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Organocatalytic and Enantioselective Transannular Reactions: Novel Strategies for the Asymmetric Synthesis of Polycyclic Structures

MEMORIA PRESENTADA POR

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PARA OPTAR AL GRADO DE DOCTOR

CON MENCIÓN "DOCTOR INTERNACIONAL"

Leioa, 2019

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Resumen extendido

Las reacciones transanulares, tal y como su propio nombre indica, son procesos cuya característica principal reside en que los puntos reactivos que participan en la formación del nuevo enlace se encuentran inicialmente formando parte de una estructura cíclica. De esta forma, las reacciones transanulares permiten acceder a estructuras policíclicas de forma sencilla y con un alto grado de economía de átomos, factores que confieren a este tipo de metodologías un gran potencial sintético.

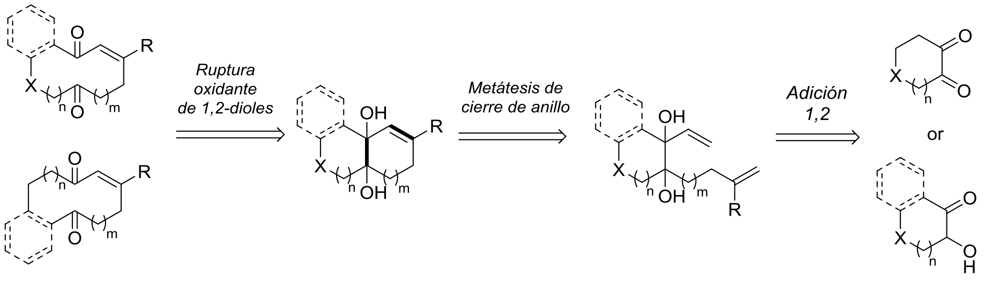
Si bien durante años se ha considerado un ámbito de gran interés dentro de la química sintética, el estudio y desarrollo de procesos transanulares eficientes se ha visto en gran medida impedido por las complicaciones inherentes a la síntesis de los substratos macrocíclicos requeridos. Afortunadamente, el desarrollo en los últimos años de nuevas metodologías sintéticas ha facilitado significativamente la obtención de estos substratos. Como consecuencia, el número de publicaciones relacionadas con el desarrollo de reacciones transanulares ha experimentado un importante aumento, siendo especialmente remarcable su aplicación como paso clave en la síntesis de numerosos productos naturales. No obstante, la gran mayoría de los ejemplos transanulares desarrollados hasta el momento consisten en procesos diastereoselectivos que requieren del empleo de substratos enantiopuros. Por el contrario, el número de ejemplos enantioselectivos es hasta la fecha muy escaso, habiéndose descrito un único ejemplo organocatalítico y enantioselectivo.

En este sentido, y en línea con los trabajos de investigación desarrollados en los últimos años en el grupo del prof. Jose Luis Vicario, el objetivo principal del presente trabajo de tesis doctoral se dirigió al estudio de reacciones transanulares enantioselectivas mediante el empleo de organocatalizadores quirales como elementos de enantiocontrol. En la presente memoria se recogen los resultados más relevantes obtenidos durante el desarrollo de este trabajo de tesis doctoral.

En un primer capítulo, se ha llevado a cabo una revisión bibliográfica acerca del empleo de reacciones transanulares como herramienta sintética para la obtención tanto de productos naturales como de compuestos con actividad biológica. A fin de aportar una visión global, se han expuesto diversos ejemplos de procesos transanulares clasificados en función del tipo de

reactividad mostrada, poniendo especial énfasis en los ejemplos catalíticos enantioselectivos desarrollados con éxito hasta la fecha.

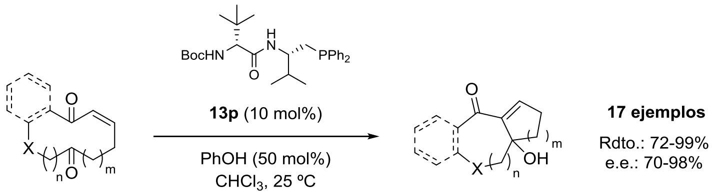
En un segundo capítulo, se recogen los principales resultados obtenidos durante el desarrollo de la primera reacción de **Morita-Baylis-Hillman transannular enantioselectiva** catalizada por fosfinas quirales. Inicialmente se describe la síntesis de los sustratos de partida, la cual ha sido específicamente diseñada a fin de permitir el acceso a sistemas cíclicos de diferente tamaño contiendo simultáneamente un sistema carbonílico α,β-insaturado así como un grupo carbonilo adicional (Esquema 1).



Esquema 1. Estrategia planteada para la síntesis de sustratos.

La metodología planteada permite acceder a ciclos de entre 9 y 12 átomos de carbono, pudiendo presentar anillos aromáticos fusionados tanto en posición α al grupo carbonilo aislado como al sistema α,β-insaturado. Esta amplia variabilidad de sustratos es posible simplemente por modificación de la dicetona de partida, de la extensión de las cadenas alquílicas adicionadas o del orden de adición de estas últimas.

En la fase inicial del proyecto, se ha demostrado la capacidad de los sustratos sintetizados para dar lugar a la reacción de Morita-Baylis-Hillman transannular proyectada. Para ello se ha evaluado el uso de diferentes fosfinas quirales nucleófilas como organocatalizadores para este proceso. De esta forma, se ha demostrado que fosfinas quirales con estructuras derivadas de esquaramidas, thioureas o aminoácidos, son capaces de promover la reacción deseada de forma enantioselectiva. Un análisis sistemático de los parámetros experimentales (naturaleza del disolvente, temperatura, concentración...), así como la optimización de las características estructurales del catalizador, ha permitido seleccionar la fosfina **13p**, derivada del aminoácido natural *L*-*tert*-leucina, como el mejor catalizador para la reacción estudiada.

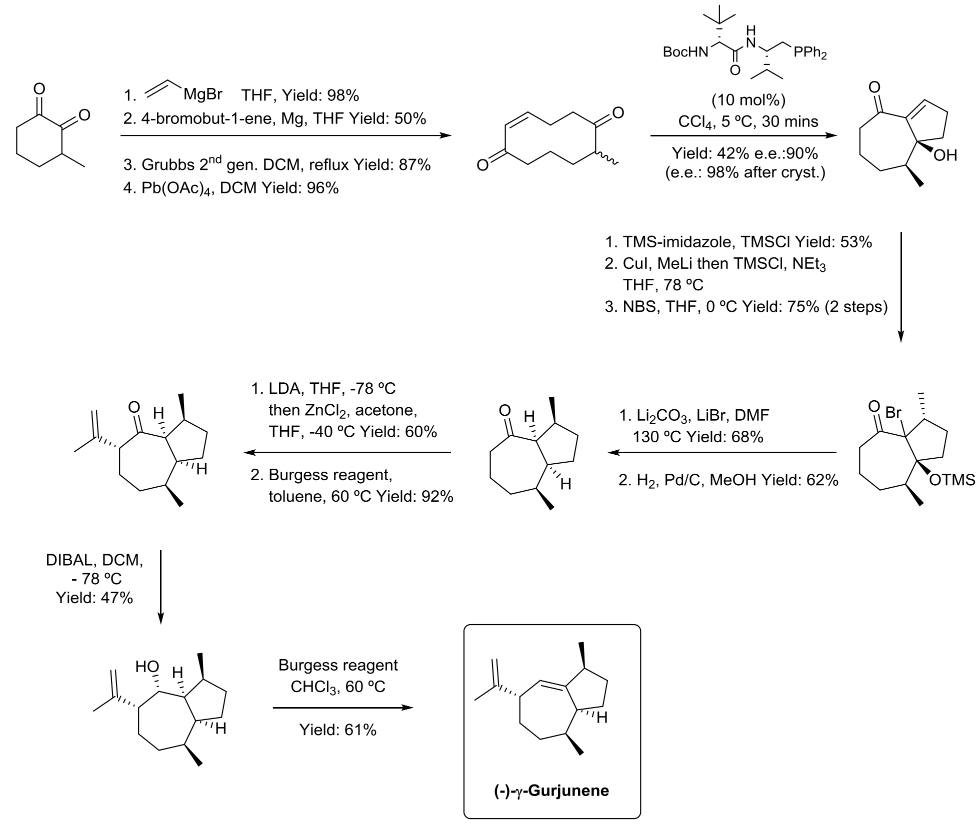


Esquema 2. Reacción de Morita-Baylis-Hillman transannular desarrollada.

Una vez optimizadas las condiciones experimentales, se ha estudiado el alcance de la reacción, pudiendo aplicarse satisfactoriamente a un total de 17 sustratos, los cuales han dado lugar a los correspondientes productos policíclicos con excelentes rendimientos y enantioselectividades. Como limitación de esta metodología, se ha observado que la reacción no tolera la sustitución en posición β del sistema carbonílico insaturado, resultando completamente inerte bajo las condiciones previamente aplicadas.

En un tercer capítulo se recogen los resultados obtenidos durante la **síntesis del compuesto (-)-γ-gurjunene**, un sesquiterpenoide natural cuya estructura base es coincidente con la de los compuestos bicíclicos previamente obtenidos en el capítulo 2. De esta forma, partiendo de la correspondiente 3-metil-ciclohexano-1,2-diona comercialmente disponible, y tras un total de 14 pasos, se ha podido acceder al producto natural γ-gurjunene con un rendimiento global del 0.46% (Esquema 3).

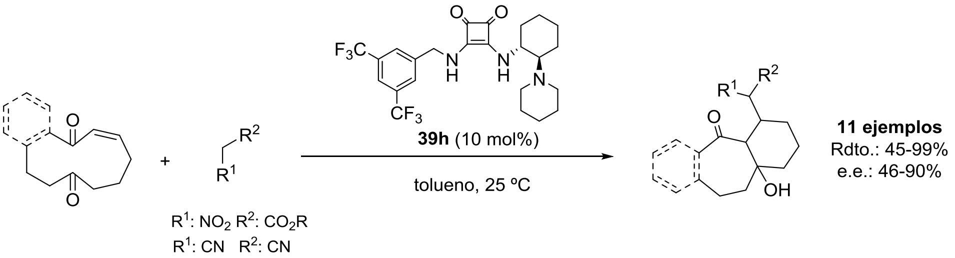
Como paso crucial de esta síntesis destaca la resolución cinética llevada a cabo en condiciones similares a las previamente empleadas en el capítulo 2, la cual es imprescindible para la obtención del producto deseado con un alto grado de enantiocontrol.



Esquema 3. Síntesis total del (-)-γ-gurjunene.

En un cuarto capítulo, y en vista de la reactividad anteriormente mostrada por los sustratos estudiados, se ha llevado a cabo el estudio de una reacción en **cascada Michael-aldólica enantioselectiva**. Para ello se han empleado catalizadores bifuncionales que contienen simultáneamente en su estructura un punto básico (capaz de desprotonar un nucleófilo externo) así como grupos susceptibles de interaccionar con electrófilos a través de la formación de puentes de hidrógeno.

De esta forma, y tras el estudio de los diferentes parámetros de reacción (temperatura, disolvente, catalizador…) se ha seleccionado la esquaramida **39h** como el catalizador bifuncional más eficiente. La reacción ha podido aplicarse satisfactoriamente a una serie de sustratos con diversos grupos funcionales en el anillo aromático (tanto dadores como atractores de electrones), obteniéndose los correspondientes productos con excelentes rendimientos y enantioselectividades. Desafortunadamente la reacción ha demostrado una gran dependencia en cuanto a la naturaleza del nucleófilo, observándose bien falta total de reactividad, bien un descenso significativo del exceso enantiomérico en el caso de nucleófilos distintos a nitroacetatos.

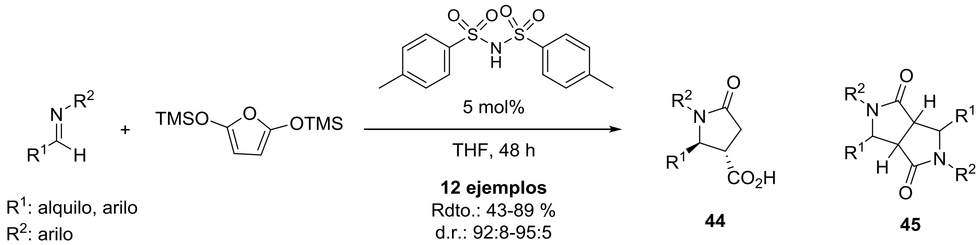


Esquema 4. Reacción en cascada Michael/aldólica transannular enantioselectiva.

Los productos obtenidos como consecuencia de la reacción organocatalítica han podido ser sometidos a diferentes transformaciones químicas, permitiendo acceder a los productos descarboxilados así como a las correspondientes nitronas de forma sencilla.

Finalmente, en un último capítulo, se recogen los resultados más relevantes obtenidos durante la estancia predoctoral de 3 meses de duración llevada a cabo en la Universidad de California – Davis (EEUU). El trabajo de investigación desarrollado durante ese periodo de tiempo ha estado enfocado al desarrollo una nueva ruta sintética que permita acceder a **compuestos γ-lactámicos** a través de una reacción de tipo **Mukaiyama-Mannich**. En este contexto, se ha demostrado que las disulfonimidas, comúnmente empleadas como ácidos de Brønsted pueden exhibir actividad como ácidos de Lewis tras un proceso de sililación en presencia de una fuente nucleofílica de silicio.

Inicialmente, se exponen los resultados obtenidos durante la optimización de las condiciones experimentales de reacción (catalizador, carga catalítica, temperatura, tiempo de reacción, disolvente…) enfocadas a controlar la selectividad de la reacción hacia la obtención de la lactama **44**, desfavoreciendo la formación de los compuestos **45** como consecuencia de un proceso doble adición.



Esquema 5. Reacción de Mukaiyama-Mannich catalizada por disulfonimidas.

De esta forma, se han podido determinar las condiciones óptimas que han permitido acceder de forma selectiva a una gran variedad de γ-lactamas con buenos rendimientos y completa diastereoselectividad *trans*. La reacción ha demostrado ser aplicable para iminas derivadas tanto de aldehídos alifáticos como aromáticos, obteniéndose buenos resultados independientemente del carácter electrónico del anillo aromático. Asimismo, se ha podido aplicar con éxito a sustratos con diferentes grupos aromáticos directamente unidos al nitrógeno. Finalmente, los compuestos γ-lactámicos han sido sometidos de forma selectiva a diferentes transformaciones químicas, siendo posible la desprotección del átomo de nitrógeno, así como la derivatización del ácido carboxílico.

EL/LA PRESIDENTE/A,	EL/LA SECRETARIO/A,
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Fdo.:

Quiero expresar mi agradecimiento a los Profesores Dr. Jose L. Vicario y Dra. Mª Luisa Carrillo por la dirección y supervisión de este trabajo, así como por la ayuda y confianza depositadas en mí. Igualmente agradezco a los Profesores Dr. Efraím Reyes y Dra. Uxue Uria, así como al resto del grupo de investigación su continuo apoyo durante el desarrollo de esta tesis doctoral.

También me gustaría agradecer a mis familiares y amigos que con su apoyo y comprensión han contribuido de una forma u otra a que este trabajo se haya podido llevar a cabo.

Asimismo, agradezco al Gobierno Vasco la concesión de una "beca predoctoral de formación de personal investigador no doctor", así como por la "ayuda para estancias en centros distintos al de aplicación del programa predoctoral de formación de personal investigador" y por la subvención a grupos de investigación IT328-10 y IT908-16; a la Universidad del País Vasco UPV/EHU por el proyecto EHUA 12/09 así como al MICINN (Proyecto CTQ2011-22790, CTQ2014-52107-P y CTQ2017-83633-P) por la financiación otorgada. Finalmente agradecer también el apoyo técnico y humano de los SGIker de la UPV/EHU.

Summary

Transannular reactions are processes with a high synthetic potential as they provide access to complex polycyclic structures in a simple way. By definition, a transannular reaction requires the use of medium or large size cyclic precursors, characterized by a ring strain inherent to this type of cyclic structures and associated to the presence of eclipsing and steric interactions, as well as bond angle distortions. A transannular reaction is therefore, favored by the strain release that takes place as consequence of the process. In the same way, the acquisition of certain energetically favored conformations by the cyclic precursor can be employed to favor the stereochemical control of the reaction. In this context, organocatalysis stands out as a promising tool for the development of stereocontrolled chemical reactions. The present manuscript complies the study and development of enantioselective transannular reactions promoted by chiral organocatalysts.

In this sense, the results obtained for a Morita-Baylis-Hillman transannular reaction employing cyclic keto-enones as substrates under chiral phosphine catalysis are summarized. In this way, it was established the capability of these catalysts as promoters of the desired reaction, providing access to a wide variety of polycyclic products in excellent yields and high enantiocontrol. Additionally, the applicability of this reaction has been demonstrated by incorporating it as a key step in the first enantioselective total synthesis of natural sesquiterpenoid (-)-γ-gurjunene.

On the other hand, the suitability of the same type of substrates to undergo a domino Michael/transannular aldol reaction initiated by the conjugate addition of active methylene compounds has been evaluated. Chiral bifunctional catalysts were employed for inducing enantiocontrol, as they are capable of interacting both with the substrate and with the nucleophile via hydrogen-bond interactions. In this way, the envisioned polycyclic compounds were obtained in excellent yields and enantioselectivities.

Finally, the results obtained in the context of a three months stay in the University of California Davis under the supervision of Prof. Jared T. Shaw are presented. The project focused on the synthesis of γ lactams through a Mukaiyama-Mannich reaction between imines and 2,5-bis(trimethylsilyloxy)furan. This process, catalyzed by disulfonimides as Lewis acids, allowed the synthesis of a wide variety of γ lactams in good yields and excellent diastereoselectivities.

Resumen

Las reacciones transanulares son procesos con un gran potencial sintético ya que permiten acceder a estructuras policíclicas de forma sencilla y con un alto grado de economía de átomos. Por definición, una reacción transannular requiere del empleo de precursores cíclicos, caracterizados por presentar una tensión de anillo inherente a estas estructuras cíclicas y asociada a la existencia de eclipsamientos e interacciones estéricas así como a la distorsión de ángulos de enlace. Una reacción transannular se encuentra, por tanto, favorecida por la liberación de tensión que se produce como consecuencia del proceso. Asimismo, la adquisición de determinadas conformaciones energéticamente favorables por parte del precursor cíclico puede emplearse para favorecer el control estereoquímico de la reacción. En este sentido, la organocatálisis destaca como herramienta de gran interés para el desarrollo de reacciones químicas estereocontroladas mediante el empleo de moléculas quirales de pequeño tamaño que no contienen elementos metálicos en su estructura, como elementos de enantiocontrol. Esta memoria recoge el estudio y desarrollo de reacciones transanulares enantioselectivas promovidas por organocatalizadores quirales.

En primer lugar, se recogen los resultados logrados en el estudio de la reacción de Morita-Baylis-Hillman transanular sobre una serie de ceto-enonas cíclicas catalizada por fosfinas quirales. De esta forma se pudo demostrar la capacidad de estos catalizadores para promover la reacción deseada, dando lugar a una gran variedad de productos policíclicos con excelentes rendimientos y un alto grado de enantiocontrol. Adicionalmente, se puso de manifiesto la aplicabilidad de esta reacción mediante la incorporación de la metodología desarrollada como paso clave en la primera síntesis total enantioselectiva del sesquiterpeno natural (-)-γ-gurjunene.

Por otro lado, se ha estudiado la capacidad de este tipo de sustratos para participar en reacciones en cascada Michael/reacción aldólica iniciadas por la adición conjugada de compuestos de metileno activo bajo el empleo de catalizadores quirales bifuncionales ácido/base de Brønsted. Estos catalizadores, cuya acción se basa en el establecimiento de interacciones no covalentes con el sustrato, permitieron obtener los productos policíclicos correspondientes con excelentes resultados.

Finalmente, se presentan los resultados obtenidos en el contexto de una estancia predoctoral de 3 meses en el grupo del profesor Jared T. Shaw en el Universidad de California – Davis. El trabajo desarrollado se centró en la síntesis de γ lactamas mediante una reacción de Mukaiyama-Mannich catalizada mediante el empleo de disulfonimidas como ácidos de Lewis.

Laburpena

Doktorego tesi hau erreakzio transanularren erabileran oinarritzen da estruktura poliziklikoen sintesi asimetrikoari aurre egiteko. Izenak adierazten duen bezala, erreakzio transanularretan sustrato ziklikoen erabilera ezinbestekoa da. Konposatu hauek zenbait tentsio erakusteagatik bereizten dira, interakzio esterikoek eta lotura anguluen distortsioak eraginda hain zuzen ere. Beraz, ikuspuntu energetikotik, edozein erreakzio transanularren ondorioz energia askapena gertatzen da, prozesu globala faboratuz. Era berean, interakzio desestabilizatzaileak minimizatzeko sustrato ziklikoek normalean hartzen dituzten konformazioak erabili ahal dira, elementu kiral batekin batera, prozesuaren estereoselektibitatea kontrolatzeko. Tesi honetan organokatalizatzaile ezberdinen erabilera aztertu da erreakzio transanular enantioselektiboetan.

Alde batetik, Morita-Baylis-Hillman erreakzio transanularra aztertu zen. Erreakzio transanularra katalizatzeko aminoazido natural deribatutako fosfina kiralen gaitasuna frogatu zen, tamaina ezberdineko sustrato ziklikoak erabiliz. Garatutako metodologia poliziklo ezberdinak sintetizatzeko erabili zen, etekin eta enantioselektibitate bikainekin. Horretaz gain, metodologia honen egokitasuna egiaztatu zen (-)-γ-gurjunene sesquiterpeno naturalaren lehenengo sintesi enantioselektiboan aplikatuz.

Beste aldetik, katalizatzaile bifuntzionalak erabili ziren Michael iniziatutako erreakzio aldoliko transanularra katalizatzeko, konposatu metileno aktiboak nukleofilo bikoitz moduan erabiliz. Katalizatzaile hauek aldi berean pro nukleofiloarekin eta elektrofiloarekin interakzionatzeko gaitasuna erakusten dute, interakzio ez kobalenteen bidez. Interakzio estu hauen ondorioz, produktu poliziklikoak enantioselektibitate altuekin lortu ziren

Bukatzeko, Davis Unibertsitatean egindako epe laburreko egonaldian, Dr. Jared T. Shaw irakasleareanpean lortutako emaitzak aurkezten dira. Denboraldi horretan, γ-lactamak sintetizatzeko metodologiaren garapenean parte hartu nuen. Proiektu honetan, disulfonimiden kapazitatea aztertu zen Lewis azido bezala, Mukaiyama-Mannich erreakzioa katalizatzeko iminen eta 2,5-bis-(trimetilsililoxi)furanoaren artean.

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Appendix

Supplementary information

The numbering of references, figures, schemes and tables has been restarted at the beginning of each chapter.

1

1

Introduction

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1. TRANSANNULAR REACTIONS

In the field of organic chemistry, the efficient synthesis of highly complex structures has been considered a challenge for years.[1] As most of the pharmaceuticals and biologically active chemical compounds contain polycyclic frameworks in their structural cores,[2] important efforts have been directed towards the development of novel strategies to access these assemblies. From a synthetic point of view, the construction of polycyclic structures can be confronted following multiple approaches which, generally speaking, can be classified into three main groups: (a) *cyclization reactions*, where new C-C or C-heteroatom bond is formed by the intramolecular reaction between a lateral chain and a functionality contained in a cyclic structure (b) *cycloaddition processes*, in which two bonds are simultaneously generated between independent molecules, being one of them necessarily cyclic and (c) *transannular reactions*, characterized by the reaction of two reactive sites initially present as part of a cyclic structure (Figure 1.1).

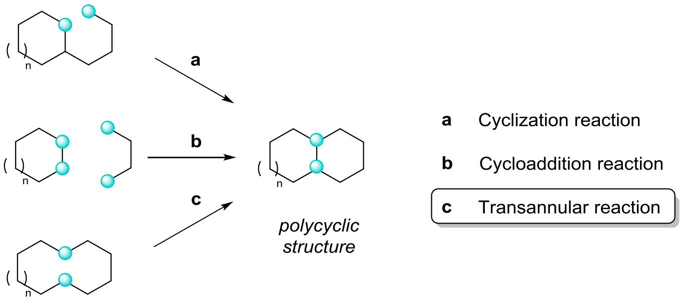

Figure 1.1. Synthetic approaches to polycyclic structures.

While there is plenty of literature focused on the two first strategies,[3] the transannular approach has not been the object of such attention by the scientific community.[4] Undoubtedly,

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[1] Andrushko, V.; Andrushko, N. In *Stereoselective Synthesis of Drugs and Natural Products*; John Wiley & Sons Inc.: Karlsruhe, 2013.

[2] (a) García-Castro, M.; Zimmermann, S.; Sankar, M. G.; Kumar, K. *Angew. Chem. Int. Ed.* **2016**, *55*, 7586. (b) Bhat, S. V.; Nagasampagi, B. A.; Sivakumar, M. In *Chemistry of Natural Products*; Springer: Berlin, 2005.

[3] For selected reviews on cyclization and cycloaddition reactions, see: (a) Barrett, A. G. M.; Ma, T.-K.; Mies, T. *Synthesis*, **2018**, *50*, 1209. (b) Albano, G.; Aronica, L. A. *Synthesis*, **2018**, *50*, 1209. (c) Klier, L.; Tur, F.; Poulsen, P. H.; Jørgensen, K. A. *Chem. Soc. Rev.* **2017**, *46*, 1080. (d) Held, F. E.; Grau, D.; Tsogoeva, S. B. *Molecules*, **2015**, *20*, 16103. (e) Ylijoki, K. E. O.; Stryker, J. M. *Chem. Rev.* **2013**, *113*, 2244. (f) Gulías, M.; López, F.; Mascareñas, J. L. *Pure Appl. Chem.* **2011**, *83*, 495.

[4] (a) Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Tetrahedron*, **2014**, *70*, 9461. (b) Clarke, P. A.; Reeder, A. T.; Winn, J. *Synthesis*, **2009**, 691.

the difficulties associated to the preparation of the required medium size (8-11 membered) and large size (>12 membered rings, also called macrocycles) cyclic substrates, has been one of the main factors that has delayed the development of this field.[5] New methodologies for the efficient synthesis of challenging medium and large size cycles,[6] such as Ring Closing Metathesis, have removed this barrier allowing a remarkable growth in the field of transannular reactions and their application to the synthesis of natural products and bioactive compounds.[4]

From a thermodynamic point of view, the course of a transannular reaction will be determined by the change on enthalpy and entropy involved in the process, which are strongly related to the structure of the cyclic precursor and the obtained polycyclic product.[7] In this sense, the inherent strain associated to any cyclic compound is strongly dependent both on the size and on the number and nature of the substituents present in the structure, affecting significantly the chemical and physical properties of these compounds. For instance, Figure 1.2 shows the strain energies of different cycloalkanes, measured as the difference in heat of combustion between the cyclic molecule and the analogous acyclic alkane.

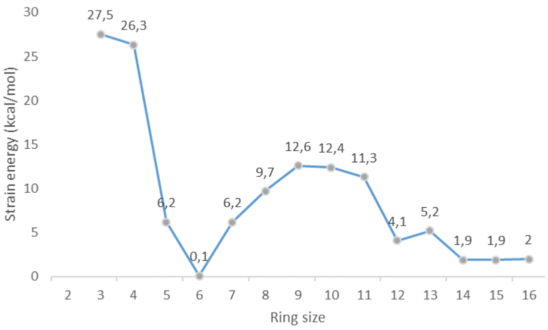

Figure 1.2. Strain energies for cycloalkanes.[8]

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[5] (a) Peterson, M. L. The synthesis of macrocycles for drug discovery. In *Macrocycles in Drug Discovery*; Levin, J. I., Eds.; RSC: Cambridge, 2015, pp 398-465. (b) Roxburgh, C. J. *Tetrahedron*, **1995**, *51*, 9767.

[6] (a) Yu, X.; Sun, D. *Molecules*, **2013**, *18*, 6230. (b) Hoveyda, A. H.; Zhugralin, A. R. *Nature*, **2007**, *450*, 243. (c) Zhang, W.; Moore, J. S. *Angew. Chem. Int. Ed.* **2006**, *45*, 4416. (d) Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086. (e) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.

[7] Dunitz, J. D.; Prelog, V. *Angew. Chem.* **1960**, *72*, 896.

[8] Yang, L.; Xie, L.; Wei, Y.; Liu, Y.; Devi, M.; Huang, W. *Steric strain in molecular organics.* In *Encyclopedia of Physical Organic Chemistry*; Wang, Z., Eds.; John Wiley & Sons, Inc.: USA, 2017.

As it can be observed, small cycles show extremely high strain energy values, which explains their instability and reactivity. In addition, medium size cycloalkanes present relatively high strain, compared to that measured for the 5, 6 and 7-membered cycles. This strain is the consequence of the combination of three independent factors: *Baeyer* or angular strain, associated to bond angle distortion; *Pitzer* or torsional strain, resulted from eclipsing interactions; and *Prelog* or transannular strain, related to unfavorable steric interactions between non-adjacent substituents in the ring chain.[9] As minimization of some of these adverse interactions will inevitably imply an increase in others, the existence of certain strain is an aspect that characterizes most cyclic compounds. For large rings a significant decrease in strain is noticed due to the high flexibility of their structures than allow acquiring conformations in which those destabilizing interactions are avoided.

As it has been mentioned before, the strain in medium size rings arises as a convergence of the three different types of strain, being the transannular component the major contributor to this factor. As a consequence, these rings show a pronounced tendency to minimize transannular repulsions by the acquisition of low energy conformations. While conformational preferences for 5 to 7-membered rings have been the subject of deep studies, medium and large cycles have not been so extensively examined.[10] Furthermore, for larger systems, the higher flexibility leads to a more complex scenario due to the increasing number of energetically similar conformations. For instance, different studies have concluded that among the 11 conformations commonly considered for cyclooctane, the *boat-chair (BC)* conformation is energetically favored (Figure 1.3).[11] In the case of analogous nine[12] and ten[13] membered cycloalkanes *twist boat-chair (TBC)* and *boat-chair-boat (BCB)* conformations have been determined as the preferred ones respectively.

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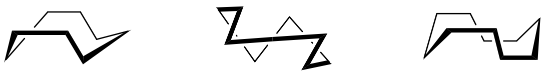
[9] (a) Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311. (b) Prelog, V. *J. Chem. Soc.* **1950**, 420. (c) Smith, M. B. *Organic Synthesis*; Wavefunction, Inc.: Connecticut, 2010.

[10] Nasipuri, D. *Stereochemistry of organic compounds. Principles and applications*: New Age International Publishers; New Dehli, 2005.

[11] (a) Wiberg, K. B.; *J. Org. Chem.* **2003**, *68*, 9322. (b) Kolossvary, I.; Guida, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 2107.

[12] Hendrickson, J. B. *J. Am. Chem. Soc.* **1964**, *86*, 4854.

[13] Still, W. C.; Galynker, I. *Tetrahedron*, **1981**, *37*, 3981.



Cyclooctane
Boat-Chair

Cyclononane
Twist Boat-Chair

Cyclodecane
Boat-Chair-Boat

Figure 1.3. Favored conformations for medium size cycloalkanes.

In the case of cycloundecane, the scenario becomes more complex, as the number of energetically similar conformations increases. Although ^{13}C-NMR studies have shown that at low temperatures there is an equilibrium between two main forms (Figure 1.4); at higher temperatures, the number of conformations in equilibria increases significantly.[14]

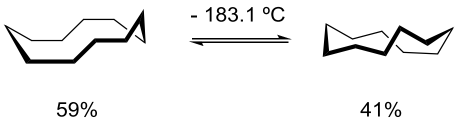


Figure 1.4. Lowest energy conformations for cycloundecane.

Another relevant aspect that should be considered in transannular reactions is the enthalpy change involved in the process. From a general perspective, for medium size rings (n = 8-11), transannular processes will be enthalpically favored by the strain release that takes place during the course of the reaction. However, this fact will be quite dependent on the nature of the polycyclic structure obtained as product of the reaction. Table 1.1 summarizes the strain energies calculated for different cycloalkanes, together with the corresponding bicyclic structures.[15] As it can be observed, in the case of cyclooctane the formation of the bicyclic product is not favored due to the high strain energy associated to this structure. On the contrary, for analogous 9-membered cycloalkane the cyclization process will be favored based on the significantly lower strain energy for the resulting polycyclic compound. In the case of a cyclodecane precursor, the formation of a [4.4.0]decane scaffold will be favored compared to [5.3.0] one, as the strain release involved in the formation of the bicyclic product is considerably higher for the first alternative. Additionally, it should not be neglected the fact that measured strain can exhibit a significant dependence on the *cis*/*trans* fusion of the bicyclic product; for

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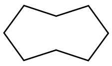
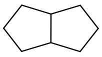
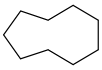
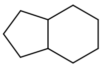
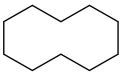
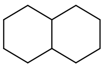
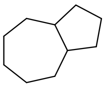
[14] Pawar, D. M.; Brown II, J.; Chen, K.-H.; Allinger, N. L.; Noe, E. A. *J. Org. Chem.* **2006**, *71*, 6512.

[15] (a) Engler, E. M.; Andose, J. D.; Schleyer, P. V. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005. (b) Chang, S.-J.; McNally, D.; Shary-Tehrany, S.; Hickey, M. J.; Boyd, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 3109.

instance, the formation of *trans* [4.4.0] bicyclo is considerably favored compared to analog *cis* product.

Table 1.1. Strain energies for different cycloalkanes.

Cycloalkane	Strain energy Kcal/mol	Product	Strain energy Kcal/mol
	11.9		*cis*: 12.0 *trans*: 18.4
	15.5		*cis*: 8.9 *trans*: 7.9
	16.4		*cis*: 4.1 *trans*: 1.0
			*cis*: 13.4 *trans*: 13.1

As it has been mentioned before, medium sized rings tend to acquire energetically favored conformations in which total strain, but especially the transannular contribution to that factor, is minimized. Unfortunately, analogous conformational study for substituted or functionalized derivatives becomes more challenging, albeit it is commonly accepted that conformations related to those acquired for the analogous simple cycloalkanes are preferred.[16]

These conformational biases can be reinforced by incorporating rigidifying elements, such as substituents or unsaturations, which increase the energy barriers both for pseudorotation and ring inversion. As an example, in the case of cyclononane the ring inversion energy is 25.0 kJ/mol, rising to 37.5 kJ/mol for 1,1-dimethyl compound and 83.5 kJ/mol for 1,1,4,4-tetramethyl derivative.[10] Therefore the existence of these elements will lead to a significant reduction in the conformational mobility of the studied cyclic molecule.

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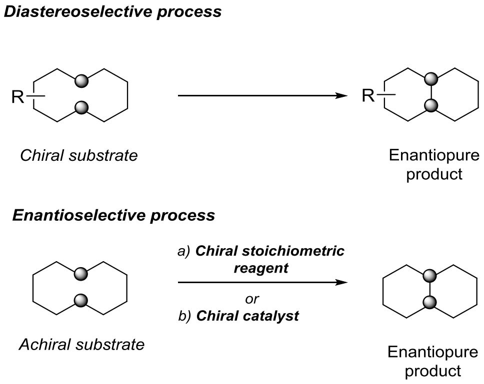
[16] Burevschi, E.; Peña, I.; Sanz, M. E.; *Phys. Chem. Chem. Phys.* **2019**, *21*, 4331.

2. TRANSANNULAR REACTIONS IN THE STEREOSELECTIVE SYNTHESIS OF ENANTIOPURE COMPOUNDS

As it has been previously stated, the conformational constraint associated to a cyclic structure plays a significant role in transannular reactions, as it conditions the approach of the reactive sites. In this sense, the intrinsic conformational preference of cyclic compounds can be used, for instance, as key factor for achieving stereochemical control, becoming a suitable strategy for the synthesis of chiral complex molecular targets.[17]

Regarding the strategy followed for achieving stereochemical control in the synthesis of enantiopure compounds by transannular reactions, reported examples can be classified into three main categories: (a) diastereoselective transannular processes where *chiral substrates* are employed for inducing enantiocontrol, (b) enantioselective processes employing *chiral stoichiometric reagents* and (c) catalytic and enantioselective reactions, in which a *chiral catalyst* is responsible of the enantioselectivity.



Scheme 1.1. General strategies for stereochemical control in transannular reactions.

Although there are different examples of transannular reactions applied to the synthesis of enantiopure compounds,[18] most of the reported works developed up to date involve

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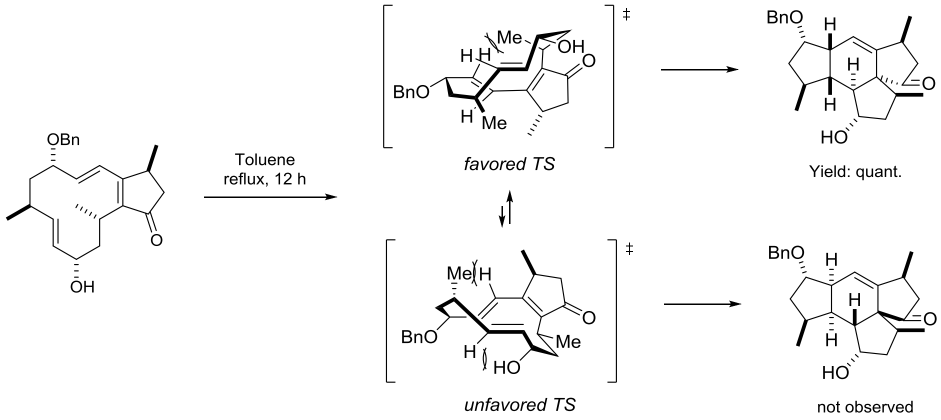
[17] Yang, J.; Xue, H. *Transannular cyclization in natural product total synthesis.* In *Stereoselective Synthesis of Drugs and Natural Products*; Andrushko, V.; Andrushko, N., Eds.; John Wiley & Sons Inc.: Karlsruhe, 2013, pp 551-579.

[18] For recent examples on transannular reactions in the synthesis of enantiopure compounds not applied to natural product synthesis, see: (a) Maiga-Wandiam, B.; Corbu, A.; Massiot, G.; Sautel, F.; Yu, P.; Lin, B. W.-Y.; Houk, K. N.; Cossy, J. *J. Org. Chem.* **2018**, *83*, 5975. (b) Chan, D.; Chen, Y.; Low, K.-H.; Chiu, P. C*hem. Eur. J.*

diastereoselective processes in which chiral enantioenriched starting materials are required. In this way, the stereocenters present in the cyclic precursor have a significant influence on the stereochemical outcome of the reaction due to the transannular repulsive interactions generated as consequence of the conformation adquired by the macrocyclic structure. This concept is clearly illustrated in the example represented in Scheme 1.2. In this transannular Diels-Alder (TADA) reaction reported by Uemura in 2004,[19] the high diastereoselectivity achieved was suggested to arise from a favored transition state in which severe transannular interactions are avoided.



Scheme 1.2. Diastereoselective TADA reaction for the synthesis of enantiopure spirotetracycles.

Alternatively, some limited examples of enantioselective transannular reactions that involve the use of stoichiometric amounts of chiral reagents have also been reported. For instance, this strategy has been applied by Inoue and coworkers for the desymmetrization of cyclic 1,4-diketones through an enantioselective transannular aldol reaction, employing stoichiometric amounts of a chiral base for the enantioselective deprotonation step.[20] A related example involving a formal transannular epoxide opening has also been reported by Hodgson employing

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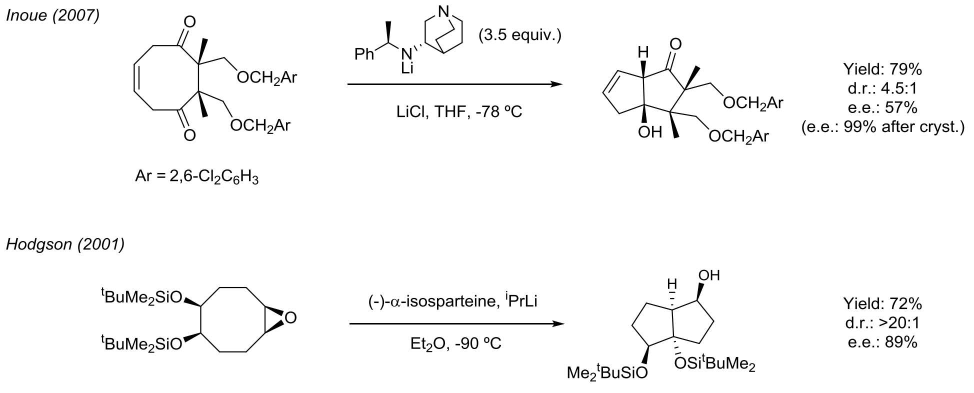
2018, *24*, 2375. (c) Riaño, I.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *J. Org. Chem.* **2018**, *83*, 4180. (d) Atmuri, N. D. P.; Reilley, D. J.; Lubell, W. D. *Org. Lett.* **2017**, *19*, 5066. (e) Kamimura, A.; Moriyama, T.; Ito, Y.; Kawamoto, T.; Uno, H. *J. Org. Chem.* **2016**, *81*, 4664. (f) Atmuri, N. D. P.; Lubell, W. D. *J. Org. Chem.* **2015**, *80*, 4904. (g) Franklin, A. I.; Bensa, D.; Adams, H.; Coldham, I. *Org. Biomol. Chem.* **2011**, *9*, 1901. (h) Surprenant, S.; Lubell, W. D. *Org. Lett.* **2006**, *8*, 2851. (i) Felzmann, W.; Arion, V. B.; Mieusset, J.-L.; Mulzer, J. *Org. Lett.* **2006**, *8*, 3849.

[19] Araki, K.; Saito, K.; Arimoto, H.; Uemura, D. *Angew. Chem. Int. Ed.* **2004**, *43*, 81.

[20] Inoue, M.; Lee, N.; Kasuya, S.; Sato, T.; Hirama, M.; Moriyama, M.; Fukuyama, Y. *J. Org. Chem.* **2007**, *72*, 3065.

iso-propyl lithium as base together with (-)-α-isosparteine as chiral ligand.[21] However, the employment of chiral reagents in transannular processes cannot be considered a common approach for the synthesis of enantiopure compounds.



Scheme 1.3. Reported transannular reactions involving the employment of chiral reagents.

On the other hand, the number of catalytic and enantioselective transannular reactions is significantly scarce, being limited to only four examples reported up to date, from which only one can be considered as organocatalytic. In order to contextualize this work, the reported catalytic and enantioselective examples of transannular reactions will be discussed in detail in the following paragraphs.

The first catalytic and enantioselective transannular reaction was reported by Jacobsen and coworkers in 2007, in which oxazaborolidine catalysts were employed as efficient promoters of an enantioselective transannular Diels-Alder reaction (Scheme 1.4).[22] Reaction worked for different sized macrocycles, including α,β-unsaturated ketones and esters, obtaining the corresponding endo products in moderate to good yields and excellent enantioselectivity. However, reaction demonstrated to be highly dependent on the conformation of the diene, being ineffective when (*E*, *Z*) or trisubstituted dienes were employed.

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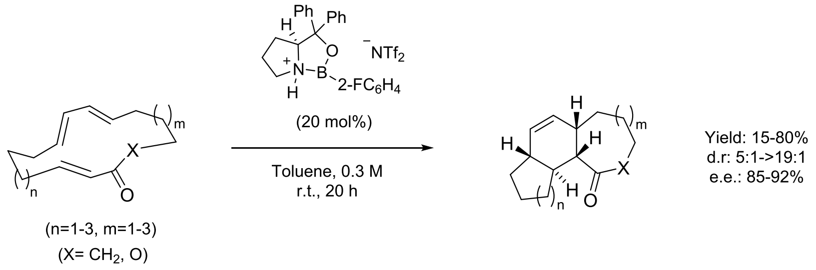
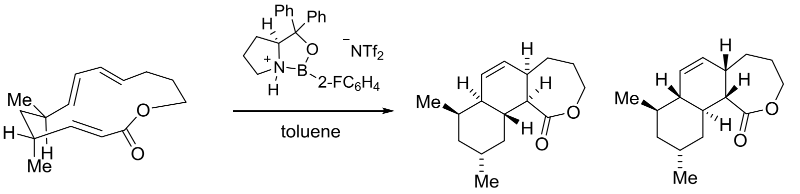
[21] Hodgson, D. M.; Cameron, I. D.; Christlieb, M.; Green, R.; Lee, G. P.; Robinson, L. A. *J. Chem. Soc. Perkin Trans. 1*, **2001**, 2161.

[22] Balskus, E. P.; Jacobsen, E. N. *Science,* **2007**, *317*, 1736.



Scheme 1.4. Organocatalytic and enantioselective transannular Diels-Alder reaction reported by Jacobsen.

Additionally, authors demonstrated that for a chiral substrate, the diastereoselectivity of the process arising as consequence of substrate-control, could be affected by the chiral catalyst, being able to work completely under catalyst-control regime. In this way, a chiral macrocyclic substrate for which no selectivity was observed under thermal conditions, provided the final adduct with high stereocontrol when the same reaction was carried out in the presence of the chiral oxazaborolidine catalyst.



Conditions:	endo A	endo B
120 ºC	45.5	54.5
cat. (20 mol%), r.t.	2.8	97.2
ent-cat. (20 mol%), r.t.	77.8	22.2

Scheme 1.5. Catalyst controlled diastereoselective transannular Diels-Alder reaction.

In a different context, some years later, the same authors reported a chromium (III) catalyzed enantioselective transannular ketone-ene reaction.[23] Developed methodology was successfully applied to a variety of medium-sized keto-olefins, including substituted, as well as heteroatomic substrates. The corresponding bicyclic alcohols were obtained in all the cases as a single diastereomer and with moderate to good enantiomeric excess (Scheme 1.6).

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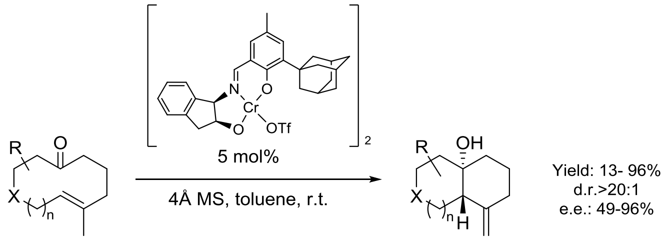
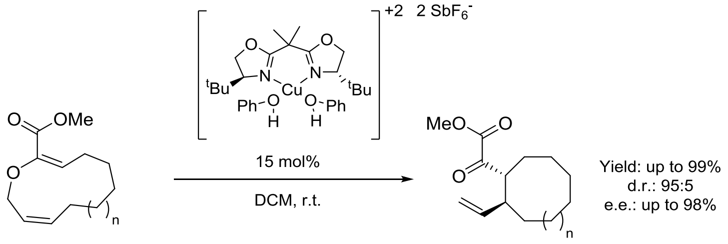
[23] Rajapaksa, N. S.; Jacobsen, E. N. *Org. Lett.* **2013**, *15*, 4238.



Scheme 1.6. Enantioselective catalytic ketone-ene reaction developed by Jacobsen.

Nearly at the same time, another catalytic and enantioselective transannular reaction was reported by Hiersemann and coworkers.[24] This work consist on a {1,6} Gosteli-Claisen rearrangement in which Lewis acid catalysts were employed to trigger the transannular process. The reaction demonstrated to be applicable to macrocycles of different size, providing the corresponding adducts in high yields and enantiomeric excess, although authors declared a significant dependence of the yield and enantiomeric excess on the configuration of both alkene moieties of the starting materials.



Scheme 1.7. Catalytic enantioselective {1,6} Gosteli-Claisen rearrangement.

Finally in 2008, List *et.al.* reported the only example developed up to date regarding an organocatalytic and enantioselective transannular reaction.[25] In this work, *trans*-4-fluoro proline was employed as catalyst in a highly enantioselective transannular aldol process using the enamine activation manifold. The reaction was successfully applied to a variety of cyclic

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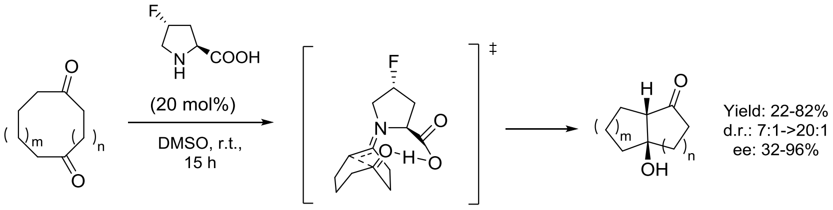
[24] Jaschinski, T.; Hiersemann, M. *Org. Lett.* **2012**, *14*, 4114.

[25] Chandler, C. L.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6737.

diketones from 8 to 10 carbon atoms, affording the corresponding enantiopure aldol products in good yields.



Scheme 1.8. Organocatalyzed enantioselective transannular aldol reaction.

The obtained *cis* ring fusion was attributed to the *E* geometry of the enamine intermediate, as well as to the relative approach of the reactive sites forced by the intramolecular H-bond between the carboxylic acid of the catalyst and the ketone. This example is especially remarkable for being the only organocatalyzed enantioselective transannular reaction developed up to date.

3. STEREOSELECTIVE TRANSANNULAR REACTIONS IN NATURAL PRODUCT SYNTHESIS

The potential of transannular reactions as synthetic tool has been fully demonstrated across several examples in the literature. In this sense, many research groups have focused their efforts on broadening the applicability of previously developed transannular methodologies to the total synthesis of enantiopure natural products.[4] It is noteworthy that almost all of the examples developed in this context imply diastereoselective processes which rely on the use of chiral enantioenriched starting materials, remaining the enantioselective approach significantly underdeveloped. In the following section the examples reported up to date in which transannular reactions are used as key step in the total synthesis of natural products will be presented classified depending on the nature of the transannular reaction involved.

3.1. Transannular cycloadditions

Among the variety of reactions developed in a transannular fashion, the transannular Diels-Alder reaction (TADA) is by far the most studied one. This fact could be attributed to the high selectivity and atom economy that characterizes this reaction, making it an ideal choice for accessing complex synthetic targets efficiently.

Since the early examples reported by Deslongchamps *et.al.* for the construction of tricyclic structures,[26] knowledge regarding the mechanism and factors affecting transannular Diels Alder reaction has allowed its efficient application as key step in many examples of total syntheses, being a recurrent strategy to access enantiopure natural products,[27] as it provides direct access to tricyclic structures, considered to be challenging through other methodologies.

In this sense, in 2008 Deslongchamps himself reported the total synthesis of (+)-cassaine, a nonsteroidal inhibitor of Na^+,K^+-ATPase originally isolated from the bark of *Erythrophleum*

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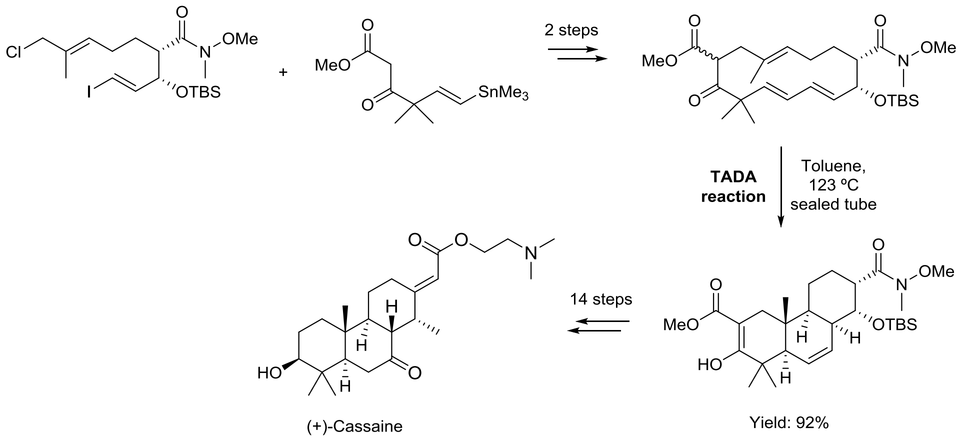
[26] (a) Deslongchamps, P. *Pure Appl. Chem.* **1992**, *64*, 1831. (b) Deslongchamps, P. *Aldrichim. Acta*, **1991**, *24*, 43. (c) Baettig, K.; Dallaire, C.; Pitteloud, R.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5249. (d) Baettig, K.; Marinier, A.; Pitteloud, R.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5253. (e) Bérubé, G.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5255.

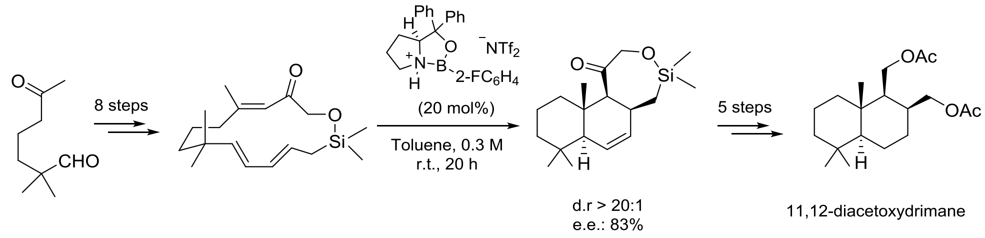
[27] For a review about TADA strategy in total synthesis, see: Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron*, **2001**, *57*, 4243.

guinneese.[28] In this synthesis, (+)-cassaine could be obtained in 14 steps from the required macrocycle, after a highly selective transannular Diels-Alder reaction that took place under thermal activation (Scheme 1.9).



Scheme 1.9. TADA reaction in the total synthesis of (+)-cassaine.

Another representative example of the applicability of this reaction in the synthesis of natural products, is the previously outlined catalytic and enantioselective transannular Diels-Alder reaction developed by Jacobsen and coworkers.[22] In this work, authors applied the previously optimized transannular Diels-Alder process as a key step in the total synthesis of natural sesquiterpenoid 11,12-diacetoxydrimane, which could be accomplished in 14 steps from a commercially available keto-aldehyde.



Scheme 1.10. Synthesis of 11,12-diacetoxydrimane by TADA reaction.

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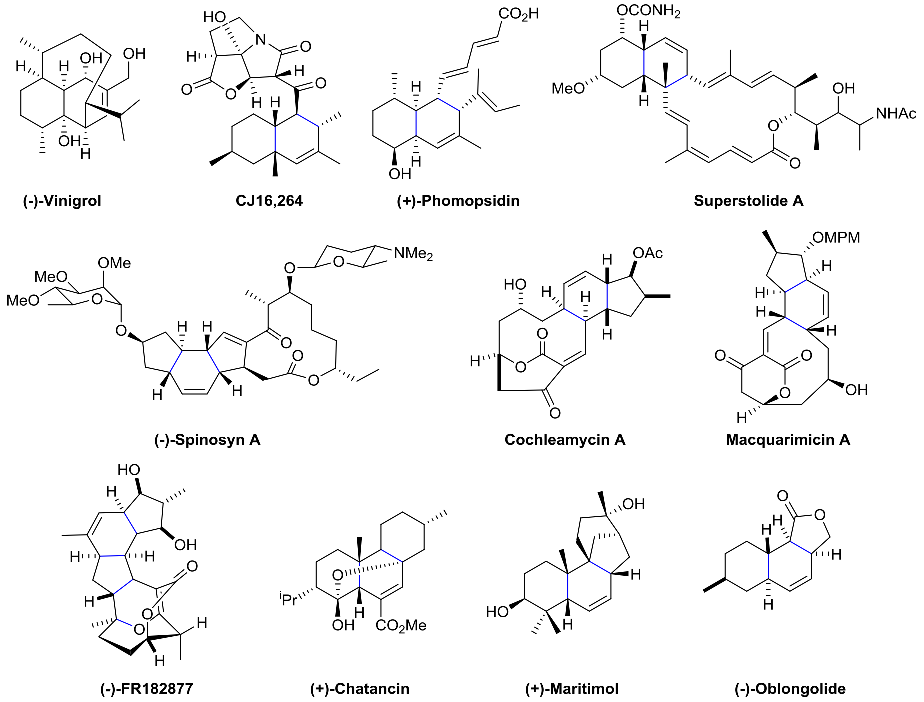
[28] Phoenix, S.; Reddy, M. S.; Deslongchamps, P. *J. Am. Chem. Soc.* **2008**, *130*, 13989.

Apart from the abovementioned examples, in the last years transannular Diels-Alder reaction has been employed as a recurrent strategy to build up the structural core of several natural products, as it is illustrated by the great variety of structures synthesized by these processes, some of them summarized in the following figure.



(-)-Vinigrol **CJ16,264** **(+)-Phomopsidin** **Superstolide A**

(-)-Spinosyn A **Cochleamycin A** **Macquarimicin A**

(-)-FR182877 **(+)-Chatancin** **(+)-Maritimol** **(-)-Oblongolide**

Figure 1.5. Natural products synthesized by diastereoselective TADA reactions. [29]

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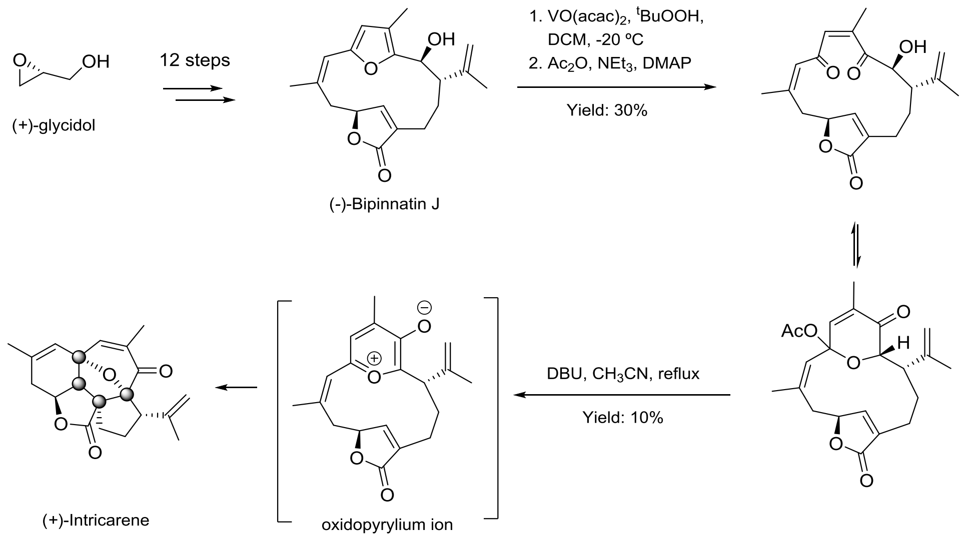
[29] (-)-Vinigrol: Yu, X.; Xiao, L.; Wang, Z.; Luo, T. *J. Am. Chem. Soc.* **2019**, *141*, 3440; CJ16,264: Nicolau, K. C.; Shah, A. A.; Korman, H.; Khan, T.; Shi, L.; Worawalai, W.; Theodorakis, E. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 9203; (+)-Phomopsidin: Hayashi, N.; Suzuki, T.; Usui, K.; Nakada, M. *Tetrahedron*, **2009**, *65*, 888; Superstolide A: Tortosa, M.; Yakelis, N. A.; Roush, W. R. *J. Am. Chem. Soc.* **2008**, *130*, 2722; (-)-Spynosyn A: Winbush, S. M.; Mergott, D. J.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1818; Cochleamycin A: Dineen, T. A.; Roush, W. R. *Org. Lett.* **2004**, *6*, 2043; Macquarimicin A: Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.-I.; Tadano, K.-I. *J. Am. Chem. Soc.* **2004**, *126*, 11254; (-)-FR182877: Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125,* 13531; (+)-Chatancin: Soucy, P.; L'Hureux, A.; Toró, A.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 9983; (+)-Maritimol: Toró, A.; Nowak, P.; Deslongchamps, P. *J. Am. Chem. Soc.* **2000**, *122*, 4526; (+)-Maritimol: Toro, A.; Lemelin, C.-A.; Préville, P.; Bélanger, G.; Deslongchamps, P. *Tetrahedron*, **1999**, *55*, 4655; (-)-Oblongolide: Shing, T. K. M.; Yang, J. *J. Org. Chem.* **1995**, *60*, 5785.

Apart from the transannular Diels-Alder reaction, other type of cycloadditions have also been employed in the total synthesis of natural products. For example, in 2006, two independent syntheses of natural diterpene (+)-intricarene were reported almost simultaneously by Pattenden[30] and Trauner.[31] Both synthetic proposals followed a very related approach for the construction of the pentacyclic core based on a transannular [5+2] cycloaddition of an *in situ* generated oxidopyrylium intermediate (Scheme 1.11). In the example reported by Pattenden, exposure of the furan moiety containing intermediate to vanadyl acetylacetonane and *tert*-butyl hydroperoxide, resulted in an oxidative ring expansion, rendering an intermediate which was acetylated *in situ*. Further treatment with DBU in acetonitrile at reflux afforded (+)-intricarene in a 20% yield as result of the transannular [5+2] reaction. On the other hand, the approach followed by Trauner, made use of alternative strategies for either the synthesis of the macrocyclic starting material or for the generation of the required oxidopyrilium ion. However, similar results were achieved in terms of overall yield and stereoselectivity.



Scheme 1.11. Total synthesis of (+)-intricarene reported by Pattenden.

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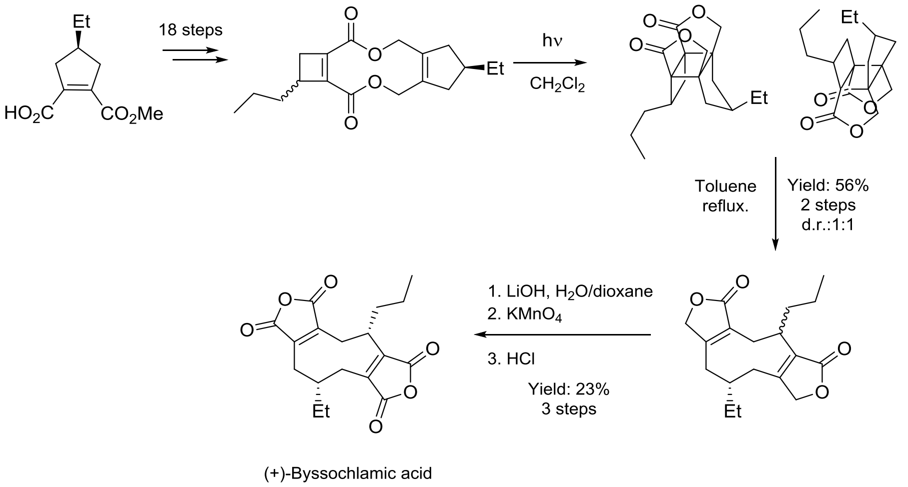
[30] (a) Tang, B.; Bray, C. D.; Pattenden, G. *Org. Biomol. Chem.* **2009**, *7*, 4448. (b) Tang, B.; Bray, C. D.; Pattenden, G. *Tetrahedron Lett.* **2006**, *47*, 6401.

[31] Roethle, P. A.; Hernandez, P. T.; Trauner, D. *Org. Lett.* **2006**, *8*, 5901.

Finally, there is one example in the literature of a transannular [2+2] cycloaddition reaction applied to the synthesis of (+)-byssochlamic acid, a nonadride natural product isolated from *Byssochlamys fulva*.[32] In this example, reported by White *et.al.* a 10-membered macrocyclic precursor was subjected to photoirradiation, which promoted the formation of the cycloaddition product as a 1:1 mixture of diastereomers. Subsequent cycloreversion reaction in refluxing toluene, followed by hydrolysis, oxidation and anhydride formation provided access to (+)-byssochlamic acid as a single product.



Scheme 1.12. Transannular [2+2] cycloaddition in total synthesis of (+)-byssochlamic acid.

3.2. Transannular aldol and Mannich type reactions

The aldol reaction is considered as one of the most suitable strategies for the α-functionalization of carbonyl compounds,[33] as therefore several relevants efforts have been applied to the extension of the well-known intermolecular or intramolecular version of this process to the transannular variant. Scheme 1.13 shows a representative example of the

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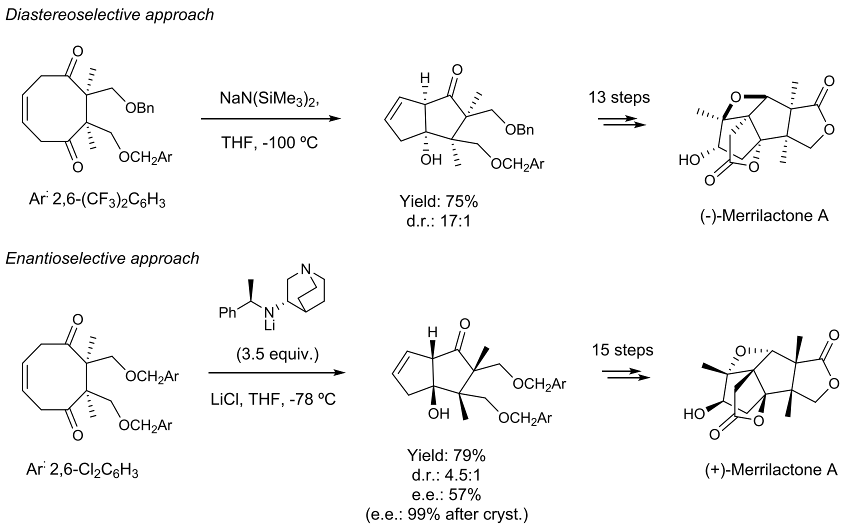
[32] White, J. D.; Kim, J.; Drapela, N. E. *J. Am. Chem. Soc.* **2000**, *122*, 8665.

[33] Gryko, D.; Walaszek, D. C-C bond formation by aldol reaction. In *Stereoselective organocatalysis: bond formation methodologies and activation modes*; Rios, R. Eds.; Wiley: Southampton, 2013; pp 81.

application of this approach to total synthesis. In this work developed by Inoue *et al.* in 2006, the total synthesis of (-)-merrilactone A, a natural sesquiterpenoid active against several neurodegenerative diseases such as Alzheimer and Parkinson disease, was accomplished involving a transannular aldol reaction as key step (Scheme 1.13).[34] While their first approach was based on the use of a chiral substrate, therefore relying on a diastereoselective process, further research allowed the authors to broaden this methodology to the use of an achiral starting material through a desymmetrization using super-stoichiometric ammount of a chiral base to promote the transannular aldol reaction (see Scheme 1.3). This strategy allowed the authors to access the unnatural enantiomer (+)-merrilactone A in a 23 step synthesis with an overall 1,3% yield.[20]



Scheme 1.13. Total synthesis of (-)-merrilactone A and (+)-merrilactone A.

The organocatalytic transannular aldol reaction proceeding under enamine activation developed by List and coworkers has also been applied to the construction of the tricyclic scaffold of natural product (+)-hirsutene.[25] Authors employed a ruthenium catalyzed ring closing metathesis for the synthesis of the required 1,4-cyclooctanedione starting material which, upon exposure to catalytic amounts of *trans*-4-fluoro proline, rendered tricyclic aldol adduct in excellent yield and enantioselectivity. Further dehydration, conjugate reduction of the enone

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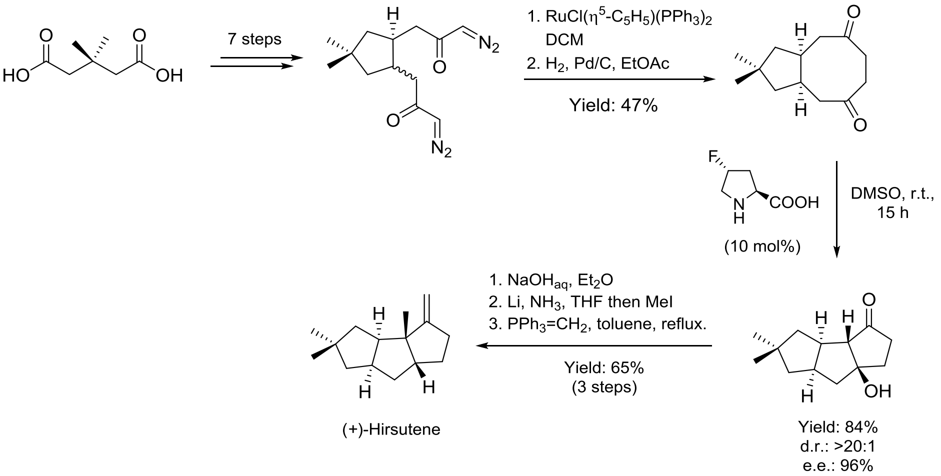
[34] Inoue, M.; Sato, T.; Hirama, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 4843.

with lithium in ammonia, followed by methylation of the enolate intermediate and final olefination step afforded (+)-hirsutene in 7% overall yield.



Scheme 1.14. Total synthesis of (+)-hirsutene.

Additionally, other related strategies involving diastereoselective transannular aldol reactions have been also developed by Barret[35] and Evans[36] for the synthesis of other interesting biologically active compounds such as LL-Z1640-3 and (+)-miyakolide respectively.

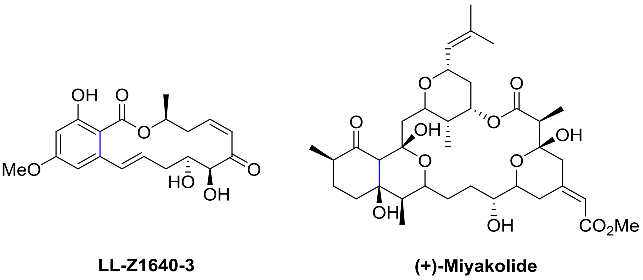


Figure 1.6. Synthetic targets accessed by Barrett and Evans via transannular aldol reaction.

The transannular variant of the Mannich reaction has also been studied and subsequently applied as key step in the total synthesis of different natural products. For instance, the total

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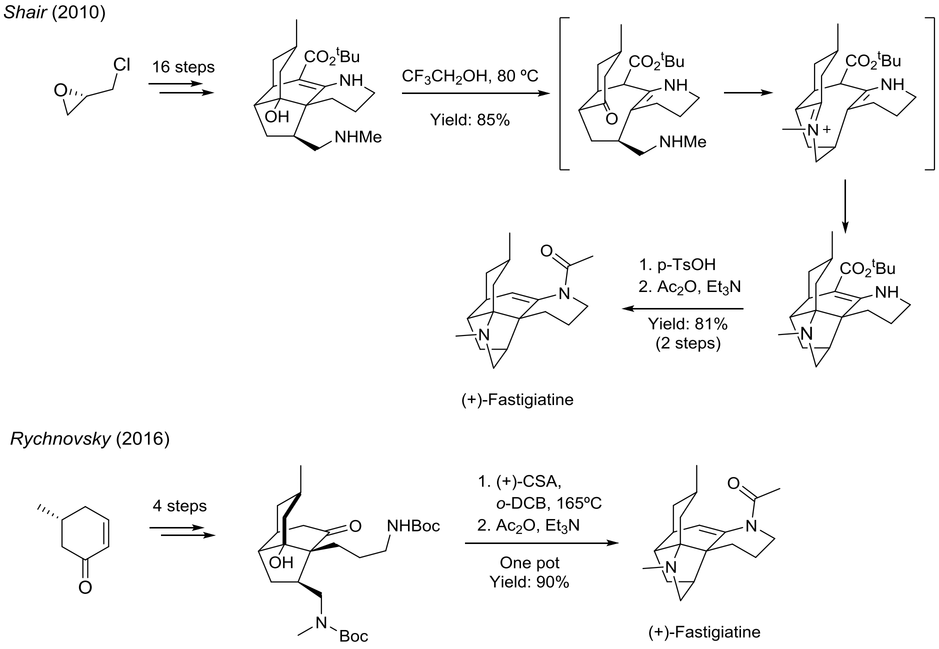
[35] Miyatake-Ondozabal, H.; Barrett, A. G. M. *Org. Lett.* **2010**, *12*, 5573.

[36] Evans, D.A.; Ripin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816.

synthesis of natural alkaloid (+)-fastigianine has been accomplished following this strategy. In the synthetic route developed by Shair,[37] the enantiopure cyclic precursor was prepared from (*S*)-epichlorohydrin. Next, it underwent the projected transannular reaction when exposed to thermal conditions affording the envisioned pentacyclic structure in excellent yield. Authors suggested that reaction proceeded through a retro-aldol/iminium ion formation sequence which subsequently underwent the transannular Mannich step. Quite recently this synthesis has been significantly improved by Rychnovsky and coworkers, which followed a related strategy to build simultaneously in a one pot procedure, two of the five cycles present in the structure.[38]



Scheme 1.15. Transannular Mannich reactions developed by Shair and Rychnovsky for the total synthesis of (+)-fastigiatine.

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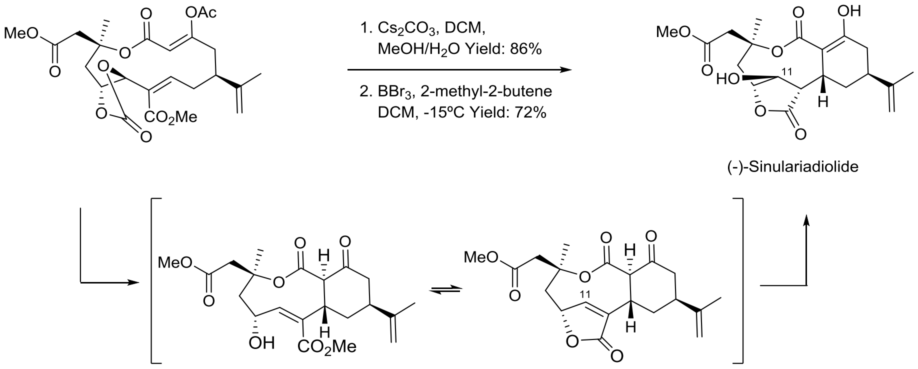
[37] Liau, B. B.; Shair, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 9594. For a related work, see: Lee, A. S.; Liau, B. B.; Shair, M. D. *J. Am. Chem. Soc.* **2014**, *136*, 13442.

[38] Samame, R. A.; Owens, C. M.; Rychnovsky, S. D. *Chem. Sci.* **2016**, *7*, 188.

3.3. Transannular Michael type reactions

Transannular conjugate additions have also been employed for the asymmetric synthesis of complex structural frameworks. Recently this year, a new example of this type of reaction was developed by Furstner *et.al.* for the construction of the tricyclic skeleton of (-)-sinulariadiolide metabolite.[39] The synthesis of the 9-membered ring, considered as challenging due to the energetically not favored nature of this ring size,[8] was achieved by a transannular Michael reaction from a 13-membered macrocyclic precursor. Subsequent intramolecular transesterification followed by spontaneous oxa-Michael addition of methanol at C-11 and final cleavage of methyl ether provided (-)-sinulariadiolide.



Scheme 1.16. Total synthesis of (-)-sinulariadiolide.

The potential of transannular Michael type reactions in natural product synthesis is clearly reflected by its application as key step in the synthesis of many other natural products such as apicularen A,[40] salvinorina A,[41] alsmaphorazine E,[42] aspergillides A and B,[43] crystamidine and erythraline alkaloids,[44] or the macrolide Sch 642305 (see Figure 1.7).[45]

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[39] Meng, Z.; Fürstner, A. *J. Am. Chem. Soc.* **2019**, *141*, 805.

[40] Hili, F.; White, J. M.; Rizzacasa, M. A. *Tetrahedron*, **2011**, *67*, 5054.

[41] Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968.

[42] Yu, K.; Gao, B.; Liu, Z.; Ding, H. *Chem. Commun.* **2016**, *52*, 4485.

[43] Kanematsu, M.; Yoshida, M.; Shishido, K. A*ngew. Chem. Int. Ed.* **2011**, *50*, 2618.

[44] Umihara, H.; Yoshino, T.; Shimokawa, J.; Kitamura, M.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 6915.

[45] Snider, B. B.; Zhou, J. *Org. Lett.* **2006**, *8*, 1283.

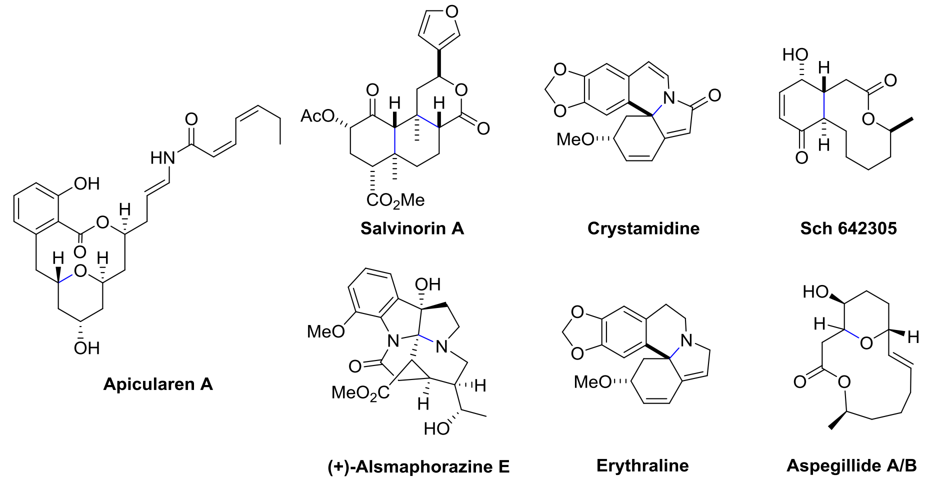
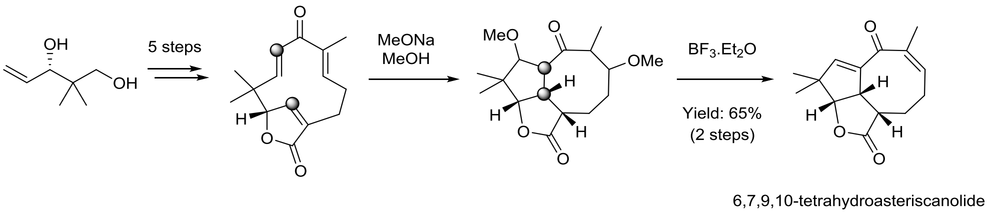


Figure 1.7. Natural products accessed by transannular Michael type reactions.

Additionally, Michael type transannular reactions have also been applied in domino processes for the total synthesis of natural products. As a representative example, in 2014 Li and coworkers successfully applied this strategy as key step in the synthesis of 6,7,9,10-tetrahydroasteriscanolide sesquiterpene lactone.[46] Although initial attempts were directed to promote a transannular Morita-Baylis-Hillman reaction, which would afford the desired tricyclic product, the exposition of the corresponding cyclic 11-membered substrate to commonly employed promoters of this reaction, such as DABCO, DBU or PPh_3, did not render the desired product. On the contrary, when the reaction was performed in the presence of MeONa and MeOH, the enantiopure cyclic precursor rendered the projected domino reaction.



Scheme 1.17. Michael initiated transannular reaction.

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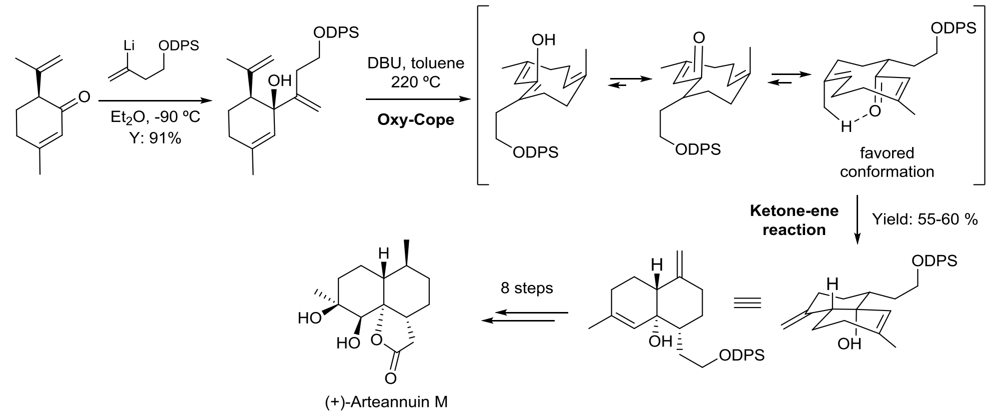
[46] Han, J.-C.; Li, F.; Li, C.-C. *J. Am. Chem. Soc.* **2014**, *136*, 13610.

MeONa was suggested to act as nucleophile in a 1,4-conjugate addition followed by transannular Michael reaction, affording the envisioned tricyclic product as complex mixture of inseparable diastereomers. Fortunately, subsequent treatment with $BF_3.Et_2O$ allowed the elimination of the methoxy group, rendering the target molecule in 65% yield for two steps.

3.4. Transannular carbonyl-ene reactions

Although the number of described examples in which ketone-ene reactions have been employed as key steps in the synthesis of natural products cannot be considered large, there are some relevant examples developed up to date. In 2001, Barriault and coworkers described a 10-step synthesis of (+)-arteannuin M which involved a cascade diastereoselective oxy-Cope rearrangement/transannular ene reaction sequence.[47] According to authors, the stereochemical information of the starting material was preserved due to the acquisition of a preferred conformation in the intermediate generated as consequence of the Oxy-Cope rearrangement, in which functionalized alkyl chain is oriented pseudoequatorial. This intermediate underwent fast transannular reaction, avoiding any interconversion to other possible conformations that would lead to the undesired epimeric macrocyclic intermediates.



Scheme 1.18. Total synthesis of (+)-arteannuim M via transannular ketone-ene reaction.

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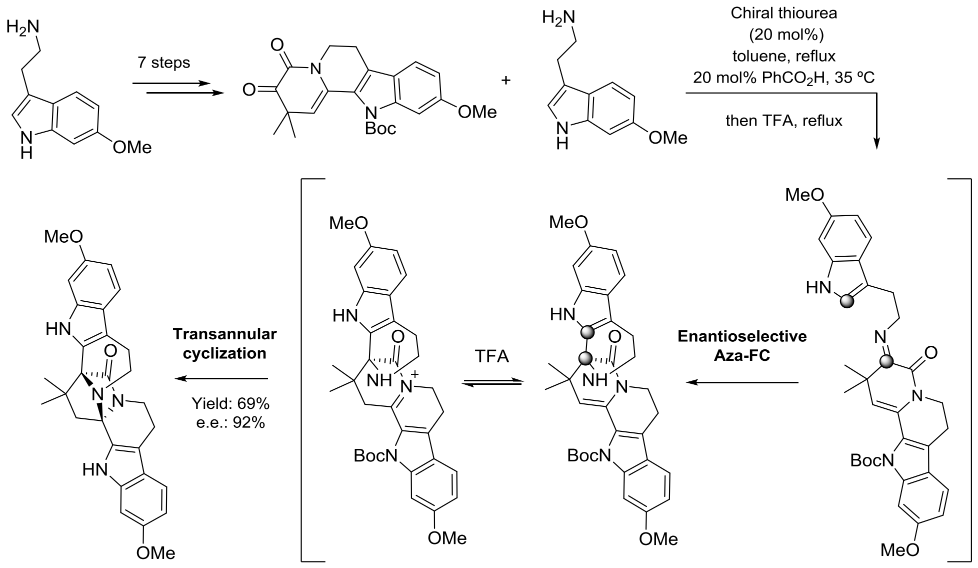
[47] Barriault, L.; Deon, D. H. *Org. Lett.* **2001**, *3*, 1925. For a related work, see: Gauvreau, D.; Barriault, L. *J. Org. Chem.* **2005**, *70*, 1382.

3.5. Other transannular reactions

As it has been shown in previous sections, in the last years the application of transannular reactions as a strategic tool in natural product synthesis have attracted great attention. Apart from the abovementioned reactions, transannular versions of other different processes have also been reported.

As a good example, Zhu and coworkers reported the first asymmetric total synthesis of natural alkaloid (+)-peganumine A in 8 steps from commercially available 6-methoxytryptamine (Scheme 1.19).[48] The key step is initiated by a chiral thiourea catalyzed enantioselective intermolecular aza-Friedel-Crafts reaction of an *in situ* generated imine. Next, the enantiopure product obtained as consequence of this process, suffers an enamine-imine tautomerization when exposed to TFA, which after a final stereospecific transannular N-addition to the N-acyliminium ion affords the desired octacyclic product.



(+)-Peganumine A

Scheme 1.19. Synthetic strategy proposed by Zhu.

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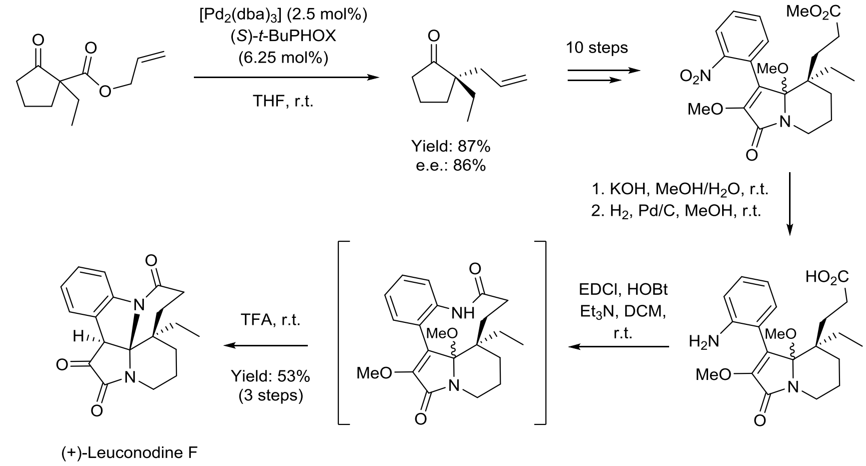
[48] Piemontesi, C.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2016**, *138*, 11148.

In a related example, the same authors applied a diastereoselective transannular aminal formation reaction for the construction of the polycyclic structural core of natural product (+)-leuconodine F.[49] The synthesis of the required 9-membered cyclic precursor started from 2,2-disubstituted cyclopentanone which after palladium catalyzed asymmetric decarboxylative allylation afforded the conveniently functionalized enantiopure cyclopentanone. This intermediate was subjected to further 12 reaction steps to afford the envisioned precursor. Subsequent exposure of this compound to lactamization conditions rendered 9-membered lactam, which after treatment with TFA, underwent diastereoselective transannular aminal formation in a one pot procedure providing access to (+)-leuconodine F.



Scheme 1.20. Total synthesis of (+)-leuconodine F.

In a different context, an example of a diastereoselective transannular Dieckmann reaction applied to natural product synthesis can be found in the literature.[50] In this work, developed by Ley and coworkers, biologically active natural product antascomicin B was synthesized in a total of 52 step synthetic route starting from dimethyl D-tartrate derivative and benzyloxyacetaldehyde. In this way, the 27-membered macrocycle underwent a deprotonation followed by Dieckmann-type condensation when treated with LHMDS. The resulting

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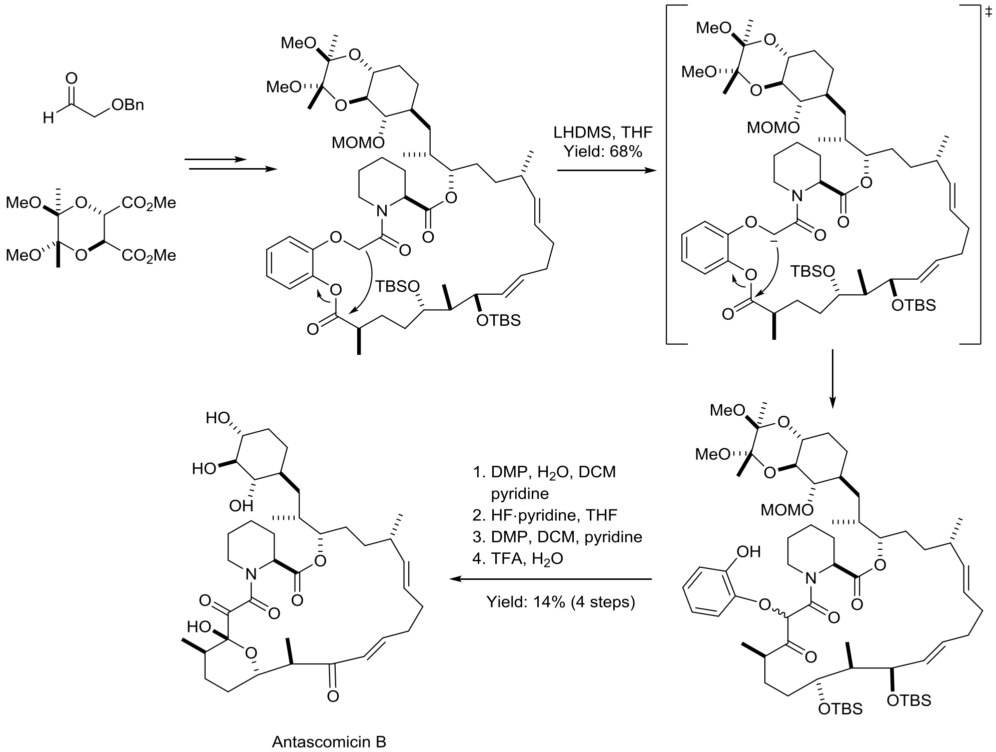
[49] Dagoneau, D.; Xu, Z.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 760.

[50] Brittain, D. E. A.; Griffiths-Jones, C. M.; Linder, M. R.; Smith, M. D.; McCusker, C.; Barlow, J. S.; Akiyama, R.; Yasuda, K.; Ley, S. V. *Angew. Chem. Int. Ed.* **2005**, *44*, 2732.

23-membered macrocycle was subjected to catechol moiety cleavage and concomitant oxidation with Dess-Martin periodinane. Finally, *tert*-butylsilyl group deprotection followed by spontaneous lactol formation, as well as, deprotection of methoxymethyl acetal and butane diacetal groups under acidic conditions rendered target molecule antascomicin B.



Scheme 1.21. Synthesis of antascomicin B.

On the other hand, transannular processes involving the opening of strained three-membered ring intermediates have also been described in the context of natural product synthesis. For example, in 2013 Davies *et al.* disclosed a synthetic route to access (-)-hyacinthacine A1 by a transannular ring opening of iodonium ion.[51] The 8-membered cyclic precursor was prepared starting from D-ribose derived α,β-unsaturated ester in a 4-step

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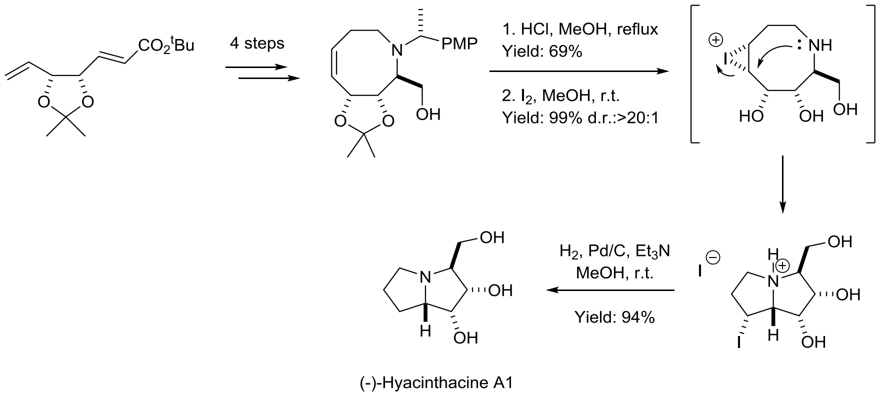
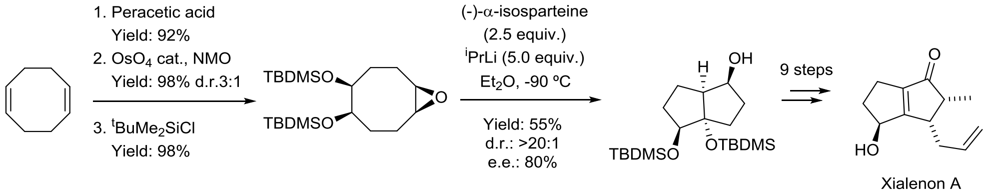
[51] Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Biomol. Chem.* **2013**, *11*, 3187.

sequence. The transannular aminoiodination reaction afforded the envisioned bicyclic product in good yield as a single diastereomer, which was further transformed into the target product.



Scheme 1.22. Synthesis of (-)-hyacintacine A1.

A related example was employed by Hodgson in the total synthesis of metabolite xialenon A, whose bicyclo[3.3.0]octane skeleton was constructed by a reaction involving α-deprotonation and C-H insertion.[52] In this example, cyclooctane-derived meso epoxide employed as substrate was prepared starting from cycloocta-1,5-diene by a synthetic sequence that comprehended an epoxidation, dihydroxylation and alcohol protection steps. The key transannular reaction was performed using (-)-α-isosparteine as chiral ligand for the enantioselective deprotonation step.



Scheme 1.23. Total synthesis of xialenon A.

As it has been demonstrated, transannular reactions have been widely employed as key steps in the total synthesis of many natural products.[53] In fact, synthetic strategies which

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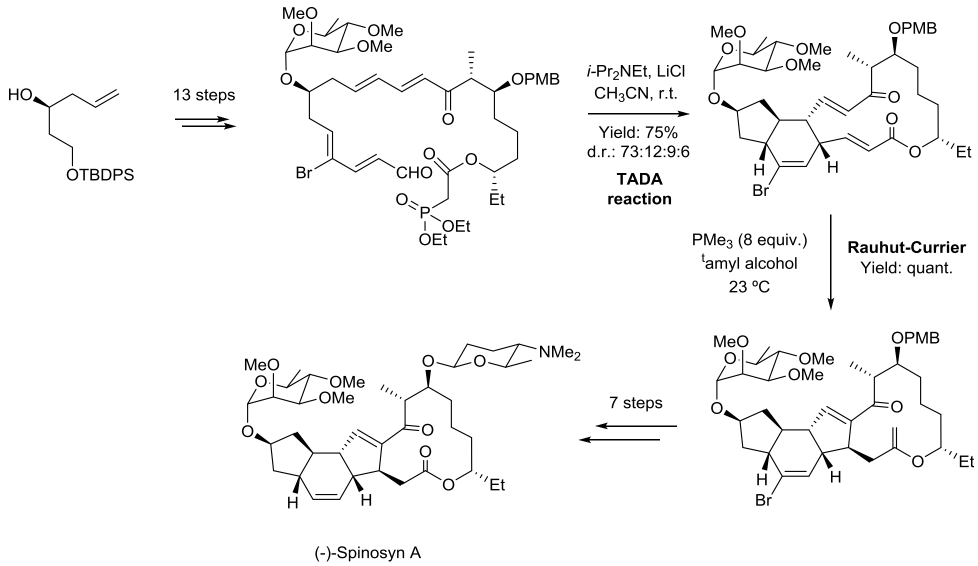
[52] Hodgson, D. M.; Galano, J.-M.; Christlieb, M. *Tetrahedron*, **2003**, *59*, 9719.

[53] For other recent examples of transannular reactions applied to natural product synthesis not described in this section, see: (a) Antropow, A. H.; Garcia, N. R.; White, K. L.; Movassaghi, M. *Org. Lett.* **2018**, *20*, 3647. (b) Kang,

combine multiple transannular steps across the synthetic route have also been described for the construction of highly complex structures. A good example of this approach is the total synthesis of (-)-spinosyn A reported by Roush and coworkers,[54] which involved an initial transannular Diels-Alder process. The direct isolation of the Diels-Alder adduct when exposed to macrocyclization conditions was suggested to arise from a tandem macrocyclization/transannular Diels-Alder reaction sequence. Further exposure of the resulting 15 membered macrocyclic intermediate, obtained as complex mixture of 4 diastereomers, to trimethylphosphine, provided the envisioned tetracyclic structure through a diastereoselective transannular Rauhut-Currier reaction. Finally, obtained intermediate was transformed into the target molecule (-)-spinosyn A by a 7-step synthetic sequence (Scheme 1.24).



Scheme 1.24. Formal total synthesis of (-)-spinosyn A developed by Roush.

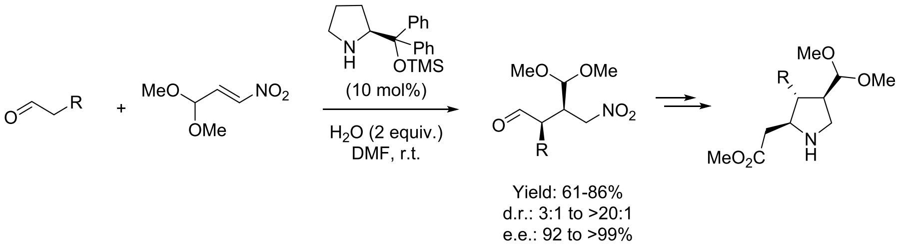
T.; White, K. L.; Mann, T. J.; Hoveyda, A. H.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 13857. (c) White, K. L.; Movassaghi, M. *J. Am. Chem. Soc.* **2016**, *138*, 11383. (d) Mewald, M.; Medley, J. W.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 11634. (e) Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 10246.

[54] Mergott, D. J.; Frank, S. A.; Roush, W. R. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11955. For a related work: Winbush, S. M.; Mergott, D. J.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1818.

4. BACKGROUND: PRECEDENTS OF THE GROUP

To set this research in context, our group has been dedicated to the development of new methodologies in the field of asymmetric synthesis, as well as to their application to the synthesis of chiral building blocks and natural products. Although initially this objective was successfully confronted mainly by the use of chiral auxiliary methodology in a wide variety of transformations,[55] in the last years our efforts have been directed to the use of organocatalysis as methodological approach.

Our first study in this field consisted in an organocatalyzed conjugate addition between enolizable aldehydes and β-nitroacroleine dimethylacetal under enamine activation.[56] This methodology allowed us to access the corresponding Michael adducts, which were subsequently transformed into enantiopure functionalized pyrrolidines.



Scheme 1.25. Michael reaction between enolizable aldehydes and β-nitroacroleine dimethylacetal under enamine activation.

Since this initial work, imizadolidinone type and diarylprolinol derived secondary amines have been deeply employed as organocatalysts in a wide variety of transformations, leading to the development of highly efficient methodologies for the synthesis of enantioenriched

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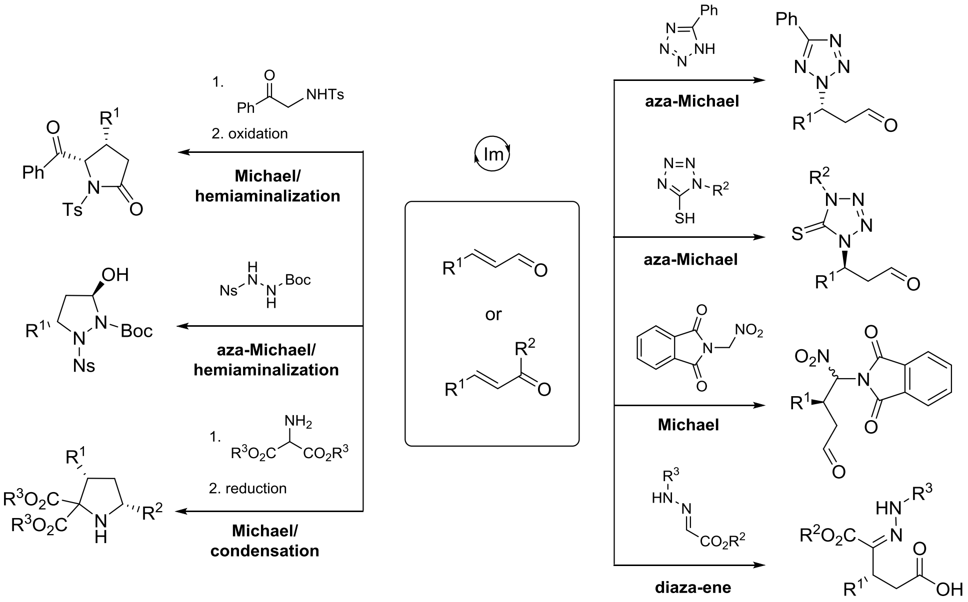
[55] Most recent examples: (a) Ocejo, M.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *J. Org. Chem.* **2011**, *76*, 460. (b) Ocejo, M.; Carrillo, L.; Badía, D.; Vicario, J. L.; Fernández, N.; Reyes, E. *J. Org. Chem.* **2009**, *74*, 4404. (c) Iza, A.; Vicario, J. L.; Badía, D.; Varrillo, L. *Synthesis* **2006**, 4065. (d) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Uria, U.; Iza, A. *J. Org. Chem.* **2006**, *71*, 7763. (e) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Iza, A.; Uria, U. *Org. Lett.* **2006**, *8*, 2535. (f) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L.; Ruiz, N. *J. Org. Chem.* **2005**, *70*, 8790. (g) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Chem.* **2004**, *69*, 2588. (h) Vicario, J. L.; Badía, D.; Carrillo, L. *Tetrahedron: Asymmetry* **2002**, *13*, 745. (i) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 5801.

[56] (a) Ruiz, N.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Uria, U. *Chem. Eur. J.* **2008**, *14*, 9357. (b) Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2006**, *8*, 6135.

compounds *via* iminium ion activation (Scheme 1.26). For instance, our group has developed protocols for the conjugate additions of tetrazoles[57] and also for the use of *N*-nitromethylphthalimide[58] and hydrazones[59] as hydroxymethanimidoyl anion and glyoxyl anion equivalents respectively in umpolung conjugate additions to enals. The extension of this strategy to bis-nucleophiles such as aminoketones,[60] hydrazides[61] and dialkylaminomalonates[62] has also been successfully accomplished as it is illustrated by different enantioselective cascade processes performed under iminium ion activation. In this way, after the initial conjugate addition, substrates tipically underwent an intramolecular hemiaminalization reaction due to the presence of a nucleophilic nitrogen atom on the conjugate adduct.



Scheme 1.26. Enantioselective transformations under iminium ion activation.

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[57] (a) Uria, U.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2011**, *13*, 336. (b) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L. *Chem. Commun.* **2007**, 2509.

[58] Alonso, B.; Reyes, E.; Carrillo, L.; Vicario, J. L.; Badía, D. *Chem. Eur. J.* **2011**, *17*, 6048.

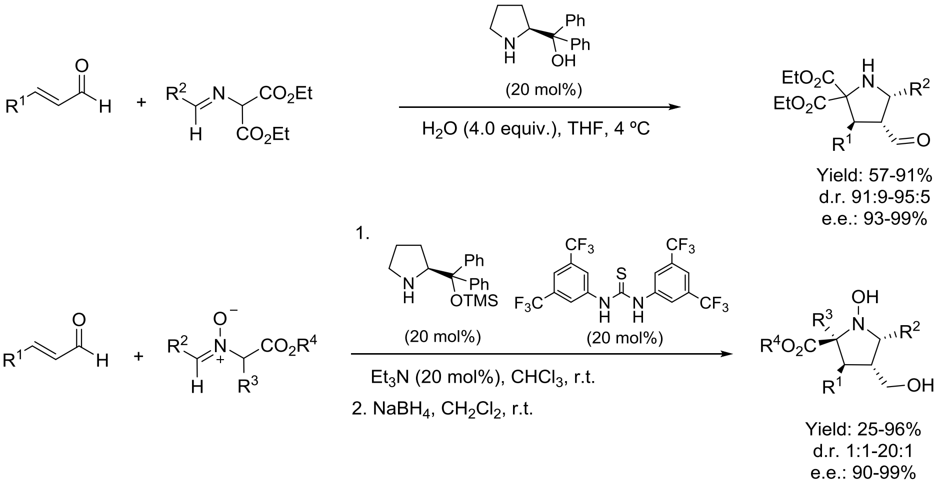
[59] Fernández, M.; Uria, U.; Vicario, J. L.; Reyes, E.; Carrillo, L. *J. Am. Chem. Soc.* **2012**, *134*, 11872.

[60] Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Adv. Synth. Catal.* **2013**, *355*, 653.

[61] Fernández, M.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Adv. Synth. Catal.* **2012**, *354*, 371.

[62] Riaño, I.; Díaz, E.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Chem. Commun.* **2016**, *52*, 2330.

Additionally, the iminium ion activation mode has also been applied in cycloaddition chemistry, such as [3+2] cycloaddition reactions between azomethine ylides and α,β-unsaturated aldehydes.[63] More recently a [3+2] cycloaddition reaction between enals and nitrones has been developed under cooperative catalysis, affording *N*-hydroxypirrolidines as enantioenriched compounds.[64]



Scheme 1.27. Organocatalytic and enantioselective [3+2] cycloadditions.

In addition, the combination of iminium and enamine activation has provided access to structurally complex molecules via organocatalyzed cascade reactions, such as oxa-Michael/aldol/hemiacetalization,[65] oxa-Michael/Michael,[66] aza-Michael/aldol/

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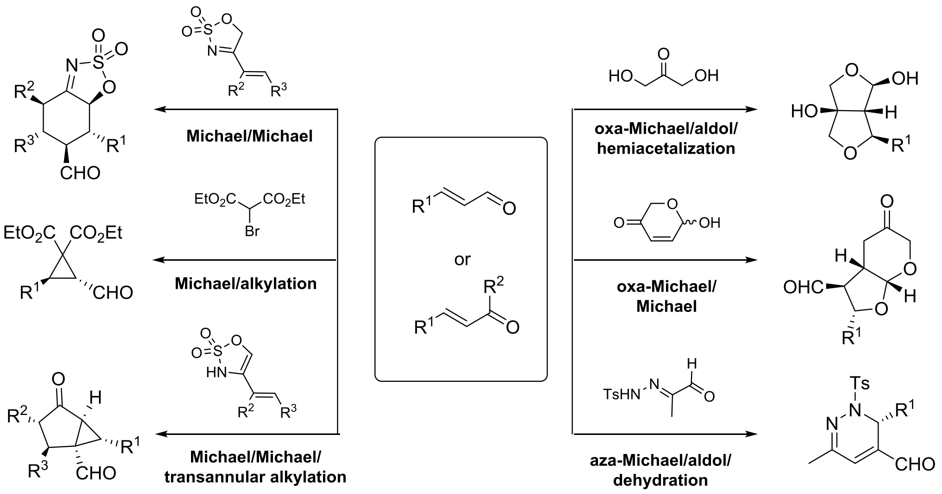
[63] Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5168.

[64] (a) Prieto, L.; Juste-Navarro, V.; Uria, U.; Delso, I.; Reyes, E.; Tejero, T.; Carrillo, L.; Merino, P.; Vicario, J. L. *Chem. Eur. J.* **2017**, *23*, 2764. (b) Juste-Navarro, V.; Prieto, L.; Delso, I.; Manzano, R.; Tejero, T.; Reyes, E.; Merino, P.; Vicario, J. L. *Adv. Synth. Catal.* **2017**, *359*, 4122.

[65] Reyes, E.; Talavera, G.; Vicario, J. L.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 5701.

[66] Orue, A.; Uria, U.; Roca-López, D.; Delso, I.; Reyes, E.; Carrillo, L.; Merino, P.; Vicario, J. L. *Chem. Sci.* **2017**, *8*, 2904.

dehydration,[67] Michael/Michael[68], Michael/α-alkylation[69] and Michael/ Michael/transannular alkylation.[18c]



Scheme 1.28. Developed cascade reactions under iminium/enamine activation.

On the other hand, the application of the principle of vinylogy has allowed us to extend the enamine activation manifold to the further remote functionalization of carbonyl compounds. In this way, dienamine activation was efficiently applied in formal [2+2],[70] [5+2][71] and [4+2][72] reactions. Trienamine activation has also been employed for the reaction between unconjugated 2,5-dienals and nitroalkenes in a Diels-Alder reaction (Scheme 1.29).[73]

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[67] Fernández, M.; Vicario, J. L.; Reyes, E.; Carrillo, L.; Badía, D. *Chem. Commun.* **2012**, *48*, 2092.

[68] Riaño, I.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Org. Chem. Front.* **2015**, *2*, 206.

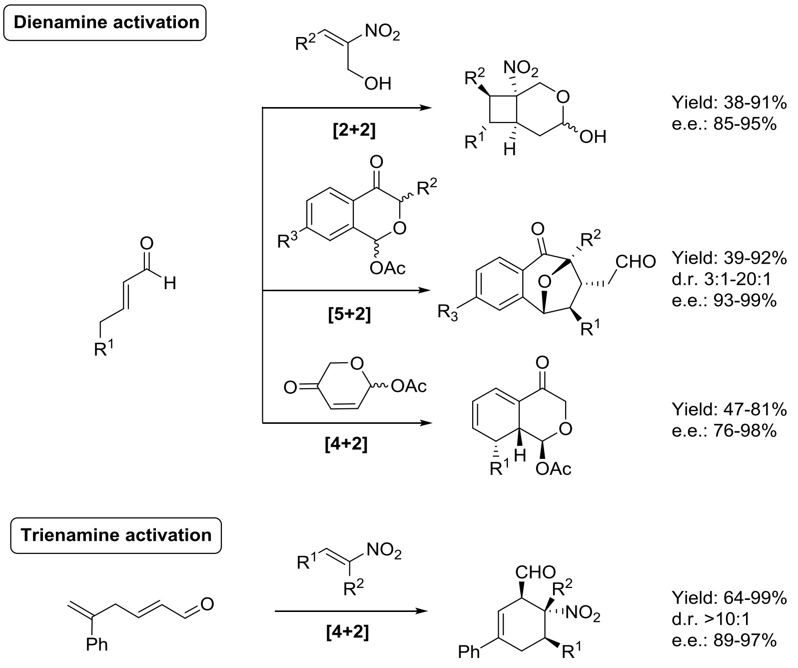
[69] (a) Martinez, J. I.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *ChemCatChem* **2013**, *5*, 2240. (b) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Pesquera, A. *Synthesis* **2010**, *4*, 701.

[70] Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 4104.

[71] Orue, A.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 3043.

[72] Orue, A.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uxue, U. *Org. Lett.* **2012**, *14*, 3740.

[73] Prieto, L.; Talavera, G.; Uria, U.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Chem. Eur. J.* **2014**, *20*, 2145.

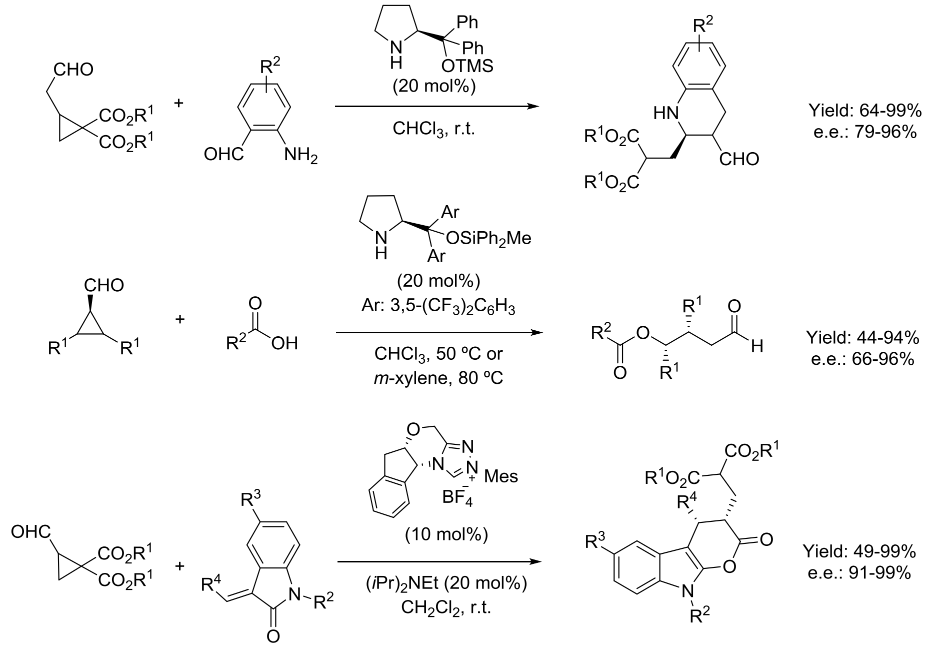


Scheme 1.29. Application of vinylogy principle to enamine activation.

In the last years, strained systems have been successfully employed as substrates in different enantioselective transformations. In this sense substituted cyclopropanes have emerged as very prolific substrates, whose reactivity is favored by the ring-strain release that takes place as consequence of the ring opening process occurring during the reaction. Aminocatalysts, as well as *N*-heterocyclic carbenes, have demonstrated to be efficient promoters of different enantioselective transformations, providing access to highly functionalized enantiopure compounds.[74]

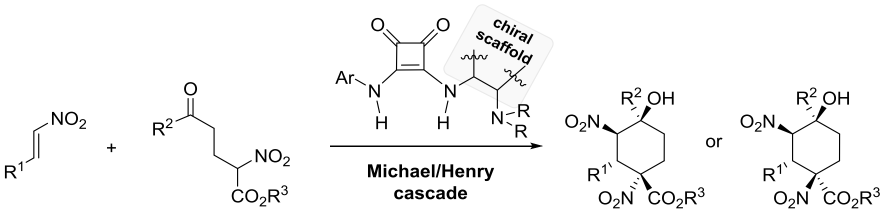
---

[74] (a) Diaz-Soto, E.; Reyes, E.; Uria, U.; Carrillo, L.; Tejero, T.; Merino, P.; Vicario, J. L. *Chem. Eur. J.* **2018**, *24*, 8764-8768. (b) Prieto, L.; Sánchez-Díez, E.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Adv. Synth. Catal.* **2017**, *359*, 1678. (c) Sánchez-Díez, E.; Vesga, D. L.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Org. Lett.* **2016**, *18*, 1270.



Scheme 1.30. Enantioselective transformations of cyclopropanes via aminocatalysis or NHC based catalysis.

Although most of the research developed in the last years relies on the use of covalent organocatalysts, in the last years non-covalent activation modes have also been explored in our group. Bifunctional Brønsted acid-Brønsted base catalysts have been employed in a diastereodivergent strategy for the enantioselective synthesis of cyclohexanes through a Michael/Henry cascade reaction between nitroalkenes and α-nitro-δ-oxo esters.[75]



Scheme 1.31. Bifunctional Brønsted acid-Brønsted base catalyzed Michael/Henry cascade reaction.

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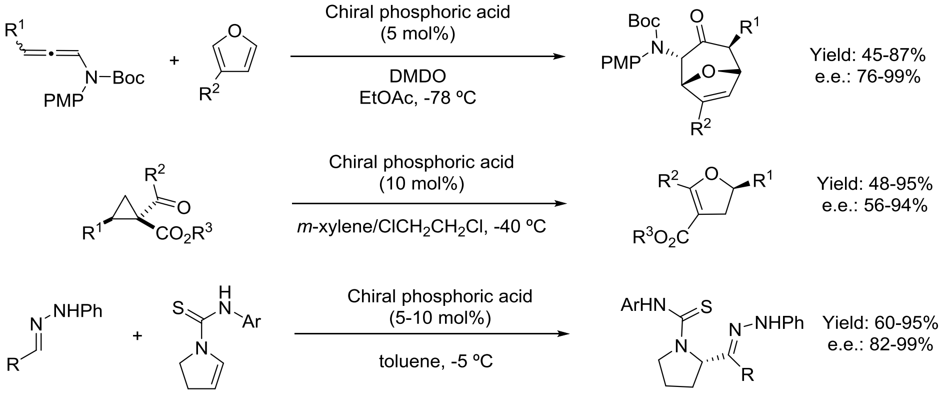
[75] (a) Martínez, J. I.; Uria, U.; Muñiz, M.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Beilstein J. Org. Chem.* **2015**, *11*, 2577. (b) Martínez, J. I.; Villar, L.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Adv. Synth. Catal.* **2014**, *356*, 3627.

Finally, chiral phosphoric acids have also been employed as Brønsted-acidic catalysts in an enantioselective oxidative [4+3] cycloaddition between allenamides and furans,[76] a Cloke-Wilson rearrangement of cyclopropanes[77] and in the asymmetric addition of hydrazones to *N*-acyldihydropyrrole derivatives (Scheme 1.32).[78]



Scheme 1.32. Enantioselective transformations under hydrogen-bond catalysis.

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[76] Villar, L.; Uria, U.; Martínez, J. I.; Prieto, L.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 10535.

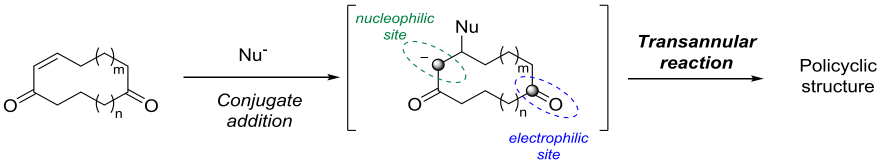
[77] Ortega, A.; Manzano, R.; Uria, M.; Carrillo, L.; Reyes, E.; Tejero, T.; Merino, P.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2018**, *57*, 8225.

[78] Zabaleta, N.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Chem. Commun.* **2018**, *54*, 8905.

5. GENERAL OBJECTIVES OF THE PRESENT WORK

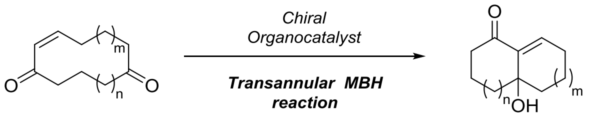
The work summarized in this thesis has been developed in line with the current research activity of the group, focused on the study of novel asymmetric transformations within the field of organocatalysis. In this sense, we oriented our research on the development of innovative strategies for enantioselective synthesis of high complexity structures in an operationally simple and environmental friendly manner. In this context, transannular reactions can be considered appealing resources as they provide direct access to polycyclic structures with high atom economy.

As it has been outlined in previous sections, most of the asymmetric transannular reactions developed up to date consist on diastereoselective processes which require chiral enantiopure starting materials, remaining the catalytic variant of these processes still significantly unexplored. Taking this into account, the general objective of this work is the **study of transannular reactions triggered by conjugate additions**.



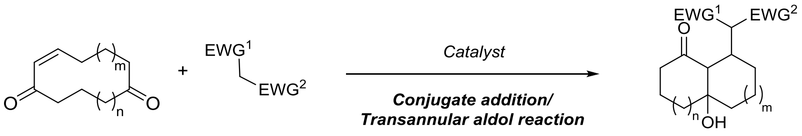
Scheme 1.33. General objective of this project.

In this context, in the first part of this work, the reactivity of **medium-sized carbocycles containing an α,β-unsaturated ketone as activated alkene and a ketone as an internal electrophile will be studied in a Morita-Baylis-Hillman reaction**. In order to induce enantioselectivity, chiral Lewis base catalysts will be surveyed as efficient promoters of the reaction. This process will provide access to structurally differing polycyclic scaffolds, commonly present as part of the structural core of natural products and biologically active compounds.



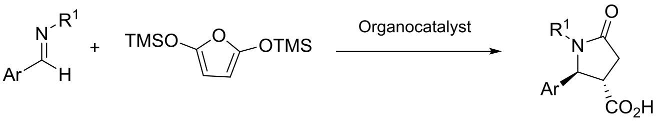
Scheme 1.34. Envisioned Morita-Baylis-Hillman reaction.

In a second related part, chiral organocatalysts will be employed in order to promote an **enantioselective conjugate addition of active methylene compounds** that will trigger the subsequent transannular aldol reaction.



Scheme 1.35. Proposed Michael initiated transannular reaction.

Finally, a chapter in which the most relevant results obtained during a three-month stay at the University of California Davis is included. This work, developed under the supervision of Prof. Jared Shaw, was oriented to the development of **the synthesis of γ-lactams through a Mukaiyama-Mannich type reaction employing disulfonimides as Lewis-Acid catalysts**.



Scheme 1.36. General scheme for the Mukaiyama-Mannich reaction.

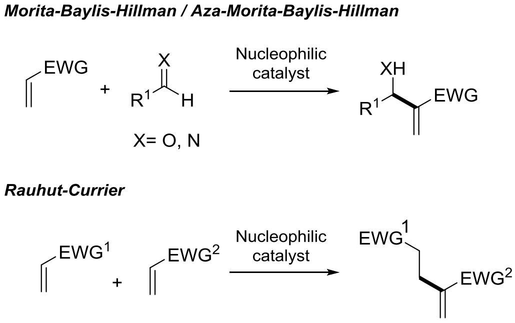
2

2

Organocatalytic enantioselective transannular Morita-Baylis-Hillman reaction

1. INTRODUCTION

The α-functionalization of an activated alkene by reaction with an electrophilic sp^2 carbon (aldehyde, ketone or imine) under tertiary amine or phosphine catalysis is known as the Morita-Baylis-Hillman (MBH) and aza-Morita-Baylis-Hillman (aza-MBH) respectively.[1] A close related process in which the new C-C bond is formed between the α carbon of an activated alkene and the β carbon of a second alkene under nucleophilic catalysis is known as the Rauhut-Currier (RC) reaction, although it is also commonly referred as the vinylogous MBH reaction.[2]



Scheme 2.1. General scheme for MBH/aza-MBH and Rauhut-Currier reaction.

Initially reported by Morita in 1968[3] as the reaction of aldehydes with acrylates or acrylonitriles catalyzed by phosphines, it was in 1972 when Baylis and Hillman broadened this methodology to different activated alkenes employing tertiary amines as catalysts (Scheme 2.2).[4]

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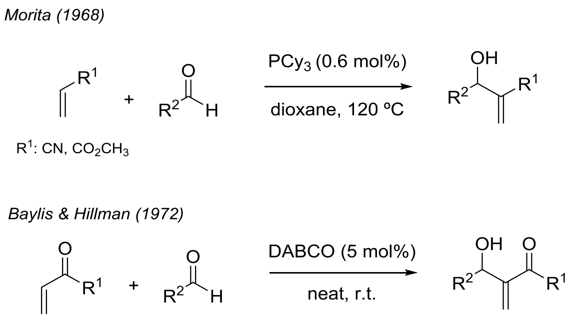
[1] Shi, M.; Wang, F.; Zhao, M.-X.; Wei, Y. *The chemistry of the Morita-Baylis-Hillman reaction;* PCS Publising, Cambridge, 2011.

[2] For a selected review on Rauhut-Currier reaction, see: Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron*, **2009**, *65*, 4069.

[3] (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815. (b) Morita, K.; Kobayashi, T. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2732.

[4] (a) Baylis, A. B.; Hillman, M. E. D. German patent 2155113, 1972, Chem. Abstr. 1972, 77, 34174q.11. (b) Hillman, M. E. D.; Baylis, A. B. U. S. Patent 3, 743, 669, 1973.12.



Scheme 2.2. Pioneering examples reported by Morita in 1968 and Baylis and Hillman in 1972.

Despite its great potential as synthetic methodology, especially due to the mild reaction conditions usually required and the excellent atom economy that characterizes this process, this transformation remained significantly unexploited for almost a decade. In fact, it was not until the early 1980s that it started to attract the interest of the scientific community.[5] Since then, different research groups have contributed to the study of the MBH reaction, allowing the development of efficient strategies for carrying out this reaction either in an intramolecular or intermolecular way. In this context, important efforts have been focused on overcoming the intrinsic drawbacks associated to MBH reaction that compress in many cases poor conversion, low reaction rates and reduced substrate scope. Although there are still certain aspects susceptible of improvement, the MBH reaction, as well as its aza counterpart, has fully demonstrated its applicability as synthetic tool, as it is reflected in the large number of literature examples reported up to date.[6]

Although as already indicated, the first examples of MBH reaction date back to early 70's, it further took a twenty-year period to develop the first moderately enantioselective examples. Following initial reports disclosed by Drewes and Roos[7] and Isaacs[8], works developed by Hirama[9]

---

[5] (a) Basavaiah, D.; Gowriswari, V. V. L. *Tetrahedron Lett.* **1986**, *27*, 2031. (b) Hoffmann, H. M. R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849. (c) Perlmutter, P.; Teo, C. C. *Tetrahedron Lett.* **1984**, *25*, 5951. (d) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 795. (e) Drewes, S. E.; Emslie, N. D. *J. Chem. Soc. Perkin Trans. 1,* **1982**, 2079.

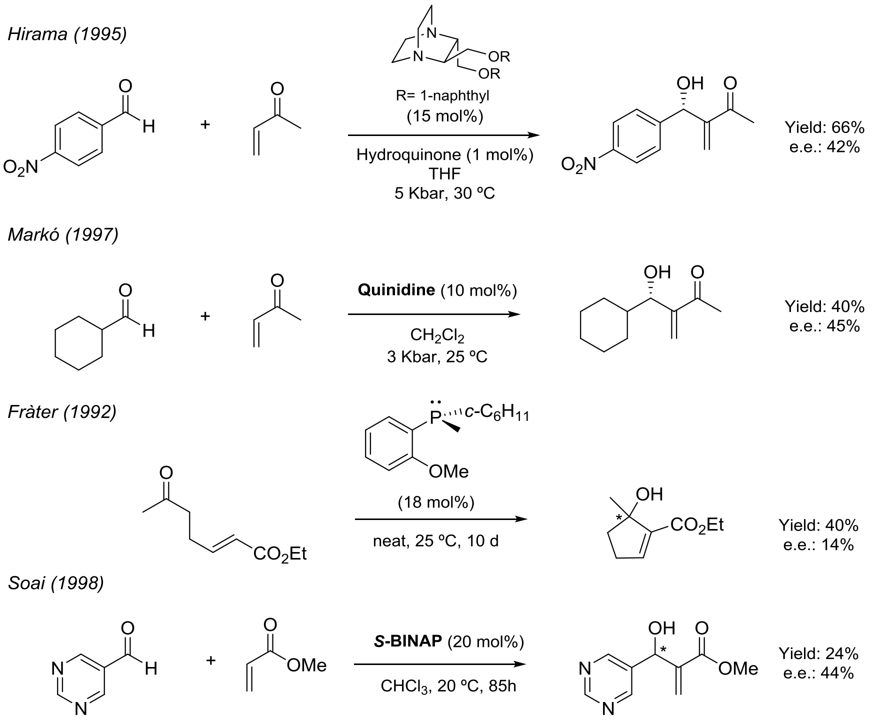
[6] For selected reviews on MBH and aza-MBH reactions in organic synthesis, see: (a) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447. (b) Declerck, V.; Martinez, J.; Lamaty, J. *Chem. Rev.* **2009**, *109*, 1.

[7] Drewes, S. E.; Roos, G. H. P. *Tetrahedron*, **1988**, *44*, 4653.

[8] Gilbert, A.; Heritage, T. W.; Isaacs, N. S. *Tetrahedron: Asymmetry*, **1991**, *2*, 969.

[9] Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry*, **1995**, *6*, 1241.

and Markò *et.al.*[10] involving chiral tertiary amines, as well as, by Fráter[11] and Soai[12] using chiral phosphines as Lewis bases, are considered the pioneering examples in this field in which moderate enantioselectivities were achieved.



Scheme 2.3. Pioneering organocatalytic and enantioselective MBH reactions.

However, it was not until 1999 that the first highly enantioselective MBH reaction was disclosed.[13] In this pioneering report, Hatakeyama and coworkers employed β-Isocupreidine (β-ICD), an amine derived from natural quinidine, as efficient catalyst for the reaction between aliphatic or aromatic aldehydes and hexafluoro isopropyl acrylate (Scheme 2.4). A comparison of the performance of related quinidine derivatives allowed them to conclude that both the rigid

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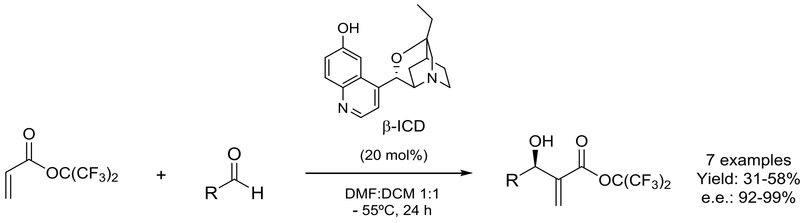
[10] Markó, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron*, **1997**, *53*, 1015.

[11] Roth, F.; Gygax, P.; Fráter, G. *Tetrahedron Lett.* **1992**, *33*, 1045.

[12] Hayase, T.; Shibata, T.; Soai, K.; Wakatsuki, Y. *Chem. Commun.* **1998**, 1271.

[13] Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.

structure of the catalyst and the phenolic hydroxyl group played a crucial role in the asymmetric induction and rate improvement.



Scheme 2.4. First highly enantioselective organocatalytic MBH reaction.

After these seminal reports, many different catalytic systems have been developed and subsequently applied as efficient promoters in enantioselective MBH and aza-MBH reactions. From a general perspective, the reported organocatalytic approaches can be classified into two main groups, depending on the nature of the nucleophilic catalyst employed, namely, ***nucleophilic chiral tertiary amine*** and ***chiral phosphine***-catalyzed reactions. In addition to the abovementioned approaches, several examples involving an achiral tertiary amine or phosphine in combination with a chiral Brønsted acid, such as BINOL-based phosphoric acids or cyclohexanediamine-based thioureas, can be also found in the literature.[14] Due to their close relation to the developed research, in the following section, the reported examples of enantioselective MBH reactions under chiral phosphine catalysis will be discussed in detail.

---

[14] For selected reviews on asymmetric MBH and aza-MBH reactions, see: (a) Pellissier, H. *Tetrahedron*, **2017**, *73*, 2831. (b) Hu, F.-L.; Shi, M. *Org. Chem. Front.* **2014**, *1*, 587. (c) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659. (d) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 4614.

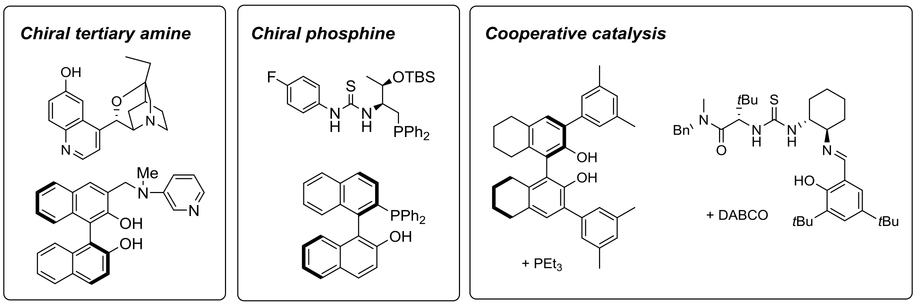
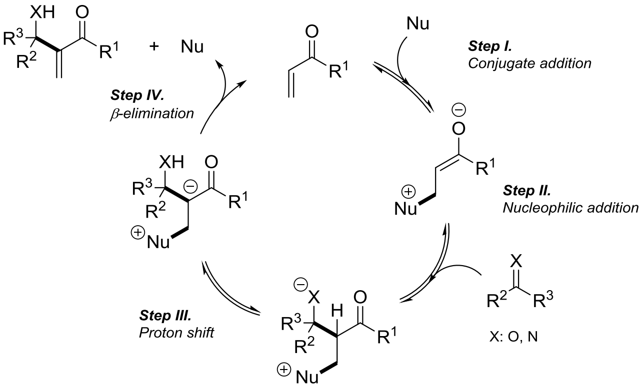


Figure 2.1. General scheme of organocatalytic approaches for enantioselective MBH, aza-MBH and RC reactions.

1.1. Mechanistic considerations

Regarding the mechanism of the reaction, the generally accepted mechanism for MBH and aza-MBH processes is shown in Scheme 2.5. The reaction sequence starts with the reversible nucleophilic addition of the Lewis base to the activated alkene, generating an enolate intermediate which subsequently takes part in an addition to the electrophilic sp^2 carbon atom affording a zwitterionic species. Finally, a proton shift followed by β-elimination affords the MBH adduct as well as allows catalyst turnover.



Scheme 2.5. General mechanism for Lewis base catalyzed MBH/aza-MBH reaction.

Initial kinetic studies performed by Hill and Isaacs in early 1980's for amine-catalyzed MBH reaction[15] proposed, as it would be expected, the C-C bond formation (Step II) as the rate-determining step. The low kinetic isotopic effect observed for the proton in alpha position (KIE = 1.03 ± 0.1) of the acrylate also supported this hypothesis. However a more comprehensive evaluation of the reaction mechanism performed by McQuade *et.al.*[16] and Aggarwal *et.al.*[17] some years later combining kinetic and theoretical studies rejected this premise, proposing the proton-transfer step as the rate-determining step.

In this sense, McQuade and coworkers found that the reaction between acrylates and aryl aldehydes in aprotic solvents exhibited four order kinetics ($\text{rate}=k\cdot[\text{aldehyde}]^2\cdot[\text{acrylate}]\cdot[\text{amine}]$). Moreover, large H/D KIE was observed when acrylates deuterated at the α position were employed as substrates; findings which are completely inconsistent with the C-C bond formation as rate-determining step. Based on these experimental observations, they proposed that in absence of a protic source, a second molecule of aldehyde had to participate in the proton transfer step via a six-membered transition state. This proposal was supported by the isolation of a dioxanone as byproduct of the reaction, which could be formed after an intramolecular nucleophilic attack over the proposed intermediate.

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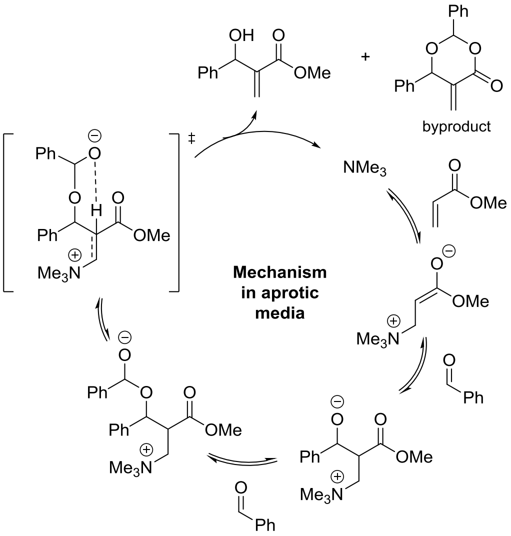
[15] (a) Hill, J. S.; Isaacs, N. S. *J. Phys. Org. Chem.* **1990**, 3, 285. (b) Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett.* **1986**, *27*, 5007.

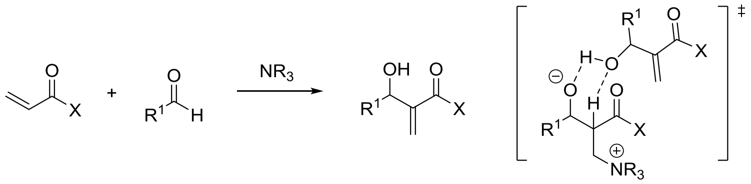
[16] (a) Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980. (b) Price, K. E.; Broadwater, S. J.; Jung, H. M.; McQuade, D. T. *Org. Lett.* **2005**, *7*, 147.

[17] (a) Robiette, R.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 15513. (b) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem. Int. Ed.* **2005**, *44*, 1706.



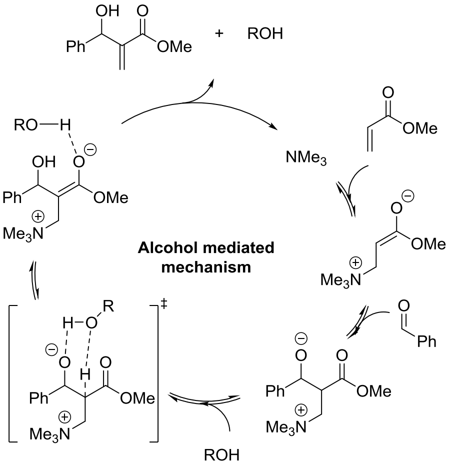
Scheme 2.6. Mechanistic pathway proposed by McQuade.

On the other hand, Aggarwal and coworkers also proposed proton-transfer step as the rate-determining step, but in this case, the autocatalysis effect experimentally observed led them to propose that the MBH adduct itself could also be involved in the hydrogen transfer process when the reaction is carried out in an aprotic media (Scheme 2.7).



Scheme 2.7. Transition state proposed by Aggarwal.

In addition, for those reactions performed in the presence of a protic source, commonly an alcohol, Aggarwal suggested a related scenario in which the alcohol itself acts as a shuttle in the proton transfer (Scheme 2.8). This assumption has been the subject of deep study for years, being supported by independent theoretical and computational studies reported by different research groups. In this context, Cantillo *et al.* analyzed by computational studies the experimentally observed acceleration of the DABCO catalyzed reaction between benzaldehyde and methylacrylate in the presence of protic additives.[18] In this way, they determined a significant decrease in energy barriers for the hydrogen transfer step, being this effect more pronounced when phenol was employed, compared to other protic additives such as methanol or water.



Scheme 2.8. Mechanistic pathway proposed for alcohol mediated MBH reaction.

More recently, Singleton has disclosed a meticulous analysis of the mechanism of the MBH reaction based on the combination of experimental observations, kinetic measurements and computational studies.[19] In this work, he emphasized the misleading conclusions reached by previous computational studies in which erroneous assumptions were made due to the high complex nature of this reaction. Results obtained by Singleton are consistent with a reaction involving two competitive rate-determining steps, concluding that rate-determining step shifts between Steps II and III depending on specific experimental conditions, due to the similarities in the energy barriers for both steps. Therefore, for the DABCO catalyzed MBH reaction between *p*-nitrobenzaldehyde and methyl acrylate in methanol, proton transfer is considered main rate-determining step under standard reaction conditions, the aldol step remaining as partially rate-limiting. On the other hand, it becomes main rate-determining step when the reaction is performed at low temperatures. In addition, further experiments allowed him to state that the

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[18] Cantillo, D.; Kappe, C. O. *J. Org. Chem.* **2010**, *75*, 8618. For other related studies, see: (a) Roy, D.; Patel, C.; Sunoj, R. B. *J. Org. Chem.* **2009**, *74*, 6936. (b) Roy, D.; Sunoj, R. B. *Org. Lett.* **2007**, *9*, 4873.

[19] Plata, R.E.; Singleton, D. A. *J. Am. Chem. Soc.* **2015**, *137*, 3811.

proton transfer that takes place in Step III occurs by acid-base chemistry and not by a proton shuttle process.

Subsequent reports have dealt with this controversial premise. For instance, computational studies recently developed by Ramasastry *et al.* for a phosphine catalyzed intramolecular MBH reaction have determined a significant decrease in energy barriers in the presence of hexafluoroisopropanol as protic additive.[20] According to the obtained results, under the studied experimental conditions the C-C bond formation is nearly barrierless, being the proton transfer the rate-determining step of the process.

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[20] Singh, N. K.; Satpathi, B.; Balanarayan, P.; Ramasastry, S. S. V. *Org. Biomol. Chem.* **2017**, *15*, 10212.

1.2. Phosphine-catalyzed enantioselective Morita-Baylis-Hillman reactions

As it has been mentioned before, three main strategies have been commonly followed regarding the development of catalytic and enantioselective Morita-Baylis-Hillman reactions, namely, using chiral tertiary amines as catalysts, employing chiral phosphines as catalysts and the cooperative use of an achiral tertiary amine or phosphine and a chiral Brønsted acid.

Although chiral tertiary amines have been successfully employed as catalysts in a wide variety of enantioselective MBH reactions,[14] the low reactivity observed for certain substrates brought to light the need of more active catalytic systems. In this sense, phosphines emerged as a promising alternative. Phosphines are able to take part in addition reactions to electrophilic substrates due to the non-bonded lone electron pair in the phosphine atom. In general, phosphines are more nucleophilic but less basic than similarly substituted amines, as it is inferred from the comparison of the nucleophilic reactivity constants for PEt_3 and NEt_3 (Table 2.1 entries 1 and 3). In addition, modifying the substituents attached to the phosphorous atom significantly affects its nucleophilicity, and hence, the reactivity of the catalyst. As an example, a significant decrease in nucleophilicity is observed when alkyl groups in a trisubstituted phosphine are replaced by phenyl groups (compare entries 1,2 and 5 Table 2.1).

Table 2.1. Nucleophilicity and basicity of different nucleophiles.[21]

Entry	Nucleophile	n_{MeI}	pk$_a$ (H_2O)
1	PEt_3	8.7	8.7
2	PBu_3	8.7	8.4
3	NEt_3	6.7	10.7
4	NH_3	5.5	9.3
5	PPh_3	1.3	2.7

In this context, a wide range of chiral phosphine catalysts have been designed and successfully applied as promoters of enantioselective MBH, aza-MBH and the related Rauhut-Currier reactions.[22] From a general perspective, most of the developed catalytic systems

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[21] Pearson, R. g.; Sobel, H. R.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319.

[22] For recent reviews on chiral phosphines as catalysts in asymmetric reactions, see: (a) Ni, H.; Chan, W.-L.; Lu, Y. *Chem. Rev.* **2018**, *118*, 9344. (b) Xiao, Y.; Guo, H.; Kwon, O. *Aldrichimica Acta*, **2016**, *49*, 3. (c) Wang, T.; Han, X.; Zhong, F.; Yao, W.; Lu, Y. *Acc. Chem. Res.* **2016**, *49*, 1369. (d) Wei, Y.; Shi, M. *Chem. Asian J.* **2014**, *9*, 2720. (e) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927. (f) Xu, L.-W. *Chem. Cat. Chem.* **2013**, *5*, 2775. (g)

are characterized by a structure containing simultaneously a nucleophilic phosphorous atom as well as a hydrogen bonding motif (Figure 2.2). These functionalities allow to stablish multiple interactions with the Michael acceptor moiety, generating less conformationally flexible transition states and therefore favoring a more efficient diastereocontrol. Additionally, this design offers a significant flexibility for the optimization of the reaction as the fine-tuning of the catalyst structure can be confronted modifying either the chiral scaffold, the phosphorous nucleophilicity or the hydrogen bond donors.

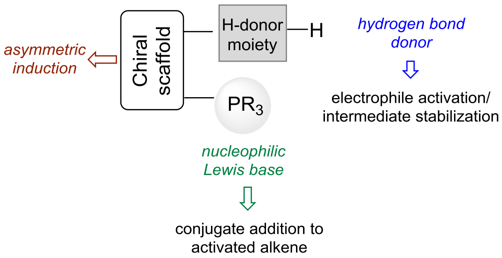


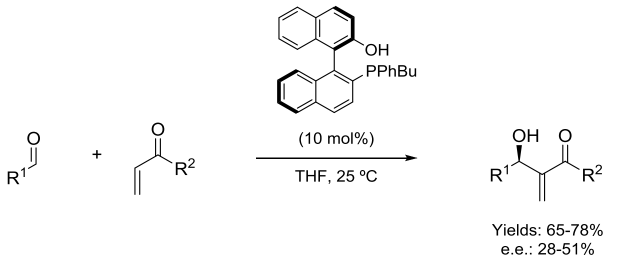
Figure 2.2. General structure of bifunctional phosphine catalysts.

In this sense, the first enantioselective examples involving chiral phosphines as catalysts made use of the binapthyl core as chiral scaffold, following the early precedent developed by Soai in 1998 for (*S*)-BINAP catalyzed MBH reaction (see Scheme 2.3).[12] In particular, Shi and coworkers reported the pioneering use of BINOL-derived phosphines as efficient catalysts in the enantioselective MBH reaction between aldehydes and vinyl ketones.[23] The employed catalysts, which were initially developed for analogous aza-MBH reaction,[24] provided the corresponding MBH adducts in good yields, albeit in moderate enantioselectivities. In order to explain the positive influence that the phenol moiety at catalyst structure had in its activity, authors proposed a hydrogen bond interaction between the hydroxyl group of the catalyst and the phosphonium enolate generated after the initial conjugate addition of the catalyst that favored the overall process.

Marinetti, A.;Voituriez, A. *Synlett*, **2010**, *02*, 174. (h) Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005. (i) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.

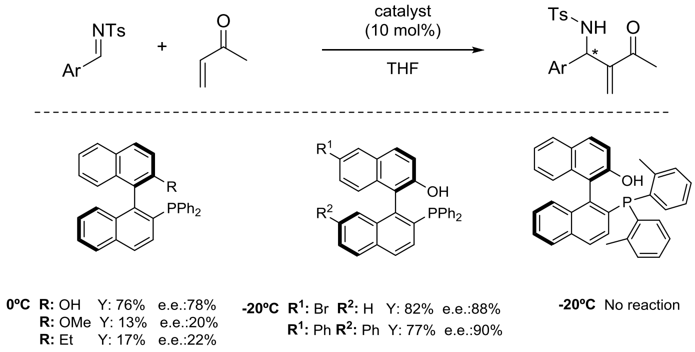
[23] Lei, Z.-Y.; Liu, X.-G.; Shi, M.; Zhao, M. *Tetrahedron: Asymmetry*, **2008**, *19*, 2058.

[24] (a) Shi, M.; Chen, L.-H.; Li, C.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790. (b) Shi, M.; Chen, L.-H. *Chem. Commun.* **2003**, 1310.



Scheme 2.9. BINOL-derived phosphine catalyzed MBH reaction.

In the following years, important efforts were directed to the development of related BINOL-derived catalysts in order to evaluate the effect that introducing substituents at different positions of the binapthyl scaffold have in the performance of MBH and aza-MBH reaction.[25] As in previous examples, the phenolic hydroxyl group in the catalyst was found to be crucial for the performance of the reaction between *N*-sulfonyl imines and methyl vinyl ketone, observing no reactivity in absence of such hydroxyl group or when it was methylated. Structural modifications of the catalyst allowed them to conclude that substituents in the 6,6′-positions of the naphthalene framework did not affect the course of the reaction, while a significant influence of the steric bulkiness around the phosphine was observed.



Scheme 2.10. Family of BINOL-derived phosphines developed by Shi.

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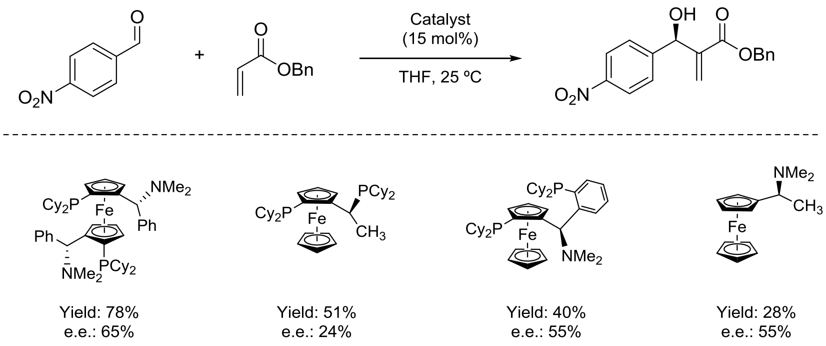
[25] For other related BINOL-derived catalysts developed by groups of Shi and Sasai applied to aza-MBH reaction, see: (a) Qi, M.-J.; Ai, T.; Shi, M.; Li, G. *Tetrahedron*, **2008**, *64*, 1181. (b) Guan, X.-Y.; Jiang, Y.-Q.; Shi, M. *Eur. J. Org. Chem.* **2008**, 2150. (c) Shi, M.; Ma, G.-N.; Gao, J. *J. Org. Chem.* **2007**, *25*, 9779. (d) Shi, Y.-L.; Shi, M. *Adv. Synth. Catal.* **2007**, *349*, 2129. (e) Li, Y.-H.; Chen, L.-H.; Shi, M. *Adv. Synth. Catal.* **2006**, *348*, 973. (f) Matsui, K.; Takizawa, S.; Sasai, H. *Synlett*, **2006**, *5*, 761. (g) Shi, M.; Chen, L.-H.; Teng, W.-D. *Adv. Synth. Catal.* **2005**, *347*, 1781. (h) Shi, M.; Chen, L.-H. *Chem. Commun.* **2003**, 1310.

Ferrocene-derived phosphines exhibiting planar chirality is another interesting design for catalysts active in enantioselective MBH reactions. In a pioneering work, Carretero *et al.* reported the use of a series of ferrocenyldialkylphosphines as highly nucleophilic catalysts for the MBH reaction between *p*-nitrobenzaldehyde and benzylacrylate (Scheme 2.11).[26] In this work, authors pursued the development of efficient phosphine catalysts which could exhibit high nucleophilicity due to the electron-rich character of ferrocene moiety, as well as, lower sensibility to oxidation. Despite obtaining excellent results for the achiral version of the reaction, the enantioselectivities observed for related chiral catalysts remained moderate in all the cases. Unfortunately, further modifications in the structure of the catalysts did not led to any improvement in the obtained results.



Scheme 2.11. Ferrocene-derived phosphine catalyzed enantioselective MBH reaction.

As pioneering examples had revealed a significant enhancement in reaction rate attributed to the presence of a hydrogen bond donor motif, subsequent efforts were directed to the development of chiral phosphine catalysts containing stronger hydrogen bond donor groups. For this purpose, the introduction of thiourea and squaramide substructures was evaluated. For instance, in 2009 Wu and coworkers reported the pioneering synthesis of a series of cyclohexane-derived phosphines containing a thiourea as hydrogen bond donor group.[27] These catalysts were successfully tested in the MBH reaction between *p*-nitrobenzaldehyde and different acrylates (Scheme 2.12), significantly improving the results previously obtained by Carretero and coworkers.

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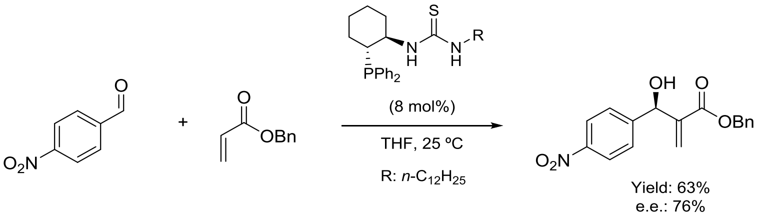
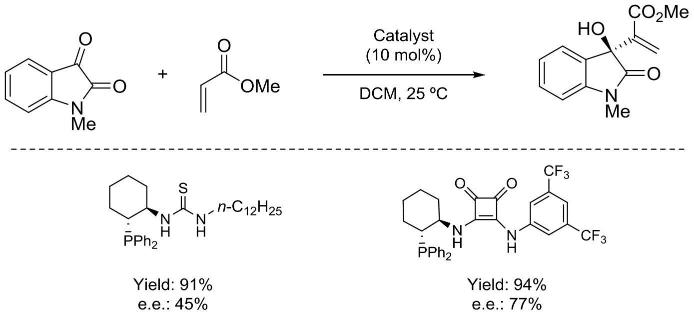
[26] Pereira, S. I.; Adrio, J.; Silva, A. M. S.; Carretero, J. C. *J. Org. Chem.* **2005**, *70*, 10175.

[27] Yuan, K.; Song, H.-L.; Hu, Y.; Wu, X.-Y. *Tetrahedron*, **2009**, *65*, 8185.



Scheme 2.12. Cyclohexane-derived thiourea phosphine catalyzed MBH reaction.

Some years later a close related squaramide-derived catalysts were reported by the same research group for the enantioselective MBH reaction between acrylates and isatines (Scheme 2.13).[28] The performance of these catalysts was compared to previously developed related thioureas, achieving significantly better results in terms of enantioselectivity. This effect was attributed to the higher ability exhibited by squaramides to stablish H bond interactions with the Michael acceptor compared to the analogous thioureas.



Scheme 2.13. Cyclohexane-derived squaramide phosphine catalyzed MBH reaction.

As a logic extension, important efforts were directed in the following years to improve the enantioselectivity induced focusing on modifying the chiral scaffold of previously designed thiourea and squaramide derived catalysts. In this context, naturally available aminoacids provided a tunable template for the design of a new type of bifunctional chiral catalysts. In line with previous works, in 2009 Wu and coworkers disclosed the use of novel thiourea derived phosphines starting from naturally available aminoacids as highly active catalysts in

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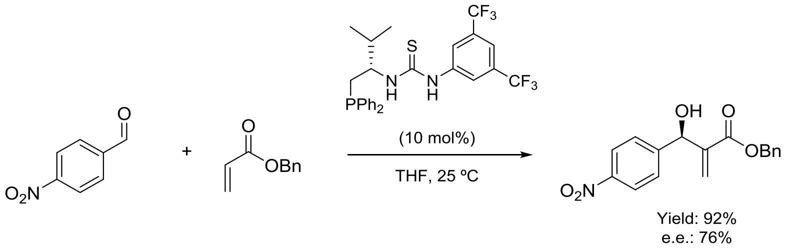
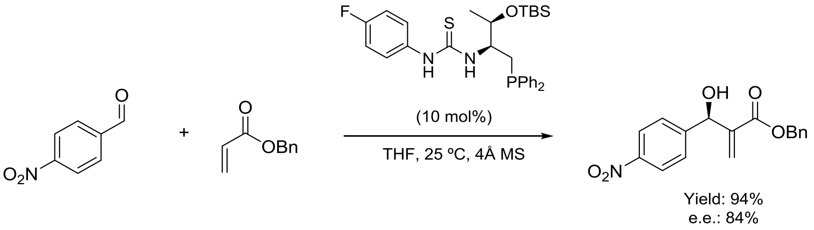
[28] Quian, J.-Y. Wang, C.-C.; Sha, F; Wu, X.-Y. *RSC Adv.* **2012**, *2*, 6042. For a related work using cyclohexane-derived thioureas, see: Wang, C.-C.; Wu, X.-Y. *Tetrahedron*, **2011**, *67*, 2974. For a related work using aminoacid-derived squaramides, see: Dong, Z.; Yan, C.; Gao, Y.; Dong, C.; Qiu, G.; Zhou, H.-B. *Adv. Synth. Catal.* **2015**, *357*, 2132.

enantioselective MBH reactions (Scheme 2.14).[29] Although these catalysts provided better results in terms of reactivity compared to analogous cyclohexane derived thioureas, they did not led to a significant improvement in the enantioselectivity (compare Scheme 2.12 and Scheme 2.14).



Scheme 2.14. Aminoacid-derived thiourea phosphine catalyzed MBH reaction.

Almost at the same time, Lu and coworkers proposed an alternative approach based on the design of a new series of aminoacid-derived phosphine catalysts containing a silyloxy group as well as a thiourea moiety (Scheme 2.15).[30] The modification of the alkyl or aryl groups attached to the silyloxy moiety, allowed them to modulate the steric bulk of the catalyst, which led to an improvement in the induced enantioselectivity. Additionally, the authors evaluated the effect of different protic additives, such as methanol, phenol or benzoic acid, among others in the outcome of the reaction. The observed negative influence of these additives in the enantioselectivity in the presence led them to propose that they would affect the intermolecular H-bond interaction stablished between the intermediate enolate and the thiourea.



Scheme 2.15. Enantioselective MBH reaction reported by Lu.

Finally, catalytic systems involving other type of chiral scaffolds not derived from α-aminoacids can also be found in the literature. For example, in 2015, Veselý and coworkers

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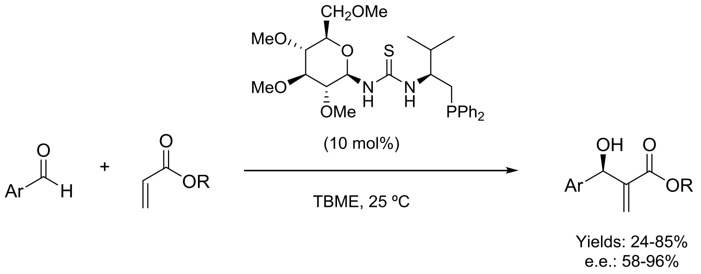
[29] Gong, J.-J.; Yuan, K.; Wu, X.-Y. *Tetrahedron: Asymmetry*, **2009**, *20*, 2117.

[30] Han, X.; Wang, Y.; Zhong, F.; Lu, Y. *Org. Biomol. Chem.* **2011**, *9*, 6734.

developed a new class of phosphine catalysts which contained a saccharide unit in their structure (Scheme 2.16).[31] Although these catalysts were employed as efficient promoters for the MBH reaction between aryl aldehydes and acrylates, the obtained results did not imply a significant improvement to previously developed catalytic systems.



Yields: 24-85%
e.e.: 58-96%

Scheme 2.16. Enantioselective MBH reaction catalyzed by saccharide-derived phosphine.

It should be highlighted that, despite most of the abovementioned catalysts have demonstrated to be useful in MBH reactions with acrylates and vinyl ketones, being also applicable as promoters of analogous aza-MBH[32] and Rauhut-Currier reactions,[33] they turned out to be unable to catalyze the MBH reaction when β-substituted Michael acceptors were employed as substrates. Moreover, achieving reactivity in these substrates has been considered a challenge for years, as they have remained unreactive against most of the chiral phosphine catalysts developed up to date. For instance, there is just one enantioselective example in which the aza-MBH reaction between *N*-sulfonyl imines and cyclic enones could be promoted under

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[31] Gergelitsová, I.; Tauchman, J.; Cisarova, I.; Veselý, J. *Synlett*, **2015**, *26*, 2690.

[32] For ferrocene-derived phosphines in aza-MBH reactions, see: Takizawa, S.; Rémond, E.; Arteaga, F. A.; Yoshida, Y.; Sridharan, V.; Bayardon, J.; Jugé, S.; Sasai, H. *Chem. Commun.* **2013**, *49*, 8392.

For BINOL-derived phosphines in aza-MBH reactions, see: (a) Takizawa, S.; Inoue, N.; Sasai, H. *Tetrahedron Lett.* **2011**, *52*, 377. (b) Takizawa, S.; Inoue, N.; Hirata, S.; Sasai, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 9725. (c) Antiss, C.; Liu, F. *Tetrahedron*, **2010**, *66*, 5486. (d) Garnier, J.-M.; Liu, F. *Org. Biomol. Chem.* **2009**, *7*, 1272. (e) Garnier, J.-M.; Antiss, C.; Liu, F. *Adv. Synth. Catal.* **2009**, *351*, 331. (f) Shi, Y.-L.; Shi, M. *Adv. Synth. Catal.* **2007**, *349*, 2129. (f) Ito, K.; Nishida, K.; Gotanda, T. *Tetrahedron Lett.* **2007**, *48*, 6147.

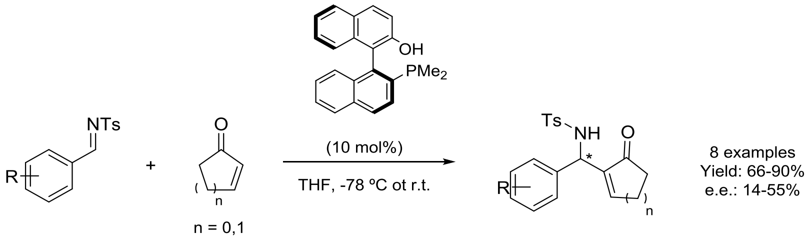
For aminoacid-derived phosphines in aza-MBH reactions, see: (a) Zhong, F.; Wang, Y.; Han, X.; Huang, K.-W.; Lu, Y. *Org. Lett.* **2011**, *13*, 1310. (b) Gao, Y.; Xu, Q.; Shi, M. *ACS Catal.* **2015**, *5*, 6608.

[33] For BINOL-derived phosphines in RC reactions, see: Zhang, X.-N.; Shi, M. *Eur. J. Org. Chem.* **2012**, 6271.

For aminoacid-derived phosphines in RC reactions, see: Takizawa, S.; Nguyen, T. M.-N.; Grossmann, A.; Suzuki, M.; Enders, D.; Sasai, H. *Tetrahedron*, **2013**, *69*, 1201.

For other nucleophilic phosphines in RC reactions, see: (a) Scanes, R. J. H.; Grossmann, O.; Grossmann, A.; Spring, D. R. *Org. Lett.* **2015**, *17*, 2462. (b) Zhao, X.; Gong, J.-J.; Yuan, K.; Sha, F.; Wu, X.-Y. *Tetrahedron Lett.* **2015**, *56*, 2526.

phosphine catalysis. In this BINOL-derived phosphine catalyzed example developed by Shi *et al.* the use of a more nucleophilic phosphine was required in order to overcome the lack of reactivity of these substrates, although the results obtained remained moderate in terms of enantioselectivity (Scheme 2.17).[34] Moreover, it should be considered that the substitution of the aromatic substituents of the phosphorous atom by alkyl groups implies an undesired increase in the sensibility to atmospheric oxidation.



Scheme 2.17. BINOL-derived phosphine catalyzed aza-MBH reaction of cyclic enones.

On the other hand, the favored nature of the intramolecular variant of this process has allowed to extend previously developed catalytic systems to β-substituted Michael acceptors that are tethered with the electrophilic carbonyl functionality. In this sense, in 2010, Wu and coworkers reported the use of bifunctional phosphine/thiourea and squaramide catalysts derived from cyclohexane[35] on the one hand, and from natural aminoacids[36] on the other, in a highly enantioselective intramolecular MBH reaction (Scheme 2.18). According to the authors, intermolecular H bonding interactions between the thiourea or squaramide and the aldehyde was responsible of the enhanced reactivity observed, as well as, of the high enantiocontrol due to the acquisition of a less flexible transition state. In addition to these examples, planar chiral ferrocene-based squaramides, as well as, saccharide-based thioureas have also been tested in the intramolecular MBH reactions, achievieng similar results in terms of yield and enantiomeric excess.[37]

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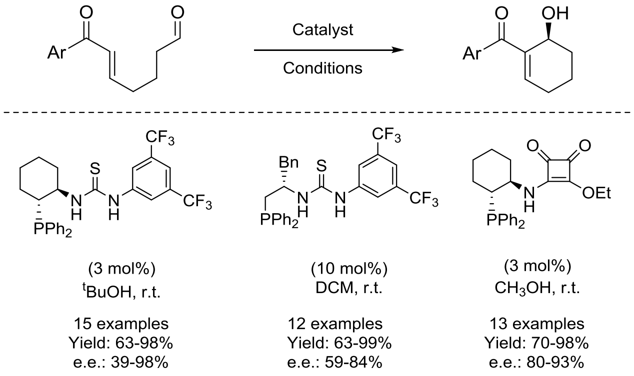
[34] Shi, M.; Li, C.-Q. *Tetrahedron: Asymmetry*, **2005**, *16*, 1385.

[35] (a) Yuan, K.; Song, H.-L.; Hu, Y.; Fang, J.-F.; Wu, X.-Y. *Tetrahedron: Asymmetry*, **2010**, *21*, 903. (b) Song, H.-L.; Yuan, K.; Wu, X.-Y. *Chem. Commun.* **2011**, *47*, 1012.

[36] Gong, J.-J.; Yuan, K.; Song, H.-L.; Wu, X.-Y. *Tetrahedron*, **2010**, *66*, 2439.

[37] (a) Yang, W.; Yuan, K.; Song, H.; Sha, F; Wu, X. *Chin. J. Chem.* **2015**, *33*, 1111. (b) Zhang, X.; Ma, P.; Zhang, D.; Lei, Y.; Zhang, S.; Jiang, R.; Chen, W. *Org. Biomol. Chem.* **2014**, *12*, 2423.



Scheme 2.18. Enantioselective intramolecular MBH reaction developed by Wu *et al*.

More challenging β,β-disubstituted enones, has also been employed by Ramasastry and coworkers as substrates in a enantioselective intramolecular MBH reaction using the cyclohexane-derived thiourea developed by Wang as catalysts (Scheme 2.19 A).[38] This reaction worked for a wide range of substrates, either containing aldehydes or ketones as electrophilic carbonyl moiety, obtaining in all the cases the corresponding bicyclic adducts in high yields and enantiomeric excess. Authors declared a significant dependence of enantioselectivity with the solvent, being necessary the use of hexafluoroisopropranol (HFIP) in order to achieve satisfactory results. This effect was attributed to the acidity of HFIP (pk_a 9.3) as well as to its strong hydrogen bond donating ability. Based on a computational analysis,[20] authors proposed that HFIP leads to a significant decrease in the energy barrier for rate-determining proton transfer step for the TS that affords the experimentally major product due to a more efficient proton transfer mediated by HFIP. Further studies allowed them to broaden the scope of this reaction to dienone susbtrates (Scheme 2.19 B),[39] albeit for these systems, the analogous urea-derived phosphine catalyst was found to provide the best results in terms of yield and enantiocontrol.

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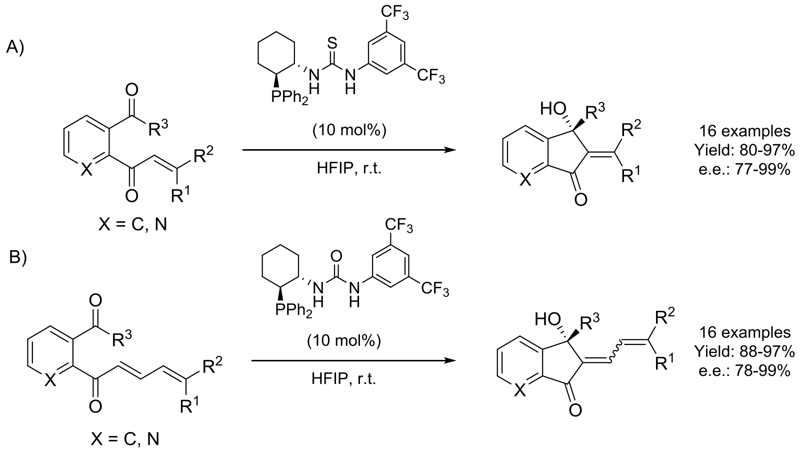
[38] (a) Satpathi, B.; Ramasastry, S. S. V. *Angew. Chem. Int. Ed.* **2016**, *55*, 1777. (b) Satpathi, B.; Ramasastry, S. S. V. *Synlett*, **2016**, *27*.

[39] Satpathi, B.; Wagulde, S. V.; Ramasastry, S. S. V. *Chem. Commun.* **2017**, *53*, 8042.

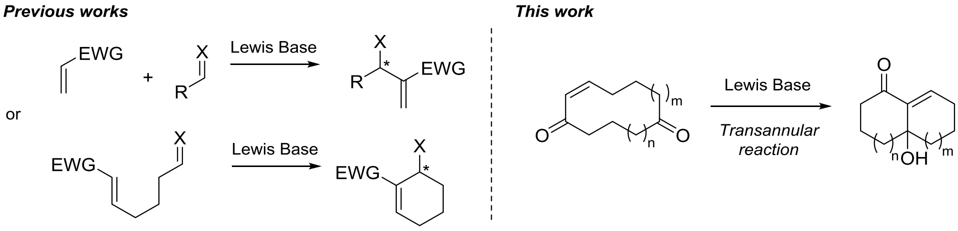


Scheme 2.19. Enantioselective intramolecular MBH reaction developed by Ramasastry.

It is noteworthy that although in the last years significant advances have been achieved in the field of phosphine-catalyzed enantioselective MBH reactions, results in terms of reactivity and enantiocontrol still remain quite dependent on the nature of the employed substrates. Moreover, most of the efficient examples reported up to date rely either on the use of unsubstituted Michael acceptors or on the intramolecular approach. In this sense, the transannular variant can be considered a suitable alternative, although it should be highlighted that there is not any precedent of enantioselective and organocatalytic MBH reaction performed in a transannular fashion.

2. SPECIFIC OBJECTIVES AND WORK PLAN

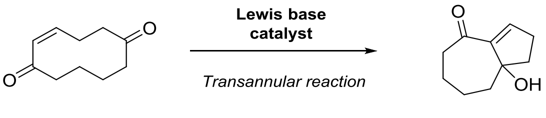
As it has been outlined in previous section, MBH reaction stands as an appealing strategy for the α-functionalization of activated alkenes. In the same way transannular reactions have been demonstrated to be a suitable method to access complex structures with high atom economy and operational simplicity. In this sense, we envisioned that combining both concepts in a **catalytic enantioselective transannular MBH reaction will offer direct access to highly functionalized polycyclic structures** (Scheme 2.20). For this purpose, medium and large size carbocycles containing simultaneously an enone as activated alkene and a ketone as internal electrophile were selected as starting materials. In order to induce enantiocontrol chiral Lewis bases, either based on nucleophilic amines or phosphines, will be surveyed as catalysts for the envisioned transannular MBH reaction.



Scheme 2.20. Specific objective of this project.

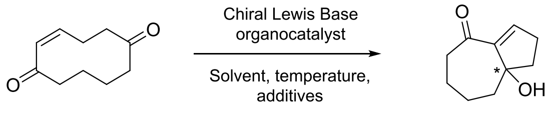
To accomplish the aforementioned objective, the subsequent work plan was outlined:

- *Proof of concept:* The viability of the envisioned reaction will be tested over a 10- membered keto-enone that would led to a bicyclo[5.3.0]decane scaffold (Scheme 2.21). The formation of this bicyclic structure is expected to be favored due to the strain release involved in the transannular process. The model reaction will be tested employing Lewis bases previously reported in the literature for MBH reaction, such as DABCO, DBU, DMAP or PMe_3.



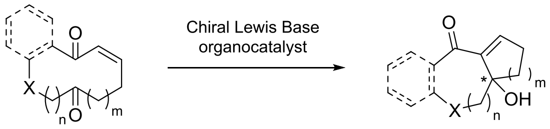
Scheme 2.21. Envisioned model reaction.

- *Optimization of the reaction conditions:* Once the viability of the reaction has been demonstrated and the most appropriate type of catalyst (amine or phosphine) has been selected, a variety of chiral catalysts will be evaluated in the enantioselective version of the reaction with the same model substrate. In the same way, different experimental parameters will be modified in order to find optimal conditions to obtain the desired products in high yields and enantioselectivities.



Scheme 2.22. Studied enantioselective reaction.

- *Scope of the reaction:* The scope and limitations of the developed method will be studied through the evaluation of structurally different substrates (Scheme 2.23). First of all, carbocycles with differing number of carbon atoms between the carbonyl moieties, as well as, between ketone and enone will be surveyed. Substrates containing an aromatic ring conjugated with the α,β-unsaturated ketone will be also evaluated, containing either electron-withdrawing and electron-donating groups. Finally substrates that contain a heteroatom in their structure will be also tested.



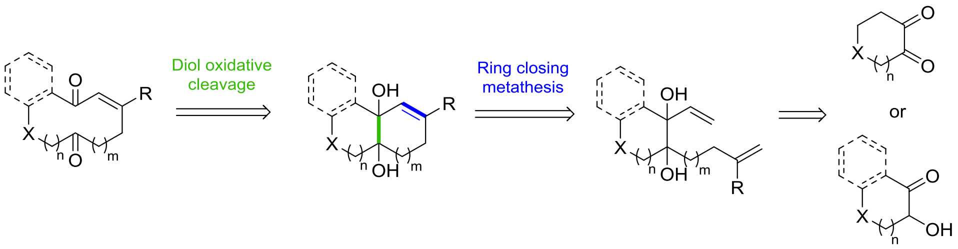
Scheme 2.23. Scope of the reaction.

3. RESULTS AND DISCUSSION

3.1. Synthesis of the precursors

Prior to start the study of the organocatalytic reaction, it was necessary to develop a synthetic strategy to access carbocycles of different size. These substrates must present an activated alkene and an electrophilic sp^2 carbon atom in their structures located at such distance that favor the transannular process. For an initial approach an α,β-unsaturated carbonyl compound and a ketone were selected as reaction partners.

Taking into consideration the disadvantages associated to strategies in which the cyclization is the final step of the synthesis, such as, high dilutions, lack of selectivity and low conversions, we decided to generate the macrocycles by a final fragmentation step. Based on a methodology developed by Paquette and coworkers,[40] we envisioned the synthesis of a different size macrocycles by an oxidative cleavage of 1,2-diols,[41] which could be, as well, accessed by a consecutive addition of Grignard reagents to 1,2-diketones followed by a ruthenium catalyzed ring closing metathesis. The modification of the length of the alkyl chain, as well as the size of the initial diketone, would provide access to different ring-size carbocycles. Additionally, the use of α-hydroxy ketones as starting materials was also contemplated.



Scheme 2.24. Proposed retrosynthetic route for the precursors.

We started the projected synthetic route with the synthesis of the envisioned model substrate. In this sense, cyclohexane-1,2-dione **1a** was subjected to the addition of

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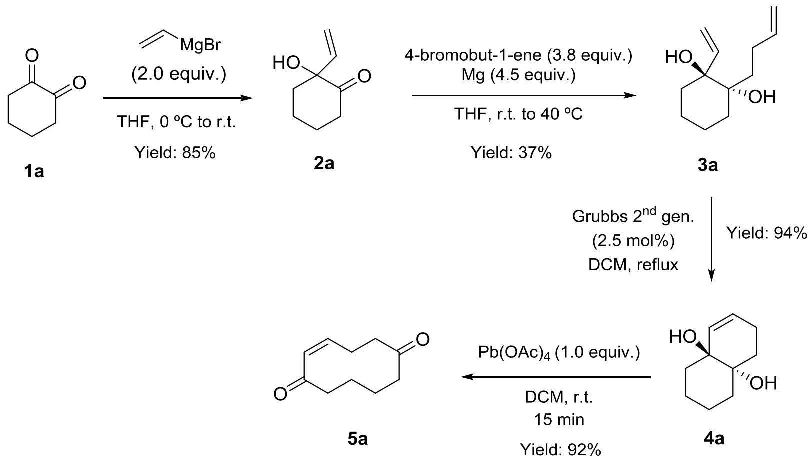
[40] (a) Balskusm E. P.; Méndez-Andino, J.; Arbit, R. M.; Paquette, L. A. *J. Org. Chem.* **2001**, *66*, 6695. (b) Méndez-Andino, J.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 1263.

[41] For a review of the use of Pb(OAc)$_4$ in the oxidative cleavage of 1,2-diols, see: Schmidt, A. C.; Stark, C. B. W. *Synthesis*, **2014**, *46*, 3283.

vinylmagnesium bromide in THF at 0 °C according to a procedure previously described in the literature,[42] which afforded 2-hydroxy-2-vinyl ketone **2a** in 85% yield (Scheme 2.25). Then, we proceeded with the introduction of the second alkyl chain, which was performed by the addition of freshly prepared but-3-en-1-ylmagnesium bromide in THF at 0 °C. After two hours at 40 °C compound **3a** was isolated in 37% yield as a single diastereomer. This product was assumed to be *trans* regarding the configuration of the hydroxyl groups, based on reported literature precedents on Grignard addition to 2-hydroxy-2-vinyl-cyclohexanone.[42b] It should be mentioned that despite several modifications of the experimental procedure were tested, isolated yield could not be improved.



Scheme 2.25. Synthesis of keto-enone **5a.**

Following the established synthetic approach, we accomplished the closure of the lateral cycle by a ruthenium catalyzed ring-closing metathesis. As initial attempts employing 1st generation Grubbs catalyst (2.5 mol%) in CH_2Cl_2 at reflux did not afford full conversion of the starting materials, 2nd generation Grubbs catalyst was tested under the same reaction conditions. This procedure allowed us to access compound **4a** in an excellent 94% yield after 2 hours. It should be highlighted that following this strategy, the configuration of the alkene would

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[42] For related precedents, see: (a) Cossy, J.; BouzBouz, S.; Laghgar, M.; Tabyaoui, B. *Tetrahedron Lett.* **2002**, *43*, 823. (b) Barnier, J. P.; Conia, J. M. *Bull. Soc. Chim. Fr.* **1975**, *304*, 1659.

certainly be *Z,* forced by the size of the cycle formed through ring closing process.[43] In addition, the configuration of the double bond was envisioned to stay unaltered under final oxidative cleavage conditions, providing selective access to *Z* substrates. This is a relevant point of the synthetic route, as controlling the *Z/E* selectivity in the synthesis of medium and large size cycles remains challenging through other methodologies.[44]

Finally, $Pb(OAc)_4$ was employed in DCM for the oxidative cleavage of cyclic 1,2-diol, providing access substrate **5a** in 92% yield after 15 minutes. ^{1}H-NMR coupling constants for alkene signals were consistent with the expected values for *Z* configuration $J_{H\text{-}H}$ ~ 12 Hz, whilst higher values would be expected for *E* $J_{H\text{-}H}$ ~ 16 Hz configurations.

Additionally, a substrate containing a heteroatom in its structure was also synthesized, although a minor modification in the synthetic route was introduced (Scheme 2.26). In this way, α-hydroxyketone **1b** was employed as starting material, which after initial Grignard addition afforded the corresponding diol. Although it was obtained as mixture of diastereomers, direct oxidation with 2-iodoxybenzoic acid (IBX) in ethyl acetate afforded the desired α-hydroxyketone **2b** as main product, which was directly subjected to Grignard addition due to its high instability, rendering product **3b** in 29% yield for 3 steps. Subsequent ring-closing metathesis afforded bicyclic diol **4b** in 77% yield, which was transformed into 10 membered keto-enone **5b** by oxidative cleavage with $Pb(OAc)_4$. This final step coursed with a 40% yield, which was significantly lower than achieved result for analogous substrate **5a** presumably due to product decomposition in the reaction media.

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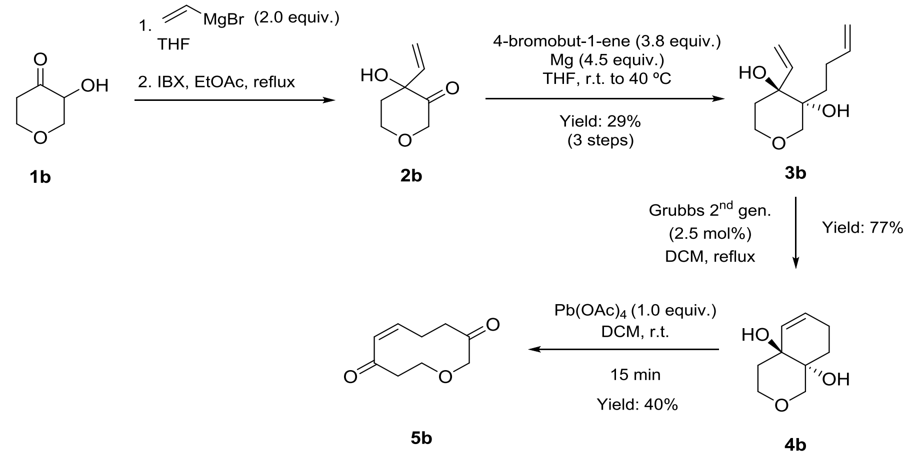
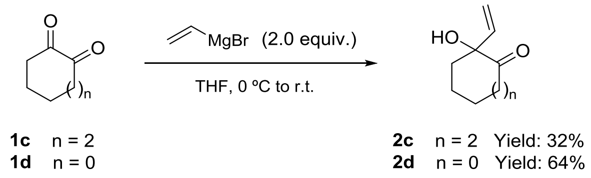
[43] It was expected that Z/E selectivity issues could be observed in the formation of larger fused cycles by ring closing metathesis due to the increasing conformational flexibility of larger rings.

[44] For more information about ring closing metathesis and stereoselective versions see: (a) Shen, X.; Nguyen, T. T.; Koh, M. J.; Xu, D.; Speed, A. W. H.; Schrock, R. R.; Hoveyda, A. H. *Nature*, **2017**, *541*, 380. (b) Hoveyda, A. H. *J. Org. Chem.* **2014**, *79*, 4763. (c) Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135*, 94. (d) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature*, **2011**, *479*, 88. (e) Hoveyda, A. H.; Zhugralin, A. R. *Nature***, 2007**, *450*, 243.



Scheme 2.26. Synthesis of substrate **5b**.

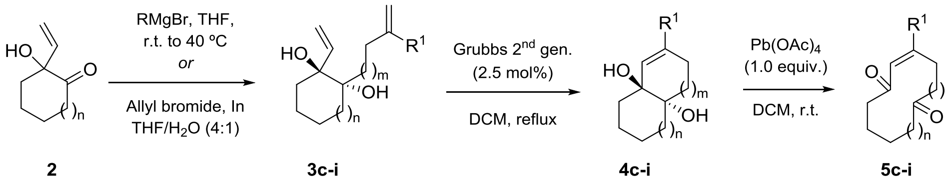
Once demonstrated the applicability of the envisioned synthetic route, we accomplished the synthesis of different sized carbocycles by the extension of previously described methodology. Hence, we started with the synthesis of a variety of α-hydroxyketones by the addition of vinylmagnesium bromide to cyclic 1,2-diketones of different size. In this way, the α-hydroxyketones derived from cycloheptane (**2c**) and cyclopentane (**2d**) were obtained in moderate yields.



Scheme 2.27. Synthesis of 2-hydroxy-2-vinyl ketones **2c-d.**

With α-hydroxyketone intermediates **2** in hand, we proceeded with the introduction of the second alkyl chain. Organometallic reagents containing an alkenyl chain of different length were employed, as they would finally led to keto-enones with differing number of carbon atoms between the carbonyl moieties. This purpose was accomplished by two parallel strategies: Grignard reagents were used for the introduction of butenyl (m=1) and pentenyl (m=2) chains; while an organoindium reagent was employed for the synthesis of the corresponding allylic derivative (compound **3i**). This organoindium reagent was generated *in situ* by reaction of allylbromide and metallic indium in a THF:H_2O mixture. The results obtained for these substrates have been summarized in Table 2.2. As it can be observed in this table, isolated yields for compounds **3** were moderate in all the cases, achieving better results for cycloheptane (60% yield for **3e**) and cyclopentane (50% yield for **3g**) derived compounds compared to analogous cyclohexane-derived products (34% yield for **3c**). The ring closing metathesis worked efficiently for most of the substrates tested, affording the corresponding bicyclic 1,2-diols (**4**) as *Z* alkenes in good to excellent yields. Finally, lead (IV) acetate promoted oxidative cleavage afforded keto-enones **5** in high yields.

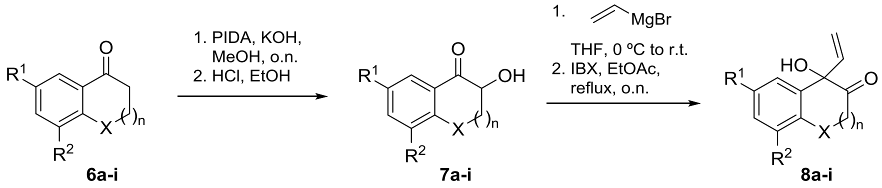
Table 2.2. Synthesis of substrates **5c-i**.



				Grignard addition		RCM		Oxidative cleavage	
Substrate	**n**	**m**	**R^1**	**3c-i**	**Yield (%)**	**4c-i**	**Yield (%)**	**5c-i**	**Yield (%)**
2a	1	1	CH_3	**3c**	34	**4c**	96	**5c**	73
2a	1	2	H	**3d**	30	**4d**	94	**5d**	78
2c	2	1	H	**3e**	60	**4e**	50	**5e**	84
2c	2	2	H	**3f**	49	**4f**	79	**5f**	95
2d	0	1	H	**3g**	50	**4g**	80	**5g**	77
2d	0	2	H	**3h**	54	**4h**	74	**5h**	75
2a	1	0	H	**3i**	67	**4i**	90	**5i**	58

Next, we proceeded with the synthesis of analogous substrates but containing an aromatic ring conjugated with the α,β-unsaturated ketone. In order to access the required α-hydroxy-vinyl ketones, an analogous strategy to that followed for substrate **5b** was employed (see Scheme 2.26). Thus, commercially available ketones **6** were converted into the corresponding α-hydroxyketones **7** and subsequently subjected to Grignard addition and IBX-mediated oxidation step to yield the desired α-hydroxy-vinyl ketones **8** (Table 2.3). Isolated yields for intermediates **7** were high in most of the cases, regardless the electronic nature of the substituents attached to the aromatic ring. On the other hand, products **8** were obtained in moderate yields, observing no improvements when alternative oxidants, such as pyridinium dichromate (PDC), pyridinium chlorochromate (PCC) or Swern oxidation were tried.

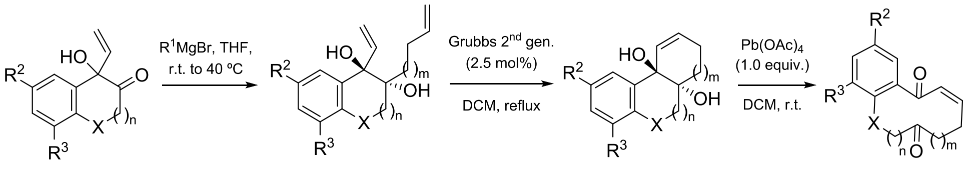
Table 2.3. Synthesis of intermediates **8a-i**.



					α-oxidation		Grignard addition	
Substrate	**n**	**X**	**R^1**	**R^2**	**7a-i**	**Yield (%)**	**8a-i**	**Yield (%)**
6a	0	CH_2	H	H	**7a**	n.d	**8a**	44
6b	1	CH_2	H	H	**7b**	87	**8b**	52
6c	1	CH_2	CH_3	CH_3	**7c**	85	**8b**	44
6d	1	CH_2	H	OCH_3	**7d**	63	**8d**	58
6e	1	CH_2	OCH_3	H	**7e**	95	**8e**	39
6f	1	CH_2	Br	H	**7f**	65	**8f**	54
6g	1	CH_2	F	H	**7g**	76	**8g**	51
6h	1	O	H	H	**7h**	70	**8h**	28
6i	2	CH_2	H	H	**7i**	n.d.	**8i**	39

Next we synthesized 1,2-diols **9** by addition of the corresponding Grignard reagents of different length over substrates **8**. At this point, and in contrast to results achieved for previous substrates, it was observed the formation of two diastereomers in almost equimolar amounts, which could be isolated separately by column chromatography. Unfortunately, the independent exposition of each product to ring-closing metathesis conditions showed complete lack of reactivity for one of the isolated diastereomers. In fact, they remained unreactive when exposed to higher catalyst loadings, higher temperatures or other catalysts, such as 1st and 2nd generation Hoveyda-Grubbs catalyst. Isolated yields for Grignard addition step described in Table 2.4, correspond to reactive diastereomers of intermediates **9**. Further ring-closing metathesis coursed in excellent yields for all the compounds rendering bicyclic adducts **10** in less than 1 hour. Finally, the oxidative cleavage step provided access to target substrates **11a-m** in moderate to good yields. As it can be observed in Table 2.4, for substrates **11d** and **11m** this final oxidative cleavage reaction did not work efficiently, affording reaction products in low yields. In contrast to other substrates, for these compounds no full consumption of the starting materials was observed by TLC after several hours. Further addition of $Pb(OAc)_4$ did not either favor completion of the reaction, albeit unreacted starting materials could be recovered by flash column chromatography. It should be mentioned that observed NMR coupling constants for alkene signals were consistent with expected values for *Z* alkenes in all the cases.

Table 2.4. Synthesis of substrates **11a-m**.

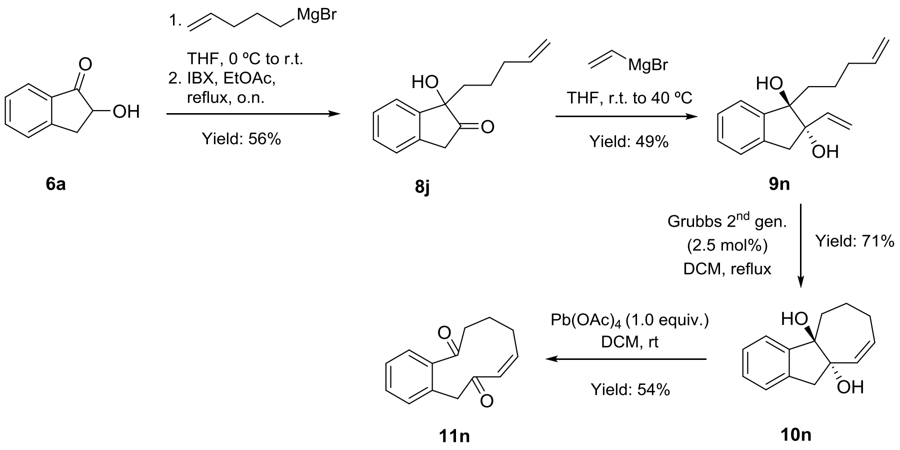


8 **9a-m** **10a-m** **11a-m**

					Grignard addition		RCM		Oxidative cleavage	
n	m	X	R^2	R^3	9a-m	Yield (%)[a]	10a-m	Yield (%)	11a-m	Yield (%)
0	2	CH_2	H	H	**9a**	21	**10a**	78	**11a**	60
1	1	CH_2	H	H	**9b**	28	**10b**	87	**11b**	90
1	1	CH_2	CH_3	CH_3	**9c**	26	**10c**	96	**11c**	79
1	1	CH_2	H	OCH_3	**9d**	25	**10d**	98	**11d**	46
1	1	CH_2	OCH_3	H	**9e**	16	**10e**	85	**11e**	64
1	2	CH_2	H	H	**9f**	24	**10f**	91	**11f**	95
1	2	CH_2	CH_3	CH_3	**9g**	32	**10g**	79	**11g**	90
1	2	CH_2	H	OCH_3	**9h**	44	**10h**	96	**11h**	88
1	2	CH_2	OCH_3	H	**9i**	32	**10i**	89	**11i**	83
1	2	CH_2	Br	H	**9j**	24	**10j**	86	**11j**	78
1	2	CH_2	F	H	**9k**	22	**10k**	95	**11k**	62
1	2	O	H	H	**9l**	54	**10l**	54	**11l**	80
2	1	CH_2	H	H	**9m**	48	**10m**	78	**11m**	54

[a] Isolated yields correspond to **9a-m** diastereomers that showed reactivity in subsequent Ring Closing Metathesis.

Additionally, a substrate containing an aromatic ring conjugated with the ketone instead of the enone was also synthesized (Scheme 2.28). To access this compound, an inversion in the order of addition of the organomagnesium reagents was required. Therefore, substrate **6a** was subjected to the addition of pent-4-en-1-ylmagnesium bromide in THF at 0 °C, followed by direct oxidation with IBX in EtOAc overnight, affording intermediate **8j** in 56% yield. Subsequent addition of vinylmagnesium bromide rendered diol **9n** in 49% yield, which was subjected to ring closing metathesis and oxidative cleavage affording compound **11n**.

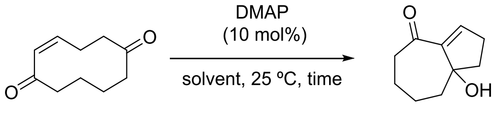


Scheme 2.28. Synthesis of substrate **11n**.

3.2. Proof of concept

We started the study of the viability of this reaction evaluating keto-enone **5a** as model substrate and employing different Lewis bases, such as DABCO and DBU as catalysts, which have been commonly used in Morita-Baylis-Hillman reactions.[45] However, none of these Lewis bases tested provided clean conversion to the desired adduct, observing multiple products attributed to unselective aldol reactions promoted by the basic character of the catalyst. On the other hand, preliminary tests showed that when substrate **5a** was subjected to reaction in the presence of 10 mol% of 4-dimethylaminepyridine (DMAP),[46] the desired bicyclic product **12a** could be detected, measuring a 66% conversion of starting material by ^{1}H-NMR of the crude reaction mixture. Preliminary tests were carried out employing ethanol as solvent (Table 2.5), as literature reports indicate that a proton source is required in order to facilitate the proton transfer step that takes place prior to catalyst turnover.[47] Moving from ethanol to other polar aprotic solvents, such as CH_2Cl_2 and CH_3CN (entries 2 and 3), led a significant decrease in reaction rate, requiring 7 days in order to achieve moderate conversions. This effect was even more significant when toluene was tested as non-polar solvent, observing 25% of conversion after 7 days (entry 4).

Table 2.5. Preliminary study of the reaction.



5a **12a**

Entry	Solvent	Time	Conv. (%)[a]
1	EtOH	24 h	66
2	CH_2Cl_2	7 d	30
3	CH_3CN	7 d	50
4	Toluene	7 d	< 25

[a]Conversions measured by ^{1}H-NMR in crude reaction mixtures.

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[45] (a) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311. (b) Shi, M.; Wang, F.-J.; Zhao, M.-X.; Wei, Y. *The Chemistry of the Morita-Baylis-Hillman Reaction*; RSC: Cambridge, 2011.

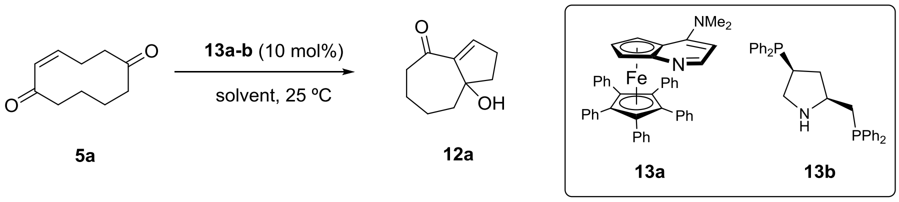
[46] For some examples of the employment of DMAP in MBH reactions: (a) Dadwal, M.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Biomol. Chem.* **2006**, *4*, 2525. (b) de Souza, R. O. M. A.; Vasconcellos, M. L. A. A. *Catal. Commun.* **2004**, *5*, 21. (c) Octavio, R.; de Souza, M. A.; Vasconcellos, M. L. A. A. *Synth. Commun.* **2003**, *33*, 1383.

[47] For more information regarding the mechanism of the reaction see section 1.

3.3. Optimization of the reaction conditions

Considering previous results as evidence of the feasibility of the reaction, next efforts were directed to the development of the asymmetric version of this reaction. In this sense, we proceeded to survey catalyst **13a**, which is considered as a chiral evolution of DMAP developed by Fu and coworkers.[48] Unfortunately, this catalyst was unable to promote the desired reaction in ethanol (Table 2.6 entry 1) or under any of the other conditions tested (entries 2-3). At this stage, we decided to change our approach and explore the performance of chiral phosphines as potential Lewis base catalysts. Initial test in EtOH with commercially available reagent **13b**, commonly used as chiral ligand for metal complexes,[49] resulted in product formation in good yields but poor enantiocontrol (entry 4). Further tests in solvents of different nature did not provide better results in terms of enantiocontrol (entries 5-8).

Table 2.6. Initial evaluation of catalysts.



Entry[a]	Catalyst	Solvent	Time (h)	Yield[b] (%)	e.e.[c] (%)
1	**13a**	EtOH	96	< 5	n.d.[d]
2	**13a**	Toluene	96	< 5	n.d.
3	**13a**	CH_3CN	96	< 5	n.d.
4	**13b**	EtOH	72	73	6
5	**13b**	Toluene	96	57	10
6	**13b**	CH_3CN	96	50	3
7	**13b**	CH_2Cl_2	96	59	0
8	**13b**	THF	96	20	n.d.

[a]Reactions were carried out at 0.06 mmol scale of **5a**, using 10 mol% of catalyst in 0.8 mL of solvent at r.t. [b]Yields refer to isolated pure product **12a**. [c]Calculated by HPLC on chiral stationary phase. [d]n.d. not determined.

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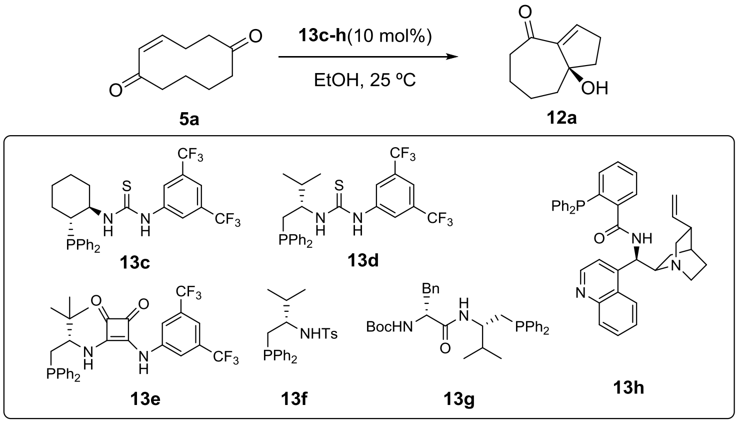
[48] (a) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542. (b) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412. (c) Ruble, J. C.; Latham, H. A.; Fu, G.C. *J. Am. Chem. Soc.* **1997**, *119*, 1492. (d) Fu catalyst used in enantioselective MBH reactions: Bugarin, A.; Connell, B.T. *Chem. Commun.* **2010**, *46*, 2644.

[49] Olszewska, B.; Kryczka, B.; Zawisza, A. *Tetrahedron*, **2013**, *69*, 9551.

In view of these results, we decided to evaluate a family of bifunctional chiral phosphines with completely different architectures (Table 2.7). In this context, we started evaluating cyclohexane-derived thiourea **13c** with after 4 hours rendered adduct **12a** in 56% yield albeit with moderate enantiomeric excess (entry 1). Aminoacid-derived thiourea **13d** significantly improved the enantiocontrol of the reaction affording adduct **12a** with a promising 64% e.e. (entry 2). The employment squaramide catalyst **13e**, which is known to exhibit a higher hydrogen bond donor tendency than analogous thiourea, led to similar results in terms of yield although a slight decrease in the enantioselectivity was observed (entry 3).

Table 2.7. Survey of chiral bifunctional phosphines as catalysts.



Entry[a]	Catalyst	Time (h)	Yield (%)[b]	e.e. (%)[c]
1	**13c**	4	56	13
2	**13d**	2	48	-64
3	**13e**	19	56	-46
4	**13f**	17	42	2
5	**13g**	13	60	6
6	**13h**	120	37	-20

[a] Reactions were carried out at 0.06 mmol scale of **5a**, using 10 mol% of catalyst in 0.8 mL of solvent at r.t. [b] Yields refer to isolated pure product **12a**. [c] Calculated by HPLC on chiral stationary phase.

On the other hand, aminoacid derived phosphine **13f** was able to promote the reaction albeit with complete loss of enantiocontrol (Table 2.7 entry 4). In the case of peptidic phosphine **13g**, it afforded adduct **12a** with the highest yield from all the catalysts tested although with poor enantiocontrol (entry 5). Finally, natural alkaloid derived catalyst **13h** was also tested in the reaction, although a significant decrease in reaction rate was observed, requiring 120 hours in order to isolate adduct **12a** in 37% yield (entry 6).

At this point, catalysts **13d**, **13e** and **13g** were selected for further screening reactions as they provided the best results in terms of yield and enantioselectivity. As previous experiments had revealed that moving from ethanol to any non-protic solvent implied a significant decrease in conversion (see Table 2.5), initial reactions were carried out in the presence of phenol as protic additive based on literature reports that indicate that phenol, as well as other mild Brønsted acids, accelerate MBH and aza-MBH reactions facilitating the protonation step of the catalytic cycle.[20,50] Under these new experimental conditions, when bifunctional thiourea **13d** was tested as catalyst, adduct **12a** was isolated in excellent yield although a decrease in the enantioselectivity was observed compared to results obtained in EtOH (Table 2.8 entry 1). Analogous enhancement in isolated yield was observed for catalyst **13e** which afforded product **12a** with a significantly higher enantiomeric excess (entry 2). Finally catalyst **13g** was tested, rendering the MBH adduct with the highest yield and enantioselectivity until this point (entry 3). Finally, as catalyst **13g** contains two stereocenters in its structure, we evaluated the possible *matched/mismatched* effect regarding the configuration of these stereocenters. Indeed, diastereomeric peptide-derived phosphine **13i** rendered adduct **12a** in a similar yield than that previously achieved by catalyst **13g** in same experimental conditions, but with a significant lower enantioselectivity. This fact suggested that both stereogenic centers play a significant role in controlling the stereochemical outcome of the reaction.

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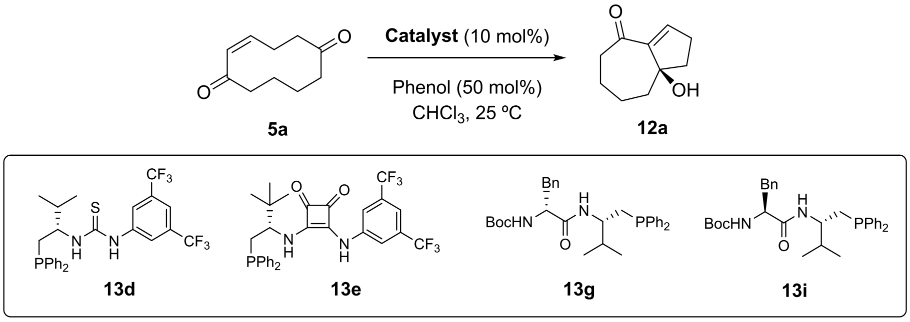
[50] For some selected examples see: (a) Abermil, N.; Masson, G.; Zhu*, J. Org. Lett.* **2009**, *11*, 4648. (b) Abermil, N.; Masson, G.; Zhu, J. *J. Am. Chem. Soc.* **2008**, *130*, 12596. (c) Shi, M.; Liu, Y-H. *Org. Biomol. Chem.* **2006**, *4*, 1468. (d) Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Letters*, **2000**, *41*, 2165.

Table 2.8. Screening for catalysts **13d**, **13e**, **13g** and **13i**.

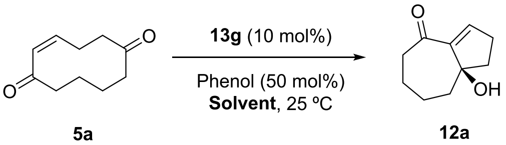


Entry[a]	Catalyst	Time (h)	Yield (%)[b]	e.e. (%)[c]
1	**13d**	0.5	79	-48
2	**13e**	0.75	82	-82
3	**13g**	16	86	84
4	**13i**	16	87	68

[a] Reactions were carried out at 0.06 mmol scale of **5a**, using 10 mol% of catalyst and 50 mol% of phenol in 0.8 mL of solvent at r.t. [b] Yields refer to isolated pure product **12a**. [c] Calculated by HPLC on chiral stationary phase.

Next we moved to study the role played by the solvent in the reaction (Table 2.9). For this reason, solvents of different nature were evaluated for catalyst **13g**. Thus when toluene was tested, a slight decrease in enantioselectivity was observed (entry 2), an effect also observed for EtOAc (entry 3). For chlorinated solvents such as DCM and 1,2-dichloroethane an improvement in the isolated yield was observed, but the enantioselectivity was negatively affected (entries 4 and 5). Tetrachloroethylene (entry 6) rendered the product in 76% yield although the e.e. was inferior to that obtained for chloroform. Finally, when THF was tested, an important decrease in reaction rate was observed, affording adduct **12a** in 73% yield after 6 days (entry 7) albeit a significantly lower enantiomeric excess was observed. After all these experiments, $CHCl_3$ still showed up as the best solvent for the reaction, enabling the formation of the transannular MBH adduct **12a** in 86% yield and 85% e.e.

Table 2.9. Solvent screening.

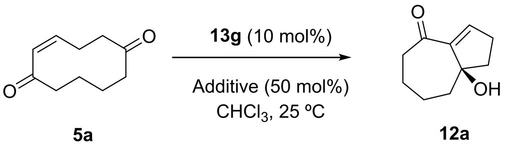


Entry[a]	Solvent	Time	Yield (%)[b]	e.e. (%)[c]
1	$CHCl_3$	16 h	86	84
2	Toluene	16 h	85	68
3	EtOAc	20 h	84	54
4	CH_2Cl_2	24 h	95	72
5	1,2-dichloroethane	18 h	95	60
6	Tetrachloroethylene	21 h	76	72
7	THF	144 h	73	38

[a]Reactions were carried out at 0.06 mmol scale of **5a**, using 10 mol% of catalyst and 50 mol% of phenol in 0.8 mL of solvent at r.t. [b]Yields refer to isolated pure product **12a**. [c]Calculated by HPLC on chiral stationary phase.

In view of the pronounced impact of the proton source in this reaction, we considered that it was necessary to survey different protic additives in order to evaluate their influence in the course of the reaction. As represented on Table 2.10, when more acidic additives as cyclohexanol and ethanol were tested, an important decrease in the enantiomeric excess was observed (entries 2 and 3). Alcohols with pK_a similar to phenol (entries 4-6) were found to promote the reaction efficiently, with the exception of 2-aminophenol (entry 5) which led to the minor formation of adduct **12a** due to the significant occurrence of side reactions. Good results were also obtained when bulkier protic additives were tested, such as, 1-naphthol or chiral (*R*)-BINOL (entries 7 and 8) rendering adduct **12a** in good yields and enantioselectivity. Additionally, other phenol derived additives were also surveyed. While 2-nitrophenol and 2,4,6-tri-*tert*-butylphenol rendered product **12a** in good yields but low enantioselectivity (entries 9 and 10); thiophenol led to a drop either in the yield of the reaction or in the enantiomeric excess (entry 11).

Table 2.10. Evaluation of different protic additives.[51]



Entry[a]	Additive	Time (h)	Yield (%)[b]	e.e. (%)[c]	pK_a
1	**Phenol**	**16**	**86**	**84**	**10.0**
2	cyclohexanol	72	95	30	17.0
3	EtOH	96	69	12	15.5
4	4-methoxyphenol	18	80	76	10.2
5	2-aminophenol	22	n.d.	80	9.97
6	4-bromophenol	7	73	74	9.37
7	1-naphthol	22	79	72	9.34
8	(*R*)-BINOL	23	82	70	8.28
9	2-nitrophenol	23	79	36	7.37
10	2,4,6-$^tBu_3C_6H_2OH$	96	80	24	--
11	thiophenol	48	37	44	6.62

[a]Reactions were carried out at 0.06 mmol scale of **5a**, using 10 mol% of catalyst and 50 mol% of additive in 0.8 mL of solvent at r.t. [b]Yields refer to isolated pure product **12a**. [c]Calculated by HPLC on chiral stationary phase.

Subsequently, the influence of the amount of protic additive in the process was evaluated. With this objective, we carried out the model reaction under the previously optimized experimental conditions but with different amounts of phenol. As it can be inferred from Table 2.12 when reaction was carried out in the presence of 20 mol% of phenol, a slight decrease in yield and e.e. was observed, an effect which was more pronounced when 10 mol% of phenol was used (entries 2 and 3). On the other hand, increasing the ammount of phenol to one equivalent led to similar results that achieved for model reaction in terms of yield, although enantioselectivity was negatively affected (entry 4).

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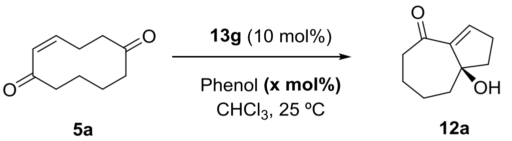
[51] Indicated pK_a values are measured in H_2O: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

Table 2.11. Evaluation of amount of additive.

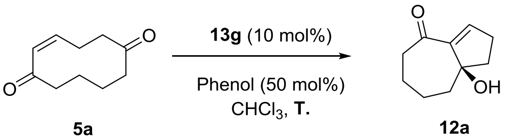


Entry[a]	Phenol (x mol%)	Time (h)	Yield (%)[b]	e.e. (%)[c]
1	**50**	**18**	**86**	**84**
2	10	18	80	78
3	20	18	82	80
4	100	18	86	82

[a]Reactions were carried out at 0.06 mmol scale of **5a**, using 10 mol% of catalyst in 0.8 mL of solvent at r.t. [b]Yields refer to isolated pure product **12a**. [c]Calculated by HPLC on chiral stationary phase.

The effect of temperature was also evaluated (Table 2.12), observing a slight decrease in enantiomeric excess when reaction was carried out at higher temperatures (entry 2). Additionally, lowering temperature from 25 °C to 0 °C (entry 3) implied slightly longer reaction times with no improvement in the outcome of the reaction regarding either the isolated yield or the enantiomeric excess.

Table 2.12. Evaluation of temperature.

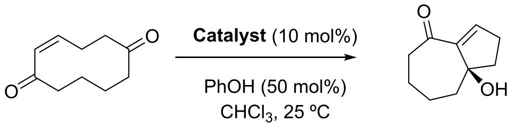


Entry[a]	T. (°C)	Time (h)	Yield (%)[b]	e.e. (%)[c]
1	**25**	**18**	**86**	**84**
2	40	15	80	78
3	0	22	81	84

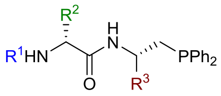
[a]Reactions were carried out at 0.06 mmol scale of **5a**, using 10 mol% of catalyst, 50 mol% of phenol in 0.8 mL of solvent. [b]Yields refer to isolated pure product **12a**. [c]Calculated by HPLC on chiral stationary phase.

Finally, we carried out a fine-tuning of the structure of the catalyst by evaluating the effect of modifying its chiral scaffold at three different positions: (a) the protecting group attached to the nitrogen atom; (b) the alkyl group of aminoacid substructure and (c) the alkyl group in the aminophosphine scaffold (Table 2.13). This systematic evaluation led us to conclude that modifying the carbamate moiety linked to the nitrogen atom from *N*-Boc to a bulkier 9-fluorenylmethyl carbamate (entry 2) did not imply an improvement in the enantioselectivity of the reaction albeit it produced a slight decrease in the yield. Alternativelly, substitution with a sulfonamide group (entry 3) that would lead to a more acidic NH group, did not result in any improvement either.

Table 2.13. Study of the catalyst structure.



5a **12a**



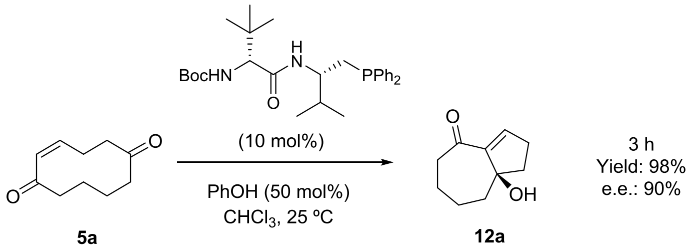
13g (R^1=Boc, R^2=Bn, R^3=^{i}Pr) **13m** (R^1=Boc, R^2=Bn, R^3=^{t}Bu)
13j (R^1=Fmoc, R^2=Bn, R^3=^{i}Pr) **13n** (R^1=Boc, R^2=Bn, R^3=Ph)
13k (R^1=Ts, R^2=Bn, R^3=^{i}Pr) **13o** (R^1=Boc, R^2=^{i}Pr, R^3=^{i}Pr)
13l (R^1=Boc, R^2=Bn, R^3=^{s}Bu) **13p** (R^1=Boc, R^2=^{t}Bu, R^3=^{i}Pr)

Entry[a]	Catalyst	Time	Yield (%)	e.e. (%)
1	**13g**	16 h	86	84
2	**13j**	16 h	77	72
3	**13k**	16 h	89	76
4	**13l**	16 h	80	84
5	**13m**	16 h	87	82
6	**13n**	16 h	99	80
7	**13o**	16 h	83	86
8	**13p**	**3 h**	**98**	**90**
9[d]	**13p**	6 h	85	90

[a]Reactions were carried out at 0.06 mmol scale of **5a**, using 10 mol% of catalyst, 50 mol% of phenol in 0.8 mL of solvent at r.t.. [b]Yields refer to isolated pure product **12a**. [c]Calculated by HPLC on chiral stationary phase. [d]Reaction was performed with 5 mol% of catalyst.

Next the effect of modifying the nature of the alkyl group present in the aminophosphine substructure was studied (Table 2.13). In this sense, no significant influence in the outcome of the reaction was observed when *iso*-propyl group was substituted by *sec*-butyl or *tert*-butyl groups (entries 4 and 5). While a slight decrease in enantioselectivity was determined for catalyst **13n** (entry 6), which contains a phenyl substituent in β position to the phosphine. On the contrary, a significant improvement was achieved when some structural modifications were applied in the alkyl substituent at the aminoacid moiety. Catalyst **13o**, in which benzyl group was substituted by an *iso*-propyl group led to a slight improvement in the enantioselectivity of the process affording product **12a** in 86% e.e. Moreover, the introduction of a bulkier *tert*-butyl group at that position (catalyst **13p** entry 8), improved the enantiocontrol of the reaction up to an excellent 90% e.e. In addition, catalyst **13p** was found to be significantly more active, allowing full consumption of the starting material in three hours compared to overall 16 hours required for other catalysts previously tested. As consequence, catalyst **13p** was selected as the most efficient catalyst for the studied enantioselective transannular reaction. Performing the reaction with lower catalyst loading (Table 2.13 entry 9) led to longer reaction times, as well as, to a slight decrease in the isolated yield.

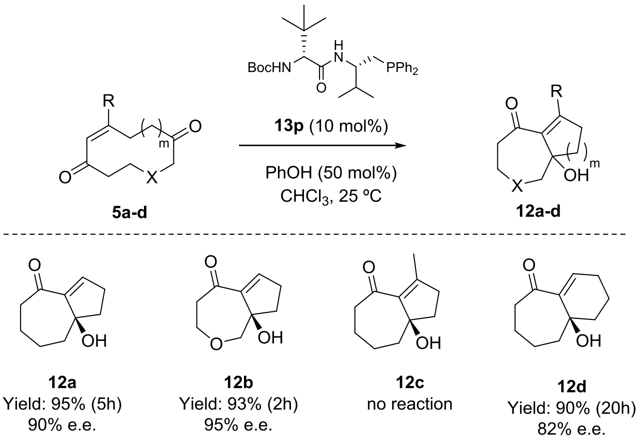
Finally, and prior to start the study of the scope of the reaction, the performance of catalyst **13p** was re-evaluated under different experimental conditions. In this context, this catalyst was tested in solvents of different nature, as well as, in the presence of other protic additives previously surveyed and under different temperatures. However no improvement in the outcome of the reaction was achieved. In this way, and despite all these final experiments, the use of 10 mol% of catalyst **13p** and 50 mol% of phenol at room temperature in chloroform remained as the best conditions, allowing the isolation of adduct **12a** in 98% yield and 90% e.e. after 3 hours (Scheme 2.29).



Scheme 2.29. Optimized conditions for enantioselective transannular MBH reaction.

3.4. Scope of the reaction

Once the optimal experimental conditions for this reaction were found, we proceeded to study its applicability towards the synthesis of a variety of bicyclic structures. First of all, a series of substrates leading to a bicyclo[5.3.0]decane scaffold (m=1, adducts **12a-c**) and bicyclo[5.4.0]undecane (m=2 adduct **12d**) were subjected to the optimized conditions (Scheme 2.30). Bicyclic adduct **12b** was obtained in excellent yield and enantioselectivity, as analogous adduct **12a**. On the other hand, product **12d** was isolated in excellent 90% yield after 20 hours, although it was required to modify reaction conditions (CCl_4 as solvent at 0 °C) in order to achieve good enantiocontrol. In the case of β,β-disubstituted substrate **5c**, no reaction was observed after prolonged reaction times, presumably due to the increased steric hindrance for this substrate.



Scheme 2.30. Synthesis of biciclo[5.3.0]decane and biciclo[5.4.0]undecane scaffolds.[52]

The developed methodology also worked efficiently for the construction of bicyclo[6.3.0]undecane system (m=1, adduct **12e**) (Scheme 2.31). In this way, when substrate **5e** was subjected to optimized conditions adduct **12e** could be isolated in 73% yield showing moderate enantioselectivity. However, analogous substrate **5f** (m=2) failed to undergo the desired transannular process that would lead to the formation of adduct **12f**, which could be

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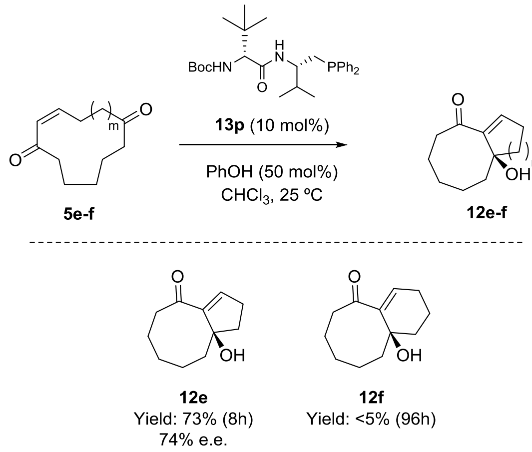
[52] Reactions were carried out at 0.2 mmol scale of substrate, using 10 mol% of catalyst, 50 mol% of phenol in 2.0 mL of solvent until consumption of starting material was observed (TLC analysis). Yields refer to isolated pure products **12** and e.e. was calculated by HPLC on chiral stationary phase.

attributed to a larger distance between the reactive points in the less energetic conformation of the cyclic substrate. For this substrate, isomerization to the *E* alkene was observed when exposed to catalyst **13p** at high temperature for several days,[53] allowing the isolation of the corresponding (*E*) keto-enone **5f** by flash column chromatography. Further exposition of pure (*E*) diastereomer of **5f** to reaction conditions did not led to the formation of desired MBH product.



Scheme 2.31. Scope of the reaction.[54]

On the other hand, when substrate **5g** that would eventually lead to the formation of bicyclo[4.3.0]nonane adduct, was subjected to the optimized experimental conditions, the formation of the desired product was not observed. Instead, product **12g** was isolated in 73% yield after 28 hours (Scheme 2.32).[55] The formation of this product can be explained by an elimination process taking place over the MBH adduct, followed by subsequent rearrangement of the double bonds. On the contrary, this reaction worked for the efficient construction of bycliclo[4.4.0]decane scaffold rendering the corresponding adduct **12h** in 72% yield and excellent 92% e.e. after 5 hours.

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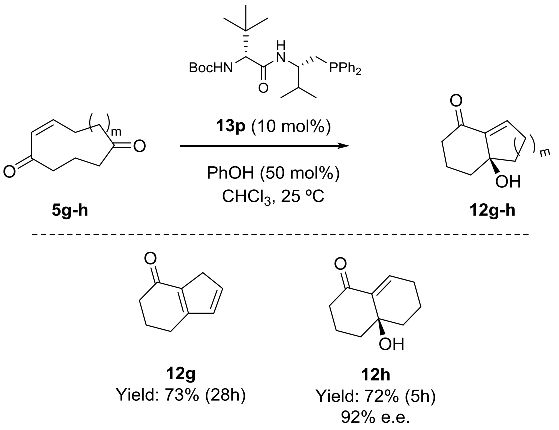
[53] The NMR spectra of the *Z* carbocycle **5f** (m=2) can be found in the experimental section as well as the corresponding to *E* isomer **5f'**. ^{1}H-NMR coupling constants for alkene signals are consistent with the expected values for *Z* ($J_{H\text{-}H}$ ~ 12 Hz) and *E* ($J_{H\text{-}H}$ ~ 16 Hz) configurations.

[54] Reactions were carried out at 0.2 mmol scale of substrate, using 10 mol% of catalyst, 50 mol% of phenol in 2.0 mL of solvent until consumption of starting material was observed (TLC analysis). Yields refer to isolated pure products **12** and e.e. was calculated by HPLC on chiral stationary phase.

[55] Spectral information matched reported data for this compound: Paquette, L. A.; Racherla, U. S. *J. Org. Chem.* **1987**, *52*, 3250.



Scheme 2.32. Scope of the reaction.[56]

This method also presented some limitations regarding the size of the fused cycle in the final adduct. When substrate **5i** was tested, it showed a particular behavior compared to the previously tested carbocycles. Instead of bicyclo[5.2.0]nonane **12i**, compound **12i'** was obtained in 86% yield and 87% e.e. after 96h (Scheme 2.33). The formation of this compound can be explained by assuming that after the conjugate addition of the phosphine catalyst, the initial enolate intermediate suffers an isomerization to enolate *intermediate II*. The transannular process is favored for this intermediate compared to the initial one, due to the high strain associated to the formation of a four membered ring.[57] Once the transannular C-C bond formation takes place, a proton transfer followed by an elimination step, allows catalyst turnover.

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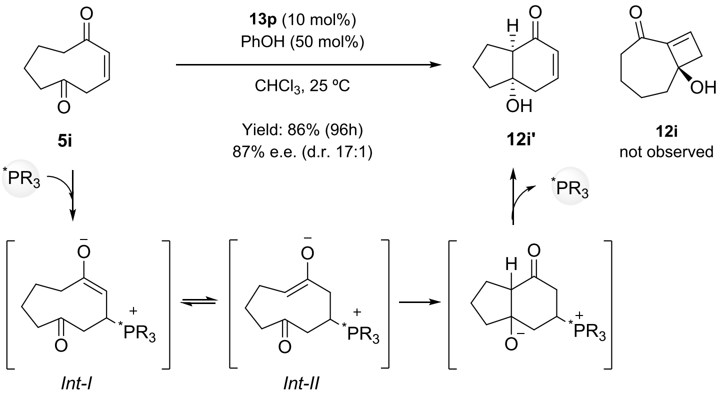
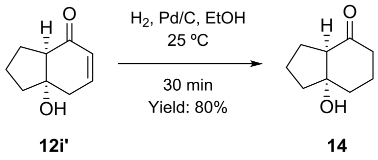
[56] Reactions were carried out at 0.2 mmol scale of substrate, using 10 mol% of catalyst, 50 mol% of phenol in 2.0 mL of solvent until consumption of starting material was observed (TLC analysis). Yields refer to isolated pure products **12** and e.e. was calculated by HPLC on chiral stationary phase.

[57] For more information regarding strain in small, medium and large size cycles see Chapter 1.



Scheme 2.33. Proposed mechanistic pathway for adduct **12i’** formation.

The relative configuration of this product was assigned after catalytic hydrogenation of the product **12i’** under standard conditions (Scheme 2.34), which afforded adduct **14** in 80% yield, being the spectral data coincident with the information previously reported by List.[58] Absolute configuration was, as well, tentatively assigned by comparison of the measured optical rotation values, $[\alpha]_D^{20}$:-24.0 (c=1.0, CH_2Cl_2, e.e.: 87%), with those reported by the same authors for the opposite enantiomer $[\alpha]_D^{20}$:+41.9 (c=1.0, CH_2Cl_2, e.e.: 94%).



Scheme 2.34. Hydrogenation of adduct **12i’**.

Next, we moved to test different substrates which contained a fused aromatic system conjugated with the α,β-unsaturated ketone. For instance, when substrate **11a** was exposed to optimized reaction conditions, adduct **15a** was isolated in 82% yield (Scheme 2.35). However, the enantioselectivity observed was significantly lower than that obtained for analogous susbtrate **5h**, which does not present the conjugated aromatic ring.

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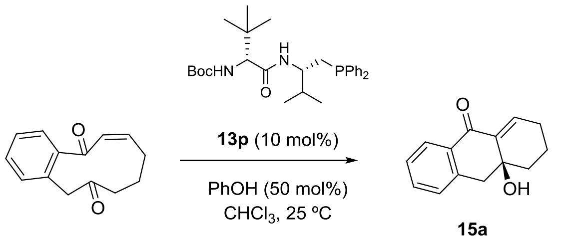
[58] Chandler, C. L.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6737.

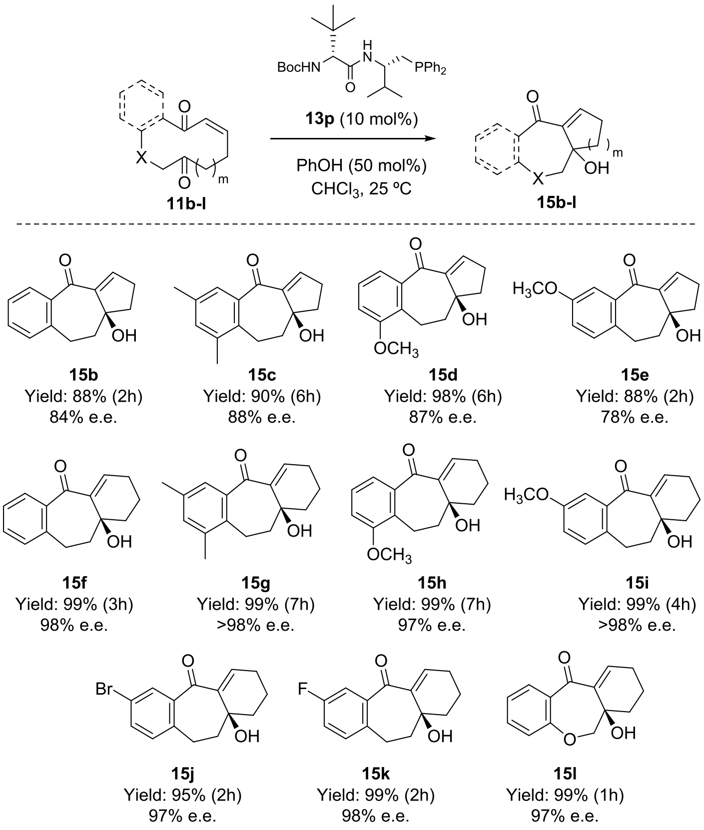


11a

15a
Yield: 82% (10h)
70% e.e.

Scheme 2.35. Synthesis of adduct **15a**.

Regarding the construction of bicyclo[5.3.0]decane core (adducts **15b-l**), the reaction was successfully applied for a variety of substrates (Scheme 2.36). In this way, unsubstituted adduct **15b** was obtained in excellent yield and enantiomeric excess, as well as, the 6,8-dimethyl-substituted analogue **15c**. On the other hand, while incorporating a methoxy group at C-8 did not affect the performance of the reaction (adduct **15d**), a slight decrease in yield and enantioselectivity was observed for 6-methoxy derived adduct (**15e**). The formation of related biciclo[5.4.0]undecane structural core was also efficiently accomplished by the developed methodology. In this way, excellent results were obtained either for unsubstituted substrate **11f** or for 7,9-dimethyl substituted substrate **11g**. The presence of a methoxy group was well tolerated both at position 9 (substrate **11h**) and 7 (substrate **11i**), rendering the corresponding adducts in almost quantitative yield and excellent enantioselectivity. Furthermore, excellent results were also obtained for substrates containing halogens as electronwithdrawing groups at C-7 (**11j-k**) although a slight decrease in yield was observed for C-7 bromo substituted substrate **11j**. Finally, substrate **11l**, which contains a heteroatom in its structure was also tested, affording adduct **15l** in excellent yield and e.e., in analogous way to related substrate **5b**.



Scheme 2.36. Scope of the reaction for substrates **11b-l**.[59]

At this point, the absolute configuration of the product **15i** was determined by X-ray diffraction on a monocrystalline sample. The absolute configuration of adducts **12a-h** and **15a-l** was tentatively assigned by analogy, assuming an identical mechanistic pathway for all the reactions.

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[59] Reactions were carried out at 0.2 mmol scale of substrate, using 10 mol% of catalyst, 50 mol% of phenol in 2.0 mL of solvent until consumption of starting material was observed (TLC analysis). Yields refer to isolated pure products **15b-l** and e.e. was calculated by HPLC on chiral stationary phase.

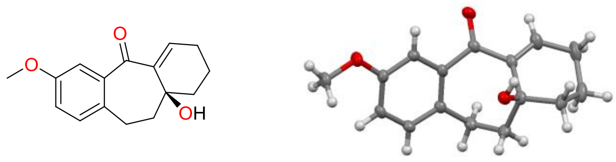
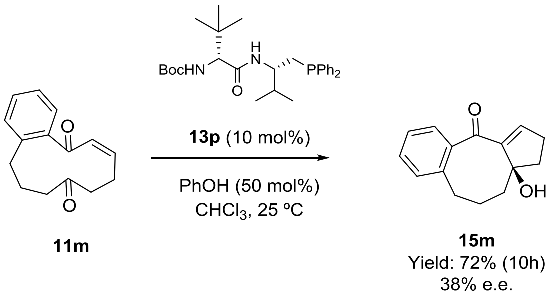


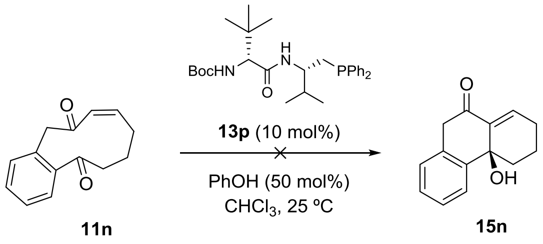
Figure 2.3. X ray structure for adduct **15i**.

On the other hand, in the case of substrate **11m**, the formation of a larger ring structure at the cycloalkanone moiety of the final adduct was accomplished, affording adduct **15m** in an acceptable 72% yield albeit with a significant decrease of the enantiocontrol (Scheme 2.37). Although different experimental conditions were tested for this substrate, results remained unsatisfactory in terms of enantioselectivity in all the cases.



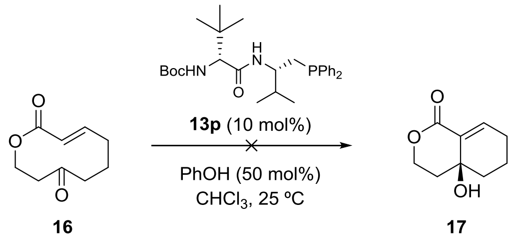
Scheme 2.37. Enantioselective MBH reaction over substrate **11m**.

Finally, a substrate containing an aromatic ring conjugated with the ketone instead of the enone was tested (substrate **11n**). Unfortunately, this substrate remained unreactive even after being exposed to catalyst **13p** at high temperatures for long reaction times (Scheme 2.38).



Scheme 2.38. Transannular Morita-Baylis-Hillman reaction for substrate **11n**.

In addition to the abovementioned substrates, an analogous 10 membered cyclic ester **16** was also prepared. This substrate, which was synthesized by an alternative methodology,[60] contained an α,β-unsaturated ester as activated alkene and a ketone as electrophile. Unfortunately, substrate **16** remained unreactive when subjected to previously optimized reaction conditions (Scheme 2.39). This fact was attributed to the lower reactivity of the α,β-unsaturated ester towards the conjugate addition of the phosphine catalyst compared to analogous α,β-unsaturated ketone.



Scheme 2.39. Enantioselective MBH reaction over substrate **16**.

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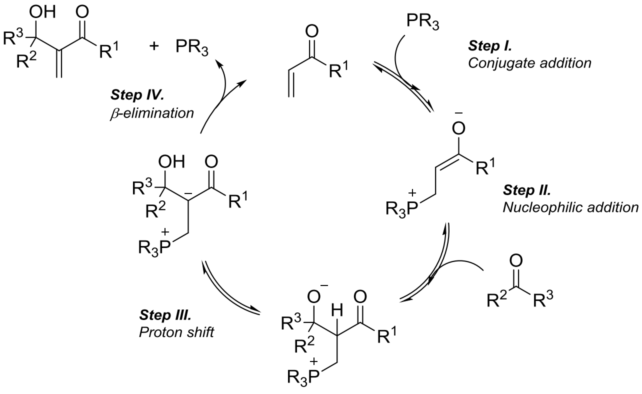
[60] For more information regarding the synthesis of substrate **16** see experimental section.

3.5. Mechanistic insights

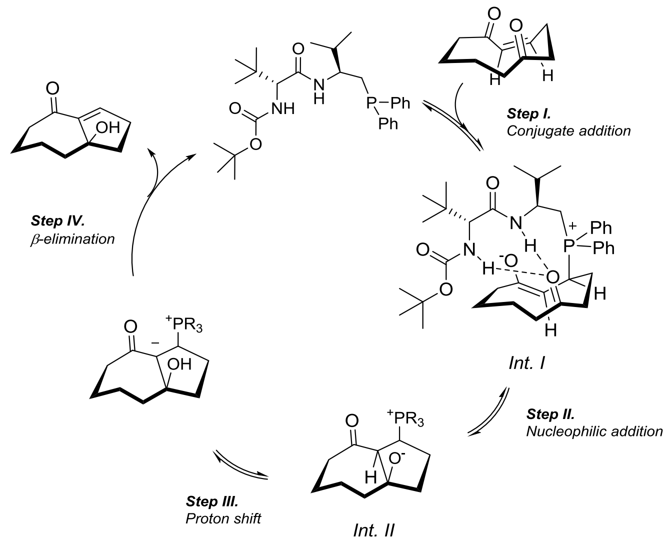
As it has been outlined in the introduction of this Chapter the generally accepted mechanism for the MBH reaction involves an initial conjugate addition of the nucleophilic phosphine to the alkene, followed by a subsequent addition of the generated enolate to the electrophilic ketone. The zwitterionic intermediate generated as consequence of this process, takes part in a proton transfer step and after a β-elimination affords the α-functionalized product and allows the catalyst turnover.



Scheme 2.40. General mechanism for phosphine catalyzed MBH reaction.

In line with the previously mentioned experimental and computational work developed by Singleton,[19] we consider an scenario in which two competitive rate-determining steps are contemplated, the aldol reaction on the one hand and the proton transfer on the other. However, there are some relevant differences between the transannular MBH reaction and the catalytic system studied by Singleton that should be considered. In this sense, Singleton studied the DABCO-catalyzed reaction between methyl acrylate and *p*-nitrobenzaldehyde employing methanol as solvent, concluding that energy barriers for the aldol reaction and the proton transfer step are comparable, being this last one main rate-determining step under standard reaction conditions. However, it should be considered that for the transannular MBH reaction the electrophilic carbonyl group is a ketone instead of an aldehyde as in the system studied by Singleton. In this sense, we propose that the lower reactivity of the ketone moiety will presumably imply a higher energy barrier for the corresponding aldol step. Additionally, the performance of the reaction in the presence of a protic solvent or additive such as phenol, favors the proton transfer step, an effect that has been commonly attributed to a decrease in the energy barrier for this step.[18] These considerations prompted us to propose the aldol reaction as the main rate-determining step of the process for the studied transannular MBH reaction.

Regarding the enantioselectivity of the process, we propose that the estereocenter formed as consequence of the initial conjugate addition would be efficiently controlled by the catalyst, rendering an enolate, which undergoes transannular aldol reaction. In this way, after the conjugate addition of the phosphine, subsequent formation of additional stereocenters will be efficiently controlled by the first stereocenter formed and conditioned by the conformation of the substrate (Scheme 2.41). The presence of hydrogen bond donor motifs in the structure of the catalyst would allow further interactions between the catalyst and the substrate, rendering less flexible transition states, a fact that would favored the stereocontrol of the process.



Scheme 2.41. Proposed catalytic cycle.

As represented in previous scheme, the addition of the enolate intermediate generated after the conjugate addition of the phosphine catalyst, takes place through the *Si* face of the ketone. This relative orientation is attributed to the formation of hydrogen bond interactions between the ketone moiety and the NH groups present either in the aminophosphine and in the aminoacid-subunit of the catalyst. These additional hydrogen bond interactions between the ketone and the NH groups has been previously suggested for related dipeptide-derived phosphine catalysts.[61] However, the comparable enantioselectivities observed for the transannular MBH reaction when different protecting groups, that would lead to more acidic NH bond, were surveyed in the aminoacid-subunit, led us to consider that the hydrogen bond interaction between the ketone and the NH group in the aminophosphine subunit is the main responsible of the high enantioselectivity observed.

Finally, experimental reactions carried out for the study of transannular MBH reaction allowed us to observe a significant drop in enantioselectivity when the reaction was performed in absence of phenol as protic additive.[62] This effect could be attributed to a shift in the rate-determining step from aldol reaction to the proton transfer due to the abovementioned similarities in energy barriers.

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[61] For a related catalyst employed in an enantioselective [3+2] annulation of allenes, see: Han, X.; Wang, Y.; Zhong, F.; Lu, Y. *J. Am. Chem. Soc.* **2011**, *133*, 1726.

[62] It has been experimentally observed a significant drop in enantioselectivity for catalyst **13g** in absence of phenol (Yield: 97%, e.e.4%) compared to analogous reaction in presence of 50 mol% of phenol (Yield: 97% e.e.78%).

4. CONCLUSIONS

Given the results presented in this chapter, the following conclusions can be outlined:

- We have been able to design a suitable methodology to synthesize medium sized cyclic keto-enones (from 9 to 12 carbon atoms), providing a novel access to these structures. The developed synthetic strategy allows to modulate the structure of the carbocycles by modifying the distance between the ketone moieties, as well as, allowing the synthesis of substrates containing either heteroatoms or aromatic rings.

- Nucelophilic phosphines have been demonstrated to be efficient catalysts for the transannular Morita-Baylis-Hillman reaction on medium sized keto-enones; in addition, the use of phenol as additive has been found to be crucial for the enhancement of the reaction rate.

- Aminoacid-derived bifunctional chiral phosphines have been employed as catalysts for the enantioselective transannular MBH reaction. The nature of the substituents in both of the stereogenic centers present in the structure of the catalyst has been found to affect the outcome of the reaction, with catalyst **13p** providing the best results in terms of yield and enantiomeric excess.

- The developed method is wide in scope for the formation of bicyclic structures of variable size at both fused rings. Moreover, substrates containing a benzo-fused system conjugated with the Michael acceptor have been successfully employed as substrates for this reaction, rendering the polycyclic MBH adducts in excellent yields and enantiomeric excess.

3

3

Catalytic enantioselective transannular Morita-Baylis-Hillman reaction in the total synthesis of sesquiterpenoid natural products

1. INTRODUCTION

As it has been clearly illustrated in previous sections, polycyclic structures are common motifs present in the structural core of many natural products.[1] The biological activity exhibited by some of these compounds, has inspired the development of many pharmaceutical drugs and therefore it has attracted the attention of the scientific community.[2] Although for decades efforts have been focused on the isolation and characterization of these polycyclic compounds from natural sources, related drawbacks such as lack of supply or isolation difficulties, have brought to light the need of new strategies for the stereocontrolled construction of polycyclic scaffolds.[3] In this sense, synthetic chemists have contributed to this field not only by the development of synthetic routes to access biologically active compounds, but also by providing critical information regarding structure-activity relationship.[4]

In the field of natural products, the hydroazulene bicyclic system is a substructure commonly present as part of the structural core of different families of sesquiterpenoids, such as aromadendrane or guaiane family, characterized by the presence of a cyclopropane unit or a lateral three carbon atom chain attached to the seven membered ring respectively (Figure 3.1).[5]

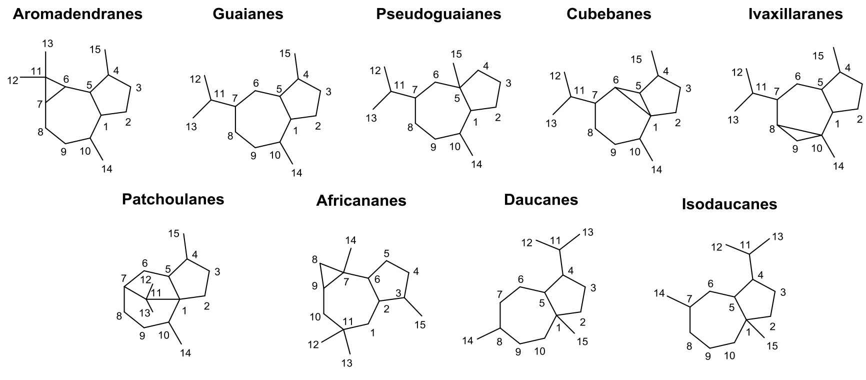

Figure 3.1. Sesquiterpenoid families containing hydroazulene core.

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[1] Singh, G. *Chemistry of terpenoids and carotenoids*; Discovery Publishing Home: New Dehli, 2007.

[2] Zhang, L.; Demain, A. L. *Natural Products: Drug discovery and therapeutic medicine*; Human Press: Totowa, 2005.

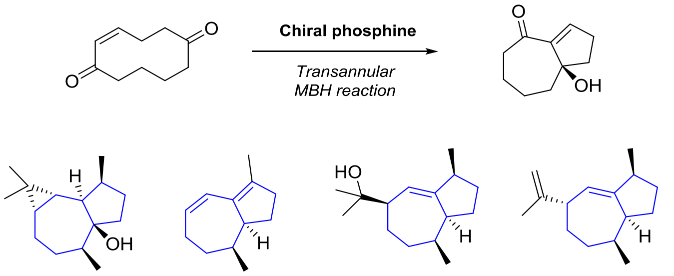
[3] Thomson, R. H. *The chemistry of natural products*; Blackie Academic & Professional: Glasgow, 1993.

[4] Pirrung, M. C.; Morehead, A. T.; Young, B. G. *The total synthesis of natural products: Bicyclic and tricyclic sesquiterpenes*; John Wiley & Sons: Atlanta, 2009.

[5] Overton, K.H. *Terpenoids and Steroids*; RSC Publishing: 1975.

Although, they have been commonly isolated from essential oils extracted from different plants and trees, in the last years marine organisms have arisen as a surprisingly prolific source of these biologically active sesquiterpenoids.[6,7] Despite this natural availability, some sesquiterpenoids still remain relatively inaccessible, being necessary the development of efficient synthetic routes.

In this sense, the enantioselective transannular Morita-Baylis-Hillman reaction presented in Chapter 2, has demonstrated to be a suitable strategy to access biciclo[5.3.0]decane scaffold, structural core found in different sesquiterpenoids such as palustrol, clavukerin A, γ-gurjunene or guaia-5(6)en-11-ol (Figure 3.2). For this reason, it has been considered that the developed enantioselective MBH reaction could be employed as key step in the total synthesis of these sesquiterpenoids.



(+)-Palustrol ***Clavukerin A*** ***Guaia-5(6)-en-11-ol*** ***(-)-γ-Gurjunene***

Figure 3.2. Representative examples of sesquiterpenoids containing biciclo[5.3.0]decane scaffold accessible by organocatalytic enantioselective MBH reaction.

In the following section, and due to its close relation to the work described in this manuscript, the reported literature examples for the synthesis of the abovementioned sesquiterpenoids will be presented in detail.

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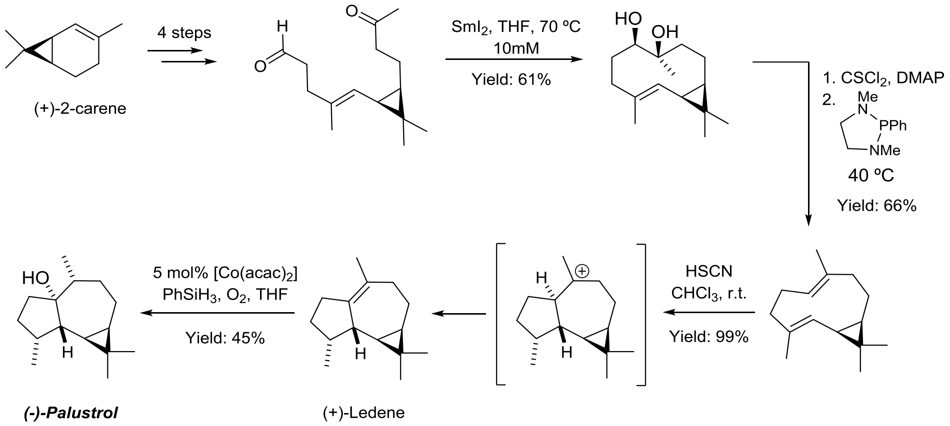
[6] Kornprobst, J.-M. *Encyclopedia of Marine Natural Products*; Wiley-Blackwell: Oxford, 2010.

[7] (a) Bideau, F. L.; Kousara, M.; Chen, L.; Wei, L.; Dumas, F. *Chem. Rev.* **2017**, *117*, 6110. (b) Mayer, A. M. S.; Rodríguez, A. D.; Taglialatela-Scafati, O.; Fusetani, N. *Mar. Drugs*, **2013**, *11*, 2510. (c) Wright, A. D.; König, G. M. *J. Nat. Prod.* **1996**, *59*, 710. (d) Fraga, B. M. *Nat. Prod. Rep.* **1998**, 15, 73.

1.1. Synthesis of palustrol

(+)-Palustrol, originally isolated by Sorm from Brasilian plant *Baccharis genistelloides*, is a representative example of aromadendrane family structurally characterized by a dimethyl cyclopropane unit fused to the hydroazulene core.[8] Although there is not any synthesis of (+)-palustrol reported up to date, a synthetic route for its also natural, but significantly less abundant enantiomer (-)-palustrol can be found in the literature. The proposed synthetic strategy, developed by Cramer in 2014, employed enantiopure (+)-2-carene as starting material (Scheme 3.1).[9] In this way, (+)-2-carene was transformed by a 4 step reaction sequence into a keto-aldehyde intermediate. Then, a SmI_2-mediated pinacol coupling afforded the ten membered cyclic diol, which was converted into the corresponding thiocarbonate that underwent cleavage when exposed to modified Corey-Winter protocol.[10] Further exposure of the so formed 10-membered cyclic intermediate to acidic conditions rendered (+)-ledene, *via* cationic cyclization. Finally, a bis(acetylacetonate)cobalt(II) catalyzed hydration in the presence of phenyl silane and molecular oxygen, also known as Mukaiyama hydration conditions,[11] afforded (-)-palustrol in 45% yield.



Scheme 3.1. Biomimetic synthesis of (-)-palustrol developed by Cramer.

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[8] Dolejs, L.; Herout, V.; Sorm, F. *Collect. Czech. Chem. Commun.* **1961**, *26*, 811.

[9] Tran, D. N.; Cramer, N. *Chem. Eur. J.* **2014**, *20*, 10654.

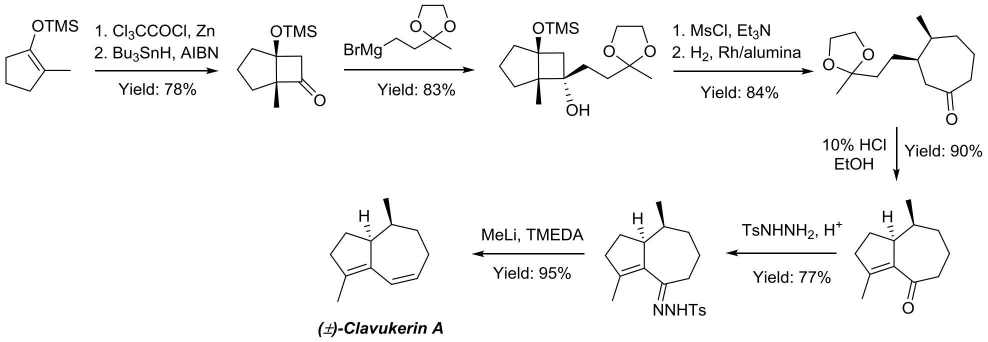
[10] Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677.

[11] S. Isayama; T. Mukaiyama. *Chem. Lett.* **1989**, *18*, 1071.

1.2. Synthesis of clavukerin A and isoclavukerin A

Clavukerin A, and its related diastereomer isoclavukerin A, are a specific type of terpenoids classified as part of norguaiane family, where *nor* prefix indicates the loss of carbon atoms compared to the general skeleton of guaiane family (Figure 3.1). This biologically active natural product, originally isolated by Kitagawa from the soft coral *Clavularia Koellikeri*,[12] has been the subject of deep study for years, which has led to the development of multiple synthetic strategies.

The first total synthesis of (±)-clavukerin A, developed by Pak and coworkers, dates back to 1991 and made use of the silyl enol ether of 2-methylcyclopentanone as starting material (Scheme 3.2).[13] Authors proposed a synthetic route which started with an initial [2+2] cycloaddition of an *in situ* generated dichloroketene followed by a dechlorination step promoted by tributyltin in the presence of 2,2-azobisisobutyronitrile (AIBN).[14] The cycloheptane core was formed by Grignard addition, followed by mesylation and Grob fragmentation. Hydrogenation of the alkene moiety led to a seven membered cyclic ketone with conveniently functionalized side chains which could be transformed into the fused cyclopentane moiety. Indeed, an acid catalyzed intramolecular aldol condensation followed by Shapiro reaction converted this keto intermediate into (±)-clavukerin A.



Scheme 3.2. Total synthesis of (±)-clavukerin A developed by Pak.

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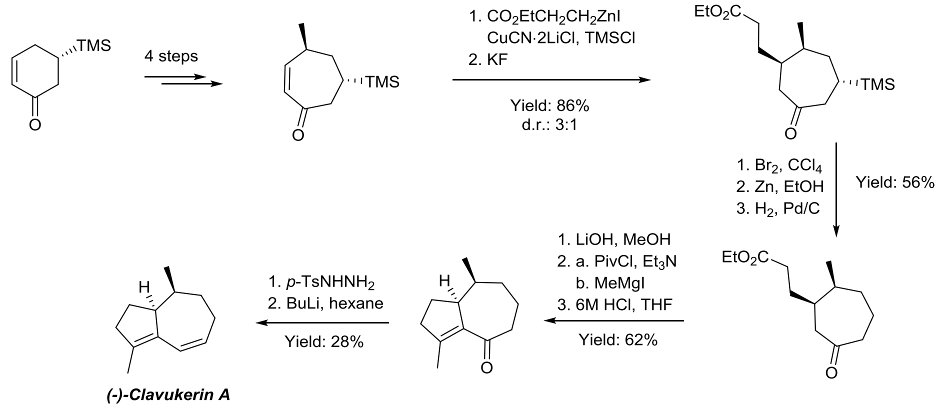
[12] Kobayashi, M.; Son, B. W.; Kido, M.; Kyogoku, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1983**, *31*, 2160.

[13] Kim, S. K.; Pak, C. S. *J. Org. Chem.* **1991**, *56*, 6829. For other racemic synthesis of Clavukerin A not described in this section, see: (a) Shimizu, I.; Ishikawa, T. *Tetrahedron Lett.* **1994**, *35*, 1905. (b) Friese, J. C.; Krause, S.; Schäfer, H. J. *Tetrahedron Lett.* **2002**, *43*, 2683.

[14] For more information about this [2+2] cycloaddition, see: Pak, C. S.; Kim, S. K. *J. Org. Chem.* **1990**, *55*, 1954.

Almost at the same time, Asaoka and coworkers reported the first asymmetric total synthesis of (-)-clavukerin A in a 14 step sequence starting from commercially available reagents.[15] The enantiopure cyclohexenone trimethylsilyl derivative was transformed into the analogous 7-membered cyclic α,β-unsaturated ketone, which after copper-catalyzed conjugate addition of the conveniently functionalized organozinc reagent rendered the corresponding cycloheptanone as 3:1 mixture of separable diasteromers. Removal of trimethylsilyl group was accomplished by its transformation into the bromo derivative followed by reduction with zinc in refluxing ethanol and hydrogenation. The ethyl ester moiety was hydrolyzed and further transformed into ketone intermediate, which was employed for the construction of the bicyclo[5.3.0]decane scaffold *via* intramolecular aldol condensation. Finally, exposition to standard Shapiro conditions provided access to (-)-clavukerin A in 28% yield.



Scheme 3.3. First asymmetric total synthesis of (-)-clavukerin A.

Later on, two independent examples were developed by Honda[16] and Srikrishna,[17] involving alternative strategies to access the bicyclic α,β-unsaturated cycloheptenone precursor previously employed by Asaoka (Scheme 3.4). While the proposal reported by Honda took advantage of a ring-expansion reaction for the construction of the cycloheptanone intermediate, which after mesylation and base-promoted elimination suffered an alkene isomerization to

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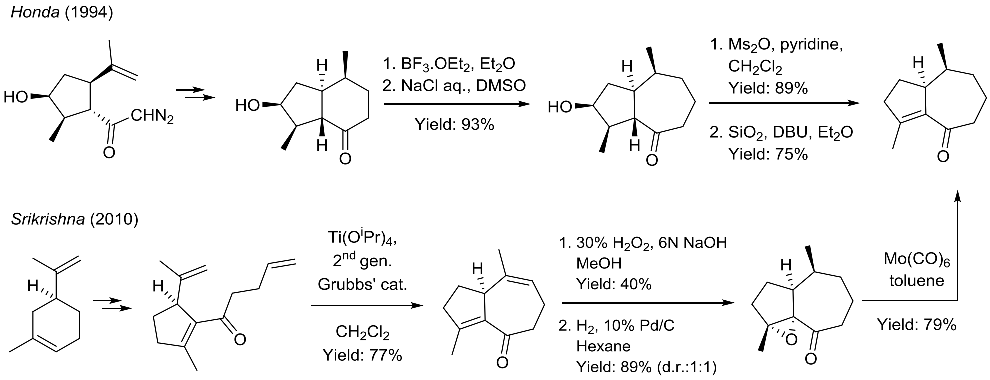
[15] Asaoka, M.; Kosaka, T.; Itahana, H.; Takei, H. *Chem. Lett.* **1991**, 1295.

[16] Honda, T.; Ishige, H.; Nagase, H. *J. Chem. Soc. Perkin Trans*, **1994**, 3305.

[17] Srikrishna, A.; Pardehi, V. H.; Satyanarayana, G. *Tetrahedron: Asymmetry*, **2010**, *21*, 746.

generate the α,β-unsaturated system; the procedure reported by Srikrishna involved a ring-closing metathesis step to access the hydroazulene core. As catalytic hydrogenation with Pd/C rendered mixture of products due to unselective hydrogenation of the trisubstituted alkene in the presence of an additional tetrasubstituted unsaturated system, an alternative approach was followed. In this way, regioselective ring epoxide formation was accomplished, followed by hydrogenation of the remaining alkene moiety. Finally, molybdenum hexacarbonyl promoted deoxygenation step rendered [5.3.0] bicyclic enone in 79% yield.



Scheme 3.4. Alternative strategies proposed by Honda and Srikrishna.

In a closely related example, Lee and coworkers disclosed a synthetic route to access (-)-clavukerin A through a chiral pool-based strategy starting form enantiopure (+)-limonene oxide, which was converted into 5-membered cyclic enal intermediate by a three step synthetic sequence (Scheme 3.5).[18] Further reduction of the aldehyde and esterification rendered bromoacetate precursor, which upon treatment with tributylstannane underwent a radical cyclization that generated the 8-membered lactone. Subsequent reduction with $LiAlH_4$ and Swern oxidation afforded the cyclopentene structure with conveniently functionalized lateral chains. Finally, titanium tetrachloride promoted reductive intramolecular coupling (McMurry type reaction) provided direct access to the target molecule.

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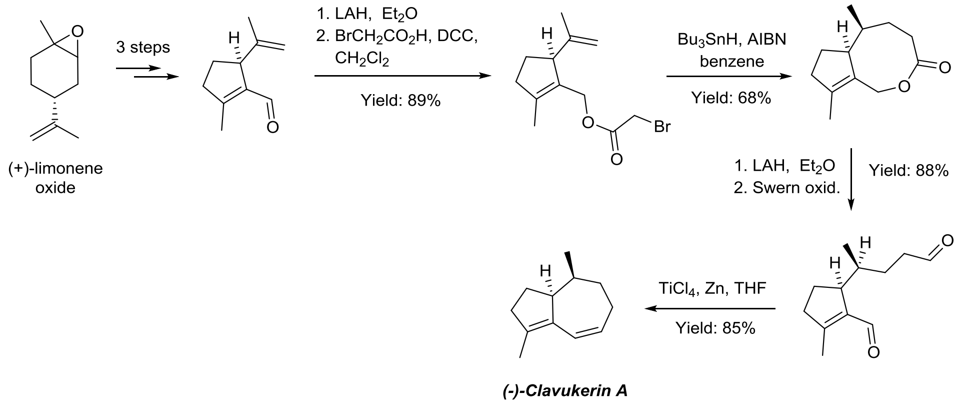
[18] Lee, E.; Yoon, C. H. *Tetrahedron Lett.* **1996**, *37*, 5929.



Scheme 3.5. Synthetic route developed by Lee *et al*.

The same enantiopure precursor was employed some years later by Shamji *et.al.* in an alternative synthesis (Scheme 3.6).[19] In this work, the initial cyclopentenal was reduced with sodium borohydride and converted into the corresponding sulfone. Hydroboration of the terminal alkene, followed by oxidative work-up and Finkelstein-type reaction provided a key intermediate which upon reaction with the sodium salt of methyl malonate allowed the required functionalization of the lateral chain. The so formed intermediate was subjected to intramolecular sulfone/ester cyclization, allowing the construction of the bicyclo[5.3.0]decane scaffold. Reduction with $NaBH_4$ rendered cyclic β-hydroxysulfone that underwent Julia elimination by treatment with sodium amalgam.

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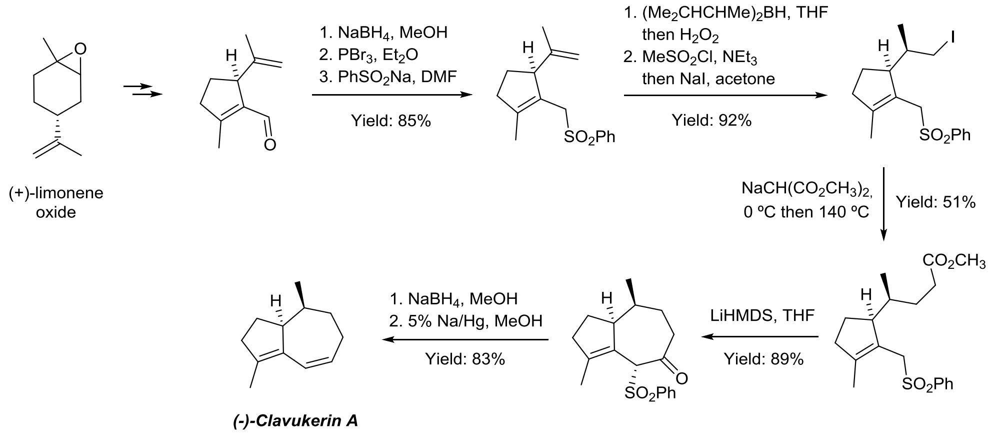
[19] Grimm, E. L.; Methot, J.-L.; Shamji, M. *Pure Appl. Chem.* **2003**, *75*, 231.



Scheme 3.6. Diastereoselective synthesis developed by Shamji *et al.*

More recently Metz and coworkers developed a highly efficient 5-step synthesis of (-)-clavukerin A based on a previously developed domino metathesis reaction starting from commercially available (*S*)-citronellal (Scheme 3.7).[20] In this way, after an initial conjugate addition of the starting material to methyl vinyl ketone under proline catalysis followed by a chemoselective dibromoolefination, the obtained product was subjected to a Wittig reaction with the corresponding ylide and alkyne formation with butyllithium in a one pot procedure. Subsequent exposition to enyne metathesis conditions afforded directly (-)-clavukerin A in 96% yield.

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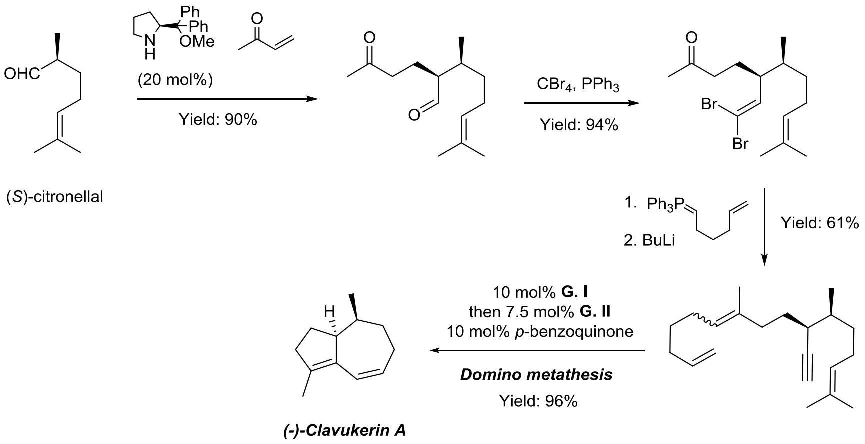
[20] (a) Barthel, A.; Kaden, F.; Jäger, A.; Metz, P. *Org. Lett.* **2016**, *18*, 3298. (b) Knüppel, S.; Rogachev, V. O.; Metz, P. *Eur. J. Org. Chem.* **2010**, 6145.



Scheme 3.7. Synthesis of (-)-clavukerin A via domino metathesis reaction.

With respect to the diastereomeric (-)-isoclavukerin A, there is just one enantioselective procedure reported up to date for the synthesis of this natural product (Scheme 3.8).[21] This synthetic route, developed by Trost and coworkers started with the silylated cyanohydrin of acrolein as acyl anion equivalent, which underwent aldol reaction with trimethylsilyl derivative of ethylacroleine affording an intermediate Michael acceptor. Enantioselective conjugate addition of an enantiopure functionalized organocuprate was followed by acetylation of the secondary alcohol and oxidation with Dess-Martin periodinane. Titanium (IV) chloride promoted Knoevenagel condensation upon the obtained aldehyde afforded appropriately functionalized acyclic intermediate, which was subjected to palladium catalyzed diastereoselective cyclization. This procedure provided access to the *trans*-fused bicyclo containing an exocyclic alkene that isomerized under basic conditions restoring the α,β-unsaturated system. Finally, (-)-isoclavukerin A was obtained after an additional 5-step sequence, including carbonyl reduction by Shapiro type reaction and two successive decarboxylation steps.

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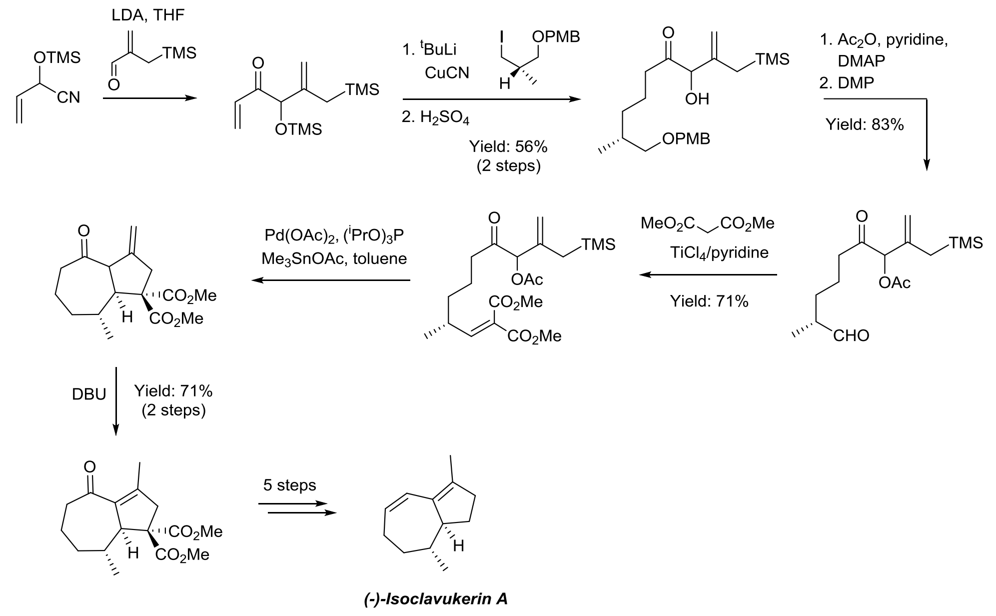
[21] Trost, B. M:; Higuchi, R. I. *J. Am. Chem. Soc.* **1996**, *118*, 10094.



Scheme 3.8. Enantioselective synthesis of (-)-isoclavukerin A reported by Trost.

1.3. Synthesis of guaia-5(6)en-11-ol

Guaia-5(6)en-11-ol is a natural sesquiterpenoid found in the essential oils of trees and shrubs from Pittosporacea family, which has exhibited anti-inflammatory activity.[22] There is no precedent of any enantioselective total synthesis of this natural product, in fact, the only reported strategy developed up to date involve the chemical manipulation of the related sesquiterpenoid guaiol.[23] In this example, guiaol, which already presents the 7,5-fused bicyclic substructure, as well as the required three carbon atom lateral chain, was subjected to initial acetylation followed by diastereoselective epoxidation of the alkene. From the different reagents tested, *m*-chloroperbenzoic acid was selected for the epoxidation reaction, as it provided best results in terms of yield and diastereoselectivity. Subsequent basic hydrolysis of acetate moiety and selective reductive opening of epoxide with $LiAlH_4$ in the presence of $AlCl_3$

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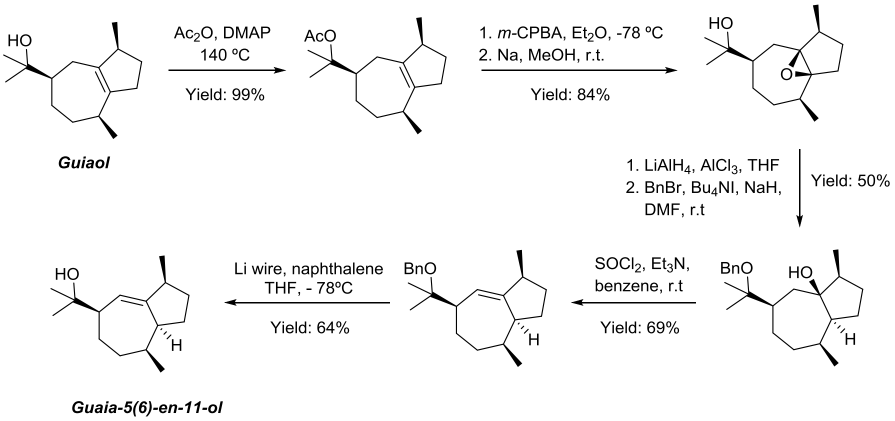
[22] Mendes, S. A. C.; Mansoor, T. A.; Rodrigues, A.; Armas, J. B.; Ferreira, M.-J. U. *Phytochemistry*, **2013**, *95*, 308.

[23] Huang, A.-C.; Sumby, C. J.; Tiekink, E. R. T.; Taylor, D. K. *J. Nat. Prod.* **2014**, *77*, 2522.

rendered diol intermediate as a single diastereomer. After benzylation of the less hindered hydroxyisopropyl group, alkene moiety was introduced by regioselective dehydration with thionyl chloride. Finally, cleavage of the benzyl ether with lithium and naphthalene afforded guaia-5(6)-en-11-ol in a 64% yield for the final step.



Scheme 3.9. Diastereoselective synthesis of guaia-5(6)-en-11-ol.

1.4. Synthesis of γ-gurjunene

γ-Gurjunene is a sesquiterpenoid compound from guaiane family isolated from the essential oil of *Cyperus rotundus*, a sedge grown in tropical and subtropical regions.[24] Even though there is not any synthetic route to access this compound described up to date, there is a literature precedent in which enantiopure sesquiterpenoids are employed as synthetic precursors.[25] In this work, (+)-aromadendrene was subjected to K/Al_2O_3 as a well-known procedure for base-catalyzed isomerization of olefins. In this way, when subjected to K/Al_2O_3 at room temperature, the formation of an isomeric sesquiterpenoid was observed, whose structure contained an internally bridgered alkene. Further exposure of this compound to high temperatures afforded (+)-γ-gurjunene in a 80% yield. It is noteworthy that when (+)-aromadendrene was directly

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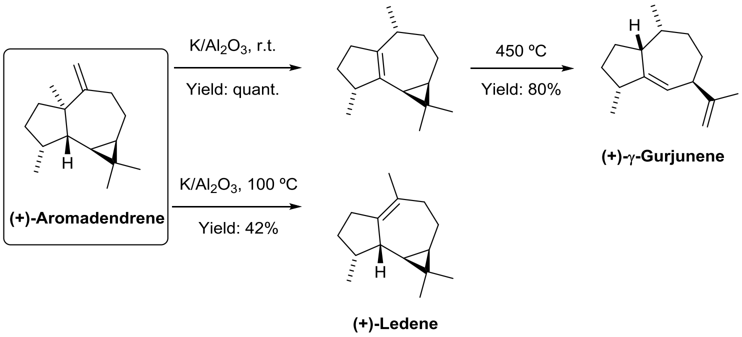
[24] (a) Sonwa, M. M.; König, W. A. *Phytochemistry*, **2001**, *58*, 799. (b) Ehret, C.; Ourisson, G. *Tetrahedron*, **1969**, *25*, 1785.

[25] Rienäcker, R.; Graefe, J. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 320.

exposed to K/Al_2O_3 at 100 °C, (+)-γ-gurjunene could only be detected in traces, whilst (+)-ledene was obtained as main product.



Scheme 3.10. Reported synthesis of (+)-γ-gurjunene.

2. SPECIFIC OBJECTIVES AND WORK PLAN

As it has been outlined in the introduction of this chapter, the potential biological activity of natural sesquiterpenoids have attracted great attention to the development of new synthetic routes to access these natural compounds. Although huge progresses have been made in this field, most of the reported synthesis rely on the use of enantiopure substrates, being in some cases necessary the employment of related sesquiterpenoids as starting materials.

In this regard, we considered that adducts previously obtained as products of the organocatalytic and enantioselective Morita-Baylis-Hillman reaction developed in the Chapter 2, contain the hydroazulene core which characterizes different sesquiterpenoid families of compounds. In this sense, (+)-palustrol, (-)-clavukerin A, (+)-isoclavukerin A, (-)-γ-gurjunene and guaia-5(6)-en-11-ol emerged as potentially accessible sesquiterpenoids.

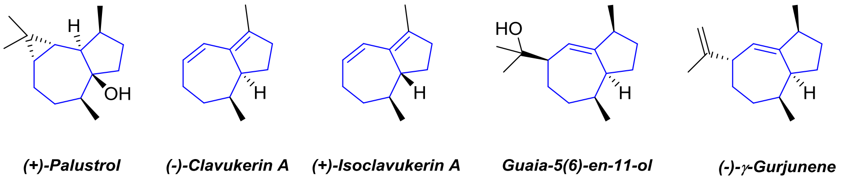
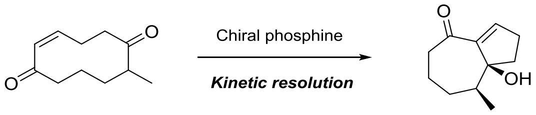


Figure 3.3. Envision of the applicability of the transannular Morita-Baylis-Hillman reaction for the synthesis of natural sesquiterpenoids.

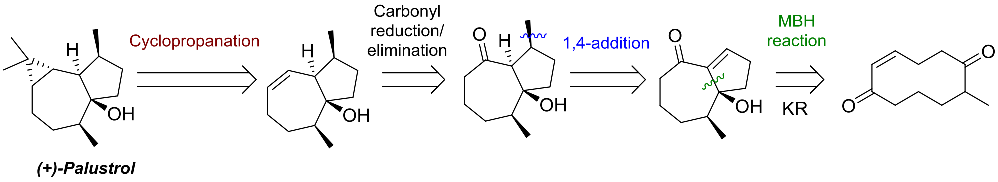
Taking into account the lack of catalytic and enantioselective alternatives to access any of the above-mentioned natural products, the objective of this work is to develop **synthetic routes to access natural sesquiterpenoids represented in Figure 3.3 employing the previously described catalytic and enantioselective transannular Morita-Baylis-Hillman reaction as a key step.**

In this regard, we envisioned that the hydroazulene core could be constructed by a chiral phosphine catalyzed Morita-Baylis-Hillman transannular reaction. As all the synthetic targets contain a methyl group at C-10 position, racemic substrate bearing a methyl group at that position was selected as starting material on the behalf that a kinetic resolution (KR) would afford the enantiopure bicyclic alcohol, which could be used as precursor of the abovementioned sesquiterpenoids.



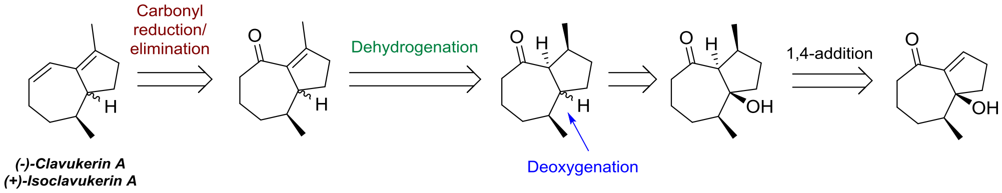
Scheme 3.11. Projected kinetic resolution through catalytic enantioselective MBH reaction.

In the case of (+)-palustrol, the cyclopropane moiety was proposed to be constructed by cyclopropanation of an alkene, which could be as well generated by reduction of the corresponding ketone and subsequent elimination. As keto-enones with substitution in the alkene did not exhibit reactivity in the transannular Morita-Baylis-Hillman reaction,[26] the methyl group at C-4 was proposed to arise from a conjugate addition over MBH bicyclic adduct.



Scheme 3.12. Retrosynthetic route proposed to access (+)-palustrol.

On the other hand, for (-)-clavukerin A and (+)-isoclavukerin A, a carbonyl reduction/elimination was proposed for the final construction of the diene system, from a bicyclic α,β-unsaturated ketone, which could be accessed by a dehydrogenation process. The C-H bond at C-1 was envisioned to be generated by a deoxygenation of the corresponding bicyclic alcohol. Additionally, and in an analogous way to the synthetic route proposed for (+)-palustrol, the methyl group at C-4 would be constructed by conjugate addition over the MBH adduct.



Scheme 3.13. Proposed strategy for (-)-clavukerin A and (+)-isoclavukerin A.

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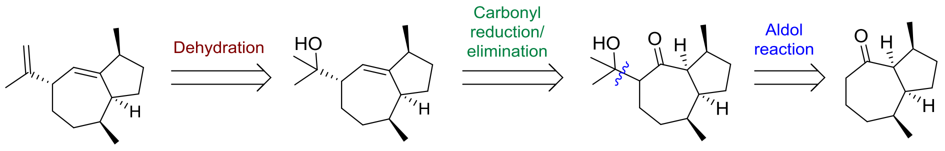
[26] For more information see Chapter 2.

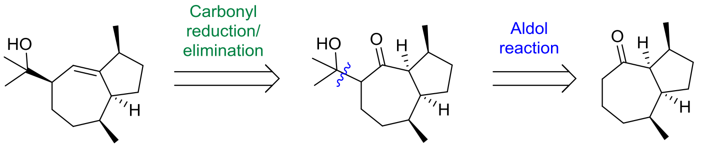
Regarding (-)-γ-gurjunene, the terminal alkene was proposed to arise from the dehydration of the corresponding alcohol, while the internal alkene could be generated by regioselective reduction/elimination of the carbonyl moiety. The lateral three carbon atom chain was proposed to be introduced by an aldol reaction over the bicyclic ketone, which could be obtained following the same strategy as previously described for (-)-clavukerin A and (+)-isoclavukerin A.



(-)-γ-Gurjunene

Scheme 3.14. Retrosynthetic route proposed for (-)-γ-gurjunene.

In the case of guaia-5(6)-en-11-ol, the synthetic proposal is analogue to that outlined for (-)-γ-gurjunene, except for the final step, which is not required for guaia-5(6)-en-11-ol, as it contains a hydroxyisopropyl group in its structure.



Guaia-5(6)-en-11-ol

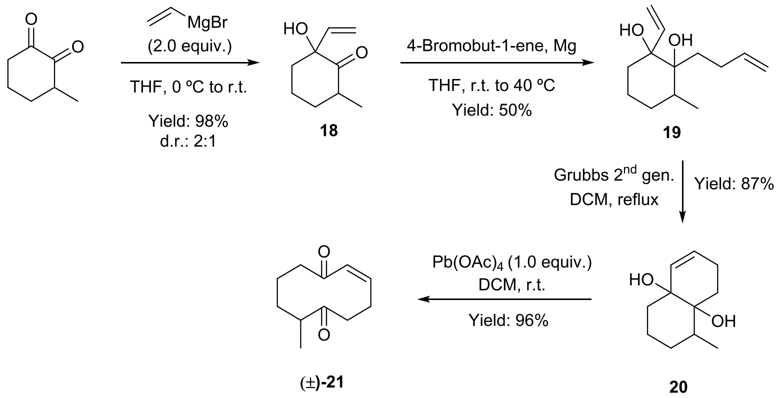
Scheme 3.15. Proposed disconnections to access guaia-5(6)-en-11-ol.

3. RESULTS AND DISCUSSION

3.1. Optimization of the kinetic resolution

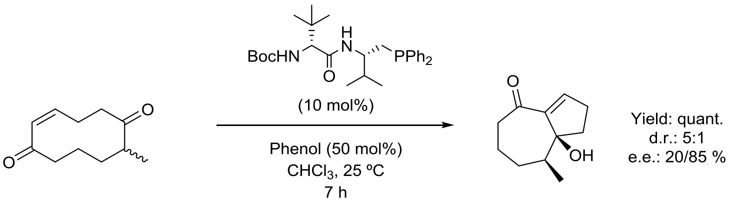
Prior to study the viability of the designed strategy, our efforts were directed to the enantioselective synthesis of bicyclo[5.3.0]decane adduct (Scheme 3.11), which is the key intermediate in all the synthetic approaches previously outlined.

First of all, the required keto-enone was prepared following the same synthetic strategy as previously applied for keto-enone substrates synthesized in Chapter 2. In this way, 3-methylcyclohexane-1,2-dione was initially subjected to the addition of vinylmagnesium bromide, followed by the addition of but-3-en-1-ylmagnesium bromide. Further ring closing metathesis catalyzed by 2nd generation Grubbs catalyst afforded conveniently functionalized bicyclic diol **20**, which was converted into the racemic 10-membered keto-enone **21** by $Pb(OAc)_4$ promoted oxidative cleavage.



Scheme 3.16. Synthesis of racemic substrate **21**.

Next we proceeded with the study of the envisioned kinetic resolution. In this sense, preliminary experiments were carried out by subjecting racemic substrate **21** to the previously optimized conditions for the transannular MBH process. The reaction was monitored by TLC and after 7 hours full conversion of the starting material was observed. Under these conditions, adduct **22** was isolated in excellent yield as a 5:1 mixture of diastereomers albeit low enantiomeric excess was obtained for major diasteromer.



rac-21

(8*S*,8a*S*)-22

Scheme 3.17. Preliminary results for the transannular MBH reaction.

However, when the analogous reaction was quenched after one hour, adduct **22** could be isolated in 50% yield as mixture of diastereomers, determining 70% e.e. for major diastereomer and 55% e.e. for minor diastereomer. In view of these preliminary results, we decided to carry out a set of reactions under the same experimental conditions, in order to evaluate the result dependence with conversion. However, NMR analysis of crude reaction mixtures showed that the reaction was continuing after work-up due to the presence of all reactive species with the catalyst in the crude mixture. For this reason, an appropriate method was necessary in order to quench the reaction at the desired times. This method should deactivate the catalyst without affecting either the product of the reaction or the unreacted starting material.

In this sense, a work-up in which the phosphine is oxidized to the corresponding phosphine oxide emerged as a suitable strategy. Based on literature precedents,[27] different oxidizing reagents were surveyed such as peracetic acid, *m*-chloroperbenzoic acid and hydrogen peroxide. Catalyst oxidation could be easily followed by ^{31}P-NMR, due to the significant shift of the NMR signal that takes place, being around -25 ppm for active catalyst whilst shifts to +30 ppm for corresponding phosphine oxide. After a survey, hydrogen peroxide was chosen as the best option as it provided immediate full deactivation of the catalyst with no side product formation.[28]

Once we found an appropriate experimental procedure for this purpose, we applied the previously optimized conditions for the enantioselective transannular process ($CHCl_3$, 50 mol%

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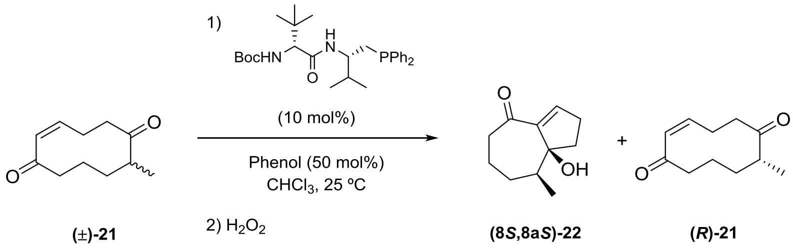
[27] (a) Sasaki, S.; Sutoh, K.; Shimizu, Y.; Kato, K.; Yoshifuji, M. *Tetrahedron Lett.* **2014**, *55*, 322. (b) Hilliard, C. R.; Bhuvanesh, N.; Gladysz, J. A.; Blümel, J. *Dalton Trans.* **2012**, *41*, 1742. (c) Bhattacharyya, P.; Slawin, A. M. Z.; Smith, M. B.; Woolins, J. D. *Inorg. Chem.* **1996**, *35*, 3675. (d) Whitaker, C. M.; Kott, K. L. ; McMahon, R. J. *J. Org. Chem.* **1995**, *60*, 3499. (e) Relles, H. M.; Schluenz, R. W. *J. Am. Chem. Soc.* **1974**, *96*, 6469.

[28] For more details about the experimental procedure for the kinetic resolution see the experimental section.

of phenol, r.t.) to a series of identical reactions (Table 3.1). However, despite different reaction times were evaluated, none of them provided satisfactory results, achieving 39% yield and 88% e.e. as best results when reaction was quenched after 50 minutes (entry 3).

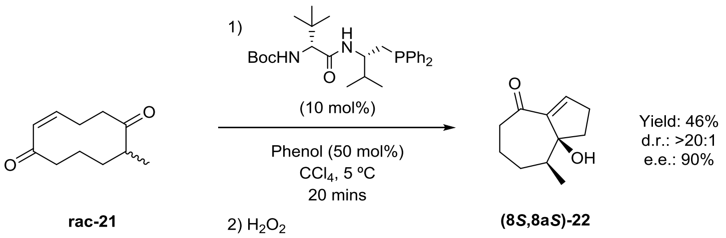
Table 3.1. Preliminary tests.



Entry^{a}	Time (min)	Yield$_{prod}$ (%)^{b,c}	e.e.$_{prod}$ (%)^{d}	Yield$_{sm}$ (%)^{c}	e.e.$_{sm}$ (%)^{d}
1	40	35	88	61	50
2	45	37	88	62	54
3	50	39	88	57	54
4	55	42	86	50	66

[a]Reactions performed at 0.1 mmol scale employing 10 mol% of catalyst and 50 mol% of phenol in $CHCl_3$ (0.1 mmol/mL) at room temperature. [b]Diastereomeric ratio for product **22** was 15:1 in all the cases. [c]Yields refer to isolated pure products. [d]Calculated by HPLC on chiral stationary phase.

Alternatively, when the solvent was changed from chloroform to carbon tetrachloride, a significant increase in reaction rate was observed, which allowed us to lower the temperature to 5°C. Under these conditions, after 20 minutes adduct **22** was isolated in 46% yield as a single diastereomer and with excellent enantioselectivity (Scheme 3.18).

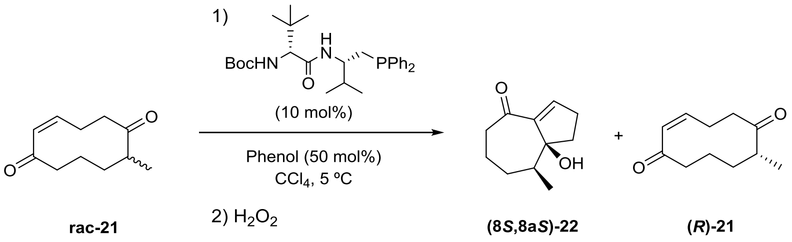


Scheme 3.18. Initial experiments in carbon tetrachloride.

At this point, it was decided to increase the working scale up to 0.8 mmol before accomplishing a more comprehensive evaluation of the reaction time parameter (Table 3.2).

Following this methodology, we were able to determine that the reaction should be quenched after 30 minutes to access adduct **22** as a single diastereomer in good yield and enantiomeric excess (Table 3.2 entry 2). Longer reaction times enhanced the isolated yield for adduct **22**, but the enantiomeric excess and diastereomeric ratio were negatively affected. Further recrystallization in hexane increased the enantiopurity of adduct **(8*S*,8a*S*)-22** up to a 98% enantiomeric excess (79% yield for recrystallization step).

Table 3.2. Optimization of the kinetic resolution.



Entry[a]	Time (mins)	Yield$_{prod}$ (%)[b]	d.r.	e.e.$_{prod}$ (%)[c]	Yield$_{sm}$ (%)[b]	e.e.$_{sm}$ (%)[c]
1	24	37	>20:1	90	58	70
2	**30**	**42**	>20:1	**90**	**56**	**76**
3	35	47	>20:1	88	46	86

[a]Reactions were performed at 0.8 mmol scale employing 10 mol% of catalyst and 50 mol% of phenol in CCl$_4$ (0.1 mmol/mL) at 5 °C. [b]Yields refer to isolated pure products. [c]Calculated by HPLC on chiral stationary phase.

The absolute configuration of adduct **22** and of the resolved unreacted starting material **21** could be determined by single-crystal X-ray diffraction and corresponded to those represented in Figure 3.4.

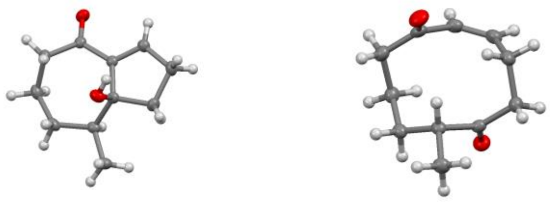
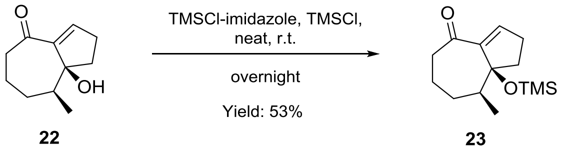


Figure 3.4. Crystal structures for bicyclic **(8*S*,8a*S*)-22** and unreacted starting material **(*R*)-21** after the kinetic resolution.

3.2. Total synthesis of (+)-palustrol

Once we found efficient experimental conditions for the synthesis of adduct **(8*S*,8a*S*)-22**, we continued with the planned strategy for the synthesis of (+)-palustrol. First of all, the protection of the alcohol moiety had to be carried out in order to prevent any interference of this functional group in the subsequent chemical transformations. Unfortunately, this protection resulted much more challenging than expected, due to either the steric hindrance and/or the allylic nature of this alcohol. Substrate **22** remained unreactive under several protection conditions tested, such as acetylation, benzylation or methoxymethyl acetal formation. Additionally, common procedures for the introduction of silyl protecting groups using the corresponding silyl chlorides did not afford the protected product,[29] while more reactive reagents such as silyl triflates or higher temperatures produced decomposition of the starting material. Fortunately, when TMS-Imidazole was employed as trimethylsilyl source,[30] product **23** could be isolated in 53% yield (Scheme 3.19). Analogous procedures for bulkier silyl protecting groups did not provide the corresponding protected products.



Scheme 3.19. Protection of bicyclic alcohol **22**.

Next, we proceeded with the projected conjugate addition of Me_2CuLi to the α,β-unsaturated system. Unfortunately, after the conjugate addition the resulting product turned out to be extremely unstable, being necessary to trap the enolate intermediate as the corresponding silyl enol ether. In this way, the preformed Gilman reagent was added at -78°C over adduct **23**, followed by the addition of TMSCl and NEt_3.[31] Resulting silyl enol ether was

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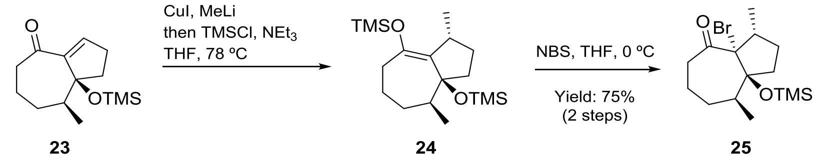
[29] Wuts, P. G. M.; Greene, T. W. In *Protective groups in organic synthesis*; Wiley: New Jersey, 2007.

[30] (a) Kociensky, P. J. In *Protecting groups*; Thieme: Stuttgart, Germany, 2005. (b) Fuchs, P. L. In *Handbook of Reagents for Organic Synthesis. Reagents for Silicon-Mediated Organic Synthesis*; John Wiley & Sons: Great Britain, 2011.

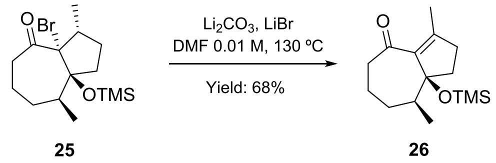
[31] For other examples of conjugate addition/silyl enol ether trapping procedure, see: (a) Kumar, J. S. R.; O'Sullivan, M.; Resiman, S. E.; Hulford, C. A.; Ovaska, T. V. *Tetrahedron Lett.* **2002**, *43*, 1939. (b) Banwell, M. G.; Hockless, D. C. R.; McLeod, M. D. *New J. Chem.* **2003**, *27*, 50. (c) Bertz, S. H.; Miao, G.; Rossiter, B. E.; Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11023.

isolated and directly subjected to bromination conditions with *N*-bromosuccinimide at 0 °C to afford compound **25** as a single diastereomer in 75% yield for two steps.[32]



Scheme 3.20. Synthesis of intermediate **25**.

Next, compound **25** was exposed to literature conditions for an elimination process to take place (Li_2CO_3, LiBr in DMF at high temperature).[33] This elimination step turned out to be quite sensitive to concentration, resulting in complex product mixtures when concentrated conditions were employed. Fortunately, high diluted conditions (0.01 M) applied by Baran *et al.*[34] significantly improved the performance of the reaction affording product **26** in 68% yield (Scheme 3.21). It should be mentioned that it was required to increase temperature to 130 °C to promote the reaction, compared to the 60 °C used in the literature procedure.



Scheme 3.21. Bromide elimination to access adduct **26**.

At this point, adduct **26** was subjected to standard hydrogenation conditions (H_2, Pd/C, MeOH) in order to afford product **27**. However, in spite of the expected hydrogenated product **27**, compound **28** was obtained, in which trimethylsilyloxy group had been lost. After 4 h, full consumption of the starting material was observed by TLC allowing the isolation of adduct **28** in 62% yield by flash column chromatography (Scheme 3.22).

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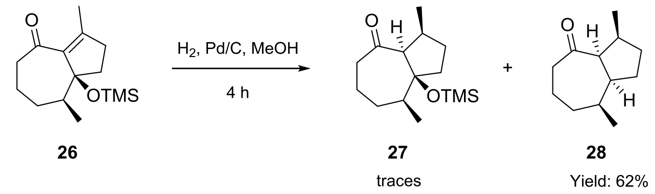
[32] Reuss, R. H.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 1785.

[33] For selected examples, see: (a) Jeganathan, A.; Richardson, S. K.; Watt, D. S. *Synth. Commun.* **1989**, *19*, 1091. (b) Roosen, P. C.; Vanderwal, C. D. *Org. Lett.* **2014**, *16*, 4368. (c) Hashimoto, S.; Katoh, S.-I.; Kato, T.; Urabe, D.; Inoue, M. *J. Am. Chem. Soc.* **2017**, *139*, 16420.

[34] Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241.



Scheme 3.22. Hydrogenation of adduct **26**.

The formation of this product was attributed to the reduction of the C-C double bond, as well as concomitant cleavage of silyl protecting group.[35] Subsequent spontaneous elimination of the alcohol and hydrogenation of the resulting product would afford adduct **28** as main product. The relative configuration of the stereocenters in the molecule could be determined by X-ray diffraction of the corresponding hydrazone **28’** (Figure 3.5), concluding that it could be employed as key intermediate in the synthesis of the envisioned natural products.

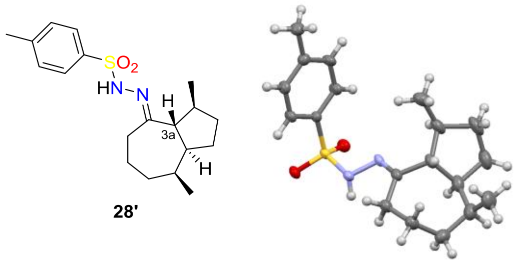


Figure 3.5. X-ray diffraction structure for hydrazone **28’**.

It should be mentioned that the absolute configuration at C-3a in compound **28** is thought to be opposite to that determine for hydrazone **28’**, taking into account that catalytic hydrogenation is expected to take place through *syn* addition. Epimerization at α position to carbonyl is believed to occur under hydrazone formation conditions ($TsNHNH_2$, EtOH, HOAc, H_2SO_4 cat., r.t.).

At this point and in order to overcome this drawback, different reported methodologies for conjugate reduction using hydrides were tested. Adduct **26** remained unreactive when exposed

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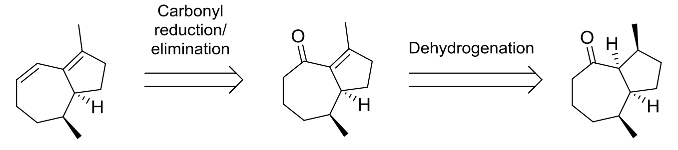
[35] Ikawa, T.; Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron*, **2004**, *60*, 6901.

to stoichiometric amounts of $[(Ph_3P)CuH]_6$, commonly known as Stryker reagent.[36] Modification of classical conditions (benzene, r.t.) by increasing temperature led to complex mixtures of products or complete decomposition of the starting material without observing in any case detectable amounts of the desired product. The use of other reported efficient catalytic systems as $Et_3SiH/[RhCl(PPh_3)_3]$[37] or PhMeSiH/CuCl[38] did not afford the desired product. After several attempts, the discouraging results obtained led us to discard the present synthetic strategy.

3.3. Total synthesis of clavukerin A

As hydrogenation of compound **26** led to the loss of the alcohol moiety present in the molecule, which prevented us from accessing (+)-palustrol, we decided to accomplish the synthesis of (-)-clavukerin A as it could be accessed from adduct **28**.



(-)-Clavukerin A

28

Scheme 3.23. Envisioned retrosynthesis for (-)-clavukerin A.

Our initial attempts were directed to restore the α,β-unsaturated system in the molecule leading to an enone intermediate, whose transformation into (-)-clavukerin A has already been described in the literature.[39] In order to achieve this objective, we considered alternative strategies. First of all, compound **28** was transformed into the corresponding silyl enol ether[40] **29** and directly exposed to phenylselenyl chloride in Et_2O at -78 °C affording selenide **30** as a

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[36] Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291. For an example of the employment of Stryker reagent in O-silylated substrates, see: Meiries, S.; Bartoli, A.; Decostanzi, M.; Parrain, J.-L.; Commeiras, L. *Org. Biomol. Chem.* **2013**, *11*, 4882.

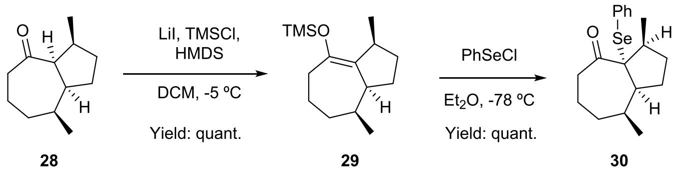
[37] Ojima, I.; Kogure, T. *Organometallics*, **1982**, *1*, 1390.

[38] Ito, H.; Ishizuka, T.; Arimoto, K.; Miura, K.; Hosomi, A. *Tetrahedron Lett.* **1997**, *38*, 8887.

[39] Reported synthesis have been described in the introduction of this chapter.

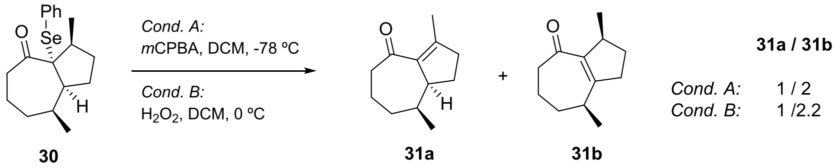
[40] (a) Miller, R. D.; McKean, D. R. *Synthesis*, **1979**, 730. (b) Ryu, I.; Murai, S.; Niwa, I.; Sonoda, N. *Synthesis*, **1977**, *12*, 874.

single diastereomer, presumably due to the formation of the new C-Se bond through the less hindered face of the silyl enol ether.



Scheme 3.24. Synthesis of selenide **30**.

Next, adduct **30** was subjected to reported conditions for oxidation to selenoxide and *in situ* elimination.[41] Unfortunately, when *m*CPBA was employed as oxidant in dichloromethane at -78 °C, a 2:1 mixture of regioisomers was obtained (Scheme 3.25). NMR analysis allowed us to identify these products as regioisomeric α,β-unsaturated ketones **31a** and **31b**, being the undesired product **31b** formed as main product. The use of H_2O_2 as an alternative oxidant did not provide any improvement on the outcome of the reaction, affording products **31a** and **31b** in a 1:2.2 ratio. The observed lack of selectivity was attributed to the *cis* orientation respect to the selenide of both hydrogens in β positions. As selenide-mediated eliminations are described to take place through a *syn* mechanism,[42] this would imply that elimination could take place in both positions. Although it was expected that β hydrogen in the cyclopentane ring would be more accessible than the β hydrogen in the fused system, experimental observations showed a preferred formation of product **31b**.



Scheme 3.25. Selenide-mediated elimination.

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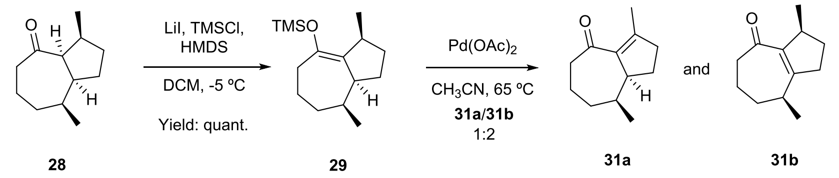
[41] For other examples of selenide mediated eliminations in bicyclic systems, see: (a) Kamikubo, T.; Ogasawara, K.; *Chem. Lett.* **1995**, *2*, 95. (b) Fernández, B.; Pérez, J. A. M.; Granja, J. R.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1992**, *57*, 3173.

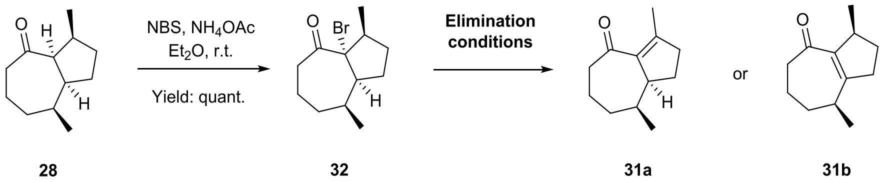
[42] (a) Sharpless, K. B.; Younh, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, *22*, 1979. (b) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137. (c) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

An alternative approach for the construction of the α,β-unsaturated system was also tested by subjecting silyl enol ether **29** to Ito-Saegusa conditions.[43] However, when adduct **29** was exposed to $Pd(OAc)_2$ in CH_3CN at 65 °C, a 2:1 mixture of regioisomers was obtained, being undesired adduct **31b** formed as main product (Scheme 3.26).



Scheme 3.26. Ito-Saegusa approach for enone synthesis.

Prior to discard this synthetic approach, other elimination procedures were also surveyed. In this sense, bromide intermediate **32** was synthesized by treatment of adduct **28** with *N*-bromosuccinimide in Et_2O at room temperature in presence of 10 mol% of NH_4OAc[44] and subsequently exposed to different bases. While DBU, NaH and LiHMDS did not promote the elimination process, even at high temperatures; pyridine, as well as previously applied conditions involving Li_2CO_3/LiBr rendered products **31a** and **31b** in a 1:4 and 1:20 ratio respectively.



Scheme 3.27. Synthesis of bromide **32** and elimination reaction.

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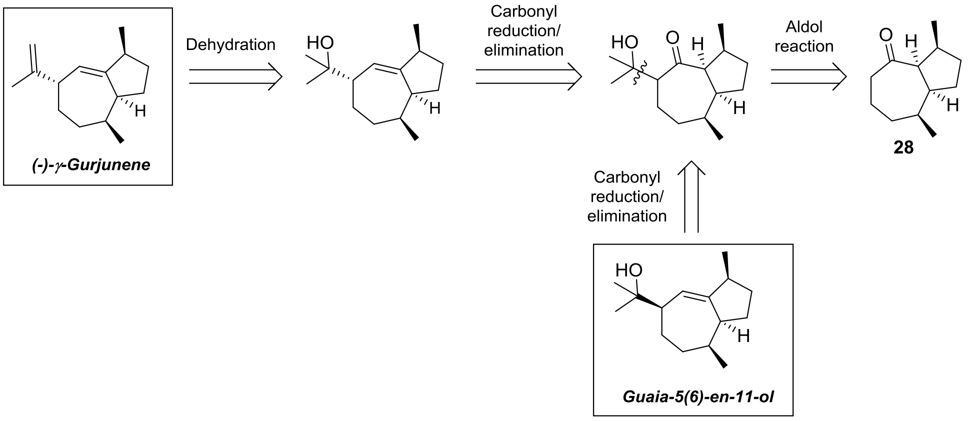
[43] For selected examples of enone synthesis under Ito-Saegusa conditions, see: (a) Angeles, A. R.; Waters, S. P.; Dnishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13765. (b) Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. *Org. Lett.* **2006**, *8*, 5311. (c) Hu, X.-D.; Tu, Y. Q.; Zhang, E.; Gao, S.; Wang, S.; Wang, A.; Fan, C.-A.; Wang, M. *Org. Lett.* **2006**, *8*, 1823. (d) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

[44] Tanemura, K.; Suzuki, T; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Commun.* **2004**, 470.

Taking into account that the performed experiments revealed our failure in controlling the regioselectivity in the synthesis of intermediate **31a**, we decided to move on and face the synthesis of other natural products previously outlined.

3.4. Total synthesis of (-)-γ-gurjunene

In view of the obtained results, we decided to focus our efforts on the synthesis of (-)-γ-gurjunene and guaia-5(6)-en-11-ol, sesquiterpenoids from guaiane family with a very related structure readily accessible from adduct **28**. As they present opposite stereochemistry at the quaternary stereocenter in the lateral chain, the generation of the C-C bond through an aldol reaction would condition the following steps of the synthetic route.



Scheme 3.28. Envisioned strategies to access (-)-γ-gurjunene and guaia-5(6)-en-11-ol.

Taking this fact into account we initially introduced the lateral three atom carbon chain through aldol reaction. For this purpose, a kinetic deprotonation was performed with LDA at -78 °C followed by zinc chloride-promoted aldol reaction,[45] affording adduct **33** as a single diastereomer in 60% yield (Scheme 3.29). The relative stereochemistry of the new stereocenter was determined by NMR analysis, by the observation of nuclear overhauser effect (nOe) between the hydrogen atom at C-7 and the methyl groups at C-4 and C-10. Therefore it was

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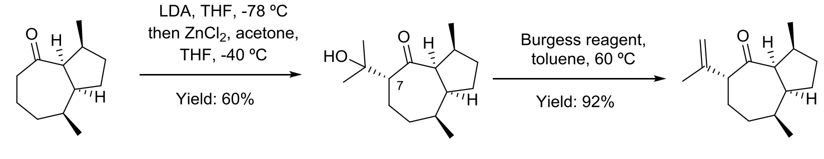
[45] For other examples of zinc chloride catalyzed aldol reactions in bicyclic systems, see: (a) Ushakov, D. B.; Navickas, V.; Ströbele, M.; Maichle-Mössmer, C.; Sasse, F.; Maier, M. E. *Org. Lett.* **2011**, *13*, 2090. (b) Gijsen, H. J. M.; Wijnberg, J. B. P. A.; Stork, G. A.; Groot, A. *Tetrahedron*, **1991**, *47*, 4409.

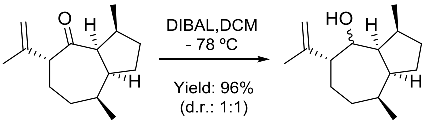
concluded that aldol **33** could be employed as precursor in the total synthesis of (-)-γ-gurjunene. Subsequent elimination of the alcohol with Burgess reagent[46] afforded compound **34** in 92% yield.



28 **33** **34**

Scheme 3.29. Synthetic route to compound **34**.

Next, the reduction of the carbonyl group was faced (Scheme 3.30). In this sense, the use of diisobutylaluminium hydride in dichloromethane at -78 °C yielded compound **35** as a 1:1 mixture of separable diastereomers. Alternative reducing reagents either remained unreactive ($NaBH_4$) or did not provide better results in terms of diastereoselectivity ($LiAlH_4$, L-selectride…).



34 **35**

Scheme 3.30. Reduction of ketone **34**.

Finally, we accomplished the dehydration of adducts **35** that would provide access to the target molecule. As expected, when alcohol **35a** was subjected to Burgess reagent in $CHCl_3$ at 60 °C, we were delighted to observe the formation of γ-gurjunene **36**, which could be isolated in 61% yield (Scheme 3.31). The ^1H and ^{13}C-NMR spectra of compound **36** were coincident with those reported for natural product. Moreover, measured optical rotation for compound **36** allowed us to identify unambiguously this product as (-)-γ-gurjunene.

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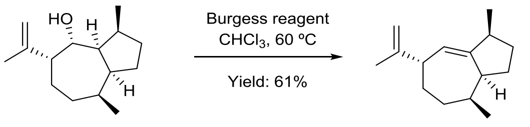
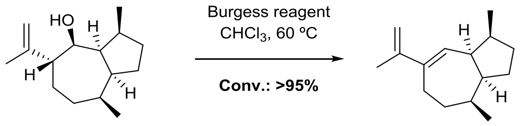
[46] For more information about Burgess reagent and its application in related eliminations, see: (a) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26. (b) Markad, S. B.; Argade, N. P. *J. Org. Chem.* **2016**, *81*, 5222. (c) Manzano, F. L.; Guerra, F. M.; Moreno-Dorado, F. J.; Jorge, Z. D.; Massanet, G. M. *Org. Lett.* **2006**, *8*, 2879.



35a **36** **(-)-γ-Gurjunene**

Scheme 3.31. Final dehydration reaction of adduct **35a.**

On the other hand, when adduct **35b** was exposed to analogous reaction conditions that those applied for product **35a** with Burgess reagent, the main formation of a new compound was detected by ^{1}H-NMR of the reaction crude mixture. Spectral data for this product did not match reported information for γ-gurjunene, although it presented a related structural core. NMR analysis allowed us to tentatively identify this product as adduct **37**, a regioisomer of γ-gurjunene.



35b **37**

Scheme 3.32. Final dehydration reaction of adduct **35b**.

It should be mentioned that although different elimination procedures *via anti* mechanisms were tried for alcohol **35b**, such as Martin's sulfurane,[47] no reaction was observed, producing decomposition of the starting material when subjected to high temperatures for long reaction times.

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[47] (a) Li, J. J.; In *Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications*; Springer International Publishing: Switzerland, 2014. (b) Li, J. J.; Corey, E. J. In *Name Reactions for functional Group Transformations*; John Wiley & Sons, Inc.: New Jersey, 2010. (c) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 2339. (d) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327.
For some selective examples of its application as dehydrating agent in complex molecules, see: (a) Myers, A. G.; Glatthar, R.; Hammond, M.; Harrington, P. M.; Kuo, E. Y.; Liang, J.; Schaus, S. E.; Wu, Y.; Xiang, J.-N. *J. Am. Chem. Soc.* **2002**, *124*, 5380. (b) Nicolau, K.C.; Rodríguez, R. M.; Fylaktakidou, K. C.; Suzuki, H.; Mitchell, H. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3340. (c) Evans, D. A.; Black, C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.

4. CONCLUSIONS

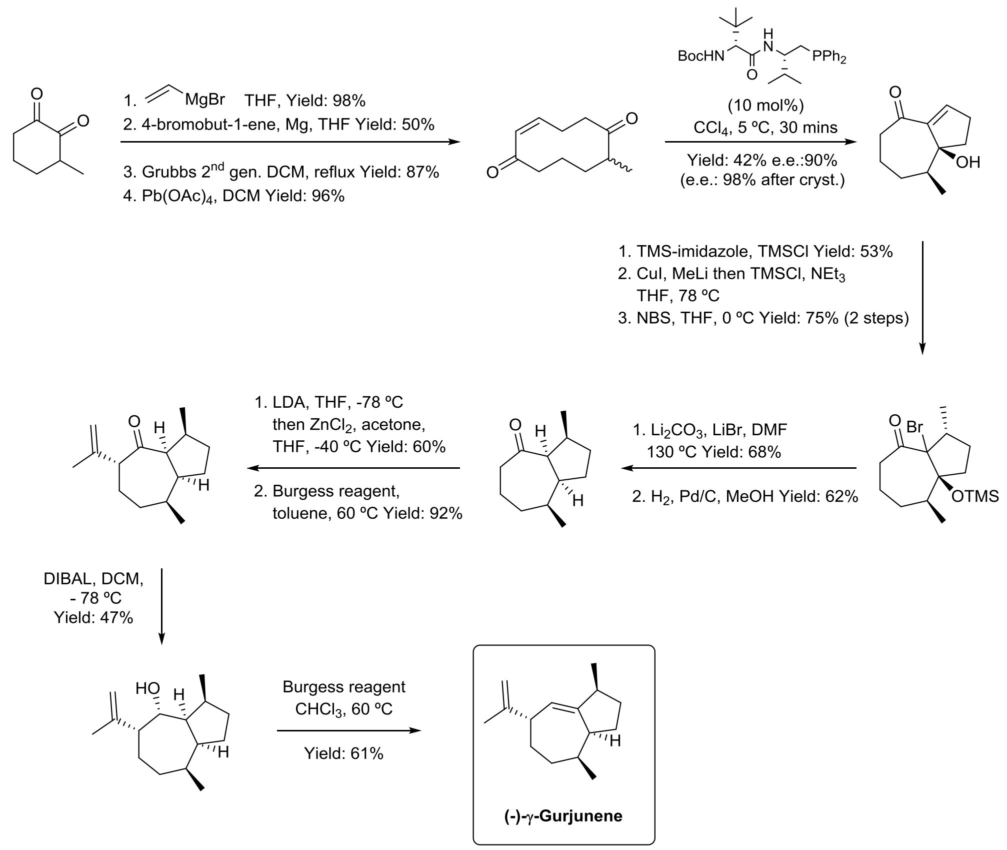
In view of the results summarized in the previous section, the following conclusion can be inferred:

- We have been able to develop the **first asymmetric total synthesis of natural sesquiterpenoid (-)-γ-gurjunene.** Unfortunately the related sesquiterpenoids (+)-palustrol, (-)-clavukerin A and guaia-5(6)-en-11-ol could not be synthesized by the developed methodology.

- Chiral aminoacid-derived phosphine catalyzed kinetic resolution developed in our group has been efficiently applied for the crucial enantioselective step, providing access to the structural core of guaiane and aremadendrane sesquiterpenoid family, which contain a methyl group at C-10 position.

- The introduction of the methyl group at C-4 has been accomplished by a conjugate addition followed by bromination of the silyl enol ether intermediate and elimination. Final catalytic hydrogenation provided access to the hydroazulene core substituted at C-4 and C-10, which was employed as a precursor in the total synthesis of (-)-clavukerin A and (-)-γ-gurjunene; Unfortunately, it prevented us from accessing (+)-palustrol. (-)-clavukerin A could not be synthesized due to the lack of selectivity in the elimination of bromide intermediate that would afford the required α,β-unsaturated ketone containing the biciclo[5.3.0]decane scaffold.

- The introduction of a functionalized lateral chain has been accomplished by an intermolecular aldol reaction. The stereochemical outcome of this process, prevented us from synthesizing guaia-5(6)-en-11-ol, while provided access to (-)-γ-gurjunene, which could be synthesized starting from 3-methyl-cyclohexane-1,2-dione in 14 step synthesis with an overall 0.46% yield.



Scheme 3.33. General overview of the asymmetric total synthesis of (-)-γ-gurjunene.

4

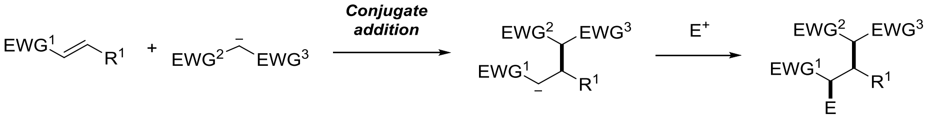
4

Organocatalytic enantioselective Michael initiated transannular aldol reaction

1. INTRODUCTION

The development of efficient methodologies for the construction of highly functionalized molecules has attracted the interest of the scientific community for years. In this context, domino reactions can be considered suitable strategies for this purpose. According to Tietze definition, a domino reaction is a process in which two or more bonds are formed under the same reaction conditions without modifying experimental parameters or adding additional reagents.[1] New bonds are, therefore, formed as consequence of the functionality generated in the previous step.

In this sense, the nucleophilic 1,4-conjugate addition of resonance-stabilized carbanions to electron deficient alkenes, commonly known as Michael reaction, has been deeply studied for the formation of new C-C bonds through domino processes.[2] Its potential as synthetic tool lies on the possibility of making use of the nucleophilic intermediate generated as consequence of the initial addition in order to react with an additional electrophilic partner.[3]



Scheme 4.1. General scheme for a Michael initiated domino reaction.

Regarding the synthesis of enantiopure compounds through Michael initiated domino reactions, different approaches have been developed, including *diastereoselective reactions*, based on the employment of enantiopure pronucleophiles or Michael acceptors; and *enantioselective reactions*, in which enantioselectivity is induced by a stoichiometric or catalytic chiral reagent which does not remain in the final structure of the product.

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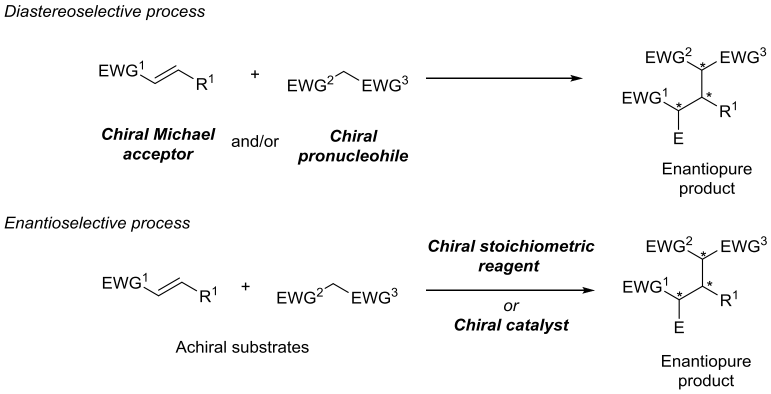
[1] (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131.

[2] Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.

[3] (a) Pellisier, H. *Chem. Rev.* **2013**, *113*, 442. (b) Düfert, S-C.; Hierold, J.; Tietze, L. F. *Domino reactions in the total synthesis of natural products. Domino reactions: concepts for efficient organic synthesis*; Tietze, L. F. Wiley-VCH: Weinheim, 2014; pp 523-578. (c) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167.



Scheme 4.2. General scheme for strategies for the synthesis of enantiopure compounds through Michael initiated domino reactions.

From the abovementioned strategies, the catalytic approach is considered more efficient as it requires the use of substoichiometric amounts of a chiral reagent. In the field of Michael initiated domino reactions the use of chiral metal catalysts for the enantioselective synthesis of highly functionalized molecules has been the subject of deep study.[4] However, in the last decades, the employment of metal-free small organic molecules as chiral catalysts, known as asymmetric organocatalysis, has emerged as an efficient alternative, being a recurrent strategy in a wide range of domino processes.[5]

Although there is plenty of literature regarding the use of covalent organocatalysts as promoters of Michael initiated domino reactions, characterized by the formation of a covalent bond between the catalyst and the substrate along the catalytic cycle; *non-covalent organocatalysts* have also demonstrated their applicability as efficient promoters of this type of reactions. In the case of non-covalent organocatalysts, the catalyst-substrate interaction is based on other kind of forces, such as hydrogen-bonds or ion-pair interactions. In this context,

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[4] For a recent review, see: Zheng, K.; Liu, X.; Feng, X. *Chem. Rev.* **2018**, *118*, 7586.

[5] Selected reviews about asymmetric organocatalytic domino reactions: (a) Chanda, T.; Zhao, J. C.-G. *Adv. Synth. Catal.* **2018**, *360*, 2. (b) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390. (c) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237. (d) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570.

bifunctional Brønsted acid – Brønsted base chiral catalysts (BA-BB) have been widely employed,[6] due to their capability to establish multiple interactions with the reaction partners involved in the chemical process, which usually implies a higher degree of stereochemical order in the transition state, therefore resulting in a better and more predictable asymmetric induction. From a general perspective bifunctional Brønsted acid – Brønsted base chiral catalysts are characterized by containing in their structure both a basic site, which deprotonates the pro-nucleophile, and a hydrogen bond donor moiety, capable of establishing additional interactions with the electrophilic Michael acceptor.

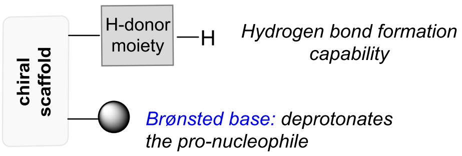
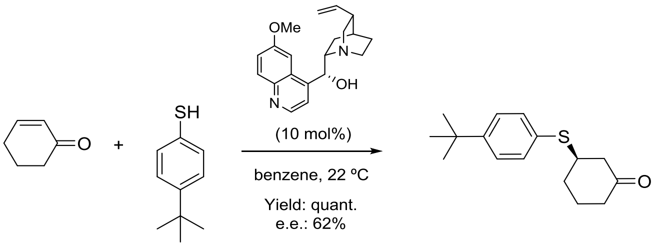


Figure 4.1. General structure of bifunctional BA-BB catalysts.

Since the first pioneering work involving an enantioselective reaction under bifunctional Brønsted acid – Brønsted base catalysis, developed in early 80's by Wynberg and Hiemstra for conjugate addition of thiols to cyclohexenone catalyzed by cinchona alkaloids (Scheme 4.3),[7] significant efforts have been applied in order to improve the performance of these catalysts.



Scheme 4.3. Initial studies developed by Wynberg and Hiemstra.

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[6] For selected reviews about bifunctional thiourea and squaramide organocatalysts, see: (a) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890. (b) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632. (c) Connon, S. J. *Chem. Commun.* **2008**, 2499.

[7] Hiemstra, K.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.

In this sense, and considering their capability to establish H-bond interactions as a fundamental aspect of their catalytic activity, efforts have been directed to enhance this hydrogen bond donor ability. For instance, in 2003, Takemoto and coworkers developed a new kind of bifunctional BA-BB catalysts containing the thiourea scaffold,[8] applying concepts previously introduced by Schreiner regarding the influence of structural modifications in the N-H acidity of thioureas.[9] As a logical extension, in 2005 two independent works were reported almost simultaneously by Dixon[10] and Connon,[11] in which the thiourea scaffold was attached to cinchona derived alkaloids. Some years later, Rawal *et.al.* reported the development of analogous squaramide catalysts.[12]

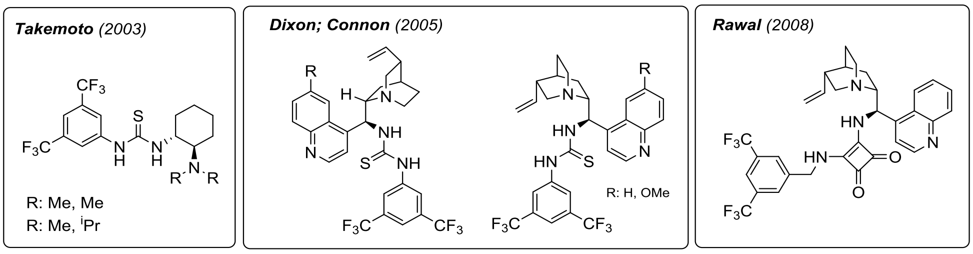

Figure 4.2. Representative examples of bifunctional Brønsted acid – Brønsted base catalysts developed by Takemoto, Dixon & Connon and Rawal.

After these preliminary reports, this specific type of organocatalysts have been subject of deep study for years. In this way, nowadays it is known that although either thioureas or squaramides can act as hydrogen bond donors, they present significant structural differences which affect their catalytic activity. While for thioureas the distance between the two N-H groups attached to the same carbon is ~2.13 Å; in the case of squaramides this distance is approximately 2.73 Å.[13]

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[8] (a) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (b) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

[9] Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407.

[10] Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481.

[11] McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367.

[12] Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416.

[13] Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253.

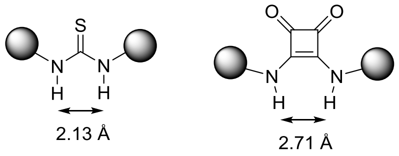

Figure 4.3. Structural differences between thioureas and squaramides.

Additionally, although in both cases the lone pair on the nitrogen is delocalized, which restricts the rotation of C-N bond, only in squaramides this delocalization can be extended to the cyclobutenedione system. This fact, apart from rigidifying the structure of the catalyst, has as consequence a higher NH acidity in the squaramide compared to urea or thiourea analogs.

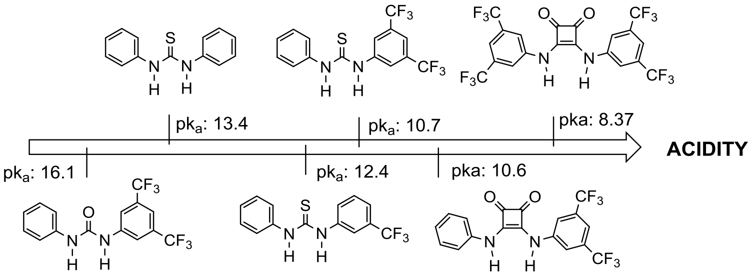

Figure 4.4. Reported pk$_a$ for urea, thiourea and squaramide analogs in DMSO.[14]

In the last years, the efficiency of thiourea and squaramide derived bifunctional chiral catalysts for promoting enantioselective transformations has been fully demonstrated, allowing to broaden their employment into domino processes.[6] Due to its close relation with the developed work, in the following section the reported enantioselective examples regarding Michael initiated domino reactions under bifunctional Brønsted acid–Brønsted base catalysis will be discussed in detail, focusing on Michael/aldol and Michael/Henry processes.

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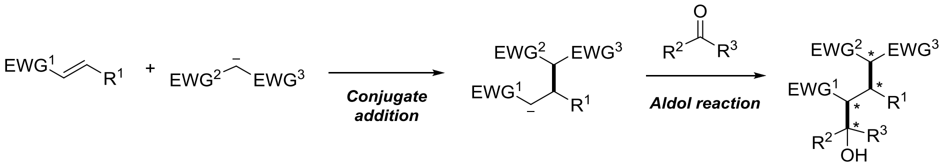
[14] (a) Ni, X.; Li, X.; Wang, Z.; Cheng, J.-P. *Org. Lett.* **2014**, *16*, 1786. (b) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *7*, 1724.

Enantioselective domino Michael/aldol and Michael/Henry reactions under bifunctional Brønsted acid – Brønsted base catalysis

A domino Michael/aldol process is a specific type of Michael reaction in which after the initial conjugate addition of the resonance-stabilized carbanion, the generated enolate reacts with the electrophilic sp^2 carbon of an aldehyde or ketone. In those cases in which a nitro alkene is employed as Michael acceptor, the process is commonly referred as Michael/Henry reaction.



Scheme 4.4. General scheme for domino Michael/aldol and Michael/Henry reactions.

As the reaction implies the formation of two new C-C bonds, domino Michael/aldol and Michael/Henry reactions have been widely employed for the construction of highly functionalized molecules. Regarding the enantiocontrol of the multiple stereocenters that are formed as consequence of the reaction, the use of bifunctional BA-BB catalysts can be considered as a recurrent strategy. In this context, the first reported example of a domino Michael/aldol reaction under bifunctional BA-BB catalysis dates back to 1998, when Terashima *et al.* employed natural alkaloid cinchonidine in the synthesis of natural product (-)-huperzine A (Scheme 4.5).[15] The developed synthetic route involved a domino Michael/aldol reaction as a key step for the construction of the structural core of this natural product. Although moderate enantioselectivities were achieved, this procedure provided access to a tricyclic key intermediate which, after mesylation and elimination, was transformed into (-)-huperzine A.

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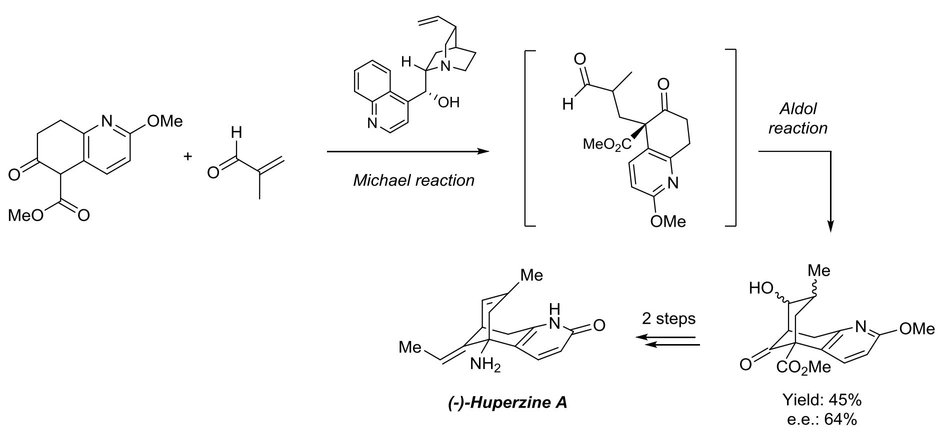
[15] Kaneko, S.; Yoshino, T.; Katoh, T.; Terashima, S. *Tetrahedron*, **1998**, *54*, 5471.



Scheme 4.5. Cinchonidine alkaloid promoted Michael/aldol reaction.

Since this initial work, different examples of BA-BB catalyzed enantioselective domino Michael/aldol reactions have been reported, most of them relying on the use of catalysts that can be considered as evolutions of those initially reported by Takemoto, Dixon&Connon and Rawal. Generally speaking, the success of most of the domino Michael/aldol reactions relies on the use of substrates containing an additional electrophilic functional group, namely an aldehyde or ketone. Thus, after the initial conjugate addition, the generated enolate reacts with the carbonyl group which is located in a distance that allows the intramolecular cyclization event. In this sense, two different approaches can be followed based on the presence of the additional carbonyl group either in the pro-nucleophile or in the Michael acceptor (Figure 4.5).

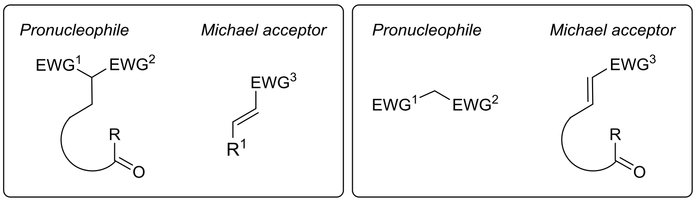
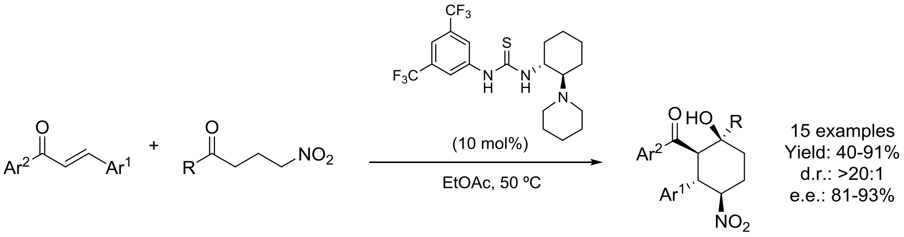


Figure 4.5. Contemplated approaches for domino Michael/aldol reactions.

Regarding the first case, nitroketones can be considered one of the most employed pro-nucleophiles with this purpose. In an example reported by Li *et al.* highly functionalized cyclohexanes were synthesized by the reaction of γ-nitroketones with enones under chiral bifunctional BA-BB catalysis. In this work, a cyclohexanediamine-derived thiourea was found to provide the best results in terms of yield and enantioselectivity (Scheme 4.6).[16]



Scheme 4.6. Enantioselective Michael/aldol reaction developed by Li.

This approach has also been employed for the enantioselective synthesis of spirocyclic compounds, which required the use of substrates containing an exocyclic alkene as Michael acceptor. Examples reported by Kanger[17] and Chen,[18] made use of nitro ketones as pro-nucleophiles in enantioselective Michael/aldol reactions with alkylidene oxindoles and 2-arylidene-1,3-indanediones respectively (Scheme 4.7). In the example developed by Kanger *et al.* authors referred a significant influence of the ester moiety, observing no reaction when methyl or ethyl esters were replaced by phenyl, cyano or *p*-nitrophenyl groups. While in the previous example, quinine-derived thiourea rendered best results in terms of enantioselectivity, in the work reported by Chen, the related quinine-derived squaramide afforded the best results. This effect was attributed to the hydrogen bond interactions established between the N-H groups of the squaramide and the Michael acceptor, while the nitroalkane is activated by the tertiary amine.

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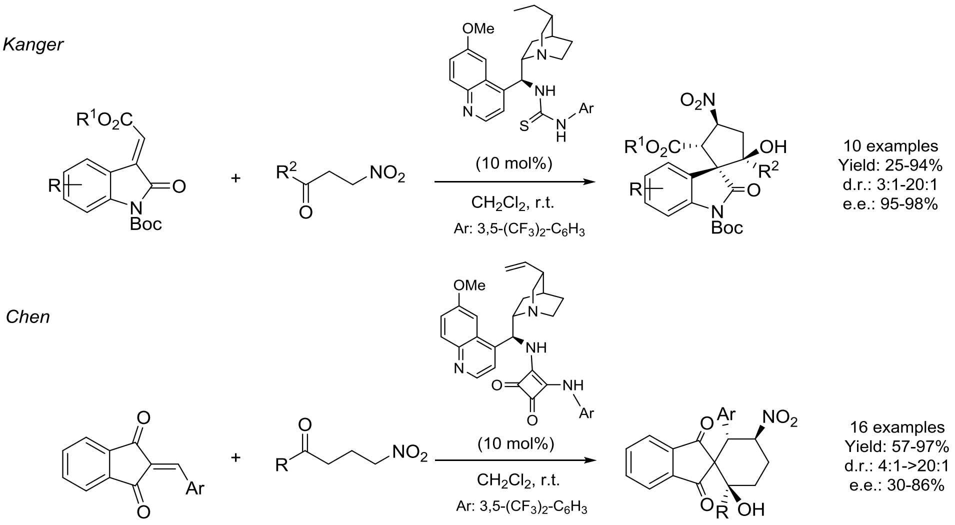
[16] Yu, L.; Yang, Z.; Peng, J.; Li, P. *Eur. J. Org. Chem.* **2016**, 535.

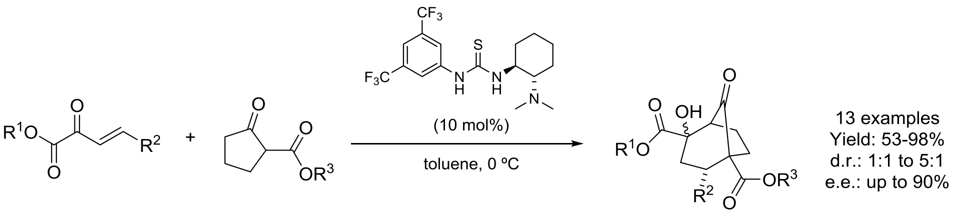
[17] Noole, A.; Ilmarinen, K.; Järving, I.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2013**, *78*, 8117.

[18] Amireddy, M.; Chen, K. *Tetrahedron*, **2015**, *71*, 8003.



Scheme 4.7. Synthesis of spiro compounds through Michael/aldol reactions.

In 2014 Alexakis and coworkers reported the enantioselective construction of bicyclo[3.2.1]octanes by reaction of β,γ-unsaturated 1,2-ketoesters and cyclic 1,3-ketoesters.[19] In this example, the substrates were not able to undergo intramolecular reaction between the enolate generated as consequence of the initial conjugate addition and the ketone moiety. Therefore, the open chain intermediate underwent a deprotonation at the α position of the cyclopentanone, subsequently proceeding to react via intramolecular aldol reaction. The use of a chiral cyclohexanediamine-derived thiourea allowed the authors to control the formation of four stereogenic centers in a highly efficient domino reaction.



Scheme 4.8. Enantioselective Michael/aldol reaction reported by Alexakis.

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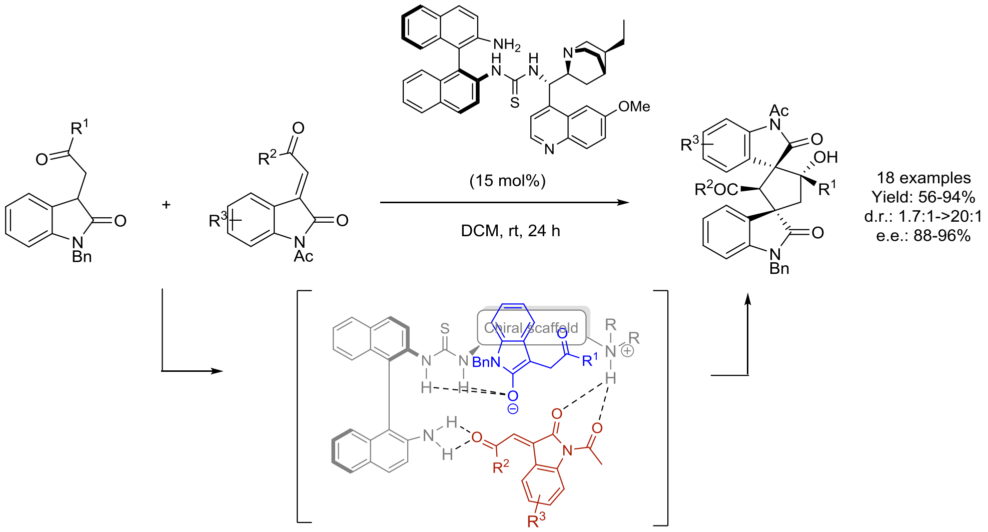
[19] Lefranc, A.; Gremaud, L.; Alexakis, A. *Org. Lett.* **2014**, *16*, 5242.

Although the most commonly employed catalysts are related to those reported by Takemoto, Dixon&Connon and Rawal, enantioselective examples involving other type of bifunctional catalysts have also been reported. In 2011, Barbas III designed a novel bifunctional organocatalyst derived from natural cinchona alkaloids which simultaneously contained a binaphthyl primary amine, a thiourea and a tertiary amine in its structure.[20] Authors proposed a dual activation mode, in which, once deprotonated, the oxindole is activated by the thiourea by multiple hydrogen bonds, while the methyleneindolinone interacts simultaneously either with the primary amine and the protonated tertiary amine. This catalyst design allowed them to access bispirooxindole derivatives in a domino Michael/aldol reaction controlling the generation of four stereogenic centers in a single step.



Scheme 4.9. Domino Michael/aldol reaction developed by Barbas III.

In addition to the abovementioned examples, the use of nitroalkenes as initial Michael acceptors has allowed the development of closely related domino Michael/Henry reactions. In this context, examples involving pro-nucleophiles which contain an additional carbonyl moiety are commonly found in the literature. For instance, in 2008, Zhong and coworkers reported a highly enantioselective domino Michael/Henry reaction for the construction of functionalized

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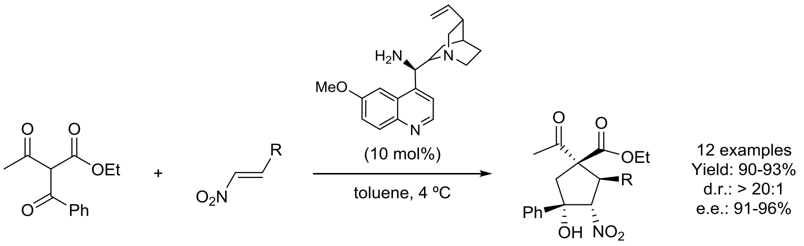
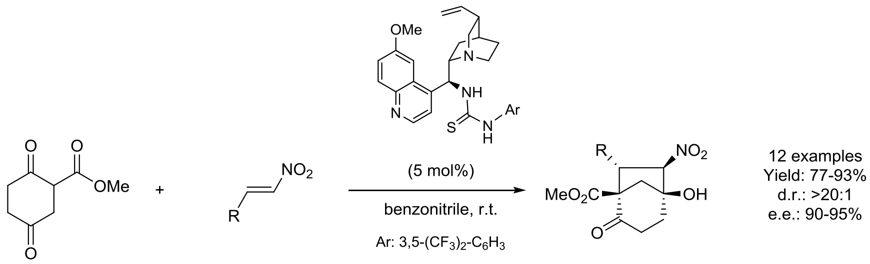
[20] Tan, B.; Candeias, N. R.; Barbas III, C. F. *Nature Chem.* **2011**, *3*, 473.

cyclopentanes under bifunctional BA-BB catalysis.[21] In this work, authors employed a cinchona alkaloid derived catalyst containing a primary amine, which instead of forming the corresponding enamine intermediate, was suggested to interact with the nitro group by hydrogen bond interactions.



Scheme 4.10. Domino Michael/Henry reaction developed by Zhong.

A related example was developed by same authors for the construction of bicyclo[3.2.1]octane scaffolds.[22] In this work, quinine derived thiourea was employed in order to control the enantioselective formation of four stereocenters in a domino Michael/Henry process between cyclic 1,3-ketoesters and nitro alkenes.



Scheme 4.11. Domino Michael/Henry reaction for the enantioselective synthesis of bicyclo[3.2.1]octane.

In an analogous way, 1,2-dicarbonyl compounds have also been used as pro-nucleophiles in domino Michael/Henry reactions under BA-BB catalysis. In this context, in 2010, Rueping[23] and Zhao[24] independently reported the enantioselective synthesis of bicyclo[3.2.1]octanones through a domino Michael/Henry reaction. Despite both works involved the use of chiral

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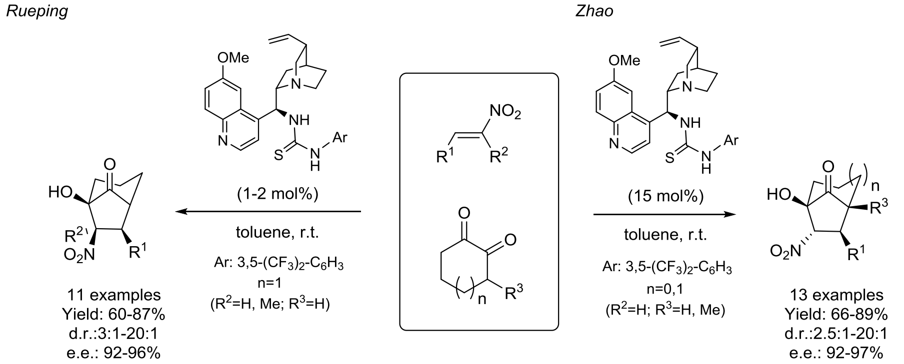
[21] Tan, B.; Chua, J.; Zeng, X.; Lu, M.; Zhong, G. *Org. Lett.* **2008**, *10*, 3489.

[22] Tan, B.; Lu, Y.; Zeng, X.; Chua, P. J.; Zhong, G. *Org. Lett.* **2010**, *12*, 2682.

[23] Rueping, M.; Kuenkel, A.; Fröhlich, R. *Chem. Eur. J.* **2010**, *16*, 4173.

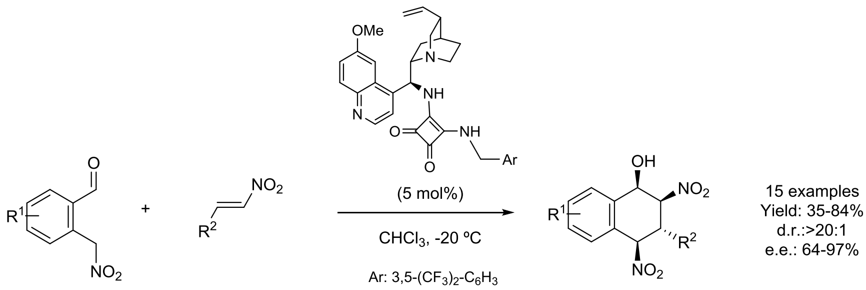
[24] Ding, D.; Zhao, C.-G.; Arman, H. *Tetrahedron*, **2010**, *66*, 4423.

thioureas derived from natural alkaloids, the example reported by Rueping was limited to cyclohexane-1,2-dione as substrate, while Zhao's work broadened the applicability of this reaction to a variety of substituted cyclic 1,2-diketones of different size (Scheme 4.12).



Scheme 4.12. Enantioselective domino Michael/Henry reactions developed by Rueping and Zhao.

Examples involving nitroalkanes as pro-nucleophiles can also be found in the literature. For instance, in 2013 Enders reported a synthetic route to access tetrahydronaphthalenes via an organocatalytic Michael/Henry reaction (Scheme 4.13).[25] In this work, quinine derived squaramide catalyst was employed in order to control the formation of 4 stereocenters in a domino process between 2-(nitromethyl)benzaldehydes and nitrostyrene.



Scheme 4.13. Domino Michael/Henry reaction developed by Enders.

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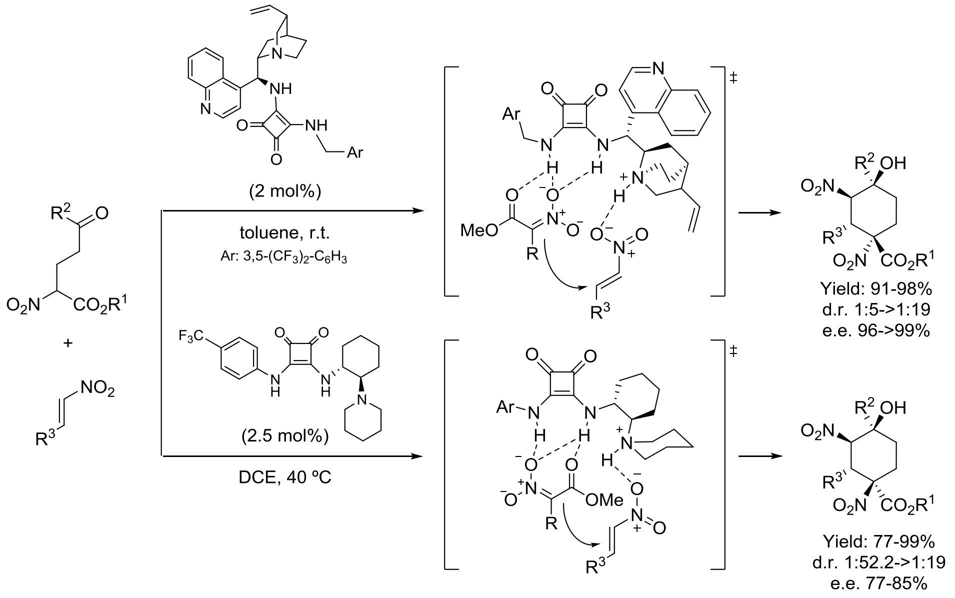
[25] Enders, D.; Hahn, R.; Atodiresei, I. *Adv. Synth. Catal.* **2013**, *355*, 1126.

Additionally, our group developed in 2014 a diastereodivergent strategy to access densely functionalized cyclohexanes employing bifunctional squaramides as organocatalysts.[26] The developed methodology provided access to diasteromeric cyclohexanes in excellent yields and high enantioselectivity (Scheme 4.14). The achieved diastereoselection was suggested to arise from the relative orientation of the nitroacetate enolate and the nitroalkene, which was affected by the structure of the catalyst that interacts with the substrates in a bifunctional manner. While cyclohexanediamine derived squaramide catalyst favored an orientation in which bulkier methoxycarbonyl group is located far from aryl group in order to avoid steric crowding, natural alkaloid derived squaramide favored opposite orientation, which led to the observed diastereoselection.



Scheme 4.14. Diastereodivergent synthesis of cyclohexanes by domino Michael/Henry reaction.

On the other hand, as it was mentioned at the beginning, the alternative approach to domino Michael/aldol and Michael/Henry reactions would involve the use of Michael acceptors containing the additional carbonyl groups. Although these strategies cannot be considered as common as previously reported ones, some examples can also be found in the literature. In this

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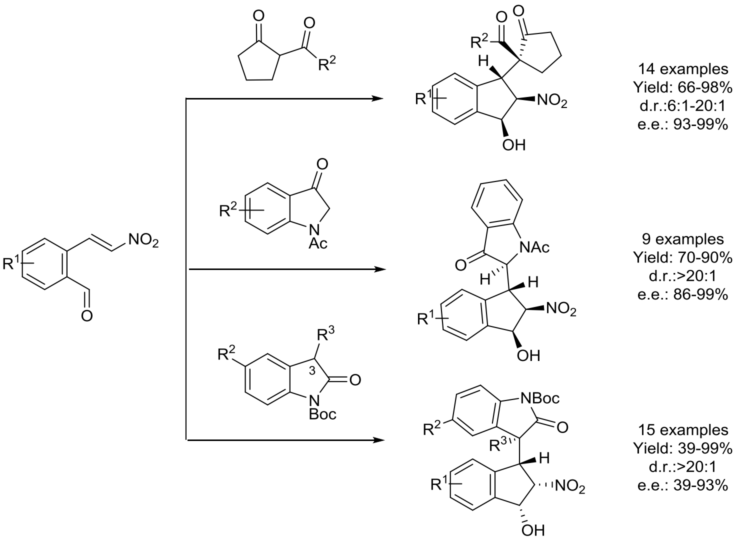
[26] Martínez, J. I.; Villar, L.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Adv. Synth. Catal.* **2014**, *356*, 3627.

sense, Enders and coworkers have reported in the last years several examples regarding the synthesis of highly functionalized indanes through domino Michael/Henry reactions between nitrovinylbenzaldehydes and different pro-nucleophiles, such as 1,3-dicarbonyl compounds,[27] indolin-3-ones[28] and oxindoles.[29] In the case of oxindoles, the presence of an aryl group at C-3 in the oxindole moiety was found to be crucial for the outcome of the reaction, observing an important drop in yield and enantioselectivity when methyl or unsubstituted substrates were employed. This fact was attributed to the stabilization of the formed carbanion at C-3 due to the aromatic groups.



Scheme 4.15. Synthesis of functionalized indanes through domino Michael/Henry reaction under bifunctional BA-BB catalysis.

It should be mentioned that apart from the abovementioned examples, bifunctional BA-BB catalysts have also been employed in enantioselective oxa-, aza- and sulfa- variant of domino Michael/aldol and Michael/Henry reactions.[30]

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[27] Loh, C. C. J.; Chauhan, P.; Hack, D.; Lehmann, C.; Enders, D. *Adv. Syth. Catal.* **2014**, *356*, 3181.

[28] Mahajan, S.; Chauhan, P.; Loh, C. C. J.; Uzungelis, S.; Raabe, G.; Enders, D. *Synthesis*, **2015**, *47*, 1024.

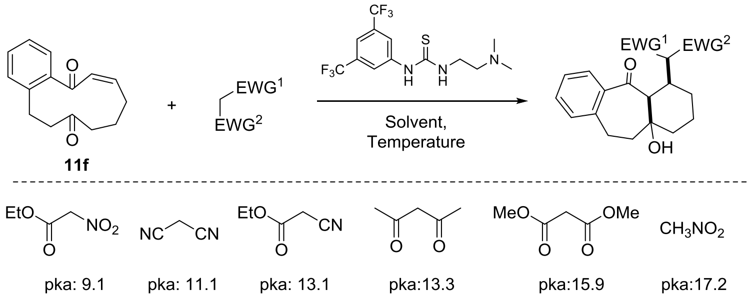
[29] Loh, C. C. J.; Hack, D.; Enders, D. *Chem. Commun.* **2013**, *49*, 10230.

[30] (a) Mahajan, S.; Chauhan, P.; Blümel, M.; Puttreddy, R.; Rissanen, K.; Raabe, G.; Enders, D. *Synthesis*, **2016**, *48*, 1131. (b) Zhu, Y.; Dong, Z.; Cheng, X.; Zhong, X.; Liu, X.; Lin, L.; Shen, Z.; Yang, P.; Li, Y.; Wang, H.; Yan, W.; Wang, K.; Wang, R. *Org. Lett.* **2016**, *18*, 3546. (c) Zhao, B.-L.; Du, D.-M. *Asian J. Org. Chem.* **2015**, *4*, 778. (d)

2. SPECIFIC OBJECTIVES AND WORK PLAN

The literature revision presented in the previous section has demonstrated the applicability of Michael initiated domino reactions for the enantioselective synthesis of complex structures. Although important efforts have been directed to the development of novel reactions, either in an intramolecular and intermolecular way, it has not been reported any enantioselective example of Michael initiated domino reaction performed in a transannular fashion. In this sense, the objective of this work is to **develop an organocatalyzed enantioselective domino Michael/transannular aldol reaction under Brønsted acid- Brønsted base catalysis.** In order to accomplish this objective, the following work plan was stated:

- *Proof of concept:* Analogously to previous sections, we will start this research by studying the viability of the envisioned reaction. In this sense, the medium-size keto-enone **11f** previously employed in Chapter 2, will be used as model substrate towards pro-nucleophiles of different acidity,[31] such as nitroacetates, 1,3-dicarbonylic compounds (including malonates and β-ketoesters) and nitroalkanes, among others. Preliminary reactions will be carried out employing an achiral bifunctional Brønsted acid-Brønsted base catalyst in order to test its capability to trigger the domino process.

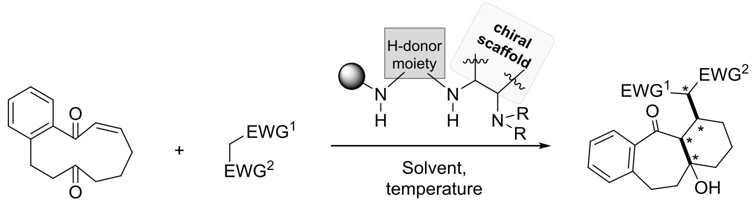


Scheme 4.16. General scheme for the envisioned domino Michael/transannular aldol reaction.

Gui, Y.-G.; Yang, J.; Qi, L.-W.; Wang, X.; Tian, F.; Li, X.-N.; Peng, L.; Wang, L.-X. *Org. Biomol. Chem.* **2015**, *13*, 6371. (e) Zhao, B.-L.; Liu, L.; Du, D.-M. *Eur. J. Org. Chem.* **2014**, 7850. (f) Su, Y.; Ling, J.-B.; Zhang, S.; Xu, P.-F. *J. Org. Chem.* **2013**, *78*, 11053. (g) Ling, J.-B.; Su, Y.; Zhu, H.-L.; Wang, G.-Y.; Xu, P.-F. *Org. Lett.* **2012**, *14*, 1090. (h) Dong, X.-Q.; Fang, X.; Tao, H.-Y.; Zhou, X.; Wang, C.-J. *Chem. Commun.* **2012**, *48*, 7238. (i) Duan, S.-W.; Li, Y.; Liu, Y.-Y.; Zou, Y.-Q.; Shi, D.-Q.; Xiao, W.-J. *Chem. Commun.* **2012**, *48*, 5160. (j) Gao, Y.; Ren, Q.; Wu, H.; Li, M.; Wang, J. *Chem. Commun.* **2010**, *46*, 9232. (k) Zu, L.; Wang, J.; Xie, H.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036. (l) Zu, L.; Xie, H.; Li, H.; Wang, J.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 1882.

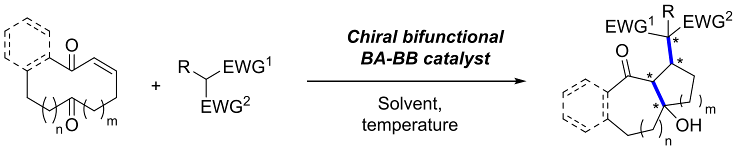
[31] Reported pka values in DMSO. (a) Arnett, E. M.; Maroldo, S. G.; Schilling, S. L.; Harrelson, J. A. *J. Am. Chem. Soc.* **1984**, *106*, 6759. (b) Matthews, W. S.; Bares, J. E.; Bartness, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006.

- *Optimization of the reaction conditions:* Once suitable nucleophiles able to trigger the reaction have been identified, the ability of different chiral bifunctional BA-BB catalysts will be tested in order to obtain the envisioned adducts with the highest possible yield and enantiocontrol. Additionally, experimental parameters, such as solvent, temperature and dilution, will be surveyed in order to achieve the best possible performance.



Scheme 4.17. Screening of experimental conditions.

- *Scope of the reaction:* Finally, the scope and limitations of the studied reaction will be evaluated. The possibility of using different pronucleophiles will be surveyed, as well as the variability offered by the keto-enone substrate in order to access bicyclic scaffolds of different sizes and functionalities.

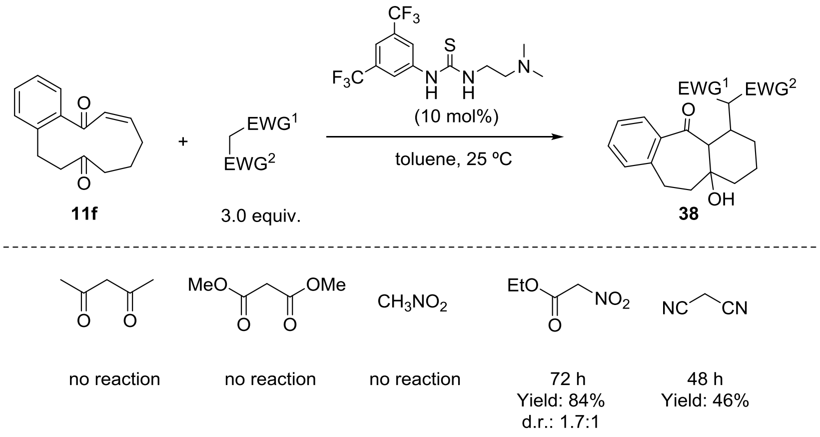


Scheme 4.18. Scope and limitations of the reaction.

3. RESULTS AND DISCUSSION

3.1. Proof of concept

As previously stated, the initial trials were directed to evaluate the capability of different pro-nucleophiles to undergo the projected domino 1,4-addition/transannular aldol reaction employing the achiral *N*,*N*-dimethyl thiourea shown in Scheme 4.19 as a bifunctional Brønsted acid-Brønsted base model catalyst. Although several of these nucleophiles remained unreactive under the initially tested conditions, when methylnitroacetate was tested, the tricyclic adduct **38a** was obtained in 84% yield. This product was isolated as a mixture of two diastereomers, due to the configurational instability of the nitro-containing stereocenter because of the acidic nature of this proton. Moreover, malononitrile turned out to be able trigger the transannular aldol reaction rendering the corresponding adduct in 46% yield.

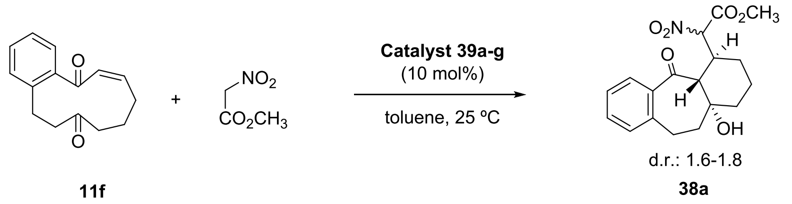


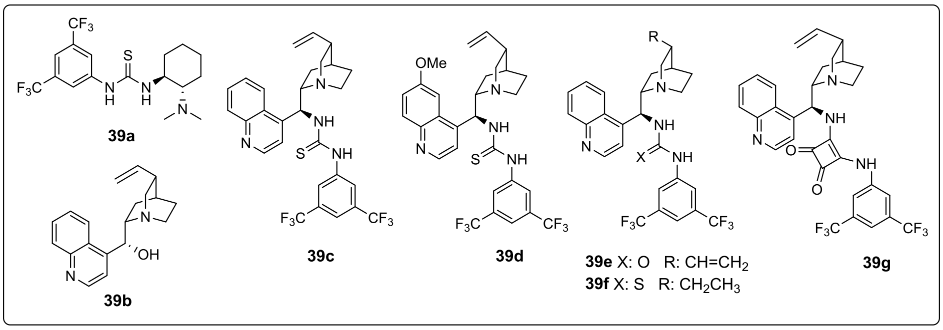
Scheme 4.19. Initial screening of pro-nucleophiles.

3.2. Optimization of experimental conditions

Considering the previous results as proof of the viability of the reaction, we focused our efforts on the development of the enantioselective version of this process using methylnitroacetate as pro-nucleophile. First of all, we decided to test a series of chiral thioureas, which have been successfully employed in enantioselective conjugate additions. Preliminary results summarized in Table 4.1 showed that bifunctional thiourea **39a**, initially reported by Takemoto,[8] was able to promote the reaction yielding the tricyclic product **38a** in excellent 90% yield and with promising enantiomeric excess (entry 1). When natural cinchonidine alkaloid **39b**, known for showing lower hydrogen bond donor tendency was tested, a significant decrease in the rate of the reaction was observed, rendering adduct **38a** in 55% yield after 10 days, but with complete loss of enantioselectivity (entry 2).

Table 4.1. Initial catalyst screening





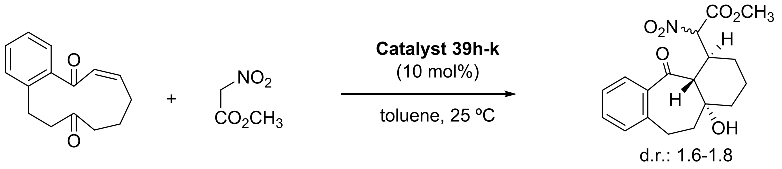
Entry[a]	Catalyst	Time	Yield (%)[b]	e.e. (%)[c]
1	**39a**	48 h	90	70/70
2	**39b**	10 d	55	8/10
3	**39c**	48 h	91	60/64
4	**39d**	48 h	93	68/72
5	**39e**	48 h	86	68/70
6	**39f**	60 h	80	58/60
7	**39g**	48 h	64	80/84

[a] Reactions were performed at 0.15 mmol scale of substrate, employing 10 mol% of catalyst, 3.0 equiv. of pronucleophile in toluene (0.25 mmol/mL). [b] Yields refer to isolated pure product **38a**. [c] Calculated by HPLC on chiral stationary phase.

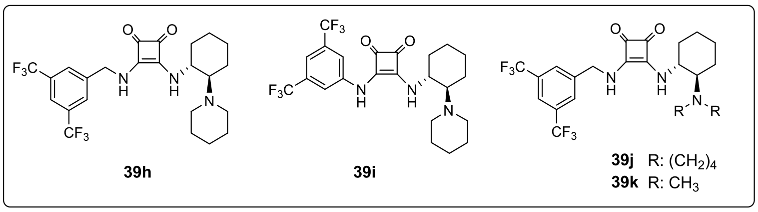
As previous tests suggested a key role played by the thiourea moiety in inducing enantiocontrol, thioureas derived from cinchonidine (**39c**) and quinine (**39d**) alkaloids were tested. Both catalysts were able to promote the reaction affording product **38a** in excellent yield and high enantioselectivity (Table 4.1 entries 3 and 4). In the same way, the analogous urea (**39e**) and hydrogenated thiourea (**39f**) catalysts derived from cinchonidine were also tested. In all the cases, formation of product **38a** was observed, although the results were inferior to those previously obtained either in yield and e.e (entries 5 and 6). On the other hand, modifying the hydrogen bond donor moiety of the catalyst from thiourea to squaramide in catalyst **39g** (entries 3 *vs* 7), had a positive influence on the enantiocontrol of the reaction yielding the product with the highest enantiomeric excess until this point (entry 7).

These preliminary results prompted us to synthesize a series of bifunctional squaramide catalysts (**39h-k**) to evaluate their performance in this reaction by modifying either the N-substituent of the squaramide or the N-substituent of the tethered amine site. As it can be inferred from results summarized in Table 4.2, benzylamine-derived squaramide **39h** turned out to be more efficient compared to aniline analogous one **39i** (entries 1 *vs* 2), allowing full consumption of the starting material in less than 48 h. Finally, the influence of the substituents in the tertiary amine was evaluated by surveying *N,N*-dimethyl and pyrrolidine-derived catalysts **39j** and **39k** (entries 3 and 4). Although both provided adduct **38a** in high yield and e.e. a slight decrease in enantioselectivity was observed compared to analogous catalyst **39h**. As a consequence, catalyst **39h**, which contains a piperidine core in its structure remained as the best catalyst as it provided the best results in terms of yield and enantiomeric excess.

Table 4.2. Catalyst screening.[a]



11f **38a**

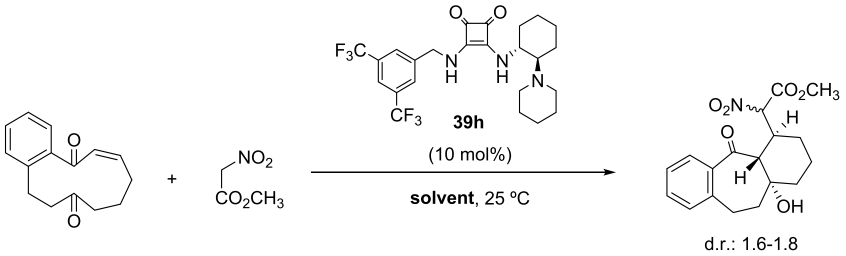


Entry[a]	Catalyst	Time	Yield (%)[b]	e.e. (%)[c]
1	**39h**	40 h	94	88/90
2	**39i**	5 d	70	82/82
3	**39j**	30 h	92	84/84
4	**39k**	48 h	99	78/78

[a] Reactions were performed at 0.15 mmol scale of substrate, employing 10 mol% of catalyst, 3.0 equiv. of pronucleophile in toluene (0.25 mmol/mL). [b] Yields refer to isolated pure product **38a**. [c] Calculated by HPLC on chiral stationary phase.

Next we moved to evaluate the influence of the solvent in the outcome of the reaction. As it is illustrated in Table 4.3, reaction proceeded in a similar way in CH_2Cl_2 (entry 2) and THF (entry 3), achieving adduct **38a** in excellent e.e., albeit a slight decrease in the isolated yield was noticed. Additionally, a drop in the enantiomeric excess was observed when a polar protic solvent like ethanol was employed (entry 4). This negative influence in the enantiocontrol of the process was specially remarkable when *N*,*N*-dimethylformamide was tested (entry 5). On the other hand, other non-polar solvents as xylenes and benzene were tested (entries 6-8). Similar results were obtained in all the cases regarding the yield and e.e., without any improvement compared to results achieved with toluene.

Table 4.3. Solvent screening.



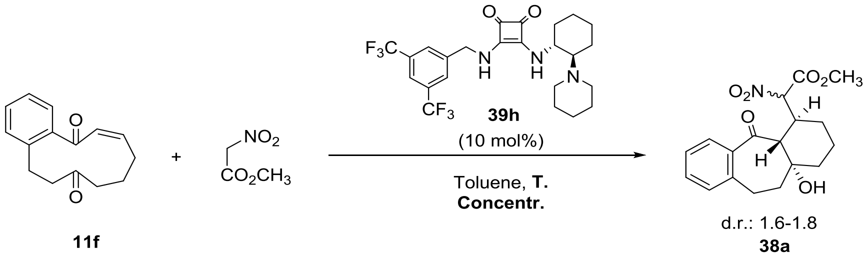
11f **38a**

Entry[a]	Solvent	Time (h)	Yield (%)[b]	e.e. (%)[c]
1	**toluene**	**40**	**94**	**88/90**
2	CH_2Cl_2	48	87	86/90
3	THF	48	86	86/90
4	EtOH	48	88	77/70
5	DMF	48	68	29/34
6	m-xylene	24	95	88/88
7	o-xylene	24	96	88/88
8	benzene	24	98	86/86

[a]Reactions were performed at 0.15 mmol scale of substrate, employing 10 mol% of catalyst, 3.0 equiv. of pronucleophile (0.25 mmol/mL). [b]Yields refer to isolated pure product **38a**. [c]Calculated by HPLC on chiral stationary phase.

At this stage, the effect of the temperature in the outcome of the reaction was evaluated (Table 4.4). Performing the reaction at lower temperatures did not have any positive influence in the enantiocontrol of the reaction; in fact, a significant decrease in the reaction rate was observed, requiring significantly longer reaction times to achieve full consumption of the starting material (entries 2 and 3). Increasing temperature to 40 °C (entry 4) did not either provide better results than those achieved at room temperature, observing a slight drop in e.e. Finally, when more diluted conditions were employed, a small improvement in the enantiocontrol of the reaction was achieved (entry 5). It should be mentioned that reaction was also performed employing 5 mol% of catalyst instead of 10 mol%, obtaining similar results in terms of yield and enantiomeric excess (95% yield, 90% e.e.) although the time required to observe full consumption of the starting materials was doubled (4 days).

Table 4.4. Screening of experimental parameters.[a]



Entry	T. (° C)	Concent. (M)	Time	Yield (%)	e.e. (%)
1	25	1.0	40 h	94	88/90
2	0	1.0	7 d	90	86/86
3	10	1.0	6 d	99	88/86
4	40	1.0	10 h	90	86/84
5	25	0.25	48 h	99	90/90

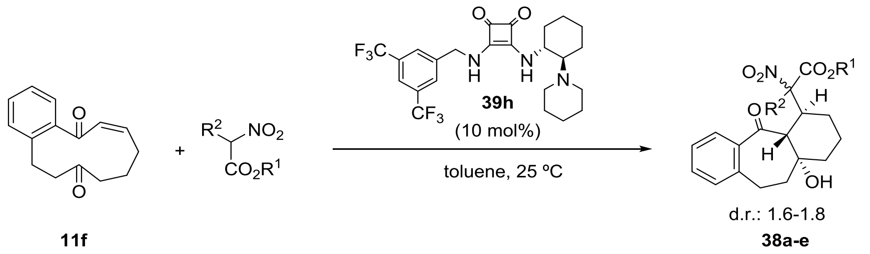
[a]Reactions were performed at 0.15 mmol scale of substrate, employing 10 mol% of catalyst, 3.0 equiv. of pronucleophile in toluene (0.25 mmol/mL). [b]Yields refer to isolated pure product **38a**. [c]Calculated by HPLC on chiral stationary phase.

The study of all these parameters led us to select 10 mol% of catalyst **39h** in toluene at room temperature as the best conditions to promote the domino conjugate addition/transannular aldol reaction with methylnitroacetate. Subsequently and following the stated work plan, the scope and limitations of this methodology were studied.

3.3. Scope of the reaction

Once the optimal experimental conditions were defined, we continued with the study of the scope and limitations of this process. First of all, the influence of modifying the alkyloxy group on the nitroacetate reagent was evaluated. As it can be observed in Table 4.5, moving from methyl to ethyl implied a slight decrease in the reactivity (entries 1 and 2), being necessary longer reaction times to achieve full consumption of the starting materials. This effect was more pronounced for bulkier *tert*-butyl group (entry 3) although adduct **38c** could be isolated in 86% yield after 7 days. In all the cases, the achieved enantiomeric excess remained excellent, regardless the bulkiness of the alkyl group. In the same way, reaction proceeded satisfactorily when benzyl nitroacetate was employed (entry 4), although the isolated yield was slightly inferior to those obtained for previous substrates.[32] In addition, we also evaluated the possibility of using an α-substituted nitroacetate as potential pro-nucleophile which would led to a quaternary sterocenter. However, when ethyl 2-nitropropionate was tested under optimized conditions, a complete suppression of the reactivity was observed (entry 5).

Table 4.5. Study of the effect of the alkyl moiety.



Entry[a]	Product	R^1	R^2	Time	Yield (%)[b]	e.e. (%)[c]
1	**38a**	Me	H	40 h	99	90/90
2	**38b**	Et	H	65 h	91	92/92
3	**38c**	^{t}Bu	H	7 d	86	90/90
4	**38d**	Bn	H	65 h	74	88/88
5	**38e**	Et	Me	72 h	< 5	n.d.

[a]Reactions performed at 0.15 mmol scale of substrate, employing 10 mol% of catalyst, 3.0 equiv. of pronucleophile in toluene (0.25 mmol/mL) at r.t. [b]Yields refer to isolated pure products **38**. [c]Calculated by HPLC on chiral stationary phase.

Regarding the substitution in the aromatic ring of the keto-enone substrate, electron-donating groups at C-1 and C-3 of the keto-enone were well tolerated, allowing the isolation of the corresponding adducts (**38f-h**) in nearly quantitative yields and with excellent enantioselectivities (Scheme 4.20). On the other hand, electron-withdrawing groups as bromine and fluorine, were also tolerated, rendering adducts **38i** and **38j** quantitatively and with excellent enantiomeric excess.

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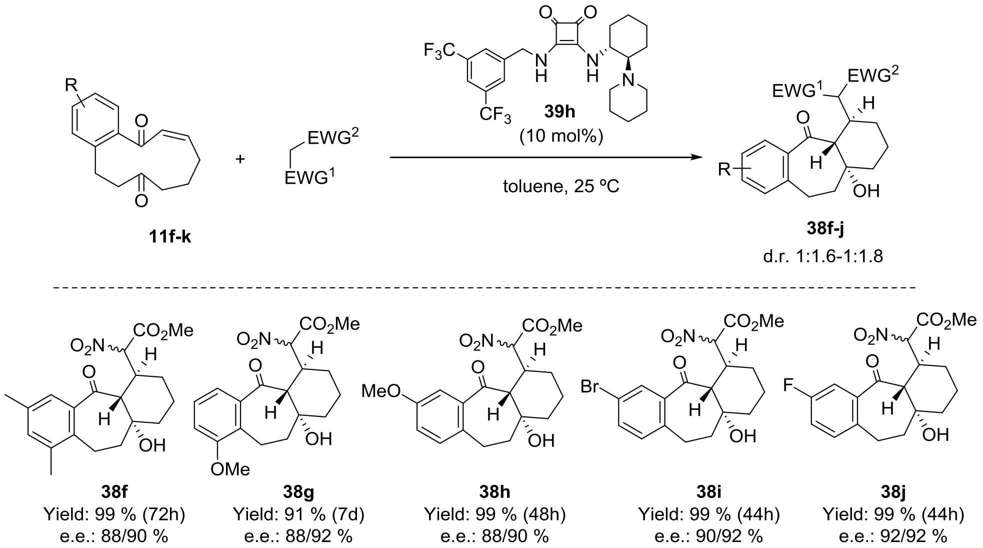
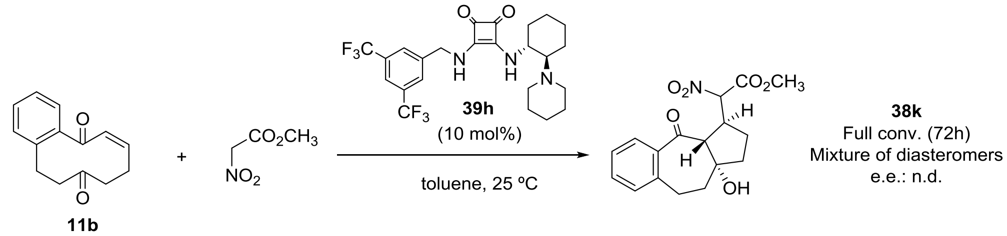
[32] This lack of influence of ester alkyl group is in agreement with previous results obtained by Yan and coworkers for nitroacetate addition to β,γ-unsaturated α-ketoesters for bifunctional thiourea catalysts: Lu, R.-J.; Wei, W.-T.; Wang, J.-J.; Nie, S.-Z.; Zhang, X.-J.; Yan, M. *Tetrahedron*, **2012**, *68*, 9397.



Scheme 4.20. Scope of benzo-fused keto-enones.[33]

It should be mentioned that this methodology could be also applied to access bicyclo[5.3.0]decane scaffolds. In this way, when substrate **11b** was subjected to optimized reaction conditions full conversion of the starting material was observed in 72 hours. However, NMR analysis of crude reaction mixture showed a complex mixture of more than 4 diasteromers attributed to an inefficient diastereocontrol of the process (Scheme 4.21).



Scheme 4.21. Construction of bicyclo[5.3.0]decane scaffold.

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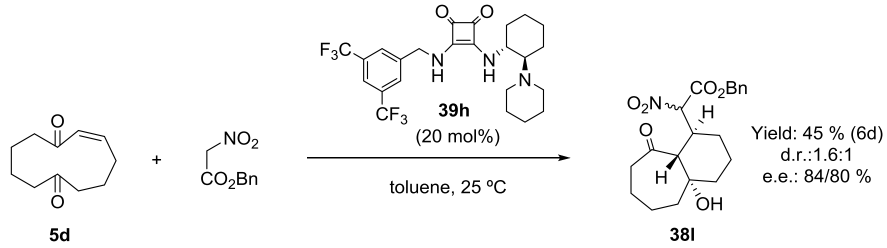
[33] [a]Reactions were performed at 0.15 mmol scale of substrate, employing 10 mol% of catalyst, 3.0 equiv. of pronucleophile in toluene (0.25 mmol/mL) at r.t. [b]Yields refer to isolated pure products **38**. [c]Calculated by HPLC on chiral stationary phase.

On the other hand, when 11-membered keto-enone **5d**, which does not contain a conjugated aromatic ring, was subjected to optimized reaction conditions, the corresponding adduct **38l** was isolated, albeit the reactivity of this substrate was significantly lower compared to previously tested analogs, being necessary to use 20 mol% of catalyst. In this way, after 6 days, bicyclic adduct **38l** was isolated in moderate yield and high enantiomeric excess (Scheme 4.22).



Scheme 4.22. Organocatalytic reaction to access adduct **38l**.

Finally, we decided to survey the performance of other active methylene compounds as pro-nucleophiles under the optimized reaction conditions (Scheme 4.23). Unfortunately, when 1,3-dicarbonyl compounds as malonates or β-ketoesters, were evaluated, they did not led to the formation of the desired products **38m-n** as it had happened in the initial studies (see Scheme 4.19). On the other hand, when malononitrile was subjected to the optimized conditions, adduct **38o** was isolated in 79% yield as a single diastereomer. The enantiomeric excess of this product was significantly lower, a fact that could be attributed to the absence of nitro functionality, which could play a crucial role in the coordination of the catalyst.[34] In the same way, nitromethyl phenyl sulfone exhibited the desired reactivity under optimized conditions, yielding to a 50% conversion of the starting material by ^{1}H NMR after 48h. However, adduct **38p** turned out to be extremely unstable and difficult to isolate, precluding further investigations.

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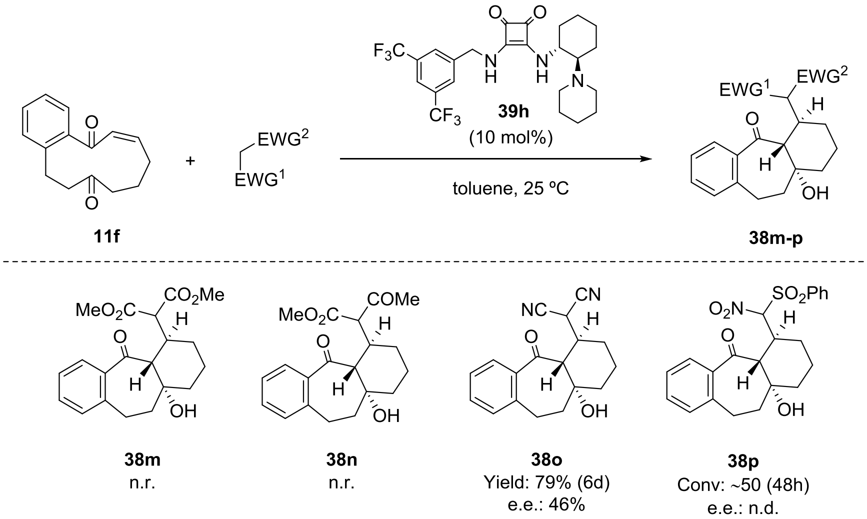
[34] For further discussion on reaction mechanism see Section 3.5.



11f **38m-p**

38m n.r.

38n n.r.

38o Yield: 79% (6d) e.e.: 46%

38p Conv: ~50 (48h) e.e.: n.d.

Scheme 4.23. Scope of pro-nucleophiles.[35]

3.4. Transformations of the adducts

Having established an efficient methodology to perform the enantioselective domino Michael/transannular aldol reaction, we focused our efforts on the transformation of the obtained adducts. For this purpose, compound **38a** was selected as model substrate, which was initially subjected to different reagents in order to obtain the decarboxylated product.

First of all, our efforts were directed to perform a decarboxylation process through initial ester hydrolysis followed by thermal treatment. In this way and after surveying different inorganic bases, such as Na_2CO_3, K_2CO_3, NaOH or LiOH, as well as several solvents and temperatures, LiOH in dioxane at 80 °C was selected as the most efficient conditions, allowing the isolation of adduct **40a** in 54% yield. This methodology could be satisfactorily applied to

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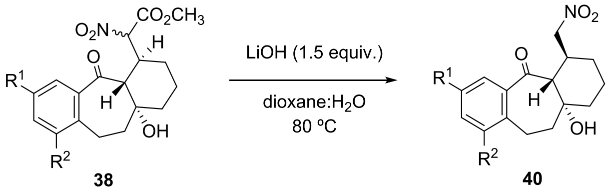
[35] [a]Reactions were performed at 0.15 mmol scale of substrate, employing 10 mol% of catalyst, 3.0 equiv. of pronucleophile in toluene (0.25 mmol/mL) at r.t. [b]Yields refer to isolated pure products **38**. [c]Calculated by HPLC on chiral stationary phase.

adducts **38f**-**j** obtaining the corresponding decarboxylated products in moderate yields (Table 4.6 entries 2 to 6).

Table 4.6. Decarboxylation of adducts **38**.



Entry	Substrate	R¹	R²	Product	Yield (%)
1	**38a**	H	H	**40a**	54
2	**38f**	CH_3	CH_3	**40f**	66
3	**38g**	H	OCH_3	**40g**	48
4	**38h**	OCH_3	H	**40h**	50
5	**38i**	Br	H	**40i**	38
6	**38j**	F	H	**40j**	34

At this point, the absolute configuration of all the stereocenters was unambiguously determined by X-ray diffraction analysis on monocrystal for decarboxylated adduct **40i** (Figure 4.6). The absolute stereostructure was presumed to be identical for the rest of the adducts assuming a common mechanistic pathway for all of them.

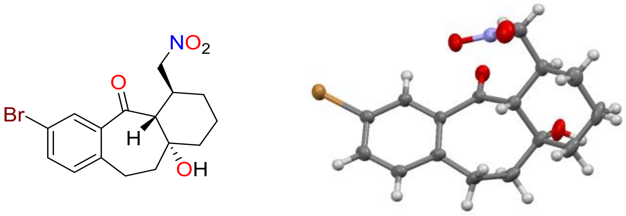
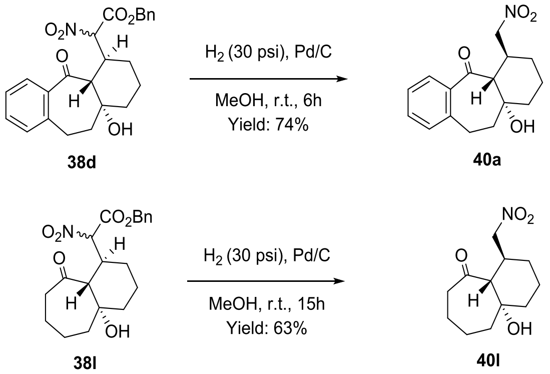


Figure 4.6. X-ray structure for compound **40i**.

In view of the low yields achieved for some of the substrates tested, alternative decarboxylation procedures were surveyed, including the Krapcho decarboxylation, a reaction in which a nucleophilic anion of an alkaline salt allows the decarboxylation of esters by the nucleophilic displacement of the alkyloxy substituent.[36] Several salts, as NaCl, LiCl, LiI and NaBr, have been reported as efficient reagents for this process, in which polar aprotic solvents and high temperatures are required. Unfortunately, although different salts were tested in DMSO, DMF and DMA, neither of them afforded product **40a** in acceptable yields. Even though product formation could be observed by ^{1}H-NMR after few hours, isolated yields remained unsatisfactory due to the formation of undesired products.

It should be mentioned that adduct **40a** could also by obtained by hydrogenolysis of the corresponding benzylic ester **38d** which underwent spontaneous decarboxylation under hydrogenation conditions (Scheme 4.24).[37] In this way, when compound **38d** was exposed to common hydrogenation conditions (H_2, Pd/C, MeOH, r.t.), adduct **40a** could be isolated after 6h in 74% yield as a single product. These reaction conditions were also successfully applied to analogous benzylic adduct **38l** affording decarboxylated product **40l** in 63% yield after 15 hours.



Scheme 4.24. Hydrogenolysis and spontaneous decarboxylation of adducts **38d** and **38l**.

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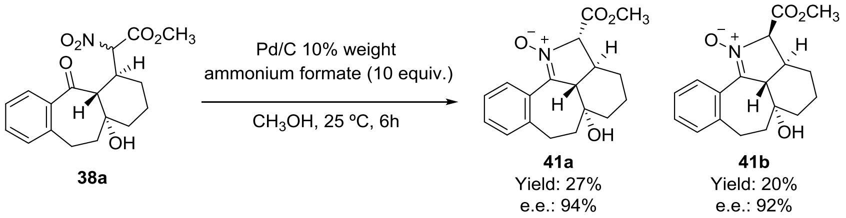
[36] (a) Krapcho, A. P. *Arkivoc* **2007**, (ii), 54. (b) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahnger, E. G. E.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138. (c) Krapcho, A. P. ; Jahnger, E. G. E.; Lovey, A. J. *Tetrahedron Lett.* **1974**, *13*, 1091. (d) Krapcho, A. P.; Glynn, G. A.; Grenon, B. J. *Tetrahedron Lett.* **1967**, *8*, 215. For an example of Krapcho decarboxylation of α-nitroacetates see: Peel, M. R.; Sternbach, D. D.; Johnson, M. R. *J. Org. Chem.* **1991**, *56*, 4990.

[37] For a reported example about in situ decarboxylation of benzyl nitroacetates, see: Ngen, A. T. Y.; Kaur, H.; Hume, P. A.; Furkert, D. P.; Brimble, M. A. *J. Org. Chem.* **2016**, *81*, 7635.

On the other hand, we decided to perform the reduction of the nitro group by the use of ammonium formate and Pd/C.[38] To our delight after 6 hours, nitrones **41a** and **41b** could be isolated separately in 47% overall yield as enantiopure compounds (Scheme 4.25). The formation of these products could be explained by the partial reduction of the nitro moiety to the corresponding hydroxylamine, which undergoes condensation with the carbonyl group. It should be mentioned that despite other reducing conditions were tried, nitrones **41a** and **41b** could not be obtained in higher yields due to the formation of undesired products.



Scheme 4.25. Synthesis of nitrones **41a** and **41b**.

Finally, nitrone **41a** could be crystallized and its structure confirmed, as well as the absolute configuration of the stereocenters, by X-ray analysis.

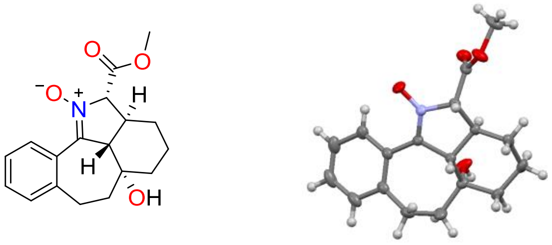


Figure 4.7. X-ray structure for compound **41a**.

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[38] (a) Ram, S.; Ehrenkaufer, R. E. *Synthesis*, **1988**¸ *02*, 91. (b) Ram, S.; Ehrenkaufer, R. E. *Synthesis*, **1986**, *2*, 133. (c) Ram, S.; Ehrenkaufer, R. E. *Tetrahedron Lett.* **1984**, *25*, 3415.

3.5. Mechanistic proposal

There are many examples in the literature in which chiral thiourea and squaramide-derived catalysts have been efficiently employed in conjugate additions between α,β-unsaturated ketones and active methylene compounds. The reaction mechanism of this process has been considered somehow unclear for years, and as consequence it has been subject of deep study.[39]

From a general point of view, two different activation modes have been classically contemplated and supported either by experimental or computational studies (Figure 4.8). Activation *mode A*, based on the model proposed by Takemoto for chiral thiourea catalyzed addition of 1,3-dicarbonyl compounds to nitroalkenes,[8a,40] contemplates electrophile (E) activation by hydrogen bond interactions with the thiourea or squaramide moiety, while pro-nucleophile (Nu-H) is activated by the amine. On the contrary, activation *mode B*, strongly supported by Pápai and coworkers,[41] predicts nucleophile activation by hydrogen bonding with the thiourea/squaramide substructure, while an additional interaction is established between the electrophile and the protonated amine.

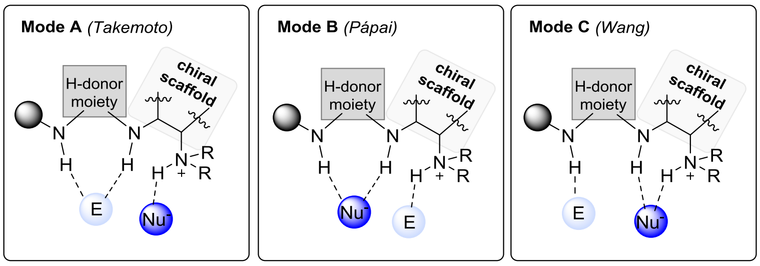

Figure 4.8. General activation modes for thiourea and squaramide catalyzed conjugate additions.

Despite considered somehow unusual, an alternative activation *mode C* was also proposed by Wang and coworkers,[42] in which electrophile interacts with the distal N-H of the thiourea and

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[39] Cheong, P. H.-Y.; Legault, C. Y.; Um, J. M.; Celebi-Ölcüm, N.; Houk, K. N. *Chem. Rev.* **2011**, *11*, 5042.

[40] (a) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 4032. (b) Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413.

[41] Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151.

[42] Zhu, J.-L.; Zhang, Y.; Liu, C.; Zheng, A.-M.; Wang, W. *J. Org. Chem.* **2012**, *77*, 9813.

nucleophile, once deprotonated, is simultaneously activated by the remaining available N-H of the thiourea and the protonated amine.

Recently, a detailed computational study of the conjugate addition of nitroalkanes to α,β-unsaturated ketones has been reported by Grayson.[43] In this work, experimental results obtained by Soós for alkaloid-derived bifunctional-thiourea catalysts[44] and Du for analogous squaramide catalysts,[45] were demonstrated to be in agreement with an activation *mode B*. It should be highlighted that author reached to the same conclusion when extended the computational study to cyclic *cis* enones. Many other independent theoretical studies have supported this activation mechanism for thiourea or squaramide catalyzed conjugate additions of different nucleophiles.[46]

Based on these precedents, we proposed that the domino Michael/transannular aldol reaction starts with the deprotonation of the pro-nucleophile, which once deprotonated interacts with the catalysts as stated by the model proposed by Pápai. Meanwhile the α,β-unsaturated ketone is activated by hydrogen bond interactions with the protonated tertiary amine. At this point, two possibilities can be considered regarding the coordination of the nitronate by the squaramide, which would led to opposite faces of the nitronate being confronted to the *cis*-enone. Note that for both possibilities represented in Figure 4.9 the orientation of the enone has remained unaltered, being the *Si* face of the enone attacked by the nucleophile. Opposite orientation has been omitted as it would imply Michael acceptor located distant to the nucleophile. Previous works developed in our group[47] for related conjugated additions, have suggested that for 1,2-cyclohexanediamine derived squaramide catalysts, nitronate is oriented as shown in Figure 4.9B. In this preferred orientation the bulkier methoxycarbonyl moiety is positioned opposite to the benzyl group at the squaramide, avoiding destabilization due to increasing steric congestion.

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[43] Grayson, M. N.; *J. Org. Chem.* **2017**, *82*, 4396.

[44] Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.

[45] Yang, W.; Du, D.-M. *Org. Lett.* **2010**, *12*, 5450.

[46] For other computational studies supporting activation *mode B*, see: (a) Guo, J.; Wong, M. W. *J. Org. Chem.* **2017**, *82*, 4362. (b) Grayson, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **2016**, *138*, 9041. (c) Manzano, R.; Andrés, J. M.; Álvarez, R.; Muruzábal, M. D.; de Lera, A. R.; Pedrosa, R. *Chem. Eur. J.* **2011**, *17*, 5931. (d) Almasi, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nájera, C. *J. Org. Chem.* **2009**, *74*, 6163. (e) Kótai, B.; Kardos, G.; Hamza, A.; Farkas, V.; Pápai, I.; Soós, T. *Chem. Eur. J.* **2014**, *20*, 5631.

[47] Martínez, J. I.; Villar, L.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Adv. Synth. Catal.* **2014**, *356*, 3627.

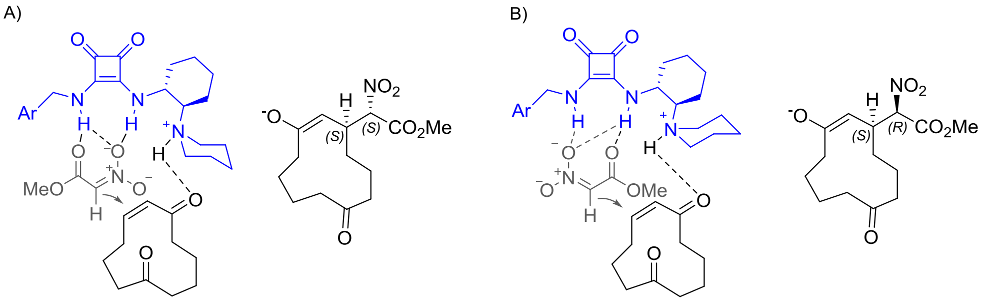

Figure 4.9. Studied scenarios for the reaction.[48]

Considering the initial addition of the nucleophile as the rate limiting step of the process, we proposed that the subsequent formation of the stereocenters is controlled by this first stereocenter formed and governed by the conformational restrictions attached to the cyclic structure.[49] In this way, the enolate intermediate generated as consequence of the initial conjugate addition (Int.I) acquires a less energetic conformation which undergoes the transannular aldol step. The resulting alcoxide, is then protonated affording the product of the reaction (Scheme 4.26). However, it is noteworthy that experimentally observed diastereoselectivity shows a *trans* relative orientation between hydrogen atoms at positions **4** and **4a** in the final product. Considering the initial *cis* configuration of α,β-unsaturated system, two plausible scenarios have been contemplated in order to explain this fact: (a) isomerization of the generated enolate in *Int.I* to afford *Int.II* which exhibits *trans* configuration (either by direct isomerization or by retro-aldol process) and (b) epimerization of the proton at position **4a** under the reaction conditions. Due to the acidic character of hydrogen atom at position **4a**, this last option is considered more reasonable.

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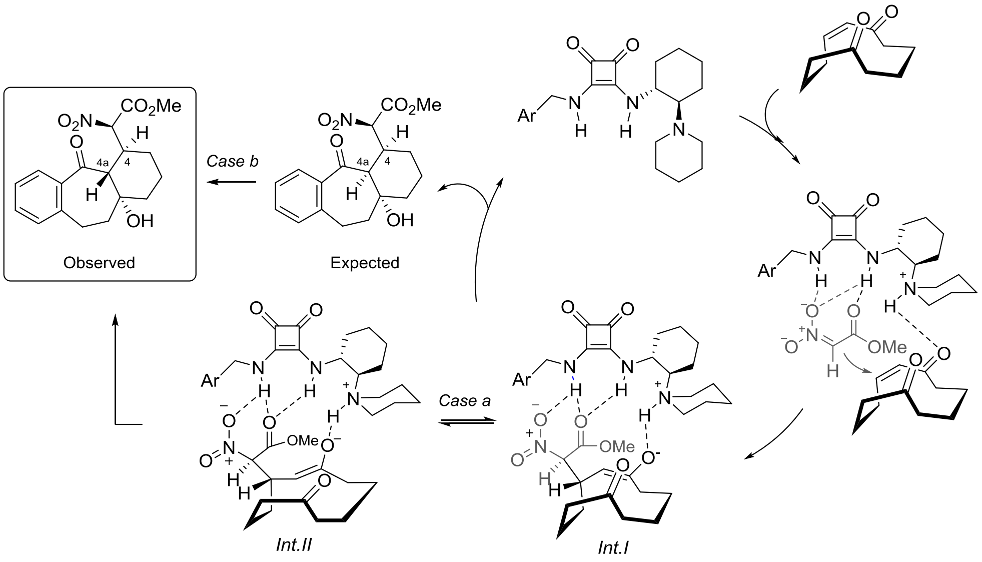
[48] For clarity aromatic ring has been omitted.

[49] For more information regarding conformations in medium and large sized cycles see Chapter 1.



Scheme 4.26. Proposed mechanistic pathway.[50]

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[50] For clarity aromatic ring has been omitted.

4. CONCLUSIONS

In view of the experimental results obtained during the research presented in this chapter, the following conclusions can be drawn:

- It has been probed that cyclic keto-enones are suitable partners for the development of enantioselective Michael initiated transannular aldol reactions employing active methylene compounds as pro-nucleophiles.

- Bifunctional Brønsted acid – Brønsted base catalysts have been employed as efficient catalysts for the reaction between different nitroacetates and medium size cyclic keto-enones.

- Under optimized conditions, cyclohexane derived squaramide **39h** has emerged as the best catalyst for the studied reaction affording the corresponding polycyclic structures in excellent yield and enantioselectivity.

- The developed methodology has demonstrated to be compatible with the presence of electron-donating and electron-withdrawing groups in the aromatic ring conjugated with the enone, albeit high dependence with the nature of the pro-nucleophile has been observed.

5

5

Synthesis of γ-lactams by disulfonimide-catalyzed Mukaiyama-Mannich reaction

1. INTRODUCTION

In the last years chiral disulfonimides (DSI) have emerged as high efficient organocatalysts for a wide variety of enantioselective transformations.[1] Regarding the structure of these catalysts, the BINOL motif is a recurrent substructure as it is considered a privileged scaffold in asymmetric catalysis. The interest of these structures as chiral templates relies on the fact that the catalytic activity can be easily modulated. In this sense, introducing bulkier groups at 3,3' positions increases the steric demand around the active site, while the electronic nature of substituents at those positions affects the acidity of N-H due to the donation or removal of electrons from the extensive π-system. Additionally, the introduction of further substitution in the chiral backbone has been demonstrated to also affect the N-H acidity through resonance contributions.

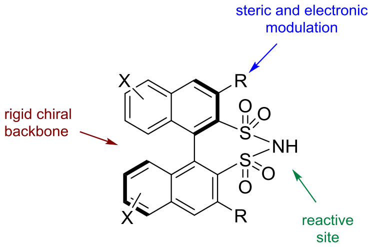

Figure 5.1. General structure of BINOL-derived disulfonimides.

From a general perspective, disulfonimides show a higher acidity of the N-H bond compared to analogous phosphoric acids and *N*-triflyl-phosphoramides (commonly referred as superacids). For instance, it has been determined that for 1,1'-bi-2-naphthyl-derived catalysts, the pK_a of the N-H is around 1.8 for disulfonimide catalyst, compared to a pK_a of 3.4 for O-H in analogous phosphoric acid. This enhancement in acidity has allowed the use of disulfonimides as highly active Brønsted acids,[2] although it is well known that these catalysts can also perform as Lewis acids under specific experimental conditions. In this sense, it has been demonstrated that when

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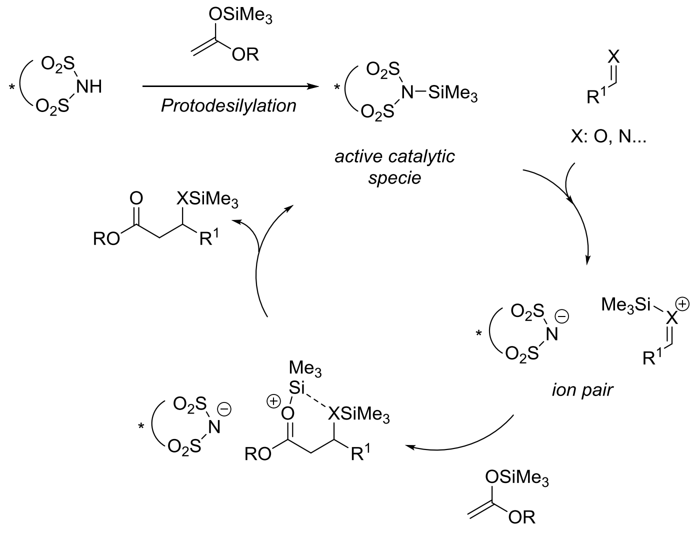
[1] For recent reviews on disulfonimides as catalysts in asymmetric transformations, see: (a) James, T.; Van Gemmeren, M.; List, B. *Chem. Rev.* **2015**, *115*, 9388. (b) Van Gemmeren, M.; Lay, F.; List, B. *Aldrichimica Acta*, **2014**, *47*, 3. (c) Hatano, M.; Ishihara, K. *Asian J. Org. Chem.* **2014**, *3*, 352. (d) Mahlau, M.; List, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 518.

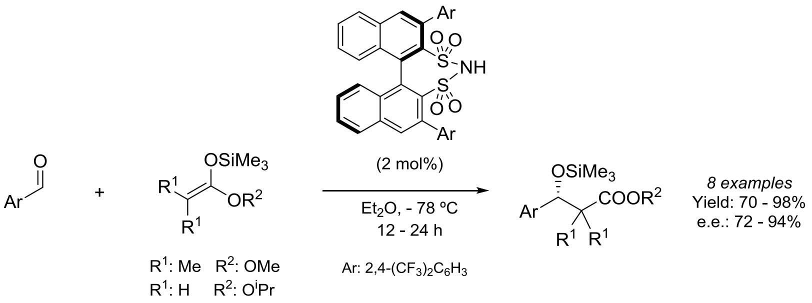
[2] For selected examples about the employment of disulfonimides as Brønsted acidic organocatalysts, see: (a) Galván, A.; González-Pérez, A. B.; Álvarez, R.; de Lera, A. R.; Fañanás, F. J.; Rodríguez, F. *Angew. Chem. Int. Ed.* **2016**, *55*, 3428. (b) Prévost, S.; Dupré, N.; Leutzsch, M.; Wang, Q.; Wakchaure, V.; List, B. *Angew. Chem. Int. Ed.* **2014**, *53*, 8770. (c) Chen, L.; He, H.; Chan, W.; Lee, A. W. M. *J. Org. Chem.* **2011**, *76*, 7141.

exposed to a silyl enol ether as nucleophile, disulfonimides suffer an instantaneous silylation process to afford the active Lewis acid catalyst (Scheme 5.1). Although there is a slight controversy about the exact catalytic mechanism for disulfonimides, the commonly accepted model suggests that after protodesilylation step, the catalyst activates the electrophile towards nucleophilic attack, remaining as a chiral counteranion. Even though initial silylation of the catalyst has been confirmed by NMR-spectroscopy, several experiments have been carried out in order to support this hypothesis. In this sense, preformed silylated catalysts have been tested in model reactions and their catalytic activity has been found to be comparable to *in situ* generated analogous catalysts. Moreover, the addition of Brønsted acid quenchers excluded the possibility that trace amounts of precursor Brønsted acid could be responsible of the catalytic activity, attributing it to the silylated compound.



Scheme 5.1. General catalytic pathway for DSI catalyzed reaction.

Regarding the use of chiral disulfonimides in asymmetric catalytic transformations, the first reports regarding BINOL-derived disulfonimides as Lewis acids date back to 2009. In this field, List and coworkers can be considered one of the major contributors, as they have developed a large number of efficient disulfonimide chiral catalysts. The first example in this area was reported in 2009 by List and it is related to a Mukaiyama aldol reaction between aromatic aldehydes and different silyl ketene acetals (Scheme 5.2).[3] It is remarkable that under optimized conditions, excellent results were achieved in terms of yield and enantioselectivity, allowing to reduce catalyst loading even to 0.1-0.05 mol%.



Scheme 5.2. Pioneering DSI catalyzed enantioselective Mukaiyama aldol reaction.

The excellent results achieved in this initial work, encouraged them to broaden the applicability of these catalytic systems to the vinylogous and bisvinylogous version of this process (Scheme 5.3).[4] After evaluating different parameters, they could conclude that the substituents of the silyl group did not have a strong influence on the reaction outcome, while the bulkiness of the alkoxy substituent of the ester considerably affected the reactivity leading to a significant decrease in yield when bulkier *tert*-butoxy-group containing substrates were tested. In the case of bisvinylogous Mukaiyama aldol reaction, different aromatic aldehydes were successfully employed, affording the corresponding products in excellent yields and e.e. Unfortunately, although structural and electronic variations in the aldehyde moiety were tested, ε/α selectivity remained low for most of the substrates. More recently, in 2016, the same research group reported the catalytic and enantioselective synthesis of allenes by alkynylogous Mukaiyama aldol reaction between aldehydes and alkynyl-substituted ketene acetals (Scheme 5.3 C).[5] In this case, a slight modification of the structure of the catalyst was required in order to afford the desired products with high enantiocontrol.

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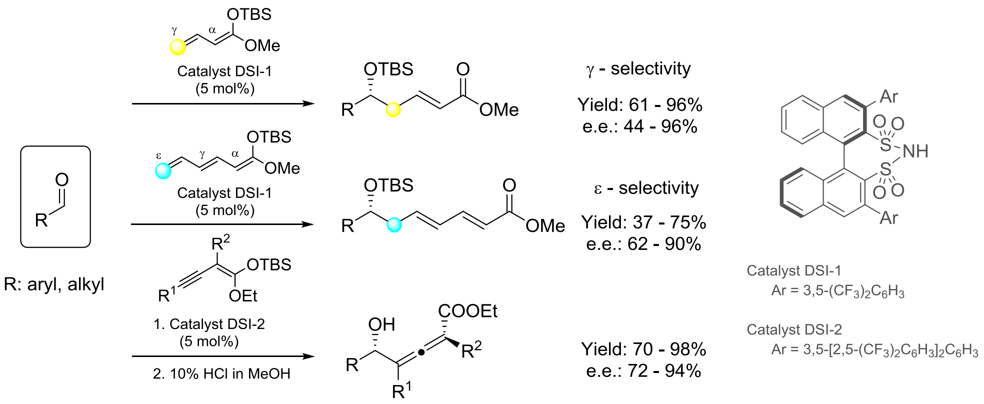
[3] García-García, P; Lay, F.; García-García, P.; Rabalakos, C.; List, B. *Angew. Chem. In. Ed.* **2009**, *48*, 4363.

[4] Ratjen, L.; García-García, P; Lay, F.; Beck, M. E.; List, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 754.

[5] Tap, A.; Blond, A.; Wakchaure, V. N.; List, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 8962.



Scheme 5.3. DSI catalyzed enantioselective reactions developed by List and coworkers.

The applicability of disulfonimides as chiral Lewis acids has not been limited to Mukaiyama aldol reactions. In fact, in recent years List and coworkers have reported different examples of enantioselective Mukaiyama-Mannich[6] and vinylogous Mukaiyama-Mannich reactions.[7] In the first work, reported in 2013, *N*-Boc imines as well as the corresponding *N*-Boc amino sulfones, which are *in situ* converted to imines, were successfully employed as substrates obtaining in all the cases, the desired products in good to excellent yields and high enantiocontrol. Reaction worked efficiently for *N*-Boc imines derived from aromatic aldehydes containing both electron-donating and electron-withdrawing groups. However, the reaction failed for imines derived from aliphatic aldehydes, for which a significant drop in the enantiocontrol of the process was observed (Scheme 5.4).

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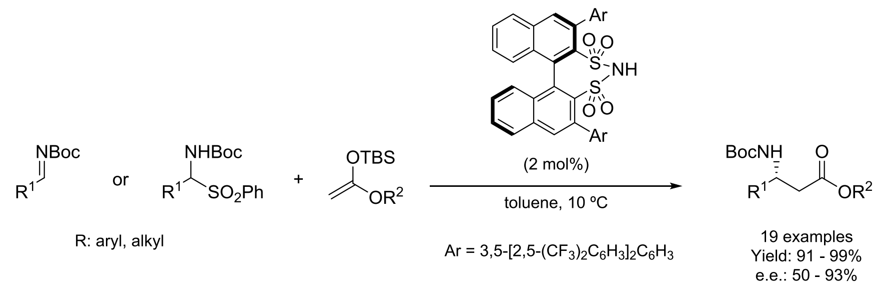
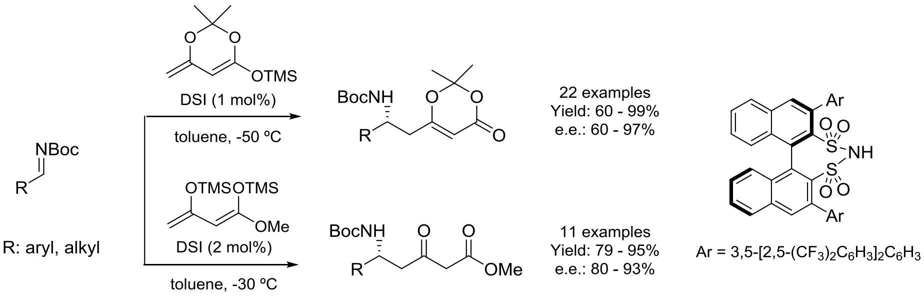
[6] Wang, Q.; Leutzsch, M.; Van Gemmeren, M.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 15334.

[7] (a) Wang, Q.; List, B. *Synlett*, **2015**, *20*, 807. (b) Wang, Q.; Van Gemmeren, M.; List, B. *Angew. Chem. Int. Ed.* **2014**, *53*, 13592. For a related example, see: Zhou, F.; Yamamoto, H. *Org. Lett.* **2016**, *18*, 4974.



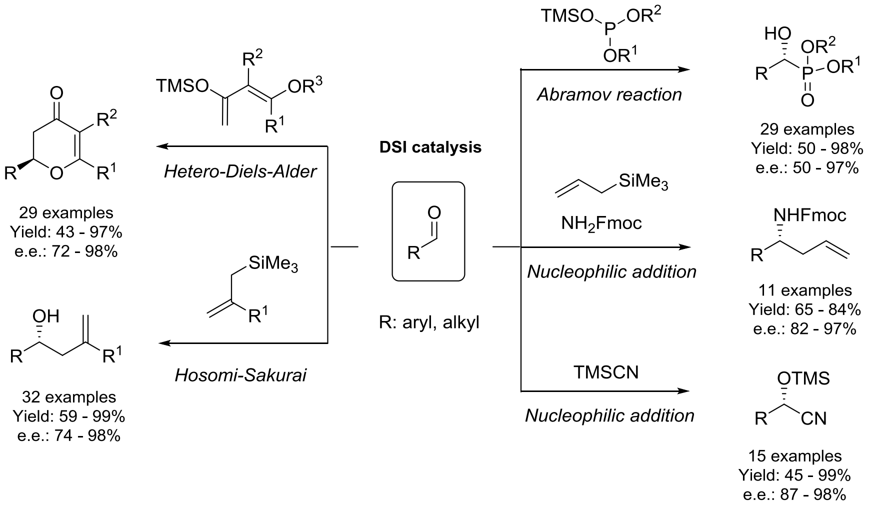
Scheme 5.4. DSI catalyzed enantioselective Mukaiyama-Mannich reaction.

This catalytic system was further applied in highly enantioselective vinylogous Mukaiyama-Mannich reactions between *N*-Boc imines and different silyloxydienes (Scheme 5.5). The reaction was successfully tested with imines derived from aromatic aldehydes, affording the corresponding products in high yields and enantiomeric excess. However, as in previous works, the reaction failed for imines derived from aliphatic aldehydes, showing a complete loss in enantiocontrol.



Scheme 5.5. DSI catalyzed enantioselective vinylogous Mukaiyama-Mannich reactions.

It should be mentioned that, in addition to the abovementioned examples, the catalytic and enantioselective variants of other reactions have also been accomplished employing chiral disulfonimides as Lewis acids, including hetero-Diels Alder,[8] Hosomi-Sakurai[9] and Abramov reactions,[10] as well as, different nucleophilic additions (Scheme 5.6).[11]



Scheme 5.6. Other catalytic and enantioselective transformations catalyzed by DSI.

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[8] Guin, J.; Rabalakaos, C.; List, B. *Angew. Chem. Int. Ed.* **2012**, *51*, 8859.

[9] Mahlau, M.; García-García, P.; List, B. *Chem. Eur. J.* **2012**, *18*, 16283.

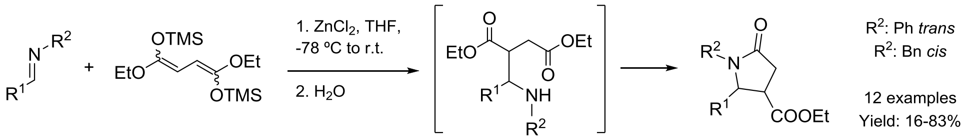
[10] Guin, J.; Wang, Q.; Van Gemmeren, M.; List, B.; *Angew. Chem. Int. Ed.* **2015**, *54*, 355.

[11] (a) Zhang, Z.; Bae, H. Y.; Guin, J.; Rabalakos, C.; Van Gemmeren, M.; Leutzsch, M.; Klussmann, M.; List, B. *Nat. Commun*. 7:12478 doi:10.1038/ncomms12478 (2016). (b) Gandhi, S.; List, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 2573.

2. SPECIFIC OBJECTIVES AND WORK PLAN

The literature precedents presented in this Chapter have clearly stated the capability of disulfonimides to act as chiral Lewis acids in different enantioselective transformations. In this sense, the success achieved by these novel catalytic systems has reinforced the interest on the development of the organocatalytic and enantioselective version of different reactions previously reported under metal Lewis acid catalysis.

In this context, the group of Prof. Shaw in University of California-Davis decided to face the construction of the γ-lactam scaffold, as these are structures found in many natural products and biologically active compounds.[12] The group of Prof. Shaw was inspired by a precedent reported by Reutrakul and coworkers for the diastereoselective synthesis of γ-lactams *via* Mukaiyama-Mannich reaction under metal Lewis acid activation.[13] In this work, the authors reported the use of stoichiometric amounts of $ZnCl_2$ in order to promote the reaction between different imines and diethylsuccinate-derived silyl dienolate (Scheme 5.7). According to authors *trans* lactams were obtained as major diastereomer when *N*-phenyl imines were tested, whilst *cis* lactams were obtained for *N*-benzyl imines.



Scheme 5.7. Metal Lewis acid catalyzed Mukaiyama-Mannich reaction for γ-lactam synthesis.

Later on, a more comprehensive study of the reaction allowed the same authors to broaden this methodology to the use of a catalytic amount of $Sc(OTf)_3$ as catalyst employing 2,5-bis(trimethylsilyloxy)furan as nucleophile (Scheme 5.8).[14] In contrast to results previously obtained for $ZnCl_2$ promoted reaction, *trans* γ-lactams were obtained regardless the nature of the N-substituent of the imine. This fact was attributed to a favored approach of the nucleophile in the transition state that avoids repulsive interactions with $Sc(OTf)_3$.

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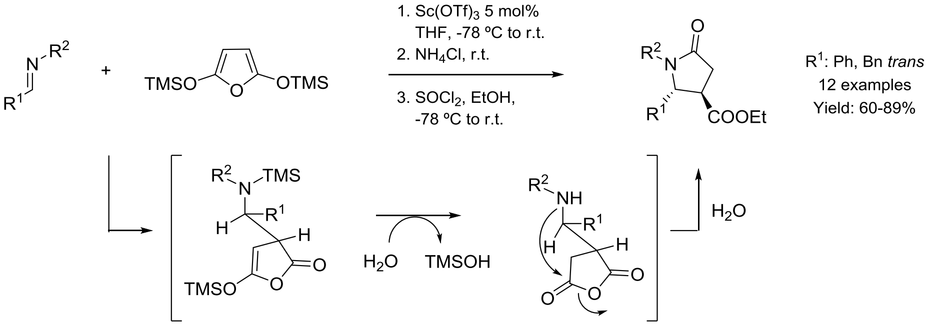
[12] For a recent review about γ-lactams as biologically active compounds, see: Caruano, J.; Muccioli, G. G.; Robiette, R. *Org. Biomol. Chem.* **2016**, *14*, 10134.

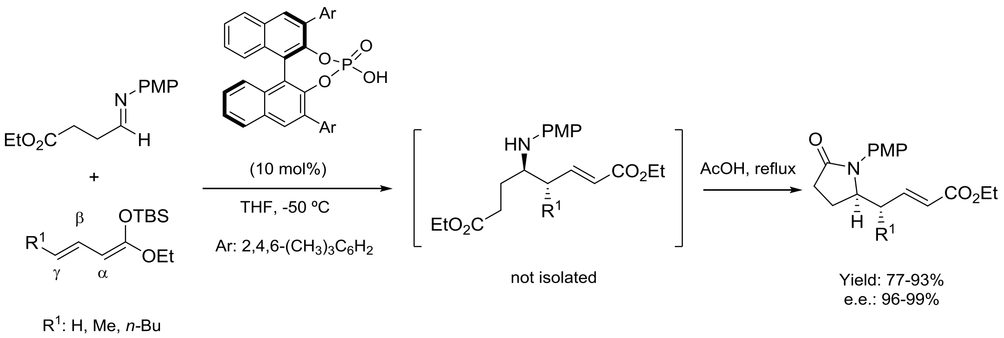
[13] Pohmakotr, M.; Yotapan, N.; Tuchinda, P.; Kuhakarn, C.; Reutrakul, V. *Tetrahedron* **2007**, 63, 4328.

[14] Pohmakotr, M.; Yotapan, N.; Tuchinda, P.; Kuhakarn, C.; Reutrakul, V. *J. Org. Chem.* **2007**, *72*, 5016.



Scheme 5.8. Sc(OTf)₃ catalyzed γ-lactam synthesis by Mukaiyama-Mannich reaction.

Despite the potential of this reaction as a suitable strategy to access γ-lactams, the organocatalytic and enantioselective version of this process has not been reported up to date. In fact, there is just one related example of γ-lactam synthesis through organocatalytic and enantioselective vinylogous Mukaiyama-Mannich reaction. In this work, developed by Schneider and coworkers, chiral phosphoric acids were employed as organocatalyts.[15] Initial experiments selectively afforded open-chain γ-addition products in high yields and with excellent diastereo- and enantio-selectivities, which could be transformed into the corresponding cyclization products by direct treatment with acetic acid at reflux.



Scheme 5.9. Phosphoric acid catalyzed enantioselective γ-lactam synthesis by vinylogous Mukaiyama-Mannich reaction.

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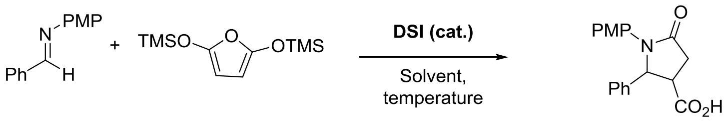
[15] Abels, F.; Lindemann, C.; Schneider, C. *Chem. Eur. J.* **2014**, *20*, 1964.

However, the reported methodology can be considered somehow limited regarding the substrate scope, a fact that did not allow a further functionalization of γ-lactam core. On the contrary, the non-asymmetric precedents under Lewis acid catalysis developed by Reutrakul and coworkers showed a more extensive scope tolerating different groups attached to the nitrogen atom, as well as, the presence of substituents in the lactam core.

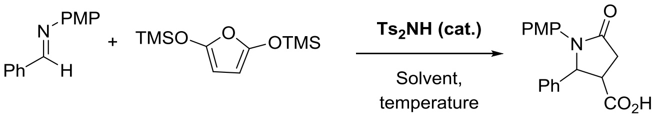
In view of these precedents, the goal of this project is to employ **disulfonimides as chiral Lewis acids to develop an organocatalytic strategy to access γ-lactams via a Mukaiyama-Mannich reaction between 2,5-bis(trimethylsilyloxy)furan and imines** (Scheme 5.10).



Scheme 5.10. γ-lactams synthesis via DSI catalyzed Mukaiyama-Mannich reaction.

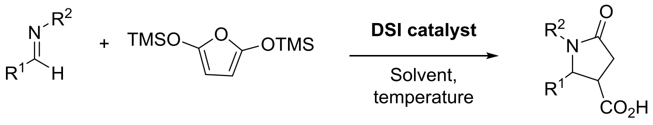
To achieve this objective, the following work plan was established:

- *Proof of concept and optimization of the reaction:* The capability of disulfonimides to act as Lewis acid catalysts for the proposed transformation will be tested in the reaction between *N*-PMP benzaldehyde derived imine and 2,5-bis(trimethylsilyloxy)furan as model substrate. The non-asymmetric version of the reaction will be studied employing ditosylsulfonimide as catalyst. Then, several experimental parameters, such as temperature or solvents, will be surveyed in order to obtain the desired products in high yields.



Scheme 5.11. Studied DSI catalyzed model reaction.

- *Scope of the reaction:* Once we determine the optimal experimental conditions to carry out the reaction, the applicability of this process will be evaluated (Scheme 5.12). To accomplish this objective several structural modifications will be introduced in the substrates, so as to study their influence in the yield and diastereoselectivity of the process. In this sense, different easily accessible imines will be tested, either by modifying the nature of the aldehyde precursor or the group attached to the nitrogen atom.



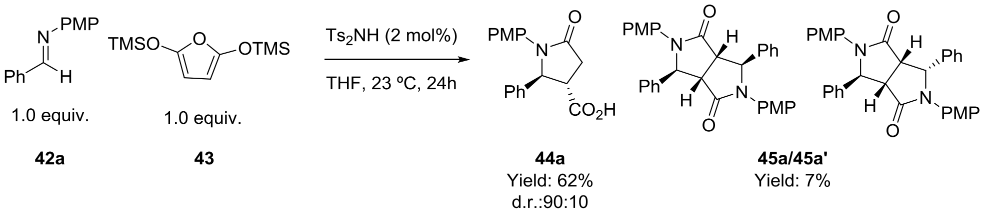
Scheme 5.12. Scope of the reaction.

- *Manipulation of the adducts:* Finally, in order to demonstrate the convenience of this methodology to access a wide variety of chemical structures, the obtained adducts will be subjected to different chemical transformations.

3. RESULTS AND DISCUSSION

3.1. Optimization of the reaction conditions

The initial studies for this reaction were carried out using (4-methoxyphenyl)-benzylidenamine **42a** and 2,5-bis(trimethylsilyloxy)furan **43** as model substrates. These compounds were prepared by condensation of benzaldehyde and *p*-methoxyaniline,[16] and by $ZnCl_2$ promoted reaction of succinic anhydride, Et_3N and chlorotrimethylsilane respectively.[17] In this way, when the model reaction was carried out in the presence of 2mol% of Ts_2NH as catalyst in THF at room temperature, the formation of desired γ-lactam **44a** was observed, although competitive formation of bislactams **45a/45a'** was detected (Scheme 5.13). ^1H-NMR analysis of unpurified reaction mixture determined 62% NMR yield for **44a** (d.r.:90:10), as well as 7% for **45a/45a'**.



Scheme 5.13. Preliminary results.[18]

The relative configuration of the obtained γ-lactam **44a** was assigned by comparison of the NMR coupling constants for protons at positions C-2 and C-3. Measured coupling constant for compound **44a** (J=5.5 Hz) was coincident with reported values[13,19] for *trans* products (J_{trans}~5.8 Hz) while higher values would be expected for *cis* lactam (J_{cis}~9.3 Hz).

On the other hand, the competitive formation of products **45a/45a'** under the experimental conditions was attributed to arise as a result of two consecutive Mukaiyama-Mannich reactions followed by intramolecular acylation, rendering an intermediate which suffers a final amidation reaction (Scheme 5.14).

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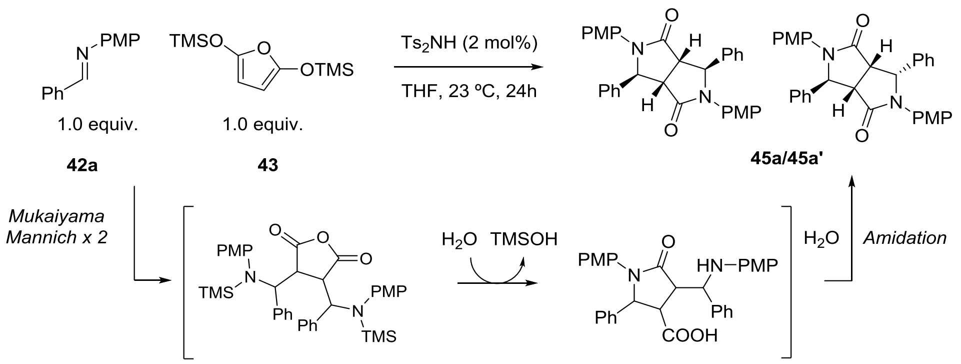
[16] Saini, A.; Smith, C. R.; Wekesa, F. S.; Helms, A. K.; Findlater, M. *Org. Biomol. Chem.* **2018**, *16*, 9368.

[17] Brownbrige, P.; Chan, T.-H. *Tetrahedron Lett.* **1980**, *21*, 3423.

[18] Determined by ^1H-NMR of crude reaction mixtures.

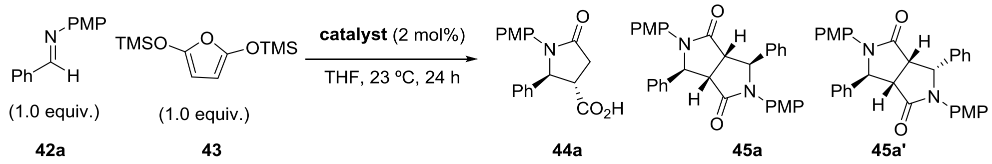
[19] Lepikhina, A.; Bakulina, O.; Darin, D.; Krasavin, M. *RSC Adv.* **2016**, *6*, 83808.



Scheme 5.14. Competitive formation of bislactams **45a/45a'**.

Next we proceeded to modify the experimental conditions in order to favor the selective formation of product **44a** (Table 5.1). In this way, when other catalysts as TfOH and Tf$_2$NH were tested in the same reaction conditions, the selectivity of the process changed to the main formation of bislactams **45a/45a'** (Table 5.1 entries 2 and 3). In view of these results it can be inferred that mono-addition product is favored when stronger Lewis acidic catalysts are employed. According to literature, while TfOH shows a higher Brønsted acidity than Tf$_2$NH, the Lewis acidities of the corresponding silylated species are reversed.[20]

Table 5.1. Preliminary studies.



Entry	Catalyst	Yield 44a (%)[a]	d.r. 44a (%)	Yield 45a/45a' (%)
1	Ts$_2$NH	62	90:10	7
2	TfOH	7	n.d.	93
3	Tf$_2$NH	54	>95:5	46

[a]Determined by ^{1}H-NMR of crude reaction mixtures.

At this point, we surveyed different modifications of the experimental parameters in order to improve the outcome of the reaction. Hence, as employing 2 mol% ditosylsulfonimide

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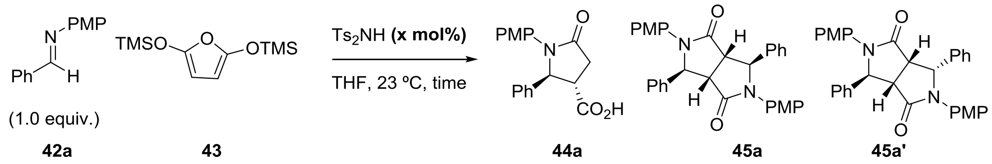
[20] Mathieu, B.; Ghosez, L. *Tetrahedron Lett.* **1997**, *38*, 5497.

rendered γ-lactam **44a** selectively albeit in a moderate 65% NMR yield**,** an increase in the catalyst loading up to 5 mol% and reaction time from 24 to 48 hours was tested (Table 5.2 entry 2). Under these conditions, a slight improvement was observed, rendering product **44a** with a 77% NMR yield as a single diastereomer. However, no further improvement was observed when the reaction was allowed to run for longer reaction times (entry 3). Finally, on the behalf that the unstability of the 2,5-bis(trimethylsilyloxy)furan **43** could be responsible of the moderate results,[21] it was decided to employ an excess of this reagent. In this way, when 2.0 equivalents of furan were employed the NMR yield was improved up to 85% (Table 5.2 entry 4). Under these conditions lactam **44a** was obtained as a single diasteromer, without observing traces either of *cis* lactam or double addition products.

Table 5.2. Preliminary studies.



Entry	Catalyst	Eq. 43	Time	Yield 44a (%)[a]	d.r. 44a (%)	Yield 45a/45a' (%)[a]
1	2 mol%	1	24 h	62	90:10	7
2	5 mol%	1	48 h	77	> 95:5	< 5
3	5 mol%	1	72 h	78	> 95:5	< 5
4	5 mol%	2	48 h	85	> 95:5	< 5

[a]Determined by ^{1}H-NMR of crude reaction mixtures.

3.2. Scope of the reaction

With the optimal conditions in hand, we proceeded to study the scope and limitations of this methodology (Scheme 5.15). First, it was decided to evaluate several *N*-PMP imines derived from aromatic aldehydes with a variety of substitution patterns in their structure. As it is shown in Scheme 5.15, reaction coursed efficiently when electron-donating groups were introduced in *para* position of the aryl substituent rendering products **44b** and **44c** in good yields. Substrate

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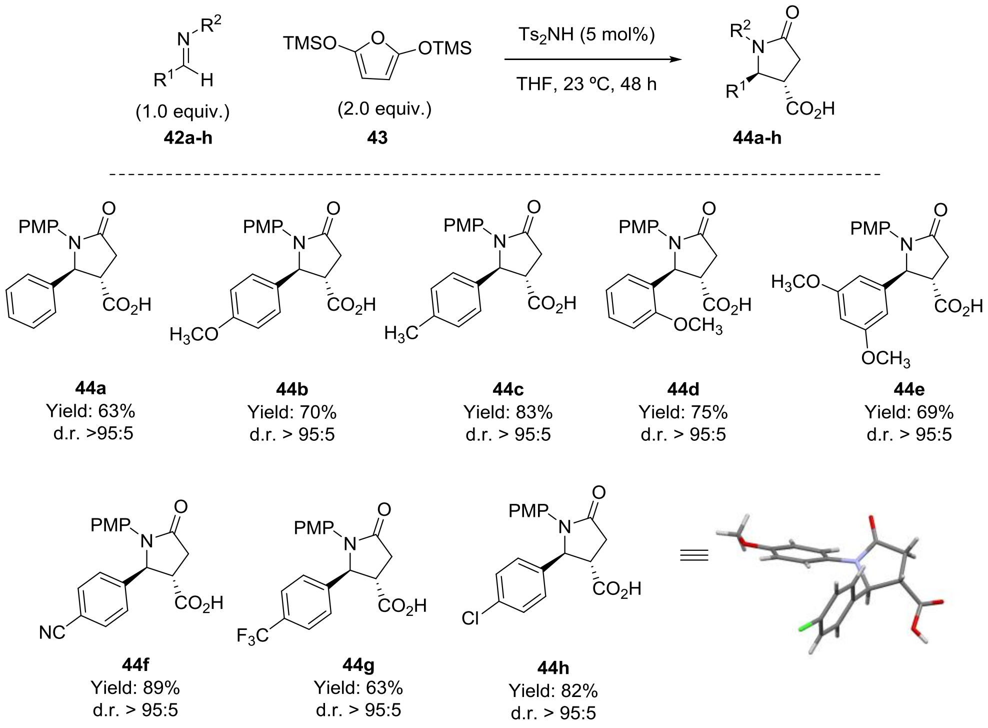
[21] It has been described in the literature its high sensitivity against moisture and air: Brownbrige, P.; Chan, T.-H. *Tetrahedron Lett.* **1980**, *21*, 3423.

containing methoxy group in *ortho* position also afforded product **44d** in good yield, albeit a slight decrease was achieved when *metha*-disubstituted benzylidenamine **42e** was tested. It should be highlighted that in all the cases products were obtained as single *trans* diastereomers. Electron-withdrawing groups were also well tolerated in *para* position, rendering compounds **44f** and **44h** in excellent yields, whilst a significant decrease was observed when a trifluoromethyl group was introduced in *para* position (**44g**). At this point the relative *trans* configuration for lactam **44h** was confirmed by X-Ray diffraction analysis.



44a Yield: 63% d.r. >95:5

44b Yield: 70% d.r. > 95:5

44c Yield: 83% d.r. > 95:5

44d Yield: 75% d.r. > 95:5

44e Yield: 69% d.r. > 95:5

44f Yield: 89% d.r. > 95:5

44g Yield: 63% d.r. > 95:5

44h Yield: 82% d.r. > 95:5

Scheme 5.15. Scope of the reaction.[22]

Notably, when *N*-PMP imines derived from mesitaldehyde **42i** and 2-naphtaldehyde **42j** were tested, no product formation was observed, which would suggest a limit in the substrate steric tolerance for this reaction (Scheme 5.16). Additionally, in the case of 2-pyridine-derived imine

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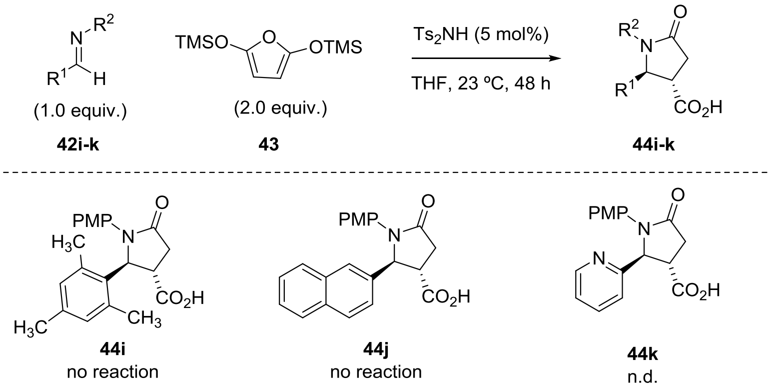
[22] Reactions were performed at 0.40 mmol scale using 5 mol% of catalyst, 2.0 equiv. of furan **43** in 2.0 mL of THF at r.t. Yields refer to isolated pure products **44**.

42k, product formation was observed by ^{1}H-NMR of the unpurified reaction mixture; however, despite different procedures were tried, no product could be isolated.



Scheme 5.16. Scope of the reaction.[23]

On the other hand, the effect of modifying the nature of the aromatic ring attached to the nitrogen atom was also tested (Scheme 5.17). In this sense, the substitution of the *p*-methoxy phenyl group by a non-activated phenyl group, led to a moderate drop in the yield of the reaction (compare compounds **44a**/**44l** and **44b**/**44m**). This behavior could be attributed to the lower nuchleophilicity of the nitrogen atom, which could affect the cyclization step that leads to γ-lactam formation.[24] Additionally, more hindered *N*-aryl substrates were tested, observing that analogous *N-metha*-substituted imine **42n** could lead to the formation of the corresponding adduct **44n** in a 92:8 diastereomeric ratio although the yield of the reaction was compromised. In the same way, when *N-ortho*-methyl substituted substrate **42o** was employed, the reaction did not take place under the optimized conditions.

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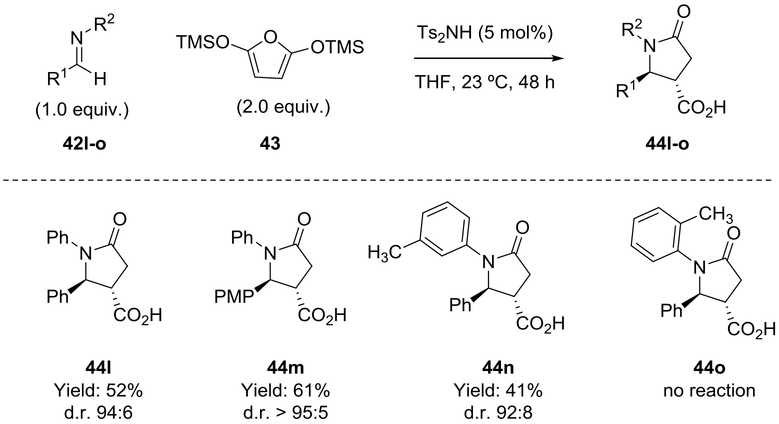
[23] Reactions were performed at 0.40 mmol scale using 5 mol% of catalyst, 2.0 equiv. of furan **43** in 2.0 mL of THF at r.t. Yields refer to isolated pure products **44**.

[24] Reaction mechanism is further discussed in this Chapter.



42l-o **43** **44l-o**

44l Yield: 52% d.r. 94:6

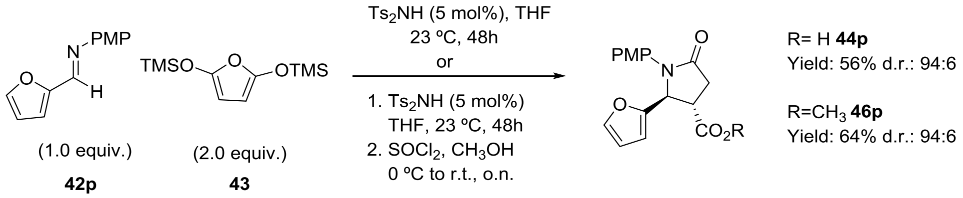
44m Yield: 61% d.r. > 95:5

44n Yield: 41% d.r. 92:8

44o no reaction

Scheme 5.17. Scope of the reaction.[25]

At this point, in view of the low isolated yields achieved for some of the γ-lactams, different procedures for the *in situ* methylation of the γ-lactam products were surveyed. In this way, while $TMSCHN_2$ in MeOH/THF mixture or methyliodide in MeOH, did not afford the desired esters in good yields, thionyl chloride in methanol rendered clean conversion to product **46**. Thus, when heteroaromatic substrate **42p** was tested under optimized conditions, the corresponding carboxylic acid **44p** was isolated in 56% yield. However, alternative procedure involving *in situ* methylation allowed us to increase the overall yield of the reaction up to a 64% (Scheme 5.18).



42p **43**

R= H **44p**
Yield: 56% d.r.: 94:6

R=CH_3 **46p**
Yield: 64% d.r.: 94:6

Scheme 5.18. Synthesis of products **44p** and **46p**.

It should be mentioned that, although it is not reflected in this memory, reaction also works for *N*-alkyl imines **42q-s**. In addition, aliphatic aldehyde-derived imines were also successfully employed in the studied Mukaiyama-Mannich reaction albeit for these substrates a slight

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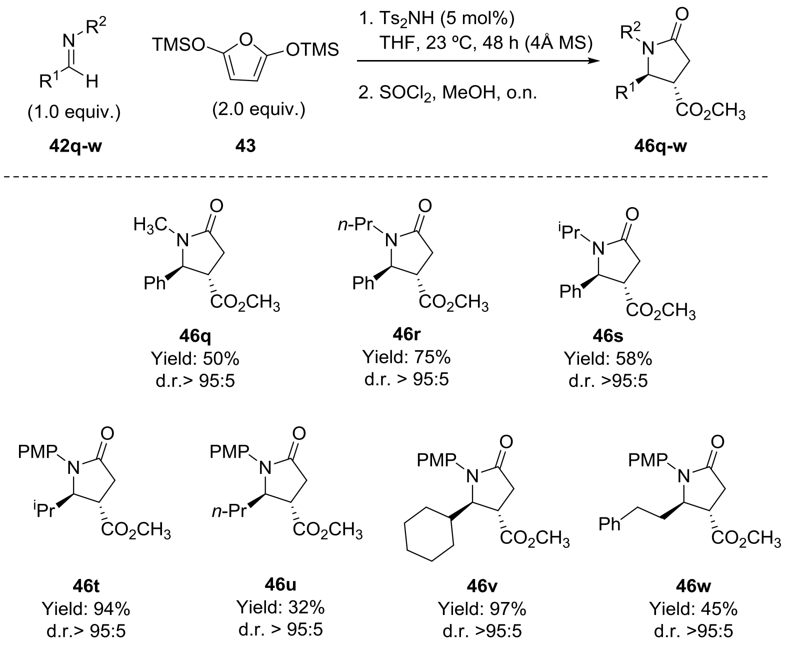
[25] Reactions were performed at 0.40 mmol scale using 5 mol% of catalyst, 2.0 equiv. of furan **43** in 2.0 mL of THF at r.t. Yields refer to isolated pure products **44**.

modification of the experimental procedure was required. The performance of the reaction in a multicomponent fashion in the presence of a desiccant, allowed the isolation of lactams **46t-w** that were not observed under previously optimized conditions. Current experiments are still on going in Prof. Shaw's group in order to broaden the scope of this methodology.



Scheme 5.19. Scope of the reaction.[26]

As a last remark, the reaction was also carried out with *N*-Boc and *N*-CBz imines showing a promising conversion by ^{1}H-NMR. Unfortunately, the products of these reactions turned out to be extremely difficult to isolate, precluding further investigations.

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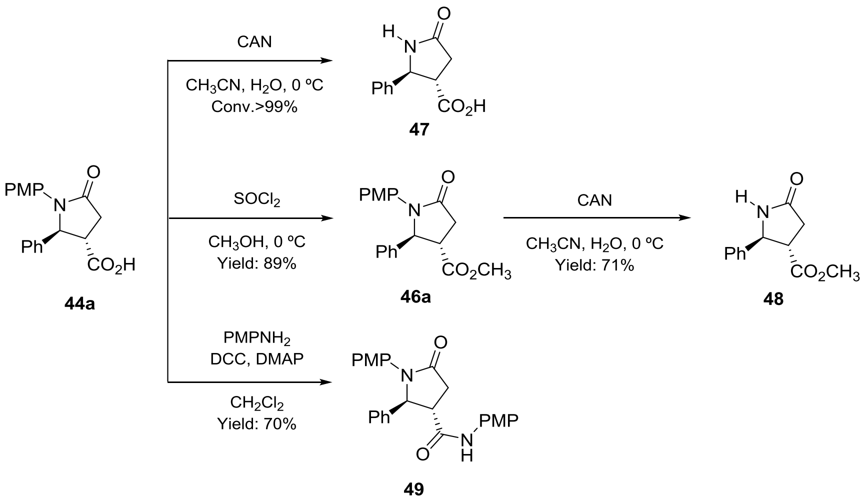
[26] Imines **42t-w** were *in situ* generated by condensation of the corresponding amine and aldehyde in the presence of 4Å MS as desiccant.

3.3. Transformations of the adducts

Having established an efficient methodology to access a wide variety of γ-lactams, a number of transformations were carried out in order to obtain related interesting structures (Scheme 5.20). Compound **44a** was chosen as model substrate for these transformations. Initially, substrate **44a** was subjected to reaction with cerium (IV) ammonium nitrate in acetonitrile:H_2O at 0 °C as it is a reported procedure for PMP cleavage.[27] Even though full conversion to the final product was observed by NMR analysis of the reaction crude, compound **47** turned out to be extremely unstable and could not be isolated. An alternative strategy involving methylation of the corresponding carboxylic acid **44a** under previously optimized conditions followed by further treatment with cerium (IV) ammonium nitrate allowed PMP cleavage, providing N-H lactam **48** in excellent yield. Additionally, amidation of the carboxylic acid **44a** with *p*-anisidine by peptidic coupling was also successfully performed affording compound **49** in good yield.



Scheme 5.20. Transformations of adducts.

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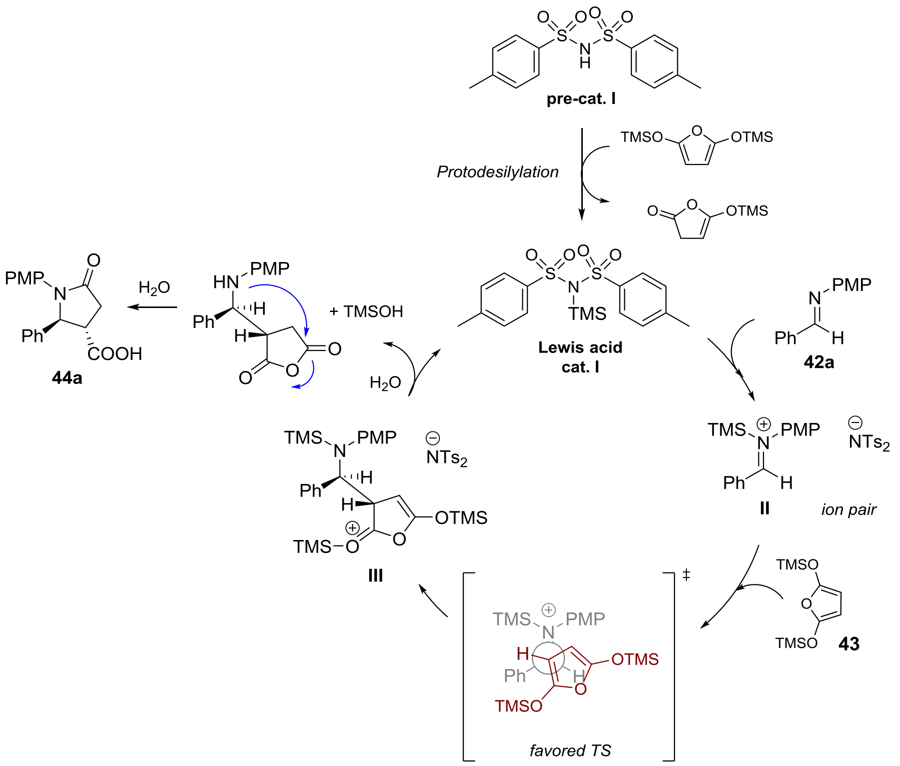
[27] Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

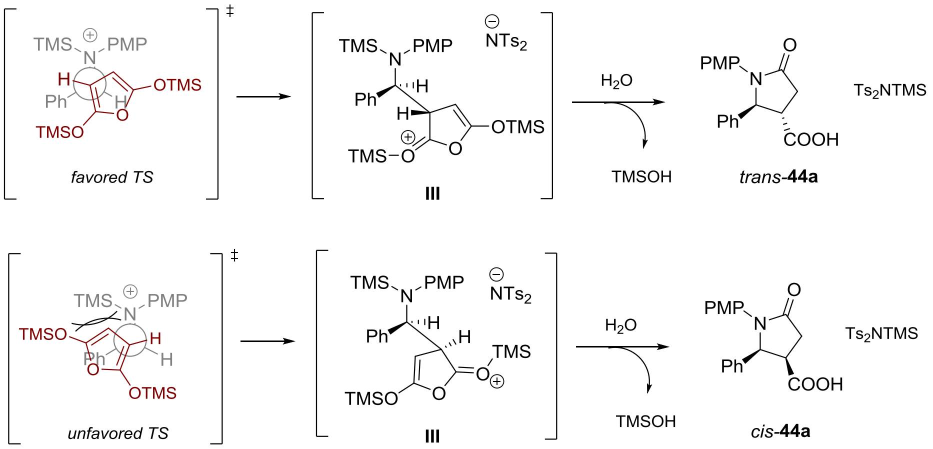
3.4. Mechanistic insights

The diastereoselectivity observed for the studied reaction is in agreement with previously reported examples for Lewis acid catalyzed Mukaiyama-Mannich reactions.[14] Based on these precedents, as well as on the commonly accepted activation mode for disulfonimides as Lewis acid catalysts,[1] the reaction mechanism represented in Scheme 5.21 was proposed. First, active Lewis acid catalyst **I** is generated by *in situ* protodesilylation of the Brønsted acidic precursor **pre-cat. I.** Then the electrophilic imine **42a** is activated by silyl group transfer, generating a cationic intermediate **II**. Subsequent reaction with 2,5-bis(trimethylsilyloxy)furan **43** affords intermediate **III**, which suffers an intramolecular cyclization rendering the corresponding adduct **44a** as well as releases the silylated catalyst.



Scheme 5.21. Proposed catalytic cycle for studied Mukaiyama-Mannich reaction.

In an analogous way that Sc(OTf)$_3$ catalyzed reaction, the reaction was proposed to proceed via an acyclic transition state. The approach of the nucleophilic furan **43** is suggested to take place in such a way that repulsive interactions between silyl group in the nitrogen atom of the imine and the hydrogen in β position of the furan ring are minimized. This is the preferred situation in the transition state that leads to the formation of *trans*-lactam **44a** observed experimentally (Scheme 5.22).



Scheme 5.22. Possible transition states.

4. CONCLUSIONS

From the work presented in this chapter, the following conclusions can be outlined:

- Disulfonimides (DSI) can be employed as efficient Lewis acid catalysts for γ-lactam synthesis via Mukaiyama-Mannich reaction between imines and 2,5-bis(trimethylsilyloxy)furan.

- Experimental conditions play a relevant role in controlling the selectivity of the reaction towards the formation of the desired mono-addition product. The use of Ts_2NH as catalyst provided the best results when THF was employed as solvent at room temperature in the presence of 2.0 equivalents of furan.

- The developed methodology is wide in scope as it has been successfully applied to different benzylidenamines either with electron-donating or electron-withdrawing groups in the aryl substituent. In all the cases, the corresponding *trans* γ-lactams were obtained as major diastereomers in good to excellent yields.

- Recent advances in the development of analogous chiral catalysts offer the possibility of studying the enantioselective variant of this process, a work that is currently under progress.

It should be mentioned that this work was developed in collaboration with Stephen W. Laws and Sara Y. Howard, who currently continue with the study of the enantioselective version of this reaction.

6

FINAL CONCLUSIONS

The present work covers the study and development of novel enantioselective transannular reactions relying on the use of organocatalysts as efficient promoters of these processes, providing access to complex polycyclic compounds. Experimental results collected during the accomplishment of present work lead to the following conclusions:

a) Chiral phosphine catalyzed enantioselective transannular Morita-Baylis-Hillman reaction. It has been demonstrated that aminoacid-derived nucleophilic chiral phosphines can be employed as efficient promoters of a highly enantioselective transannular Morita-Baylis-Hillman reaction. Medium and large size keto-enones have been employed as substrates in this reaction, providing access to a wide variety of bicyclo[4.4.0]decane, bicyclo[5.3.0]decane and bicyclo[5.4.0]undecane scaffolds. The reaction rendered the desired polycyclic adducts in high yields and enantiocontrol, showing reasonably broad tolerance to electron-withdrawing and electron-donating groups in the aromatic ring conjugated with the enone, as well as, to the presence of heteroatoms in the backbone of the cyclic precursor.

b) Total synthesis of (-)-γ-gurjunene. The applicability of the previously developed organocatalytic reaction has been demonstrated by incorporating this process as the key step in the first enantioselective total synthesis of (-)-γ-gurjunene.

c) Organocatalytic enantioselective Michael initiated transannular aldol reaction. Chiral Brønsted acid- Brønsted base bifunctional catalysts have been employed in order to trigger a highly enantioselective domino Michael/aldol transannular reaction. Different nitroacetates were selected as efficient pro-nucleophiles for this process affording the corresponding polycyclic compounds in excellent yields and high enantioselectivity, although as mixtures of diastereomers. Additionally, the developed methodology has demonstrated to be compatible with the presence of electron-donating and electron-withdrawing groups in the aromatic ring conjugated with the enone. Further hydrolysis and decarboxylation of the obtained adducts allowed them to converge in a single product in moderate to good yields.

d) γ-lactam synthesis by disulfonimide catalyzed Mukaiyama-Mannich reaction. Disulfonimides have been found to be able to promote a highly diastereoselective

Mukaiyama-Mannich reaction between different *N*-alkyl and *N*-aryl imines and 2,5-bis(trimethylsilyloxy)furan as nucleophile. The developed methodology, which tolerated the presence of both electron-donating and electron-withdrawing groups, afforded *trans* γ-lactams in moderate to good yields showing an excellent diastereoselectivities.

7

7

Experimental

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5. ORGANOCATALYTIC ENANTIOSELECTIVE MICHAEL INITIATED TRANSANNULAR ALDOL REACTION

5.1. Synthesis of adducts **38a-o**

5.2. Synthesis of adducts **40**

5.3. Synthesis of nitrones **41a/41b**

6. SYNTHESIS OF γ-LACTAMS BY DISULFONIMIDE-CATALYZED MUKAIYAMA-MANNICH REACTION

6.1. Synthesis of imines **42a-s**

6.2. Synthesis of γ-lactams **44** and methyl esters **46**

6.3. Transformations of the adducts

1. GENERAL METHODS AND MATERIALS[1]

Monodimensional and/or bidimensional nuclear magnetic resonance proton and carbon spectra (^1H NMR, ^{13}C NMR, ^{19}F NMR, ^{31}P NMR) were acquired at 25 °C on a Bruker AC-300 spectrometer (300 MHz for ^1H, 75.5 MHz for ^{13}C, 283 MHz for ^{19}F and 121.5 MHz for ^{31}P) or a Bruker AC-500 spectrometer (500 MHz for ^1H and 125.7 MHz for ^{13}C) at the indicated temperature. Chemical shifts (δ) are reported in ppm relative to residual solvent signals[2] ($CHCl_3$, 7.26 ppm for ^1H NMR, $CDCl_3$, 77.16 ppm for ^{13}C NMR) and coupling constants (J) in hertz (Hz). The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; app, apparent; m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired on a broad band decoupled mode using DEPT experiments (Distorsionless Enhancement by Polarization Transfer) for assigning different types of carbon environment. Selective n.O.e., NOESY, COSY, HSQC and HMBC experiments were acquired to confirm precise molecular configurations and to assist in convoluting complex multiplet signals.[3] **Infrared spectra** (IR) were measured in a Jasco FT/IR 4100 (ATR) in the interval between 4000 and 400 cm^{-1} with a 4 cm^{-1} resolution. Only characteristic bands are given in each case. **Mass spectra** (MS) were recorded on an Agilent 7890A gas chromatograph coupled to an Agilent 5975 quadrupole mass spectrometer under electronic impact ionization (EI) 70 eV. The obtained data is presented in mass units (m/z) and the values found in brackets belong to the relative intensities comparing to the base peak (100%). **High-resolution mass spectra** were recorded on an Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionization (ESI^+ or ESI^-). **Melting points** (M.p.) were measured in a Stuart SMP30 apparatus in open capillary tubes and are uncorrected. The **enantiomeric excess** (e.e.) of the products was determined by High Performance Liquid Chromatography (HPLC) on a chiral stationary phase in a Waters chromatograph coupled to a Waters photodiode array detector. Daicel Chiralpak IA, IC, AD-H, ASH, AZ-3, AY-3 and Chiralcel OD and OD-3 columns (0.46 × 25 cm) were used; specific conditions are indicated for each case. Specific optical rotations ($[\alpha]_D{}^{20}$) were measured at 20 °C on a Jasco P-2000 polarimeter with sodium lamp at 589 nm and a path of length of 1 dm. Solvent and concentration are specified in each case. **X-ray** data collections were performed in an Agilent Supernova diffractometer equipped with an Atlas CCD area detector, and a CuKα micro-focus source with multilayer optics (λ = 1.54184 Å, 250 µm FWHM beam size). The sample was kept at 150 K with an Oxford Cryosystems Cryostream 700 cooler. The quality of the crystals was checked under a polarizing microscope, and a suitable crystal or fragment was

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[1] SGIker technical support (MEC, GV/EJ and European Social Fund) is gratefully acknowledged (NMR and X-ray analysis).

[2] Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **62**, 7512-7515 (1997).

[3] Kinss, M.; Sanders, J. K. M. *J. Mag. Res*. **56**, 518-520 (1984).

mounted on a Mitegen Micromount™ using Paratone N inert oil and transferred to the diffractometer.

Analytical grade solvents and commercially available reagents were used without further purification. Anhydrous solvents were purified and dried with activated molecular sieves prior to use.[4] For reactions carried out under inert conditions, the argon was previously dried through a column of P_2O_5 $CaCl_2$. All the glassware was dried for 12 hours prior to use in an oven at 140 °C, and allowed to cool under a dehumidified atmosphere. Reactions at reduced temperatures were carried out using a Thermo Haake EK90 refrigerator. Reactions were monitored using analytical thin layer chromatography (TLC), in pre-coated silica-backed plates (Merck Kiesegel 60 F254). These were visualized by ultraviolet irradiation, *p*-anisaldehyde, phosphomolybdic acid or potassium permanganate stains.[5] For flash chromatography Silicycle 40-63, 230-400 mesh silica gel was used.[6] For the removal of the solvents under reduced pressure Büchi R-210 rotatory evaporators were used. For precision weighing Sartorius Analytical Balance Practum 224-1S was used (± 0.1 mg).

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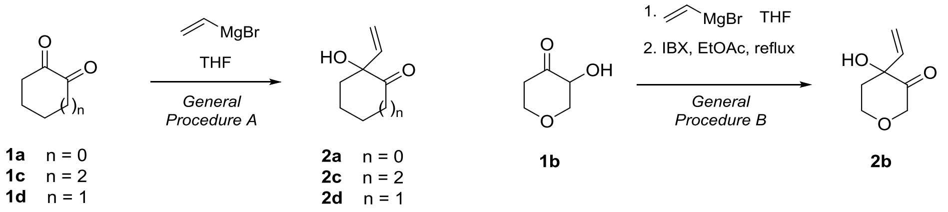
[4] (a) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 7th ed.; Elsevier: Oxford, 2012. (b) Williams, D. B. G.; Lawton, M. *J. Org. Chem*. **2010**, *75*, 8351.

[5] Stahl, E. *Thin Layer Chromatography*, Springer Verlag: Berlin, 1969.

[6] Still, W. C.; Kahn, H.; Mitra, A. J. *J. Org. Chem*. **1978**, *43*, 2923.

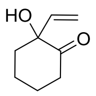
2. SYNTHESIS OF STARTING MATERIALS

2.1. Synthesis of 2-hydroxy-2-vinyl ketones 2a-d



1a was commercially available and used without further purification. Compounds **1b**,[7] **1c**[8] and **1d**[9] were synthesized according to procedures previously described in the literature.

General Procedure A: To an ice-cooled solution of the corresponding ketone (1.0 equiv.) in anhydrous THF (1 mmol/mL) was added dropwise a solution of vinylmagnesium bromide (2.0 equiv., 1 mmol/mL in THF). After the addition, the reaction mixture was allowed to reach room temperature and stirred overnight. It was quenched by the slow addition of aq. NH_4Cl solution, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/ EtOAc) to yield the desired product.



2-hydroxy-2-vinylcyclohexan-1-one (2a). Following the *General Procedure A*, compound **2a** (6.70 g, 48.0 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 7:3) starting from **1a** (6.30 g, 56.2 mmol) and vinylmagnesium bromide (112.0 mL, 112.0 mmol). Yield: 85%. Yellow oil. ^1H NMR (δ, ppm) (300 MHz, $CDCl_3$): 6.12 (dd, *J* = 17.1, 10.6 Hz, 1H, $C\mathbf{H}{=}CH_2$), 5.38 (dd, *J* = 17.1, 1.2 Hz, 1H, $CH{=}CH_{cis}\mathbf{H_{trans}}$), 5.20 (dd, *J* = 10.6, 1.2 Hz, 1H, $CH{=}C\mathbf{H_{cis}}H_{trans}$), 4.10 (s, 1H, O**H**), 2.53-2.45 (m, 2H, $C\mathbf{H_2}CO$), 2.25-2.16 (m, 1H, $C\mathbf{H_a}H_bCOH$), 2.13-2.03 (m, 1H, $CH_a\mathbf{H_b}COH$), 1.83-1.57 (m, 4H, $C\mathbf{H_2}CH_2COH$ and $C\mathbf{H_2}CH_2CO$). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 211.3 (**C**=O), 137.4 ($\mathbf{C}H{=}CH_2$), 116.6 ($CH{=}\mathbf{C}H_2$), 79.3 (**C**-OH), 41.3 ($\mathbf{C}H_2CO$), 38.5 ($\mathbf{C}H_2COH$), 27.8 ($\mathbf{C}H_2CH_2CO$), 22.4 ($\mathbf{C}H_2CH_2COH$). IR (ATR) cm^{-1}: 3479 (O-H st), 1712 (C=O st). MS (EI, 70 eV) *m/z* (%): 140 (M^+, 9), 122 (5),

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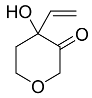
[7] Kothandaraman, S.; Donnely, K. L.; Butora, G.; Jiao, R.; Pasternak, A.; Morriello, G. J.; Goble, S. D.; Zhou, C.; Mills, S. G.; MacCoss, M.; Vicario, P. P.; Ayala, J. M.; Demartino, J. A.; Struthers, M.; Cascieri, M. A.; Yang, L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1830.

[8] Miller, C.P. Fused indole derivatives as androgen receptor modulators and their preparation and use for the treatment of diseases. PCT Int. Appl., 2011097496, 11 Aug 2011.

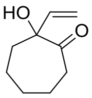
[9] Tomari, K.; Machiya, K.; Ichimoto, I.; Ueda, H. *Agric. Biol. Chem.* **1980**, *44*, 2135.

112 (16), 97 (54), 83 (100), 70 (27), 55 (78). HRMS (UPLC MS ESI$^+$): Calculated for [$C_8H_{12}NaO_2$]$^+$: 163.0735 [(M+Na)$^+$]; found: 163.0739.

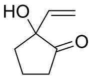
4-hydroxy-4-vinyldihydro-2*H*-pyran-3(4*H*)-one (2b). *General Procedure B:* To an ice-cooled solution of **1b** (325 mg, 2.8 mmol) in anhydrous THF (10 mL) was added dropwise a solution of vinylmagnesium bromide (5.6 mmol, 1 mmol/mL in THF). After the addition, the reaction mixture was allowed to reach room temperature and stirred until full conversion was observed by TLC. It was quenched by the slow addition of aq. NH_4Cl solution, extracted with EtOAc (3 x 20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in EtOAc (10 mL) followed by the addition of IBX (15 mmol). Then it was heated at reflux temperature overnight. The reaction mixture was filtered through Celite to remove solids, concentrated under reduced pressure and the unstable compound directly used to avoid decomposition.



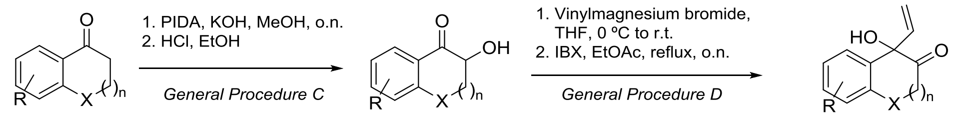
2-hydroxy-2-vinylcycloheptan-1-one (2c). Following the *General Procedure A*, compound **2c** (195 mg, 1.27 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 9:1) starting from **1c** (500 mg, 3.96 mmol) and vinylmagnesium bromide (7.9 mL, 7.90 mmol). Yield: 32%. Pale yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 5.85 (dd, *J*=17.1, 10.5 Hz, 1H, C**H**=CH_2), 5.36 (dd, *J*=17.1, 1.3 Hz, 1H, CH=CH$_{cis}$**H$_{trans}$**), 5.12 (dd, *J*=10.5, 1.3 Hz, 1H, CH=C**H$_{cis}$**H$_{trans}$), 4.01 (s, 1H, O**H**), 2.86-2.55 (m, 1H, C**H$_a$**H$_b$CO), 2.55-2.31 (m, 1H, CH$_a$**H$_b$**CO), 2.06-1.93 (m, 2H, C**H$_2$**COH), 1.93-1.71 (m, 3H, C**H$_2$**CH$_2$CO and C**H$_a$**H$_b$CH$_2$COH), 158-1.19 (m, 3H, CH$_a$**H$_b$**CH$_2$COH and C**H$_2$**CH$_2$CH$_2$CO). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 213.1 (**C**=O), 138.9 (**C**H=CH$_2$), 116.0 (CH=**C**H$_2$), 82.3 (**C**-OH), 39.1 (**C**H$_2$CO), 36.8 (**C**H$_2$COH), 30.5 (**C**H$_2$CH$_2$CH$_2$COH), 27.5 (**C**H$_2$CH$_2$CO), 23.7 (**C**H$_2$CH$_2$COH). IR (ATR) cm^{-1}: 3483 (O-H st), 1707 (C=O st). MS (EI, 70 eV) *m/z* (%): 154 (M$^+$, 2), 136 (6), 111 (24), 99 (39), 83 (100), 70 (35), 55 (61). HRMS (UPLC MS ESI$^+$): Calculated for [$C_9H_{14}NaO_2$]$^+$: 177.0892 [(M+Na)$^+$]; found: 177.0896.



2-hydroxy-2-vinylcyclopentan-1-one (2d). Following the *General Procedure A*, compound **2d** (0.83 g, 6.60 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **1d** (1.00 g, 10.2 mmol) and vinylmagnesium bromide (20.4 mL, 20.4 mmol). Yield: 64%. Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 5.85 (dd, *J* = 17.4, 10.6 Hz, 1H, C**H**=CH$_2$), 5.36-5.17 (m, 2H, CH=C**H$_2$**), 2.93 (s, 1H, O**H**), 2.46-2.27 (m, 2H, C**H$_2$**CO), 2.26-2.12 (m, 1H, C**H$_a$**H$_b$COH), 2.10-1.75 (m, 3H, CH$_a$**H$_b$**COH and C**H$_2$**CH$_2$CO). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 218.0 (**C**=O), 136.8 (**C**H=CH$_2$), 116.4 (CH=**C**H$_2$), 80.1 (**C**-OH), 35.8 (**C**H$_2$CO), 34.8 (**C**H$_2$COH), 17.0 (**C**H$_2$CH$_2$CO). IR (ATR) cm^{-1}: 3447 (O-H st), 1738 (C=O st). MS (EI, 70 eV) *m/z* (%): 126 (M$^+$, 10), 108 (3), 98 (20), 83 (17), 70 (100), 55(48). HRMS (UPLC MS ESI$^+$): Calculated for [$C_7H_{10}NaO_2$]$^+$: 149.0579 [(M+Na)$^+$]; found: 149.0582.



2.2. Synthesis of 2-hydroxy-2-vinyl ketones 8a-i

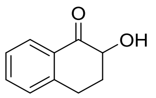


6a	n=0 X=CH$_2$	**7a**	n=0 X=CH$_2$	**8a**	n=0 X=CH$_2$
6b-g	n=1 X=CH$_2$	**7b-g**	n=1 X=CH$_2$	**8b-g**	n=1 X=CH$_2$
6h	n=1 X=O	**7h**	n=1 X=O	**8h**	n=1 X=O
6i	n=2 X=CH$_2$	**7i**	n=2 X=CH$_2$	**8i**	n=2 X=CH$_2$

6a-i were commercially available and used without further purification. Compound **7a**[10] and **7i**[11] were synthesized according to procedures previously described in the literature.

General Procedure C: A solution of the corresponding ketone **6a-i** (1.0 equiv.) in MeOH (0.2 mmol/mL) was added to a previously prepared ice-cooled solution of KOH (3.0 equiv.) in MeOH (1.2 mmol/mL) over 5 min. Solid iodobenzene diacetate (1.1 equiv.) was added in portions at 0 °C during 5 min and the resulting mixture was stirred at 0 °C for 1 hour and then at room temperature overnight. Organic solvents were removed under reduced pressure to give a residue which was dissolved in Et_2O, washed with water and evaporated. The residue was dissolved in EtOH and 6*M* HCl aq. (6.0 equiv.) was added. It was stirred at room temperature for 30 min, then basified with K_2CO_3 and extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give the corresponding α-hydroxy ketone **7a-i**.

2-hydroxy-3,4-dihydronaphtalen-1(2*H*)-one (7b). Following the *General Procedure C*, **7b** (9.64 g, 59.4 mmol) was isolated by FC (hexanes/EtOAc 8:2) starting from **6b** (9.0 mL, 68.0 mmol), iodobenzene diacetate (24.10 g, 74.8 mmol) and KOH (9.42 g, 204 mmol). Yield: 87%. Orange oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 8.04 (dd, *J* = 7.8, 1.5 Hz, 1H, C**H**$_{arom}$), 7.59-7.47 (m, 1H, C**H**$_{arom}$), 7.41-7.23 (m, 2H, 2 x C**H**$_{arom}$), 4.39 (dd, *J* = 13.7, 5.2 Hz, 1H, **H**-2), 3.91 (s, 1H, O**H**), 3.25-2.96 (m, 2H, **H**-4), 2.62-2.46 (m, 1H, **H**$_a$-3), 2.16-1.94 (m, 1H, **H**$_b$-3). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 199.7 (**C**-1), 144.4 (**C**$_{arom}$), 134.3 (**C**H$_{arom}$), 130.6 (**C**$_{arom}$), 129.0 (**C**H$_{arom}$), 127.7 (**C**H$_{arom}$), 127.0 (**C**H$_{arom}$), 74.0 (**C**-2), 32.0 (**C**-3), 27.9 (**C**-4). IR (ATR) cm^{-1}: 2940 (O-H st), 1680 (C=O st). MS (EI, 70



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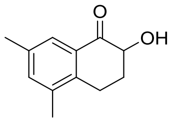
[10] Matsuo, K.; Shindo, M. *Org. Lett.* **2010**, *12*, 5346.

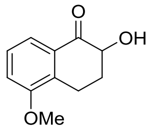
[11] Koprowski, M.; Luczak, J.; Krawczyk, E. *Tetrahedron*. **2006**, *62*, 12363.

eV) *m/z* (%): 162 (M^+, 34), 144 (20), 130 (41), 118 (100), 102 (35), 90 (67), 77 (17). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{10}H_{10}NaO_2]^+$: 185.0576 [$(M+Na)^+$]; found 185.0579.

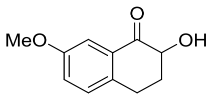
2-hydroxy-5,7-dimethyl-3,4-dihydronaphtalen-1(2*H*)-one (7c). Following the *General Procedure C*, **7c** (9.17 g, 48.2 mmol) was isolated by FC (hexanes/EtOAc 8:2) starting from **6c** (10.0 g, 57.0 mmol), iodobenzene diacetate (20.2 g, 62.7 mmol) and KOH (9.58 g, 171 mmol). Yield: 85%. Orange solid. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 7.68 (s, 1H, C**H**$_{arom}$), 7.20 (s, 1H, C**H**$_{arom}$), 4.33 (dd, *J* = 13.8, 5.5 Hz, 1H, **H**-2), 3.97 (s, 1H, O**H**), 2.97 (ddd, *J* = 17.4, 5.2, 2.5 Hz, 1H, **H**$_a$-4), 2.81 (ddd, *J* = 17.4, 12.4, 4.7 Hz, 1H, **H**$_b$-4), 2.62 - 2.44 (m, 1H, **H**$_a$-3), 2.31 (s, 3H, C**H**$_3$), 2.25 (s, 3H, C**H**$_3$), 1.94 (dtd, *J* = 13.8, 12.4, 5.2 Hz, 1H, **H**$_b$-3). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 200.1 (**C**-1), 139.6 (**C**$_{arom}$), 136.6 (**C**H$_{arom}$), 136.5 (**C**$_{arom}$), 136.3 (**C**$_{arom}$), 130.5 (**C**$_{arom}$), 125.4 (**C**H$_{arom}$), 73.3 (**C**-2), 31.2 (**C**-3), 24.7 (**C**-4), 20.8 (**C**H$_3$), 19.2 (**C**H$_3$). IR (ATR) cm^{-1}: 3472 (O-H st), 1673 (C=O st). MS (EI, 70 eV) *m/z* (%): 190 (M^+, 80), 172 (46), 158 (34), 146 (100), 129 (38), 118 (83), 103 (19), 91 (22), 77 (13), 63 (7), 51 (7). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{12}H_{14}NaO_2]^+$: 213.0892 [$(M+Na)^+$]; found 213.0892. M.p.: 56-58 °C (hexanes/EtOAc).



2-hydroxy-5-methoxy-3,4-dihydronaphtalen-1(2*H*)-one (7d). Following the *General Procedure C*, **7d** (3.44 g, 18.0 mmol) was isolated by FC (hexanes/EtOAc 8:2) starting from **6d** (5.00 g, 28.0 mmol), iodobenzene diacetate (9.92 g, 30.8 mmol) and KOH (4.70 g, 84.0 mmol). Yield: 63%. Orange solid. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 7.59 (dd, *J* = 8.0, 1.1 Hz, 1H, C**H**$_{arom}$), 7.28 (t, *J* = 8.0 Hz, 1H, C**H**$_{arom}$), 7.08-6.96 (m, 1H, C**H**$_{arom}$), 4.34 (ddd, *J* = 13.7, 5.5, 2.1 Hz, 1H, **H**-2), 3.93 (d, *J* = 2.1 Hz, 1H, O**H**), 3.84 (s, 3H, OC**H**$_3$), 3.19 (ddd, *J* = 18.0, 5.0, 2.3 Hz, 1H, **H**$_a$-4), 2.73 (ddd, *J* = 18.0, 12.8, 4.8 Hz, 1H, **H**$_b$-4), 2.57-2.42 (m, 1H, **H**$_a$-3), 2.04-1.82 (m, 1H, **H**$_b$-3). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 199.9 (**C**-1), 156.8 (**C**$_{arom}$), 133.2 (**C**$_{arom}$), 131.5 (**C**$_{arom}$), 127.5 (**C**H$_{arom}$), 118.9 (**C**H$_{arom}$), 114.9 (**C**H$_{arom}$), 73.5 (**C**-2), 55.7 (O**C**H$_3$), 31.0 (**C**-3), 21.6 (**C**-4). IR (ATR) cm^{-1}: 3479 (O-H st), 1670 (C=O st). MS (EI, 70 eV) *m/z* (%): 192 (M^+, 100), 174 (45), 160 (34), 148 (70), 131 (27), 120 (77), 105 (30), 90 (66), 77 (43), 63 (18), 51 (21). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{11}H_{12}NaO_3]^+$: 215.0684 [$(M+Na)^+$]; found 215.0684. M.p.: 109-111 °C (hexanes/EtOAc).

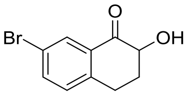


2-hydroxy-7-methoxy-3,4-dihydronaphtalen-1(2*H*)-one (7e). Following the *General Procedure C*, **7e** (5.30 g, 27.5 mmol) was isolated by FC (hexanes/EtOAc 8:2) starting from **6e** (5.00 g, 28.0 mmol), iodobenzene diacetate (9.92 g, 30.8 mmol) and KOH (4.70 g, 84.0 mmol). Yield: 95%. Orange oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 7.42 (d, *J* = 2.8 Hz, 1H, **H**-8), 7.10 (d, *J* = 8.5 Hz, 1H, **H**-5), 7.03 (dd, *J* = 8.5, 2.8 Hz, 1H, **H**-6), 4.30 (ddd, *J* = 13.5, 5.4, 2.0 Hz, 1H, **H**-2), 4.00 (d, *J* = 2.0 Hz, 1H, O**H**), 3.77 (s, 3H, OC**H**$_3$), 3.14-2.82 (m, 2H, **H**-4), 2.51-2.36 (m, 1H, **H**$_a$-3), 2.06-1.85 (m, 1H, **H**$_b$-3). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 199.5 (**C**-

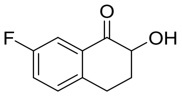


1), 158.4 (**C**$_{arom}$), 136.8 (**C**$_{arom}$), 131.2 (**C**$_{arom}$), 130.0 (**C**H$_{arom}$), 122.4 (**C**H$_{arom}$), 109.3 (**C**H$_{arom}$), 73.9 (**C**-2), 55.4 (O**C**H$_3$), 32.1 (**C**-3), 26.9 (**C**-4). IR (ATR) cm^{-1}: 3482 (O-H st), 1680 (C=O st). MS (EI, 70 eV) *m/z* (%): 192 (M$^+$, 50), 174 (41), 160 (26), 146 (35), 131 (11), 120 (100), 103 (9), 91 (24), 77(23), 63(14), 51(14). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{11}H_{12}NaO_3$]$^+$: 215.0684 [(M+Na)$^+$]; found 215.0682.

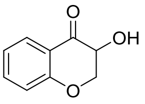
7-bromo-2-hydroxy-3,4-dihydronaphtalen-1(2*H*)-one (7f). Following the *General Procedure C*, **7f** (3.47 g, 14.4 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **6f** (5.00 g, 22.2 mmol), iodobenzene diacetate (7.86 g, 24.4 mmol) and KOH (3.73 g, 66.6 mmol). Yield: 65%. Brown solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 8.13 (d, *J* = 2.2 Hz, 1H, **H**-8), 7.60 (dd, *J* = 8.2, 2.2 Hz, 1H, **H**-6), 7.15 (d, *J* = 8.2 Hz, 1H, **H**-5), 4.36 (ddd, *J* = 13.5, 5.4, 1.8 Hz, 1H, **H**-2), 3.85 (d, *J* = 1.8 Hz, 1H, O**H**), 3.16-2.91 (m, 2H, **H**-4), 2.60-2.43 (m, 1H, **H$_a$**-3), 2.17-2.06 (m, 1H, **H$_b$**-3). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 198.5 (**C**-1), 143.1 (**C**$_{arom}$), 137.0 (**C**H$_{arom}$), 132.1 (**C**$_{arom}$), 130.8 (**C**H$_{arom}$), 130.4 (**C**H$_{arom}$), 121.0 (**C**$_{arom}$), 73.8 (**C**-2), 31.6 (**C**-3), 27.4 (**C**-4). IR (ATR) cm^{-1}: 3468 (O-H st), 1682 (C=O st). MS (EI, 70 eV) *m/z* (%): 239 (M$^+$, 43), 242 (37), 239 (43), 224 (32), 197 (83), 196 (100), 170 (66), 143 (18), 115 (79), 89 (69), 63 (36), 51 (15). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{10}H_9BrNaO_2$]$^+$: 262.9684 [(M+Na)$^+$]; found 262.9670. M.p.: 115-117 °C (hexanes/EtOAc).



7-fluoro-2-hydroxy-3,4-dihydronaphtalen-1(2*H*)-one (7g). Following the *General Procedure C*, **7g** (4.17 g, 23.2 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **6g** (5.00 g, 30.4 mmol), iodobenzene diacetate (10.8 g, 33.4 mmol) and KOH (5.11 g, 91.2 mmol). Yield: 76%. Orange solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.59 (dd, *J* = 8.8, 2.7 Hz, 1H, C**H**$_{arom}$), 7.28-7.09 (m, 2H, 2 x C**H**$_{arom}$), 4.34 (dd, *J* = 13.5, 5.4 Hz, 1H, **H**-2), 3.99 (s, 1H, O**H**), 3.15-2.89 (m, 2H, **H**-4), 2.46 (m, 1H, **H$_a$**-3), 2.10-1.87 (m, 1H, **H$_b$**-3). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 198.7 (d, $^4J_{CF}$ = 1.9 Hz, **C**-1), 161.4 (d, $^1J_{CF}$ = 247.0 Hz, **C**-7), 140.1 (d, $^4J_{CF}$ = 3.1 Hz, **C**-4a), 132.0 (d, $^3J_{CF}$ = 6.3 Hz, **C**-8a), 130.8 (d, $^3J_{CF}$ = 7.4 Hz, **C**-5), 121.4 (d, $^2J_{CF}$ = 22.1 Hz, **C**H$_{arom}$), 113.2 (d, $^2J_{CF}$ = 22.0 Hz, **C**H$_{arom}$), 73.8 (**C**-2), 31.8 (**C**-3), 27.1 (**C**-4). ^{19}F NMR (δ, ppm) (282 MHz, CDCl$_3$): -114.7. IR (ATR) cm^{-1}: 3478 (O-H st), 1683 (C=O st). MS (EI, 70 eV) *m/z* (%): 180 (M$^+$, 26), 162 (39), 148 (20), 136 (62), 120 (21), 108 (100), 94 (8), 75 (10), 63 (7), 51 (5). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{10}H_9FNaO_2$]$^+$: 203.0484 [(M+Na)$^+$]; found 203.0480. M.p.: 65-67 °C (hexanes/EtOAc).



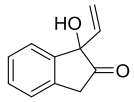
3-hydroxychroman-4-one (7h). Following the *General Procedure C*, **7h** (7.79 g, 47.4 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **6h** (10.0 g, 67.5 mmol), iodobenzene diacetate (23.9 g, 74.2 mmol) and KOH (11.3 g, 0.20 mol). Yield: 70%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.83 (dd, *J* = 7.9, 1.8 Hz, 1H, C**H**$_{arom}$), 7.47 (ddd, *J* = 8.6, 7.2, 1.8 Hz, 1H, C**H**$_{arom}$), 7.07-6.91 (m, 2H, 2 x C**H**$_{arom}$), 4.69-4.53



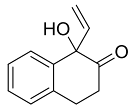
(m, 2H, **H**-2), 4.19-4.05 (m, 1H, **H**-3), 3.98 (d, *J* = 2.1 Hz, 1H, O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 194.5 (**C**-4), 162.1 (**C**$_{\mathrm{arom}}$), 136.6 (**C**H$_{\mathrm{arom}}$), 127.3 (**C**H$_{\mathrm{arom}}$), 121.8 (**C**H$_{\mathrm{arom}}$), 118.8 (**C**$_{\mathrm{arom}}$), 117.9 (**C**H$_{\mathrm{arom}}$), 70.5 (**C**-2), 69.1 (**C**-3). IR (ATR) cm^{-1}: 3422 (O-H st), 1691 (C=O st), 1208 (C-O-C st). MS (EI, 70 eV) *m/z* (%): 164 (M$^+$, 27), 147 (4), 136 (4), 120 (100), 105 (4), 92 (69), 77 (9), 63 (16), 51 (5). HRMS (UPLC MS ESI$^+$): Calculated for $[C_9H_9O_3]^+$: 165.0552 [(M+H)$^+$]; found 165.0551. M.p.: 66-68 °C (hexanes/EtOAc).

General Procedure D: To an ice-cooled solution of α-hydroxyketone **7a-i** (1.0 equiv.) in anhydrous THF (0.5 mmol/mL) was added dropwise a solution of vinylmagnesium bromide (3.8 equiv., 1 mmol/mL in THF). After the addition, the reaction mixture was allowed to reach room temperature and stirred until full conversion. It was quenched by slow addition of aq. NH_4Cl solution, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in EtOAc followed by the addition of 2-iodoxybenzoic acid (1.5 equiv.).[12] Then it was heated at reflux temperature overnight. The reaction mixture was filtered through Celite to remove solids, concentrated under reduced pressure and purified by flash column chromatography.

1-hydroxy-1-vinyl-1,3-dihydro-2*H*-inden-2-one (8a). Following the *General Procedure D*, **8a** (1.60 g, 9.18 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 8:2) starting from **7a** (3.06 g, 20.7 mmol), vinylmagnesium bromide (79 mL, 79 mmol) and 2-iodoxybenzoic acid (8.68 g, 31.0 mmol). Yield: 44%. Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 7.53-7.30 (m, 4H, 4 x C**H**$_{\mathrm{arom}}$), 5.96 (dd, *J* = 17.1, 10.4 Hz, 1H, C**H**=CH$_2$), 5.26 (dd, *J* = 10.4, 0.7 Hz, 1H, CH=C**H**$_{\mathbf{cis}}$H$_{\mathrm{trans}}$), 5.10 (dd, *J* = 17.1, 0.7 Hz, 1H, CH=CH$_{\mathrm{cis}}$**H**$_{\mathbf{trans}}$), 3.70 (d, *J* = 21.7 Hz, 1H, **H**$_{\mathbf{a}}$-3), 3.51 (d, *J* = 21.7 Hz, 1H, **H**$_{\mathbf{b}}$-3), 3.11 (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 214.3 (**C**-2), 141.4 (**C**$_{\mathrm{arom}}$), 137.6 (**C**H=CH$_2$), 135.6 (**C**$_{\mathrm{arom}}$), 129.5 (**C**H$_{\mathrm{arom}}$), 128.4 (**C**H$_{\mathrm{arom}}$), 125.3 (**C**H$_{\mathrm{arom}}$), 125.0 (**C**H$_{\mathrm{arom}}$), 117.3 (CH=**C**H$_2$), 82.0 (**C**-1), 40.2 (**C**-3). IR (ATR) cm^{-1}: 3440 (O-H st), 1756 (C=O st). MS (EI, 70 eV) *m/z* (%): 174 (M$^+$, 12), 156 (32), 146 (100), 131 (67), 115 (40), 103 (12), 91 (35), 77 (14), 63 (19), 51 (14). HRMS (UPLC MS ESI+): Calculated for $[NaC_{11}H_{10}O_2]^+$: 197.0579 [(M+Na)$^+$]; found 197.0580.



1-hydroxy-1-vinyl-3,4-dihydronaphthalen-2(1*H*)-one (8b). Following *the General Procedure*, **8b** (1.95 g, 10.4 mmol) was isolated by FC (hexanes/EtOAc 8:2) starting from **7b** (3.26 g, 20.1 mmol), vinylmagnesium bromide (76.4 mL, 76.4 mmol) and 2-iodoxybenzoic acid (8.44 g, 30.1 mmol). Yield: 52%. Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 7.61 (dd, *J* = 7.5, 1.7 Hz, 1H, C**H**$_{\mathrm{arom}}$), 7.38-7.25 (m, 2H, 2 x C**H**$_{\mathrm{arom}}$), 7.22-7.15 (m, 1H, C**H**$_{\mathrm{arom}}$), 5.89



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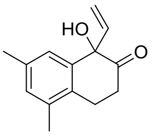
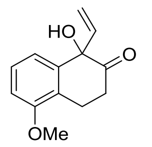
[12] Other oxidants were tested but provided lower yields.

(dd, *J* = 17.1, 10.3 Hz, 1H, C**H**=CH$_2$), 5.26 (dd, *J* = 10.2, 0.7 Hz, 1H, CH=C**H**$_{\mathbf{cis}}$H$_{\text{trans}}$), 5.11 (dd, *J* = 17.1, 0.7 Hz, 1H, CH=CH$_{\text{cis}}$**H**$_{\mathbf{trans}}$), 4.25 (s, 1H, O**H**), 3.27 (m, 1H, **H**$_{\mathbf{a}}$-3), 3.11-2.83 (m, 2H, **H**$_{\mathbf{b}}$-3 and **H**$_{\mathbf{a}}$-4), 2.62 (m, 1H, **H**$_{\mathbf{b}}$-4). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 210.4 (**C**-2), 138.0 (**C**$_{\text{arom}}$), 137.5 (**C**H=CH$_2$), 135.1 (**C**$_{\text{arom}}$), 128.1 (**C**H$_{\text{arom}}$), 127.64 (**C**H$_{\text{arom}}$), 127.59 (**C**H$_{\text{arom}}$), 126.4 (**C**H$_{\text{arom}}$), 117.7 (CH=**C**H$_2$), 80.1 (**C**-1), 33.7 (**C**-3), 27.7 (**C**-4). IR (ATR) cm^{-1}: 3468 (O-H st), 1713 (C=O st). MS (EI, 70 eV) *m/z* (%): 188 (M$^+$, 30), 168 (98), 145 (100), 131 (58), 115 (77), 103 (21), 91 (33), 77 (34), 65 (12), 55 (27). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{12}$H$_{12}$NaO$_2$]$^+$: 211.0735 [(M+Na)$^+$]; found 211.0730.

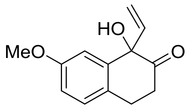
1-hydroxy-5,7-dimethyl-1-vinyl-3,4-dihydronaphthalen-2(1*H*)-one (8c). Following the *General Procedure D*, **8c** (1.50 g, 6.95 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 8:2) starting from **7c** (3.00 g, 15.8 mmol), vinylmagnesium bromide (60.0 mL, 60.0 mmol) and 2-iodoxybenzoic acid (6.64 g, 23.7 mmol). Yield: 44%. Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.26 (s, 1H, C**H**$_{\text{arom}}$), 6.98 (s, 1H, C**H**$_{\text{arom}}$), 5.93 (dd, *J* = 17.0, 10.3 Hz, 1H, C**H**=CH$_2$), 5.37-5.11 (m, 2H, CH=C**H**$_{\mathbf{2}}$), 4.27 (s, 1H, O**H**), 3.12-30.3 (m, 2H, **H**-3), 3.03-2.90 (m, 1H, **H**$_{\mathbf{a}}$-4), 2.61 (dt, *J* = 16.6, 6.8 Hz, 1H, **H**$_{\mathbf{b}}$-4), 2.32 (s, 3H, C**H**$_{\mathbf{3}}$), 2.29 (s, 3H, C**H**$_{\mathbf{3}}$). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 210.6 (**C**-2), 138.6 (**C**$_{\text{arom}}$), 138.5 (**C**H=CH$_2$), 137.1 (**C**$_{\text{arom}}$), 135.0 (**C**$_{\text{arom}}$), 130.6 (**C**H$_{\text{arom}}$), 130.2 (**C**$_{\text{arom}}$), 125.0 (**C**H$_{\text{arom}}$), 117.2 (CH=**C**H$_2$), 80.0 (**C**-1), 33.7 (**C**-3), 24.6 (**C**-4), 21.2 (**C**H$_3$), 19.8 (**C**H$_3$). IR (ATR) cm^{-1}: 3472 (O-H st), 1720 (C=O st). MS (EI, 70 eV) *m/z* (%): 216 (M$^+$, 47), 196 (100), 183 (38), 173 (60), 159 (71), 146 (31), 128 (34), 115 (44), 103 (10), 91 (23), 77 (16), 55 (19). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{14}$H$_{16}$NaO$_2$]$^+$: 239.1048 [(M+Na)$^+$]; found 239.1053.



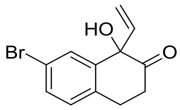
1-hydroxy-5-methoxy-1-vinyl-3,4-dihydronaphthalen-2(1*H*)-one (8d). Following the *General Procedure D*, **8d** (1.99 g, 9.12 mmol) was isolated by FC (hexanes/EtOAc 8:2) starting from **7d** (3.00 g, 15.6 mmol), vinylmagnesium bromide (59.3 mL, 59.3 mmol) and 2-iodoxybenzoic acid (6.55 g, 23.4 mmol). Yield: 58%. Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.27 (t, *J* = 8.0 Hz, 1H, **H**-7), 7.22-7.14 (m, 1H, C**H**$_{\text{arom}}$), 6.81 (d, *J* = 8.1 Hz, 1H, C**H**$_{\text{arom}}$), 5.99-5.84 (m, 1H, C**H**=CH$_2$), 5.28-5.11 (m, 2H, CH=C**H**$_{\mathbf{2}}$), 4.33 (s, 1H, O**H**), 3.83 (s, 3H, OC**H**$_{\mathbf{3}}$), 3.25 (ddd, *J* = 16.2, 7.4, 5.2 Hz, 1H, **H**$_{\mathbf{a}}$-3), 3.11-2.85 (m, 2H, **H**$_{\mathbf{b}}$-3 and **H**$_{\mathbf{a}}$-4), 2.56 (dt, *J* = 16.9, 7.1 Hz, 1H, **H**$_{\mathbf{b}}$-4). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 210.4 (**C**-2), 155.8 (**C**$_{\text{arom}}$), 139.9 (**C**$_{\text{arom}}$), 138.1 (**C**H=CH$_2$), 128.1 (**C**H$_{\text{arom}}$), 123.5 (**C**$_{\text{arom}}$), 118.5 (**C**H$_{\text{arom}}$), 117.1 (CH=**C**H$_2$), 109.2 (**C**H$_{\text{arom}}$), 79.8 (**C**-1), 55.5 (O**C**H$_3$), 33.2 (**C**-3), 21.1 (**C**-4). IR (ATR) cm^{-1}: 3465 (O-H st), 1716 (C=O st). MS (EI, 70 eV) *m/z* (%): 218 (M$^+$, 43), 200 (100), 190 (17), 175 (46), 161 (54), 145 (22), 128 (36), 115 (30), 103 (11), 91 (28), 77 (21), 65 (8), 55 (15). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{13}$H$_{14}$NaO$_3$]$^+$: 241.0841 [(M+Na)$^+$]; found 241.0841.



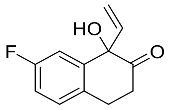
1-hydroxy-7-methoxy-1-vinyl-3,4-dihydronaphthalen-2(1*H*)-one (8e). Following the *General Procedure D*, **8e** (1.36 g, 6.23 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) starting from **7e** (3.07 g, 16.0 mmol), vinylmagnesium bromide (60.8 mL, 60.8 mmol) and 2-iodoxybenzoic acid (6.72 g, 24 mmol). Yield: 39%. Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.14 (d, *J* = 2.7 Hz, 1H, **H**-8), 7.07 (d, *J* = 8.3 Hz, 1H, **H**-5), 6.81 (dd, *J* = 8.3, 2.7 Hz, 1H, **H**-6), 5.86 (dd, *J* = 17.0, 10.3 Hz, 1H, C**H**=CH$_2$), 5.23 (dd, *J* = 10.3, 0.8 Hz, 1H, CH=C$\mathbf{H_{cis}}$H$_{trans}$), 5.11 (dd, *J* = 17.0, 0.8 Hz, 1H, CH=CH$_{cis}\mathbf{H_{trans}}$), 4.33 (s, 1H, O**H**), 3.78 (s, 3H, OC$\mathbf{H_3}$), 3.24-3.06 (m, 1H, $\mathbf{H_a}$-3), 2.99-2.78 (m, 2H, $\mathbf{H_b}$-3 and $\mathbf{H_a}$-4), 2.56 (ddd, *J* = 18.0, 9.1, 7.3 Hz, 1H, $\mathbf{H_b}$-4). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 210.2 (**C**-2), 159.1 ($\mathbf{C}_{arom}$), 139.1 ($\mathbf{C}_{arom}$), 137.2 (**C**H=CH$_2$), 128.7 (**C**H$_{arom}$), 127.1 ($\mathbf{C}_{arom}$), 117.6 (CH=**C**H$_2$), 114.6 (**C**H$_{arom}$), 110.5 (**C**H$_{arom}$), 80.0 (**C**-1), 55.4 (O**C**H$_3$), 33.8 (**C**-3), 26.6 (**C**-4). IR (ATR) cm^{-1}: 3461 (O-H st), 1713 (C=O st). MS (EI, 70 eV) *m/z* (%): 218 (M$^+$, 80), 198 (100), 189 (12), 176 (76), 155 (96), 145 (39), 134 (20), 121(55), 103 (16), 91 (36), 77 (39), 65 (13), 55 (24). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{13}H_{14}NaO_3]^+$: 241.0841 [(M+Na)$^+$]; found 241.0842.



7-bromo-1-hydroxy-1-vinyl-3,4-dihydronaphthalen-2(1*H*)-one (8f). Following the G*eneral Procedure D*, **8f** (1.72 g, 6.44 mmol) was isolated by FC (hexanes/EtOAc 9:1) starting from **7f** (3.00 g, 12.4 mmol), vinylmagnesium bromide (47.1 mL, 47.1 mmol) and 2-iodoxybenzoic acid (5.20 g, 18.6 mmol). Yield: 54%. Orange oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.76 (d, *J* = 2.1 Hz, 1H, **H**-8), 7.40 (dd, *J* = 8.1, 2.1 Hz, 1H, **H**-6), 7.06 (d, *J* = 8.1 Hz, 1H, **H**-5), 5.85 (dd, *J* = 17.1, 10.3 Hz, 1H, C**H**=CH$_2$), 5.28 (d, *J* = 10.3 Hz, 1H, CH=C$\mathbf{H_{cis}}$H$_{trans}$), 5.12 (d, *J* = 17.1 Hz, 1H, CH=CH$_{cis}\mathbf{H_{trans}}$), 4.25 (s, 1H, O**H**), 3.20 (dt, *J* = 16.9, 8.3 Hz, 1H, $\mathbf{H_a}$-3), 3.03-2.83 (m, 2H, $\mathbf{H_b}$-3 and $\mathbf{H_a}$-4), 2.59 (ddd, *J* = 18.1, 9.3, 7.4 Hz, 1H, $\mathbf{H_b}$-4). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 209.3 (**C**-2), 139.9 ($\mathbf{C}_{arom}$), 136.6 (**C**H=CH$_2$), 134.0 ($\mathbf{C}_{arom}$), 130.9 (**C**H$_{arom}$), 129.3 (**C**H$_{arom}$), 129.2 (**C**H$_{arom}$), 121.2 ($\mathbf{C}_{arom}$), 117.9 (CH=**C**H$_2$), 79.6 (**C**-1), 33.2 (**C**-3), 26.8 (**C**-4). IR (ATR) cm^{-1}: 3465 (O-H st), 1713 (C=O st). MS (EI, 70 eV) *m/z* (%): 266 (M$^+$, 30), 248 (100), 236 (6), 223 (36), 211 (44), 196 (15), 181 (10), 168 (42), 157 (7), 144 (77), 131 (28), 115 (69), 102 (28), 89 (31), 77 (30), 55 (40). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{12}H_{11}BrNaO_2]^+$: 288.9840 [(M+Na)$^+$]; found 288.9832.

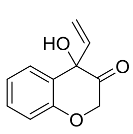


7-fluoro-1-hydroxy-1-vinyl-3,4-dihydronaphthalen-2(1*H*)-one (8g). Following the *General Procedure D*, **8g** (1.73 g, 8.40 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 8:2) starting from **7g** (3.00 g, 16.6 mmol), vinylmagnesium bromide (63.0 mL, 63.0 mmol) and 2-iodoxybenzoic acid (6.97 g, 24.9 mmol). Yield: 51%. Orange oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.28 (dd, *J* = 9.6, 2.8 Hz, 1H, C$\mathbf{H}_{arom}$), 7.11 (dd, *J* = 8.4, 5.4 Hz, 1H, C$\mathbf{H}_{arom}$), 6.91 (m, 1H, C$\mathbf{H}_{arom}$), 5.82 (dd, *J* = 17.1, 10.3 Hz, 1H, C**H**=CH$_2$), 5.22 (d, *J* = 10.3 Hz, 1H, CH=C$\mathbf{H_{cis}}$H$_{trans}$), 5.07 (d, *J* = 17.1 Hz, 1H, CH=CH$_{cis}\mathbf{H_{trans}}$), 4.35 (s, 1H, O**H**), 3.25-3.08 (m, 1H, $\mathbf{H_a}$-3), 2.89 (m, 2H, $\mathbf{H_b}$-3 and $\mathbf{H_a}$-4), 2.53 (ddd, *J* = 18.3, 9.4, 7.0 Hz, 1H, $\mathbf{H_b}$-4). ^{13}C NMR (δ, ppm) (75 MHz, CDCl$_3$):

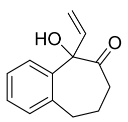


209.6 (**C**=O), 162.2 (d, $^{1}J_{CF}$ = 244.9 Hz, **C**-7), 140.1 (d, $^{3}J_{CF}$ = 7.5 Hz, **C**-8a), 136.7 (**C**H=CH$_2$), 130.8 (d, $^{4}J_{CF}$ = 3.2 Hz, **C**-4a), 129.1 (d, $^{3}J_{CF}$ = 8.1 Hz, **C**-5), 117.8 (CH=**C**H$_2$), 114.9 (d, $^{2}J_{CF}$ = 21.6 Hz, **C**H$_{arom}$), 113.1 (d, $^{2}J_{CF}$ = 23.2 Hz, **C**H$_{arom}$), 79.7 (**C**-1), 33.4 (**C**-3), 26.6 (**C**-4). ^{19}F NMR (δ, ppm) (282 MHz, CDCl$_3$): -114.65. IR (ATR) cm^{-1}: 3468 (O-H st), 1719 (C=O st). MS (EI, 70 eV) *m/z* (%): 206 (M$^+$, 37), 188 (93), 178 (26), 159 (100), 149 (67), 133 (72), 108 (43), 95 (10), 75 (14), 55 (37). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{12}H_{11}FNaO_2$]$^+$: 229.0641 [(M+Na)$^+$]; found 229.0639.

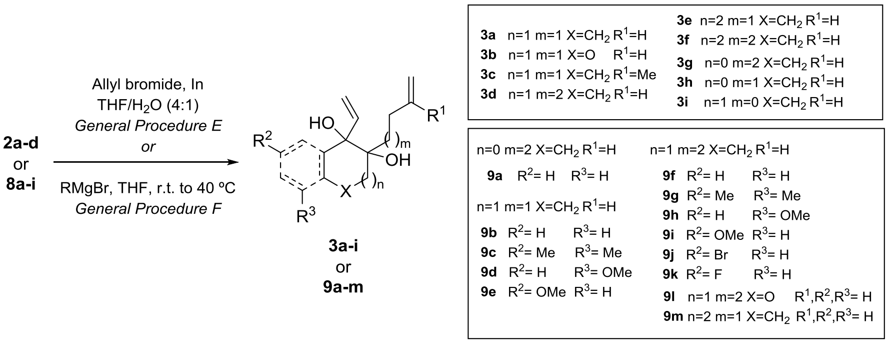
4-hydroxy-4-vinylchroman-3-one (8h). Following the *General Procedure D*, **8h** (1.24 g, 6.45 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 8:2) starting from **7h** (3.75 g, 22.8 mmol), vinylmagnesium bromide (86.6 mL, 86.6 mmol) and 2-iodoxybenzoic acid (9.58 g, 34.2 mmol). Yield: 28% yield. Orange oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.55 (dd, *J* = 7.7, 1.7 Hz, 1H, C**H**$_{arom}$), 7.40-7.22 (m, 1H, C**H**$_{arom}$), 7.13 (td, *J* = 7.5, 1.2 Hz, 1H, C**H**$_{arom}$), 7.04 (dd, *J* = 8.1, 1.2 Hz, 1H, C**H**$_{arom}$), 5.99 (dd, *J* = 17.0, 10.3 Hz, 1H, C**H**=CH$_2$), 5.42-5.18 (m, 2H, CH=C**H$_2$**), 4.82 (d, *J* = 18.6 Hz, 1H, **H$_a$**-2), 4.44 (d, *J* = 18.6 Hz, 1H, **H$_b$**-2), 4.16 (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 207.6 (**C**-3), 153.2 (**C**$_{arom}$), 135.8 (**C**H=CH$_2$), 129.6 (**C**H$_{arom}$), 127.2 (**C**$_{arom}$), 125.9 (**C**H$_{arom}$), 123.9 (**C**H$_{arom}$), 117.6 (**C**H$_{arom}$), 117.4 (CH=**C**H$_2$), 78.6 (**C**-4), 70.4 (**C**-2). IR (ATR) cm^{-1}: 3483 (O-H st), 1734 (C=O st). MS (EI, 70 eV) *m/z* (%): 190 (M$^+$, 5), 172 (29), 162 (21), 147 (48), 135 (29), 121 (100), 105 (10), 92 (16), 77 (28), 63 (13), 51 (10). HRMS (UPLC MS ESI$^-$): Calculated for: [$C_{11}H_9O_3$]$^-$: 189.0552 [(M-H)$^-$]; found 189.0553.



5-hydroxy-5-vinyl-5,7,8,9-tetrahydro-6*H*-benzo[7]annulen-6-one (8i). Following the *General Procedure D*, **8i** (326 mg, 1.61 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 8:2) starting from **7i** (720 mg, 4.09 mmol), vinylmagnesium bromide (15.5 mL, 15.5 mmol) and 2-iodoxybenzoic acid (1.72 g, 6.15 mmol). Yield: 39%. Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.73 – 7.62 (m, 1H, C**H**$_{arom}$), 7.28 (m, 2H, 2 x C**H**$_{arom}$), 7.18 – 7.03 (m, 1H, C**H**$_{arom}$), 6.18 (dd, *J* = 16.9, 10.4 Hz, 1H, C**H**=CH$_2$), 5.69 – 5.37 (m, 2H, CH=C**H$_2$**), 4.44 (s, 1H, O**H**), 3.09 – 2.77 (m, 3H, **H$_a$**-7 and **H**-9), 2.67 (m, 1H, **H$_b$**-7), 2.18 – 1.89 (m, 2H, **H**-8). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 210.6 (**C**-6), 138.5 (**C**$_{arom}$), 137.7 (**C**$_{arom}$), 137.5 (**C**H=CH$_2$), 130.6 (**C**H$_{arom}$), 129.0 (**C**H$_{arom}$), 128.6 (**C**H$_{arom}$), 127.4 (**C**H$_{arom}$), 118.1 (CH=**C**H$_2$), 84.5 (**C**-5), 37.8 (**C**-7), 33.2 (**C**-9), 26.2 (**C**-8). IR (ATR) cm^{-1}: 3462 (O-H st), 1716 (C=O st). MS (EI, 70 eV) *m/z* (%): 202 (M$^+$, 3), 184 (45), 156 (14), 147 (100), 128 (76), 115 (48), 103 (11), 91 (54), 77 (19), 65 (9), 55 (14). HRMS (UPLC MS ESI$^+$): Calculated for: [$NaC_{13}H_{14}O_2$]$^+$: 225.0892 [(M+Na)$^+$]; found 225.0886.



2.3. Synthesis of 1,2-diols 3a-i and 9a-m



General Procedure E: To a solution of the corresponding 2-hydroxy-2-vinyl ketone (1.0 equiv.) in a 4:1 mixture of THF/H$_2$O (3.0 mmol/mL) was added indium beads (2.0 equiv.) and allyl bromide (3.0 equiv.) and stirred overnight at room temperature. The reaction mixture was treated with a saturated aqueous solution of KHSO$_4$. The aqueous phase was extracted with EtOAc, washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/ EtOAc) to yield the desired product.

General Procedure F: A previously prepared solution of the corresponding Grignard reagent[13] (3.8 equiv.) was added under inert atmosphere to a THF solution (0.50 mmol/mL) of the corresponding 2-hydroxy-2-vinyl ketone **2a-d** or **8a-i** (1.0 equiv.). It was stirred at room temperature and then heated at 40 °C for 2 hours before quenching by the addition of aq. NH$_4$Cl solution. The reaction mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/ EtOAc) to yield the desired product.

For aromatic substrates **9a-m**, two diastereomers were obtained in almost equimolar amounts. Although several modifications of metathesis methodology were tried, only one of the diastereomers yield the subsequent ring closing metathesis product. Described yields and experimental data correspond to reactive diastereomer of **9a-m**.

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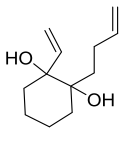
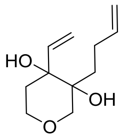
[13] Grignard reagents were synthesized following procedures previously described in the literature. But-3-en-1-ylmagnesium bromide: Davies, J.; Booth, S. G.; Essafi, S.; Dryfe, R. A. W.; Leonori, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 14017; pent-4-en-1-ylmagnesium bromide: Li, X.-H.; Zheng, B.-H.; Ding, C.-H.; Hou, X.-L. *Org. Lett.* **2013**, *15*, 6086; and (3-methylbut-3-en-1-yl) magnesium bromide: Berkowitz, W. F.; Wu, Y. *J. Org. Chem.* **1997**, *62*, 1536.

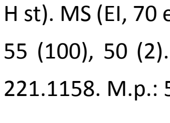
1-(but-3-en-1-yl)-2-vinylcyclohexane-1,2-diol (3a).[14] Following the *General Procedure F*, **3a** (318 mg, 1.62 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **2a** (614 mg, 4.38 mmol) and but-3-en-1-ylmagnesium bromide (17.50 mmol). Yield: 37%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 6.10 (dd, *J*=17.3, 10.9 Hz, 1H, C-2-C**H**=CH_2), 5.80 (ddt, *J*=16.9, 10.1, 6.6 Hz, 1H, CH_2C**H**=CH_2), 5.34 (dd, *J*=17.3, 1.6 Hz, 1H, C-2-CH=CH_{cis}**H_{trans}**), 5.16 (dd, *J*=10.9, 1.6 Hz, 1H, C-2-CH=C**H_{cis}**H_{trans}), 5.09-4.83 (m, 2H, CH_2CH=C**H_2**), 2.34 (s, 1H, O**H**), 2.24-1.95 (m, 2H, C**H_2**CH=CH_2), 2.07* (s, 1H, O**H**) 1.86-1.71 (m, 2H, **H**-6), 1.69-1.28 (m, 8H, **H**-3, **H**-4, **H**-5 and C-1-C**H_2**). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 140.6 (C-2-**C**H=CH_2), 139.3 (CH_2**C**H=CH_2), 114.5 (CH_2CH=**C**H_2), 114.2 (C-2-CH=**C**H_2), 76.6 (**C**-OH), 75.2 (**C**-OH), 35.0 (**C**-6), 34.4 (**C**-3), 31.3 (C-1-**C**H_2), 27.5 (C-1-CH_2**C**H_2), 21.9 (**C**-5), 21.6 (**C**-4). IR (ATR) cm^{-1}: 3425 (O-H st), 2944 (=C-H st). MS (EI, 70 eV) *m/z* (%): 160 (M^+ - 2·H_2O, 1), 136 (7), 124 (16), 95 (41), 79 (39), 67 (30), 55 (100). HRMS (UPLC MS ESI^+): Calculated for $[C_{12}H_{20}NaO_2]^+$: 219.1361 [$(M+Na)^+$]; found: 219.1362. M.p.: 50-52 °C (hexanes/EtOAc).



3-(but-3-en-1-yl)-4-vinyltetrahydro-2*H*-pyran-3,4-diol (3b). Following the *General Procedure F*, **3b** (160 mg, 0.81 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) starting from **2b** (400 mg, 2.80 mmol) and but-3-en-1-ylmagnesium bromide (10.6 mmol). Yield: 29%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 6.27 (dd, *J* = 17.6, 10.9 Hz, 1H, C-4-C**H**=$CH_{cis}H_{trans}$), 5.78 (ddt, *J* = 16.8, 10.0, 6.5 Hz, 1H, CH_2C**H**=$CH_{cis}H_{trans}$), 5.36-5.18 (m, 2H, C-4-CH=C**H_2**), 5.09-4.86 (m, 2H, CH_2CH=C**H_2**), 3.85-3.70 (m, 3H, **H**-6 and **H_a**-2), 3.57 (d, *J* = 11.6 Hz, 1H, **H_b**-2), 2.60 (s, 1H, O**H**), 2.31-2.10 (m, 2H, C**H_2**CH=CH_2), 2.03-1.86 (m, 1H, **H_a**-5), 1.59* (s, 1H, O**H**), 1.66-1.42 (m, 2H, **H_b**-5 and C-3-C**H_a**H_b), 1.27 (dt, *J* = 14.4, 2.2 Hz, 1H, C-3-CH_a**H_b**). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 141.7 (C-4-**C**H=CH_2), 139.0 (CH_2**C**H=CH_2), 114.6 (CH_2CH=**C**H_2), 113.8 (C-4-CH=**C**H_2), 74.4 (**C**-OH), 72.6 (**C**-OH), 70.6 (**C**-2), 63.6 (**C**-6), 35.3 (**C**-5), 30.1 (C-3-CH_2**C**H_2), 26.9 (C-3-**C**H_2). IR (ATR) cm^{-1}: 3379 (O-H st), 2959 (=C-H st). MS (EI, 70 eV) *m/z* (%): 157 (1), 151 (1), 135 (2), 114 (10), 97 (12), 91 (5), 83 (80), 77 (6), 67 (13), 55 (100), 50 (2). HRMS (UPLC MS ESI^+): Calculated for $[C_{11}H_{18}NaO_3]^+$: 221.1154 [$(M+Na)^+$]; found: 221.1158. M.p.: 58-60 °C (hexanes/EtOAc).



1-(3-methylbut-3-en-1-yl)-2-vinylcyclohexane-1,2-diol (3c). Following the *General Procedure D*, **3c** (500 mg, 2.38 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **2a** (1.00 g, 7.10 mmol) and (3-methylbut-3-en-1-yl) magnesium bromide (28.4 mmol). Yield: 34%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$):



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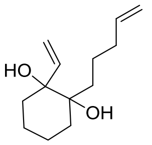
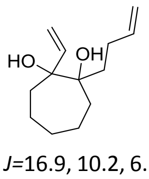
[14] Relative configuration of the isolated product is assumed to be *trans* based on reported literature on Grignard addition to 2-hydroxy-2-vinyl-cyclohexanone: Barnier, J. P.; Conia, J. M. *Bull. Soc. Chim. Fr.* **1975**, *304*, 1659.

(*denotes partially overlapped resonances): 6.10 (dd, *J* = 17.3, 10.9 Hz, 1H, C-2-C**H**=CH$_2$), 5.33 (dd, *J* = 17.3, 1.6 Hz, 1H, C-2-CH=CH$_{cis}$$\mathbf{H_{trans}}$), 5.14 (dd, *J* = 10.9, 1.6 Hz, 1H, C-2-CH=C$\mathbf{H_{cis}}$H$_{trans}$), 4.64 (s, 2H, CCH$_3$=C$\mathbf{H_2}$), 2.45 (s, 1H, O**H**), 2.17 (s, 1H, O**H**), 2.12 – 1.89 (m, 2H, C-1-CH$_2$C$\mathbf{H_2}$), 1.84 – 1.66 (m, 2H, **H**-6), 1.69* (s, 3H, C$\mathbf{H_3}$), 1.66 – 1.49 (m, 5H, **H**-3, **H**-4 and $\mathbf{H_a}$-5), 1.49 – 1.25 (m, 3H, $\mathbf{H_b}$-5 and C-1-C$\mathbf{H_2}$). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 146.5 (**C**CH$_3$=CH$_2$), 140.6 (C-2-**C**H=CH$_2$), 114.1 (C-2-CH=**C**H$_2$), 109.7 (CCH$_3$=**C**H$_2$), 76.6 (**C**-OH), 75.2 (**C**-OH), 35.0 (**C**-6), 33.2 (**C**-3), 31.3 (C-1-CH$_2$**C**H$_2$), 31.1 (C-1-**C**H$_2$), 22.8 (C**C**H$_3$=CH$_2$), 21.9 (**C**-5), 21.6 (**C**-4). IR (ATR) cm^{-1}: 3433 (O-H st), 3339 (O-H st), 2945(=C-H st), 2934 (=C-H st). MS (EI, 70 eV) *m/z* (%): 192 (5), 174 (5), 159 (7), 138 (52), 125 (21), 115 (17), 105 (16), 95 (98), 79 (45), 69 (45), 55 (100). HRMS (UPLC MS ESI$^+$): Calculated for [NaC$_{13}$H$_{22}$O$_2$]$^+$: 233.1518 [(M+Na)$^+$]; found: 233.1526. M.p.: 58-60 °C (hexanes/EtOAc).



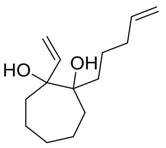
1-(pent-4-en-1-yl)-2-vinylcyclohexane-1,2-diol (3d). Following the *General Procedure F*, **3d** (160 mg, 0.76 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **2a** (358 mg, 2.55 mmol) and pent-4-en-1-ylmagnesium bromide (10.2 mmol). Yield: 30%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 6.09 (dd, *J*=17.3, 10.8 Hz, 1H, C-2-C**H**=CH$_2$), 5.78 (ddt, *J*=16.9, 10.1, 6.6 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.33 (dd, *J*=17.3, 1.6 Hz, 1H, C-2-CH=CH$_{cis}$$\mathbf{H_{trans}}$), 5.15 (dd, *J*=10.8, 1.7 Hz, 1H, C-2-CH=C$\mathbf{H_{cis}}$H$_{trans}$), 5.07-4.81 (m, 2H, CH$_2$CH=C$\mathbf{H_2}$), 2.34 (s, 1H, O**H**), 2.09-1.93 (m, 2H, C$\mathbf{H_2}$CH=CH$_2$), 2.00* (s, 1H, O**H**), 1.87-1.20 (m, 12H, C-1-C$\mathbf{H_2}$, C-1-CH$_2$C$\mathbf{H_2}$, **H**-3, **H**-4, **H**-5 and **H**-6). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 140.8 (C-2-**C**H=CH$_2$), 138.8 (CH$_2$**C**H=CH$_2$), 114.6 (CH$_2$CH=**C**H$_2$), 114.1 (C-2-CH=**C**H$_2$), 76.6 (**C**-OH), 75.4 (**C**-OH), 35.0 (**C**H$_2$CH=CH$_2$), 34.6 (**C**-6), 34.3 (**C**-3), 31.3 (C-1-**C**H$_2$), 22.4 (**C**-5), 22.0 (C-1-CH$_2$**C**H$_2$), 21.5 (**C**-4). IR (ATR) cm^{-1}: 3418 (O-H st), 2948(=C-H st), 2862 (=C-H st). MS (EI, 70 eV) *m/z* (%): 192 (M$^+$ - H$_2$O, 1), 151 (15), 138 (15), 123 (21), 109 (21), 95 (51), 84 (31), 69 (57), 55 (100). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{13}$H$_{22}$NaO$_2$]$^+$: 233.1518 [(M+Na)$^+$]; found: 233.1519. M.p.: 51-53 °C (hexanes/EtOAc).



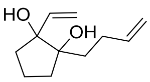
1-(but-3-en-1-yl)-2-vinylcycloheptane-1,2-diol (3e). Following the *General Procedure F*, **3e** (129 mg, 0.61 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **2c** (157 mg, 1.02 mmol) and but-3-en-1-ylmagnesium bromide (4.08 mmol). Yield: 60% yield. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 6.06 (dd, *J*=17.2, 10.8 Hz, 1H, C-2-C**H**=CH$_2$), 5.82 (ddt, *J*=16.9, 10.2, 6.6 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.34 (dd, *J*=17.3, 1.6 Hz, 1H, C-2-CH=CH$_{cis}$$\mathbf{H_{trans}}$), 5.16 (dd, *J*=10.8, 1.6 Hz, 1H, C-2-CH=C$\mathbf{H_{cis}}$H$_{trans}$), 5.08-4.86 (m, 2H, CH$_2$CH=C$\mathbf{H_2}$), 2.46 (s, 1H, O**H**), 2.29-2.00 (m, 3H, C$\mathbf{H_2}$CH=CH$_2$ and $\mathbf{H_a}$-7), 1.98-1.87 (m, 1H, $\mathbf{H_b}$-7), 1.95* (s, 1H, O**H**), 1.85-1.39 (m, 10H, **H**-3, **H**-4, **H**-5, **H**-6 and C-1-C$\mathbf{H_2}$). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 142.2 (C-2-**C**H=CH$_2$), 139.3 (CH$_2$**C**H=CH$_2$), 114.5 (CH$_2$CH=**C**H$_2$), 113.7 (C-2-CH=**C**H$_2$), 79.1 (**C**-OH), 78.2 (**C**-OH), 36.6 (**C**-3), 35.5 (**C**-7), 31.8 (C-1-**C**H$_2$), 27.9

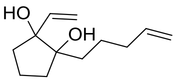
(**C**H$_2$CH=CH$_2$), 26.2 (**C**-5), 20.3 (**C**-4), 20.1 (**C**-6). IR (ATR) cm^{-1}: 3386 (O-H st), 2949 (=C-H st), 2918 (=C-H st). MS (EI, 70 eV) *m/z* (%): 192 (M$^+$ - H$_2$O, 1), 176 (2), 137 (11), 109 (21), 91 (27), 83 (36), 67 (46), 55 (100). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{13}H_{22}NaO_2]^+$: 233.1518 [(M+Na)$^+$]; found: 233.1523. M.p.: 47-49 °C (hexanes/EtOAc).

1-(pent-4-en-1-yl)-2-vinylcycloheptane-1,2-diol (3f). Following the *General Procedure F*, **3f** (450 mg, 2.00 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **2c** (630 mg, 4.08 mmol) and pent-4-en-1-ylmagnesium bromide (16.3 mmol). Yield: 49%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 6.06 (dd, *J*=17.2, 10.8, 1H, C-2-C**H**=CH$_2$), 5.80 (ddt, *J*=16.9, 10.1, 6.6, 1H, CH$_2$C**H**=CH$_2$), 5.35 (dd, *J*=17.2, 1.6, 1H, C-2-CH=CH$_{cis}\mathbf{H}_{\mathbf{trans}}$), 5.17 (dd, *J*=10.8, 1.6, 1H, C-2-CH=C$\mathbf{H}_{\mathbf{cis}}H_{trans}$), 5.08-4.89 (m, 2H, CH$_2$CH=C$\mathbf{H_2}$), 2.41 (s, 1H, O**H**), 2.27-1.31 (m, 16H, C-1-C$\mathbf{H_2}$, C-1-CH$_2$C$\mathbf{H_2}$, C$\mathbf{H_2}$CH=CH$_2$, **H**-3, **H**-4, **H**-5, **H**-6 and **H**-7), 1.80* (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 142.4 (C-2-**C**H=CH$_2$), 138.8 (CH$_2$**C**H=CH$_2$), 114.7 (CH$_2$CH=**C**H$_2$), 113.5 (C-2-CH=**C**H$_2$), 79.0 (**C**-OH), 78.4 (**C**-OH), 36.5 (**C**H$_2$CH=CH$_2$), 35.6 (**C**-3), 34.4 (**C**-7), 31.6 (C-1-**C**H$_2$), 26.2 (**C**-5), 22.7 (**C**-4), 20.3 (**C**-6), 20.0 (C-1-CH$_2$**C**H$_2$). IR (ATR) cm^{-1}: 3440 (O-H st), 3321 (O-H st), 2940 (=C-H st), 2920 (=C-H st). MS (EI, 70 eV) *m/z* (%): 188 (M$^+$ - 2·H$_2$O, 2), 165 (11), 147 (8), 119 (32), 109 (), 91 (39), 79 (44), 67 (82), 55 (100). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{14}H_{24}NaO_2]^+$: 247.1674 [(M+Na)$^+$]; found: 247.1678. M.p.: 54-56 °C (hexanes/EtOAc).

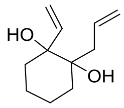


1-(but-3-en-1-yl)-2-vinylcyclopentane-1,2-diol (3g). Following the *General Procedure F,* **3g** (390 mg, 2.14 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **2d** (545 mg, 4.30 mmol) and but-3-en-1-ylmagnesium bromide (17.2 mmol). Yield: 50%. Orange oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 6.09 (dd, *J* = 17.6, 11.0 Hz, 1H, C-2-C**H**=CH$_2$), 5.82 (ddt, *J* = 16.8, 10.3, 6.6 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.32 (dd, *J* = 17.6, 1.5 Hz, 1H, C-2-CH=CH$_{cis}\mathbf{H}_{\mathbf{trans}}$), 5.22 (dd, *J* = 11.0, 1.5 Hz, 1H, C-2-CH=C$\mathbf{H}_{\mathbf{cis}}H_{trans}$), 5.06-4.86 (m, 2H, CH$_2$CH=C$\mathbf{H_2}$), 2.28-2.13 (m, 2H, C$\mathbf{H_2}$CH=CH$_2$), 2.13-1.98 (m, 1H, $\mathbf{H_a}$-3), 1.96-1.86 (m, 1H, $\mathbf{H_b}$-3), 1.83-1.63 (m, 4H, **H**-5 and C-1-C$\mathbf{H_2}$), 1.80* (s, 1H, O**H**), 1.60-1.36 (m, 2H, **H**-4), 1.50* (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 139.9 (C-2-**C**H=CH$_2$), 139.3 (CH$_2$**C**H=CH$_2$), 115.4 (CH$_2$CH=**C**H$_2$), 114.4 (C-2-CH=**C**H$_2$), 85.05 (**C**-OH), 85.01 (**C**-OH), 37.4 (**C-5**), 35.6 (**C**-3), 33.1 (C-1-**C**H$_2$), 28.6 (C-1-CH$_2$**C**H$_2$), 19.5 (**C**-4). IR (ATR) cm^{-1}: 3468 (O-H st), 2974 (=C-H st). MS (EI, 70 eV) *m/z* (%): 146 (M-2.H$_2$O, 3), 135 (4), 127 (11), 117 (6), 111 (21), 105 (14), 98 (11), 91 (9), 83 (43), 77 (11), 70 (12), 55 (100). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{11}H_{18}NaO_2]^+$: 205.1205 [(M+Na)$^+$]; found: 205.1204.

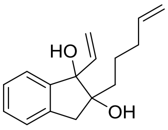




1-(pent-4-en-1-yl)-2-vinylcyclopentane-1,2-diol (3h). Following the *General Procedure F*, **3h** (500 mg, 2.55 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **2d** (603 mg, 4.75 mmol) and pent-4-en-1-ylmagnesium bromide (19.00 mmol). Yield: 54%. Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 6.10 (dd, *J*=17.5, 10.9 Hz, 1H, C-2-C**H**=CH$_2$), 5.79 (ddt, *J*=16.9, 10.2, 6.6 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.50-5.16 (m, 2H, CH$_2$CH=C**H$_2$**), 5.10-4.76 (m, 2H, C-2-CH=C**H$_2$**), 2.32-2.15 (m, 1H, C**H$_a$**H$_b$CH=CH$_2$), 2.08-1.98 (m, 2H, **H**-3), 1.97-1.86 (m, 1H, CH$_a$**H$_b$**CH=CH$_2$), 1.85-1.23 (m, 10H, **H**-4, **H**-5, C-1-C**H$_2$**, C-1-CH$_2$C**H$_2$** and 2 x O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 140.0 (C-2-**C**H=CH$_2$), 138.9 (CH$_2$**C**H=CH$_2$), 115.4 (CH$_2$CH=**C**H$_2$), 114.6 (C-2-CH=**C**H$_2$), 85.11 (**C**-OH), 85.05 (**C**-OH), 37.4 (**C**H$_2$CH=CH$_2$), 35.7 (**C**-5), 34.4 (**C**-3), 33.5 (C-1-**C**H$_2$), 23.5 (C-1-CH$_2$**C**H$_2$), 19.5 (**C**-4). IR (ATR) cm^{-1}: 3465 (O-H st), 2973 (=C-H st), 2942 (=C-H st). MS (EI, 70 eV) *m/z* (%): 167 (1), 155 (12), 137 (11), 125 (23), 109 (11), 83 (58), 55(100). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{12}$H$_{20}$NaO$_2$]$^+$: 219.1361 [(M+Na)$^+$]; found: 219.1360.



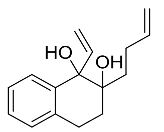
1-allyl-2-vinylcyclohexane-1,2-diol (3i). Following the *General Procedure E*, **3i** (385 mg, 2.12 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) starting from **2a** (445 mg, 3.17 mmol). Yield: 67%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 6.14 (dd, *J* = 17.2, 10.9 Hz, 1H, C-2-C**H**=CH$_2$), 5.88 (ddt, *J* = 17.4, 10.2, 7.4, 1H, C-1-CH$_2$C**H**=CH$_2$), 5.36 (dd, *J* = 17.2, 1.7, 1H, C-1-CH$_2$CH=CH$_{cis}$**H$_{trans}$**), 5.12 (m, 3H, C-1-CH$_2$CH=C**H$_{cis}$**H$_{trans}$ and C-2-CH=C**H$_2$**), 2.39* (s, 1H, O**H**), 2.36-2.25 (m, 1H, C-1-C**H$_a$**H$_b$CH=CH$_2$), 2.23-2.13 (m, 1H, C-1-CH$_a$**H$_b$**CH=CH$_2$), 2.20* (s, 1H, O**H**), 1.87-1.32 (m, 8H, **H**-3, **H**-4, **H**-5 and **H**-6). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 140.1 (C-2-**C**H=CH$_2$), 134.1 (C-1-CH$_2$**C**H=CH$_2$), 118.6 (C-1-CH$_2$CH=**C**H$_2$), 114.3 (C-2-CH=**C**H$_2$), 76.4 (**C**-OH), 74.7 (**C**-OH), 40.4 (C-1- **C**H$_2$CH=CH$_2$), 35.5 (**C**-6), 32.7 (**C**-3), 21.9 (**C**-5), 21.5 (**C**-4). IR (ATR) cm^{-1}: 3391 (O-H st), 2924 (=C-H st). MS (EI, 70 eV) *m/z* (%): 164 (M$^+$ - H$_2$O, 2), 123 (41), 95 (100), 79 (34), 67 (42), 55 (94). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{11}$H$_{18}$NaO$_2$]$^+$: 205.1205 [(M+Na)$^+$]; found: 205.1209. M.p.: 50-52 °C (hexanes/EtOAc).



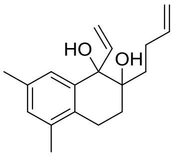
2-(pent-4-en-1-yl)-1-vinyl-2,3-dihydro-1*H*-indene-1,2-diol (9a). Following the G*eneral Procedure F*, **9a** (298 mg, 1.22 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 8:2) starting from **6a** (1.00 g, 5.74 mmol) and pent-4-en-1-ylmagnesium bromide (21.8 mmol). Yield: 21% (major diastereomer). Yellow solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 7.34-7.14 (m, 4H, 4 x C**H$_{arom}$**), 6.23 (dd, *J* = 17.4, 10.9 Hz, 1H, C-1-C**H**=CH$_2$), 5.86 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.55-5.41 (m, 2H, C-1-CH=C**H$_2$**), 5.13-4.93 (m, 2H, CH$_2$CH=C**H$_2$**), 3.16 (d, *J* = 16.0 Hz, 1H, **H$_a$**-3), 2.85 (d, *J* = 16.0 Hz, 1H, **H$_b$**-3), 2.21-2.04 (m, 2H, C**H$_2$**CH=CH$_2$), 1.84* (s, 1H, O**H**), 1.93-1.78 (m, 1H, C-2-C**H$_a$**H$_b$), 1.63* (s, 1H, O**H**), 1.78-1.57 (m, 2H, C-2-CH$_a$**H$_b$** and C-2-CH$_2$C**H$_a$**H$_b$), 1.56-1.39 (m, 1H, C-2-CH$_2$CH$_a$**H$_b$**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 145.4 (**C**$_{arom}$), 141.9 (**C**$_{arom}$), 138.9 (C-1-**C**H=CH$_2$), 137.6

(CH$_2$**C**H=CH$_2$), 129.1 (**C**H$_{\text{arom}}$), 127.1 (**C**H$_{\text{arom}}$), 125.8 (**C**H$_{\text{arom}}$), 124.4 (**C**H$_{\text{arom}}$), 117.3 (CH$_2$CH=**C**H$_2$), 114.7 (C-1-CH=**C**H$_2$), 86.4 (**C**-OH), 86.0 (**C**-OH), 42.9 (**C**-3), 34.4 (**C**H$_2$CH=CH$_2$), 33.4 (C-2-**C**H$_2$), 23.3 (C-2-CH$_2$**C**H$_2$). IR (ATR) cm^{-1}: 3526 (O-H st), 3436 (O-H st), 2930 (=C-H st). MS (EI, 70 eV) *m/z* (%): 226 (M$^+$ - H$_2$O, 8), 215 (39), 197 (15), 185 (9), 172 (33), 161 (34), 144 (38), 129 (100), 115 (59), 102 (9), 91 (34), 78 (5), 69 (38), 55 (55). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{16}$H$_{20}$NaO$_2$]$^+$: 267.1361 [(M+Na)$^+$]; found 267.1362. M.p.: 73-75 °C (hexanes/EtOAc).

2-(but-3-en-1-yl)-1-vinyl-1,2,3,4-tetrahydronapthalene-1,2-diol (9b). Following the G*eneral Procedure F*, **9b** (311 mg, 1.27 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **8b** (845 mg, 4.49 mmol) and but-3-en-1-ylmagnesium bromide (17.1 mmol). Yield: 28% (major diastereomer). Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 7.46-7.40 (m, 1H, C**H**$_{\text{arom}}$), 7.26-7.15 (m, 2H, 2 x C**H**$_{\text{arom}}$), 7.14-7.06 (m, 1H, C**H**$_{\text{arom}}$), 6.04 (dd, *J* = 17.1, 10.6 Hz, 1H, C-1-C**H**=CH$_2$), 5.87 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.39-5.21 (m, 2H, C-1-CH=C**H$_2$**), 5.13-4.91 (m, 2H, CH$_2$CH=C**H$_2$**), 3.02 (ddd, *J* = 17.4, 8.9, 6.2 Hz, 1H, **H$_a$**-4), 2.89-2.72 (m, 1H, **H$_b$**-4), 2.82* (s, 1H, O**H**), 2.42-2.04 (m, 3H, C**H$_2$**CH=CH$_2$ and **H$_a$**-3), 2.13* (s, 1H, O**H**) 1.99-1.73 (m, 2H, **H$_b$**-3 and C-2-C**H$_a$**H$_b$), 1.55 (ddd, *J* = 14.1, 11.2, 5.3 Hz, 1H, C-2-CH$_a$**H$_b$**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 140.9 (C-1-**C**H=CH$_2$), 139.7 (**C**$_{\text{arom}}$), 139.2 (CH$_2$**C**H=CH$_2$), 135.4 (**C**$_{\text{arom}}$), 128.9 (**C**H$_{\text{arom}}$), 128.5 (**C**H$_{\text{arom}}$), 127.6 (**C**H$_{\text{arom}}$), 126.6 (**C**H$_{\text{arom}}$), 115.4 (CH$_2$CH=**C**H$_2$), 114.8 (C-1-CH=**C**H$_2$), 78.1 (**C**-OH), 74.8 (**C**-OH), 34.7 (C-2-**C**H$_2$), 28.4 (**C**-4), 27.8 (**C**H$_2$CH=CH$_2$), 25.7 (**C**-3). IR (ATR) cm^{-1}: 3468 (O-H st), 2941 (=C-H st). MS (EI, 70 eV) *m/z* (%): 226 (M$^+$ - H$_2$O, 8), 208 (10), 172 (24), 143 (100), 128 (65), 115 (41), 91 (16), 83 (13), 55 (20). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{16}$H$_{20}$NaO$_2$]$^+$: 267.1361 [(M+Na)$^+$]; found 267.1360.

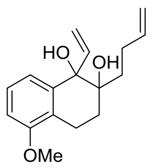


2-(but-3-en-1-yl)-5,7-dimethyl-1-vinyl-1,2,3,4-tetrahydronapthalene -1,2-diol (9c). Following the *General Procedure F*, **9c** (350 mg, 1.28 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **8c** (1.05 g, 4.85 mmol) and but-3-en-1-ylmagnesium bromide (18.4 mmol). Yield: 26% (major diastereomer). Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 7.13 (d, *J* = 1.9 Hz, 1H, C**H**$_{\text{arom}}$), 6.93 (d, *J* = 1.9 Hz, 1H, C**H**$_{\text{arom}}$), 6.05 (dd, *J* = 17.1, 10.7 Hz, 1H, C-1-C**H**=CH$_2$), 5.88 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.38 (dd, *J* = 17.1, 1.7 Hz, 1H, C-1-CH=CH$_{\text{cis}}$**H$_{\text{trans}}$**), 5.27 (dd, *J* = 10.7, 1.7 Hz, 1H, C-1-CH=C**H$_{\text{cis}}$**H$_{\text{trans}}$), 5.14-4.94 (m, 2H, CH$_2$CH=C**H$_{\text{cis}}$H$_{\text{trans}}$**), 2.82 (s, 1H, O**H**), 2.79-2.69 (m, 1H, **H$_a$**-4), 2.70-2.54 (m, 1H, **H$_b$**-4), 2.29* (s, 3H, C**H$_3$**), 2.24* (s, 3H, C**H$_3$**), 2.37-2.11 (m, 4H, C**H$_2$**CH=CH$_2$, **H$_a$**-3 and O**H**), 1.98-1.74 (m, 2H, **H$_b$**-3 and C-2-C**H$_a$**H$_b$), 1.64-1.47 (m, 1H, C-2-CH$_a$**H$_b$**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 140.9 (C-1-**C**H=CH$_2$), 139.4 (**C**$_{\text{arom}}$), 139.1 (CH$_2$**C**H=CH$_2$), 135.72 (**C**$_{\text{arom}}$), 135.67 (**C**$_{\text{arom}}$), 130.7 (**C**$_{\text{arom}}$), 130.0 (**C**H$_{\text{arom}}$), 126.8 (**C**H$_{\text{arom}}$), 115.0 (CH$_2$CH=**C**H$_2$), 114.5 (C-1-CH=**C**H$_2$), 78.2 (**C**-OH), 74.3 (**C**-OH), 34.5 (C-2-**C**H$_2$), 28.0 (C-2-CH$_2$**C**H$_2$), 27.7

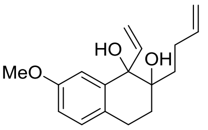


(**C**-4), 23.2 (**C**-3), 21.0 (**C**H$_3$), 19.6 (**C**H$_3$). IR (ATR) cm^{-1}: 3500 (O-H st), 2933 (=C-H st). MS (EI, 70 eV) *m/z* (%): 254 (M$^+$ - H$_2$O, 5), 236 (7), 200 (18), 185 (8), 171 (100), 156 (39), 141 (28), 128 (22), 115 (20), 102 (3), 91 (10), 83 (11), 65 (3), 55 (41). HRMS (UPLC MS ESI+): Calculated for [C$_{18}$H$_{24}$NaO$_2$]$^+$: 295.1674 [(M+Na)$^+$]; found 295.1673.

2-(but-3-en-1-yl)-5-methoxy-1-vinyl-1,2,3,4-tetrahydronapthalene-1,2-diol (9d). Following the *General Procedure F*, **9d** (582 mg, 2.12 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **8d** (1.85 g, 8.48 mmol) and but-3-en-1-ylmagnesium bromide (32.0 mmol). Yield: 25% (major diastereomer). Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 7.19 (t, *J* = 7.9 Hz, 1H, **H**-7), 7.05 (d, *J* = 7.9 Hz, 1H, **H**-8), 6.75 (d, *J* = 7.9 Hz, 1H, **H**-6), 6.03 (dd, *J* = 17.1, 10.7 Hz, 1H, C1-C**H**=CH$_2$), 5.86 (ddt, *J* = 16.8, 9.9, 6.6 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.41-5.17 (m, 2H, CH$_2$CH=C**H$_2$**), 5.13-4.92 (m, 2H, C1-CH=C**H$_2$**), 3.83 (s, 3H, OC**H$_3$**), 2.82* (s, 1H, O**H**), 2.89-2.65 (m, 2H, **H**-4), 2.40-2.10 (m, 3H, C**H$_2$**CH=CH$_2$ and **H$_a$**-3), 2.06 (s, 1H, O**H**), 1.96-1.76 (m, 2H, **H$_b$**-3 and C-2-C**H$_a$**H$_b$), 1.61-1.47 (m, 1H, C-2-CH$_a$**H$_b$**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 156.6 (**C**-5), 141.0 (**C**-8$_a$), 140.8 (C-1-**C**H=CH$_2$), 139.2 (CH$_2$**C**H=CH$_2$), 127.1 (**C**H$_{arom}$), 124.5 (**C**-4$_a$), 120.7 (**C**H$_{arom}$), 115.4 (CH$_2$CH=**C**H$_2$), 114.7 (C-1-CH=**C**H$_2$), 108.5 (**C**H$_{arom}$), 78.0 (**C**-OH), 74.5 (**C**-OH), 55.5 (O**C**H$_3$), 34.6 (C-2-**C**H$_2$), 27.8 (**C**H$_2$CH=CH$_2$), 27.7 (**C**-4), 20.1 (**C**-3). MS (EI, 70 eV) *m/z* (%): 256 (M$^+$ - H$_2$O, 11), 238 (11), 202 (31), 189 (18), 173 (100), 158 (52), 145 (21), 128 (35), 115 (54), 103 (7), 91 (22), 77 (15), 55 (54). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{17}$H$_{22}$NaO$_3$]$^+$: 297.1467 [(M+Na)$^+$]; found 297.1415.

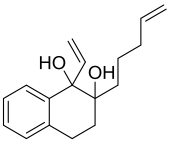


2-(but-3-en-1-yl)-7-methoxy-1-vinyl-1,2,3,4-tetrahydronapthalene-1,2-diol (9e). Following the *General Procedure F*, **9e** (358 mg, 1.30 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **8e** (1.78 g, 8.15 mmol) and but-3-en-1-ylmagnesium bromide (31.0 mmol). Yield: 16% (major diastereomer). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 7.02 (d, *J* = 8.4 Hz, 1H, **H**-5), 6.97 (d, *J* = 2.7 Hz, 1H, **H**-8), 6.77 (dd, *J* = 8.4, 2.7 Hz, 1H, **H**-6), 6.01 (dd, *J* = 17.1, 10.7 Hz, 1H, C-1-C**H**=CH$_2$), 5.86 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.31 (dd, *J* = 17.1, 1.6 Hz, 1H, C-1-CH=CH$_{cis}$**H$_{trans}$**), 5.24 (dd, *J* = 10.7, 1.6 Hz, 1H, C-1-CH=C**H$_{cis}$**H$_{trans}$), 5.13-4.90 (m, 2H, CH$_2$CH=C**H$_2$**), 3.76 (s, 3H, OC**H$_3$**), 2.90* (s, 1H, O**H**), 3.01-2.83 (m, 1H, **H$_a$**-4), 2.74 (dt, *J* = 17.2, 5.8 Hz, 1H, **H$_b$**-4), 2.12*(s, 1H, O**H**), 2.40-2.05 (m, 3H, C**H$_2$**CH=CH$_2$ and **H$_a$**-3), 1.96-1.76 (m, 2H, **H$_b$**-3 and C-2-C**H$_a$**H$_b$), 1.65-1.43 (m, 1H, C-2-CH$_a$**H$_b$**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 158.3 (**C**-7), 140.9 (**C**$_{arom}$), 140.7 (C-1-**C**H=CH$_2$), 139.2 (CH$_2$**C**H=CH$_2$), 129.5 (**C**H$_{arom}$), 127.4 (**C**$_{arom}$), 115.5 (CH$_2$CH=**C**H$_2$), 114.7 (**C**H$_{arom}$), 114.5 (C-1-CH=**C**H$_2$), 113.0 (**C**H$_{arom}$), 78.2 (**C**-OH), 74.8 (**C**-OH), 55.4 (O**C**H$_3$), 34.6 (C-2-**C**H$_2$), 28.5 (**C**-4), 27.8 (**C**H$_2$CH=CH$_2$), 24.8 (**C**-3). IR (ATR) cm^{-1}: 3480 (O-H st), 2946 (=C-H st). MS (EI, 70 eV) *m/z* (%): 256 (M$^+$ - H$_2$O, 12), 238 (M$^+$ - 2.H$_2$O, 14), 202 (22), 189 (10), 173

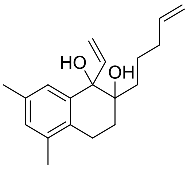


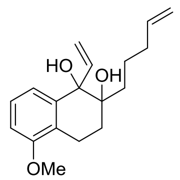
(100), 158 (46), 141 (23), 128 (47), 115 (60), 102 (15), 91 (18), 77 (21), 65 (8), 55 (74). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{17}H_{22}NaO_3$]$^+$: 297.1467 [(M+Na)$^+$]; found 297.2467.

2-(pent-4-en-1-yl)-1-vinyl-1,2,3,4-tetrahydronapthalene-1,2-diol (9f). Following the *General Procedure F*, **9f** (323 mg, 1.25 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **8b** (966 mg, 5.13 mmol) and pent-4-en-1-ylmagnesium bromide (19.5 mmol). Yield: 24% (major diastereomer). Yellow solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.48-7.36 (m, 1H, C**H**$_{arom}$), 7.30-7.14 (m, 2H, 2 x C**H**$_{arom}$), 7.16-7.08 (m, 1H, C**H**$_{arom}$), 6.04 (ddd, *J* = 17.1, 10.7, 1.2 Hz, 1H, C-1-C**H**=CH$_2$), 5.92-5.73 (m, 1H, CH$_2$C**H**=CH$_2$), 5.39-5.19 (m, 2H, C-1-CH=C**H$_2$**), 5.11-4.92 (m, 2H, CH$_2$CH=C**H$_2$**), 3.14-2.91 (m, 1H, **H$_a$**-4), 2.90-2.69 (m, 1H, **H$_b$**-4), 2.79* (s, 1H, O**H**), 2.23-2.00 (m, 3H, C**H$_2$**CH=CH$_2$ and **H$_a$**-3), 2.03* (s, 1H, O**H**), 1.97-1.82 (m, 1H, **H$_b$**-3), 1.79-1.40 (m, 4H, C-2-C**H$_2$** and C-2-CH$_2$C**H$_2$**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 140.9 (C-1-**C**H=CH$_2$), 139.7 (**C**$_{arom}$), 138.8 (CH$_2$**C**H=CH$_2$), 135.5 (**C**$_{arom}$), 129.0 (**C**H$_{arom}$), 128.5 (**C**H$_{arom}$), 127.6 (**C**H$_{arom}$), 126.6 (**C**H$_{arom}$), 115.4 (CH$_2$CH=**C**H$_2$), 114.8 (C-1-CH=**C**H$_2$), 78.2 (**C**-OH), 74.8 (**C**-OH), 35.0 (**C**H$_2$CH=CH$_2$), 34.4 (C-2-**C**H$_2$), 28.3 (**C**-4), 25.8 (**C**-3), 22.7 (C-2-CH$_2$**C**H$_2$). IR (ATR) cm^{-1}: 3472 (O-H st), 2940 (=C-H st). MS (EI, 70 eV) *m/z* (%): 240 (M$^+$ - H$_2$O, 3), 222 (6), 171 (18), 153 (12), 143 (100), 128 (56), 115 (34), 102 (3), 91 (12), 69 (9), 55 (10). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{17}H_{22}NaO_2$]$^+$: 281.1518 [(M+Na)$^+$]; found 281.1524. M.p.: 67-69 °C (hexanes/EtOAc).

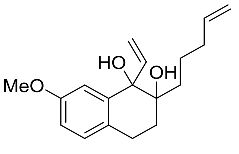


5,7-dimethyl-2-(pent-4-en-1-yl)-1-vinyl-1,2,3,4-tetrahydronapthalene-1,2-diol (9g). Following the *General Procedure F*, **9g** (726 mg, 2.54 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 8:2) starting from **8c** (1.70 g, 7.86 mmol) and pent-4-en-1-ylmagnesium bromide (30.0 mmol). Yield: 32% (major diastereomer). White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 7.13 (s, 1H, C**H**$_{arom}$), 6.94 (s, 1H, C**H**$_{arom}$), 6.05 (dd, *J* = 17.1, 10.6 Hz, 1H, C-1-C**H**=CH$_2$), 5.86 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.44-5.21 (m, 2H, C-1-CH=C**H$_2$**), 5.11-4.95 (m, 2H, CH$_2$CH=C**H$_2$**), 2.85 (s, 1H, O**H**), 2.84-2.54 (m, 2H, **H**-4), 2.30 (s, 3H, C**H$_3$**), 2.24 (s, 3H, C**H$_3$**), 2.22-2.04 (m, 3H, **H$_a$**-3 and C**H$_2$**CH=CH$_2$), 2.12* (s, 1H, O**H**), 1.96-1.85 (m, 1H, **H$_b$**-3), 1.78-1.41 (m, 4H, C-2-C**H$_2$** and C-2-CH$_2$C**H$_2$**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 141.0 (C-1-**C**H=CH$_2$), 139.5 (**C**$_{arom}$), 138.8 (CH$_2$**C**H=CH$_2$), 135.7 (**C**$_{arom}$), 135.6 (**C**$_{arom}$), 130.8 (**C**$_{arom}$), 130.04 (**C**H$_{arom}$), 126.9 (**C**H$_{arom}$), 115.0 (CH$_2$CH=**C**H$_2$), 114.7 (C-1-CH=**C**H$_2$), 78.2 (**C**-OH), 74.4 (**C**-OH), 34.8 (**C**H$_2$CH=CH$_2$), 34.4 (C-2-**C**H$_2$), 27.9 (**C**-4), 23.3 (**C**-3), 22.7 (C-2-CH$_2$**C**H$_2$), 21.1 (**C**H$_3$), 19.6 (**C**H$_3$). IR (ATR) cm^{-1}: 3379 (O-H st), 2947 (=C-H st), 2926 (=C-H st). MS (EI, 70 eV) *m/z* (%): 268 (M$^+$, 4), 250 (14), 235 (6), 221 (2), 208 (4), 195 (12), 181 (10), 171 (100), 156 (29), 141 (15), 128 (10), 115 (8), 105 (2), 91 (3), 55 (4). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{19}H_{26}NaO_2$]$^+$: 309.1831 [(M+Na)$^+$]; found 309.1831. M.p.: 95-97 °C (hexanes/EtOAc).



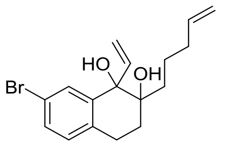


5-methoxy-2-(pent-4-en-1-yl)-1-vinyl-1,2,3,4-tetrahydronapthalene-1,2-diol (9h). Following the *General Procedure F*, **9h** (274 mg, 0.95 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 7:3) starting from **8d** (470 mg, 2.15 mmol) and pent-4-en-1-ylmagnesium bromide (8.17 mmol). Yield: 44% (major diastereomer). Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 7.19 (t, *J* = 8.0 Hz, 1H, C**H**$_{arom}$), 7.05 (dd, *J* = 8.0, 1.1 Hz, 1H, C**H**$_{arom}$), 6.74 (dd, *J* = 8.0, 1.1 Hz, 1H, C**H**$_{arom}$), 6.02 (dd, *J* = 17.1, 10.7 Hz, 1H, C-1-C**H**=CH$_2$), 5.83 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.38-5.22 (m, 2H, CH$_2$CH=C**H$_2$**), 5.08-4.93 (m, 2H, C-1-CH=C**H$_2$**), 3.83 (s, 3H, OC**H$_3$**), 2.87 (s, 1H, O**H**), 2.85-2.61 (m, 2H, **H**-4), 2.19-2.01 (m, 3H, C**H$_2$**CH=CH$_2$ and **H$_a$**-3), 2.05* (s, 1H, O**H**) 1.86 (m, 1H, **H$_b$**-3), 1.77-1.39 (m, 4H, C-2-C**H$_2$** and C-2-CH$_2$C**H$_2$**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 156.5 (**C**$_{arom}$), 141.0 (**C**$_{arom}$), 140.8 (C-1-**C**H=CH$_2$), 138.8 (CH$_2$**C**H=CH$_2$), 127.0 (**C**H$_{arom}$), 124.6 (**C**$_{arom}$), 120.7 (**C**H$_{arom}$), 115.3 (CH$_2$CH=**C**H$_2$), 114.7 (C-1-CH=**C**H$_2$), 108.4 (**C**H$_{arom}$), 78.0 (**C**-OH), 74.5 (**C**-OH), 55.4 (O**C**H$_3$), 34.8 (**C**H$_2$CH=CH$_2$), 34.4 (C-2-**C**H$_2$), 27.6 (**C**-4), 22.7 (**C**-3), 20.1 (C-2-CH$_2$**C**H$_2$). IR (ATR) cm^{-1}: 3493 (O-H st), 2941 (=C-H st). MS (EI, 70 eV) *m/z* (%): 288 (M$^+$, 2), 270 (9), 252 (31), 201 (19), 173 (100), 158 (33), 128 (17), 115 (23), 91 (10), 69 (7), 55 (12). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{18}$H$_{24}$NaO$_3$]$^+$: 311.1623 [(M+Na)$^+$]; found 311.1614.

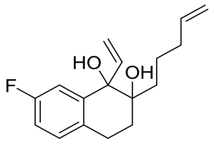


7-methoxy-2-(pent-4-en-1-yl)-1-vinyl-1,2,3,4-tetrahydronapthalene-1,2-diol (9i). Following the *General Procedure F*, **9i** (572 mg, 1.98 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 8:2) starting from **8e** (1.36 g, 6.23 mmol) and pent-4-en-1-ylmagnesium bromide (23.7 mmol). Yield: 32% (major diastereomer). Yellow solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.06-6.93 (m, 2H, 2 x C**H**$_{arom}$), 6.76 (dd, *J* = 8.4, 2.7 Hz, 1H, C**H**$_{arom}$), 6.00 (dd, *J* = 17.1, 10.6 Hz, 1H, C-1-C**H**=CH$_2$), 5.82 (ddt, *J* = 16.7, 9.9, 6.5 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.37-5.18 (m, 2H, CH$_2$CH=C**H$_2$**), 5.10-4.92 (m, 2H, C-1-CH=C**H$_2$**), 3.74 (s, 3H, OC**H$_3$**), 3.00 (s, 1H, O**H**), 2.97-2.81 (m, 1H, **H$_a$**-4), 2.71 (dt, *J* = 17.1, 5.9 Hz, 1H, **H$_b$**-4), 2.17 (s, 1H, O**H**), 2.15-2.01 (m, 3H, C**H$_2$**CH=CH$_2$ and **H$_a$**-3), 1.93-1.78 (m, 1H, **H$_b$**-3), 1.79-1.37 (m, 4H, C-2-C**H$_2$** and C-2-CH$_2$C**H$_2$**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$) 158.2 (**C**-7), 140.9 (**C**$_{arom}$), 140.7 (C-1-**C**H=CH$_2$), 138.8 (CH$_2$**C**H=CH$_2$), 129.5 (**C**H$_{arom}$), 127.4 (**C**$_{arom}$), 115.4 (CH$_2$CH=**C**H$_2$), 114.8 (C-1-CH=**C**H$_2$), 114.5 (**C**H$_{arom}$), 113.1 (**C**H$_{arom}$), 78.2 (**C**-OH), 74.8 (**C**-OH), 55.4 (O**C**H$_3$), 34.9 (**C**H$_2$CH=CH$_2$), 34.4 (C-2-**C**H$_2$), 28.4 (**C**-4), 24.9 (**C**-3), 22.7 (C-2-CH$_2$**C**H$_2$). IR (ATR) cm^{-1}: 3487 (O-H st), 3397 (O-H st). MS (EI, 70 eV) *m/z* (%): 288 (M$^+$, 5), 270 (10), 252 (22), 237 (5), 201 (24), 189 (15), 173 (100), 145 (20), 128 (32), 115 (38), 102 (7), 91 (14), 80 (1), 69 (13), 55 (27). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{18}$H$_{24}$NaO$_3$]$^+$: 311.1623 [(M+Na)$^+$]; found 311.1629. M.p.: 71-73 °C (hexanes/EtOAc).

7-bromo-2-(pent-4-en-1-yl)-1-vinyl-1,2,3,4-tetrahydronapthalene-1,2-diol (9j). Following the *General Procedure F*, **9j** (527 mg, 1.56 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **8f** (1.72 g, 6.44 mmol) and pent-4-en-1-ylmagnesium bromide (24.5 mmol). Yield: 24% (major diastereomer). White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 7.57 (d, *J* = 2.2 Hz, 1H, **H**-8), 7.36-7.20 (m, 1H, **H**-6), 6.98 (d, *J* = 8.2 Hz, 1H, **H**-5), 5.98 (dd, *J* = 17.1, 10.7 Hz, 1H, C-1-C**H**=CH$_2$), 5.81 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.37-5.20 (m, 2H, CH$_2$CH=C**H$_2$**), 5.09-4.89 (m, 2H, C-1-CH=C**H$_2$**), 3.01-2.87 (m, 1H, **H$_a$**-4), 2.85 (s, 1H, O**H**), 2.72 (dt, *J* = 17.6, 5.8 Hz, 1H, **H$_b$**-4), 2.17-1.99 (m, 3H, **H$_a$**-3 and C**H$_2$**CH=CH$_2$), 1.96-1.78 (m, 1H, **H$_b$**-3), 1.94* (s, 1H, O**H**), 1.78-1.37 (m, 4H, C-2-C**H$_2$** and C-2-CH$_2$C**H$_2$**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 142.2 (**C**$_{\text{arom}}$), 140.4 (C-1-**C**H=CH$_2$), 138.6 (CH$_2$**C**H=CH$_2$), 134.4 (**C**$_{\text{arom}}$), 131.9 (**C**H$_{\text{arom}}$), 130.6 (**C**H$_{\text{arom}}$), 130.2 (**C**H$_{\text{arom}}$), 120.1 (**C**$_{\text{arom}}$), 116.0 (CH$_2$CH=**C**H$_2$), 115.0 (C-1-CH=**C**H$_2$), 78.0 (**C**-OH), 74.6 (**C**-OH), 35.0 (**C**H$_2$CH=CH$_2$), 34.3 (C-2-**C**H$_2$), 28.2 (**C**-4), 25.3 (**C**-3), 22.6 (C-2-CH$_2$**C**H$_2$). IR (ATR) cm^{-1}: 3332 (O-H st), 2945 (=C-H st). MS (EI, 70 eV) *m/z* (%): 336 (M^{+}, 1), 320 (4), 302 (14), 252 (19), 239 (20), 221 (54), 207 (20), 191 (11), 178 (24), 165 (65), 153 (30), 141 (100), 128 (48), 115 (100), 97 (64), 82 (12), 69 (60), 55 (67). HRMS (UPLC MS ESI^{+}): Calculated for [$C_{17}H_{21}BrNaO_2$]$^{+}$: 359.0623 [(M+Na)$^{+}$]; found 359.0618. M.p.: 110-112 °C (hexanes/EtOAc).

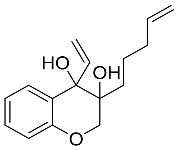


7-fluoro-2-(pent-4-en-1-yl)-1-vinyl-1,2,3,4-tetrahydronapthalene-1,2-diol (9k). Following the G*eneral Procedure F*, **9k** (514 mg, 1.86 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **8g** (1.70 g, 8.24 mmol) and pent-4-en-1-ylmagnesium bromide (31.3 mmol). Yield: 22% (major diastereomer). White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 7.13 (m, 1H, C**H**$_{\text{arom}}$), 7.06 (dd, *J* = 8.5, 5.8 Hz, 1H, C**H**$_{\text{arom}}$), 6.89 (td, *J* = 8.3, 2.7 Hz, 1H, C**H**$_{\text{arom}}$), 5.98 (dd, *J* = 17.1, 10.7 Hz, 1H, C-1-C**H**=CH$_2$), 5.82 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.34-5.21 (m, 2H, CH$_2$CH=C**H$_2$**), 5.08-4.92 (m, 2H, C-1-CH=C**H$_2$**), 3.03-2.86 (m, 1H, **H$_a$**-4), 2.92* (s, 1H, O**H**), 2.74 (dt, *J* = 17.3, 5.8 Hz, 1H, **H$_b$**-4), 2.19-2.02 (m, 3H, C**H$_2$**CH=CH$_2$ and **H$_a$**-3), 1.99 (s, 1H, O**H**), 1.94-1.81 (m, 1H, **H$_b$**-3), 1.81-1.37 (m, 4H, C-2-C**H$_2$** and C-2-CH$_2$C**H$_2$**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 161.7 (d, $^{1}J_{CF}$=243.7 Hz, **C**-7), 142.0 (d, $^{3}J_{CF}$=6.4 Hz, **C**-8a), 140.5 (C-1-**C**H=CH$_2$), 138.7 (CH$_2$**C**H=CH$_2$), 130.9 (d, $^{4}J_{CF}$ =3.2 Hz, **C**-4a), 129.9 (d, $^{3}J_{CF}$ =7.7 Hz, **C**-5), 115.8 (CH$_2$CH=**C**H$_2$), 115.2 (d, $^{2}J_{CF}$ =21.7 Hz, **C**H$_{\text{arom}}$), 114.91 (C-1-CH=**C**H$_2$), 114.86 (d, $^{2}J_{CF}$ =21.7 Hz, **C**H$_{\text{arom}}$), 78.1 (**C**-OH), 74.6 (**C**-OH), 35.0 (**C**H$_2$CH=CH$_2$), 34.3 (C-2-**C**H$_2$), 28.4 (**C**-4), 25.0 (**C**-3), 22.6 (C-2-CH$_2$**C**H$_2$). ^{19}F NMR (δ, ppm) (282 MHz, CDCl$_3$): -116.3. IR (ATR) cm^{-1}: 3487 (O-H st), 3349 (O-H st). MS (EI, 70 eV) *m/z* (%): 276 (M^{+}, 1), 258 (4), 240 (12), 197 (18), 183 (35), 161 (99), 146 (100), 133 (81), 109 (37), 97

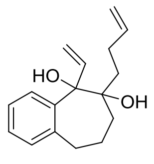


(32), 69 (33), 55 (38). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{17}H_{21}FNaO_2$]$^+$: 299.1423 [(M+Na)$^+$]; found 299.1426. M.p.: 101-103 °C (hexanes/EtOAc).

3-(pent-4-en-1-yl)-4-vinylchromane-3,4-diol (9l). Following the *General Procedure F*, **9l** (905 mg, 3.48 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 7:3) starting from **8h** (1.24 g, 6.52 mmol) and pent-4-en-1-ylmagnesium bromide (24.8 mmol). Yield: 54% (mixture of diastereoisomers). Red solid. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes minor diastereoisomer resonances): 7.34* (m, 2H, 2 x C**H**$_{arom}$), 7.21 (m, 2H, 2 x C**H**$_{arom}$), 6.89 (m, 2H, 2 x C**H**$_{arom}$), 6.19 (dd, *J* = 17.2, 10.7 Hz, 1H, C-4-C**H**=CH$_2$), 6.02* (dd, *J* = 17.1, 10.6 Hz, 1H, C-4-C**H**=CH$_2$), 5.83 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.67-5.46 (m, 2H, CH$_2$CH=C**H$_2$**), 5.40-5.15* (m, 2H, CH$_2$CH=C**H$_2$**), 5.16-4.91 (m, 2H, C-4-CH=C**H$_2$**), 4.23 (d, *J* = 11.2 Hz, 1H, **H$_a$**-2), 4.12-3.97 (d, *J* = 11.2 Hz, 1H, **H$_b$**-2), 3.06* (s, 1H, O**H**), 2.61* (s, 1H, O**H**), 2.20 (s, 1H, O**H**), 2.15 (s, 1H, O**H**), 2.12-1.99 (m, 2H, C**H$_2$**CH=CH$_2$), 1.75-1.55 (m, 3H, C3-C**H$_2$** and C3-CH$_2$C**H$_a$**H$_b$), 1.50-1.28 (m, 1H, C3-CH$_2$CH$_a$**H$_b$**). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$) (*denotes minor diastereoisomer resonances): 153.2 (**C**$_{arom}$), 153.1* (**C**$_{arom}$), 139.9* (C-4-**C**H=CH$_2$), 138.6 (C-4-**C**H=CH$_2$), 138.5 (CH$_2$**C**H=CH$_2$), 129.8 (**C**H$_{arom}$), 129.7* (**C**H$_{arom}$), 129.3* (**C**H$_{arom}$), 129.2 (**C**H$_{arom}$), 126.2* (**C**$_{arom}$), 125.3 (**C**$_{arom}$), 121.7* (**C**H$_{arom}$), 121.4 (**C**H$_{arom}$), 117.3* (CH$_2$CH=**C**H$_2$), 117.09 (CH$_2$CH=**C**H$_2$), 117.03 (**C**H$_{arom}$), 116.3* (**C**H$_{arom}$), 114.9* (C-4-CH=**C**H$_2$), 114.8 (C-4-CH=**C**H$_2$), 75.2* (**C**-OH), 74.8 (**C**-OH), 71.8 (**C**-OH), 71.6* (**C**-OH), 68.39 (**C**-2), 68.36* (**C**-2), 34.3 (**C**H$_2$CH=CH$_2$), 34.2* (**C**H$_2$CH=CH$_2$), 31.4* (C-3-**C**H$_2$), 30.3 (C-3-**C**H$_2$), 22.3* (C-3-CH$_2$**C**H$_2$), 22.2 (C-3-CH$_2$**C**H$_2$). IR (ATR) cm^{-1}: 3426 (O-H st), 3361 (O-H st). MS (EI, 70 eV) *m/z* (%): 260 (M$^+$, 1), 242 (3), 224 (2), 207 (3), 180 (2), 163 (5), 147 (100), 131 (18), 121 (38), 103 (10), 90 (1), 77 (9), 55 (20). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{16}H_{20}NaO_3$]$^+$: 283.1310 [(M+Na)$^+$]; found 283.1311. M.p.: 87-89 °C (hexanes/EtOAc).

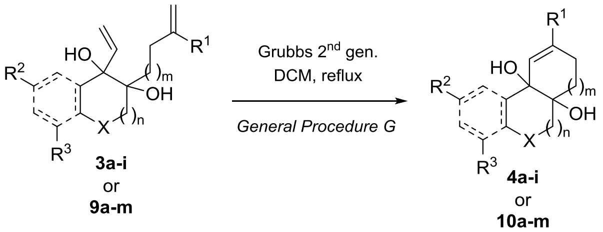


6-(but-3-en-1-yl)-5-vinyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-5,6-diol (9m). Following the *General Procedure F*, **9m** (335 mg, 1.30 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from **8i** (550 mg, 2.72 mmol) and but-3-en-1-ylmagnesium bromide (10.4 mmol). Yield: 48%. Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 7.61 – 7.44 (m, 1H, C**H**$_{arom}$), 7.25 – 6.94 (m, 3H, 3 x C**H**$_{arom}$), 6.67 (dd, *J* = 17.1, 10.8 Hz, 1H, C-5-C**H**=CH$_2$), 5.77 (ddt, *J* = 16.9, 10.0, 6.6 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.63 – 5.38 (m, 2H, CH$_2$CH=C**H$_2$**), 5.12 – 4.74 (m, 2H, C-5-CH=C**H$_2$**), 3.29 (dd, *J* = 14.0, 10.8 Hz, 1H, **H$_a$**-9), 2.73 (dd, *J* = 14.1, 8.0 Hz, 1H, **H$_b$**-9), 2.43 (s, 1H, O**H**), 2.36 – 2.14 (m, 2H, C**H$_2$**CH=CH$_2$), 2.07 (m, 1H, **H$_a$**-7), 2.01 – 1.76 (m, 2H, **H$_b$**-7 and C-6-C**H$_a$**H$_b$), 1.61* (s, 1H, O**H**), 1.76 – 1.33 (m, 3H, C-6-CH$_a$**H$_b$** and **H**-8). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 142.3 (**C**$_{arom}$), 141.0 (**C**$_{arom}$), 140.4 (C-5-**C**H=CH$_2$), 139.2 (CH$_2$**C**H=CH$_2$), 131.1 (**C**H$_{arom}$), 128.9 (**C**H$_{arom}$), 128.2 (**C**H$_{arom}$), 126.2 (**C**H$_{arom}$), 116.5 (CH$_2$CH=**C**H$_2$), 114.6 (C-5-CH=**C**H$_2$), 84.0 (**C**-OH), 77.5 (**C**-OH), 36.5 (**C**-9),

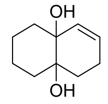


36.2 (**C**-7), 34.4 (C-6-**C**H_2), 27.9 (**C**$H_2CH=CH_2$), 24.8 (**C**-8). IR (ATR) cm^{-1}: 3547 (O-H st), 3447 (O-H st), 2934 (=C-H st). MS (EI, 70 eV) *m/z* (%): 240 (M^+ - H_2O, 4), 199 (7), 185 (24), 161 (100), 152 (19), 141 (57), 129 (87), 119 (32), 103 (9), 91 (30), 77 (15), 65 (6), 55 (45). HRMS (UPLC MS ESI$^+$): Calculated for $[NaC_{17}H_{22}O_2]^+$: 281.1518 [$(M+Na)^+$]; found 281.1512.

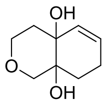
2.4. Synthesis of 1,2-diols 4a-i and 10a-m by Ring-Closing Metathesis (RCM)



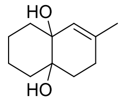
General Procedure G: Under inert atmosphere a solution of 2nd generation Grubbs catalyst (required amount indicated in each case) in anhydrous CH_2Cl_2 (5 mL) was added *via* cannula to a solution of the corresponding 1,2-diol **3a-i** or **9a-m** in anhydrous CH_2Cl_2 (0.033 M). It was refluxed until full conversion monitored by TLC and then opened to the atmosphere and stirred at room temperature for an additional 30 min. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel (hexanes/EtOAc) to yield the desired product.



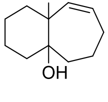
1,2,3,4,5,6-hexahydronaphthalene-4a,8a-diol (4a). Following the *General Procedure G*, **4a** (400 mg, 2.40 mmol) was isolated by FC (hexanes/EtOAc 1:1) starting from **3a** (500 mg, 2.55 mmol) and 2nd generation Grubbs catalyst (54 mg, 0.06 mmol). Yield: 94%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 5.67 (dt, *J* = 9.9, 3.6 Hz, 1H, **H**-7), 5.46 (d, *J* = 9.9, 1H, **H**-8), 2.73 (s, 2H, 2 x O**H**), 2.27-1.93 (m, 2H, **H**-6), 1.84-1.06 (m, 10H, **H**-1, **H**-2, **H**-3, **H**-4 and **H**-5). ^{13}C NMR (δ, ppm) (126 MHz, DMSO-d^6, 60 °C): 134.2 (**C**-8), 127.8 (**C**-7), 70.8 (**C**-OH), 70.4 (**C**-OH), 36.7 (**C**-1), 34.1 (**C**-4), 31.4 (**C**-5), 24.3 (**C**-6), 22.7 (**C**-3), 21.8 (**C**-2). IR (ATR) cm^{-1}: 3422 (O-H st), 2934 (=C-H st). MS (EI, 70 eV) *m/z* (%): 168 (M^+, 5), 150 (100), 132 (20), 107 (82), 91 (41), 79 (69), 68 (93), 55 (37). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{10}H_{16}NaO_2]^+$: 191.1048 [$(M+Na)^+$]; found: 191.1048.



3,4,7,8-tetrahydro-1*H*-isochromene-4a,8a-diol (4b). Following the *General Procedure G*, **4b** (95 mg, 0.56 mmol) was isolated by FC (hexanes/EtOAc 1:1) from **3b** (145 mg, 0.73 mmol) and 2nd generation Grubbs catalyst (15 mg, 0.018 mmol). Yield: 77% (2:1 mixture of diastereomers). Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes minor diastereomer): 5.87 (dt, *J* = 9.9, 3.6 Hz, 1H, **H**-6), 5.79* (dt, *J* = 10.0, 3.6 Hz, 1H, **H**-6*), 5.58 (dt, *J* = 9.8, 2.2 Hz, 1H, **H**-5), 5.52* (dt, *J* = 9.9, 2.2 Hz, 1H, **H**-5*), 3.93-3.70 (m, 4H, **H**-1 and **H**-3), 3.61* (d, *J* = 11.6 Hz, 2H, **H**-1*), 3.49-3.32* (m, 2H, **H**-3*), 2.86 (s, 1H, O**H**), 2.81* (s, 1H, O**H***), 2.49-1.50 (m, 6 H, **H**-4, **H**-7, **H$_a$**-8 and O**H**), 1.49-1.32 (m, 1H, **H$_b$**-8). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$) (*denotes minor diastereomer): 131.3 (**C**-5), 130.6 (**C**-6), 129.8* (**C**-5'), 72.1* (**C**-1'), 71.5 (**C**-1), 70.2 (**C**-OH), 70.1* (**C**-OH), 68.9* (**C**-OH), 66.9 (**C**-OH), 65.0* (**C**-3'), 63.5 (**C**-3), 36.9* (**C**-4'), 32.9 (**C**-4), 27.8* (**C**-7'), 23.9 (**C**-7), 23.5* (**C**-8'), 22.0 (**C**-8). IR (ATR) cm^{-1}: 3379 (O–H st), 2922 (=C-H st). MS (EI, 70 eV) *m/z* (%) major diastereomer: 170 (M$^+$, 1), 152 (5), 134 (33), 122 (68), 104 (72), 91 (36), 79 (100), 68 (19), 51 (27); minor diastereomer: 152 (M$^+$ - H$_2$O, 5), 134 (29), 122 (72), 104 (61), 91 (38), 79 (100), 65 (19), 51 (27). HRMS (UPLC MS ESI$^+$): Calculated for [C$_9$H$_{14}$NaO$_3$]$^+$: 193.0841 [(M+Na)$^+$]; found: 193.0847.

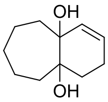


7-methyl-1,2,3,4,5,6-hexahydronaphthalene-4a,8a-diol (4c). Following the *General Procedure G*, **4c** (460 mg, 2.52 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 7:3) starting from **3c** (550 mg, 2.61 mmol) and 2nd generation Grubbs catalyst (55 mg, 0.065 mmol). Yield: 96%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 5.18 (s, 1H, **H**-8), 2.62 (s, 1H, O**H**), 2.51 (s, 1H, O**H**), 2.09 – 1.82 (m, 2H, **H**-6), 1.82 – 1.63 (m, 2H, **H**-5), 1.63 – .22 (m, 7H, **H**-1 and **H**-2 and **H$_a$**-3 and **H**-4), 1.60* (s, 3H, C**H$_3$**), 1.22 – 1.04 (m, 1H, **H$_b$**-3). ^{13}C NMR (δ, ppm) (126 MHz, DMSO-d^6, 60 °C): 135.0 (**C**-7), 129.1 (**C**-8), 70.8 (**C**-OH), 70.7 (**C**-OH), 36.9 (**C**-1), 33.9 (**C**-4), 31.8 (**C**-6), 29.1 (**C**-5), 23.2 (**C**H$_3$), 22.8 (**C**-3), 21.8 (**C**-2). IR (ATR) cm^{-1}: 3408 (O-H st), 2929 (=C-H st). MS (EI, 70 eV) *m/z* (%): 182 (M$^+$, 1), 164 (M$^+$ - H$_2$O, 29), 146 (78), 131 (100), 118 (81), 105 (33), 91 (46), 77 (29), 63 (15), 51 (16). HRMS (UPLC MS ESI+): Calculated for [NaC$_{11}$H$_{18}$O$_2$]$^+$: 205.1205 [(M+Na)$^+$]; found: 205.1209.

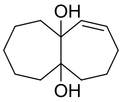


1,2,3,4,6,7-hexahydro-4a*H*-benzo[7]annulene-4a,9a(5*H*)-diol (4d). Following the *General Procedure G*, **4d** (300 mg, 1.65 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) starting from **3d** (440 mg, 2.09 mmol) and 2nd generation Grubbs catalyst (27 mg, 0.03 mmol). Yield: 94%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, DMSO-d^6): 5.65 (dt, *J* = 12.0, 6.0 Hz, 1H, **H**-8), 5.39 (dt, *J* = 12.2, 1.4 Hz, 1H, **H**-9), 4.14 (s, 1H, O**H**), 3.69 (s, 1H, O**H**), 2.20-2.02 (m, 1H, **H$_a$**-7), 2.02-1.87 (m, 2H, **H$_b$**-7 and **H$_a$**-1), 1.82-1.61 (m, 3H, **H$_b$**-1 and **H**-4), 1.61-1.20 (m, 8H, **H**-2, **H**-3, **H**-5 and **H**-6). ^{13}C NMR (δ, ppm) (126 MHz, DMSO-d^6, 60 °C): 138.5 (**C**-9), 130.5 (**C**-8), 76.4 (**C**-OH), 73.2 (**C**-OH), 36.8 (**C**-5), 36.5 (**C**-7), 28.2 (**C**-1), 28.2 (**C**-4), 23.0 (**C**-6), 22.0 (**C**-2), 21.8 (**C**-3). IR (ATR) cm^{-1}: 3425 (O-H st), 2920 (=C-H st), 2840 (=C-H st). MS (EI, 70 eV) *m/z* (%): 182 (M$^+$, 1), 146 (33), 135 (46), 120 (53), 108 (58), 93 (83), 79 (100), 67 (60), 55 (53). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{11}H_{18}NaO_2]^+$: 205.1205 [(M+Na)$^+$]; found: 205.1207.

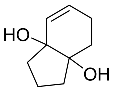
1,2,6,7,8,9-hexahydro-4a*H*-benzo[7]annulene-4a,9a(5*H*)-diol (4e). Following the *General Procedure G*, **4e** (140 mg, 0.77 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 7:3) starting from **3e** (330 mg, 1.57 mmol) and 2nd generation Grubbs catalyst (20 mg, 0.02 mmol). Yield: 50%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 5.78 (dt, *J* = 9.9, 3.6 Hz, 1H, **H**-3), 5.48 (dt, *J* = 9.9, 2.1 Hz, 1H, **H**-4), 2.54 (s, 1H, O**H**), 2.31 (s, 1H, O**H**), 2.25-2.00 (m, 2H, **H**-2), 1.98-1.55 (m, 8H, **H**-1, **H**-5, **H**-6 and **H**-9), 1.54-1.33 (m, 4H, **H**-7 and **H**-8). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 133.7 (**C**-4), 128.8 (**C**-3), 74.2 (**C**-OH), 73.9 (**C**-OH), 35.9 (**C**-5), 34.5 (**C**-9), 34.1 (**C**-7), 26.8 (**C**-1), 23.5 (**C**-2), 20.2 (**C**-6), 19.1 (**C**-8). IR (ATR) cm^{-1}: 3417 (O-H st), 2921 (=C-H st), 2875 (=C-H st). MS (EI, 70 eV) *m/z* (%): 182 (M$^+$, 1), 164 (92), 146 (100), 131 (63), 122 (99), 104 (88), 91 (91), 79 (94), 68 (42), 55 (28). HRMS (UPLC MS ESI+): Calculated for $[C_{11}H_{18}NaO_2]^+$: 205.1205 [(M+Na)$^+$]; found: 205.1203.



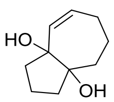
2,3,4,5,7,8-hexahydroheptalene-5a,10a(1*H*, 6*H*)-diol (4f). Following the *General Procedure G*, **4f** (360 mg, 1.84 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) starting from **3f** (520 mg, 2.32 mmol) and 2nd generation Grubbs catalyst (98 mg, 0.05 mmol). Yield: 79%. Brown solid. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 5.79 (ddd, *J* = 12.2, 6.9, 5.3 Hz, 1H, **H**-9), 5.58 (dd, *J* = 12.2, 1.8 Hz, 1H, **H**-10), 2.55 (s, 1H, **O**H), 2.27-1.97 (m, 4H, **H**-6 and **H**-8), 2.06* (s, 1H, **O**H), 1.96-1.84 (m, 2H, **H**-1), 1.79-1.39 (m, 10H, **H**-2, **H**-3, **H**-4, **H**-5 and **H**-7). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 139.0 (**C**-10), 131.0 (**C**-9), 80.3 (**C**-OH), 76.8 (**C**-OH), 39.3 (**C**-6), 37.5 (**C**-1), 35.5 (**C**-5), 27.8 (**C**-8), 26.0 (**C**-3), 22.6 (**C**-2), 20.9 (**C**-4), 20.5 (**C**-7). IR (ATR) cm^{-1}: 3414 (O-H st), 2916 (=C-H st), 2855 (=C-H st). MS (EI, 70 eV) *m/z* (%): 178 (M$^+$ - H_2O, 17), 160 (22), 149 (50), 117 (40), 107 (54), 91 (81), 79 (100). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{12}H_{20}NaO_2]^+$: 219.1361 [(M+Na)$^+$]; found: 219.1372. M.p.: 53-55 °C (hexanes/EtOAc).



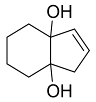
2,3,4,5-tetrahydro-1*H*-indene-3a,7a-diol (4g). Following the *General Procedure G*, **4g** (447 mg, 2.90 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **3g** (660 mg, 3.62 mmol) and 2nd generation Grubbs catalyst (77 mg, 0.09 mmol). Yield: 80%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 6.04 (dt, *J* = 9.9, 2.2 Hz, 1H, **H**-7), 5.92 (dt, *J* = 9.9, 3.4 Hz, 1H, **H**-6), 2.34-2.24 (m, 2H, **H**-5), 2.15-1.95 (m, 2H, **H**-4), 1.94-1.82 (m, 4H, **H**-1 and **H**-3), 1.76-1.64 (m, 2H, **H**-2), 1.53 (s, 1H, **O**H), 1.38 (s, 1H, **O**H). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 131.6 (**C**-7), 129.0 (**C**-6), 80.7 (**C**-OH), 77.7 (**C**-OH), 33.2 (**C**-1), 32.8 (**C**-3), 26.0 (**C**-4), 22.9 (**C**-5), 19.5 (**C**-2). IR (ATR) cm^{-1}: 3354 (O-H st), 3324 (O-H st). MS (EI, 70 eV) *m/z* (%): 154 (M$^+$, 2), 136 (7), 126 (5), 117 (100), 108 (6), 103 (6), 96 (18), 91 (26), 84 (11), 79 (12), 71 (15), 65 (9), 55 (8).



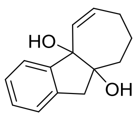
2,3,5,6-tetrahydroazulene-3a,8a(1*H*, 4*H*)-diol (4h). Following the *General Procedure G*, **4h** (317 mg, 1.88 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **3h** (500 mg, 2.55 mmol) and 2nd generation Grubbs catalyst (54 mg, 0.06 mmol). Yield: 74%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 6.06 (ddd, *J* = 11.0, 8.8, 4.2 Hz, 1H, **H**-7), 5.74 (dd, *J* = 11.0, 2.8 Hz, 1H, **H**-8), 2.47-2.28 (m, 1H, $\mathbf{H_a}$-6), 2.28-2.06 (m, 3H, $\mathbf{H_b}$-6 and **H**-4), 1.94-1.66 (m, 8H, **H**-1, **H**-2, **H**-3 and 2 x O**H**), 1.66-1.53 (m, 2H, **H**-5). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 137.2 (**C**-8), 133.6 (**C**-7), 83.6 (**C**-OH), 81.5 (**C**-OH), 40.2 (**C**-4), 38.0 (**C**-1), 35.1 (**C**-3), 27.5 (**C**-6), 22.1 (**C**-5), 19.6 (**C**-2). IR (ATR) cm^{-1}: 3379 (O-H st), 2964 (=C-H st), 2931 (=C-H st). MS (EI, 70 eV) *m/z* (%): 168 (M$^+$, 1), 150 (47), 132 (67), 117 (100), 104 (42), 91 (78), 79 (99), 55 (72). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{10}H_{16}NaO_2]^+$: 191.1048 [(M+Na)$^+$]; found: 191.1041.



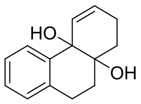
4,5,6,7-tetrahydro-1*H*-indene-3a,7a-diol (4i). Following the *General Procedure G*, **4i** (230 mg, 1.49 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) starting from **3i** (300 mg, 1.64 mmol) and 2nd generation Grubbs catalyst (35 mg, 0.04 mmol). Yield: 90%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 5.86 (dt, *J* = 6.1, 2.3 Hz, 1H, **H**-2), 5.77 (dt, *J* = 6.1, 1.9 Hz, 1H, **H**-3), 2.68 (s, 1H, O**H**), 2.55-2.12 (m, 3H, **H**-1 and O**H**), 1.97-1.71 (m, 2H, **H**-4), 1.69-1.46 (m, 4H, **H**-5 and **H**-7), 1.44-1.06 (m, 2H, **H**-6). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 138.1 (**C**-3), 132.2 (**C**-2), 81.8 (**C**-OH), 79.2 (**C**-OH), 44.3 (**C**-1), 34.4 (**C**-7), 34.2 (**C**-4), 22.1 (**C**-6), 21.6 (**C**-5). IR (ATR) cm^{-1}: 3404 (O-H st), 2930 (=C-H st), 2858 (=C-H st). MS (EI, 70 eV) *m/z* (%): 154 (M$^+$, 2), 136 (77), 117 (94), 108 (100), 93 (97), 79 (84), 67 (52), 55 (34). HRMS (UPLC MS ESI$^+$): Calculated for $[C_9H_{14}NaO_2]^+$: 177.0892 [(M+Na)$^+$]; found: 177.0888.



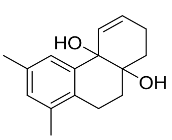
8,9-dihydrobenzo[*a*]azulene-4b,9a(7*H*,10*H*)-diol (10a). Following the *General Procedure G*, **10a** (232 mg, 1.07 mmol) was isolated by FC (hexanes/EtOAc 8:2) starting from **9a** (337 mg, 1.38 mmol) and 2nd generation Grubbs catalyst (29 mg, 0.034 mmol). Yield: 78%. Brown solid. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 7.37 (dd, *J* = 6.6, 1.7 Hz, 1H, C**H**$_{arom}$), 7.33-7.22 (m, 3H, 3 x C**H**$_{arom}$), 6.37 (ddd, *J* = 11.0, 8.7, 4.3 Hz, 1H, **H**-6), 6.22 (dd, *J* = 11.0, 2.7 Hz, 1H, **H**-5), 3.10 (d, *J* = 15.8, 1H, $\mathbf{H_a}$-10), 2.86 (d, *J* = 15.8 Hz, 1H, $\mathbf{H_b}$-10), 2.77-2.60 (m, 1H, $\mathbf{H_a}$-7), 2.52 (ddd, *J* = 14.0, 9.9, 7.0 Hz, 1H, $\mathbf{H_b}$-7), 2.22 (ddd, *J* = 15.3, 8.8, 4.1 Hz, 1H, $\mathbf{H_a}$-9), 1.99 (dt, *J* = 14.1, 4.0 Hz, 1H, $\mathbf{H_b}$-9), 1.93* (s, 1H, O**H**), 1.92* (s, 1H, O**H**), 1.74 (m, 2H, **H**-8). ^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$): 146.7 (**C**$_{arom}$), 142.7 (**C**$_{arom}$), 139.6 (**C**-5), 130.7 (**C**-6), 129.0 (**C**H$_{arom}$), 127.0 (**C**H$_{arom}$), 126.0 (**C**H$_{arom}$), 123.0 (**C**H$_{arom}$), 83.9 (**C**-OH), 82.3 (**C**-OH), 44.1 (**C**-9), 34.5 (**C**-10), 27.3 (**C**-7), 21.9 (**C**-8). IR (ATR) cm^{-1}: 3551 (O-H st), 3418 (O-H st), 2915 (=C-H st). MS (EI, 70 eV) *m/z* (%): 180 (M$^+$ - $2\cdot H_2O$, 88), 165 (100), 152 (29), 139 (5), 127 (4), 115 (5), 89 (11), 76 (9), 62 (4), 51 (5). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{14}H_{16}NaO_2]^+$: 239.1048 (M+Na)$^+$]; found: 239.1052. M.p.: 114-116 °C (hexanes/EtOAc).



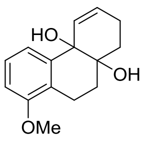
1,2,9,10-tetrahydrophenanthrene-4a,10a-diol (10b). Following the G*eneral Procedure G*, **10b** (203 mg, 0.94 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **9b** (264 mg, 1.08 mmol) and 2nd generation Grubbs catalyst (23 mg, 0.027 mmol). Yield: 87%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 7.65 (dd, *J* = 7.8, 1.5 Hz, 1H, C**H**$_{arom}$), 7.32-7.15 (m, 2H, 2 x C**H**$_{arom}$), 7.08 (d, *J* = 7.5 Hz, 1H, C**H**$_{arom}$), 5.88 (dt, *J* = 9.8, 2.0 Hz, 1H, **H**-4), 5.74 (ddd, *J* = 9.8, 4.3, 2.8 Hz, 1H, **H**-3), 3.12 (ddd, *J* = 16.4, 9.1, 6.8 Hz, 1H, **H$_a$**-9), 2.78-2.64 (m, 1H, **H$_b$**-9), 2.66* (s, 1H, O**H**), 2.62 (s, 1H, O**H**), 2.36-2.06 (m, 2H, **H**-2), 2.05-1.91 (m, 3H, **H**-1 and **H$_a$**-10), 1.71 (ddd, *J* = 13.0, 5.8, 3.9 Hz, 1H, **H$_b$**-10). ^{13}C NMR (δ, ppm) (75 MHz, CDCl$_3$): 140.6 (**C**$_{arom}$), 135.4 (**C**$_{arom}$), 133.2 (**C**-4), 128.2 (**C**-3), 128.1 (**C**H$_{arom}$), 127.7 (**C**H$_{arom}$), 127.1 (**C**H$_{arom}$), 126.5 (**C**H$_{arom}$), 71.3 (**C**-OH), 70.7 (**C**-OH), 31.5 (**C**-9), 29.8 (**C**-1), 25.3 (**C**-2), 23.8 (**C**-10). IR (ATR) cm^{-1}: 3404 (O-H st). MS (EI, 70 eV) *m/z* (%): 208 (20), 179 (23), 165 (32), 143 (100), 128 (77), 115 (75), 83 (42), 55 (58). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{14}$H$_{16}$NaO$_2$]$^+$: 239.1048 [(M+Na)$^+$]; found 239.1048.



6,8-dimethyl-1,2,9,10-tetrahydrophenanthrene-4a,10a-diol (10c). Following the *General Procedure G*, **10c** (300 mg, 1.23 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) starting from **9c** (350 mg, 1.28 mmol) and 2nd generation Grubbs catalyst (27 mg, 0.032 mmol). Yield: 96%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 7.38 (s, 1H, C**H**$_{arom}$), 6.95 (s, 1H, C**H**$_{arom}$), 5.93 (dt, *J* = 9.9, 2.0 Hz, 1H, **H**-4), 5.74 (dt, *J* = 9.9, 3.5 Hz, 1H, **H**-3), 3.04 (s, 1H, O**H**), 2.89* (s, 1H, O**H**), 2.86-2.78 (m, 1H, **H$_a$**-9), 2.60 (dt, *J* = 17.2, 5.5 Hz, 1H, **H$_b$**-9), 2.37 (s, 3H, C**H$_3$**), 2.25* (s, 3H, C**H$_3$**), 2.33-2.24 (m, 1H, **H$_a$**-2), 2.19-2.05 (m, 1H, **H$_b$**-2), 2.04-1.92 (m, 3H, **H**-10 and **H$_a$**-3), 1.70 (ddd, *J* = 13.0, 5.9, 4.0 Hz, 1H, **H$_b$**-3). ^{13}C NMR (δ, ppm) (75 MHz, CDCl$_3$): 140.4 (**C**$_{arom}$), 135.6 (**C**$_{arom}$), 135.4 (**C**$_{arom}$), 133.4 (**C**-4), 130.9 (**C**$_{arom}$), 129.7 (**C**-3), 127.5 (**CH**$_{arom}$), 126.1 (**CH**$_{arom}$), 71.4 (**C**-OH), 70.3 (**C**-OH), 31.3 (**C**-9), 29.5 (**C**-1), 23.8 (**C**-2), 22.6 (**C**-10), 21.1 (**C**H$_3$), 19.6 (**C**H$_3$). IR (ATR) cm^{-1}: 3408 (O-H st), 2921 (=C-H st). MS (EI, 70 eV) *m/z* (%): 208 (M$^+$ - 2·H$_2$O, 100), 193 (93), 178 (58), 165 (19), 151 (8), 139 (2), 127 (2), 115 (3), 95 (8), 82 (4), 63 (5), 51 (3). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{16}$H$_{20}$NaO$_2$]$^+$: 267.1361 [(M+Na)$^+$]; found 267.1359.

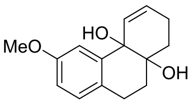


8-methoxy-1,2,9,10-tetrahydrophenanthrene-4a,10a-diol (10d). Following the *General Procedure G*, **10d** (192 mg, 0.78 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **9d** (220 mg, 0.80 mmol) and 2nd generation Grubbs catalyst (17 mg, 0.02 mmol). Yield: 98%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 7.32-7.14 (m, 2H, 2 x C**H$_{arom}$**), 6.73 (dd, *J* = 6.7, 2.4 Hz, 1H, C**H$_{arom}$**), 5.87 (d, *J* = 10.0 Hz, 1H, **H**-4), 5.70 (dt, *J* = 10.0, 3.4 Hz, 1H, **H**-3), 3.81 (s, 3H, OC**H$_3$**), 3.06 (s, 1H, O**H**), 2.80* (s, 1H, O**H**), 2.94-2.62 (m, 2H, **H**-9), 2.38-2.15 (m, 1H, **H$_a$**-2), 2.17-1.78 (m, 4H, **H$_b$**-2, **H**-1 and **H$_a$**-10),



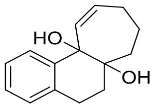
1.76-1.55 (m, 1H, **H$_b$**-10). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 156.2 (**C**-8), 141.8 (**C**-4b), 133.0 (**C**-4), 127.7 (**C**-3), 127.0 (**C**H$_{arom}$), 124.6 (**C**-8a), 119.9 (**C**H$_{arom}$), 108.2 (**C**-7), 71.2 (**C**-OH), 70.4 (**C**-OH), 55.3 (O**C**H$_3$), 31.2 (**C**-9), 29.2 (**C**-1), 23.8 (**C**-2), 19.4 (**C**-10). MS (EI, 70 eV) *m/z* (%): 210 (M^+ - 2·H_2O, 100), 179 (87), 165 (29), 151 (11), 121 (12), 88 (12), 62 (8), 51 (4). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{15}H_{18}NaO_3]^+$: 269.1154 [$(M+Na)^+$]; found 269.1163.

6-methoxy-1,2,9,10-tetrahydrophenanthrene-4a,10a-diol (10e). Following the G*eneral Procedure G*,



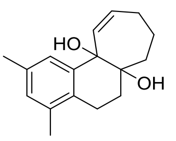
10e (270 mg, 1.10 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) starting from **9e** (350 mg, 1.29 mmol) and 2nd generation Grubbs catalyst (27 mg, 0.032 mmol). Yield: 85%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 7.17 (d, *J* = 2.7 Hz, 1H, **H**-5), 6.98 (d, *J* = 8.4 Hz, 1H, **H**-8), 6.76 (dd, *J* = 8.4, 2.7 Hz, 1H, **H**-7), 5.84 (d, *J* = 10.0 Hz, 1H, **H**-4), 5.71 (dt, *J* = 10.0, 3.5 Hz, 1H, **H**-3), 3.78 (s, 3H, OC**H$_3$**), 3.00* (s, 1H, O**H**), 3.11-2.92 (m, 1H, **H$_a$**-9), 2.78 (s, 1H, O**H**), 2.62 (dt, *J* = 16.6, 5.2 Hz, 1H, **H$_b$**-9), 2.34-1.81 (m, 5H, **H**-2, **H**-10 and **H$_a$**-1), 1.71-1.57 (m, 1H, **H$_b$**-1). ^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$): 158.3 (**C**-6), 141.7 (**C**$_{arom}$), 133.1 (**C**-4), 129.3 (**C**H$_{arom}$), 128.0 (**C**-3), 127.6 (**C**$_{arom}$), 114.0 (**C**H$_{arom}$), 112.5 (**C**H$_{arom}$), 71.5 (**C**-OH), 70.7 (**C**-OH), 55.4 (O**C**H$_3$), 31.6 (**C**-9), 30.0 (**C**-1), 24.5 (**C**-2), 23.9 (**C**-10). IR (ATR) cm^{-1}: 3401 (O-H st), 2926 (=C-H st). MS (EI, 70 eV) *m/z* (%): 210 (M^+ - 2.H_2O, 63), 208 (100), 193 (8), 176 (4), 162 (6), 85 (5), 70 (4). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{15}H_{18}NaO_3]^+$: 269.1154 [$(M+Na)^+$]; found 269.1157.

5,6,8,9-tetrahydro-6a*H*-cyclohepta[*a*]naphthalene-6a,11a(7*H*)-diol (10f). Following the *General*



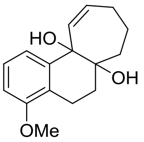
Procedure G, **10f** (260 mg, 1.13 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) starting from **9f** (320 mg, 1.24 mmol) and 2nd generation Grubbs catalyst (26 mg, 0.031 mmol). Yield: 91%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 7.57 (dt, *J* = 7.2, 3.5 Hz, 1H, C**H**$_{arom}$), 7.19 (dt, *J* = 7.2, 3.5 Hz, 2H, 2 x C**H**$_{arom}$), 7.10 (dd, *J* = 5.6, 3.5 Hz, 1H, C**H**$_{arom}$), 5.93 (dt, *J* = 12.2, 6.1 Hz, 1H, **H**-10), 5.72 (dt, *J* = 12.0, 1.4 Hz, 1H, **H**-11), 3.03 (dt, *J* = 17.7, 6.9 Hz, 1H, **H$_a$**-5), 2.95-2.76 (m, 1H, **H$_b$**-5), 2.92* (s, 1H, O**H**) 2.32 (s, 1H, O**H**), 2.29-1.69 (m, 7H, **H**-6, **H**-7, **H$_a$**-8 and **H**-9), 1.54 (m, 1H, **H$_b$**-8). ^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$): 142.3 (**C**$_{arom}$), 136.3 (**C**-11), 135.1 (**C**$_{arom}$), 133.3 (**C**-10), 128.6 (**C**H$_{arom}$), 127.4 (**C**H$_{arom}$), 126.9 (**C**H$_{arom}$), 126.4 (**C**H$_{arom}$), 78.0 (**C**-OH), 74.0 (**C**-OH), 38.9 (**C**-7), 32.0 (**C**-9), 28.0 (**C**-5), 26.0 (**C**-8), 22.2 (**C**-6). IR (ATR) cm^{-1}: 3440 (O-H st), 2922 (=C-H st). MS (EI, 70 eV) *m/z* (%): 212 (M^+ - H_2O, 100), 194 (18), 183 (75), 169 (31), 155 (23), 141 (71), 128 (32), 115 (42), 102 (4), 89 (13), 76 (9), 63 (8), 51 (6). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{15}H_{18}NaO_2]^+$: 253.1205 [$(M+Na)^+$]; found 253.1207. M.p.: 85-87 °C (hexanes/EtOAc).

2,4-dimethyl-5,6,8,9-tetrahydro-6a*H*-cyclohepta[*a*]naphthalene-6a,11a(7*H*)-diol (10g). Following



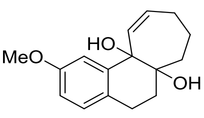
the *General Procedure G*, **10g** (500 mg, 1.93 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) starting from **9g** (700 mg, 2.45 mmol) and 2nd generation Grubbs catalyst (52 mg, 0.060 mmol). Yield: 79%. Brown solid. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 7.30 (d, *J* = 2.0 Hz, 1H, C**H**$_{arom}$), 6.92 (d, *J* = 2.0 Hz, 1H, C**H**$_{arom}$), 5.92 (dt, *J* = 12.0, 6.1 Hz, 1H, **H**-10), 5.74 (d, *J* = 12.0 Hz, 1H, **H**-11), 2.89* (s, 1H, O**H**), 2.86-2.56 (m, 2H, **H**-5), 2.33* (s, 1H, O**H**), 2.30 (s, 3H, C**H$_3$**), 2.21* (s, 3H, C**H$_3$**), 2.18-1.70 (m, 7H, **H**-6, **H**-7, **H$_a$**-8 and **H**-9), 1.55 (m, 1H, **H$_b$**-8). ^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$): 142.2 (**C**$_{arom}$), 136.8 (**C**-11), 135.9 (**C**$_{arom}$), 135.6 (**C**$_{arom}$), 132.9 (**C**-10), 130.3 (**C**$_{arom}$), 129.9 (**C**H$_{arom}$), 125.1 (**C**H$_{arom}$), 78.1 (**C**-OH), 73.6 (**C**-OH), 38.8 (**C**-7), 31.8 (**C**-9), 28.0 (**C**-5), 23.6 (**C**-6), 22.2 (**C**-8), 21.1 (**C**H$_3$), 19.6 (**C**H$_3$). IR (ATR) cm^{-1}: 3361 (O-H st), 3278 (O-H st), 2932 (=C-H st). MS (EI, 70 eV) *m/z* (%): 240 (M^+ - H_2O, 100), 225 (10), 211 (31), 197 (27), 183 (20), 169 (32), 155 (15), 141 (12), 128 (12), 115 (10), 91 (5), 77 (5). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{17}H_{22}NaO_2]^+$: 281.1518 [(M+Na)$^+$]; found 281.1518. M.p.**:** 114-116 °C (hexanes/EtOAc).

4-methoxy-5,6,8,9-tetrahydro-6a*H*-cyclohepta[*a*]naphthalene-6a,11a(7*H*)-diol (10h). Following the



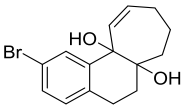
General Procedure G, **10h** (236 mg, 0.91 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **9h** (274 mg, 0.95 mmol) and 2nd generation Grubbs catalyst (20 mg, 0.024 mmol). Yield: 96%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 7.23-7.12 (m, 2H, 2 x C**H**$_{arom}$), 6.73 (dd, *J* = 6.6, 2.6 Hz, 1H, C**H**$_{arom}$), 5.89 (dt, *J* = 12.1, 6.1 Hz, 1H, **H**-10), 5.70 (dt, *J* = 12.0, 1.2 Hz, 1H, **H**-11), 3.81 (s, 3H, OC**H$_3$**), 2.99 (s, 1H, O**H**), 2.94-2.60 (m, 2H, **H**-5), 2.36 (s, 1H, O**H**), 2.29-1.66 (m, 7H, **H**-6, **H**-7, **H**-9 and **H$_a$**-8), 1.76-1.55 (m, 1H, **H$_b$**-8). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 156.6 (**C**$_{arom}$), 143.5 (**C**$_{arom}$), 136.4 (**C**-11), 133.0 (**C**-10), 127.0 (**C**H$_{arom}$), 123.9 (**C**$_{arom}$), 118.8 (**C**H$_{arom}$), 108.4 (**C**H$_{arom}$), 77.8 (**C**-OH), 73.6 (**C**-OH), 55.3 (O**C**H$_3$), 38.7 (**C**-7), 31.4 (**C**-9), 27.9 (**C**-5), 22.1 (**C**-8), 20.4 (**C**-6). IR (ATR) cm^{-1}: 3447 (O-H st), 2930 (=C-H st). MS (EI, 70 eV) *m/z* (%): 242 (M^+ - H_2O, 100), 224 (11), 213 (45), 199 (20), 185 (11), 171 (25), 141 (16), 128 (21), 115 (22), 91 (4), 77 (5), 63 (3), 51 (3). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{16}H_{20}NaO_3]^+$: 283.1310 [(M+Na)$^+$]; found 283.1310.

2-methoxy-5,6,8,9-tetrahydro-6a*H*-cyclohepta[*a*]naphthalene-6a,11a(7*H*)-diol (10i). Following the

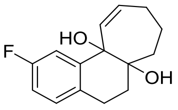


General Procedure G, **10i** (460 mg, 1.77 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **9i** (570 mg, 1.98 mmol) and 2nd generation Grubbs catalyst (42 mg, 0.050 mmol). Yield: 89%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 7.16 (d, *J* = 2.8 Hz, 1H, **H**-1), 7.03 (d, *J* = 8.4 Hz, 1H, **H**-4), 6.78 (dd, *J* = 8.4, 2.8 Hz, 1H, **H**-3), 5.95 (ddd, *J* = 12.1, 6.7, 5.5 Hz, 1H, **H**-10), 5.73-5.64 (m, 1H, **H**-11), 3.79 (s, 3H, OC**H$_3$**), 3.02-2.77 (m, 2H, **H**-5), 2.75 (s, 1H, O**H**), 2.36-2.14 (m, 2H, **H**-9), 2.14-

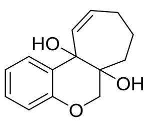
1.70 (m, 5H, **H**-6, **H**-7 and $\mathbf{H_a}$-8), 2.08* (s, 1H, O**H**), 1.66-1.49 (m, 1H, $\mathbf{H_b}$-8). ^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$): 158.4 (**C**$_{arom}$), 143.9 (**C**$_{arom}$), 136.0 (**C**-11), 133.7 (**C**-10), 129.6 (**C**H$_{arom}$), 126.9 (**C**$_{arom}$), 113.9 (**C**H$_{arom}$), 111.4 (**C**H$_{arom}$), 78.0 (**C**-OH), 74.1 (**C**-OH), 55.4 (O**C**H$_3$), 39.1 (**C**-7), 32.0 (**C**-9), 28.0 (**C**-5), 25.0 (**C**-8), 22.4 (**C**-6). IR (ATR) cm^{-1}: 3443 (O-H st), 2926 (=C-H st). MS (EI, 70 eV) *m/z* (%): 242 (M^+ - H_2O, 100), 224 (9), 213 (39), 199 (18), 185 (9), 171 (31), 152 (9), 141 (13), 128 (21), 115 (17), 102 (4), 91 (4), 77 (5), 63 (3), 51 (3). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{16}H_{20}NaO_3]^+$: 283.1310 [$(M+Na)^+$]; found 283.1311.



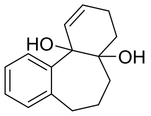
2-bromo-5,6,8,9-tetrahydro-6a*H*-cyclohepta[*a*]naphthalene-6a,11a(7*H*)-diol (10j). Following the *General Procedure G*, **10j** (415 mg, 1.34 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **9j** (525 mg, 1.56 mmol) and 2nd generation Grubbs catalyst (33 mg, 0.039 mmol). Yield: 86%. Brown solid. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 7.72 (d, *J* = 2.1 Hz, 1H, **H**-1), 7.36-7.23 (m, 1H, **H**-3), 6.99 (d, *J* = 8.2 Hz, 1H, **H**-4), 5.96 (dt, *J* = 12.2, 6.3 Hz, 1H, **H**-10), 5.66 (dt, *J* = 12.0, 1.4 Hz, 1H, **H**-11), 2.98 (dt, *J* = 17.5, 7.2 Hz, 1H, $\mathbf{H_a}$-5), 2.86-2.72 (m, 1H, $\mathbf{H_b}$-5), 2.78* (s, 1H, O**H**), 2.33-2.14 (m, 2H, **H**-9), 2.14-1.92 (m, 4H, **H**-7, $\mathbf{H_a}$-6 and O**H**), 1.92-1.69 (m, 2H, $\mathbf{H_b}$-6 and $\mathbf{H_a}$-8), 1.67-1.51 (m, 1H, $\mathbf{H_b}$-8). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 144.9 (**C**$_{arom}$), 135.7 (**C**-11), 134.2 (**C**$_{arom}$), 134.1 (**C**-10), 130.4 (**C**H$_{arom}$), 130.3 (**C**H$_{arom}$), 129.9 (**C**H$_{arom}$), 120.1 (**C**$_{arom}$), 77.7 (**C**-OH), 73.9 (**C**-OH), 39.3 (**C**-7), 31.6 (**C**-9), 28.0 (**C**-5), 25.5 (**C**-8), 22.3 (**C**-6). IR (ATR) cm^{-1}: 3368 (O-H st), 3303 (O-H st). MS (EI, 70 eV) *m/z* (%): 290 (M^+ - H_2O, 100), 272 (18), 261 (59), 248 (11), 236 (10), 221 (15), 193 (27), 178 (51), 165 (40), 153 (40), 141 (51), 128 (31), 115 (34), 89 (14), 76 (14), 63 (13), 51 (9). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{15}H_{17}BrNaO_2]^+$: 331.0310 [$(M+Na)^+$]; found 331.0303. M.p.: 120-122 °C (hexanes/EtOAc).



2-fluoro-5,6,8,9-tetrahydro-6a*H*-cyclohepta[*a*]naphthalene-6a,11a(7*H*)-diol (10k). Following the *General Procedure G*, **10k** (438 mg, 1.77 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **9k** (514 mg, 1.86 mmol) and 2nd generation Grubbs catalyst (40 mg, 0.046 mmol). Yield: 95%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 7.31-7.19 (m, 1H, **H**-1), 7.04 (dd, *J* = 8.4, 5.8 Hz, 1H, **H**-3), 6.86 (td, *J* = 8.4, 2.7 Hz, 1H, **H**-4), 6.01-5.84 (m, 1H, **H**-10), 5.61 (dt, *J* = 12.0, 1.4 Hz, 1H, **H**-11), 3.11 (s, 1H, O**H**), 2.95 (dt, *J* = 17.1, 7.2 Hz, 1H, $\mathbf{H_a}$-5), 2.78 (dt, *J* = 17.3, 6.8 Hz, 1H, $\mathbf{H_b}$-5), 2.37 (s, 1H, O**H**), 2.29-2.07 (m, 2H, **H**-9), 2.06-1.86 (m, 3H, **H**-6 and $\mathbf{H_a}$-7), 1.87-1.66 (m, 2H, $\mathbf{H_b}$-7 and $\mathbf{H_a}$-8), 1.62-1.45 (m, 1H, $\mathbf{H_b}$-8). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 161.6 (d, $^1J_{CF}$ = 243.2 Hz, **C**-2), 144.7 (d, $^3J_{CF}$ = 6.4 Hz, **C**$_{arom}$), 135.6 (**C**-11), 133.9 (**C**-10), 130.6 (d, $^4J_{CF}$ = 3.2 Hz, **C**$_{arom}$), 129.9 (d, $^3J_{CF}$ = 7.7 Hz, **C**-4), 114.4 (d, $^2J_{CF}$ = 21.5 Hz, **C**H$_{arom}$), 113.4 (d, $^2J_{CF}$ = 22.1 Hz, **C**H$_{arom}$), 77.6 (d, $^4J_{CF}$ = 28.8 Hz, **C**-11a), 73.8 (**C**-4a), 39.2 (**C**-7), 31.8 (**C**-9), 28.0 (**C**-5), 25.2 (**C**-8), 22.2 (**C**-6). ^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$): -116.4. IR (ATR) cm^{-1}: 3353 (O-H st), 3289 (O-H st), 2944 (=C-H st). MS (EI, 70 eV) *m/z* (%): 230 (M^+ - H_2O, 100), 212 (41), 196 (64), 183 (43), 170 (28), 159 (77), 146 (48), 133 (52), 120 (6), 109 (15), 98 (8), 81 (7), 72 (1), 63 (5), 51 (4). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{15}H_{17}FNaO_2]^+$: 271.1110 [(M+Na)$^+$]; found 271.1118.

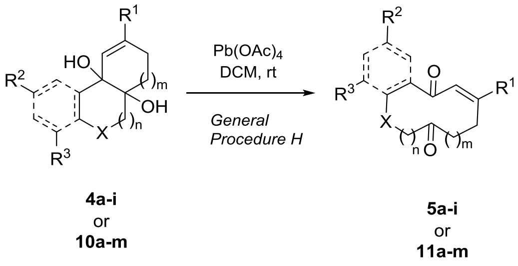


3-(pent-4-en-1-yl)-4-vinylchromane-3,4-diol (10l). Following the *General Procedure G*, **10l** (207 mg, 0.89 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) starting from **9l** (430 mg, 1.65 mmol) and 2nd generation Grubbs catalyst (70 mg, 0.082 mmol). Yield: 54%. Brown solid. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) : 7.50 (dd, *J* = 7.4, 1.7 Hz, 1H, **H**-4), 7.20 (ddd, *J* = 8.4, 7.4, 1.7 Hz, 1H, **H**-2), 6.95 (td, *J* = 7.4, 1.2 Hz, 1H, **H**-3), 6.83 (dd, *J* = 8.4, 1.2 Hz, 1H, **H**-1), 5.95 (dt, *J* = 11.0, 5.3 Hz, 1H, **H**-10), 5.80 (d, *J* = 11.0 Hz, 1H, **H**-11), 4.20 (d, *J* = 10.8 Hz, 1H, $\mathbf{H_a}$-6), 4.01 (d, *J* = 10.8 Hz, 1H, $\mathbf{H_b}$-6), 2.80 (s, 1H, O**H**), 2.57 (s, 1H, O**H**), 2.39-2.20 (m, 1H, $\mathbf{H_a}$-9), 2.20-2.07 (m, 1H, $\mathbf{H_b}$-9), 2.02-1.84 (m, 2H, **H**-7), 1.64-1.46 (m, 2H, **H**-8). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 152.7 ($\mathbf{C}_{arom}$), 134.3 (**C**-11), 133.8 (**C**-10), 129.6 ($\mathbf{C}H_{arom}$), 128.4 ($\mathbf{C}_{arom}$), 128.0 ($\mathbf{C}H_{arom}$), 121.5 ($\mathbf{C}H_{arom}$), 116.6 ($\mathbf{C}H_{arom}$), 74.7 (**C**-OH), 72.0 (**C**-6), 70.8 (**C**-OH), 36.2 (**C**-7), 28.6 (**C**-9), 20.8 (**C**-8). IR (ATR) cm^{-1}: 3447 (O-H st), 2934 (=C-H st). MS (EI, 70 eV) *m/z* (%): 214 (M$^+$ - H_2O, 17), 185 (15), 171 (33), 158 (17), 145 (41), 131 (28), 115 (16), 91 (8), 77 (11), 55 (5). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{14}H_{16}NaO_3]^+$: 255.0997 [(M+Na)$^+$]; found 255.1004. M.p.: 102-103 °C (hexanes/EtOAc).



3,4,6,7-tetrahydro-4a*H*-dibenzo[a,c][7]annulene-4a, 11b(5*H*)-diol (10m). Following the *General Procedure G*, **10m** (235 mg, 1.02 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **9m** (335 mg, 1.30 mmol) and 2º generation Grubbs catalyst (27.2 mg, 0.032 mmol). Yield: 78%. Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 7.43 (dd, *J* = 7.3, 1.8 Hz, 1H, $C\mathbf{H}_{arom}$), 7.23 – 7.06 (m, 3H, 3 x $C\mathbf{H}_{arom}$), 6.01 (dddd, *J* = 10.0, 4.5, 2.6, 0.9 Hz, 1H, **H**-2), 5.60 (dt, *J* = 10.0, 2.2 Hz, 1H, **H**-1), 3.54 (ddd, *J* = 14.7, 9.4, 5.2 Hz, 1H, $\mathbf{H_a}$-7), 3.06 (s, 1H, O**H**), 2,67* (s, 1H, O**H**), 2.80 – 2.62 (m, 1H, $\mathbf{H_b}$-7), 2.39 – 2.23 (m, 1H, $\mathbf{H_a}$-3), 2.23 – 1.98 (m, 2H, $\mathbf{H_b}$-3 and $\mathbf{H_a}$-5), 1.81 – 1.58 (m, 2H, $\mathbf{H_b}$-5 and $\mathbf{H_a}$-4), 1.57 – 1.39 (m, 3H, $\mathbf{H_b}$-4 and **H**-6). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 140.8 ($\mathbf{C}_{arom}$), 140.6 ($\mathbf{C}_{arom}$), 132.2 (**C**-1), 131.2 (**C**-2), 128.8 ($\mathbf{C}H_{arom}$), 128.6 ($\mathbf{C}H_{arom}$), 128.0 ($\mathbf{C}H_{arom}$), 125.4 ($\mathbf{C}H_{arom}$), 77.5 (**C**-OH), 72.4 (**C**-OH), 38.5 (**C**-7), 32.9 (**C**-5), 32.4 (**C**-4), 22.2 (**C**-3), 18.9 (**C**-6). IR (ATR) cm^{-1}: 3389 (O-H st), 2930 (=C-H st). MS (EI, 70 eV) *m/z* (%): 230 (M$^+$, 4), 212 (21), 194 (100), 179 (91), 165 (63), 152 (27), 141 (37), 128 (36), 115 (38), 103 (5), 89 (13). HRMS (UPLC MS ESI+): Calculated for $[NaC_{15}H_{18}O_2]^+$: 253.1205 [(M+Na)$^+$]; found 253.1199.

2.5. Synthesis of substrates 5a-l and 11a-m



4a-i or **10a-m**

5a-i or **11a-m**

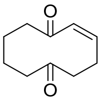
5a n=1 m=1 X=CH$_2$ R^1=H
5b n=1 m=1 X=O R^1=H
5c n=1 m=1 X=CH$_2$ R^1=Me
5d n=1 m=2 X=CH$_2$ R^1=H
5e n=2 m=1 X=CH$_2$ R^1=H
5f n=2 m=2 X=CH$_2$ R^1=H
5g n=0 m=2 X=CH$_2$ R^1=H
5h n=0 m=1 X=CH$_2$ R^1=H
5i n=1 m=0 X=CH$_2$ R^1=H

n=0 m=2 X=CH$_2$ R^1=H
11a R^2= H R^3= H

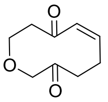
n=1 m=1 X=CH$_2$ R^1=H
11b R^2= H R^3= H
11c R^2= Me R^3= Me
11d R^2= H R^3= OMe
11e R^2= OMe R^3= H

n=1 m=2 X=CH$_2$ R^1=H
11f R^2= H R^3= H
11g R^2= Me R^3= Me
11h R^2= H R^3= OMe
11i R^2= OMe R^3= H
11j R^2= Br R^3= H
11k R^2= F R^3= H
11l n=1 m=2 X=O R^1,R^2,R^3= H
11m n=2 m=1 X=CH$_2$ R^1,R^2,R^3= H

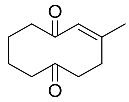
General Procedure H: To a solution of Pb(OAc)$_4$ (1.0 equiv.) in CH$_2$Cl$_2$ (0.4 mmol/mL) was added a solution of the corresponding 1,2-diol (1.0 equiv.) in CH$_2$Cl$_2$ (0.4 mmol/mL) and it was stirred at room temperature for 30 min. The reaction mixture was concentrated, taken up in ether and the solids were removed by filtration through a short pad of silica gel. The filtrate was concentrated and purified by column chromatography on silica gel (hexanes/EtOAc) to yield the desired product.



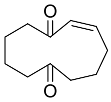
(*Z*)-cyclodec-2-ene-1,6-dione (5a). Following the G*eneral Procedure H*, compound **5a** (680 mg, 4.10 mmol) was isolated by FC (hexanes/EtOAc 1:1) starting from **4a** (750 mg, 4.46 mmol) and Pb(OAc)$_4$ (1.98 g, 4.46 mmol). Yield: 92%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 6.09 (d, *J* = 12.0 Hz, 1H, **H**-2), 5.75 (dt, *J* = 12.0, 8.4 Hz, 1H, **H**-3), 2.73 (m, 2H, **H**-10), 2.41-2.24 (m, 6H, **H**-4, **H**-5 and **H**-7), 1.73 (m, 4H, **H**-8 and **H**-9). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 211.1 (**C**-6), 208.3 (**C**-1), 136.9 (**C**-3), 132.0 (**C**-2), 44.1 (**C**-10), 42.0 (**C**-5), 36.0 (**C**-7), 23.7 (**C**-4), 23.3 (**C**-9), 23.0 (**C**-8). IR (ATR) cm^{-1}: 1699 (C=O st), 1678 (C=O st). MS (EI, 70 eV) *m/z* (%): 166 (M$^+$, 3), 148 (53), 128 (65), 115 (38), 104 (71), 91 (100), 79 (53), 68 (35), 55 (65). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{10}$H$_{14}$NaO$_2$]$^+$: 189.0892 [(M+Na)$^+$]; found: 189.0889. M.p.: 85-87 °C (hexanes/EtOAc).



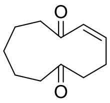
(*Z*)-4,5,9,10-tetrahydro-2*H*-oxecine-3,8-dione (5b). Following the G*eneral Procedure H*, compound **5b** (35 mg, 0.21 mmol) was isolated by FC (hexanes/EtOAc 1:1) starting from **4b** (90 mg, 0.53 mmol) and Pb(OAc)$_4$ (230 mg, 0.53 mmol). Yield: 40%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 6.09 (d, *J* = 12.2 Hz, 1H, **H**-7), 5.87 (dt, *J* = 12.1, 7.3 Hz, 1H, **H**-6), 3.94 (s, 2H, **H**-2), 3.87 (t, *J* = 5.5 Hz, 2H, **H**-10), 2.74-2.56 (m, 6H, **H**-4, **H**-5 and **H**-9). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 209.4 (**C**-3), 205.9 (**C**-8), 136.5 (**C**-6), 131.7 (**C**-7), 76.3 (**C**-2), 68.3 (**C**-10), 43.6 (**C**-9), 40.0 (**C**-4), 24.2 (**C**-5). IR (ATR) cm^{-1}: 1691 (C=O st). MS (EI, 70 eV) *m/z* (%): 150 (M$^+$ - H$_2$O, 8), 140 (8), 126 (77), 110 (28), 95 (64), 82 (63), 68 (100), 54 (85). HRMS (UPLC MS ESI$^+$): Calculated for $[C_9H_{12}NaO_3]^+$: 191.0684 [(M+Na)$^+$]; found: 191.0691.



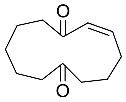
(*Z*)-3-methylcyclodec-2-ene-1,6-dione (5c). Following the *General Procedure H*, compound **5c** (269 mg, 1.49 mmol) was isolated by FC (hexanes/EtOAc 1:1) starting from **4c** (370 mg, 2.03 mmol) and $Pb(OAc)_4$ (900 mg, 2.03 mmol). Yield: 73%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 5.88 (s, 1H, **H**-2), 2.74 (t, *J* = 6.9 Hz, 2H, **H**-10), 2.41 – 2.30 (m, 4H, **H**-5 and **H**-7), 2.30 – 2.20 (m, 2H, **H**-4), 1.78 – 1.62 (m, 4H, **H**-8 and **H**-9), 1.73* (s, 3H, C**H₃**). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 210.3 (**C**-6), 208.6 (**C**-1), 147.0 (**C**-3), 128.2 (**C**-2), 44.3 (**C**-10), 40.8 (**C**-7), 36.1 (**C**-5), 27.6 (**C**-4), 23.1 (**C**-9), 23.0 (**C**-8), 22.6 (**C**H_3). IR (ATR) cm^{-1}: 1703 (C=O st), 1672 (C=O st), 1635 (C=O st). MS (EI, 70 eV) *m/z* (%): 162 (M^+ - H_2O, 39), 123 (45), 120 (11), 109 (48), 107 (29), 95 (100), 81 (59), 67 (80), 55 (65), 51 (33). HRMS (UPLC MS ESI+): Calculated for $[NaC_{11}H_{16}O_2]^+$: 203.1048 [(M+Na)$^+$]; found: 203.1058. M.p.: 86-88 °C (hexanes/EtOAc).



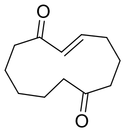
(*Z*)-cycloundec-7-ene-1,6-dione (5d). Following the G*eneral Procedure H*, compound **5d** (166 mg, 0.92 mmol) was isolated by FC (hexanes/EtOAc 1:1) starting from **4d** (215 mg, 1.18 mmol) and $Pb(OAc)_4$ (520 mg, 1.18 mmol). Yield: 78%. Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 6.11 (d, *J*=11.9 Hz, 1H, **H**-2), 5.96 (dt, *J*=11.9, 8.5 Hz, 1H, **H**-3), 2.60-2.51 (m, 2H, **H**-11), 2.49-2.32 (m, 6H, **H**-4, **H**-6 and **H**-8), 1.95-1.80 (m, 4H, **H**-5 and **H**-9), 1.79-1.65 (m, 2H, **H**-10). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 211.4 (**C**-7), 205.6 (**C**-1), 144.7 (**C**-3), 129.6 (**C**-2), 43.8 (**C**-6), 43.2 (**C**-8), 41.3 (**C**-11), 28.0 (**C**-4), 22.8 (**C**-5), 22.66 (**C**-9), 22.66 (**C**-10). IR (ATR) cm^{-1}: 1707 (C=O st), 1685 (C=O st). MS (EI, 70 eV) *m/z* (%): 180 (M^+, 7), 162 (21), 144 (27), 133 (49), 120 (56), 95 (78), 81 (100), 68 (94), 55 (89). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{11}H_{17}O_2]^+$: 181.1229 [(M+H)$^+$]; found: 181.1231.



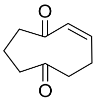
(*Z*)-cycloundec-7-ene-1,6-dione (5e). Following the *General Procedure H*, compound **5e** (117 mg, 0.65 mmol) was isolated by FC (hexanes/EtOAc 1:1) starting from **4e** (140 mg, 0.77 mmol) and $Pb(OAc)_4$ (340 mg, 0.77 mmol). Yield: 84%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 6.26 (dt, *J*=11.8, 1.6 Hz, 1H, **H**-3), 5.94 (dt, *J*=11.7, 8.1 Hz, 1H, **H**-2), 2.89-2.67 (m, 2H, **H**-11), 2.54-2.23 (m, 6H, **H**-4, **H**-5 and **H**-7), 1.76-1.46 (m, 4H, **H**-8 and **H**-10), 1.40-1.18 (m, 2H, **H**-9). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 211.2 (**C**-6), 205.4 (**C**-1), 140.7 (**C**-3), 131.1 (**C**-2), 43.2 (**C**-7), 42.8 (**C**-11), 39.1 (**C**-5), 25.2 (**C**-4), 24.5 (**C**-10), 23.2 (**C**-8), 21.4 (**C**-9). IR (ATR) cm^{-1}: 2937 (=C-H st), 1687 (C=O st), 1628 (C=O st). MS (EI, 70 eV) *m/z* (%): 180 (M^+, 3), 162 (14), 134 (16), 109 (32), 95 (100), 81 (60), 68 (28), 55 (91). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{11}H_{16}NaO_2]^+$: 203.1048 [(M+Na)$^+$]; found: 203.1048. M.p.: 58-60 °C (hexanes/EtOAc).



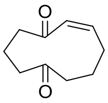
(*Z*)-cyclododec-2-ene-1,7-dione (5f). Following the G*eneral Procedure H*, compound **5f** (300 mg, 1.55 mmol) was isolated by FC (hexanes/EtOAc 1:1) starting from **4f** (320 mg, 1.63 mmol) and Pb(OAc)$_4$ (720 mg, 1.63 mmol). Yield: 95%. Yellow solid. ^{1}H NMR (δ, ppm) (500 MHz, CDCl$_3$): 6.26 (dt, *J*=11.8, 1.9 Hz, 1H, **H**-2), 5.76 (dt, *J*=11.8, 7.6 Hz, 1H, **H**-3), 2.46-2.31 (m, 8H, **H**-4, **H**-7, **H**-8 and **H**-12), 1.88-1.73 (m, 2H, **H**-5), 1.75-1.52 (m, 4H, **H**-9 and **H**-11), 1.25-1.11 (m, 2H, **H**-10). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 211.2 (**C**-7), 204.5 (**C**-1), 143.1 (**C**-3), 131.4 (**C**-2), 41.6 (**C**-6), 41.5 (**C**-8), 38.7 (**C**-12), 26.9 (**C**-4), 25.1 (**C**-9), 23.4 (**C**-5), 23.2 (**C**-11), 21.8 (**C**-10). IR (ATR) cm^{-1}: 1941 (=C-H st), 1700 (C=O st), 1677 (C=O st). MS (EI, 70 eV) *m/z* (%): 194 (M$^+$, 6), 176 (9), 151 (10), 133 (26), 109 (25), 95 (51), 81 (100), 68 (43), 55 (69). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{12}$H$_{18}$NaO$_2$]$^+$: 217.1205 [(M+Na)$^+$]; found: 217.1208. M.p.: 63-65 °C (hexanes/EtOAc).



(*E*)-cyclododec-2-ene-1,7-dione (5f'). Compound **5f'** could be isolated as a consecuence of the isomerization of the double bond when substrate **5f** was subjected to the reaction conditions. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 6.40 (dt, *J* = 15.6, 7.8 Hz, 1H, **H**-3), 6.22-6.13 (d, *J* = 15.6, 1H, **H**-2), 2.48-2.42 (m, 2H, **H**-12), 2.41-2.35 (m, 4H, **H**-6 and **H**-8), 2.21 (m, 2H, **H**-4), 1.97 (m, 2H, **H**-5), 1.67-1.53 (m, 4H, **H**-9 and **H**-11), 1.24 (m, 2H, **H**-10). ^{13}C NMR (75 MHz, CDCl$_3$) δ 210.1 (**C**-7), 203.0 (**C**-1), 145.6 (**C**-3), 131.1 (**C**-2), 41.8 (**C**-12), 40.99 (**C**H$_2$CO), 40.91 (**C**H$_2$CO), 33.9 (**C**-4), 24.6 (**C**-11), 23.1 (**C**H$_2$), 21.9 (**C**H$_2$), 21.1 (**C**H$_2$). IR (ATR) cm^{-1}: 2926 (=C-H st), 1700 (C=O st), 1683 (C=O st), 1630 (C=O st). MS (EI, 70 eV) *m/z* (%): 194 (M$^+$, 4), 176 (4), 165 (6), 133 (11), 123 (10), 109 (13), 95 (29), 81 (100), 68 (42), 55 (58), 53 (32).



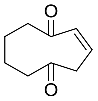
(*Z*)-cyclonon-6-ene-1,5-dione (5g). Following the G*eneral Procedure H*, compound **5g** (138 mg, 0.91 mmol) was isolated by FC (hexanes/EtOAc 1:1) as starting from **4g** (187 mg, 1.21 mmol) and Pb(OAc)$_4$ (526 mg, 1.21 mmol). Yield: 75%. Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 6.23 (dt, *J* = 12.6, 8.5 Hz, 1H, **H**-7), 6.12 (d, *J* = 12.6 Hz, 1H, **H**-6), 2.79-2.69 (m, 2H, **H**-4), 2.67-2.48 (m, 6H, **H**-2, **H**-8 and **H**-9), 2.06-1.94 (m, 2H, **H**-3). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 212.3 (**C**-1), 204.0 (**C**-5), 139.1 (**C**-7), 134.4 (**C**-6), 44.2 (**C**-2), 41.9 (**C**-9), 39.4 (**C**-4), 23.6 (**C**-8), 21.9 (**C**-3). IR (ATR) cm^{-1}: 2971 (=C-H st), 1703 (C=O st), 1652 (C=O st). MS (EI, 70 eV) *m/z* (%): 152 (M$^+$, 1), 134 (35), 124 (50), 117 (7), 105 (39), 96 (100), 91 (24), 82 (45), 77 (21), 68 (29), 63 (7), 55 (40). HRMS (UPLC MS ESI$^+$): Calculated for [C$_9$H$_{12}$NaO$_2$]$^+$: 175.0735 [(M+Na)$^+$]; found: 175.0735.



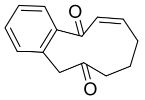
(*Z*)-cyclodec-6-ene-1,5-dione (5h). Following the *General Procedure H*, compound **5h** (230 mg, 1.38 mmol) was isolated by FC (hexanes/EtOAc 1:1) starting from **4h** (300 mg, 1.79 mmol) and Pb(OAc)$_4$ (790 mg, 1.79 mmol). Yield: 77%. Orange oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 6.17 (d, *J*=12.0 Hz, 1H, **H**-3), 5.76 (dt, *J*=12.0, 8,8 Hz, 1H, **H**-2), 2.49-2.28 (m, 8H, **H**-4, **H**-6, **H**-8 and **H**-10), 2.22-2.05 (m, 2H, **H**-5), 1.79-1.66 (m, 2H, **H**-9). ^{13}C NMR (δ, ppm)

(75.5 MHz, CDCl$_3$): 212.3 (**C**-7), 204.8 (**C**-1), 141.1 (**C**-3), 132.3 (**C**-2), 43.8 (**C**-6), 43.4 (**C**-8), 39.0 (**C**-10), 25.0 (**C**-4), 22.5 (**C**-5), 22.0 (**C**-9). IR (ATR) cm^{-1}: 1703 (C=O st), 1686 (C=O st). MS (EI, 70 eV) *m/z* (%): 166 (M$^+$, 2), 148 (21), 130 (18), 120 (33), 104 (67), 95 (79), 81 (100), 68 (66), 55 (70). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{10}$H$_{14}$NaO$_2$]$^+$: 189.0892 [(M+Na)$^+$]; found: 189.0896.

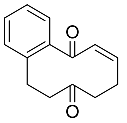
(*Z*)-cyclonon-2-ene-1,5-dione (5i). Following the *General Procedure H*, compound **5i** (210 mg, 1.38 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) starting from **4i** (355 mg, 2.30 mmol) and Pb(OAc)$_4$ (1.02 g, 2.30 mmol). Yield: 58%. Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 6.15 (d, *J*=12.0 Hz, 1H, **H**-2), 5.90 (dt, *J*=12.0, 7.9 Hz, 1H, **H**-3), 3.18 (d, *J*=7.9 Hz, 2H, **H**-4), 2.50-2.21 (m, 4H, **H**-6 and **H**-9), 1.86-1.54 (m, 4H, **H**-7 and **H**-8). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 208.5 (**C**-5), 207.3 (**C**-1), 134.7 (**C**-3), 128.8 (**C**-2), 42.8 (**C**-6), 42.5 (**C**-9), 42.3 (**C**-4), 24.6 (**C**-8), 23.9 (**C**-7). IR (ATR) cm^{-1}: 2937 (=C-H st), 1704 (C=O st), 1691 (C=O st). MS (EI, 70 eV) *m/z* (%): 152 (M$^+$, 4), 133 (34), 124 (18), 107 (51), 95 (41), 79 (40), 68 (100), 55 (47). HRMS (UPLC MS ESI$^+$): Calculated for [C$_9$H$_{13}$O$_2$]$^+$: 153.0916 [(M+H)$^+$]; found: 153.0919.



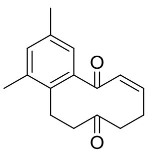
(*Z*)-9,10-dihydrobenzo[10]annulene-5,11(8*H*,12*H*)-dione (11a). Following the *General Procedure H*, compound **11a** (108 mg, 0.50 mmol) was isolated by FC (pentane/Et$_2$O gradient from 100:0 to 1:1) starting from **10a** (180 mg, 0.83 mmol) and Pb(OAc)$_4$ (369 mg, 0.83 mmol). Yield: 60%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.54-7.44 (m, 2H, 2 x C**H**$_{arom}$), 7.43-7.37 (m, 1H, C**H**$_{arom}$), 7.32 (d, *J* = 7.5 Hz, 1H, C**H**$_{arom}$), 6.31 (d, *J* = 12.2 Hz, 1H, **H**-6), 6.10 (dt, *J* = 12.2, 8.9 Hz, 1H, **H**-7), 3.72 (s, 2H, **H**-12), 2.47-2.32 (m, 2H, **H**-10), 1.96-1.82 (m, 2H, **H**-8), 1.74-1.60 (m, 2H, **H**-9). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 210.8 (**C**-11), 198.4 (**C**-5), 144.8 (**C**-7), 142.4 (**C**$_{arom}$), 142.4 (**C**$_{arom}$), 132.45 (**C**H$_{arom}$), 132.39 (**C**H$_{arom}$), 131.8 (**C**H$_{arom}$), 128.2 (**C**H$_{arom}$), 128.1 (**C**-6), 51.1 (**C**-12), 38.5 (**C**-10), 28.1 (**C**-8), 24.7 (**C**-9). IR (ATR) cm^{-1}: 1692 (C=O st), 1645 (C=O st). MS (EI, 70 eV) *m/z* (%): 214 (M$^+$, 6), 196 (19), 186 (20), 167 (8), 158 (100), 145 (18), 132 (39), 115 (40), 103 (7), 89 (32), 77 (10), 63 (14), 51 (7). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{14}$H$_{15}$O$_2$]$^+$: 215.1072 [(M+H)$^+$]; found 215.1074. M.p.: 68-70 °C (hexanes/EtOAc).



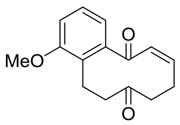
(*Z*)-8,9,11,12-tetrahydrobenzo[10]annulene-5,10-dione (11b). Following the *General Procedure H*, compound **11b** (185 mg, 0.86 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) starting from **10b** (205 mg, 0.95 mmol) and Pb(OAc)$_4$ (420 mg, 0.95 mmol). Yield: 90%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.36 (td, *J* = 7.2, 2.0 Hz, 1H, C**H**$_{arom}$), 7.28-7.15 (m, 3H, 3 x C**H**$_{arom}$), 6.38 (dt, *J* = 12.1, 1.0 Hz, 1H, **H**-6), 6.23 (dt, *J* = 12.1, 8.6 Hz, 1H, **H**-7), 3.06-2.95 (m, 2H, **H**-12), 2.71-2.55 (m, 2H, **H**-11), 2.46-2.33 (m, 2H, **H**-9), 2.20-2.10 (m, 2H, **H**-8). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 210.6 (**C**-10), 199.0 (**C**-5), 142.9 (**C**-7), 141.6 (**C**$_{arom}$), 138.6 (**C**$_{arom}$), 133.6 (**C**H$_{arom}$), 130.6 (**C**H$_{arom}$), 130.5 (**C**H$_{arom}$), 126.8 (**C**H$_{arom}$), 126.6 (**C**-6), 44.0 (**C**-



11), 43.4 (**C**-9), 29.1 (**C**-12), 22.1 (**C**-8). IR (ATR) cm^{-1}: 1699 (C=O st), 1645 (C=O st). MS (EI, 70 eV) *m/z* (%): 214 (M^{+}, 7), 196 (45), 180 (39), 167 (45), 157 (10), 144 (28), 128 (51), 115 (48), 103 (31), 89 (31), 77 (45), 63 (21), 51 (22). HRMS (UPLC MS ESI^{+}): Calculated for $[C_{14}H_{14}NaO_2]^+$: 239.1048 [(M+Na)$^{+}$]; found 239.1049. M.p.: 58-60 °C (hexanes/EtOAc).

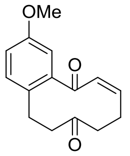


(*Z*)-1,3-dimethyl-8,9,11,12-tetrahydrobenzo[10]annulene-5,10-dione (11c). Following the *General Procedure H*, compound **11c** (235 mg, 0.97 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **10c** (300 mg, 1.23 mmol) and Pb(OAc)$_4$ (545 mg, 1.23 mmol). Yield: 79%. Yellow solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.07 (s, 1H, C**H**$_{\text{arom}}$), 6.83 (s, 1H, C**H**$_{\text{arom}}$), 6.40 (d, *J* = 12.2 Hz, 1H, **H**-6), 6.25 (dt, *J* = 12.2, 8.5 Hz, 1H, **H**-7), 3.05-2.96 (m, 2H, **H**-12), 2.62-2.52 (m, 2H, **H**-11), 2.45-2.37 (m, 2H, **H**-9), 2.31 (s, 3H, C**H$_3$**), 2.28 (s, 3H, C**H$_3$**), 2.25-2.14 (m, 2H, **H**-8). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 210.9 (**C**-10), 199.7 (**C**-5), 142.9 (**C**-7), 142.4 (**C**$_{\text{arom}}$), 136.9 (**C**$_{\text{arom}}$), 136.0 (**C**$_{\text{arom}}$), 134.0 (**C**H$_{\text{arom}}$), 133.10 (**C**$_{\text{arom}}$), 133.09 (**C**H$_{\text{arom}}$), 124.0 (**C**-6), 43.6 (**C**-11), 42.3 (**C**-9), 25.0 (**C**-12), 21.7 (**C**-8), 20.7 (**C**H$_3$), 19.6 (**C**H$_3$). IR (ATR) cm^{-1}: 1701 (C=O st), 1645 (C=O st). MS (EI, 70 eV) *m/z* (%): 242 (M^{+}, 4), 223 (51), 185 (100), 140 (7), 115 (43), 79 (5), 53 (13). HRMS (UPLC MS ESI^{+}): Calculated for $[C_{16}H_{18}NaO_2]^+$: 265.1205 [(M+Na)$^{+}$]; found 265.1215. M.p.: 119-122 °C (hexanes/EtOAc).

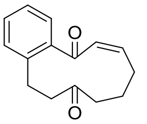


(*Z*)-1-methoxy-8,9,11,12-tetrahydrobenzo[10]annulene-5,10-dione (11d). Following the *General Procedure H*, compound **11d** (90 mg, 0.37 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) starting from **10d** (196 mg, 0.80 mmol) and Pb(OAc)$_4$ (355 mg, 0.80 mmol). Yield: 46%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.31-7.22 (m, 1H, C**H**$_{\text{arom}}$), 6.96 (d, *J* = 8.2 Hz, 1H, C**H**$_{\text{arom}}$), 6.79 (d, *J* = 7.6 Hz, 1H, C**H**$_{\text{arom}}$), 6.38 (d, *J* = 12.3 Hz, 1H, **H**-6), 6.28 (dt, *J* = 12.3, 8.3 Hz, 1H, **H**-7), 3.88 (s, 3H, OC**H$_3$**), 3.02-2.93 (m, 2H, **H**-12), 2.68-2.58 (m, 2H, **H**-11), 2.49-2.38 (m, 2H, **H**-9), 2.26-2.11 (m, 2H, **H**-8). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 211.6 (**C**-10), 198.7 (**C**-5), 157.5 (**C**-1), 144.0 (**C**-7), 143.6 (**C**$_{\text{arom}}$), 133.8 (**C**H$_{\text{arom}}$), 128.1 (**C**-6), 126.8 (**C**$_{\text{arom}}$), 118.2 (**C**H$_{\text{arom}}$), 112.0 (**C**H$_{\text{arom}}$), 55.8 (O**C**H$_3$), 44.0 (**C**-11), 42.8 (**C**-9), 23.0 (**C**-8), 21.8 (**C**-12). IR (ATR) cm^{-1}: 1702 (C=O st), 1645 (C=O st). MS (EI, 70 eV) *m/z* (%): 244 (M^{+}, 46), 243 (100), 227 (27), 209 (42), 186 (42), 171 (65), 145 (42), 142 (38), 128 (35), 120 (42), 89 (58), 51 (23). HRMS (UPLC MS ESI^{+}): Calculated for $[C_{18}H_{17}O_3]^+$: 245.1178 [(M+H)$^{+}$]; found 245.1187. M.p.: 138-140 °C (hexanes/EtOAc).

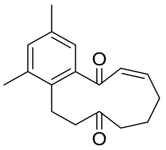
(*Z*)-3-methoxy-8,9,11,12-tetrahydrobenzo[10]annulene-5,10-dione (11e). Following the *General Procedure H*, compound **11e** (170 mg, 0.70 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) starting from **10e** (270 mg, 1.10 mmol) and Pb(OAc)$_4$ (488 mg, 1.10 mmol). Yield: 64%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.16 (d, *J* = 8.5 Hz, 1H, **H**-1), 6.94 (dd, *J* = 8.5, 2.8 Hz, 1H, **H**-2), 6.76 (d, *J* = 2.8 Hz, 1H, **H**-4), 6.41 (d, *J* = 12.0 Hz, 1H, **H**-6), 6.28 (dt, *J* = 12.0, 8.4 Hz, 1H, **H**-7), 3.80 (s, 3H, OC**H**$_3$), 3.04-2.95 (m, 2H, **H**-12), 2.71-2.61 (m, 2H, **H**-11), 2.50-2.39 (m, 2H, **H**-9), 2.28-2.15 (m, 2H, **H**-8). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 210.9 (**C**-10), 198.7 (**C**-5), 158.4 (**C**-3), 143.4 (**C**-7), 142.6 (**C**$_{\text{arom}}$), 133.5 (**C**H$_{\text{arom}}$), 132.0 (**C**-6), 130.7 (**C**$_{\text{arom}}$), 116.9 (**C**H$_{\text{arom}}$), 111.5 (**C**H$_{\text{arom}}$), 55.6 (O**C**H$_3$), 44.3 (**C**-11), 43.7 (**C**-9), 28.4 (**C**-12), 22.4 (**C**-8). IR (ATR) cm^{-1}: 1688 (C=O st), 1641 (C=O st). MS (EI, 70 eV) *m/z* (%): 244 (25, M$^+$), 226 (33), 187 (100), 173 (22), 159 (14), 144 (34), 128 (40), 115 (70), 91 (74), 77 (65), 63 (53), 51 (53). HRMS (UPLC MS ESI+): Calculated for [C$_{15}$H$_{17}$O$_3$]$^+$: 245.1178 [(M+H)$^+$]; found 245.1177. M.p.: 94-96 °C (hexanes/EtOAc).



(*Z*)-9,10,12,13-tetrahydro-5*H*-benzo[11]annulene-5,11(8*H*)-dione (11f). Following the *General Procedure H*, compound **11f** (245 mg, 1.07 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) starting from **10f** (260 mg, 1.13 mmol) and Pb(OAc)$_4$ (500 mg, 1.13 mmol). Yield: 95%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.41-7.28 (m, 2H, 2 x C**H**$_{\text{arom}}$), 7.28-7.14 (m, 2H, 2 x C**H**$_{\text{arom}}$), 6.37 (dt, *J* = 12.1, 1.3 Hz, 1H, **H**-6), 6.14 (dt, *J* = 12.1, 8.8 Hz, 1H, **H**-7), 3.14 (t, *J* = 6.9 Hz, 2H, **H**-13), 2.70 (dd, *J* = 7.5, 6.3 Hz, 2H, **H**-12), 2.33-2.18 (m, 2H, **H**-10), 1.94-1.80 (m, 2H, **H**-8), 1.65 (m, 2H, **H**-9). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 211.3 (**C**-11), 199.2 (**C**-5), 146.3 (**C**-7), 141.5 (**C**$_{\text{arom}}$), 137.0 (**C**$_{\text{arom}}$), 132.2 (**C**H$_{\text{arom}}$), 130.7 (**C**H$_{\text{arom}}$), 130.4 (**C**H$_{\text{arom}}$), 127.2 (**C**H$_{\text{arom}}$), 126.7 (**C**-6), 44.8 (**C**-12), 38.2 (**C**-10), 27.8 (**C**-8), 27.6 (**C**-13), 22.3 (**C**-9). IR (ATR) cm^{-1}: 1705 (C=O st), 1639 (C=O st). MS (EI, 70 eV) *m/z* (%): 228 (M$^+$, 6), 210 (51), 192 (44), 178 (69), 165 (52), 152 (39), 132 (49), 115 (44), 93 (100), 77 (62), 63 (22), 51 (22). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{15}$H$_{16}$NaO$_2$]$^+$: 251.1048 [(M+Na)$^+$]; found 251.1051. M.p.: 66-68 °C (hexanes/EtOAc).

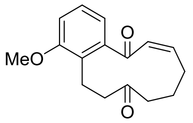


(*Z*)-1,3-dimethyl-9,10,12,13-tetrahydro-5*H*-benzo[11]annulene-5,11(8*H*)-dione (11g). Following the *General Procedure H*, compound **11g** (445 mg, 1.74 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) starting from **10g** (500 mg, 1.93 mmol) and Pb(OAc)$_4$ (858 mg, 1.93 mmol). Yield: 90%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.03-6.98 (s, 1H, C**H**$_{\text{arom}}$), 6.87 (s, 1H, C**H**$_{\text{arom}}$), 6.34 (dt, *J* = 12.0, 1.2 Hz, 1H, **H**-6), 6.14 (dt, *J* = 12.0, 9.0 Hz, 1H, **H**-7), 3.18 (t, *J* = 7.1 Hz, 2H, **H**-13), 2.61 (t, *J* = 7.1 Hz, 2H, **H**-12), 2.33 (s, 3H, C**H**$_3$), 2.30-2.22 (m, 2H, **H**-10), 2.20 (s, 3H, C**H**$_3$), 1.95-1.84 (m, 2H, **H**-8), 1.66-1.53 (m, 2H, **H**-9). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 210.9 (**C**-11), 199.7 (**C**-5), 145.4 (**C**-7), 141.9 (**C**$_{\text{arom}}$), 138.3 (**C**$_{\text{arom}}$), 135.8, (**C**$_{\text{arom}}$) 133.6 (**C**H$_{\text{arom}}$), 132.6 (**C**H$_{\text{arom}}$), 132.2 (**C**$_{\text{arom}}$), 125.4 (**C**-6),

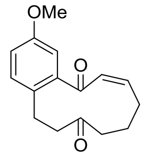


42.0 (**C**-12), 38.1 (**C**-10), 27.1 (**C**-8), 24.1 (**C**-13), 21.6 (**C**-9), 20.7 (**C**H$_3$), 20.0 (**C**H$_3$). IR (ATR) cm^{-1}: 1707 (C=O st), 1632 (C=O st). MS (EI, 70 eV) *m/z* (%): 256 (M$^+$, 3), 238 (24), 220 (13), 207 (14), 193 (10), 178 (13), 163 (100), 147 (12), 128 (10), 115 (17), 105 (7), 93 (43), 77 (18), 65 (6), 51 (5). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{17}H_{20}NaO_2]^+$: 279.1361 [(M+Na)$^+$]; found 279.1365. M.p.: 97-99 °C (hexanes/EtOAc).

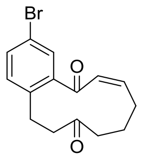
(*Z*)-1-methoxy-9,10,12,13-tetrahydro-5*H*-benzo[11]annulene-5,11(8*H*)-dione (11h). Following the *General Procedure H*, compound **11h** (205 mg, 0.79 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) starting from **10h** (235 mg, 0.90 mmol) and Pb(OAc)$_4$ (400 mg, 0.90 mmol). Yield: 88%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.19 (dd, *J* = 8.2, 7.7 Hz, 1H, **H**-3), 6.92 (d, *J* = 8.2 Hz, 1H, **H**-4), 6.83 (d, *J* = 7.7 Hz, 1H, **H**-2), 6.35 (d, *J* = 12.2 Hz, 1H, **H**-6), 6.21 (dt, *J* = 12.2, 9.0 Hz, 1H, **H**-7), 3.88 (s, 3H, OC**H$_3$**), 3.16 (t, *J* = 6.9 Hz, 2H, **H**-13), 2.74 (t, *J* = 6.9 Hz, 2H, **H**-12), 2.33-2.19 (m, 2H, **H**-10), 1.82 (m, 2H, **H**-8), 1.69-1.53 (m, 2H, **H**-9). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 211.4 (**C**-11), 199.2 (**C**-5), 158.8 (**C**-1), 146.3 (**C**-7), 143.1 (**C**$_{\text{arom}}$), 132.6 (**C**H$_{\text{arom}}$), 127.8 (**C**-6), 125.2 (**C**$_{\text{arom}}$), 119.0 (**C**H$_{\text{arom}}$), 112.5 (**C**H$_{\text{arom}}$), 55.8 (O**C**H$_3$), 41.4 (**C**-12), 37.6 (**C**-10), 27.6 (**C**-8), 23.3 (**C**-9), 21.0 (**C**-13). IR (ATR) cm^{-1}: 1699 (C=O st), 1633 (C=O st). MS (EI, 70 eV) *m/z* (%): 258 (M$^+$, 6), 240 (16), 222 (8), 207 (9), 197 (4), 178 (10), 165 (100), 153 (30), 128 (8), 115 (12), 105 (2), 91 (33), 77 (23), 65 (8), 51 (8). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{16}H_{18}NaO_3]^+$: 281.1154 [(M+Na)$^+$]; found 281.1152. M.p.: 145-147 °C (hexanes/EtOAc).



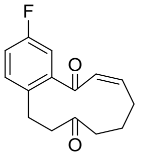
(*Z*)-3-methoxy-9,10,12,13-tetrahydro-5*H*-benzo[11]annulene-5,11(8*H*)-dione (11i). Following the *General Procedure H*, compound **11i** (410 mg, 1.59 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) starting from **10i** (500 mg, 1.92 mmol) and Pb(OAc)$_4$ (850 mg, 1.92 mmol). Yield: 83%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.18 (d, *J* = 8.6 Hz, 1H, **H**-1), 6.87 (dd, *J* = 8.6, 2.8 Hz, 1H, **H**-2), 6.69 (d, *J* = 2.8 Hz, 1H, **H**-4), 6.30 (dt, *J* = 12.1, 1.2 Hz, 1H, **H**-6), 6.10 (dt, *J* = 12.1, 8.8 Hz, 1H, **H**-7), 3.69 (s, 3H, OC**H$_3$**), 3.02 (t, *J* = 6.8 Hz, 2H, **H**-13), 2.72-2.58 (m, 2H, **H**-12), 2.25-2.14 (m, 2H, **H**-10), 1.90-1.75 (m, 2H, **H**-8), 1.68-1.53 (m, 2H, **H**-9). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 211.3 (**C**-11), 198.6 (**C**-5), 157.9 (**C**-3), 146.5 (**C**-7), 142.3 (**C**$_{\text{arom}}$), 131.9 (**C**H$_{\text{arom}}$), 131.4 (**C**-6), 128.6 (**C**$_{\text{arom}}$), 116.6 (**C**H$_{\text{arom}}$), 111.7 (**C**H$_{\text{arom}}$), 55.3 (O**C**H$_3$), 44.7 (**C**-12), 38.0 (**C**-10), 27.6 (**C**-8), 26.9 (**C**-13), 22.0 (**C**-9). IR (ATR) cm^{-1}: 1698 (C=O st), 1637 (C=O st). MS (EI, 70 eV) *m/z* (%): 158 (M$^+$, 4), 240 (8), 222 (4), 207 (4), 194 (2), 178 (6), 165 (100), 153 (3), 139 (3), 121 (6), 109 (3), 91 (8), 77 (9), 65 (3), 51 (3). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{16}H_{18}NaO_3]^+$: 281.1154 [(M+Na)$^+$]; found 281.1150. M.p.: 104-106 °C (hexanes/EtOAc).



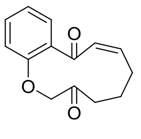
(*Z*)-3-bromo-9,10,12,13-tetrahydro-5*H*-benzo[11]annulene-5,11(8*H*)-dione (11j). Following the *General Procedure H*, compound **11j** (245 mg, 0.80 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) starting from **10j** (329 mg, 1.03 mmol) and Pb(OAc)$_4$ (458 mg, 1.03 mmol). Yield: 78%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.51 (dd, J = 8.3, 2.2 Hz, 1H, **H**-2), 7.39 (d, J = 2.2 Hz, 1H, **H**-4), 7.22 (d, J = 8.3 Hz, 1H, **H**-1), 6.39 (d, J = 12.2 Hz, 1H, **H**-6), 6.22 (dt, J = 12.2, 8.7 Hz, 1H, **H**-7), 3.12 (t, J = 6.9 Hz, 2H, **H**-13), 2.72 (t, J = 6.9 Hz, 2H, **H**-12), 2.35-2.24 (m, 2H, **H**-10), 2.03-1.87 (m, 2H, **H**-8), 1.81-1.06 (m, 2H, **H**-9). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 211.2 (**C**-11), 197.4 (**C**-5), 147.4 (**C**-7), 143.2 (**C**$_{\text{arom}}$), 136.1 (**C**$_{\text{arom}}$), 133.7 (**C**H$_{\text{arom}}$), 132.3 (**C**H$_{\text{arom}}$), 131.8 (**C**H$_{\text{arom}}$), 130.0 (**C**-6), 120.6 (**C**-3), 44.6 (**C**-12), 38.4 (**C**-10), 28.0 (**C**-8), 27.5 (**C**-13), 22.5 (**C**-9). IR (ATR) cm^{-1}: 1702 (C=O st), 1649 (C=O st) cm^{-1}. MS (EI, 70 eV) *m/z* (%): 306 (M$^+$, 4), 288 (62), 258 (20), 207 (58), 178 (63), 152 (48), 131 (9), 115 (14), 93 (100), 77 (32), 51 (10). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{15}$H$_{15}$BrNaO$_2$]$^+$: 329.0153 [(M+Na)$^+$]; found 329.0148. M.p.: 85-88 °C (hexanes/EtOAc).



(*Z*)-3-fluoro-9,10,12,13-tetrahydro-5*H*-benzo[11]annulene-5,11(8*H*)-dione (11k). Following the *General Procedure H*, compound **11k** (305 mg, 1.24 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) starting from **10k** (500 mg, 2.01 mmol) and Pb(OAc)$_4$ (893 mg, 2.01 mmol). Yield: 62%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.25 (dd, J = 8.6, 5.2 Hz, 1H, **H**-2), 7.03 (m, 1H, **H**-4), 6.89 (dd, J = 8.6, 2.8 Hz, 1H, **H**-1), 6.31 (dt, J = 12.1, 1.2 Hz, 1H, **H**-6), 6.15 (dt, J = 12.1, 8.8 Hz, 1H, **H**-7), 3.06 (t, J = 6.9 Hz, 2H, **H**-13), 2.64 (t, J = 6.9 Hz, 2H, **H**-12), 2.29-2.14 (m, 2H, **H**-10), 1.91-1.76 (m, 2H, **H**-8), 1.71-1.57 (m, 2H, **H**-9). ^{13}C NMR (δ, ppm) (75 MHz, CDCl$_3$): 211.0 (**C**-11), 197.4 (d, $^4J_{CF}$ = 1.9 Hz, **C**-5), 161.0 (d, $^1J_{CF}$ = 247.9 Hz, **C**-3), 147.1 (**C**-7), 142.9 (d, $^3J_{CF}$ = 6.0 Hz, **C**-4a), 132.6 (d, $^4J_{CF}$ = 3.5 Hz, **C**-13a), 132.3 (d, $^3J_{CF}$ = 7.7 Hz, **C**-1), 131.6 (**C**-6), 117.6 (d, $^2J_{CF}$ = 21.3 Hz, **C**H$_{\text{arom}}$), 113.7 (d, $^2J_{CF}$ = 22.5 Hz, **C**H$_{\text{arom}}$), 44.6 (**C**-12), 38.0 (**C**-10), 27.6 (**C**-8), 27.0 (**C**-13), 22.2 (**C**-9). ^{19}F NMR (δ, ppm) (282 MHz, CDCl$_3$): -115.1. IR (ATR) cm^{-1}: 1706 (C=O st), 1636 (C=O st). MS (EI, 70 eV) *m/z* (%): 246 (M$^+$, 7), 228 (26), 196 (32), 171 (15), 146 (33), 121 (13), 93 (100), 55 (9). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{15}$H$_{15}$FNaO$_2$]$^+$: 269.0954 [(M+Na)$^+$]; found 269.0948. M.p.: 102-104 °C (hexanes/EtOAc).

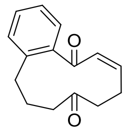


(*Z*)-5,6-dihydrobenzo[*b*][1]oxacycloundecine-3,9(2*H*,4*H*)-dione (11l). Following the G*eneral Procedure H*, compound **1l** (150 mg, 0.65 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **10l** (188 mg, 0.81 mmol) and Pb(OAc)$_4$ (359 mg, 0.81 mmol). Yield: 80%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.53-7.32 (m, 2H, 2 x C**H**$_{\text{arom}}$), 7.17-6.93 (m, 2H, 2 x C**H**$_{\text{arom}}$), 6.35 (dt, J = 12.1, 1.5 Hz, 1H, **H**-8), 5.90 (dt, J = 12.1, 8.1 Hz, 1H, **H**-7), 4.47 (s, 2H, **H**-2), 2.72-2.44 (m, 2H, **H**-4), 2.25-2.05 (m, 2H, **H**-6), 1.97-1.79 (m, 2H, **H**-5). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 208.4 (**C**-3), 197.1 (**C**-9), 155.7 (**C**$_{\text{arom}}$), 142.2 (**C**-7), 133.0 (**C**H$_{\text{arom}}$),

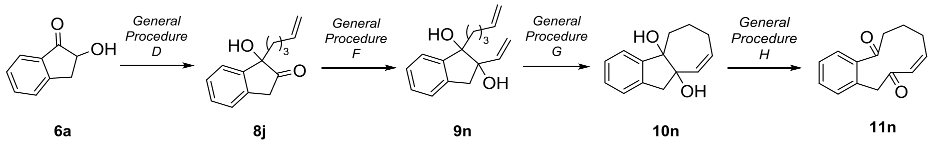


132.6 (**C**$_{arom}$), 132.4 (**C**H$_{arom}$), 128.8 (**C**-8), 123.2 (**C**H$_{arom}$), 115.6 (**C**H$_{arom}$), 75.6 (**C**-2), 37.2 (**C**-4), 28.2 (**C**-6), 24.9 (**C**-5). IR (ATR) cm^{-1}: 1720 (C=O st), 1635 (C=O st), 1628 (C=O st). MS (EI, 70 eV) *m/z* (%): 230 (M$^+$, 9), 212 (13), 174 (86), 157 (34), 144 (100), 131 (32), 121 (86), 105 (36), 93 (94), 77 (71), 63 (40), 51 (26). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{14}H_{15}O_3]^+$: 231.1021 [(M+H)$^+$]; found 231.1023. M.p.: 83-85 °C (hexanes/EtOAc).

(*Z*)-8,9,12,13-tetrahydro-5*H*-benzo[11]annulene-5,10(11*H*)-dione (11m). Following the *General Procedure H*, compound **11m** (125 mg, 0.55 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **10m** (230 mg, 1.01 mmol) and Pb(OAc)$_4$ (447 mg, 1.01 mmol). Yield: 54%. Yellow solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.37 (ddd, *J* = 8.3, 6.3, 2.4 Hz, 1H, CH$_{arom}$), 7.28 – 7.17 (m, 3H, 3 x C**H**$_{arom}$), 6.33 (d, *J* = 12.0 Hz, 1H, **H**-6), 6.18 (dt, *J* = 12.0, 8.2 Hz, 1H, **H**-7), 2.72 (t, *J* = 6.4 Hz, 2H, **H**-13), 2.42 – 2.17 (m, 6H, **H**-8, **H**-9 and **H**-11), 2.04 – 1.91 (m, 2H, **H**-12). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 210.2 (**C**-10), 198.4 (**C**-5), 143.5 (**C**-7), 142.4 (**C**$_{arom}$), 138.3 (**C**$_{arom}$), 132.6 (**C**H$_{arom}$), 130.6 (**C**H$_{arom}$), 129.6 (**C**H$_{arom}$), 127.0 (**C**H$_{arom}$), 126.3 (**C**-6), 42.2 (**C**-11), 37.8 (**C**-9), 28.6 (**C**-13), 24.8 (**C**-12), 23.1 (**C**-8). IR (ATR) cm^{-1}: 1703 (C=O st), 1635 (C=O st). MS (EI, 70 eV) *m/z* (%): 228 (M$^+$, 17), 210 (36), 195 (15), 170 (88), 157 (100), 144 (44), 128 (72), 115 (81), 91 (62), 77 (41), 63 (27). HRMS (UPLC MS ESI+): Calculated for $[C_{15}H_{17}O_2]^+$: 229.1229 [(M+H)$^+$]; found 229.1227. M.p.: 115-117 °C (hexanes/EtOAc).

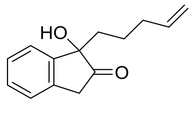


2.6. Synthesis of substrate 11n



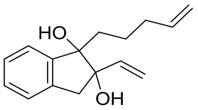
For the preparation of substrate **11n**, the same methodology previously described for aromatic substrates was followed except for the order of addition of the Grignard reagents.

1-hydroxy-1-(pent-4-en-1-yl)-1,3-dihydro-2*H*-inden-2-one (8j). Following *General Procedure D* (see Section 2.1) *c*ompound **8j** (555 mg, 2.56 mmol) was isolated by FC (hexanes/EtOAc 8:2) starting from **6a** (680 mg, 4.60 mmol), 5-bromo-1-pentene (2.07 mL, 17.5 mmol) and magnesium turnings (630 mg, 26.2 mmol). Yield: 56%. Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.53 – 7.41 (m, 1H, C**H**$_{arom}$), 7.41 – 7.29 (m, 3H, 3 x

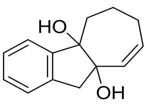


C**H**$_{\text{arom}}$), 5.69 (ddt, J = 17.0, 10.3, 6.7 Hz, 1H, C**H**=CH$_2$), 5.06 – 4.86 (m, 2H, CH=C**H$_2$**), 3.70 – 3.42 (m, 2H, **H**-3), 2.74 (s, 1H, O**H**), 2.08 – 1.94 (m, 2H, C**H$_2$**COH), 1.88 – 1.74 (m, 2H, C**H$_2$**CH=CH$_2$), 1.47 – 1.20 (m, 2H, C**H$_2$**CH$_2$CH=CH$_2$). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 217.3 (**C**-2), 142.8 (**C**$_{\text{arom}}$), 138.0 (**C**H=CH$_2$), 135.4 (**C**$_{\text{arom}}$), 129.1 (**C**H$_{\text{arom}}$), 128.2 (**C**H$_{\text{arom}}$), 125.1 (**C**H$_{\text{arom}}$), 124.6 (**C**H$_{\text{arom}}$), 115.2 (CH=**C**H$_2$), 80.6 (**C**-1), 40.9 (**C**H$_2$COH), 39.2 (**C**-3), 33.8 (**C**H$_2$CH=CH$_2$), 22.6 (**C**H$_2$CH$_2$CH=CH$_2$). IR (ATR) cm^{-1}: 3436 (O–H st), 1752 (C=O st). MS (EI, 70 eV) *m/z* (%): 198 (M$^+$ - H$_2$O, 25), 188 (22), 169 (10), 147 (21), 134 (23), 119 (100), 103 (6), 91 (32), 77 (9), 65 (9), 55 (11). HRMS (UPLC MS ESI$^+$): Calculated for [NaC$_{14}$H$_{16}$O$_2$]$^+$: 239.1048 [(M+Na)$^+$]; found 239.1048.

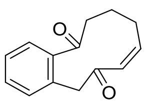
1-(pent-4-en-1-yl)-2-vinyl-2,3-dihydro-1*H*-indene-1,2-diol (9n). Following *General Procedure F* (see Section 2.3) compound **9n** (135 mg, 0.55 mmol) was isolated by FC (hexanes/EtOAc 8:2) starting from **8j** (245 mg, 1.13 mmol) and vinylmagnesium bromide (4.30 mL, 4.30 mmol). Yield: 49%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 7.45 – 7.12 (m, 4H, 4 x C**H**$_{\text{arom}}$), 6.07 (dd, *J* = 17.5, 10.9 Hz, 1H, C-2-C**H**=CH$_2$), 5.80 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, CH$_2$C**H**=CH$_2$), 5.45 (dd, *J* = 17.5, 1.2 Hz, 1H, C-2-CH=CH$_{\text{cis}}$**H$_{\text{trans}}$**), 5.26 (dd, *J* = 10.9, 1.2 Hz, 1H, CH$_2$CH=C**H$_{\text{cis}}$**H$_{\text{trans}}$), 5.05 – 4.87 (m, 2H, CH$_2$CH=CH$_{\text{cis}}$**H$_{\text{trans}}$** and C-2-CH=C**H$_{\text{cis}}$**H$_{\text{trans}}$), 3.14 (d, *J* = 15.6 Hz, 1H, **H$_a$**-3), 3.01 (d, *J* = 15.5 Hz, 1H, **H$_b$**-3), 2.12 – 2.01 (m, 2H, C**H$_2$**CH=CH$_2$), 2.01 – 1.74 (m, 2H, C-1-C**H$_2$**), 1.97* (s, 1H, O**H**), 1.79* (s, 1H, O**H**), 1.74 – 1.62 (m, 1H, C-1-CH$_2$C**H$_a$**H$_b$), 1.55 – 1.41 (m, 1H, C-1-CH$_2$CH$_a$**H$_b$**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 145.8 (**C**$_{\text{arom}}$), 140.3 (C-2-**C**H=CH$_2$), 138.9 (CH$_2$**C**H=CH$_2$), 138.6 (**C**$_{\text{arom}}$), 128.5 (**C**H$_{\text{arom}}$), 127.1 (**C**H$_{\text{arom}}$), 125.2 (**C**H$_{\text{arom}}$), 124.3 (**C**H$_{\text{arom}}$), 115.1 (CH$_2$CH=**C**H$_2$), 114.7 (C-2-CH=**C**H$_2$), 86.7 (**C**-OH), 85.1 (**C**-OH), 43.7 (**C**-3), 34.4 (**C**H$_2$CH=CH$_2$), 34.4 (C-1-**C**H$_2$), 22.9 (C-1-CH$_2$**C**H$_2$). IR (ATR) cm^{-1}: 3360 (O-H st), 3306 (O-H st), 2946 (=C-H st). MS (EI, 70 eV) *m/z* (%): 226 (M$^+$ - H$_2$O, 5), 208 (14), 175 (100), 157 (43), 144 (39), 129 (91), 115 (43), 105 (24), 91 (24), 77 (16), 65 (7), 55 (29). HRMS (UPLC MS ESI$^+$): Calculated for [NaC$_{16}$H$_{20}$O$_2$]$^+$: 263.1361 [(M+Na)$^+$]; found 263.1357. M.p.: 101-103 °C (hexanes/EtOAc).



6,7-dihydrobenzo[a]azulene-4b,9a(5*H*,10*H*)-diol (10n). Following *General Procedure G* (see Section 2.4) compound **10n** (200 mg, 0.92 mmol) was isolated by FC (hexanes/EtOAc 7:3) starting from **9n** (318 mg, 1.30 mmol) and 2$^{\text{nd}}$ generation Grubbs catalyst (28 mg, 0.03 mmol). Yield: 71%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 7.41 – 7.17 (m, 4H, 4 x C**H**$_{\text{arom}}$), 6.25 (ddd, *J* = 11.0, 8.5, 4.3 Hz, 1H, **H**-8), 5.98 (dd, *J* = 10.9, 2.6 Hz, 1H, **H**-9), 3.45 (d, *J* = 15.8 Hz, 1H, **H$_a$**-10), 2.90 (d, *J* = 15.8 Hz, 1H, **H$_b$**-10), 2.72 – 2.53 (m, 1H, **H$_a$**-5), 2.45 – 2.36 (m, 2H, **H**-7), 2.30 – 2.17 (m, 1H, **H$_b$**-5), 2.03 (s, 1H, O**H**), 1.94 – 1.77 (m, 2H, **H**-6), 1.85* (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 145.6 (**C**$_{\text{arom}}$), 141.8 (**C**$_{\text{arom}}$), 138.3 (**C**-9), 132.1 (**C**-8), 128.9 (**C**H$_{\text{arom}}$), 127.1 (**C**H$_{\text{arom}}$), 126.0 (**C**H$_{\text{arom}}$), 123.2 (**C**H$_{\text{arom}}$), 84.8 (**C**-OH), 81.9 (**C**-OH), 45.5 (**C**-10), 32.1 (**C**-5), 27.4 (**C**-7), 22.3 (**C**-6). IR (ATR) cm^{-1}: 3508 (O-H st), 3393 (O-H st). MS

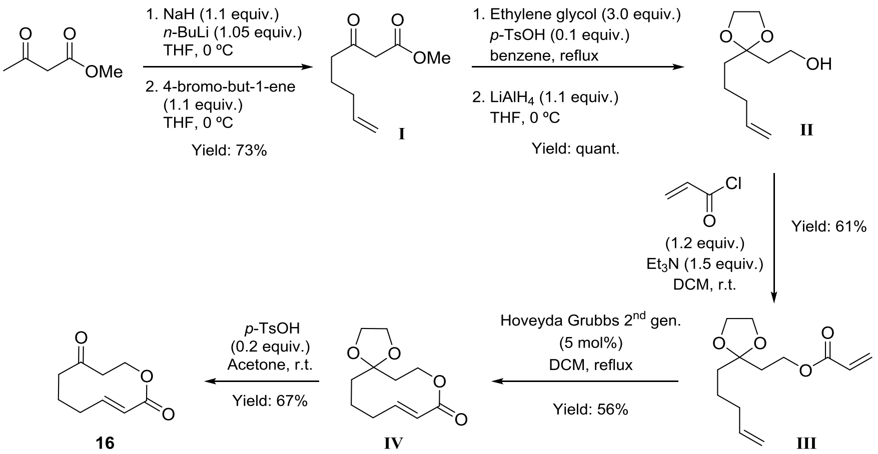


(EI, 70 eV) *m/z* (%): 198 (M^+ - H_2O, 100), 180 (28), 170 (41), 155 (31), 141 (72), 128 (36), 115 (37), 91 (14), 77 (12), 63 (9). M.p.: 113-115 °C (hexanes/EtOAc).



(Z)-7,8-dihydrobenzo[10]annulene-5,11(6*H*,12*H*)-dione (11n). Followin *General Procedure H* (see Section 2.5) compound **11n** (105 mg, 0.50 mmol) was isolated by FC (CH_2Cl_2/CH_3OH 1%) starting from **10n** (200 mg, 0.92 mmol) and $Pb(OAc)_4$ (410 mg, 0.92 mmol). Yield: 54%. White solid. ^1H NMR (δ, ppm) (300 MHz, $CDCl_3$): 7.46 – 7.16 (m, 4H, 4 x C**H**$_{arom}$), 5.91 – 5.70 (m, 2H, **H**-9 and **H**-10), 3.94 (s, 2H, **H**-12), 2.84 (t, *J* = 6.5 Hz, 2H, **H**-6), 2.59 – 2.36 (m, 2H, **H**-8), 2.11 – 1,94 (m, 2H, **H**-7). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 207.1 (**C**-5), 202.5 (**C**-11), 142.7 (**C**$_{arom}$), 139.8 (**C**-9), 133.0 (**C**-10), 132.3 (**C**$_{arom}$), 131.8 (**C**H$_{arom}$), 130.7 (**C**H$_{arom}$), 127.2 (**C**H$_{arom}$), 126.3 (**C**H$_{arom}$), 48.4 (**C**-12), 38.9 (**C**-6), 24.5 (**C**-8), 23.5 (**C**-7). IR (ATR) cm^{-1}: 1682 (C=O st). MS (EI, 70 eV) *m/z* (%): 214 (M^+, 6), 207 (15), 185 (20), 160 (38), 119 (100), 90 (43), 67 (16), 50 (9). HRMS (UPLC MS ESI^+): Calculated for $[NaC_{14}H_{14}O_2]^+$: 237.0892 [$(M+Na)^+$]; found 237.0896. M.p.: 93-95 °C (hexanes/EtOAc).

2.7. Synthesis of substrate 16



To an ice-cold suspension of NaH (816 mg, 60% dispersion in mineral oil, 20.4 mmol) in THF (50 mL) was added dropwise methylacetoacetate (2.0 mL, 18.5 mmol). Reaction mixture was stirred at 0 °C for 10 minutes and then *n*-buthyllithium (7.8 mL, 2.5 M in hexanes, 19.4 mmol) was added at that temperature, followed by 4-bromo-but-1-ene (2.1 mL, 20.4 mmol). It was allowed to reach room temperature and stirred for further 15 minutes. Reaction was quenched by the addition of 4 mL of

$HCl_{conc.}$ and subsequently diluted with water (10 mL) and Et_2O (30 mL). Phases were separated and aqueous phase was extracted with Et_2O (3x15 mL). Combined organic layers were dried over anhydrous Na_2SO_4, filetered and evaporated. The residue was purified by FC (petroleum ether/EtOAc 8:2) to afford pure product **I** (2.29 g, 13.5 mmol) in 73% yield as an orange oil.

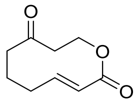
To a solution of **I** (715 mg, 4.2 mmol) in benzene (10 mL) was added ethylene glycol (0.70 mL, 12.6 mmol) followed by *p*-toluenesulfonic acid (80.0 mg, 0.42 mmol) and it was heated at reflux temperature in a Dean-Stark apparatus overnight. Reaction mixture was washed with $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The resulting colorless oil was dissolved in anhydrous THF (20 mL) and added dropwise to a THF solution (20 mL) of $LiAlH_4$ (1.75 g, 4.6 mmol) at 0 °C. After 20 minutes, the reaction was quenched by the addition of a saturated aqueous solution of Rochelle salt, filtered through Celite to remove solids and extracted with EtOAc (3x15 mL). Combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The resulting residue was filtered through a plug of silica rendering product **II** (780 mg, 4.19 mmol) in quantitative yield.

To a solution of compound **II** (760 mg, 4.10 mmol) in anhydrous DCM (20 mL) was added acryloyl chloride (0.4 mL, 4.92 mmol) followed by Et_3N (0.86 mL, 6.15 mmol). After stirring at room temperature for 10 minutes, reaction mixture was washed with water, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by FC (petroleum ether/EtOAc 8:2) to afford product **III** (600 mg, 2.49 mmol) in 61% yield as a yellow oil.

Compound **III** (350 mg, 1.46 mmol) was dissolved in anhydrous DCM (150 mL, 0.01 M). A solution of 2nd generation Hoveyda-Grubbs catalyst (45.7 mg, 0.073 mmol) in anhydrous DCM (5 mL) was added and it was heated at reflux temperature for 3 hours. After that time, solvent was removed under vacuum and resulting residue was purified by FC (petroleum ether/EtOAc 7:3) to afford compound **IV** (174 mg, 0.82 mmol) in 56% yield.

Finally, product **IV** (170 mg, 0.80 mmol) was dissolved in anhydrous acetone (4.0 mL) and *p*-TsOH (28.0 mg, 0.16 mmol) was added. After 2 hours, reaction mixture was diluted with DCM (10 mL), washed with water (5 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by FC (petroleum ether/EtOAc 1:1) to afford desired cyclic ester **16** (90.8 mg, 0.54 mmol) in 67% yield as a white solid.

(*E*)-6,7,9,10-tetrahydro-2*H*-oxecine-2,8(5*H*)-dione (16). ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 6.86 (dt, *J* = 15.7, 6.9 Hz, 1H, **H**-4), 5.72 (dt, *J* = 15.7, 1.6 Hz, 1H, **H**-3), 4.47-4.35 (m, 2H, **H**-10), 2.81-2.57 (m, 2H, **H**-9), 2.51-2.35 (m, 2H, **H**-7), 2.35- 2.17 (m, 2H, **H**-5), 1.86-1.66 (m, 2H, **H**-6). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 208.4 (**C**-8), 165.9 (**C**-2), 148.8 (**C**-4), 121.7 (**C**-3), 60.0 (**C**-10), 42.3 (**C**-7), 41.2 (**C**-9), 30.8 (**C**-5), 21.5 (**C**-6).

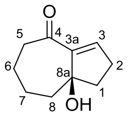


3. ORGANOCATALYTIC ENANTIOSELECTIVE TRANSANNULAR MORITA-BAYLIS-HILLMAN REACTION

3.1. Synthesis of Morita-Baylis-Hillman adducts

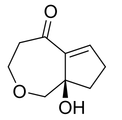
General Procedure I: To a solution of substrate **5a-i** or **11a-m** (0.2 mmol) in anhydrous $CHCl_3$ or CCl_4 (2 mL) was added phenol (0.1 mmol) and catalyst **13p** (0.02 mmol) under inert atmosphere. The reaction mixture was stirred at the indicated temperature in each case until consumption of the starting material was observed by TLC. The product was isolated directly by flash column chromatography (FC) with the indicated eluent, obtaining the Morita-Baylis-Hillman adducts. The racemic standards for HPLC separation conditions were prepared under the same reaction conditions, using 4-dimethylaminopyridine (DMAP) (0.04 mmol) as catalyst.

(*R*)-8a-hydroxy-2,5,6,7,8,8a-hexahydroazulen-4(1*H*)-one (12a). Following the *General Procedure*, compound **12a** (31.5 mg, 0.19 mmol) was isolated by FC (hexanes/EtOAc 1:1) after 5 hours at room temperature, starting from **5a** (33.2 mg, 0.20 mmol) in the presence of phenol (9.40 mg, 0.10 mmol) and catalyst **13p** (9.70 mg, 0.02 mmol) using dry $CHCl_3$ (2 mL) as solvent. Yield: 95% (e.e.: 90%). Yellow oil. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$): 6.83 (t, *J* = 2.7 Hz, 1H, **H**-3), 2.80 (ddd, *J* = 14.7, 13.1, 1.9 Hz, 1H, $\mathbf{H_a}$-5), 2.58-2.47 (m, 2H, $\mathbf{H_b}$-5 and $\mathbf{H_a}$-2), 2.38 (dddd, *J* = 19.2, 8.1, 5.2, 2.7 Hz, 1H, $\mathbf{H_b}$-2), 2.20-2.12 (m, 2H, $\mathbf{H_a}$-1 and $\mathbf{H_a}$-8), 2.10-2.02 (m, 1H, $\mathbf{H_b}$-1), 2.02-1.89 (m, 2H, $\mathbf{H_a}$-6 and $\mathbf{H_a}$-7), 1.82-1.74 (m, 2H, $\mathbf{H_b}$-7 and O**H**), 1.72-1.59 (m, 1H, $\mathbf{H_b}$-8), 1.46-1.35 (m, 1H, $\mathbf{H_b}$-6). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 201.5 (**C**-4), 149.0 (**C**-3a), 144.2 (**C**-3), 83.1 (**C**-8a), 43.8 (**C**-5), 43.2 (**C**-1), 41.1 (**C**-8), 29.2 (**C**-2), 25.4 (**C**-7), 24.7 (**C**-6). IR (ATR) cm^{-1}: 3411 (O-H st), 2926 (=C-H st), 1665 (C=O st), 1604 (C=O st). MS (EI, 70 eV) *m/z* (%): 166 (M$^+$, 4), 148 (81), 137 (37), 120 (24), 105 (63), 91 (100), 78 (27), 65 (17). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{10}H_{14}NaO_2]^+$: 189.0892 $[(M+Na)^+]$; found: 189.0896. The e.e. was determined by HPLC using a Chiralpak AD-H

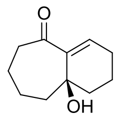


column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 8.14 min, τ_{minor} = 9.52 min (90% e.e.). $[\alpha]_D^{20}$: + 93.2 (*c*=1.60, $CHCl_3$).

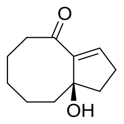
(*R*)-8a-hydroxy-1,3,4,7,8,8a-hexahydro-5*H*-cyclopenta[*c*]oxepin-5-one (12b). Following the *General Procedure*, compound **12b** (31.2 mg, 0.19 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 3:7) after 2 hours at room temperature, starting from **5b** (33.6 mg, 0.20 mmol) in the presence of phenol (9.40 mg, 0.1 mmol) and catalyst **13p** (9.70 mg, 0.02 mmol) using dry $CHCl_3$ (2 mL) as solvent. Yield: 93% (e.e.: 95%). White solid. ^1H NMR (δ, ppm) (500 MHz, $CDCl_3$): 6.93 (t, *J* = 2.7 Hz, 1H, **H**-6), 4.14 (ddd, *J* = 13.0, 4.5, 3.1 Hz, 1H, $\mathbf{H_a}$-3), 4.00 (d, *J* = 12.4 Hz, 1H, $\mathbf{H_a}$-1), 3.59-3.50 (m, 1H, $\mathbf{H_b}$-3), 3.44 (d, *J* = 12.4 Hz, 1H, $\mathbf{H_b}$-1), 3.15 (s, 1H, O**H**), 3.06 (ddd, *J* = 16.1, 11.9, 3.1 Hz, 1H, $\mathbf{H_a}$-4), 2.67-2.59 (m, 1H, $\mathbf{H_b}$-4), 2.58-2.53 (m, 1H, $\mathbf{H_a}$-7), 2.39 (dddd, *J* = 19.6, 9.1, 3.9, 2.8 Hz, 1H, $\mathbf{H_b}$-7), 2.07 (ddd, *J* = 14.3, 8.8, 3.9 Hz, 1H, $\mathbf{H_a}$-8), 1.91 (ddd, *J* = 14.5, 9.1, 5.7 Hz, 1H, $\mathbf{H_b}$-8). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 197.7 (**C**-5), 147.1 (**C**-5a), 145.8 (**C**-6), 82.4 (**C**-8a), 78.7 (**C**-1), 67.6 (**C**-3), 46.8 (**C**-4), 36.0 (**C**-8), 29.7 (**C**-7). IR (ATR) cm^{-1}: 3343 (O-H st), 3260 (O-H st), 1673 (C=O st), 1607 (C=O st), 1253 (C-O-C st). MS (EI/70 eV) *m/z* (%): 168 (M$^+$, 2), 150 (53), 138 (43), 122 (44), 109 (100), 93 (47), 82 (56), 65 (52), 53 (26). HRMS (UPLC MS ESI$^+$): Calculated for $[C_9H_{12}NaO_3]^+$: 191.0684 [(M+Na)$^+$]; found: 191.0687. M.p.: 64-66 °C (*n*-hexane/EtOAc). The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 15.83 min, τ_{minor} = 19.00 min (95% e.e.). $[\alpha]_D^{20}$: + 114.9 (*c*=0.90, $CHCl_3$).



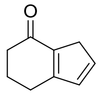
(*R*)-9a-hydroxy-1,2,3,6,7,8,9,9a-octahydro-5*H*-benzo[7]annulen-5-one (12d). Following the *General Procedure*, compound **12d** (32.4 mg, 0.18 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 20 hours at 0 °C, starting from **5d** (36.0 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.10 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry CCl_4 (2 mL) as solvent. Yield: 90% (e.e.: 82%). Yellow oil. ^1H NMR (δ, ppm) (500 MHz, $CDCl_3$): 6.64 (t, *J* = 3.9 Hz, 1H, **H**-4), 2.89-2.76 (m, 1H, $\mathbf{H_a}$-6), 2.46 (dd, *J* = 14.4, 6.7 Hz, 1H, $\mathbf{H_b}$-6), 2.22-2.05 (m, 2H, **H**-3), 2.00-1.89 (m, 1H, $\mathbf{H_a}$-8), 1.89-1.81 (m, 2H, $\mathbf{H_a}$-1 and $\mathbf{H_a}$-7), 1.76-1.58 (m, 6H, $\mathbf{H_b}$-1, **H**-2, $\mathbf{H_b}$-8 and **H**-9), 1.53 (s, 1H, O**H**), 1.44-1.28 (m, 1H, $\mathbf{H_b}$-7). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 205.0 (**C**-5), 144.6 (**C**-4a), 137.9 (**C**-4), 70.0 (**C**-9a), 43.7 (**C**-6), 42.0 (**C**-1), 41.5 (**C**-9), 25.9 (**C**-3), 25.1 (**C**-8), 24.9 (**C**-7), 18.9 (**C**-2). IR (ATR) cm^{-1}: 3418 (O-H st), 2934 (=C-H st), 1670 (C=O st), 1607 (C=O st). MS (EI/70 eV) *m/z* (%): 180 (M$^+$, 8), 162 (63), 133 (41), 105 (57), 91 (100), 77 (35), 55 (19). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{11}H_{16}NaO_2]^+$: 203.1048 [(M+Na)$^+$]; found: 203.1048. The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 8.98 min, τ_{minor} = 8.17 min (82% e.e.). $[\alpha]_D^{20}$: + 84.8 (*c*=2.50, $CHCl_3$).



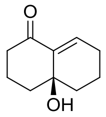
(*R*)-9a-hydroxy-1,2,5,6,7,8,9,9a-octahydro-4*H*-cyclopenta[8]annulen-4-one (12e). Following the *General Procedure*, compound **12e** (26.6 mg, 0.15 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 8 hours at room temperature, starting from **5e** (36.0 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.10 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry CHCl$_3$ (2 mL) as solvent. Yield: 73% (e.e.: 74%). Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 6.64 (t, *J* = 2.7 Hz, 1H, **H**-3), 3.25 (td, *J* = 12.1, 5.3 Hz, 1H, **H$_a$**-5), 2.52-2.37 (m, 1H, **H$_a$**-2), 2.38-2.26 (m, 2H, **H$_b$**-2 and **H$_b$**-5), 2.21-1.98 (m, 4H, **H**-1, **H$_a$**-9 and O**H**), 1.91-1.78 (m, 1H, **H$_a$**-6), 1.75-1.59 (m, 5H, **H$_b$**-6, **H**-7, **H$_a$**-8 and **H$_b$**-9), 1.36-1.18 (m, 1H, **H$_b$**-8). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 205.0 (**C**-4), 148.3 (**C**-3a), 141.7 (**C**-3), 84.8 (**C**-9a), 43.9 (**C**-1), 41.4 (**C**-9), 39.2 (**C**-5), 28.5 (**C**-2), 26.5 (**C**-6), 26.0 (**C**-8), 21.9 (**C**-7). IR (ATR) cm^{-1}: 3440 (O-H st), 2934 (=C-H st), 2862 (=C-H st), 1705 (C=O st), 1637 (C=O st). MS (EI/70 eV) *m/z* (%): 180 (M$^+$, 6), 162 (61), 147 (9), 137 (95), 119 (71), 105 (61), 91 (100), 78 (38), 65 (20), 55 (19). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{11}$H$_{16}$NaO$_2$]$^+$: 203.1048 [(M+Na)$^+$]; found: 203.1047. The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.0 mL/min; τ_{major} = 15.13 min, τ_{minor} = 17.12 min (74% e.e.). $[\alpha]_D^{20}$: + 60.7 (*c*=1.29, CHCl$_3$).



3,5,6,7-tetrahydro-4*H*-inden-4-one (12g).[15] Following the *General Procedure*, compound **12g** (20.1 mg, 0.15 mmol) was isolated by FC (hexanes/EtOAc 7:3) after 28 hours at room temperature, starting from **5g** (30.3 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.10 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry CHCl$_3$ (2 mL) as solvent. Yield: 73%. Colorless oil. ^{1}H NMR (δ, ppm) (500 MHz, CDCl$_3$): 6.79 (dt, *J* = 5.2, 1.3 Hz, 1H, **H**-1), 6.52 (dt, *J* = 5.3, 1.5 Hz, 1H, **H**-2), 3.29-3.24 (m, 2H, **H**-3), 2.66-2.59 (m, 2H, **H**-7), 2.49-2.41 (m, 2H, **H**-5), 2.10 (p, *J* = 6.2 Hz, 2H, **H**-6). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 195.1 (**C**-4), 164.4 (**C**-7a), 141.8 (**C**-1), 139.1 (**C**-3a), 134.3 (**C**-2), 38.8 (**C**-3), 37.9 (**C**-5), 25.5 (**C**-7), 24.2 (**C**-6).



(*S*)-4a-hydroxy-3,4,4a,5,6,7-hexahydronapthalen-1(2*H*)-one (12h). Following the *General Procedure*, compound **12h** (23.9 mg, 0.14 mmol) was isolated by FC (pentane/Et$_2$O gradient from 100:0 to 1:1) after 5 hours at room temperature, starting from **1h** (33.2 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.10 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry CHCl$_3$ (2 mL) as solvent. Yield: 72% (e.e.: 92%). White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 6.71 (dd, *J* = 4.9, 2.7 Hz, 1H, **H**-8), 2.68-2.51 (m, 1H, **H$_a$**-2), 2.38-2.08 (m, 4H, **H$_b$**-2, **H$_a$**-3 and **H**-7), 2.05-1.78 (m, 4H, **H$_b$**-3, **H$_a$**-4, **H$_a$**-5 and O**H**), 1.78-1.47 (m, 4H, **H$_b$**-4, **H$_b$**-5 and **H**-6). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 201.6 (**C**-1), 140.6 (**C**-8a), 138.6 (**C**-8), 69.4 (**C**-4a), 40.3 (**C**-2), 37.4 (**C**-4),



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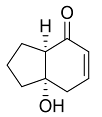
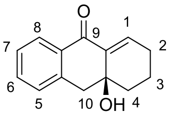
[15] Spectral information matched reported data for this compound: Paquette, L. A.; Racherla, U. S. *J. Org. Chem.* **1987**, *52*, 3250.

37.3 (**C**-5), 26.3 (**C**-7), 18.2 (**C**-3), 17.2 (**C**-6). IR (ATR) cm^{-1}: 3404 (O-H st), 2940 (=C-H st), 1677 (C=O st), 1615 (C=O st). MS (EI, 70 eV) *m/z* (%): 166 (M$^+$, 9), 148 (77), 138 (37), 120 (50), 110 (38), 91(100), 77 (26), 65 (16). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{10}H_{14}NaO_2]^+$: 189.0892 [(M+Na)$^+$]; found: 189.0902. M.p.: 57-59 °C (hexanes/EtOAc). The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 13.52 min, τ_{minor} = 10.86 min (92% e.e.). $[\alpha]_D^{20}$: +108.6 (*c*=0.46, CHCl$_3$).

(3a*R*,7a*S*)-7a-hydroxy-1,2,3,3a,7,7a-hexahydro-4*H*-inden-4-one (12i').[16] Following the *General Procedure*, compound **12i'** (26.2 mg, 0.17 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 3:7) after 96 hours at room temperature, starting from **5i** (30.5 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.1 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry CHCl$_3$ (2 mL) as solvent. Yield: 86% (d.r.: 17:1 and e.e.: 87%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 6.83 (dt, *J* = 10.0, 4.2 Hz, 1H, **H**-6), 6.02 (dt, *J* = 10.1, 2.2 Hz, 1H, **H**-5), 2.73-2.63 (m, 2H, **H**-7), 2.62-2.52 (m, 1H, **H**-3a), 2.24-2.05 (m, 2H, **H**-3), 2.19* (s, 1H, O**H**), 1.93-1.56 (m, 4H, **H**-1 and **H**-2). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$) (*denotes minor diastereomer): 200.9 (**C**-4), 200.1* (**C**-4*), 146.5 (**C**-6), 145.6* (**C**-6*), 130.4* (**C**-5*), 128.3 (**C**-5), 82.7* (**C**-7a*), 81.5 (**C**-7a), 57.9* (**C**-3a*), 57.7 (**C**-3a), 39.5* (**C**-1*), 39.0* (**C**-7*), 38.3 (**C**-1), 36.1 (**C**-7), 26.4 (**C**-3), 21.3* (**C**-3*), 21.2 (**C**-2), 20.2* (**C**-2*). IR (ATR) cm^{-1}: 3412 (O-H st), 2956 (=C-H st), 1663 (C=O st). MS (EI/70 eV) *m/z* (%): 152 (M$^+$, 22), 133 (53), 123 (14), 117 (20), 110 (7), 105 (15), 96 (6), 91 (18), 84 (100), 77 (21), 69 (41), 63 (6), 55 (37), 51 (14). HRMS (UPLC MS ESI$^+$): Calculated for $[C_9H_{12}NaO_2]^+$: 153.0916 [(M+Na)$^+$]; found: 153.0915. The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 8.38 min, τ_{minor} = 10.16 min (87% e.e.). $[\alpha]_D^{20}$: -12.6 (*c*=0.75, CHCl$_3$).



(*S*)-4a-hydroxy-3,4,4a,10-tetrahydroanthracen-9(2*H*)-one (15a). Following the *General Procedure*, compound **15a** (35.3 mg, 0.16 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 10 hours at room temperature, starting from **11a** (43.0 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.10 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry CHCl$_3$ (2 mL) as solvent. Yield: 82% (e.e.: 70%). Yellow solid. ^{1}H NMR (δ, ppm) (500 MHz, CDCl$_3$): 8.13 (dd, *J* = 7.8, 1.4 Hz, 1H, **H**-8), 7.54 (td, *J* = 7.5, 1.5 Hz, 1H, **H**-6), 7.42-7.37 (m, 1H, **H**-7), 7.33-7.29 (m, 2H, **H**-1 and **H**-5), 3.17 (d, *J* = 16.1 Hz, 1H, **H$_a$**-10), 3.11 (d, *J* = 16.1 Hz, 1H, **H$_b$**-10), 2.55-2.42 (m, 1H, **H$_a$**-2), 2.37-2.25 (m, 1H, **H$_b$**-2), 2.18-2.11 (m, 1H, **H$_a$**-4),



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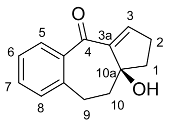
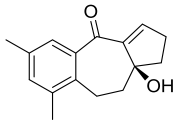
[16] The relative and absolute configuration of this product was assigned after hydrogenation of the product **12i'** (H$_2$, Pd-C in EtOH, 30 min) and by comparison with the NMR spectra and optical rotation values described by B. List at *J. Am. Chem. Soc.* **2008**, *130*, 6737. Reported value for (3a*S*,7a*R*) product $[\alpha]_D^{20}$: + 41.9 (*c*=1.0, CH$_2$Cl$_2$, e.e.: 94%), measured value $[\alpha]_D^{20}$: -24.0 (*c*=1.0, CH$_2$Cl$_2$, e.e.: 87%).

1.95 (s, 1H, O**H**), 1.89-1.72 (m, 4H, **H$_b$**-4 and **H**-3). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 185.8 (**C**-9), 141.5 (**C**-1), 140.2 (**C**$_{arom}$), 137.80 (**C**-9a), 133.7 (**C**-7), 132.3 (**C**$_{arom}$), 129.3 (**C**-5), 128.0 (**C**H$_{arom}$), 127.2 (**C**H$_{arom}$), 68.9 (**C**-4a), 42.8 (**C**-10), 37.0 (**C**-4), 26.5 (**C**-2), 17.3 (**C**-3). IR (ATR) cm^{-1}: 3418 (O-H st), 2940 (=C-H st), 1659 (C=O st). MS (EI/70 eV) *m/z* (%): 214 (M$^+$, 3), 196 (100), 181 (53), 165 (58), 139 (10), 115 (8), 98 (5), 82 (13), 63 (7). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{14}H_{15}O_2]^+$: 215.1072 [(M+H)$^+$]; found: 215.1075. M.p.: 126-128 °C (hexanes/EtOAc). The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.0 mL/min; τ_{major} = 17.28 min, τ_{minor} = 25.11 min (70% e.e.). $[\alpha]_D^{20}$: -33.1 (*c*=1.9, $CHCl_3$).

(*S*)-10a-hydroxy-2,9,10,10a-tetrahydrobenzo[*f*]azulen-4(1*H*)-one (15b). Following the *General Procedure*, compound **15b** (37.8 mg, 0.18 mmol) was isolated by FC (hexanes/EtOAc 7:3) after 2 hours at room temperature, starting from **11b** (43.0 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.10 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry $CHCl_3$ (2 mL) as solvent. Yield: 88% (e.e.: 84%). Yellow oil. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$): 7.81-7.76 (m, 1H, **H**-5), 7.46 (td, *J* = 7.5, 1.5 Hz, 1H, **H**-7), 7.35 (td, *J* = 7.6, 1.2 Hz, 1H, **H**-6), 7.24 (dd, *J* = 7.5, 1.2 Hz, 1H, **H**-8), 7.03 (t, *J* = 2.6 Hz, 1H, **H**-3), 2.94 (ddd, *J* = 14.1, 12.5, 5.9 Hz, 1H, **H$_a$**-9), 2.79 (ddd, *J* = 14.2, 4.8, 3.3 Hz, 1H, **H$_b$**-9), 2.60-2.52 (m, 1H, **H$_a$**-2), 2.46 (dtd, *J* = 18.9, 7.5, 2.4 Hz, 1H, **H$_b$**-2), 2.37-2.19 (m, 3H, **H$_a$**-1 and **H**-10), 2.14-2.04 (m, 1H, **H$_b$**-1), 1.69 (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 192.5 (**C**-4), 149.0 (**C**-3a), 144.2 (**C**-3), 141.4 (**C**-8a), 138.5 (**C**-4a), 132.8 (**C**-7), 129.7 (**C**-8), 129.4 (**C**-5), 127.2 (**C**-6), 83.9 (**C**-10a), 42.6 (**C**-1), 40.8 (**C**-10), 31.3 (**C**-9), 29.2 (**C**-2). IR (ATR) cm^{-1}: 3436 (O-H st), 1634 (C=O st), 1594 (C=O st). MS (EI, 70 eV) *m/z* (%): 196 (M$^+$ - H_2O, 100), 181 (33), 167 (73), 152 (30), 139 (8), 128 (7), 118 (39), 105 (5), 90 (33), 83 (11), 76 (5), 63 (11), 51 (9). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{14}H_{14}NaO_2]^+$: 237.0892 [(M+Na)$^+$]; found: 237.0893. The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 14.71 min, τ_{minor} = 13.92 min (84% e.e.). $[\alpha]_D^{20}$: - 39.5 (*c*=1.00, $CHCl_3$).

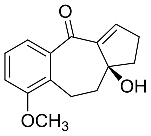


(*S*)-10a-hydroxy-6,8-dimethyl-2,9,10,10a-tetrahydrobenzo[*f*]azulen-4(1*H*)-one (15c). Following the *General Procedure*, compound **15c** (44.3 mg, 0.18 mmol) was isolated by FC (hexanes/CH_2Cl_2/EtOAc gradient from 1:1:0.1 to 1:1:0.2) after 6 hours at room temperature, starting from **11c** (49.0 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.10 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry $CHCl_3$ (2 mL) as solvent. Yield: 90% (e.e.: 88%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$): 7.37 (d, *J* = 2.0 Hz, 1H, **C**H$_{arom}$), 7.17 (d, *J* = 2.0 Hz, 1H, **C**H$_{arom}$), 7.10 (t, *J* = 2.7 Hz, 1H, **H**-3), 2.96 (ddd, *J* = 14.4, 5.0, 2.6 Hz, 1H, **H$_a$**-9), 2.73-2.64 (m, 1H, **H$_b$**-9), 2.55 (ddt, *J* = 19.0, 8.9, 2.7 Hz, 1H, **H$_a$**-2), 2.51-2.41 (m, 1H, **H$_b$**-2), 2.37 (s, 3H, C**H$_3$**), 2.34 (s, 3H, C**H$_3$**), 2.32-2.22 (m, 2H, **H$_a$**-1 and **H$_a$**-10), 2.18 (td, *J* = 13.7, 5.0 Hz, 1H, **H$_b$**-



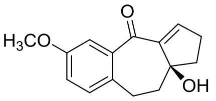
10), 2.11-2.02 (m, **H$_b$**-1), 1.42 (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 193.0 (**C**-4), 148.5 (**C**-3a), 144.0 (**C**-3), 139.7 (**C**$_{\text{arom}}$), 136.6 (**C**$_{\text{arom}}$), 135.7 (**C**$_{\text{arom}}$), 135.5 (**C**$_{\text{arom}}$), 135.3 (**C**H$_{\text{arom}}$), 127.5 (**C**H$_{\text{arom}}$), 83.9 (**C**-10a), 42.0 (**C**-1), 40.2 (**C**-10), 29.1 (**C**-2), 25.7 (**C**-9), 20.9 (**C**H$_3$), 19.6 (**C**H$_3$). IR (ATR) cm^{-1}: 3432 (O-H st), 1640 (C=O st), 1595 (C=O st). MS (EI, 70 eV) *m/z* (%): 226 (3, M$^+$ - H$_2$O), 224 (65), 196 (72), 165 (100), 115 (54), 78 (79), 50 (18). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{16}$H$_{18}$NaO$_2$]$^+$: 265.1205 [(M+Na)$^+$]; found 265.1212. M.p.: 90-92 °C (*n*-hexane/EtOAc). The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 9.53 min, τ_{minor} = 10.86 min (88% e.e.). $[\alpha]_D^{20}$: - 110.6 (*c*=1.70, CHCl$_3$).

(*S*)-10a-hydroxy-8-methoxy-2,9,10,10a-tetrahydrobenzo[*f*]azulen-4(1*H*)-one (15d). Following the



G*eneral Procedure*, compound **15d** (49.1 mg, 0.20 mmol) was isolated by FC (hexanes/CH$_2$Cl$_2$/EtOAc gradient from 1:1:0.2 to 1:1:0.4) after 6 hours at room temperature, starting from **11d** (50.2 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.10 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry CHCl$_3$ (2 mL) as solvent. Yield: 98% (e.e.: 87%). Yellow solid. ^{1}H NMR (δ, ppm) (500 MHz, CDCl$_3$): 7.33 (dd, *J* = 7.7, 1.4 Hz, 1H, C**H$_{\text{arom}}$**), 7.28 (t, *J* = 7.8 Hz, 1H, **H**-6), 7.07 (dd, *J* = 3.1, 2.3 Hz, 1H, **H**-3), 7.04 (dd, *J* = 8.0, 1.4 Hz, 1H, C**H$_{\text{arom}}$**), 3.86 (s, 3H, OC**H$_3$**), 3.38 (ddd, *J* = 14.0, 5.0, 2.8 Hz, 1H, **H$_a$**-9), 2.58-2.40 (m, 3H, **H**-2 and **H$_b$**-9), 2.31-2.22 (m, 2H, **H$_a$**-1 and **H$_a$**-10), 2.17 (ddd, *J* = 14.3, 13.0, 5.0 Hz, 1H, **H$_b$**-10), 2.09-2.01 (m, 1H, **H$_b$**-1), 1.60 (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 192.5 (**C**-4), 156.4 (**C**$_{\text{arom}}$), 148.7 (**C**-3a), 144.2 (**C**-3), 140.4 (**C**$_{\text{arom}}$), 129.2 (**C**$_{\text{arom}}$), 127.8 (**C**H$_{\text{arom}}$), 121.0 (**C**H$_{\text{arom}}$), 114.5 (**C**H$_{\text{arom}}$), 84.0 (**C**-10a), 56.0 (O**C**H$_3$), 42.3 (**C**-1), 40.2 (**C**-10), 29.1 (**C**-2), 21.7 (**C**-9). IR (ATR) cm^{-1}: 3487 (O-H st), 2941 (=C-H st), 1641 (C=O st), 1579 (C=O st). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{15}$H$_{16}$NaO$_3$]$^+$: 267.0997 [(M+Na)$^+$]; found 267.1007. M.p.: 134-136 °C (hexanes/EtOAc). The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 21.38 min, τ_{minor} = 12.13 min (87% e.e.). $[\alpha]_D^{20}$: - 75.4 (*c*=1.95, CHCl$_3$).

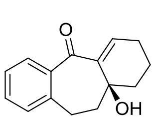
(*S*)-10a-hydroxy-6-methoxy-2,9,10,10a-tetrahydrobenzo[*f*]azulen-4(1*H*)-one (15e). Following the



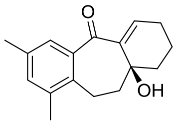
General Procedure, compound **15e** (43.2 mg, 0.18 mmol) was isolated by FC (hexanes/EtOAc 1:1), starting from **11e** (49.0 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.10 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry CHCl$_3$ (2 mL) as solvent. Yield: 88% (e.e.: 78%). Colorless oil. ^{1}H NMR (δ, ppm) (500 MHz, CDCl$_3$): 7.31 (d, *J* = 2.9 Hz, 1H, **H**-5), 7.14 (d, *J* = 8.3 Hz, 1H, **H**-8), 7.03-6.97 (m, 2H, **H**-3 and **H**-7), 3.83 (s, 3H, OC**H$_3$**), 2.86 (ddd, *J* = 14.4, 12.5, 5.7 Hz, 1H, **H$_a$**-9), 2.73 (ddd, *J* = 14.4, 5.0, 3.2 Hz, 1H, **H$_b$**-9), 2.54 (ddt, *J* = 18.9, 8.6, 2.9 Hz, 1H, **H$_a$**-2), 2.44 (dtd, *J* = 18.9, 7.6, 2.3 Hz, 1H, **H$_b$**-2), 2.33-2.23 (m, 2H, **H$_a$**-1 and **H$_a$**-10), 2.19 (ddd, *J* = 14.3, 12.5, 5.0 Hz, 1H, **H$_b$**-10), 2.12-2.03 (m, 1H, **H$_b$**-1), 1.82 (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (126 MHz, CDCl$_3$): 192.3 (**C**-4), 158.8 (**C**-6), 149.0 (**C**-3a), 144.3 (**C**-3), 139.3 (**C**$_{\text{arom}}$), 133.6 (**C**$_{\text{arom}}$), 131.1

(**C**-8), 119.7 (**C**-7), 113.1 (**C**-5), 84.1 (**C**-10a), 55.6 (O**C**H_3), 42.4 (**C**-1), 41.0 (**C**-10), 30.4 (**C**-9), 29.2 (**C**-2). IR (ATR) cm^{-1}: 3443 (O-H st), 2937 (=C-H st), 1644 (C=O st), 1599 (C=O st). MS (EI, 70 eV) *m/z* (%): 226 (100), 211 (32), 198 (22), 183 (24), 165 (34), 152 (42), 120 (50), 78 (46), 63 (19), 51 (19). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{15}H_{16}NaO_3]^+$: 267.0997 [$(M+Na)^+$]; found 267.1001. M.p.: The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 16.95 min, τ_{minor} = 20.49 min (78% e.e.). $[\alpha]_D^{20}$: - 22.8 (*c*=2.40, $CHCl_3$).

(*S*)-11a-hydroxy-1,2,3,10,11,11a-hexahydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (15f). Following the *General Procedure*, compound **15f** (45.1 mg, 0.20 mmol) was isolated by FC (hexanes/EtOAc 7:3) after 3.5 hours at room temperature, starting from **11f** (45.6 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.10 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry $CHCl_3$ (2 mL) as solvent. Yield: 99% (e.e.: 98%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$): 7.83 (dd, *J* = 7.8, 1.4 Hz, 1H, **H**-6), 7.43 (td, *J* = 7.5, 1.4 Hz, 1H, **H**-8), 7.33 (t, *J* = 7.8 Hz, 1H, **H**-7), 7.22 (d, *J* = 7.5 Hz, 1H, **H**-9), 7.00 (t, *J* = 3.9 Hz, 1H, **H**-4), 3.02 (td, *J* = 13.8, 5.4 Hz, 1H, $\mathbf{H_a}$-10), 2.75 (ddd, *J* = 14.1, 4.5, 3.0 Hz, 1H, $\mathbf{H_b}$-10), 2.39-2.18 (m, 3H, **H**-3 and $\mathbf{H_a}$-11), 2.01 (td, *J* = 13.9, 4.5 Hz, 1H, $\mathbf{H_b}$-11), 1.88 (m, 2H, $\mathbf{H_a}$-1 and $\mathbf{H_a}$-2), 1.74-1.54 (m, 2H, $\mathbf{H_b}$-1 and $\mathbf{H_b}$-2), 1.40 (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 194.5 (**C**-5), 143.8 (**C**-4a), 141.5 (**C**-9a), 139.03 (**C**-5a), 138.97 (**C**-4), 132.6 (**C**-8), 129.30 ($\mathbf{C}H_{arom}$), 129.28 ($\mathbf{C}H_{arom}$), 127.2 (**C**-7), 72.4 (**C**-11a), 41.9 (**C**-11), 38.5 (**C**-1), 31.8 (**C**-10), 25.8 (**C**-3), 19.9 (**C**-2). IR (ATR) cm^{-1}: 3443 (O-H st), 2937 (=C-H st), 1654 (C=O st), 1611 (C=O st). MS (IE, 70 eV) *m/z* (%): 228 (M$^+$, 7), 210 (100), 195 (39), 178 (47), 165 (46), 152 (27), 141 (14), 133 (22), 115 (20), 103 (14), 89 (24), 77 (20), 63 (10), 51 (9). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{15}H_{16}NaO_2]^+$: 251.1048 [$(M+Na)^+$]; found: 251.1046. The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 13.54 min, τ_{minor} = 14.82 min (98% e.e.). $[\alpha]_D^{20}$: -128.7 (*c*=2.35, $CHCl_3$).

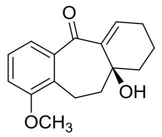


(*S*)-11a-hydroxy-7,9-dimethyl-1,2,3,10,11,11a-hexahydro-5*H*-dibenzo[*a,d*][7] annulen-5-one (15g). Following the *General Procedure*, compound **15g** (50.8 mg, 0.20 mmol) was isolated by FC (hexanes/EtOAc 1:1) after 7 hours at room temperature, starting **11g** (51.3 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.10 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry $CHCl_3$ (2 mL) as solvent. Yield: 99% (e.e.: >98%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 7.43 (s, 1H, **H**-6), 7.16 (s, 1H, **H**-8), 7.10 (t, *J* = 3.7 Hz, 1H, **H**-4), 2.99 (dt, *J* = 14.4, 3.7 Hz, 1H, $\mathbf{H_a}$-10), 2.73 (td, *J* = 14.1, 5.0 Hz, 1H, $\mathbf{H_b}$-10), 2.34 (m, 1H, $\mathbf{H_a}$-3), 2.36*(s, 3H, C$\mathbf{H_3}$), 2.33* (s, 3H, C$\mathbf{H_3}$), 2.32-2.21 (m, 2H, $\mathbf{H_b}$-3 and $\mathbf{H_a}$-11), 1.94-1.84 (m, 3H, $\mathbf{H_a}$-1, $\mathbf{H_a}$-2 and $\mathbf{H_b}$-11), 1.73-1.57 (m, 2H, $\mathbf{H_b}$-1 and $\mathbf{H_b}$-2), 1.52 (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 194.7 (**C**-5), 143.2 (**C**-4a), 140.0 (**C**-9a), 139.2 (**C**-4), 136.4 ($\mathbf{C}_{arom}$), 136.1 ($\mathbf{C}_{arom}$), 135.24 ($\mathbf{C}_{arom}$), 135.21 (**C**-8), 127.7 (**C**-6), 72.3 (**C**-11a), 41.0



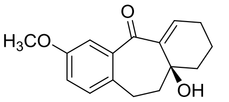
(**C**-11), 38.0 (**C**-1), 25.9 (**C**-10), 25.7 (**C**-3), 20.9 (**C**H_3), 19.9 (**C**-2), 19.7 (**C**H_3). IR (ATR) cm^{-1}: 3422 (O-H st), 2934 (=C-H st), 1659 (C=O st), 1597 (C=O st). MS (EI, 70 eV) *m/z* (%): 256 (M$^+$, 2), 238 (100), 223 (33), 209 (23), 195 (25), 178 (28), 165 (28), 152 (13), 141 (8), 128 (12), 115 (20), 103 (9), 91 (16), 77 (12), 63 (5), 51 (5). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{17}H_{20}NaO_2]^+$: 279.1361 [(M+Na)$^+$]; found: 279.1359. M.p.: 100-102 °C (hexanes/EtOAc). The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 8.89 min, τ_{minor} = 9.94 min (>98% e.e.). $[\alpha]_D^{20}$: -99.7 (*c*=0.57, $CHCl_3$).

(*S*)-11a-hydroxy-9-methoxy-1,2,3,10,11,11a-hexahydro-5*H*-dibenzo[*a*,*d*][7] annulen-5-one (15h).



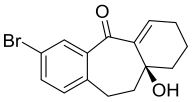
Following the *General Procedure*, compound **15h** (51.1 mg, 0.20 mmol) was isolated by FC (hexanes/EtOAc 7:3) after 7 hours at room temperature, starting from **11h** (51.7 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.10 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry $CHCl_3$ (2 mL) as solvent. Yield: 99% (e.e.: 97%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 7.41 (dd, *J* = 7.8, 1.2 Hz, 1H, **H**-6), 7.30-7.27 (m, 1H, **H**-7), 7.07 (td, *J* = 3.2, 1.5 Hz, 1H, **H**-4), 7.04* (dd, *J* = 8.2, 1.2 Hz, 1H, **H**-8), 3.87 (s, 3H, OC**H₃**), 3.44 (ddd, *J* = 14.1, 4.4, 3.0 Hz, 1H, $\mathbf{H_a}$-10), 2.54 (td, *J* = 13.9, 5.1 Hz, 1H, $\mathbf{H_b}$-10), 2.41-2.32 (m, 1H, $\mathbf{H_a}$-3), 2.32-2.18 (m, 2H, $\mathbf{H_b}$-3 and $\mathbf{H_a}$-11), 1.96 (dd, *J* = 14.0, 4.4 Hz, 1H, $\mathbf{H_b}$-11), 1.93-1.84 (m, 2H, $\mathbf{H_a}$-1 and $\mathbf{H_a}$-2), 1.75-1.65 (m, 1H, $\mathbf{H_b}$-2), 1.65-1.57 (m, 1H, $\mathbf{H_b}$-1), 1.48 (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 194.4 (**C**-5), 156.2 (**C**-9), 143.5 (**C**-4a), 140.9 (**C**-5a), 139.2 (**C**-4), 129.7 (**C**-9a), 127.6 (**C**-7), 121.2 (**C**-6), 114.4 (**C**-8), 72.4 (**C**-11a), 56.1 (O**C**H_3), 41.1 (**C**-11), 38.2 (**C**-1), 25.9 (**C**-3), 21.7 (**C**-10), 19.9 (**C**-2). IR (ATR) cm^{-1}: 3465 (O-H st), 2934 (=C-H st), 1657 (C=O st). MS (EI, 70 eV) *m/z* (%): 258 (M$^+$, 4), 240 (100), 225 (29), 212 (12), 202 (18), 178 (16), 165 (37), 152 (17), 128 (9), 115 (15), 91 (16), 77 (14), 51 (7). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{16}H_{18}NaO_3]^+$: 281.1154 [(M+Na)$^+$]; found: 281.1148. M.p.: 96-98 °C (hexanes/EtOAc). The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 16.22 min, τ_{minor} = 21.08 min (97% e.e.). $[\alpha]_D^{20}$: -134.3 (*c*=0.95, $CHCl_3$).

(*S*)-11a-hydroxy-7-methoxy-1,2,3,10,11,11a-hexahydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-one (15i).



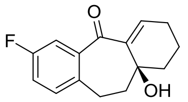
Following the *General Procedure*, compound **15i** (51.2 mg, 0.20 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 4 hours at room temperature, starting from **11i** (51.7 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.10 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry $CHCl_3$ (2 mL) as solvent. Yield: 99% (e.e.: >98%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$): 7.38 (d, *J* = 2.8 Hz, 1H, **H**-6), 7.14 (d, *J* = 8.3 Hz, 1H, **H**-9), 7.02-6.97 (m, 2H, **H**-8 and **H**-4), 3.84 (s, 3H, OC**H₃**), 2.96 (td, *J* = 13.9, 5.3 Hz, 1H, $\mathbf{H_a}$-10), 2.72 (ddd, *J* = 14.2, 4.6, 2.9 Hz, 1H, $\mathbf{H_b}$-10), 2.40-2.20 (m, 3H, **H**-3 and $\mathbf{H_a}$-11), 1.99 (td, *J* = 14.0, 4.6 Hz, 1H, $\mathbf{H_b}$-11), 1.94-1.83 (m, 2H, $\mathbf{H_a}$-1 and $\mathbf{H_a}$-2), 1.77-1.64 (m, 1H, $\mathbf{H_b}$-2), 1.64-1.59 (m, 1H, **H**$_b$-1), 1.59 (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 194.3 (**C**-5), 158.7 (**C**-7), 143.8 (**C**-4a), 139.7 (**C**-5a), 138.9 (**C**-4), 133.8 (**C**-9a), 130.6 (**C**-9), 119.5 (**C**-8), 112.9 (**C**-6), 72.4 (**C**-11a), 55.5 (O**C**H$_3$), 42.0 (**C**-11), 38.4 (**C**-1), 30.8 (**C**-10), 25.8 (**C**-3), 19.9 (**C**-2). IR (ATR) cm^{-1}: 3422 (O-H st), 2937 (=C-H st), 1654 (C=O st). MS (70 eV) *m/z* (%): HRMS (UPLC MS ESI$^+$): Calculated for $[C_{16}H_{18}NaO_3]^+$: 281.1154 [(M+Na)$^+$]; found: 281.1161. M.p.: 108-110 °C (hexanes/EtOAc). The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 17.98 min, τ_{minor} = 22.43 min (>98% e.e.). $[\alpha]_D^{20}$: -108.8 (*c*=1.58, CHCl$_3$).

(*S*)-7-bromo-11a-hydroxy-1,2,3,10,11,11a-hexahydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (15j).



Following the *General Procedure*, compound **15j** (58.4 mg, 0.19 mmol) was isolated by FC (pentane/Et$_2$O gradient from 2:1 to 1:2) after 2 hours at room temperature, starting from **11j** (61.4 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.10 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry CHCl$_3$ (2 mL) as solvent. Yield: 95% (e.e.: 97%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, CDCl$_3$): 7.93 (d, *J* = 2.2 Hz, 1H, **H**-6), 7.53 (dd, *J* = 8.0, 2.2 Hz, 1H, **H**-8), 7.10 (d, *J* = 8.1 Hz, 1H, **H**-9), 7.01-6.97 (m, 1H, **H**-4), 2.96 (td, *J* = 13.8, 5.4 Hz, 1H, **H**$_a$-10), 2.74 (ddd, *J* = 14.2, 4.5, 2.9 Hz, 1H, **H**$_b$-10), 2.42-2.32 (m, 1H, **H**$_a$-3), 2.33-2.19 (m, 2H, **H**$_b$-3 and **H**$_a$-11), 2.00 (td, *J* = 14.0, 4.5 Hz, 1H, **H**$_b$-11), 1.95-1.85 (m, 2H, **H**$_a$-1 and **H**$_a$-2), 1.76-1.63 (m, 1H, **H**$_b$-2), 1.60-1.53 (m, 1H, **H**$_b$-1), 1.53 (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 193.4 (**C**-5), 143.5 (**C**-4a), 140.6 (**C**$_{arom}$), 140.4 (**C**$_{arom}$), 139.7 (**C**-4), 135.1 (**C**-8), 131.8 (**C**-6), 131.0 (**C**-9), 120.9 (**C**-7), 72.2 (**C**-11a), 41.3 (**C**-11), 38.8 (**C**-1), 31.3 (**C**-10), 25.8 (**C**-3), 19.9 (**C**-2). IR (ATR) cm^{-1}: 3462 (O-H st), 1651 (C=O st). MS (EI, 70 eV) *m/z* (%): 288 (M$^+$ - H$_2$O, 100), 273 (14), 258 (25), 209 (29), 194 (19), 178 (69), 165 (28), 152 (25), 128 (16), 115 (14), 102 (10), 89 (26), 76 (23), 63 (15). HRMS (UPLC MS ESI+): Calculated for $[C_{15}H_{15}BrNaO_2]^+$: 329.0153 [(M+Na)$^+$]; found: 329.0148. M.p.: 156-158 °C (hexanes/EtOAc). The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 9.66 min, τ_{minor} = 14.33 min (97% e.e.). $[\alpha]_D^{20}$: -135.4 (*c*=1.70, CHCl$_3$).

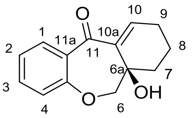
(*S*)-7-fluoro-11a-hydroxy-1,2,3,10,11,11a-hexahydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (15k).



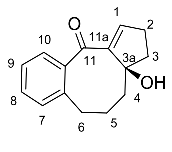
Following the *General Procedure*, compound **15k** (48.8 mg, 0.20 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 1,5 hours at room temperature, starting from **11k** (49.3 mg, 0.20 mmol) in the presence of phenol (9.4 mg, 0.10 mmol) and catalyst **13p** (9.7 mg, 0.02 mmol) using dry CHCl$_3$ (2 mL) as solvent. Yield: 99% (e.e.: 98%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, CDCl$_3$): 7.56-7.50 (m, 1H, **H**-6), 7.20 (dd, *J* = 8.3, 5.3 Hz, 1H, **H**-9), 7.12 (td, *J* = 8.2, 2.8 Hz, 1H, **H**-8), 7.00 (t, *J* = 3.7 Hz, 1H, **H**-4), 2.99 (td, *J* = 14.0, 5.1 Hz, 1H, **H**$_a$-10), 2.81-2.72 (m, 1H, **H**$_b$-10), 2.42-2.20 (m, 3H, **H**-3 and **H**$_a$-11), 2.01 (td, *J* = 14.0, 4.4 Hz, 1H, **H**$_b$-11), 1.97-1.85 (m, 2H, **H**$_a$-1 and **H**$_a$-2), 1.76-1.64 (m, 1H, **H**$_b$-2), 1.58 (td, *J* = 12.7, 2.7 Hz, 1H,

H$_b$-1), 1.46 (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 193.6 (d, $^{4}J_{CF}$ = 1.9 Hz, **C**-5), 161.8 (d, $^{1}J_{CF}$ = 245.8 Hz, **C**-7), 143.5 (**C**-4a), 140.7 (d, $^{3}J_{CF}$ = 6.4 Hz, **C**-5a), 139.6 (**C**-4), 137.3 (d, $^{4}J_{CF}$ = 3.2 Hz, **C**-9a), 130.9 (d, $^{3}J_{CF}$ = 7.4 Hz, **C**-9), 119.2 (d, $^{2}J_{CF}$ = 21.4 Hz, **C**-8), 115.6 (d, $^{2}J_{CF}$ = 22.6 Hz, **C**-6), 72.3 (**C**-11a), 41.6 (**C**-11), 38.8 (**C**-1), 31.0 (**C**-10), 25.8 (**C**-3), 19.9 (**C**-2). ^{19}F NMR (δ, ppm) (282 MHz, CDCl$_3$): -115.5. IR (ATR) cm^{-1}: 3467 (O-H st), 2946 (=C-H st), 1656 (C=O st). MS (EI, 70 eV) *m/z* (%): 246 (M$^+$, 4), 228 (100), 213 (27), 196 (51), 183 (37), 170 (23), 159 (15), 146 (16), 133 (20), 121 (5), 107 (15), 91 (9), 75 (8), 63 (7), 51 (7). HRMS (UPLC MS ESI+): Calculated for [$C_{15}H_{15}FNaO_2$]$^+$: 269.0954 [(M+Na)$^+$]; found: 269.0946. M.p.: 110-112 °C (hexanes/EtOAc). The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 10.58 min, τ_{minor} = 13.84 min (98% e.e.). [α]$_D^{20}$: -102.5 (*c*=1.35, CHCl$_3$).

(*R*)-6a-hydroxy-6a,7,8,9-tetrahydrodibenzo[*b,e*]oxepin-11(6*H*)-one (15l). Following the *General Procedure*, compound **15l** (22.8 mg, 0.10 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 1 hour at room temperature, starting from **11l** (23.0 mg, 0.10 mmol) in the presence of phenol (4.7 mg, 0.05 mmol) and catalyst **13p** (4.8 mg, 0.01 mmol) using dry CHCl$_3$ (1 mL) as solvent. Yield: 99% yield (e.e.: 97%). Colorless oil. ^{1}H NMR (δ, ppm) (500 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 7.93 (dd, *J* = 7.9, 1.8 Hz, 1H, **H**-1), 7.46 (ddd, *J* = 8.5, 7.2, 1.8 Hz, 1H, **H**-3), 7.19-7.11 (m, 1H, **H**-2), 7.09 (dd, *J* = 8.2, 1.2 Hz, 1H, **H**-4), 6.78 (t, *J* = 3.9 Hz, 1H, **H**-10), 4.30 (d, *J* = 12.2 Hz, 1H, **H$_a$**-6), 4.17 (d, *J* = 12.2 Hz, 1H, **H$_b$**-6), 2.40* (s, 1H, O**H**), 2.44-2.21 (m, 2H, **H**-9), 2.04-1.92 (m, 1H, **H$_a$**-8), 1.92-1.85 (m, 1H, **H$_a$**-7), 1.82-1.71 (m, 2H, **H$_b$**-7 and **H$_b$**-8). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 192.2 (**C**-11), 160.7 (**C**-4a), 143.6 (**C**-10a), 139.3 (**C**-10), 134.4 (**C**-3), 130.8 (**C**-1), 129.1 (**C**-11a), 123.4 (**C**-2), 121.1 (**C**-4), 80.4 (**C**-6), 71.0 (**C**-6a), 34.5 (**C**-7), 25.7 (**C**-9), 18.2 (**C**-8). IR (ATR) cm^{-1}: 3411 (O-H st), 2937 (=C-H), 1656 (C=O). MS (EI, 70 eV) *m/z* (%): 230 (M$^+$, 18), 212 (58), 200 (60), 181 (54), 165 (19), 144 (32), 131 (14), 121 (100), 105 (19), 91 (25), 77 (34), 63 (29), 51 (19). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{14}H_{24}NaO_3$]$^+$: 253.0841 [(M+Na)$^+$]; found 253.0841. The e.e. was determined by HPLC using a Chiralcel OD column [*n*-hexane/*i*-PrOH (98:02)]; flow rate 1.0 mL/min; τ_{major} = 26.29 min, τ_{minor} = 22.17 min (97% e.e.). [α]$_D^{20}$: + 65.7 (*c*=0.98, CHCl$_3$).



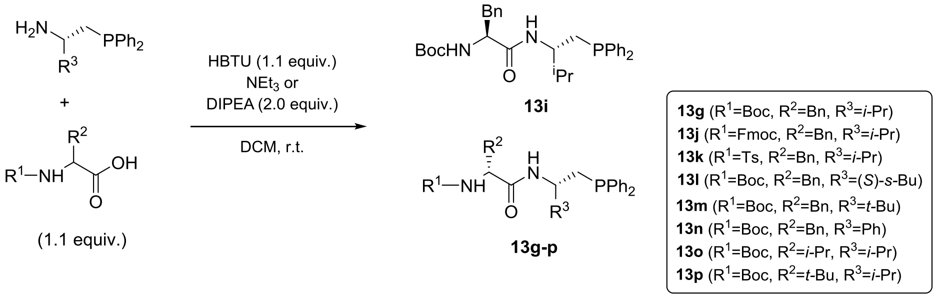
(*R*)-3a-hydroxy-2,3,3a,4,5,6-hexahydro-11*H*-benzo[*a*]cyclopenta[*d*][8]annulen-11-one (15m). Following the *General Procedure*, compound **15m** (32.9 mg, 0.14 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 10 hours at room temperature, starting from **11m** (45.6 mg, 0.20 mmol) in the presence of phenol (9.40 mg, 0.10 mmol) and catalyst **13p** (9.70 mg, 0.02 mmol) using dry CHCl$_3$ (2 mL) as solvent. Yield: 72% (e.e.: 38%). Yellow solid. ^{1}H NMR (δ, ppm) (500 MHz, CDCl$_3$): 7.79 (dd, *J* = 7.8, 1.4 Hz, 1H, **H**-10), 7.49 (td, *J* = 7.5, 1.4 Hz, 1H, **H**-8), 7.33 (td, *J* = 7.6, 1.3 Hz, 1H, **H**-9), 7.16 (d, *J* =



7.6, 1H, **H**-7), 6.75 (dt, *J* = 4.7, 2.7 Hz, 1H, **H**-1), 3.15 (td, *J* = 13.3, 6.0 Hz, 1H, $\mathbf{H_a}$-6), 2.74 – 2.60 (m, 2H, $\mathbf{H_a}$-2 and $\mathbf{H_b}$-6), 2.51 (ddt, *J* = 18.8, 8.9, 2.4 Hz, 1H, $\mathbf{H_b}$-2), 2.40 (ddd, *J* = 15.8, 8.8, 7.0 Hz, 1H, $\mathbf{H_a}$-3), 2.11 – 1.88 (m, 3H, $\mathbf{H_b}$-3, $\mathbf{H_a}$-5 and O**H**), 1.83 (dt, *J* = 14.1, 3.8 Hz, 1H, $\mathbf{H_a}$-4), 1.74 (m, 1H, $\mathbf{H_b}$-5), 1.61 (td, *J* = 13.7, 4.0 Hz, 1H, $\mathbf{H_b}$-4). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 194.4 (**C**-11), 152.9 (**C**-11a), 143.0 (**C**-1), 140.2 ($\mathbf{C}_{arom}$), 139.1 ($\mathbf{C}_{arom}$), 132.9 (**C**-8), 129.8 (**C**-7), 129.5 (**C**-10), 126.8 (**C**-9), 84.5 (**C**-3a), 37.6 (**C**-3), 33.0 (**C**-4), 30.3 (**C**-6), 29.2 (**C**-2), 24.9 (**C**-5). IR (ATR) cm^{-1}: 3400 (O-H st), 2916 (=C-H st), 1629 (C=O st), 1620 (C=O st). MS (EI, 70 eV) *m/z* (%): 210 (M^+ - H_2O, 54), 191 (14), 182 (68), 165 (26), 152 (17), 141 (6), 131 (100), 115 (13), 103 (26), 91 (25), 77 (21), 65 (10), 51 (9). HRMS (UPLC MS ESI+): Calculated for $[NaC_{15}H_{16}O_2]^+$: 251.1048 [$(M+Na)^+$]; found: 251.1053. The e.e. was determined by HPLC using a Chiralpak ADH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 20.67 min, τ_{minor} = 13.65 min (38% e.e.). M.p.: 138-140 °C (hexanes/EtOAc). $[\alpha]_D^{20}$: - 28.1 (*c*=1.35, $CHCl_3$).

3.2. Synthesis of catalysts

Catalysts **13a** and **13b** were commercially available and directly used without purification. Catalysts **13c**[17], **13d**[18], **13e**,[19] **13f**[20] and **13h**[21] were prepared following procedures previously described in the literature. NMR spectra of the obtained products matched the reported data. The experimental procedure for the synthesis of catalysts **13g** and **13i-p** was based on previously described literature procedure.[22]



General Procedure J: To a solution of the corresponding phosphine (1.0 equiv.) in anhydrous DCM (0.3 mmol/mL) was added the corresponding aminoacid (1.1 equiv.), HBTU (1.1 equiv.) and NEt_3 (2.0

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[17] Yuan, K.; Zhang, L.; Song, H.; Hu, Y.; Wu, X. *Tetrahedron Lett.* **2008**, *49*, 6262.

[18] Deng, H.; Wei, Y.; Shi, M. *Adv. Synth. Catal.* **2012**, *354*, 783.

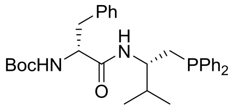
[19] Dong, Z.; Yan, C.; Gao, Y.; Dong, C.; Qiu, G.; Zhou, H. *Adv. Synth. Catal.* **2015**, *357*, 2132.

[20] Kawamura, K.; Fukuzawa, H.; Hayashi, M. *Org. Lett.* **2008**, *16*, 3509.

[21] Sladojevigch, F.; Trabocchi, A.; Guarna, A.; Dixon, D. J. *J. Am. Chem. Soc.* **2011**, *133*, 1710.

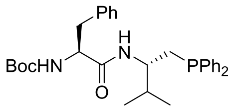
[22] Scanes, R. J. H.; Grossmann, O.; Grossmann, A.; Spring, D. R. *Org.Lett.* **2015**, *17*, 2462.

equiv.) or *N*,*N*-diisopropylethylamine (2.0 equiv.) under inert atmosphere. The reaction mixture was degassed by bubbling argon through the solution and it was stirred at room temperature for three days. After that time, the reaction mixture was washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/ EtOAc) to yield the desired product, which was stored under inert atmosphere to avoid oxidation.



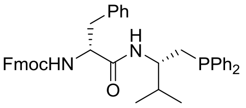
***tert*-butyl ((*R*)-1-(((*S*)-1-(diphenylphosphanyl)-3-methylbutan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (13g).** Following the *General Procedure*, catalyst **13g** (205 mg, 0.40 mmol) was isolated by FC (hexanes/EtOAc 8:2) as a white solid starting from (*S*)-1-(Diphenylphosphino)-3-methyl-2-butylamine (175 mg, 0.65 mmol), Boc-D-phenylalanine (190 mg, 0.72 mmol), HBTU (275 mg, 0.72 mmol) and NEt$_3$ (0.18 mL, 1.30 mmol) in 62% yield. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.62 – 7.08 (m, 15H, 15 x C**H**$_{\text{arom}}$), 5.71 (s, 1H, N**H**), 4.69 (s, 1H, N**H**), 4.22 – 4.16 (m, 1H, C**H**CO), 4.06 – 3.92 (m, 1H, C**H**CH$_2$PPh$_2$), 3.05 (dd, *J* = 13.9, 6.9 Hz, 1H, C**H$_a$**H$_b$CHCO), 2.98 – 2.86 (m, 1H, CH$_a$**H$_b$**CHCO), 2.28 – 2.10 (m, 2H, C**H$_2$**PPh$_2$), 1.93 – 1.81 (m, 1H, CH(CH$_3$)$_2$), 1.40 (s, 9H, OC(C**H$_3$**)$_3$), 0.75 (d, *J* = 6.7 Hz, 6H, CH(C**H$_3$**)$_2$). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 170.4 (NH**C**O), 155.3 (**C**OOC(CH$_3$)$_3$), 138.7 (d, $^1J_{CP}$ = 13.4 Hz, **C**$_{\text{arom}}$), 138.5 (d, $^1J_{CP}$ = 12.9 Hz, **C**$_{\text{arom}}$), 137.0 (**C**$_{\text{arom}}$), 132.9 (d, $^2J_{CP}$ = 19.4 Hz, **C**$_{\text{arom}}$), 132.8 (d, $^2J_{CP}$ = 19.3 Hz, **C**$_{\text{arom}}$), 129.3 (**C**H$_{\text{arom}}$), 128.8 (**C**H$_{\text{arom}}$), 128.8 (**C**H$_{\text{arom}}$), 128.7 (**C**H$_{\text{arom}}$), 128.6 (**C**H$_{\text{arom}}$), 128.5 (**C**H$_{\text{arom}}$), 126.9 (**C**H$_{\text{arom}}$), 80.1 (O**C**(CH$_3$)$_3$), 56.1 (**C**HCO), 52.4 (d, $^2J_{CP}$ =14.8 Hz, **C**HCH(CH$_3$)$_2$), 38.3 (C**H$_2$**CHCO), 32.2 (d, $^3J_{CP}$ = 8.4 Hz, **C**H(CH$_3$)$_2$), 31.6 (d, $^1J_{CP}$ = 15.0 Hz, **C**H$_2$CHCH(CH$_3$)$_2$), 28.3 (C(**C**H$_3$)$_3$), 18.8 (CH(CH$_3$)$_2$), 17.5 (CH(**C**H$_3$)$_2$). ^{31}P NMR (δ, ppm) (121.5 MHz, CDCl$_3$): -23.3. IR (ATR) cm^{-1}: 3307 (N-H st), 1687 (C=O st), 1652 (C=O st), 1529 (N-C=O st), 1497 (N-C=O st). HRMS (UPLC MS ESI+): Calculated for [C$_{31}$H$_{40}$N$_2$O$_3$P]$^+$: 519.2777 [(M+H)$^+$]; found: 519.2800. M.p.: 108-110 °C (hexanes/EtOAc). $[\alpha]_D^{20}$: + 22.0 (*c*=0.83, CHCl$_3$).

***tert*-butyl ((*S*)-1-(((*S*)-1-(diphenylphosphanyl)-3-methylbutan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (13i).** Following the *General Procedure*, catalyst **13i** (200 mg, 0.39 mmol) was isolated by FC (hexanes/EtOAc 8:2) as a white solid starting from (*S*)-1-(Diphenylphosphino)-3-methyl-2-butylamine (202 mg, 0.75 mmol), Boc-L-phenylalanine (218 mg, 0.82 mmol), HBTU (310 mg, 0.82 mmol) and NEt$_3$ (0.21 mL, 1.50 mmol) in 52% yield. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.52 – 7.12 (m, 15H, 15 x C**H**$_{\text{arom}}$), 5.81 (d, *J* = 9.2 Hz, 1H, N**H**), 5.03 (s, 1H, N**H**), 4.18 (m, 1H, C**H**CO), 3.87 (m, 1H, C**H**CH$_2$PPh$_2$), 3.03 (d, *J* = 7.1 Hz, 2H C**H$_2$**CHCO), 2.08 (d, *J* = 7.2 Hz, 2H, C**H$_2$**PPh$_2$), 1.94 (m, 1H C**H**(CH$_3$)$_2$), 1.40 (s, 9H, OC(C**H$_3$**)$_3$), 0.79 (d, *J* = 6.7 Hz, 3H, CH(C**H$_3$**)$_2$), 0.76 (d, *J* = 6.8 Hz, 3H, CH(C**H$_3$**)$_2$). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 170.6 (NH**C**O), 155.6 (**C**OOC(CH$_3$)$_3$), 138.5 (d, $^1J_{CP}$ = 12.7 Hz, **C**$_{\text{arom}}$), 138.2 (d, $^1J_{CP}$ = 12.0

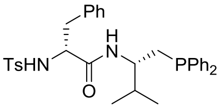


Hz, **C**$_{arom}$), 137.2 (**C**$_{arom}$), 133.2 (**C**H$_{arom}$), 132.9 (**C**H$_{arom}$), 132.6 (**C**H$_{arom}$), 129.5 (**C**H$_{arom}$), 128.9(**C**H$_{arom}$), 128.8 (**C**H$_{arom}$), 128.7 (**C**H$_{arom}$), 128.6 (**C**H$_{arom}$), 128.5 (**C**H$_{arom}$), 126.9 (**C**H$_{arom}$), 80.1 (O**C**(CH$_3$)$_3$), 55.9 (**C**HCO), 52.1 (d, $^2J_{CP}$ =14.9 Hz, **C**HCH(CH$_3$)$_2$), 38.1 (C**H$_2$**CHCO), 32.0 (**C**H(CH$_3$)$_2$), 31.8 (d, $^1J_{CP}$ = 7.3 Hz, **C**H$_2$CHCH(CH$_3$)$_2$), 28.4 (C(**C**H$_3$)$_3$), 19.2 (CH(**C**H$_3$)$_2$), 17.0 (CH(**C**H$_3$)$_2$). ^{31}P NMR (δ, ppm) (121.5 MHz, CDCl$_3$): -23.71. IR (ATR) cm^{-1}: 3280 (N-H st), 1685 (C=O st), 1630 (C=O st), 1540 (N-C=O st). HRMS (UPLC MS ESI+): Calculated for [C$_{31}$H$_{40}$N$_2$O$_3$P]$^+$: 519.2777 [(M+H)$^+$]; found: 519.2804. M.p.: 163-165 °C (hexanes/EtOAc). [α]$_D$^{20}: + 20.52 (*c*=0.65, CHCl$_3$).

(9*H*-fluoren-9-yl)methyl ((*R*)-1-(((*S*)-1-(diphenylphosphanyl)-3-methylbutan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl) carbamate (13j). Following the *General Procedure*, **13j** (205 mg, 0.32 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 2:8) as a white solid starting from (*S*)-1-(Diphenylphosphino)-3-methyl-2-butylamine (170 mg, 0.63 mmol), Fmoc-D-phenylalanine (265 mg, 0.69 mmol), HBTU (265 mg, 0.69 mmol) and *N*,*N*-diisopropylethylamine (0.2 mL, 1.26 mmol) in 51% yield. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.79 (d, *J* = 7.6 Hz, 2H, 2 x C**H**$_{arom}$), 7.62 – 7.50 (m, 2H, 2 x C**H**$_{arom}$), 7.46 – 7.11 (m, 19H, 19 x C**H**$_{arom}$), 5.54 (d, *J* = 9.3 Hz, 1H, N**H**), 4.95 (d, *J* = 8.1 Hz, 1H, N**H**), 4.50 – 4.29 (m, 2H, C**H$_2$**OCONH), 4.31 – 4.10 (m, 2H, C**H**CH$_2$OCONH and C**H**CO), 3.98 (qt, *J* = 9.3, 5.0 Hz, 1H, C**H**CH$_2$PPh$_2$), 3.12 – 2.81 (m, 2H, C**H$_2$**CHCO), 2.31 – 2.06 (m, 2H, C**H$_2$**PPh$_2$), 1.92 – 1.74 (m, 1H, C**H**(CH$_3$)$_2$), 0.74 (d, *J* = 6.9 Hz, 6H, CH(C**H$_3$**)$_2$). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 169.8 (NHCO), 156.0 (COOCH$_2$), 143.9 (C$_{arom}$), 143.8 (C$_{arom}$), 141.44 (C$_{arom}$), 141.42 (C$_{arom}$), 138.6 (d, $^1J_{CP}$ = 13.5 Hz, C$_{arom}$), 138.5 (d, $^1J_{CP}$ = 12.8 Hz, C$_{arom}$), 136.8 (C$_{arom}$), 132.9 (d, $^2J_{CP}$ = 19.3 Hz, CH$_{arom}$), 132.8 (d, $^2J_{CP}$ = 19.3 Hz, CH$_{arom}$), 129.4 (CH$_{arom}$), 128.9 (CH$_{arom}$), 128.83 (CH$_{arom}$), 128.80 (CH$_{arom}$), 128.74 (CH$_{arom}$), 128.66 (CH$_{arom}$), 128.56 (CH$_{arom}$), 127.85 (CH$_{arom}$), 127.84 (CH$_{arom}$), 127.19 (CH$_{arom}$), 127.16 (CH$_{arom}$), 127.0 (CH$_{arom}$), 125.11 (CH$_{arom}$), 125.06 (CH$_{arom}$) 120.1 (CH$_{arom}$), 66.9 (CH$_2$O), 56.4 (CHCO), 52.8 (d, $^2J_{CP}$ = 14.4 Hz, CHCH(CH$_3$)$_2$), 47.2 (CHCH$_2$O), 38.4 (CH$_2$CHCO), 32.4 (d, $^3J_{CP}$ = 8.6 Hz, CH(CH$_3$)$_2$), 31.5 (d, $^1J_{CP}$ = 15.0 Hz, CH$_2$CHCH(CH$_3$)$_2$), 18.8 (CH(CH$_3$)$_2$), 17.8 (CH(CH$_3$)$_2$). ^{31}P NMR (δ, ppm) (121.5 MHz, CDCl$_3$): -23.07. IR (ATR) cm^{-1}: 3297 (N-H st), 1690 (C=O st), 1647 (C=O st), 1528 (N-C=O st). HRMS (UPLC MS ESI+): Calculated for [C$_{41}$H$_{42}$N$_2$O$_3$P]$^+$: 641.2933 [(M+H)$^+$]; found: 641.2949. M.p.: 135-138 °C (hexanes/EtOAc). [α]$_D$^{20}: + 13.34 (*c*=1.33, CHCl$_3$).

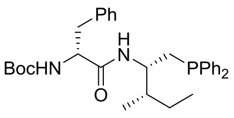


(*R*)-*N*-((*S*)-1-(diphenylphosphanyl)-3-methylbutan-2-yl)-2-((4-methylphenyl) sulfonamido)-3-phenylpropanamide (13k). Following the *General Procedure*, catalyst **13k** (340 mg, 0.59 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) as a white solid starting from (*S*)-1-(Diphenylphosphino)-3-methyl-2-butylamine (250 mg, 0.92 mmol), *N*-Tosyl-D-phenylalanine (320 mg, 1.01 mmol), HBTU (380 mg, 1.01 mmol) and NEt$_3$ (0.26 mL, 1.84 mmol) in 64% yield. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.52 –

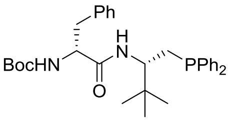


7.26 (m, 12H, 12 x C**H**$_{arom}$), 7.21 – 7.04 (m, 5H, 5 x C**H**$_{arom}$), 6.94 – 6.84 (m, 2H, 2 x C**H**$_{arom}$), 6.48 (d, *J* = 9.5 Hz, 1H, N**H**), 4.80 (d, *J* = 6.4 Hz, 1H, N**H**), 4.10 – 3.98 (m, 1H, C**H**CO), 3.87 – 3.78 (m, 1H, C**H**CH(CH$_3$)$_2$), 3.02 (dd, *J* = 14.1, 5.2 Hz, 1H, C**H$_a$**H$_b$CHCO), 2.67 (dd, *J* = 14.1, 8.4 Hz, 1H, CH$_a$**H$_b$**CHCO), 2.35 (s, 3H, C**H$_3$**), 2.22 (d, *J* = 7.2 Hz, 2H, C**H$_2$**PPh$_2$), 2.04 – 1.84 (m, *J* = 6.7 Hz, 1H, C**H**(CH$_3$)$_2$), 0.88 (d, *J* = 6.7 Hz, 6H, CH(C**H$_3$**)$_2$). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 169.4 (NHC**O**), 143.6 (**C**$_{arom}$), 138.6 (d, $^1J_{CP}$ = 13.8 Hz, **C**$_{arom}$), 138.5 (d, $^3J_{CP}$ = 12.8 Hz, **C**$_{arom}$), 135.6 (**C**$_{arom}$), 135.5 (**C**$_{arom}$), 132.9 (d, $^2J_{CP}$ = 20.1 Hz, **C**H$_{arom}$), 132.6 (d, $^2J_{CP}$ = 19.6 Hz, **C**H$_{arom}$), 129.7 (**C**H$_{arom}$), 129.1 (**C**H$_{arom}$), 128.8 (**C**H$_{arom}$), 128.7 (**C**H$_{arom}$), 128.58 (**C**H$_{arom}$), 128.55 (**C**H$_{arom}$), 128.46 (**C**H$_{arom}$), 127.0 (**C**H$_{arom}$), 126.9 (**C**H$_{arom}$), 58.0 (**C**HCO), 52.8 (d, $^2J_{CP}$ = 15.0 Hz, **C**HCH(CH$_3$)$_2$), 38.0 (**C**H$_2$CHCO), 32.5 (d, $^3J_{CP}$ = 8.3 Hz, **C**H(CH$_3$)$_2$), 31.5 (d, $^1J_{CP}$ = 14.7 Hz, **C**H$_2$CHCH(CH$_3$)$_2$), 21.5 (**C**H$_3$), 18.8 (CH(**C**H$_3$)$_2$), 17.4 (CH(**C**H$_3$)$_2$). ^{31}P NMR (δ, ppm) (121.5 MHz, CDCl$_3$): -22.9. IR (ATR) cm^{-1}: 1655 (C=O st), 1522 (N-C=O st). HRMS (UPLC MS ESI+): Calculated for [C$_{33}$H$_{38}$N$_2$O$_3$PS]$^+$: 573.2341 [(M+H)$^+$]; found: 573.2360. M.p.: 58-60 °C (hexanes/EtOAc). [α]$_D$^{20}: + 54.6 (*c*=1.00, CHCl$_3$).

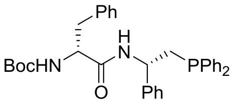
***tert*-butyl ((*R*)-1-(((2*S*,3*S*)-1-(diphenylphosphanyl)-3-methylpentan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (13l).** Following the *General Procedure*, catalyst **13l** (340 mg, 0.64 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 8:2) as a white solid starting from (2*S*,3*S*)-1-(Diphenylphosphino)-3-methylpentan-2-amine (225 mg, 0.79 mmol), Boc-D-phenylalanine (230 mg, 0.87 mmol), HBTU (330 mg, 0.87 mmol) and NEt$_3$ (0.22 mL, 1.58 mmol) in 81% yield. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.59 – 7.10 (m, 15H, 15 x C**H**$_{arom}$), 5.79 (d, *J* = 9.2 Hz, 1H, N**H**), 4.78 (s, 1H, N**H**), 4.29 – 4.12 (m, 1H, C**H**CO), 4.12 – 3.93 (m, 1H, C**H**CH$_2$PPh$_2$), 3.14 – 3.00 (m, 1H, C**H$_a$**H$_b$CHCO), 2.99 – 2.82 (m, 1H, CH$_a$**H$_b$**CHCO), 2.32 – 2.02 (m, 2H, C**H$_2$**PPh$_2$), 1.70 – 1.52 (m, 1H, C**H**CHCH$_2$PPh$_2$), 1.41 (s, 9H, OC(C**H$_3$**)$_3$), 1.38 – 1.22 (m, 1H, C**H$_a$**H$_b$CHCHCH$_2$PPh$_2$), 1.07 – 0.84 (m, 1H, CH$_a$**H$_b$**CHCHCH$_2$PPh$_2$), 0.88 – 0.68 (m, 6H, 2 x C**H$_3$**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 170.2 (NHC**O**), 155.2 (**C**OOC(CH$_3$)$_2$), 138.7 (d, $^1J_{CP}$ = 13.0 Hz, **C**$_{arom}$), 138.5 (d, $^1J_{CP}$ = 13.7 Hz, **C**$_{arom}$), 137.0 (**C**$_{arom}$), 132.9 (d, $^2J_{CP}$ = 19.6 Hz, **C**H$_{arom}$), 132.7 (d, $^1J_{CP}$ = 19.3 Hz, **C**H$_{arom}$), 129.2 (**C**H$_{arom}$), 128.8 (**C**H$_{arom}$), 128.7 (**C**H$_{arom}$), 128.6 (**C**H$_{arom}$), 128.5 (**C**H$_{arom}$), 128.4 (**C**H$_{arom}$), 126.8 (**C**H$_{arom}$), 79.9 (O**C**(CH$_3$)$_3$), 56.0 (**C**HCO), 51.5 (d, $^2J_{CP}$ = 14.8 Hz, **C**HCH$_2$PPh$_2$), 38.8 (d, $^3J_{CP}$ = 7.8 Hz, **C**HCHCH$_2$PPh$_2$), 38.3 (**C**H$_2$CHCO), 30.6 (d, $^1J_{CP}$ = 14.9 Hz, **C**H$_2$PPh$_2$), 28.3 (OC(**C**H$_3$)$_3$), 24.8 (**C**H$_2$**C**HCHCH$_2$PPh$_2$), 14.8 (**C**H$_3$CH), 11.6 (**C**H$_3$CH$_2$). ^{31}P NMR (δ, ppm) (121.5 MHz, CDCl$_3$): -23.0. IR (ATR) cm^{-1}: 3270 (N-H st), 1645 (C=O st). HRMS (UPLC MS ESI+): Calculated for [C$_{32}$H$_{42}$N$_2$O$_3$P]$^+$: 533.2933 [(M+H)$^+$]; found: 533.2952. M.p.: 133-135 °C (hexanes/EtOAc). [α]$_D$^{20}: + 25.4 (*c*=0.95, CHCl$_3$).



***tert*-butyl ((*R*)-1-(((*S*)-1-(diphenylphosphanyl)-3,3-dimethylbutan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (13m).** Following the *General Procedure*, catalyst **13m** (245 mg, 0.46 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 8:2) as a white solid starting from (*S*)-1-(Diphenylphosphino)-3,3-dimethylbutan-2-amine (235 mg, 0.82 mmol), Boc-D-phenylalanine (240 mg, 0.90 mmol), HBTU (340 mg, 0.90 mmol) and NEt$_3$ (0.29 mL, 1.64 mmol) in 56% yield. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.57 – 7.12 (m, 15H, 15 x C**H**$_{\text{arom}}$), 5.87 (d, J = 10.3 Hz, 1H, N**H**), 4.66 (s, 1H, N**H**), 4.30 – 4.18 (m, 1H, C**H**CO), 4.17 – 3.90 (m, 1H, C**H**CH$_2$PPh$_2$), 3.15 (dd, J = 14.2, 6.5 Hz, 1H, C**H$_a$**H$_b$CHCO), 3.01 – 2.85 (m, 1H, CH$_a$**H$_b$**CHCO), 2.32 (dt, J = 13.9, 2.9 Hz, 1H, C**H$_a$**H$_b$PPh$_2$), 2.11 – 1.94 (m, 1H, CH$_a$**H$_b$**PPh$_2$), 1.40 (s, 9H, OC(C**H$_3$**)$_3$), 0.80 (s, 9H, CH(C**H$_3$**)$_3$). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 170.4 (NH**C**O), 155.3 (**C**OOC(CH$_3$)$_3$), 139.2 (d, $^1J_{CP}$ = 13.9 Hz, **C**$_{\text{arom}}$), 138.5 (d, $^1J_{CP}$ = 14.6 Hz, **C**$_{\text{arom}}$), 137.2 (**C**$_{\text{arom}}$), 133.0 (d, $^2J_{CP}$ = 19.3 Hz, **C**H$_{\text{arom}}$), 132.6 (d, $^2J_{CP}$ = 19.2 Hz, **C**H$_{\text{arom}}$), 129.2 (**C**H$_{\text{arom}}$), 128.69 (**C**H$_{\text{arom}}$), 128.65 (**C**H$_{\text{arom}}$), 128.61 (**C**H$_{\text{arom}}$), 128.57 (**C**H$_{\text{arom}}$), 128.47 (**C**H$_{\text{arom}}$), 128.4 (**C**H$_{\text{arom}}$), 126.7 (**C**H$_{\text{arom}}$), 80.0 (O**C**(CH$_3$)$_3$), 56.0 (**C**HCO), 55.1 (d, $^2J_{CP}$ = 14.5 Hz, **C**HC(CH$_3$)$_3$), 37.8 (C**H$_2$**CHCO), 35.4 (d, $^3J_{CP}$ = 6.8 Hz, **C**(CH$_3$)$_3$), 30.3 (d, $^1J_{CP}$ = 14.0 Hz, **C**H$_2$CHC(CH$_3$)$_3$), 28.2 (OC(**C**H$_3$)$_3$), 26.0 (C(**C**H$_3$)$_3$). ^{31}P NMR (δ, ppm) (121.5 MHz, CDCl$_3$): -21.4. IR (ATR) cm^{-1}: 3300 (N-H st), 1685 (C=O st), 1652 (C=O st). HRMS (UPLC MS ESI+): Calculated for [C$_{32}$H$_{42}$N$_2$O$_3$P]$^+$: 533.2933 [(M+H)$^+$]; found: 533.2939. M.p.: 108-110 °C (hexanes/EtOAc). [α]$_D^{20}$: +29.6 (*c*=1.0, CHCl$_3$).

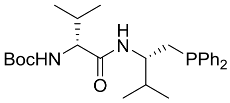


***tert*-butyl ((*R*)-1-(((*S*)-1-(diphenylphosphanyl)-1-phenylethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (13n).** Following the *General Procedure*, catalyst **13n** (214 mg, 0.39 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) as a white solid starting from (*S*)-2-Diphenylphosphino-1-phenylethylamine (165 mg, 0.54 mmol), Boc-D-phenylalanine (155 mg, 0.59 mmol), HBTU (225 mg, 0.59 mmol) and NEt$_3$ (0.15 mL, 1.08 mmol) in 72% yield. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.53 – 7.02 (m, 20H, 20 x C**H**$_{\text{arom}}$), 6.28 (d, J = 7.9 Hz, 1H, N**H**), 5.14 – 5.04 (m, 1H, C**H**CH$_2$PPh$_2$), 4.94 (s, 1H, N**H**), 4.32 – 4.17 (m, 1H, C**H**CO), 2.99 (d, J = 6.5 Hz, 2H, C**H$_2$**CHCO), 2.64 (dd, J = 13.9, 8.5 Hz, 1H, C**H$_a$**H$_b$PPh$_2$), 2.50 (dd, J = 13.9, 6.4 Hz, 1H, CH$_a$**H$_b$**PPh$_2$), 1.43 (s, 9H, OC(C**H$_3$**)$_3$). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 170.2 (NH**C**O), 155.4 (**C**OOC(CH$_3$)$_3$), 141.9 (d, $^3J_{CP}$ = 5.6 Hz, **C**$_{\text{arom}}$), 138.3 (d, $^1J_{CP}$ = 13.1 Hz, **C**$_{\text{arom}}$), 137.9 (d, $^1J_{CP}$ = 12.9 Hz, **C**$_{\text{arom}}$), 136.8 (**C**$_{\text{arom}}$), 133.0 (d, $^2J_{CP}$ = 20.2 Hz, **C**H$_{\text{arom}}$), 132.8 (d, $^2J_{CP}$ = 20.2 Hz, **C**H$_{\text{arom}}$), 129.4 (**C**H$_{\text{arom}}$), 129.1 (**C**H$_{\text{arom}}$), 128.83 (**C**H$_{\text{arom}}$), 128.80 (**C**H$_{\text{arom}}$), 128.73 (**C**H$_{\text{arom}}$), 128.66 (**C**H$_{\text{arom}}$), 128.57 (**C**H$_{\text{arom}}$), 127.6 (**C**H$_{\text{arom}}$), 126.9 (**C**H$_{\text{arom}}$), 126.5 (**C**H$_{\text{arom}}$), 80.2 (O**C**(CH$_3$)$_3$), 56.0 (**C**HCO), 51.9 (d, $^2J_{CP}$ = 18.0 Hz, **C**HCH$_2$PPh$_2$), 38.5 (C**H$_2$**CHCO), 36.4 (d, $^1J_{CP}$ = 16.0 Hz, **C**H$_2$PPh$_2$), 28.4 (OC(**C**H$_3$)$_3$). ^{31}P NMR (δ, ppm) (121.5 MHz, CDCl$_3$): -23.4. IR (ATR) cm^{-1}: 3278 (N-H st), 1688 (C=O st), 1651 (C=O st). HRMS (UPLC

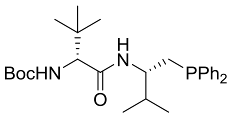


MS ESI+): Calculated for [$C_{34}H_{38}N_2O_3P$]$^+$: 553.2620 [(M+H)$^+$]; found: 553.2635. M.p.: 140-142 °C (hexanes/EtOAc). [α]$_D$^{20}: + 24.8 (*c*=0.75, CHCl$_3$).

***tert*-butyl ((*R*)-1-(((*S*)-1-(diphenylphosphanyl)-3-methylbutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl) carbamate (13o).** Following the *General Procedure*, catalyst **13o** (370 mg, 0.79 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 8:2) as a white solid starting from (*S*)-1-(Diphenylphosphino)-3-methyl-2-butylamine (330 mg, 1.22 mmol), Boc-D-Valine (290 mg, 1.34 mmol), HBTU (510 mg, 1.34 mmol) and NEt$_3$ (0.35 mL, 2.44 mmol) in 65% yield. ^{1}H NMR **(**δ, ppm) (300 MHz, CDCl$_3$): 7.50 – 7.28 (m, 10H, 10 x C**H**$_{arom}$), 5.78 (d, *J* = 9.2 Hz, 1H, N**H**), 4.86 (s, 1H, N**H**), 4.04 – 3.90 (m, 1H, C**H**CH$_2$PPh$_2$), 3.82 – 3.71 (m, 1H, C**H**CO), 2.31 – 2.09 (m, 3H, C**H$_2$**PPh$_2$ and C**H**(CH$_3$)$_2$), 2.07 – 1.87 (m, 1H, C**H**(CH$_3$)$_2$), 1.45 (s, 9H, OC(C**H$_3$**)$_3$), 0.99 – 0.80 (m, 12H, 4 x CH(C**H$_3$**)$_2$). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 170.8 (NH**C**O), 155.8 (**C**OOC(CH$_3$)$_3$), 138.5 (d, $^1J_{CP}$ = 13.7 Hz, **C**$_{arom}$), 138.4 (d, $^1J_{CP}$ = 12.6 Hz, **C**$_{arom}$), 133.0 (d, $^2J_{CP}$ = 19.4 Hz, **C**H$_{arom}$), 132.6 (d, $^2J_{CP}$ = 19.0 Hz, **C**H$_{arom}$), 128.8 (**C**H$_{arom}$), 128.7 (**C**H$_{arom}$), 128.60 (**C**H$_{arom}$), 128.56 (**C**H$_{arom}$), 128.52(**C**H$_{arom}$), 128.47 (**C**H$_{arom}$), 79.7 (O**C**(CH$_3$)$_3$), 60.2 (**C**HCO), 52.1 (d, $^2J_{CP}$ = 14.5 Hz, **C**HCH$_2$PPh$_2$), 32.1 (d, $^3J_{CP}$ = 8.4 Hz, **C**H(CH$_3$)$_3$), 31.8 (d, $^1J_{CP}$ = 8.4 Hz, **C**H$_2$PPh$_2$), 30.4 (**C**HCHCO), 28.4 (OC(**C**H$_3$)$_3$), 19.5 (**C**H$_3$), 19.0 (**C**H$_3$), 17.7 (**C**H$_3$), 17.4 (CH$_3$). ^{31}P NMR (δ, ppm) (121.5 MHz, CDCl$_3$): -23.7. IR (ATR) cm^{-1}: 3318 (N-H st), 1686 (C=O st), 1649 (C=O st), 1517 (N-C=O st). HRMS (UPLC MS ESI+): Calculated for [$C_{27}H_{40}N_2O_3P$]$^+$: 471.2777 [(M+H)$^+$]; found: 471.2798. M.p.: 76-79 °C (hexanes/EtOAc). [α]$_D$^{20}: + 28.8 (*c*=0.95, CHCl$_3$).



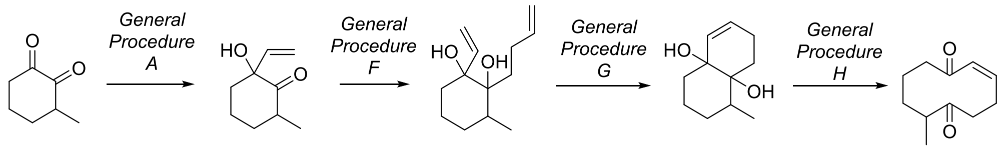
***tert*-butyl ((*R*)-1-(((*S*)-1-(diphenylphosphanyl)-3-methylbutan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl) carbamate (13p).** Following the *General Procedure*, catalyst **13p** (400 mg, 0.83 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a white solid starting from (*S*)-1-(Diphenylphosphino)-3-methyl-2-butylamine (300 mg, 1.10 mmol), Boc-D-*tert*-leucine (280 mg, 1.21 mmol), HBTU (459 mg, 1.21 mmol) and NEt$_3$ (0.31 mL, 2.2 mmol) in 76% yield. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.61 – 7.21 (m, 10H, 10 x C**H**$_{arom}$), 5.65 (d, *J* = 9.1 Hz, 1H, N**H**), 5.24 (d, *J* = 9.1 Hz, 1H, N**H**), 4.00 – 3.86 (m, 1H, C**H**CH(CH$_3$)$_2$), 3.71 (d, *J* = 9.1 Hz, 1H, C**H**CO), 2.39 – 2.10 (m, 2H, C**H$_2$**PPh$_2$), 2.06 – 1.93 (m, 1H, C**H**(CH$_3$)$_2$), 1.45 (s, 9H, OC(C**H$_3$**)$_3$), 0.98 (s, 9H, C(C**H$_3$**)$_3$), 0.87 (d, *J* = 6.8 Hz, 6H, CH(C**H$_3$**)$_2$). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 170.4 (NH**C**O), 155.9 (**C**OOC(CH$_3$)$_3$), 138.5 (d, $^1J_{CP}$ = 12.5 Hz, **C**$_{arom}$), 138.4 (d, $^1J_{CP}$ = 13.7 Hz, **C**$_{arom}$), 133.1 (d, $^2J_{CP}$ = 19.6 Hz, **C**H$_{arom}$), 132.7 (d, $^2J_{CP}$ = 18.9 Hz, **C**H$_{arom}$), 128.9 (**C**H$_{arom}$), 128.70 (**C**H$_{arom}$), 128.67 (**C**H$_{arom}$), 128.62 (**C**H$_{arom}$), 128.57 (**C**H$_{arom}$), 79.7 (O**C**(CH$_3$)$_3$), 63.0 (**C**HCO), 52.3 (d, $^2J_{CP}$ = 14.6 Hz, **C**HCH(CH$_3$)$_2$), 34.5 (**C**(CH$_3$)$_3$), 31.9 (d, $^1J_{CP}$ = 14.8 Hz, **C**H$_2$CHCH(CH$_3$)$_2$), 31.8 (d, $^3J_{CP}$ = 8.3 Hz, **C**H(CH$_3$)$_2$), 26.8 (C(**C**H$_3$)$_3$), 19.2 (CH(**C**H$_3$)$_2$), 17.5 (CH(**C**H$_3$)$_2$). ^{31}P NMR (δ, ppm) (121.5 MHz, CDCl$_3$): -23.7. IR (ATR) cm^{-1}: 1700 (C=O st), 1661 (C=O st), 1506 (N-C=O st).



HRMS (UPLC MS ESI+): Calculated for $[C_{28}H_{42}N_2O_3P]^+$: 485.2933 $[(M+H)^+]$; found: 485.2957. M.p.: 58-60 °C (hexanes/EtOAc). $[\alpha]_D^{20}$: + 6.90 (*c*=0.83, $CHCl_3$).

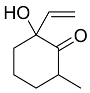
4. CATALYTIC ENANTIOSELECTIVE TRANSANNULAR MORITA-BAYLIS-HILLMAN REACTION IN THE TOTAL SYNTHESIS OF SESQUITERPENOID NATURAL PRODUCTS

4.1. Synthesis of racemic substrate 21



18a / 18b **19** **20** **21**

Substrate **21** was prepared following the same synthetic strategy employed for the synthesis of substrates **5a-i** and **11a-m**, starting from commercially available 3-methylcyclohexane-1,2-dione.



2-hydroxy-6-methyl-2-vinylcyclohexan-1-one (18). Following *General Procedure A* (see Section 2.1) compounds **18a** and **18b** were isolated by FC (hexanes/EtOAc gradient from 19:1 to 8:2) starting from 3-methylcyclohexane-1,2-dione (1.50 g, 12.0 mmol) and vinylmagnesium bromide (24.0 mL, 1.0 M in THF, 24.0 mmol) in 98% yield (d.r.:2:1).[23]

Yellow oil. Major diastereoisomer (**18a**): ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 6.10 (dd, *J* = 17.0, 10.5 Hz, 1H, C**H**=CH$_2$), 5.36 (dd, *J* = 17.0, 1.3 Hz, 1H, CH=CH$_{cis}$**H**$_{\mathbf{trans}}$), 5.16 (dd, *J* = 10.5, 1.3 Hz, 1H, CH=C**H**$_{\mathbf{cis}}$H$_{trans}$), 4.21 (s, 1H, O**H**), 2.74-2.55 (m, 1H, **H**-6), 2.26-2.15 (m, 1H, **H**$_{\mathbf{a}}$-3), 2.15-1.99 (m, 1H, **H**$_{\mathbf{b}}$-3), 1.90-1.54 (m, 3H, **H**-5 and **H**$_{\mathbf{a}}$-4), 1.44-1.23 (m, 1H, **H**$_{\mathbf{b}}$-4), 1.00 (d, *J* = 6.4 Hz, 3H, C**H**$_{\mathbf{3}}$). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 212.7 (**C**-1), 137.6 (**C**H=CH$_2$), 116.3 (CH=**C**H$_2$), 79.3 (**C**-2), 41.9 (**C**-6), 41.8 (**C**-3), 36.7 (**C**-5), 21.8 (**C**-4), 14.3 (**C**H$_3$). IR (ATR) cm^{-1}: 3479 (O-H st), 2934 (=C-H st), 1713 (C=O st). MS (EI, 70 eV) *m/z* (%): 154 (M$^+$, 6), 136 (24), 131 (3), 126 (5), 121 (36), 111 (61), 96 (38), 91 (14), 83 (100), 77

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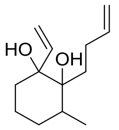
[23] Although substrate **21** can be synthesized applying the aforementioned synthesis to both diastereomers, higher efficiency was achieved starting from compound **18a**. Treatment of **18b** with 1M KOH in EtOH led to a 2:1 mixture of **18a**/**18b**, which could be separated by flash chromatography. Described compounds correspond to those obtained starting from product **18a**.

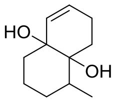
(13), 70 (80), 65 (7), 55 (79), 50 (3). HRMS (UPLC MS ESI+): Calculated for $[C_9H_{18}NO_2]^+$: 172.1338 $[(M+NH_4)^+]$; found: 172.1333.

Yellow oil. Minor diastereoisomer (**18b**): ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 6.19 (dd, *J* = 17.4, 10.8 Hz, 1H, C**H**=CH_2), 5.32 (dd, *J* = 17.4, 1.1 Hz, 1H, CH=$CH_{cis}\mathbf{H}_{\mathbf{trans}}$), 5.20 (dd, *J* = 10.8, 1.1 Hz, 1H, CH=$C\mathbf{H}_{\mathbf{cis}}H_{trans}$), 3.11-2.97 (m, 2H, **H**-6 and O**H**), 2.06-1.79 (m, 4H, **H**-3 and **H**-5), 1.76-1.60 (m, 1H, $\mathbf{H}_\mathbf{a}$-4), 1.51-1.35 (m, 1H, $\mathbf{H}_\mathbf{b}$-4), 1.02 (d, *J* = 6.8 Hz, 3H, $C\mathbf{H}_\mathbf{3}$). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 213.6 (**C**-1), 139.5 (**C**H=CH_2), 114.5 (**C**H_2=CH), 78.3 (**C**-2), 41.4 (**C**-6), 40.2 (**C**-3), 35.6 (**C**-5), 19.8 (**C**-4), 15.4 (**C**H_3). IR (ATR) cm^{-1}: 3479 (O-H st), 2934 (=C-H st), 1715 (C=O st). MS (EI, 70 eV) *m/z* (%): 154 (M^+, 6), 136 (M^+-H_2O, 32), 121 (39), 111 (55), 96 (34), 83 (100), 70 (81), 55 (84). HRMS (UPLC MS ESI+): Calculated for $[NaC_9H_{18}NO_2]^+$: 177.0892 $[(M+Na)^+]$; found: 177.0886.

2-(but-3-en-1-yl)-3-methyl-1-vinylcyclohexane-1,2-diol (19). Following *General Procedure F* (see Section 2.3), compound **19** (445 mg, 2.12 mmol) was isolated by FC (hexanes/EtOAc 9:1) starting from **18a** (650 mg, 4.22 mmol) and but-3-en-1-ylmagnesium bromide (12.7 mmol). Yield: 50%. White solid. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 6.24 (dd, *J* = 17.1, 10.9 Hz, 1H, C-1-C**H**=CH_2), 5.74 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H, CH_2C**H**=CH_2), 5.42 (dd, *J* = 17.1, 1.8 Hz, 1H, C-1-CH=$C\mathbf{H}_{\mathbf{cis}}H_{trans}$), 5.14 (dd, *J* = 10.9, 1.8 Hz, 1H, C-1-CH=$CH_{cis}\mathbf{H}_{\mathbf{trans}}$), 4.92 (m, 2H, $CH_2CH=C\mathbf{H}_\mathbf{2}$), 2.183* (s, 1H, O**H**), 2.176* (s, 1H, O**H**), 2.23-2.08 (m, 2H, $C\mathbf{H}_\mathbf{2}CH=CH_2$), 1.96-1.79 (m, 1H, $\mathbf{H}_\mathbf{a}$-6), 1.77-1.35 (m, 8H, $\mathbf{H}_\mathbf{b}$-6, **H**-4, **H**-5, C**H**CH_3 and C-2-$C\mathbf{H}_\mathbf{2}$), 0.98 (d, *J* = 6.7 Hz, 3H, $C\mathbf{H}_\mathbf{3}$). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 139.9 (C-1-**C**H=CH_2), 139.5 (CH_2**C**H=CH_2), 114.1 ($CH_2CH=\mathbf{C}H_2$), 113.5 (C-1-CH=**C**H_2), 77.7 (**C**-OH), 76.3 (**C**-OH), 37.6 (**C**-6), 37.0 (**C**HCH_3), 35.0 (**C**-4), 30.0 (C-2-**C**H_2), 29.6 (**C**$H_2CH=CH_2$), 21.9 (**C**-5), 15.9 (**C**H_3). IR (ATR) cm^{-1}: 3368 (O-H st), 2937 (=C-H st). MS (EI, 70 eV) *m/z* (%): 192 (M^+ - H_2O, 1), 174 (2), 159 (2), 150 (5), 138 (13), 125 (11), 109 (38), 95 (17), 83 (39), 67 (36), 55 (100). HRMS (UPLC MS ESI+): Calculated for $[C_{13}H_{22}O_2Na]^+$: 233.1518 $[(M+Na)^+]$; found: 233.1515. M.p.: 80-82 °C (hexanes/EtOAc).

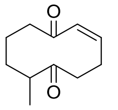


4-methyl-1,2,3,4,5,6-hexahydronaphthalene-4a,8a-diol (20). Following *General Procedure G* (see Section 2.4) compound **20** (695 mg, 3.82 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) starting from **19** (920 mg, 4.38 mmol) and 2nd generation Grubbs catalyst (56 mg, 0.066 mmol). Yield: 87%. Brown oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 5.87 (dt, *J* = 9.8, 3.6 Hz, 1H, **H**-7), 5.57 (dt, *J* = 9.8, 2.3 Hz, 1H, **H**-8), 2.35-2.07 (m, 2H, **H**-6), 2.04-1.88 (m, 1H, **H**-4), 1.88-1.62 (m, 4H, **H**-1 and **H**-5), 1.46* (s, 1H, O**H**), 1.56-1.36 (m, 4H, **H**-2 and **H**-3), 1.34 (s, 1H, O**H**), 0.88 (d, *J* = 6.9 Hz, 3H, $C\mathbf{H}_\mathbf{3}$). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 132.4 (**C**-8), 130.4 (**C**-7), 73.1 (**C**-OH), 69.4 (**C**-OH), 33.4 (**C**HCH_3), 32.2 (**C**-1), 29.5 (**C**-4), 25.3 (**C**-6), 22.4 (**C**-5), 20.2 (**C**-2), 14.6 (**C**H_3). IR (ATR) cm^{-1}: 3479 (O-H st), 2930 (=C-H



st). MS (EI, 70 eV) *m/z* (%): 164 (M^+ - H_2O, 26), 146 (34), 131 (100), 122 (12), 115 (25), 109 (26), 91 (31), 79 (24), 68 (13), 62 (2), 55 (10). HRMS (UPLC MS ESI+): Calculated for $[C_{11}H_{18}O_2Na]^+$: 205.1205 $[(M+Na)^+]$; found: 205.1209.

(*Z*)-7-methylcyclodec-2-ene-1,6-dione (21). Following *General Procedure H* (see Section 2.5)



compound **21** (325 mg, 1.80 mmol) was isolated by FC (hexanes/EtOAc 1:1) starting from **20** (340 mg, 1.87 mmol) and $Pb(OAc)_4$ (822 mg, 1.86 mmol). Yield: 96%. White solid. ^1H NMR (δ, ppm) (300 MHz, $CDCl_3$): 6.12 (d, *J* = 12.0 Hz, 1H, **H**-2), 5.83 (td, *J* = 12.0, 5.2 Hz, 1H, **H**-3), 3.39-3.18 (m, 1H, $\mathbf{H_a}$-4), 2.87 (dqd, *J* = 11.7, 7.0, 3.0 Hz, 1H, **H**-7), 2.73 (dt, *J* = 13.5, 4.2 Hz, 1H, $\mathbf{H_a}$-5), 2.52 (ddd, *J* = 14.5, 7.6, 2.6 Hz, 1H, $\mathbf{H_a}$-10), 2.36-2.11 (m, 3H, $\mathbf{H_b}$-4 and $\mathbf{H_b}$-5 and $\mathbf{H_b}$-10), 1.99 (dddd, *J* = 14.3, 11.7, 5.0, 2.9 Hz, 1H, $\mathbf{H_a}$-8), 1.91-1.67 (m, 2H, **H**-9), 1.36-1.18 (m, 1H, $\mathbf{H_b}$-8), 0.97 (d, *J* = 7.0 Hz, 3H, $C\mathbf{H_3}$). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 215.2 (**C**-6), 208.5 (**C**-1), 137.5 (**C**-3), 131.8 (**C**-2), 44.6 (**C**-10), 40.0 (**C**-5), 39.8 (**C**-7), 33.1 (**C**-8), 23.8 (**C**-4), 22.8 (**C**-9), 19.8 ($\mathbf{C}H_3$). IR (ATR) cm^{-1}: 2937 (=C-H st), 1699 (C=O st), 1675 (C=O st). MS (EI, 70 eV) *m/z* (%): 180 (M^+, 8), 162 (32), 152 (21), 131 (22), 119 (31), 109 (47), 95 (100), 82 (71), 68 (49), 55 (74). HRMS (UPLC MS ESI+): Calculated for $[C_{11}H_{16}O_2Na]^+$: 203.1048 $[(M+Na)^+]$; found: 203.1045. M.p.: 72-74 °C (hexanes/EtOAc).

4.2. Kinetic resolution procedure

To a cooled solution (5 °C) of substrate **21** (150 mg, 0.83 mmol) in anhydrous CCl_4 (8.0 mL) was added phenol (39.0 mg, 0.41 mmol) and catalyst **13p** (40.5 mg, 0.083 mmol) under inert atmosphere. The reaction mixture was stirred at this temperature for the indicated minutes in each case. The reaction was stopped by the addition of 30% aq. H_2O_2 (0.1 mL)[24] and stirred for a further 1 minute. Then the reaction mixture was diluted with CH_2Cl_2, washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and product **(8*S*,8a*S*)-22** and unreacted starting material **(*R*)-21** were isolated by flash column chromatography (hexanes/Et_2O 1:1).The racemic standards for HPLC separation conditions were prepared under the same reaction conditions, using 4-dimethylaminopyridine (DMAP) (10 mol%) as catalyst.

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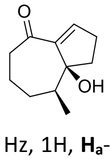
[24] H_2O_2 was employed due to its capability to oxidize the catalyst without producing any transformation in the reaction product and unreacted starting material.

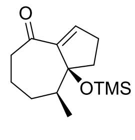
(8*S*, 8a*S*)-8a-hydroxy-8-methyl-2,5,6,7,8,8a-hexahydroazulen-4(1*H*)-one (22). Following the previously described procedure, adduct **22** was isolated by FC (hexanes/Et_2O 1:1) after 30 min as a single diastereomer (64.0 mg, 0.35 mmol). Yield: 42% (e.e.: 90%). White solid. ^1H NMR (δ, ppm) (500 MHz, $CDCl_3$): 6.90 (t, *J* = 2.6 Hz, 1H, **H**-3), 2.72 (t, *J* = 13.4 Hz, 1H, $\mathbf{H_a}$-5), 2.48 (m, 2H, $\mathbf{H_b}$-5 and $\mathbf{H_a}$-2), 2.40 – 2.30 (m, 1H, $\mathbf{H_b}$-2), 2.22 (ddd, *J* = 14.6, 8.4, 6.5 Hz, 1H, $\mathbf{H_a}$-1), 2.01 – 1.87 (m, 2H, $\mathbf{H_b}$-1 and $\mathbf{H_a}$-6), 1.87 – 1.78 (m, 1H, $\mathbf{H_a}$-7), 1.76 – 1.64 (m, 3H, $\mathbf{H_b}$-7 and **H**-8 and O**H**), 1.44 (m, 1H, $\mathbf{H_b}$-6), 1.07 (d, *J* = 6.4 Hz, 3H, C$\mathbf{H_3}$). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 201.4 (**C**-4), 149.5 (**C**-3a), 145.5 (**C**-3), 85.1 (**C**-8a), 43.3 (**C**-5), 43.1 (**C**-8), 40.9 (**C**-1), 34.5 (**C**-7), 28.8 (**C**-2), 24.0 (**C**-6), 17.8 (**C**H_3). IR (ATR) cm^{-1}: 3443 (O-H st), 2930 (=C-H st), 1670 (C=O st). MS (EI, 70 eV) *m/z* (%): 180 (M^+, 7), 162 (58), 147 (21), 137 (47), 129 (5), 119 (67), 105 (52), 91 (100), 83 (3), 77 (24), 65 (23), 55 (14). HRMS (UPLC MS ESI^+): Calculated for $[C_{11}H_{16}NaO_2]^+$: 203.1048 [$(M+Na)^+$]; found: 203.1044. M.p.: 58-60 °C (hexanes/EtOAc). The e.e. was improved up to a 98% by recrystallization in *n*-hexane (79% yield). The e.e. was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (97:03)]; flow rate 1.0 mL/min; τ_{major} = 16.6 min, τ_{minor} = 13.77 min (98% e.e.). $[\alpha]_D^{20}$: + 53.0 (*c*=0.77, $CHCl_3$).



Following the previously described procedure, unreacted starting material **(*R*)-21** was isolated (85.0 mg, 0.47 mmol) in 56% yield (e.e.: 76%) as a white solid. The e.e. was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (99:01)]; flow rate 1.0 mL/min; τ_{major} = 14.78 min, τ_{minor} = 14.07 min (90% e.e.). $[\alpha]_D^{20}$: +136.5 (*c*=5.60, $CHCl_3$).

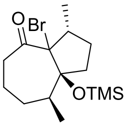
4.3. Synthesis of (-)-γ-gurjunene

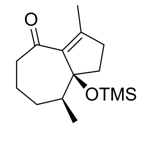
(8S,8aS)-8-methyl-8a-((trimethylsilyl)oxy)-2,5,6,7,8,8a-hexahydroazulen-4(1*H*)-one (23). Chlorotrimethylsilane (2.5 mL, 20.0 mmol) was added to a solution of alcohol **22** (901 mg, 5.0 mmol) in 1-(trimethylsilyl)imidazole (2.2 mL, 15.0 mmol) under argon and the resulting heterogeneous mixture was stirred at r.t. until consumption of starting material (1-2 h, TLC). Volatiles were thoroughly removed under a stream of air and the residue was purified by FC (petroleum ether/EtOAc 40:1) to afford pure compound **23** (669 mg, 2.7 mmol). Yield: 53%. Colorless oil. ^1H NMR (δ, ppm) (300 MHz, $CDCl_3$): 6.83 (t, *J* = 2.7 Hz, 1H, **H**-3), 2.66 (t, *J* = 13.3 Hz, 1H, $\mathbf{H_a}$-5), 2.52 – 2.26 (m, 3H, $\mathbf{H_b}$-5 and $\mathbf{H_a}$-2), 2.25 – 2.13 (m, 1H), 2.13 – 1.99 (m, 1H), 1.93 – 1.70 (m, 2H), 1.67 – 1.50 (m, 2H), 1.50 – 1.32 (m, 1H), 1.00 (d, *J* = 6.4 Hz, 3H, C$\mathbf{H_3}$), 0.06 (s,



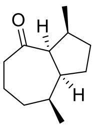
9H, SiC(C**H**$_3$)$_3$). 13C NMR (δ, ppm) (75.5 MHz, CDCl3): 201.6 (**C**-4), 150.2 (**C**-3a), 143.8 (**C**-3), 87.9 (**C**-8a), 44.8 (**C**-8), 43.4 (**C**-5), 39.0 (**C**-1), 34.9 (**C**-7), 29.2 (**C**-2), 24.2 (**C**-6), 18.0 (**C**H$_3$), 1.9 (SiC(**C**H$_3$)$_3$). IR (ATR) cm^{-1}: 2924 (=C-H st), 1681 (C=O st). MS (EI, 70 eV) *m/z* (%): 252 (M$^+$, 1), 237 (M$^+$ - CH$_3$, 100), 223 (7), 209 (28), 195 (12), 181 (21), 105 (12), 91 (26), 75 (100), 73 (77), 55 (14). HRMS (UPLC MS ESI+): Calculated for $[C_{12}H_{15}O]^+$: 163.1123 [(M-OSi(C(CH$_3$)$_3$)$^+$]; found: 163.1128. $[\alpha]_D^{20}$: + 211.28 (*c*=1.30, CHCl$_3$).

(3*R*,8*S*,8a*S*)-3a-bromo-3,8-dimethyl-8a-((trimethylsilyl)oxy)octahydroazulen-4(1*H*)-one (25). A solution of methyllithium (3.4 mL, 1.6 M in Et$_2$O, 5.4 mmol) was added dropwise to a suspension of copper(I) iodide (539 mg, 2.8 mmol) in dry THF (13 mL) at 0 °C and the mixture was stirred for 15 min. The resulting colorless solution was cooled to -78 °C and a solution of enone **23** (650 mg, 2.6 mmol) in THF (13 mL) was slowly added, followed by Et$_3$N (distilled from NaOH, 1.4 mL, 10.3 mmol) and TMSCl (distilled from CaH$_2$, 0.98 mL, 7.7 mmol). The reaction mixture was stirred at -78 °C until completion (30 min, TLC) and it was diluted with Et$_2$O (100 mL). While still cold, a saturated solution of NH$_4$Cl (50 mL) was added and the biphasic mixture was transferred to a separation funnel and vigorously shaken. The phases were separated and the organic layer was washed with sat. aq. NH$_4$Cl solution (4 × 50 mL) until disappearance of blue color from aq. phase. The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude silyl enol ether (870 mg, 2.6 mmol) was dissolved in dry THF (30 mL) and N-bromosuccinimide (481 mg, 2.7 mmol) was added in one portion at 0 °C. The colorless solution was stirred at 0 °C for 1 h and then poured onto sat. aq. NaHCO$_3$ (50 mL). The organic layer was diluted with petroleum ether (50 mL), the phases were separated and the aq. phase was extracted with petroleum ether (3 × 50 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and evaporated. The residue was purified by FC (petroleum ether/EtOAc 30:1) affording pure compound **25** (670 mg, 1.9 mmol). Yield: 75%. Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 2.88 – 2.70 (m, 2H, **H**-5), 2.62 – 2.47 (m, 1H), 2.47 – 2.28 (m, 2H), 2.12 – 1.97 (m, 1H), 1.92 – 1.74 (m, 2H), 1.73 – 1.61 (m, 1H), 1.59 – 1.35 (m, 3H), 1.12 (d, *J* = 6.3 Hz, 3H, C**H$_3$**), 0.92 (d, *J* = 6.8 Hz, 3H, C**H$_3$**), 0.12 (s, 9H, Si(C**H$_3$**)$_3$). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 203.4 (**C**-4), 91.8 (**C**-8a), 84.6 (**C**-3a), 42.3 (**C**-5), 41.4 (**C**H), 40.0 (**C**H), 35.1 (**C**-1), 32.8 (**C**-7), 27.7 (**C**-2), 22.0 (**C**-6), 18.8 (**C**H$_3$), 18.7 (**C**H$_3$), 2.3 (Si(**C**H$_3$)$_3$). IR (ATR) cm^{-1}: 1698 (C=O st), 1102 (C-Br st), 837 (C-Br st). MS (EI, 70 eV) *m/z* (%): 348 (M$^+$, 2), 309 (4), 267 (M$^+$-Br, 40), 197 (11), 177 (84), 159 (65), 135 (27), 121 (20), 107 (25), 93 (32), 73 (100), 55 (22). $[\alpha]_D^{20}$: -76.0 (*c*=1.00, CH$_2$Cl$_2$).

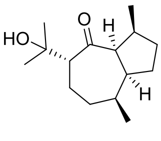




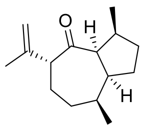
(8*S*,8a*S*)-3,8-dimethyl-8a-((trimethylsilyl)oxy)-2,5,6,7,8,8a-hexahydroazulen-4(1*H*)-one (26). Lithium bromide (3.33 g, 38.3 mmol) and lithium carbonate (2.83 g, 38.3 mmol) were sequentially added to a solution of compound **25** (665 mg, 1.9 mmol) in dry DMF (192 mL, 0.01 M) at rt. The heterogeneous mixture was heated to 130 °C for 14 h until full conversion was observed. After cooling, the mixture was diluted with EtOAc (200 mL) and aq. sat. $NaHCO_3$ (100 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with H_2O (75 mL) and brine (3 × 75 mL) dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was purified by FC (petroleum ether/EtOAc 40:1) to afford pure compound **26** (344 mg, 1.3 mmol). Yield: 68%. Yellow oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 2.75 – 2.59 (m, 1H, **H$_a$**-5), 2.49 – 2.28 (m, 3H, **H$_b$**-5 and **H**-2), 2.14 – 2.04 (m, 1H), 2.02 (s, 3H, C**H$_3$**-C), 1.94 – 1.68 (m, 3H), 1.64 – 1.53 (m, 2H), 1.50 – 1.35 (m, 1H), 0.98 (d, *J* = 6.3 Hz, 3H, C**H$_3$**-CH), 0.05 (s, 9H, Si(C**H$_3$**)$_3$). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 204.0 (**C**-4), 155.1 (**C**-3), 142.6 (**C**-3a), 89.6 (**C**-8a), 44.1 (**C**-5), 43.6 (**C**-8), 37.3 (**C**H$_2$), 36.2 (**C**H$_2$), 35.0 (**C**H$_2$), 24.2 (**C**-6), 18.3 (**C**H$_3$), 17.4 (**C**H$_3$), 1.8 (Si(**C**H$_3$)$_3$). IR (ATR) cm^{-1}: 1673 (C=O st). MS (EI, 70 eV) *m/z* (%): 266 (M$^+$, 9), 251 (83), 223 (99), 209 (30), 195 (38), 176 (47), 161 (23), 147 (16), 133 (53), 119 (28), 105 (59), 91 (44), 75 (100). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{15}H_{26}NaSiO_2]^+$: 289.1600 [(M+Na)$^+$]; found: 289.1601. $[\alpha]_D^{20}$: +148.4 (*c*=1.00, CH_2Cl_2).



(3*S*,3a*S*,8*S*,8a*S*)-3,8-dimethyloctahydroazulen-4(1*H*)-one (28). Palladium on carbon (10%, 36 mg) was added to a solution of enone **26** (340 mg, 1.3 mmol) in methanol (25 mL), and the heterogenous mixture was stirred under H_2 atmosphere (balloon pressure) for 12 h. The reaction mixture was filtered through celite and eluted with methanol. Volatiles were evaporated and the residue was purified by FC (petroleum ether/EtOAc 30:1) to afford compound **28** (143 mg, 0.8 mmol). Yield: 62%. Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 2.79 (t, *J* = 7.9 Hz, 1H, **H**-3a), 2.48 – 2.35 (m, 1H), 2.40 – 2.19 (m, 3H), 2.04 – 1.65 (m, 6H), 1.62 – 1.44 (m, 2H), 1.46 – 1.29 (m, 1H), 0.98 (d, *J* = 7.1 Hz, 3H, C**H$_3$**), 0.95 (d, *J* = 7.1 Hz, 3H, C**H$_3$**). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 215.2 (**C**-4), 62.3 (**C**-3a), 46.0 (**C**-8a), 44.9 (**C**-5), 38.6 (**C**-3), 35.3 (**C**-8), 32.5 (**C**H$_2$), 31.4 (**C**H$_2$), 25.6 (**C**H$_2$), 24.0 (C-8-C**H$_3$**), 22.7 (**C**-1), 16.2 (C-3-C**H$_3$**). IR (ATR) cm^{-1}: 1691 (C=O st). MS (EI, 70 eV) *m/z* (%): 180 (M$^+$, 3), 165 (3), 137 (7), 125 (42), 109 (37), 95 (19), 81 (100), 67 (87), 55 (73). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{12}H_{20}NaO]^+$: 203.1412 [(M+Na)$^+$]; found: 203.1414. $[\alpha]_D^{20}$: +90.6 (*c*=1.00, CH_2Cl_2).

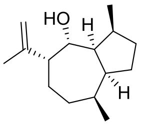


(3*S*,3a*S*,5*R*,8*S*,8a*S*)-5-(2-hydroxypropan-2-yl)-3,8-dimethyloctahydroazulen-4(1*H*)-one (33). A solution of butyllithium (1.2 mL, 1.6 M in hexanes, 1.9 mmol) was added dropwise to a solution of diisopropylamine (distilled from NaOH, 0.33 mL, 2.3 mmol) in dry THF (2 mL) at -78 °C. The reaction mixture was stirred at 0 °C for 30 min and the resulting colorless solution was cooled down to -78 °C. A solution of ketone **28** (140 mg, 0.8 mmol) in dry THF (3 mL) was then slowly added and stirred at -78 °C for 1 h, then it was warmed to -40 °C and a solution of $ZnCl_2$ (1.3 mL, 0.7 M in THF, 0.9 mmol) was added, followed by dry acetone (0.63 mL, 8.5 mmol). The mixture was stirred at that temperature for 60-90 min (full conversion was not achieved). The reaction was quenched by addition of aq. sat NH_4Cl (5 mL) and diluted with EtOAc (10 mL). The phases were separated and the aq. layer was extracted with EtOAc (4 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was purified by FC (petroleum ether/EtOAc 15:1 to 8:1) to afford compound **33** (111 mg, 0.5 mmol). Yield: 60%. Colorless oil. ^{1}H NMR (δ, ppm) (500 MHz, C_6D_6) (*denotes partially overlapped resonances): 3.31 (s, 1H, O**H**), 2.81 (td, *J* = 7.1, 2.4 Hz, 1H, **H**-3a), 2.30 (dd, *J* = 11.3, 2.4 Hz, 1H, **H**-5), 2.11 – 1.94 (m, 3H, **H**-3 and **H**$_a$-6 and **H**-8a), 1.87 – 1.76 (m, 1H, **H**$_a$-2), 1.72 – 1.51 (m, 4H, **H**-1 and **H**$_b$-2 and **H**-8), 1.46 – 1.28 (m, 3H, **H**$_b$-6 and **H**-7), 1.39* (s, 3H, C(C**H**$_3$)$_2$), 1.32* (s, 3H, C(C**H**$_3$)$_2$), 1.19 (d, *J* = 7.1 Hz, 3H, C-3-C**H**$_3$), 0.89 (d, *J* = 6.9 Hz, 3H, C-8-C**H**$_3$). ^{13}C NMR (δ, ppm) (126 MHz, C_6D_6): 217.8 (**C**-4), 72.1 (**C**-OH), 63.3 (**C**-5), 62.6 (**C**-3a), 46.8 (**C**-8a), 40.6 (**C**-3), 35.8 (**C**-8), 32.1 (**C**-2), 31.6 (**C**-7), 29.5 (**C**H$_3$), 28.14 (**C**-6), 28.10 (**C**H$_3$), 23.4 (C-8-**C**H$_3$), 22.4 (**C**-1), 16.5 (C-3-**C**H$_3$). IR (ATR) cm^{-1}: 3451 (O-H st), 2954 (C-H st), 1676 (C=O st), 1458 (C-O st), 1378 (C-O st). MS (EI, 70 eV) *m/z* (%): 220 (M^+ - H_2O, 2), 205 (2), 180 (9), 163 (12), 149 (9), 137 (16), 125 (26), 109 (74), 98 (77), 81 (100), 67 (71), 55 (53). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{15}H_{26}NaO_2]^+$: 261.1831 [$(M+Na)^+$]; found: 261.1838. $[\alpha]_D^{20}$: +68.5 (*c*=1.00, CH_2Cl_2).

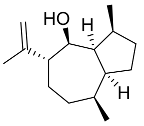


(3*S*,3a*S*,5*R*,8*S*,8a*S*)-3,8-dimethyl-5-(prop-1-en-2-yl)octahydroazulen-4(1*H*)-one (34). Burgess reagent (333 mg, 1.4 mmol) was added to a solution of alcohol **33** (111 mg, 0.5 mmol) in benzene (4 mL), and the solution was heated to 60 °C until full conversion (30 min, TLC). Volatiles were evaporated in vacuo and the residue was purified by FC (petroleum ether/EtOAc 30:1) to afford pure compound **34** (94 mg, 0.4 mmol). Yield: 92%. Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 4.85 (d, *J* = 1.6 Hz, 1H, C=C**H**$_a$H$_b$), 4.78 – 4.68 (m, 1H, C=CH$_a$**H**$_b$), 3.03 – 2.92 (m, 1H, **H**-3a), 2.84 (t, *J* = 7.0 Hz, 1H, **H**-5), 2.33 – 2.12 (m, 2H), 1.98 – 1.67 (m, 5H), 1.76* (s, 3H, C**H**$_3$C=), 1.65 – 1.56 (m, 1H), 1.55 – 1.41 (m, 2H), 0.99 – 0.90 (m, 6H, 2 x CHC**H**$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 214.2 (**C**-4), 144.7 (**C**=CH$_2$), 111.8 (CH=**C**H$_2$), 61.0 (**C**HCO), 60.8 (**C**HCO), 46.9 (**C**-8a), 39.4 (**C**H), 36.0 (**C**H), 31.8 (**C**H$_2$), 30.8 (**C**H$_2$), 30.6 (**C**H$_2$), 23.2 (**C**H$_3$), 22.8 (**C**-1), 22.3 (**C**H$_3$), 16.5 (C-3-**C**H$_3$). IR (ATR) cm^{-1}: 2953 (=C-H st), 2928 (=C-H st), 1696 (C=O st). MS (EI, 70 eV) *m/z* (%): 220 (M^+, 1), 205 (2), 177 (1), 163 (13), 149 (9), 137 (7), 121 (13), 109 (49), 95 (16), 81 (74), 67 (100), 55 (53). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{15}H_{24}NaO]^+$: 243.1725 [$(M+Na)^+$]; found: 243.1727. $[\alpha]_D^{20}$: +151.7 (*c*=1.00, CH_2Cl_2).

(3*S*,3a*S*,5*R*,8*S*,8a*S*)-3,8-dimethyl-5-(prop-1-en-2-yl)decahydroazulen-4-ol (35a/35b). A solution of DIBAL-H (1.3 mL, 1 M in CH_2Cl_2, 1.3 mmol) was added to a solution of ketone **34** (94 mg, 0.4 mmol) in dry DCM (4 mL) at -78 °C. The mixture was stirred at that temperature until full conversion (30 min, TLC). The reaction was quenched by addition of water (5 mL) and 1 M HCl (approx. 1 mL) and diluted with CH_2Cl_2 (5 mL). The phases were separated and the aq. phase was extracted with DCM (4 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. The resulting residue was determined to be a 1:1 mixture of diastereomeric alcohols (^{1}H-NMR), which could be separated by FC (toluene) to afford pure products **35a** (45 mg, 0.2 mmol) and **35b** (46 mg, 0.2 mmol) in overall 96% yield.

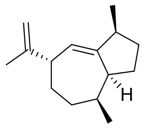


Product **35a**: 47% yield. Colorless oil. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$): 4.88 (s, 1H, C=C**H_a**H_b), 4.80 (s, 1H, C=CH_a**H_b**), 3.89 (ddd, *J* = 9.7, 4.8, 3.2 Hz, 1H), 2.75 – 2.63 (m, 2H), 2.42 – 2.33 (m, 1H), 2.32 – 2.22 (m, 1H), 1.82 – 1.78 (m, 1H), 1.76 (d, *J* = 3.4 Hz, 1H), 1.74 (s, 3H, C**H_3**C=CH_2), 1.72 – 1.66 (m, 1H), 1.65 – 1.59 (m, 1H), 1.58 – 1.49 (m, 2H), 1.49 – 1.31 (m, 4H), 1.17 (d, *J* = 7.4 Hz, 3H, C**H_3**CH), 0.92 (d, *J* = 7.0 Hz, 3H, C**H_3**CH). ^{13}C NMR (126 MHz, $CDCl_3$) (δ, ppm): 148.9 (**C**=CH_2), 112.6 (CH=**C**H_2), 74.8 (**C**-4), 51.5 (**C**H), 47.6 (**C**H), 45.3 (**C**H), 38.1 (**C**H), 35.9 (**C**H), 34.7 (**C**H_2), 34.3 (**C**H_2), 30.8 (**C**H_2), 25.4 (**C**H_2), 23.8 (**C**H_3), 20.1 (**C**H_3), 19.2 (**C**H_3). IR (ATR) cm^{-1}: 3479 (O-H st), 2951 (C-H st), 2922 (C-H st), 1455 (O-H δ). MS (EI, 70 eV) *m/z* (%): 222 (M^+, 2), 207 (22), 204 (M^+ - H_2O, 19), 189 (22), 161 (21), 149 (25), 139 (36), 123 (29), 109 (100), 93 (40), 81 (67), 67 (44), 55 (39). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{15}H_{25}]^+$: 205.1956 [$(M-H_2O+H)^+$]; found: 205.1949. $[\alpha]_D^{20}$: +18.5 (*c*=0.3, CH_2Cl_2).



Product **35b**: 49% yield. Colorless oil. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$): 4.76 (s, 1H, C=C**H_a**H_b), 4.74 (s, 1H, C=CH_a**H_b**), 3.92 (broad signal, s, 1H, **H**-4), 2.39 – 2.28 (m, 1H), 2.25 (td, *J* = 8.4, 2.4 Hz, 1H), 2.22 – 2.08 (m, 2H), 2.04 (d, *J* = 12.0 Hz, 1H), 2.00 – 1.86 (m, 1H), 1.80 (s, 3H, C**H_3**C=CH_2), 1.77 – 1.67 (m, 1H), 1.68 – 1.54 (m, 2H), 1.50 (s, 1H, O**H**), 1.49 – 1.38 (m, 3H), 1.33 – 1.21 (m, 1H), 1.05 (d, *J* = 7.1 Hz, 3H, C**H_3**CH), 0.91 (d, *J* = 7.0 Hz, 3H, C**H_3**CH).^{13}C NMR (126 MHz, $CDCl_3$) (δ, ppm): 151.2 (**C**=CH_2), 109.8 (C=**C**H_2), 72.7 (**C**-4), 51.7 (**C**H), 50.3 (**C**H), 48.7 (**C**H), 38.8 (**C**H), 34.0 (**C**H), 33.4 (**C**H_2), 31.8 (**C**H_2), 27.2 (**C**H_2), 24.4 (**C**H_3), 23.7 (**C**H_2), 23.3 (**C**H_3), 16.6 (C-3-**C**H_3). IR (ATR) cm^{-1}: 3472 (O-H st), 2950 (C-H st), 1455 (O-H δ). MS (EI, 70 eV) *m/z* (%): 222 (M^+, 1), 204 (M^+ - H_2O, 18), 189 (18), 161 (23), 149 (18), 139 (30), 123 (23), 109 (100), 93 (39), 81

(72), 67 (47), 55 (45). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{15}H_{25}]^+$: 205.1956 $[(M-H_2O+H)^+]$; found: 205.1956. $[\alpha]_D^{20}$: -41.2 (*c*=0.3, CH_2Cl_2).



(-)-γ-gurjunene (36).[25,26] Burgess reagent (95 mg, 0.4 mmol) was added to a solution of alcohol **35a** (22 mg, 0.1 mmol) in chloroform (1 mL) and the solution was heated to 60 °C until full conversion (1 h, TLC). The solution was filtered through a pad of silica gel and eluted with pentane. Solvents were evaporated below room temperature due to the volatility of the target product. The residue was purified by column chromatography using silver nitrate-impregnated silica gel[27,28](pentane as eluent for column chromatography; pentane/Et_2O 20:1 for TLC monitoring) to afford pure γ-gurjunene **36** (12 mg, 0.06 mmol). Yield: 61%. Colorless oil. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 5.39 (ddd, *J* = 5.2, 2.4, 2.4 Hz, 1H, **H**-6), 4.78 – 4.73 (m, 2H, C=C$\mathbf{H_2}$), 2.95 – 2.86 (m, 1H, **H**-7), 2.85 – 2.78 (m, 1H, **H**-1), 2.54 – 2.47 (m, 1H, **H**-4), 1.95 – 1.89 (m, 1H, **H**-10), 1.87 – 1.76 (m, 2H, $\mathbf{H_a}$-8 and $\mathbf{H_a}$-9), 1.75 – 1.66 (m, 3H, $\mathbf{H_a}$-2, $\mathbf{H_a}$-3, and $\mathbf{H_b}$-8), 1.72* (s, 3H, C$\mathbf{H_3}$C=), 1.58 – 1.55 (m, 1H, $\mathbf{H_b}$-2), 1.43 – 1.35 (m, 1H, $\mathbf{H_b}$-9), 1.25 – 1.19 (m, 1H, $\mathbf{H_b}$-3), 1.01 (d, *J* = 6.9 Hz, 3H, C4-C$\mathbf{H_3}$), 0.84 (d, *J* = 7.0 Hz, 3H, C10-C$\mathbf{H_3}$). ^{13}C NMR (126 MHz, $CDCl_3$) (δ, ppm): 150.7 (**C**-5), 147.2 (**C**=CH_2), 122.3 (**C**-6), 110.7 (C=**C**H_2), 47.6 (**C**-7), 45.9 (**C**-1), 41.2 (**C**-4), 33.93 (**C**-10), 33.90 (**C**-3), 33.4 (**C**-9), 30.1 (**C**-2), 25.8 (**C**-8), 21.5 (**C**H_3C=), 19.8 (C-4-**C**H_3), 15.7 (C-10-**C**H_3). $[\alpha]_D^{20}$: -121.1 (*c*=0.1, $CHCl_3$).

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[25] Spectral data matches reported values for γ-gurjunene: König, G. M.; Wright, A. D. *J. Org. Chem.* **1997**, *62*, 3837.

[26] Absolute configuration of the product was confirmed by comparison of optical rotation values. Measured value for (-)-γ-gurjunene $[\alpha]_D^{20}$: -121.1 (*c*=0.1, $CHCl_3$); reported value for (+)-γ-gurjunene $[\alpha]_D^{20}$: +147.0 (*c*=0.1, $CHCl_3$) Ehret, C.; Ourisson, G. *Tetrahedron*, **1969**, *25*, 1785.

[27] (a) Williams, C. M.; Mander, L. N. *Tetrahedron,* **2001**, *57*, 425. (b) Li, T.-S. ; Li, J.-T. ; Li, H.-Z. *J. Chromatogr. A*, **1995**, *715*, 372.

[28] *Preparation of silica gel impregnated with silver nitrate*: An aqueous solution of silver nitrate (5.5 g in 30 mL water) was mixed with 50 g silica gel. The mixture was ground for 5 min in a mortar and the wet solid was dried in an oven at 150 °C for 1 h and then in a vacuum desiccator over phosphorus pentoxide overnight. The solid was protected from light by wrapping the container with aluminum foil.

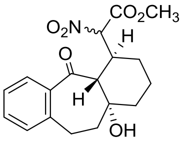
Preparation of TLC plates impregnated with silver nitrate: Regular TLC plates were developed once with an aqueous solution of silver nitrate (1.0 g in 10 mL water) and reactivated in an oven at 110 °C for 1-2 h. The resulting TLC plates were protected from light with aluminum foil.

5. ORGANOCATALYTIC ENANTIOSELECTIVE MICHAEL INITIATED TRANSANNULAR ALDOL REACTION

Catalysts **39a** and **39b** were commercially available and used without further purification. Catalysts **39c-k** were prepared following procedures previously reported in the literature.[29] *Tert*-butylnitroacetate and benzylnitroacetate were synthesized following procedures described in the literature.[30]

5.1. Synthesis of adducts 38a-o

General Procedure K: To a solution of the corresponding substrate (1.0 equiv.) in anhydrous toluene (0.25 mmol/mL) was added catalyst **39h** (0.1 equiv.) and nucleophile (3.0 equiv.) under inert atmosphere. The reaction mixture was stirred at 25 °C until consumption of the starting material was observed by TLC. The reaction mixture was concentrated under reduced pressure and the product was isolated by flash column chromatography (FC) with the indicated eluent in each case. The racemic standards for HPLC separation conditions were prepared under the same reaction conditions, using 1-(3,5-bis(trifluoromethyl)phenyl) -3-(2-(dimethylamino)ethyl)thiourea as catalyst.[31]



methyl 2-((4*S*,4a*R*,11a*R*)-11a-hydroxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo [*a,d*][7]annulen-4-yl)-2-nitroacetate (38a). Following the *General Procedure K*, compound **38a** (53.0 mg, 0.15 mmol) was isolated by FC (DCM/MeOH 0.3%) after 40h starting from **11f** (35.0 mg, 0.15 mmol) and methyl nitroacetate (42 µL, 0.45 mmol) in the presence of catalyst **39h** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 99% (d.r.: 1.8:1) (e.e.: 90/90%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, CDCl$_3$) (*denotes minor diastereomer): 7.72-7.61 (m, 1H, C**H**$_{arom}$), 7.44-7.34 (m, 1H, C**H**$_{arom}$), 7.34-7.17 (m, 2H, 2 x C**H**$_{arom}$), 5.50 (d, *J* = 3.6, 1.7 Hz, 1H, C**H**NO$_2$), 5.24* (d, *J* = 3.4, 1.7 Hz, 1H, C**H**NO$_2$), 3.84 (s, 3H, COOC**H$_3$**), 3.56* (s, 3H, COOC**H$_3$**), 3.39* (t, *J* = 11.8 Hz, 1H, **H**-4), 3.27 (t, *J* = 11.6 Hz, 1H, **H**-4), 3.14* (d, *J* = 11.3 Hz, 1H, **H**-4a), 3.09-2.92 (m, 3H, **H**-4a and **H**-10), 2.35-2.21 (m, 1H, **H$_a$**-11), 2.08-1.77 (m, 3H, , **H$_a$**-2, **H$_a$**-3 and O**H**), 1.79-1.60 (m, 4H, **H$_b$**-2, **H$_b$**-11 and **H**-1), 1.51-1.32 (m, 1H, **H$_b$**-3), 1.32-1.17* (m, 1H, **H$_b$**-3). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$) (*denotes minor diastereomer): 203.93 (**C**-

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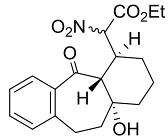
[29] (a) Iriarte, I.; Olaizola, O.; Vera, S.; Gamboa, I.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2017**, *56*, 8860. (b) Baran, R.; Ververkov′a, E.; Skvorcová, A.; Sebesta, R. *Org. Biomol. Chem.* **2013**, *11*, 7705. (c) Mailhol, D.; Duque, M. S.; Raimondi, W.; Bonne, D.; Constantieux, T.; Coquerel, Y.; Rodriguez, J. *Adv. Synth. Catal.* **2012**, *354*, 3523. (d) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028. (e) Malerich, J. P.; Hagiharam, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416. (f) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. (g) McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367. (h) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett*, **2005**, *4*, 603.

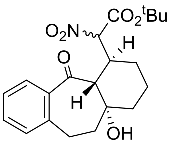
[30] Sylvain, C.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **1999**, *40*, 875.

[31] Achiral thiourea was prepared following a literature reported methodology: Dolan, N.; Gavin, D. P.; Eshwika, A.; Kavanagh, K.; McGinley, J.; Stephens, J. C. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 630.

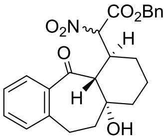
5), 203.88* (**C**-5), 164.5 (**C**O$_2$CH$_3$), 164.4* (**C**O$_2$CH$_3$), 143.4 (**C**$_{arom}$), 139.4 (**C**$_{arom}$), 131.99 (**C**H$_{arom}$), 131.88* (**C**H$_{arom}$), 130.26 (**C**H$_{arom}$), 130.22* (**C**H$_{arom}$), 128.6 (**C**H$_{arom}$), 128.4* (**C**H$_{arom}$), 126.8 (**C**H$_{arom}$), 126.7* (**C**H$_{arom}$), 88.5 (**C**HNO$_2$), 87.9* (**C**HNO$_2$), 73.5 (**C**-11a), 73.2* (**C**-11a), 57.8* (**C**-4a), 57.7 (**C**-4a), 53.4 (O**C**H$_3$), 52.9* (O**C**H$_3$), 44.2 (**C**-11), 44.1* (**C**-11), 36.9 (**C**-1), 36.7* (**C**-1), 35.3 (**C**-4), 35.2* (**C**-4), 31.0 (**C**-10), 26.1* (**C**-3), 25.2 (**C**-3), 20.7 (**C**-2), 20.5* (**C**-2). IR (ATR) cm^{-1}: 3500 (O-H st), 1757 (C=O st), 1673 (C=O st), 1556 (N-O st), 1250 (N-O st). MS (EI, 70 eV) *m/z* (%): 329 (M$^+$ - H$_2$O, 3), 282 (17), 167 (14), 250 (33), 221 (32), 209 (23), 165 (19), 133 (100), 115 (26), 103 (26), 91 (37), 77 (27), 55 (15). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{18}$H$_{21}$NNaO$_6$]$^+$: 370.1267 [(M+Na)$^+$]; found: 370.1268.The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major1} = 50.83 min, τ_{minor1} = 127.06 min (90% e.e.); τ_{major2} = 66.98 min, τ_{minor2} = 90.34 min (90% e.e.).

ethyl 2-((4*S*,4a*R*,11a*R*)-11a-hydroxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo [*a,d*][7]annulen-4-yl)-2-nitroacetate (38b). Following the *General Procedure K*, compound **38b** (50.4 mg, 0.14 mmol) was isolated by FC (DCM/MeOH 0.3%) after 65h starting from **11f** (34.9 mg, 0.15 mmol) and ethyl nitroacetate (50 µL, 0.45 mmol) in the presence of catalyst **39h** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 91% (d.r.: 1.6:1) (e.e.: 92/92%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes minor diastereomer): 7.68 (t, *J* = 6.7 Hz, 1H, C**H**$_{arom}$), 7.43-7.33 (m, 1H, C**H**$_{arom}$), 7.34-7.17 (m, 2H, C**H**$_{arom}$), 5.48 (d, *J* = 3.4 Hz, 1H, C**H**NO$_2$), 5.21* (d, *J* = 3.2 Hz, 1H, C**H**NO$_2$), 4.29 (q, *J* = 7.0 Hz, 2H, OC**H$_2$**CH$_3$), 4.02* (q, *J* = 7.0 Hz, 2H, OC**H$_2$**CH$_3$), 3.46-3.33 (m, 1H, **H**-4), 3.32-3.20* (m, 1H, **H**-4), 3.18-2.92 (m, 3H, **H**-4a and **H**-10), 2.34-2.19 (m, 1H), 2.12-1.80 (m, 3H), 1.80-1.63 (m, 4H), 1.49-1.36 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H$_3$**), 0.93* (t, *J* = 7.0 Hz, 3H, OCH$_2$C**H$_3$**). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$) (*denotes minor diastereomer): 203.9 (**C**-5), 203.8* (**C**-5), 163.95* (**C**O$_2$Et), 163.89 (**C**O$_2$Et), 143.5* (**C**$_{arom}$), 143.4 (**C**$_{arom}$), 139.39 (**C**$_{arom}$), 139.36* (**C**$_{arom}$), 131.92 (**C**H$_{arom}$), 131.92 (**C**H$_{arom}$), 130.24* (**C**H$_{arom}$), 130.18 (**C**H$_{arom}$), 128.51 (**C**H$_{arom}$), 128.48* (**C**H$_{arom}$), 126.75 (**C**H$_{arom}$), 126.66* (**C**H$_{arom}$), 88.62 (**C**HNO$_2$), 87.68* (**C**HNO$_2$), 73.4 (**C**-11a), 73.2* (**C**-11a), 62.9 (O**C**H$_2$CH$_3$), 62.5* (O**C**H$_2$CH$_3$), 57.8* (**C**-4a), 57.7 (**C**-4a), 44.1 (**C**-11), 44.0* (**C**-11), 36.9 (**C**-1), 36.7* (**C**-1), 35.2 (**C**-4), 35.0* (**C**-4), 31.06* (**C**-10), 30.99 (**C**-10), 25.9* (**C**-3), 25.1 (**C**-3), 20.7 (**C**-2), 20.4* (**C**-2), 14.1 (OCH$_2$**C**H$_3$), 13.6* (OCH$_2$**C**H$_3$). IR (ATR) cm^{-1}: 3522 (O-H st), 1748 (C=O st), 1674 (C=O st), 1554 (N-O st). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{19}$H$_{23}$NNaO$_6$]$^+$: 384.1423 [(M+Na)$^+$]; found: 384.1426. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major1} = 15.28 min, τ_{minor1} = 48.12 min (92% e.e.); τ_{major2} = 19.98 min, τ_{minor2} = 25.05 min (92% e.e.).



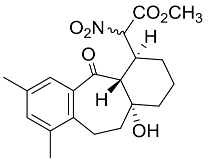


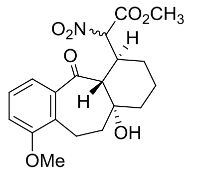
***tert*-butyl-2-((4*S*,4a*R*,11a*R*)-11a-hydroxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a,d*][7]annulen-4-yl)-2-nitroacetate (38c).** Following the *General Procedure K*, compound **38c** (50.6 mg, 0.13 mmol) was isolated by FC (DCM/MeOH 0.3%) after 7d starting from **11f** (34.5 mg, 0.15 mmol) and *tert*-butyl nitroacetate (72.0 mg, 0.45 mmol) in the presence of catalyst **39h** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 86% (d.r.: 1.7:1) (e.e.: 90/90%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes minor diastereomer): 7.70 (t, *J* = 6.4 Hz, 1H, C$\mathbf{H}_{\mathbf{arom}}$), 7.45-7.34 (m, 1H, C$\mathbf{H}_{\mathbf{arom}}$), 7.34-7.28 (m, 1H, C$\mathbf{H}_{\mathbf{arom}}$), 7.24-7.16 (m, 1H, C$\mathbf{H}_{\mathbf{arom}}$), 5.40 (d, *J* = 3.4 Hz, 1H, C**H**NO$_2$), 5.08* (d, *J* = 3.1 Hz, 1H, C**H**NO$_2$), 3.40-3.26 (m, 1H, **H**-4a), 3.26-3.14 (m, 1H, **H**-4), 3.04-2.92 (m, 2H, **H**-10), 2.33-2.21 (m, 1H), 2.16-1.98 (m, 1H), 1.94-1.60 (m, 6H), 1.50 (s, 9H, C(C$\mathbf{H_3}$)$_3$), 1.44-1.20 (m, 1H), 1.16* (s, 9H, C(C$\mathbf{H_3}$)$_3$). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$) (*denotes minor diastereomer): 204.1* (**C**-5), 203.6 (**C**-5), 162.9* (**C**O$_2{}^t$Bu), 162.8 (**C**O$_2{}^t$Bu), 143.8 (**C**$_{\mathrm{arom}}$), 143.3* (**C**$_{\mathrm{arom}}$), 139.5 (**C**$_{\mathrm{arom}}$), 139.4* (**C**$_{\mathrm{arom}}$), 132.0 (**C**H$_{\mathrm{arom}}$), 131.9* (**C**H$_{\mathrm{arom}}$), 130.3 (**C**H$_{\mathrm{arom}}$), 130.2* (**C**H$_{\mathrm{arom}}$), 128.6* (**C**H$_{\mathrm{arom}}$), 128.5 (**C**H$_{\mathrm{arom}}$), 126.7 (**C**H$_{\mathrm{arom}}$), 89.1 (**C**HNO$_2$), 88.0* (**C**HNO$_2$), 84.6 (**C**(CH$_3$)$_3$), 84.4* (**C**(CH$_3$)$_3$), 73.5* (**C**-11a), 73.2 (**C**-11a), 57.9 (**C**-4a), 57.8* (**C**-4a), 44.2* (**C**-11), 44.1 (**C**-11), 36.9* (**C**-1), 36.8 (**C**-1), 35.2* (**C**-4), 34.8 (**C**-4), 31.2 (**C**-10), 31.0* (**C**-10), 28.0* (**C**H$_3$), 27.6 (**C**H$_3$), 25.5 (**C**-3), 25.0* (**C**-3), 20.8* (**C**-2), 20.5 (**C**-2). IR (ATR) cm^{-1}: 3479 (O-H st), 1744 (C=O st), 1672 (C=O st), 1552 (N-O st). MS (EI, 70 eV) *m/z* (%): 355 (1), 281 (14), 207 (88), 181 (21), 165 (24), 147 (18), 133 (100), 107 (67), 91 (76), 77 (69), 55 (42). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{21}$H$_{27}$NNaO$_6$]$^+$: 412.1736 [(M+Na)$^+$]; found: 412.1736. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major1} = 10.97 min, τ_{minor1} = 30.52 min (90% e.e.); τ_{major2} = 13.68 min, τ_{minor2} = 15.76 min (90% e.e.).



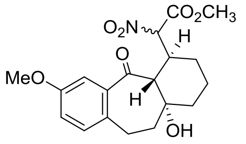
benzyl-2-((4*S*,4a*R*,11a*R*)-11a-hydroxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a,d*][7]annulen-4-yl)-2-nitroacetate (38d). Following the *General Procedure K*, compound **38d** (47.8 mg, 0.11 mmol) was isolated by FC (hexanes/Et$_2$O gradient from 2:1 to 1:2) after 65h starting from **11f** (34.6 mg, 0.15 mmol) and benzyl nitroacetate (88.0 mg, 0.45 mmol) in the presence of catalyst **39h** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 74% (d.r.: 1.6:1) (e.e.: 88/88%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes minor diastereomer): 7.74-7.61 (m, 1H, C$\mathbf{H}_{\mathbf{arom}}$), 7.47-7.17 (m, 7H, 7 x C$\mathbf{H}_{\mathbf{arom}}$), 7.07-7.01 (m, 1H, C$\mathbf{H}_{\mathbf{arom}}$), 5.54* (d, *J* = 3.6 Hz, 1H, C**H**NO$_2$), 5.30-5.22 (m, 3H, C**H**NO$_2$ and OC$\mathbf{H_2}$Ph), 5.13* (d, *J* = 11.9 Hz, 1H, OC$\mathbf{H_a}$H$_b$Ph), 4.89* (d, *J* = 11.9 Hz, 1H, OCH$_a\mathbf{H_b}$Ph), 3.42-3.21 (m, 1H, **H**-4), 3.08-2.93 (m, 2H, **H**-10), 2.93-2.67 (m, 1H, **H**-4a), 2.32-2.13 (m, 1H), 2.12-1.83 (m, 2H), 1.79-1.60 (m, 4H), 1.55-0.99 (m, 2H). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$) (*denotes minor diastereomer): 203.90 (**C**-5), 203.86* (**C**-5), 164.0* (**C**O$_2$CH$_3$), 163.8 (**C**O$_2$CH$_3$), 143.5 (**C**$_{\mathrm{arom}}$), 143.4* (**C**$_{\mathrm{arom}}$), 139.4 (**C**$_{\mathrm{arom}}$), 139.3* (**C**$_{\mathrm{arom}}$), 134.5 (**C**$_{\mathrm{arom}}$), 134.4* (**C**$_{\mathrm{arom}}$), 131.96 (**C**H$_{\mathrm{arom}}$), 131.87* (**C**H$_{\mathrm{arom}}$), 130.3* (**C**H$_{arom}$), 130.2 (**C**H$_{arom}$), 128.9 (**C**H$_{arom}$), 128.81 (**C**H$_{arom}$), 128.78* (**C**H$_{arom}$), 128.6 (**C**H$_{arom}$), 128.5 (**C**H$_{arom}$), 128.4* (**C**H$_{arom}$), 126.8 (**C**H$_{arom}$), 126.7* (**C**H$_{arom}$), 88.5 (**C**HNO$_2$), 87.6* (**C**HNO$_2$), 73.5 (**C**-11a), 73.2* (**C**-11a), 68.4 (CO$_2$**C**H$_2$Ph), 68.0* (CO$_2$**C**H$_2$Ph), 57.8 (**C**-4a), 57.7* (**C**-4a), 44.2 (**C**-11), 44.0* (**C**-11), 36.9 (**C**-1), 36.7* (**C**-1), 35.3 (**C**-4), 35.0* (**C**-4), 31.0 (**C**-10), 30.9* (**C**-10), 26.0 (**C**-3), 25.1* (**C**-3), 20.6 (**C**-2), 20.4* (**C**-2). IR (ATR) cm^{-1}: 3487 (O-H st), 1749 (C=O st), 1654 (C=O st), 1556 (N-O st). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{24}$H$_{25}$NNaO$_6$]$^+$: 446.1580 [(M+Na)$^+$]; found: 446.1584. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (70:30)]; flow rate 1.0 mL/min; τ_{major1} = 17.79 min, τ_{minor1} = 35.38 min (88% e.e.); τ_{major2} = 18.97 min, τ_{minor2} = 24.52 min (88% e.e.).

methyl 2-((4*S*,4a*R*,11a*R*)-11a-hydroxy-7,9-dimethyl-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a,d*][7]annulen-4-yl)-2-nitroacetate (38f). Following the *General Procedure K*, compound **38f** (56.3 mg, 0.15 mmol) was isolated by FC (DCM/MeOH 0.3%) after 72h starting from **11g** (37.9 mg, 0.15 mmol) and methyl nitroacetate (42 µL, 0.45 mmol) in the presence of catalyst **39h** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 99% (d.r.: 1.7:1) (e.e.: 88/90%). White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes minor diastereomer): 7.37-7.30 (m, 1H, C**H$_{arom}$**), 7.08 (t, *J* = 2.6 Hz, 1H, C**H$_{arom}$**), 5.44 (d, *J* = 3.5 Hz, 1H, C**H**NO$_2$), 5.19* (d, *J* = 3.4 Hz, 1H, C**H**NO$_2$), 3.83 (s, 3H, CO$_2$C**H$_3$**), 3.52* (s, 3H, CO$_2$C**H$_3$**), 3.37 (tt, *J* = 12.1, 3.3 Hz, 1H, **H**-4), 3.24* (tt, *J* = 11.9, 3.1 Hz, 1H, **H**-4), 3.14-2.93 (m, 2H, **H**-4a and **H$_a$**-11), 2.76-2.58 (m, 1H, **H$_b$**-11), 2.33-2.18 (m, 7H, 2 x C**H$_3$** and O**H**), 2.06-1.82 (m, 3H), 1.76-1.60 (m, 4H), 1.47-1.16 (m, 1H). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$) (*denotes minor diastereomer): 204.7 (**C**-5), 164.41 (**C**O$_2$CH$_3$), 164.39* (**C**O$_2$CH$_3$), 140.0* (**C**$_{arom}$), 139.9 (**C**$_{arom}$), 139.04 (**C**$_{arom}$), 138.94* (**C**$_{arom}$), 136.78* (**C**$_{arom}$), 136.71 (**C**$_{arom}$), 135.8 (**C**$_{arom}$), 135.7* (**C**$_{arom}$), 134.6 (**C**H$_{arom}$), 134.5* (**C**H$_{arom}$), 126.9 (**C**H$_{arom}$), 126.7* (**C**H$_{arom}$), 88.5 (**C**HNO$_2$), 87.8* (**C**HNO$_2$), 73.6 (**C**-11a), 73.4* (**C**-11a), 58.0* (**C**-4a), 57.9 (**C**-4a), 53.4 (CO$_2$**C**H$_3$), 52.8* (CO$_2$**C**H$_3$), 43.8 (**C**-11), 43.6* (**C**-11), 36.2 (**C**-1), 36.0* (**C**-1), 35.2 (**C**-4), 35.1* (**C**-4), 26.3* (**C**-10), 26.2 (**C**-10), 26.0* (**C**-3), 25.1 (**C**-3), 20.78 (**C**H$_3$), 20.75* (**C**H$_3$), 20.66 (**C**-2), 20.5* (**C**-2), 20.4 (**C**H$_3$). IR (ATR) cm^{-1}: 3508 (O-H st), 1755 (C=O st), 1672 (C=O st), 1554 (N-O st). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{20}$H$_{25}$NNaO$_6$]$^+$: 398.1580 [(M+Na)$^+$]; found: 398.1574. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (80:20)]; τ_{major1} = 16.54 min, τ_{minor1} = 22.68 min (90% e.e.); τ_{major2} = 21.16 min, τ_{minor2} = 25.19 min (88% e.e.). M.p.: 126-128 °C (hexanes/EtOAc).



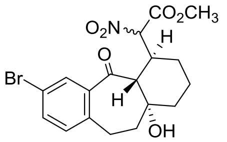


methyl 2-((4*S*,4a*R*,11a*R*)-11a-hydroxy-9-methoxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a,d*][7]annulen-4-yl)-2-nitroacetate (38g). Following the *General Procedure K*, compound **38g** (50.7 mg, 0.13 mmol) was isolated by FC (DCM/MeOH 0.3%) after 7d starting from **11h** (38.1 mg, 0.15 mmol) and methyl nitroacetate (42 µL, 0.45 mmol) in the presence of catalyst **39h** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 91% (d.r.: 1.7:1) (e.e.: 88/92%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes minor diastereomer): 7.35-7.16 (m, 2H, 2 x C**H$_{\text{arom}}$**), 7.04-6.91 (m, 1H, C**H$_{\text{arom}}$**), 5.45 (d, *J* = 3.6 Hz, 1H, C**H**NO$_2$), 5.20* (d, *J* = 3.4 Hz, 1H, C**H**NO$_2$), 3.87 (s, 3H, OC**H$_3$**), 3.86 (s, 3H, OC**H$_3$**), 3.84* (s, 3H, OC**H$_3$**), 3.55* (s, 3H, OC**H$_3$**), 3.47-3.33 (m, 1H, **H**-4), 3.31-3.19* (m, 1H, **H**-4), 3.15* (d, *J* = 11.4 Hz, 1H, **H**-4a), 3.03 (d, *J* = 11.2 Hz, 1H, **H**-4a), 2.65-2.47 (m, 1H), 2.28* (d, *J* = 7.4 Hz, 1H), 2.23 (d, *J* = 7.4 Hz, 1H), 2.06-1.85 (m, 2H), 1.77-1.52 (m, 6H), 1.48-1.22 (m, 1H). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$) (*denotes minor diastereomer): 204.2 (**C**-5), 164.4 (**C**O$_2$CH$_3$), 157.04* (**C**$_{\text{arom}}$), 157.01 (**C**$_{\text{arom}}$), 141.0* (**C**$_{\text{arom}}$), 140.9 (**C**$_{\text{arom}}$), 132.4 (**C**$_{\text{arom}}$), 132.3* (**C**$_{\text{arom}}$), 127.4 (**C**H$_{\text{arom}}$), 127.3* (**C**H$_{\text{arom}}$), 120.3 (**C**H$_{\text{arom}}$), 120.2* (**C**H$_{\text{arom}}$), 113.7 (**C**H$_{\text{arom}}$), 113.5* (**C**H$_{\text{arom}}$), 88.5 (**C**HNO$_2$), 87.9* (**C**HNO$_2$), 73.8 (**C**-11a), 73.6* (**C**-11a), 58.2* (**C**-4a), 58.0 (**C**-4a), 56.0 (O**C**H$_3$), 53.5 (CO$_2$**C**H$_3$), 52.9* (CO$_2$**C**H$_3$), 43.8 (**C**-11), 43.6* (**C**-11), 36.3 (**C**-1), 36.1* (**C**-1), 35.25 (**C**-4), 35.18* (**C**-4), 26.2* (**C**-3), 25.2 (**C**-3), 22.6* (**C**-10), 22.5 (**C**-10), 20.7 (**C**-2), 20.5* (**C**-2). IR (ATR) cm^{-1}: 3518 (O-H st), 1755 (C=O st), 1677 (C=O st), 1557 (N-O st). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{19}$H$_{23}$NNaO$_7$]$^+$: 400.1372 [(M+Na)$^+$]; found: 400.1375. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.0 mL/min; τ_{major1} = 93.91 min, τ_{minor1} = 217.44 min (88% e.e.); τ_{major2} = 123.75 min, τ_{minor2} = 197.62 min (92% e.e.).

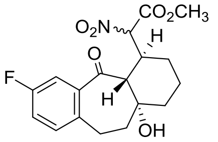


methyl 2-((4*S*,4a*R*,11a*R*)-11a-hydroxy-7-methoxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a,d*][7]annulen-4-yl)-2-nitroacetate (38h). Following the *General Procedure K*, compound **38h** (57.0 mg, 0.15 mmol) was isolated by FC (hexanes/Et$_2$O 2:1) after 48 starting from **11i** (39.1 mg, 0.15 mmol) and methyl nitroacetate (42 µL, 0.45 mmol) in the presence of catalyst **39h** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 99% (d.r.: 1.6:1) (e.e.: 88/90%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes minor diastereomer): 7.17 (dd, *J* = 8.5, 3.0 Hz, 1H, C**H**$_{\text{arom}}$), 7.11 (d, *J* = 8.7 Hz, 1H, C**H**$_{\text{arom}}$), 6.99-6.86 (m, 1H, C**H**$_{\text{arom}}$), 5.50 (d, *J* = 3.5 Hz, 1H, C**H**NO$_2$), 5.23* (d, *J* = 3.3 Hz, 1H, C**H**NO$_2$), 3.84* (s, 3H, OC**H$_3$**), 3.81 (s, 3H, OC**H$_3$**), 3.58 (s, 3H, OC**H$_3$**), 3.47-3.19 (m, 1H, **H**-4), 3.14* (d, *J* = 11.4 Hz, 1H, **H**-4a), 3.02 (d, *J* = 11.2 Hz, 1H, **H**-4a), 2.96-2.84 (m, 2H), 2.37-2.18 (m, 1H), 2.08-1.76 (m, 3H), 1.74-1.61 (m, 4H), 1.49-1.14 (m, 1H). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$) (*denotes minor diastereomer): 203.6 (**C**-5), 203.5* (**C**-5), 164.5* (**C**O$_2$CH$_3$), 164.4 (**C**O$_2$CH$_3$), 158.22 (**C**$_{\text{arom}}$), 158.18* (**C**$_{\text{arom}}$), 140.1 (**C**$_{\text{arom}}$), 135.97* (**C**$_{\text{arom}}$), 135.93 (**C**$_{\text{arom}}$), 131.56* (**C**H$_{\text{arom}}$), 131.50 (**C**H$_{\text{arom}}$), 118.9 (**C**H$_{arom}$), 118.8* (**C**H$_{arom}$), 112.0 (**C**H$_{arom}$), 111.9* (**C**H$_{arom}$), 88.5 (**C**HNO$_2$), 87.9* (**C**HNO$_2$), 73.5 (**C**-11a), 73.3* (**C**-11a), 57.8* (**C**-4a), 57.7 (**C**-4a), 55.63* (O**C**H$_3$), 55.59 (O**C**H$_3$), 53.4 (CO$_2$**C**H$_3$), 52.9* (CO$_2$**C**H$_3$), 44.5 (**C**-11), 44.4* (**C**-11), 36.9* (**C**-1), 36.8 (**C**-1), 35.3 (**C**-4), 35.2* (**C**-4), 30.3* (**C**-10), 30.2 (**C**-10), 26.0* (**C**-3), 25.1 (**C**-3), 20.7 (**C**-2), 20.4* (**C**-2). IR (ATR) cm^{-1}: 3526 (O-H st), 1754 (C=O st), 1673 (C=O st), 1553 (N-O st). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{19}H_{23}NNaO_7$]$^+$: 400.1372 [(M+Na)$^+$]; found: 400.1377. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major1} = 23.56 min, τ_{minor1} = 39.20 min (88% e.e.); τ_{major2} = 28.17 min, τ_{minor2} = 30.13 min (90% e.e.).

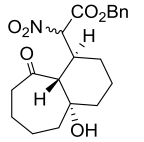
methyl 2-((4*S*,4a*R*,11a*R*)-7-bromo-11a-hydroxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a,d*][7]annulen-4-yl)-2-nitroacetate (38i). Following the *General Procedure K*, compound **38i** (64.0 mg, 0.15 mmol) was isolated by FC (DCM/MeOH 0.3%) after 44h starting from **11j** (46.5 mg, 0.15 mmol) and methyl nitroacetate (42 µL, 0.45 mmol) in the presence of catalyst **39h** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 99% (d.r.: 1.7:1) (e.e.: 90/92%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, CDCl$_3$) (*denotes minor diastereomer): 7.81 (d, *J* = 2.2 Hz, 1H, C**H**$_{arom}$), 7.76* (d, *J* = 2.2 Hz, 1H, C**H**$_{arom}$), 7.53-7.47 (m, 1H, C**H**$_{arom}$), 7.13* (d, *J* = 8.4 Hz, 1H, C**H**$_{arom}$), 7.10 (d, *J* = 8.2 Hz, 1H, C**H**$_{arom}$), 5.44 (d, *J* = 3.5 Hz, 1H, C**H**NO$_2$), 5.21* (d, *J* = 3.3 Hz, 1H, C**H**NO$_2$), 3.85 (s, 3H, CO$_2$C**H$_3$**), 3.63* (s, 3H, CO$_2$C**H$_3$**), 3.41-3.32* (m, 1H, **H**-4), 3.29-3.22 (m, 1H, **H**-4), 3.14* (d, *J* = 11.4 Hz, 1H, **H**-4a), 2.99 (d, *J* = 11.2 Hz, 1H, **H**-4a), 2.94 (dt, *J* = 10.7, 5.3 Hz, 1H, **H$_a$**-10), 2.33-2.24 (m, 1H, **H$_a$**-11), 2.07-1.96 (m, 1H, **H$_a$**-3), 1.96-1.83 (m, 1H, **H$_a$**-2), 1.76-1.65 (m, 5H, **H**-1, **H$_b$**-2, **H$_b$**-11 and O**H**), 1.36 (td, *J* = 12.9, 3.9 Hz, 1H, **H$_b$**-3), 1.32-1.21 (m, 1H, **H$_b$**-10). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 202.4* (**C**-5), 202.3 (**C**-5), 164.4* (**C**O$_2$CH$_3$), 164.2 (**C**O$_2$CH$_3$), 142.2 (**C**$_{arom}$), 142.1* (**C**$_{arom}$), 140.9* (**C**$_{arom}$), 140.8 (**C**$_{arom}$), 134.7 (**C**H$_{arom}$), 134.6* (**C**H$_{arom}$), 132.0 (**C**H$_{arom}$), 131.3 (**C**H$_{arom}$), 131.1* (**C**H$_{arom}$), 120.8 (**C**$_{arom}$), 120.7* (**C**$_{arom}$), 88.4 (**C**HNO$_2$), 87.9* (**C**HNO$_2$), 73.5 (**C**-11a), 73.3* (**C**-11a), 57.9* (**C**-4a), 57.8 (**C**-4a), 53.5 (CO$_2$**C**H$_3$), 53.1* (CO$_2$**C**H$_3$), 44.0 (**C**-11), 43.9* (**C**-11), 37.0 (**C**-1), 36.9* (**C**-11), 35.2 (**C**-4), 30.6 (**C**-10), 30.5* (**C**-10), 26.3* (**C**-3), 25.1 (**C**-3), 20.6 (**C**-2), 20.4* (**C**-2). IR (ATR) cm^{-1}: 3465 (O-H st), 1764 (C=O st), 1659 (C=O st), 1555 (N-O st). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{18}H_{20}BrNNaO_6$]$^+$: 448.0372 [(M+Na)$^+$]; found: 448.0370. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major1} = 20.03 min, τ_{minor1} = 27.90 min (90% e.e.); τ_{major2} = 25.25 min, τ_{minor2} = 21.36 min (90% e.e.). M.p.: 126-129 °C (hexanes/EtOAc).



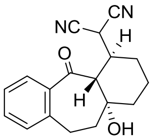
methyl 2-((4*S*,4a*R*,11a*R*)-7-fluoro-11a-hydroxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a,d*][7]annulen-4-yl)-2-nitroacetate (38j). Following the *General Procedure K*, compound **38j** (55.0 mg, 0.15 mmol) was isolated by FC (DCM/MeOH 0.3%) after 44h starting from **11k** (37.1 mg, 0.15 mmol) and methyl nitroacetate (42 µL, 0.45 mmol) in the presence of catalyst **39h** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 99% (d.r.: 1.7:1) (e.e.: 92/92%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$) (*denotes minor diastereomer): 7.42-7.30 (m, 1H, C**H**$_{\text{arom}}$), 7.24-7.14 (m, 1H, C**H**$_{\text{arom}}$), 7.14-7.03 (m, 1H, C**H**$_{\text{arom}}$), 5.53-5.38 (m, 1H, C**H**NO_2), 5.26-5.17* (m, 1H, C**H**NO_2), 3.84 (s, 3H, $CO_2C\mathbf{H_3}$), 3.63* (s, 3H, $CO_2C\mathbf{H_3}$), 3.45-3.10 (m, 1H, **H**-4), 3.06-2.86 (m, 3H, **H**-4a and **H**-10), 2.40-2.20 (m, 1H), 2.10-1.82 (m, 2H), 1.82-1.56 (m, 5H), 1.47-1.20 (m, 1H). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 202.4 (**C**-5), 164.5 (**C**O_2CH_3), 164.3* (**C**O_2CH_3), 161.3 (d, $^1J_{CF}$ = 246.8 Hz, **C**-7), 140.8 (**C**$_{\text{arom}}$), 140.7* (**C**$_{\text{arom}}$), 139.30 (**C**$_{\text{arom}}$), 139.26* (**C**$_{\text{arom}}$), 132.0 (d, $^3J_{CF}$ = 7.2 Hz, **C**-9), 118.9 (d, $^2J_{CF}$ = 21.5 Hz, **C**-8), 118.7* (d, $^2J_{CF}$ = 21.5 Hz, **C**-8), 115.0 (d, $^2J_{CF}$ = 22.7 Hz, **C**-6), 114.8* (d, $^2J_{CF}$ = 22.7 Hz, **C**-6), 88.4 (**C**HNO_2), 88.0* (**C**HNO_2), 73.5 (**C**-11a), 73.2* (**C**-11a), 57.8 (**C**-4a), 57.7* (**C**-4a), 53.4 ($CO_2\mathbf{C}H_3$), 53.0* ($CO_2\mathbf{C}H_3$), 44.1 (**C**-11), 44.0* (**C**-11), 37.0 (**C**-1), 36.9* (**C**-1), 35.23 (**C**-4), 35.17* (**C**-4), 30.3 (**C**-10), 26.3* (**C**-3), 25.1 (**C**-3), 20.6 (**C**-2), 20.4* (**C**-2). IR (ATR) cm^{-1}: 3500 (O-H st), 1763 (C=O st), 1673 (C=O st), 1553 (N-O st). MS (EI, 70 eV) *m/z* (%): 347 (M^+ - H_2O, 3), 300 (23), 268 (48), 239 (45), 207 (25), 175 (23), 151 (100), 133 (70), 109 (53), 79 (53), 55 (30). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{18}H_{20}FNNaO_6]^+$: 388.1172 [$(M+Na)^+$]; found: 388.1172. The e.e. was determined by HPLC using a Chiralpak AY3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major1} = 14.80 min, τ_{minor1} = 25.44 min (92% e.e.); τ_{major2} = 20.27 min, τ_{minor2} = 47.99 min (92% e.e.). M.p.: 112-116 °C (hexanes/EtOAc).



benzyl 2-((1*S*,4a*S*,9a*R*)-4a-hydroxy-9-oxodecahydro-1*H*-benzo[7]annulen-1-yl)-2-nitroacetate (38l). Following the *General Procedure*, compound **38l** (26.2 mg, 0.07 mmol) was isolated by FC (hexanes/Et_2O 2:1) after 6d starting from **5d** (29.2 mg, 0.15 mmol) and benzyl nitroacetate (58.0 mg, 0.30 mmol) in the presence of catalyst **39h** (15.0 mg, 0.030 mmol) using dry toluene (0.6 mL) as solvent. Yield: 45% (d.r.: 1.7:1) (e.e.: 84/80%). Colorless oil. . ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes minor diastereomer): 7.50-7.31 (m, 5H, 5 x C**H**$_{\text{arom}}$), 5.33* (d, *J* = 11.9 Hz, 1H, $CO_2C\mathbf{H_a}H_bPh$), 5.27-5.19 (m, 2H, $CO_2C\mathbf{H_2}Ph$), 5.15* (d, *J* = 12.0 Hz, 1H, $CO_2CH_a\mathbf{H_b}Ph$), 5.10 (d, *J* = 3.4 Hz, 1H, C**H**NO_2), 4.89* (d, *J* = 2.9 Hz, 1H, C**H**NO_2), 3.20-2.92 (m, 1H, **H**-9a), 2.86 (d, *J* = 11.5 Hz, 1H, **H**-1), 2.75-2.61 (m, 1H), 2.59-2.31 (m, 1H), 2.07-1.42 (m, 11H), 1.42-0.98 (m, 2H). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 214.5* (**C**-9), 214.4 (**C**-9), 164.0* (**C**O_2Bn), 163.4 (**C**O_2Bn), 134.45* (**C**$_{\text{arom}}$), 134.40 (**C**$_{\text{arom}}$), 129.2* (**C**H$_{\text{arom}}$), 129.1 (**C**H$_{\text{arom}}$), 128.97* (**C**H$_{\text{arom}}$), 128.93* (**C**H$_{\text{arom}}$), 128.8 (**C**H$_{\text{arom}}$), 128.6 (**C**H$_{\text{arom}}$), 89.5 (**C**HNO_2), 88.7 (**C**HNO_2), 70.7 (**C**-4a), 70.3* (**C**-4a), 68.6* (**C**H_2Ph), 68.5 (**C**H_2Ph), 57.0 (**C**-9a), 56.4* (**C**-9a), 46.4 (**C**-8), 46.3* (**C**-8), 45.2 (**C**-5),



44.8 (**C**-5), 40.0 (**C**-4), 39.9* (**C**-4), 36.6 (**C**-1), 26.3* (**C**H$_2$), 25.1 (**C**H$_2$), 22.8 (**C**H$_2$), 21.6 (**C**-6), 21.5* (**C**-6), 20.5 (**C**-2), 20.2* (**C**-2). IR (ATR) cm^{-1}: 3544 (O-H st), 1751 (C=O st), 1692 (C=O st), 1554 (N-O st). MS (EI, 70 eV) *m/z* (%): 281 (6), 207 (35), 108 (61), 91 (49), 79(95), 77 (100), 51 (58). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{20}H_{25}NNaO_6]^+$: 398.1580 [(M+Na)$^+$]; found: 398.1590. The e.e. was determined by HPLC using a Chiralpak AY3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major1} = 23.11 min, τ_{minor1} = 20.34 min (84% e.e.); τ_{major2} = 52.96 min, τ_{minor2} = 33.44 min (80% e.e.). M.p.: 112-116 °C (hexanes/EtOAc).

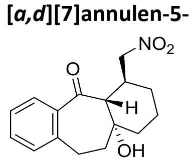


2-((4*R*,4a*R*,11a*R*)-11a-hydroxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a,d*][7] annulen-4-yl)malononitrile (38o). Following the *General Procedure K*, compound **38o** (35.4 mg, 0.12 mmol) was isolated by FC (Et$_2$O/hexanes gradient from 1:2 to 1:1) after 5 days starting from **11f** (34.8 mg, 0.15 mmol) and malononitrile (29.7 mg, 0.45 mmol) in the presence of catalyst **39h** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 79% (e.e.: 46%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, CDCl$_3$): 7.75 (dd, *J* = 7.8, 1.4 Hz, 1H,C**H**$_{arom}$), 7.50-7.43 (m, 1H, C**H**$_{arom}$), 7.36-7.31 (m, 1H, C**H**$_{arom}$), 7.31-7.26 (m, 1H, C**H**$_{arom}$), 4.18 (d, *J* = 3.8 Hz, 1H, C**H**-CN), 3.15-3.00 (m, 4H, **H**-4, **H**-4a and **H**-10), 2.36 (ddd, *J* = 14.6, 7.3, 1.4 Hz, 1H, **H$_a$**-11), 2.25 (dt, *J* = 13.0, 3.5 Hz, 1H, **H$_a$**-3), 2.02-1.92 (m, 1H, **H$_a$**-2), 1.91-1.73 (m, 5H, **H**-1, **H$_b$**-2, **H$_b$**-11 and O**H**), 1.52-1.41 (m, 1H, **H$_b$**-3). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$): 202.4 (**C**-5), 144.2 (**C**$_{arom}$), 138.2 (**C**$_{arom}$), 132.7 (**C**H$_{arom}$), 130.6 (**C**H$_{arom}$), 128.7 (**C**H$_{arom}$), 127.0 (**C**H$_{arom}$), 112.4 (**C**N), 111.3 (**C**N), 73.5 (**C**-11a), 58.7 (**C**-4a), 44.2 (**C**-11), 37.0 (**C**-1), 35.2 (**C**-4), 31.2 (**C**-10), 27.0 (**C**-3), 26.2 (**C**H-CN), 20.1 (**C**-2). IR (ATR) cm^{-1}: 3526 (O-H st), 1666 (C=O st). MS (EI, 70 eV) *m/z* (%): 294 (M$^+$, 5), 276 (M$^+$ - H$_2$O, 11), 240 (25), 211 (41), 193 (17), 133 (100), 118 (21), 103 (22), 91 (25), 79 (27), 67 (13), 55 (9). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{18}H_{17}N_2O_2]^-$: 293.1290 [(M-H)$^-$]; found: 293.1284. The e.e. was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 43.98 min, τ_{minor} = 23.98 min (46% e.e.). M.p.: 133-137 °C (hexanes/EtOAc). $[\alpha]_D^{20}$: +19.4 (*c*=1.15, CHCl$_3$).

5.2. Synthesis of adducts 40

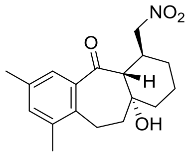
General procedure L: To a solution of the corresponding adduct in dioxane (0.10 mmol/mL) at 80 °C was added aqueous solution of LiOH (1.7 eq, 1.0 mmol/mL) and it was stirred at that temperature for the time indicated in each case. Then reaction mixture was diluted with Et$_2$O and aqueous phase was extracted with Et$_2$O. Combined organic layers were dried with anhydrous Na$_2$SO$_4$, concentrated under reduced pressure and purified by column chromatography to afford pure products.

General procedure M: To a solution of the corresponding adduct in MeOH (3mL) was added Pd/C and it was subjected to hydrogenation conditions at room temperature (H_2, 30 psi) until full conversion was observed by TLC. Reaction crude was filtered through a plug of Celite, concentrated under reduced pressure and purified by column chromatography.



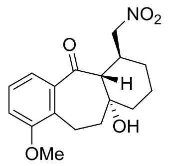
(4S,4a*R*,11a*R*)-11a-hydroxy-4-(nitromethyl)-1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo [*a,d*][7]annulen-5-one (40a). Following the *General Procedure L* compound **40a** (12.5 mg, 0.043 mmol) was isolated by FC (hexanes/EtOAc 8:2) after 3 days, starting from adduct **38a** (27.8 mg, 0.08 mmol) and LiOH (5.7 mg, 0.13 mmol). Yield: 54% (e.e.: 90%). Colorless oil. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$): 7.74 (dd, *J* = 7.7, 1.5 Hz, 1H, C**H**$_{arom}$), 7.43 (td, *J* = 7.5, 1.6 Hz, 1H, C**H**$_{arom}$), 7.36-7.31 (m, 1H, C**H**$_{arom}$), 7.27 (d, *J* = 7.6 Hz, 1H, C**H**$_{arom}$), 4.49-4.29 (m, 2H, C**H$_2$**NO$_2$), 3.14-2.95 (m, 4H, **H**-4, **H**-4a and **H**-10), 2.31 (ddd, *J* = 14.6, 6.9, 1.8 Hz, 1H, **H$_a$**-11), 2.00-1.87 (m, 2H, **H$_a$**-2 and **H$_a$**-3), 1.82-1.65 (m, 5H, **H$_a$**-1, **H$_b$**-1, **H$_b$**-2, **H$_b$**-11 and O**H**), 1.24 (dddd, *J* = 16.6, 14.7, 10.0, 2.7 Hz, 1H, **H$_b$**-3). ^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$): 203.8 (**C**-5), 143.5 (**C**$_{arom}$), 139.6 (**C**$_{arom}$), 131.9 (**C**H$_{arom}$), 130.3 (**C**H$_{arom}$), 128.4 (**C**H$_{arom}$), 126.8 (**C**H$_{arom}$), 79.2 (**C**H$_2$NO$_2$), 73.1 (**C**-11a), 57.9 (**C**-4a), 44.1 (**C**-11), 36.8 (**C**-1), 32.8 (**C**-4), 31.2 (**C**-10), 28.4 (**C**-3), 20.5 (**C**-2). IR (ATR) cm^{-1}: 3497 (O-H st), 1677 (C=O st), 1544 (N=O st), 735 (C-N st). MS (EI, 70 eV) *m/z* (%): 271 (M$^+$ - H_2O, 2), 242 (8), 223 (19), 195 (23), 181 (20), 157 (18), 147 (15), 133 (100), 117 (23), 107 (73), 91 (59), 77 (41), 67 (16), 55 (24). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{16}H_{19}NNaO_4]^+$: 312.1212 [(M+Na)$^+$]; found: 312.1222. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 25.38 min, τ_{minor} = 34.74 min (90% e.e.). $[\alpha]_D^{20}$: +4.58 (*c*=1.19, $CHCl_3$).

Alternatively, following the *General Procedure M* compound **40a** (19.4 mg, 0.067 mmol) was isolated by FC (hexanes/EtOAc 7:3) after 6 h, starting from adduct **38d** (38.6 mg, 0.09 mmol) and Pd/C (6.0 mg) in 3.0 mL of MeOH. Yield: 74% (90% e.e).

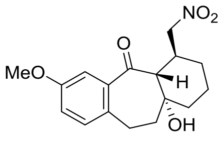


(4S,4a*R*,11a*R*)-11a-hydroxy-7,9-dimethyl-4-(nitromethyl)-1,2,3,4,4a,10,11,11a-octahydro -5*H*-dibenzo[*a,d*][7]annulen-5-one (40f). Following the *General Procedure L* compound **40f** (9.80 mg, 0.031 mmol) was isolated by FC (hexanes/EtOAc 8:2) after 3 days, starting from adduct **38f** (17.5 mg, 0.047 mmol) and LiOH (3.4 mg, 0.08 mmol). Yield: 66% (e.e.: 90%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$): 7.34 (s, 1H, C**H**$_{arom}$), 7.11 (s, 1H, C**H**$_{arom}$), 4.36 (dd, *J* = 11.4, 2.9 Hz, 1H, C**H$_a$**H$_b$NO$_2$), 4.30-4.22 (m, 1H, CH$_a$**H$_b$**NO$_2$), 3.09-2.94 (m, 3H, **H**-4, **H**-4a and **H$_a$**-10), 2.69 (dd, *J* = 18.0, 12.0 Hz, 1H, **H$_b$**-10), 2.31 (s, 3H, C**H$_3$**), 2.30 (s, 3H, C**H$_3$**), 2.25 (ddd, *J* = 14.7, 7.4, 1.2 Hz, 1H, **H$_a$**-11), 1.97-1.84 (m, 2H, **H$_a$**-2 and **H$_a$**-3), 1.78-1.65 (m, 5H, **H$_b$**-2, **H$_b$**-11, **H**-1 and O**H**), 1.23-1.13 (m, 1H, **H$_b$**-3). ^{13}C NMR (δ, ppm) (75 MHz, CDCl$_3$): 204.7 (**C**-5), 140.2 (**C**$_{arom}$), 139.1 (**C**$_{arom}$), 136.9 (**C**$_{arom}$), 136.0 (**C**$_{arom}$), 134.6 (**C**H$_{arom}$), 126.7 (**C**H$_{arom}$), 79.1 (**C**H$_2$NO$_2$), 73.2 (**C**-11a), 58.2 (**C**-4a), 43.8 (**C**-11), 36.0 (**C**-1), 32.7 (**C**-4), 28.4 (**C**-10), 26.5 (**C**-3), 20.8 (**C**H$_3$), 20.51 (**C**-2), 20.46 (**C**H$_3$). IR (ATR) cm^{-1}: 3443 (O-H st), 1663 (C=O st), 1544 (N=O st), 754 (C-N st). MS (EI, 70 eV) *m/z* (%): 317 (M$^+$, 1), 175 (12), 163 (100), 161 (18), 145 (8), 119 (16), 107 (11), 91 (20), 79 (9), 67 (4), 55 (7). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{18}$H$_{23}$NNaO$_4$]$^+$: 340.1525 [(M+Na)$^+$]; found: 340.1534. The e.e. was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ$_{major}$ = 10.89 min, τ$_{minor}$ = 13.42 min (90% e.e.). M.p.: 65-68 °C (hexanes/EtOAc). [α]$_D^{20}$: +30.26 (*c*=0.58, CHCl$_3$).

(4*S*,4a*R*,11a*R*)-11a-hydroxy-9-methoxy-4-(nitromethyl)-1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (40g). Following the *General Procedure L* compound **40g** (13.1 mg, 0.041 mmol) was isolated by FC (hexanes/EtOAc 8:2) after 3 days, starting from adduct **38g** (32.0 mg, 0.085 mmol) and LiOH (6.0 mg, 0.144 mmol). Yield: 48% (e.e.: 90%). Colorless oil. ^{1}H NMR (δ, ppm) (500 MHz, CDCl$_3$): 7.34-7.27 (m, 2H, 2 x **CH$_{arom}$**), 7.01 (dd, *J* = 7.4, 1.9 Hz, 1H, **CH$_{arom}$**), 4.38 (dd, *J* = 11.4, 3.1 Hz, 1H, **CH$_a$**H$_b$NO$_2$), 4.34-4.30 (m, 1H, CH$_a$**H$_b$**NO$_2$), 3.89 (s, 3H, OC**H$_3$**), 3.44 (ddd, *J* = 18.5, 7.5, 1.3 Hz, 1H, **H$_a$**-10), 3.08-2.98 (m, 2H, **H**-4 and **H**-4a), 2.59 (dd, *J* = 18.5, 12.2 Hz, 1H, **H$_b$**-10), 2.27 (ddd, *J* = 14.7, 7.5, 1.2 Hz, 1H, **H$_a$**-11), 2.02-1.86 (m, 2H, **H$_a$**-2 and **H$_a$**-3), 1.78-1.64 (m, 5H, **H**-1, **H$_b$**-2, **H$_b$**-11 and O**H**), 1.21 (ddt, *J* = 15.1, 12.7, 5.7 Hz, 1H, **H$_b$**-3). ^{13}C NMR (δ, ppm) (75 MHz, CDCl$_3$): 204.1 (**C**-5), 157.1 (**C**-9), 141.2 (**C**$_{arom}$), 132.5 (**C**$_{arom}$), 127.4 (**C**H$_{arom}$), 120.1 (**C**H$_{arom}$), 113.6 (**C**H$_{arom}$), 79.1 (**C**H$_2$NO$_2$), 73.4 (**C**-11a), 58.3 (**C**-4a), 56.0 (O**C**H$_3$), 43.7 (**C**-11), 36.2 (**C**-1), 32.7 (**C**-4), 28.4 (**C**-3), 22.6 (**C**-10), 20.5 (**C**-2). IR (ATR) cm^{-1}: 3493 (O-H st), 1677 (C=O st), 1546 (N=O st), 1259 (C-O st). MS (EI, 70 eV) *m/z* (%): 319 (M$^+$, 12), 281 (4), 207 (20), 187 (10), 165 (100), 147 (9), 128 (7), 115 (14), 91 (32), 77 (23), 55 (12). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{17}$H$_{21}$NNaO$_5$]$^+$: 342.1317 [(M+Na)$^+$]; found: 342.1324. The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ$_{major}$ = 28.99 min, τ$_{minor}$ = 40.59 min (90% e.e.). [α]$_D^{20}$: +12.15 (*c*=0.05, CHCl$_3$).

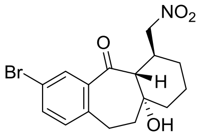


(4S,4a*R*,11a*R*)-11a-hydroxy-7-methoxy-4-(nitromethyl)-1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (40h). Following the *General Procedure L* compound **40h** (13.9 mg, 0.043 mmol) was isolated by FC (hexanes/EtOAc 8:2) after 3 days, starting from adduct **38h** (33.0 mg, 0.087 mmol) and LiOH (6.2 mg, 0.15 mmol). Yield: 50% (e.e.: 90%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.22 (d, *J* = 2.8 Hz, 1H, **H**-6), 7.15 (d, *J* = 8.4 Hz, 1H, **H**-9), 6.96 (dd, *J* = 8.4, 2.9 Hz, 1H, **H**-8), 4.47-4.28 (m, 2H, C**H$_2$**NO$_2$), 3.83 (s, 3H, OC**H$_3$**), 3.09-2.99 (m, 2H, **H**-10), 2.99-2.90 (m, 2H, **H**-4 and **H**-4a), 2.27 (ddd, *J* = 14.6, 6.1, 2.6 Hz, 1H, **H$_a$**-11), 1.96-1.83 (m, 2H, **H$_a$**-a and **H$_a$**-3), 1.76-1.61 (m, 5H, **H**-1, **H$_b$**-2, **H$_b$**-11 and O**H**), 1.30-1.14 (m, 1H, **H$_b$**-3). ^{13}C NMR (δ, ppm) (75 MHz, CDCl$_3$): 203.5 (**C**-5),

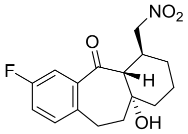


158.3 (**C**-7), 140.3 (**C**$_{\text{arom}}$), 136.0 (**C**$_{\text{arom}}$), 131.6 (**C**H$_{\text{arom}}$), 118.9 (**C**H$_{\text{arom}}$), 111.9 (**C**H$_{\text{arom}}$), 79.2 (**C**H_2NO_2), 73.1 (**C**-11a), 57.9 (**C**-4a), 55.7 (O**C**H_3), 44.5 (**C**-11), 36.8 (**C**-1), 32.8 (**C**-4), 30.4 (**C**-10), 28.4 (**C**-3), 20.5 (**C**-2). IR (ATR) cm^{-1}: 3558 (O-H st), 1677 (C=O st), 1547 (N=O st), 754 (C-N st). MS (EI, 70 eV) *m/z* (%): 319 (M^+, 12), 254 (5), 225 (4), 211 (4), 187 (8), 165 (100), 147 (4), 121 (13), 91 (12), 77 (11). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{17}H_{21}NNaO_5]^+$: 342.1317 $[(M+Na)^+]$; found: 342.1323. The e.e. was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 19.17 min, τ_{minor} = 23.19 min (90% e.e.). $[\alpha]_D^{20}$: +47.31 (*c*=0.34, $CHCl_3$).

(4*S*,4a*R*,11a*R*)-7-bromo-11a-hydroxy-4-(nitromethyl)-1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (40i). Following the *General Procedure L* compound **40i** (8.70 mg, 0.024 mmol) was isolated by FC (hexanes/EtOAc 8:2) after 3 days, starting from adduct **38i** (26.3 mg, 0.062 mmol) and LiOH (4.4 mg, 0.10 mmol). Yield: 38% (e.e.: 90%). White solid. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 7.83 (d, *J* = 2.3 Hz, 1H, **H**-6), 7.50 (dd, *J* = 8.1, 2.2 Hz, 1H, **H**-8), 7.13 (d, *J* = 8.2 Hz, 1H, **H**-9), 4.43-4.31 (m, 2H, C**H$_2$**NO$_2$), 3.08-2.88 (m, 4H), 2.38-2.20 (m, 1H), 1.98-1.80 (m, 2H), 1.81-1.60 (m, 5H), 1.56 (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$): 202.3 (**C**-5), 142.2 (**C**$_{\text{arom}}$), 141.1 (**C**$_{\text{arom}}$), 134.6 (**CH**$_{\text{arom}}$), 132.1 (**CH**$_{\text{arom}}$), 131.2 (**CH**$_{\text{arom}}$), 120.8 (**C**-7), 79.0 (**C**H_2NO_2), 73.1 (**C**-11a), 57.9 (**C**-4a), 43.9 (**C**-11), 36.9 (**C**-1), 32.8 (**C**-4), 30.7 (**C**H_2), 28.4 (**C**H_2), 20.5 (**C**-2). IR (ATR) cm^{-1}: 3522 (O-H st), 1680 (C=O st), 1544 (N=O st), 758 (C-N st). MS (EI, 70 eV) *m/z* (%): 369 (1), 303 (13), 288 (10), 212 (53), 194 (14), 165 (22), 128 (31), 107 (100), 89 (42), 69 (13), 55 (30). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{16}H_{18}BrNNaO_4]^+$: 390.0317 $[(M+Na)^+]$; found: 390.0314. The e.e. was determined by HPLC using a Chiralpak ADH column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.0 mL/min; τ_{major} = 39.71 min, τ_{minor} = 51.34 min (90% e.e.). $[\alpha]_D^{20}$: +16.57 (*c*=0.95, $CHCl_3$). M.p.: 68-70 °C (hexanes/EtOAc).

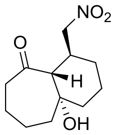


(4*S*,4a*R*,11a*R*)-7-fluoro-11a-hydroxy-4-(nitromethyl)-1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (40j). Following the *General Procedure L* compound **40j** (10.3 mg, 0.033 mmol) was isolated by FC (hexanes/EtOAc 7:3) after 4 days, starting from adduct **38j** (35.8 mg, 0.098 mmol) and LiOH (7.0 mg, 0.17 mmol). Yield: 34% (e.e.: 90%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 7.41 (dd, *J* = 8.9, 2.8 Hz, 1H, **H**-9), 7.22 (dd, *J* = 8.5, 5.2 Hz, 1H, **H**-8), 7.18 - 7.03 (m, 1H, **H**-6), 4.46-4.34 (m, 2H, C**H$_2$**NO$_2$), 3.06-2.91 (m, 4H), 2.36-2.23 (m, 1H), 1.97-1.83 (m, 2H), 1.79-1.61 (m, 5H), 1.57 (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$): 202.4 (**C**-5), 161.5 (d, $^1J_{CF}$ =246.8 Hz, **C**-7), 141.1 (d, $^3J_{CF}$ = 5.9 Hz, **C**-5a), 139.2 (d, $^4J_{CF}$ = 3.2 Hz, **C**-9a), 132.1 (d, $^3J_{CF}$ = 7.2 Hz, **C**-9), 118.8 (d, $^2J_{CF}$ =21.4 Hz, **C**H$_{\text{arom}}$), 115.0 (d, $^2J_{CF}$ = 22.6 Hz, **C**H$_{\text{arom}}$), 79.1 (**C**H_2NO_2), 73.1 (**C**-11a), 57.8 (**C**-4a), 44.2 (**C**-11), 36.9 (**C**-1), 32.8 (**C**-4), 30.5 (**C**H_2), 28.4 (**C**H_2), 20.5 (**C**-2). IR (ATR) cm^{-1}: 3526 (O-H st), 1679 (C=O st), 1547 (N=O st). MS (EI, 70 eV) *m/z* (%): 261 (M^+-NO_2, 2), 241 (14), 213 (16), 199 (15), 175 (22), 151 (72), 133 (35), 122 (21),



107 (100), 93 (28), 79 (30), 67 (20), 55 (31). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{16}H_{18}FNNaO_4]^+$: 330.1118 [(M+Na)$^+$]; found: 330.1124. The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 23.69 min, τ_{minor} = 27.55 min (90% e.e.). $[\alpha]_D^{20}$: +20.13 (*c*=1.42, $CHCl_3$).

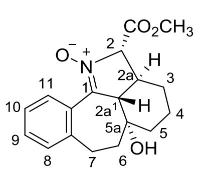
(4S,4a*R*,9a*S*)-9a-hydroxy-4-(nitromethyl)decahydro-5*H*-benzo[7]annulen-5-one (40l). Following the *General Procedure M* compound **40l** (6.9 mg, 0.029 mmol) was isolated by FC (hexanes/EtOAc 7:3) after 15 h, starting from adduct **38l** (17.0 mg, 0.045 mmol) and Pd/C (3.3 mg) in 3.0 mL of MeOH. Yield: 63%. Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes partially overlapped resonances): 4.37-4.19 (m, 2H, C**H$_2$**NO$_2$), 2.91 (d, *J* = 11.6 Hz, 1H, **H**-4a), 2.84-2.65 (m, 2H, **H**-6), 2.61-2.45 (m, 1H, **H**-4), 2.04-1.88 (m, 1H), 2.00* (s, 1H, O**H**), 1.88-1.52 (m, 7H), 1.42-1.13 (m, 4H). ^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$): 214.6 (**C**-5), 79.9 (**C**H$_2$NO$_2$), 70.5 (**C**-9a), 56.9 (**C**-4a), 46.5 (**C**-6), 45.1 (**C**-9), 39.8 (**C**-1), 34.2 (**C**-4), 28.4 (**C**H$_2$), 23.0 (**C**H$_2$), 21.7 (**C**H$_2$), 20.5 (**C**H$_2$). IR (ATR) cm^{-1}: 3483 (O-H st), 1695 (C=O st), 1548 (N=O st). MS (EI, 70 eV) *m/z* (%): 234 (1), 147 (22), 133 (18), 121 (17), 110 (69), 93 (51), 81 (66), 67 (50), 55 (100). $[\alpha]_D^{20}$: + 234.0 (*c*=0.34, $CHCl_3$).



5.3. Synthesis of nitrones 41a/41b

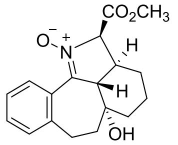
To a solution of adduct **38a** (66.0 mg, 0.19 mmol) in anhydrous MeOH (0.6 mL) was added under inert atmosphere Pd/C 10% weight (6.6 mg) and ammonium formate (120 mg, 1.9 mmol). The mixture was stirred at room temperature for 6h, filtered through a celite pad and concentrated under reduced pressure. The crude was then purified by FC (hexanes/EtOAc gradient from 3:7 to 2:8) to afford pure nitrones **41a** (16.3 mg, 0.052 mmol) and **41b** (12.0 mg, 0.038) in 47% overall yield.

(2S,2a*S*,2a^1*S*,5a*R*)-5a-hydroxy-2-(methoxycarbonyl)-2a,2a^1,3,4,5,5a,6,7-octahydro-2*H*-benzo[6,7]cyclohepta[1,2,3-*cd*]isoindole 1-oxide (41a): White solid. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$): 9.14-9.06 (m, 1H, **H**-11), 7.33-7.30 (m, 2H, 2 x C**H**$_{arom}$), 7.23-7.16 (m, 1H, C**H**$_{arom}$), 4.64-4.55 (m, 1H, **H**-2), 3.93 (s, 3H, OC**H$_3$**), 3.04-2.91 (m, 3H, **H**-2a, **H**-2a^1 and **H$_a$**-7), 2.86 (ddd, *J* = 14.8, 6.0, 3.6 Hz, 1H, **H$_b$**-7), 2.15-2.00 (m, 2H, **H**-6), 1.98-1.83 (m, 2H, **H$_a$**-3 and **H$_a$**-5), 1.81-1.71 (m, 2H, **H**-4), 1.54-1.41 (m, 2H, **H$_b$**-3 and **H$_b$**-5), 1.36 (s, 1H, O**H**). ^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$): 168.1 (**C**O$_2$CH$_3$), 143.5 (**C**$_{arom}$), 141.0 (**C**=N), 130.8 (**C**H$_{arom}$), 130.2 (**C**H$_{arom}$), 128.6 (**C**$_{arom}$), 128.4 (**C**H$_{arom}$), 126.7 (**C**H$_{arom}$), 79.3 (**C**-2), 71.2 (**C**-5a), 56.1 (**C**-2a^1), 53.1 (O**C**H$_3$), 42.6 (**C**-6), 40.73 (**C**-2a), 40.68 (**C**-5), 31.6 (**C**-



7), 26.5 (**C**-3), 21.9 (**C**-4). IR (ATR) cm^{-1}: 3361 (O-H st), 1752 (C=O st), 1199 (C-O st). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{18}H_{21}FNNaO_4]^+$: 338.1368 [(M+Na)$^+$]; found: 338.1373. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (70:30)]; flow rate 1.0 mL/min; τ_{major} = 36.50 min, τ_{minor} = 53.82 min (94% e.e.). M.p.: 170-173 °C (hexanes/EtOAc). $[\alpha]_D^{20}$: -29.77 (*c*=0.89, CHCl$_3$).

(2*R*,2a*S*,2a^1*S*,5a*R*)-5a-hydroxy-2-(methoxycarbonyl)-2a,2a^1,3,4,5,5a,6,7-octahydro-2*H*-benzo[6,7]cyclohepta[1,2,3-*cd*]isoindole 1-oxide (41b): Colorless oil. ^{1}H NMR (δ, ppm) (500 MHz, Acetone-d_6): 9.18 (dd, *J* = 7.7, 1.7 Hz, 1H, **H**-11), 7.33-7.17 (m, 3H, 3 x C**H**$_{arom}$), 4.69 (dd, *J* = 9.1, 1.0 Hz, 1H, **H**-2), 3.80 (s, 3H, OC**H$_3$**), 3.23-3.12 (m, 2H, **H**-2a and **H$_a$**-7), 3.00 (d, *J* = 11.2 Hz, 1H, **H**-2a^1), 2.90-2.78 (m, 2H, **H$_b$**-7 and O**H**), 2.06-1.97 (m, 1H, **H$_a$**-6), 1.96-1.82 (m, 3H, **H$_a$**-3, **H$_a$**-4 and **H$_b$**-6), 1.77-1.64 (m, 2H, **H$_b$**-4 and **H$_a$**-5), 1.58-1.47 (m, 1H, **H$_b$**-5), 1.26-1.10 (m, 1H, **H$_b$**-3). ^{13}C NMR (δ, ppm) (75 MHz, Acetone): 168.8 (**C**O$_2$CH$_3$), 143.1 (**C**=N), 131.1 (**C**H$_{arom}$), 130.90 (**C**$_{arom}$), 130.90 (**C**$_{arom}$), 130.74 (**C**H$_{arom}$), 129.0 (**C**H$_{arom}$), 126.5 (**C**H$_{arom}$), 80.2 (**C**-2), 71.5 (**C**-5a), 57.4 (**C**-2a^1), 52.7 (O**C**H$_3$), 42.1 (**C**-6), 41.1 (**C**-5), 37.4 (**C**-2a), 31.9 (**C**-7), 26.5 (**C**-3), 22.6 (**C**-4). IR (ATR) cm^{-1}: 3322 (O-H st), 1745 (C=O st), 1207 (C-O st). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{18}H_{21}FNNaO_4]^+$: 338.1368 [(M+Na)$^+$]; found: 338.1374. The e.e. was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 22.92 min, τ_{minor} = 39.06 min (92% e.e.). $[\alpha]_D^{20}$: -85.29 (*c*=0.33, CHCl$_3$).



6. SYNTHESIS OF γ-LACTAMS BY DISULFONIMIDE-CATALYZED MUKAIYAMA-MANNICH REACTION

Catalyst $NHTs_2$[32] and 2,5-bis(trimethylsilyloxy)furan **43**[33] were synthesized following procedures previously described in the literature.

6.1. Synthesis of imines 42a-s

Imines **42a-s** were synthesized by condensation of the corresponding aldehyde (4.0 mmol) and aryl amine (4.0 mmol) in CH_2Cl_2 (8 mL) in the presence of $MgSO_4$ (6.0 mmol).[34] After stirring at room temperature overnight, the reaction mixture was filtered and solvent was removed in vacuo to yield the corresponding imine pure enough to be used without further purification. In those cases that unreacted starting material was observed, imines were purified by recrystallization in EtOH. 2-furaldehyde derived imine **42p** was synthesized in a similar procedure using MeOH as solvent and 3A molecular shieves (0.25 g/mmol amine) as dehydrating agent.

6.2. Synthesis of γ-lactams 44 and methyl esters 46

General procedure N: The imine (1.0 equiv.) and catalyst (0.05 equiv.) were placed in a flame-dried vial under argon atmosphere and a 0.4M THF solution of 2,5-bis(trimethylsilyloxy)furan (2.0 equiv.) was added. The reaction mixture was allowed to stir at room temperature for 48 h, then 1.00 mL of sat. NH_4Cl aq. solution was added and it was stirred at room temperature for 1h. The biphasic mixture was extracted with EtOAc and the combined organic layers were dried over anhydrous Na_2SO_4 and solvent was evaporated *in vacuo*. The crude mixture was purified by flash column chromatography (80% EtOAc:hex/0.25%HAc) or recrystallized in EtOH:H_2O to yield pure *trans* diastereomers.[35]

General procedure O: The reaction was performed in a similar way to *General Procedure N* except that after aqueous work-up with sat. NH_4Cl and extraction with EtOAc, the combined organic layers

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[32] Kiyokawa, K.; Yahata, S.; Kojima, T.; Minakata, S. *Org. Lett.* **2014**, *16*, 4646.

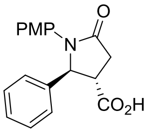
[33] Brownbrige, P.; Chan, T.-H. *Tetrahedron Lett.* **1980**, *21*, 3423.

[34] The NMR spectra of the imines matched data previously described in the literature: (a) Pezzetta, C.; Veiros, L. F.; Oble, J.; Poli, G. *Chem. Eur. J.* **2017**, *23*, 8385. (b) Zhang, Y.-F.; Wu, B.; Shi, Z.-J. *Chem. Eur. J.* **2016**, *22*, 17808. (c) Novacek, J.; Roiser, L.; Zielke, K.; Robiette, R.; Waser, M. *Chem. Eur. J.* **2016**, *22*, 11422. (c) Hong, X.; Wang, H.; Liu, B.; Xu, B. *Chem. Commun.* **2014**, *50*, 14129. (d) Harding, P.; Harding, D. J.; Soponrat, N.; Tinpun, K.; Samuadnuan, S.; Adams, H. *Austr. J. Chem.* **2010**, *63*, 75. (e) Naeimi, H.; Salimi, F.; Rabiei, K. *J. Mol. Catal. A: Chem.* **2006**, *260*, 100. (f) Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 5665.

[35] Relative configuration of the products was determined by comparison of the ^1H-NMR coupling constants with literature data and confirmed by X-Ray diffraction: (a) Lepikhina, A.; Bakulina, O.; Dar'in, D.; Krasavin, M. *RSC Adv.*, **2016**, *6*, 83808. (b) Pohmakotr, M.; Yotapan, N.; Tuchinda, P.; Kuhakarn, C.; Reutrakul, V. *Tetrahedron* **2007**, *63*, 4328. (c) Pohmakotr, M.; Yotapan, N.; Tuchinda, P.; Kuhakarn, C.; Reutrakul, V. *J. Org. Chem.* **2007**, *72*, 5016.

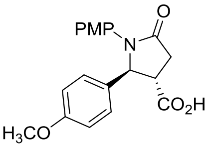
were dried over anhydrous Na_2SO_4 and solvent was evaporated *in vacuo*. The crude mixture was dissolved in MeOH (2 mL), cooled to 0 °C and thionyl chloride (1.1 equiv.) was added dropwise. Reaction mixture was allowed to reach room temperature and stirred overnight. Solvent was removed *in vacuo*, diluted with DCM and washed with water. Aqueous phase was extracted with DCM (2x10 mL) and organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography to yield the corresponding lactam.

(2*R,3*R**)-1-(4-methoxyphenyl)-5-oxo-2-phenylpyrrolidine-3-carboxylic acid (44a).** Following the



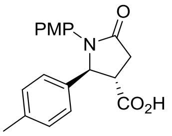
General Procedure N, lactam **44a** (79.1 mg, 0.25 mmol) was isolated after flash column chromatography (80% EtOAc:hex/0.25%HAc) in 63% yield as an orange pale solid starting from imine **42a** (84.3 mg, 0.40 mmol), $NHTs_2$ catalyst (6.5 mg, 0.02 mmol) and THF solution of 2,5-bis(trimethylsilyloxy)furan (2.0 mL, 0.80 mmol). ^1H NMR (δ, ppm) (400 MHz, DMSO-d_6): 12.86 (s, 1H), 7.35 – 7.25 (m, 6H), 7.25 – 7.17 (m, 1H), 6.80 (d, J = 8.7 Hz, 2H), 5.48 (d, J = 5.5 Hz, 1H), 3.66 (s, 3H), 3.10 (m, 1H), 2.94 (dd, J = 17.0, 9.5 Hz, 1H), 2.74 (dd, J = 17.0, 6.9 Hz, 1H). ^{13}C NMR (δ, ppm) (100 MHz, DMSO): 173.6, 171.6, 156.4, 140.4, 130.6, 128.6, 127.8, 126.9, 124.8, 113.7, 65.2, 55.1, 45.7, 34.0. IR cm^{-1}: 2927, 1714, 1652, 1512, 1248. HRMS (ESI-TOF): Calculated for [$C_{18}H_{16}NO_4^-$]: 310.1085 [M-H]$^-$, found 310.1076. M.p.: 171-174 °C.

(2*R,3*R**)-1,2-bis(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (44b).** Following the



General Procedure N, lactam **44b** (95.2 mg, 0.28 mmol) was isolated after flash column chromatography (80% EtOAc:hex/0.25%HAc) in 70% yield as a white solid starting from imine **42b** (96.4 mg, 0.40 mmol), $NHTs_2$ catalyst (6.5 mg, 0.02 mmol) and THF solution of 2,5-bis(trimethylsilyloxy)furan (2.0 mL, 0.80 mmol). ^1H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.27 – 7.21 (m, 2H), 7.21 – 7.14 (m, 2H), 6.89 – 6.82 (m, 2H), 6.82 – 6.76 (m, 2H), 5.41 (d, J = 5.1 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.20 (ddd, J = 9.4, 6.7, 5.0 Hz, 1H), 3.09 (dd, J = 17.2, 9.4 Hz, 1H), 2.99 (dd, J = 17.2, 6.7 Hz, 1H). ^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$): 176.4, 172.7, 159.6, 157.6, 131.4, 130.2, 127.8, 125.3, 114.6, 114.2, 66.3, 55.45, 55.37, 46.4, 34.3. HRMS (ESI-TOF): Calculated for [$C_{19}H_{18}NO_5^-$]: 340.1190 [M-H]$^-$, found 340.1192. M.p.: 149-151 °C.

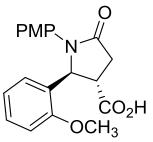
(2*R,3*R**)-1-(4-methoxyphenyl)-5-oxo-2-(*p*-tolyl)pyrrolidine-3-carboxylic acid (44c).** Following the



General Procedure N, lactam **44c** (109 mg, 0.34 mmol) was isolated after flash column chromatography (80% EtOAc:hex/0.25%HAc) in 83% yield as a yellow pale solid starting from imine **42c** (90.8 mg, 0.40 mmol), $NHTs_2$ catalyst (6.5 mg, 0.02 mmol) and THF solution of 2,5-bis(trimethylsilyloxy)furan (2.0 mL, 0.80 mmol). ^1H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.34 – 7.21 (m, 3H), 7.20 – 7.07 (m, 4H), 6.90 – 6.70 (m, 2H), 5.44 (d,

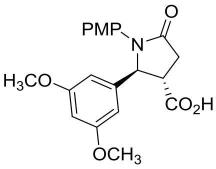
J = 4.7 Hz, 1H), 3.74 (s, 3H), 3.19 (ddd, J = 9.2, 6.3, 4.6 Hz, 1H), 3.10 (dd, J = 17.2, 9.4 Hz, 1H), 3.00 (dd, J = 17.2, 6.3 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 176.7, 172.5, 157.5, 138.4, 136.5, 130.3, 129.9, 126.4, 125.1, 114.2, 66.4, 55.5, 46.3, 34.2, 21.2. HRMS (ESI-TOF): Calculated for [$C_{19}H_{18}NO_4^-$]: 324.1241 [M-H]$^-$, found 324.1240. M.p.: 164-166 °C.

(2*R,3*R**)-2-(2-methoxyphenyl)-1-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (44d).**



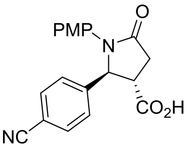
Following the *General Procedure N*, lactam **44d** (102.3 mg, 0.30 mmol) was isolated after flash column chromatography (80% EtOAc:hex/0.25%HAc) in 75% yield as a yellow pale solid starting from imine **42d** (97.0 mg, 0.40 mmol), $NHTs_2$ catalyst (6.5 mg, 0.02 mmol) and THF solution of 2,5-bis(trimethylsilyloxy)furan (2.0 mL, 0.80 mmol). ^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 10.71 (s, 1H), 7.30 (dd, J = 20.2, 7.8 Hz, 3H), 7.12 (d, J = 7.5 Hz, 1H), 6.94 – 6.85 (m, 2H), 6.80 (d, J = 8.6 Hz, 2H), 5.76 (d, J = 3.3 Hz, 1H), 3.88 (s, 3H), 3.73 (s, 3H), 3.23 (m, 1H), 3.08 (dd, J = 17.4, 9.7 Hz, 1H), 2.96 (dd, J = 17.3, 4.4 Hz, 1H). ^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 177.7, 173.1, 157.4, 156.9, 130.6, 129.6, 127.6, 127.0, 124.6, 120.8, 114.1, 111.0, 62.8, 55.6, 55.4, 43.9, 34.6. HRMS (ESI-TOF): Calculated for [$C_{19}H_{18}NO_5^-$]: 340.1190 [M-H]$^-$, found 340.1193. M.p.: 183-185 °C.

(2*R,3*R**)-2-(3,5-dimethoxyphenyl)-1-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (44e).**



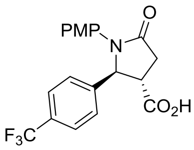
Following the *General Procedure N*, lactam **44e** (104 mg, 0.28 mmol) was isolated after flash column chromatography (80% EtOAc:hex/0.25%HAc) in 69% yield as a yellow pale solid starting from imine **42e** (110 mg, 0.40 mmol), $NHTs_2$ catalyst (6.5 mg, 0.02 mmol) and THF solution of 2,5-bis(trimethylsilyloxy)furan (2.0 mL, 0.80 mmol). ^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.33 – 7.22 (m, 2H), 6.85 – 6.73 (m, 2H), 6.39 (d, J = 2.2 Hz, 2H), 6.34 (t, J = 2.2 Hz, 1H), 5.39 (d, J = 4.4 Hz, 1H), 3.74 (s, 9H), 3.18 (m, 1H), 3.07 (dd, J = 17.3, 9.5 Hz, 1H), 2.96 (dd, J = 17.2, 5.8 Hz, 1H). ^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 176.4, 172.5, 161.5, 157.5, 142.2, 130.4, 124.8, 114.3, 104.4, 100.0, 66.45, 55.52, 55.50, 45.9, 34.2. HRMS (ESI-TOF): Calculated for [$C_{20}H_{20}NO_6^-$]: 370.1296 [M-H]$^-$, found 370.1291. M.p.: 167-170 °C.

(2*R,3*R**)-2-(4-cyanophenyl)-1-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (44f).**

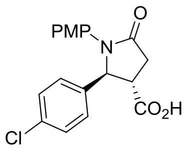


Following the *General Procedure N*, lactam **44f** (120 mg, 0.36 mmol) was isolated after flash column chromatography (80% EtOAc:hex/0.25%HAc) in 89% yield as a yellow pale solid starting from imine **42f** (95.8 mg, 0.40 mmol), $NHTs_2$ catalyst (6.5 mg, 0.02 mmol) and THF solution of 2,5-bis(trimethylsilyloxy)furan (2.0 mL, 0.80 mmol). ^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.31 (s, 1H), 7.63 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.26 – 7.16 (m, 2H), 6.86 – 6.75 (m, 2H), 5.57 (d, J = 5.0 Hz, 1H), 3.74 (s, 3H), 3.17 (ddd, *J* = 9.4, 7.6, 5.4 Hz, 1H), 3.12 – 3.00 (m, 2H). ^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 175.2, 172.6, 157.9, 144.8, 133.1, 129.4, 127.5, 124.9, 118.2, 114.5, 112.6, 65.8, 55.5, 45.8, 34.0. HRMS (ESI-TOF): Calculated for [$C_{19}H_{15}N_2O_4^-$]: 335.1037 [M-H]$^-$, found 335.1097. M.p.: 185-187 °C.

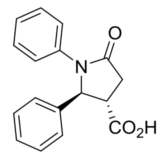
(2*R,3*R**)-1-(4-methoxyphenyl)-5-oxo-2-(4-(trifluoromethyl)phenyl)pyrrolidine-3-carboxylic acid (44g).** Following the *General Procedure N*, lactam **44g** (95.8 mg, 0.25 mmol) was isolated after flash column chromatography (80% EtOAc:hex/0.25%HAc) in 63% yield as a yellow pale solid starting from imine **42g** (111.8 mg, 0.40 mmol), $NHTs_2$ catalyst (6.5 mg, 0.02 mmol) and THF solution of 2,5-bis(trimethylsilyloxy)furan (2.0 mL, 0.80 mmol). ^{1}H NMR (δ, ppm) (400 MHz, DMSO-d_6) 12.93 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.9 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 5.62 (d, *J* = 5.8 Hz, 1H), 3.65 (s, 3H), 3.14 (m, 1H), 2.93 (dd, *J* = 17.0, 9.6 Hz, 1H), 2.76 (dd, *J* = 17.0, 7.3 Hz, 1H). ^{13}C NMR (δ, ppm) (100 MHz, DMSO-d_6) 173.3, 171.7, 156.5, 145.2, 130.3, 128.3 (q, $^2J_{C-F}$ = 31.7 Hz), 128.0, 125.5 (m), 124.8, 124.1 (q, $^1J_{C-F}$ = 272.2 Hz), 113.7, 64.4, 55.1, 45.4, 33.8. HRMS (ESI-TOF): Calculated for [$C_{19}H_{15}F_3NO_4^-$]: 378.0959 [M-H]$^-$, found 378.0950. M.p.: 190-193 °C.



(2*R,3*R**)-2-(4-chlorophenyl)-1-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (44h).** Following the *General Procedure N*, lactam **44h** (113.5 mg, 0.33 mmol) was isolated after flash column chromatography (80% EtOAc:hex/0.25%HAc) in 82% yield as a white solid starting from imine **42h** (98.4 mg, 0.40 mmol), $NHTs_2$ catalyst (6.5 mg, 0.02 mmol) and THF solution of 2,5-bis(trimethylsilyloxy)furan (2.0 mL, 0.80 mmol). ^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.84 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.25 – 7.17 (m, 4H), 6.79 (d, *J* = 8.5 Hz, 2H), 5.46 (d, *J* = 4.8 Hz, 1H), 3.74 (s, 3H), 3.15 (td, *J* = 9.0, 4.6 Hz, 1H), 3.03 (m, 2H). ^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 176.0, 172.9, 157.8, 138.1, 134.5, 129.9, 129.6, 128.1, 125.3, 114.4, 66.1, 55.6, 46.3, 34.2. HRMS (ESI-TOF): Calculated for [$C_{18}H_{15}ClNO_4^-$]:344.0695 [M-H]$^-$, found 344.0695. M.p.: 153-156 °C.

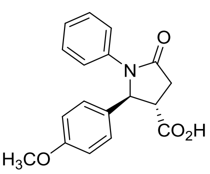


(2*R,3*R**)-5-oxo-1,2-diphenylpyrrolidine-3-carboxylic acid (44l).** Following the *General Procedure N*, lactam **44l** (59.2 mg, 0.21 mmol) was isolated after recrystallization in EtOH:H_2O in 52% yield (94:6 dr) as a white solid starting from imine **42l** (73.7 mg, 0.41 mmol), $NHTs_2$ catalyst (6.5 mg, 0.02 mmol) and THF solution of 2,5-bis(trimethylsilyloxy)furan (2.0 mL, 0.80 mmol). ^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.13 (s, 1H), 7.36 (d, *J* = 7.7 Hz, 2H), 7.33 – 7.18 (m, 7H), 7.07 (t, *J* = 7.4 Hz, 1H), 5.55 (d, *J* = 4.4 Hz, 1H), 3.17 (ddd, *J* = 9.2, 6.1, 4.4 Hz, 1H), 3.12 – 2.94 (m, 2H). ^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 176.5, 172.9, 139.5, 137.3, 129.3, 129.0, 128.5, 126.3, 125.9, 123.1, 66.2, 46.3, 34.2.

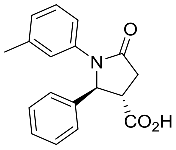


IR cm^{-1}: 2924, 1713, 1659. HRMS (ESI-TOF): Calculated for [$C_{17}H_{14}NO_3^-$]: 280.0979 [M-H]$^-$, found 280.0971. M.p.: 174-176 °C.

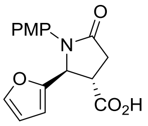
(2*R,3*R**)-2-(4-methoxyphenyl)-5-oxo-1-phenylpyrrolidine-3-carboxylic acid (44m).** Following the *General Procedure N*, lactam **44m** (75.5 mg, 0.24 mmol) was isolated after recrystallization in EtOH:H_2O in 61% yield as a white solid starting from imine **42m** (83.9 mg, 0.40 mmol), $NHTs_2$ catalyst (6.5 mg, 0.02 mmol) and THF solution of 2,5-bis(trimethylsilyloxy)furan (2.0 mL, 0.80 mmol). ^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.44 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.20 (m, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 5.49 (d, *J* = 4.8 Hz, 1H), 3.74 (s, 3H), 3.15 (ddd, *J* = 9.1, 6.4, 4.7 Hz, 1H), 3.07 (dd, *J* = 17.2, 9.2 Hz, 1H), 2.98 (dd, *J* = 17.2, 6.4 Hz, 1H). ^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 176.7, 172.8, 159.6, 137.3, 131.3, 128.9, 127.6, 125.9, 123.3, 114.6, 65.8, 55.4, 46.5, 34.3. HRMS (ESI-TOF): Calculated for [$C_{18}H_{16}NO_4^-$]: 310.1085 [M-H]$^-$, found 310.1075. M.p.: 134-137 °C.



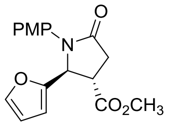
(2*R,3*R**)-5-oxo-2-phenyl-1-(*m*-tolyl)pyrrolidine-3-carboxylic acid (44n).** Following the *General Procedure N*, lactam **44n** (48.9 mg, 0.16 mmol) was isolated after recrystallization in EtOH:H_2O in 41% yield (92:8 dr) as a yellow solid starting from imine **42n** (79.1 mg, 0.40 mmol), $NHTs_2$ catalyst (6.5 mg, 0.02 mmol) and THF solution of 2,5-bis(trimethylsilyloxy)furan (2.0 mL, 0.80 mmol). ^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 8.64 (s, 1H), 7.41 – 7.23 (m, 6H), 7.20 – 7.07 (m, 2H), 7.01 – 6.83 (m, 1H), 5.56 (d, *J* = 4.3 Hz, 1H), 3.19 (ddd, *J* = 9.9, 6.0, 4.4 Hz, 1H), 3.09 (dd, *J* = 17.3, 9.2 Hz, 1H), 3.01 (dd, *J* = 17.2, 6.0 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 176.6, 172.7, 139.6, 138.8, 137.3, 129.3, 128.7, 128.5, 126.8, 126.3, 123.9, 120.2, 66.2, 46.3, 34.2, 21.6. HRMS (ESI-TOF): Calculated for [$C_{18}H_{16}NO_3^-$]: 294.1136 [M-H]$^-$, found 294.1129. M.p.: 139-143 °C.



(2*R,3*R**)-2-(furan-2-yl)-1-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (44p).** Following the *General Procedure N*, lactam **44p** (67.2 mg, 0.22 mmol) was isolated after flash column chromatography (80% EtOAc:hex/0.25%HAc) in 56% yield as an orange pale solid starting from imine **42p** (80.2 mg, 0.40 mmol), $NHTs_2$ catalyst (6.5 mg, 0.02 mmol) and THF solution of 2,5-bis(trimethylsilyloxy)furan (2.0 mL, 0.80 mmol). ^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 9.66 (s, 1H), 7.39 (d, *J* = 1.9 Hz, 1H), 7.12 – 7.06 (m, 2H), 6.86 – 6.79 (m, 2H), 6.27 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.21 (d, *J* = 3.3 Hz, 1H), 5.40 (d, *J* = 4.3 Hz, 1H), 3.76 (s, 3H), 3.49 (m, 1H), 3.19 (dd, *J* = 17.4, 9.9 Hz, 1H), 2.99 (dd, *J* = 17.4, 5.4 Hz, 1H). ^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 176.1, 172.7, 158.4, 150.8, 143.3, 129.5, 126.6, 114.4, 110.6, 109.7, 60.8, 55.5, 42.5, 34.2. HRMS (ESI-TOF): Calculated for [$C_{16}H_{14}NO_5^-$]: 300.0877 [M-H]$^-$, found 300.0865. M.p.: 154-157 °C.



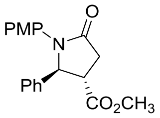
Methyl (2*R,3*R**)-2-(furan-2-yl)-1-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylate (46p).**



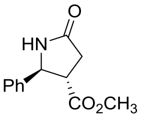
Following the *General Procedure O*, lactam **46p** (80.2 mg, 0.25 mmol) was isolated after flash column chromatography (7:3 hex/EtOAc) in 64% yield as a yellow oil (94:6 dr) starting from imine **42p** (80.2 mg, 0.40 mmol), $NHTs_2$ catalyst (6.5 mg, 0.02 mmol) and THF solution of 2,5-bis(trimethylsilyloxy)furan (2.0 mL, 0.80 mmol). ^1H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.39 – 7.34 (m, 1H), 7.14 – 7.06 (m, 2H), 6.86 – 6.77 (m, 2H), 6.25 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.18 (d, *J* = 3.2 Hz, 1H), 5.38 (d, *J* = 4.5 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.50 – 3.40 (m, 1H), 3.10 (dd, *J* = 17.2, 9.8 Hz, 1H), 2.89 (dd, *J* = 17.2, 5.7 Hz, 1H). ^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$) 172.7, 171.8, 158.2, 151.2, 143.2, 130.0, 126.4, 114.4, 110.6, 109.5, 60.6, 55.5, 52.9, 42.7, 34.4. HRMS (ESI-TOF): Calculated for $[C_{17}H_{18}NO_5^+]$: 316.1179 $[M+H]^+$, found 316.1179.

6.3. Transformations of the adducts

Synthesis of methyl (2*R,3*R**)-1-(4-methoxyphenyl)-5-oxo-2-phenylpyrrolidine-3-carboxylate (46a).** Lactam **44a** (32.8 mg, 0.10 mmol) was dissolved in MeOH (2 mL), cooled to 0 °C and thionyl chloride (8.0 µL, 0.11 mmol) was added dropwise. Reaction mixture was allowed to reach room temperature and stirred overnight. Solvent was removed *in vacuo*, reaction crude dissolved in DCM and washed with water. Aqueous phase was extracted with DCM (2 x 10 mL) and organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (7:3 hex/EtOAc) to yield lactam **46a** (28.9 mg, 0.09 mmol) in 89% yield as a yellow oil; ^1H NMR (400 MHz, CDCl3) δ 7.33 (ddd, *J* = 7.7, 6.6, 1.3 Hz, 2H), 7.30 – 7.22 (m, 5H), 6.82 – 6.76 (m, 2H), 5.47 (d, *J* = 5.0 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.17 (ddd, *J* = 9.3, 6.7, 5.0 Hz, 1H), 3.04 (dd, *J* = 17.2, 9.4 Hz, 1H), 2.94 (dd, *J* = 17.2, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.1, 157.3, 139.8, 130.5, 129.2, 128.4, 126.5, 124.8, 114.2, 66.4, 55.4, 52.8, 46.4, 34.4; IR 2924, 1737, 1699, 1513, 1249 cm^{-1}; AMM (ESI-TOF) *m/z* calcd for $C_{19}H_{20}NO_4^+$ $[M+H]^+$ 326.1387, found 326.1389.

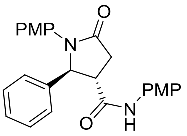


Synthesis of methyl (2*R,3*R**)-5-oxo-2-phenylpyrrolidine-3-carboxylate (48).** To a cooled solution (0 °C) of methylated lactam **46a** (28.9 mg, 0.089 mmol) in CH_3CN/H_2O (5:1, 3 mL) was added cerium ammonium nitrate (214 mg, 0.39 mmol) under argon atmosphere and the reaction was allowed to reach room temperature and stirred for 1 h. Reaction mixture was diluted in EtOAc and washed with $NaHCO_3$, then with 1M HCl, and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified



by flash column chromatography (50:50 EtOAc/hexanes + 0.25% AcOH) to yield lactam **48** (13.8 mg, 0.063 mmol) in 71% yield as an amorphous yellow solid; ^{1}H NMR (400 MHz, CDCl3) δ 7.43 – 7.31 (m, 5H), 6.24 (s, 1H), 5.00 (d, *J* = 6.6 Hz, 1H), 3.73 (s, 3H), 3.14 (td, *J* = 9.1, 6.6 Hz, 1H), 2.74 (d, *J* = 9.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 172.6, 140.8, 129.2, 128.6, 126.1, 60.3, 52.6, 49.0, 33.8; IR 3226, 2924, 1734, 1700 cm^{-1}; AMM (ESI-TOF) *m/z* calcd for $C_{12}H_{14}NO_3^+$ [M+H]$^+$ 220.0968, found 220.0959.

Synthesis of (2*R,3*R**)-N,1-Bis(4-methoxyphenyl)-5-oxo-2-phenylpyrrolidine-3-carboxamide (49).**



Lactam **44a** (124.0 mg, 0.40 mmol) was dissolved in CH_2Cl_2 (1 mL) under argon and HOBt (66.0 mg, 1.2 mmol), *p*-anisidine (148.0 mg, 1.2 mmol), *N*-methylmorpholine (0.017 mL, 1.6 mmol), and EDC (84.0 mg, 0.44 mmol) were added in succession. The reaction mixture was stirred at 0 °C for 2 h, then warmed to room temperature and stirred for further 16 h. The reaction mixture was diluted with EtOAc, then washed with 3 x 20 mL of 1.2 N HCl, 3 x 20 mL of sat. $NaHCO_3$, and 30 mL of brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (60-100% EtOAc/Hexanes) to afford pure lactam **49** (116.0 mg, 0.28 mmol). 70 % yield. Yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 5H), 7.26 – 7.23 (m, 2H), 7.22 – 7.16 (m, 2H), 6.93 (s, 1H), 6.86 (dd, *J* = 7.4, 4.8 Hz, 2H), 6.80 – 6.74 (m, 2H), 5.41 (d, *J* = 7.3 Hz, 1H), 3.79 (d, *J* = 2.5 Hz, 3H), 3.71 (s, 3H), 3.18 (dd, *J* = 16.7, 9.0 Hz, 1H), 3.06 – 2.98 (m, 1H), 2.95 (dd, *J* = 16.7, 9.1 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 168.8, 157.3, 156.9, 139.7, 130.2, 130.1, 129.2, 128.5, 126.8, 125.2, 121.9, 114.2, 114.1, 67.0, 55.5, 55.3, 50.1, 35.1.; AMM (ESI-TOF) *m/z* calcd for $C_{25}H_{25}N_2O_4^+$ [M+H]$^+$: 417.1809, found: 417.1827.

Appendix

Abbreviations, acronyms and symbols[1]

$acac^-$	Acetylacetonate anion
Ac	Acetyl group
AIBN	Azobisisobutyronitrile
Ar	Aryl group
ATR	Attenuated total reflectance
BA	Brønsted acid
BB	Brønsted base
BINAP	(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
BINOL	1,1′-Binaphthalene-2,2′-diol
Boc	*tert*-Butyloxycarbonyl
c	Concentration (measured in g/100 mL)
C_{arom}	Aromatic carbon
Cat.	Catalyst
Conv.	Conversion
CSA	10-Camphorsulfonic acid
Cy	Cyclohexyl group
DABCO	1,4-Diazabicicylo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DIBAL	Diisobutylaluminum hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMDO	Dimethyldioxirane
DSI	Disulfonimide
E	Electrophile
EDG	Electron-donating group
e.e.	Enantiomeric excess
Ent.	Enantiomer
Equiv.	Equivalent
EWG	Electron-withdrawing group
FC	Flash column chromatography

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[1] For Standard Abbreviations and Acronyms, see: “Guidelines for Authors” *J. Org. Chem.* **2017**.

Fmoc	9-Fluorenylmethoxycarbonyl
HBTU	*N,N,N′,N′*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HFIP	Hexafluoroisopropanol
IBX	2-Iodoxybenzoic acid
ICD	Isocupreidine
Ile	Isoleucine
J	Coupling constant
LA	Lewis acid
LB	Lewis base
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
Leu	Leucine
LHDMS	Lithium bis(trimethylsilyl)amide
MBH	Morita-Baylis-Hillman reaction
***m*CPBA**	*meta*-chloroperoxybenzoic acid
M.p.	Melting point
MS	Mass spectrometry
M.S.	Molecular sieves
NAHDMS	Sodium bis(trimethylsilyl)amide
NBS	*N*-Bromosuccinimide
n.d.	Not determined
Nu	Nucleophile
o-DCB	*ortho*-Dichlorobenzene
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PG	Protecting group
Phe	Phenylalanine
PIDA	(Diacetoxyiodo)benzene
Piv	Pivaloyl group
PMB	*para*-Methoxybenzyl group
PMP	*para*-Methoxyphenyl group
QTOF	Quadrupole-time of flight
R	Alkyl group or substituent
r.t.	Room temperature

TADA	Transannular Diels-Alder reaction
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
Tf	Trifluoromethanesulfonate group
TMEDA	*N,N,N′,N′*-Tetramethylethylenediamine
Thr	Threonine
TMS	Trimethylsilyl
Ts	Tosyl
TS	Transition state
Val	Valine
vs	Versus
X	Halogen or heteroatom
δ	Chemical shift
τ_1	Retention time for first enantiomer
τ_2	Retention time for second enantiomer

Resumen extendido

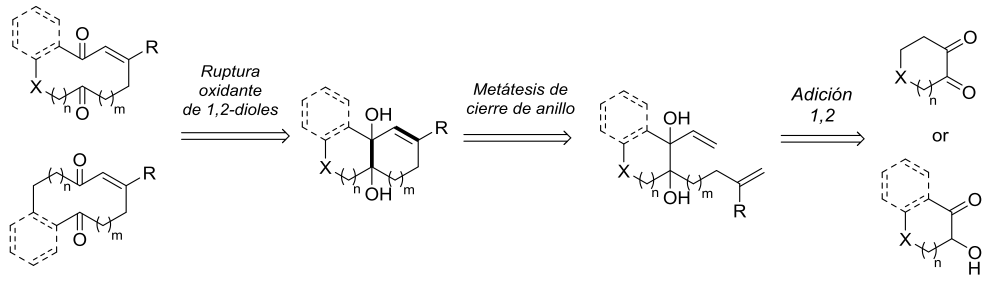
Las reacciones transanulares, tal y como su propio nombre indica, son procesos cuya característica principal reside en que los puntos reactivos que participan en la formación del nuevo enlace se encuentran inicialmente formando parte de una estructura cíclica. De esta forma, las reacciones transanulares permiten acceder a estructuras policíclicas de forma sencilla y con un alto grado de economía de átomos, factores que confieren a este tipo de metodologías un gran potencial sintético.

Si bien durante años se ha considerado un ámbito de gran interés dentro de la química sintética, el estudio y desarrollo de procesos transanulares eficientes se ha visto en gran medida impedido por las complicaciones inherentes a la síntesis de los substratos macrocíclicos requeridos. Afortunadamente, el desarrollo en los últimos años de nuevas metodologías sintéticas ha facilitado significativamente la obtención de estos substratos. Como consecuencia, el número de publicaciones relacionadas con el desarrollo de reacciones transanulares ha experimentado un importante aumento, siendo especialmente remarcable su aplicación como paso clave en la síntesis de numerosos productos naturales. No obstante, la gran mayoría de los ejemplos transanulares desarrollados hasta el momento consisten en procesos diastereoselectivos que requieren del empleo de substratos enantiopuros. Por el contrario, el número de ejemplos enantioselectivos es hasta la fecha muy escaso, habiéndose descrito un único ejemplo organocatalítico y enantioselectivo.

En este sentido, y en línea con los trabajos de investigación desarrollados en los últimos años en el grupo del prof. Jose Luis Vicario, el objetivo principal del presente trabajo de tesis doctoral se dirigió al estudio de reacciones transanulares enantioselectivas mediante el empleo de organocatalizadores quirales como elementos de enantiocontrol. En la presente memoria se recogen los resultados más relevantes obtenidos durante el desarrollo de este trabajo de tesis doctoral.

En un primer capítulo, se ha llevado a cabo una revisión bibliográfica acerca del empleo de reacciones transanulares como herramienta sintética para la obtención tanto de productos naturales como de compuestos con actividad biológica. A fin de aportar una visión global, se han expuesto diversos ejemplos de procesos transanulares clasificados en función del tipo de reactividad mostrada, poniendo especial énfasis en los ejemplos catalíticos enantioselectivos desarrollados con éxito hasta la fecha.

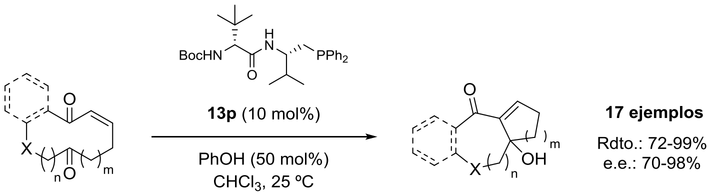
En un segundo capítulo, se recogen los principales resultados obtenidos durante el desarrollo de la primera reacción de **Morita-Baylis-Hillman transannular enantioselectiva** catalizada por fosfinas quirales. Inicialmente se describe la síntesis de los sustratos de partida, la cual ha sido específicamente diseñada a fin de permitir el acceso a sistemas cíclicos de diferente tamaño contiendo simultáneamente un sistema carbonílico α,β-insaturado así como un grupo carbonilo adicional (Esquema 1).



Esquema 1. Estrategia planteada para la síntesis de sustratos.

La metodología planteada permite acceder a ciclos de entre 9 y 12 átomos de carbono, pudiendo presentar anillos aromáticos fusionados tanto en posición α al grupo carbonilo aislado como al sistema α,β-insaturado. Esta amplia variabilidad de sustratos es posible simplemente por modificación de la dicetona de partida, de la extensión de las cadenas alquílicas adicionadas o del orden de adición de estas últimas.

En la fase inicial del proyecto, se ha demostrado la capacidad de los sustratos sintetizados para dar lugar a la reacción de Morita-Baylis-Hillman transannular proyectada. Para ello se ha evaluado el uso de diferentes fosfinas quirales nucleófilas como organocatalizadores para este proceso. De esta forma, se ha demostrado que fosfinas quirales con estructuras derivadas de esquaramidas, thioureas o aminoácidos, son capaces de promover la reacción deseada de forma enantioselectiva. Un análisis sistemático de los parámetros experimentales (naturaleza del disolvente, temperatura, concentración...), así como la optimización de las características estructurales del catalizador, ha permitido seleccionar la fosfina **13p**, derivada del aminoácido natural *L*-*tert*-leucina, como el mejor catalizador para la reacción estudiada.

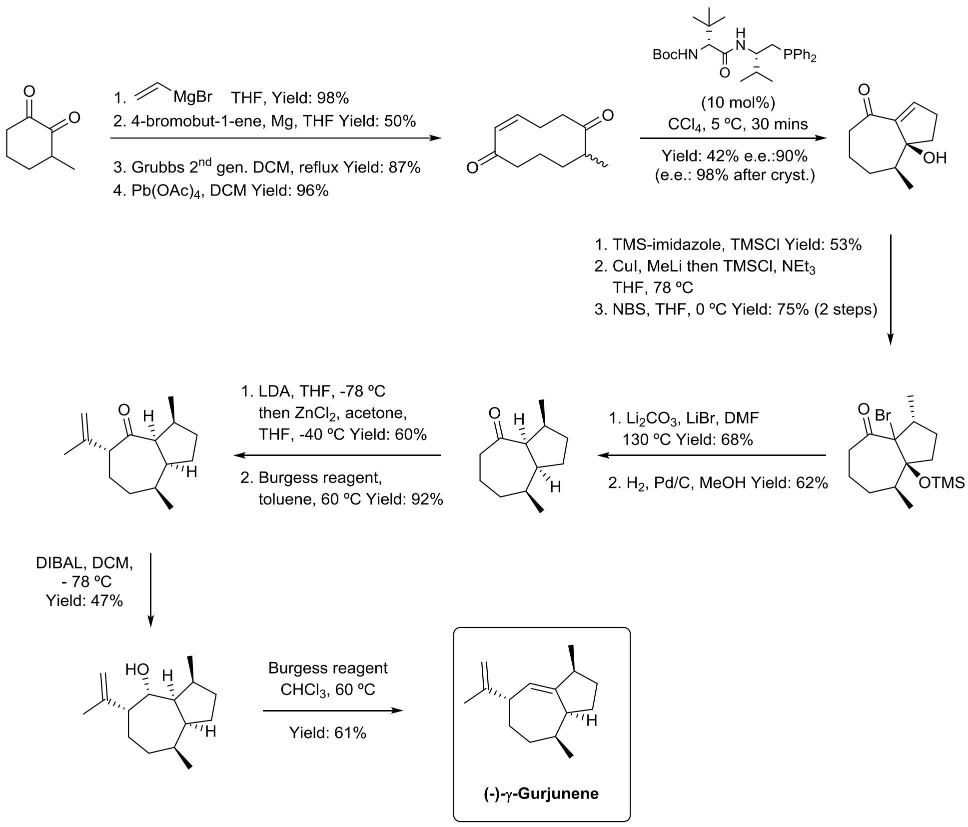


Esquema 2. Reacción de Morita-Baylis-Hillman transannular desarrollada.

Una vez optimizadas las condiciones experimentales, se ha estudiado el alcance de la reacción, pudiendo aplicarse satisfactoriamente a un total de 17 sustratos, los cuales han dado lugar a los correspondientes productos policíclicos con excelentes rendimientos y enantioselectividades. Como limitación de esta metodología, se ha observado que la reacción no tolera la sustitución en posición β del sistema carbonílico insaturado, resultando completamente inerte bajo las condiciones previamente aplicadas.

En un tercer capítulo se recogen los resultados obtenidos durante la **síntesis del compuesto (-)-γ-gurjunene**, un sesquiterpenoide natural cuya estructura base es coincidente con la de los compuestos bicíclicos previamente obtenidos en el capítulo 2. De esta forma, partiendo de la correspondiente 3-metil-ciclohexano-1,2-diona comercialmente disponible, y tras un total de 14 pasos, se ha podido acceder al producto natural γ-gurjunene con un rendimiento global del 0.46% (Esquema 3).

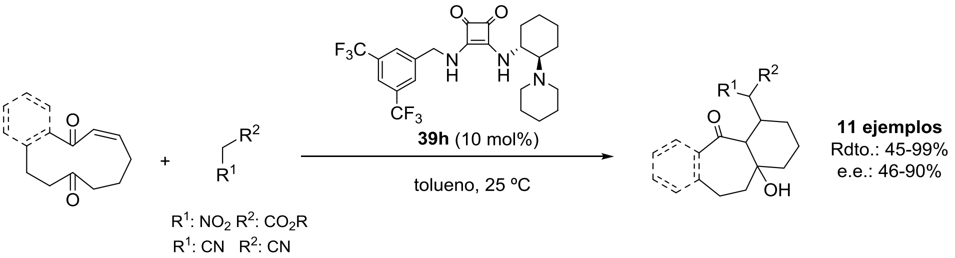
Como paso crucial de esta síntesis destaca la resolución cinética llevada a cabo en condiciones similares a las previamente empleadas en el capítulo 2, la cual es imprescindible para la obtención del producto deseado con un alto grado de enantiocontrol.



Esquema 3. Síntesis total del (-)-γ-gurjunene.

En un cuarto capítulo, y en vista de la reactividad anteriormente mostrada por los sustratos estudiados, se ha llevado a cabo el estudio de una reacción en **cascada Michael-aldólica enantioselectiva**. Para ello se han empleado catalizadores bifuncionales que contienen simultáneamente en su estructura un punto básico (capaz de desprotonar un nucleófilo externo) así como grupos susceptibles de interaccionar con electrófilos a través de la formación de puentes de hidrógeno.

De esta forma, y tras el estudio de los diferentes parámetros de reacción (temperatura, disolvente, catalizador…) se ha seleccionado la esquaramida **39h** como el catalizador bifuncional más eficiente. La reacción ha podido aplicarse satisfactoriamente a una serie de sustratos con diversos grupos funcionales en el anillo aromático (tanto dadores como atractores de electrones), obteniéndose los correspondientes productos con excelentes rendimientos y enantioselectividades. Desafortunadamente la reacción ha demostrado una gran dependencia en cuanto a la naturaleza del nucleófilo, observándose bien falta total de reactividad, bien un descenso significativo del exceso enantiomérico en el caso de nucleófilos distintos a nitroacetatos.

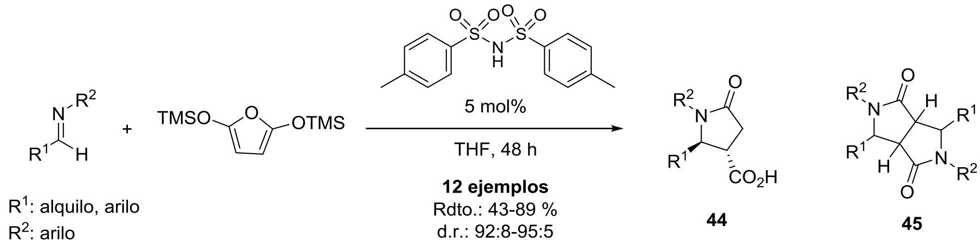


Esquema 4. Reacción en cascada Michael/aldólica transannular enantioselectiva.

Los productos obtenidos como consecuencia de la reacción organocatalítica han podido ser sometidos a diferentes transformaciones químicas, permitiendo acceder a los productos descarboxilados así como a las correspondientes nitronas de forma sencilla.

Finalmente, en un último capítulo, se recogen los resultados más relevantes obtenidos durante la estancia predoctoral de 3 meses de duración llevada a cabo en la Universidad de California – Davis (EEUU). El trabajo de investigación desarrollado durante ese periodo de tiempo ha estado enfocado al desarrollo una nueva ruta sintética que permita acceder a **compuestos γ-lactámicos** a través de una reacción de tipo **Mukaiyama-Mannich**. En este contexto, se ha demostrado que las disulfonimidas, comúnmente empleadas como ácidos de Brønsted pueden exhibir actividad como ácidos de Lewis tras un proceso de sililación en presencia de una fuente nucleofílica de silicio.

Inicialmente, se exponen los resultados obtenidos durante la optimización de las condiciones experimentales de reacción (catalizador, carga catalítica, temperatura, tiempo de reacción, disolvente…) enfocadas a controlar la selectividad de la reacción hacia la obtención de la lactama **44**, desfavoreciendo la formación de los compuestos **45** como consecuencia de un proceso doble adición.



Esquema 5. Reacción de Mukaiyama-Mannich catalizada por disulfonimidas.

De esta forma, se han podido determinar las condiciones óptimas que han permitido acceder de forma selectiva a una gran variedad de γ-lactamas con buenos rendimientos y completa diastereoselectividad *trans*. La reacción ha demostrado ser aplicable para iminas derivadas tanto de aldehídos alifáticos como aromáticos, obteniéndose buenos resultados independientemente del carácter electrónico del anillo aromático. Asimismo, se ha podido aplicar con éxito a sustratos con diferentes grupos aromáticos directamente unidos al nitrógeno. Finalmente, los compuestos γ-lactámicos han sido sometidos de forma selectiva a diferentes transformaciones químicas, siendo posible la desprotección del átomo de nitrógeno, así como la derivatización del ácido carboxílico.