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Four-Step Synthesis of (−)-4-*epi*-Presilphiperfolan-8α-ol by Intramolecular Iron Hydride Atom Transfer-Mediated Ketone-Alkene Coupling and Studies to Access *trans*-Hydrindanols with a Botryane Scaffold

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Abstract: From an (*R*)-(+)-pulegone-derived building block that incorporates the stereo-defined tertiary carbon bearing a methyl group, as found in the targeted sesquiterpenoid, a four-step synthesis of (−)-4-*epi*-presilphiperfolan-8-α-ol was achieved. The key processes involved are a ring-closing metathesis leading to a bridged alkene-tethered ketone and its subsequent Fe^{III}-mediated metal-hydride atom transfer (MHAT) transannular cyclization. This synthetic method, implying an irreversible addition of a carbon-centered radical upon a ketone by means of a hydrogen atom transfer upon the alkoxy radical intermediate, was also applied in the synthesis of *trans*-fused hydrindanols structurally related to botrydial compounds.

Introduction

Presilphiperfolanols[1] constitute a small group of sesquiterpenoids produced by fungi with antimycobacterial and insect-repelling effects. The flagship member of this family of natural products is presilphiperfolan-8α-ol (**I**),[2] a biosynthetic precursor of other triquinane-type molecules[3] and botryanes.[4] Structurally, presilphiperfolanols are characterized by a sterically demanding tricyclic core embodying a 6,5,5-fused ring system with five contiguous stereogenic carbon atoms. Due to their structurally challenging nature,[5] few synthetic approaches to these natural products have been published (Figure 1). Among them, only Snyder has reported a total synthesis of the highly strained presilphiperfolan-8α-ol, which was achieved in 14 synthetic steps, the key one being a Pd-catalyzed tandem cyclization.[6] Notably, this synthetic route involves the generation of a tricyclic intermediate bearing an embedded *trans*-indane, which provides access to the highly demanding 1,2-*trans*-bicyclo[3.3.0]octane framework of the presilphiperfolanol skeleton after a ring contraction step. Additional achievements in the presilphiperfolanol synthetic field are as follows: (a) the first synthesis was reported by Weyerstahl;[7] (b) the first asymmetric synthesis was described by Stoltz;[8] (c) a tandem process involving Pauson-Khand and 6π-electrocyclization reactions was developed by Gong and Yang to access the presilphiperfolane ring system, the overall synthetic process

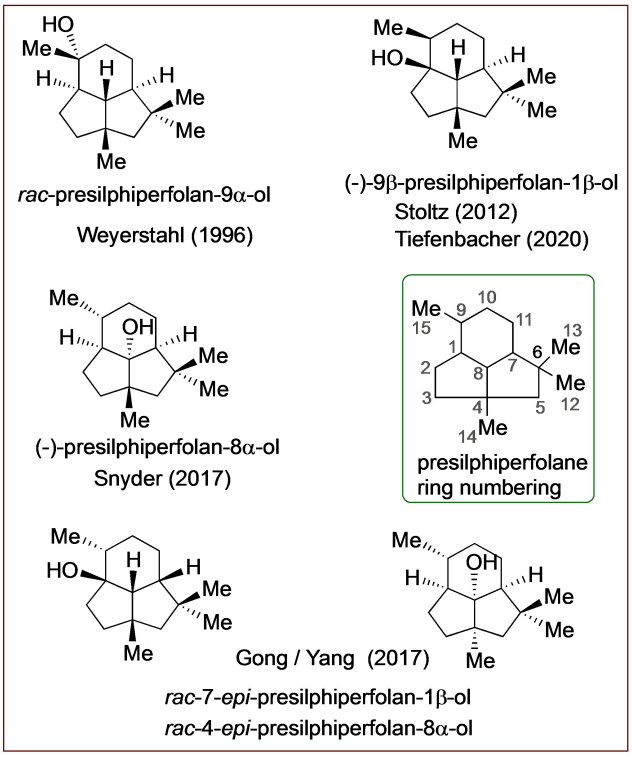

Figure 1. Presilphiperfolanol compounds: previous syntheses.

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leading to two novel unnatural presilphiperfonalol-type compounds,[9] and (d) the shortest synthesis to date of a presilphiperfolanol sesquiterpenoid was achieved by Tiefenbacher using supramolecular catalysis.[10]

In the present study, we examined the applicability of a radical ring closure to access the presiphiperfolane[11,12] and botryane[13] scaffolds. By increasing the arsenal of synthetic methods for C–C bond formation, metal-hydride atom transfer (MHAT)-promoted reactions have opened new perspectives for the retrosynthetic analysis of complex molecules and natural products.[14] In recent years, various researchers,[15] including our group,[16] have described diverse hydrofunctionalizations and couplings of unactivated alkenes based on MHAT reactions. These processes represent powerful new tools in organic synthesis, as they generate radical intermediates that allow otherwise challenging combinations between certain functional groups.

A noteworthy contribution in this field by our group is the intramolecular coupling of alkenes with ketones,[16a] there being no equivalent reaction in the literature (Figure 2a). Previously reported methodologies that couple alkenes with carbonyls differ in a carbonyl being used as the radical precursor.[17,18] In our radical conditions, the more challenging intermolecular version of the reaction was achieved by controlling the highly unstable alkoxy radical intermediate through the addition of Fe^{II} salts, which enhances the reversibility of the process.[16d] By allowing the assembly of sterically congested structures containing tertiary alcohols and quaternary centers as well as novel disconnections of strategic bonds, the application of our radical methodology could greatly facilitate the design of synthetic approaches in the natural products field.

The goal of the present work was to explore the applicability of the aforementioned Fe-HAT methodology in synthetic strategies towards compounds embodying presilphiperfolane and botryane scaffolds (Figure 2b). As functionalized hydrindanes, compounds bearing the botryane structure are of particular interest, with potential application as building-blocks to access the presilphiperfolanol tricyclic ring.

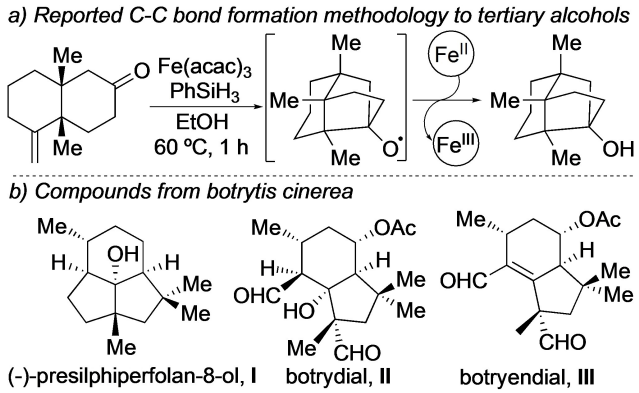


Figure 2. (a) Our previously reported procedure: intramolecular MHAT alkene-ketone coupling. (b) Sesquiterpenes with presilphiperfolane (**I**) and botryane (**II** and **III**) scaffolds.

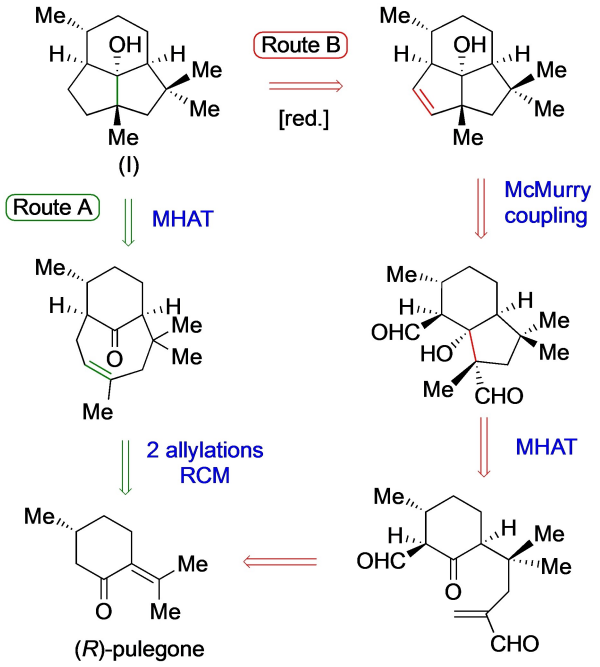
Results and Discussion

Synthesis of (−)-4-epi-presilphiperfolan-8α-ol

The structural complexity of presilphiperfolan-8-ol renders the total synthesis of this tricyclic sesquiterpene alcohol a particularly demanding proposition. The challenge resides above all in the uncommon and compact tricyclo[5.3.1.$0^{4,11}$]undecane framework[6,8] and the highly strained *trans* fusion between the 5-membered rings.[19]

To explore new synthetic approaches to presilphiperfolan-8-ol (**I**), we proposed two retrosynthetic routes (Scheme 1). In a straightforward pathway (A), an eight-membered ring would be synthesized from the commercially available (*R*)-pulegone, the key steps involving a bisallylation and a ring-closing metathesis, followed by an MHAT-based alkene-ketone transannular cyclization. The uncertainty of this approach lies in the *trans*-fusion of **I**, which would imply a high degree of ring strain[20] in the ring-closing step required to achieve the sterically congested core of this natural product. In an alternative route (B), the stereochemistry would be controlled by starting from a precursor similar to botrydial and using an MHAT-promoted ring closure for the polyfunctionalized hydrindane synthesis. The stereochemistry of the newly formed ring would be key to attaining the tricyclic framework of **I** by an additional cyclization from the bicyclic dialdehyde using a McMurry coupling. Route B (from a botryane compound to the presilphiperfolanol target) would constitute a reverse biosynthetic approach.

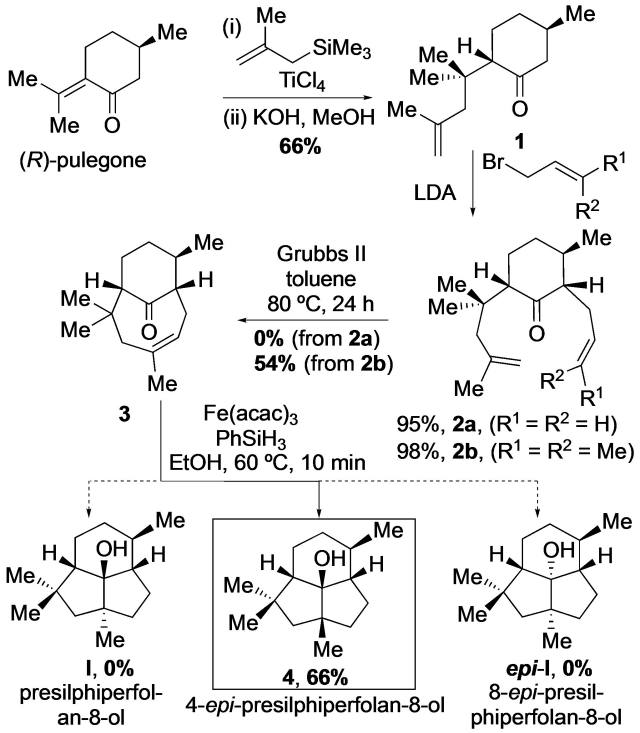
In the synthetic studies focused on route A, compound **2a** was synthesized by an initial Sakurai allylation of (*R*)-pulegone followed by an epimerization process leading to a 4:1 epimeric mixture of **1**[11] and a subsequent LDA-based allylation[6,11]



Scheme 1. Retrosynthetic analysis of presilphiperfolanol **I**.

(Scheme 2). Although a range of conditions were tried, the ring-closing metathesis reaction from **2a** did not give the desired bridged eight-membered ring **3**, and instead the dimerization product was obtained by cross-metathesis of the less substituted alkene **2a**.[21] It was envisaged that the cross-metathesis could be avoided by the use of the highly substituted dialkene **2b**.[22] In this case, the ruthenium would be forced to insert into the disubstituted alkene and react intramolecularly with the trisubstituted double bond. Thus, the cross-metathesis would lead to the formation of a highly disfavored tetrasubstituted double bond. Gratifyingly, our hypothesis proved correct and after some refinements, such as the slow addition of ruthenium by syringe pump, we were able to isolate the desired keto-alkene **3** in 54% yield.

With synthetic intermediate **3** in hand, we proceeded to evaluate the key MHAT radical coupling conditions. Although the reaction gave a good clean yield of coupled product, only 4-*epi*-presilphiperfolan-8-ol (**4**) was obtained, as corroborated by comparison with the NMR spectra of the racemic compound reported by Yang (see Supporting Information).[9] The synthesis of **4** through such a short synthetic sequence emphasizes the robustness and operational simplicity of our methodology for C–C bond formation. Notably, the new reported synthesis of **4** has four steps, compared to the 10 steps of the only synthetic precedent.[9] However, the stereocontrolled process did not furnish the targeted compound **I** in any of the modified reaction conditions, in which variable catalyst quantities, temperature, and reaction times were tested. As a last resort, we evaluated other radical methodologies to couple ketones to alkenes (*inter alia*, Bu_3SnH[23] and SmI_2[24]) in the hope of a more favourable stereochemical outcome, but no desired product was obtained.

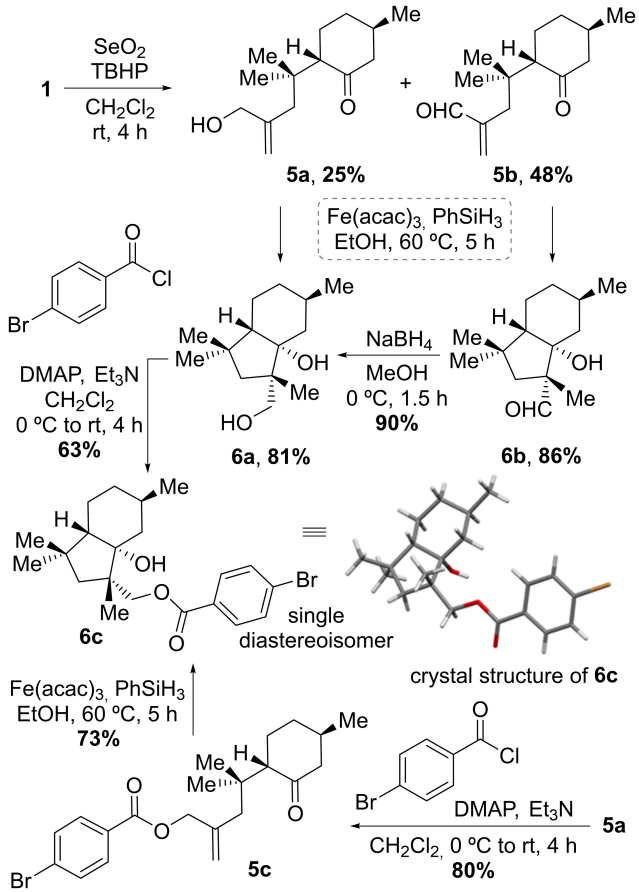


Scheme 2. Four-step synthesis of 4-*epi*-presilphiperfolan-8β-ol.

Synthesis of trans-hydrindan-3a-ol compounds

At this point, we decided to evaluate an approach to the 6,5,5-membered ring system of **I** from a *cis*-hydrindane synthesis of the tricarbonyl compound needed to prepare the hydrindanol with the requisite stereoparent commenced with a Riley oxidation[25] of alkene **1** (Scheme 3). The process rendered a separable mixture of allylic alcohol **5a** and the α,β-unsaturated aldehyde **5b**. Both compounds underwent MHAT-promoted radical cyclization to give tertiary hydrindanols **6a** and **6b** with a *trans*-diastereoselectivity and excellent yield. The stereostructure of **6a** was confirmed by X-Ray crystallographic analysis of bromobenzoate **6c**.

It is noteworthy that compound **5b** underwent MHAT cyclization, even though the radical precursor was an electron-deficient alkene[26] Reduction of the resulting aldehyde **6b** with sodium borohydride demonstrated that the stereochemical outcome of this reaction was identical to that of **6a**. To account for this result, we speculated that the primary alcohol in **5a** might be responsible for the formation of the tertiary alcohol on the lower face. However, when the alcohol was protected



Scheme 3. Synthesis of *trans*-hydrindanes **6**.

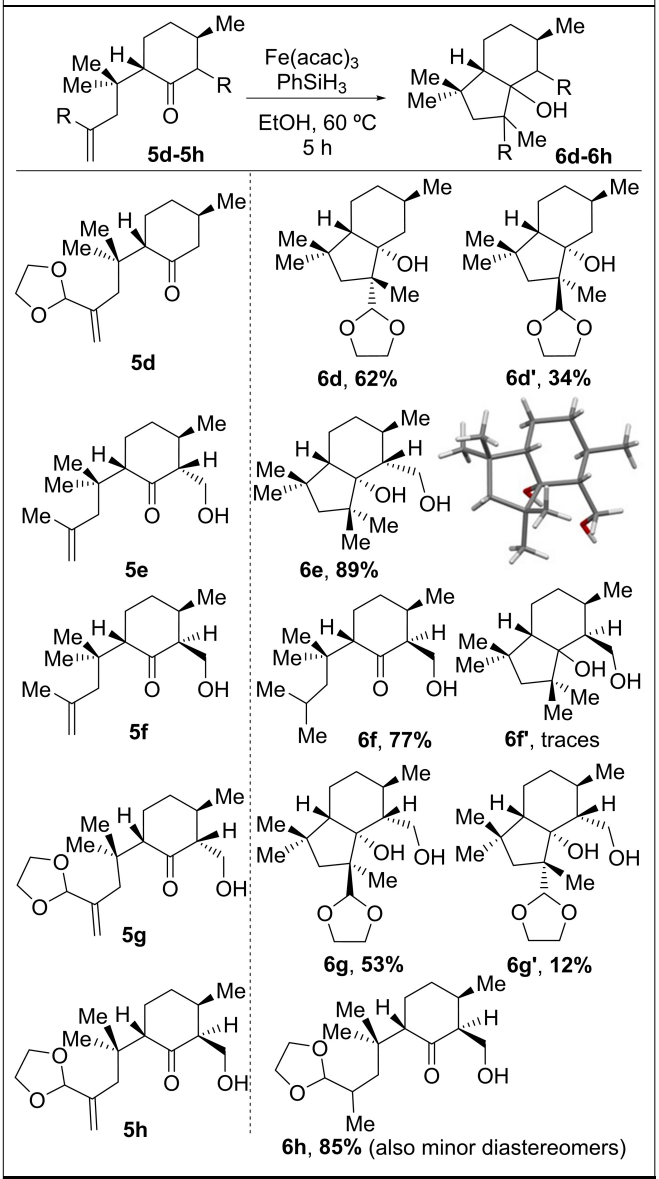
(**5c**) to avoid hydrogen bond formation in the intermediate, and **5c** was submitted to MHAT conditions, the stereochemistry was the same as for **5a** and **5b**. The generation of the *trans* product indicated that the oxygen atom did not exert a directing effect in the cyclization process.

To gain more insight into the stereochemical outcome of this radical cyclization reaction leading to substituted hydrindanol compounds, we decided to evaluate if modifying the functionalities in the radical precursors (e.g., synthesizing compounds **5d**–**5h**, Scheme 4) would overturn the diastereomeric course of the annulation. Aldehyde **5b** was protected, using ethyleneglycol and tartaric acid[27] to give acetal **5d**. The alcohol chain was then installed in **5b** and **5d** using benzotriazole-1-yl-methanol for the in situ generation of formaldehyde[28] to obtain compounds **5e**–**5h** in good yields.

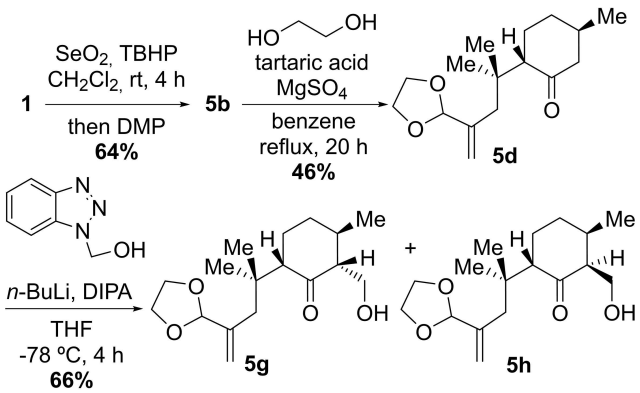
With the alkene-tethered ketones **5d**–**5h** in hand, the radical cyclization for hydrindane formation was explored (Table 1). Cyclization of compound **5d**, with a bulky acetal group, led to a mixture of the *trans*-diastereomers **6d** and **6d'**. To evaluate the influence of the hydroxyl group in the side chain on the resulting stereochemistry, cyclization of the substrates **5e** and **5f** was carried out under the same MHAT conditions. Surprisingly, ring closure only occurred from substrate **5e**, which again rendered a *trans*-diastereomer, **6e**, with good yields, whereas compound **5f** was mostly reduced to give **6f**, among other products, including traces of the coupled product **6f'**. Analogously to the results obtained for **5e** and **5f**, when substrates **5g** and **5h** were submitted to our reaction conditions, only compound **5g** gave the desired product **6g** with good yields. Keto-alkene **5h** provided the reduced product **6h** and some minor compounds. These results led us to conclude that the configuration of the carbon atom linked to the hydroxymethyl side chain in compounds **5e**–**5h** has a strong influence on the reaction, either by steric or coordination effects.

Once compound **6g** had been obtained, a Dess-Martin oxidation, followed by cleavage of acetal **7** with iodine in acetone, provided the botrydial-type compounds **8** and ***epi*-8**. The latter arose from a partial epimerization at C-4 through a retro-aldol process involving β-aldol fragmentation and subsequent recyclization,[29] which even the mild reaction conditions used could not avoid (Scheme 5). The NMR data of *epi*-**8** correlated well with those reported for 8,9-epibotrydial,[30] considering that *trans*-hydrindanol *epi*-**8** lacks the acetoxy substituent present in the terpene.

Table 1. Fe-catalyzed HAT cyclzation of keto-alkenes: substrate scope.[a]



[a] X-ray data for compounds **6e**, **6g**, and the corresponding 4-bromobenzoates of **6f'** and **6g'** are reported in the Supporting Information.



Scheme 4. Preparation of substrates **5d**–**5h**.

During these studies of keto-alkene radical cyclization, the regular formation of *trans*-hydrindanes was observed (e.g. **8**. Scheme 5 and Figure 3). However, *cis*-hydrindane compounds (e.g. **9**, Figure 3) were not isolated due to an unfavorable steric interaction attributed to the presence of a *gem*-dimethyl unit adjacent to the ring fusion (Figure 3). In contrast, relief of these steric interactions in the *trans*-hydrindanes **8** sufficiently compensates for the strain introduced by formation of the *trans*-ring fusion in the radical cyclization and allows compounds with the stereostructure of **8** to be isolated.

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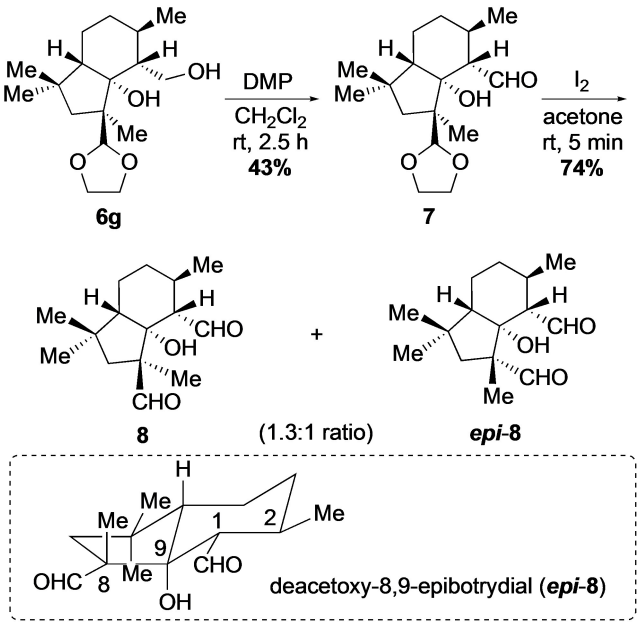

Scheme 5. Synthesis of botrydial-type analogs and botryane numbering.

In order to establish the thermodynamic stability of deacetoxybotrydial diastereomers with a *cis* (not isolated)/*trans* ring fusion as well as those epimeric at C-8 (Figure 3), DFT calculation of the stability of structures corresponding to the isolated compounds **8** and deacetoxy-8,9-epibotrydial (*epi*-**8**) and deacetoxybotrydial (**9**) and its epimer at C-8 (*epi*-**9**) were carried out.[31]

The formation of the final products was hypothesized to occur in thermodynamic conditions. Thus, DFT calculations were carried out with the pairs of diastereoisomers **8**/***epi*-8** and **9**/***epi*-9**, and the evaluation of their relative stabilities confirmed the expected energy trends, according to the experimental ratios. Indeed, isomers **8** and *epi*-**8** were found to be close in energy, with a slight difference of 0.7 kcal/mol in favor of the experimental major **8**. This value corresponds to a theoretical preference slightly over the limit of the method differentiation capability, in fair agreement with the very narrow experimental 1.3 : 1 selectivity. Exploration of both isomers of **8** does not show crucial structural differences. Indeed, all computed structures show highly distorted five and six membered rings. In any case, a weak H-bond can be observed in **8**, which is absent in the rest of the isomers. Also, one of the critical methyl groups in **8** seems to be in a *pseudo* equatorial disposition, while two of the methyl groups in *epi*-**8** are at a distance short enough to induce some negative steric hindrance (Figure 3). On the other hand, isomer **9** is remarkably more stable than *epi*-**9**, by more than 6.0 kcal/mol. That energy difference would ensure the complete absence of the *epi*-**9** isomer in the final reaction mixture, as was found experimentally.

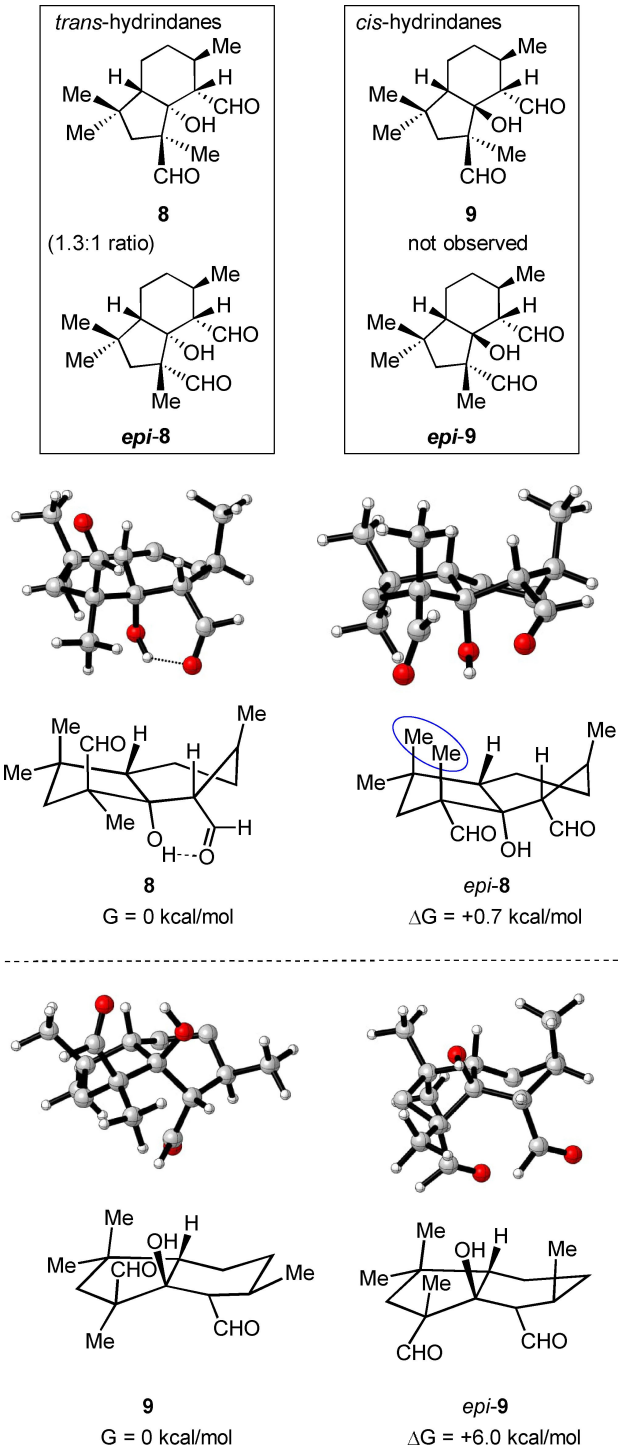

Figure 3. Structure and stability relative (DFT calculations) of isolated *trans*-hydrindanols **8** and unobserved *cis*-hydrindanols **9**.

The Conclusion

In summary, we have shown that the Fe^{III} hydrogen atom transfer to promote alkene-ketone coupling reactions can be employed to synthesize 4-*epi*-presilphiperfolan-8-ol in only four synthetic steps. It was also demonstrated that this radical

methodology can provide polysubstituted *trans*-fused hydrindane ring compounds, related to the botryane skeleton, which bear five contiguous chiral centers, two of them being quaternary carbons.

Experimental Section

Synthesis of presilphiperfolanol 4: To a solution of keto-alkene **3** (16 mg, 0.073 mmol) and $Fe(acac)_3$ (26 mg, 0.073 mmol) in absolute EtOH (1.25 mL) and ethylene glycol (0.25 mL), $PhSiH_3$ (22 μL, 0.182 mmol) was added. The resulting mixture was heated to 60 °C with stirring for 1 h. The reaction was then cooled to room temperature and diluted with brine. The aqueous layer was extracted three times with Et_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (hexane→hexane/EtOAc 95:5) to furnish compound **4** (11 mg, 66% yield) as a yellowish oil.

Deposition Numbers 2128943 (for **6c**), 2128944 (for **6e**), 2154245 (for **6g**), and 2128945 (for **6g''**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Supporting Information

Supporting Information includes detailed experimental procedures, X-Ray data, DFT calculations, and copies of NMR spectra.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting material of this article.

Keywords: C–C coupling · natural products · radical reactions · strained molecules · triquinanes

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