molbank

MDPI

Short Note

Diethyl(benzamido(diisopropoxyphosphoryl)methyl)phosphonate

Adrián López-Francés, Francisco Palacios, Aitor Maestro * and Javier Vicario *

Departamento de Química Orgánica I, Centro de Investigación y Estudios Avanzados "Lucio Lascaray", Facultad de Farmacia, University of the Basque Country, UPV/EHU Paseo de la Universidad 7, 01006 Vitoria-Gasteiz, Spain

* Correspondence: aitor.maestro@ehu.eus (A.M.); javier.vicario@ehu.eus (J.V.); Tel.: +34-945013087 (J.V.)

Abstract: Bisphosphonates are widely used in medicine and related areas, mainly for the treatment of bone diseases, such as osteoporosis. However, their synthesis is usually performed under harsh reaction conditions. In order to overcome this limitation, the present work illustrates a new synthetic route to access the title α-aminobisphosphonate in milder reaction conditions using α-phosphorylated imines as key intermediates.

Keywords: bisphosphonates; α-iminophosphonates; Pudovik reaction

check for updates

Citation: López-Francés, A.; Palacios, F.; Maestro, A.; Vicario, J. Diethyl (benzamido(diisopropoxyphosphoryl) methyl)phosphonate. *Molbank* **2022**, *2022*, M1424. https://doi.org/10.3390/M1424

Academic Editors: Bartolo Gabriele, Raffaella Mancuso and Zhengguo Cai

Received: 19 July 2022
Accepted: 9 August 2022
Published: 11 August 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Phosphonate-containing organic molecules such as aminophosphonate and bisphosphonate derivatives are well-known for their biological activities [1–5]. Consequently, many routes have been reported for their synthesis [6–10]. In particular, bisphosphonates have shown high potential as enzyme inhibitors [11–13], anti-inflammatory agents [14] or cancer treatments [15–17]. In particular, zoledronic acid, considered an essential medicine by the World Health Organization [18,19], and other bisphosphonate analogues, are broadly used for the treatment of osteoporosis and other bone diseases (Figure 1).

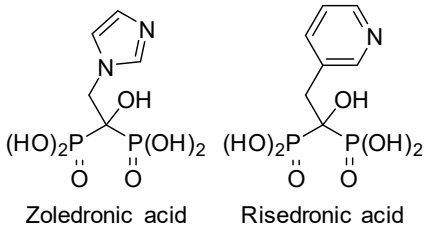
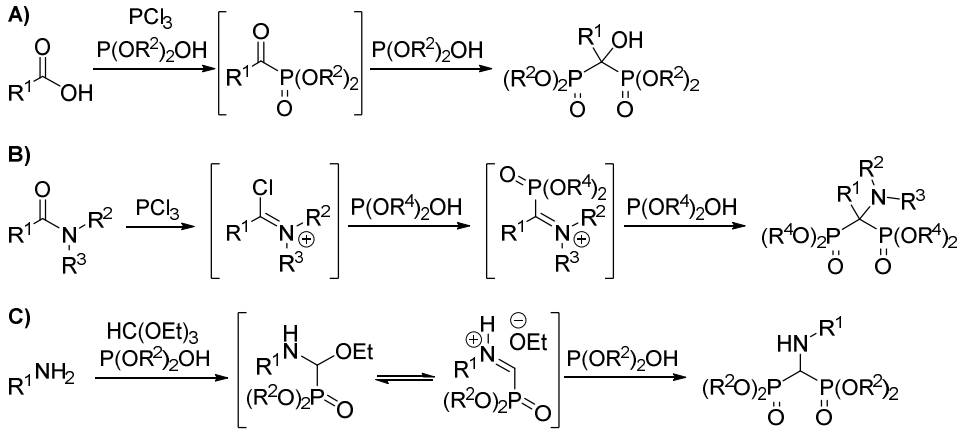


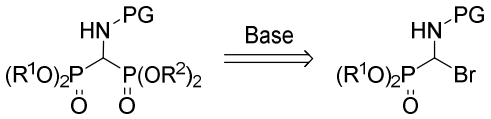
Figure 1. Bisphosphonate drugs.

Concerning the synthetic routes to α-hydroxy and α-aminobisphosphonates, the most widely used methods make use of carboxylic acids, amides or amines as starting materials (Scheme 1) [6,8]. However, these methodologies often require harsh reaction conditions or high temperatures.

In this context, α-iminophosphonates have emerged as promising substrates to access α-aminophosphonate derivatives [20,21] that allow phosphorylated imine intermediates and make them suitable for subsequent transformations [22–24]. It should be noted that all those methodologies require milder reaction conditions when compared with the previously known strategies (Scheme 1B,C). Over the last decade, our group has been working on the synthesis of organophosphorus compounds [22,25–30]. Based on Steglich's [31] and Kobayashi's reports [32–34], as well as our previous experience with nucleophilic additions to imines [22,26,28,35,36], in this case, we propose the synthesis of chiral diethyl (benzamido (diisopropoxyphosphoryl) methyl) phosphonate through a Pudovik reaction using α-bromo aminophosphonates as the starting material of the corresponding imine (Scheme 2).



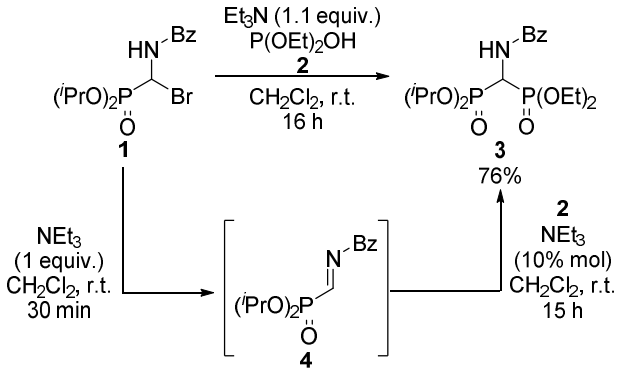
Scheme 1. Main synthetic routes to bisphosphonates. (**A**) Synthesi of α hydroxy bisphosphonates from car-boxylic acids; (**B**) Synthesis of α aminobisphosphonates from amides; (**C**) Synthesis of α amino bisphosphonates from amines.



Scheme 2. Our proposal to access amino bisphosphonates.

2. Results

The proposed synthesis requires two base-catalyzed steps. For this reason, we initially tested the direct addition of diethyl phosphite **2** to α-bromo aminophosphonate **1** in presence of an excess of triethylamine, which is known to promote the elimination of hydrobromic acid as well as to act as a catalyst in the Pudovik reaction. In order to demonstrate the formation of the α-iminophosphonate intermediate **4**, the reaction was monitored by ^{31}P NMR (^{31}P NMR of α-iminophosphonate **4** (δ = 1.7 ppm)). The addition of the phosphite 2 with 0.1 equivalents of trimethylamine afforded the bisphosphonate product **3.** However, the low stability of α-iminophosphonates makes this two-step procedure less efficient. Therefore, the synthesis of 3 was performed using a single-step procedure, affording the bisphosphonate **3** in 76% yield after purification (Scheme 3).



Scheme 3. Synthesis of diethyl (benzamido (diisopropoxyphosphoryl) methyl) phosphonate **3**.

Aminobisphosphonate **3** was extensively characterized by ^{1}H, ^{13}C{^{1}H] NMR, DEPT, ^{31}P NMR, 2D-COSY NMR {^{1}H-^{1}H}, 2D-HSQC NMR {^{1}H-^{13}C}, 2D-HMBC NMR {^{1}H-^{13}C}, FTIR spectra and HRMS experiments (Supplementary Materials).

The most relevant signal of compound **3** in the ^{1}H NMR spectrum ($CDCl_3$) is the proton corresponding to the P-C<u>H</u>-P moiety, which is seen as a representative triplet doublet at δ_H = 5.19 ppm ($^{2}J_{PH}$ = 21.5 Hz and $^{3}J_{HH}$ = 10.2 Hz), the result of the coupling

between CH and the NH of the amide moiety and the coupling of CH with each of the contiguous phosphonates. In addition, due to the low interchange ratio of the NH belonging to the amide group, a doublet is observed at 6.54 ppm, showing coupling only with the neighboring CH moiety ($^3J_{HH}$ = 10.2 Hz). Likewise, in the ^{13}C NMR spectrum of phosphorylated derivative **3**, the two doublets corresponding to the two diastereotopic CH carbons of the *iso*-propyl moiety appear at δ_C = 72.8 ppm ($^2J_{CP}$ = 17.4 Hz) and δ_C = 72.7 ppm ($^2J_{CP}$ = 17.7 Hz). The methylene carbons corresponding to the two ethoxy groups can be also detected as two doublets with chemical shifts at δ_C = 63.7 ppm (d, $^2J_{CP}$ = 29.3 Hz) and δ_C = 63.6 ppm (d, $^2J_{CP}$ = 29.7 Hz). A very characteristic signal corresponding to the CH carbon appears as a double doublet at δ_C = 44.9 ppm with strong coupling with the two adjacent phosphorus atoms ($^1J_{CP}$ = 148.4 Hz and $^1J_{CP}$ = 146.6 Hz). Finally, due to the presence of a chiral center in the structure, the two carbons corresponding to the four methyl groups at the isopropyl moieties appear as two doublets at 24.7 ppm ($^3J_{CP}$ = 3.3 Hz) and 23.9 ppm ($^3J_{CP}$ = 5.4 Hz) for isopropyl groups. However, both methyl groups of the ethoxy group appear overlapped as one doublet at 16.5 ppm ($^3J_{CP}$ = 6.0 Hz). As expected, the ^{31}P NMR spectrum of substrate **3** shows two doublets at δ_P = 16.5 and 14.3 ppm ($^2J_{PP}$ = 31.3 Hz).

The FTIR spectrum of compound **3** shows a stretching vibration around ν = 3218 cm^{-1}, which is typical for N-H moiety. In addition, several absorptions within the interval ν = 3056–2986 cm^{-1} correspond to the stretching vibration of aromatic and aliphatic C-H bonds. One of the most relevant absorption signals observed in the IR spectrum corresponds to the stretching vibration of the amide C=O bond at ν = 1657 cm^{-1}. The vibration of the P=O bonds corresponding to the ethyl and isopropyl phosphonates results in moderate absorption bands at ν = 1258 cm^{-1} and ν = 1163 cm^{-1}. Due to the presence of the phosphorylated groups, the IR spectrum shows two signals at ν = 1144 cm^{-1} and ν = 1109 cm^{-1} which correspond to the P-O-C stretching bonds of both phosphonate moieties.

The high-resolution mass spectrometry (HRMS (ESI-TOF) m/z) experiment shows a peak corresponding to the molecular ion with an exact mass of 436.1642 $(M + H)^+$ that fits with the predicted mass ($(M + H)^+$ = 436.1654) of the calculated molecular formula ($C_{18}H_{32}NO_7P_2$) far within the standard tolerated deviation.

3. Materials and Methods

3.1. General Experimental Information

Solvents used for extraction and chromatography were technical grade. All the solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with silica gel 60 F254 plates. Visualization was accomplished by UV light. ^{1}H and ^{13}C-NMR spectra were recorded on a Varian Unity Plus (Varian Inc., NMR Systems, Palo Alto, Santa Clara, CA, USA) (at 300 MHz, 75 MHz, 120 MHz and 282 MHz) and on a Bruker Avance 400 (Bruker BioSpin GmbH, Rheinstetten, Germany) (at 400 MHz for ^{1}H and 100 MHz for ^{13}C). Chemical shifts (δ) were reported in ppm relative to residual CHCl3 (δ = 7.26 ppm for ^{1}H and δ = 77.16 ppm for ^{13}C NMR). Coupling constants (J) were reported in Hertz. Data for ^{1}H NMR spectra were reported as follows: chemical shift, multiplicity, coupling constant and integration. Multiplicity abbreviations were as follows: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. ^{13}C-NMR peak assignments were supported by distortionless enhanced polarization transfer (DEPT). High resolution mass spectra (HRMS) were obtained by positive-ion electrospray ionization (ESI). Data were reported in the form m/z (intensity relative to base = 100). Infrared spectra (IR) were taken in a Nicolet iS10 Thermo Scientific spectrometer (Thermo Scientific Inc., Waltham, MA, USA) as neat solids. Peaks were reported in cm^{-1}.

*3.2. Experimental Procedures and Characterization Data for Aminobisphosphonate **3***

Synthetic procedure: To a solution of **1** (2 mmol, 756 mg, 1.0 equiv.) in dry CH_2Cl_2 (3 mL) under N_2 atmosphere, triethylamine (2.2 mmol, 307 µL, 1.1 equiv.) and diethyl phosphite **2** (2 mmol, 260 µL, 1 equiv.) were sequentially added. Then, the reaction was stirred at room temperature for 16 h, concentrated under vacuum and purified by column chromatography (hexane/EtOAc) to afford 662 mg (76%) of **3** as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.78 (d, $^3J_{HH}$ = 7.2 Hz, 2H, 2 × CH_{Ar}), 7.54 (t, $^3J_{HH}$ = 7.4 Hz, H, CH_{Ar}), 7.46 (t, $^3J_{HH}$ = 7.4 Hz, 2H, 2 × CH_{Ar}), 6.54 (d, $^3J_{PH}$ = 10.2 Hz, 1H, NH), 5.19 (td, $^2J_{PH}$ = 21.5 Hz, $^3J_{HH}$ = 10.2 Hz, 1H, CH), 4.87–4.74 (m, 2H, 2 × CH O^{i}Pr), 4.35–4.11 (m, 4H, 2 × CH_2 OEt), 1.65–0.97 (m, 18H, 2 × CH_3 OEt + 4 × CH_3 O^{i}Pr) ppm.

^{13}C-NMR {^{1}H} (101 MHz, $CDCl_3$) δ 166.5 (t, $^3J_{CP}$ = 4.0 Hz, C = O), 133.7 (C_{quat}), 132.2 (CH_{Ar}), 128.9 (2 × CH_{Ar}), 127.2 (2 × CH_{Ar}), 72.8 (d, $^2J_{CP}$ = 17.4 Hz, CH O^{i}Pr), 72.7 (d, $^2J_{CP}$ = 17.7 Hz, CH O^{i}Pr), 63.7 (d, $^2J_{CP}$ = 29.3 Hz, CH_2 OEt), 63.6 (d, $^2J_{CP}$ = 29.7 Hz, CH_2 OEt), 44.9 (dd, $^1J_{CP}$ = 148.4 Hz, $^1J_{CP}$ = 146.6 Hz, CH), 24.7 (d, $^3J_{CP}$ = 3.3 Hz, 2 × CH_3 O^{i}Pr), 23.9 (d, $^3J_{CP}$ = 5.4 Hz, 2 × CH_3 O^{i}Pr), 16.5 (d, $^3J_{CP}$ = 6.0 Hz, 2 × CH_3 OEt) ppm.

^{31}P-NMR (162 MHz, $CDCl_3$) δ 16.5 (d, $^2J_{PP}$ = 31.3 Hz), 14.3 (d, $^2J_{PP}$ = 31.3 Hz) ppm.

M.p. (Et_2O) = 153–155 °C.

FTIR (neat) $\boldsymbol{\nu_{max}}$: 3218 (NH), 3056 (=CH), 2987 (C-H), 1657 (C=O), 1258 (P=O), 1163 (P=O), 1144 (P-O-C), 1109 (P-O-C) cm^{-1}.

HRMS (ESI-TOF) *m*/*z*: [M + H] $^+$ calcd for $C_{18}H_{32}NO_7P_2$ 436.1654, Found 436.1642.

4. Conclusions

The synthesis of bisphosphonate derivative **3** was accomplished by the direct addition of diethyl phosphite **2** to a solution of α-bromo aminophosphonate **1** under the presence of an excess of triethylamine. ^{1}H, ^{13}C, ^{31}P and 2D-NMR, and FTIR and HRMS experiments unequivocally confirm the structure of the obtained compound.

Supplementary Materials: The following are available online, ^{1}H, ^{13}C, ^{31}P and 2D-NMR, and FTIR, HRMS and UV spectra copies of compound **3**.

Author Contributions: Conceptualization, A.L.-F., F.P., A.M. and J.V.; methodology, A.L.-F. and A.M.; software, A.L.-F. and A.M.; validation, A.M. and J.V.; formal analysis, A.L.-F. and A.M.; investigation, A.L.-F. and A.M.; resources, F.P. and J.V.; data curation, A.L.-F. and A.M.; writing—original draft preparation, A.L.-F. and A.M.; writing—review and editing, A.L.-F., F.P., A.M. and J.V.; visualization, A.M. and J.V.; supervision, A.M. and J.V.; project administration, A.M. and J.V.; funding acquisition, F.P. and J.V. All authors have read and agreed to the published version of the manuscript.

Funding: Financial support by Ministerio de Economía, Industria y Competividad (RTI2018-101818-B-I00) and Gobierno Vasco (GV, IT 992-16) is gratefully acknowledged. A.L.-F. thanks the Basque Country Government for a predoctoral grant.

Data Availability Statement: The data presented in this study are available in the supplementary materials file or on request from the corresponding author (^{1}H, ^{13}C, ^{31}P, 2D-COSY, 2D-HSQC and 2D-HMBC NMR, FTIR, HRMS and HPLC spectra.

Acknowledgments: The authors give thanks for technical and human support provided by SGIker (UPV/EHU/ERDF, EU).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Krečmerová, M.; Majer, P.; Rais, R.; Slusher, B.S. Phosphonates and Phosphonate Prodrugs in Medicinal Chemistry: Past Successes and Future Prospects. *Front. Chem.* **2022**, *10*, 889737. [CrossRef]
2. Kudzin, Z.H.; Kudzin, M.H.; Drabowicz, J.; Stevens, C.V. Aminophosphonic Acids—Phosphorus Analogues of Natural Amino Acids.Part 1: Syntheses of α-Aminophosphonic Acids. *Curr. Org. Chem.* **2012**, *15*, 2015–2071. [CrossRef]
3. Orsini, F.; Sello, G.; Sisti, M. Aminophosphonic Acids and Derivatives. Synthesis and Biological Applications. *Curr. Med. Chem.* **2009**, *17*, 264–289. [CrossRef]

4. Barbosa, J.S.; Braga, S.S.; Almeida Paz, F.A. Empowering the Medicinal Applications of Bisphosphonates by Unveiling Their Synthesis Details. *Molecules* **2020**, *25*, 2821. [CrossRef]
5. Kaboudin, B.; Daliri, P.; Faghih, S.; Esfandiari, H. Hydroxy- and Amino-Phosphonates and -Bisphosphonates: Synthetic Methods and Their Biological Applications. *Front. Chem.* **2022**, *10*, 890696. [CrossRef]
6. Chmielewska, E.; Kafarski, P. Synthetic Procedures Leading towards Aminobisphosphonates. *Molecules* **2016**, *21*, 1474. [CrossRef]
7. Maestro, A.; del Corte, X.; López-Francés, A.; Martinez De Marigorta, E.; Palacios, F.; Vicario, J. Asymmetric Synthesis of Tetrasubstituted α-Aminophosphonic Acid Derivatives. *Molecules* **2021**, *26*, 3202. [CrossRef]
8. Dussart, J.; Deschamp, J.; Migianu-Griffoni, E.; Lecouvey, M. From Industrial Method to the Use of Silylated P(III) Reagents for the Synthesis of Relevant Phosphonylated Molecules. *Org. Process Res. Dev.* **2020**, *24*, 637–651. [CrossRef]
9. Skarpos, H.; Osipov, S.N.; Vorob'Eva, D.V.; Odinets, I.L.; Lork, E.; Röschenthaler, G.V. Synthesis of Functionalized Bisphosphonates via Click Chemistry. *Org. Biomol. Chem.* **2007**, *5*, 2361–2367. [CrossRef]
10. Bortolamiol, E.; Chiminazzo, A.; Sperni, L.; Borsato, G.; Fabris, F.; Scarso, A. Functional Bisphosphonate Synthesis for the Development of New Anti-Resorption Bone Drug Candidates. *New J. Chem.* **2019**, *43*, 12641–12649. [CrossRef]
11. Leung, C.Y.; Langille, A.M.; Mancuso, J.; Tsantrizos, Y.S. Discovery of Thienopyrimidine-Based Inhibitors of the Human Farnesyl Pyrophosphate Synthase—Parallel Synthesis of Analogs via a Trimethylsilyl Ylidene Intermediate. *Bioorg. Med. Chem.* **2013**, *21*, 2229–2240. [CrossRef]
12. Lacbay, C.M.; Mancuso, J.; Lin, Y.S.; Bennett, N.; Götte, M.; Tsantrizos, Y.S. Modular Assembly of Purine-like Bisphosphonates as Inhibitors of HIV-1 Reverse Transcriptase. *J. Med. Chem.* **2014**, *57*, 7435–7449. [CrossRef]
13. Lee, H.F.; Lacbay, C.M.; Boutin, R.; Matralis, A.N.; Park, J.; Waller, D.D.; Guan, T.L.; Sebag, M.; Tsantrizos, Y.S. Synthesis and Evaluation of Structurally Diverse C-2-Substituted Thienopyrimidine-Based Inhibitors of the Human Geranylgeranyl Pyrophosphate Synthase. *J. Med. Chem.* **2022**, *65*, 2471–2496. [CrossRef]
14. Shaddy, A.A.; Kamel, A.A.; Abdou, W.M. Synthesis, Quantitative Structure-Activity Relationship, and Anti-Inflammatory Profiles of Substituted 5-and 6-N-Heterocycle Bisphosphonate Esters. *Synth. Commun.* **2013**, *43*, 236–252. [CrossRef]
15. Monteil, M.; Migianu-Griffoni, E.; Sainte-Catherine, O.; Di Benedetto, M.; Lecouvey, M. Bisphosphonate Prodrugs: Synthesis and Biological Evaluation in HuH7 Hepatocarcinoma Cells. *Eur. J. Med. Chem.* **2014**, *77*, 56–64. [CrossRef]
16. Stresing, V.; Daubiné, F.; Benzaid, I.; Mönkkönen, H.; Clézardin, P. Bisphosphonates in Cancer Therapy. *Cancer Lett.* **2007**, *257*, 16–35. [CrossRef]
17. Coleman, R. The Use of Bisphosphonates in Cancer Treatment. *Ann. N. Y. Acad. Sci.* **2011**, *1218*, 3–14. [CrossRef]
18. WHO World Health Organization. World Health Organization Model List of Essential Medicines: 21st List (2019). 2019. Available online: https://apps.who.int/iris/handle/10665/325771 (accessed on 19 July 2022).
19. WHO World Health Organization. World Health Organization Model List of Essential Medicines: 22nd List (2021). 2021. Available online: http://apps.who.int/iris/handle/10665/345533 (accessed on 19 July 2022).
20. Maestro, A.; de Marigorta, E.M.; Palacios, F.; Vicario, J. α-Iminophosphonates: Useful Intermediates for Enantioselective Synthesis of α-Aminophosphonates. *Asian J. Org. Chem.* **2020**, *9*, 538–548. [CrossRef]
21. Turcheniuk, K.V.; Kukhar, V.P.; Röschenthaler, G.V.; Aceña, J.L.; Soloshonok, V.A.; Sorochinsky, A.E. Recent Advances in the Synthesis of Fluorinated Aminophosphonates and Aminophosphonic Acids. *RSC Adv.* **2013**, *3*, 6693–6716. [CrossRef]
22. Vicario, J.; Ezpeleta, M.; Palacios, F. Asymmetric Cyanation of α-Ketiminophosphonates Catalyzed by Cinchona Alkaloids: Enantioselective Synthesis of Tetrasubstituted α-Aminophosphonic Acid Derivatives from Trisubstituted α-Aminophosphonates. *Adv. Synth. Catal.* **2012**, *354*, 2641–2647. [CrossRef]
23. Yan, Z.; Wu, B.; Gao, X.; Chen, M.W.; Zhou, Y.G. Enantioselective Synthesis of α-Amino Phosphonates via Pd-Catalyzed Asymmetric Hydrogenation. *Org. Lett.* **2016**, *18*, 692–695. [CrossRef]
24. Inokuma, T.; Sakakibara, T.; Someno, T.; Masui, K.; Shigenaga, A.; Otaka, A.; Yamada, K.I. Asymmetric Synthesis of α-Amino Phosphonic Acids Using Stable Imino Phosphonate as a Universal Precursor. *Chem. Eur. J.* **2019**, *25*, 13829–13832. [CrossRef]
25. Vicario, J.; Ortiz, P.; Palacios, F. Synthesis of Tetrasubstituted α-Aminophosphonic Acid Derivatives from Trisubstituted α-Aminophosphonates. *Eur. J. Org. Chem.* **2013**, *2013*, 7095–7100. [CrossRef]
26. Vicario, J.; Ortiz, P.; Ezpeleta, J.M.; Palacios, F. Asymmetric Synthesis of Functionalized Tetrasubstituted α-Aminophosphonates through Enantioselective Aza-Henry Reaction of Phosphorylated Ketimines. *J. Org. Chem.* **2015**, *80*, 156–164. [CrossRef]
27. Maestro, A.; Martinez De Marigorta, E.; Palacios, F.; Vicario, J. Enantioselective Aza-Reformatsky Reaction with Ketimines. *Org. Lett.* **2019**, *21*, 9473–9477. [CrossRef]
28. Maestro, A.; De Marigorta, E.M.; Palacios, F.; Vicario, J. Enantioselective α-Aminophosphonate Functionalization of Indole Ring through an Organocatalyzed Friedel-Crafts Reaction. *J. Org. Chem.* **2019**, *84*, 1094–1102. [CrossRef]
29. López-Francés, A.; del Corte, X.; Martinez De Marigorta, E.; Palacios, F.; Vicario, J. Ugi Reaction on α-Phosphorated Ketimines for the Synthesis of Tetrasubstituted α-Aminophosphonates and Their Applications as Antiproliferative Agents. *Molecules* **2021**, *26*, 1654. [CrossRef]
30. Maestro, A.; del Corte, X.; Martinez de Marigorta, E.; Palacios, F.; Vicario, J. Enantioselective Synthesis of Functionalized α-Aminophosphonic Acid Derivatives. *Phosphorus Sulfur Silicon Relat. Elem.* **2019**, *194*, 287–291. [CrossRef]
31. Schrader, T.; Kober, R.; Steglich, W. Synthese von 1-Aminophosphonsäure-Derivaten Über Acyliminophosphonsäure-Ester. *Synthesis* **1986**, *5*, 372–375. [CrossRef]

32. Kobayashi, S.; Kiyohara, H.; Nakamura, Y.; Matsubara, R. Catalytic Asymmetric Synthesis of α-Amino Phosphonates Using Enantioselective Carbon-Carbon Bond-Forming Reactions. *J. Am. Chem. Soc.* **2004**, *126*, 6558–6559. [CrossRef]
33. Kiyohara, H.; Nakamura, Y.; Matsubara, R.; Kobayashi, S. Enantiomerically Enriched Allylglycine Derivatives through the Catalytic Asymmetric Allylation of Iminoesters and Iminophosphonates with Allylsilanes. *Angew. Chem. Int. Ed.* **2006**, *45*, 1615–1617. [CrossRef]
34. Kiyohara, H.; Matsubara, R.; Kobayashi, S. High Turnover Frequency Observed in Catalytic Enantioselective Additions of Enecarbamates and Enamides to Iminophosphonates. *Org. Lett.* **2006**, *8*, 5333–5335. [CrossRef]
35. Del Corte, X.; Maestro, A.; Vicario, J.; Martinez De Marigorta, E.; Palacios, F. Brönsted-Acid-Catalyzed Asymmetric Three-Component Reaction of Amines, Aldehydes, and Pyruvate Derivatives. Enantioselective Synthesis of Highly Functionalized γ-Lactam Derivatives. *Org. Lett.* **2018**, *20*, 317–320. [CrossRef]
36. del Corte, X.; López-Francés, A.; Maestro, A.; Martinez de Marigorta, E.; Palacios, F.; Vicario, J. Brönsted Acid Catalyzed Multicomponent Synthesis of Phosphorus and Fluorine-Derived γ-Lactam Derivatives. *J. Org. Chem.* **2020**, *85*, 14369–14383. [CrossRef]