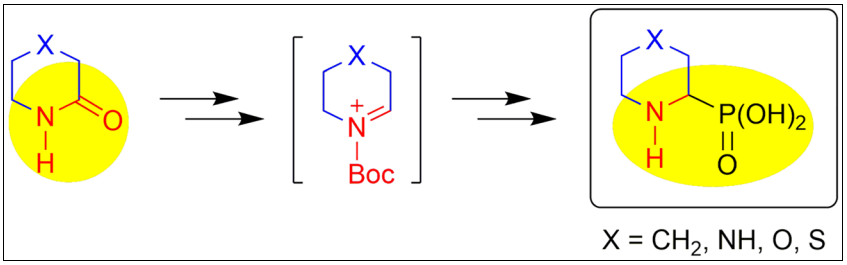
A Straightforward Synthesis of Six-Membered-Ring Heterocyclic α-Aminophosphonic Acids from *N*-Acyliminium Ions

Rubén Oswaldo Argüello-Velasco,[a] Grecia Katherine Sánchez-Muñoz,[a] José Luis Viveros-Ceballos,[a] Mario Ordóñez,[a]* and Pawel Kafarski[b]*

[a]Centro de Investigaciones Químicas-IICBA, Universidad Autónoma del Estado de Morelos, Avenue Universidad 1001, 62209, Cuernavaca, Morelos, Mexico
[b]Department of Bioorganic Chemistry, Wroclaw University of Science and Technology, Wybrzeże Wyspiańskiego 27, 50-370, Wrocław, Poland
*E-mail: palacios@uaem.mx; pawel.kafarski@pwr.wroc.pl
Received December 10, 2018
DOI 10.1002/jhet.3593
Published online 00 Month 2019 in Wiley Online Library (wileyonlinelibrary.com).

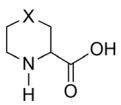


A convenient synthesis of phosphonic analogues of pipecolic acid and its heterocyclic analogues is reported. The major step of the elaborated procedure is the introduction of the phosphonate group into the skeleton of the appropriate cyclic amide through *N*-acyliminium ions. The former ones were obtained by preparation of the hemiaminals or their methyl ethers from the *N*-protected cyclic amides. Finally, the reaction with trimethyl phosphite in the presence of $BF_3{\cdot}OEt_2$ afforded the desired phosphonates, which were converted into phosphonic acids by the hydrolysis of phosphonate moiety with simultaneous cleavage of the nitrogen protecting groups.

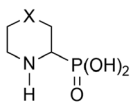
J. Heterocyclic Chem., **00,** 00 (2019).

INTRODUCTION

The development of new peptidomimetics is now receiving substantial interest because these compounds might be considered as mimics of therapeutic peptides in their preferable conformations. The introduction of such scaffolds usually results in their greater bioavailability and stability and limits undesirable physiologic effects. In this regard, the synthesis of conformationally restricted amino acids, where the nitrogen is introduced into aliphatic ring, has been the focus of extensive search as they may induce secondary structural and functional alterations in peptidomimetics, becoming synthetic tools for drug discovery [1–3]. It is well known that the presence of proline in peptide chain is crucial for protein structural and dynamic properties; thence, cyclic amino acids attract increasing attention in medicinal chemistry, and thus, structurally variable six-membered-ring heterocyclic amino acids have been introduced as building blocks for the preparation of bioactive compounds [4–7]. Thus, intensive research efforts have been dedicated to their preparation, particularly pipecolic acid **1** [8–11], piperazine-2-carboxylic acid **2** [12–14], morpholine-3-carboxylic acid **3** [15,16], and thiomorpholine-3-carboxylic acid **4** [17–19]. Additionally, these cyclic amino acids have also been used as precursors for the preparation of more complex scaffolds exhibiting pharmacological activities [20–24] or acting as organocatalysts [25–27]. The preparation of their phosphonic analogues **5**–**8** has not been explored sufficiently with scarce reports being published so far [28–34], despite the acknowledgement of the importance of α-aminophosphonic acids and their derivatives in organic and medicinal chemistry [35–38]. Hence, there is still strong need to develop new procedures for the preparation of this class of compounds [39–41].



1; X = CH_2
2; X = NH
3; X = O
4; X = S



5; X = CH_2
6; X = NH
7; X = O
8; X = S

Considering the possible importance of these non-proteinogenic amino acids analogues, which is in line with our current research interest in the synthesis of conformationally restricted α-aminophosphonic acids [42–45], we now report a straightforward synthesis of phosphopipecolic acid **5**, piperazine-2-phosphonic acid **6**, morpholine-3-phosphonic acid **7**, and thiomorpholine-3-phosphonic acid **8**. *N*-Acyliminium ions were chosen as key substrates here.

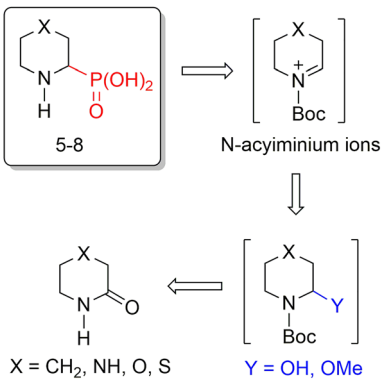
RESULTS AND DISCUSSION

Retrosynthetic analysis of possible procedures leading to acids **5–8** indicated the *N*-acyliminium ions as appropriate precursors. Preparation of *N*-acyliminium ions might be achieved on a synthetic pathway composed of (i) reduction of the carbonyl group of imides obtained from the corresponding cyclic amides leading to hemiaminals (Y = OH) and (ii) their conversion into appropriate methyl ethers (Y = OMe), (iii) followed by their transformation into *N*-acyliminium ions by means of elimination reaction. Action of phosphite allows the incorporation of the phosphonate functionality into the α position to a nitrogen atom [34]. The excellent results in our previous work [42–45] stimulated our interest in the use of *N*-acyliminium ions for the synthesis of the target compounds (Scheme 1).

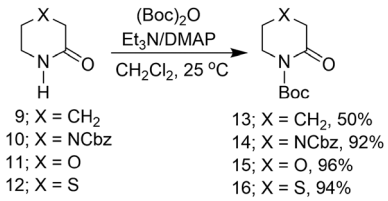
In order to protect reactive nitrogen atom from substrate lactams *tert*-butoxycarbonyl (Boc) group was selected because its subsequent deprotection to generate the amino function can be accomplished under mild conditions. In order to avoid interference of the amino group at *N*-4 position in the piperazine derivative (X = NH), we decided to use the *N*-Cbz-2-ketopiperazine **10** as starting material, considering that orthogonal deprotection could be valuable in further potential applications of this compound for the preparation of peptidomimetics. In this context, and following the protocol described in the literature [46], the cyclic amides **9–12** were reacted with $(Boc)_2O$, Et_3N, and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 at room temperature, yielding *N*-Boc protected derivatives **13–16** in moderate to excellent yields (Scheme 2).

Once the *N*-Boc protected cyclic amides **13–16** were obtained, the incorporation of phosphonate group was carried out in the next step. Thus, the amide functionality in **13–16** was transformed into the desired cyclic α-aminophosphonates **17–20** by three consecutive steps

Scheme 1. Retrosynthetic analysis of phosphonic acids **5–8**. [Color figure can be viewed at wileyonlinelibrary.com]



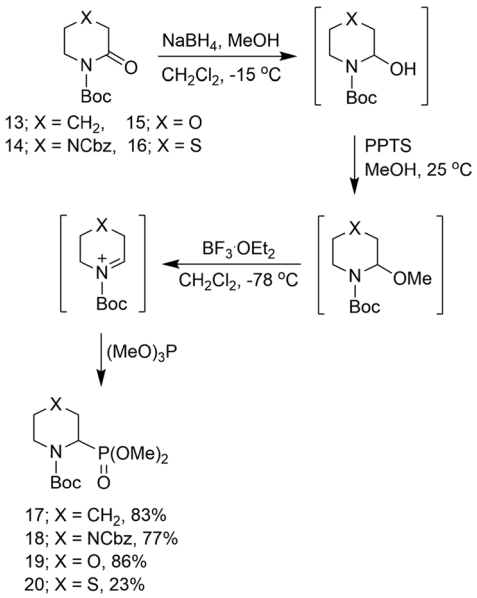
Scheme 2. Synthesis of *N*-Boc protected cyclic amides **13–16**.



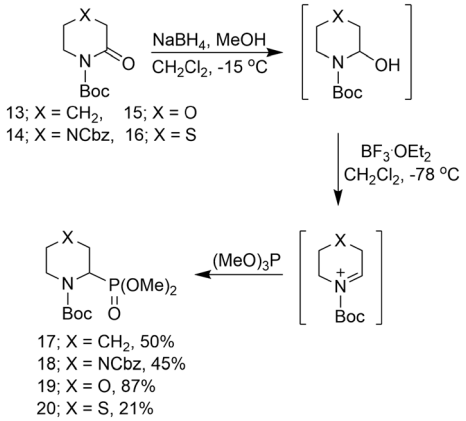
without isolation of the intermediates. Thus, we carried out the reduction of carbonyl function of the *N*-Boc protected cyclic amides **13–16** with sodium borohydride in a $MeOH:CH_2Cl_2$ mixture at −15°C, obtaining the hemiaminals [47]. As hemiaminal derivatization to its methyl ether was used previously as *N*-acyliminium reagent in the synthesis of cyclic amino acids [34,48], we had treated unisolated hemiaminals with methanol in the presence of catalytic amounts of pyridinium *p*-toluenesulfonate to obtain the corresponding hemiaminal methyl ethers. These ethers were reacted with trimethyl phosphite in the presence of boron trifluoride etherate ($BF_3{\cdot}OEt_2$) in dichloromethane at −78°C and afforded the cyclic *N*-Boc α-aminophosphonates **17–20** in 23 to 86% yield (Scheme 3).

In order to reduce the number of synthetic steps of the procedure and taking into consideration reports that describe that Lewis acids can mediate the direct addition of nucleophiles to hemiaminals [49–51], we carried out the reduction of the carbonyl function in the *N*-Boc protected cyclic amides **13–16** with sodium borohydride in a $MeOH:CH_2Cl_2$ mixture at −15°C, which resulted in the corresponding hemiaminals [47], which without

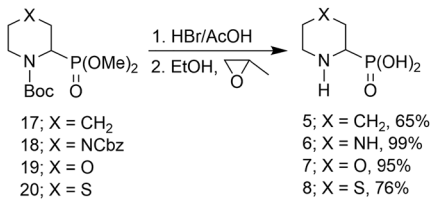
Scheme 3. Synthesis of cyclic *N*-Boc α-aminophosphonates **17–20**.



Scheme 4. Short synthesis of *N*-Boc protected α-aminophosphonates **17**–**20**.



Scheme 5. Preparation of the target compounds **5**–**8**.



purification were reacted with trimethyl phosphite using boron trifluoride diethyl ether ($BF_3{\cdot}OEt_2$) as catalyst. Reaction carried out in dichloromethane at −78°C yielded cyclic *N*-Boc α-aminophosphonates **17**–**20** in 21 to 87% yield. The synthesis of compounds similar to **17** and **18** through radical fragmentation-phosphorylation reaction from heterocyclic α-amino acids [33] has already been described in the literature. The new procedure described in this article provides a proof of concept of a general alternative, which might be especially useful when the parent α-amino acids are unavailable (Scheme 4).

Total removal of the protecting groups in **17**–**20** (hydrolysis of phosphonic ester moiety and removal of Boc from nitrogen) was accomplished through acidolysis with a 33% solution of hydrogen bromide in glacial acetic acid. Treatment of ethanolic solutions of obtained hydrobromides with propylene oxide resulted in obtaining corresponding heterocyclic α-aminophosphonic acids **5**–**8** in good yields (Scheme 5).

CONCLUSIONS

A new general, practical, and efficient procedure for the synthesis of phosphopipecolic acid **5**, piperazine-2-phosphonic acid **6**, morpholine-3-phosphonic acid **7**, and thiomorpholine-3-phosphonic acid **8** was elaborated. It is based on the reduction of *N*-Boc protected cyclic amides **13**–**16** and later use of hemiaminals or their corresponding methyl ethers as substrates for *in situ* generation of *N*-acyliminium ions. Direct reaction of these ions with trimethyl phosphite gave desired phosphonic analogues of heterocyclic amino acids. The use of hemiaminals as substrates resulted in a shorter route of reaction, however, on the cost of lower chemical yield. The total cleavage of the protecting groups (from both phosphonate and amino moieties) was accomplished by acidolysis by hydrogen bromide in glacial acetic acid. The obtained results show the utility of the *N*-acyliminium ions as valuable intermediates for the synthesis of novel scaffolds, which are of interest for medicinal and organic chemistry.

EXPERIMENTAL

All commercial materials were used as received unless otherwise noted. Flash chromatography was performed with 230–400 mesh Silica Flash 60. Thin-layer chromatography was performed with pre-coated TLC sheets of silica gel (60 F_{254}, Merck, Kenilworth, NJ), and the plates were visualized with UV light and ninhydrin. Melting points were determined with a Fisher–Johns apparatus and are uncorrected. NMR spectra were recorded on a Varian instrument (400 MHz for ^1H; Varian, Inc., Palo Alto, CA) or a Mercury instrument (200 MHz for ^1H) and calibrated using tetramethylsilane, $P(O)Ph_3$, and the residual solvent signal as internal standards; chemical shifts (δ) are expressed in parts per million (ppm) and coupling constants (*J*) in Hertz, and an asterisk (*) indicates a duplicate signal corresponding to the minor rotamer. High-resolution FAB^+ and CI^+ mass spectra [high-resolution mass spectrometry (HRMS)] were obtained on a JEOL MStation MS-700. ^1H and ^{13}C NMR data for the compounds **13**–**15** [46,52,53] and **5** [54] were identical to those described in the literature.

***tert*-Butyl 3-oxothiomorpholine-4-carboxylate (16).** To a solution of **12** (0.3 g, 2.6 mmol), Et_3N (0.26 g, 0.4 mL, 2.6 mmol), and DMAP (0.31 g, 2.6 mmol) in CH_2Cl_2 (13 mL) was slowly added di-*tert*-butyl dicarbonate (0.84 g, 3.8 mmol). The reaction mixture was stirred at room temperature for 16 h, then diluted with CH_2Cl_2, and washed with a saturated solution of $NaHCO_3$. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography to give 0.523 g (94%) of **16** as a white solid; m.p. 52–54°C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.54 (s, 9H, C $(CH_3)_3$), 2.96–2.99 (m, 2H, H-6), 3.34 (s, 2H, H-2), 4.03–4.09 (m, 2H, H-5). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 26.4 (C-6), 28.2 ($(CH_3)_3C$), 31.6 (C-2), 44.2 (C-5), 84.1 (*C* $(CH_3)_3$), 151.9 (C═O), 168.0

(C═O). HRMS (FAB$^+$): calcd. for $C_9H_{16}NO_3S$ [M + H]$^+$, *m/z* 218.0851; found for [M + H]$^+$, *m/z* 218.0867.

General procedure for the preparation of cyclic *N*-Boc α-aminophosphonates 17–20. To a stirred solution of the appropriate *N*-Boc protected cyclic amide (0.2 g, 1 eq) in MeOH:CH_2Cl_2 (3:1, 8 mL) at 0°C was slowly added $NaBH_4$ (3 eq). The reaction mixture was stirred at 0°C for 1.0 h and then quenched by the successive addition of a saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to obtain the corresponding hemiaminal as a colorless oil. It was dissolved in MeOH (7 mL), and catalytic amounts of pyridinium *p*-toluenesulfonate (0.1 eq) were added. The mixture was allowed to reach at room temperature and stirred for an additional 2 h. The reaction was quenched with Et_3N (0.1 eq), and the solvent was evaporated under reduced pressure, to give the hemiaminal methyl ether as a colorless oil, which was dissolved in anhydrous CH_2Cl_2 (5 mL) and kept under nitrogen. Trimethyl phosphite (2 eq) was added, and the resulting solution was cooled at −78°C. Boron trifluoride diethyl ether (2 eq) was added dropwise, and the reaction mixture was stirred for 1.0 h at −78°C, 1.0 h at 0°C, and 1 h at room temperature. The reaction was then quenched with water and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Finally, the crude product was purified by flash column chromatography.

Dimethyl 1-(tert-butoxycarbonyl)piperidine-2-phosphonate (17). White solid (0.243 g, 83%); m.p. 50–52°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24–1.30* (m, 1H, H-4), 1.41 (s, 9H, C $(CH_3)_3$), 1.55–1.59* (m, 2H, H-3, H-4), 1.78–1.83 (m, 1H, H-5), 1.83–1.89 (m, 1H, H-5)* 1.93–2.03 (m, 1H, H-6), 2.03–2.13* (m, 1H, H-6), 2.90–3.09* (m, 1H, H-3), 3.10–3.22 (m, 1H, H-3), 3.71 (d, *J* = 10.6 Hz, 6H, $(CH_3O)_2P$), 3.86–4.00 (m, 1H, H-6), 4.00–4.12* (m, 1H, H-6), 4.43–4.60* (m, 1H, H-2), 4.60–4.78 (m, 1H, H-2). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 20.4 (C-5), 24.7 (C-6), 25.4 (C-4), 28.5 ($(CH_3)_3C$), 40.7* (C-3), 42.0 (C-3), 46.9 (d, *J* = 148.5 Hz, C-2), 48.8* (d, *J* = 149.4 Hz, C-2), 52.7 (d, *J* = 6.1 Hz, $(CH_3O)_2P$), 53.0 (d, *J* = 6.9 Hz, $(CH_3O)_2P$), 80.4 (*C* $(CH_3)_3$), 155.0 (C═O). ^{31}P NMR (202 MHz, $CDCl_3$) δ = 28.0. HRMS (FAB$^+$): calcd. for $C_{12}H_{25}NO_5P$ [M + H]$^+$, *m/z* 294.1470; found for [M + H]$^+$, *m/z* 294.1437.

Dimethyl 4-(benzyloxycarbonyl)-1-(tert-butoxycarbonyl) piperazine-2-phosphonate (18). White solid (0.64 g, 85%); m.p. 88–90°C. ^{1}H NMR (400 MHz, $CDCl_3$, 50°C): δ = 1.47 (s, 9H, C $(CH_3)_3$), 2.79–2.92 (m, 1H, H-3), 3.08–3.25 (m, 1H, H-5), 3.35 (bs, 1H, H-6), 3.66 (d, *J* = 10.9 Hz, 6H, $(CH_3O)_2P$), 3.90 (bs, 1H, H-6), 4.08–4.16 (m, 1H, H-3), 4.45–4.56 (m, 2H, H-2, H-5), 5.14 (d, *J* = 12.5 Hz, 1H, CH_2Ph), 5.18 (d, *J* = 12.5 Hz, 1H, CH_2Ph), 7.25–7.41 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 (($CH_3)_3C$), 41.1 (C-6), 42.6 (C-5), 43.3 (C-3), 46.8 (d, *J* = 158.2 Hz, C-2), 52.8 (d, *J* = 7.2 Hz, $(CH_3O)_2P$), 53.0 (d, *J* = 7.1 Hz, $(CH_3O)_2P$), 67.6 (CH_2Ph), 81.3 (*C* $(CH_3)_3$), 128.2, 128.6, 136.6, 155.1 (C═O). ^{31}P NMR (81 MHz, $CDCl_3$): δ = 21.9, 22.8*. HRMS (FAB$^+$): calcd. for $C_{19}H_{30}N_2O_7P$ [M + H]$^+$, *m/z* 429.1791; found for [M + H]$^+$, *m/z* 429.1799.

Dimethyl 4-(tert-butoxycarbonyl)morpholine-3-phosphonate (19). Colorless oil (0.254 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (s, 9H, C $(CH_3)_3$), 3.28–3.59 (m, 2H, H-5, H-6), 3.63* (dd, *J* = 12.16 Hz, 1H, H-2), 3.70 (dd, *J* = 12.18 Hz, 1H, H-2), 3.79 (d, *J* = 10.7 Hz, 6H, $(CH_3O)_2P$), 3.82* (d, *J* = 10.7 Hz, 6H, $(CH_3O)_2P$), 3.85–3.98 (m, 1H, H-5), 4.21–4.36 (m, 1H, H-2), 4.37–4.54 (m, 1H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.5 (($CH_3)_3C$), 40.2* (C-6), 41.7 (C-6), 47.8 (d, *J* = 148.8 Hz, C-3), 49.9* (d, *J* = 140.1 Hz, C-3), 53.0 ($(CH_3O)_2P$), 53.1 ($(CH_3O)_2P$), 65.7 (C-2), 66.8 (C-6), 81.1 (*C* $(CH_3)_3$), 154.4 (C═O). ^{31}P NMR (202 MHz, $CDCl_3$) δ = 30.5. HRMS (FAB$^+$): calcd. for $C_{11}H_{23}NO_6P$ [M + H]$^+$, *m/z* 296.1263; found for [M + H]$^+$, *m/z* 296.1277.

Dimethyl 4-(tert-butoxycarbonyl)thiomorpholine-3-phosphonate (20). Yellow oil (0.071 g, 23%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 (s, 9H, C $(CH_3)_3$), 2.43* (s, 1H, H-6), 2.46 (s, 1H, H-6), 2.59–2.63 (m, 1H, H-6), 2.64–2.71* (m, 1H, H-6), 2.81–2.90* (m, 2H, H-2), 2.90–2.95 (m, 2H, H-2), 3.21–3.44* (m, 1H, H-5), 3.44–3.64 (m, 1H, H-5), 3.72 (d, *J* = 10.7 Hz, 6H, $(CH_3O)_2P$), 3.77* (d, *J* = 10.6 Hz, 6H, $(CH_3O)_2P$), 4–06-4.25 (m, 1H, H-5), 4.25–4.50* (m, 1H, H-5), 4.66–4.87* (m, 1H, H-3), 4.87–5.19 (m, 1H, H-3). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 26.3 (C-2), 27.2 (C-6), 28.4 (($CH_3)_3C$), 40.7* (C-5), 42.1 (C-5),47.8 (d, *J* = 154.6 Hz, C-3), 49.9* (d, *J* = 156.3 Hz, C-3), 52.9 ($(CH_3O)_2P$), 53.2 ($(CH_3O)_2P$), 81.2 (*C* $(CH_3)_3$), 154.7 (C═O). ^{31}P NMR (202 MHz, $CDCl_3$) δ = 25.7. HRMS (FAB$^+$): calcd. for $C_{11}H_{23}NO_5PS$ [M + H]$^+$, *m/z* 312.1035; found for [M + H]$^+$, *m/z* 312.1035.

General procedure for the preparation of heterocyclic α-aminophosphonic acids 5–8. The appropriate cyclic α-aminophosphonate (0.2 g, 1 eq) was treated with a 33% solution of hydrogen bromide in acetic acid (10 mL). The reaction mixture was stirred at room temperature for 4 h, and the volatiles were evaporated under reduced pressure. The crude product was dissolved in the minimal amount of ethanol, and the resulting solution was treated with propylene oxide and stirred at room temperature for 12 h. The precipitate formed was filtered; washed successively

with CH_2Cl_2, AcOEt, and MeOH; and dried under reduced pressure.

Piperazine-2-phosphonic acid (6). White solid (0.163 g, 99%); m.p. 270–272°C. ^{1}H NMR (400 MHz, D_2O): δ = 3.05–3.23 (m, 4H, H-2, H-5, H-6), 3.31–3.44 (m, 2H, H-3, H-6), 3.45–3.55 (m, 1H, H-3). ^{13}C NMR (100 MHz, D_2O): δ = 40.5 (C-6), 41.1 (C-5), 43.0 (C-3), 51.0 (d, *J* = 127.9 Hz, C-2). ^{31}P NMR (81 MHz, D_2O): δ = 5.7. HRMS (FAB$^+$): calcd. for $C_4H_{12}N_2O_3P$ [M + H]$^+$, *m/z* 167.0586; found for [M + H]$^+$, *m/z* 167.0827.

Morpholine-3-phosphonic acid (7). White solid (0.152 g, 95%); m.p. 261–265°C. ^{1}H NMR (500 MHz, D_2O): δ = 3.25–3.33 (m, 1H, H-3), 3.34–3.40 (m, 1H, H-5), 3.48–3.55 (m, 1H, H-5), 3.79–3.87 (m, 2H, H-6), 4.06–4.12 (m, 1H, H-2), 4.20–4.26 (m, 1H, H-2). ^{13}C NMR (126 MHz, D_2O): δ = 44.1 (C-5), 53.2 (d, *J* = 133.7 Hz, C-3), 63.4 (C-6), 65.2 (C-2). ^{31}P NMR (202 MHz, D_2O): δ = 6.8. HRMS (FAB$^+$): calcd. for $C_4H_{10}NO_4PNa$ [M + Na]$^+$, *m/z* 190.0245; found for [M + Na]$^+$, *m/z* 190.0241.

Thiomorpholine-3-phosphonic acid (8). White solid (0.150 g, 76%); m.p. 255–258°C. ^{1}H NMR (500 MHz, D_2O): δ = 2.11–2.18 (m, 1H, H5), 2.32–2.40 (m, 1H, H5), 2.52–2.57 (m, 4H, H2, H3, H6), 2.96–3.03 (m, 1H, H2). ^{13}C NMR (125 MHz, D_2O): δ = 26.46 (C5), 28.27 (C6), 47.76 (d, *J* = 11.7 Hz, C2), 58.04 (d, *J* = 137.1 Hz, C3). ^{31}P NMR (202 MHz, D_2O): δ = 15.20. HRMS (FAB$^+$): calcd. for $C_4H_{10}NO_3PSNa$ [M + Na]$^+$, *m/z* 206.0017; found for [M + Na]$^+$, *m/z* 206.0010.

Acknowledgments. The authors thank the Consejo Nacional de Ciencia y Tecnología (CONACyT) for financial support through projects 256985 and 248868. We also thank Victoria Labastida for their valuable technical support in obtaining MS spectra. G. K.S.M. and R.O.A.V. also wish to thank CONACyT for Graduate Scholarships 623427 and 332980.

REFERENCES AND NOTES

[1] Ko, E.; Liu, J.; Pérez, L. M.; Lu, G.; Schaefer, A.; Burgess, K. J Am Chem Soc 2011, 133, 462.

[2] Hruby, V. J. Nat Rev Drug Discov 2002, 1, 847.

[3] Venkatraman, J.; Shankaramma, S. C.; Balaram, P. Chem Rev 2001, 101, 3131.

[4] Jørgensen, F. P.; Bols, M. J Org Chem 2018, 83, 6050.

[5] Blizzard, T. A.; Singh, S.; Patil, B.; Chidurala, N.; Komanduri, V.; Debnath, S.; Belyakov, S.; Crespo, A.; Struck, A.; Kurtz, M.; Wiltsie, J.; Shen, X.; Sonatore, L.; Arocho, M.; Lewis, D.; Ogletree, M.; Biftu, T. Bioorg Med Chem Lett 2014, 24, 1111.

[6] Narsimha, S.; Kumar, T. R.; Kumar, N. S.; Yakoob, S.; Reddy, N. V. Med Chem Res 2014, 23, 5321.

[7] Hicks, F.; Hou, Y.; Langston, M.; McCarron, A.; O'Brien, E.; Ito, T.; Ma, C.; Matthews, C.; O'Bryan, C.; Provencal, D.; Zhao, Y.; Huang, J.; Yang, Q.; Heyang, L.; Johnson, M.; Sitang, Y.; Yuqiang, L. Org Process Res Dev 2013, 17, 829.

[8] Yu, X.; Nie, R.; Zhang, H.; Lu, X.; Zhou, D.; Xia, Q. Micropor Mesopor Mat 2018, 256, 10.

[9] Chavan, S. P.; Khairnar, L. B.; Pawar, K. P.; Chavan, P. N.; Kawale, S. RSC Adv 2015, 5, 50580.

[10] Byun, S. M.; Jeong, S. W.; Cho, D. H.; Kim, Y. H. Biotechnol Bioprocess Eng 2015, 20, 73.

[11] Barluenga, J.; Aznar, F.; Valdés, C.; Ribas, C. J Org Chem 1998, 63, 3918.

[12] Firth, J. D.; O'Brien, P.; Ferris, L. J Am Chem Soc 2016, 138, 651.

[13] Komeda, H.; Harada, H.; Washika, S.; Sakamoto, T.; Ueda, M.; Asano, Y. Eur J Biochem 2004, 271, 1465.

[14] Kukula, P.; Prins, R. J Catal 2002, 208, 404.

[15] Jagodzinski, J. J.; Aubele, D. L.; Quincy, D. A.; Dappen, M. S.; Latimer, L. H.; Homa, R. K.; Galemmo, R. A. Jr.; Konradi, A. W.; Sham, H. L. Tetrahedron Lett 2011, 52, 2471.

[16] Ciofi, C.; Morvillo, M.; Sladojevich, F.; Guarna, A.; Trabocchi, A. Tetrahedron Lett 2010, 51, 6282.

[17] Králová, P.; Fülöpová, V.; Maloň, M.; Volná, T.; Popa, I.; Soural, M. ACS Comb Sci 2017, 19, 173.

[18] Larsson, U.; Carlson, R. Acta Chem Scand 1994, 48, 517.

[19] Kogami, Y.; Okawa, K. Bull Chem Soc Jpn 1987, 60, 2963.

[20] Tereshchenko, A. D.; Myronchuk, J. S.; Leitchenko, L. D.; Knysh, I. V.; Tokmakova, G. O.; Litsis, O. O.; Tolmachev, A.; Liubchak, K.; Mykhailiuk, P. Tetrahedron 2017, 73, 750.

[21] Clark, R. B.; Lamppu, D.; Libertine, L.; McDonough, A.; Kumar, A.; LaRosa, G.; Rush, R.; Elbaum, D. J Med Chem 2014, 57, 3966.

[22] Trabocchi, A.; Krachmalnicoff, A.; Menchi, G.; Guarna, A. Tetrahedron 2012, 68, 9701.

[23] Sladojevich, F.; Guarna, A.; Trabocchi, A. Org Biomol Chem 2010, 7, 916.

[24] Gao, H.; Renslo, A. R. J Org Chem 2007, 72, 8591.

[25] Laars, M.; Raska, H.; Lopp, M.; Kanger, T. Tetrahedron: Asymmetry 2010, 21, 562.

[26] Wang, Z.; Cheng, M.; Wu, P.; Wei, S.; Sun, J. Org Lett 2006, 8, 3045.

[27] Inoue, T.; Sato, D.; Komura, K.; Itsuno, S. Tetrahedron Lett 1999, 40, 5379.

[28] Das, D.; Seidel, D. Org Lett 2013, 15, 4358.

[29] Wardle, N. J.; Hudson, H. R.; Matthews, R. W.; Nunn, C. M.; Vella, C.; Bligh, S. W. A. Chem Med Chem 2013, 8(8), 719.

[30] Han, W.; Mayer, P.; Ofiala, A. R. Adv Synth Catal 2010, 352, 1667.

[31] Odinets, I. L.; Artyushin, O. I.; Shevchenko, N.; Petrovskii, P. V.; Nenajdenko, V. G.; Röschenthaler, G.-V. Synthesis 2009, 2009, 577.

[32] Mumford, P. M.; Tarver, G. J.; Shipman, M. J Org Chem 2009, 74, 3573.

[33] Boto, A.; Gallardo, J. A.; Hernández, R.; Saavedra, C. J. Tetrahedron Lett 2005, 46, 7807.

[34] Shono, T.; Matsumura, Y.; Tsubata, K. Tetrahedron Lett 1981, 22, 3249.

[35] Mucha, A.; Kafarski, P.; Berlicki, L. J Med Chem 2011, 54, 5955.

[36] Orsini, F.; Sello, G.; Sisti, M. Curr Med Chem 2010, 17, 264.

[37] Naydenova, E. D.; Todorov, P. T.; Troev, K. D. Amino Acids 2010, 38, 23.

[38] Lejczak, B.; Kafarski, P. Phosphorous Heterocycles I 2009, 20, 31.

[39] Ordóñez, M.; Viveros-Ceballos, J. L.; Cativiela, C.; Sayago, F. J. Tetrahedron 2015, 71, 1745.

[40] Ordóñez, M.; Sayago, F. J.; Cativiela, C. Tetrahedron 2012, 68, 6369.

[41] Ordóñez, M.; Viveros-Ceballos, J. L.; Cativiela, C.; Arizpe, A. Curr Org Synth 2012, 9, 310.

[42] Ordóñez, M.; Arizpe, A.; Sayago, F. J.; Jiménez, A. I.; Cativiela, C. Molecules 2016, 21, 1140.

[43] Ramírez-Marroquín, O. A.; Romero-Estudillo, I.; Viveros-Ceballos, J. L.; Cativiela, C.; Ordoñez, M. Eur J Org Chem 2016, 2016, 308.

[44] Viveros-Ceballos, J. L.; Sayago, F. J.; Cativiela, C.; Ordóñez, M. Eur J Org Chem 2015, 2015, 1084.

[45] Bonilla-Landa, I.; Viveros-Ceballos, J. L.; Ordóñez, M. Tetrahedron: Asymmetry 2014, 25, 485.
[46] Taylor, R. R. R.; Twin, H. C.; Wen, W. W.; Mallot, R. J.; Lough, A. J.; Gray-Owen, S. D.; Batey, R. A. Tetrahedron 2010, 66, 3370.
[47] Viveros-Ceballos, J. L.; Cativiela, C.; Ordóñez, M. Tetrahedron: Asymmetry 2011, 22, 1479.
[48] Medina, J. R.; Blackledge, C. W.; Erhard, K. F.; Axten, J. M.; Miller, W. H. J Org Chem 2008, 73, 3946.
[49] Butters, M.; Davies, C. D.; Elliott, M. C.; Hill-Cousins, J.; Kariuki, B. M.; Ooi, L.; Wood, J. L.; Wordingham, S. V. Org Biomol Chem 2009, 7, 5001.
[50] Van der Veken, P.; Soroka, A.; Brandt, I.; Chen, Y. S.; Maes, M. B.; Lambeir, A. M.; Chen, X.; Haemers, A.; Scharpé, S.; Augustyns, K.; De Meester, I. J Med Chem 2007, 50, 5568.
[51] Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. J Org Chem 1990, 55, 215.
[52] Garnier, E. C.; Liebeskind, L. S. J Am Chem Soc 2008, 130, 7449.
[53] Chandrakumar, N. S.; Stapelfeld, A.; Beardsley, P. M.; Lopez, O. T.; Drury, B.; Anthony, E.; Savage, M. A.; Williamson, L. N.; Reichman, M. J Med Chem 1992, 35, 2928.
[54] Maury, C.; Wang, Q.; Gharbaoui, T.; Chiadmi, M.; Tomas, A.; Royer, J.; Husson, H.-P. Tetrahedron 1997, 53, 3627.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.