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Diastereoselective synthesis of novel 5-substituted morpholine-3-phosphonic acids: further exploitation of *N*-acyliminium intermediates

Israel Bonilla-Landa, José Luis Viveros-Ceballos, Mario Ordóñez *

Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, 62209 Cuernavaca, Morelos, Mexico

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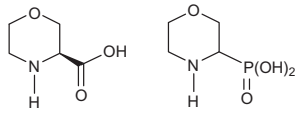
ABSTRACT

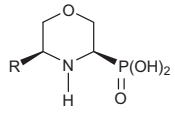
The first diastereoselective total synthesis of 5-substituted morpholine-3-phosphonic acids is reported. The principal feature of the synthesis is the introduction of a dimethyl phosphonate group into 5-substituted morpholin-3-ones. The procedure is based on the preparation of *N*-Boc-(*S*)-5-phenyl- and *N*-Boc-(*S*)-5-benzylmorpholin-3-one from L-phenylglycine and L-phenylalanine methyl esters, followed by the formation of the 3-methoxylated compounds and subsequent reaction with trimethyl phosphite in the presence of $BF_3{\cdot}OEt_2$. Diastereoselectivity in the formation of *cis*-disubstituted products is in agreement with the nucleophilic addition to other methoxylated derivatives.

1. Introduction

Over the last few years, the synthesis and the incorporation of cyclic amino acids, where the nitrogen atom of the amino functional group is part of a ring, has led to a better understanding of the bioactive conformation of peptidomimetic molecules, due to the inability of the nitrogen atom to act as a hydrogen bond donor, unless it is located at the N-terminal position of the molecule, and to the conformational strain imparted by the cyclic structure.[1] Also, the *cis*/*trans* isomerism of the tertiary amide bond formed by cyclic amino acids is responsible for the modulation of conformational preferences.[2] In particular, morpholine-3-carboxylic acid (Mor) **1**, as a proline surrogate, that has been used as a key intermediate in the synthesis of several compounds with medical purposes, such as Alzheimer's disease,[3] neurotrophic agents,[4] modulators of cell growth,[5] TORC1/2 inhibitors,[6] as imaging probes for diagnostic in melanoma growth,[7] β-lactamase inhibitors,[8] T-type Ca^{2+} channel blockers,[9] TACE inhibitors,[10] potent VLA-4 antagonists,[11] as ligands for $\alpha_v\beta_3/\alpha_v\beta_5$ integrins,[12] ICE inhibitors,[13] and MMP and TNF inhibitors.[14] Furthermore, Mor **1** has also been used in organic synthesis as a precursor in the preparation of more complex compounds[15] and as catalysts.[16] Due to the relevant utility exhibited by **1** and its derivatives, much effort has been dedicated to the preparation of these compounds.[17] However, to the best of our knowledge, the synthesis of its analogue morpholine-3-phosphonic acid (Mor^P) **2** in enantio- or diastereoisomerically pure form has not yet been described in the literature,[18] despite the great importance that these compounds could have in medicinal and organic synthesis, such as that shown by the α-aminophosphonic acids and their derivatives,[19,20] hence there is great importance in the development of new methods for the preparation of these compounds.[21]



1 **2**



3a; R = Ph
3b; R = Bn

Considering the high value of these non-coded compounds in connection with our current research interest in the synthesis of novel conformationally restricted α-aminophosphonic acids,[22] we herein report the first stereoselective synthesis of (3*R*,5*S*)-5-phenyl- and (3*R*,5*S*)-5-benzylmorpholine-3-phosphonic acids **3a** and **3b**.

2. Results and discussion

The synthesis of the target chiral 5-substituted morpholine-3-phosphonic acids **3a**,**b** began with the preparation of Boc-protected morpholin-3-ones **7a**,**b** from readily available α-amino acid methyl

* Corresponding author. Tel./fax: +52 7773297997.
E-mail address: palacios@uaem.mx (M. Ordóñez).

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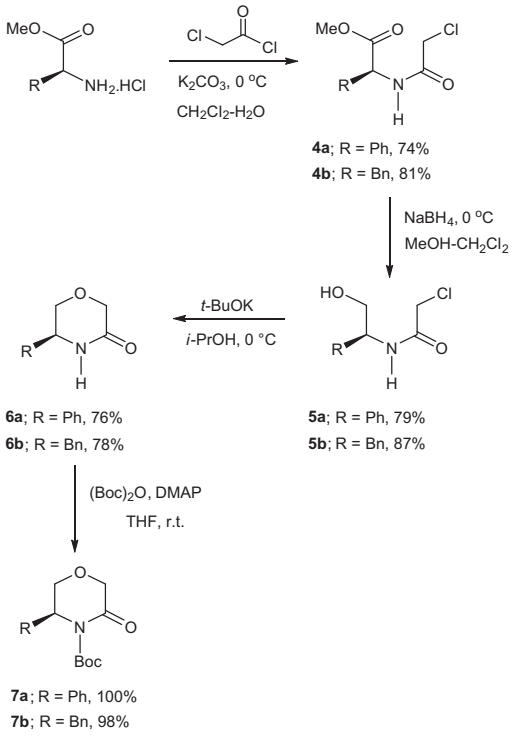
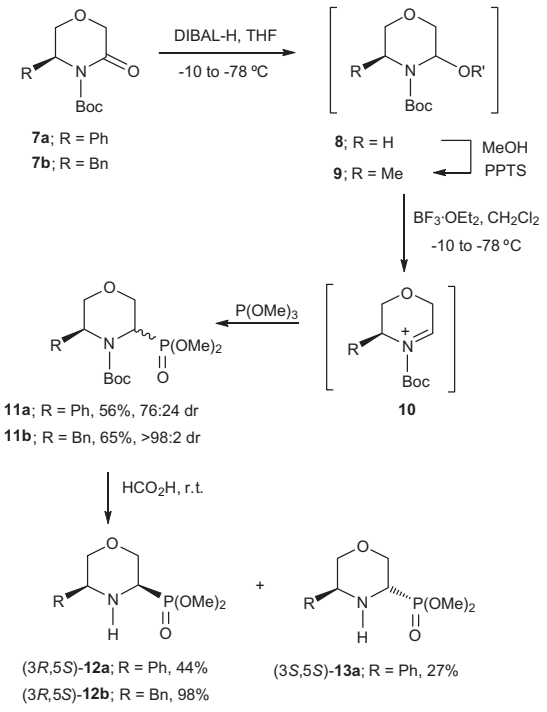
esters as shown in Scheme 1. In the first step, L-phenylglycine and L-phenylalanine methyl esters hydrochlorides were reacted with chloroacetyl chloride and K_2CO_3 in a dichloromethane/water mixture at 0 °C, to give the corresponding chloroacetamides (*S*)-**4a**,**b** in 74% and 81% yields.[23] Next, the methyl esters **4a**,**b** were reduced with $NaBH_4$ in a methanol/dichloromethane mixture at 0 °C to afford the *N*-chloroacetamido alcohols **5a**,**b** in 79% and 87% yields,[24] which upon treatment with potassium *tert*-butoxide in isopropyl alcohol at 0 °C,[25] provided the (*S*)-5-phenylmorpholin-3-one **6a** and (*S*)-5-benzylmorpholin-3-one **6b** in 76% and 78% yields, respectively.[26] The resulting morpholin-3-ones **6a**,**b** were transformed into *tert*-butylcarbamates **7a**,**b** in excellent yield by reaction with $(Boc)_2O$ and a catalytic amount of 4-dimethylaminopyridine (DMAP) in THF at room temperature (Scheme 1).[27]



Scheme 1.

To further expand upon the synthetic potential of *N*-acyliminium ions **10**[28] obtained from methoxylated derivatives of type **9** in the synthesis of cyclic α-aminophosphonates,[22,29] the *tert*-butylcarbamate **7a** was reduced with diisobutylaluminium hydride (DIBAL-H) at −10 to −78 °C to obtain the corresponding hemiaminal **8**, which was not isolated but treated immediately with methanol and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS), to obtain the methoxyaminal **9**. Subsequent treatment of **9** with trimethyl phosphite and boron trifluoride–diethyl ether at −78 °C, gave the (3*R*,5*S*)- and (3*S*,5*S*)-cyclic α-aminophosphonates **11a** in 56% yield and a 76:24 diastereoisomeric ratio, through the *N*-acyliminium ion intermediate **10**. Selective *N*-Boc bond cleavage in **11a** with formic acid gave, after chromatographic separation the cyclic α-aminophosphonates (3*R*,5*S*)-**12a** (more polar diastereoisomer) and (3*S*,5*S*)-**13a** (less polar diastereoisomer) in 44% and 27% yields, respectively.[30] In a similar manner, **7b** gave the α-aminophosphonate (3*R*,5*S*)-**11b** in 65% yield and with >98:2 diastereoisomeric ratio, which upon treatment with formic acid afforded the α-aminophosphonate (3*R*,5*S*)-**12b** in quantitative yield (Scheme 2).[31]

The diastereoselectivity in the nucleophilic addition of dimethyl phosphite to *N*-acylaminium cation **10** is in agreement with the



Scheme 2.

nucleophilic addition of diethyl phosphite to 2-methoxylated proline[29a] and the allylation of a 3-methoxylated morpholine-3-carboxylic acid derivative.[32]

The stereochemistry assignment in the diastereoisomers (3*R*,5*S*)-**12a** and (3*R*,5*S*)-**12b** was assigned based on the 2D NOESY experiments. The key nOe signals are the cross-peaks between H-3 and H-5 and the axial correlation exhibited by H-2 and H-6. The nOe effect was not observed for the diastereoisomer (3*S*,5*S*)-**13a**. Additionally, H-3 for (3*R*,5*S*)-**12a** appears at 3.53 ppm as a ddd signal ($J_{H/P}$ = 10.8 Hz, J_{anti} = 10.8 Hz, and J_{gauche} = 2.8 Hz), and the H-3 for (3*R*,5*S*)-**12b** appears in 3.27 also as a ddd signal ($J_{H/P}$ = 11.8, J_{anti} = 10.8, and J_{gauche} = 3.0 Hz), (Fig. 1).

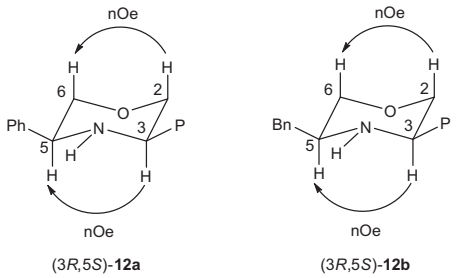
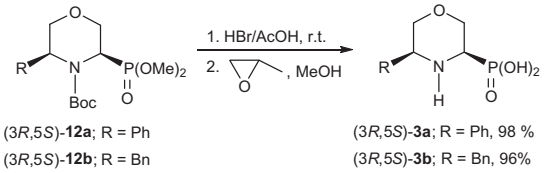


Figure 1. Relative stereochemistry assignment of phosphonates **12a** and **12b**.

Finally, hydrolysis of (3*R*,5*S*)-**12a** and (3*R*,5*S*)-**12b** with hydrogen bromide (33% solution in acetic acid) followed by treatment with propylene oxide in methanol afforded 5-phenyl morpholine-3-phosphonic acid (3*R*,5*S*)-**3a** in 98% yield and 5-benzyl morpholine-3-phosphonic acid (3*R*,5*S*)-**3b** in 96% yield (Scheme 3).[33]



Scheme 3.

3. Conclusion

In conclusion, we have demonstrated the utility of this methodology in the diastereoselective nucleophilic addition of trimethyl phosphite to 3-methoxylated (5*S*)-5-phenyl- and (5*S*)-5-benzylmorpholine via the intermediacy of *N*-acyliminium cation **10**, which allows the construction of cyclic α-aminophosphonates from L-amino acids. The *N*-Boc cleavage and hydrolysis of the dimethyl phosphonate moiety produced, for the first time, the synthesis of (3*R*,5*S*)-5-phenyl- and (3*R*,5*S*)-5-benzylmorpholine-3-phosphonic acids **3a**,**b**. Additionally, we anticipate that the use of *N*-acyliminium cations as templates could be extremely important in the synthesis of large libraries of cyclic α-aminophosphonic acids with significant potential in pharmacology and organic synthesis areas.

Acknowledgments

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30. (3*R*,5*S*)-**12a**. $[\alpha]_D = +60.0$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.30 (br s, 1H, NH), 3.32 (dd, *J* = 10.7, 10.7 Hz, 1H, H-6), 3.53 (ddd, *J* = 10.7, 10.7, 2.8 Hz, 1H, H-3), 3.63 (ddd, *J* = 10.8, 10.7, 3.1 Hz, 1H, H-2), 3.79–3.83 (m, 1H, H-6), 3.81 (d, *J* = 10.7 Hz, 3H, OCH_3), 3.89 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.89–3.93 (m, 1H, H-5), 4.06 (dd, *J* = 10.8, 2.8 Hz, 1H, H-2), 7.25–7.41 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.9 (d, *J* = 6.9 Hz, OCH_3), 53.3 (d, *J* = 156.1 Hz, C-3), 54.0 (d, *J* = 6.4 Hz, OCH_3), 60.4 (d, *J* = 14.9 Hz, C-5), 66.6 (C-2), 73.3 (C-6), 127.3, 128.1, 128.6, 139.6. ^{31}P NMR (81 MHz, $CDCl_3$) δ 24.8. HRMS (FAB^+): calcd for $C_{12}H_{19}NO_4P$ $[M+H]^+$, *m*/*z* 272.1052; found for $[M+H]^+$, *m*/*z* 272.1057. (3*S*,5*S*)-**13a**. $[\alpha]_D = +53.3$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.97 (ddd, *J* = 12.0, 8.5, 3.7 Hz, 1H, H-3), 3.20 (dd, *J* = 10.6, 3.6 Hz, 1H, H-5), 3.36 (dd, *J* = 11.1, 11.1 Hz, 1H, H-6), 3.70–3.75 (m, 1H, H-6), 3.77–3.81 (m, 1H, H-2), 3.80 (d, *J* = 10.8 Hz, 3H, OCH_3), 3.90 (d, *J* = 10.6 Hz, 3H, OCH_3), 4.16–4.21 (m, 1H, H-2), 7.24–7.43 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.5 (d, *J* = 7.0 Hz, OCH_3), 53.7 (d, *J* = 6.6 Hz, OCH_3), 61.1 (d, *J* = 156.3 Hz, C-3), 67.8 (C-2), 69.1 (d, *J* = 15.2 Hz, C-5), 73.4 (C-6), 127.9, 128.0, 128.7, 139.2. ^{31}P NMR (81 MHz, $CDCl_3$) δ 25.1. HRMS (FAB^+): calcd for $C_{12}H_{19}NO_4P$ $[M+H]^+$, *m*/*z* 272.1052; found for $[M+H]^+$, *m*/*z* 272.1088.
31. (3*R*,5*S*)-**12b**. $[\alpha]_D = -65.3$ (*c* 3.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 2.16 (br s, 1H, NH), 2.53 (dd, *J* = 12.8, 7.2 Hz, 1H, CH_2Ph), 2.58 (dd, *J* = 12.8, 5.6 Hz, 1H, CH_2Ph), 2.92–2.99 (m, 1H, H-5), 3.16 (dd, *J* = 10.4, 10.4 Hz, 1H, H-6), 3.27 (ddd, *J* = 11.8, 10.8, 3.0 Hz, 1H, H-3), 3.47 (ddd, *J* = 11.0, 10.8, 3.4 Hz, 1H, H-2), 3.70–3.76 (m, 1H, H-6), 3.72 (d, *J* = 10.4 Hz, 3H, OCH_3), 3.76 (d, *J* = 10.4 Hz, 3H, OCH_3), 3.93 (dd, *J* = 11.0, 3.0 Hz, 1H, H-2), 7.11–7.28 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.1 (CH_2Ph), 53.2 (d, *J* = 7.3 Hz, OCH_3), 53.4 (d, *J* = 155.2 Hz, C-3), 53.6 (d, *J* = 7.3 Hz, OCH_3), 56.6 (d, *J* = 13.2 Hz, C-5), 66.9 (C-2), 72.1 (C-6), 126.9, 128.8, 129.3, 137.5. ^{31}P NMR (81 MHz, $CDCl_3$) δ 22.5. HRMS (FAB^+): calcd for $C_{13}H_{21}NO_4P$ $[M+H]^+$, *m*/*z* 286.1208; found for $[M+H]^+$, *m*/*z* 286.1219.
32. (a) O'Neil, S. V. O.; Wang, Y.; Laufersweiler, M. C.; Oppong, K. A.; Soper, D. L.; Wos, J. A.; Ellis, C. D.; Baize, M. W.; Bosch, G. K.; Fancher, A. N.; Lu, W.; Suchanek, M. K.; Wang, R. L.; De, B.; Demuth, T. P., Jr. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5434–5438; (b) Shono, T.; Mataumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590–2592.
33. (3*R*,5*S*)-**3a**. Mp = 256–258 °C, $[\alpha]_D = +32.0$ (*c* 1.0, 1 M NaOH). ^1H NMR (400 MHz, NaOD-D_2O) δ 2.91 (ddd, *J* = 14.4, 11.4, 2.9 Hz, 1H, H-3), 3.33 (dd, *J* = 11.0, 11.0 Hz, 1H, H-6), 3.46 (ddd, *J* = 11.5, 11.4, 2.7 Hz, 1H, H-2), 3.72–3.80 (m, 2H, H-5, H-6), 3.93 (dd, *J* = 11.5, 2.9 Hz, 1H, H-2), 7.18–7.35 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, NaOD-D_2O) δ 56.2 (d, *J* = 136.1 Hz, C-3), 59.8 (d, *J* = 11.7 Hz, C-5), 68.4 (C-2), 71.3 (C-6), 127.0, 128.1, 128.8, 139.4. ^{31}P NMR (162 MHz, NaOD-D_2O) δ 8.9. HRMS (FAB^+): calcd for $C_{10}H_{15}NO_4P$ $[M+H]^+$, *m*/*z* 244.0739; found for $[M+H]^+$, *m*/*z* 244.0726. (3*R*,5*S*)-**3b**. Mp = 280–281 °C, $[\alpha]_D = -42.7$ (*c* 3.0, 1 M NaOH). ^1H NMR (400 MHz, NaOD-D_2O) δ 2.39 (dd, *J* = 13.6, 7.6 Hz, 1H, CH_2Ph), 2.44 (dd, *J* = 13.6, 6.4 Hz, 1H, CH_2Ph), 2.61 (ddd, *J* = 14.0, 11.2, 2.8 Hz, 1H, H-3), 2.77–2.84 (m, 1H, H-5), 3.03 (dd, *J* = 10.8, 10.8 Hz, 1H, H-6), 3.27 (ddd, *J* = 11.2, 11.2, 3.0 Hz, 1H, H-2), 3.54 (d, *J* = 10.8 Hz, 1H, H-6), 3.77 (dd, *J* = 11.2, 2.8 Hz, 1H, H-2), 7.06–7.18 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, NaOD-D_2O) δ 37.7 (CH_2Ph), 56.3 (d, *J* = 136.1 Hz, C-3), 56.6 (d, *J* = 11.7 Hz, C-5), 68.5 (C-2), 70.6 (C-6), 126.6, 128.7, 129.3, 137.9. ^{31}P NMR (81 MHz, NaOD-D_2O) δ 15.2. HRMS (FAB^+): calcd for $C_{11}H_{17}NO_4P$ $[M+H]^+$, *m*/*z* 258.0895; found for $[M+H]^+$, *m*/*z* 258.0922.