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One-pot synthesis of α-amino phosphonates from α-amino acids and β-amino alcohols

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Abstract—The one-pot radical fragmentation–phosphorylation reaction of α-amino acids and β-amino alcohols affords α-amino phosphonates in good yields. The reaction was applied to the synthesis of potentially bioactive phosphonates.

The α-amino phosphonates are amino acid analogues, which have elicited considerable attention due to their interesting biological properties.[1] For instance, the leucine surrogate **1** (Fig. 1) is a potent inhibitor of leucine aminopeptidase.[2] The proline analogue **2** is an angiotensin inhibitor, useful as an antihypertensive agent.[3] The amino phosphonate **3** possesses herbicidal activity.[4] Other amino phosphonates are promising antitumoural, fungicidal, antibacterial and antiviral agents.[1–4] As a result, different synthetic methodologies to obtain these compounds have been developed.[1]

We report now on a mild and efficient preparation of these compounds from β-amino alcohols and α-amino acid derivatives, using a sequential fragmentation–phosphorylation reaction (Scheme 1).

It is known that on treatment with $PhI(OAc)_2$–I_2, the β-amino alcohol derivatives **4a** (X = H,H) generate an alkoxyl radical **5a**, while the amino acids **4b** (X = O) generate a carboxyl radical **5b**.[5] These *O*-radicals were expected to undergo a radical β-fragmentation to afford a *C*-radical **6**,[5,6] which would be oxidized in the reaction medium to an *N*-acyliminium ion **7**.[6] This intermediate could be trapped by phosphorous nucleophiles, namely dimethyl phosphonate or trialkylphosphites, to afford α-amino phosphonates **8**.

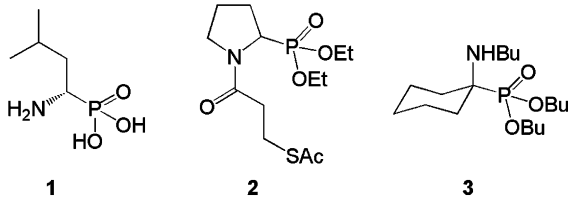
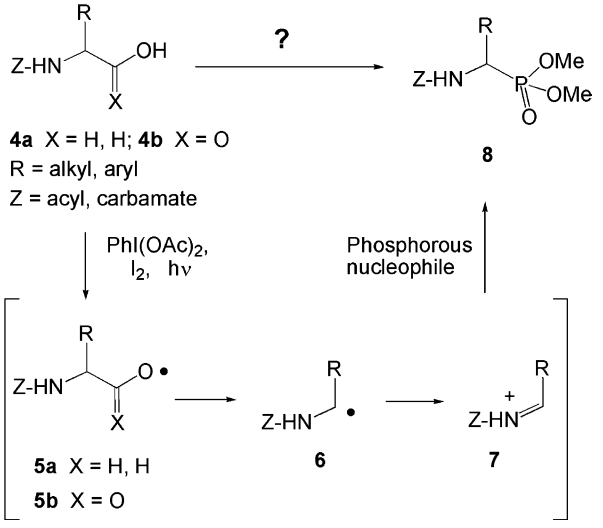


Figure 1. Bioactive α-amino phosphonates.



Scheme 1. Proposed one-pot radical fragmentation–phosphorylation for the synthesis of α-amino phosphonates.

To explore the feasibility and scope of this reaction, several amino alcohol and amino acid derivatives **9**–**15** were prepared in a few steps from commercial products, using standard methodologies.

Keywords: Amino acids; Amino phosphonates; Radicals; Fragmentation; Decarboxylation; Hypervalent iodine reagents.
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Table 1. One-pot β-fragmentation–phosphorylation reaction[a]

Entry	Substrate	Conditions[b]	Products (%)[c]
1	**9**	A	**16** (64)
2	**9**	B	**16** (62)
3	**9**	C	**16** (26), **17** (27)
4	**9**	D	**16** (4), **17** (64)
5	**10**	D	**17** (86)
6	**11**	D	**18** (81)
7	**12**	D	**19** (85)
8	**13**	D	**20** (67)
9	**14**	D	**21b** (89)
10	**15**	D	**22** (26)

[a] General procedure: The substrate (1 mmol) in dry dichloromethane (15 ml) was treated with DIB (2.5 mmol) and iodine (1 mmol) and irradiated with visible light (sunlight, or a 100 W tungsten-filament lamp). The reaction mixture was stirred at room temperature under nitrogen until no starting material was observed by TLC analysis (about 3 h). Then it was cooled to 0 °C and the Lewis acid ($BF_3{\cdot}OEt_2$ or TMSOTf, 2 equiv) and the nucleophile [$HP(O)(OMe)_2$ or $P(OMe)_3$, 5 equiv] were added. The reaction was allowed to reach rt and stirred for 4 h, and afterwards it was poured into aqueous $NaHCO_3$–10% $Na_2S_2O_3$ and extracted with CH_2Cl_2.

[b] Condition A: TMSOTf as Lewis acid and $HP(O)(OMe)_2$ as nucleophile. Condition B: $BF_3{\cdot}OEt_2$ as Lewis acid and $HP(O)(OMe)_2$ as nucleophile. Condition C: TMSOTf as Lewis acid and $P(OMe)_3$ as nucleophile. Condition D: $BF_3{\cdot}OEt_2$ as Lewis acid and $P(OMe)_3$ as nucleophile.

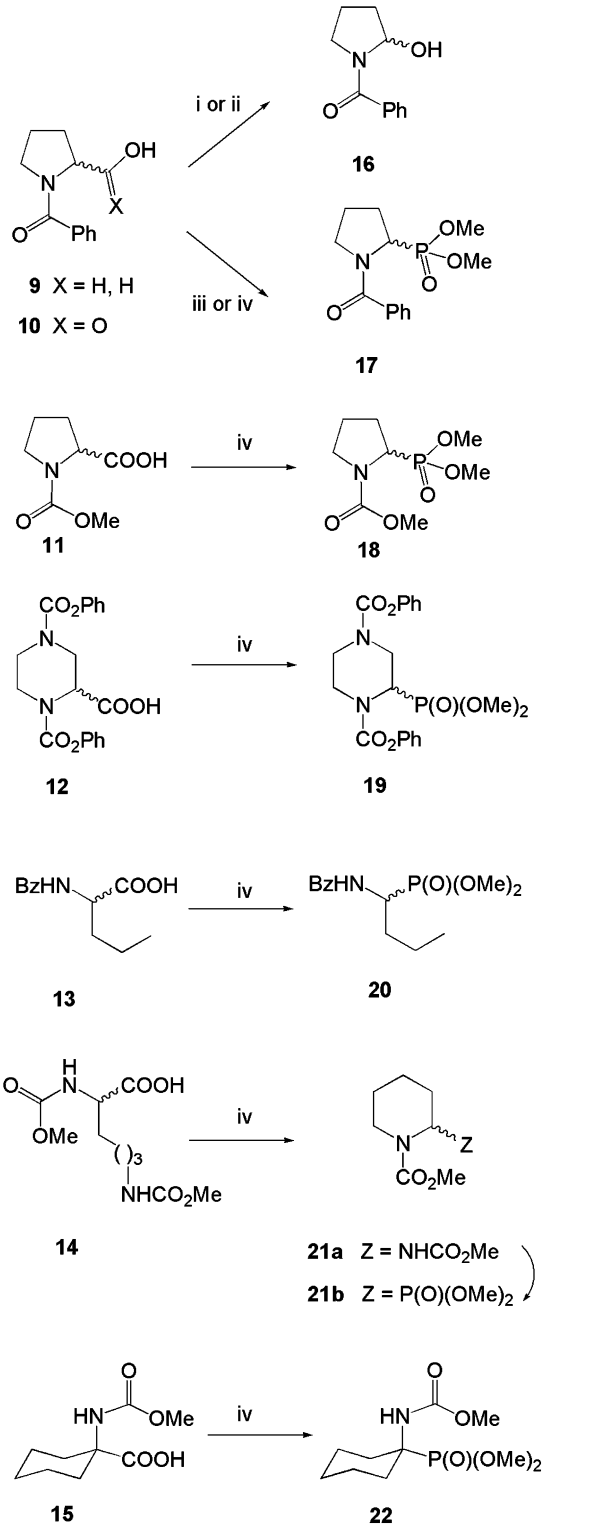
[c] Yields are given for products purified by chromatography on silica gel.

The sequential fragmentation–phosphorylation was studied first with substrate **9** (Table 1, entries 1–4), which was treated with DIB–I_2 and irradiated with visible light to carry out the fragmentation. Once this step was completed, a Lewis acid (TMSOTf or $BF_3{\cdot}OEt_2$)[7] and the nucleophile [$HP(O)(OMe)_2$ or $P(OMe)_3$] were added.[8]

When dimethyl phosphonate was used as nucleophile (entries 1 and 2), no phosphonates were obtained, and the 2-hydroxypyrrolidine **16**[6g,7] was isolated instead. This result implies that this nucleophile was not reactive enough to trap the *N*-acyliminium intermediate, which therefore reacted with water during the work-up. However, by using $P(OMe)_3$ as nucleophile (entries 3 and 4) the desired α-amino phosphonate **17**[9b] was obtained as the major product.

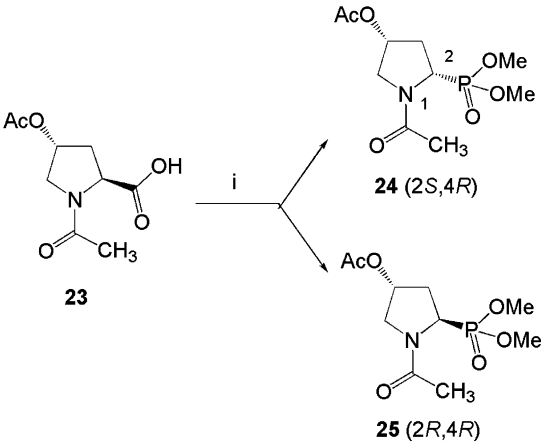
The fragmentation of the amino acid analogue **10** (Scheme 2) was studied next (entry 5) in order to determine whether the reaction results improved by using amino acids as substrates.[10] The one-pot fragmentation–phosphorylation proceeded in good yield, affording the amino phosphonate **17**. The decarboxylation–phosphorylation of proline methyl carbamate **11** (entry 6) also proceeded in good yield, affording product **18**.

When the piperazic acid derivative **12** was used as substrate (entry 7), the reaction gave the desired phosphonate **19** in very good yield.[11] The same occurred with the fragmentation of the unnatural amino acid **13** (entry 8), which afforded the phosphonate analogue **20**.[12]

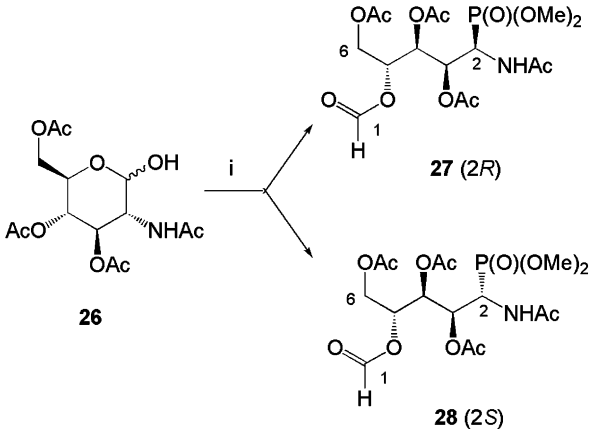


Scheme 2. Reagents and conditions: (i) DIB, I_2, *hv*; then 0 °C, TMSOTf, $HP(O)(OMe)_2$; (ii) DIB, I_2, *hv*; then 0 °C, $BF_3{\cdot}OEt_2$, $HP(O)(OMe)_2$; (iii) DIB, I_2, *hv*; then 0 °C, TMSOTf, $P(OMe)_3$; (iv) DIB, I_2, *hv*; then 0 °C, $BF_3{\cdot}OEt_2$, $P(OMe)_3$. See Table 1 for product yields.

The fragmentation of the lysine derivative **14** (entry 8) surprisingly gave the pipecolinic acid surrogate **21b**[13a] in good yields. This result can be explained via an intermediate **21a**, formed by addition of the ε-carbamate



Scheme 3. Use of precursors from the chiral pool to obtain functionalized amino phosphonates. Reagents and conditions: (i) DIB (2.5 mmol), I_2 (1 mmol), rt, sunlight, 3 h; then 0 °C, $P(OMe)_3$ (5 equiv) and $BF_3{\cdot}OEt_2$ (2 equiv); **24** (64%) and **25** (15%).



Scheme 4. Use of precursors from the chiral pool to obtain functionalized amino phosphonates. Reagents and conditions: (i) DIB (2.5 mmol), I_2 (1 mmol), rt, sunlight, 3 h; then 0 °C, $P(OMe)_3$ (5 equiv) and $BF_3{\cdot}OEt_2$ (2 equiv); **27** (40%) and **28** (26%).

group to the initial *N*-acyliminium ion.[13b] On treatment with the Lewis acid, **21a** generated a cyclic acyliminium ion, which was trapped by the phosphorous nucleophile to afford **21b**.

The fragmentation–phosphorylation of the amino acid **15** (entry 9) posed a challenge since a quaternary centre would be formed. However, the reaction proceeded in low yield, generating the interesting α,α-disubstituted amino phosphonate **22**.[14]

The sequential decarboxylation–phosphorylation reaction was also studied with substrates bearing stereogenic centres next to the reacting centre. For instance, when the (4*R*)-acetoxyproline derivative **23** (Scheme 3) was treated with DIB–iodine and then with $BF_3{\cdot}OEt_2$ and $P(OMe)_3$, the amino phosphonate **24**[15a,16a] and its 2-epimer **25**[15b,16b] were obtained in 64% and 15% yield, respectively (79% overall yield).

The carbohydrate pool can also provide a variety of precursors. For instance, the substrate **26** (Scheme 4) was obtained in two steps from commercial 2-acetamide D-glucopyranose.

The fragmentation of the alkoxyl radical derived from **26**, followed by phosphorylation with $BF_3{\cdot}OEt_2$ and $P(OMe)_3$, afforded a separable 3:2 mixture of the polyhydroxylated products **27**[17a] and **28**[17b] in 66% global yield. Since in this case the reaction proceeded via an acyclic acyliminium ion, a low diastereoselectivity was observed.[18] However, the use of differently protected, more rigid carbohydrate substrates, should increase the stereocontrol.[19] As shown in this example, the fragmentation–phosphorylation of precursors from the chiral pool can allow the synthesis of highly functionalized amino phosphonates.

In summary, the one-pot fragmentation–phosphorylation reaction is a versatile and efficient pathway to obtain many different amino phosphonates from readily available precursors. The biological activity of compounds **17**–**22**, **24**, **25** and **27**, **28**, is currently under study and will be reported in due course.

Acknowledgements

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9. (a) All new compounds were characterized by ^{1}H and ^{13}C NMR, MS, HRMS, IR and elemental analysis. 2D-COSY, HSQC and NOESY experiments were also carried out. Selected NMR and mass spectra data are given. The NMR spectra were recorded in $CDCl_3$ at 70 °C unless otherwise stated; (b) Compound **17**: ^{1}H NMR (500 MHz) δ 7.51 (2H, d, $J = 8.1$ Hz), 7.4–7.3 (3H, m), 4.82 (1H, m), 3.77 (3H, d, $J_{H,P} = 10.5$ Hz), 3.76 (3H, d, $J_{H,P} = 10.5$ Hz), 3.59 (1H, ddd, $J = 7.6$, 7.7, 10.6 Hz), 3.47 (1H, m), 2.2–2.1 (2H, m), 1.78 (1H, m); ^{13}C NMR (125.7 MHz): δ 170.3 (C), 136.6 (C), 130.2 (CH), 128.2 (2×CH), 127.6 (2×CH), 53.0 (CH_3, d, $J_{C,P} = 7.0$ Hz), 52.7 (CH_3, d, $J_{C,P} = 6.4$ Hz), 52.2 (CH, d, $J_{C,P} = 163$ Hz), 49.9 (CH_2), 26.0 (CH_2), 25.0 (CH_2). MS (EI, 70 eV), *m*/*z*: 283 (M^+, 8), 178 (4), 174 (69), 105 (100); HRMS: calcd for $C_{13}H_{18}NO_4P$ 283.0973, found 283.0968.
10. The fragmentation of carboxyl radicals proceeds much faster than the fragmentation of alkoxyl radicals. Thus, K_{frag} ($RCOO^{\cdot}$) = 10^{10} s^{-1}, K_{frag} ($PhCOO^{\cdot}$) = 10^{6} s^{-1} and K_{frag} ($^{t}BuO^{\cdot}$) = 10^{5} s^{-1}. For a discussion on the subject, see: Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley: Chichester, 1995; pp 96, 148–149, 223–225 and 295.
11. Compound **19**: ^{1}H NMR (500 MHz) δ 7.35 (2H, dd, $J = 7.8$, 8.1 Hz), 7.34 (2H, dd, $J = 8.1$, 8.0 Hz), 7.21–7.13 (6H, m), 4.70 (1H, m), 4.66 (1H, dd, $J = 5.0$, 16.8 Hz), 4.30 (1H, d, $J = 13.5$ Hz), 4.16 (1H, d, $J = 12.1$ Hz), 3.79 (3H, d, $J_{H,P} = 11$ Hz), 3.78 (3H, d, $J_{H,P} = 11$ Hz), 3.70 (1H, m), 3.40 (1H, m), 3.08 (1H, m); ^{13}C NMR (125.7 MHz): δ 153.6 (C), 153.2 (C), 151.6 (C), 151.4 (C), 129.2 (2×CH), 129.1 (2×CH), 125.5 (CH), 125.2 (CH), 121.5 (2×CH), 121.3 (2×CH), 53.0 (CH_3, d, $J_{C,P} = 7.0$ Hz), 52.8 (CH_3, d, $J_{C,P} = 7.0$ Hz), 48.5 (CH, d, $J_{C,P} = 151.0$ Hz), 43.6 (CH_2), 43.0 (CH_2), 41.2 (CH_2); MS (EI, 70 eV), *m*/*z*: 435 (M^++H, 1), 434 (M^+, 1), 342 (18), 341 (99), 93 (100); HRMS: calcd for $C_{20}H_{23}N_2O_7P$ 434.1243, found 434.1248.
12. For very similar compounds, see: (a) Yuan, C.; Wang, G.; Chen, S. *Synthesis* **1990**, 522–524; (b) Shono, T.; Matsumura, Y.; Tsubata, K. *Tetrahedron Lett.* **1981**, *22*, 3249–3252.
13. (a) Compound **21b**: ^{1}H NMR (500 MHz) δ 4.55 (1H, dd, $J = 6.3$ Hz, $J_{H,P} = 17.4$ Hz), 3.95 (1H, d, $J = 12.8$ Hz), 3.65 (3H, d, $J_{H,P} = 10.5$ Hz), 3.64 (3H, d, $J_{H,P} = 10.6$ Hz), 3.61 (3H, s), 3.14 (1H, ddd, $J = 2.6$, 13.1, 13.3 Hz), 1.96 (1H, m), 1.81 (1H, m), 1.64 (1H, m), 1.55 (2H, m), 1.29 (1H, m); ^{13}C NMR (125.7 MHz): δ 155.9 (C), 52.6 (CH_3), 52.4 (CH_3, d, $J_{C,P} = 6.9$ Hz), 52.1 (CH_3, d, $J_{C,P} = 7.1$ Hz), 48.2 (CH, d, $J_{C,P} = 152.0$ Hz), 41.5 (CH_2), 25.0 (CH_2), 24.5 (CH_2), 20.0 (CH_2); MS (EI, 70 eV), *m*/*z*: 251 (M^+, 8), 143 (30), 142 (100); HRMS: calcd for $C_9H_{18}NO_5P$ 251.0923, found 251.0935. For a similar result, see: (b) Boto, A.; Hernández, R.; Suárez, E. *Tetrahedron Lett.* **1999**, *40*, 5945–5948.
14. Compound **22**: ^{1}H NMR (500 MHz) δ 4.47 (1H, br b, NH), 3.77 (6H, d, $J_{H,P} = 10.5$ Hz), 3.64 (3H, s), 2.33 (2H, m), 1.76 (2H, dddd, $J = 3.9$, 4.0, 13.1, 13.3 Hz), 1.67–1.55 (2H, m), 1.49 (2H, m), 1.27 (2H, m); ^{13}C NMR (125.7 MHz): δ 155.3 (C), 55.9 (C, d, $J_{C,P} = 160$ Hz), 53.1 (2×CH_3, d, $J_{C,P} = 7.2$ Hz), 51.6 (CH_3), 30.0 (2×CH_2), 25.1 (CH_2), 20.4 (CH_2), 20.2 (CH_2); MS (EI, 70 eV), *m*/*z*: 266 (M^++H, 1), 265 (M^+, 1), 234 (2), 191 (3), 156 (100); HRMS: calcd for $C_{10}H_{20}NO_5P$ 265.1079, found 265.1089.
15. (a) Compound **24**: ^{1}H NMR (500 MHz, 26 °C) δ 5.10 (1H, m), 4.48 (1H, m), 3.89 (1H, dd, $J = 6.5$, 11.5 Hz), 3.71 (3H, d, $J_{H,P} = 10.7$ Hz), 3.70 (3H, d, $J_{H,P} = 10.6$ Hz), 3.45 (1H, dd, $J = 4.7$, 11.5 Hz), 2.5–2.3 (2H, m), 2.00 (3H, s), 1.99 (3H, s); ^{1}H NMR (400 MHz, C_6D_6, 26 °C) δ 4.80 (1H, m), 4.53 (1H, m), 3.74 (3H, d, $J_{H,P} = 10.8$ Hz), 3.57 (3H, d, $J_{H,P} = 10.5$ Hz), 3.33 (2H, m), 2.46 (1H, m), 1.93 (1H, m), 1.82 (3H, s), 1.68 (3H, s); ^{13}C NMR (125.7 MHz, 26 °C): δ 170.5 (C), 168.9 (C), 71.8 (CH), 53.2 (CH_3, d, $J_{C,P} = 6.8$ Hz), 52.6 (CH_3, d, $J_{C,P} = 6.3$ Hz), 52.6 (CH_2), 50.7 (CH, d, $J_{C,P} = 160$ Hz), 31.9 (CH_2), 22.0 (CH_3), 20.8 (CH_3); MS (EI, 70 eV), *m*/*z*: 280 (M^++H, 2), 219 (M^+, 20), 110 (90), 109 (3), 68 (100); HRMS: calcd for $C_{10}H_{19}NO_6P$ 280.0950, found 280.0947; (b) The spectroscopic data of compound **25** were very similar, the main differences being observed in the ^{1}H NMR spectrum (500 MHz, 26 °C) δ 5.36 (1H, m), 4.73 (1H, m), 3.83 (1H, m), 3.78 (6H, d, $J_{H,P} = 10.3$ Hz), 3.60 (1H, m), 2.61 (1H, m), 2.23 (1H, m), 2.09 (3H, m), 2.01 (3H, s).
16. (a) The stereochemistry of compound **24** was determined with a COSY experiment (400 MHz, C_6D_6). Thus, a strong coupling was observed between 4-H (δ_H 4.80) and 3β-H (δ_H 1.93) and between 3β-H (δ_H 1.93) and 2-H (δ_H 4.53). In contrast, the coupling between 3α-H (δ_H 2.46) and 4-H or 2-H was very weak, as expected for 2-H,3α-H *trans* and 4-H,3α-H *trans* relationships; (b) In the case of compound **25**, the COSY experiment (500 MHz, $CDCl_3$) showed a strong coupling between 4-H (δ_H 5.36) and 3β-H (δ_H 2.61). The coupling between 3α-H (δ_H 2.23) and 2-H (δ_H 4.73) was also observe. The nucleophile was added from the apparently more hindered face. For similar results, see: (c) Yoda, H.; Egawa, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 1643–1646, and references cited therein.
17. (a) Compound **27**: ^{1}H NMR (500 MHz, −50 °C) δ 7.94 (1H, s, OCHO), 6.44 (1H, d, $J = 9.8$ Hz, NH), 5.59 (1H, dd, $J = 7.1$, 7.4 Hz, 3-H), 5.50 (1H, dd, $J = 4.9$, 6.4 Hz, 4-H), 5.23 (1H, ddd, $J = 5.1$, 5.1, 5.3 Hz, 5-H), 4.89 (1H, ddd, $J = 2.4$, 10.4 Hz, $J_{H,P} = 22.7$ Hz, 2-H), 4.30 (1H, dd, $J = 4.7$, 12.1 Hz, 6-H_a), 4.10 (1H, dd, $J = 6.4$, 11.8 Hz, 6-H_b), 3.77 (3H, d, $J_{H,P} = 9.8$ Hz, OMe), 3.75 (3H, d, $J_{H,P} = 10.3$ Hz, OMe), 2.15 (3H, s, Ac), 2.12 (3H, s, Ac), 2.10 (6H, s, 2×Ac); ^{13}C NMR (125.7 MHz, 26 °C): δ 170.5 (C, CO), 170.1 (C, CO), 169.8 (C, CO), 169.6 (C, CO), 159.4 (CH, CHO), 70.1 (CH, d, $J_{C,P} = 11.5$ Hz, 4-C), 69.0

(CH, 5-C), 68.5 (CH, $J_{C,P} = 4$ Hz, 3-C), 61.3 (CH_2, 6-C), 53.9 (CH_3, d, $J_{C,P} = 6.8$ Hz, OMe), 53.4 (CH_3, d, $J_{C,P} = 6.4$ Hz, OMe), 45.0 (CH, d, $J_{C,P} = 159$ Hz, 2-C), 23.0 (CH_3), 20.6 ($3\times CH_3$); MS (EI, 70 eV), *m*/*z*: 456 (M^++H, 6), 57 (100); HRMS: calcd for $C_{16}H_{27}NO_{12}P$ 456.1271, found 456.1286; (b) The spectroscopic data of compound **28** were very similar, the main differences being observed in the ^{1}H NMR spectrum (500 MHz, −50 °C): δ 8.07 (1H, s, OCHO), 7.14 (1H, br b, NH), 5.64 (1H, dd, $J = 9.9$, 10.0 Hz, 3-H), 5.44 (1H, dd, $J = 1.0$, 8.9 Hz, 4-H), 5.28 (1H, m, 5-H), 4.77 (1H, ddd, $J = 10.4$, 10.5 Hz, $J_{H,P} = 14.3$ Hz, 2-H), 4.21 (1H, br d, $J = 11.7$ Hz, 6-H_a), 4.00 (1H, dd, $J = 6.6$, 12.7 Hz, 6-H_b), 3.73 (6H, d, $J_{H,P} = 11.9$ Hz, OMe), 2.14 (3H, s, Ac), 2.12 (3H, s, Ac), 2.05 (3H, s, Ac), 1.99 (3H, s, Ac).

18. (a) The stereochemistry of compounds **27** and **28** was tentatively assigned by comparing the theoretical coupling constants calculated over the minimized structures for both diastereomers and the experimental coupling constants at −50 °C. Since at this temperature the interconversion between conformers is very slow, signals for each conformer are recorded in the NMR experiment; the intensity of the signals is related to the conformer population. In our case, the signals of the minor conformations were hardly observed. Presuming that the minimum-energy conformation was the major one, the experimental *J* would match the theoretical ones; The theoretical *J* were calculated by using the Karplus–Altona equation implemented in the Macromodel 7.0 program. See: (b) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792; (c) Experimental *J* for product **27**: $J_{2,3} = 2.4$ Hz, $J_{3,4} = 6.0$ Hz, and for compound **28**: $J_{2,3} = 10.0$ Hz, $J_{3,4} = 10.0$ Hz. Calculated *J* for the 2*R* diastereomer: $J_{2,3} = 0.3$ Hz, $J_{3,4} = 5.0$ Hz, and for the 2*S* diastereomer: $J_{2,3} = 8.0$ Hz and $J_{3,4} = 4.4$ Hz.
19. Boto, A.; Hernández, R.; Suárez, E. *Tetrahedron Lett.* **2001**, *42*, 9167–9170.