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Synthesis of (1*R*,2*S*)- and (1*S*,2*S*)-3-azido-1,2-dihydroxypropylphosphonates

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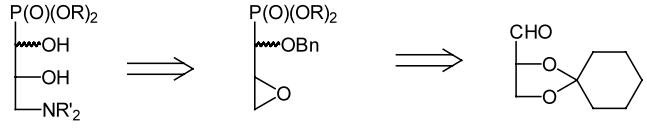
Abstract—An efficient synthesis of diastereomerically pure dimethyl (1*R*,2*S*)- and (1*S*,2*S*)-3-azido-1,2-dihydroxypropylphosphonates from L-ascorbic acid, via new chirons: (2*S*,3*S*)-4-azido-3-benzyloxy-1,2-*O*-isopropylidene-1,2-butanediol and (2*S*)-3-azido-2-benzyloxypropanal was elaborated. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Of the various aminoalkylphosphonates, α-amino derivatives form the most prominent subclass because they serve as analogues of α-aminoacids.[1] Alkylphosphonates bearing an amino group in the β or γ positions are less known, although β-aminoethylphosphonic acid (ciliatine) was the first aminophosphonate found in nature.[2] Phosphoalanine[3] and 2-amino-1-hydroxyethylphosphonic acid[4] are other examples of β-aminophosphonates isolated from natural sources. Fosfidomycin and structurally related γ-aminophosphonates are active as antibiotics.[5–8] Additionally, a number of γ- and δ-aminophosphonates have been synthesised and their ability as ligands for glutamate receptors has been investigated.[9]

For some time we have been involved in stereochemical studies on β-aminoalkylphosphonates. Enantiomeric *N*-substituted 2-amino-1-hydroxy-2-phenylethylphosphonates have recently been synthesised as phosphonate analogues of paclitaxel and docetaxel C-13 side chains.[10,11] Highly enantiomerically enriched substituted 2-amino-1,3-dihydroxypropylphosphonates were obtained from Garner aldehyde and dialkyl phosphites.[12] These achievements have stimulated our interest in the synthesis of 3-amino-1,2-dihydroxypropylphosphonates of the type **1**. To secure the 2*R* configuration in **1**, 2,3-*O*-cyclohexylidene-D-glyceraldehyde was selected as a starting material, and diastereoisomeric trihydroxypropylphosphonates obtained in the Abramov reaction[13] were transformed into stereochemically homogeneous 2,3-epoxy-1-benzyloxypropylphosphonates as precursors to (2*R*)-**1** (Scheme 1).[14]

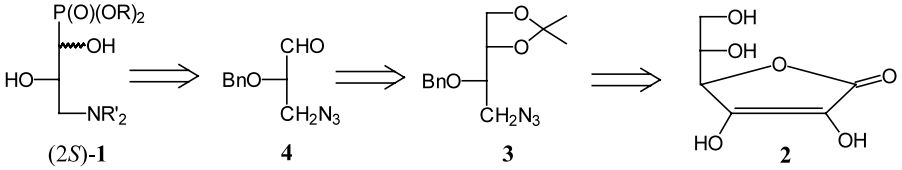


(2*R*)-**1**

Scheme 1. Retrosynthesis of (2*R*)-**1**.

In order to synthesise the phosphonates (2*S*)-**1** we turned to L-ascorbic acid **2** as a source of chirality (Scheme 2).[15]

Herein, we describe the transformation of **2** into a new four-carbon chiron, (2*S*,3*S*)-4-azido-3-benzyloxy-1,2-



(2*S*)-**1** **4** **3** **2**

Scheme 2. Retrosynthesis of (2*S*)-**1**.

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O-isopropylidene-1,2-butanediol **3**, one-step deisopropylidenation–periodate oxidation of **3** to (2*S*)-3-azido-2-benzyloxypropanal **4** and the addition of dialkyl phosphites to **4** to afford diastereoisomeric 3-azidoalkylphosphonates **9** and **10**.

2. Results and discussion

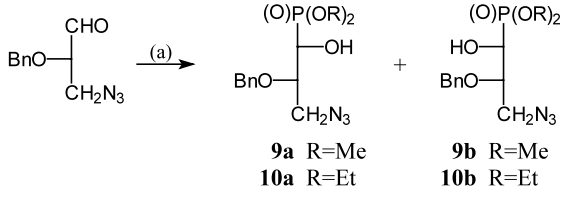
The protected α-hydroxy ester **5** was prepared according to the literature procedure[16] in 78% overall yield. After *O*-benzylation of **5** the known compound **6** was obtained (Scheme 3).[17] It was reduced with $NaBH_4$–LiCl mixture[18] to produce (2*S*,3*S*)-2-*O*-benzyl-3,4-*O*-isopropylidenebutanetetrol **7** in 90% yield. Alternative procedures for preparation of **7** employ L-tartrates as a source of chirality and $LiAlH_4$ as a reducing agent.[19–21] Quantitative mesylation of **7** led to the mesylate **8**,[22] which after azidation gave unknown (2*S*,3*S*)-4-azido-3-benzyloxy-1,2-*O*-isopropylidene-1,2-butanediol **3** in 35% overall yield from L-ascorbic acid. The synthesis of the aldehyde **4** from the 1,2-*O*-isopropylidene derivative **3** was accomplished with periodic acid in AcOEt.[23] However, the aldehyde **4** appeared to be very unstable and after removal of inorganic impurities by filtration through a pad of silica gel it was used immediately in the next step.

The crude aldehyde **4** was reacted separately with dimethyl and diethyl phosphites in the presence of NEt_3 as a catalyst to give phosphonates **9a**/**9b** and **10a**/**10b** in ca. 1:1 ratios (Scheme 4). The diastereoselectivity of the addition remained unchanged using $Ti(O\textit{i}\text{-}Pr)_4$ as a catalyst or when dimethyl trimethylsilyl phosphite was applied. Separation of the diastereoisomeric phosphonates was readily achieved for the methyl esters only to afford less polar **9a** as white needles (43%) and the more polar **9b** as a colorless oil (42%).

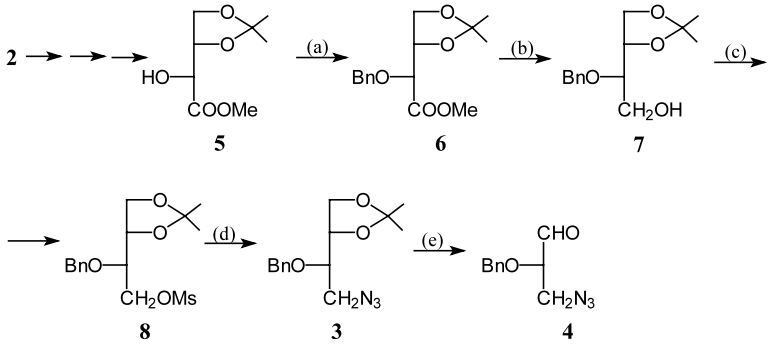
Finally, the γ-azidophosphonates **9a** and **9b** were transformed into 3-acetamido-1,2-dihydroxypropylphosphonates **12a** and **12b**, respectively, as shown in Scheme 5. After quantitative acetylation of the C(1) hydroxyl group, the acetates **11a** and **11b** were subjected to hydrogenation under atmospheric pressure at room temperature in the presence of 10% Pd/C or 20% $Pd(OH)_2$/C as catalysts. We found that hydrogenation of the azido group is much faster than hydrogenolysis of the benzyl group, which takes 1 week for completion irrespective of the catalyst used.

To assign the absolute configurations at C(1) in **9a** and **9b**, the diols **12a** and **12b** were reacted with 2,2-dimethoxypropane to form substituted 1,3-dioxolanes **13a** and **13b**, respectively (Scheme 5). Analysis of vicinal coupling constants (H(4)–H(5) 9.1 Hz, H(5)–P 10.8 Hz, *P*–C(4)–C(5)–*C* 0 Hz and *P*–C(4)–O(3)–*C*(2) 10.4 Hz) strongly supports the existence of **13a** in a single E_4 conformation, in which the *O*,*O*-dimethylphosphoryl group is equatorial, while the acetamidomethyl group occupies pseudoequatorial position (Scheme 6). On the other hand, the 1,3-dioxolane **13b** exists in the E_1 conformation having the largest substituents positioned pseudoequatorially. Again, a set of vicinal couplings (H(4)–H(5) 6.9 Hz, H(5)–P 23.2 Hz, *P*–C(4)–C(5)–*C* 4.8 Hz and *P*–C(4)–O(3)–*C*(2) 6.3 Hz)[24–31] is in a full agreement with the proposed conformation. Based on the results of the conformational studies on **13a** and **13b**, it was concluded that the absolute configurations at C(1) in **9a** and **9b** are 1*S* and 1*R*, respectively.

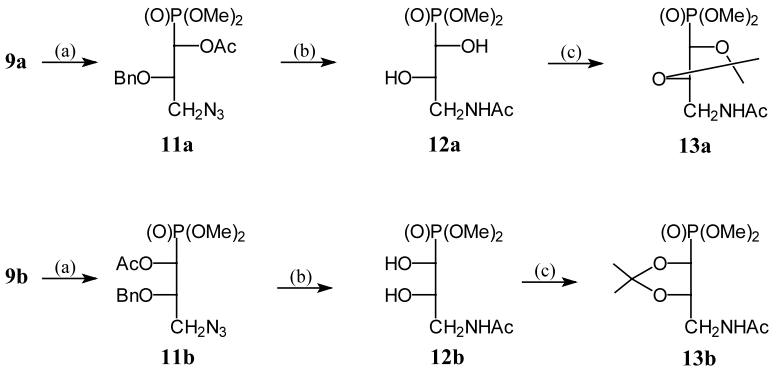
Before we decided to employ isopropylidene derivatives **13a** and **13b** for configurational assignments of **9a** and **9b**, conformational analysis of acyclic systems in the diastereoisomeric azides **9** and acetamides **12** was performed. It was noticed that the *O*,*O*-dimethylphosphoryl and azidomethyl groups in **9** prefer antiperiplanar arrangements, but because of significant contributions from the *gauche* conformers, reliable configurational conclusions could not be drawn. Although diastereoiso-



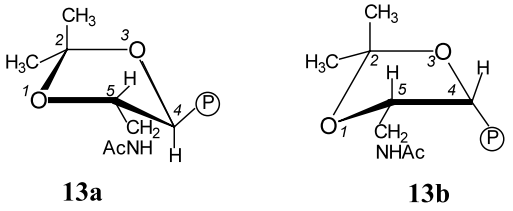
Scheme 4. Synthesis of the diastereoisomeric phosphonates **9** and **10**. *Reagents and conditions*: (a) $(RO)_2P(O)H$, NEt_3, rt.



Scheme 3. Synthesis of the aldehyde **4**. *Reagents and conditions*: (a) BnBr, Ag_2O; (b) $NaBH_4$, LiCl; (c) MsCl, pyridine, CH_2Cl_2; (d) NaN_3, DMF, 60°C; (e) H_5IO_6.



Scheme 5. Synthesis of diastereoisomeric 3-amino-1,2-dihydroxypropylphosphonates. *Reagents and conditions*: (a) Ac_2O, NEt_3, DMAP; (b) H_2, Pd–C; (c) $Me_2C(OMe)_2$, TosOH.



Scheme 6. Preferred conformations of 1,3-dioxolanes **13a** and **13b**.

meric acetamides **12** exist predominantly as *anti*-conformers ($^3J_{P-C3}=13.2$ and 13.6 Hz)[30–32] and spatial relationships of H(1) and H(2) in **12a** and **12b** are *gauche* (2.7 Hz) and *anti* (9.8 Hz), respectively, signal overlaps prohibited extraction of stereochemically relevant vicinal P–H(2) couplings, thus making configurational assignments at C(1) doubtful.

3. Conclusions

An efficient synthesis of a four-carbon chiron, (2*S*,3*S*)-4-azido-3-benzyloxy-1,2-*O*-isopropylidene-1,2-butanediol, was elaborated starting from L-ascorbic acid. Using a one-pot procedure it was transformed into unstable (2*S*)-3-azido-2-benzyloxypropanal, which was readily phosphonylated with dialkyl phosphites.

4. Experimental

General procedures and instrumentation have been described earlier.[14] In addition, some ^1H, ^{13}C and ^{31}P NMR spectra were obtained on a Varian-Mercury spectrometer at 300, 75.5 and 121.5 MHz, respectively.

4.1. Methyl (2*R*,3*S*)-2-benzyloxy-3,4-*O*-isopropylidene-3,4-dihydroxybutanoate 6

A suspension of **5** (1.67 g, 8.78 mmol), benzyl bromide (1.62 mL, 14.05 mmol), Ag_2O (3.26 g, 14.1 mmol) and powdered molecular sieves was stirred at room temperature for 4 h. After filtration through a pad of Celite, the solvent was evaporated and the crude product was purified on a silica gel column with chloroform–methanol (100:1, v/v) to give **6** as a colorless oil (1.757 g, 72%). IR (film): $\nu=2998$, 1744, 1372, 1210, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.40$–7.26 (m, 5H), 4.79 and 4.51 (AB, $J=11.9$ Hz, 2H), 4.40 (ddd ~ q, $J=6.5$ Hz, $J=6.5$ Hz, $J=5.6$ Hz, 1H), 4.01 (dAB, $J=8.7$ Hz, $J=6.5$ Hz, 1H), 4.00 (d, $J=5.6$ Hz, 1H), 3.97 (dAB, $J=8.7$ Hz, $J=6.5$ Hz, 1H), 3.77 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=170.43$, 136.92, 128.34, 128.09, 127.94, 109.85, 78.34, 75.85, 72.83, 65.49, 52.16, 26.36, 25.40.

4.2. (2*S*,3*S*)-3-Benzyloxy-1,2-*O*-isopropylidene-1,2,4-butanetriol 7

To a cooled (0°C) solution of **6** (1.435 g, 5.12 mmol) in THF–EtOH (22 mL, 1:2, v/v), LiCl (0.651 g, 15.4 mmol) and $NaBH_4$ (0.581 g, 15.4 mmol) were added. The reaction mixture was allowed to warm to room temperature and was stirred for 20 h. After quenching with acetone (6 mL), chloroform (30 mL) was added followed by $MgSO_4$ (5 g). The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified on a silica gel column with chloroform–methanol (100:1, v/v) to afford **7** as a colorless oil (1.161 g, 90%). IR (film): $\nu=3410$, 2934, 2882, 1455, 1372, 1214, 1057 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.38$–7.25 (m, 5H), 4.77 and 4.69 (AB, $J=11.7$ Hz, 2H), 4.31 (ddd, $J=6.9$ Hz, $J=6.5$ Hz, $J=6.0$ Hz, 1H), 4.01 (dd, $J=8.3$ Hz, $J=6.5$ Hz, 1H), 3.82 (dd, $J=8.3$ Hz, $J=6.9$ Hz, 1H), 3.78–3.69 (m, 1H), 3.64–3.54 (m, 2H), 1.44 (s, 3H), 1.37 (s, 3H).

4.3. Mesylation of 7

To a solution of **7** (1.16 g, 4.60 mmol) and pyridine (1.2 mL) in CH_2Cl_2 (6 mL) mesyl chloride (0.47 mL, 6.0 mmol) was added dropwise at 0°C and the reaction mixture was left at room temperature for 20 h. After diluting with CH_2Cl_2 (15 mL), the solution was washed with water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3×20 mL) and organic phases were dried ($MgSO_4$) and concentrated. The residue was coevaporated with toluene (3×20 mL) and finally kept in vacuo for 8 h to afford the crude mesylate **8** as a pale yellow oil (1.504 g, 99%). ^1H NMR (300 MHz, $CDCl_3$): $\delta=$ 7.37–7.26 (m, 5H), 4.74 and 4.70 (AB, $J=11.9$ Hz, 2H),

4.39 (dAB, $J=10.9$ Hz, $J=3.8$ Hz, 1H), 4.27 (dt, $J=5.2$ Hz, $J=6.5$ Hz, 1H), 4.26 (dAB, $J=10.9$ Hz, $J=6.1$ Hz, 1H), 4.02 (dd, $J=8.5$ Hz, $J=6.7$ Hz, 1H), 3.83 (dd, $J=8.5$ Hz, $J=6.5$ Hz, 1H), 3.76 (ddd, $J=6.2$ Hz, $J=5.2$ Hz, $J=3.8$ Hz, 1H), 2.99 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H).

4.4. (2*S*,3*S*)-4-Azido-3-benzyloxy-1,2-*O*-isopropylidene-1,2-butanediol 3

A mixture of **8** (1.504 g, 4.55 mmol) and NaN_3 (0.355 g, 5.46 mmol) in DMF (5 mL) was heated at 60°C for 48 h. After diluting with AcOEt (15 mL), the precipitate was filtered off, and the organic phase was washed with aqueous $NaHCO_3$ (5%, 2×20 mL) and brine (2×30 mL), dried with $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel column with chloroform–methanol (100:1, v/v) to afford **3** as a colorless oil (1.016 g, 81%). $[\alpha]_D=+10.5$ ($c=2.47$ in $CHCl_3$). IR (film): $\nu=2987$, 2935, 2886, 2102, 1214, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.40$–7.26 (m, 5H), 4.75 and 4.72 (AB, $J=11.7$ Hz, 2H), 4.26 (ddd ~ q, $J=6.8$ Hz, $J=6.6$ Hz, $J=5.6$ Hz, 1H), 3.99 (dAB, $J=8.6$ Hz, $J=6.6$ Hz, 1H), 3.79 (dAB, $J=8.6$ Hz, $J=6.8$ Hz, 1H), 3.64 (ddd, $J=6.5$ Hz, $J=5.6$ Hz, $J=4.4$ Hz, 1H), 3.37 (dAB, $J=13.1$ Hz, $J=4.2$ Hz, 1H), 3.33 (dAB, $J=13.1$ Hz, $J=6.5$ Hz, 1H), 1.43 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=137.76$, 128.34, 127.87, 127.79, 109.45, 78.36, 75.84, 73.22, 65.31, 51.32, 26.44, 25.23. Anal. calcd for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.90; N, 15.15. Found: C, 60.71; H, 6.80; N, 15.28%.

4.5. (2*S*)-3-Azido-2-benzyloxypropanal 4

A solution of **3** (0.932 g, 3.36 mmol) and H_5IO_6 (0.843 g, 3.70 mmol) in AcOEt (6 mL) was stirred at room temperature for 1 h. The reaction mixture was filtered through a pad of silica gel and the solution was concentrated to give unstable **4** as a yellowish oil (0.642 g, 93%). ^1H NMR (300 MHz, $CDCl_3$): $\delta=9.69$ (d, $J=1.0$ Hz, 1H), 7.40–7.30 (m, 5H), 4.76 (s, 2H), 3.96 (ddd, $J=5.7$ Hz, $J=4.2$ Hz, $J=1.0$ Hz, 1H), 3.55 (dAB, $J=12.3$ Hz, $J=4.2$ Hz, 1H), 3.52 (dAB, $J=12.3$ Hz, $J=5.7$ Hz, 1H).

4.6. Addition of dimethyl phosphite to (2*S*)-4

A mixture of the crude aldehyde (2*S*)-**4** (0.303 g, 1.48 mmol), dimethyl phosphite (0.168 mL, 1.48 mmol) and triethylamine (0.021 mL, 0.15 mmol) was stirred at room temperature for 20 h. After addition of CH_2Cl_2 (10 mL), the solution was washed with water (2×20 mL), dried over $MgSO_4$ and concentrated to leave a yellowish oil, which was chromatographed on a silica gel column with a chloroform–methanol–triethylamine mixture (100:1:0.2, v/v). The appropriate fractions were collected to give: **9a** (0.184 g, 43%), a mixture of **9a** and **9b** (0.053 g, 12%) and **9b** (0.180 g, 42%).

4.6.1. Dimethyl (1*S*,2*S*)-3-azido-2-benzyloxy-1-hydroxypropylphosphonate 9a. White needles. Mp 71–72°C (from diethyl ether). $[\alpha]_D=+16.6$ ($c=2.19$ in $CHCl_3$). IR (KBr): $\nu=3214$, 2956, 2863, 2163, 2096, 1241, 1064, 838, 756, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.41$–7.31 (m, 5H), 4.75 (s, 2H), 4.01 (dAB, $J_{AB}=3.6$ Hz, $J=10.1$ Hz, 1H, H-1), 3.96 (dddAB, $J=3.6$ Hz, $J=5.8$ Hz, $J=5.8$ Hz, $J=9.3$ Hz, 1H, H-2), 3.810 and 3.806 (2d, $J=10.7$ Hz, 6H), 3.524 and 3.517 (AB part of ABX system, $J_{AB}=12.6$ Hz, $J=5.8$ Hz, $J=5.8$ Hz, 2H), 2.8–1.8 (brs, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=137.27$, 128.53, 128.34, 128.17, 77.13 (d, $J=3.4$ Hz), 73.91, 67.92 (d, $J=162.0$ Hz), 53.81 (d, $J=8.0$ Hz), 53.32 (d, $J=6.9$ Hz), 51.19 (d, $J=10.3$ Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta=24.40$. Anal. calcd for $C_{12}H_{18}N_3O_5P$: C, 45.72; H, 5.75; N, 13.33. Found: C, 45.76; H, 5.54; N, 13.14%.

4.6.2. Dimethyl (1*R*,2*S*)-3-azido-2-benzyloxy-1-hydroxypropylphosphonate 9b. Colorless oil. $[\alpha]_D=+23.4$ ($c=1.02$ in $CHCl_3$). IR (film): $\nu=3274$, 2956, 2855, 2103, 1224, 1053, 836, 743, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.41$–7.26 (m, 5H), 4.72 and 4.66 (AB, $J_{AB}=11.1$ Hz, 2H), 4.14 (dd, $J=7.5$ Hz, $J=6.3$ Hz, 1H), 3.90 (dddd, $J=9.7$ Hz, $J=6.3$ Hz, $J=5.6$ Hz, $J=3.4$ Hz, 1H), 3.78 and 3.75 (2×d, $J=10.6$ Hz, 6H), 3.61 and 3.60 (AB part of ABX system, $J_{AB}=13.5$ Hz, $J=5.6$ Hz, $J=3.4$ Hz, 2H), 3.4–1.8 (brs, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=137.36$, 128.55, 128.31, 128.13, 78.38 (d, $J=4.0$ Hz), 73.14, 67.59 (d, $J=160.6$ Hz), 58.68 and 58.67 (2d, $J=6.0$ Hz), 51.33 (d, $J=8.0$ Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta=26.14$. Anal. calcd for $C_{12}H_{18}N_3O_5P$: C, 45.72; H, 5.75; N, 13.33. Found: C, 45.51; H, 5.91; N, 13.07%.

4.7. Dimethyl 3-acetamido-1,2-dihydroxypropylphosphonates 12

4.7.1. Acetylation of 9a and 9b, general procedure. A solution of **9** (1.0 mmol), Ac_2O (3.0 mmol) and NEt_3 (3.3 mmol) in CH_2Cl_2 (1 mL) containing a few crystals of DMAP was stirred at room temperature for 0.5 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with H_2O (2×20 mL), aqueous $NaHCO_3$ (25 mL), dried over $MgSO_4$ and concentrated. The crude product was purified on a silica gel column with chloroform–methanol–triethylamine (100:1:0.1, v/v).

Compound (1*S*,2*S*)-11a: From (1*S*,2*S*)-**9a** (0.109 g, 0.360 mmol), (1*S*,2*S*)-**11a** (0.113 g, 92%) was obtained as a colorless oil. $[\alpha]_D=-2.9$ ($c=1.75$ in $CHCl_3$). IR (film): $\nu=2956$, 2930, 2857, 2104, 1753, 1219, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.39$–7.27 (m, 5H), 5.50 (dd, $J=11.1$ Hz, $J=5.8$ Hz, 1H), 4.73 (s, 2H), 3.99 (dddd, $J=9.2$ Hz, $J=6.0$ Hz, $J=5.8$ Hz, $J=4.8$ Hz, 1H), 3.78 and 3.77 (2×d, $J=10.8$ Hz, 6H), 3.50 (dAB, $J_{AB}=13.0$ Hz, $J=6.0$ Hz, 1H), 3.46 (dAB, $J_{AB}=13.0$ Hz, $J=4.8$ Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=169.30$ (d, $J=4.9$ Hz), 137.24, 128.50, 128.14, 128.09, 76.79 (d, $J=3.8$ Hz), 67.36 (d, $J=164.6$ Hz), 53.74 (d, $J=6.8$ Hz), 53.54 (d, $J=6.0$ Hz), 51.62 (d, $J=6.3$ Hz), 20.79; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta=20.78$. Anal. calcd for $C_{14}H_{20}N_3O_6P$: C, 47.06; H, 5.64; N, 11.76. Found: C, 46.80; H, 5.52; N, 11.69%.

Compound (1*R*,2*S*)-11b: From (1*R*,2*S*)-**9b** (0.095 g, 0.30 mmol), (1*R*,2*S*)-**11b** was obtained as a colorless oil (0.090 g, 81%). $[\alpha]_D = +2.0$ ($c = 1.38$ in $CHCl_3$). IR (film): $\nu = 2956$, 2854, 2101, 1753, 1216, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.41$–7.29 (m, 5H), 5.63 (dd, $J = 12.93$ Hz, $J = 3.8$ Hz, 1H), 4.73 and 4.62 (AB, $J_{AB} = 11.1$ Hz, 2H), 3.98 (dddd, $J = 7.9$ Hz, $J = 7.1$ Hz, $J = 3.8$ Hz, $J = 3.6$ Hz, 1H), 3.78 and 3.75 (2×d, $J = 10.7$ Hz, 6H), 3.55 (dAB, $J_{AB} = 13.3$ Hz, $J = 3.6$ Hz, 1H), 3.51 (dAB, $J_{AB} = 13.3$ Hz, $J = 7.1$ Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 169.12$ (d, $J = 4.9$ Hz), 136.84, 128.49, 128.43, 128.12, 77.15, 72.72, 66.37 (d, $J = 164.6$ Hz), 53.75 (d, $J = 7.2$ Hz), 53.47 (d, $J = 6.7$), 51.30 (d, $J = 2.9$ Hz), 20.77; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 20.67$. Anal. calcd for $C_{14}H_{20}N_3O_6P$: C, 47.06; H, 5.64; N, 11.76. Found: C, 47.25; H, 5.36; N, 11.58%.

4.7.2. Hydrogenolysis of azides 11a and 11b, general procedure. A solution of the azide (0.3 mmol) in methanol (0.5 mL) was kept under a hydrogen atmosphere over Pd/C catalyst (5 mg) at room temperature for 7 days. The suspension was filtered through a pad of Celite and washed with methanol. After evaporation of the solvent, the residue was chromatographed on a silica gel column with chloroform–methanol (10:1, v/v).

Compound (1*S*,2*S*)-12a: From (1*S*,2*S*)-**11a** (0.113 g, 0.32 mmol) in the presence of 10% Pd–C, (1*S*,2*S*)-**12a** (0.061 g, 86%) was obtained as a colorless oil. $[\alpha]_D = -12.4$ ($c = 2.12$ in $CHCl_3$). IR (film): $\nu = 3297$, 2959, 2856, 1654, 1558, 1219, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.73$ (brt, 1H), 4.54 (brdd, $J = 11.0$ Hz, $J = 7.1$ Hz, 1H, HO-C1), 4.40 (brd, $J = 5.4$ Hz, 1H, HO-C2), 4.06–3.98 (m, 1H, H-2), 3.93 (ddd, $J = 11.7$ Hz, $J = 7.1$ Hz, $J = 2.7$ Hz, 1H, H-1), 3.86 and 3.82 (2d, $J = 10.5$ Hz, 6H), 3.61 (ddAB, $J_{AB} = 14.1$ Hz, $J = 7.0$ Hz, $J = 6.0$ Hz, 1H, H-3a), 3.68 (ddAB, $J_{AB} = 14.1$ Hz, $J = 7.2$ Hz, $J = 5.6$ Hz, 1H, H-3b), 2.04 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 172.31$, 69.67 (d, $J = 1.5$ Hz, C-2), 68.72 (d, $J = 164.3$ Hz, C1), 54.14 and 53.34 (2d, $J = 7.0$ Hz), 42.39 (d, $J = 13.2$ Hz, C-3), 23.15; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 25.67$. Anal. calcd for: $C_7H_{18}NO_7P$: C, 32.44; H, 7.00; N, 5.38. Found: C, 32.68; H, 7.29; N, 5.57%.

Compound (1*R*,2*S*)-12b: From (1*R*,2*S*)-**11b** (0.137 g, 0.38 mmol) in the presence of 20% $Pd(OH)_2/C$, (1*R*,2*S*)-**12b** (0.085 g, 82%) was obtained as a colorless oil. $[\alpha]_D = +35.6$ ($c = 1.81$ in $CHCl_3$); IR (film): $\nu = 3307$, 2959, 2856, 1647, 1556, 1226, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.61$ (brm, 1H), 5.49 (dd, $J = 25.5$ Hz, $J = 5.4$ Hz, 1H, HO-C1), 4.36 (brs, 1H, HO-C2), 4.02–3.82 (m, 2H, H-2, H-3a), 3.89 and 3.86 (2d, $J = 10.6$ Hz, 6H), 3.67 (ddd, $J = 9.8$ Hz, $J = 9.8$ Hz, $J = 5.4$ Hz, 1H, H-1), 3.24 (dddd, $J = 14.7$ Hz, $J = 5.0$ Hz, $J = 3.0$ Hz, $J = 3.0$ Hz, 1H, H-3b), 2.08 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 173.37$, 70.52 (d, $J = 2.9$ Hz, C-2), 67.59 (d, $J = 164.6$ Hz, C-1), 54.20 and 53.81 (2d, $J = 6.8$ Hz), 41.68 (d, $J = 13.6$ Hz, C-3), 23.07; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 27.58$. Anal. calcd for $C_7H_{18}NO_7P$: C, 32.44; H, 7.00; N, 5.40. Found: C, 32.24; H, 7.06; N, 5.38%.

4.8. Dimethyl 1,2-*O*-isopropylidene-3-acetamido-1,2-dihydroxypropylphos-phonates 13, general procedure

A solution of the diol **12** (1.0 mmol) and 2,2-dimethoxypropane (2.0 mmol) in CH_2Cl_2 (1 mL) containing a few crystals of *p*-toluenesulfonic acid was left at room temperature for 4.5 h. The catalyst was neutralized with NEt_3 (0.2 mL) and the volatiles were removed in vacuo. The crude products were purified on a silica gel column with chloroform–methanol–triethylamine (50:1:0.1, v/v).

Compound (1*S*,2*S*)-13a: From (1*S*,2*S*)-**12a** (0.054 g, 0.21 mmol), (1*S*,2*S*)-**13a** (0.049 g, 78%) was obtained as a colorless oil. $[\alpha]_D = -2.0$ ($c = 0.98$ in $CHCl_3$); IR (film): $\nu = 3438$, 3297, 2990, 2960, 2939, 2856, 1659, 1555, 1248, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.4$ (brs, 1H), 4.34 (dddd, $J = 10.8$ Hz, $J = 9.1$ Hz, $J = 5.2$ Hz, $J = 5.2$ Hz, 1H), 3.91 (dd, $J = 9.1$ Hz, $J = 2.4$ Hz, 1H), 3.87 and 3.86 (2×d, $J = 10.7$ Hz, 6H), 3.68 (ddAB, $J_{AB} = 13.9$ Hz, $J = 6.7$ Hz, $J = 5.2$ Hz, 1H), 3.46 (ddAB, $J_{AB} = 13.9$ Hz, $J = 5.2$ Hz, $J = 5.2$ Hz, 1H), 2.01 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 170.30$, 111.41 (d, $J = 10.4$ Hz), 75.93 (d, $J = 5.0$ Hz), 73.38 (d, $J = 172.2$ Hz), 53.87 (d, $J = 7.0$ Hz), 53.55 (d, $J = 6.7$ Hz), 40.79, 26.57, 25.91, 23.06; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 22.30$. Anal. calcd for $C_{10}H_{20}NO_6P$: C, 42.71; H, 7.17; N, 4.98. Found: C, 42.42; H, 7.19; N, 4.74%.

Compound (1*R*,2*S*)-13b: From (1*R*,2*S*)-**12b** (0.051 g, 0.18 mmol), (1*R*,2*S*)-**13b** (0.048 g, 63%) was obtained as a colorless oil. $[\alpha]_D = +31.3$ ($c = 0.97$ in $CHCl_3$); IR (film): $\nu = 3407$, 3300, 2989, 2959, 2856, 1659, 1552, 1224, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.66$ (brs, 1H), 4.48 (dddd, $J = 23.2$ Hz, $J = 6.9$ Hz, $J = 6.9$ Hz, $J = 6.1$ Hz, 1H), 4.37 (dd, $J = 6.9$ Hz, $J = 1.0$ Hz, 1H), 3.88 and 3.84 (2×d, $J = 10.6$ Hz, 6H), 3.80 (ddd, $J = 13.9$ Hz, $J = 6.4$ Hz, $J = 6.1$ Hz, 1H), 3.57 (ddd, $J = 13.9$ Hz, $J = 6.9$ Hz, $J = 6.6$ Hz, 1H), 2.00 (s, 3H), 1.53 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 170.36$, 110.95 (d, $J = 6.3$ Hz), 75.45, 72.73 (d, $J = 169.9$ Hz), 53.98 (d, $J = 7.1$ Hz), 53.41 (d, $J = 7.2$ Hz), 39.74 (d, $J = 4.8$ Hz), 26.91, 25.08, 23.59; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 22.32$. Anal. calcd for $C_{10}H_{20}NO_6P$: C, 42.71; H, 7.17; N, 4.98. Found: C, 42.55; H, 7.46; N, 4.83%.

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