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

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Abstract—Diastereomeric diethyl (1*R*,2*R*)- and (1*S*,2*R*)-2,3-epoxy-1-benzyloxypropylphosphonates were obtained from the respective 2,3-*O*-cyclohexylidene-1-hydroxypropylphosphonates via the following sequence of reactions: benzylation, acetal hydrolysis and transformation of the terminal diol into the epoxide using the Sharpless protocol. These epoxides were regioselectively opened with dibenzylamine to afford the title compounds after acetylation and hydrogenolysis. © 2002 Published by Elsevier Science Ltd.

1. Introduction

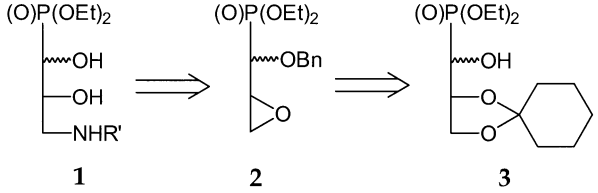
The biological activity of several phosphonate and phosphinate derivatives containing amino and hydroxy groups has been well documented.[1–4] Synthetic approaches to these compounds rely mostly on connecting *H*-phosphonates or phosphinates with appropriate carbon chirons. For the synthesis of α-aminoalkylphosphonates various modifications of the Fields–Kabachnik reaction have been applied[5] including the most recent examples.[6,7] When β-amino-α-hydroxyalkylphosphonates are required, addition to protected β-amino aldehydes is the method of choice.[1–4,8–12] The same strategy seems to be appropriate for the synthesis of γ-amino-α,β-dihydroxyalkylphosphonates.

Terminal epoxides are extremely useful precursors to vicinal ω-amino alcohols. We have recently shown that highly enantiomerically enriched 3-amino-2-hydroxypropylphosphonates can be prepared by regioselective opening of diethyl 2,3-epoxypropylphosphonate obtained via HKR of the racemic epoxide in the presence of the Jacobsen catalyst.[13] In order to synthesise substituted 3-amino-1,2-dihydroxypropylphosphonates **1** (Scheme 1) a similar strategy was applied. Our approach takes advantage of the mild conditions and full regiochemistry of the epoxide ring opening while preserving the phosphonate ester functionality. Herein, we present the efficient transformation of diethyl (1*R*,2*R*)- and (1*S*,2*R*)-2,3-*O*-cyclohexylidene-1-hydroxypropylphosphonates **3** into 2,3-epoxy-1-benzyloxypropylphosphonates **2** and 3-amino-1,2-dihydroxypropylphosphonates **1**.

2. Results and discussion

The reaction sequence leading to diethyl (1*R*,2*R*)- and (1*S*,2*R*)-2,3-epoxy-1-benzyloxypropylphosphonates **2** is outlined in Scheme 2.

Enantiomerically pure (1*R*,2*R*)-**3a** and (1*S*,2*R*)-**3b**[14] were subjected to benzylation with benzyl bromide in the presence of silver oxide and powdered molecular sieves. Under these slightly alkaline conditions the *retro*-Abramov reaction[15] was suppressed, and the corresponding 1-*O*-benzylated phosphonates (1*R*,2*R*)-**4a** and (1*S*,2*R*)-**4b** were separated as pure diastereoisomers in 93 and 86% yield, respectively. However, in the ^{31}P NMR spectra of the crude products, small resonances



1 **2** **3**

Scheme 1. Retrosynthesis of 3-amino-1,2-hydroxypropylphosphonates.

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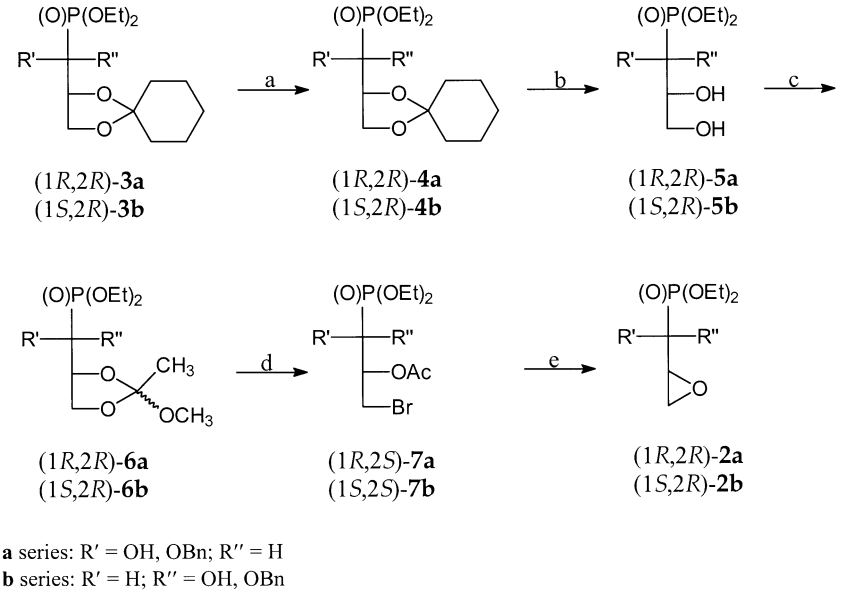


a series: R′ = OH, OBn; R″ = H
b series: R′ = H; R″ = OH, OBn

Scheme 2. *Reagents and conditions*: (a) BnBr, Ag_2O, A4, 24 h; (b) HCl, H_2O, dioxane, 24 h; (c) $MeC(OMe)_3$, PPTS; (d) AcBr; (e) K_2CO_3, MeOH, 2 h.

at −0.25 ppm were found, i.e. ca. 1% and up to 8% during benzylation of **3a** and **3b**, respectively. This is probably (2,3-*O*-cyclohexylidene-2,3-dihydroxypropyl)-diethyl phosphate, which is formed by the α-hydroxyphosphonate–phosphate rearrangement.[16] Deprotection of the cyclohexylidene group was accomplished under standard conditions[17] to give the terminal diols (1*R*,2*R*)-**5a** and (1*S*,2*R*)-**5b** almost quantitatively. Several attempts to achieve a clean transformation of **5** into terminal epoxides **2** have been reported in the literature.[18–20] The best results were obtained when the Sharpless three-step (5→6→7→2) one-pot procedure[21] was applied. Under these conditions the epoxides (1*R*,2*R*)-**2a** and (1*S*,2*R*)-**2b** were formed from the corresponding diols in 77 and 53% yield, respectively. In preliminary experiments intermediate bromides **7** were separated and characterized by ^1H, ^{13}C and ^{31}P NMR spectroscopy.

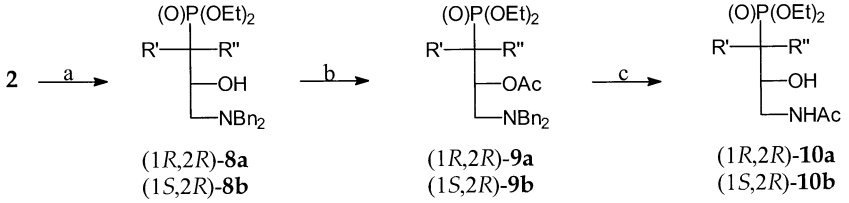
O-Benzylated phosphonates **2** were used as starting materials in the synthesis of 3-amino-1,2-dihydroxypropylphosphonates **1** (Scheme 3).

Following our previous experience with the regioselective opening of the epoxide ring in structurally related systems[13] dibenzylamine was selected. In the presence of 1.1 equiv. of this amine the phosphonates **2** were cleanly and completely reacted at 50°C after 3 days. In order to accelerate hydrogenolysis of the dibenzylamino group and to prevent future nucleophilic attack of the H_2N–C(3) group at the phosphorus atom,[22] the intermediates **8** were first acetylated and the fully protected phosphonates **9** were subjected to hydrogenolysis over Pearlman's catalyst to give the title compounds **10**.

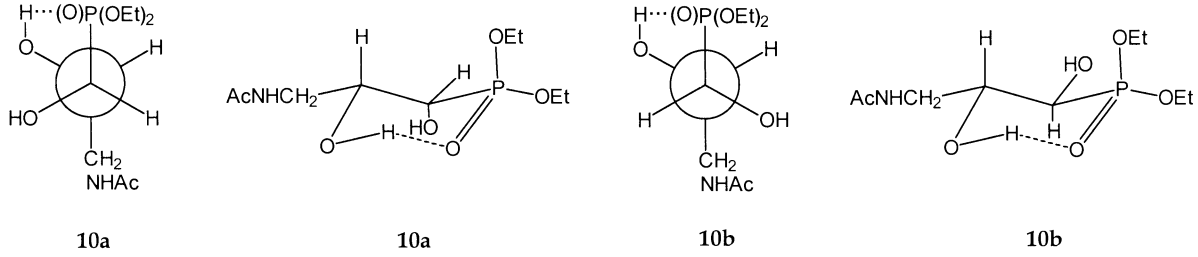
Diastereoisomeric 3-acetamido-1,2-dihydroxypropylphosphonates **10a** and **10b** exist preferentially as *anti*-conformers (Scheme 4). They are stabilised by the antiperiplanar disposition of the largest substituents about the C(1)–C(2) bond and by the formation of the hydrogen bond between the *H*O–C(2) and P=*O* groups, possibly within six-membered rings, which adopt a chair conformation. These conclusions are based on the large $^3J_{CCCP}$ coupling constant values (12.9 Hz for **10a** and 13.5 Hz for **10b**) together with vicinal C(1)H–C(2)H couplings (3.0 Hz for **10a** and 10.0 Hz for **10b**).[23–26]

3. Conclusions

Diastereoisomerically pure diethyl (1*R*,2*R*)- and (1*S*,2*R*)-2,3-*O*-cyclohexylidene-1-hydroxypropylphosphonates were efficiently transformed into the respective diethyl 1-benzyloxy-2,3-epoxypropylphosphonates,



Scheme 3. *Reagents and conditions*: (a) $HNBn_2$, 3 days; (b) Ac_2O, TEA, cat. DMAP, 1.5 h; (c) H_2–$Pd(OH)_2$/C, 6 days.



Scheme 4. Preferred conformations of **10a** and **10b**.

which are useful starting materials for the synthesis of 3-substituted 1,2-dihydroxypropylphosphonates. Fully C(3)-regioselective oxirane ring opening in these 2,3-epoxyphosphonates was achieved with dibenzylamine leading after acetylation and hydrogenolysis to diethyl (1*R*,2*R*)- and (1*S*,2*R*)-3-acetamido-1,2-dihydroxypropylphosphonates.

4. Experimental

General procedures and instrumentation were described earlier.[14] In addition, some ^{1}H, ^{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. Diethyl (1*R*,2*R*)-1-benzyloxy-2,3-*O*-cyclohexylidene-2,3-dihydroxypropylphosphonate 4a

A solution of (1*R*,2*R*)-**3a** (4.50 g, 0.015 mol) in dry CH_2Cl_2 (120 mL) was added to a mixture of ground molecular sieves (1.5 g) and freshly prepared silver oxide (5.35 g, 0.022 mol). After addition of benzyl bromide (5.17 g, 0.0291 mol) the suspension was vigorously stirred at room temperature for 24 h. The reaction mixture was filtered through Celite, washed with CH_2Cl_2, and the solution was concentrated in vacuo. The residue was purified on a silica gel column with chloroform–methanol (100:1, v/v) to give (1*R*,2*R*)-**4a** as a colorless oil (5.42 g, 93%). $[\alpha]_D=-6.5$ ($c=2.38$, $CHCl_3$); IR (film): $\nu=2982$, 2936, 2863, 1252, 1028, 741 and 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.40$–7.26 (m, 5H), 4.88 and 4.83 (AB, $J=11.6$ Hz, 2H), 4.40 (dddd, $J=7.8$ Hz, $J=7.2$ Hz, $J=6.2$ Hz, $J=3.4$ Hz, 1H, H-2), 4.23–4.10 (m, 4H), 4.05 (dd, $J=8.7$ Hz, $J=6.2$ Hz, 1H, H-3a), 3.82 (dd, $J=8.7$ Hz, $J=7.2$ Hz, 1H, H-3b), 3.69 (dd, $J=9.1$ Hz, $J=7.8$ Hz, 1H, H-1), 1.64–1.54 (m, 8H), 1.44–1.36 (m, 2H), 1.33 and 1.32 (2t, $J=7.1$ Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=$ 137.32, 128.29, 128.16, 127.72, 109.86, 76.44 (d, $J=$ 160.5 Hz, C-1), 75.60 (d, $J=11.0$ Hz, O*C*H_2Ph), 74.67 (d, $J=5.4$ Hz, C-2), 65.75 (d, $J=2.8$ Hz, C-3), 62.67 (d, $J=7.6$ Hz), 62.44 (d, $J=6.8$ Hz), 36.08, 34.97, 25.00, 23.84, 23.74, 16.31 (d, $J=5.8$ Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta=20.16$. Anal. calcd for $C_{20}H_{31}O_6P$: C, 60.28; H, 7.84. Found: C, 60.05; H, 7.64%.

In a similar manner, from (1*S*,2*R*)-**3b** (4.50 g, 0.015 mol), (1*S*,2*R*)-**4b** (5.02 g, 86%) was obtained as a colorless oil. $[\alpha]_D=+16.4$ ($c=1.78$, $CHCl_3$); IR (film): $\nu=2981$, 2935, 2862, 1255, 1101, 1027, 740 and 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.40$–7.27 (m, 5H), 4.86 and 4.80 (AB, $J=11.3$ Hz, 2H), 4.43 (dddd, $J=7.0$ Hz, $J=7.0$ Hz, $J=3.2$ Hz, $J=1.9$ Hz, 1H, H-2), 4.20–4.03 (m, 7H), 1.66–1.60 (m, 8H), 1.40–1.35 (m, 2H), 1.32 and 1.30 (2t, $J=7.0$ Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=137.41$, 128.22, 128.11, 127.80, 109.47, 75.64 (d, $J=5.3$ Hz, C-2), 75.09 (d, $J=12.7$ Hz, O*C*H_2Ph), 74.57 (d, $J=163.6$ Hz, C-1), 64.35 (d, $J=2.6$ Hz, C-3), 62.69 (d, $J=6.8$ Hz), 62.53 (d, $J=7.2$ Hz), 35.74, 34.91, 25.08, 23.92, 23.78, 16.41 (d, $J=5.8$ Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta=20.60$. Anal. calcd for $C_{20}H_{31}O_6P$: C, 60.28; H, 7.84. Found: C, 59.99; H, 8.02%.

4.2. Diethyl (1*R*,2*R*)-1-benzyloxy-2,3-dihydroxypropylphosphonate 5a

A solution of (1*R*,2*R*)-**4a** (3.24 g, 8.13 mmol) in dioxane (42 mL) containing aqueous HCl (4.5%–82 mL) was left at room temperature for 24 h. The volatiles were evaporated at 20 mmHg (bath 40°C). The residue was evaporated with dry dioxane (5×20 mL), dissolved in CH_2Cl_2 (50 mL), neutralised with NEt_3 and dried over $MgSO_4$. After removal of the solvent the crude product (2.48 g) was purified on a silica gel column with chloroform:methanol (50:1, v/v) to give (1*R*,2*R*)-**5a** as a colorless syrup (2.22 g, 89%). $[\alpha]_D=-14.1$ ($c=4.45$, $CHCl_3$); IR (film): $\nu=3380$, 2983, 2932, 1217, 1028, 970, 743 and 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.40$–7.26 (m, 5H), 4.90 (d, $J=11.3$ Hz, 1H), 4.62 (dd, $J=11.3$ Hz, $J=1.2$ Hz, 1H), 4.30–4.15 (m, 4H), 3.96 (dddd, $J=9.9$ Hz, $J=5.2$ Hz, $J=5.1$ Hz, $J=4.8$ Hz, 1H, H-2), 3.83 (dd, $J=7.1$ Hz, $J=4.8$ Hz, 1H, H-1), 3.77 (dAB, $J_{AB}=11.7$ Hz, $J=5.2$ Hz, 1H, H-3a), 3.62 (dAB, $J=11.7$ Hz, $J=5.1$ Hz, 1H, H-3b), 2.9–1.9 (brs, 2H), 1.36 (t, $J=6.9$ Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=136.89$, 128.45, 128.41, 128.21, 74.97 (d, $J=161.7$ Hz, C-1), 74.67 (d, $J=2.9$ Hz, O*C*H_2Ph), 71.04 (d, $J=4.1$ Hz, C-2), 63.08 (d, $J=7.0$ Hz), 62.83 (d, $J=9.0$ Hz, C-3), 62.48 (d, $J=7.0$ Hz), 16.43 and 16.42 (2d, $J=5.7$ Hz); ^{31}P NMR (101.3 MHz, $CDCl_3$): $\delta=23.24$. Anal. calcd for $C_{14}H_{23}O_6P$: C, 52.82; H, 7.29. Found: C, 52.63; H, 7.55%.

In a similar manner from (1*S*,2*R*)-**4b** (0.357 g, 0.896 mmol), (1*S*,2*R*)-**5b** (0.253 g, 89%) was obtained as a colorless syrup. $[\alpha]_D=+46.5$ ($c=1.10$, $CHCl_3$); IR (film): $\nu=3392$, 2983, 2931, 1221, 1048, 1027, 743 and 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.40$–7.30

(m, 5H), 4.81 (d, $J=10.9$ Hz, 1H), 4.64 (d, $J=10.9$ Hz, 1H), 4.30–4.08 (m, 4H), 3.97 (dddd, $J=9.7$ Hz, $J=7.7$ Hz, $J=3.8$ Hz, $J=3.4$ Hz, 1H, H-2), 3.88 (dd, $J=7.7$ Hz, $J=4.8$ Hz, 1H, H-1), 3.82 (ddAB, $J=11.9$ Hz, $J=3.4$ Hz, $J=1.2$ Hz, 1H, H-3a), 3.75 (dAB, $J=11.9$ Hz, $J=3.8$ Hz, 1H, H-3b), 2.9–41.5 (2brs, 2H), 1.36 (t, $J=7.0$ Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=$ 137.12, 128.57, 128.38, 128.24, 75.52 (d, $J=159.8$ Hz, C-1), 75.03 (d, $J=3.2$ Hz, O*C*H$_2$Ph), 71.07 (d, $J=4.3$ Hz, C-2), 63.58 (d, $J=7.2$ Hz), 62.91 (d, $J=10.0$ Hz, C-3), 62.80 (d, $J=7.2$ Hz), 16.81 and 16.77 (2d, $J=5.5$ Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta=24.38$. Anal. calcd for $C_{14}H_{23}O_6P$: C, 52.82; H, 7.29. Found: C, 52.64; H, 7.57%.

4.3. Diethyl (1*R*,2*R*)-1-benzyloxy-2,3-epoxypropylphosphonate 2a

A solution of (1*R*,2*R*)-**5a** (0.647 g, 2.03 mmol) and trimethyl orthoacetate (0.293 g, 2.44 mmol) in CH_2Cl_2 (6 mL) containing pyridinium *p*-toluenesulfonate (0.005 g) was stirred at room temperature for 30 min. After evaporation of solvents (finally at 0.1 mmHg), the residue was dissolved in CH_2Cl_2 (6 mL), treated with NEt_3 (5.7 μL) followed by acetyl bromide (0.303 g, 2.46 mmol), while maintaining temperature of the reaction mixture below 40°C. When the formation of the bromoacetate intermediate **7a** was complete (TLC, ca. 40 min), the solution was concentrated, the residue was dissolved in methanol (5 mL) and K_2CO_3 (0.313 g, 2.26 mmol) was added. The suspension was vigorously stirred at room temperature for 2 h. Saturated NH_4Cl (20 mL) was added and the solution was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The crude product was chromatographed on a silica gel column with chloroform:methanol (100:1, v/v) to give (1*R*,2*R*)-**2a** as a colorless oil (0.393 g, 77%). $[\alpha]_D=$ +20.7 ($c=1.23$, $CHCl_3$); IR (film): $\nu=2985$, 2932, 2872, 1257, 1049, 1027, 971, 743 and 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.41$–7.27 (m, 5H), 4.88 and 4.77 (AB, $J=11.9$ Hz, 2H), 4.25–4.09 (m, 4H), 3.39 (dd, $J=13.0$ Hz, $J=7.2$ Hz, 1H, H-1), 3.29 (ddd, $J=7.2$ Hz, $J=4.2$ Hz, $J=2.5$ Hz, 1H, H-2), 2.88 (dd, $J=4.7$ Hz, $J=4.2$ Hz, 1H, H-3a), 2.68 (dd, $J=4.7$ Hz, $J=2.5$ Hz, 1H, H-3b), 1.34 and 1.33 (2d, $J=7.2$ Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=136.95$, 128.27, 128.14, 127.83, 76.76 (d, $J=164.6$ Hz, C-1), 73.37 (d, $J=10.8$ Hz, O*C*H$_2$Ph), 62.88 and 62.74 (2d, $J=6.9$ Hz), 51.47 (d, $J=10.1$ Hz, C-2), 43.63 (d, $J=1.1$ Hz, C-3), 16.39 and 16.37 (2d, $J=5.8$ Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta=18.68$. Anal. calcd for $C_{14}H_{21}O_5P$: C, 55.98; H, 7.06. Found: C, 55.67; H, 7.04%.

In a similar way, from (1*S*,2*R*)-**5b** (1.483 g, 4.661 mmol), the epoxide (1*S*,2*R*)-**2b** was obtained as a colorless oil (0.741 g, 53%). $[\alpha]_D=+22.1$ ($c=0.997$, $CHCl_3$); IR (film): $\nu=2986$, 2932, 2872, 1254, 1026, 970, 744 and 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.36$–7.26 (m, 5H), 4.72 (s, 2H), 4.23–4.10 (m, 4H), 3.93 (dd, $J=11.9$ Hz, $J=3.2$ Hz, 1H), 3.33 (dddd, $J=3.9$ Hz, $J=3.2$ Hz, $J=2.6$ Hz, $J=1.2$ Hz, 1H, H-2), 2.88 (ddAB, $J_{AB}=5.5$ Hz, $J=2.6$ Hz, $J=0.4$ Hz, 1H, H-3a), 2.79 (ddAB, $J_{AB}=5.5$ Hz, $J=3.9$ Hz, $J=1.0$ Hz, 1H, H-3b), 1.34 and 1.33 (2t, $J=7.1$ Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=137.19$, 128.38, 128.22, 128.03, 75.11 (d, $J=7.6$ Hz, O*C*H$_2$Ph), 72.51 (d, $J=164.5$ Hz, C-1), 62.91 and 62.88 (2d, $J=6.8$ Hz), 50.46 (d, $J=10.0$ Hz, C-2), 44.04 (d, $J=4.5$ Hz, C-3), 16.54 and 16.52 (2d, $J=5.7$ Hz); ^{31}P NMR (101.3 MHz, $CDCl_3$): $\delta=$ 19.74. Anal. calcd for $C_{14}H_{21}O_5P$: C, 55.98; H, 7.06. Found: C, 56.03; H, 7.05%.

4.3.1. Diethyl (1*R*,2*S*)-2-acetyloxy-1-benzyloxy-3-bromopropylphosphonate 7a

This compound was obtained as follows: when the formation of **7a** was complete, the solution was concentrated and the residue was chromatographed to give a yellowish oil, which slowly decomposed. $[\alpha]_D=-55.8$ ($c=0.76$, $CHCl_3$); IR (film): $\nu=3032$, 2983, 2934, 1746, 1227, 1026, 971, 764, 701 and 598 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.40$–7.30 (m, 5H), 5.34 (dddd, $J=6.9$ Hz, $J=6.3$ Hz, $J=6.3$ Hz, $J=4.2$ Hz, 1H, H-2), 4.95 (d, $J=11.1$ Hz, 1H), 4.69 (dd, $J=11.1$ Hz, $J=1.1$ Hz, 1H), 4.25–4.15 (m, 4H), 4.15 (dd, $J=9.3$ Hz, $J=4.2$ Hz, 1H, H-1), 3.55 (dAB, $J_{AB}=10.5$ Hz, $J=6.3$ Hz, 1H, H-3a), 3.51 (dAB, $J_{AB}=$ 10.5 Hz, $J=6.3$ Hz, 1H, H-3b), 2.08 (s, 3H), 1.35 (t, $J=7.0$ Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=$ 169.71, 136.83, 128.63, 128.60, 128.37, 75.47 (d, $J=2.3$ Hz, O*C*H$_2$Ph), 73.99 (d, $J=166.9$ Hz, C-1), 71.78 (d, $J=4.3$ Hz, C-2), 63.26 (d, $J=6.6$ Hz), 63.00 (d, $J=7.1$ Hz), 29.66 (d, $J=8.3$ Hz, C-3), 21.13, 16.83 and 16.73 (2d, $J=5.4$ Hz); ^{31}P NMR (101.3 MHz, $CDCl_3$): $\delta=$ 19.81. Anal. calcd for $C_{16}H_{24}BrO_6P$: C, 45.40; H, 5.73. Found: C, 45.34; H, 5.97%.

In a similar way (1*S*,2*S*)-**7b** was isolated as a yellowish oil, which slowly became brownish. $[\alpha]_D=+32.9$ ($c=$ 1.01, $CHCl_3$); IR (film): $\nu=3032$, 2984, 2934, 1747, 1241, 1025, 973, 737 and 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.38$–7.29 (m, 5H), 5.31 (dddd, $J=$ 8.7 Hz, $J=7.3$ Hz, $J=4.8$ Hz, $J=3.2$ Hz, 1H, H-2), 4.88 (d, $J=11.3$ Hz, 1H), 4.69 (dd, $J=11.3$ Hz, $J=1.1$ Hz, 1H), 4.25–4.10 (m, 4H), 4.00 (dd, $J=8.7$ Hz, $J=4.8$ Hz, 1H, H-1), 3.83 (dd, $J=11.3$ Hz, $J=3.2$ Hz, 1H, H-3a), 3.66 (dd, $J=11.3$ Hz, $J=7.3$ Hz, 1H, H-3b), 2.04 (s, 3H), 1.35 and 1.34 (2t, $J=7.1$ Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=169.76$, 136.75, 128.57, 128.53, 128.31, 75.09 (d, $J=3.7$ Hz, O*C*H$_2$Ph), 74.83 (d, $J=164.9$ Hz, C-1), 72.04 (d, $J=8.9$ Hz, C-2), 63.17 and 63.08 (2d, $J=6.9$ Hz), 31.42 (d, $J=4.9$ Hz, C-3), 21.06, 16.78 and 16.75 (2d, $J=5.7$ Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta=19.58$. Anal. calcd for $C_{16}H_{24}BrO_6P$: C, 45.40; H, 5.73. Found: C, 45.57; H, 5.90%.

4.4. Diethyl (1*R*,2*R*)-3-(*N*,*N*-dibenzylamino)-1-benzyloxy-2-hydroxypropyl-phosphonate 8a

A mixture of (1*R*,2*R*)-**2a** (100 mg, 0.333 mmol) and dibenzylamine (66.7 μL, 0.347 mmol) was kept at 50°C (bath) for 72 h. The crude product was chromatographed on a silica gel column using chloroform:methanol (100:1, v/v) to give (1*R*,2*R*)-**8a** as a colorless oil (131 mg, 79%). Crystallisation from ethyl acetate gave white needles. Mp 87.2–87.5°C; $[\alpha]_D=-4.0$ ($c=0.73$, $CHCl_3$); IR (film): $\nu=3467$, 2988, 2924, 2838,

1230, 1026, 752 and 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.35–7.14$ (m, 15H), 4.70 (d, $J = 11.1$ Hz, 1H); 4.25–4.10 (m, 5H), 4.11 (d, $J = 11.1$ Hz, 1H), 3.78 (dd, $J = 7.1$ Hz, $J = 2.4$ Hz, 1H, H-1), 3.60 and 3.55 (AB, $J_{AB} = 13.5$ Hz, 4H), 2.66 (ddAB, $J_{AB} = 12.8$ Hz, $J = 7.2$ Hz, $J = 1.2$ Hz, 1H, H-3a), 2.58 (dAB, $J_{AB} = 12.8$Hz, $J = 6.4$ Hz, 1H, H-3b), 1.32 and 1.30 (2t, $J = 6.9$ Hz, 6H): ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 138.74$, 137.41, 129.30, 128.45, 128.38, 128.33, 127.94, 127.30, 75.29 (d, $J = 164.0$ Hz, C-1), 74.67 (d, $J = 2.0$ Hz), 67.92 (d, $J = 2.0$ Hz, C-2), 62.80 and 62.60 (2d, $J = 6.9$ Hz), 58.65, 56.04 (d, $J = 12.0$ Hz, C-3), 16.83 (d, $J = 5.7$ Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 23.18$. Anal. calcd for $C_{28}H_{36}NO_5P$: C, 67.58; H, 7.31; N, 2.81. Found: C, 67.58; H, 7.36; N, 2.95%.

In a similar fashion, from (1*S*,2*R*)-**2b** (299 mg, 0.996 mmol) and dibenzylamine (0.201 mL, 1.045 mmol), (1*S*,2*R*)-**8b** (360 mg, 73%) was obtained as a white solid after crystallisation from heptane–ether. Mp 56–57°C; $[\alpha]_D = +45.4$ ($c = 0.82$, $CHCl_3$); IR (KBr): $\nu = 3314$, 3030, 2977, 2926, 2866, 1226, 1059, 750 and 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.40–7.20$ (m, 13H), 7.18–7.10 (m, 2H), 4.59 and 4.52 (AB, $J_{AB} = 11.3$ Hz, 2H), 4.16–4.02 (m, 5H), 3.90 (dd, $J = 12.0$ Hz, $J = 3.4$ Hz, 1H, H-1), 3.85 (d, $J = 13.5$ Hz, 2H), 3.75 (brs, 1H), 3.44 (d, $J = 13.5$ Hz, 2H), 2.88 (dAB, $J_{AB} = 13.0$ Hz, $J = 10.0$ Hz, 1H, H-3a), 2.77 (dAB, $J = 13.0$ Hz, $J = 3.8$ Hz, 1H, H-3b), 1.28 (t, $J = 7.0$ Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$); $\delta = 138.53$, 137.56, 129.26, 128.67, 128.49, 128.26, 127.79, 127.33, 77.06 (d, $J = 163.2$ Hz, C-1), 75.40 (d, $J = 7.2$ Hz), 67.92 (d, $J = 10.6$ Hz, C-2), 63.07 and 62.45 (2d, $J = 6.9$ Hz), 58.67, 54.36 (d, $J = 3.7$ Hz, C-3), 16.82 and 16.77 (2d, $J = 5.4$ Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 21.60$. Anal. calcd for $C_{28}H_{36}NO_5P$: C, 67.58; H, 7.31; N, 2.81. Found: C, 67.48; H, 7.24; N, 3.08%.

4.5. Diethyl (1*R*,2*R*)-2-acetyloxy-3-(*N*,*N*-dibenzylamino)-1-benzyloxypropyl-phosphonate 9a

Standard acetylation of (1*R*,2*R*)-**8a** (88 mg, 0.18 mmol) with acetic anhydride (20.0 μL, 0.22 mmol) in the presence of NEt_3 (38.0 μL, 0.27 mmol) and DMAP (one crystal) in CH_2Cl_2 (1 mL) gave after chromatography on a silica gel column (1*R*,2*R*)-**9a** as a colorless oil (70 mg, 73%). $[\alpha]_D = -11.3$ ($c = 1.42$, $CHCl_3$); IR (film): $\nu = 2982$, 2915, 2836, 1738, 1239, 1045, 1026, 969, 739, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.38–7.17$ (m, 15H), 5.37 (dddd, $J = 7.3$ Hz, $J = 6.8$ Hz, $J = 5.7$ Hz, $J = 2.5$ Hz, 1H, H-2), 4.74 (d, $J = 11.5$ Hz, 1H), 4.23–4.04 (m, 4H), 4.02 (d, $J = 11.5$ Hz, 1H), 3.96 (dd, $J = 8.5$ Hz, $J = 2.5$ Hz, 1H, H-1), 3.64 and 3.49 (AB, $J = 13.1$ Hz, 4H), 2.83 (dd, $J = 13.1$ Hz, $J = 7.3$ Hz, 1H, H-3a), 2.58 (ddd, $J = 13.1$ Hz, $J = 5.7$ Hz, $J = 3.2$ Hz), (1H, H-3b), 2.05 (s, 3H), 1.28 (t, $J = 7.0$ Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta =$ 170.13, 139.01, 137.50, 129.25, 128.36, 128.28, 128.27, 127.86, 127.19, 74.93 (d, $J = 1.7$ Hz, OCH_2Ph), 74.38 (d, $J = 167.5$ Hz, C-1), 70.12 (s, C-2), 63.16 and 62.39 (2d, $J = 7.1$ Hz), 58.76, 53.82 (d, $J = 9.7$ Hz, C-3), 21.43, 16.85 and 16.77 (2d, $J = 5.5$ Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 20.77$. Anal. calcd for $C_{30}H_{38}NO_6P$: C, 66.77; H, 7.11; N, 2.59. Found: C, 67.01; H, 7.35; N, 2.32%.

In a similar fashion, from (1*S*,2*R*)-**8b** (250 mg, 0.502 mmol), the acetate (1*S*,2*R*)-**9b** was obtained as a colorless oil (219 mg, 80%). $[\alpha]_D = +37.5$ ($c = 0.841$, $CHCl_3$); IR (film): $\nu = 3086$, 2982, 2931, 2910, 2799, 1738, 1240, 1039, 968, 747 and 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.35–7.19$ (m, 15H), 5.42 (dddd, $J = 10.7$ Hz, $J = 7.7$ Hz, $J = 4.8$ Hz, $J = 2.7$ Hz, 1H, H-2), 4.66 and 4.54 (AB, $J = 11.7$ Hz, 2H), 4.15–4.00 (m, 4H), 3.85 (dd, $J = 12.8$ Hz, $J = 2.7$ Hz, 1H, H-1), 3.75 and 3.43 (AB, $J = 13.7$ Hz, 4H), 2.92 (dAB, $J = 14.4$ Hz, $J = 4.8$ Hz, 1H, H-3a), 2.88 (dAB, $J = 14.4$ Hz, $J = 7.7$ Hz, 1H, H-3b), 1.98 (s, 3H), 1.29 and 1.27 (2t, $J = 7.0$ Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 170.13$, 139.40, 137.12, 129.08, 128.41, 128.37, 128.19, 128.02, 126.94, 76.05 (d, $J = 164.0$ Hz, C-1), 74.47 (d, $J = 6.3$ Hz, OCH_2Ph), 71.40 (d, $J = 9.4$ Hz, C-2), 62.91 and 62.75 (2d, $J = 7.0$ Hz), 58.88, 53.44 (s, C-3), 21.46, 16.81 and 16.73 (2d, $J = 5.6$ Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 19.73$. Anal. calcd for $C_{30}H_{38}NO_6P$: C, 66.77; H, 7.11; N, 2.59. Found: C, 66.98; H, 7.15; N, 2.89%.

4.6. Diethyl (1*R*,2*R*)-3-acetamido-1,2-dihydroxypropyl-phosphonate 10a

A solution of (1*R*,2*R*)-**9a** (0.442 g, 0.819 mmol) in anhydrous ethanol (5 mL) was hydrogenated over $Pd(OH)_2/C$ (20%, 136 mg) at room temperature for 6 days. The catalyst was removed by filtration, the solution was concentrated, and the residue was chromatographed on a silica gel column with chloroform:methanol (20:1, v/v) to give (1*R*,2*R*)-**10a** as a colorless oil (0.170 g, 77%). $[\alpha]_D = +19.0$ ($c = 0.98$, $CHCl_3$); IR (film): $\nu = 3285$, 2984, 2921, 2852, 1648, 1559, 1218, 1045, 971 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.40$ (brt, $J = 5.5$ Hz, 1H), 4.23 (qu, $J = 7.1$ Hz, 2H), 4.19 (dq, $J = 7.3$ Hz, $J = 7.1$ Hz, 2H), 4.3–4.1 (brs, 2H), 4.01 (dddd, $J = 7.1$ Hz, $J = 6.1$ Hz, $J = 3.5$ Hz, $J = 3.0$ Hz, 1H, H-2), 3.85 (dd, $J = 11.0$ Hz, $J = 3.0$ Hz, 1H, H-1), 3.65 (ddd, $J = 14.0$ Hz, $J = 7.1$ Hz, $J = 5.5$ Hz, 1H, H-3b), 3.32 (ddd, $J = 14.0$ Hz, $J = 6.1$ Hz, $J = 5.5$ Hz, 1H, H-3a), 2.02 (s, 3H), 1.36 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 171.92$, 69.82 (d, $J = 2.0$ Hz, C-2), 68.99 (d, $J = 163.8$ Hz, C-1), 63.64 and 62.99 (2d, $J = 7.2$ Hz), 42.57 (d, $J = 12.9$ Hz, C-3), 16.73 and 16.69 (2d, $J = 5.7$ Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 23.09$. Anal. calcd for $C_9H_{20}NO_6P$: C, 40.14; H, 7.50; N, 5.20. Found: C, 39.87; H, 7.19; N, 5.02%.

In a similar manner, from (1*S*,2*R*)-**9b** (0.260 g, 0.491 mmol), the acetamide (1*S*,2*R*)-**10b** (0.098 g, 74%) was obtained as an almost colorless oil. $[\alpha]_D = -77.2$ ($c = 1.01$, $CHCl_3$); IR (film): $\nu = 3304$, 2985, 2913, 1643, 1556, 1226, 1044, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.29$ (brt, $J = 4.8$ Hz, 1H), 5.33 (dd, $J = 27.0$ Hz, $J = 5.3$ Hz, 1H, HOC-1), 4.35–4.15 (m, 5H), 4.05–3.90 (m, 2H, H-2, H-3b), 3.58 (dt, $J = 10.0$ Hz, $J = 10.0$ Hz, $J = 5.3$ Hz, 1H, H-1), 3.19 (dddd, $J = 14.7$ Hz, $J = 4.8$ Hz, $J = 3.0$ Hz, $J = 3.0$ Hz, 1H, H-3a), 2.08 (s, 3H), 1.38 and 1.37 (2t, $J = 7.0$ Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 172.0$, 69.25 (d, $J = 2.9$ Hz, C-2), 66.25 (d, $J = 164.0$ Hz, C-1), 62.40 and 62.08 (2d, $J = 7.0$ Hz), 40.21 (d, $J = 13.5$ Hz, C-3), 21.77, 15.45 and 15.37

(2d, $J=6.3$ Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta=$ 25.27. Anal. calcd for $C_9H_{20}NO_6P$: C, 40.14; H, 7.50; N, 5.20. Found: C, 40.15; H, 7.80; N, 4.93%.

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