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An efficient synthesis of enantiomerically pure diethyl 2,3-dihydroxypropylphosphonate

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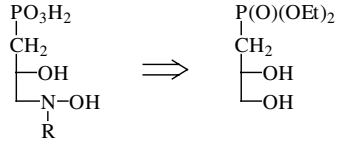
Abstract—A reliable method for the synthesis of the enantiomerically pure diethyl (*R*)-2,3-dihydroxypropylphosphonate from 1,2;5,6-di-*O*-cyclohexylidene-D-mannitol is elaborated.

1. Introduction

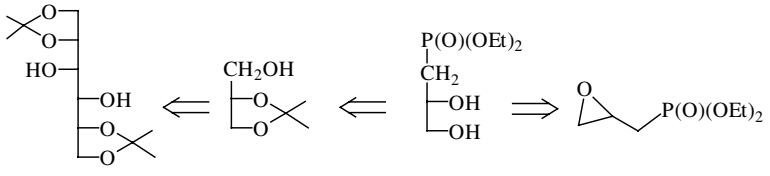
The search for lipid analogues having a nonhydrolyzable P–C bond have prompted Baer and Basu to synthesise optically active diethyl (*R*)- and (*S*)-2,3-dihydroxypropylphosphonates **1**.[1] They applied 1,2;5,6-di-*O*-isopropylidene-D- (or L)-mannitols **2** as starting materials and prepared 2,3-*O*-isopropylidene-D- (or L)-glycerols **3** as key intermediates (Scheme 1). Further transformations included the formation of a tosylate, an iodide, Michaelis–Arbuzov reaction and the acetal hydrolysis. The total yield of (*R*)-**1** from D-**3** was about 24%. A similar approach to (*R*)-**1** (total yield 18% from D-**2**) has recently been presented by Thomas et al. in their study on phosphonate lipid tubules II.[2] In both strategies all the intermediates had to be purified, and the enantiomeric purity of (*R*)-**1** was not established. On the other hand, the phosphonate (*R*)-**1** (ee up to 98%) was obtained in a one-step procedure by a hydrolytic kinetic resolution (HKR) of racemic diethyl 2,3-epoxypropylphosphonate **4** in the presence of the Jacobsen's catalyst (Scheme 1).[3,4]

Besides applications in the studies on modified lipids, the phosphonate (*R*)-**1** has also been used in configurational studies and chemical synthesis of **5** (FR-33289) and **6** (FR-33699), antibiotics from the fosmidomycin family (Scheme 2).[5,6]



5 R=Ac
6 R=CHO
(*R*)-**1**

Scheme 2.



D-**2** D-**3** (*R*)-**1** **4**

Scheme 1.

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Because the enantiomeric purity of (*R*)-**1** obtained through the intermediacy of the racemisation prone[7] D-**3** has never been measured and the ee of the phosphonate prepared by HKR was found to be at best 98%, an unambiguous method for the synthesis of the enantiomerically pure (*R*)-**1** is required.

2. Results and discussion

Our strategy for the synthesis of the enantiomerically pure (*R*)-**1** is based on the application of the configurationally stable 2,3-*O*-cyclohexylidene-D-glyceraldehyde,[8] formation of the P–C bond via the Abramov reaction and deoxygenation at C(1) (Scheme 3).

Addition of diethyl phosphite to D-**8** was carried out as described earlier[9] and gave a 35:65 mixture of (1*R*,2*R*)- and (1*S*,2*R*)-**9**, quantitatively. The crude 1-hydroxyphosphonates **9** were reacted with thiocarbonyldiimidazole[10] to furnish a mixture of diastereoisomeric thiocarbamates (1*R*,2*R*)- and (1*S*,2*R*)-**10** in 93% yield, which was found to be pure by ^{1}H and ^{31}P NMR spectroscopy. In the presence of tributyltin hydride (the Barton procedure[11]) the phosphonates **10** were cleanly deoxygenated to afford (*R*)-**11** in 91% yield, which was pure enough to be used in the next step. Hydrolysis of the cyclohexylidene protecting group in (*R*)-**11** was accomplished with 0.1 N HCl in dioxane[9] and the phosphonate (*R*)-**1** was finally purified on a silica gel column. The total yield of (*R*)-**1** from D-**8** exceeds 67%.

The enantiomeric purity of (*R*)-**1** (100%) was established after derivatisation with (*S*)-*O*-methylmandelic acid[12] as described earlier.[3,4]

3. Conclusions

A stereochemically unequivocal synthesis of enantiomerically pure diethyl (*R*)-2,3-dihydroxypropylphosphonate from 2,3-*O*-cyclohexylidene-D-glyceraldehyde has been elaborated. The reaction sequence, which involves only one chromatographic purification, can be easily extended for the preparation of other esters, since the addition of dialkyl(aryl)phosphites (the Abramov reaction) is less sterically demanding than alternative approach through the Arbuzov reaction.

4. Experimental

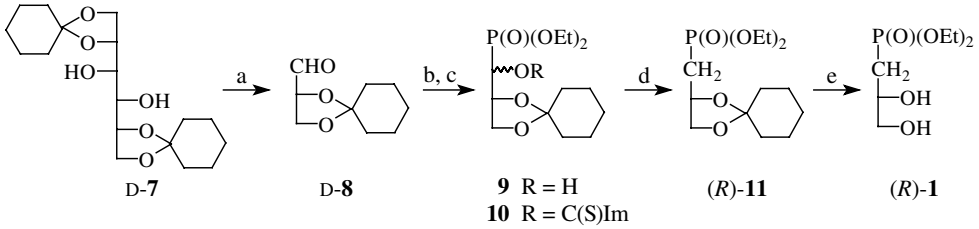
^{1}H NMR spectra were recorded with a Varian Mercury-300 spectrometer; chemical shifts δ in ppm with respect to TMS; coupling constants J in Hz. ^{13}C and ^{31}P NMR spectra were recorded on a Varian Mercury-300 machine at 75.5 and 121.5 MHz, respectively. IR spectral data were measured on an Infinity MI-60 FT-IR spectrometer. Polarimetric measurements were conducted on a Perkin Elmer 241 MC apparatus.

1,2;5,6-Di-*O*-cyclohexylidene-D-mannitol was prepared according to the literature procedure.[13]

4.1. Diethyl (*R*)-2,3-dihydroxypropylphosphonate, (*R*)-1

A mixture of the aldehyde D-**8** (2.625 g, 15.40 mmol) and diethyl phosphite (1.98 mL, 15.4 mmol) containing triethylamine (0.202 mL, 1.46 mmol) was left at room temperature for 16 h. After removal of the catalyst in vacuo, a mixture of diastereoisomeric phosphonates **9** (4.75 g, 100%) was obtained as a yellowish oil. ^{31}P NMR ($CDCl_3$): $\delta = 21.60$ ppm for (1*R*,2*R*)-**9** and 22.14 ppm for (1*S*,2*R*)-**9**.

A solution of diastereoisomeric phosphonates **9** (4.67 g, 15.1 mmol) in dry 1,2-dichloroethane (250 mL) containing 1,1′-thiocarbonyldiimidazole (5.40 g, 30.3 mmol) was stirred at 70 °C for 3 h. The cooled solution was washed with 1 M HCl (2×200 mL), saturated aqueous sodium bicarbonate (200 mL) and water (200 mL). The organic phase was dried over $MgSO_4$ and solvents were evaporated in vacuo to leave a crude diastereoisomeric mixture of the phosphonates **10** (5.872 g, 93%) as a yellowish oil. ^{1}H NMR ($CDCl_3$): $\delta = 1.28$–1.60 (m, 16H, $CH_3CH_2OPOCH_2CH_3$ and cyclohexylidene), 4.09–4.30 (m, 6H, CH_2OPOCH_2 and H_2CO), 4.60–4.72 (m, 1H, HCCP), 6.07 (dd, $J = 9.7$, 6.8 Hz, 0.35H, HCP), 6.33 (dd, $J = 11.1$, 2.7 Hz, 0.65H, HCP), 7.15 (br s, 1H), 7.71 (br s, 1H), 8.52 (br s, 1H). ^{13}C NMR ($CDCl_3$): major diastereoisomer: $\delta = 16.5$ (d, $J = 5.7$ Hz, CH_3CH_2OP), 23.8, 23.9, 25.1, 34.3, 35.8, 63.5 and 63.6 (2d, $J = 7.1$ Hz, CH_2OPOCH_2), 64.8 (d, $J = 1.7$ Hz, *C*CCP), 73.7 (d, $J = 9.4$ Hz, *C*CP), 75.8 (d, $J = 161.8$ Hz, *C*P), 110.4, 118.1, 131.0, 137.2, 183.2 (d, $J = 5.8$ Hz, O*C*=S); minor diastereoisomer: $\delta = 16.5$ and 16.6 (2d, $J = 5.7$ Hz, $CH_3CH_2OPOCH_2CH_3$), 23.9, 24.0, 25.1, 34.8, 36.1, 63.4 and 63.6 (2d, $J = 6.5$ Hz, CH_2OPOCH_2), 65.3 (d, $J = 5.4$ Hz, *C*CCP), 73.4 (d,



Scheme 3. Reagents and conditions: (a) $NaIO_4$, ether–water; (b) $(EtO)_2P(O)H$, cat. NEt_3; (c) Im_2C=S, 1,2-dichloroethane, 70 °C, 3 h; (d) Bu_3SnH, refluxing toluene, 2.5 h; (e) 0.1 N HCl in dioxane, reflux, 1 h.

$J = 5.2$ Hz, *C*CP), 77.0 (d, $J = 160.6$ Hz, *C*P), 110.9, 118.4, 131.0, 137.0, 183.5 (d, $J = 5.7$ Hz, O*C*=S). ^{31}P NMR ($CDCl_3$): $\delta = 15.65$.

A solution of a crude mixture of diastereoisomeric phosphonates **10** (3.00 g, 7.17 mmol) in dry toluene (190 mL) was treated under argon atmosphere with tributyltin hydride (3.28 mL, 12.4 mmol). The reaction mixture was refluxed for 2.5 h, cooled to room temperature and all volatiles were evaporated, finally in vacuo (0.05 mmHg). The residue was dissolved in acetonitrile (200 mL) and the solution was extracted with hexanes (200 mL and 2×100 mL). Concentration of the acetonitrile solution left crude (*R*)-**11** (1.905 g, 91%) as a colourless oil. A part of this material was purified on a silica gel column with chloroform/methanol (100:1, v/v). $[\alpha]_D^{20} = +8.3$ (*c* 1.05, $CHCl_3$). IR (film): $\nu = 2981$, 2936, 1448, 1366, 1252, 1030, 964 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 1.33$ (t, $J = 7.0$ Hz, CH_3CH$_2$OP), 1.30–1.45 (m, 2H), 1.5–1.7 (m, 8H), 1.98 (ddd, $J = 18.3$, 15.0, 8.7 Hz, 1H, H_aH$_b$CP), 2.26 (ddd, $J = 19.0$, 15.0, 5.2 Hz, 1H, H$_a$$H_b$CP), 3.67 (dd, $J = 8.1$, 6.6 Hz, 1H, H_aH$_b$CO), 3.99–4.20 (m, 5H, CH$_3$CH_2OP, H$_a$$H_b$CO), 4.32–4.43 (m, 1H, *H*CO). ^{13}C NMR ($CDCl_3$): $\delta = 16.6$ and 16.7 (2d, $J = 6.3$ Hz, *C*H$_3$CH$_2$OPOCH$_2$*C*H$_3$), 24.1, 24.2, 25.3, 31.3 (d, $J = 138.3$ Hz, *C*P), 35.4, 36.8, 61.9 and 62.1 (2d, $J = 6.6$ Hz, *C*H$_2$OPO*C*H$_2$), 69.7 (d, $J = 6.6$ Hz, *C*CCP), 70.7, 109.7. ^{31}P NMR ($CDCl_3$): $\delta = 27.86$. HRMS (FAB+) $C_{13}H_{26}O_5P$ (m/z): calcd 293.1518. Found 293.1520.

A solution of the crude phosphonate (*R*)-**11** (1.22 g, 4.17 mmol) in dioxane (25 mL) containing 0.1 N HCl (46 mL) was maintained under reflux for 1 h. The cooled solution was concentrated and co-evaporated with anhydrous dioxane (5×20 mL). The residue was dissolved in methylene chloride, dried over $MgSO_4$/$NaHCO_3$ and chromatographed on a silica gel column with chloroform/methanol (20:1, v/v) to give (*R*)-**1** (0.705 g, 80%) as a colourless oil. $[\alpha]_D^{20} = -15.3$ (*c* 1.94, ethanol). ^{1}H, ^{13}C and ^{31}P NMR spectral data of this material were identical to those described in the literature.[4]

Acknowledgements

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References and notes

1. Baer, E.; Basu, H. *Can. J. Biochem.* **1969**, *47*, 955–960.
2. Thomas, B. N.; Lindemann, C. M.; Corcoran, R. C.; Cotant, C. L.; Kirsch, J. E.; Persichini, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 1227–1233.
3. Wróblewski, A. E.; Hałajewska-Wosik, A. *Tetrahedron: Asymmetry* **2000**, *11*, 2053–2055.
4. Wróblewski, A. E.; Hałajewska-Wosik, A. *Eur. J. Org. Chem.* **2002**, 2758–2763.
5. Hashimoto, M.; Hemmi, K.; Takeno, H.; Kamiya, T. *Tetrahedron Lett.* **1980**, *21*, 99–102.
6. Hemmi, K.; Takeno, H.; Hashimoto, M.; Kamiya, T. *Chem. Pharm. Bull.* **1981**, *29*, 646–650.
7. Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447–488.
8. Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585–587.
9. Wróblewski, A. E.; Balcerzak, K. B. *Tetrahedron* **1998**, *54*, 6833–6840.
10. Oshikawa, T.; Yamashita, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2728–2730.
11. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585.
12. Bonner, W. A. *J. Am. Chem. Soc.* **1951**, *73*, 3126–3132.
13. Sugiyama, T.; Sugawara, H.; Watanabe, M.; Yamashita, K. *Agric. Biol. Chem.* **1984**, *48*, 1841–1844.