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LETTERS TO THE EDITOR

Asymmetric Synthesis of Phosphathreoninic Acid

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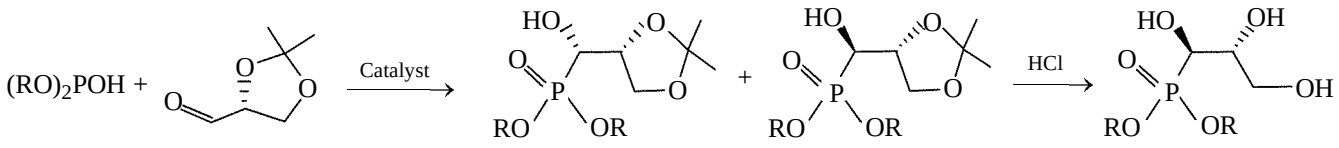
Hydroxy- and aminophosphonic acids exhibit interesting biological and pharmacological properties and therefore have been intensively studied [1–3]. In the present work we prepared phosphathreoninic esters **V** and **VI** and free phosphathreoninic acid **VII**, phosphorus analogs of the natural treoninic acid (threonate) which plays an important role in the metabolism of ascorbic acid and in some other biological processes [4].



I **II** (*S*,*R*)-**III, IV** (*R*,*R*)-**III, IV** **V**–**VII**

Catalyst = DBU and aluminum lithium (*S*)- and (*R*)-bis(binaphtholates) [(*S*)- and (*R*)-ALB]; R = (1*R*,2*S*,5*R*)-menthyl (**III, V**), Et (**IV, VI**), H (**VII**).

The asymmetric synthesis of chiral compounds **III** and **IV** was carried out by reaction of dialkyl hydrogen phosphites **I** with (*R*)-glyceraldehyde acetonide (**II**). The ordinary stereoselectivity of the reaction of the achiral diethyl hydrogen phosphite with the chiral aldehyde **II** is very low (*de* 10%). Therefore, for a more stereoselective reaction we made use of multiple asymmetric induction [5, 6]. The chiral dimenthyl hydrogen phosphite reacted with the chiral aldehyde **II** in the presence of the achiral DBU with double asymmetric induction. As a result, the stereoselectivity of the reaction increased to *de* 60%. A still higher stereoselectivity (80% *de*) was observed in the reaction of the chiral di[(1*R*,2*S*,5*R*)-mentyl] hydrogen phosphite with the chiral (*R*)-glyceraldehyde acetonide in the presence of the chiral (*S*)-ALB [7, 8]. With the (*R*)-ALB catalyst, no stereoselectivity increase was observed.

Hence, introduction of two or three asymmetric inductors in the reacting system additively increases the stereoselectivity of the reaction of (*R*)-glyceraldehyde acetonide phosphorous diesters if the absolute configurations of the chiral inductors, like in the (*R*)-glyceraldehyde/(1*R*,2*S*,5*R*)-menthyl/(*S*)-ALB, act concordantly in one direction. If the absolute configurations of chiral inductors act discordantly, like in the (*R*)-glyceraldehyde/(1*R*,2*S*,5*R*)-menthyl/(*R*)-ALB system, no stereoselectivity increase was observed.

The diastereomers of compound **IV** were separated and purified by crystallization from acetonitrile. Hydrolysis with HCl in dioxane was used to successively remove the isopropylidene and ester groups of compounds **III** and **IV** to obtain chiral phosphasugars **V** and **VII**. The absolute configuration of compounds **III** and **IV** (*S*) was established by NMR spectroscopy and X-ray diffraction analysis.

Di[(1*R*,2*S*,5*R*)-menthyl] (*S*)-[hydroxy[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]phosphonate (III). Catalyst [1-2 drops of DBU or 25 mol% of ALB] was added to a cold (0°C) mixture of 0.01 mol of dimenthyl hydrogen phosphite and 0.01 mol of glyceraldehyde acetonide in 5 ml of THF. The resulting mixture was left to stand at this temperature for 12 h. The ^{31}P NMR spectrum of the reaction mixture showed the presence of two diastereomers (δ_P 19.98 and 20.9 ppm) in the above-mentioned ratio. An

optically pure *S*,*R* diastereomer was isolated by crystallization from acetonitrile. Yield 50%, mp 98–100°C (prisms), $[\alpha]_D^{20}$ –65° (*c* 2, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.76 d (6H, CH_3–Mnt, J_{HH} 7.0), 0.87 d [12H, $(CH_3)_2CH$–Mnt, J_{HH} 6.6], 1,1–2.2 m CH_2 + CH–Mnt), 1.33 s, 1.40 s [6H, $(CH_3)_2C$)], 1.62 d (2H, mentyl CH, J_{HH} 11.1), 2.1–2.27 m (2H, menthyl CH), 2.65 br (1H, OH, J_{HH} 12), 4.05 d.t ($OCHCH_2$, J_{HH} 6.5, PCH, J_{HP} 10.5), 4.23 d.t (CH_2, *ABX* system, J_{AX} 7, J_{AB} 6), 4.39 m (2H, CH_2). ^{31}P NMR spectrum ($CDCl_3$): δ_P 20.9 ppm.

The *R*,*R* diastereomer containing a small admixture of the *S*,*R* diastereomer was isolated as an oil by column chromatography (eluent ethyl acetate–hexane, 4 : 1). Yield 5–15% (depending on the nature of the catalyst). ^{31}P NMR spectrum ($CDCl_3$): δ_P 20.0 ppm. Found, %: 6.2. $C_{26}H_{49}O_6P$. Calculated, %: P 6.34.

Diethyl (*R*/*S*)-[hydroxy[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]phosphonate (IV) was obtained analogously to compound **III**. Yield 85%, $[\alpha]_D^{20}$ –8.5 (*c* 2, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$) δ, ppm (*J*, Hz): 1.30 t (6H, CH_3, J_{HH} 7), 1.35 s, 1,43 s [6H, $(CH_3)_2C$], 2.8 br (1H, OH), 3.8 d.d (1H, H^1, J_{HP} 9.5, J_{HH} 6.5), 3.95 m (1H, H^3), 4.07 m (1H, H^3, J_{HH} 8.5), 4.18 m (4H, CH_2O), 4.45 d.d.t (1H, CH_2, J_{HH} 6.6, J_{HH} 6.4, J_{HH} 4.0). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 23.0, 24.5

Di[(1*R*,1*S*,5*R*)-menthyl] (*S*,*R*)-(1,2,3-trihydroxypropyl)phosphonate (V). To a solution of 0.005 mol of compound **I** in 5 ml of dioxane, 2–3 ml of concentrated sulfuric acid was added. The resulting mixture was left overnight and then thoroughly evaporated in a vacuum. The residue was crystallized from hexane. Yield 90%, mp 108–109°C (needles). $[\alpha]_D^{20}$ –60 (*c* 2, $CHCl_3$). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.782 d [3H, $(CH_3)_2C$, J_{HH} 6.9 Hz], 0.887 d (6H, menthyl CH_3, J_{HH} 6.0), 0.895 d (6H, CH_3–Mnt, J_{HH} 6.6), 1.0–1.5 m (CH_2 + menthyl CH), 1.626 m (2H, menthyl H), 1.662 m (2H, menthyl H), 2.131 m (2H, menthyl H), 2.234 m (2H, menthyl H), 2.74 br (3H, OH), 3.831 m (POCH, 2H), 3.899 m (PCH, 1H), 4.234 m (2H, CH_2). ^{31}P NMR spectrum ($CDCl_2$), δ, ppm: 22.51.

Diethyl (1,2,3-trihydroxypropyl)phosphonate (VI) was obtained analogously, $[\alpha]_D^{20}$ 3.6 (*c* 5, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.30 t (6H, CH_3, J_{HH} 7), 3.30–3.45 br (1H, OH), 3.65–3.80 br (2H, OH), 4.18 d.q (CH_2, 2H, J_{HH} 8), 4.15–4.35 m (6H, CH_2OP). ^{31}P NMR spectrum ($CDCl_3$) δ, ppm: 23.0, 24.5. Found, %: P 13.00. $C_7H_{17}O_6P$. Calculated, %: P 13.57.

(1,2,3-Trihydroxypropyl)phosphonic acid (VII). A solution of 0.005 mol of compound **I** in a 1 : 1 mixture of 40% hydrochloric acid and dioxane, left to stand at 80°C for 48 h, and then thoroughly evaporated in a vacuum. The residue was dissolved in 4 ml of ethanol, and 0.01 mol of cyclohexylamine was added. The cyclohexylammonium salt that precipitated was filtered off, yield 65%, mp > 200°C (decomp.) ^1H NMR spectrum (CD_3OD + $CDCl_3$), δ, ppm : 0.9–1.2 m (2H, CH_2), 1.6 m (4H, CH_2), 1.75 m (4H, CH_2), 2.7 m (2H, CH_2), 3.1 s (4H, OH), 3.4–3.6 m (2H, NH + CH). ^{31}P NMR spectrum (CD_3OD), δ_P 18.1 ppm. Found, %: P 11.03. $C_9H_{22}NO_6P$. Calculated, %: P 11.42.

The NMR spectra were recorded on a Varian-300 spectrometer against internal TMS (^1H in CD_3OD + $CDCl_3$) and 85% phosphoric acid (^{31}P in D_2O). The optical rotations were measured on a Polax-2L polarymeter (Japan).

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