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LETTERS TO THE EDITOR

Enantioselective Synthesis of α-Hydroxyalkylphosphonates

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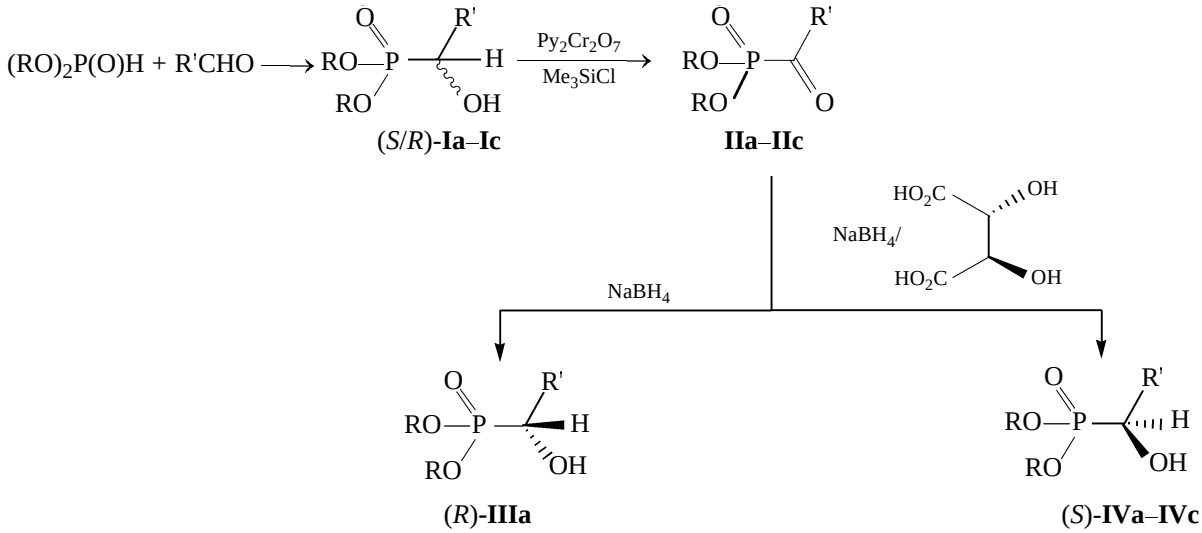
In this communication we report on the synthesis of optically active α-hydroxyalkylphosphonates by asymmetric reduction of dialkyl arylketophosphonates **II**.



R = Et, R' = Ph (**a**); R = (1*R*,2*S*,5*R*)-Mnt, R' = Ph (**b**), C_6H_4F-2 (**c**).

Arylketophosphonates **II** were synthesized by a two-step one-pot procedure. In the first step, dialkyl phosphites were reacted with aldehydes to obtain racemic α-hydroxyphosphonates in quantitative yields. The products without isolation and purification were oxidized with pyridinium dichromate [1, 2] to form dketophosphonates **II** in high yields. The chemical purity of ketophosphonates **II** prepared in this way was 90% or higher. Therefore, they were brought in further transformations without purification. If necessary, they could be easily purified by column chromatography on silica gel.

The reduction of dimenthyl ketophosphonates with sodium borohydride in ethanol affords (*R*)-α-hydroxyphosphonates with a low stereoselectivity (30–35% *de*). The products were purified by crystallization from acetonitrile (procedure *a*).

The stereoselectivity of the hydroborination of ketophosphonates could be enhanced via generation of a chiral complex of sodium borohydride with natural *L*-(+)-tartaric acid (procedure *b*). This procedure gave diethyl α-hydroxy(phenyl)methylphosphonate [(*S*)-**IVa**] with the enantiomeric purity ~60% *ee* and dimenthyl α-hydroxy(aryl)methylphosphonates (*S*)-**IVb** (93% *de*) and (*S*)-**IVc** (80% *de*). We explain the high stereoselectivity of the reduction of dimenthyl arylketophosphonates by the effect of dual asymmetric induction [3]: In this case, the asymmetric inductions of the menthyl group and tartaric acid acted in the same direction. α-Hydroxyphosphonates (*S*)-**IVb** and

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(*S*)-**IVc** were purified by crystallization from acetonitrile to 100% optical purity.

Di-(1*R*,2*S*,5*R*)-(–a)-menthyl benzoylphosphonate (IIb). Chlorotrimethylsilane, 0.6 g (5.5 mmol) was added to a stirred suspension of 1.68 g (4.47 mmol) of pyridinium dichromate in 30 ml of methylene chloride at 0°C, after which racemic dimenthyl α-hydroxyphosphonate (**Ib**) prepared from 1.75 mol of dimenthyl phosphite and 1.75 mol of benzaldehyde was added. The mixture of stirred for 2–4 h, the solvent was evaporated, and the product was isolated as a colorless liquid. Yield 90%, R_f 0.3 (eluent hexane–ethyl acetate, 4 : 1), $[\alpha]_D^{20}$ –62 (*c* 1.5, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.7–1.0 m (CH_3); 1.1–2.2 m (CH_2 + CH); 4.15 d.t (OCH, J_{HH} 2.3, J_{HH} 4.1); 7.35 m (C_6H_5); 7.45 m (C_6H_5). ^{31}P NMR spectrum ($CDCl_3$): δ_P –2.3 ppm. Ketophosphonates **IIa** and **IIc** were prepared similarly.

Di-(1*R*,2*S*,5*R*)-(3a)-menthyl (*R*)-hydroxy(phenyl)methylphosphonate (IIIb). *a*. Yield 40%, mp 139°C (acetonitrile), $[\alpha]_D^{20}$ –70 (*c* 1, toluene). ^{31}P NMR spectrum ($CDCl_3$): δ_P –22.4 ppm, in agreement with [5].

Di-(1*R*,2*S*,5*R*)-(–)-menthyl (*S*)-hydroxy(phenyl)methylphosphonate (IVb). *b*. *L*-(+)-Tartaric acid, 4 mmol, was added to 4 mmol of sodium borohydride in 15 ml of THF, and the reaction mixture was refluxed for 4 h. After cooling to –30°C, 0.99 mol of ketophosphonate in 5 ml of THF was added, the mixture was kept for 24 h at –30°C, after which 8 ml of ethyl acetate was added, and 20 ml of 1 N HCl was added dropwise. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The solvent was evaporated in a vacuum, and the residue was crystallized from acetonitrile. Yield 95%, mp 112–113, $[\alpha]_D^{20}$ –87.6 (*c* 1.3, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.01 d (3H, CH_3, J_{HH} 6.9); 1.04 d (3H, CH_3, J_{HH} 6.9); 1.08 d (3H, CH_3, J_{HH} 6.9); 1.18 d (3H, CH_3, J_{HH} 6.9); 1.20 d (3H, CH_3, J_{HH} 6.9); 1.21 d (3H, CH_3, J_{HH} 6.9); 1.40–2.6 m (14H, C*H*$_3$ and CH); 2.00 m [1H, $CH(CH_3)_2$]; 2.4 m [1H, $CH(CH_3)_2$]; 4.49 m (2H, OCH); 5.2 d (1H, CHP, J_{HH} 10.5); 5.10 br (1H, OH); 7.48 m (3H, ArH); 7.8 m (2H, Ar*H*). ^{31}P NMR spectrum ($CDCl_3$): δ_P 22.3 ppm. Found, %: P 6.38. $C_{27}H_{45}O_4P$. Calculated, %: P 6.67.

Diethyl (*S*)-hydroxy(phenyl)methylphosphonate (IVa) was prepared similarly to compound **IVb**. Yield 95%, mp 74–76°C, $[\alpha]_D^{20}$ –15.4 (*c* 2.6, $CHCl_3$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 22.00 ppm, in agreement with [4–6].

Di-2-(1*R*,2*S*,5*R*)-(–)-menthyl (*S*)-(2-fluorophenyl)(hydroxyl)methylphosphonate (IVc) was prepared similarly to compound **IVb**. Yield 97%, mp 137.5–138.5oC, $[\alpha]_D^{20}$ –83.7 (*c* 1.3, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.71 d (3H, CH_3, J_{HH} 6.9); 0.76 d (6H, CH_3, J_{HH} 6.9); 0.86 d (6H, CH_3, J_{HH} 6.9); 0.91 d (3H, CH_3, J_{HH} 6.9); 1.00–2.25 m (14H, C*H*$_3$ and CH); 1.74 m [1H, $CH(CH_3)_2$]; 2.0 m [1H, $CH(CH_3)_2$]; 4.04 d (1H, CHP, J_{HH} 22.5); 4.2 m (2H, OCH); 5.18 br (1H, OH); 6.9 t (3H, J_{HH} 8.2, Ar*H*); 7.45 m (2H, Ar*H*). ^{31}P NMR spectrum ($CDCl_3$): δ_P 19.8 ppm.

The NMR spectra were measured on a Varian-300 instrument against internal TMS (^{1}H) and external reference 85% H_3PO_4 in D_2O (^{31}P).

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