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TETRAHEDRON: *ASYMMETRY*

Towards enantiomeric 2,3-epoxypropylphosphonates†

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Abstract

Hydrolysis of diethyl 2,3-epoxypropylphosphonate in the presence of (*R*,*R*)-salen–Co(III)-OAc after 19 h afforded a mixture of (*S*)-epoxide (82% ee) and diethyl (*R*)-2,3-dihydroxypropylphosphonate (98% ee). Improved enantiomeric excess (93%) of the (*S*)-epoxide was obtained in the 72 h hydrolytic kinetic resolution experiment. Acid-catalyzed hydrolysis of (*S*)-epoxide (91% ee) gave (*S*)-diol (72% ee) due to low C-3 regioselectivity of the reaction.

Enantiomeric 2,3-epoxypropylphosphonates would be useful three-carbon phosphonate chirons for the syntheses of various phosphonate analogs, such as phosphocarnitine,[1] phosphonic acid antibiotics FR-33289 and FR-33699,[2] and isosters of glycerophosphoric acid.[3] However, standard protocols for the oxirane ring closure require the application of basic reagents, and it was shown that in the presence of bases diethyl 2,3-epoxypropylphosphonate isomerizes to 3-hydroxy-1-propenylphosphonate.[4–6]

Design of low-molecular weight catalysts capable of reaching enantioselectivities similar to those obtained in enzymatic reactions has become an important goal of asymmetric synthesis. Hydrolytic kinetic resolution (HKR) processes introduced by Jacobsen[7] are recent examples of achievements in this area. Enantioselective hydrolyses of terminal epoxides[7–12] have been extended to oxirane ring openings with azides[13] and thiols.[14] A recent report on the application of HKR to oxiranephosphonate[15] has prompted us to communicate our results on enantioselectivity of hydrolysis of diethyl 2,3-epoxypropylphosphonate **1**.[16]

In the presence of 0.2 mol% (*R*,*R*)-salen–Co(III)-OAc **2** and 0.55 equiv. of water racemic **1** was transformed into (*S*)-(–)-**1** and diethyl (*R*)-(–)-2,3-dihydroxypropylphosphonate **3** (Scheme 1). Based on signs of the optical rotation of the obtained diol and that synthesized from 2,3-*O*-isopropylidene-D-glyceraldehyde by Baer and Basu,[3] application of (*R*,*R*)-**2** produced (*S*)-**1** and (*R*)-**3**. The stereochemical outcome of the reaction followed that observed by Jacobsen.[7]

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† Dedicated to Professor Jan Michalski on the occasion of his 80th birthday.

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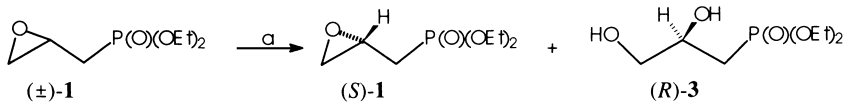
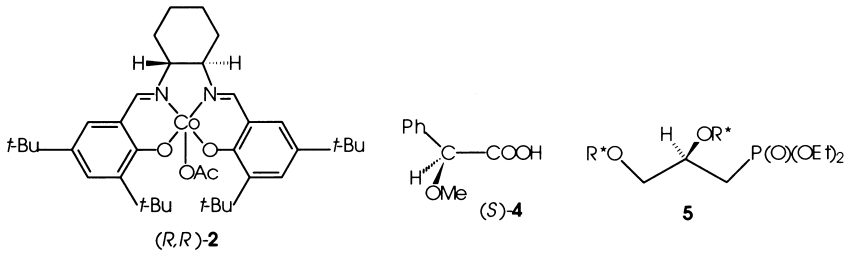


(±)-**1** (*S*)-**1** (*R*)-**3**

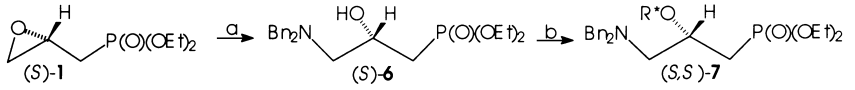
Scheme 1. Reagents and conditions: (a) (*R*,*R*)-salen–Co(III)-OAc (0.2 mol%), H_2O (0.55 equiv.)



(*R*,*R*)-**2** (*S*)-**4** **5**

Comparison of specific rotations of the prepared diol: $[\alpha]_D = -17.8$ (*c* 1.43, ethanol) and the literature value: $[\alpha]_D = -12.2$ (*c* 4.1, ethanol)[3] does not allow the enantiomeric purity to be estimated. However, complete esterification of the obtained diol with (*S*)-*O*-methylmandelic acid **4**[17] (**4** = 3.0 equiv., DCC = 3.0 equiv., DMAP = 0.2 equiv.)[18] gave diester **5** which showed 96% ee by ^{31}P NMR spectroscopy [(*R*,*S*,*S*)-**5**, δ $^{31}P = 25.02$ ppm; (*S*,*S*,*S*)-**5**, δ $^{31}P = 24.95$ ppm]. After correction for the enantiomeric purity of (*S*)-**4** (97.6%),[19] the ee of the prepared diol (*R*)-**3** was estimated as 98%.[20]

The enantiomeric excess of the unreacted epoxide (*S*)-**1** was established in the following way: Despite claims of the C-3 regioselectivity of the oxirane ring opening in (±)-**1**,[6,16] we found that, among various amines tried, dibenzylamine attacted C-3 exclusively.[21] Thus, after 20 h at 60°C in the presence of 1.1 equiv. of Bn_2NH the unreacted (*S*)-**1** was quantitatively transformed into diethyl (*S*)-3-(*N*,*N*-dibenzylamino)-2-hydroxypropylphosphonate **6** (Scheme 2). Again, complete esterification[18] with (S)-**4** led to monoesters **7** [(*S*,*S*)-**7**, δ $^{31}P = 27.13$ ppm; (*R*,*S*)-**7**, δ $^{31}P = 27.59$ ppm], and the enantiomeric excess of (*S*)-**1** was estimated[20] as 82%.

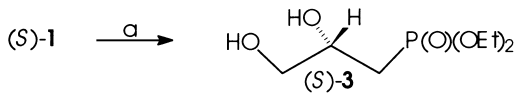


(*S*)-**1** (*S*)-**6** (*S*,*S*)-**7**

Scheme 2. Reagents and conditions: (a) Bn_2NH, 1.1 equiv., 60°C, 20 h; (b) **4** = 1.5 equiv., DCC = 1.5 equiv., DMAP = 0.1 equiv., CH_2Cl_2

These results were obtained in the HKR experiment lasting 19 h which produced a 52:48 mixture of (*S*)-**1** and (*R*)-**3** (by ^{31}P NMR). After chromatography of this mixture on silica gel, (*S*)-**1** and (*R*)-**3** were obtained in 44 and 41% yield, respectively. However, the epoxide (S)-**1** was contaminated with traces of the catalyst and for this reason reliable measurements of the optical rotation were not obtained. The 45 h hydrolysis led to a 46:54 mixture of (*S*)-**1** and (*R*)-**3** having ee's of 86 and 95%, respectively. When hydrolysis was carried out for 72 h, a mixture of (*S*)-**1** (93% ee) and (*R*)-**3** (74% ee) in a 38:62 ratio was obtained. Summing up, shorter reaction times gave the diol in high enantiomeric purity, while extended hydrolyses significantly improved the ee of the epoxide.

Attempts at preparing the (*S*)-**3** diol from the (*S*)-**1** epoxide via acid-catalyzed opening of the oxirane ring with water (Scheme 3) were partially successful. Under conditions described by Griffin and Kundu[16] the epoxide was quantitatively transformed into the diol, which was contaminated with ca. 5% of unidentified organophosphorus compounds (δ ^{31}P 29.98 and 29.22 ppm). However, from (*S*)-**1** (91% ee), the (*S*)-**3** diol (72% ee) was obtained. This result clearly showed concomitant attack of water at C-2 in **1**.



Scheme 3. Reagents and conditions: (a) H_2O, H_2SO_4, 100°C, 2.5 h

In conclusion, two important three-carbon phosphonate chirons, diethyl (*S*)-2,3-epoxypropylphosphonate (93% ee) and diethyl (*R*)-2,3-dihydroxypropylphosphonate (98% ee) were synthesized by the application of the Jacobsen's HKR process.

Acknowledgements

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