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An enantioselective synthesis of (*R*)-2-amino-1-hydroxyethylphosphonic acid by hydrolytic kinetic resolution of (±)-diethyl oxiranephosphonate

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Abstract

(±)-Diethyl oxiranephosphonate undergoes efficient hydrolytic kinetic resolution by (*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(III) acetate; opening of the resultant (*R*)-epoxide by benzylamine, followed by phosphonate ester hydrolysis and hydrogenolysis, affords the protozoal plasma membrane component (*R*)-2-amino-1-hydroxyethylphosphonic acid.

Keywords: phosphonic acid; phosphonic acid derivatives; asymmetric reactions; epoxides.

It is evident from a recent review[1] that the chemistry of 1,2-epoxyalkylphosphonates is of great significance for the synthesis of naturally occurring phosphonic acids, such as the antibiotic fosfomycin (**1**) and the protozoal plasma membrane component (*R*)-2-amino-1-hydroxyethylphosphonic acid (**2**). Despite the advances in catalytic asymmetric epoxidation of various types of C=C bond, there is a lack of a published methodology for obtaining enantiomerically pure 1,2-epoxyalkylphosphonates directly and without resorting to classical resolution. We now report a successful hydrolytic kinetic resolution of (±)-diethyl oxiranephosphonate (**3**) using the (*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(III) acetate catalyst (**7**) pioneered by Jacobsen.[2]

The racemic epoxide (±)-(**3**) was prepared by a modification of the procedure of Sturtz.[3] Treatment of diethyl vinylphosphonate with NaOCl/HCl yielded (±)-diethyl 1-chloro-2-hydroxyethylphosphonate (59%); cyclization of this intermediate with KO^{t}Bu/^{t}BuOH then gave (±)-(**3**) in 65% yield. With (±)-(**3**) in hand we sought a method for determination of the enantiomeric excess of this epoxide. ^{31}P NMR in the presence of chiral lanthanide shift reagents [Eu(hfc)$_3$ or Yb(hfc)$_3$; hfc=3-(trifluoromethylhydroxymethylene-(+)-camphorato] did not distinguish between the enantiomers present and gave only a single, broadened peak. However, derivatization with (*S*)-1-phenylethylamine (5 equivalents; 16 h; 20°C) led to complete conversion into a 1:1 mixture of the two diastereoisomeric products (**4**)

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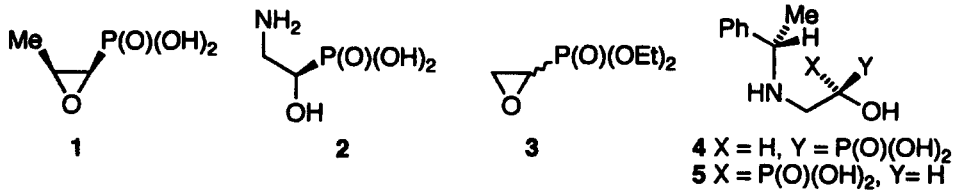
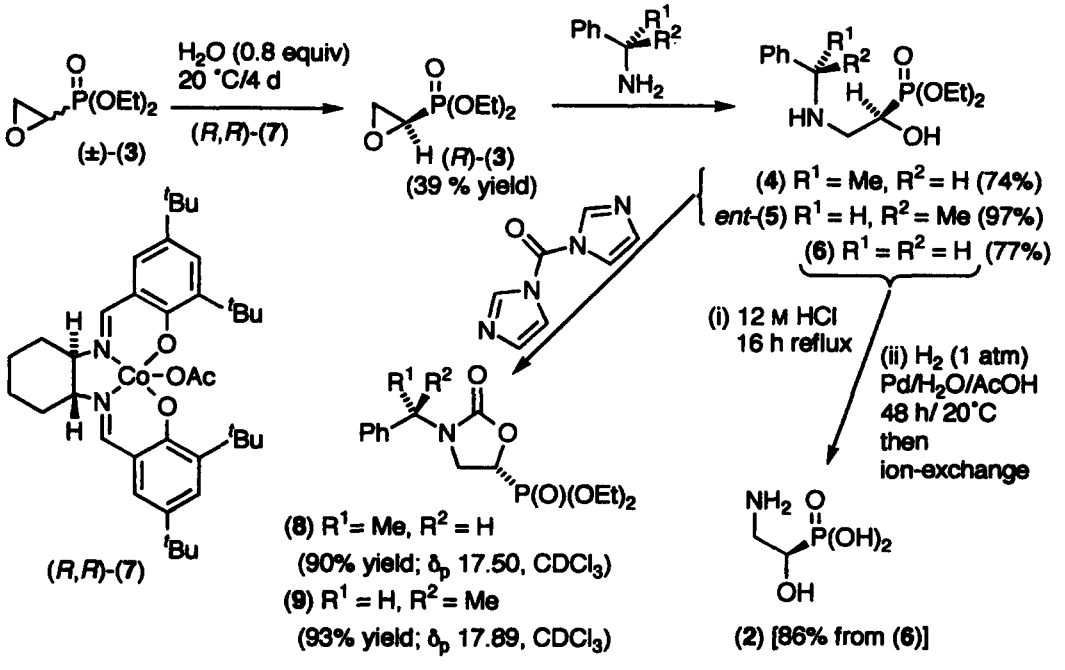
and (**5**), which had appreciably different ^{31}P chemical shift values ($\Delta\delta_P$=0.04, 0.15 and 0.24 in $CDCl_3$, C_5D_5N and C_6D_6, respectively).



Kinetic resolution of (±)-(**3**) (5.55 mmol) was achieved by stirring the epoxide in the presence of the catalyst (*R,R*)-(**7**) (0.05 mmol) and H_2O (4.44 mmol) at 20°C for 4 days (Scheme 1). Although we have yet to devise a method for monitoring this hydrolysis quantitatively, we noted that the reaction mixture became very viscous within the first few hours, consistent with the rapid conversion of some of the epoxide into the corresponding diol. The epoxide (**3**) which remained unreacted after 4 days (2.18 mmol, 39%) was isolated by flash chromatography (3:1 CH_2Cl_2:EtOAc) and had $[\alpha]_D^{28}$=+14.8 (*c* 1.65, CH_2Cl_2). It was shown to consist of essentially a single enantiomer since reactions with (*S*)- and (*R*)-1-phenylethylamine gave two single, diastereoisomeric amino alcohols (**4**) and *ent*-(**5**) as judged by ^{31}P NMR. Furthermore, the oxazolidinones (**8**) and (**9**) which were obtained by cyclization of the amino alcohols using 1,1′-carbonyldiimidazole were obtained as single diastereoisomers with distinct differences in their physical properties, including ^{31}P NMR.



Scheme 1. All compounds shown were homogeneous by TLC, with ^1H, ^{13}C and ^{31}P NMR and IR spectra consistent with their formulation as single isomers. The mass spectra of new compounds (**4**), *ent*-(**5**), (**8**) and (**9**) all gave the expected molecular ions, which were measured at high resolution

Finally the (*R*)-configuration of the resolved epoxide (+)-(**3**) was established by conversion into the natural product (*R*)-2-amino-1-hydroxyethylphosphonic acid (**2**) of $[\alpha]_D^{27}$=–31.9 (*c* 0.53, H_2O) {lit.[4] $[\alpha]_D^{20}$ for natural material=–30.5 (*c* 0.525, H_2O)}; a similar synthetic sequence has been used before in the racemic series.[5] A sample of (–)-(**2**) prepared by a procedure involving a classical resolution was

reported to have $[\alpha]_D^{20}=-31.4$ (*c* 0.525, H_2O) and its absolute configuration was related to that of (*R*)-(+)-1-phenylethyl isocyanate through a combination of X-ray crystallography and synthetic chemistry.[4] Thus the orientation of the substituent relative to the oxirane ring in (+)-(3) is analogous to that observed by Jacobsen for alkyl- and haloalkyl-monosubstituted epoxides resolved using the same catalyst.[2] Note, however, that some of these epoxides are of (*R*)-configuration and some are (*S*)-, depending on the relative priorities of the groups under the Cahn–Ingold–Prelog rules.

In conclusion, Jacobsen's kinetic resolution of monosubstituted epoxides has been shown to be applicable to diethyl oxiranephosphonate, providing easy access to a useful new homochiral building block.

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