Synthesis of Novel Enantiomerically Pure C_3-Symmetric Trialkanolamine Ligand Containing Phosphoryl Groups

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This paper is respectfully dedicated to Professor John G. Verkade on the occasion of his 70th birthday.

Abstract: Catalytic activity of ten metal salts in the reaction of benzhydrylamine and benzylamine with diethyl 2,3-epoxypropylphosphonate (**1**) was studied. Only in the presence of copper(I) iodide pure diethyl 3-benzhydrylamino- and 3-benzylamino-2-hydroxypropylphosphonates were produced quantitatively. Although the reactions catalysed by calcium(II) triflate were the fastest, they led to the contamination of the major products with the respective bisphosphonates. Enantiomerically pure (*S*,*S*)-bis[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amine (**10**) was prepared in a $Ca(OTf)_2$-catalysed reaction of (*S*)-**1** (ee 94%) with 0.4 equivalent benzylamine followed by hydrogenolysis. The bisphosphonate (*S*,*S*)-**10** was transformed into enantiomerically pure (*S*,*S*,*S*)-tris[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amine (**2**), when reacted with (*S*)-**1** (ee 94%) or into (*R*,*S*,*S*)-**2**, when (*R*)-**1** (ee 94%) was used.

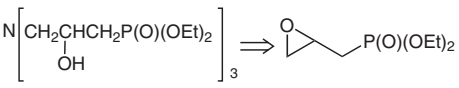
Key words: amino alcohols, epoxides, ligands, phosphonates, ring opening

Chiral triisopropanolamine was first synthesised by Farina and used in stereochemical studies on trimethylboratrane.[1] Later Nugent and Harlow prepared other trialkanolamines in order to study transition metal alkoxide complexes.[2] The rigid atrane framework of these complexes provides an asymmetric environment for a metal and thus implies potential applications in asymmetric catalysis.[3] So far the most useful complexes in this area are those of titanium(IV) and zirconium(IV), which are known to catalyse sulfide to sulfoxide oxidations,[4,5] meso-epoxide ring openings,[6] halohydrin synthesis[7] and oxidation of secondary amines to nitrones.[8] Other chiral titanium(IV) complexes have been applied as catalysts in a variety of oxidative processes, e.g. epoxidation of allylic alcohols[9] and N-oxidation of β-hydroxyamines.[10] Also vanadium(V) complexes have been found to efficiently catalyse oxidation of, for example, allylic alcohols to epoxides[11] and sulfides to sulfoxides.[12]

The interest in the synthesis of C_3-symmetric ligands has been increasing in recent years. For example, efficiency of several chiral trialkanolamine-based quaternary salts in alkylation of glycinate-benzophenone Schiff bases under PTC conditions has been examined.[13] A series of 3′-*O*-silatranylthymidines has been prepared and shown to possess anticancer activity.[14] Chiral trisoxazoline-based ligands were studied as models for zinc hydrolases[15] and in chiral molecular recognition.[16] Chiral C_3-symmetric ligands having a mesitylene core have also been obtained[17,18] and successfully applied as catalysts in the asymmetric addition of dialkylzinc to aldehydes.[18] Very recently chiral trialkanolamine-based hemicryptophanes, which may serve as model of enzymes, have been described.[19]

On the other hand, chelating properties of phosphonic derivatives of amino acids have been recognised and their biomedical applications as ligands in MRI contrast agents, fluorescent complexes and radiopharmaceuticals are well known.[20]

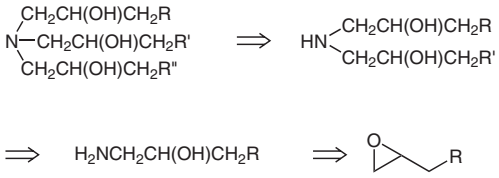
We have recently synthesised several enantiopure γ-amino-β-hydroxypropylphosphonates[21–23] employing Jacobsen's hydrolytic kinetic resolution (HKR)[24] of diethyl 2,3-epoxypropylphosphonate (**1**) and noticed the formation of respective secondary amines, when benzhydrylamine[22] or *O*-benzylhydroxylamine[23] were reacted with **1**. These observations have prompted us to synthesise chiral trialkanolamines **2** containing the *O*,*O*-diethylphosphoryl groups at terminal carbon atoms (Scheme 1).



2 **1**

Scheme 1 Retrosynthetic plan

Although syntheses of chiral trialkanolamines take advantage of reactions of ammonia with 3 equivalents of appropriate terminal epoxides[1,2,13,25] or of β-amino alcohols with two equivalents of the epoxide,[2,19] we preferred a stepwise approach, which would allow us to design synthetic pathways to chiral and unsymmetrically substituted trialkanolamine ligands (Scheme 2).



Scheme 2 Synthetic strategy to unsymmetrically substituted trialkanolamines

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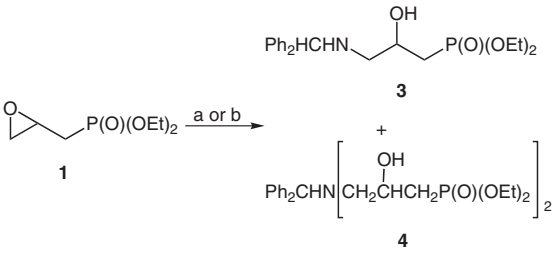
In this paper we describe our studies on the optimisation of the catalyst efficient in opening of the epoxide ring in **1** with primary amines, a two-step approach to (*S*,*S*)-bis[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amine [(*S*,*S*)-**10**] and finally the syntheses of (*S*,*S*,*S*)- and (*R*,*S*,*S*)-tris[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amines [(*S*,*S*,*S*)- and (*R*,*S*,*S*)-**2**].

Regiospecific opening of the epoxide **1** at C-3 with amines was quantitatively accomplished without catalysts, but it required heating at elevated temperatures sometimes for several days.[21,22] To shorten the reaction time and to lower the reaction temperature several metal salts, recently introduced as catalysts for the epoxide ring opening,[26–29] have been tried with the phosphonate **1** and benzhydrylamine, selected as a model primary amine (Scheme 3). The progress of the reactions carried out in the presence of 5 mol% of catalysts was monitored by ^{31}P NMR spectroscopy and compositions of the crude products were calculated from ^{31}P NMR spectra (Table 1). The by-products **5**, **6** and **7** (Figure 1) were identified based on our recent spectroscopic characterisation.[21,22]

Although in the reaction catalysed by copper(I) iodide the phosphonate **3** was formed as a single product, we conducted further studies using calcium triflate as catalyst, since the epoxide ring opening in **1** could be accomplished at room temperature in a few hours and the reaction mixture was contaminated with negligible amounts of the bisphosphonate **4**.

To further shorten the reaction time benzhydrylamine was replaced by less sterically hindered benzylamine



Scheme 3 Reaction of phosphonate **1** with benzhydrylamine. *Reagents and conditions:* a) Ph_2CHNH_2 (1.1 equiv), see Table 1; or b) Ph_2CHNH_2 (0.4 equiv), $Ca(OTf)_2$ (5 mol%), 50 °C, 19 h.

(Scheme 4). Application of Cu_2I_2 as catalyst led to the formation of the phosphonate **8** as a single product after four hours at 50 °C. At the same temperature, in the presence of $Ca(OTf)_2$, the reaction of **1** with benzylamine was finished after 20 minutes. However, the major phosphonate **8** was contaminated with ca 20% of the bisphosphonate **9**. The latter transformation was also carried out at room temperature to give an 85:15 mixture of **8** and **9** after two hours.

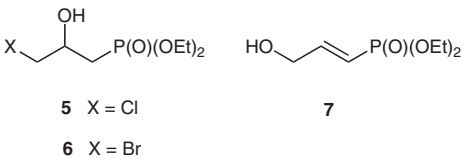
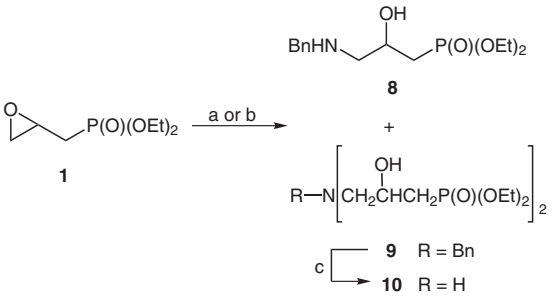


Figure 1 Structure of by-products **5**–**7**

Table 1 Products of the Catalysed Epoxide Opening in the Phosphonate **1** with Benzhydrylamine

Entry	Catalyst	Conditions	Ratio of phosphonates (%)					
			1	**3**	**4**	**5**	**6**	**7**
1	$FeSO_4 \cdot 7H_2O$	50 °C; 46 h	1	93	6	0	0	0
2	$ZnCl_2$	50 °C; 24 h	7	83	5	5	0	0
3	$ZnBr_2$	50 °C; 24 h	0	95	0	0	5	0
4	AgF	50 °C; 24 h	3	91	3	–[a]	0	0
5	CsF	50 °C; 24 h	0	91	3	0	0	6
6	$NiCl_2 \cdot 6H_2O$	50 °C; 2 h	22	73	0	5	0	0
7	$ZrCl_4$	50 °C; 10 h	2	87	6	5	0	0
8	$ZrCl_4$	20 °C; 12 h	10	82	3	5	0	0
9	LiBr	50 °C; 3 h	0	84	3	0	4	9
10	LiBr	20 °C; 4.5 h	48	45	0	0	5	2
11	Cu_2I_2	50 °C; 21 h	0	100	0	0	0	0
12	$Ca(OTf)_2$	50 °C; 3 h	0	96	4	0	0	0
13	$Ca(OTf)_2$	20 °C; 6 h	0	97	3	0	0	0

[a] Contains 3% of an unknown phosphonate (^{31}P NMR: $\delta = 29.77$).



Scheme 4 Reaction of phosphonate **1** with benzylamine. *Reagents and conditions:* a) $BnNH_2$ (1.1 equiv), Cu_2I_2 or $Ca(OTf)_2$ (5 mol%), r.t.; or b) $BnNH_2$ (0.4 equiv), $Ca(OTf)_2$ (5 mol%), 50 °C, 20 min; c. H_2, Pd/C and $Pd(OH)_2$/C, 20 h.

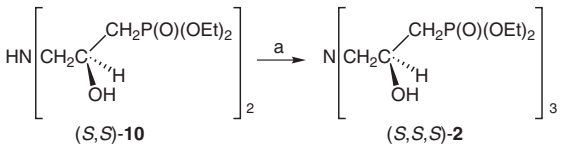
Syntheses of pure bisphosphonates **4** and **9** were accomplished by reacting the epoxyphosphonate **1** with 0.4 equivalent of the amine at 50 °C in the presence of $Ca(OTf)_2$. It took 19 hours for benzhydrylamine to completely react with a slight excess of **1** (Scheme 3), while with benzylamine (Scheme 4) only one hour was needed to produce the bisphosphonate **9** quantitatively. In both cases, approximate 1:1 *dl* and *meso* mixtures of the respective bisphosphonates were formed.

Hydrogenolysis of the benzyl protecting group in **9** was performed in the presence of a 1:1 Pd/C and $Pd(OH)_2$/C mixture to afford pure secondary amine **10** quantitatively (Scheme 4). However, this compound had to be used in further transformations as a crude material, since attempts to purify it on silica gel led to partial decomposition.

When the epoxyphosphonate (*S*)-**1** (ee 94%) was reacted with 0.4 equivalent benzylamine, enantiomerically pure (*S*,*S*)-*N*-benzyl-bis[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amine [(*S*,*S*)-**9**] was formed quantitatively. The enantiomeric purity of this compound was confirmed (within detection limits) by disappearance of signals of *meso*-**9** from the ^{1}H and ^{13}C NMR spectra of the obtained material. The absence of a singlet at 3.75 ppm (H_2CPh in *meso*-**9**) was especially indicative. Hydrogenolysis of (*S*,*S*)-**9** led to (*S*,*S*)-bis[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amine [(*S*,*S*)-**10**], which was pure to be used in the next step as a crude product.

To synthesise the trisamine (*S*,*S*,*S*)-**2**, the enantiomerically pure bisphosphonate (*S*,*S*)-**10** was reacted with three equivalents of epoxyphosphonate (*S*)-**1** (ee 94%) in the presence of $Ca(OTf)_2$ (10 mol%) at 50 °C for 20 hours (Scheme 5). After removal of an excess (*S*)-**1** (ee 90%) and residual vinylphosphonate **7** as less polar materials, (*S*,*S*,*S*)-tris[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amine [(*S*,*S*,*S*)-**2**] was cleanly separated in 72% yield. Since the ^{1}H and ^{13}C NMR spectra of this compound exhibited single sets of resonances for the homotopic substituents at the nitrogen atom, we consider it as enantiomerically pure.

To confirm this conclusion we undertook the synthesis of (*R*,*S*,*S*)-**2**. To this end, the enantiomerically pure bisphosphonate (*S*,*S*)-**10** was reacted with three equivalents epoxyphosphonate (*R*)-**1** (ee 94%)[21] in the presence of $Ca(OTf)_2$ (10 mol%) at 50 °C for 20 h. After chromatographic purification, the trisphosphonate (*R*,*S*,*S*)-**2** (Figure 2) was separated in 67% yield. Its enantiomeric purity was proved by absence of ^{1}H, ^{13}C and ^{31}P NMR resonances characteristic of (*S*,*S*,*S*)-**2** in the spectra of the obtained material. For example, the ^{31}P NMR chemical shifts for methanol solutions are well separated and appeared as a single line at 31.48 ppm for (*S*,*S*,*S*)-**2**, while for (*R*,*S*,*S*)-**2**, two lines (a 2:1 ratio) were observed at 31.70 and 31.92 ppm, respectively.



Scheme 5 Synthesis of (*S*,*S*,*S*)-**2**. *Reagents and conditions:* a) (*S*)-**1** (3 equiv), $Ca(OTf)_2$ (10 mol%), toluene, 50 °C, 20 h.

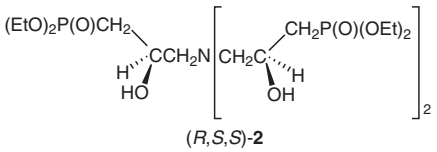


Figure 2 (*R*,*S*,*S*)-Tris[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amine

In conclusion, among the 10 metal salts tried as catalysts in opening of the epoxide ring in diethyl 2,3-epoxypropylphosphonate (**1**) with benzhydrylamine and benzylamine, only Cu_2I_2 cleanly gave diethyl 3-benzhydrylamino- and 3-benzylamino-2-hydroxypropylphosphonates, while in the reactions catalysed by calcium(II) triflate, which were the fastest, the major products were contaminated with the respective bisphosphonates. Tagging the terminal epoxide residue with the *O*,*O*-diethylphosphoryl group made possible identification of impurities, which were formed by nucleophilic attack of chloride or bromide (from catalysts) at terminal carbon atom.

Synthesis of enantiomerically pure (*S*,*S*)-bis[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amine (**10**) was accomplished in a $Ca(OTf)_2$-catalysed reaction of the epoxyphosphonate (*S*)-**1** (ee 94%) with 0.4 equivalent of benzylamine followed by hydrogenolysis. Enantiomerically pure (*S*,*S*,*S*)- and (*R*,*S*,*S*)-tris[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amines [(*S*,*S*,*S*)- and (*R*,*S*,*S*)-**2**] were obtained, when the bisphosphonate (*S*,*S*)-**10** was reacted with (*S*)-**1** (ee 94%) or with (*R*)-**1** (ee 94%).

^{1}H NMR spectra were recorded with a Varian Mercury-300 spectrometer; chemical shifts δ are given in ppm with respect to TMS; coupling constants *J* are reported 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 spectra were measured on an Infinity MI-60 FT-IR spectrometer. Elemental analyses were performed by the Microanalytical Laboratory of this Faculty on a Perkin-Elmer PE 2400 CHNS analyser. Polarimetric measurements were conducted on a Perkin-Elmer 241 MC apparatus.

The following absorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh); analytical TLC, Merck TLC plastic sheets silica gel 60 F_{254}.

Diethyl (*R*)- and (*S*)-2,3-epoxypropylphosphonates (**1**, ee 94%, both) were prepared according to the literature procedure.[21]

Reaction of the Epoxyphosphonate 1 with Benzhydrylamine or Benzylamine (1:1.1 Mixture) in the Presence of Catalysts; General Procedure

A mixture of the phosphonate **1** (1.00 mmol) and the amine (1.10 mmol) containing the respective catalyst (5 mol%) was stirred at 50 °C or at r.t. under argon for the time indicated in Table 1.

Diethyl 3-Benzylamino-2-hydroxypropylphosphonate (8)

The crude product obtained from **1** (0.200 g, 1.03 mmol) and benzylamine (0.124 mL, 1.13 mmol) in the presence of Cu_2I_2 (0.010 g, 0.05 mmol) was dissolved in CH_2Cl_2 (3 mL) and the solution was washed with H_2O (3 × 2 mL). The aqueous washings were extracted with CH_2Cl_2 (2 × 2 mL) and the combined organic phases were dried ($MgSO_4$). After concentration, the crude product was chromatographed on a silica gel column with chloroform–MeOH mixture (50:1) to give the phosphonate **8** (0.264 g, 85%) as a yellowish oil.

IR (film): 3376, 2984, 2909, 2854, 1601, 1456, 1223, 1027, 964, 807, 747, 705 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.34–7.23 (m, 5 H), 4.22–4.03 (m, 5 H), 3.88 (d, *J* = 13.2 Hz, 1 H, H_aH_bCPh), 3.77 (d, *J* = 13.2 Hz, 1 H, H_aH_b-CPh), 2.83 (dd, *J* = 12.0, 3.6 Hz, 1 H, H_aH_bCN), 2.66 (dd, *J* = 12.0, 7.8 Hz, 1 H, H_aH_bCN), 2.02 (dd, AB, J_{AB} = 15.3 Hz, *J* = 16.8, 8.4 Hz, 1 H, H_aH_bCP), 1.94 (dd, AB, J_{AB} = 15.3 Hz, *J* = 18.6, 4.2 Hz, 1 H, H_aH_bCP), 1.32 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR ($CDCl_3$): δ = 139.4, 128.5, 127.4, 127.3, 65.2, 62.1 and 62.0 (2 d, *J* = 6.9 Hz, COP), 55.1 (d, *J* = 16.0 Hz, CN), 53.7 (s, *C*Ph), 31.8 (d, *J* = 139.0 Hz, CP), 16.7 and 16.7 (2 d, *J* = 6.0 Hz, CH_3).

^{31}P NMR ($CDCl_3$): δ = 30.37.

Anal. Calcd for $C_{14}H_{24}NO_4P{\cdot}0.8\ H_2O$: C, 53.26; H, 8.20; N, 4.44. Found: C, 53.25; H, 8.48; N, 4.20.

Reaction of the Epoxyphosphonate 1 with Benzhydrylamine or Benzylamine (1:0.4 mixture) in the Presence of $Ca(OTf)_2$; General Procedure

A mixture of the phosphonate **1** (2.50 mmol) and the amine (1.00 mmol) containing $Ca(OTf)_2$ (5 mol%) was stirred at 50 °C under argon for 19 h (benzhydrylamine) or 1 h (benzylamine).

***N*-Benzylbis[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amine [*dl*- and *meso*-9]**

The crude product obtained from **1** (0.500 g, 2.57 mmol) and benzylamine (0.112 mL, 1.03 mmol) in the presence of $Ca(OTf)_2$ (0.044 g, 0.13 mmol, 5 mol%) was dissolved in CH_2Cl_2 (5 mL) and the solution was washed with H_2O (3 × 3 mL). Aqueous washings were back extracted with CH_2Cl_2 (3 mL) and the combined organic phases were dried ($MgSO_4$). After concentration, the crude product was chromatographed on a silica gel column with acetone–toluene mixture (10:1) to give *dl*- and *meso*-**9** (0.457 g, 90%) as a colourless oil.

IR(film): 3373, 3085, 2982, 2932, 2908, 2828, 1603, 1451, 1391, 1225, 1034, 963, 832, 806, 744, 702 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.30–7.20 (m, 5 H), 4.20–4.00 (m, 9 H), 4.00–3.80 (m, 1 H, C*H*OH in *meso*-**9**), 3.84 (d, *J* = 13.8 Hz, 1 H, H_aH_bCPh in *dl*-**9**), 3.75 (s, 2 H, H_2CPh in *meso*-**9**), 3.65 (d, *J* = 13.8 Hz, 1 H, H_aH_bCPh in *dl*-**9**), 2.74 (dd, *J* = 13.2, 4.2 Hz, 1 H, H_aH_bCN in *meso*-**9**), 2.67–2.57 (m, 3 H, H_aH_bCN in *meso*-**9** and H_2CN in *dl*-**9**), 1.96–1.74 (m, 4 H, H_2CP in *meso*-**9** and *dl*-**9**), 1.32 (t, *J* = 7.1 Hz, 6 H, CH_3 in *dl*-**9**), 1.32 and 1.31 (2 t, *J* = 7.1 Hz, 6 H, 2 CH_3 in *meso*-**9**).

^{13}C NMR ($CDCl_3$): δ = 138.3, 128.9, 128.2, 128.1, 127.1, 127.0, 65.0 (d, *J* = 4.3 Hz, CHOH in *dl*-**9**), 64.1 (d, *J* = 2.9 Hz, CHOH in *meso*-**9**), 62.1, 62.0, 61.9, 61.9 (4 d, *J* = 6.5 Hz, COP in *meso*-**9** and *dl*-**9**), 61.2 and 61.2 (2 d, *J* = 16.3 Hz, C-N in *meso*-**9** and *dl*-**9**), 60.3 (s, *C*Ph in *dl*-**9**), 60.1 (s, *C*Ph in *meso*-**9**), 31.7 (d, *J* = 139.7 Hz, CP in *dl*-**9**), 31.6 (d, *J* = 139.7 Hz, CP in *meso*-**9**), 16.7 (d, *J* = 6.0 Hz, CH_3 in *dl*-**9**), 16.6 (d, *J* = 6.0 Hz, 2 CH_3 in *meso*-**9**).

^{31}P NMR ($CDCl_3$): δ = 30.81 (*meso*-**9**), 30.75 (*dl*-**9**).

Anal. Calcd for $C_{21}H_{39}NO_8P_2{\cdot}0.5\ H_2O$: C, 49.99; H, 7.99; N, 2.78. Found: C, 50.02; H, 8.02; N, 2.78.

(*S*,*S*)-*N*-Benzylbis[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amine [(*S*,*S*)-9]

The crude product obtained from **1** (0.500 g, 2.57 mmol) (ee 94%) and benzylamine (0.112 mL, 1.03 mmol) in the presence of $Ca(OTf)_2$ (0.044 g, 0.13 mmol, 5 mol%) was purified as described above to give (*S*,*S*)-**9** (0.397 g, 78%) as a colourless oil; $[\alpha]_D^{20}$ –35.0 (*c* = 1.5, $CHCl_3$).

^1H NMR ($CDCl_3$): δ = 7.30–7.20 (m, 5 H), 4.20–4.00 (m, 10 H), 3.84 (d, *J* = 13.8 Hz, 1 H, H_aH_bCPh), 3.65 (d, *J* = 13.8 Hz, 1 H, H_aH_bCPh), 2.70–2.56 (m, 4 H, H_2CN), 1.88 (dd, AB, J_{AB} = 15.3 Hz, *J* = 22.5, 8.1 Hz, 2 H, H_aH_bCP), 1.83 (dd, AB, J_{AB} = 15.3 Hz, *J* = 23.4, 4.8 Hz, 2 H, H_aH_bCP), 1.32 (t, *J* = 7.1 Hz, 6 H, 2 CH_3).

^{13}C NMR ($CDCl_3$): δ = 138.6, 129.1, 128.5, 127.3, 64.4 (d, *J* = 3.8 Hz, COH), 62.1 and 61.9 (2 d, *J* = 6.8 Hz, COP), 61.3 (d, *J* = 16.6 Hz, CN), 60.3 (s, *C*Ph), 31.7 (d, *J* = 140.0 Hz, CP), 16.7 (d, *J* = 6.0 Hz).

^{31}P NMR ($CDCl_3$): δ = 30.75.

Anal. Calcd for $C_{21}H_{39}NO_8P_2{\cdot}0.5\ H_2O$: C, 49.99; H, 7.99; N, 2.78. Found: C, 49.81; H, 7.93; N, 2.76.

Bis[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amine [*dl*- and *meso*-10]

A solution of the phosphonate *dl*- and *meso*-**9** (0.240 g, 0.520 mmol) in EtOH (2.5 mL) containing 10% Pd/C (4 mg) and $Pd(OH)_2$/C (4 mg) was stirred under H_2 atmosphere for 20 h. Catalysts were removed on a layer of Celite, and the solution was concentrated in vacuo to afford *dl*- and *meso*-**10** (0.181 g, 86%) as a yellowish oil.

IR (film): 3355, 2984, 2910, 1445, 1393, 1226, 1029, 964, 834 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.22–3.98 (m, 10 H), 2.78 (dd, *J* = 12.3, 3.6 Hz, 1 H, H_aH_bCN in *meso*-**10**), 2.77 (dd, *J* = 12.3, 3.9 Hz, 1 H, H_aH_bCN in *dl*-**10**), 2.70 (dd, *J* = 12.3, 8.1 Hz, 1 H, H_aH_bCN in *meso*-**10**), 2.69 (dd, *J* = 12.3, 7.5 Hz, 1 H, H_aH_bCN in *dl*-**10**), 2.07–1.84 (m, 4 H, H_2CP in *meso*-**10** and *dl*-**10**), 1.34 (t, *J* = 7.0 Hz, 12 H, CH_3 in *meso*-**10** and *dl*-**10**).

^{13}C NMR ($CDCl_3$): δ= 65.4 (d, *J* = 3.8 Hz, CHOH in *meso*-**10**), 65.3 (d, *J* = 3.8 Hz, CHOH in *dl*-**10**), 62.0 and 61.9 (2 d, *J* = 6.8 Hz, COP in *meso*-**10** and *dl*-**10**), 55.9 and 55.7 (2 d, *J* = 15.4 Hz, CN in *meso*-**10** and *dl*-**10**), 31.7 (d, *J* = 139.6 Hz, CP in *meso*-**10**), 31.7 (d, *J* = 139.6 Hz, CP in *dl*-**10**), 16.6 and 16.6 (2 d, *J* = 6.0 Hz, CH_3 in *meso*-**10** and *dl*-**10**).

^{31}P NMR ($CDCl_3$): δ = 30.94 and 30.95 (*meso*-**10** and *dl*-**10**).

Anal. Calcd for $C_{14}H_{33}NO_8P{\cdot}0.75\ H_2O$: C, 40.14; H, 8.30; N, 3.34. Found: C, 40.16; H, 8.30; N, 3.22.

(*S*,*S*)-Bis[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amine [(*S*,*S*)-10]

From the phosphonate (*S*,*S*)-**9** (0.315 g, 0.680 mmol) dissolved in EtOH (3 mL) in the presence of 10% Pd/C (6 mg) and $Pd(OH)_2$/C

(6 mg), the phosphonate (*S*,*S*)-**10** (0.259 g, 94%) was obtained as a yellowish oil following the procedure described for the racemic **10**; $[\alpha]_D^{20}$ +38.0 (*c* = 2.16, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 4.22–4.00 (m, 10 H), 2.77 (dd, *J* = 12.3, 3.9 Hz, 2H, H_aH_bCN), 2.69 (dd, *J* = 12.3, 7.5 Hz, 2 H, H_aH_bCN), 2.65–1.90 (br s, 3 H), 2.02 (ddAB, J_{AB} = 15.3 Hz, *J* = 16.8, 8.4 Hz, 2 H, H_aH_bCP), 1.92 (ddAB, J_{AB} = 15.3 Hz, *J* = 19.1, 4.2 Hz, 2 H, H_aH_bCP), 1.34 (t, *J* = 7.0 Hz, 12 H).

^{1}H NMR (CD_3OD): δ = 4.18–4.00 (m, 10 H), 2.75 (dd, *J* = 12.3, 4.1 Hz, 2 H, H_aH_bCN), 2.68 (dd, *J* = 12.3, 7.8 Hz, 2 H, H_aH_bCN), 2.08 (ddAB, J_{AB} = 15.6 Hz, *J* = 18.6, 5.7 Hz, 2 H, H_aH_bCP), 2.05 (ddAB, J_{AB} = 15.6 Hz, *J* = 18.0, 7.2 Hz, 2 H, H_aH_bCP), 1.33 (t, *J* = 7.1 Hz, 12 H).

^{13}C NMR ($CDCl_3$): δ = 65.2 (d, *J* = 3.0 Hz, CHOH), 62.0 and 61.9 (2 d, *J* = 6.8 Hz, COP), 55.7 (d, *J* = 15.1 Hz, CN), 31.7 (d, *J* = 138.8 Hz, CP), 16.6 and 16.6 (2 d, *J* = 6.0 Hz).

^{13}C NMR (CD_3OD): δ = 66.3 (d, *J* = 3.0 Hz, CHOH), 63.5 and 63.3 (2 d, *J* = 6.3 Hz, COP), 56.7 (d, *J* = 12.9 Hz, CN), 32.7 (d, *J* = 138.8 Hz, CP), 16.9 (d, *J* = 6.3 Hz).

^{31}P NMR ($CDCl_3$): δ = 30.97.

^{31}P NMR (CD_3OD): δ = 29.57.

Anal. Calcd for $C_{14}H_{33}NO_8P \cdot 0.25\ H_2O$: C, 41.03; H, 8.24; N, 3.42. Found: C, 41.06; H, 8.51; N, 3.41.

(*S*,*S*,*S*)-Tris[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amine [(*S*,*S*,*S*)-2]

A mixture of the bisphosphonate (*S*,*S*)-**10** (0.050 g, 0.12 mmol) and the epoxyphosphonate (*S*)-**1** (0.070 g, 0.36 mmol) (ee 94%) containing $Ca(OTf)_2$ (0.012 g, 0.036 mmol) in toluene (1 mL) was stirred at 50 °C for 20 h. After concentration in vacuo, the residue was filtered through a short pad of silica gel to remove the excess (*S*)-**1** (with acetone) and to collect the product (*S*,*S*,*S*)-**2** (0.052 g, 72%) as a yellowish oil, after washing with MeOH; $[\alpha]_D^{20}$ –32.3 (*c* = 1.0, MeOH).

^{1}H NMR ($CDCl_3$): δ = 4.20–4.00 (m, 15 H), 2.55 (dd, *J* = 12.9, 1.0 Hz, 3 H, H_aH_bCN), 2.46 (dd, *J* = 12.9, 9.7 Hz, 3 H, H_aH_bCN), 2.20–1.90 (br s, 3 H), 1.95 (dd, AB, J_{AB} = 15.3 Hz, *J* = 17.7, 8.4 Hz, 3 H, H_aH_bCP), 1.79 (dd, AB, J_{AB} = 15.3 Hz, *J* = 18.6, 4.8 Hz, 3 H, H_aH_bCP), 1.32 (t, *J* = 7.0 Hz, 18 H).

^{1}H NMR (CD_3OD): δ = 4.20–4.07 (m, 12 H), 4.07–3.93 (m, 3 H), 2.65 (dd, *J* = 13.5, 3.5 Hz, 3 H, H_aH_bCN), 2.56 (dd, *J* = 13.5, 8.6 Hz, 3 H, H_aH_bCN), 2.04 (dd, AB, J_{AB} = 15.6 Hz, *J* = 18.7, 5.4 Hz, 3 H, H_aH_bCP), 1.96 (ddAB, J_{AB} = 15.6 Hz, *J* = 17.9, 7.5 Hz, 3 H, H_aH_bCP), 1.33 (t, *J* = 7.0 Hz, 18 H).

^{13}C NMR ($CDCl_3$): δ = 63.8 (d, *J* = 3.8 Hz, CHOH), 63.7 (d, *J* = 16.6 Hz, CN), 62.2 and 61.7 (2 d, *J* = 6.8 Hz, COP), 31.3 (d, *J* = 141.2 Hz, CP), 16.7 and 16.6 (2 d, *J* = 6.0 Hz).

^{13}C NMR (CD_3OD): δ = 65.6 (d, *J* = 3.0 Hz, CHOH), 64.2 (d, *J* = 15.1 Hz, CN), 63.5 and 63.3 (2 d, *J* = 6.8 Hz, COP), 32.2 (d, *J* = 139.6 Hz, CP), 16.9 (d, *J* = 6.0 Hz).

^{31}P NMR ($CDCl_3$): δ = 30.97.

^{31}P NMR (CD_3OD): δ = 31.48.

Anal. Calcd for $C_{21}H_{48}NO_{12}P_3 \cdot 2\ H_2O$: C, 39.67; H, 7.95; N, 2.20. Found: C, 39.50; H, 8.02; N, 2.24.

(*R*,*S*,*S*)-Tris[2-(*O*,*O*-diethylphosphorylmethyl)ethanol]amine [(*R*,*S*,*S*)-2]

In a manner described for (*S*,*S*,*S*)-**2**, the bisphosphonate (*S*,*S*)-**10** (0.082 g, 0.20 mmol) and the epoxyphosphonate (*R*)-**1** (0.120 g, 0.606 mmol) (ee 94%) in the presence of $Ca(OTf)_2$ (0.020 g, 0.061 mmol) in toluene (1.5 mL), gave the trisphosphonate (*R*,*S*,*S*)-**2** (0.081 g, 67%) as a yellowish oil; $[\alpha]_D^{20}$ –11.0 (*c* = 2.5, MeOH).

^{1}H NMR (CD_3OD): δ = 4.40–4.15 (m, 12 H), 4.15–3.90 (m, 3 H), 2.72 (dd, *J* = 13.4, 4.4 Hz, 1 H, H_aH_bCN in *R*), 2.70 (dd, *J* = 13.4, 4.4 Hz, 2 H, H_aH_bCN in *S*,*S*), 2.66–2.54 (m, 3 H, H_aH_bCN), 2.15 (dd, AB, J_{AB} = 15.4 Hz, *J* = 18.6, 4.5 Hz, 1 H, H_aH_bCP in *R*), 2.08 (dd, AB, J_{AB} = 15.4 Hz, *J* = 18.6, 4.9 Hz, 2 H, H_aH_bCP in *S*,*S*), 1.94 (dd, AB, J_{AB} = 15.4 Hz, *J* = 17.8, 7.8 Hz, 1 H, H_aH_bCP in *R*), 1.94 (dd, AB, J_{AB} = 15.4 Hz, *J* = 17.8, 8.1 Hz, 2 H, H_aH_bCP in *S*,*S*), 1.33 (t, *J* = 6.9 Hz, 18 H).

^{13}C NMR (CD_3OD): δ = 66.6 (d, *J* = 3.4 Hz, CHOH in *R*), 66.1 (d, *J* = 3.4 Hz, CHOH in *S*,*S*), 64.8 (d, *J* = 14.6 Hz, CN in *R*), 64.5 (d, *J* = 14.6 Hz, CN in *S*,*S*), 63.5 and 63.2 (2 d, *J* = 6.3 Hz, COP), 32.5 (d, *J* = 139.7 Hz, CP in *R*), 32.3 (d, *J* = 140.0 Hz, CP in *S*,*S*), 16.9 (d, *J* = 6.3 Hz).

^{31}P NMR (CD_3OD): δ = 31.96 (s, 1 P in *R*) and 31.70 (s, 2 P in *S*,*S*).

Anal. Calcd for $C_{21}H_{48}NO_{12}P_3$: C, 42.07; H, 8.07; N, 2.34. Found: C, 42.15; H, 7.97; N, 2.11.

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