Di(1*R*,2*S*,5*R*)-menthyl 2-Hydroxy-3-chloropropylphosphonate as a Useful Chiral Synthon for the Preparation of Enantiomerically Pure Phosphonic Acids

Vitaly V. Nesterov, Oleg I. Kolodiazhnyi*

Institute of Bioorganic Chemistry of the National Academy of Sciences, Murmanska Str. 1, 02094 Kyiv, Ukraine
Fax 38(44)5732554; E-mail: oikol123@rambler.ru

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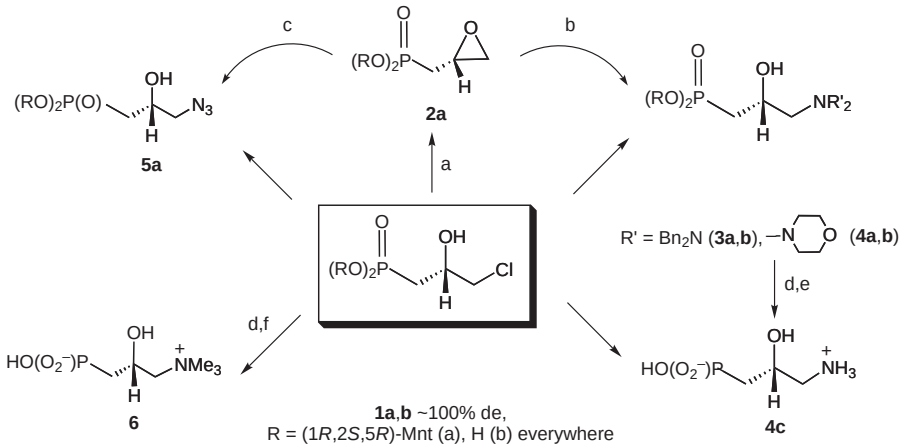
Abstract: Stereochemically pure di(1*R*,2*S*,5*R*)-menthyl (*S*)- and (*R*)-2-hydroxy-3-chloropropylphosphonates were synthesized by reaction of di(1*R*,2*S*,5*R*)-menthyl ketophosphonate with chiral complexes prepared from sodium borohydride and (*R*,*R*)-(+)-tartaric acid or with (*S*,*S*)-(–)-tartaric acid. Dimenthyl 2-hydroxy-3-chloropropylphosphonate was utilized as a chiron for the preparation of biologically active products.

Key words: asymmetric synthesis, reductions, double stereoselectivity, phosphono-GABOB, phosphono-carnitine

Hydroxyphosphonic acids are an important class of compounds occurring in nature.[1] Many of these compounds have attracted considerable attention in recent years for their role in biologically relevant processes.[1–3] They possess antibacterial, antiviral, antibiotic, pesticidal, anticancer, and enzyme inhibitor properties.[1,2] In our previous publications we have reported methods for the preparation of optically active α- and β-hydroxyphosphonic acids, including efficient methods for the enantioselective reduction of ketophosphonates.[2–4] Herein, we describe an extension of this approach to the synthesis of the *R*- and *S*-stereoisomers of dimenthyl 2-hydroxy-3-chloropropylphosphonate (**1a**) and 2-hydroxy-3-chloropropylphosphonic acid (**1b**) of high optical purity, which represent useful chiral synthetic building blocks (chirons) for the synthesis of enantiomerically pure β-hydroxyphosphonates. By means of these chirons we have obtained biologically important β-hydroxyphosphonic acids **2**–**6**, including 2,3-epoxypropylphosphonate (**2a**), chiral compounds **3**–**5**, γ-amino-β-hydroxypropylphosphonic acid (phosphono-GABOB, **4c**) and phosphono-carnitine (**6**, Scheme 1).

The hydroxyphosphonates **1a** were prepared by diastereoselective reduction of the corresponding di(1*R*,2*S*,5*R*)-menthyl 2-keto-3-chloropropylphosphonate (**7a**). Asymmetric reduction of prochiral ketophosphonates is a common method to obtain enantiomerically pure hydroxyphosphonic acids and their derivatives.[2,5,6] For the reduction of the ketophosphonate **7a** we have used a chiral reactant prepared from sodium borohydride and natural (*R*,*R*)-tartaric acid or synthetic (*S*,*S*)-tartaric acid (TA, Scheme 2).[4]

The reduction of chiral di(1*R*,2*S*,5*R*)-menthyl ketophosphonate (**7a**) with the chiral complex (*R*,*R*)-TA/$NaBH_4$ proceeded under control of double stereoselectivity[7] to yield the (*S*)-β-hydroxyphosphonate **1a** with 96% de that was considerably higher than the single stereoselectivity



Scheme 1 Representative transformations of (*S*)-**1a** to optically pure β-hydroxyphosphonates **2**–**6**. *Reagents and conditions*: (a) K_2CO_3/KI in MeCN–DMF; (b) HNR'_2, 80 °C; (c) NaN_3/NH_4Cl; (d) HCl–dioxane, 80–85 °C; (e) H_2, Pd/C; (f) Me_3N, H_2O.

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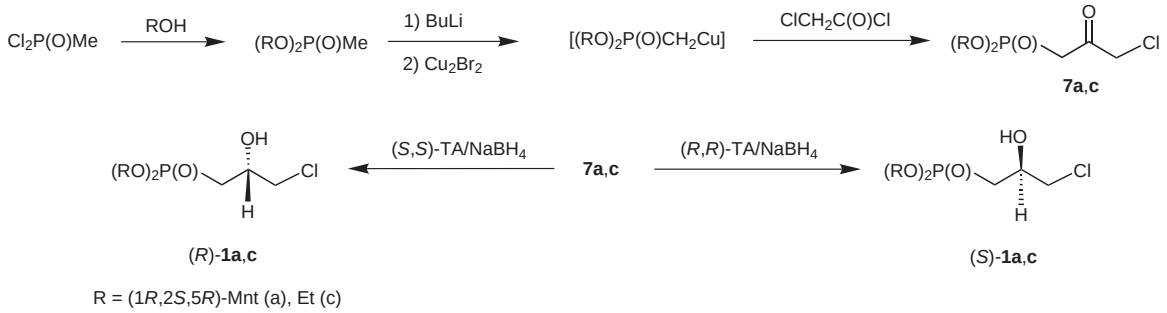


Scheme 2 Synthesis of (*R*)- and (*S*)-2-hydroxy-3-chloropropylphosphonates **1a**,**c**.

when the achiral diethyl 2-keto-3-chloropropylphosphonate (**7c**) was reduced with (*R*,*R*)-TA/$NaBH_4$ (80% ee, Table 1). The diastereomeric ratio of (*R*)-**1a**/(*S*)-**1a** was determined by means of ^1H NMR and ^{31}P NMR spectroscopy. The enantiomeric purity of diethyl β-hydroxy-γ-chloropropylphosphonates (**1c**) was analyzed using cinchonidine as a chiral solvated reagent,[8a] and dimenthylchlorophosphite as a chiral derivatizing reagent.[8b] The absolute configurations of the new stereogenic centers at C(2) in the β-hydroxyphosphonates **1a**,**c** were determined by chemical correlation.[2b] The di(1*R*,2*S*,5*R*)-menthyl 2-hydroxy-3-chloropropylphosphonates [(*S*)-**1a** and (*R*)-**1a**] were crystallized in acetonitrile or hexane and obtained as chemically and stereochemically pure crystalline compounds (ca. 100% de).[9]

The (*S*)- and (*R*)-**1a** were used for the synthesis of *R*- and *S*-enantiomers of phosphono-carnitine (**6**), which are phosphonate analogues of natural L-carnitine playing an important role in the transport of fatty acids into the mitochondrial matrix.[10] Previously, the synthesis of phosphono-carnitine has been performed by chemoenzymatic methods on the milligram scale.[11] We have developed the synthesis of (*R*)- and (*S*)-phosphono-carnitines on the multigram scale. As shown in the Scheme 1, the hydrolysis of (*S*)-**1a** or (*R*)-**1a** with hydrochloric acid in dioxane at 85 °C afforded acids (*S*)-**1b** and (*R*)-**1b**, which were treated with an aqueous solution of trimethylamine to give the crystalline enantiomerically pure (*R*)- and (*S*)-phosphono-carnitines **6** in good yields (Figure 1).[12]

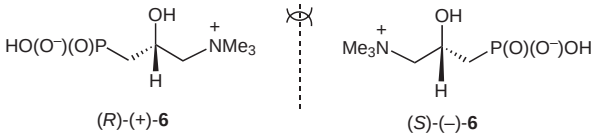


Figure 1

The treatment of (*S*)-**1a** with K_2CO_3 in acetonitrile–DMF in the presence of potassium iodide led quantitatively to the formation of epoxide (*R*)-**2a** with 99% de (Scheme 1).[13] The epoxyphosphonate (*R*)-**2a** added dibenzylamine and morpholine on heating to 80 °C to afford crystalline optically pure (*R*)-hydroxyaminophosphonates **3a** and **4a** in ca. 90% yield. Regiospecific opening of the epoxide cycle in dimenthyl (*R*)-2,3-epoxypropylphosphonate (**2a**) with secondary amines proceeded at C(3) and, after crystallization, the diastereomerically pure phosphonates **3a** and **4a** were isolated as colorless solids. The reaction of epoxide **2a** with sodium azide in the presence of ammonium chloride in methanol afforded the (*R*)-2-hydroxy-3-azidopropylphosphonate (**5a**) in very high yield (Figure 2).

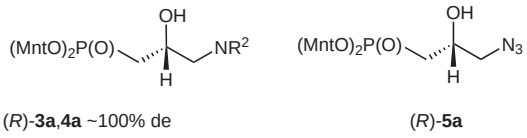


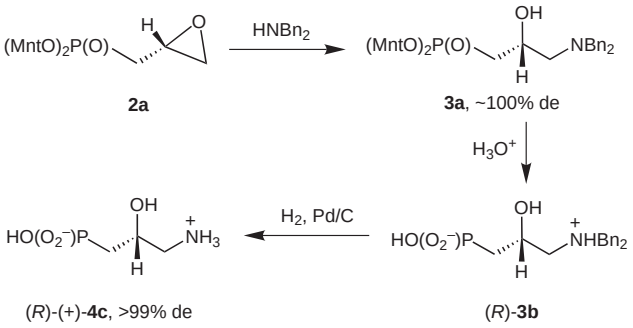
Figure 2

Table 1 Stereoselective Reduction of β-Ketophosphonates **7a**,**c**

R	Reductant	ee or de (%)	Config of **1**	Stereoselectivity
Et	$NaBH_4$	0	–	–
Et[a]	(*R*,*R*)-TA/$NaBH_4$	81	*S*	Single
Et[a]	(*S*,*S*)-TA/$NaBH_4$	81	*R*	Single
(1*R*,2*S*,5*R*)-Mnt	$NaBH_4$	<30	*R*	Single
(1*R*,2*S*,5*R*)-Mnt	(*R*,*R*)-TA/$NaBH_4$	96	*S*	Matched double
(1*R*,2*S*,5*R*)-Mnt	(*S*,*S*)-TA/$NaBH_4$	80	*R*	Mismatched double

[a] The reduction of diethyl 2-keto-3-chloropropylphosphonate **7c** with $NaBH_4$/TA was reported earlier, see ref. 4.

The epoxyphosphonate (*R*)-**2a** was used for the asymmetric synthesis of the phosphonic analogue of γ-amino-β-hydroxybutyric acid (L-GABOB) **4c**, which is used for the treatment of schizophrenia, epilepsy, and other illnesses.[14–16] Phosphonate analogues of GABA and GABOB have been synthesized in recent years.[17] We report here an efficient approach to enantiomerically pure γ-amino-β-hydroxypropylphosphonic acid (**4c**), which delivers this compounds in high stereochemical purity starting from the dimenthyl (*R*)- or (*S*)-2-hydroxy-3-chloropropylphosphonate (**1a**). In the first step the reaction of optically pure epoxide (*R*)-**2a** with dibenzylamine proceeded at C(3) to yield the hydroxyaminophosphonate (*R*)-**3a**, which was dealkylated by heating with hydrochloric acid in dioxane to afford the crystalline phosphonic acid (*R*)-**3b** in 74% yield and with ca. 100% ee. Then (*R*)-**3b** was debenzylated by hydrogenolysis in methanol in the presence of Pd/C to result in the phosphonic analogue of natural β-hydroxy-γ-aminobutyric acid (*R*)-(+)-**4c**, which was isolated as a solid in good yield and with high optical purity.[18] The crystalline compound **3a** bearing menthyl groups was purified by crystallization in acetonitrile (Scheme 3), and its stereochemical purity was determined by means of NMR spectroscopy. The *R*-configuration of **4c** was determined from the value of the optical rotation, which is coincident with that of the previously described phosphono-GABOB.[17]



Scheme 3 Synthesis of (*R*)-(+)-phosphono-GABOB (**4c**).

In summary, a series of optically active γ-amino-β-hydroxyphosphonic acids can be synthesized starting from the dimenthyl (*S*)- or (*R*)-2-hydroxy-3-chloropropylphosphonates. These compounds give access to (*R*)- or (*S*)-phosphono-carnitines, phosphono-GABOB, and 2-hydroxy-3-aminophosphonates. Di(1*R*,2*S*,5*R*)-menthyl (*S*)-2-hydroxy-3-cloropropylphosphonate via the formation of the epoxide and reaction with sodium azide was converted into the (*S*)-2-hydroxy-3-azidopropylphosphonate. All these products represent important biologically active structures.

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(9) **Synthesis of Dimenthyl 2-Hydroxy-3-chloropropylphosphonates (1a)**

Compound (*S*)-1a

(*R*,*R*)-Tartaric acid (5.35 g, 19.56 mmol) was added to a suspension of $NaBH_4$ (1.35 g, 19.56 mmol) in abs. THF (195 mL) and then the reaction mixture was refluxed with stirring for 4 h. The reaction mixture was cooled to –30 °C, a solution of 4.0 g of **7a**[19] in THF (15 mL) was added and the mixture was left overnight at –30 °C with stirring. Then EtOAc (50 mL) and 1 N HCl (40 mL) were added consecutively to the mixture, the organic and the aqueous layers were separated, and the latter was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with sat. aq Na_2CO_3 and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by crystallization in MeCN to give (*S*)-**1a** as a colorless solid (2.4 g, 60%). Mp 86.2 °C; $[\alpha]_D^{20}$ –97.2 (*c* 3, $CHCl_3$). IR (film): 1256 (P=O), 3200 (OH) cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ = 0.71 (d, *J* = 6.9 Hz, 3 H, CH_3), 0.76 (d, *J* = 6.9 Hz, 3 H, CH_3), 0.81–0.84 (m, 12 H, CH_3), 0.88–2.18 (m, 17 H, CH_2 and CH), 1.53 [m, 1 H, $CH(CH_3)_2$], 1.73 (m, 1 H, CH^aP), 1.97 (m, 1 H, CH^bP), 1.96 [m, 1 H, $CH(CH_3)_2$], 3.29 (dd, *J* = 10.8, 6.7 Hz, 1 H, CH^aCl), 3.43 (ddd, *J* = 10.8, 4.7, 2.8 Hz, 1 H, CH^bCl), 3.90–4.10 (m, 2 H, OCH), 4.15 (m, 1 H, CHOH), 4.44 (br, 1 H, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.13, 16.37, 21.34, 21.41, 22.24, 22.25, 23.40, 23.43, 26.00, 26.12, 31.98, 32.01, 32.64 (d, *J* = 141.2 Hz, CH_2P), 34.49, 34.49, 43.62, 44.13, 49.07 (d, *J* = 6.5 Hz, CH), 49.08 (d, *J* = 6.5 Hz, CH), 49.36 (d, *J* = 18.2 Hz, CH_2Cl), 67.29 (d, *J* = 3.6 Hz, CHOH), 78.33 (d, *J* = 7.5 Hz, OCH), 78.36 (d, *J* = 7.5 Hz, OCH). ^{31}P NMR (161.96 MHz, $CDCl_3$): δ = 28.81. Anal. Calcd for $C_{23}H_{44}ClO_4P$: C, 61.25; H, 9.83; P, 6.87. Found: C, 61.28; H, 9.86; P, 6.88.

Compound (*R*)-1a

Colorless solid, mp 76.5 °C(hexane); $[\alpha]_D^{20}$ –64.3 (*c* 2, $CHCl_3$). IR (film): 1256 (P=O), 3200 (OH) cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ = 0.72 (d, *J* = 6.9 Hz, 3 H, CH_3), 0.73 (d, *J* = 6.9 Hz, 3 H, CH_3), 0.81–0.84 (m, 12 H, CH_3), 0.88–2.18 (m, 17 H, CH_2 and CH), 1.53 [m, 1 H, $CH(CH_3)_2$], 1.71 (ddd, *J* = 15.7, 15.5, 9.1 Hz, 1 H, CH^aP), 1.97 (m, 1 H, CH^bP), 1.96 [m, 1 H, $CH(CH_3)_2$], 3.29 (dd, *J* = 10.8, 7.4 Hz, 1 H, CH^aCl), 3.43 (ddd, *J* = 10.8, 4.4, 3.4 Hz, 1 H, CH^bCl), 3.90–4.05 (m, 2 H, OCH), 3.95 (m, 1 H, CHOH), 4.25 (br, 1 H, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.13, 16.36, 21.34, 21.41, 22.24, 22.25, 23.40, 23.41, 26.00, 26.12, 31.98, 32.01, 32.61 (d, *J* = 141.2 Hz, CH_2P), 34.49, 34.49,

43.62, 44.13, 49.07 (d, *J* = 6.5 Hz, CH), 49.08 (d, *J* = 6.5 Hz, CH), 49.36 (d, *J* = 18.2 Hz, CH_2Cl), 67.29 (d, *J* = 3.6 Hz, CHOH), 78.34 (d, *J* = 7.5 Hz, OCH), 78.37 (d, *J* = 7.5 Hz, OCH). ^{31}P NMR (161.96 MHz, $CDCl_3$): δ = 28.7. Anal. Calcd for $C_{23}H_{44}ClO_4P$: C, 61.25; H, 9.83; P, 6.87. Found: C, 61.25; H, 9.88; P, 6.85.

Synthesis of Compound (*S*)-1b

To a solution of dimenthyl hydroxyphosphonate (*S*)-**1a** (4.5 g, 9.97 mmol) in dioxane (270 mL) was added concd HCl (80 mL) and the reaction mixture was left for 3 d at 85 °C. Then the solvent was removed under reduced pressure, to the residue was added H_2O (50 mL) and the mixture was washed with toluene (3 × 15 mL). Afterwards H_2O was removed in vacuo, the residue was dissolved in EtOH, and treated with activated charcoal. The solvent was evaporated to give (*S*)-**1b** as a colorless oil (1.63 g, 93.5%). The spectroscopically pure product was used without further purification. ^{1}H NMR (300 MHz, C_6D_6): δ = 1.6–1.9 (m, 2 H, PCH_2), 3.2–3.4 (m, 2 H, CH_2Cl), 4.8 (m, 1 H, CHO), 4.9 (br, OH). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 25.5.[20]

Compound (*R*)-1b

Colorless oil; yield 90%. ^{1}H NMR (300 MHz, C_6D_6): δ = 1.6–1.9 (m, 2 H, PCH_2), 3.2–3.4 (m, 2 H, CH_2Cl), 4.8 (m, 1 H, CHOH). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 25.5.

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(12) **Phosphono-carnitine (*R*)-(+)-6**

A solution of 30% trimethylamine (80 mL) was added to a solution of (*S*)-**1b** (1.74 g, 10 mmol) in H_2O. The mixture was left for 48 h at 40 °C, the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (MeOH–H_2O, 1:1) to give (*R*)-**6** (2g, 80%) as a white solid; yield 80%; mp >250 °C (decomp.); $[\alpha]_D^{20}$ +26 (*c* 1, H_2O). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.80 (ddd, *J* = 18, 14.7, 6.6 Hz, 1 H, PC^aH), 1.89 (ddd, *J* = 17.7, 14.8, 6.9 Hz, 1 H, PC^bH), 3.20 [s, 9 H, $(CH_3)_3N$], 3.40 (dd, *J* = 13.8, 9.8 Hz, 1 H, CH^aN), 3.60 (dd, *J* = 13.8, 1.2 Hz, 1 H, CH^bN), 4.50 (m, 1 H, CHOH). ^{13}C NMR (100.6 MHz, D_2O): δ = 35.55 (d, *J* = 131.7 Hz, CH_2P), 54.91, 54.94, 54.98, 63.65, 71.57. ^{31}P NMR (161.96 MHz, D_2O): δ = 18.1.

Phosphono-carnitine (*S*)-(–)-6

White solid; yield 80%; mp >250 °C (decomp.); $[\alpha]_D^{20}$ –26.0 (*c* 1, H_2O). The NMR spectroscopy data are identical to (*R*)-(+)-**6**.

(13) **Compound (*R*)-2a**

To a stirred solution of (*S*)-(–)-**1a** (4.5 g, 10 mmol) in a 10:3.5 mixture of MeCN–DMF (100 mL) were added K_2CO_3 (3.0 g) and KI (0.3 g). The mixture was refluxed for 8 h, filtered off, and the filtrate was evaporated to give (*R*)-**2a** (4.05 g, 98%) as a colorless oil; $[\alpha]_D^{20}$ –62.4 (*c* 7.0, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.80 (d, *J* = 7 Hz, 3 H, CH_3), 0.88 (d, *J* = 7 Hz, 3 H, CH_3), 0.89 (d, *J* = 7 Hz, 3 H, CH_3), 0.90 (d, *J* = 7 Hz, 3 H, CH_3), 0.91 (d, *J* = 7 Hz, 3 H, CH_3), 0.80–1.65 (m, 16 H CH_2C), 2.15–2.05 (m, 5 H, PCH_2, CH_2, and CH), 2.40 (dd, *J* = 5.1, 2.1 Hz, 1 H, CH^aO), 3.0 (dd, *J* = 5.1, 4.0 Hz, 1 H, CH^bO), 3.00 (m 1 H, CHO), 4.24 (m, 2 H, CHOP). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 25.3.

Compound (*R*)-3a

Colorless solid; yield 70%; mp 73 °C; $[\alpha]_D^{20}$ –45.92 (*c* 4.57, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6): δ = 0.73 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.80 d (3H, *J* = 7.0 Hz, CH_3), 0.87 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.90 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.91 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.92 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.96–2.25 (m, 19 H, CH_2C, CH, and CH^aP), 1.82 (ddd, *J* = 18.3, 15.1, 3.4 Hz, 1 H, CH^bP), 2.48 (m, 2 H, CH_2N), 3.55 (s, 4 H, CH_2Ph), 3.60 (m, 1 H, OH), 3.90–4.00 (m, 3 H, OCH and CHOH), 7.10–7.30 (m, 10 H, 2 C_6H_5). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 30.0.

Compound (*R*)-3b

Colorless solid; yield 3.1 g (85%). ^{1}H NMR (300 MHz, CD_3OD): δ = 1.73 (ddd, J_{HP} = 32.4 Hz, J_{HH} = 17.4 Hz, J_{HH} = 8.1 Hz, CH^aP), 1.93 (ddd, *J* = 34.5, 14.7, 4.5 Hz, 1 H, CH^bP), 2.96 (dd, *J* = 13.2, 9.3 Hz, 1 H, CH^aN), 3.20 (dd, *J* = 13.2, 9.3 Hz, CH^bN), 4.08–4.21 (m, 1 H, CHOH), 7.52–7.54 (m, 10 H, C_6H_5). ^{31}P NMR (121.4 MHz, H_2O): δ = 26.5.

Compound (*R*)-4a

Colorless solid; yield 70%; mp 93 °C; $[\alpha]_D^{20}$ –63.9 (*c* 1.17, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6): δ = 0.75–1.63 (m, 13 H, 8 CH_2 and 5 CH) 0.80 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.81 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.90 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.91 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.92 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.93 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.79 (m, 1 H, C^aH_2P), 1.85 (m, 1 H, C^bH_2P), 2.02–2.49 [m, 10 H, CH_2N, $O(CH_2CH_2)_2N$, 2 CH_2, and CH], 3.54 [m, 4 H, $O(CH_2CH_2)_2N$], 3.59 (br, 1 H, OH), 3.96 (m, 1 H, CHOH), 4.10 (m, 2 H, 2 CHOH). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 30.0.

Compound (*R*)-5a

Colorless oil; yield 96%; $[\alpha]_D^{20}$ –74.2 (*c* 2.5, $CHCl_3$). IR (film): ν_{max} = 2120 (N_3), 1200 (P=O) cm^{-1}. ^{1}H NMR (300 MHz, C_6D_6): δ = 0.79 (d, *J* = 7 Hz, 3 H, CH_3), 0.81 (d, *J* = 7 Hz, 3 H, CH_3), 0.91 (d, *J* = 7 Hz, 3 H, CH_3), 0.92 (d, *J* = 7 Hz, 3 H, CH_3), 0.93 (d, *J* = 7 Hz, 3 H, CH_3), 0.94 (d, *J* = 7 Hz, 3 H, CH_3), 1.00–2.00 (m, 16 H, CH_2C), 1.80 (m, 2 H, PCH), 3.15 (m, 2 H, CH_2N), 4.05 (m, 2 H, CHO), 4.14 (m, 2 H, CHOH and OH). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 27.4.

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(18) **Phosphono-GABOB (*R*)-(+)-4c**

A solution of (*R*)-**3b** (1.85 g, 5 mmol) in MeOH (210 mL) was hydrogenated over 10% Pd/C (1.75 g) for 20 h at r.t. The mixture was filtered off and concentrated under reduced pressure, washed with acetone, and dried in vacuo. The residue was purified by ion-exchange chromatography to give a colorless hygroscopic solid (0.69 g, 90%); $[\alpha]_D^{20}$ +10.2 (*c* 1, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 1.78 (ddd, *J* = 31.2, 15.0, 6.3 Hz, CH^aP), 1.86 (ddd, *J* = 32.1, 14.7, 6.3 Hz, CH^bP), 2.99 (dd, *J* = 13.5, 8.5 Hz, CH^aN), 3.27 (dd, *J* = 13.1, 3.4 Hz, CH^bN), 4.14 (m, 1 H, CHOH). ^{13}C NMR (100.6 MHz, D_2O): δ = 37.01 (d, *J* = 128.3 Hz, CH_2P), 48.13 (d, *J* = 9.0 Hz, CH_2N), 67.41. ^{31}P NMR (161.96 MHz, D_2O): δ = 18.1.

(19) **Di(1*R*,2*S*,5*R*)-menthyl 2-keto-3-chloropropylphosphonate (7a)**
Yield 70%; mp 65.5–65.6 °C; $[\alpha]_D^{20}$ –78.0 (*c* 1, $CHCl_3$). IR (film): 1256 (P=O), 1725 (C=O) cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ = 0.79 (d, *J* = 7 Hz, 3 H, CH_3), 0.81 (d, *J* = 7 Hz, 3 H, CH_3), 0.89 (d, *J* = 7 Hz, 3 H, CH_3), 0.90 (d, *J* = 7 Hz, 3 H, CH_3) 0.91 (d, *J* = 7 Hz, 3 H, CH_3), 0.93 (d, *J* = 7 Hz, 3 H, CH_3), 0.90–2.10 (m, 16 H, CH_2 and CH), 1.52 [m, 1 H, $CH(CH_3)_2$], 1.94 [m, 1 H, $CH(CH_3)_2$], 3.04 (d, *J* = 23.5 Hz, 2 H, PCH_2), 4.04 (s, 2 H, CH_2Cl), 4.07 (m, 2 H, 2 OCH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 15.64, 15.81, 20.93, 20.99, 21.85, 22.88, 22.95, 25.53, 25.65, 31.58, 31.66, 33.98, 41.58 (d, *J* = 128.6 Hz, CH_2P), 42.90, 43.54, 48.49 (d, *J* = 9.3 Hz, CH), 48.51 (d, *J* = 9.3 Hz, CH), 48.53 (d, *J* = 19.3 Hz, CH_2Cl), 78.62 (d, *J* = 7.5 Hz, OCH), 78.90 (d, *J* = 7.5 Hz, OCH), 193.10 [d, *J* = 6.1 Hz, C(O)]. ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 16.7.

(20) All new compounds gave satisfactory analytical data in C, H, P (or N).