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Efficient method for the asymmetric reduction of α- and β-ketophosphonates

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Abstract—An efficient and versatile method for the asymmetric reduction of α- and β-ketophosphonates using chiral reactant derived from sodium borohydride and L-(+)- or D-(−)-tartaric acid is developed. The methodology was used for the preparation of a number of biologically interesting enantiomerically pure products: including 2,3-epoxypropylphosphonate **11**, 2-hydroxy-3-aminopropylphosphonic acid **14** (phospho-GABOB), phospho-carnitine **19**, and others in multigram scale.

1. Introduction

Asymmetric reduction of prochiral ketones is the most common method used to obtain optically active hydroxy derivatives.[1] The reductions with chirally modified metal hydrides, catalytic hydrogenation in the presence of chiral metal complexes, asymmetric hydrosilylation, hydroboration, etc. are widely used for their preparation.[2]

In this work we have developed a simple method for the asymmetric reduction of C=O compounds with a reagent obtained from sodium borohydride and optically active tartaric acid (TA), which we have also applied to the reduction of ketophosphonates. The asymmetric reduction of ketophosphonates is one of the most convenient methods for the synthesis of chiral hydroxyphosphonates, which are an important class of compounds occurring in the nature.[3] Many of these compounds have attracted considerable attention in recent years for their role in biologically relevant processes such as inhibition of renin and HIV protease, human calpain I. Hydroxyphosphonates act as antibacterial, antiviral, antibiotic, and anticancer drugs.[3,4] For these reasons, many synthetic routes toward their synthesis have been developed.[4,5] Ketophosphonates were reduced to the corresponding hydroxyphosphonates by borane or catecholborane in the presence of chiral oxazaborolidine catalysts.[5,6] The reduction of ketophosphonates with chiral chlorodiisopinocampheylboranes,[7] and enantioselective hydrogenation in the presence of chiral BINAP-ruthenium(II) catalyst[8] [BINAP=2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] was also used for the preparation of hydroxyphosphonates. However, these methods require expensive reagents and special reaction conditions (such as low temperatures or high pressures), which are experimentally inconvenient.[9]

Therefore as part of our ongoing program directed toward the development of reagents for the asymmetric synthesis,[9–17] derived from readily available natural compounds, we report here a simple method for the asymmetric reduction of ketophosphonates by reducing reactant obtained from sodium borohydride and L- and D-tartaric acids.

2. Results and discussion

2.1. Synthesis of starting ketophosphonates

Two methods were used to prepare the starting *α-ketophosphonates* **1**: the one-step reaction of trialkylphosphites with aroyl chlorides (method a) and two-step method (method b) according to the reaction of dialkylphosphites with aldehydes affording racemic α-hydroxyphosphonates, which were then oxidized by pyridinium dichromate/trimethylchlorosilane with the formation of the ketophosphonates **1a–f** in 90–100% yields. The ketophosphonates **1a–d** prepared by method a were purified by column chromatography and isolated in good yields. The ketophosphonates **1a–f** prepared by method b were stereochemically pure and used without further purification (Scheme 1).

The *β-ketophosphonates* **6a–c** were prepared by a three-step one-pot procedure, from dialkyl methylphosphonates **3a** and

Keywords: Phospho-GABOB; Phospho-carnitine; Di(1*R*,2*S*,5*R*)-menthyl (*S*)-2-hydroxy-3-chloropropylphosphonate; Asymmetric reduction; Double asymmetric induction; Sodium borohydride/tartaric acid adduct.
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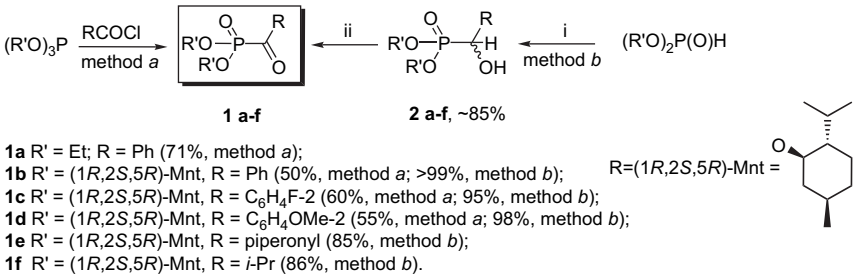


Scheme 1. Synthesis of α-ketophosphonates **1**. Reagents and conditions: method *a*: RCOCl, toluene, 0 °C; method *b*: (i) RCHO, DBU (cat.), rt, 12 h; (ii) $Py_2Cr_2O_7$/TMSCl, CH_2Cl_2, rt, 5–12 h.

b by reaction in THF with butyllithium to form carbanion **4** followed by the reaction with carboxylic acid chlorides. To decrease the effect of an undesired inter-metallation reaction between **6** and **4**, the lithium derivative **4** by reaction with the cuprous bromide was converted into cuprous derivative **5**, which reacted with acyl chlorides to give the corresponding β-ketophosphonates **6a–c** in good yields (Scheme 2).

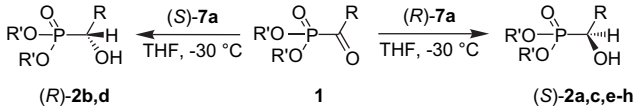
2.2. Reduction of ketophosphonates with the chiral adduct $NaBH_4$/TA

Having efficiently prepared α-ketophosphonates **1a–f** and β-ketophosphonates **6a–c**, we turned out our attention to their diastereoselective reduction to obtain α- or β-hydroxyphosphonate.

Reduction of ketophosphonates **1b–f** and **6c** with sodium borohydride in THF afforded the corresponding hydroxyphosphonates **2** with low stereoselectivity (≤30% de). Therefore for this purpose we have used chiral reactants **7a–c** prepared by addition of sodium (lithium or tetrabutylammonium) borohydrides to natural L-(+)-tartaric acid or synthetic D-(−)-tartaric acid, which were recently described by us.[12–14] These adducts were isolated as colorless high-melting solids (mp >250 °C) (M=Na and Li) or oil (M=Bu_4N) (Scheme 3).

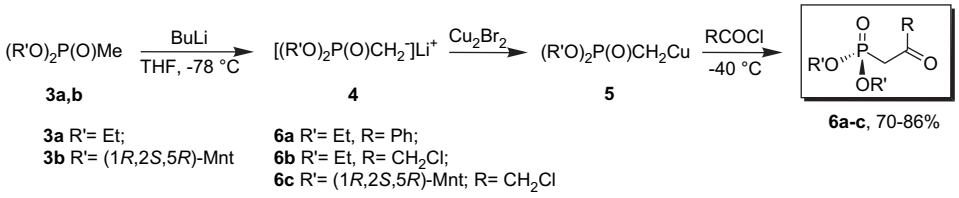
The reduction of ketophosphonates with chiral adducts of borohydrides (of sodium, tetrabutylammonium or lithium) with (*R*,*R*)-(+)-tartaric acid proceeded with higher stereoselectivity. Reagents **7a** and **c** (M=Li and Na) are more active, than **7b** (M=Bu_4N^+). The reduction of ketophosphonates with the reagents **7a** and **c** proceeded readily at −30 °C in THF, whereas the reaction with **7b** occurred only at ambient temperature or with heating. The best results in stereoselectivity were obtained with **7a**, which is also the most convenient and readily accessible.

The stereochemistry of the reduction of α- and β-ketophosphonates with **7a** depended on the absolute configuration of tartaric acid. Thus, the reduction of α-ketophosphonates **1a–f** with (*R*)-**7a** yielded α-hydroxyalkyl(aryl)phosphonates **2a**,**c**, and **e–h** of (*S*)-configuration, whereas the reduction of α-ketophosphonates **1a** and **b** with (*S*)-**7a** resulted in the formation of (*R*)-α-hydroxybenzylphosphonates **2b** and **d** (Scheme 4).

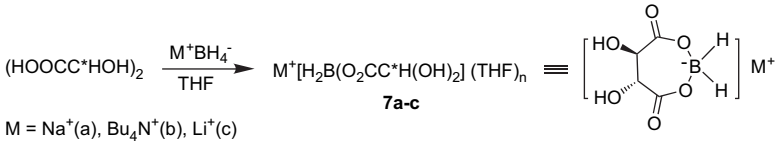


Scheme 4. Reduction of α-ketophosphonates **1** with **7a**.

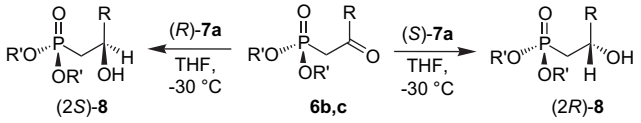
The reduction of β-ketophosphonates **6b** and **c** with (*R*)-**7a** afforded (*S*)-β-hydroxyphosphonates **8b** and **d**, and the reduction with (*S*)-**7a** yielded β-hydroxyphosphonates **8c** and **e** of (*R*)-absolute configuration at C-2 (Scheme 5). Table 1 summarizes the conditions used in the reduction and results obtained.



Scheme 2. Synthesis of β-ketophosphonates **6a–c**.



Scheme 3. The chiral reactants **7a–c**.



Scheme 5. Reduction of β-ketophosphonates **6b** and **c** with **7a**.

The reduction of dimenthyl ketophosphonates with (*R*)-**7a** proceeded with higher stereoselectivity than the reduction of diethyl ketophosphonates because of the effect of double asymmetric induction (Table 1).[14,15]

At the same time the reduction of dimenthyl aryl(alkyl)ketophosphonates **1** with (*S*)-**7a** proceeded with moderate stereoselectivity. For example, the reduction of dimenthyl benzoylphosphonate **1b** with this adduct yielded the corresponding hydroxyphosphonate **2d** only with 45% de, that is lower than that from the reaction of diethyl benzoylphosphonate **1b** with (*S*)-**7a** (60% ee).

Similar stereoselectivities and yields were obtained when the reduction of **6a–c** was carried out with (*S*)-**7a** or (*R*)-**7a** (Entries 9–13). A very good yield and diastereoselectivity of the β-hydroxyphosphonate **8d** was obtained when the β-ketophosphonate **6c** was reduced with (*R*)-**7a** at −30 °C in absolute THF (Entry 12).

Evidently, the asymmetric inductions of chiral (1*R*,2*S*,5*R*)-menthyl groups and (*R*,*R*)-tartaric acid act in one direction increasing the diastereofacial selectivity of the reagents, whereas asymmetric inductions of (1*R*,2*S*,5*R*)-menthyl groups and (*S*,*S*)-tartaric acid are mismatched and act in opposite directions decreasing the resulting stereoselectivity (Table 2).

All hydroxyphosphonates mentioned in the Table 1 were purified and isolated in optically pure form. The diethyl α- and β-hydroxyphosphonates **2a**,**b** and **8a–c** were purified by column chromatography or by crystallization, the dimenthyl hydroxyphosphonates **2c–h** and **8d** were crystallized from acetonitrile. Even dimenthyl (*R*)-α-hydroxyphosphonate **2b** (Entry 2) and (*R*)-β-hydroxyphosphonate **8e** (Entry 13), prepared by reaction of corresponding ketophosphonates with (*S*)-**7a** under the condition of mismatched double asymmetric induction (moderate stereoselectivity) were purified by crystallization from hexane and obtained with ~100 de.

Table 2. Multiple stereoselectivity in the reduction of ketophosphonates **1a**,**b** and **6b**,**c**

R′	R	TA	Stereoselectivity (ee or de, %)	Config of **2**	Asymmetric induction
Et	Ph	*R*,*R*	80	*S*	Single
Et	Ph	*S*,*S*	80	*R*	Single
Mnt	Ph	*R*,*R*	92.5	*S*	Matched double
Mnt	Ph	*S*,*S*	46	*R*	Mismatched double
Mnt	CH_2Cl	*R*,*R*	96	*S*	Matched double
Mnt	CH_2Cl	*S*,*S*	80	*R*	Mismatched double

2.3. Optical purity and absolute configuration

The optical purity of diastereomeric dimenthyl hydroxyphosphonates **2c–h** and **8d**,**e** obtained by reduction of ketophosphonates **1b–f** and **6c** was determined by ^1H and ^{31}P NMR of the crude reaction mixtures.

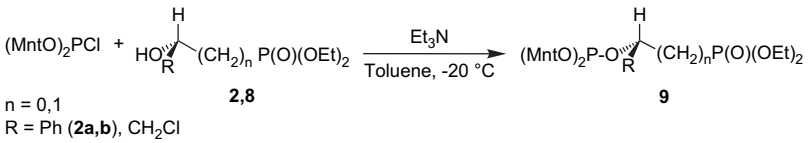
Enantiomeric purity of homochiral diethyl hydroxyphosphonates **2a**,**b** and **8b**,**c** was determined by ^{31}P NMR, using the dimenthylchlorophosphite as derivatizing reagent or cinchona alkaloids (cinchonidine and cinchonine) as chiral solvating agents.[16] These alkaloids discriminate the signals of (*R*)- and (*S*)-stereomers of hydroxyphosphonates **2** and **8** in ^1H and ^{31}P NMR spectra, give high values of $\Delta\delta$ (~0.2–0.4 ppm), allow to integrate the split signals. For example, the ^{31}P NMR spectra of **8b** in the presence of cinchonidine disclosed two signals δ_P 29.2 and 29.51 ppm in the ratio 90:10 according to the enantiomeric excess of this compound.

The optical purity of homochiral diethyl hydroxyphosphonates **2a**,**b** and **8b**,**c** was also determined by derivatization with the di(1*R*,2*S*,5*R*)-menthylchlorophosphite and conversion into diastereomers **9** according to the earlier reported methodology (Scheme 6).[17] For example, ^{31}P NMR spectra of derivatized compound **9** obtained from **2a** showed two double doublets in downfield at ~145 ppm, $^3J_{PP}$ 18 Hz and in up field at ~20 ppm, $^3J_{PP}$ 18 Hz, which provided accurate

Table 1. Asymmetric reduction of ketophosphonates $(R'O)_2P(O)(CH_2)_nC(O)R$ with $NaBH_4$/TA [(*S*)-**7a** or (*R*)-**7a**]

Entry	Compd	R	R′	*n*	TA	Yield, %	*R*/*S*[b,c]	Config[a]
1	**2a**	Ph	Et	0	*R*,*R*	95	20:80	*S*
2	**2b**	Ph	Et	0	*S*,*S*	94	80:20	*R*
3	**2c**	Ph	Mnt	0	*R*,*R*	95	3.8:96.2	*S*
4	**2d**	Ph	Mnt	0	*S*,*S*	98	73:27	*R*
5	**2e**	2-FC_6H_4	Mnt	0	*R*,*R*	97	9.8:90.1	*S*
6	**2f**	2-$MeOC_6H_4$	Mnt	0	*R*,*R*	96	13:87	*S*
7	**2g**	Piperonyl	Mnt	0	*R*,*R*	97	2:98	*S*
8	**2h**	*i*-Pr	Mnt	0	*R*,*R*	97.6	16:84	*S*
9	**8a**	Ph	Et	1	*R*,*R*	95	72:28	*R*
10	**8b**	CH_2Cl	Et	1	*R*,*R*	86	10:90	*S*
11	**8c**	CH_2Cl	Et	1	*S*,*S*	82	90:10	*R*
12	**8d**	CH_2Cl	Mnt	1	*R*,*R*	94	2:98	*S*
13	**8e**	CH_2Cl	Mnt	1	*S*,*S*	80	91:9	*R*

[a] The configuration of major enantiomer was determined by comparison of optical rotation with the literary data.
[b] Determined by ^{31}P NMR after derivatization with dimenthylchlorophosphite.
[c] Determined by ^{31}P NMR with cinchonidine as chiral solvating agent.



Scheme 6. Derivatization of diethyl hydroxyphosphonates **2** and **8** with the di(1*R*,2*S*,5*R*)-menthylchlorophosphite.

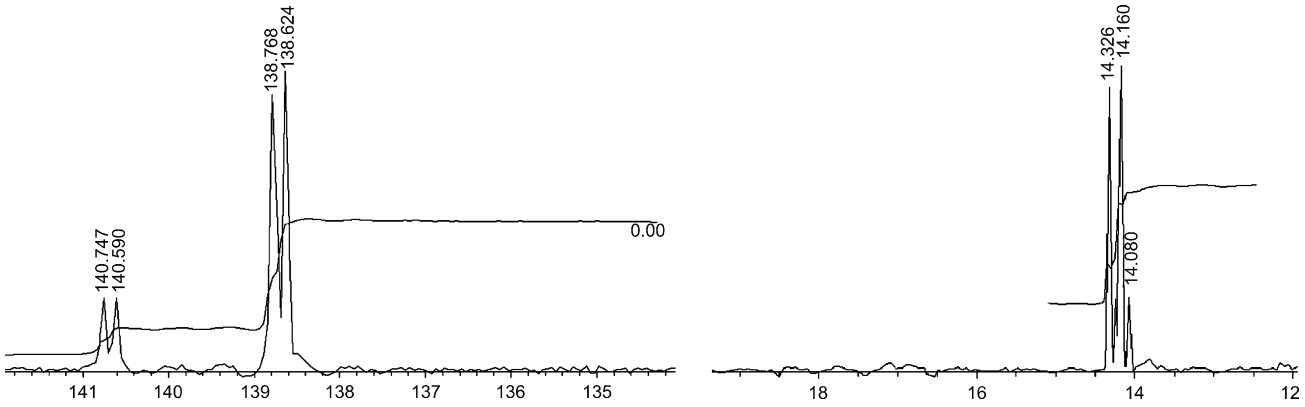
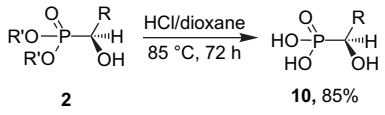


Figure 1. ^{31}P NMR spectra of the derivatized hydroxyphosphonates **9** (R=Ph, *n*=0).

integration of signals and correct measuring of their diastereomeric ratio (Fig. 1).

The absolute configurations of hydroxyphosphonates **2** were verified by chemical correlation after conversion of hydroxyphosphonates to the corresponding phosphonic acids **10** whose configuration was determined earlier (Scheme 7).[5,17]



Scheme 7. Hydrolysis of hydroxyphosphonates.

2.4. Stereochemistry of reduction

These results can be rationalized by referring to appropriate models of transition states in the reduction of ketophosphonates **1** and **6** with (*R*)-**7a**. The minimum energy conformers of α- and β-ketophosphonates were determined by applying the PC MM$^+$ method for the geometry minimization and energy assessment.[18,19] Examination of the lowest energy conformations for the ketophosphonates **1a** and **6c** showed that the nucleophilic attack of the hydride may occurs via the less hindered *Si* face, leading to the corresponding (*S*)-α-hydroxyphosphonate **2c** or (*S*)-β-hydroxyphosphonate **8d** as the major isomer (Fig. 2).

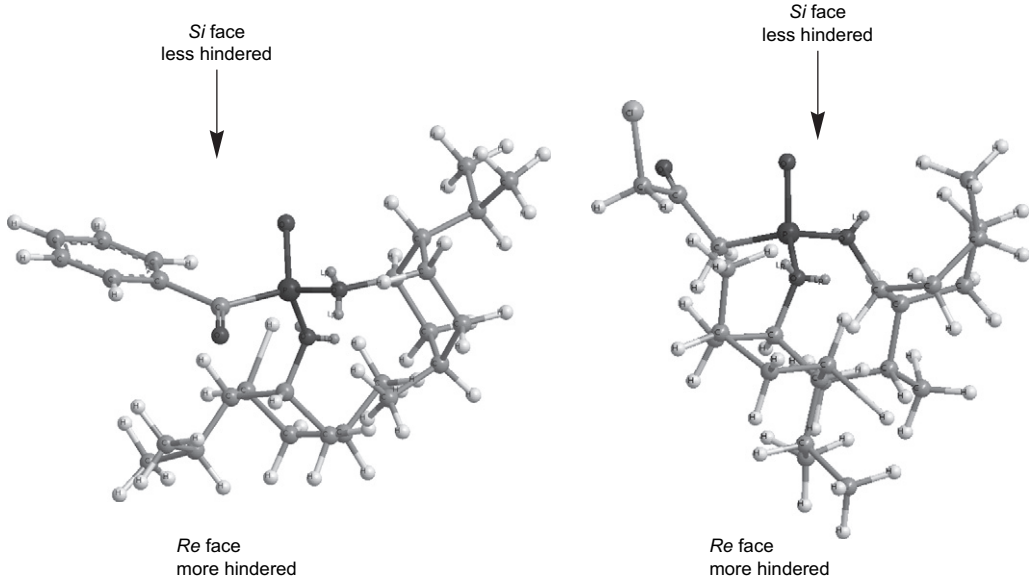


Figure 2. MM$^+$ conformations of minimum energy for α- and β-ketophosphonates **1a** and **6c**.

Since the reduction of ketophosphonates **1a**–**g** with (*R*)-**7** resulted in the formation of (*S*)-hydroxyphosphonates, it is probable that the participation of P═O group in the transition state favors the attack of the hydride ion to the *Si*-side of C═O group. These theoretical calculations are in good agreement with the experimental data, that is the observed stereoselectivities depend on the size of the RO group at the phosphorus, as has been shown with the reduction of α- and β-ketophosphonates (Table 1, Entries 1, 3, 10, and 12).

We have applied the developed methodology for the synthesis of a number of biologically important functionalized phosphonic acids, including phospho-GABOB, phosphocarnitine, phosphono-epoxides, phosphono aziridines, and 2-hydroxy-3-aminoalkylphosphonates.

2.5. Synthesis of phospho-GABOB

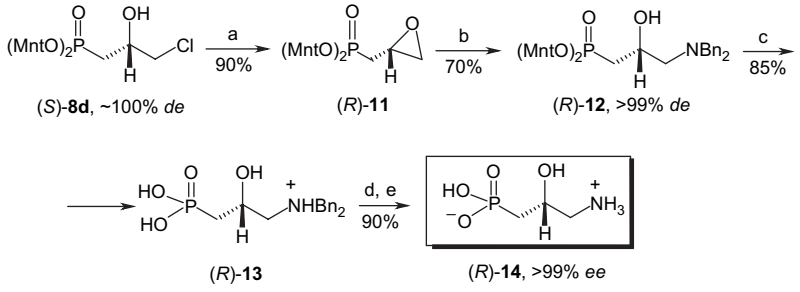
Thus, we have developed a simple method for the asymmetric synthesis of phosphonic analogue of natural 2-hydroxy-3-aminobutyric acid (GABOB), which is an important amino acid, acting as an antimimetic and hypotensive drug, and is an agonist of γ-aminobutyric acid (GABA).[20] As a neuromodulator it is effective in managing a variety of clinical conditions including schizophrenia, epilepsy, and other character-based disorders.[21] For these reasons, many synthetic routes to GABOB analogues have been developed.[22–24] Enantioselective syntheses of (*S*)-phospho-GABOB were achieved using a Baker's yeast mediated bio-reduction of diethyl 2-oxo-3-azidopropylphosphonate.[22] Wróblewski reported the synthesis of phospho-GABOB by means of the regioselective opening of the oxirane ring of diethyl (*S*)-2,3-epoxypropylphosphonate with tritylamine, followed by hydrogenolysis of the trityl group and hydrolysis of the ester group.[23] Herein, we report an efficient approach to prepare enantiomerically pure (*R*)-2-hydroxy-3-aminopropylphosphonic acid P-GABOB, which takes advantage of the highly diastereoselective reduction of β-ketophosphonates.

In the first step optically pure dimenthyl (*S*)-2-hydroxy-3-chloropropylphosphonate **8d** was treated with K_2CO_3 in acetonitrile in presence of KI to afford the optically pure epoxide (*R*)-**11** in good yield. Then the epoxide ring in the phosphonate **11** was opened regioselectively with *N*,*N*-dibenzylamine at C-3 to yield the crystalline dimenthyl (*R*)-2-hydroxy-3-(*N*,*N*-dibenzylamino)propylphosphonate **12** (Scheme 8). The 2-hydroxy-3-aminophosphonate (*R*)-**12** was hydrolyzed on heating with hydrochloric acid in dioxane to yield 2-hydroxy-3-aminopropylphosphonic acid (*R*)-**13** and without further purification was treated with hydrogen under Pd/C in methanol at 20 °C to afford the crystalline (*R*)-γ-amino-β-hydroxypropylphosphonic acid (*R*)-**14** in 74% yield and with 99% ee, that is the phosphonic analogue of naturally occurring GABOB. The crystalline compounds **8d** and **12** bearing menthyl groups were purified by crystallization from acetonitrile.

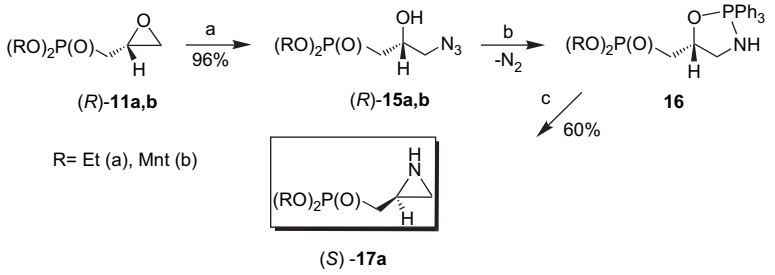
The structure of (*R*)-**14** was confirmed by elemental analysis and NMR spectroscopy, the (*R*)-absolute configuration was found from comparison of the measured values of optical rotation with published data.[23,24]

2.6. Synthesis of 2,3-aziridinopropylphosphonates

The epoxide **11** was converted consequently into azides **15a**,**b** and aziridine **17**. To the best of our knowledge, optically active 2,3-aziridinoalkylphosphonates have not been earlier reported in the literature. The diethyl (2*R*)-2,3-epoxypropylphosphonate (*R*)-**11** reacted readily with sodium azide in the presence of ammonium chloride in methanol to afford dialkyl (2*R*)-2-hydroxy-3-azidopropylphosphonate **15** (Scheme 9). The reaction of azidophosphonates **15a**,**b**



Scheme 8. Asymmetric synthesis of phospho-GABOB (*R*)-**14**. Reagents and conditions: (a) K_2CO_3, KI, CH_3CN/DMF (10:3.5), reflux, 8 h; (b) Bn_2NH, MeOH, reflux, 10 h; (c) HCl/dioxane, 80–85 °C, 72 h; (d) H_2, Pd/C, MeOH, rt; and (e) ion-exchange chromatography.



Scheme 9. Asymmetric synthesis of aziridinophosphonate (*S*)-**17**. Reagents and conditions: (a) NaN_3, NH_4Cl, MeOH, reflux, 4 h; (b) Ph_3P, toluene, rt; and (c) reflux, 1 h, $–Ph_3PO$.

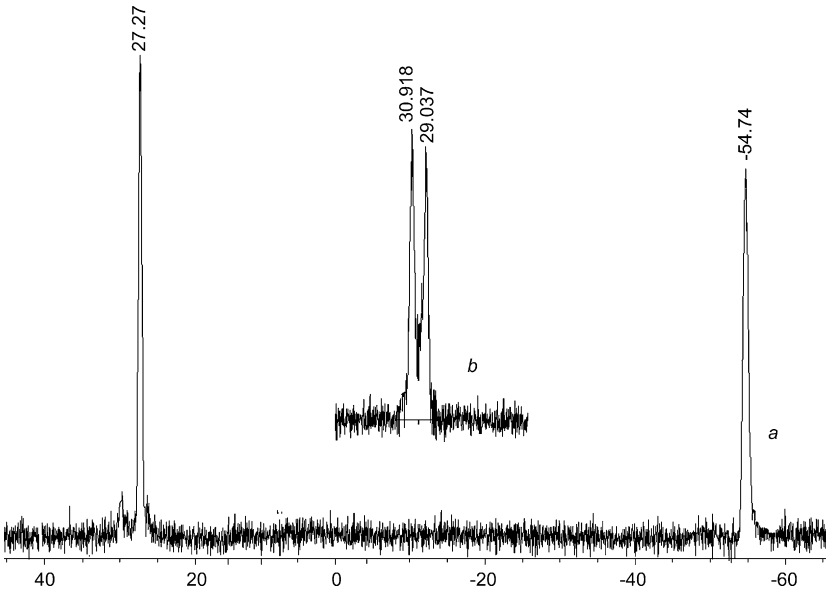


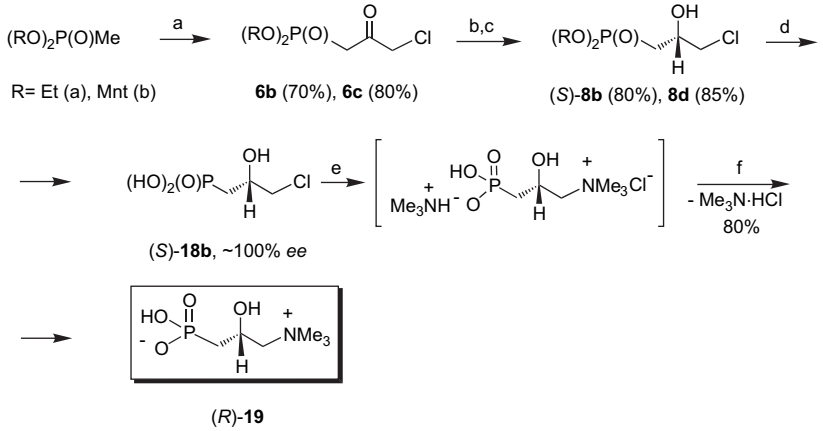
Figure 3. ^{31}P NMR monitoring (120 MHz, C_6D_6) of the reaction of azidophosphonate **15** with Ph_3P: (a) the reaction mixture in 1 h after mixing of reagents at room temperature and (b) the reaction mixture after reflux in toluene for 1 h.

with triphenylphosphine at room temperature proceeded via the formation of unstable intermediate **16** bearing pentacoordinated phosphorus. In ^{31}P NMR spectra of the intermediate **16** were found two signals: δ_P −55.1 (pentacoordinated phosphorus) and +26.9 ppm (tetracoordinated phosphorus) according to the structure of this compound. Upon heating, **16** converts into triphenylphosphine oxide (δ_P 30.2 ppm) and aziridinophosphonates **17** (δ_P 29 ppm), which were isolated in good yield. The aziridinophosphonate (*S*)-**17a** was purified by distillation under vacuum and isolated as colorless liquid (Fig. 3).

2.7. Synthesis of phospho-carnitine

The phospho-carnitine, which is phosphonate analogue of natural L-carnitine plays an important role in the transport of fatty acids into the mitochondrial matrix.[25–27] Earlier the synthesis of phospho-carnitine was performed by a chemoenzymatic method and only *in milligram scale*.[28,29] The literature data concerning the phospho-carnitine are ambiguous (compare the $[\alpha]_D$ and absolute configurations of this compound in the publications[28–30]).

We have performed the synthesis of (*R*)-phospho-carnitine *in multigram scale*, using the stereoselective reduction of 2-keto-3-chloropropylphosphonates as shown in Scheme 10. In the first step the reduction of β-ketophosphonates **6b** and **c** led to the formation of optically active 2-hydroxy-3-chloropropylphosphonates **8b** and **d**, which are precursors of (*R*)-phospho-carnitine.[31] The diethyl 2-hydroxy-3-chloropropylphosphonate **8b** was obtained with good stereoselectivity (80% ee), whereas the dimenthyl derivative **8d** was obtained with excellent stereoselectivity (96% de). The crystallization of **8d** from hexane provided the optically pure compound (~100% de). Further, the β-hydroxypropylphosphonates **8b** and **d** were treated with Me_3SiBr/EtOH or hydrolyzed with HCl in dioxane to afford the β-hydroxypropylphosphonic acids (*S*)-**18**. The free phosphonic acid **18**



Scheme 10. Asymmetric synthesis of phospho-carnitine (*R*)-**19**. Reagents and conditions: (a) BuLi, Cu_2Br_2, $ClCH_2COCl$, THF, −78 to −40 °C; (b) (*R*)-**7a**, THF, −30 °C; (c) crystallization from MeCN; (d) HCl/dioxane, 85 °C, 72 h; (e) Me_3N, 40 °C, 72 h; and (f) column chromatography.

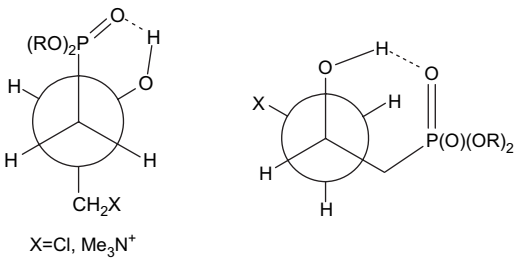


Figure 4. Conformational analysis of β-hydroxyphosphonates: (a) Newman projection relatively to C-1/C-2 bond (b) Newman projection relatively to C-2/C-3 bond.

was reacted with water solution of trimethylamine to yield the trimethylammonium salt. The reaction mixture was purified by column chromatography with silica gel to give optically pure (*R*)-phospho-carnitine (*R*)-**19** in high yield. The structure of compound **19** was confirmed by elemental analysis and NMR spectroscopy. The (*R*)-phospho-carnitine **19** is a hygroscopic crystalline compound, which decomposes on heating (>250 °C).

NMR spectra allow conformational analysis of the obtained compounds **8**, **18**, and **19** to be performed. The ^{1}H NMR spectra of β-hydroxyphosphonates disclose signals of diastereotopic protons in PCH_2 and CH_2X groups as doublet of double doublets due to spin–spin coupling with the phosphorus atom, the proton of CHOH group (vicinal constant $^{3}J_{HH}$), and due to geminal coupling $^{2}J_{HH}$. Diastereoisomeric 2-hydroxypropylphosphonates exist mainly as *anti*-conformers at the C-1/C-2 bond, as follows from the values of constants $^{2}J_{HP}$ ~18 Hz, $^{3}J_{H}1a_{H}2$ ~9.5 Hz, and $^{3}J_{H}1b_{H}2$=3.0–3.5 Hz (Fig. 4a), and as cis-conformers at the C-2/C-3 bond in agreement with the values of vicinal constants: $^{3}J_{H}2_{H}3a$ 6.9 Hz and $^{3}J_{H}2_{H}3b$ 6.6 Hz (Fig. 4b).[30]

The β-hydroxyphosphonates **8** and **19** are stabilized by the antiperiplanar disposition of the largest substituents about the C-1/C-2 bond and by the formation of the intramolecular hydrogen bond between the *H*O–C and P=*O* groups, possibly within six-membered rings, which adopt a chair conformation. In NMR spectra of these compounds the signal of hydroxyl proton is shifted to downfield 4.75–5.0 ppm because of intramolecular hydrogen bonding. Stability of the *anti*-conformers probably is higher due to formation six-membered ring with conformation approaching the chair form.

Modeling of a molecule by means of MM^{+} calculations allows the values of dihedral angles in the most energetically favorable conformations of hydroxyphosphonates **8** and **19** to be calculated.[18] These theoretical values coincide with the experimental data obtained on the basis of NMR spectra by means of Karplus equation, thus confirming our conclusions.[19]

3. Conclusion

In summary, the method of asymmetric reduction of α- and β-ketophosphonates by means of a chiral reactant obtained from the sodium borohydride and D- or L-tartaric acid is developed. The reduction of chiral di(1*R*,2*S*,5*R*)-menthyl ketophosphonates with chiral $NaBH_4$/(*R*,*R*)-TA adduct was controlled by matched double asymmetric induction to result in increased stereoselectivity and the formation of hydroxyphosphonates with ≥90% ee (de). At the same time the reduction of di(1*R*,2*S*,5*R*)-menthyl ketophosphonates with $NaBH_4$/(*S*,*S*)-TA was accompanied by mismatched double asymmetric induction decreasing the stereoselectivity and resulting in the formation of hydroxyphosphonates with ~45–80% ee (de). The methodology was applied for the preparation of a number of biologically important enantiomerically pure products: including 2-hydroxy-3-aminopropylphosphonic acid **2** (phospho-GABOB), 2,3-epoxypropylphosphonate **11**, phospho-carnitine **19**, and others in multigram scale.

4. Experimental

4.1. General

NMR measurements were recorded on a Varian VXR-300 spectrometer at 300 (^{1}H) and 121.4 (^{31}P) MHz or on a Varian Gemini2000 (400 MHz) spectrometer at 400 (^{1}H), 100.6 (^{13}C), and 161.96 (^{31}P) MHz with TMS (^{1}H, ^{13}C) as an internal standard and 85% H_3PO_4 in D_2O (^{31}P). Chemical shifts are given as δ value in parts per million with reference to TMS as an internal standard. IR spectra were recorded on Perkin–Elmer Paragon 1000 infrared spectrophotometer. For ^{1}H NMR spectra the deuterated solvents indicated were used. Polarimetric measurements were conducted on a Polax 2L apparatus (Japan). Products were purified by column chromatography on silica gel Merck 60 (60–200 mesh). TLC analysis was performed on Merck silica gel 60 F_{254} plates. Visualization of spots was effected with iodine vapors, with UV illumination and charring with 0.3% *p*-anisaldehyde in EtOH. Melting points are uncorrected. All solvents were dried by standard methods and all reactions were performed under an inert atmosphere. Tetrahydrofuran was distilled from Na/benzophenone ketyl under a nitrogen atmosphere. Tartaric acid, sodium borohydride, and (1*R*,2*S*,5*R*)-menthol were obtained from commercial firms (Fluck, Merck, and Acros).

4.2. General procedure for the preparation of α-ketophosphonates 1a–f

To a suspension of pyridinium dichromate (9.6 g, 25 mmol) in 190 mL of CH_2Cl_2 at 0–5 °C was added with stirring trimethylchlorosilane (6.43 g, 59 mmol) and after 15 min a solution of racemic dialkyl α-hydroxyalkyl(aryl)phosphonates (8.3 mmol) **2a–f** in 10 mL of CH_2Cl_2 (**2a–f** were prepared by reaction of dialkylphosphite (10 mmol) with corresponding aldehyde (10 mmol) in the presence of catalytic quantity of DBU). The reaction mixture was stirred at room temperature for 5–12 h, then filtered through a short column with silica gel and flushed with AcOEt. The solution was evaporated under reduced pressure to afford **1a–f** as colorless oils, which were purified by column chromatography using hexane/ethyl acetate.

4.2.1. Di(1*R*,2*S*,5*R*)-menthyl benzoylphosphonate 1b. Yield: ~99%, colorless oil; [found: C, 69.9; H, 9.78; P,

6.61. $C_{27}H_{43}O_4P$ requires C, 70.10; H, 9.37; P, 6.70%]; R_f (25% ethyl acetate/hexane) 0.3; $[\alpha]_D^{20}$ −62 (*c* 1.5, $CHCl_3$); ν_{max} (liquid film) 2959, 1661, 1456, 1252, 993 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35 (5H, m, C_6H_5), 4.15 (2H, dt, *J* 4.1, 2.3 Hz, 2OCH), 2.2–1.1 (18H, m, CH_2 and CH), 1.0–0.7 (18H, m, CH_3); δ_C (100.6 MHz, $CDCl_3$) 199.28 (d, *J* 178.3 Hz), 136.04 (d, *J* 64.5 Hz), 133.93, 129.74 (d, *J* 1.3 Hz), 128.34 (d, *J* 0.8 Hz), 79.85 (d, *J* 8.2 Hz), 79.82 (d, *J* 8.2 Hz), 48.61 (d, *J* 6.2 Hz), 48.55 (d, *J* 6.2 Hz), 43.54, 42.91, 34.02, 34.02, 31.69, 31.66, 25.60, 25.50, 22.98, 22.95, 21.86, 21.83, 20.93, 20.90, 15.75, 15.65; δ_P (121.4 MHz, $CDCl_3$) −2.3.

4.2.2. Di(1*R*,2*S*,5*R*)-menthyl 2-fluorobenzoylphosphonate 1c. Yield: 95%, colorless oil; [found: C, 67.45; H, 8.71; P, 6.38. $C_{27}H_{42}O_4P$ requires C, 67.48; H, 8.81; P, 6.44%]; R_f (20% ethyl acetate/hexane) 0.4; $[\alpha]_D^{20}$ −72 (*c* 1, toluene); δ_H (300 MHz, $CDCl_3$) 7.4 (4H, m, C_6H_4), 4.0 (2H, dt, *J* 4.1, 2.3 Hz, OCH), 2.0–0.8 (18H, m, CH_2+CH), 0.9–0.6 (18H, m, CH_3); δ_P (121.4 MHz, $CDCl_3$) −3.1.

4.2.3. Di(1*R*,2*S*,5*R*)-menthyl 2-methoxybenzoylphosphonate 1d. Yield: 98%, colorless oil; [found: C, 68.25; H, 9.18; P, 6.25. $C_{28}H_{45}O_5P$ requires C, 68.27; H, 9.21; P, 6.29%]; R_f (25% ethyl acetate/hexane) 0.33; $[\alpha]_D^{20}$ −65 (*c* 1.5, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.2–7.0 (m, C_6H_4), 6.8–6.6 (4H, m, C_6H_4), 4.15 (2H, dt, *J* 4.1, 2.3 Hz, 2OCH), 3.9 (3H, s, OCH_3), 2.2–1.1 (18H, m, CH_2+CH), 1.0–0.7 (18H, m, CH_3); δ_P (121.4 MHz, $CDCl_3$) −3.5; δ_C (100.6 MHz, $CDCl_3$) 199.28 (d, *J* 170 Hz), 136.04 (d, *J* 64 Hz), 133.93, 129.74 (d, *J* 1.3 Hz), 128.34 (d, *J* 0.8 Hz), 79.85 (d, *J* 8.2 Hz), 79.82 (d, *J* 8.2 Hz), 55, 48.61 (d, *J* 6.2 Hz), 48.55 (d, *J* 6.2 Hz), 43.8, 34.09, 33.9, 31.5, 25.24, 22.7, 21.97, 21.87, 21.21, 21.05, 15.72, 15.62.

4.2.4. Di(1*R*,2*S*,5*R*)-menthyl piperonoylphosphonate 1e. Yield: 85%, colorless oil; [found: C, 66.24; H, 9.02; P, 6.09. $C_{28}H_{43}O_6P$ requires C, 66.38; H, 8.56; P, 6.11%]; R_f (25% ethyl acetate/hexane) 0.51; $[\alpha]_D^{20}$ −63.8 (*c* 5.48, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 8.25 (1H, d, *J* 10 Hz, C_6H_3), 6.75 (1H, d, *J* 10 Hz, C_6H_3), 7.66 (1H, s, C_6H_3), 5.8 (2H, s, O_2CH_2), 4.15 (2H, dt, *J* 4.1, 2.3 Hz, 2OCH), 2.2–1.1 (18H, m, CH_2+CH), 1.0–0.7 (18H, m, CH_3); δ_P (121.4 MHz, $CDCl_3$) −1.8.

4.2.5. Di(1*R*,2*S*,5*R*)-menthyl 2-methylpropionylphosphonate 1f. Yield: 86%, colorless oil; [found: C, 67.18; H, 10.41; P, 7.18. $C_{24}H_{45}O_4P$ requires C, 67.26; H, 10.58; P, 7.23%]; R_f (10% ethyl acetate/hexane) 0.42; $[\alpha]_D^{20}$ −90.4 (*c* 0.75, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 4.2 (2H, dt, *J* 4.1, 2.3 Hz, 2OCH), 3.15 (1H, m, C*H*CH_3), 2.2–1.1 (18H, m, CH_2+CH), 1.06 (3H, d, *J* 3.3 Hz, CH(C*H*$_3$)$_2$), 1.04 (3H, d, *J* 3.3 Hz, CH(C*H*$_3$)$_2$), 1.0–0.7 (18H, m, CH_3); δ_P (121.4 MHz, $CDCl_3$) −3.4.

4.3. General procedure for the preparation of β-ketophosphonates 6a–c

A solution of butyllithium (1.84 M, 0.1 mol) in hexane was cooled to −78 °C and mixed with 60 mL of anhydrous THF before the slow addition of dialkyl methylphosphonate **3a** and **b** (0.1 mol) in 30 mL of THF. The resultant solution was stirred at −78 °C for 20 min, then Cu_2Br_2 (0.1 mol) was added and the reaction mixture was stirred at −60 to −30 °C for 0.5 h and then at −30 °C for 1 h. After that acylchloride (0.1 mol) in 30 mL of THF was added at −40 °C. The reaction mixture was stirred at −40 to −30 °C for 2 h and was left overnight at this temperature. Then 70 mL of water was added to the mixture, the precipitate was separated, and extracted with chloroform (2×50 mL). The combined organic extracts were treated first with water (2×30 mL), then with aqueous solution of Na_2CO_3 (2×30 mL) and water (2×25 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by distillation under vacuum or crystallization.

4.3.1. Diethyl 2-oxo-2-phenylethylphosphonate 6a. Yield: 86%, colorless viscous liquid, bp 140 °C (0.2 mmHg); δ_P (121.4 MHz, $CDCl_3$) 29, that corresponds to the earlier described compound.[6]

4.3.2. Diethyl 2-oxo-3-chloropropylphosphonate 6b. Yield: 70%, colorless viscous liquid, bp 94–95 °C (0.07 mmHg); ν_{max} (liquid film) 2985, 1725, 1396, 1257, 1027, 969 cm^{-1}; δ_P (121.4 MHz, $CDCl_3$) 18.8, that corresponds to the earlier described compound.[22]

4.3.3. Di(1*R*,2*S*,5*R*)-(−)-menthyl 2-oxo-3-chloropropylphosphonate 6c.

4.3.3.1. Di(1*R*,2*S*,5*R*)-menthyl methylphosphonate 3b. To a solution of (1*R*,2*S*,5*R*)-menthol (8.74 g, 55.9 mmol) and pyridine (4.53 mL, 55.9 mmol) in 20 mL of dried toluene was added dropwise with stirring a solution of methyldichlorophosphine oxide (3.7 g, 27.8 mmol) in 20 mL of toluene. The mixture was stirred at 90 °C for 10 h, then was filtered and the mother liquor was washed with a saturated aqueous solution of Na_2CO_3 (2×10 mL), water (15 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated, the residue was distilled under vacuum to give the *title compound* **3b** (8.81 g, 85%) as a colorless viscous liquid, bp 137 °C (0.06 mmHg); [found: C, 67.68; H, 11.04; P, 8.29. $C_{21}H_{41}O_3P$ requires C, 67.71; H, 11.09; P, 8.31%]; $[\alpha]_D^{20}$ −78.8 (*c* 17.8, $CHCl_3$); δ_H (300 MHz, C_6D_6), 4.02 (2H, m, 2OCH), 2.15–0.9 (16H, m, CH_2 and CH), 1.98 (1H, m, C*H*$(CH_3)_2$), 1.83 (3H, s, CH_3), 1.52 (1H, m, C*H*$(CH_3)_2$), 0.82 (12H, m, CH_3), 0.73 (3H, d, *J* 6.9 Hz, CH_3), 0.72 (3H, d, *J* 6.9 Hz, CH_3); δ_P (121.4 MHz, $CDCl_3$) 29.2.

4.3.3.2. Synthesis of 6c. The ketophosphonate **6c** was obtained in 80% yield as a white solid after crystallization from *i*-PrOH/H_2O, mp 65.5–65.6 °C; [found: C, 61.5; H, 9.57; Cl, 7.77; P, 6.88. $C_{23}H_{42}ClO_4P$ requires C, 61.52; H, 9.43; Cl, 7.9; P, 6.9%]; $[\alpha]_D^{20}$ −78 (*c* 1, $CHCl_3$); ν_{max} (liquid film) 2960, 1725, 1456, 1256, 1001, 992 cm^{-1}; δ_H (300 MHz, C_6D_6) 4.07 (2H, m, 2OCH), 4.04 (2H, s, CH_2Cl), 3.04 (2H, d, *J* 23.5, PCH_2), 1.94 (1H, m, C*H*$(CH_3)_2$), 1.52 (1H, m, C*H*$(CH_3)_2$), 2.1–0.9 (16H, m, CH_2 and CH), 0.93 (3H, d, *J* 7 Hz, CH_3), 0.91 (3H, d, *J* 7 Hz, CH_3), 0.90 (3H, d, *J* 7 Hz, CH_3), 0.89 (3H, d, *J* 7 Hz, CH_3), 0.81 (3H, d, *J* 7 Hz, CH_3), 0.79 (3H, d, *J* 7 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 193.10 (d, *J* 6.1 Hz), 78.90 (d, *J* 7.5 Hz), 78.62 (d, *J* 7.5 Hz), 48.53 (d, *J* 19.3 Hz), 48.51 (d, *J* 9.3 Hz), 48.49 (d, *J* 9.3 Hz), 43.54, 42.90, 41.58 (d, *J* 128.6 Hz), 33.98, 31.66, 31.58, 25.65, 25.53, 22.95, 22.88, 21.85, 21.85, 20.99, 20.93, 15.81, 15.64; δ_P (121.4 MHz, $CDCl_3$) 16.7.

4.4. General procedure for the reduction of ketophosphonates 1a–f with $NaBH_4$/(*R*,*R*)-TA adduct

To a suspension of sodium borohydride (0.36 g, 10 mmol) in 50 mL of THF was added (*R*,*R*)-(+)-tartaric acid (1.5 g, 10 mmol), then the reaction mixture was refluxed for 4 h. After that a solution of ketophosphonate (2.5 mmol) in 10 mL of THF was added at −30 °C and the reaction mixture was stirred at this temperature for 24 h. Then to the reaction mixture was added 20 mL of ethyl acetate and 30 mL of 1 N hydrochloric acid dropwise. The organic layer was separated, the aqueous phase was saturated with NaCl and extracted two times with ethyl acetate (15 mL). The organic extracts were washed with a saturated solution of Na_2CO_3 (3×20 mL) and dried with Na_2SO_4. The solvent was removed under vacuum, the residue was crystallized from acetonitrile.

4.4.1. Diethyl (*S*)-hydroxy(phenyl)methylphosphonate 2a (Table 1, entry 1). Yield: 95%, white solid, mp 74–76 °C; [found: C, 54.08; H, 6.98; P, 12.66. $C_{11}H_{17}O_4P$ requires C, 54.10; H, 7.02; P, 12.68%]; $[\alpha]_D^{20}$ −15.4 (*c* 2.6, $CHCl_3$); δ_H (300 MHz, C_6D_6) 7.49 (2H, m, Ph), 7.3–7.38 (3H, m, Ph), 5.01 (1H, d, *J* 10.9 Hz, C*H*OH), 3.90–4.13 (4H, m, $2CH_2$), 3.8 (1H, br, OH), 1.26 (3H, t, *J* 7.1 Hz, CH_3), 1.21 (3H, t, *J* 7.1 Hz, CH_3); δ_P (121.4 MHz, $CDCl_3$) 22.00.[5]

4.4.2. Diethyl (*R*)-hydroxy(phenyl)methylphosphonate 2b (Table 1, entry 2). Yield: 94%, white solid, mp 74–76 °C; $[\alpha]_D^{20}$ +28.3 (*c* 2.1, $CHCl_3$), that corresponds to.[32a]

4.4.3. Di(1*R*,2*S*,5*R*)-menthyl (*S*)-hydroxy(phenyl)methylphosphonate 2d (Table 1, entry 3). Yield: 80%, white solid, mp 112–113 °C (MeCN); [found: C, 69.53; H, 9.80; P, 6.38. $C_{27}H_{45}O_4P$ requires C, 69.80; H, 9.76; P, 6.67%]; $[\alpha]_D^{20}$ −87.6 (*c* 1.3, $CHCl_3$); δ_H (300 MHz, C_6D_6) 7.8 (2H, m, Ph), 7.48 (3H, m, Ph), 5.2 (1H, d, *J* 10.5 Hz, CHP), 5.10 (1H, br, OH), 4.49 (2H, m, 2OCH), 2.6–1.40 (14H, m, CH_3 and CH), 2.4 (1H, m, $CH(CH_3)_2$), 2.00 (1H, m, $CH(CH_3)_2$), 1.21 (3H, d, *J* 6.9 Hz, CH_3), 1.20 (3H, d, *J* 6.9 Hz, CH_3), 1.18 (3H, d, *J* 6.9 Hz, CH_3), 1.08 (3H, d, *J* 6.9 Hz, CH_3), 1.01 (3H, d, *J* 6.9 Hz, CH_3), 1.04 (3H, d, *J* 6.9 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 127.98 (d, *J* 2.5 Hz), 127.8 (d, *J* 2.5 Hz), 127.4 (d, *J* 9.6 Hz), 71.8 (d, *J* 160 Hz), 48.4 (d, *J* 14 Hz), 48.3 (d, *J* 13.2 Hz,), 45.66, 42.53, 34.01, 31.5, 25.33, 22.7, 21.98, 21.13, 21.03, 15.73, 15.61; δ_P (121.4 MHz, $CDCl_3$) 22.3.

4.4.4. Di(1*R*,2*S*,5*R*)-menthyl (*R*)-hydroxy(phenyl)methylphosphonate 2c (Table 1, entry 4). Yield: 95%, white solid, mp 139 °C (hexane); [found: C, 69.75; H, 9.60; P, 6.56. $C_{27}H_{45}O_4P$ requires C, 69.80; H, 9.76; P, 6.67%]; $[\alpha]_D^{20}$ −70 (*c* 1.07, $CHCl_3$); δ_H (300 MHz, C_6D_6) 7.5–7.3 (2H, m, Ph), 7.3–7.2 (3H, m, Ph), 4.92 (1H, d, *J* 11 Hz, CHP), 4.2 (2H, dt, *J* 4.1, 2.3 Hz, 2OCH), 3.7 (1H, br, OH), 1.23–1.1 (18H, m, CH_2+CH), 1.0–0.7 (18H, m, CH_3); δ_C (100.6 MHz, $CDCl_3$) 127.99 (d, *J* 2.5 Hz), 127.8 (d, *J* 2.5 Hz), 127.3 (d, J_{CP} 9.6 Hz), 71.6 (d, *J* 160 Hz), 48.6 (d, *J* 14 Hz), 48.5 (d, *J* 13.2 Hz), 45.66, 42.53, 34.00, 31.5, 25.31, 22.7, 21.97, 21.13, 21.03, 15.74, 15.60; δ_P ($CDCl_3$) 23.71.

4.4.5. Di(1*R*,2*S*,5*R*)-menthyl (*S*)-hydroxy(2-fluorophenyl)methylphosphonate 2e (Table 1, entry 5). Yield: 97%, white solid, mp 137.5–138.5 °C (MeCN); [found: C, 67.00; H, 9.20; P, 6.38. $C_{27}H_{44}FO_4P$ requires C, 67.20; H, 9.19; P, 6.42%]; $[\alpha]_D^{20}$ −83.7 (*c* 1.3, $CHCl_3$); δ_H (300 MHz, C_6D_6) 7.45 (2H, m, C_6H_4), 6.9 (3H, t, *J* 8.2, C_6H_4), 5.18 (1H, br, OH), 4.2 (2H, m, OCH), 4.04 (1H, d, *J* 22.5 Hz, CHP), 2.25–1.00 (14H, m, CH_3 and CH), 2.0 (1H, m, C*H*$(CH_3)_2$), 1.74 (1H, m, C*H*$(CH_3)_2$), 0.91 (3H, d, *J* 6.9 Hz, CH_3), 0.86 (6H, d, *J* 6.9 Hz, CH_3), 0.76 (6H, d, *J* 6.9 Hz, CH_3), 0.71 (3H, d, *J* 6.9 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 164.2, 164.1, 161.6, 161.5, 130.7, 130.4, 130.3, 130.2, 125.8, 116.4, 116.1, 114.2, 114.4, 72.4, 70.8, 49.3, 49.16, 49.0, 48.3, 45.7, 42.5, 34.0, 31.5, 25.3, 22.7, 22.0, 21.1, 21.0, 15.7, 15.6; δ_P (121.4 MHz, $CDCl_3$) 19.8.

4.4.6. Di(1*R*,2*S*,5*R*)-menthyl (*S*)-hydroxy(2-methoxyphenyl)methylphosphonate 2f (Table 1, entry 6). Yield: 74%, white solid, mp 116–117 °C (MeCN); [found: C, 68.16; H, 9.50; P, 6.25. $C_{28}H_{47}O_5P$ requires C, 67.99; H, 9.58; P, 6.26%]; $[\alpha]_D^{20}$ −75.2 (*c* 0.66, $CHCl_3$); δ_H (300 MHz, C_6D_6) 7.60 (1H, d, *J* 7.5 Hz, C_6H_4), 7.04 (1H, t, *J* 7.9 Hz, C_6H_4), 6.80 (1H, t, *J* 7.9 Hz, C_6H_4), 6.59 (1H, d, *J* 8.1 Hz, C_6H_4), 5.24 (1H, d, *J* 13.2 Hz, CHP), 4.54 (1H, br, OH), 4.17 (1H, m, OCH), 4.03 (1H, m, OCH), 3.59 (3H, s, OCH_3), 2.40 (1H, m, C*H*$(CH_3)_2$), 2.14 (1H, m, C*H*$(CH_3)_2$), 1.54–0.92 (14H, m, CH_2 and CH), 0.84 (3H, d, *J* 6.9 Hz, CH_3), 0.79 (6H, m, $2CH_3$), 0.73 (3H, d, *J* 6.9 Hz, CH_3), 0.52 (3H, d, *J* 6.9 Hz, CH_3), 0.60 (3H, d, *J* 6.9 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 157.10 (d, *J* 6.5 Hz), 129.00 (d, *J* 2.8 Hz), 128.8 (d, *J* 2.8 Hz), 128.8 (d, *J* 2.0 Hz), 125.3 (d, *J* 5.5 Hz), 120.6 (d, *J* 2.0 Hz), 110.5, 66.6 (d, *J* 161 Hz), 55 (s), 48.8 (d, *J* 35 Hz), 48.5 (d, *J* 34 Hz), 43.8, 34.09, 33.9, 31.5, 25.24, 22.7, 21.97, 21.87, 21.21, 21.05, 15.72, 15.62; δ_P (121.4 MHz, $CDCl_3$) 20.98.

4.4.7. Di(1*R*,2*S*,5*R*)-menthyl (*S*)-hydroxy(piperonyl)methylphosphonate 2g (Table 1, entry 7). Yield: 70%, white solid, mp 96 °C (MeCN); [found: C, 66.17; H, 8.83; P, 6.14. $C_{28}H_{45}O_6P$ requires C, 66.12; H, 8.92; P, 6.09%]; $[\alpha]_D^{20}$ −74 (*c* 1, $CHCl_3$); δ_H (300 MHz, C_6D_6) 6.98 (1H, s, C_6H_3), 6.85 (1H, d, *J* 7.9 Hz, C_6H_3), 6.57 (1H, d, *J* 7.9 Hz, C_6H_3), 5.65 (2H, s, O_2CH_2), 5.38 (1H, br, OH), 4.7 (1H, d, *J* 10.5 Hz, CHP), 4.09 (2H, m, OCH), 1.94 (1H, m, C*H*$(CH_3)_2$), 1.48 (1H, m, C*H*$(CH_3)_2$), 2.27–0.9 (16H, m, CH_2 and CH), 0.81 (3H, d, *J* 6.9 Hz, CH_3), 0.77 (3H, d, *J* 6.9 Hz, CH_3), 0.76 (3H, d, *J* 6.9 Hz, CH_3), 0.67 (3H, d, *J* 6.9 Hz, CH_3), 0.66 (3H, d, *J* 6.9 Hz, CH_3), 0.62 (3H, d, *J* 6.9 Hz, CH_3); δ_P (121.4 MHz, $CDCl_3$) 19.8.

4.4.8. Di(1*R*,2*S*,5*R*)-menthyl (*S*)-hydroxy(isopropyl)methylphosphonate 2h (Table 1, entry 8). Yield: 97.6%, white solid, mp 71 °C (MeCN); [found: C, 66.90; H, 10.93; P, 7.18. $C_{24}H_{47}O_4P$ requires C, 66.94; H, 11.0; P, 7.19%]; $[\alpha]_D^{20}$ −82.8 (*c* 2.2, $CHCl_3$); δ_H (300 MHz, C_6D_6) 4.09 (2H, m, 2OCH), 3.33 (1H, m, C*H*OH), 2.3–0.87 (18H, m, CH_2 and CH), 1.94 (1H, m, C*H*$(CH_3)_2$), 0.97 (3H, d, *J* 6.3 Hz, CH(C*H*$_3)_2$), 0.95 (3H, d, *J* 6.3 Hz, CH(C*H*$_3)_2$), 0.73–0.84 (18H, m, CH_3); δ_P (121.4 MHz, $CDCl_3$) 24.04.

4.4.9. Diethyl (*R*)-2-hydroxy-2-phenylethylphosphonate 8a (Table 1, entry 9). Yield: 95%, yellow oil; [found: C, 55.86; H, 7.47; P, 11.90. $C_{12}H_{19}O_4P$ requires C, 55.81; H, 7.42; P, 11.99%]; $[\alpha]_D^{20}$ −25 (*c* 2.38, $CHCl_3$); δ_H (300 MHz, C_6D_6) 7.28 (2H, d, *J* 7.2 Hz, C_6H_5), 7.14 (2H, t, *J* 7.2 Hz, C_6H_5), 7.05 (1H, t, *J* 7.2 Hz, C_6H_5), 5.06–4.96 (1H, m, C*H*OH), 4.75 (1H, br, OH), 3.99–3.77 (4H, m, $2CH_2$),

2.12–1.90 (2H, m, CH_2), 1.11 (3H, t, *J* 6.9 Hz, CH_3), 1.10 (3H, t, *J* 6.9 Hz, CH_3); δ_P (121.4 MHz, $CDCl_3$) 29.6.[8a,32b]

4.4.10. Diethyl (*S*)-(−)-2-hydroxy-3-chloropropylphosphonate 8b (Table 1, entry 10). Yield: 85%, yellow oil; [found: C, 36.2; H, 6.4; P, 13.50. $C_7H_{16}ClO_4P$ requires C, 36.46; H, 6.99; P, 13.43%]; $[\alpha]_D^{20}$ −12.42 (*c* 3.22, $CHCl_3$); δ_H (300 MHz, C_6D_6) 4.62 (1H, m, OH), 3.96 (5H, m, CH_2O+C*H*OH), 3.44 (1H, ddd, *J* 10.8, 4.4, 3.4 Hz, C^bHCl), 3.26 (1H, dd, *J* 10.8, 7.2 Hz, C^aHCl), 2.02 (1H, ddd, *J* 18.9, 15.3, 3.4 Hz, PC^bH), 1.79 (1H, ddd, *J* 17.1, 15.3, 9.4 Hz, PC^aH), 1.18 (6H, t, *J* 7.2 Hz, CH_3CH_2); δ_P (121.4 MHz, $CDCl_3$) 29.4, that corresponds to.[12,13]

4.4.11. Diethyl (*R*)-(+)-2-hydroxy-3-chloropropylphosphonate 8c (Table 1, entry 11). Yield: 85%, yellow oil; [found: C, 36.27; H, 6.54; P, 13.51. $C_7H_{16}ClO_4P$ requires C, 36.46; H, 6.99; P, 13.43%]; $[\alpha]_D^{20}$ +12.4 (*c* 3.2, $CHCl_3$); δ_H (300 MHz, C_6D_6) 4.62 (1H, m OH), 3.96 (5H, m, CH_2O+C*H*OH), 3.44 (1H, ddd, *J* 10.8, 4.4, 3.4 Hz, C^bHCl), 3.26 (1H, dd, *J* 10.8, 7.2 Hz, C^aHCl), 2.02 (1H, ddd, *J* 18.9, 15.3, 3.4 Hz, PC^bH), 1.79 (1H, ddd, *J* 17.1, 15.3, 9.4 Hz, PC^aH), 1.18 (6H, t, *J* 7.2 Hz, CH_3CH_2); δ_P (121.4 MHz, $CDCl_3$) 29.4, that corresponds to.[12]

4.4.12. Di(1*R*,2*S*,5*R*)-menthyl (*S*)-(−)-2-hydroxy-3-chloropropylphosphonate 8d (Table 1, entry 12). (*R*,*R*)-Tartaric acid (7.49 g, 50 mmol) was added to a suspension of $NaBH_4$ (1.89 g, 50 mmol) in 270 mL of absolute THF and then the reaction mixture was refluxed with stirring for 4 h. The reaction mixture was cooled up to −30 °C, the solution of di(1*R*,2*S*,5*R*)-menthyl 2-oxo-3-chloropropylphosphonate **6c** (5.6 g, 12.5 mmol) in 30 mL of THF was added and the mixture was left overnight at −30 °C with stirring. Then 70 mL of ethyl acetate and 60 mL of 1 N hydrochloric acid were added consecutively to the mixture. The organic phase was separated and the aqueous layer was saturated with NaCl and extracted with ethyl acetate (2×25 mL). The combined organic extracts were washed with saturated solution of sodium carbonate (3×60 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue (5.3 g, 95%) was crystallized from acetonitrile to give the *title compound* **8d** (~99% de) as a colorless solid, mp 86.2 °C; [found: C, 61.28; H, 9.86; P, 6.88. $C_{23}H_{44}ClO_4P$ requires C, 61.25; H, 9.83; P 6.87%]; $[\alpha]_D^{20}$ −97.16 (*c* 3, $CHCl_3$); δ_H (300 MHz, C_6D_6) 4.44 (1H, br, OH), 4.15 (1H, m, C*H*OH), 4.10–3.9 (2H, m, OCH), 3.43 (1H, ddd, *J* 10.8, 4.7, 2.8 Hz, CH^bCl), 3.29 (1H, dd, *J* 10.8, 6.7 Hz, CH^aCl), 1.96 (1H, m, $CH(CH_3)_2$), 1.97 (1H, m, CH^bP), 1.73 (1H, m, CH^aP), 1.53 (1H, m, $CH(CH_3)_2$), 2.18–0.88 (17H, m, CH_2+CH), 0.84–0.81 (12H, m, CH_3), 0.76 (3H, d, *J* 6.9 Hz, CH_3), 0.71 (3H, d, *J* 6.9 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 78.36 (d, *J* 7.5 Hz), 78.33 (d, *J* 7.5 Hz), 67.29 (d, *J* 3.6 Hz), 49.36 (d, *J* 18.2 Hz), 49.08 (d, *J* 6.5 Hz), 49.07 (d, *J* 6.5 Hz), 44.13, 43.62, 34.49, 34.49, 32.64 (d, *J* 141.2 Hz), 32.01, 31.98, 26.12, 26.00, 23.43, 23.40, 22.25, 22.24, 21.41, 21.34, 16.37, 16.13; δ_P (161.96 MHz, $CDCl_3$) 28.81.

4.4.13. Di(1*R*,2*S*,5*R*)-menthyl (*R*)-(−)-2-hydroxy-3-chloropropylphosphonate 8e (Table 1, entry 13). Compound **8e** was prepared analogously to **8d** by reduction with $NaBH_4$ and (*S*,*S*)-tartaric acid. Yield: 80% as a colorless solid after crystallization from hexane, mp 76.5 °C; [found: C, 61.27; H, 9.86; P, 6.88. $C_{23}H_{44}ClO_4P$ requires C, 61.25; H, 9.83; P, 6.87%]; $[\alpha]_D^{20}$ −64.3 (*c* 2, $CHCl_3$); δ_H (300 MHz, C_6D_6) 4.25 (1H, br, OH), 3.95 (1H, m, C*H*OH), 4.05–3.9 (2H, m, OCH), 3.43 (1H, ddd, *J* 10.8, 4.4, 3.4 Hz, CH^bCl), 3.29 (1H, dd, *J* 10.8, 7.4 Hz, CH^aCl), 1.96 (1H, m, $CH(CH_3)_2$), 1.97 (1H, m, CH^bP), 1.71 (1H, ddd, *J* 15.7, 15.5, 9.1 Hz, CH^aP), 1.53 (1H, m, $CH(CH_3)_2$), 2.18–0.88 (17H, m, CH_2+CH), 0.84–0.81 (12H, m, CH_3), 0.73 (3H, d, *J* 6.9 Hz, CH_3), 0.72 (3H, d, *J* 6.9 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 78.37 (d, *J* 7.5 Hz), 78.34 (d, *J* 7.5 Hz), 67.29 (d, *J* 3.6 Hz), 49.36 (d, *J* 18.2 Hz), 49.08 (d, *J* 6.5 Hz), 49.07 (d, *J* 6.5 Hz), 44.13, 43.62, 34.49, 34.49, 32.61 (d, *J* 141.2 Hz), 32.01, 31.98, 26.12, 26.00, 23.41, 23.40, 22.25, 22.24, 21.41, 21.34, 16.36, 16.13; δ_P (161.96 MHz, $CDCl_3$) 28.75.

4.5. (−)-(*S*)-1-Phenyl(1-hydroxy)methylphosphonic acid 10a

To a solution of hydroxyphosphonate **2a** (1.15 g, 2.5 mmol) in 50 mL of dioxane was added 25 mL of 6 N hydrochloric acid. The reaction mixture was left for 3 days at 80 °C. The course of reaction was monitored by ^{31}P NMR spectroscopy. When the reaction was complete, the solvent was evaporated, the residue was dissolved in ethanol and an excess of cyclohexylamine (~1.5 mL) was added. The dicyclohexylammonium salt was filtered off. Yield: 50%, colorless solid, mp 226 °C; δ_P (121.4 MHz, D_2O) 16.1; $[\alpha]_D^{20}$ −14.0 (*c* 1, MeOH/water 1:1) corresponds to the (*S*)-configuration of **10a**.[12,32c]

4.6. The preparing of phospho-GABOB

4.6.1. Di(1*R*,2*S*,5*R*)-menthyl (2*R*)-(oxirane-2-yl)methylphosphonate 11. To a stirred solution of di(1*R*,2*S*,5*R*)-menthyl (2*S*)-3-chloro-2-hydroxypropylphosphonate **8d** (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. Then the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (60 mL), washed with water (2×15 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the *title compound* **11** (4.05 g, 90%) as a colorless oil; [found: C, 66.34; H, 10.27; P, 7.11. $C_{23}H_{43}O_4P$ requires C, 66.64; H, 10.45; P, 7.47%]; $[\alpha]_D^{20}$ −62.4 (*c* 7.0, $CHCl_3$); δ_H (300 MHz, C_6D_6) 4.24 (2H, m, 2OCH), 3.0 (1H, m, CHO), 3.0 (1H, dd, *J* 5.1, 4.0 Hz, CH^bO), 2.4 (1H, dd, *J* 5.1, 2.1 Hz, CH^aO), 2.15–2.05 (5H, m, PCH_2+CH_2+CH), 1.65–0.8 (16H, m, CH_2C), 0.91 (3H, d, *J* 7 Hz, CH_3), 0.90 (3H, d, *J* 7 Hz, CH_3), 0.89 (3H, d, *J* 7 Hz, CH_3), 0.88 (3H, d, *J* 7 Hz, CH_3), 0.8 (3H, d, *J* 7 Hz, CH_3); δ_P (161.96 MHz, $CDCl_3$) 25.3.[31]

4.6.2. Di(1*R*,2*S*,5*R*)-menthyl (*R*)-2-hydroxy-3-(*N*,*N*-dibenzylamino)propylphosphonate 12. To a solution of 2,3-epoxypropylphosphonate **11** (2.1 g, 5 mmol) in 40 mL of methanol was added dibenzylamine (1.1 g, 5.1 mmol). The mixture was refluxed for 20 h. The solvent was removed under reduced pressure and the residue was crystallized from acetonitrile to give the *title compound* **12** (70%) as colorless crystals, mp 73 °C; [found: C, 72.64; H, 9.51; P, 5.08. $C_{37}H_{58}NO_4P$ requires C, 72.63; H, 9.55; P, 5.06%]; $[\alpha]_D^{20}$

−45.92 (*c* 4.57, $CHCl_3$); δ_H (300 MHz, C_6D_6) 7.3–7.1 (10H, m, $2C_6H_5$), 4.0–3.9 (3H, m, 2OCH+C*H*OH), 3.6 (1H, m, OH), 3.55 (4H, s, CH_2Ph), 2.48 (2H, m, CH_2N), 1.82 (1H, ddd, *J* 18.3, 15.1, 3.4 Hz, CH^bP), 2.25–0.96 (19H, m, CH_2C, CH, and CH^aP), 0.92 (3H, d, *J* 7.0 Hz, CH_3), 0.91 (3H, d, *J* 7.0 Hz, CH_3), 0.90 (3H, d, *J* 7.0 Hz, CH_3), 0.87 (3H d, *J* 7.0 Hz, CH_3), 0.80 (3H, d, *J* 6.9 Hz, CH_3), 0.73 (3H, d, *J* 7.2 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 139.13, 129.22, 128.44, 127.26, 77.78 (d, *J* 7.3 Hz), 77.71 (d, *J* 7.3 Hz), 64.72, 60.14 (d, *J* 14.3 Hz), 59.33, 49.12 (d, *J* 6.5 Hz), 49.10 (d, *J* 6.5 Hz), 44.19, 44.63, 34.57, 34.55, 33.74 (d, J_{CP} 140.9 Hz), 32.00, 31.96, 26.06, 26.00, 23.44, 23.44, 22.28, 22.28, 21.46, 21.40, 16.42, 16.19; δ_P (161.96 MHz, $CDCl_3$) 30.0.

4.6.3. (*R*)-2-Hydroxy-3-(*N*,*N*-dibenzylamino)propylphosphonic acid hydrochloride 13. To a solution of di(1*R*,2*S*,5*R*)-menthyl (*R*)-2-hydroxy-3-(*N*,*N*-dibenzylamino)propylphosphonate **12** (6.1 g, 10 mmol) in 250 mL of dioxane was added 90 mL of concd hydrochloric acid. The mixture was heated at 83–85 °C for 72 h. Then the solvent was evaporated under reduced pressure and the residue was dissolved in 15 mL of water, and washed with benzene (3×15 mL). The volatile components of the mixture were evaporated to give the *title compound* **13** (3.1 g, 85%) as a colorless solid; δ_H (300 MHz, CD_3OD) 7.54–7.52 (10H, m, $2C_6H_5$), 4.21–4.08 (1H, m, C*H*OH), 3.00 (1H, dd, *J* 13.2, 9.3 Hz, CH^bN), 1.93 (1H, ddd, *J* 34.5, 14.7, 4.5 Hz, CH^bP), 1.73 (1H, ddd, *J* 32.4, 17.4, 8.1 Hz, CH^aP); δ_P (121.4 MHz, D_2O) 26.5.

4.6.4. (*R*)-2-Hydroxy-3-aminopropylphosphonic acid (phospho-GABOB) 14. A solution of **13** (1.85 g, 5 mmol) in 190 mL of methanol was hydrogenated over 10% Pd/C (1.79 g) for 20 h at room temperature. Then the mixture was filtered off and concentrated under reduced pressure, washed with acetone (2×10 mL), and dried in vacuo. The residue was purified by ion-exchange chromatography to afford the *title compound* **14** (0.69 g, 90%) as a colorless hygroscopic solid; [found: C, 23.37; H, 6.72; N, 9.43. $C_3H_{10}NO_4P$ requires C, 23.23; H, 6.50; N, 9.03%]; $[\alpha]_D^{20}$ +10.2 (*c* 1, H_2O); δ_H (300 MHz, D_2O) 4.14 (m, 1H, C*H*OH), 3.27 (1H, dd, *J* 13.1, 3.4 Hz, CH^bN), 2.99 (1H, dd, *J* 13.5, 8.5 Hz, CH^aN), 1.86 (1H, ddd, *J* 32.1, 14.7, 6.3 Hz, CH^bP), 1.78 (1H, ddd, *J* 31.2, 15.0, 6.3 Hz, CH^aP); δ_C (100.6 MHz, D_2O) 67.41, 48.13 (d, *J* 9.0 Hz), 37.01 (d, *J* 128.3 Hz); δ_P (121.4 MHz, D_2O) 18.1.

4.7. Di(1*R*,2*S*,5*R*)-menthyl (*R*)-2-hydroxy-3-azidopropylphosphonate 15a

To a solution of 2,3-epoxypropylphosphonate **11** (0.5 g, 1.2 mmol) in 8 mL of methanol were added the sodium azide (0.188 g, 2.89 mmol) and ammonium chloride (0.115 g, 2.15 mmol). The mixture was refluxed for 4 h. Then the solvent was evaporated under vacuum and the residue was dissolved in ethyl acetate and the solution was washed with water. The organic layer was separated, dried with Na_2SO_4, and concentrated to give the *title compound* **15a** (0.53 g, 96%) as a yellow oil; [found: C, 60.28; H, 9.57; N, 8.84. $C_{23}H_{44}N_3O_4P$ requires C, 60.37; H, 9.69; N, 9.18%]; $[\alpha]_D^{20}$ −74.2 (*c* 2.5, $CHCl_3$); ν_{max} (liquid film) 3352, 2960, 2107, 1732, 1456, 1256, 992 cm^{-1}; δ_H (300 MHz, C_6D_6) 4.14 (2H, m, C*H*OH), 4.05 (2H, m, 2OCH), 3.15 (2H, m, CH_2N), 2.0–1.0 (16H, m, CH_2C), 1.8 (2H, m, PCH), 0.94 (3H, d, *J* 7 Hz, CH_3), 0.93 (3H, d, *J* 7 Hz, CH_3), 0.92 (3H, d, *J* 7 Hz, CH_3), 0.81 (3H, d, *J* 7 Hz, CH_3), 0.91 (3H, d, *J* 7 Hz, CH_3), 0.79 (3H, d, *J* 7 Hz, CH_3); δ_P (121.4 MHz, $CDCl_3$) 27.4.

4.8. Phosphono aziridines

4.8.1. Diethyl (*R*)-2-hydroxy-3-azidopropylphosphonate 15b. Compound **15b** was prepared analogously to **15a**. Yield: 90%, yellow oil; [found: C, 35.30; H, 6.71; P, 12.99. $C_7H_{16}N_3O_4P$ requires C, 35.45; H, 6.80; P, 13.06%]; ν_{max} (liquid film) 3681, 2984, 2105, 1225, 1099, 967 cm^{-1}; δ_H (300 MHz, C_6D_6) 4.03 (5H, m, OCH_2 and C*H*OH), 3.6 (1H, br, OH), 3.24 (2H, m, CH_2N_3), 1.87 (2H, m, CH_2P), 1.23 (6H, t, *J* 7.0 Hz, CH_3); δ_P (121.4 MHz, $CDCl_3$) 29.5.

4.8.2. Diethyl (2*S*)-aziridine-2-yl-propylphosphonate 17. To a solution of diethyl (*R*)-2-hydroxy-3-azidopropylphosphonate **15b** (1.487 g, 6.27 mmol) in 45 mL of toluene was added triphenylphosphine (1.65 g, 6.29 mmol). The reaction mixture was stirred at room temperature for 30–40 min and then refluxed for 1 h. The solvent was removed under reduced pressure and diethyl ether (10 mL) was added to the residue. The precipitate was filtered off, the filtrate was evaporated and the residue was distilled under vacuum to afford the *title compound* **17** (60%) as a colorless liquid, bp 92–93 °C (0.07 mmHg); [found: C, 43.48; H, 8.29; N, 7.23; P, 16.00. $C_7H_{16}NO_3P$ requires C, 43.52; H, 8.35; N, 7.25; P, 16.03%]; ν_{max} (liquid film) 3278, 3008, 2984, 1392, 1245, 1032, 964 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.14 (4H, $2CH_2O$), 2.25 (1H, m, CHN), 2.02 (1H, m, CH_2P), 1.91 (1H, m, NCH_2), 1.75 (1H, m, CH_2P), 1.46 (1H, m, NCH_2), 1.347 (3H, t, *J* 6.9 Hz, CH_3), 1.34 (3H, t, *J* 6.9 Hz, CH_3), 0.37 (1H, br, NH); δ_C (100.6 MHz, $CDCl_3$) 61.98, 61.91, 31.46 (d, *J* 142.7 Hz), 25.65, 24.58, 16.83, 16.76; δ_P (161.96 MHz, $CDCl_3$) 26.2.

4.9. The preparing of phospho-carnitine

4.9.1. (*S*)-2-Hydroxy-3-chloropropylphosphonic acid 18. *Method a*. To a solution of dimenthyl hydroxyphosphonate **8d** (4.5 g, 10 mmol) in 270 mL of dioxane was added 80 mL of concd hydrochloric acid. The reaction mixture was left for 3 days at 85 °C. Then the solvent was removed under reduced pressure, to the residue was added 50 mL of water and the mixture was washed with toluene (3×25 mL). The water was removed in vacuo, the residue was dissolved in ethanol (35 mL) and treated with activated charcoal. The solvent was evaporated under reduced pressure to give **18a** as a colorless oil. Yield: 1.56 g (~90%). Spectroscopically pure product was used without further purification.

Method b. A solution of hydroxyphosphonate **8b** (2.3 g, 10 mmol) in 50 mL of CH_2Cl_2 was treated with 10.5 mL (80 mmol) of trimethylbromosilane and was left overnight. The solvent was evaporated and the residue was dissolved in 25 mL of 60% aqueous ethanol. Then the solvent was removed under reduced pressure, to the residue was added 100 mL of water and the mixture was washed with toluene (3×25 mL). The solvent was evaporated under reduced

pressure to give **18b** as a colorless oil. Yield: 1.7 g (~98%) spectroscopically pure oil, which was used without further purification. δ_H (300 MHz, CD_3OD) 4.8 (1H, m, C*H*OH), 3.4–3.2 (2H, m, CH_2Cl), 1.9–1.6 (2H, m, PCH_2); δ_P (121.4 MHz, D_2O) 25.5.

4.9.2. (*R*)-(+)-2-Hydroxy-3-(*N*,*N*,*N*-trimethylammonium)propylphosphonic acid [(*R*)-(+)-phospho-carnitine] 19. A solution of 30% trimethylamine (85 mL) was added to the (*S*)-2-hydroxy-3-chloropropylphosphonic acid **18a** (1.74 g, 10 mmol). The mixture was left for 72 h at 40 °C, then the solvent was evaporated under reduced pressure, the residue was purified by column chromatography on silica gel (gradient from 100 to 50% methanol/water) to give the *title compound* (*R*)-**19** (2 g, 80%) as a white solid, mp >250 °C (decomp.); [found: C, 36.52; H, 8.15; P, 15.62. $C_6H_{16}NO_4P$ requires C, 36.55; H, 8.18; P, 15.71%]; $[\alpha]_D^{20}$ +26 (*c* 1, H_2O); δ_H (300 MHz, CD_3OD) 4.5 (1H, m, C*H*OH), 3.6 (1H, dd, *J* 13.8, 1.2 Hz, CH^bN), 3.4 (1H, dd, *J* 13.8, 9.8 Hz, CH^aN), 3.2 (9H, s, CH_3N), 1.89 (1H, ddd, *J* 17.7, 14.8, 6.9 Hz, PC^bH), 1.80 (1H, ddd, *J* 18, 14.7, 6.6 Hz, PC^aH); δ_C (100.6 MHz, D_2O) 71.57, 63.65, 54.98, 54.94, 54.91, 35.55 (d, *J* 131.7 Hz); δ_P (161.96 MHz, D_2O) 18.7.

References and notes

1. (a) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd ed.; Wiley-VCH: New York, NY, 1997; p 6; (b) Hudlicky, M. *Reductions in Organic Chemistry*; Ellis Horwood, John Wiley: New York, NY, 1984; 309 pp.
2. (a) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, NY, 1983; Vol. 2, Chapters 2 and 3; (b) Cho, B. T. *Aldrichimica Acta* **2002**, *35*, 3–16; (c) Kanth, J. V. B. *Aldrichimica Acta* **2002**, *35*, 57–66.
3. (a) Fields, S. C. *Tetrahedron* **1999**, *55*, 12237–12273; (b) Hildebrand, R. L.; Henderson, T. O. *The Role of Phosphonates in Living Systems*; Hildebrand, R. L., Ed.; Chemical Rubber: Boca Raton, FL, 1983; pp 5–29.
4. (a) Kolodiazhnyi, O. I. *Advances in Asymmetric Synthesis*; JAI: Stamford, London, 1998; Vol. 3, pp 273–357; (b) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **1998**, *9*, 1279–1332.
5. Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **2005**, *16*, 3295–3340.
6. (a) Meier, C.; Laux, W. H. G. *Tetrahedron: Asymmetry* **1995**, *6*, 1089–1092; (b) Meier, C.; Laux, W. H. G. *Tetrahedron* **1996**, *52*, 589–598.
7. Meier, C.; Laux, W. H. G. *Tetrahedron: Asymmetry* **1996**, *7*, 89–94.
8. (a) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2931–2932; (b) Bilenko, V.; Spannenberg, A.; Baumann, W.; Komarov, I.; Börner, A. *Tetrahedron: Asymmetry* **2006**, *17*, 2082–2087.
9. Kolodiazhnyi, O. I. *Russ. Chem. Rev.* **2006**, *75*, 227–255.
10. Kolodiazhnyi, O. I.; Gulyaiko, I. V. *Russ. J. Gen. Chem.* **2003**, *73*, 1825–1826.
11. Gulyaiko, I. V.; Kolodiazhnyi, O. I. *Russ. J. Gen. Chem.* **2004**, *74*, 1623–1624.
12. Nesterov, V. V.; Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1023–1025.
13. Nesterov, V. V.; Kolodiazhnyi, O. I. *Russ. J. Gen. Chem.* **2005**, *75*, 1161–1162.
14. Nesterov, V. V.; Kolodiazhnyi, O. I. *Russ. J. Gen. Chem.* **2006**, *76*, 1510–1511.
15. Kolodiazhnyi, O. I. *Tetrahedron* **2003**, *59*, 5923–6018.
16. Kolodiazhnyi, O. I.; Kolodyazhnaya, A. O.; Kukhar', V. P. *Russ. J. Gen. Chem.* **2006**, *76*, 1342–1343.
17. (a) Nesterov, V. V.; Grishkun, E. V.; Kolodiazhnyi, O. I. *Russ. J. Gen. Chem.* **2004**, *74*, 1947–1948; (b) Kolodiazhnyi, O. I.; Sheiko, O.; Grishkun, E. V. *Heteroat. Chem.* **2000**, *11*, 138.
18. (a) Burkert, U.; Allinger, N. L. *Molecular Mechanics*. Monograph 177; American Chemical Society: Washington, DC, 1982; (b) *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis (Methods in Stereochemical Analysis)*; Verkade, J. G., Quin, L. D., Eds.; John Wiley and Sons: New York, NY, 1987.
19. Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121–1162.
20. (a) Tacano, S.; Yanase, M.; Sekiguchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1987**, *28*, 1783–1784; (b) Otzuka, M.; Obata, K.; Miyata, Y.; Yaneka, Y. *J. Neurochem.* **1971**, *18*, 287–296; (c) Falch, E.; Hegegaard, A.; Nielsen, L.; Jensen, B. R.; Hjeds, H.; Krogsgaard-Larsen, P. *J. Neurochem.* **1986**, *47*, 898–903; (d) Kristiansen, U.; Fjalland, B. *Pharmacol. Toxicol.* **1991**, *68*, 332–339.
21. (a) Banfi, S.; Fonio, W.; Allievi, E.; Raimondo, S. *Pharmacol. Res. Commun.* **1983**, *15*, 553–558; (b) Garcia-Flores, E.; Farias, R. *Stereotact. Funct. Neurosurg.* **1997**, *69*, 243–246.
22. Yuan, C.; Wang, K.; Li, Z. *Heteroat. Chem.* **2001**, *12*, 551–556.
23. Wróblewski, A. E.; Halajewska-Wosik, A. *Tetrahedron: Asymmetry* **2003**, *14*, 3359–3363.
24. (a) Ordóñez, M.; González-Morales, A.; Ruiz, C.; De la Cruz-Cordero, R.; Fernández-Zertuche, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1775–1779; (b) Ordóñez, M.; González-Morales, A.; Salazar-Fernarndez, H. *Tetrahedron: Asymmetry* **2004**, *15*, 2719–2725.
25. (a) De Simone, C.; Famularo, G. *Carnitine Today*; Springer: Heilderberg, 1997; (b) Ferrari, R.; Di Mauro, S.; Sherwood, G. *L-Carnitine and its Role in Medicine: From Function to Therapy*; Academic: San Diego, CA, 1992; (c) Vary, T. C.; Neely, J. R. *Am. J. Physiol.* **1982**, *242*, H585–H592.
26. (a) Giannessi, F.; Chiodi, P.; Marzi, M.; Minetti, P.; Pessotto, P.; De Angelis, F.; Tassoni, E.; Conti, R.; Giorgi, F.; Mabilia, M.; Dell'Uomo, N.; Muck, S.; Tinti, M. O.; Carminati, P.; Arduini, A. *J. Med. Chem.* **2001**, *44*, 2383–2386; (b) Giannessi, F.; Pessotto, P.; Tassoni, E.; Chiodi, P.; Conti, R.; De Angelis, F.; Dell'Uomo, N.; Catini, R.; Deias, R.; Tinti, M. A.; Carminati, P.; Arduini, A. *J. Med. Chem.* **2003**, *46*, 303–309.
27. Yamagishi, T.; Fujii, K.; Shibuya, S.; Yokomatsu, T. *Tetrahedron* **2006**, *62*, 54–65.
28. Kielbasinski, P.; Luczak, J.; Mikolajczyk, M. *J. Org. Chem.* **2002**, *67*, 7872–7875.
29. (a) Yuan, C.; Wang, K.; Li, J.; Li, Z. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 2391–2397; (b) Wang, K.; Zhang, Y.; Yuan, C. *Org. Biomol. Chem.* **2003**, *1*, 3564–3569.
30. Wróblewski, A. E.; Halajewska-Wosik, A. *Eur. J. Org. Chem.* **2002**, 2758–2763.
31. Nesterov, V. V.; Kolodiazhnyi, O. I. *Russ. J. Gen. Chem.* **2006**, *76*, 1677–1678.
32. (a) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1779; (b) Zymanczyk-Duda, E.; Lejczak, B.; Kafarski, P.; Grimaud, J.; Fischer, P. *Tetrahedron* **1995**, *51*, 11809–11814; (c) Blazis, V. J.; Koeller, K. J.; Spilling, C. D. *J. Org. Chem.* **1995**, *60*, 931–940.