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New method for the asymmetric hydroboration of ketophosphonates and the synthesis of phospho-carnitine

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Abstract—The reduction of α- or β-ketophosphonates with a chiral reactant **1**, prepared from sodium borohydride and (*R*)- or (*S*)-tartaric acids, led to the formation of both (*S*)- and (*R*)-α- or β-hydroxyphosphonates in high yields. The stereoselectivity of the reaction depended on the absolute configurations of **1** and the ketophosphonates. The reduction of di(1*R*,2*S*,5*R*)-menthyl ketophosphonates with (*R*)-**1** proceeded with matched double asymmetric induction to give high diastereomeric excesses of hydroxyphosphonates (up to 96% de). This methodology was used for the preparation of enantiomerically pure phosphonate modified carnitine on a multigram scale.

1. Introduction

Asymmetric reduction of prochiral ketones is the most common method for obtaining hydroxy acids and their derivatives, possessing biological activity.[1] The reductions with chirally modified metal hydrides, catalytic hydrogenation in the presence of chiral metal complexes, asymmetric hydrosilylation, hydroboration, etc., are all widely used for the asymmetric reduction of ketones.[2]

Herein we have developed a simple method for the asymmetric reduction of carbonyl compounds with a reagent obtained from sodium borohydride and optically active tartaric acid (TA). The addition of $NaBH_4$ to a THF solution of tartaric acid causes the formation of a colorless solid, which is very sensitive to moisture. The structure of this chiral adduct is probably similar to one of the achiral adducts obtained from sodium borohydride and acetic or trifluoroacetic acid, which are used in organic synthesis as hydroborating reagents.[2,3] The experimental data support the assignment of the structure of **1** to this adduct.[4] This structure is consistent with the results of the hydrolysis, NMR and IR spectra, and elemental analysis. In particular, the IR spectrum exhibits a B–H bond at 2550 cm^{-1}, two bands of C=O groups at 1720, 1740 cm^{-1} and the frequency of OH group at 3525 cm^{-1}. Compound **1** contains solvated THF (Scheme 1).

$$(HOOCC^{*}HOH)_2 \xrightarrow{NaBH_4} \underset{\mathbf{1}}{Na[H_2B(O_2CC^{*}H(OH)_2]\cdot(THF)_{0.5}}$$

Scheme 1. Synthesis of chiral hydroborating reagent **1**.

2. Results and discussion

We have applied this reactant to the asymmetric reduction of ketophosphonates, resulting in chiral hydroxyphosphonates as a part of our ongoing program investigating biologically active organophosphorus compounds.[5,6] Ketophosphonates have previously been reduced with borane, catecholborane in the presence of chiral oxazaborolidine catalysts, chiral chlorodiisopinocampheylboranes, and hydrogenated in the presence of chiral BINAP-ruthenium(II)-catalysts.[5,7–9] However, these methods need the application of rather expensive reagents, the reaction conditions of application of which cannot always be reproduced[5] (Scheme 2).

Reagent **1** was used for the hydroboration of both α- and β-ketophosphonates **2**. The reduction of either diethyl α- or β-ketophosphonates **2** with (*R*,*R*)-**1** at −30 °C in THF led to the formation of diethyl (*S*)-β-hydroxyphosphonates **3** in yield of 82–95% and with ~50–80% ee.[10] Conversely, (*S*,*S*)-**1** yielded (*R*)-hydroxyphosphonates **3** with the same stereoselectivity and chemical yields. Assignment of the absolute configuration of the new stereogenic center in the stereoisomers was attained by chemical correlation. Compounds **3** were purified by column chromatography

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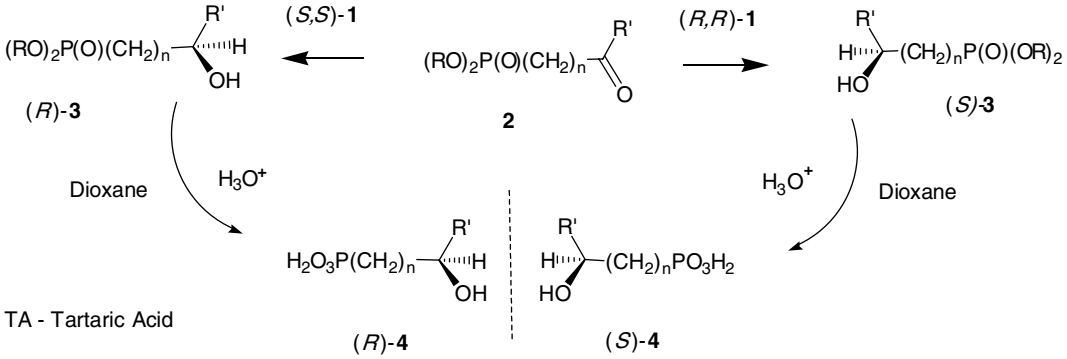


Scheme 2. Reduction of ketophosphonates **3** with (*S*)-**1** or (*R*)-**1**.

or crystallization and then converted into chiral hydroxyphosphonic acids **4** by hydrolysis with hydrochloric acid. The yields and ee (or de) of compounds are summarized in Table 1.

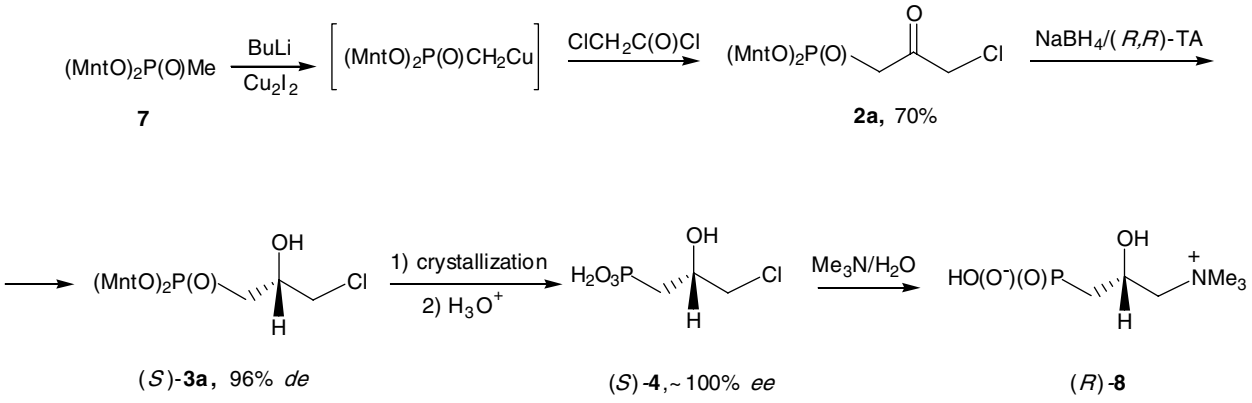
The stereoselectivity of hydroboration was increased when (1*R*,2*S*,5*R*)-dimenthyl ketophosphonates **2** were reduced with (*R*,*R*)-**1** due to the double asymmetric induction.[17,18] In this case, the reaction afforded (1*S*)-α-hydroxybenzylphosphonates **3e**,**g**,**i** with 80–96% de, higher than in the analogous reaction of diethyl ketophosphonates (Table 1, entries 3 and 4). However, the reduction of (1*R*,2*S*,5*R*)-dimenthyl ketophosphonates with (*S*,*S*)-**1** proceeded with lower stereoselectivity than in case of diethyl ketophosphonates (Table 1, entries 4 and 6). Evidently, the asymmetric induction of the (1*R*,2*S*,5*R*)-menthyl groups and (*R*,*R*)-tartaric acid act in coordination in one direction, increasing the resulting stereoselectivity (matched double asymmetric induction), whereas the asymmetric induction of the (1*R*,2*S*,5*R*)-menthyl groups and (*S*,*S*)-tartaric acid act in opposite directions, thus reducing the resulting stereoselectivity (mismatched double asymmetric induction). The reduction of dimenthyl ketophosphonates **2** with unmodified $NaBH_4$ proceeded with low stereoselectivity (~30% de, Table 1, entry 7). Dimenthyl hydroxyphosphonates (*S*)-**3a**,**3e**–**i** were recrystallized from acetonitrile and obtained in an enantiomerically pure state.[19]

The methodology developed was applied to the synthesis of phospho-carnitine, which is a phosphonate analogue of natural L-carnitine, which plays an important role in the transport of fatty acids into the mitochondrial matrix.[20] The synthesis of phospho-carnitine has been performed by a chemoenzymatic method and only on a milligram scale.[13,21] The literature data concerning phospho-carnitine is ambiguous (see Refs. 21–23). We have developed the total synthesis of (*R*)-phospho-carnitine on a multigramme scale, using the enantioselective hydroboration of 2-keto-3-chloropropylphosphonates as shown in Scheme 3. In the first step, dimenthyl 3-chloro-2-oxopropylphosphonate **2a** was prepared starting from the readily available dimenthyl methylphosphonate **7**. The enantioselective reduction of β-ketophosphonate **2a** led to the formation of optically active dialkyl 3-chloro-2-hydroxypropylphosphonate **3a**, which is the precursor of (*R*)-phospho-carnitine.[13] The dimenthyl derivative **3a** was obtained with very good stereoselectivity (96% de). The crystallization of **3a** in hexane or acetonitrile provided the enantiomerically pure compound. Phosphonate **3a** was dealkylated by heating with hydrochloric acid in dioxane to give acid (*S*)-**4**. The (*S*)-configuration of compound **4** was confirmed by the specific rotation value.[13] The free phosphonic acid **4** was treated with an aqueous solution of trimethylamine to provide the enantiomerically pure (*R*)-phospho-carnitine **8** in good yield.[24,25]

Table 1. Asymmetric reduction of ketophophonates with reagent (*S*)-**1** or (*R*)-**1** $(R'O)_2P(O)(CH_2)_nCH(OH)R$

Entry	Compd	R	R′	*n*	TA	$[\alpha]_D^{20}$ (*c*, solvent)[d]	Yield,%	ee (or de), %[a]	Config
1	**3a**	CH_2Cl	Mnt	1	*R*,*R*	−97.2 (*c* 3.0, $CHCl_3$)	**93**	**96**	*S*
2	**3b**	CH_2Cl	Et	1	*R*,*R*	−12.4 (*c* 3.2, $CHCl_3$)	**82**	**80**[c]	*S*[5,13]
3	**3c**	Ph	Et	0	*R*,*R*	−15.4 (*c* 2.6, $CHCl_3$)	95	60[b,c]	*S*[5,14]
4	**3d**	Ph	Et	0	*S*,*S*	+28.3 (*c* 2.1, $CHCl_3$)	**94**	**60**[b,c]	*R*[5,16]
5	**3e**	Ph	Mnt	0	*R*,*R*	−87.6 (*c* 1.3, $CHCl_3$)	**95**	**92.5**	*S*[5,15]
6	**3f**	Ph	Mnt	0	*S*,*S*	−70.0 (*c* 1.0, $CHCl_3$)	**98**	**46**	*R*[5,15]
7	**3e**/**3f**	Ph	Mnt	0	—	—	80	30	*S*/*R*
8	**3g**	2-FC_6H_4	Mnt	0	*R*,*R*	−83.7 (*c* 1.3, $CHCl_3$)	97	82	*S*
9	**3h**	2-An	Mnt	0	*R*,*R*	−75.2 (*c* 0.7, $CHCl_3$)	96	74	*S*[5,15]
10	**3i**	Pyperonyl	Mnt	0	*R*,*R*	−74.0 (*c* 1.0, $CHCl_3$)	97	96	*S*

[a] ee (or de) are given for unpurified products.
[b] ee was determined by derivatization with dimenthylchlorophosphite.[11,12]
[c] ee was determined by ^{31}P NMR with cinchonidine as a chiral solvating agent.[12b]
[d] Specific rotations are given for purified products.



Scheme 3. Synthesis of phospho-carnitine (*R*)-**8**.

3. Conclusion

In conclusion, we have developed a simple method for the asymmetric hydroboration of ketophosphonates and their conversion to hydroxyphosphonates. This methodology can as well be applied for the hydroboration of organic ketones.

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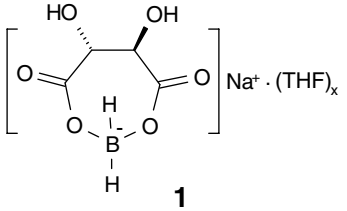
4. Compound **1**: Mp > 200 °C. ^{1}H NMR (DMSO): δ 1.7 m (CH_2C); 3.29 br (OH); 3.7 m (CH_2O); 4.5 m (C*H*OH). IR (KBr, cm^{-1}) 1720, 1740 (C=O), 2550 (B–H), 2970 (CH), 3525 (OH). The **1** contains solvated THF: 0.75 equiv (dried under vacuum at 20 °C) or 0.5 equiv (dried under vacuum at +50 °C). Anal. calcd for $C_7H_{11}BNaO_{6.75}$: C, 35.48, H, 4.68; found C, 35.56, H, 4.97.



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10. General methodology of reduction of ketophosphonates with chiral reagent **1**. Tartaric acid (7.16 mmol) was added to a suspension of $NaBH_4$ (7.16 mmol) in 25 ml of THF and the reaction mixture refluxed with stirring for 4 h. The mixture was cooled to −30 °C, at which point a solution of ketophosphonate (1.79 mol) in 8 ml THF was added and the mixture left overnight at −30 °C with stirring. 15 ml of ethyl acetate and 25 ml of 1 M hydrochloric acid were then added consecutively to the mixture. The organic layer was separated and the aqueous layer extracted with ethyl acetate. The combined extracts were washed out with a saturated solution of sodium carbonate and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was recrystallized in acetonitrile or purified by column chromatography.
11. The ee values of compounds **3** were estimated by ^{31}P NMR-{^{1}H}, using dimenthylchlorophosphite as derivatizing agent[12a] or cinchonidine[12b] as a chiral solvating agent.
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19. Compounds **3a**: Mp 86.2 °C; **3c**: mp 76 °C; **3e**: mp 113 °C; **3f**: mp 139 °C; **3g**: mp 138.5 °C; **3h**: mp 117 °C; **3i**: mp 96 °C.
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21. The (*S*)-phospho-carnitine was described as an *oil*, $[\alpha]_D^{20} = -24$ (*c* 2.3, MeOH–H_2O), 100% ee[13] *as a crystalline* product, mp 270°, $[\alpha]_D^{20} = -17.4$ (*c* 1.15, H_2O), 100% ee[22] and as a solid, $[\alpha]_D^{20} = -15$ (*c* 2.1, H_2O), 100% ee.[23]
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24. Phospho-carnitine (*R*)-**8** was purified by column chromatography with silica gel using methanol–water as eluent. Yield

80%, mp > 250 °C (decomp.), $[\alpha]_D^{20} = +24$ (*c* 1, H_2O). ^1H NMR (CD_3OD): δ 1.80 ddd (1H, $^3J_{HH}$ 6.6, $^2J_{HH}$ 14.7, $^2J_{HP}$ 18, PC^aH), 1.89 ddd (1H, $^3J_{HH}$ 6.9, $^2J_{HH}$ 14.8, $^2J_{HP}$ 17.7, PC^bH), 3.2 s (9H, CH_3N), 3.4 dd ($^2J_{HH}$ 13.8, $^3J_{HH}$ 9.8, CH^aN), 3.6 dd ($^2J_{HH}$ 13.8, $^3J_{HH}$ 1.2, CH^bN), 4.5 m (1H, CHOH), 4.9–5.0 br (1H, IH).

25. All new compounds gave satisfactory analytical data in C, H, and P.