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Asymmetric Synthesis of Chiral, Nonracemic Dialkyl-α-, β-, and γ-Hydroxy*alkyl*phosphonates via a Catalyzed Enantioselective Catecholborane Reduction

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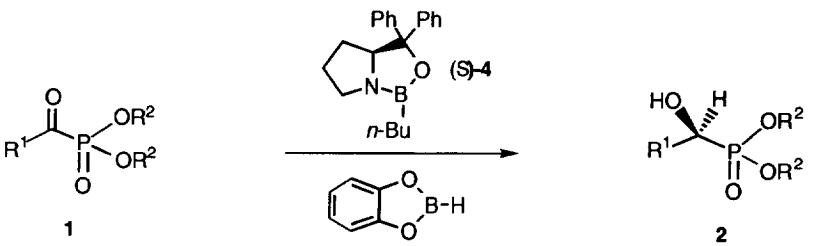
Abstract: A highly enantioselective synthesis of dialkyl α-hydroxyphosphonates achieved by a oxazaborolidine catalyzed reduction with catecholborane starting with α-ketophosphonates is described. Both α-aryl- and α-alkylketophosphonates were reduced using the (S)-enantiomer of the catalyst **4** leading also to the (S)-configuration in the products **2**. The reaction gave good chemical yields and excellent enantiomeric excesses (up to >99 % ee).

In the last years α-hydroxyphosphonates have received increasing interest because these compounds are biologically active: It has been shown, that α-hydroxyphosphonates act as inhibitor of renin[1], EPSP synthetase[2] and HIV protease[3]. It was demonstrated that the absolute configuration at the α-position is important for biological activity[4]. Chiral, nonracemic α-hydroxyphosphonates may serve as precursors for the synthesis of α-aminophosphonates. These compounds are used as analogues of α-amino acids[5]. In contrast to the α-aminophosphonates, there is only a limited number of synthetic approaches to optically active, nonracemic α-hydroxyphosphonates with one stereogenic center described. Chirality was introduced by i) the addition of chiral aldehydes to phosphorus nucleophiles[6], ii) the enantioselective addition of chiral phosphites to aldehydes[7], iii) the use of the Pudovik reaction in the presence of chiral base catalysts[8] and iv) reductions of ketophosphonates[9,10]. As part of our ongoing program investigating nucleoside α-hydroxyphosphonate esters as prodrugs[11] and prooligonucleotides[12], we were interested in the development of a stereoselective synthesis of α-hydroxybenzyl- and α-hydroxyalkylphosphonates. We report here on the enantioselective reduction of α-ketophosphonates **1** to α-hydroxybenzyl- and α-hydroxyalkylphosphonate dialkyl esters **2** with catecholborane **3** as reductant via *n*-butyl-oxazaborolidine **4** catalysis.

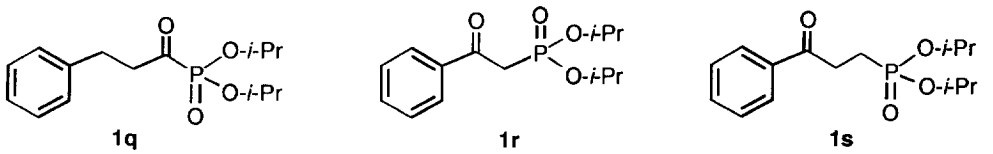
The starting materials **1** were synthesized via two different pathways: a) the aromatic α–ketophosphonates **1a-1i, 1k-1m, 1q-1s** were obtained by the reaction of the appropriate benzoylchlorides or alkylchlorides and tri-*i*-propyl phosphite as described before[13]; b) the aliphatic α-ketophosphonates **1n-1p** and the aryl-α-ketophosphonate **1j** were obtained by a two step reaction sequence: first the aldehydes were reacted in the presence of 1.2 equiv. sodium hydride with di-*t*-butylphosphite[14] to yield the racemic α-hydroxyalkylphosphonate di-*t*-butyl esters[15]. These racemic mixtures were subsequently transformed via the PDC-oxidation into the corresponding α-ketophosphonates **1** (scheme 1)[16]. The α-ketophosphonates were subsequently treated in toluene with 1.1 equiv. of catecholborane **3** in the presence of 12 mol% (S)-5,5-diphenyl-2-butyl-3,4-propano-

1,3,2-oxazaborolidine **4** as catalyst[17]. The reactants were mixed at -80 °C where no reaction occurred[18]. Then we stored the reaction mixture at -20 °C for 5 h. After this time no starting material **1** could be detected by TLC analysis (scheme 1)[19].

Scheme 1



1a R^1: Ph, R^2: *i*-Pr
1b R^1: 2-F-Ph, R^2: *i*-Pr
1c R^1: 2-Cl-Ph, R^2: *i*-Pr
1d R^1: 2-Br-Ph, R^2: *i*-Pr
1e R^1: 2-I-Ph, R^2: *i*-Pr
1f R^1: 3-Cl-Ph, R^2: *i*-Pr
1g R^1: 4-Cl-Ph, R^2: *i*-Pr
1h R^1: 2-Me-Ph, R^2: *i*-Pr
1i R^1: 2-OMe-Ph, R^2: *i*-Pr
1j R^1: 4-Me-Ph, R^2: *t*-Bu
1k R^1: 4-OMe-Ph, R^2: *i*-Pr
1l R^1: 2,6-F-Ph, R^2: *i*-Pr
1m R^1: 2,4-Cl-Ph, R^2: *i*-Pr
1n R^1: Me, R^2: *t*-Bu
1o R^1: *i*-Pr, R^2: *t*-Bu
1p R^1: *i*-Pr-CH_2, R^2: *t*-Bu



1q **1r** **1s**

After work-up the obtained chiral, nonracemic α-hydroxyphosphonates **2** were converted into their (1S)-(-)-camphanic esters or their (R)-(+)-Mosher esters. From these diastereomers we were able to determine the enantiomeric excess of the original reaction product **2** by ^{31}P NMR spectroscopy. The results are summarized in table 1.

As can be seen from table 1 all reactions proceeded with good to excellent yields. Additionally and even more important, all reactions yielded in high to very high enantiomeric excesses. This is valid for the α-hydroxy*aryl*- **1a-1m** as well as the α-hydroxy*alkyl* phosphonate esters **1n-1q**. Also from table 1, the reduction reaction proceeded with predictable stereochmistry. So the (S)-configurated oxazaborolidine catalyst **4** leads in all cases to (S)-configuration at the new stereogenic center[20]. This leads to the conclusion that in the reaction complex of **1**, the catalyst and the catecholborane the phosphoryl group represents the "large" residue whereas the aryl or alkyl moiety represents the "small" residue. Hence, the hydride of the borane attacks the carbonyl carbon from it's *re*-face. As can be seen from table 1, we observed only marginal differences in the stereochemical outcome of the chiral reduction between the α-aryl- and α-alkylketophosphonates. Within the series of α-arylketophosphonates **1a-1m** the 2-substituted compounds gave better enantioselectivities than the 3- or 4-substituted derivatives. This was exemplified by the reactions of the 2-, 3- and 4-chlorobenzoylphosphonates (**1c** vs. **1f** vs. **1g**), respectively. Additionally, we observed no effect of the size of the substituent in the 2-position. This conclusion can be drawn from the reaction series with the 2-halogen atom in the starting material (**1b** vs. **1c**, **1d** vs. **1e**). Donor and acceptor activity of the substituents had no effect on the enantioselectivity.

Table 1. Enantioselective reduction of α-ketophosphonates **1** in the presence of catecholborane **3** and (S)-5,5-diphenyl-2-butyl-3,4-propano-1,3,2-oxazaborolidine **4**

	1	Product 2	Yield (%)[a]	E.e. (%)[b]	Config.[c]	α_D (c)[d]
1	**a**	**2a**	92	65	S	-17.3 (1.0)
2	**b**	**2b**	68	91	S	-18.1 (0.7)
3	**c**	**2c**	96	97	S	-65.8 (0.9)
4	**d**	**2d**	82	95	S	-59.0 (1.5)
5	**e**	**2e**	79	92	S	-65.2 (1.2)
6	**f**	**2f**	84	77	S	-16.8 (0.8)
7	**g**	**2g**	98	70	S	-22.4 (1.0)
8	**h**	**2h**	89	97	S	-60.0 (0.9)
9	**i**	**2i**	82	51	S	-22.5 (0.9)
10	**j**	**2j**	85	76	S	-12.8 (0.8)
11	**k**	**2k**	76	55	S	-12.3 (0.8)
12	**l**	**2l**	96	>99[21]	S	-6.9 (1.0)
13	**m**	**2m**	85	94	S	-55.0 (1.0)
14	**n**	**2n**	89	81	S	+2.0 (1.3)
15	**o**	**2o**	91	80	S	-2.5 (1.0)
16	**p**	**2p**	85	90	S	+12.7 (0.7)
17	**q**	**2q**	85	95	S	+14.1 (0.8)
18	**r**	**2r**	66	91	R	+25.1 (0.8)
19	**s**	**2s**	58	68	R	+18.7 (0.8)

a) Most of the compounds were isolated as solids; b) Determined by ^{31}P-NMR analysis of the corresponding (R)-(+)-Mosher or (1S)-(-)-camphanic acid esters; c) Stereochemistry was determined by chemical correlation[8c] and CD-spectroscopy[8d]; d) Measured in $CHCl_3$ at 20°C.

Additionally, we reduced the ketophosphonates **1q**, **1r** and **1s** derived from benzoylphosphonate **1a**: we "introduced" in **1q** an ethylene spacer between the keto group and the aryl ring (so "making" the aryl group even smaller) and we "introduced" a methylene and an ethylene spacer between the keto group and the phosphoryl moiety to obtain the β-ketophosphonate **1r** and the γ-ketophosphonate **1s**, respectively. The results of these reactions, which were carried out under the same conditions (also same enantiomer of the oxazaborolidine catalyst **4**) are also listed in table 1. As expected the first experiment lead the (S)-configuration in the product **2q**, whereas in the other two experiments the (R)-configurated compounds **2r,s** was isolated, as a consequence of the inversion of the large/small attribution. To the best of our knowledge these are the first examples of an enantioselective synthesis of β- and γ-hydroxyphosphonate diesters. The α-hydroxyalkylphosphonates **1n-p** were transformed into their α-aminophosphonates by a known method described by T. Gajda[22].

In summary, the described *n*-butyl-oxazaborolidine catalyzed enantioselective reduction of α-ketophosphonates **1** with catecholborane **3** is a very easy to handle reaction, which leads to high or very high enantiomeric excesses in the stereospecific synthesis of chiral, nonracemic α-hydroxybenzyl-, α-, β- and γ-hydroxyalkylphosphonates.

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18. In previous reactions using the borane THF or Me_2S complexes we observed even at -80°C the reduction but without any enantiomeric excess (unpublished results).
19. In a typical experiment to a solution of 1 mmol of the acylphosphonate **1** and (S)-5,5-diphenyl-2-butyl-3,4-propano-1,3,2-oxazaborolidine **4** in 3 ml toluene a THF solution of 1.1 ml of catecholborane **3** (1 M) was added at -80°C. The reaction mixture was stored for 5 h at -20°C. After that time the mixture was diluted by the addition of 20 ml Et_2O and extracted 4x with a saturated solution of $NaHCO_3$. The organic phases were dried over $MgSO_4$. The solvent was evaporated and the residue was purified on a Chromatotron on silica gel plates using a 0-5% gradient of MeOH in CH_2Cl_2.
20. Compounds **1** and **2** were characterized by ^1H, ^{13}C, ^{31}P NMR spectroscopy and showed satisfactory analytical data. If products **2** are solids, one recrystallisation lead to enantiomerically pure compounds.
21. In this case only one diastereomer was observed in the ^{31}P NMR spectrum. We knew before that the (1S)-(-)-camphanic acid ester of racemic **2** showed two well separated signals in the ^{31}P NMR spectrum.
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