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Asymmetric Synthesis of Chiral, Nonracemic Dialkyl-α-Hydroxy*alkyl*phosphonates via a (-)-Chlorodiisopinocampheylborane (Ipc_2B-Cl) Reduction

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Abstract: The enantioselective synthesis of dialkyl α-hydroxybenzylphosphonates **2** using a (-)-chlorodiisopinocampheylborane (Ipc_2B-Cl) **3** catalyzed reduction starting with α-ketophosphonates **1** is described. The reaction gave the target compounds **2** in good yields with predictable stereochemistry and enantiomeric excesses up to 65 % ee.

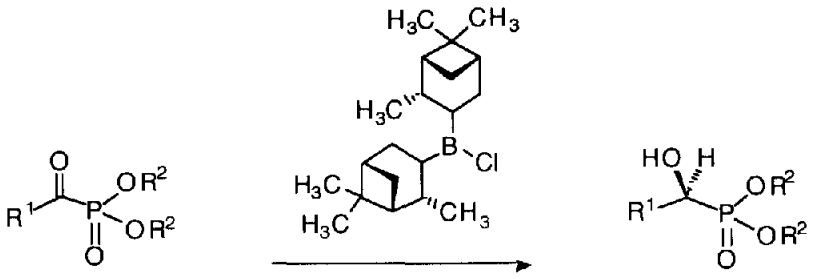
α-Hydroxyphosphonates have received increasing interest because these compounds are biologically active as inhibitors of different enzymes, e. g. renin[1], EPSP synthetase[2] and HIV protease[3]. It was demonstrated that the absolute configuration at the α-position is important for biological activity[4]. Chiral, nonracemic α-hydroxyphosphonates may serve as precursors for the synthesis of α-aminophosphonates. These compounds are used as analogues of α-amino acids. There is only a limited number of synthetic approaches to optically active, nonracemic α-hydroxyphosphonates with one stereogenic center described and chirality was introduced by the addition of aldehydes to phosphorus nucleophiles[5,6], the Pudovik reaction in the presence of chiral base catalysts[7], by enzymatic resolution of racemic α-hydroxyphosphonates[8] and reductions of ketophosphonates[9,10,11]. As part of our ongoing program investigating nucleoside α-hydroxyphosphonate esters as prodrugs[12] and prooligonucleotides[13], we were interested in the development of a stereoselective synthesis of α-hydroxybenzylphosphonates[14]. We report here on the enantioselective reduction of α-ketophosphonates **1** to dialkyl α-hydroxybenzylphosphonates **2** with (-)-chlorodiisopinocampheylborane **3** as reductant and stereodifferentiating catalyst. The results will be compared to our catecholborane / oxazaborolidine reduction described before[9,14].

All starting compounds **1** were synthesized by the Arbusov reaction[15] using the appropriate benzoylchlorides and trialkyl phosphite as described before[9,14] (Scheme 1). The different dialkylesters of the α-ketophosphonates **1** were subsequently treated with 1.08 equiv. (-)-chlorodiisopinocampheylborane **3**[16] in different THF quantities at -20°C for 3 d. After this time no starting material **1** could be detected by TLC analysis.

After workup the obtained chiral, nonracemic dialkyl α-hydroxybenzylphosphonates **2** were converted into their (1S)-(-)-camphanic acid esters or their (R)-(+)-Mosher esters in order to determine the enantiomeric excess of the original product **2** by ^{31}P NMR spectroscopy. The results are summarized in dependence of the alkyl groups of the ester moiety and the THF quantities in Table 1.

As can be seen from Table 1 all reactions proceeded with varying enantiomeric excesses but with good to excellent chemical yields and with predictable stereochemistry.

Scheme 1



1a	R^1: Ph, R^2: Me	**1g**	R^1: 2-MeO-Ph, R^2: *i*Pr
1b	R^1: Ph, R^2: Et	**1h**	R^1: 3-MeO-Ph, R^2: *i*Pr
1c	R^1: Ph, R^2: *i*Pr	**1i**	R^1: 4-MeO-Ph, R^2: *i*Pr
1d	R^1: 2-Cl-Ph, R^2: *i*Pr	**1j**	R^1: 4-*t*-Bu-Ph, R^2: *i*Pr
1e	R^1: 3-Cl-Ph, R^2: *i*Pr	**1k**	R^1: 4-MeS-Ph, R^2: *i*Pr
1f	R^1: 4-Cl-Ph, R^2: *i*Pr		

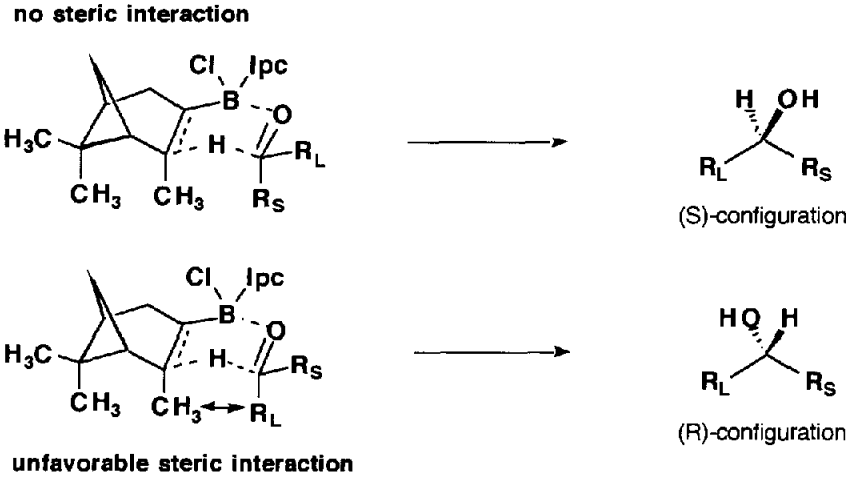
Table 1 Enantioselective reduction of α-ketophosphonates **1** using (-)-Ipc$_2$B-Cl **3** in THF at -20°C

Entry	**2**	THF (ml)	Yield (%)	E.e. (%)[a]	Config.[b]	α_D[°] (c)[c]
1	**a**	0.75	40	34	S	-15.7 (0.8)
2	**b**	0.75	56	42	S	-13.5 (1.0)
3	**c**	0.75	58	60	S	-16.0 (1.0)
4	**d**	0.40	77	38	S	-25.8 (1.0)
5	**d**	0.75	89	41	S	-27.8 (0.9)
6	**d**	2.25	83	25	S	-17.0 (0.9)
7	**d**	4.50	81	17	S	-11.5 (0.9)
8	**e**	0.75	65	42	S	-9.2 (0.8)
9	**f**	0.75	61	42	S	-13.4 (1.0)
10	**g**	0.75	75	54	S	-17.6 (0.9)
11	**h**	0.75	87	52	S	-9.0 (1.0)
12	**i**[17]	0.75	88	65	S	-14.5 (0.8)
13	**j**	0.75	94	52	S	-15.6 (1.0)
14	**k**	0.75	75	63	S	-18.8 (1.1)

a) Determined by ^{31}P NMR analysis of the corresponding (R)-(+)-Mosher or (1S)-(-)-camphanic acid esters; b) Stereochemistry was determined as described before[14]; c) Measured in $CHCl_3$ at 20°C.

In accordance to the (S)-oxazaborolidine catalyzed catecholborane reductions described before, the (-)-chlorodiisopinocampheylborane catalyst **3** led in all cases to (S)-configuration at the new stereogenic center[18]. This result leads to the conclusion that in the Ipc_2B-Cl reaction reported here the "large / small" assignment of the residues flanking the carbonyl group of **1** in the complex[19] with the (-)-Ipc_2B-Cl **3** is inversed with respect to the catecholborane reduction. So here the aryl moiety represents the "large"- and the phosphonyl residue is the "small" group. The reason for this inversion should be an unfavorable steric interaction of the "large"-group with one of the methyl groups in **3** as depicted in Scheme 2. Hence, the hydride of the borane attacks the carbonyl carbon from it's *re*-face.

Scheme 2



Within the series of dialkyl α-arylketophosphonates **1**, the diisopropyl esters (examplified by **1c**) gave significantly higher enantiomeric excesses than the dimethyl **1a** or diethyl esters **1b** (entries 1-3, Table 1). The same correlation was observed in the catecholborane / oxazaborolidine catalyzed reductions of compounds of type **1**. Additionally the reduction was surprisingly sensitive to concentration effects. As examplified by diisopropyl 2-chlorophenylketophosphonate **1d** the enantiomeric excess decreases in high diluted solutions for some unknown reason (entries 4,5 vs. 6,7). We have never found such an effect in the catecholborane reductions. Again in contrast to the catecholborane reduction method, we observed nearly no influence of the position of the substituent in the aromatic ring (entries 5 [2-Cl, **1d**], 8 [3-Cl, **1e**], 9 [4-Cl, **1f**] and 10 [2-MeO, **1g**], 11 [3-MeO, **1h**], 9 [4-MeO, **1i**]). Also in contrast to the catecholborane reduction method, we observed no decrease of the ee value for the 2-MeO substituted derivative **1g**. As a consequence the postulated two-point catalyst-ketone complexation for the oxazaborolidine case plays no role in the Ipc_2B-Cl **3** reduction method. As can be seen from Table 1, the acceptor substituted α-ketophosphonate derivatives **1d**-**1e** yielded somewhat lower ee values than the unsubstituted or the donor substituted compounds. An explanation therefor could be that the electron-withdrawing aryl residue further activates the carbonyl group and as a result a less stereoselective reduction takes place. Nevertheless, in contrast to the catecholborane / oxazaborolidine reduction method the formation of the complex between Ipc_2B-Cl **3** and the ketophosphonates **1** is obligatory for the reduction and hence to yield the α-hydroxybenzylphosphonates **2**. Without complexation no reduction takes place. As a consequence the stereodifferentiation between the *re*- or the *si*-face hydride attack is obviously not sufficiently pronounced to obtain higher ee values using the α-ketophosphonates **1**.

In summary, the described Ipc_2B-Cl **3** catalyzed enantioselective reduction of α-ketophosphonates **1** is a useful completion to the catecholborane / oxazaborolidine method for the availability of the 3- and 4-substituted derivatives of chiral, nonracemic dialkyl α-hydroxybenzylphosphonates **2**.

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EXPERIMEMTAL

Melting points (uncorrected): Apparatus of Tottoli (Büchi). - Optical rotations: Perkin-Elmer 241; solvent was $CHCl_3$ p. a. (Merck, Darmstadt). - FTIR: Perkin-Elmer 1600. - ^{31}P (162 MHz), ^{13}C (100.6 MHz) and ^{1}H NMR (400 MHz): Bruker AMX 400; OH signals regularly confirmed by D_2O exchange; solvent was $CDCl_3$; internal standards: tetramethylsilane (^{1}H NMR), $CDCl_3$ (^{13}C NMR), phosphorus acid was used as external standard for the ^{31}P NMR spectra. All ^{13}C and the ^{31}P NMR spectra were recorded in the proton-decoupled mode. Chemical shifts are given in δ (ppm) and coupling constants, J, are in Hz. - Elemental analyses: Foss Heraeus CHN-O-Rapid. - Preparative thin-layer chromatography: Chromatotron Harrison Research Model 7924 T; silica gel 60 PF_{254} gipshaltig (Merck, Darmstadt). - Analytical thin-layer chromatographies (all reactions were monitored using TLC) were performed on silica gel 60 F_{254} aluminium plates (0.2 mm; Merck, Darmstadt) containing a fluorescent indicator. - Solvents: THF was purchased from Fluka. - (1S)-(-)-camphanic acid and R-(+)-α-methoxy-α-trifluoromethylphenylacetic acid are commercially available from Fluka.

General Experimental Procedure: To a solution of 0.35 g of (-)-Ipc_2BCl (1.08 equiv., 1.08 mmol) in 0.75 ml of dry THF at -20 °C under an argon-atmosphere was added 1.0 mmol of the α-ketophosphonate. The reaction mixture was stored at -20 °C for 3 d and then dried at 10^{-2} Torr for 6 h. The residue was dissolved in 3.8 ml of diethylether and 0.23 g of diethanolamine (2.2 equiv., 2.2 mmol) were added. The precipitate was filtered of and the filtrate was dried in vacuo. The residue was subjected to preparative TLC using a gradient of 0-5 % CH_3OH in CH_2Cl_2 to afford the α-hydroxyphenylmethylphosphonates.

The characterization of compounds **1b-1g**, **2b-2g**, **2k** has been described in ref. 14.

Dimethyl benzoylphosphonate (1a):
IR (film) 3065, 3008, 2958, 2854, 1655, 1596, 1260, 1034, 783, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.23, 7.67-7.62, 7.53-7.49 (m, 5H), 3.91 (d, J = 10.8 Hz, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.6 (d, J = 175 Hz), 135.7 (d, J = 63.9 Hz), 135.2, 130.0, 129.1, 54.4 (d, J = 7.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 1.4. Anal. Calcd. for $C_9H_{11}O_4P$: C, 50.48; H, 5.18. Found: C, 50.22; H, 5.32.

Diisopropyl 3-methoxybenzoylphosphonate (1h):
IR (film) 3072, 2981, 2938, 2839, 1655, 1597, 1582, 1268, 995, 765 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.94, 7.72-7.71, 7.42-7.38, 7.17-7.15 (m, 4H), 4.88-4.76 (m, 2H), 3.84 (s, 3H), 1.37, 1.36, 1.31 (d, J = 6.2 Hz, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 199.2 (d, J = 177 Hz), 159.6, 136.8 (d, J = 63.8 Hz),

129.6, 123.0, 121.5, 112.6, 72.7 (d, J = 6.0 Hz), 72.5 (d, J = 6.0 Hz), 55.3, 24.1, 23.9, 23.7, 23.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ -2.1. Anal. Calcd. for $C_{14}H_{21}O_5P$: C, 56.00; H, 7.05. Found: C, 55.89; H, 7.04.

Diisopropyl 4-tert-butylbenzoylphosphonate (1j):
M.p. 81-82 °C; IR (KBr) 3072, 2976, 2872, 1652, 1601, 1561, 1257, 994, 847 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22-8.20, 7.51-7.49 (m, 4H), 4.87-4.79 (m, 2H), 1.38, 1.37 (d, J = 6.1 Hz, 12H), 1.34 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.8 (d, J = 176 Hz), 158.5, 133.2 (d, J = 63.8 Hz), 129.8, 125.7, 72.9 (d, J = 7.4 Hz), 35.2, 30.9, 24.0, 23.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.8. Anal. Calcd. for $C_{17}H_{27}O_4P$: C, 62.56; H, 8.34. Found: C, 62.85; H, 8.41.

Diisopropyl 4-methylthiobenzoylphosphonate (1k):
M.p. 28-33 °C; IR (film) 3060, 2981, 2933, 1647, 1584, 1550, 1255, 993, 831 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.18, 7.30-7.26 (m, 4H), 4.87-4.76 (m, 2H), 2.53 (s, 3H), 1.37, 1.36 (d, J = 6.2 Hz, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.0 (d, J = 177 Hz), 148.3, 132.0 (d, J = 63.7 Hz), 130.1, 124.7, 72.9 (d, J = 7.4 Hz), 24.0, 23.8, 14.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.8. Anal. Calcd. for $C_{14}H_{21}O_4PS$: C, 53.15; H, 6.69. Found: C, 53.23; H, 6.61.

(S)-Dimethyl 1-hydroxy-1-phenylmethylphosphonate (2a + ent-2a):
M.p. 88-90 °C; IR (KBr) 3269, 3060, 3016, 2956, 2895, 2851, 1242, 1051, 1026, 774, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.40, 7.30-7.13 (m, 5H), 4.98 (d, J = 11.5 Hz, 1H), 4.69 (br, s, 1H), 3.60, 3.57 (d, J = 11.2 Hz, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.6, 128.3, 128.1, 127.1, 70.5 (d, J = 160 Hz), 53.9 (d, J = 7.2 Hz), 53.6 (d, J = 7.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.5. Anal. Calcd. for $C_9H_{13}O_4P$: C, 50.01; H, 6.06. Found: C, 49.99; H, 6.09.

(S)-Diisopropyl 1-hydroxy-1-(3-methoxyphenyl)methylphosphonate (2h + ent-2h):
M.p. 61-63 °C; IR (KBr) 3285, 3027, 2985, 2931, 1607, 1588, 1226, 997, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.20, 7.10-7.04, 6.83-6.81 (m, 4H), 4.93 (d, J = 11.2 Hz, 1H), 4.70-4.56 (m, 3H), 3.79 (s, 3H), 1.27, 1.26, 1.15 (d, J = 6.2 Hz, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.4, 138.5, 128.9, 119.7, 113.8, 112.4, 71.9 (d, J = 7.5 Hz), 71.6 (d, J = 7.5 Hz), 71.0 (d, J = 160 Hz), 55.2, 24.1, 24.0, 23.8, 23.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.4. Anal. Calcd. for $C_{14}H_{23}O_5P$: C, 55.62; H, 7.67. Found: C, 55.71; H, 7.67.

(S)-Diisopropyl 1-hydroxy-1-(4-tert-butylphenyl)methylphosphonate (2j + ent-2j):
M.p. 77-79 °C; IR (KBr) 3339, 3096, 2978, 2867, 1612, 1512, 1238, 984, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.35 (m, 4H), 4.91 (d, J = 10.7 Hz, 1H), 4.66-4.57 (m, 2H), 3.04 (br, s, 1H), 1.30 (s, 9H), 1.28, 1.26, 1.24, 1.09 (d, J = 6.1 Hz, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 150.7, 133.7, 126.9, 124.9, 71.7 (d, J = 7.0 Hz), 71.4 (d, J = 7.0 Hz), 70.8 (d, J = 161 Hz), 37.6, 31.2, 24.0, 23.9, 23.7, 23.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.8. Anal. Calcd. for $C_{17}H_{29}O_4P$: C, 62.18; H, 8.90. Found: C, 62.09; H, 8.92.

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17. In contrast to the other reaction in this case the precipitation (see General Experimental Procedure) using diethanolamine was omitted because of the instability of **2i**. The reaction mixture was directly isolated by chromotography.
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