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# Enantioselective Synthesis of Diisopropyl $\alpha$ -, $\beta$ -, and $\gamma$ -Hydroxyarylalkylphosphonates from Ketophosphonates: A Study on the Effect of the Phosphonyl Group

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**Abstract:** A comparative study of different reduction conditions to an enantioselective synthesis of diisopropyl  $\alpha$ -,  $\beta$ - and  $\gamma$ -hydroxyphosphonates **4-6** by 1.3.2-oxazaborolidine catalysis using catecholborane **7** or BH<sub>3</sub>•Me<sub>2</sub>S **8** is described. The comparison to acetophenone reductions gave information's on the effect of the phosphonyl group during the reduction of ketophosphonate. So very efficient syntheses to chiral dialkyl  $\alpha$ -,  $\beta$ - and  $\gamma$ -hydroxyphosphonates were elaborated.

 $\alpha$ -Hydroxyphosphonates have received increasing interest because these compounds are biologically active in the inhibition of renin<sup>1</sup>, EPSP synthetase<sup>2</sup> and HIV protease<sup>3</sup>. It was demonstrated that the absolute configuration at the  $\alpha$ -position is important for biological activity<sup>4</sup>. Chiral, nonracemic  $\alpha$ -hydroxyphosphonates may serve also as precursors for the synthesis of  $\alpha$ -aminophosphonates which are analogues of  $\alpha$ -amino acids (P-amino acids)<sup>5</sup>. There is only a limited number of synthetic approaches to optically active, nonracemic  $\alpha$ hydroxyphosphonates with one stereogenic center described. Chirality was introduced by i) the addition of chiral aldehydes to phosphorus nucleophiles<sup>6</sup>, ii) the enantioselective addition of chiral phosphites to aldehydes7, iii) the use of the Pudovik reaction8 in the presence of chiral base catalysts9, iv) different approaches of stereoselective reductions of  $\alpha^{-10}$  and  $\beta$ -ketophosphonates<sup>11</sup> or v) by enzymatic resolution of racemic  $\alpha$ -hydroxyphosphonates<sup>12</sup>. As part of our ongoing program investigating nucleoside  $\alpha$ -hydroxyphosphonate esters as prodrugs<sup>13</sup> and prooligonucleotides<sup>14</sup>, we were interested in the development of a stereoselective synthesis of  $\alpha$ -hydroxybenzyl- and  $\alpha$ -hydroxyalkylphosphonates<sup>15</sup>. We already have investigated the effect of the substituted aromatic ring residues<sup>16</sup> and in this paper we report about the effect of the phosphonyl group on the enantioselective reduction of the diisopropyl  $\alpha$ -1,  $\beta$ -2, and  $\gamma$ -ketophosphonates 3 to the diisopropyl  $\alpha$ -hydroxybenzyl- 4 and  $\beta$ - 5, and  $\gamma$ -hydroxyalkylphosphonates 6<sup>17</sup> using catecholborane 7 as well as the borane-dimethylsulfide complex 8 as reducing agent via n-butyl-oxazaborolidine 9 catalysis. The same reaction conditions were also applied to the appropriate acetophenone derivatives 10 leading to the substituted 1phenylethanols 11 for comparison.

All starting compounds 1, 2 and 3 were synthesized by the Arbusov reaction using the appropriate benzoylchlorides or phenylalkylchlorides/bromides and triisopropyl phosphite as described before<sup>16,18</sup> (Scheme 1). All substituted acetophenone derivatives, except the 2-OMEM derivative 10b, were commercially available. Acetophenone 10b was prepared starting with 2-hydroxyacetophenone and MEM chloride in the presence of

sodium hydride<sup>19</sup>. The  $\alpha$ -,  $\beta$ -, and  $\gamma$ -ketophosphonates 1, 2 and 3 as well as the acetophenone derivatives 10 were subsequently treated with 1.1 equiv. catecholborane 7 or 0.66 equiv. of the borane-dimethylsulfide complex 8 in the presence of 12 mol-% (S)-5,5-diphenyl-2-butyl-3,4-propano-1.3.2-oxazaborolidine 9 as catalyst<sup>20</sup>. Additionally we conducted the reactions in different ways. In the case of the catecholborane reaction (Method 1) the reactants were mixed at -80 °C in toluene where no reaction occurred<sup>21</sup>. Subsequently we stored the reaction mixture at -20 °C for 5 h. Then no starting material 1, 2, 3 and 10 could be detected by TLC analysis (Scheme 1)<sup>16</sup>. In the case of the borane complex reactions two different reaction methods were investigated: i) mixing the starting materials 1, 2, 3 and 10 with catalyst 9 followed by the addition of the borane 8 within 5.5 h at room temperature in THF (Method 2); or ii) mixing the borane 8 with the catalyst 9 in THF and addition of the ketones 1, 2, 3 and 10 within 10 minutes. The reaction mixture was then stored for additional 10 minutes at room temperature (Corey's reaction conditions<sup>22</sup>; Method 3).





After workup the obtained chiral, nonracemic diisopropyl hydroxyphosphonates 4, 5,  $6^{23}$  and the 1phenylethanol derivatives  $11^{23}$  were transformed into their (1S)-(-)-camphanic acid esters or their (R)-(+)-Mosher esters in order to determine the enantiomeric excess of the original reaction products by <sup>31</sup>P NMR or <sup>1</sup>H NMR spectroscopy<sup>16,24</sup>. The results are summarized in dependence of methods 1-3 in Table 1. As can be seen all reactions proceeded with good to excellent yields. Also from Table 1, all reductions - independent of the method used - proceeded with predictable stereochemistry: the (S)-configurated oxazaborolidine catalyst 9 led in the cases of the  $\alpha$ -ketophosphonates 1a-1i to the (S)-configuration at the new stereogenic center<sup>25</sup>. In contrast, 2, 3 and the acetophenone derivatives 10 gave the (R)-configurated hydroxyphosphonates 5, 6 and 1phenylethanols 11 (Table 1). This result is in full agreement with our postulated reaction complex<sup>15,16</sup>: As expected the configuration changes because of the inversion of the "large/small"-assignment of the residues flanking the carbonyl group. Henceforth, the hydride of the reducing reagents attacks the carbonyl carbon from its *re*-face or from its *si*-face, respectively.

					Method 1[a]		Method 2 <sup>[b]</sup>		Method 3[c]	
Entry	Ketone	Product	R or X	Config.[d]	Yield (%)	E.e. (%)[e]	Yield (%)	E.e. (%)[e]	Yield (%)	E.e. (%)[e]
1	1a	4a	2-MeO-Ph	S	82	69	81	46	65	20
2	1 b	4b	2-Me-Ph	S	89	97	95	76	78	41
3	1 c	4 c	2-Cl-Ph	S	96	97	85	79	78	49
4	1 d	4d	$\alpha$ -Naphthyl	S	<b>8</b> 0	88	87	73	81	30
5	1 e	4e	3-Cl-Ph	S	84	77	95	53	76	39
6	1 <b>f</b>	4 f	β-Naphthyl	S	93	74	84	30	91	34
7	1 g	4 g	4-Cl-Ph	S	98	70	80	4	89	<b>3</b> 9
8	1 h	4h	2-F-Ph	S	68	91	78	57	81	67
9	1 i	<b>4</b> i	2-Br-Ph	S	82	95	79	58	79	43
10	2	5		R	66	91	88	68	74	83
11	3	6		R	58	68	81	76	94	>9826
12	10a	11a	2-MeO	R	80	91	94	76	75	95
13	10b	11b	2-MEMO	R	96	67	87	53	78	98
14	10c	11c	2-Me	R	88	90	91	85	69	92
15	10d	11d	2-F	R	78	92	93	75	73	95
16	10e	11e	2-Cl	R	77	88	87	72	80	91
17	10f	11f	2-Br	R	76	88	84	78	77	93

Table 1. Enantioselective reduction of carbonyl compounds 1, 2, 3 and 10 in the presence of catecholborane 7 or the borane-dimethylsulfide complex 8 and (S)-5,5-diphenyl-2-butyl-3,4-propano-1.3.2-oxazaborolidine 9 using Methods 1-3

[a] Method 1: Reduction was performed with catecholborane 7. - [b] Method 2: Reduction was performed with borane-dimethylsulfide 8 (addition of the reducing reagent to a mixture of the catalyst and the keto compound). - [c] Method 3: Reduction was performed with borane-dimethylsulfide 8 (addition of the keto compound to a mixture of the catalyst and the reducing reagent; Corey's conditions<sup>22</sup>). - [d] Stereochemistry was determined by an X-ray crystal structure of  $4e^{25}$ , chemical correlation<sup>9c</sup> and CD spectroscopy<sup>9d</sup>. - [e] Determined by <sup>3</sup>P and <sup>1</sup>H NMR analysis of the corresponding (R)-(+)-Mosher or (1S)-(-)-camphanic acid esters. Surprisingly we observed some marked differences in the enantiomeric excesses using the three different reducing conditions. First of all, the reactions conducted with catecholborane 7 (Method 1) yielded excellent enantiomeric excesses for the 2-substituted diisopropyl  $\alpha$ -hydroxybenzyl- 1 and the diisopropyl  $\beta$ -hydroxyalkylphosphonate 5<sup>15,16</sup>. Only the enantiomeric excesses found in the reaction of the  $\alpha$ - 1a and the  $\gamma$ -ketophosphonate 6 were markedly lower for some unknown reasons. We explain the lower ee values for the 3-chlorophenyl- 4e, the  $\beta$ -naphthyl- 4f and the 4-chlorophenyl derivate 4g with the structural differences of the keto compounds 1e-1g as compared to the 2-substituted compounds as mentioned before (entries 5-7)<sup>16</sup>. Nevertheless, according to Method 1, the acetophenone derivatives 10, especially the 2-OMEM-acetophenone 10b (entry 13), yielded somewhat lower enantiomeric excesses of the hydroxyl compounds 11.

As compared to the catecholborane reductions, the introduction of the borane-dimethylsulfide complex 8 resulted in a more complicated picture. According to Method 2 we obtained lower ee values as compared to Method 1. Again the 3-chloro- le and the 4-chloro derivate lg yielded the lowest ee values. Additionally, the two 2-OR substituted keto compounds 1a and 10b showed lower ee's as compared to the other 2-substituted starting compounds. In this case we observed no dramatic difference in stereoselectivity between the ketophosphonates 1, 2 and 3 and the acetophenones 10. This changed using Method 3: Here the  $\alpha$ -ketophosphonates 1 yielded substantially lower ee's as compared to all acetophenones 10 and surprisingly also to the  $\beta$ -2 and  $\gamma$ -ketophosphonate 3. As a consequence, these compounds 2 and 3 represent the links between the acetophenone and the  $\alpha$ -ketophosphonate reductions. The  $\gamma$ -ketophosphonate 3 reacted as the acetophenones and no influence of the phosphonyl group could be detected. It should be mentioned that to the best of our knowledge, this is the best approach towards chiral, nonracemic y-hydroxyphosphonates reported so far (ee >98%<sup>26</sup>, entry 11, Method 3; Table 1). On the other hand the  $\beta$ -ketophosphonate 2 represents the borderline case: it yielded lower ee's than the acetophenones and higher ee's than the  $\alpha$ -ketophosphonates. The pronounced difference in stereoselectivity in the reduction of the  $\alpha$ -ketophosphonates 1 according to Method 2 and Method 3 is obviously a result of the phosphonyl group: following Method 2 we added the borane complex to a mixture of the catalyst and 1. As a consequence only a small amount of the borane reagent is present in the reaction mixture. In contrast, according to Corey's conditions a high excess of reducing agent is present because the starting ketones 1 were added to the ketone and the catalyst. We observed before that reductions using the borane-dimethylsulfide complex 8 occurred in the presence and in the absence of the oxazaborolidine catalyst in comparable reaction times. On the other hand the reduction of the acetophenones 10 occurred with very different reaction times. These data clearly show that the phosphonyl group represents an activator leading to a more reactive carbonyl group in the  $\alpha$ -ketophosphonates 1 (acceptor substituent<sup>27</sup>) and we have two concurrent reactions taking place: the catalyzed, stereodifferentiating reaction and the uncatalyzed reaction leading to the racemic products. So for 1 the function of the catalyst 9 is more the stereodifferentiating function than the rate acceleration. The situation is different in the case of the catecholborane reductions because catecholborane is a much less reactive reducing agent than the borane-dimethylsulfide or the borane-THF complexes<sup>28</sup> and consequently the complexation with the catalyst has two functions: the stereodifferentiation and the rate acceleration<sup>29</sup>. So the higher reactivity of the  $\alpha$ -ketophosphonates 1 is compensated for the lower reactivity of the reducing agent. The reason why the 2-OR substituted compounds 1a and 10b (entry 1 and 13; Table 1) led to lower ee values is presumably an effect of the proximal heteroatom and a two-point catalyst-substrate binding or distortion<sup>30</sup>. Another effect of the phosphonyl group could be assumed from the results listed in Table 1, Method 1). As described above the ee values of the  $\alpha$ -ketophosphonates 1 were somewhat higher than those of the acetophenones 10. A better complexation of 1 as compared to 10 could be the reason because the nucleophilicity of the oxygen atom in 1 seems to be higher than in 10. Evidence for this explanation was taken from the IR spectra of the ketones 1 and 10. In all cases the wave number of the C=O-absorption band of the

ketones 1 was about 25-40 cm<sup>-1</sup> lower than that of the acetophenones  $(1690-1700 \text{ cm}^{-1})^{31}$ . Consequently the force constant of the carbonyl bond is also smaller for the  $\alpha$ -ketophosphonates and a higher electron density at the oxygen atom results ( $\sigma$ -acceptor- $\pi$ -donor activity of the phosphonyl group). This conclusion is also supported by the results obtained from the  $\beta$ - and  $\gamma$ -ketophosphonates were the influence of the phosphonyl group decreases (entry 10,11; Table 1).

In summary, by comparison with the acetophenones 10, the described oxazaborolidine catalyzed enantioselective reduction of  $\alpha$ - 1,  $\beta$ - 2, and  $\gamma$ -ketophosphonates 3 with catecholborane 7 and the boranedimethylsulfide complex 8 demonstrated the effect of the phosphonyl group. So beside the influence of the substituted aryl moiety studied before<sup>16</sup> also the phosphonyl group influences the enantioselective reductions of the  $\alpha$ - and  $\beta$ -ketophosphonates in contrast to the  $\gamma$ -ketophosphonates. Whereas the reason for the effect of the aryl residue is a structural one the effect of the phosphonyl group is more a tuning of the reactivity of the carbonyl group. Additionally, a consequence of our study is that for activated ketones (here the acceptor group phosphonyl) the reaction condition could be adapted in order to obtain an efficient stereoselectivity in the synthesis of chiral, nonracemic  $\alpha$ -hydroxybenzyl-,  $\beta$ - and  $\gamma$ -hydroxyalkylphosphonates.

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## EXPERIMENTAL

Melting points (uncorrected): Apparatus of Tottoli (Büchi). - Optical rotations: Perkin-Elmer 241; solvent was CHCl<sub>3</sub> p. a. (Merck, Darmstadt). - FTIR: Perkin-Elmer 1600. - <sup>31</sup>P (162 MHz), <sup>13</sup>C (100.6 MHz) and <sup>1</sup>H NMR (400 MHz): Bruker AMX 400; OH signals regularly confirmed by D<sub>2</sub>O exchange; solvent was CDCl<sub>3</sub>; internal standards: tetramethylsilane (<sup>1</sup>H NMR), CDCl<sub>3</sub> (<sup>13</sup>C NMR), phosphorus acid was used as external standard for the <sup>31</sup>P NMR spectra. All <sup>13</sup>C and the <sup>31</sup>P NMR spectra were recorded in the proton-decoupled mode. Chemical shifts are given in  $\delta$  (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<sub>254</sub> gipshaltig (Merck, Darmstadt). - Analytical thin-layer chromatographies (all reactions were monitored using TLC) were performed on silica gel 60 F<sub>254</sub> aluminium plates (0.2 mm; Merck, Darmstadt) containing a fluorescent indicator. - Solvents: THF and toluene were purchased from (Fluka). - (1S)-(-)-camphanic acid (Fluka), R-(+)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetic acid (Fluka); borane•DMS complex (2M in THF, Aldrich) and catecholborane (1M in THF, Aldrich) are commercially available. - (S)-5,5-Diphenyl-2-butyl-3,4-propano-1.3.2-oxazaborolidine was prepared according to the literature<sup>20</sup> from *n*-butylboronic acid and (S)-2-(diphenylhydroxymethyl)pyrrolidine in toluene or THF solution just prior to use.

#### **General Experimental Procedures**

Method 1: In a typical experiment to a solution of 1.00 mmol of the ketophosphonates 1, 2, 3 or the acetophenone 10 and (S)-5,5-diphenyl-2-butyl-3,4-propano-1.3.2-oxazaborolidine 9 (0.12 mmol, 0.12 equiv.)

in 3.0 ml toluene a THF solution of 1.1 ml of catecholborane 7 (1 M; 1.1 equiv.) was added at -80°C. The reaction mixture was stored 5 h at -20°C. After that time the mixture was diluted at room temperature by the addition of 20 ml Et<sub>2</sub>O, extracted 4x with 5 ml each of a saturated NaHCO<sub>3</sub> solution, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was subjected to preparative TLC using a 0-5 % gradient of CH<sub>3</sub>OH in CH<sub>2</sub>Cl<sub>2</sub>.

Method 2: 1.00 mmol of the ketophosphonates 1, 2, 3 or the acetophenones 10 were added to a solution of *n*butyl-oxazoborolidine 9 (0.12 mmol, 0.12 equiv.) in 1.5 ml of dry THF. Subsequently, the borane 8 (0.66 mmol, 0.66 equiv.) was added dropwise at room temperature within 5.5 h. The reaction mixture was stirred for 30 min, the reaction was quenched with 1.0 ml of CH<sub>3</sub>OH, the mixture filtered through Celite and concentrated in vacuo. The residue was purified as mentioned above (Method 1).

*Method 3*: The borane **8** (0.66 mmol, 0.66 equiv.) was added to a solution of the catalyst **9** (0.12 mmol, 0.12 equiv.) in 1.5 ml of dry THF. 1.00 mmol of the ketophosphonates **1**, **2**, **3** or 1.00 mmol of the acetophenones **10** solubilized in 1.0 ml THF were added dropwise at room temperature within 10 min. The reaction mixture was stirred for further 10 min, then the reaction was quenched with 1.0 ml of CH<sub>3</sub>OH, the mixture filtered through Celite and concentrated in vacuo. The residue was purified as mentioned above (Method 1).

#### Diisopropyl 1-naphthoylphosphonate (1d)

0.95 g of 1-Naphthoyl chloride (5.0 mmol) were heated to 80 °C in an argon atmosphere. 1.04 g Triisopropyl phosphite (1.0 equiv., 5.0 mmol) were added dropwise over 2 h. The reaction mixture was stirred for another 2 h at 80 °C, dried at 10<sup>-2</sup> Torr and finally subjected to preparative TLC using a gradient of 20-50 % ethyl acetate in *n*-hexane. 1d was obtained as an yellow solid (1.51 g, 94 %), m.p. 42-44 °C. [Found, C, 63.83; H, 6.44 %. C<sub>17</sub>H<sub>21</sub>O<sub>4</sub>P requires C, 63.74; H, 6.61 %];  $v_{max}$  (KBr)/cm<sup>-1</sup> 1648 (CO), 1241 (PO) and 996 (POC);  $\delta_{H}$  1.38 [12H, d, J 6.2, CH(CH<sub>3</sub>)<sub>2</sub>], 4.82-4.93 [2H, m, CH(CH<sub>3</sub>)<sub>2</sub>] and 7.53-7.66, 7.87-7.90, 8.06-8.08, 8.85-8.87 (7H, m, Ar*H*);  $\delta_{C}$  23.7, 24.0 [CH(CH<sub>3</sub>)<sub>2</sub>], 73.0 [d, J 8.0, CH(CH<sub>3</sub>)<sub>2</sub>], 124.4, 125.3, 126.7, 128.6, 128.9, 130.2, 130.3, 133.8, 135.0 (Ar), 132.1 (d, J 64.4, CCO) and 201.9 (d, J 174, CO);  $\delta_{P}$  -2.2.

#### Diisopropyl 2-naphthoylphosphonate (1f)

If was prepared analogously to 1d. 1f was obtained as an yellow oil (1.38 g, 86 %). [Found, C, 63.47; H, 6.57 %.  $C_{17}H_{21}O_4P$  requires C, 63.74; H, 6.61 %];  $v_{max}$  (film)/cm<sup>-1</sup> 1650 (CO), 1249 (PO) and 992 (POC);  $\delta_H$  1.38, 1.39 [12H, d, J 5.8, CH(CH<sub>3</sub>)<sub>2</sub>], 4.83-4.91 [2H, m, CH(CH<sub>3</sub>)<sub>2</sub>] and 7.53-7.63, 7.84-7.90, 8.01-8.03, 8.11-8.13, 9.07 (7H, m, ArH);  $\delta_C$  23.9, 24.1 [CH(CH<sub>3</sub>)<sub>2</sub>], 73.1 [d, J 7.3, CH(CH<sub>3</sub>)<sub>2</sub>], 123.6, 127.0, 127.8, 128.7, 129.4, 130.3, 132.4, 134.0, 136.2 (Ar), 133.2 (d, J 63.9, CCO) and 199.4 (d, J 177, CO);  $\delta_P$  -2.1.

#### 2-Methoxyethoxymethoxyacetophenone (10b)

To a suspension of 0.25 g of sodium hydride (1.3 equiv., 10.4 mmol) in 16.0 ml of dry THF were added at 0 °C 1.09 g of 2-hydroxyacetophenone (8.0 mmol) and 1.60 g of chloromethyl methoxyethyl ether (1.6 equiv., 12.8 mmol) simultaneously within 15 min. The reaction mixture was stirred for 30 min at 0 °C and for 2 h at room temperature, quenched with 5 ml of water and extracted 3x with 40 ml of CH<sub>2</sub>Cl<sub>2</sub>. The combined

organic phases were dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was subjected to preparative TLC using a 0-15 % gradient of CH<sub>3</sub>OH in CH<sub>2</sub>Cl<sub>2</sub> to afford **10b** as a colorless oil (1.48 g, 83 %). [Found, C, 64.00; H, 7.25 %. C<sub>12</sub>H<sub>16</sub>O<sub>4</sub> requires C, 64.27; H, 7.19 %];  $v_{max}$  (film)/cm<sup>-1</sup> 1678 (CO);  $\delta_{H}$  2.62 (3H, s, CH<sub>3</sub>CO), 3.37 (3H, s, OCH<sub>3</sub>), 3.54-3.62, 3.82-3.86 (4H, m, OCH<sub>2</sub>CH<sub>2</sub>O), 5.37 (2H, s, OCH<sub>2</sub>O) and 7.00-7.06, 7.20-7.23, 7.39-7.46, 7.67-7.71 (4H, m ArH);  $\delta_{C}$  32.0 (CH<sub>3</sub>CO), 59.3 (OCH<sub>3</sub>), 68.4, 71.8 (OCH<sub>2</sub>CH<sub>2</sub>O), 93.8 (OCH<sub>2</sub>O), 115.2, 122.0, 130.4, 133.7 (Ar), 129.3 (CCO), 156.6 (COCH<sub>2</sub>) and 200.0 (CO).

# (S)-Diisopropyl 1-hydroxy-(1-naphthyl)methylphosphonate (4d) + ent-4d

The mixtures of **4d** + *ent*-**4d** were obtained according to methods 1-3 as colorless solids, m.p. 123-125 °C. [Found, C, 63.53; H, 7.20 %.  $C_{17}H_{23}O_4P$  requires C, 63.34; H, 7.19 %];  $v_{max}$  (KBr)/cm<sup>-1</sup> 3264 (OH), 1230, 1211 (PO) and 997 (POC);  $\delta_H 0.88$ , 1.14, 1.17, 1.24 [12H, d, J 6.2, CH(CH<sub>3</sub>)<sub>2</sub>], 4.49-4.67 [3H, m, OH and CH(CH<sub>3</sub>)<sub>2</sub>], 5.80 (1H, dd, J 22.9, J 3.6, CHOH) and 7.43-7.50, 7.70-7.84, 7.89-7.92, 8.07-8.09 (7H, m, ArH);  $\delta_C$  23.2, 23.8, 23.9, 24.1 [CH(CH<sub>3</sub>)<sub>2</sub>], 67.3 (d, J 163, CHOH), 71.6, 72.1 [d, J 7.5, CH(CH<sub>3</sub>)<sub>2</sub>], 124.0, 125.2, 125.4, 125.5, 125.7, 128.4, 128.5, 131.0, 133.3 and 133.5 (Ar);  $\delta_P$  20.9.

#### (S)-Diisopropyl 1-hydroxy-(2-naphthyl)methylphosphonate (4f) + ent-4f

The mixtures of **4f** + *ent*-**4f** were obtained according to methods 1-3 as colorless solids, m.p. 110-111 °C. [Found, C, 63.22; H, 7.25 %.  $C_{17}H_{23}O_4P$  requires C, 63.34; H, 7.19 %];  $v_{max}$  (KBr)/cm<sup>-1</sup> 3280 (OH), 1234 (PO) and 993 (POC);  $\delta_H$  1.09, 1.17, 1.24 [12H, d, J 6.2, CH(CH<sub>3</sub>)<sub>2</sub>], 4.55-4.71 [3H, m, OH and CH(CH<sub>3</sub>)<sub>2</sub>], 5.13 (1H, d, J 11.4, CHOH) and 7.42-7.47, 7.59-7.66, 7.77-7.84, 7.94 (7H, m, ArH);  $\delta_C$  23.6, 23.9, 24.0, 24.1 [CH(CH<sub>3</sub>)<sub>2</sub>], 71.2 (d, J 161, CHOH), 71.9, 72.1 [d, J 7.5, CH(CH<sub>3</sub>)<sub>2</sub>], 115.6, 120.3, 125.2, 126.0, 126.2, 126.3, 127.6, 128.1, 133.1 and 134.4 (Ar);  $\delta_P$  20.4.

## (R)-1-(2-Methoxyphenyl)ethanol (11a) + ent-11a

The mixtures of **11a** + *ent*-**11a** were obtained according to methods 1-3 as colorless oils. [Found, C, 70.85; H, 8.18 %. C<sub>9</sub>H<sub>12</sub>O<sub>2</sub> requires C, 71.03; H, 7.95 %];  $\nu_{max}$  (film)/cm<sup>-1</sup> 3402 (OH);  $\delta_{H}$  ref. 32;  $\delta_{C}$  23.2 (CH<sub>3</sub>), 55.5 (OCH<sub>3</sub>), 66.6 (CHOH), 110.7, 121.0, 126.3, 128.5 (Ar), 133.8 (CCHOH) and 156.8 (COCH<sub>3</sub>).

# (R)-1-(2-Methoxyethoxymethoxyphenyl)ethanol (11b) + ent-11b

The mixtures of **11b** + *ent*-**11b** were obtained according to methods 1-3 as colorless oils. [Found, C, 63.43; H, 8.29 %.  $C_{12}H_{18}O_4$  requires C, 63.70; H, 8.02 %];  $v_{max}$  (film)/cm<sup>-1</sup> 3427 (OH);  $\delta_H$  1.50 (3H, d, J 6.6, CH<sub>3</sub>), 2.33 (1H, s, OH), 3.36 (3H, s, OCH<sub>3</sub>), 3.54-3.62, 3.77-3.89 (4H, m, OCH<sub>2</sub>CH<sub>2</sub>O), 5.15 (1H, q, J 6.5, CHOH), 5.33 (2H, s, OCH<sub>2</sub>O) and 6.99-7.05, 7.11-7.14, 7.19-7.25, 7.37-7.40 (4H, m, ArH);  $\delta_C$  23.4 (CH<sub>3</sub>), 59.2 (OCH<sub>3</sub>), 66.0 (CHOH), 68.2, 71.9 (OCH<sub>2</sub>CH<sub>2</sub>O), 93.8 (OCH<sub>2</sub>O), 114.4, 122.3, 126.4, 128.5 (Ar), 134.6 (CCHOH) and 154.3 (COCH<sub>2</sub>).

#### (R)-1-(2-Methylphenyl)ethanol (11c) + ent-11c

The mixtures of 11c + *ent*-11c were obtained according to methods 1-3 as colorless oils. [Found, C, 79.10; H, 8.93 %. C<sub>9</sub>H<sub>12</sub>O requires C, 79.37; H, 8.88 %];  $\nu_{max}$  (film)/cm<sup>-1</sup> 3357 (OH);  $\delta_{H}$  ref. 33;  $\delta_{C}$  18.8 (ArCH<sub>3</sub>), 23.9 (CH<sub>3</sub>), 66.7 (CHOH), 124.5, 126.3, 127.1, 130.3 (Ar), 134.2 (CCH<sub>3</sub>) and 143.8 (CCHOH).

## (R)-1-(2-Fluorophenyl)ethanol (11d) + ent-11d

The mixtures of **11d** + *ent*-**11d** were obtained according to methods 1-3 as colorless oils. [Found, C, 68.46; H, 6.49 %. CgH9FO requires C, 68.56; H, 6.47 %];  $v_{max}$  (film)/cm<sup>-1</sup> 3360 (OH);  $\delta_{H}$  ref. 34;  $\delta_{C}$  23.9 (CH<sub>3</sub>), 64.4 (d, J 3.1, CHOH), 115.2 (d, J 21.8). 124.2 (d, J 3.5), 126.6 (d, J 4.6), 128.6 (d, J 8.3, Ar), 132.6 (d, J 13.3, CCHOH) and 159.6 (d, J 245, CF).

# (R)-1-(2-Chlorophenyl)ethanol (11e) + ent-11e

The mixtures of **11e** + *ent*-**11e** were obtained according to methods 1-3 as colorless oils. [Found, C, 61.07; H, 6.03 %. C<sub>8</sub>H<sub>9</sub>ClO requires C, 61.35; H, 5.79 %];  $v_{max}$  (film)/cm<sup>-1</sup> 3356 (OH);  $\delta_{H}$  ref. 32, 33;  $\delta_{C}$  23.4 (CH<sub>3</sub>), 66.8 (CHOH), 126.4, 127.1, 128.3, 129.3 (Ar), 131.5 (CCl) and 143.0 (CCHOH).

#### (R)-1-(2-Bromophenyl)ethanol (11f) + ent-11f

The mixtures of 11f + *ent*-11f were obtained according to methods 1-3 as colorless oils. [Found, C, 48.03; H, 4.64 %. C<sub>8</sub>H<sub>9</sub>BrO requires C, 47.79; H, 4.51 %];  $v_{max}$  (film)/cm<sup>-1</sup> 3351 (OH);  $\delta_{H}$  and  $\delta_{C}$  ref. 35.

		Method 1	Method 2	Method 3	Derivative	Spectroscopy		
Product	R	$[\alpha]_{D}^{20}(c)$	$[\alpha]_{D}^{20}(c)$	$\left[\alpha\right]_{D}^{20}\left(c\right)$	A <sup>[a]</sup> or	1H[c]	13C[c]	31p[c]
<b>4</b> a	2-MeO-Ph	-22.5 (0.9)	-14.6 (0.8)	-6.5 (0.9)	А	[16]	[16]	[16]
4b	2-Me-Ph	-60.0 (0.9)	-47.0 (0.9)	-25.3 (0.8)	А	[16]	[16]	[16]
4c	2-Cl-Ph	-65.8 (0.9)	-53.6 (0.9)	-33.2 (0.9)	Α	[16]	[16]	[16]
4d	$\alpha$ -Naphthyl	-108.4 (1.1)	-89.8 (1.1)	-36.9 (1.1)	Α	s. below		
4e	3-Cl-Ph	-16.8 (0.8)	-11.5 (0.8)	-8.5 (0.9)	А	[16]	[16]	[16]
4f	β-Naphthyl	-17.9 (1.1)	-7.3 (1.0)	-8.2 (1.0)	В	s. below		
4 g	4-Cl-Ph	-22.4 (1.0)	-1.2 (1.0)	-12.5 (0.9)	А	[16]	[16]	[16]
4h	2-F-Ph	-18.1 (0.7)	-11.3 (0.7)	-13.3 (0.8)	В	[16]	[16]	[16]
4 i	2-Br-Ph	-59.0 (1.5)	-36.0 (1.5)	-26.7 (1.5)	А	[16]	[16]	[16]
5		+25.1 (0.8)	+18.6 (0.8)	+22.9 (0.8)	В	[16]	[16]	[16]
6		+18.7 (0.8)	+20.8 (0.8)	+27.0 (0.9)	В	s. below	[16]	[16]
11a	2-MeO	+23.4 (1.0)	+19.6 (0.9)	+24.4 (1.0) <sup>[d]</sup>	Α	[32]	s. below	
11b	2-MEMO	+11.7 (0.9)	+9.3 (0.9)	+17.1 (1.0)	Α	s. below		
11c	2-Me	+67.8 (1.1)	+64.1 (1.0)	+69.3 (1.0)[e]	А	[33]	s. below	
11d	2-F	+44.0 (1.4)	+35.8 (1.3)	+45.4 (1.4)	А	[34]	s. below	
11e	2-Cl	+58.4 (1.1)	+47.8 (1.1)	+60.3 (1.1)[f]	Α	[32,33]	s. below	
11f	2-Br	+47.1 (1.3)	+41.8 (1.3)	+49.8 (1.3) <sup>[g]</sup>	Α	[3 <i>5</i> ]	[35]	

Table 2. Characterization of the target compounds 4, 5, 6 and 11

[a] Determined by <sup>31</sup>P or <sup>1</sup>H NMR analysis of the corresponding (1S)-(-)-camphanic acid ester derivative. - [b] Determined by <sup>31</sup>P or <sup>1</sup>H NMR analysis of the corresponding (R)-(+)-Mosher ester derivative. - [c] reference to the literature. - [d]  $\left[\alpha\right]_{D}^{20}$  = +22.4 (CHCl<sub>3</sub>), 82 % ee (R), ref. 36. - [e]  $\left[\alpha\right]_{D}^{22}$  = +50.46 (neat), 91 % ee (R), ref. 37. - [f]  $\left[\alpha\right]_{D}^{22}$  = -35.88 (benzene, c 1.14), 77 % ee (S), ref. 37. - [g]  $\left[\alpha\right]_{D}^{22}$  = -58.8 (CH<sub>2</sub>Cl<sub>2</sub>, c 0.17), > 99 % ee (S), ref. 35.

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- 26. In this case only one diastereomer was observed in the <sup>31</sup>P NMR spectrum. We knew before that the (1S)-(-)-camphanic acid ester of racemic **6** showed two well separated signals.
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