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Stereochemistry of the addition of dialkyl phosphites to (*S*)-*N*,*N*-dibenzylphenylglycinal

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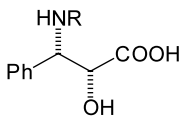
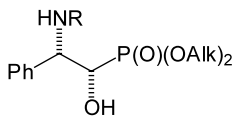
Abstract—The addition of various dialkyl phosphite derivatives to (*S*)-*N*,*N*-dibenzylphenylglycinal **6** led to the preponderance of *anti* over *syn* diastereoisomers: from 75:25 when NEt_3 or $Ti(OiPr)_4$ were used to 51:49 for Li or Mg salts. In the NEt_3-catalysed reaction, partially racemised phosphonates were formed, while enantiomeric products were obtained after addition of lithium *O*,*O*-dimethylphosphonate to (*S*)-**6** at −70°C. Because the *syn*-isomers were found to be resistant to *O*-benzoylation, mixtures of diastereoisomers were easily separated after esterification of the *anti* products. Hydrogenation of the *syn*-phosphonates in the presence of Boc_2O gave enantiomeric dialkyl *N*-Boc-2-amino-1-hydroxy-2-phenylethylphosphonates—phosphonate analogues of the docetaxel C-13 side chain.

1. Introduction

Paclitaxel and its semi-synthetic analogue docetaxel are among the most important anti-cancer agents clinically used for the treatment of various tumours.[1]

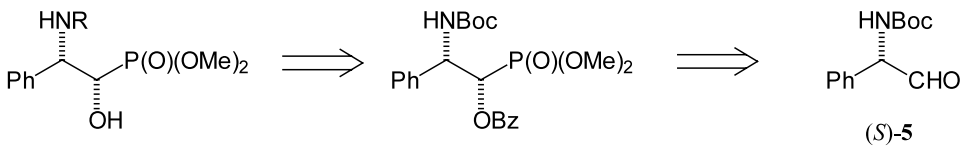


1 R = Bz
2 R = Boc



3 R = Bz
4 R = Boc
Alk = Me, Et

The search for structural analogues of **1** and **2** has focused on the modification of the C-13 side chains, i.e. *N*-benzoyl- and *N*-Boc-(2*R*,2*S*)-3-phenylisoserine **1** and **2** and has included replacement of the phenyl group with various substituents[2–16] or *H*-C_α with alkyl groups.[17,18] For some time we have been involved in the synthesis of dialkyl (1*S*,2*S*)-2-(benzoylamino)- and 2-[(*tert*-butoxycarbonyl)amino]-1-hydroxy-2-phenylethylphosphonates **3**[19] and **4**[20] as possible bioisosteric analogues[21] of the paclitaxel and docetaxel C-13 side chains. Having accomplished the synthesis of enantiomers of **3** and **4** we turned to the asymmetric synthesis of these compounds. Our experience with the chemistry of the phosphonates **3** and **4** led us to conclude that the most straightforward approach would involve the addition of dimethyl phosphite to *N*-Boc-(*S*)-phenylglycinal **5**, separation of the *syn*- and *anti*-α-hydroxyphosphonates via the *O*-benzoyl derivatives, followed by two one-step transformations of the *syn*-diastereoisomer into **3** and **4** (Alk = Me) (Scheme 1). Unfortunately in our hands attempts at preparation of



3 R = Bz
4 R = Boc

(*S*)-**5**

Scheme 1.

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enantiomerically pure (*S*)-**5** by the DIBAL-H reduction of methyl *N*-Boc-(*S*)-phenylglycinate[22] failed.†

For this reason a search for other phenylglycinal derivatives was conducted and a recent review[23] brought to our attention *N*,*N*-dibenzylphenylglycinal[24–27] as a stereochemically stable alternative to (*S*)-**5**. However, several literature reports[23,24,28–30] noticed the predominance of the *anti* products in nucleophilic additions to *N*,*N*-disubstituted α-amino aldehydes opposite to *N*-monosubstituted analogues, which afforded *syn*-isomers as the major products (Scheme 2). Herein, the stereochemistry of the addition of dialkyl phosphites to (*S*)-*N*,*N*-dibenzylphenylglycinal **6** will be described followed by transformation of the *syn* adducts into diastereoisomeric *N*-Boc-2-amino-1-hydroxy-2-phenylethylphosphonates.

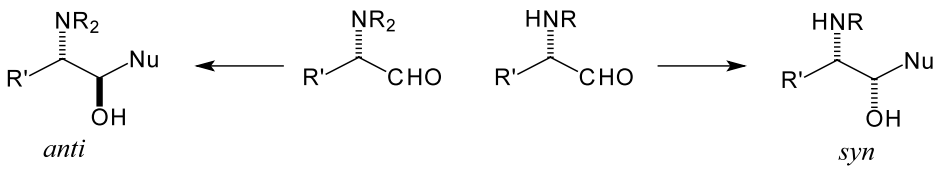
2. Results and discussion

Oxidation of (*S*)-*N*,*N*-dibenzylphenylglycinol to the respective aldehyde (*S*)-**6** was accomplished with the DMSO–oxalyl chloride–NEt_3 mixture (Swern oxidation[31]). The crude product was sufficiently pure by ^1H NMR to be used in the next step. We found that a chloroform solution of **6** was stable at room temperature for at least 24 h. Addition of dialkyl phosphites was, however, carried out immediately after the purification of the aldehyde. In NEt_3-catalysed reactions, mixtures of diastereoisomeric dimethyl or diethyl 2-(*N*,*N*-dibenzylamino)-1-hydroxy-2-phenylethylphosphonates were obtained (Scheme 3). Ratios of 78:22 and 80:20 for **7**:**8** and **9**:**10**, respectively, were established from the ^{31}P NMR spectra. Attempts at separating these mixtures by chromatography on silica gel with various solvent systems met with partial success.

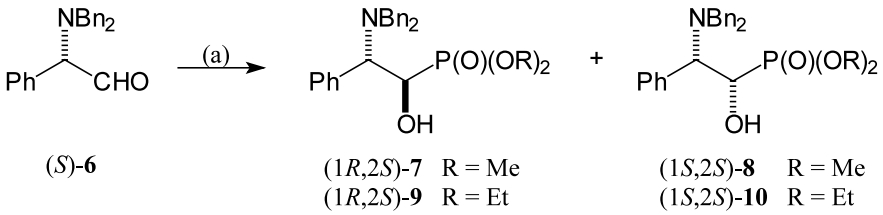
The e.e. of the α-hydroxyphosphonates **7** and **8** (methyl esters), and **9** and **10** (ethyl esters) obtained in the NEt_3-catalysed reactions were studied by the ^{31}P NMR spectroscopy after esterification of the crude reaction mixtures with (*S*)-*O*-methylmandelic acid.[32] It appeared that after the 24 h usually required to complete the esterification, the *anti*-diastereoisomers **7** and **9** were quantitatively transformed into esters, while the *syn*-isomers remained unreacted. Based on these data, the e.e.s of (1*R*,2*S*)-**7** and (1*R*,2*S*)-**9** were established as 84 and 55%, respectively. It is reasonable to assume that the e.e. of the *syn*-diastereoisomers (1*S*,2*S*)-**8** and (1*S*,2*S*)-**10** are the same as those measured for the respective *anti*-isomers.

We suspect that the application of NEt_3 as a catalyst in the Abramov reaction was responsible for the partial racemisation of the aldehyde (*S*)-**6**, and in consequence, phosphonates **7** and **8** (*O*-methyl) and **9** and **10** (*O*-ethyl) were obtained with lower e.e. Significantly diminished e.e. of the ethyl ester **9** could be associated with the lower rate of the addition of diethyl phosphite in comparison with its methyl analogue, in agreement with our previous observations for the additions to Garner aldehyde.[33] We reasoned that in the presence of NEt_3 dialkyl phosphites are not sufficiently nucleophilic to add to the carbonyl group of (*S*)-**6** faster than the rate of racemisation of the aldehyde.

To further support these conclusions, a preliminary study of the racemisation of (*S*)-**6** in the presence of NEt_3 was undertaken. A mixture of (*S*)-**6** and NEt_3 (30



Scheme 2.



(*S*)-**6**

(1*R*,2*S*)-**7** R = Me
(1*R*,2*S*)-**9** R = Et

(1*S*,2*S*)-**8** R = Me
(1*S*,2*S*)-**10** R = Et

Scheme 3. *Reagents and conditions*: (a) $(MeO)_2P(O)H$ or $(EtO)_2P(O)H$ 1 equiv., NEt_3 10 mol%.

† Removal of aluminium salts was an extremely time consuming step which led to significant racemisation.

mol%)[‡] was kept at room temperature for 24 h. Samples were withdrawn after 1, 2 and 3 h after the addition of the amine and were immediately reduced with sodium borohydride at 0°C.[22] The e.e. of the (*S*)-*N*,*N*-dibenzylphenylglycinols were estimated by ^{1}H NMR spectroscopy after derivatisation with (*S*)-*O*-methylmandelic acid.[32] Including the e.e. of (*S*)-*N*,*N*-dibenzylphenylglycinol obtained from (*S*)-**6** just before addition of NEt_3 (time 0 h), the following rate of the racemisation was observed: $t=0$ h, e.e. 90%; $t=1$ h, e.e. 44%; $t=2$ h, e.e. 28% and $t=3$ h, e.e. = 20%. Furthermore, in the presence of NEt_3 (*S*)-**6** was simultaneously undergoing decomposition to unidentified products and no aldehyde resonance was found in the ^{1}H NMR spectrum after 24 h.

In order to circumvent the problem of the low nucleophilicity of the dialkyl phosphite and, at the same time, minimise racemisation of (*S*)-**6** by triethylamine, lithium *O*,*O*-dimethylphosphonate was added at −70°C to the in situ generated aldehyde (*S*)-**6**. Under these conditions a 75:25 mixture of (1*R*,2*S*)-**7** and (1*S*,2*S*)-**8** was formed, while using $Li^{+-}P(O)(OEt)_2$ the respective diastereoisomeric phosphonates were produced in a 72:28 ratio. After purification on a silica gel column, the e.e. of (1*R*,2*S*)-**7** was estimated by ^{31}P NMR spectroscopy as 100% after derivatisation with ω-camphanyl chloride.

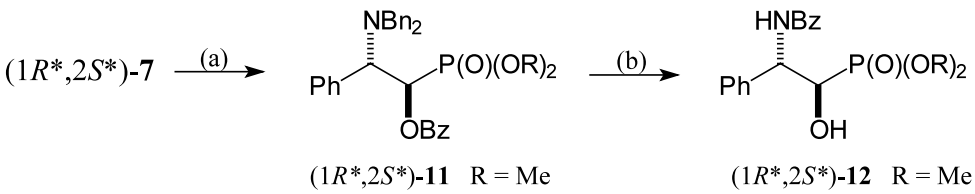
In establishing the relative configurations of the diastereoisomeric phosphonates **7**/**8** and **9**/**10** we relied on the transformation of **7** into the known compounds **12** and **13**. Pure **7** was isolated as a racemate[§] after crystallisation of a 78:22 mixture of diastereoisomeric dimethyl phosphonates **7** and **8** obtained in NEt_3-catalysed addition of dimethyl phosphite to (*S*)-**6**. At first, the *O*-benzoate **11** was subjected to hydrogenolysis (Scheme 4). The reaction was extremely sluggish, leading to traces of dimethyl 2-(benzoylamino)-2-phenyl-1-hydroxyethylphosphonate **12** (δ ^{31}P NMR = 24.45 ppm).

Although both diastereoisomers of this compound are known,[19] we noticed that their ^{31}P NMR chemical shifts are solvent and concentration dependent and for this reason we were unable to assign the configuration unequivocally. However, the (1*R**,2*S**) configuration was extremely likely to be in agreement with our previous observations of slow intramolecular *O*–*N* transbenzoylation in structurally similar systems.[34] On the other hand, hydrogenolysis of racemic **7** in the presence of Boc_2O gave dimethyl (1*R**,2*S**)-2-[(*tert*-butoxycarbonyl)amino]-1-hydroxy-2-phenylethylphosphonate **13**[19] in almost quantitative yield (Scheme 5).

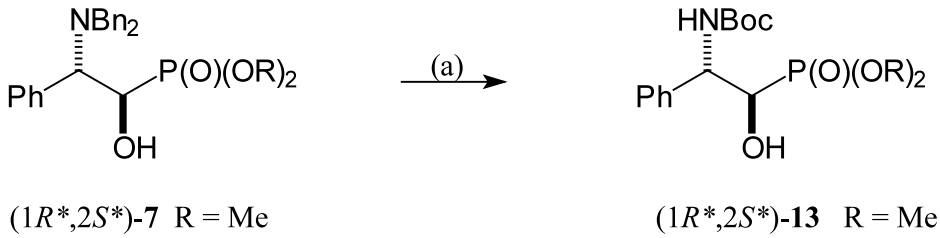
This assignment clearly showed that the addition of dialkyl phosphites to the aldehyde (*S*)-**6** in the presence of NEt_3 led to *anti*-diastereoisomers as the major products. In connection with our synthetic efforts directed

Table 1. Diastereoselectivity of the addition to (*S*)-**6**

Reagent	**7**	**8**	**9**	**10**
$(MeO)_2P(O)H/NEt_3$	78	22	–	–
$(EtO)_2P(O)H/NEt_3$	–	–	80	20
$(MeO)_2P(O)Li$	57	43	–	–
$(EtO)_2P(O)MgBr$	–	–	51	49
$(EtO)_2POTMS$	–	–	61	39
$(EtO)_2P(O)H/Ti(OiPr)_4$	–	–	72	28



Scheme 4. *Reagents and conditions*: (a) PhCOOH, DCC, DMAP; (b) H_2–$Pd(OH)_2$/C, methanol, 14 days.



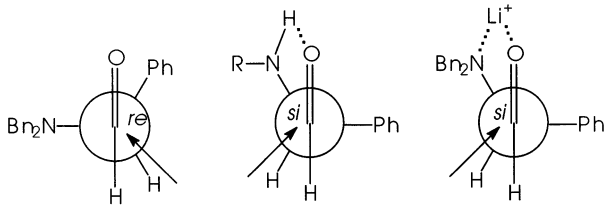
Scheme 5. *Reagents and conditions*: (a) H_2–$Pd(OH)_2$/C, Boc_2O, methanol, 24 h.

[‡] Although 10 mol% of NEt_3 was usually applied in the Abramov reaction, a three-fold excess of the amine was used to speed the racemisation up.

[§] Esterification of this material with (*S*)-*O*-methylmandelic acid gave a 1:1 mixture (by ^{31}P NMR) of the respective esters.

towards asymmetric synthesis of the phosphonate analogues of the paclitaxel and docetaxel C-13 side chains, we were interested in the preponderance of the *syn* diastereoisomers. For this reason, the diastereoselectivity of additions to (*S*)-**6** using other phosphonylating reagents was examined. The results collected in Table 1 left no doubt that the protection of the nitrogen atom in phenylglycinal with two benzyl groups led to a reversal of the stereochemistry of the reaction in comparison to those of the monosubstituted aldehydes, e.g. **5**.[20,35]

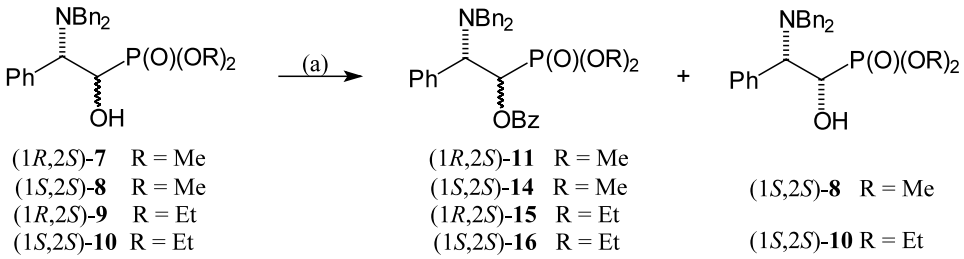
These results can be rationalised by referring to appropriate models of transition states in the additions to (*S*)-**5** or (*S*)-**6**.[23–25,28–30,36] Dimethyl phosphite approaches the *re* face of the carbonyl group in (*S*)-**6** preferentially, because in the presence of NEt_3 chelation is not possible (model **A**). On the other hand, in (*S*)-**5** (*N*-Boc) the intramolecular hydrogen bond stabilises conformation **B**, and the dialkyl phosphite attacks the *si* face of the carbonyl group, thus leading to the formation of the *syn*-adduct. This bonding is apparently stronger in (*S*)-**5** than in *N*-benzoylphenylglycinal, since in the presence of NEt_3 better diastereoselectivity was observed for the former.[20] Additions of metalated phosphites (Li^+, Mg^{2+}) to (*S*)-**6** gave increased amounts of *syn*-diastereoisomers due to involvement of the chelated conformation **C**.



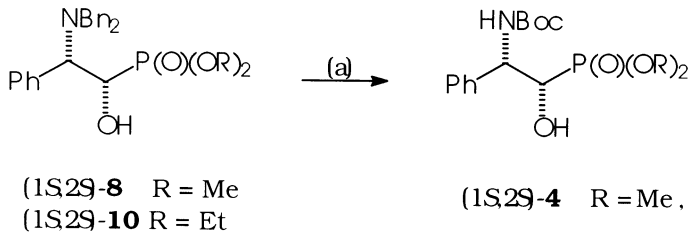
As mentioned above, esterification of mixtures of *syn*- and *anti*-diastereoisomers with (*S*)-*O*-methylmandelic acid revealed unexpected selectivity leading to formation of the *anti* esters while leaving the *syn* alcohols remained unreacted. We thought that this observation could be employed for the separation of the *syn*- and *anti*-diastereoisomers. Benzoylation of the 6:4 mixture of (1*R*,2*S*)-**7** and (1*S*,2*S*)-**8** (left after crystallisation of (±)-**7**) with 1 equiv. of benzoic acid gave *O*-benzoates (1*R*,2*S*)-**11** and (1*S*,2*S*)-**14** containing unreacted (1*S*,2*S*)-**8** in a 62:6:32 ratio (Scheme 6). Column chromatography of this mixture allowed us to separate pure (1*R*,2*S*)-**11**, (1*S*,2*S*)-**14** and (1*S*,2*S*)-**8** in 58, 1 and 14% yield, respectively.

Encouraged by the successful separation of (1*R*,2*S*)-**7** (as the *O*-benzoate) from (1*S*,2*S*)-**8** prepared from the partially racemised aldehyde (*S*)-**6**, we applied this procedure to the phosphonates obtained from the enantiomerically pure (*S*)-**6** and $Li^{+-}P(O)(OMe)_2$. A sample of enantiomerically pure (1*R*,2*S*)-**7** was separated from the crude product by column chromatography leaving a 1:1 mixture of (1*R*,2*S*)-**7** and (1*S*,2*S*)-**8**. In the next step this mixture was benzoylated with 0.5 equiv. of benzoic acid in the presence of DCC and DMAP,[32] and the less polar (1*R*,2*S*)-**11** was cleanly separated from the unreacted (1*S*,2*S*)-**8**, which was obtained in 13% yield. In a similar way the phosphonate (1*S*,2*S*)-**10** was also obtained in 13% yield.

Hydrogenolysis of the *syn*-diastereoisomers (1*S*,2*S*)-**8** and (1*S*,2*S*)-**10** (Scheme 7) in the presence of Boc_2O led to the methyl and ethyl *N*-Boc-phosphonates (1*S*,2*S*)-**4**, respectively, in 91 and 89% yield. After derivatisation with ω-camphanyl chloride, both phosphonates were found to be enantiomerically pure.



Scheme 6. *Reagents and conditions*: (a) PhCOOH, DCC, DMAP.



Scheme 7. *Reagents and conditions*: (a) H_2–$Pd(OH)_2$/C, Boc_2O, methanol or ethanol, 24 h.

3. Conclusions

It was found that the stereochemistry of the addition of dialkyl phosphites to *N*,*N*-dibenzylphenylglycinal is opposite to that observed earlier for the additions to *N*-Boc- and *N*-benzoylphenylglycinal. Mixtures of *anti*- and *syn*-2-(*N*,*N*-dibenzylamino)-1-hydroxy-2-phenylethylphosphonates were easily separated after selective benzoylation of the *anti*-isomers. Enantioselective synthesis of the phosphonate analogue of docetaxel C-13 side chain was accomplished, when the in situ generated (*S*)-*N*,*N*-dibenzylphenylglycinal (Swern oxidation) was treated with lithium dialkyl phosphonates at −70°C followed by separation of the *syn*- and *anti*-diastereoisomers and hydrogenolysis in the presence of Boc_2O.

4. Experimental

General procedures and instrumentation were as described earlier.[19,20] However, ^1H, ^{13}C and ^{31}P NMR spectra were obtained on a Varian-Mercury spectrometer at 300, 75.5 and 121.5 MHz, respectively. In addition, some ^{13}C NMR spectra were taken at 62.9 MHz on a Bruker DPX (250 MHz). Bromomagnesium *O*,*O*-diethylphosphonate was obtained from diethyl phosphite and ethylmagnesium bromide in THF at room temperature by analogy to the literature.[37]

4.1. (*S*)-*N*,*N*-Dibenzylphenylglycinal 6

To a stirred solution of oxalyl chloride (0.700 mL, 8.18 mmol) in CH_2Cl_2 (15 mL) under argon atmosphere, DMSO (1.2 mL, 17 mmol) dissolved in CH_2Cl_2 (5 mL) was added dropwise at −60°C. After 30 min a solution of (*S*)-2-(*N*,*N*-dibenzylamino)-2-phenyl-1-ethanol (2.1 g, 6.6 mmol) in CH_2Cl_2 (10 mL) was added over 15 min. The reaction mixture was stirred for 30 min at −70°C followed by addition of triethylamine (2.80 mL, 19.8 mmol). The cooling bath was removed, and saturated aqueous $NaHCO_3$ (10 mL) was added at 0°C. Aqueous layer was re-extracted with CH_2Cl_2 (10 mL). The organic phases were combined, dried ($MgSO_4$) and then concentrated to yield the crude aldehyde **6** as a yellowish oil (2.47 g, 119%). ^1H NMR: $\delta=9.72$ (d, $J=2.1$ Hz, 1H), 7.90–7.22 (m, 15H), 4.33 (d, $J=2.1$ Hz, 1H), 3.85 (d, $J=13.9$ Hz, 2H), 3.44 (d, $J=13.9$ Hz, 2H).

4.2. Addition of dialkyl phosphites to (*S*)-6

A mixture of the crude aldehyde **6** (1.24 g, 3.30 mmol), dimethyl phosphite (0.275 mL, 2.97 mmol) and NEt_3 (0.046 mL, 0.33 mmol) was stirred at room temperature for 24 h. The crude product was dissolved in CH_2Cl_2 (50 mL), washed with water (4×20 mL) and dried ($MgSO_4$). After evaporation of the solvent, the residue was crystallised from ethyl acetate–hexanes to give pure racemic **7** as white needles (0.360 g, 28%).

4.2.1. (1*R,2*S**)-7**. Mp: 133.7–134.7°C; IR (KBr): $\nu=$ 3307, 2952, 1495, 1233, 1075, 1057, 1032 cm^{-1}; ^1H NMR: $\delta=7.48$–7.18 (m, 15H), 4.67 (ddd, $J=8.4$ Hz, $J=6.9$ Hz, $J=4.5$ Hz, 1H, H-1), 4.21 (dd, $J=8.4$ Hz, $J=6.9$ Hz, 1H, H-2), 3.96 (d, $J=13.8$ Hz, 2H), 3.62 (d, $J=10.5$ Hz, 3H), 3.54 (d, $J=10.5$ Hz, 3H), 3.23 (d, $J=13.8$ Hz, 2H), 2.16 (dd, $J=13.3$ Hz, $J=4.5$ Hz, 1H, OH); ^{13}C NMR (75.5 MHz): $\delta=139.53$, 134.64 (d, $J=8.6$ Hz), 130.42, 128.96, 128.24, 128.00, 127.74, 126.97, 69.25 (d, $J=161.5$ Hz, C-1), 64.10 (brs, C-2), 55.16, 53.26 (d, $J=7.4$ Hz), 53.15 (d, $J=7.5$ Hz); ^{31}P NMR: $\delta=25.52$. Anal calcd for $C_{24}H_{28}O_4NP$: C, 67.75; H, 6.63; N, 3.29. Found: C, 67.93; H, 6.65; N, 3.23%.

The residue from crystallisation was subjected to column chromatography on silica gel using ethyl acetate–hexanes (2:1, v/v). The appropriate fractions were collected to give a 6:4 mixture of **7** and **8** (0.782 g, 62%).

In a similar way from diethyl phosphite (0.383 mL, 2.97 mmol) and (*S*)-**6** (1.24 g, 3.30 mmol) a 80:20 mixture of phosphonates **9** and **10** was obtained. Column chromatography on silica gel with ethyl acetates–hexanes (2:1, v/v) gave fractions containing **9** (0.478 g, 35%), which were recrystallised from ethyl acetate–hexanes leaving racemic **9** as a white amorphous solid (0.144 g, 11%).

4.2.2. (1*R,2*S**)-9**. Mp: 148.9–149.4°C; IR (KBr): $\nu=$ 3293, 2982, 2928, 1494, 1454, 1229, 1055, 1020 cm^{-1}; ^1H NMR: $\delta=7.46$–7.21 (m, 15H), 4.64 (ddd, $J=8.8$ Hz, $J=5.4$ Hz, $J=5.3$ Hz, 1H, H-1), 4.16 (dd, $J=8.1$ Hz, $J=5.4$ Hz, 1H, H-2), 4.03–3.78 (m, 4H), 3.99 (d, $J=$ 13.9 Hz, 2H), 3.27 (d, $J=13.9$ Hz, 2H), 2.38 (dd, $J=11.0$ Hz, $J=5.3$ Hz, 1H, OH), 1.11 (t, $J=7.2$ Hz, 3H), 1.10 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (75.5 MHz): $\delta=139.73$, 135.02 (d, $J=6.3$ Hz), 130.58, 128.79, 128.10, 127.73, 127.44, 126.78, 70.23 (d, $J=160.5$ Hz, C-1), 63.38 (d, $J=6.2$ Hz, C-2), 62.52 (d, $J=7.0$ Hz), 62.31 (d, $J=7.3$ Hz), 55.05, 16.17 (d, $J=5.8$ Hz), 16.08 (d, $J=5.6$ Hz); ^{31}P NMR: $\delta=23.78$. Anal. calcd for $C_{26}H_{32}NO_4P$: C, 68.86; H, 7.11; N, 3.09. Found: C, 68.63; H, 7.29; N, 3.30%.

Further elution afforded fractions containing **9** and **10** (total 0.421 g, 31%).

4.3. Benzoylation of 7 and 8

To a 6:4 mixture of **7** and **8** (0.719 g, 1.69 mmol) and benzoic acid (0.206 g, 1.69 mmol) in CH_2Cl_2 (5 mL) was added DCC (0.348 g, 1.69 mmol) followed by DMAP (0.020 g, 0.169 mmol). The reaction mixture was stirred at room temperature for 24 h. After removal of DCU by filtration, the residue was chromatographed on silica gel with ethyl acetate–hexanes (2:1, v/v) containing methanol (0.1%) to give **11** (0.520 g, 58%), **14** (0.010 g, 1%) and **8** (0.103 g, 14%).

4.3.1. (1*R*,2*S*)-11. IR (film): $\nu=3061$, 3027, 2952, 2847, 1725, 1495, 1453, 1249, 1053, 1028 cm^{-1}; ^1H NMR: $\delta=7.71$–7.68 (m, 2H), 7.56–7.52 (m, 4H), 7.49–7.42 (m, 1H), 7.37–7.20 (m, 13H), 6.35 (dd, $J=9.6$ Hz, $J=8.4$

Hz, 1H, H-1), 4.58 (t, $J=9.6$ Hz, 1H, H-2), 3.97 (d, $J=13.5$ Hz, 2H), 3.72 (d, $J=10.8$ Hz, 3H), 3.57 (d, $J=10.8$ Hz, 3H), 3.18 (d, $J=13.5$ Hz, 2H); ^{13}C NMR (62.9 MHz): $\delta=165.10$ (d, $J=2.9$ Hz, C=O), 138.96, 133.57 (d, $J=11.3$ Hz), 133.15, 129.55, 129.31, 129.09, 128.25, 128.13, 127.98, 127.73, 126.97, 67.07 (d, $J=166.2$ Hz, C-1), 62.72 (d, $J=3.0$ Hz, C-2), 54.43, 53.21 (d, $J=6.2$ Hz), 52.84 (d, $J=7.3$ Hz); ^{31}P NMR: $\delta=21.83$. Anal. calcd for $C_{31}H_{32}NO_5P$: C, 70.31; H, 6.09; N, 2.64. Found: C, 70.09; H, 5.91; N, 2.84%.

4.3.2. (1*S*,2*S*)-14. IR (film): $\nu=3061$, 3028, 2953, 2850, 1724, 1494, 1454, 1259, 1051, 1028 cm^{-1}; ^{1}H NMR: $\delta=8.26$–8.21 (m, 2H), 7.75–7.68 (m, 1H), 7.63–7.54 (m, 2H), 7.50–7.40 (m, 3H), 7.38–7.31 (m, 2H), 7.22–7.12 (m, 10H), 6.36 (dd, $J=11.4$ Hz, $J=10.5$ Hz, 1H, H-1), 4.40 (dd, $J=11.4$ Hz, $J=8.4$ Hz, 1H, H-2), 3.93 (d, $J=13.8$ Hz, 2H), 3.50 (d, $J=10.8$ Hz, 3H), 3.11 (d, $J=10.8$ Hz, 3H), 3.03 (d, $J=13.8$ Hz, 2H); ^{13}C NMR (75.5 MHz): $\delta=165.34$ (d, $J=5.2$ Hz, C=O), 139.15, 133.68, 131.59, 130.72, 130.42, 129.58, 128.81, 128.67, 128.36, 128.23, 128.00, 126.97, 66.93, (d, $J=168.1$ Hz, C-1), 62.58 (d, $J=9.2$ Hz, C-2), 53.61, 52.70 (d, $J=6.6$ Hz), 52.69 (d, $J=6.6$ Hz); ^{31}P NMR: $\delta=22.84$. Anal. calcd for $C_{31}H_{32}NO_5P$: C, 70.31; H, 6.09; N, 2.64. Found: C, 70.21; H, 6.34; N, 2.52%.

4.3.3. (1*S*,2*S*)-8. IR (film): $\nu=3347$, 3061, 3028, 2954, 2850, 1602, 1494, 1452, 1249, 1048, 1030 cm^{-1}; ^{1}H NMR: $\delta=7.48$–7.38 (m, 3H), 7.38–7.24 (m, 12H), 4.98 (brs, 1H, OH), 4.49 (dd, $J=11.5$ Hz, $J=3.6$ Hz, 1H, H-2), 4.12 (dd, $J=12.5$ Hz, $J=11.5$ Hz, 1H, H-1), 3.91 (d, $J=12.9$ Hz, 2H), 3.50 (d, $J=10.5$ Hz, 3H), 3.22 (d, $J=10.5$ Hz, 3H), 3.11 (d, $J=12.9$ Hz, 2H); ^{13}C NMR (75.5 MHz): $\delta=137.68$ (brs), 132.27 (brs), 130.34, 129.30, 128.84, 128.73 (brs), 128.40, 127.77, 65.47 (d, $J=173.2$ Hz, C-1), 63.18 (brs, C-2), 53.51, 52.87 (d, $J=6.6$ Hz); ^{31}P NMR: $\delta=25.34$. Anal. calcd for $C_{24}H_{28}NO_4P$: C, 67.75; H, 6.63; N, 3.29. Found: C, 67.81; H, 6.40; N, 3.39%.

4.4. General procedures for the e.e. determinations of the α-hydroxyphosphonates 7/8 and 9/10

4.4.1. Via mandelate. To a solution of the corresponding phosphonates (0.1 mmol) in CH_2Cl_2 (2 mL), (*S*)-*O*-methylmandelic acid (20.5 mg, 0.12 mmol) was added followed by DCC (25 mg, 0.12 mmol) and DMAP (two crystals). The mixture was stirred for 24 h at room temperature. DCU was filtered off and washed with CH_2Cl_2 (4 mL). The organic solution was concentrated, the residue was dissolved in benzene-d_6 (0.7 mL), and the solution was subjected to ^{31}P NMR analysis.

4.4.2. Via camphanate. To a solution of (−)-camphanyl chloride (16.0 mg, 0.075 mmol) and corresponding phosphonates (0.03 mmol) in benzene-d_6 (0.7 mL), NEt_3 (14.0 μL, 0.10 mmol) was injected followed by two crystals of DMAP. The progress of the esterification was monitored by ^{31}P NMR spectroscopy.

4.5. Addition of lithium dialkyl phosphonates to (*S*)-6

The crude aldehyde **6** was obtained from the corresponding alcohol (3.74 g, 11.8 mmol) as described in 4.1. After addition of NEt_3 (4.90 mL, 35.4 mmol) at −60°C, the reaction mixture was cooled to −78°C and a solution of lithium dimethyl phosphonate [from reaction of diisopropylamine (1.98 mL, 14.5 mmol) 1.6 M *n*-BuLi (8.85 mL, 14.5 mmol) and dimethyl phosphite (1.30 mL, 14.5 mmol), in THF (25 mL) at −70°C] was added dropwise via cannula. After 3 h the reaction mixture was quenched with saturated aqueous NH_4Cl (25 mL) and the temperature was allowed to reach 25°C. The organic layer was separated, washed with brine (20 mL), dried ($MgSO_4$) and concentrated to leave a 75:25 mixture of phosphonates (1*R*,2*S*)-**7** and (1*S*,2*S*)-**8** as a yellowish oil (5.60 g, 111%).

In a similar way a crude 72:28 mixture of phosphonates (1*R*,2*S*)-**9** and (1*S*,2*S*)-**10** (2.91 g, 104%) was obtained after treatment of the aldehyde **6** [from (1.967 g, 6.196 mmol) of the corresponding alcohol] with lithium diethyl phosphonate (7.44 mmol).

4.6. Separation of (1*R*,2*S*)-7 and (1*S*,2*S*)-8

The crude mixture of the phosphonates **7** and **8** (5.6 g) was chromatographed on silica gel with chloroform–methanol (50:1, v/v) to give a 1:1 mixture of (1*R*,2*S*)-**7** and (1*S*,2*S*)-**8** (1.190 g, 24%), the phosphonate (1*R*,2*S*)-**7** (2.019 g, 40%) and (1*R*,2*S*)-**7** (0.82 g, 16%) with a small amount of unidentified organophosphorus compound. To the fraction containing a 1:1 mixture of **7** and **8** (1.190 g, 2.79 mmol) dissolved in CH_2Cl_2 (5 mL), benzoic acid (0.161 g, 0.132 mmol) and DCC (0.271 g, 1.32 mmol) were added followed by DMAP (0.016 g, 0.13 mmol). After stirring the mixture for 24 h DCU was filtered off and the solution was concentrated in vacuo. The residue was chromatographed on silica gel using ethyl acetate–hexanes (2:1, v/v) to afford (1*R*,2*S*)-**11** (0.566 g), (1*S*,2*S*)-**8** (0.330 g, 7%) and (1*S*,2*S*)-**8** (0.297 g, 6%) containing small amounts of unidentified impurities.

4.6.1. (1*R*,2*S*)-7. Colourless oil; $[\alpha]_D=+73.8$ ($c=2.0$, ethyl acetate). Anal. calcd for $C_{24}H_{28}NO_4P$: C, 67.75; H, 6.63; N, 3.29. Found: C, 67.86; H, 6.58; N, 3.17%.

4.6.2. (1*R*,2*S*)-11. Colourless oil; $[\alpha]_D=+79.2$ ($c=1.25$, ethyl acetate). Anal. calcd for $C_{31}H_{32}NO_5P$: C, 70.31; H, 6.09; N, 2.64. Found: C, 70.57; H, 5.89; N, 2.84%.

4.6.3. (1*S*,2*S*)-8. Colourless oil; $[\alpha]_D=+73.5$ ($c=0.95$, ethyl acetate). Anal. calcd for $C_{24}H_{28}NO_4P$: C, 67.75; H, 6.63; N, 3.29. Found: C, 68.01; H, 6.85; N, 3.36%.

4.7. Separation of (1*R*,2*S*)-9 and (1*S*,2*S*)-10

The crude mixture of phosphonates **9** and **10** (2.91 g) was chromatographed on silica gel with chloroform–methanol to give several fractions containing various ratios of phosphonates **9** and **10** (total 2.080 g, 4.586 mmol, 74%). This mixture was treated with benzoic

acid (0.377 g, 2.92 mmol), DCC (0.637 g, 2.92 mmol) and DMAP (0.037 g, 0.29 mmol). After stirring the mixture for 24 h at room temperature, DCU was filtered off. After concentration the residue was twice purified on silica gel with ethyl acetate–hexanes (2:1, v/v) to give less polar benzoate (1*R*,2*S*)-**15** (1.03 g), unreacted phosphonate (1*S*,2*S*)-**10** (0.202 g, 7%) and the phosphonate **10** contaminated with minute quantities of unidentified organophosphorus compound (0.163 g, 6%).

4.7.1. (1*R*,2*S*)-15. Colourless oil; $[\alpha]_D = +42.1$ ($c = 1.07$, ethyl acetate). IR (film): $\nu = 3061$, 3028, 2960, 2910, 1726, 1494, 1452, 1246, 1025 cm^{-1}; ^{1}H NMR: $\delta = 7.78$–7.71 (m, 2H), 7.54–7.20 (m, 18H), 6.34 (t, $J = 9.1$ Hz, 1H, H-1), 4.58 (t, $J = 9.1$ Hz, 1H, H-2), 4.17–3.83 (m, 4H), 3.95 (d, $J = 13.7$ Hz, 2H), 3.23 (d, $J = 13.7$ Hz, 2H), 1.15 (t, $J = 6.9$ Hz, 3H), 1.10 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75.5 MHz): $\delta = 165.13$ (d, $J = 3.1$ Hz, C=O), 139.14, 134.07 (d, $J = 10.9$ Hz), 133.19, 129.77, 129.59, 129.38, 129.31, 128.36, 128.20, 127.98, 127.71,127.02, 67.92 (d, $J = 165.5$ Hz, C-1), 62.89 (d, $J = 6.3$ Hz), 62.84 (d, $J = 7.2$ Hz), 62.79 (d, $J = 3.8$ Hz, C-2), 54.64, 16.58 (d, $J = 6.0$ Hz), 16.50 (d, $J = 6.0$ Hz); ^{31}P NMR: $\delta =$ 19.80. Anal. calcd for $C_{33}H_{36}NO_5P$: C, 71.08; H, 6.51; N, 2.51. Found: C, 71.11; H, 6.26; N, 2.72%.

4.7.2. (1*S*,2*S*)-10. Colourless oil; $[\alpha]_D = +81.4$ ($c = 1.88$, ethyl acetate). IR (film): $\nu = 3309$, 3061, 3028, 2980, 2929, 1443, 1246, 1045, 1028 cm^{-1}; ^{1}H NMR: $\delta = 7.50$–7.22 (m, 15H), 4.47 (dd, $J = 11.4$ Hz, $J = 3.3$ Hz, 1H, H-2), 4.10 (dd, $J = 12.6$ Hz, $J = 11.4$ Hz, 1H, H-1), 3.91 (d, $J = 12.9$ Hz, 2H), 3.88–3.75 (m, 3H), 3.66–3.52 (m, 1H), 3.07 (d, $J = 12.9$ Hz, 2H), 0.95 (t, $J = 7.5$ Hz, 3H), 0.93 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75.5 MHz): $\delta =$ 138.06, 132.72, 130.27, 129.26, 128.76, 128.42, 128.22, 127.61, 65.13 (d, $J = 173.6$ Hz, C-1), 62.94 (d, $J = 3.8$ Hz, C-2), 62.50 (d, $J = 6.0$ Hz), 62.43 (d, $J = 7.5$ Hz), 53.29, 16.32 (d, $J = 5.3$ Hz), 16.24 (d, $J = 5.3$ Hz); ^{31}P NMR: $\delta = 22.52$. Anal. calcd for $C_{26}H_{32}NO_4P$: C, 68.91; H, 7.11; N, 3.09. Found: C, 68.86; H, 7.16; N, 3.37%.

4.8. Hydrogenation of the phosphonates (1*S*,2*S*)-7 and (1*S*,2*S*)-9

The phosphonate (1*S*,2*S*)-**7** (0.096 g, 0.225 mmol) was dissolved in methanol (2 mL) containing $(Boc)_2O$ (0.049 g, 0.225 mmol) and hydrogenated over $Pd(OH)_2$–C (20 mg). After filtration through a pad of Celite, methanol was removed and the product was chromatographed on silica gel with ethyl acetate–hexanes (2:1, v/v) to give (1*S*,2*S*)-**4** (R = Me) as a colourless oil (0.070 g, 91%). $[\alpha]_D = +22.4$ ($c = 1.16$, ethyl acetate). Anal. calcd for $C_{15}H_{24}NO_6P$: C, 52.17; H, 7.00; N, 4.06. Found: C, 52.26; H, 7.28; N, 3.77%.

Following the same procedure, using ethanol as a solvent, from (1*S*,2*S*)-**9** (0.065 g, 0.14 mmol) the phosphonate (1*S*,2*S*)-**4** (R = Et) (0.047 g, 89%) was obtained as a colourless oil. $[\alpha]_D = +18.1$ ($c = 0.91$, ethyl acetate). Anal. calcd for $C_{17}H_{28}NO_6P$: C, 54.68; H, 7.56; N, 3.75. Found: C, 54.57; H, 7.36; N, 3.58%.

4.9. Racemisation of (*S*)-6

The aldehyde (*S*)-**6** was prepared from (*S*)-*N*,*N*-dibenzylphenylglycinol (0.317 g, 1.00 mmol) as described in 4.1. A sample (ca. 50 mg) was withdrawn and immediately added to a mixture of $NaBH_4$ (12 mg, 0.32 mmol) and methanol (1 mL) cooled to 0°C. Then the aldehyde was treated with NEt_3 (34 μL, 0.24 mmol) and the mixture was stirred at room temperature for 24 h. Samples (ca. 50 mg) of this mixture were withdrawn after 1, 2 and 3 h and reduced with $NaBH_4$ at 0°C. After derivatisation of the *N*,*N*-dibenzylphenylglycinols with (*S*)-*O*-methylmandelic acid as described in Section 4.4.1. ^{1}H NMR spectra in $CDCl_3$ were taken. Integrals of signals at 4.714 and 4.695 ppm (**H**–C–OCH_3) and at 3.366 and 3.334 ppm (CH_3O–C–H) were selected for calculation of e.e.

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