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Enantiomeric phosphonate analogs of the paclitaxel C-13 side chain

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Abstract

Both enantiomers of *syn* diethyl 2-(benzoylamino)-1-hydroxy-2-phenylethylphosphonate have been obtained by resolution via *O*-methylmandelate derivatives. Removal of the resolving ester moiety was easily achieved by ammonolysis with no trace of the *retro*-Abramov reaction. Absolute configurations of the enantiomeric phosphonate analogs were established from ^{1}H (the Trost model) and ^{31}P NMR data of the *O*-methylmandelate derivatives.

1. Introduction

Paclitaxel is considered as one of the most promising anticancer drugs.[1] In the search for more powerful and less toxic analogs and in order to study structure–activity relationships (SARs) a significant number of derivatives have been reported.[2–4] It appears that the structure of the C-13 side chain is extremely important for the antitumor activity.

Recently, we have disclosed the synthesis of racemic *syn* and *anti* diethyl 2-[(*tert*-butoxycarbonyl)amino]-1-hydroxy-2-phenylethylphosphonates **1** and **2**, respectively, and the transformation of **1** into diethyl 2-(benzoylamino)-1-hydroxy-2-phenylethylphosphonate **3**, the phosphonate analogs of docetaxel and paclitaxel C-13 side chains, respectively.[5] Growing interest in the modification of (2*R*,3*S*)-3-phenylisoserine has prompted our further studies in this area and herein we wish to describe an improved synthesis of racemic **3** and its resolution via *O*-methylmandelate derivatives. In addition, the absolute configurations of the enantiomers of **3** were established based on ^{1}H and ^{31}P NMR spectral data.

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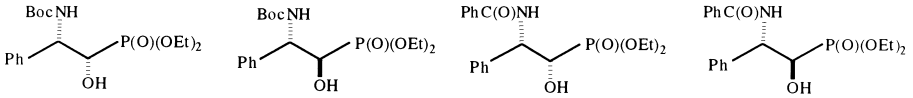
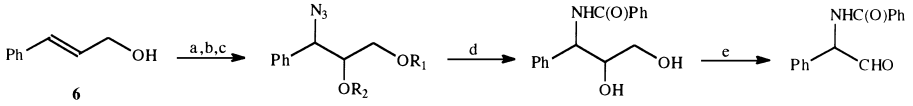


(1*S*,2*S*)- **1** (1*R*,2*S*)- **2** (1*S*,2*S*)- **3** (1*R*,2*S*)- **4**

2. Results and discussion

A synthetic pathway to racemic **5** followed by analogy with the Sharpless asymmetic epoxidation process on 3-phenyl-2-propen-1-ol[6] with minor modifications is shown in Scheme 1.



6 **9a** R_1 = Bz, R_2 = H; **9b** R_1 = H, R_2 = Bz **10** **5**

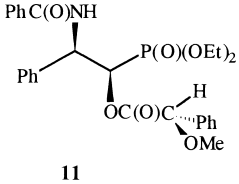
Scheme 1. Reagents and conditions: (a) MCPBA, 0.5 M $NaHCO_3$; (b) PhC(O)Cl, NEt_3, CH_2Cl_2; (c) NaN_3, MeOH–H_2O, 65°C; (d) H_2, Pd–C, MeOH; (e) $NaIO_4$, CH_2Cl_2–H_2O

Epoxide **7** prepared from **6** under standard conditions was benzoylated to give **8**, which was subjected to azidolysis to produce a 4:1 mixture of benzoates **9a** and **9b**. Hydrogenation of **9a**/**9b** led to the diol **10** which was purified by crystallization. The periodate cleavage supplied *N*-benzoylphenylglycinal **5** which was used immediately in the next step without purification.

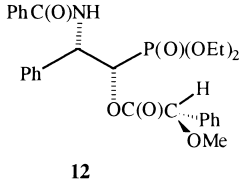
Racemic **5** was reacted with diethyl phosphite in the presence of various basic catalysts to produce mixtures of diastereoisomeric diethyl (1*S**,2*S**)- and (1*R**,2*S**)-2-(benzoylamino)-1-hydroxy-2-phenylethylphosphonates **3** and **4**. The diastereoselectivity of the addition changed significantly from those observed when *N*-Boc-phenylglycinal was used (in brackets):[5] $(EtO)_2P(O)H/NEt_3$ 65:35 (75:25); $(EtO)_2P(O)Li$ 54:46 (70:30); $(EtO)_2P(O)Na$ 78:22 (87:13);[7] $(EtO)_2POTMS$ 81:19 (87:13);[7] $(EtO)_2P(O)H/Ti(OiPr)_4$ 46:54 (67:33).[7]

The mixture of diastereoisomeric *N*-Boc-phosphonates (1*S**,2*S**)-**1** and (1*R**,2*S**)-**2** was found to be inseparable on silica gel.[5] On the other hand, *N*-benzoyl analogs (1*S**,2*S**)-**3** and (1*R**,2*S**)-**4** were separated by column chromatography, and the required *syn* diastereoisomer (1*S**,2*S**)-**3** was obtained in satisfactory yield from the mixture prepared using diethyl trimethylsilyl phosphite.

Resolution of **3** was achieved via *O*-methylmandelate derivatives. Thus, **3** was esterified with (*S*)-*O*-methylmandelic acid[8] in the presence of DCC[9] to form the respective mandelates quantitatively. They were cleanly separated on a silica gel column into a resinous less polar diastereomer **11** (43%) and a crystalline more polar diastereomer **12** (36%), and their diastereoisomeric purity was ascertained from ^1H, ^{13}C and ^{31}P NMR spectra.



11



12

Absolute configurations of the phosphonate fragments in **11** and **12** were assigned, based on the analysis of ^1H and ^{31}P NMR spectral data of mandelates. Thus, according to the Trost model[10] the phenyl ring of the mandelic ester is expected to shield the $P(O)(OEt)_2$ group in **11** as well as the CHPh-NH-C(O)Ph residue in **12** (Fig. 1). Indeed, we noticed significant upfield shifts for one OCH_2CH_3 group

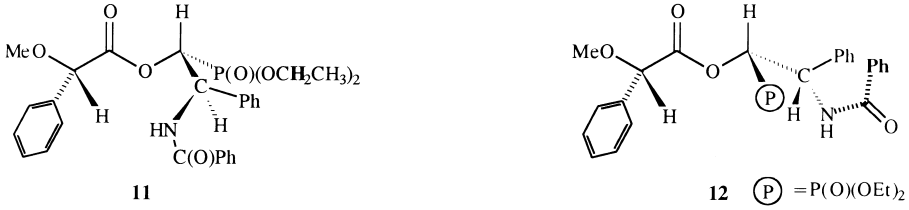


Figure 1. Preferred conformations of *O*-methylmandelates **11** and **12**

in **11** (from 4.2–3.8 ppm in **3** and **12**, to 3.64 and 3.41 ppm in **11**) leading even to a first-order pattern for the diastereotopic protons, and resonances of the *Ph*-C(O) in **12** were moved to 7.2–7.05 ppm (*m*- and *p*-) and to 7.0–6.9 ppm (*o*-) regions. Although better probes for configurational assignments of secondary alcohols than *O*-methylmandelates have been proposed very recently,[11,12] the ^{1}H NMR upfield shifts observed for **11** and **12** were used with confidence. On the other hand, extensive configurational studies of α-hydroxyphosphonates[13] showed that for (*R*)-*O*-methylmandelates, esters of (*S*)-alcohols are less polar and their ^{31}P NMR chemical shifts appear in a higher field than (*R*)-*O*-methylmandelates of (*R*)-alcohols. Our less polar (*S*)-*O*-methylmandelate **11** contains (1*R*)-alcohol and also absorbs at higher field (17.01 ppm) than (*S*)-*O*-methylmandelate of (1*S*)-alcohol **12** (17.54 ppm). For this reason removal of the resolving group from **11** would lead to (1*R*,2*R*)-**3**, while from **12**, (1*S*,2*S*)-**3** would be obtained.

The resolving moiety was simply removed with 25% aqueous ammonia at room temperature. Although the ammonolysis was carried out in a basic solution no epimerization at C-1 (the retro-Abramov reaction) was observed as judged from ^{31}P NMR spectra, i.e. from **11** (δ^{31}P=17.01 ppm) and from **12** (δ^{31}P=17.54 ppm) only enantiomeric *syn* phosphonates (δ^{31}P=22.6 ppm) were obtained. Thus, mandelate **11** gave (1*R*,2*R*)-**3**, while from **12** the enantiomer (1*S*,2*S*)-**3**, having the same configuration as the C-13 side chain of paclitaxel, was formed. On the other hand, attempts at cleaving *O*-methylmandelates **11**/**12** with methanol in the presence of potassium carbonate[10] led to complete decomposition of the phosphonate via the retro-Abramov reaction. The present procedure for racemization-free deprotection of esters of α-hydroxyphosphonates by ammonolysis seems superior to the method using NEt_3–MeOH described by Hammerschmidt[14] (1–2 h vs. 1–11 days, respectively). The generality of this new deprotection method is under extensive studies in this laboratory.

The enantiomeric purity of (1*R*,2*R*)-**3** and (1*S*,2*S*)-**3** was proved by esterification of small samples (NMR tube experiments) with (−)-camphanyl chloride. After disappearance of the ^{31}P NMR signals of the hydroxyphosphonates **3** only single resonances for the corresponding camphanates at δ^{31}P=17.74 ppm from (1*R*,2*R*)-**3** and at δ^{31}P=17.54 ppm from (1*S*,2*S*)-**3** were observed at 202.5 MHz. Thus, within NMR spectroscopy detection limits we judge the enantiomeric purity of both samples as better than 99%.

In conclusion, it was shown that preparation of pure **3** was efficiently accomplished from racemic *N*-benzoylphenylglycinal and diethyl trimethylsilyl phosphite. Enantiomerically pure (1*S*,2*S*)-**3** and (1*R*,2*R*)-**3** were obtained in good yield by resolution using *O*-methylmandelates. Ammonolysis (25% aqueous NH_3) of the mandelates of α-hydroxyphosphonates did not cause epimerization at C-1 of enantiomeric phosphonates. Studies on asymmetric synthesis of (1*S*,2*S*)-**3** and related phosphonates are under way in this laboratory.

3. Experimental

^{1}H NMR spectra were taken in $CDCl_3$ on the following spectrometers: Tesla BM 567 (100 MHz) and Bruker DPX (250 MHz) with TMS as an internal standard. ^{13}C and ^{31}P NMR spectra were recorded for

$CDCl_3$ solutions on a Bruker DPX spectrometer at 62.9 and 101.25 MHz, respectively. For enantiomeric excess determinations ^{31}P NMR spectra were obtained with a Bruker DRX spectrometer at 202.5 MHz. IR spectral data were measured on an Infinity MI-60 FT-IR spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this Institute on a Perkin–Elmer PE 2400 CHNS analyzer. Polarimetric measurements were conducted on a Perkin–Elmer 241 MC apparatus.

The following absorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh); analytical TLC, Merck TLC plastic sheets silica gel 60 F254. TLC plates were developed in various ethyl acetate–hexanes or $CHCl_3$–CH_3OH solvent systems. Visualization of spots was effected with iodine vapors.

All solvents were purified by methods described in the literature.

3.1. N-*(2,3-Dihydroxy-1-phenylpropyl)benzamide* ***10***

To a suspension of cinnamyl alcohol (**6**, 6.71 g, 50.0 mmol) in aqueous $NaHCO_3$ (0.5 M, 200 ml) was added MCPBA (70%, 13.56 g, 55.00 mmol) at 0–3°C. The reaction mixture was stirred vigorously for 4 h at 25°C. After saturation with solid NaCl the aqueous phase was extracted with CH_2Cl_2 (4×50 ml) and organic extracts were dried over $MgSO_4$. Evaporation of the solvent left crude **7** (7.73 g, 103%) as a colorless oil.[15]

To a solution of **7** in CH_2Cl_2 (40 ml) was added NEt_3 (7.63 ml, 55.0 mmol), benzoyl chloride (6.70 ml, 57.75 mmol) and a few crystals of DMAP. After stirring for 3 h, the reaction mixture was washed with water (3×30 ml). The organic layer was dried ($MgSO_4$) and concentrated to give crude **8** (13.45 g, 106%) as yellowish oil. ^1H NMR (250 MHz): δ=8.5–8.2 (m, 2H), 7.5–7.2 (m, 8H), 4.75 (dd, *J*=12.3 Hz, *J*=3.3 Hz, 1H), 4.36 (dd, *J*=12.3 Hz, *J*=5.8 Hz, 1H), 3.90 (d, *J*=2.0 Hz, 1H), 3.41 (ddd, *J*=5.8 Hz, *J*=3.3 Hz, *J*=2.0 Hz, 1H).

The epoxide **8** was dissolved in methanol:water (8:1, v/v, 450 ml) containing NaN_3 (16.25 g, 0.25 mol) and NH_4Cl (5.84 g, 0.11 mol). The solution was gently refluxed for 10 h and then methanol was evaporated. After addition of water (20 ml) the reaction mixture was extracted with CH_2Cl_2 (4×70 ml), the organic layer was washed with brine (2×50 ml), dried ($MgSO_4$), and concentrated to leave a 4:1 mixture of **9a** and **9b** (13.37 g, 90%) as a brownish oil. ^1H (250 MHz): δ=8.1–7.9 (m, 2H), 7.6–7.3 (m, 8H), 5.36 (ddd, *J*=6.2 Hz, *J*=5.2 Hz, *J*=3.5 Hz, **9b**), 5.05 (d, *J*=6.2 Hz, **9b**), 4.72 (d, *J*=6.4 Hz, **9a**), 4.47 (dAB, J_{AB}=11.8 Hz, *J*=3.8 Hz, **9a**), 4.41 (dAB, J_{AB}=11.8 Hz, *J*=5.6 Hz, **9a**), 4.2–4.1 (m, **9a**), 3.9–3.7 (m, **9b**).

The crude mixture of azides **9a** and **9b** (13.37 g, 45.00 mmol) was dissolved in methanol (100 ml) and hydrogenated over 10% Pd–C (500 mg) overnight. After filtration through a pad of Celite, methanol was removed and the product was recrystallized from ethyl acetate–hexanes leaving **10** (7.40 g, 55%) as a white amorphous solid. Mp 160–161°C; ^1H NMR (100 MHz, CD_3OD): δ=7.8–7.7 (m, 2H), 7.5–7.1 (m, 9H), 5.14 (d, *J*=6.1 Hz, 1H), 4.0–3.8 (m, 1H), 3.60 (dAB, J_{AB}=11.2 Hz, *J*=3.7 Hz, 1H), 3.40 (dAB, J_{AB}=11.2 Hz, *J*=5.0 Hz, 1H).

3.2. N-*(2-Oxo-1-phenylethyl)benzamide* ***5***

A mixture of *N*-benzoylaminodiol **10** (2.71 g, 10.0 mmol), $NaIO_4$ (2.57 g, 12.0 mmol), water (30 ml) and CH_2Cl_2 (50 ml) was stirred at room temperature for 2 h. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2×15 ml). The organic solution was dried ($MgSO_4$) and concentrated in vacuo to leave a crude **5** as a white solid (2.63 g, 110%), which was immediately used

in the next step without purification. ^{1}H NMR (250 MHz): δ=9.65 (s, 1H), 7.9–7.8 (m, 2H), 7.5–7.2 (m, 9H), 5.77 (d, *J*=5.8 Hz, 1H).

3.3. Diethyl (1S,2S*)- and (1R*,2S*)-2-(benzoylamino)-1-hydroxy-2-phenylethylphosphonates **3** and **4***

(a) A mixture of the crude **5** (0.248 g, obtained from 0.271 g, 1.00 mmol of **10**), diethyl phosphite (0.116 ml, 0.90 mmol) and NEt_3 (0.014 ml, 0.10 mmol) was stirred at room temperature for 24 h. After removal of volatiles in vacuo the ratio of diastereoisomeric α-hydroxyphosphonates was estimated by ^{31}P NMR spectroscopy. Column chromatography on silica gel with ethyl acetate:hexanes (2:1, v/v) gave several fractions of poorly separated mixtures of **3** and **4** (total 0.252 g, 74%).

(b) To a solution of lithium diethyl phosphonate [from diethyl phosphite (0.93 ml, 7.2 mmol), diisopropylamine (0.94 ml, 7.2 mmol), and 1.6 M BuLi (4.5 ml, 7.2 mmol) in THF (10 ml) cooled to −60°C] was added crude **5** (2.48 g, obtained from 2.14 g, 8.00 mmol of **10**) in THF (10 ml). The reaction mixture was stirred at this temperature for 3 h and allowed to reach 25°C. A saturated aqueous NH_4Cl (5 ml) was added followed by CH_2Cl_2 (100 ml). The suspension was washed with water (2×70 ml), the organic layer was dried ($MgSO_4$) and concentrated to leave a 54:46 mixture of **3** and **4** as a viscous oil. Column chromatography on silica gel with ethyl acetate:hexanes (2:1, v/v) gave fractions containing **4** (1.162 g, 43%), which were recrystallized from ethyl acetate–hexanes leaving **4** (0.667 g, 25%) as a white amorphous solid. Mp 117–118°C; IR (KBr): ν=3284, 1638, 1548, 1221, 1076, 1054, 1026 and 698 cm^{-1}; ^{1}H NMR (250 MHz): δ=8.33 (brd, *J*=8.2 Hz, 1H), 8.0–7.9 (m, 2H), 7.6–7.2 (m, 8H), 5.72 (ddd, *J*=25.5 Hz, *J*=8.2 Hz, *J*=4.6 Hz, 1H), 4.39 (ddd, *J*=8.5 Hz, *J*=6.2 Hz, *J*=4.6 Hz, 1H), 4.2–4.0 (m, 2H), 3.9–3.6 (m, 3H), 1.27 (t, *J*=7.1 Hz, 3H), 0.97 (t, *J*=7.1 Hz, 3H); ^{13}C NMR: δ=167.52, 137.77 (d, *J*=2.1 Hz), 133.87, 131.65, 128.56, 128.27, 127.54, 127.30, 127.25, 70.76 (d, *J*=161.6 Hz), 63.61 (d, *J*=7.0 Hz), 62.05 (d, *J*=7.3 Hz), 56.37 (d, *J*=1.8 Hz), 16.39 (d, *J*=5.7 Hz), 15.83 (d, *J*=6.3 Hz); ^{31}P NMR: δ=22.50. Anal. calcd for $C_{19}H_{24}NO_5P$: C, 60.47; H, 6.41; N, 3.71. Found: C, 60.31; H, 6.61; N, 3.98.

Further elution afforded mixed fractions of **4** and **3** (total 1.335 g, 49%).

(c) To a solution of sodium diethyl phosphite [from diethyl phosphite (0.26 ml, 2.0 mmol) and NaH (55% suspension, 0.098 g, 2.2 mmol) in THF (5 ml)] a crude **5** (0.529 mg, obtained from 0.542 g, 2.0 mmol of **10**) in THF (2 ml) was added at room temperature. The reaction mixture was stirred for 3 h and CH_3COOH (0.13 ml, 2.2 mmol) was injected. After dilution with CH_2Cl_2 (25 ml), anhydrous $MgSO_4$ (3 g) was added and inorganic salts were filtered off. The organic phase was concentrated to leave a crude mixture of **3** and **4** (78:22, by ^{31}P NMR).

(d) To a cooled (0°C) solution of diethyl phosphite (0.129 ml, 1.00 mmol) in THF (1.0 ml) was injected $Ti(OiPr)_4$ (0.059 ml, 0.2 mmol). After 30 min at this temperature the crude aldehyde **5** (0.284 g, obtained from 0.271 g, 1.00 mmol of **10**) was added as a solution in THF (2 ml). The reaction mixture was stirred at 0–5°C for 24 h and aqueous HCl (1.0 ml, 0.1 M) was added. The extraction with ether (3×10 ml) followed by a brine wash (3×5 ml), drying ($MgSO_4$) and concentration in vacuo led to crude **3** and **4** in a 46:54 ratio. After filtration through a pad of silica gel a mixture of **3** and **4** (0.300 g, 80%) was obtained.

(e) A solution of crude aldehyde **5** (4.35 g, obtained from 4.07 g, 15.0 mmol of **10**) and $(EtO)_2$POTMS (3.10 ml, 13.5 mmol) in CH_2Cl_2 (5 ml) was kept at room temperature for 24 h. After removal of solvents the residue was dissolved in THF (40 ml) containing aqueous H_2SO_4 (2%, 4 ml) and refluxed for 3 h. Evaporation of THF led to a mixture which was diluted in CH_2Cl_2 (50 ml) and carefully treated with solid $NaHCO_3$ until evolution of CO_2 ceased followed by anhydrous $MgSO_4$. The inorganic salts were filtered off, washed with CH_2Cl_2, and the solution was concentrated in vacuo to give a crude 81:19 mixture of

3 and **4**. Column chromatography on silica gel with ethyl acetate:hexanes (2:1, v/v) containing 0.1% of methanol gave various mixtures of **3** and **4** (1.594 g, 31%) and **3** (3.427 g, 67%), which were crystallized from ethyl acetate–hexanes leaving pure **3** (2.230 g, 44%). Mp 127–128°C.[5]

*3.4. Esterification of (1*S**,2*S**)-**3** with (*S*)-O-methylmandelic acid*

To a solution of **3** (1.132 g, 3.00 mmol) and (*S*)-*O*-methylmandelic acid[8] (0.648 g, 3.00 mmol) in CH_2Cl_2 (10 ml) containing DMAP (0.037 mg, 0.30 mmol), DCC (0.805 g, 3.90 mmol) was added. After stirring for 2 h at room temperature DCU was filtered off and the residue was concentrated. The crude product was purified on silica gel with ethyl acetate:hexanes (2:1, v/v) containing 0.1% of methanol to give **11** (0.684 g, 43%) as a colorless resin and **12** (0.727 g, 46%), which was recrystallized from ethyl acetate–hexanes leaving **12** (0.567 g, 36%) as white needles.

11: $[\alpha]_D^{20}$=+29.0 (*c*=1.4, ethyl acetate); IR (film): ν=3303, 1760, 1646, 1524, 1256, 1028 cm^{-1}; ^1H NMR (250 MHz): δ=7.9–7.8 (m, 2H), 7.65 (brd, *J*=7.1 Hz, 1H), 7.6–7.2 (m, 13H), 5.7–5.6 (m, 2H), 4.71 (s, 1H), 4.1–3.9 (m, 2H), 3.64 (dqu, *J*=10.1 Hz, *J*=7.1 Hz, 1H), 3.41 (ddq, *J*=10.1 Hz, *J*=8.4 Hz, *J*=7.1 Hz, 1H), 3.21 (s, 3H), 1.19 (t, *J*=7.1 Hz, 3H), 0.91 (t, *J*=7.1 Hz, 3H); ^{13}C NMR: δ=168.85 (d, *J*=4.7 Hz), 166.28, 137.35 (d, *J*=8.9 Hz), 135.43, 133.82, 131.61, 128.80, 128.54, 128.53, 128.39, 127.79, 127.09, 126.80, 82.12, 69.84 (d, *J*=166.0 Hz), 63.05 (d, *J*=6.7 Hz), 62.98 (d, *J*=7.1 Hz), 57.48, 53.40 (d, *J*=1.2 Hz), 16.14 (d, *J*=5.7 Hz), 15.95 (d, *J*=6.1 Hz); ^{31}P NMR: δ=17.01. Anal. calcd for $C_{28}H_{32}NO_7P$: C, 63.99; H, 6.14; N, 2.67. Found: C, 64.19; H, 6.41; N, 2.36.

12: mp 110–111°C. $[\alpha]_D^{20}$=−33.3 (*c*=1.3, ethyl acetate); IR (KBr): ν=3394, 1750, 1645, 1523, 1265, 1030 cm^{-1}; ^1H NMR (250 MHz): δ=7.85–7.80 (m, 2H), 7.6–7.4 (m, 3H), 7.4–7.3 (m, 6H), 7.2–7.05 (m, 3H), 7.0–6.9 (m, 2H), 5.68 (dAB, J_{AB}=3.8 Hz, J_{AP}=10.0 Hz, 1H), 5.59 (ddAB, J_{AB}=3.8 Hz, J_{BP}=12.0 Hz, $J_{B,H\text{-}N}$=8.3 Hz, 1H), 4.81 (s, 1H), 4.3–4.1 (m, 2H), 4.0–3.8 (m, 2H), 3.36 (s, 3H), 1.26 (t, *J*=7.1 Hz, 3H), 1.13 (t, *J*=7.1 Hz, 3H); ^{13}C NMR: δ=168.68 (d, *J*=4.8 Hz), 166.08, 137.30 (d, *J*=9.4 Hz), 135.51, 133.94, 131.63, 129.05, 128.78, 128.56, 128.33, 127.66, 127.36, 127.11, 126.57, 82.30, 70.11 (d, *J*=165.8 Hz), 63.30 (d, *J*=6.6 Hz), 63.09 (d, *J*=7.3 Hz), 57.42, 52.66, 16.32 (d, *J*=5.6 Hz), 16.19 (d, *J*=6.0 Hz); ^{31}P NMR: δ=17.54. Anal. calcd for $C_{28}H_{32}NO_7P$: C, 63.99; H, 6.14; N, 2.67. Found: C, 64.00; H, 6.20; N, 2.64.

*3.5. Diethyl (1*R,*2*R*)- and (1*S,*2*S*)-2-(benzoylamino)-1-hydroxy-2-phenylethylphosphonates **3***

A solution of **11** (0.550 g, 1.05 mmol) in ethanol (7 ml) containing aqueous NH_3 (25%, 6 ml) was left at room temperature for 2 h. The volatiles were removed in vacuo and the residue was evaporated with anhydrous ethanol (3×10 ml), chloroform (3×20 ml) and chromatographed on silica gel with ethyl acetate:hexanes (2:1, v/v) containing methanol (0.1%). Appropriate fractions were recrystallized from ethyl acetate–hexanes to give (1*R*,2*R*)-**3** (0.274 g, 73%). Mp 157.5–158.0°C; $[\alpha]_D^{20}$=+35.1 (*c*=1.0, ethyl acetate). Anal. calcd for $C_{19}H_{24}NO_5P$: C, 60.47; H, 6.41; N, 3.71. Found: C, 60.40; H, 6.41; N, 3.49.

Following the same procedure, from **12** (0.430 g, 0.82 mmol) (1*S*,2*S*)-**3** (0.252 g, 82%) was obtained. Mp 156.5–157.0°C; $[\alpha]_D^{20}$=−37.7 (*c*=1.4, ethyl acetate). Anal. calcd for $C_{19}H_{24}NO_5P$: C, 60.47; H, 6.41; N, 3.71. Found: C, 60.62; H, 6.41; N, 3.61.

*3.6. Determination of the optical purity of (1*R,*2*R*)-**3** and (1*S,*2*S*)-**3***

To a solution of (−)-camphanyl chloride (14.0 mg, 0.065 mmol) and enantiomeric alcohols **3** (10.0 mg, 0.026 mmol) in chloroform-*d* (0.6 ml) NEt_3 (14.0 μl, 0.10 mmol) was injected followed by one

crystal of DMAP. The progress of the esterification was monitored by ^{31}P NMR spectroscopy. The phosphonates (1*R*,2*R*)-**3** and (1*S*,2*S*)-**3** were transformed into corresponding camphanates: δ^{31}P=17.74 ppm and δ^{31}P=17.54 ppm, respectively.

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