Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2615–2624

TETRAHEDRON: *ASYMMETRY*

Enantiomeric phosphonate analogs of the docetaxel C-13 side chain†

Andrzej E. Wróblewski* and Dorota G. Piotrowska

Institute of Chemistry, Faculty of Pharmacy, Medical University of Łódź, 90-151 Łódź, Muszyńskiego 1, Poland

Received 9 May 2000; accepted 23 May 2000

Abstract

Addition of dimethyl phosphite to racemic *N*-Boc-phenylglycinal led to a 75:25 mixture of *syn* and *anti* dimethyl 2-[(*tert*-butoxycarbonyl)amino]-1-hydroxy-2-phenylethylphosphonates. The *syn*-diastereoisomer was obtained in 50% yield after a single crystallization. Resolution of the *syn*-isomer was achieved via the (*S*)-*O*-methylmandelate esters. Racemization-free ammonolysis gave both enantiomers in high enantiomeric excess. Benzoates of both *N*-Boc *syn*-enantiomers were transformed into dimethyl (1*R*,2*R*)- and (1*S*,2*S*)-2-(benzoylamino)-1-hydroxy-2-phenylethylphosphonates in good yields.

1. Introduction

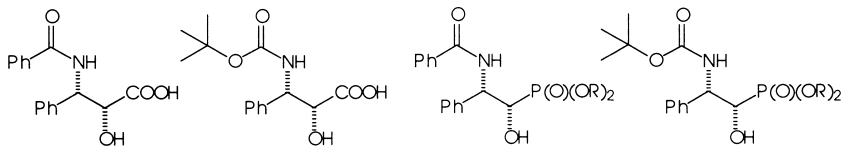
The natural anticancer agent paclitaxel and its semisynthetic analog docetaxel are used clinically against various tumors, especially breast and ovarian cancers.[1] The importance of the C-13 side chains, *N*-benzoyl- and *N*-Boc-(2*R*,2*S*)-3-phenylisoserine **1** and **2**, for achieving the antitumor activity has prompted the search for structural analogs, by replacing the phenyl group with other substituents,[2–9] and also by introducing alkyl groups at C_α.[10,11] We proposed another modification of this important amino acid based on the idea that phosphonates can serve as bioisosters[12] of carboxylic acids.[13,14] So far, we have described the synthesis of phosphonate analogs of **1** and **2**, i.e. diethyl (1*S**,2*S**)-2-(benzoylamino)- and 2-[(*tert*-butoxycarbonyl)amino]-1-hydroxy-2-phenylethylphosphonates (±)-**3a**[15,16] and (±)-**5a**,[15] respectively, and the resolution of racemic **3a**.[16] However, when a future coupling of these esters to Baccatin III (the diterpene part of paclitaxel and docetaxel) was considered, the major problems to overcome would have been the selective monodeprotection of diethyl phosphonates under neutral conditions and, most importantly, extreme steric congestion of *HO*–C-13 in the Baccatin III skeleton.[17–20] Although thermal (100°C) monodealkylation of diethyl phosphonates has recently been described,[21] clean and quantitative removal of one methyl group from dimethyl α-hydroxyphosphonates can be

* Corresponding author. Fax: 48-42-678-83-98; e-mail: aewplld@ich.pharm.am.lodz.pl

† Dedicated to Professor John G. Verkade on the occasion of his 65th birthday.

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00203-2

achieved with NaI in boiling acetone.[22] On steric grounds, one can expect faster coupling of the monomethyl phosphonates in comparision with the monoethyl analogs.

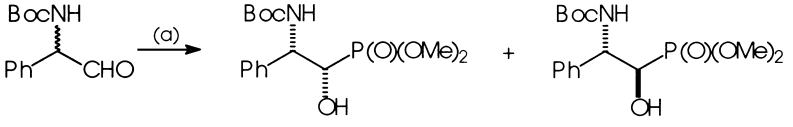


1 **2** (1*S*,2*S*)-**3a** R=Et (1*S*,2*S*)-**4a** R=Me (1*S*,2*S*)-**5a** R=Et (1*S*,2*S*)-**6a** R=Me

For these reasons, and prompted by the recent publication from the Sharpless group on the asymmetric synthesis of structurally related phosphonates,[23] we decided to study the synthetic availability and stability of dimethyl (1*S**,2*S**)-2-(benzoylamino)- and 2-[(*tert*-butoxycarbonyl]-1-hydroxy-2-phenylethylphosphonates **4a** and **6a** as prospective starting materials in the synthesis of phosphonate analogs of paclitaxel and docetaxel, respectively. In this paper, significant improvements in the preparation of the racemic analog of docetaxel side chain **6a**, the resolution of **6a** and the transformation of both enantiomeric phosphonates **6a** into (1*R*,2*R*)- and (1*S*,2*S*)-**4a** via the respective benzoates will be described.

2. Results and discussion

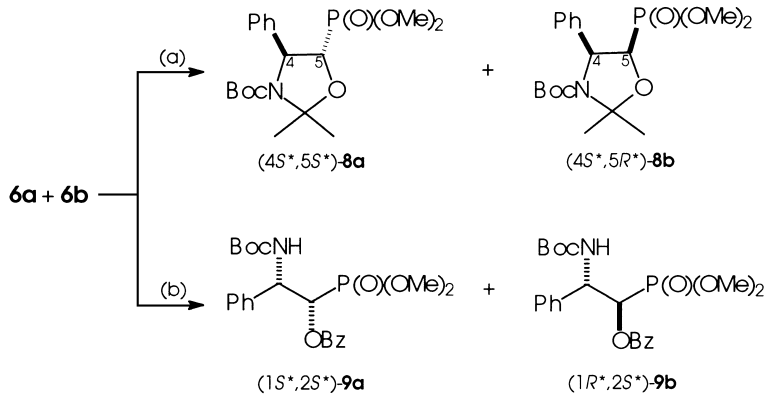
Phosphonate (1*S**,2*S**)-**5a** and its C-1 epimer (1*R**,2*S**)-**5b** were first obtained as a 75:25 mixture by the addition of diethyl phosphite to racemic *N*-Boc-phenylglycinal **7**.[15] The *syn*-diastereoisomer **5a** having the same relative configurations as the natural (2*R*,3*S*)-phenylisoserine could not be separated from the crude product either by column chromatography or fractional crystallization from various solvent mixtures. The stereochemistry of the addition did not change when dimethyl phosphite was used instead of the diethyl derivative. In the presence of NEt_3 the aldehyde **7** was transformed into a 75:25 mixture of the phosphonates (1*S**,2*S**)-**6a** and (1*R**,2*S**)-**6b**, respectively (Scheme 1). However, after a single crystallization of the crude product, pure *syn*-diastereoisomer **6a** was obtained in 50% yield. Attempts at separating diastereoisomeric methyl esters **6a** and **6b** on silica gel proved ineffective, as had been observed for the diethyl phosphonates **5a** and **5b**.



7 (1*S**,2*S**)-**6a** (1*R**,2*S**)-**6b**

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

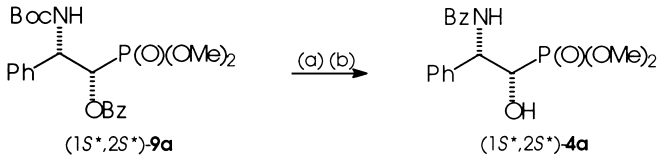
The *anti*-diastereoisomer (1*R**,2*S**)-**6b** was isolated in the following way: The mother liquors after crystallization of **6a** containing **6a** and **6b** in a 1:1 ratio were subjected to isopropylidenation (Scheme 2) to produce a mixture of **8a** (51%), **8b** (27%) and unreacted **6b** (13%) together with an unidentified organophosphorus compound (δ $^{31}P = 18.14$ ppm) (9%). After column chromatography pure **8a** and **8b** were obtained followed by more polar **6b**.



Scheme 2. Reagents and conditions: (a) $H_2C{=}C(OCH_3)CH_3$, PPTS, (b) PhCOCl, NEt_3, DMAP

Alternatively, benzoylation of a 4:6 mixture of **6a** and **6b** was carried out, and the respective benzoates **9a** and **9b** (Scheme 2) were separated on silica gel to give **9b** in 47% yield. The analogous approach to separating mixtures of the benzoates of **5a** and **5b** (ethyl derivatives) met with partial success and led to pure products in significantly lower yields.[15] The benzoates **9a** and **9b** were subjected to ammonolysis[16,24] to afford pure **6a**[24] and **6b** in 65 and 77% yield, respectively.

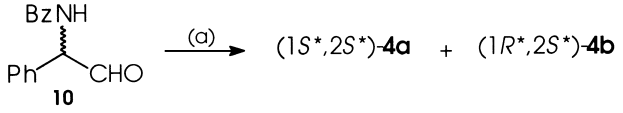
After removal of the *tert*-butoxycarbonyl group the benzoates **9a** and **9b** were transformed into the racemic phosphonate analog of the paclitaxel C-13 side chain **4a** and its C-1 epimer **4b** in excellent yields (Scheme 3). High concentration of anhydrous hydrogen chloride in ethyl acetate did not appear to be deleterious for the $(MeO)_2P(O)$ group. Furthermore, an excess of NEt_3 caused neither epimerization at C-1 (via the *retro*-Abramov reaction) nor demethylation of the ester function.



Scheme 3. Reagents and conditions: (a) 3 M HCl–AcOEt, (b) NEt_3

The relative configurations in diastereoisomeric pairs **4a** and **4b**, and **6a** and **6b** were assigned based on similarities of ^1H and ^{13}C NMR spectra of the respective ethyl and methyl esters, e.g. **3a**[15] and **4a** or **5a**[15] and **6a**. Furthermore, the stereochemistry of the addition to the carbonyl group of **7** would be expected to be unaltered between diethyl and dimethyl phosphites.

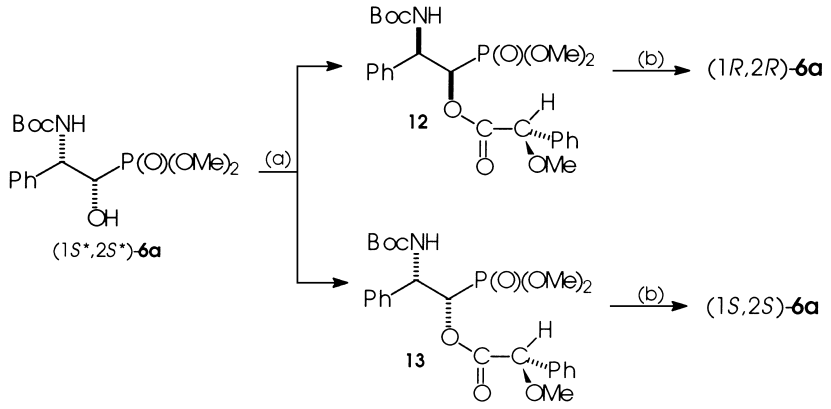
In an alternative approach to the phosphonates **4a** and **4b** NEt_3-catalyzed addition of dimethyl phosphite to the racemic *N*-benzoylphenylglycinal **10**[16] was explored (Scheme 4). However, a 63:38 mixture of diastereoisomers **4a** and **4b** was contaminated with several impurities, and separation



Scheme 4. Reagents and conditions: (a) $(MeO)_2P(O)H$, NEt_3

of **4a** and **4b** on silica gel proved extremely tedious. This observation is in contrast with our findings for **3a** and **3b** (ethyl esters) which were separated on silica gel to afford **3a** in 67% yield.[16]

The resolution of (1*S**,2*S**)-**6a** was achieved via esters with (*S*)-*O*-methylmandelic acid **11**.[25] To this end racemic **6a** was quantitatively esterified with **11** in the presence of DCC/DMAP,[26] and pure esters **12** (less polar) and **13** (more polar) were obtained after column chromatography in 45 and 43% yield, respectively (Scheme 5).



Scheme 5. Reagents and conditions: (a) (*S*)-Ph(MeO)CHCOOH, DCC, DMAP, (b) aqueous NH_3, THF

Treatment of **12** with aqueous ammonia followed by separation of *O*-methylmandelamide by column chromatography gave (1*R*,2*R*)-**6a** in 94% yield. In a similar manner, (1*S*,2*S*)-**6a** was obtained from **13** in 92% yield. Absolute configurations of (1*R*,2*R*)- and (1*S*,2*S*)-**6a** were assigned from the similarities of ^{1}H NMR spectral patterns for **12** or **13** and their ethyl analogs.[16] The Trost model[27] was applied once again.[16] The ^{31}P NMR chemical shifts of **12** (19.48 ppm) and **13** (20.14 ppm) were also useful for the assignments.[16,28] Since we were able to obtain minute quantities of pure racemic **5a**,[15] the enantiomeric phosphonate analogs of docetaxel side chain became available as methyl esters **6a** only.

Enantiomeric excesses of enantiomeric phosphonates **6a** were estimated based on ^{31}P NMR spectral data for the respective (–)-camphanyl esters. After completion of the esterification (NMR tube experiments) the camphanate derivative obtained from (1*S*,2*S*)-**6a** showed a single resonance at 20.08 ppm, while from (1*R*,2*R*)-**6a** two esters were formed as judged from the appearance of the two ^{31}P NMR signals at 20.34 and 20.08 ppm in a 99:1 ratio. Thus, the prepared samples of (1*R*,2*R*)- and (1*S*,2*S*)-**6a** had 98 and 100% enantiomeric excess, respectively. The enantiomeric excess of our resolving acid **11** was 97.6%,[‡] and (*S*)-*O*-methylmandelic esters **12** and **13** were finally purified by crystallization.

With the enantiomeric phosphonates **6a** in hand, we decided to synthesize phosphonates **4a** taking advantage of a clean transformation of racemic *N*-Boc phosphonates **5a** into *N*-benzoyl derivatives **3a**.[15] Benzoylation of (1*R*,2*R*)-**6a** and (1*S*,2*S*)-**6a** provided crystalline benzoates (1*R*,2*R*)-**9a** and (1*S*,2*S*)-**9a** in 58 and 57% yield, respectively. They were treated with hydrogen chloride in ethyl acetate followed by an excess of triethylamine (Scheme 3) to give crystalline

[‡] Estimated by ^{1}H NMR spectroscopy after esterification with natural menthol. Integrals of Me_8–C–Me_9 doublets[29] at δ 0.40 ppm for the ester of (*R*)-**11** and ^{13}C satellites at δ 0.46 ppm for the ester of (*S*)-**11** were compared. This region of the ^{1}H NMR spectrum is free from other ^{13}C satellites or spinning side-bands. Enantiomeric excess of natural menthol (100%) was proved in a similar way after derivatization with (–)-camphanyl chloride.

phosphonates (1*R*,2*R*)-**4a** and (1*S*,2*S*)-**4a**. Their enantiomeric excesses were again estimated by ^{31}P NMR spectroscopy as camphanyl esters and it appeared that ee's of both enantiomers were 100%.

In conclusion, it was demonstrated that the racemic phosphonate analog of the docetaxel C-13 side chain was easily obtained in gram quantities as the methyl ester **6a**. Enantiomers of this analog were obtained by resolution of the (*S*)-*O*-methylmandelate esters followed by racemization-free ammonolysis. Benzoates of these enantiomeric phosphonates were quantitatively transformed into enantiomeric phosphonate analogs of the paclitaxel C-13 side chain **4a**.

3. Experimental

^1H NMR spectra were taken in $CDCl_3$ on the following spectrometers: Bruker DPX (250 MHz) and Varian Mercury-300 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, or a Varian Mercury-300 machine at 75.5 and 121.5 MHz, respectively. 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 F_{254}. TLC plates were developed in various ethyl acetate–hexanes or $CHCl_3$–CH_3OH solvent systems. Visualization of spots was effected with iodine vapours. All solvents were purified by methods described in the literature.

3.1. Addition of dimethyl phosphite to the aldehyde 7

A mixture of the crude aldehyde **7** prepared[15] from 1,1-dimethylethyl-(2,3-dihydroxy-1-phenylpropyl)carbamate (3.385 g, 12.66 mmol), dimethyl phosphite (1.16 ml, 12.66 mmol) and NEt_3 (0.176 ml, 1.27 mmol) was stirred at room temperature for 24 h. The crude product was recrystallized from ethyl acetate–hexanes to give dimethyl (1*S**,2*S**)-2-[(*tert*-butoxycarbonyl)amino]-1-hydroxy-2-phenylethylphosphonate **6a** (2.045 g, 47%) as colorless plates. Mp 119.5–120.5°C; IR (KBr): $\nu = 3357$, 3314, 1704, 1525, 1238, 1163 and 1040 cm^{-1}; ^1H NMR (250 MHz): $\delta = 7.41$–7.22 (m, 5H), 6.09 (d, $J = 10.0$ Hz, 1H), 5.09 (brs, 1H), 4.48 (brs, 1H), 4.21 (brs, 1H), 3.79 (d, $J = 10.5$ Hz, 3H), 3.74 (d, $J = 10.5$ Hz, 3H), 1.40 (s, 9H); ^{13}C NMR (62.9 MHz): $\delta = 155.41$, 140.20 (brd, $J = 13.7$ Hz), 128.19, 127.24, 126.80, 79.41 (brs), 71.02 (d, $J = 161.3$ Hz), 54.52 (vbrs), 53.67 (d, $J = 7.1$ Hz), 53.12 (d, $J = 7.3$ Hz), 28.18; ^{31}P NMR (101.25 MHz): $\delta = 24.73$. Anal. calcd for $C_{15}H_{24}NO_6P$: C, 52.17; H, 7.00; N, 4.06. Found: C, 52.17; H, 7.18; N, 4.02.

Mother liquors were concentrated to leave a 1:1 mixture of **6a** and **6b** as a yellowish oil (0.520 g).

When this reaction was repeated using **7** [from the carbamate (0.802 g, 3.00 mmol)], dimethyl phosphite (0.250 ml, 2.70 mmol) and NEt_3 (0.042 ml, 0.30 mmol), the phosphonate **6a** (0.480 g, 51%) was obtained after crystallization from acetate–hexanes.

3.2. Isopropylidenation of a mixture of 6a and 6b

A 1:1 mixture of **6a** and **6b** (1.45 g, 4.19 mmol) was dissolved in toluene (40 ml) and 2-methoxypropene (4.01 ml, 41.9 mmol) followed by PPTS (53 mg, 0.21 mmol) were added. The solution

was kept at 80–90°C (bath) for 2 h. The toluene solution was washed with water (2×20 ml), dried over $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed on silica gel using ethyl acetate:hexanes (2:1, v/v) containing methanol (0.1%) to give **8a** (0.639 g, 40%), various mixtures of **8a** and **8b** (0.134 g, 8%), **8b** (0.105 g, 7%) and **6b** (0.140 g, 10%).

1,1-Dimethyl (4*S**,5*S**)-5-(dimethoxyphosphinyl)-2,2-dimethyl-4-phenyl-3-oxazolidinecarboxylate **8a**: colorless needles after crystallization from ethyl acetate–hexanes (0.308 g, 19%). Mp 101–102°C; IR (KBr): $\nu = 1707$, 1387, 1261, 1094, 1048 and 1026 cm^{-1}; ^1H NMR (250 MHz): $\delta = 7.38$–7.24 (m, 5H), 5.04 (vbrdd, $J_{H-P} = \sim 14$ Hz, $J_{H-H} = \sim 8$ Hz, 1H), 4.20 (d, $J = 8.3$ Hz, 1H), 3.75 (d, $J = 10.5$ Hz, 6H), 1.75 (s, 6H), 1.09 (brs, $\nu_{1/2} = 21$ Hz, 9H); ^{13}C NMR (62.9 MHz): $\delta = 151.61$, 140.45 (brs), 128.45, 127.70, 126.61, 96.82 (d, $J = 9.3$ Hz), 80.27 (brs), 77.77 (d, $J = 172.3$ Hz), 63.01 (d, $J = 3.4$ Hz), 53.74 (d, $J = 6.6$ Hz), 53.39 (d, $J = 6.8$ Hz), 28.02, 26.3 (vbrs, $\nu_{1/2} = 21$ Hz), 26.0 (vbrs, $\nu_{1/2} = 13$ Hz); ^{31}P NMR (101.25 MHz): $\delta = 22.22$. Anal. calcd for $C_{18}H_{28}NO_6P$: C, 56.10; H, 7.32; N, 3.63. Found: C, 56.13; H, 6.97; N, 3.54.

1,1-Dimethyl (4*S**,5*R**)-5-(dimethoxyphosphinyl)-2,2-dimethyl-4-phenyl-3-oxazolidinecarboxylate **8b**: a colorless oil. IR (film): $\nu = 3483$, 2978, 1699, 1456, 1377, 1247, 1099 and 1047 cm^{-1}; ^1H NMR (300 MHz): $\delta = 7.44$–7.22 (m, 5H), 5.18 (vbrd, $J = \sim 6$ Hz, 0.25×H, *E*), 5.05 (dd, $J = 6.6$ Hz, $J = 2.1$ Hz, 0.75×H, *Z*), 4.66 (dd, $J = 8.1$ Hz, $J = 6.6$ Hz, 1H), 3.63 (d, $J = 10.8$ Hz, 0.75×3H, *Z*), 3.60 (brd, $J = 11$ Hz, 0.25×3H, *E*), 3.19 (brd, $J = 11$ Hz, 0.25×3H, *E*), 3.14 (d, $J = 11.1$ Hz, 0.75×3H, *Z*), 1.95 (brs, 0.75×3H, *Z*), 1.84 (brs, 0.25×3H, *E*), 1.61 (s, 3H), 1.44 (brs, $\nu_{1/2} = 4.8$ Hz, 0.25×9H, *E*), 1.14 (brs, $\nu_{1/2} = 2.4$ Hz, 0.75×9H, *Z*); ^{13}C NMR (75.5 MHz): $\delta = 151.5$ (brs, *E*), 151.45 (s, *Z*), 139.40 (d, $J = 4.3$ Hz, 75%, *Z*), 138.6 (brs, 25%, *E*), 128.34 (75%, *Z*), 128.19 (25%, *E*), 128.03 (25%, *E*), 127.86 (25%, *E*), 127.74 (75%, *Z*), 95.74 (d, $J = 13.7$ Hz, 75%, *Z*), 95.27 (d, $J = 14.6$ Hz, 25%, *E*), 81.00 (25%, *E*), 80.26 (75%, *Z*), 73.81 (d, $J = 179.5$ Hz, *Z*), 73.74 (d, $J = 179.0$ Hz, *E*), 62.88 (brs, 25%, *E*), 62.73 (d, $J = 3.8$ Hz, 75%, *Z*), 53.20 (d, $J = 6.6$ Hz, *E*+*Z*), 53.02 (d, $J = 6.6$ Hz, *E*+*Z*), 28.58 (25%, *E*), 28.25 (75%, *Z*), 27.16 (25%, *E*), 26.31 (75%, *Z*), 24.17 (25%, *E*), 23.03 (75%, *Z*); ^{31}P NMR (121.5 MHz): $\delta = 19.00$. Anal. calcd for $C_{18}H_{28}NO_6P$: C, 56.10; H, 7.32; N, 3.63. Found: C, 55.80; H, 7.51; N, 3.86.

Dimethyl (1*R**,2*S**)-2-[(*tert*-butoxycarbonyl)amino]-1-hydroxy-2-phenylethylphosphonate **6b**: a white amorphous solid after crystallization from ether–hexanes (0.072 g, 5%). Mp 96.2–96.8°C; IR (KBr): $\nu = 3256$, 1694, 1389, 1248, 1165, 1086 and 1047 cm^{-1}; ^1H NMR (300 MHz): $\delta = 7.4$–7.2 (m, 5H), 6.02 (brd, $J = 8.1$ Hz, 1H), 5.17 (vbrd, $J = \sim 20$ Hz, 1H), 4.32 (ddd, $J = 8.1$ Hz, $J = 8.1$ Hz, $J = 4.5$ Hz, 1H), 3.71 (brd, $J = 10.5$ Hz, 3H), 3.38 (brd, $J = 10.0$ Hz, 3H), 3.29 (brs, 1H), 1.43 (brs, 9H); ^{13}C NMR (75.5 MHz): $\delta = 155.63$, 138.00, 128.28, 127.70, 127.56, 80.02, 70.99 (d, $J = 159.7$ Hz), 56.55 (brd, $J = 3.0$ Hz), 53.72 (d, $J = 6.6$ Hz), 53.12 (d, $J = 7.2$ Hz), 28.55; ^{31}P NMR (121.5 MHz): $\delta = 23.94$. Anal. calcd for $C_{15}H_{24}NO_6P$: C, 52.17; H, 7.00; N, 4.06. Found: C, 52.53; H, 7.34; N, 4.17.

When pure **6a** (0.652 g, 1.89 mmol) was subjected to isopropylidenation as described above, **8a** (0.658 g, 90%) was obtained after column chromatography. Crystallization of this material from ethyl acetate–hexanes gave **8a** (0.439 g, 60%). Mp 102.1–102.3°C.

3.3. Benzoylation of *6a* and *6b*

A 4:6 mixture of **6a** and **6b** (0.540 g, 1.56 mmol) was subjected to benzoylation (PhCOCl 1.05 equiv., NEt_3 1.1 equiv., DMAP 0.1 equiv.) to give crude benzoates **9a** and **9b** (0.745 g). This material was chromatographed three times on silica gel using ethyl acetate:hexanes (2:1, v/v) containing methanol (0.1%) to give **9b** (0.333 g, 47%) after crystallization from ethyl acetate–hexanes.

Dimethyl (1*R**,2*S**)-1-(benzoyloxy)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylethylphosphonate **9b**. Colorless plates. Mp 140.0–140.5°C; IR (KBr): $\nu = 3391$, 1728, 1711, 1521, 1303, 1262, 1244 and 1016 cm^{-1}; ^1H NMR (300 MHz): $\delta = 8.09$–8.05 (m, 2H), 7.63–7.57 (m, 1H), 7.5–7.4 (m, 4H), 7.4–7.3 (m, 2H), 7.3–7.24 (m, 1H), 6.38 (brd, $J = \sim 7$ Hz, 1H), 5.82 (dd, $J = 10.5$ Hz, $J = 5.1$ Hz, 1H), 5.42 (vbrd, $J_{H-P} \sim 26$ Hz, 1H), 3.67 (d, $J = 10.8$ Hz, 3H), 3.30 (brd, $J = 10.8$ Hz, 3H), 1.42 (s, $\nu_{1/2} = 7$ Hz) and ~1.30 (vbrs) total 9H; ^{13}C NMR (75.5 MHz): $\delta = 164.69$ (d, $J = 6.3$ Hz), 155.25 (brs), 137.10 (brs), 133.48, 129.82, 128.76, 128.37, 128.30, 127.69, 126.92, 79.63 (brs), 70.12 (d, $J = 166.1$ Hz), 54.88 (brs), 53.78 (d, $J = 6.6$ Hz), 52.61 (d, $J = 6.6$ Hz), 28.36; ^{31}P NMR (121.5 MHz): $\delta = 21.32$. Anal. calcd for $C_{22}H_{28}NO_7P$: C, 58.79; H, 6.28; N, 3.12. Found: C, 58.87; H, 6.59; N, 3.27.

In a similar manner pure **6a** (0.690 g, 2.00 mmol) was transformed into **9a** (0.817 g, 91%) after column chromatography. Crystallization from ethyl acetate–hexanes gave pure **9a** (0.661 g, 74%) as colorless needles.[24]

3.4. Dimethyl (1S*,2S*)- and (1R*,2S*)-2-(benzoylamino)-1-hydroxy-2-phenylethylphosphonates **4a** and **4b**

To a solution of the phosphonate **9a** (0.759 g, 1.69 mmol) in CH_2Cl_2 (4 ml) 3.8 M HCl–AcOEt (2 ml) was added at room temperature and the reaction mixture was stirred for 3 h. Methylene chloride (5 ml) was added followed by NEt_3 (1.4 ml, 10 mmol). The suspension was stirred at room temperature for 2 h. After dilution with CH_2Cl_2 (10 ml) the organic phase was washed with water (3×10 ml), dried ($MgSO_4$) and concentrated. The crude product was chromatographed on silica gel using ethyl acetate:hexanes (3:1, v/v) containing methanol (0.5%) to afford **4a** (0.534 g, 91%). Crystallization from ethyl acetate–hexanes gave pure **4a** (0.485 g, 82%) as a white amorphous solid. Mp 139.6–140.0°C; IR (KBr): $\nu = 3372$, 3233, 1645, 1523, 1487, 1202 and 1042 cm^{-1}; ^1H NMR (300 MHz): $\delta = 7.51$–7.24 (m, 11H), 5.59 (ddd, $J = 9.5$ Hz, $J = 8.4$ Hz, $J = 3.0$ Hz, 1H), 4.60 (brs, 1H), 4.33 (ddd, $J = 8.9$ Hz, $J = 7.3$ Hz, $J = 3.0$ Hz, 1H), 3.76 and 3.68 (2×d, $J = 10.5$ Hz, 2×3H); ^{13}C NMR (75.5 MHz): $\delta = 166.94$, 139.12 (d, $J = 12.9$ Hz), 134.06, 131.42, 128.32, 128.26, 127.42, 127.14, 126.89, 70.75 (d, $J = 161.8$ Hz), 54.02 (d, $J = 1.6$ Hz), 53.76 and 53.46 (2×d, $J = 7.5$ Hz): ^{31}P NMR (121.5 MHz): $\delta = 24.66$. Anal. calcd for $C_{17}H_{20}NO_5P$: C, 58.45; H, 5.77; N, 4.01. Found: C, 58.35; H, 5.86; N, 3.87.

In a similar way, from **9b** (0.334 g, 0.74 mmol) phosphonate **4b** (0.213 g, 83%) was obtained after column chromatography on silica gel with chloroform:methanol (50:1, v/v). Crystallization from chloroform–hexanes gave pure **4b** (0.189 g, 73%) as a white amorphous solid. Mp 163.8–164.0°C; IR (KBr): $\nu = 3250$, 1632, 1545, 1232, 1081 and 1058 cm^{-1}; ^1H NMR (300 MHz): $\delta = 8.27$ (brd, $J = 8.1$ Hz, 1H), 7.96–7.90 (m, 2H), 7.55–7.40 (m, 4H), 7.40–7.25 (m, 2H), 5.73 (ddd, $J = 26.2$ Hz, $J = 8.1$ Hz, $J = 4.8$ Hz, 1H), 4.44 (ddd, $J = 8.4$ Hz, $J = 6.6$ Hz, $J = 4.8$ Hz, 1H), 3.85–3.65 (brs, 1H), 3.77 (d, $J = 10.5$ Hz, 3H), 3.33 (brd, $J = 10.8$ Hz, 3H); ^{31}P NMR (121.5 MHz): $\delta = 24.65$. Anal. calcd for $C_{17}H_{20}NO_5P$: C, 58.45; H, 5.77; N, 4.01. Found: C, 58.84; H, 6.08; N, 4.23.

3.5. Ammonolysis of the benzoate **9b**

To a solution of **9b** (0.045 g, 0.10 mmol) in methanol (1 ml) 25% aqueous ammonia (1 ml) was added at room temperaure. When the ester **9b** disappeared (4 h), all volatiles were removed in vacuo. The residue was evaporated with anhydrous ethanol (3×5 ml) and chromatographed on silica gel with ethyl acetate–hexanes to give **6b** (0.028 g, 80%). After crystallization from ether–hexanes pure **6b** (0.027 g, 77%) was obtained. Mp 96.4–97.0°C.

3.6. Optical resolution of racemic **6a**

To a solution of **6a** (2.00 g, 5.80 mmol) and (*S*)-*O*-methylmandelic acid (1.16 g, 6.96 mmol) in CH_2Cl_2 (20 ml) DCC (1.44 g, 6.96 mmol) was added followed by DMAP (0.071 mg, 0.58 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 **12** (1.275 g, 45%) and **13** (1.222 g, 43%). Crystallizations from ethyl acetate–hexanes afforded **12** (1.113 g, 39%) and **13** (0.939 g, 33%).

Compound **12**: mp 114.4–114.9°C; $[\alpha]_D = +6.6$ ($c = 1.4$, ethyl acetate); IR (KBr): $\nu = 3411$, 1757, 1696, 1512, 1267 and 1043 cm^{-1}; ^1H NMR (300 MHz): $\delta = 7.4$–7.3 (m, 5H), 7.3–7.2 (m, 5H), 5.66–5.50 (brm, 2H), 5.32-5.18 (brs, 1H), 4.73 (s, 1H), 3.52 (d, $J = 10.8$ Hz, 3H), 3.27 (s, 3H), 3.25 (brd, $J = 11$ Hz, 3H), 1.44 (brs) and ~1.32 (vbrs)-total 9H; ^{13}C NMR (75.5 MHz): $\delta = 168.74$ (d, $J = 4.2$ Hz), 154.60, 137.90 (brd, $J = \sim 10$ Hz), 135.23, 128.78, 128.49, 128.39, 127.73, 127.09, 126.58 (brs), 82.12, 79.93 (brs), 70.31 (d, $J = 166.6$ Hz), 57.55, 53.97 (brs), 53.11 (brd, $J = \sim 6$ Hz), 53.05 (d, $J = 6.3$ Hz), 28.36; ^{31}P NMR (121.5 MHz): $\delta = 19.48$. Anal. calcd for $C_{24}H_{32}NO_8P$: C, 58.41; H, 6.54; N, 2.84. Found: C, 58.58; H, 6.51; N, 3.12.

Compound **13**: mp 122.4–122.8°C; $[\alpha]_D = +22.6$ ($c = 1.3$, ethyl acetate); IR (KBr): $\nu = 3300$, 1765, 1720, 1523, 1251, 1164 and 1065 cm^{-1}; ^1H NMR (300 MHz): $\delta = 7.41$–7.30 (m, 5H), 7.14–7.04 (m, 3H), 6.89-6.82 (m, 2H), 5.6-5.4 (brm, 2H), 5.16 (brt, $J = \sim 9$ Hz, 1H), 4.79 (s, 1H), 3.73 (d, $J = 10.5$ Hz, 3H), 3.60 (brd, $J = \sim 10$ Hz, 3H), 3.34 (s, 3H), 1.42 (brs) and ~1.34 (vbrs) total 9H; ^{13}C NMR (75.5 MHz): $\delta = 168.43$ (d, $J = 4.3$ Hz), 154.43, 137.93 (brd, $J = \sim 12$ Hz), 135.27, 128.91, 128.66, 128.17, 127.35, 127.22, 126.02, 82.08, 79.83 (brs), 70.27 (brd, $J = 166.0$ Hz), 57.33, 53.37 (d, $J = 6.3$ Hz), 53.29 (d, $J = 6.3$ Hz), 53.3 (vbrs), 28.29; ^{31}P NMR (121.5 MHz): $\delta = 20.14$. Anal. calcd for $C_{24}H_{32}NO_8P$: C, 58.41; H, 6.54; N, 2.84. Found: C, 58.74; H, 6.83; N, 2.92.

To a solution of **12** (0.602 g, 1.22 mmol) in THF (6 ml) aqueous ammonia (25%, 4 ml) was added and the reaction mixture was stirred at room temperature for 2 h. After removal of all volatiles the crude product was chromatographed on silica gel with ethyl acetate:hexanes (3:1, v/v) containing methanol (0.1%) to give (1*R*,2*R*)-**6a** (0.394 g, 94%) as a colorless oil; $[\alpha]_D = -21.7$ ($c = 1.3$, ethyl acetate). Anal. calcd for $C_{15}H_{24}NO_6P$: C, 52.17; H, 7.00; N, 4.06. Found: C, 51.71; H, 6.86; N, 4.39.

In a similar way, from **13** (0.610 g, 1.24 mmol) (1*S*,2*S*)-**6a** (0.393 g, 92%) was obtained as a colorless oil; $[\alpha]_D = +20.4$ ($c = 1.4$, ethyl acetate). Anal. calcd for $C_{15}H_{24}NO_6P$: C, 52.17; H, 7.00; N, 4.06. Found: C, 52.31; H, 6.80; N, 4.10.

3.7. Benzoylation of (1R,2R)- and (1S,2S)-6a

Enantiomeric phosphonates **6a** were subjected to benzoylation as described above. From (1*R*,2*R*)-**6a** (0.307 g, 0.89 mmol) the benzoate (1*R*,2*R*)-**9a** (0.387 g, 97%) was obtained after chromatography on silica gel using chloroform:methanol (50:1, v/v). This material was recrystallized from ether–hexanes to give pure ester (0.230 g, 58%) as colorless plates. Mp 92.5–93.5°C; $[\alpha]_D = -60.5$ ($c = 1.1$, ethyl acetate). Anal. calcd for $C_{22}H_{28}NO_7P$: C, 58.79; H, 6.28; N, 3.12. Found: C, 58.65; H, 6.14; N, 3.08.

From (1*S*,2*S*)-**6a** (0.364 g, 1.06 mmol) the benzoate (1*S*,2*S*)-**9a** (0.463 g, 98%) was obtained after chromatography. Crystallization from ether–hexanes gave pure ester (0.272 g, 57%) as colorless plates. Mp 93.6–94.2°C; $[\alpha]_D = +63.9$ ($c = 1.1$, ethyl acetate). Anal. calcd for $C_{22}H_{28}NO_7P$: C, 58.79; H, 6.28; N, 3.12. Found: C, 58.66; H, 6.30; N, 3.07.

3.8. Enantiomeric phosphonates (1R,2R)- and (1S,2S)-**4a**

A solution of the benzoate (1*R*,2*R*)-**9a** (0.200 g, 0.445 mmol) in methylene chloride (5 ml) containing 3.7 M HCl–AcOEt (1 ml) was left at room temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2 (10 ml), neutralized with NEt_3 (0.56 ml, 4.0 mmol) and left for 2 h. After washing with water (3×10 ml) the organic layer was dried ($MgSO_4$) and concentrated. The crude product was chromatographed on silica gel with chloroform:methanol (50:1, v/v) to give (1*R*,2*R*)-**4a** (0.155 g, 100%). After crystallization from chloroform–ether pure phosphonate (0.106 g, 68%) was obtained as a white amorphous solid. Mp 117.4–118.4°C; $[\alpha]_D = +42.4$ ($c = 1.3$, ethyl acetate). Anal. calcd for $C_{17}H_{20}NO_5P$: C, 58.45; H, 5.77; N, 4.01. Found: C, 58.55; H, 5.66; N, 3.97.

In a similar manner from the benzoate (1*S*,2*S*)-**9a** (0.230 g, 0.512 mmol), (1*S*,2*S*)-**4a** (0.179 g, 100%) was obtained. Crystallization of this material from chloroform–ether gave pure product (0.130 g, 73%) as a white amorphous solid. Mp 117.4–118.1°C; $[\alpha]_D = -44.6$ ($c = 1.2$, ethyl acetate). Anal. calcd for $C_{17}H_{20}NO_5P$: C, 58.48; H, 5.77; N, 4.01. Found: C, 58.54; H, 5.71; N, 3.98.

3.9. Determination of the enantiomeric excess of (1R,2R)- and (1S,2S)-**4a** and (1R,2R)- and (1S,2S)-**6a**

A general procedure described earlier[16] was followed. ^{31}P NMR spectra of (–)-camphanyl esters of (1*R*,2*R*)-**4a** and (1*S*,2*S*)-**4a** were taken for the chloroform-*d* solutions; ^{31}P NMR (121.5 MHz): 20.14 and 19.42 ppm, respectively. ^{31}P NMR spectra of (–)-camphanyl derivatives of (1*R*,2*R*)-**6a** and (1*S*,2*S*)-**6a** were obtained for the benzene-d_6 solutions; ^{31}P NMR (121.5 MHz): 20.34 and 20.08 ppm, respectively.

3.10. Determination of the enantiomeric excess of (S)-O-methylmandelic acid **11**

To a solution of the acid **11** (17.0 mg, 0.1 mmol) in CH_2Cl_2 (2 ml), natural menthol (31.0 mg, 0.2 mmol) was added followed by DCC (43.0 mg, 0.21 mmol) and DMAP (two crystals). After 24 h at room temperature DCU was filtered off and washed with CH_2Cl_2 (4 ml). The organic solution was concentrated, dissolved in chloroform-*d* (0.7 ml) and ^1H NMR spectrum was taken at 300 MHz; NS = 256.

Acknowledgements

We thank Mrs. Jolanta Plocka for her skilled experimental contributions. Financial support from the Medical University of Łódz (503-302-4) is gratefully acknowledged.

References

1. Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15–44.
2. Oijma, I.; Kuduk, S. D.; Pera, P.; Veith, J. M.; Bernacki, R. J. *J. Med. Chem.* **1997**, *40*, 279–285.
3. Oijma, I.; Slater, J. C.; Kuduk, S. D.; Takeuchi, C. S.; Gimi, R. H.; Sun, C.-M.; Park, Y. H.; Pera, P.; Veith, J. M.; Bernacki, R. J. *J. Med. Chem.* **1997**, *40*, 267–278.
4. Ali, S. M.; Hoemann, M. Z.; Aube, J.; Georg, G. I.; Mitscher, L. A.; Jayasinghe, L. R. *J. Med. Chem.* **1997**, *40*, 236–241.

5. Moyna, G.; Williams, H. J.; Scott, A. I. *Synth. Commun.* **1997**, *27*, 1561–1567.
6. Georg, G. I.; Harriman, G. C. B.; Hepperle, M.; Clowers, J. S.; Vander Velde, D. G.; Himes, R. H. *J. Org. Chem.* **1996**, *61*, 2664–2676.
7. Rossi, F. M.; Powers, E. T.; Yoon, R.; Rosenberg, L.; Meinwald, J. *Tetrahedron* **1996**, *52*, 10279–10286.
8. Kant, J.; Schwartz, W. S.; Fairchild, C.; Gao, Q.; Huang, S.; Long, B. H.; Kadow, J. F.; Langley, D. R.; Farina, V.; Vyas, D. *Tetrahedron Lett.* **1996**, *37*, 6495–6498.
9. Kingston, D. G. I.; Chordia, M. D.; Jagtap, P. G. *J. Org. Chem.* **1999**, *64*, 1814–1822.
10. Cardillo, G.; Tolomelli, A.; Tomasini, C. *Eur. J. Org. Chem.* **1999**, 155–161.
11. Nocioni, A. M.; Papa, C.; Tomasini, C. *Tetrahedron Lett.* **1999**, *40*, 8453–8456.
12. Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147–3176.
13. Hilderbrand, R. L. *The Role of Phosphonates in Living Systems*; CRC Press: Boca Raton, 1983.
14. Engel, R. *Synthesis of Carbon–Phosphorus Bond*; CRC Press: Boca Raton, 1988.
15. Wróblewski, A. E.; Piotrowska, D. G. *Tetrahedron* **1998**, *54*, 8123–8132.
16. Wróblewski, A. E.; Piotrowska, D. G. *Tetrahedron: Asymmetry* **1999**, *10*, 2037–2043.
17. Gennari, C.; Carcano, M.; Donghi, M.; Mongelli, N.; Vanotti, E.; Vulpetti, A. *J. Org. Chem.* **1997**, *62*, 4746–4755.
18. Bourzat, J. D.; Comerçon, A. *Tetrahedron Lett.* **1993**, *38*, 6049–6052.
19. Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985–7012.
20. Yamaguchi, T.; Harada, N.; Ozaki, K.; Hayashi, M.; Arakawa, H.; Hashiyama, T. *Tetrahedron* **1999**, *55*, 1005–1016.
21. Krawczyk, H. *Synth. Commun.* **1997**, *27*, 3151–3161.
22. Jacques, J.; Leclercq, M.; Brienne, M.-J. *Tetrahedron* **1981**, *37*, 1727–1733.
23. Thomas, A. A.; Sharpless, K. B. *J. Org. Chem.* **1999**, *64*, 8379–8385.
24. Piotrowska, D. G.; Hałajewska-Wosik, A.; Wróblewski, A. E. *Synth. Commun.* **2000**, *30*, accepted.
25. Bonner, W. A. *J. Am. Chem. Soc.* **1951**, *73*, 3126–3132.
26. Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978,** 4475–4478.
27. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370–2374.
28. Kozlowski, J. K.; Rath, N. P.; Spilling, C. D. *Tetrahedron* **1995**, *51*, 6385–6396.
29. Chataigner, I.; Lebreton, J.; Durand, D.; Guingant, A.; Villiéras, J. *Tetrahedron Lett.* **1998**, *39*, 1759–1762.