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# Enantiomerically pure *N*-Boc- and *N*-benzoyl-(*S*)-phenylglycinals

Andrzej E. Wróblewski* and Dorota G. Piotrowska

*Bioorganic Chemistry Laboratory, Faculty of Pharmacy, Medical University of Łódź, 90-151 Łódź, Muszyńskiego 1, Poland*

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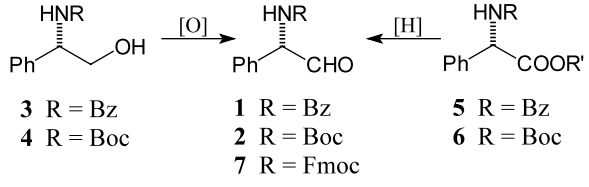
**Abstract**—Enantiomerically pure *N*-Boc- and *N*-benzoyl-(*S*)-phenylglycinals were prepared by oxidation of the respective alcohols with Dess–Martin periodinane. The glycinals were phosphonylated with lithium *O*,*O*-dimethyl phosphonate at −70°C or $(MeO)_2POTMS$ at −20°C without racemisation. In the presence of 10 mol% of $NEt_3$ at 20°C the aldehydes racemised instantaneously, while it took a few hours for the reacemisation processes to reach completion after addition of 1 mol% of $NEt_3$.


## 1. Introduction

*N*-Benzoyl- and *N*-Boc-phenylglycinals, **1** and **2**, belong to a group of α-amino aldehydes[1] usually considered as chemically unstable and easily racemised compounds. Since they have been employed in syntheses of several important natural products[2–4] including paclitaxel[5–10] and paclitaxel analogues,[11–14] the preparation of enantiomerically pure **1** and **2** is an important goal. However, in almost all synthetic applications of **1** and **2** the materials prepared in situ were immediately used in further transformations. An attempt of purification by vacuum distillation of *N*-Boc-D-phenylglycinal was described by Shioiri.[4]

In general, α-amino aldehydes **1** and **2** were synthesised (Scheme 1) by oxidation of the respective α-amino alcohols **3** and **4**[2–5,10,11,15] and by reduction of esters **5** and **6**[6,7,9] or Weinreb amides.[8] Other methods are also known.[16,17] Oxidations were performed under Swern conditions using ethyldiisopropylamine[2,5,10,11] or with sulphur trioxide–pyridine complex.[4] The crude aldehydes were further subjected to nucleophilic additions, and their e.e.'s were estimated by the analysis of the enantiomeric purities of the addition products. DIBAL-H reduction of esters **5** and **6** elaborated by Dondoni[9] led to the aldehydes **1** and **2**, and their e.e.'s were established as 84 and 90%, respectively, after $NaBH_4$ reduction to the known phenylglycinols **3** and **4**.




**3** R = Bz
**4** R = Boc

**1** R = Bz
**2** R = Boc
**7** R = Fmoc

**5** R = Bz
**6** R = Boc

**Scheme 1.**

The recent achievements of Myers in the synthesis of enantiomerically pure Fmoc-phenylglycinal[18–20] **7** and scarce examples of the application of the Dess–Martin reagent to the oxidation of **4**[5,15] prompted us to investigate the preparation of enantiomerically pure **1** and **2** and their racemisation-free transformation into the respective α-hydroxy phosphonates.

## 2. Results and discussion

(*S*)-Phenylglycinol **8** was obtained from L-phenylglycine according to the described procedure.[21] In the presence of $Boc_2O$ **8** was transformed into *N*-Boc derivative **4**,[22] while benzoylation led to *N*-benzoyl-(*S*)-phenylglycinol **3**.[22] Oxidation of **4** with the Swern reagent[23,24] was initially attempted. Despite the poor solubility of **4** in dichloromethane at low temperature, the aldehyde formed in situ was treated with lithium *O*,*O*-dimethyl phosphonate at −70°C to give a 74:26 mixture of the phosphonates **9a** and **9b** (Scheme 2).[14] The e.e. of **9a** and **9b** was established as only 76% by the $^{31}P$ NMR analysis of the ω-camphanate derivatives.[14]

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

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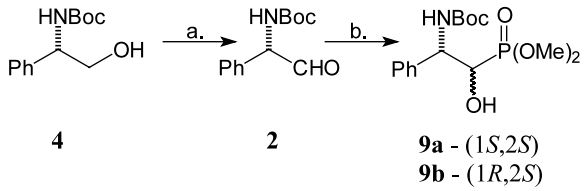
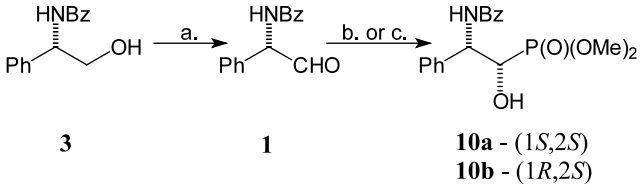



**Scheme 2.** *Reagents and conditions*: (a) Swern ($NEt_3$) or Dess–Martin reagents; (b) $LiP(O)(OMe)_2$, −70°C or $(MeO)_2POTMS$, −20°C and $Bu_4NF$.




**Scheme 4.** *Reagents and conditions*: (a) Dess–Martin reagent; (b) $LiP(O)(OMe)_2$, −70°C; (c) $(MeO)_2POTMS$, −20°C, then $Bu_4NF$.

However, when Dess–Martin periodinane[25–28] was applied, the aldehyde **2** was obtained as a white amorphous solid after crystallisation from $CH_2Cl_2$–ether–hexanes at −15°C. Reduction of a sample of **2** with $NaBH_4$ at 0°C[9] led to **4**, which was esterified with (*S*)-*O*-methylmandelic acid and found to be enantiomerically pure by $^1H$ NMR analysis of the reaction mixture. Phosphonylation of **2** was accomplished with $(MeO)_2POTMS$ at −20°C, and after desilylation with $Bu_4NF$, a 83:17 mixture of **9a** and **9b** was produced. The 100% e.e. of the phosphonates obtained was proved by the $^{31}P$ NMR analysis of their ω-camphanates.

In order to verify whether lithium *O*,*O*-dimethyl phosphonate could cause racemisation of **2** at −70°C, the aldehyde prepared after Dess–Martin oxidation of **4** was subjected to phosphonylation under these conditions. The 100% e.e. of the addition products was proved by the $^{31}P$ NMR spectroscopy. Enantiomerically pure phosphonate analogues of paclitaxel and docetaxel side chain **10a** and **9a**, respectively, were next obtained as follows. After benzoylation of the crude mixture of diastereoisomers **9a** and **9b**, the benzoate **11a** was separated in 31% yield after silica gel chromatography. The ester **11a** was subjected to a two-step one-pot procedure[14] to produce the phosphonate **10a** in 82% yield, while ammonolysis[29] of **11a** gave **9a** in 40% yield (Scheme 3). Both phosphonates were shown to be 100% e.e. by HPLC.

Dess–Martin periodinane oxidation of *N*-benzoyl-(*S*)-phenylglycinol **3** afforded enantiomerically pure aldehyde **1** as a white amorphous solid after crystallisation from $CH_2Cl_2$–ether–hexanes at −15°C. The aldehyde was reacted with either lithium *O*,*O*-dimethyl phosphonate at −70°C or dimethyl (trimethylsilyl)phosphite at −20°C to give 1:1 and 87:13 mixtures of the phosphonates **10a** and **10b**, respectively (Scheme 4).

Again, 100% e.e.'s of the phosphonates formed were established by the $^{31}P$ NMR spectroscopy after esterification with ω-camphanyl chloride[14] and further proved by HPLC.

After successful preparation of the enantiomerically pure *N*-Boc- and *N*-benzoyl-(*S*)-phenylglycinals, **1** and **2**, we addressed the problem of configurational stability of these compounds. Even crude products isolated after oxidation with Dess–Martin periodinane retained their 100% enantiomeric purity when left at 20°C for 24 h. At 0°C the purified aldehydes kept their configurational integrity for at least 3 months. However, at 20°C in the presence of 10 mol% of triethylamine, the purified aldehydes underwent complete racemisation instantaneously. The rates of racemisation of (*S*)-**1** and (*S*)-**2** were qualitatively followed at 20°C after addition of 1 mol% of $NEt_3$ (Table 1).

**Table 1.** The rate of racemisation of the aldehydes (*S*)-**1** and (*S*)-**2**

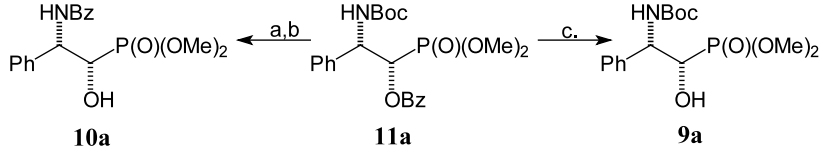
| Time (h) | 0 | 1 | 2 | 3 | 24 |
|---|---|---|---|---|---|
| (*S*)-**1** | 90[a] | 38 | 32 | 30 | 0 |
| (*S*)-**2** | 100 | 55 | 50 | 40 | 0 |

[a] E.e. from $^1H$ NMR spectroscopy.

Undoubtedly, the lower enantiomeric purity of the aldehyde **2** obtained by oxidation of **4** with Swern reagent was caused by the presence of triethylamine.

## 3. Conclusions

Dess–Martin periodinane was successfully applied to a racemisation-free oxidation of *N*-Boc- and *N*-benzoyl-(*S*)-phenylglycinols, while the Swern reagent caused some racemisation even at −60°C. The conditions of phosphonylation of enantiomerically pure *N*-Boc- and *N*-benzoyl-(*S*)-phenylglycinals were elaborated, namely with lithium *O*,*O*-dimethyl phosphonate at −70°C or with dimethyl(trimethylsilyl)phosphite at −20°C. In the presence of 1 mol% of $NEt_3$ the aldehydes racemised




**Scheme 3.** *Reagents and conditions*: (a) HCl–AcOEt, $CH_2Cl_2$; (b) $NEt_3$; (c) $NH_3$ aq., MeOH.

within a few hours at 20°C, while after addition of 10 mol% of $NEt_3$, racemisation occurred instantaneously.

## 4. Experimental

$^1H$, $^{13}C$ and $^{31}P$ NMR spectra were taken in $CDCl_3$ on the Varian Mercury-300 spectrometer at 300, 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 analysis were performed by the Microanalytical Laboratory of this Faculty on a Perkin–Elmer PE 2400 CHNS analyser. Polarimetric measurements were conducted on a Perkin–Elmer 241 MC apparatus. HPLC analyses were carried out on a LDC Analytical apparatus (column: Chiracel OD, 0.46 cm $\phi$×25 cm; detection: UV at 256 nm; isopropanol–hexanes, 1:9; 1 mL/min; rt).

The following adsorbents 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 chloroform–methanol solvent systems. Visualisation of spots was effected with iodine vapours.

### 4.1. *N*-Benzoyl- and *N*-Boc-(*S*)-phenylglycinals, 1 and 2

To a solution of amino alcohol **3** or **4** (482 mg or 475 mg, 2.00 mmol) in water-saturated $CH_2Cl_2$ (7.5 mL) was added Dess–Martin periodinane (1.78 g, 4.20 mmol). The suspension was stirred at 23°C for 30 min while water-saturated $CH_2Cl_2$ (2×3 mL) was added every 15 min. After disappearance of the starting alcohols (TLC), ethyl ether (6.7 mL) was added followed by a solution of sodium thiosulphate (5.46 g) in 80% saturated sodium bicarbonate (7.3 mL). Organic layer was separated, and the aqueous phase was extracted with ether (15 mL). Organic solution was washed with saturated aqueous $NaHCO_3$ (10 mL), water (2x10 mL) and brine (2×10 mL). After drying over $MgSO_4$ at 0°C, the solvents were partially evaporated (water bath below 20°C). The residue was triturated with hexanes until turbidity and left at −15°C for 1 h (in the case of **1**) or overnight (in the case of **2**). Solvents were removed, solid aldehydes were washed with a 4:1 hexane–ether mixture and dried in a stream of argon at rt.

**4.1.1. *N*-Benzoyl-(*S*)-phenylglycinal, (*S*)-1**. Yield 230 mg (48%). Mp: 121–122°C; $[\alpha]_D^{20}$ +269 (*c* 0.8 in $CH_2Cl_2$); $[\alpha]_D^{20}$ +260 (*c* 0.85 in $CHCl_3$).

**4.1.2. *N*-Boc-(*S*)-phenylglycinal, (*S*)-2**. Yield 250 mg (53%). Mp: 75.9–76.4°C, lit.[4] 55–56°C; $[\alpha]_D^{20}$ +272 (*c* 0.9 in $CH_2Cl_2$), lit.[4] $[\alpha]_D^{19.5}$ −95.5 (*c* 0.53 in $CH_2Cl_2$) for (*R*)-**2**; $[\alpha]_D^{20}$ +308 (*c* 0.75 in $CHCl_3$).

### 4.2. General procedure for the e.e. determination of (*S*)-1 and (*S*)-2

**4.2.1. Method 1: by $^1H$ NMR spectroscopy**. A sample (50 mg, 0.20 mmol) of the aldehyde **1** or **2** was dissolved in methanol (1 mL), cooled to 0°C and $NaBH_4$ (12 mg, 0.32 mmol) was added. After 30 min the reaction mixture was allowed to reach rt and was neutralised to pH 7 with 1N HCl. Methanol was evaporated, the residue was suspended in $CH_2Cl_2$ (5 mL) and anhydrous $MgSO_4$ (1 g) was added. The solids were removed and the solution was evaporated to give crude phenylglycinols **3** and **4** quantitatively.

A sample of **3** or **4** (10 mg, 0.041 mmol) was dissolved in $CH_2Cl_2$ (1.0 mL) and (*S*)-*O*-methylmandelic acid (8.0 mg, 0.046 mmol) was added followed by DCC (9.0 mg, 0.046 mmol) and a crystal of DMAP. After 2 h at rt the precipitated DCU was filtered off, washed with $CH_2Cl_2$, and the residue was subjected to $^1H$ NMR analysis as a solution in chloroform-*d* (ester of **3**) or benzene-$d_6$ (ester of **4**). Integrals of signals at 4.695 and 4.684 ppm (*H*-C-OMe) and 3.294 and 3.254 ppm ($CH_3$O-C-H) in the spectra of *O*-methylmandelate of **3** and 4.618 and 4.586 ppm (*H*-C-OMe) and 3.176 and 3.144 ppm ($CH_3$O-C-H) in the spectra of *O*-methylmandelate of **4** were selected for calculation of e.e.

**4.2.2. Method 2: by HPLC**. Retention times: $t_R$(*R*)-**3** = 15.16 min, $t_R$(*S*)-**3** = 11.40 min; $t_R$(*R*)-**4** = 6.34 min, $t_R$(*S*)-**4** = 7.55 min.

### 4.3. Phosphonylation of aldehydes (*S*)-1 and (*S*)-2

**4.3.1. Method 1: with dimethyl(trimethylsilyl)phosphite**. To a solution of a crude aldehyde (*S*)-**2** [prepared from (*S*)-**4** (1.66 g, 7.00 mmol)] in $CH_2Cl_2$ (3 mL), $(MeO)_2$POTMS (1.34 mL, 7.00 mmol) was added at −20°C. The reaction mixture was left at −20°C for 24 h. The solvent was evaporated, and the residue was dissolved in 1 M $Bu_4NF$ in THF (8.4 mL, 8.4 mmol). After 1 h at rt the solvent was evaporated, the crude product was dissolved in $CH_2Cl_2$ (10 mL), washed with water (2×5 mL) and dried over $MgSO_4$. Column chromatography on silica gel gave a 83:17 mixture of (1*S*,2*S*)-**9a** and (1*R*,2*S*)-**9b** (1.92 g, 80%).

In the same way, from crude aldehyde (*S*)-**1** [prepared from (*S*)-**3** (0.241 g, 1.00 mmol)] and $(MeO)_2$POTMS (0.19 mL, 1.00 mmol), a 87:13 mixture of (1*S*,2*S*)-**10a** and (1*R*,2*S*)-**10b** (0.216 g, 62%) was obtained after chromatography on a silica gel column.

**4.3.2. Method 2: with lithium *O*,*O*-dimethyl phosphite**. Crude aldehyde (*S*)-**2** [prepared from (*S*)-**4** (1.42 g, 6.00 mmol)] was subjected to the reaction with lithium *O*,*O*-dimethyl phosphite (6.00 mmol) at −70°C as described in Ref. 12. After chromatography on a silica gel column a 75:25 mixture of the phosphonates (1*S*,2*S*)-**9a** and (1*R*,2*S*)-**9b** (1.347 g, 80%) was obtained.

In the same way, from crude aldehyde (*S*)-**1** [prepared from (*S*)-**3** (0.668 g, 2.77 mmol)] and lithium *O*,*O*-dimethyl phosphite (2.77 mmol), a 1:1 mixture of the phosphonates (1*S*,2*S*)-**10a** and (1*R*,2*S*)-**10b** (0.490 g, 51%) was obtained after chromatography on a silica gel column.

### 4.4. Phosphonates (1*S*,2*S*)-9a and (1*S*,2*S*)-10a

**4.4.1. Benzoate, 11a**. A 3:1 mixture of (1*S*,2*S*)-**9a** and (1*R*,2*S*)-**9b** (1.025 g, 2.968 mmol) was esterified with benzoyl chloride as described earlier[14] to give crude product (0.666 g, 83%), which was purified on a silica gel column followed by crystallisation. The benzoate (1*S*,2*S*)-**11a** was obtained in 30% yield (0.392 g). Mp 93.0–93.8°C.

**4.4.2. Phosphonate (1*S*,2*S*)-10a**. The benzoate (1*S*,2*S*)-**11a** (0.130 g, 0.289 mmol) was treated with 3.7 M HCl–AcOEt as described earlier[14] to afford (1*S*,2*S*)-**10a** (0.082 g, 82%). Mp. 117–118°C. Retention time: $t_R =$ 21.92 min.

Retention times for the racemic mixture: $t_R$(1*R*,2*R*)-**10a** = 16.73 min, $t_R$(1*S*,2*S*)-**10a** = 21.95 min.

**4.4.3. Phosphonate (1*S*,2*S*)-9a**. The benzoate (1*S*,2*S*)-**11a** (0.075 g. 0.167 mmol) was dissolved in methanol (0.5 mL) and treated with aqueous ammonia (25%, 1 mL) for 24 h.[14] After column chromatography on a silica gel column, (1*S*,2*S*)-**9a** (0.022g, 40%) was obtained as a colourless oil. Retention time: $t_R = 8.30$ min.

Retention times for the racemic mixture: $t_R$(1*R*,2*R*)-**9a** = 10.04 min, $t_R$(1*S*,2*S*)-**9a** = 8.86 min.

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