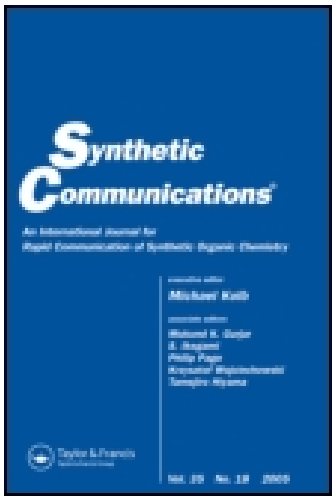

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A PRACTICAL AND EFFICIENT SYNTHESIS OF TAXOL C-13 SIDE CHAIN

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A PRACTICAL AND EFFICIENT SYNTHESIS OF TAXOL C-13 SIDE CHAIN

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ABSTRACT

A practical and efficient synthesis of taxol C-13 side chain from cheap and easily available starting material is described.

Taxol **1**, an antimicrotubule agent isolated from the bark of *Taxus brevifolia*,[1] has recently attracted much attention because of its efficacy in the treatment of various types of cancer. In view of promising results in cancer treatment, a demand for large quantities of taxol is anticipated in the near future. The most favourable solution to supply the problem is a semi-synthetic approach involving the synthesis and attachment of

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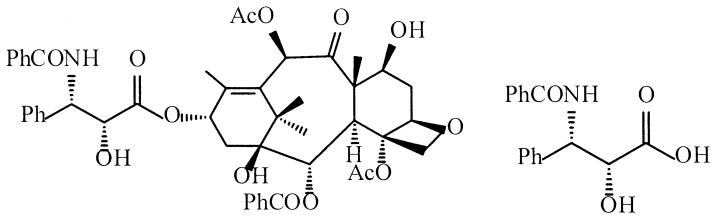
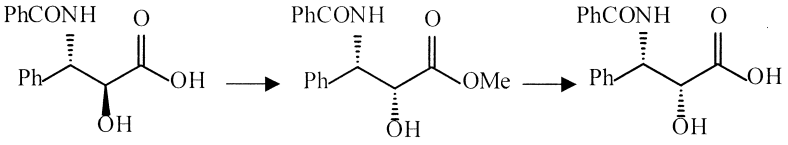


1 2

(2R,3S)-*N*-benzoyl-3-phenylisoserine **2** to baccatin III obtained from the leaves of readily available *taxus* species.[2] Several synthesis of chirally pure phenylisoserine are known,[3–9] but most are unsuitable for large scale production. In view of the demand for large quantities of phenylisoserine. We attempted to design a practical and efficient synthetic route to compound **2**.

In our previous paper,[10] we have reported the synthesis of erythro-*N*- benzoyl-3-phenylisoserine, resolution of erythro-*N*-benzoyl-3-phenylisoserine with S-(−)-α-methyl benzylamine provided (2S,3S)-*N*-benzoyl-3-phenylisoserine **3**. The compound **3** can be transformed to the (2R,3S)-*N*-benzoyl-3-phenylisoserine **2** by inversion of configuration at the C-**2**.[11] The reaction sequence is illustrated in Scheme 1.

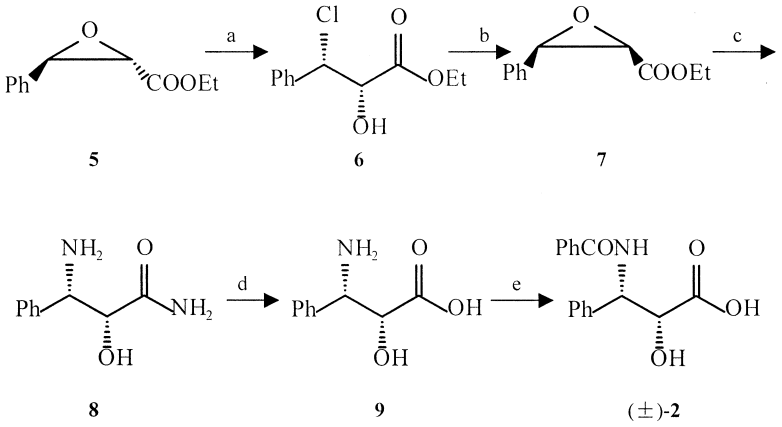


3 4 2

Scheme 1.

The present report describes a highly practical and efficient synthesis of **2** in terms of production cost and handling of the reaction process. Reaction of *trans*-epoxide **5**[12] with HCl gas in benzene furnished the highly stereoselective ring opened product **6** which upon treatment with inexpensive Amberlite IRA-420(OH^-) resin gave *cis*-epoxide **7**. Ammonolysis of **7** by methanolic ammonia under high pressure provided the isoserineamide **8** as the major product. Any serine byproduct was easily removed by washing with methanol. Hydrolysis of the amide **8** using $Ba(OH)_2$ gave threo-3-phenylisoserine **9**. This material was converted to

threo-*N*-benzoyl-3-phenylisoserine (±)-**2** by treatment with benzoyl chloride/$NaHCO_3$ in a two-phase reaction in good yield. Resolution of (±)-**2** with *R*-(+)-α-methyl benzylamine provided **2**. (Scheme 2)



(a) HCl,benzene,3h,70%;(b) Amberlite IRA-420(HO^-),THF,3h,61%;(c) NH_3,MeOH,100℃, 22h,65%;(d) $Ba(OH)_2 \cdot 8H_2O$,8h,88%;(e) PhCOCl,$NaHCO_3$,4℃,6h,69%

Scheme 2.

EXPERIMENTAL

Melting points were uncorrected. IR spectra were determined on a IDP-435 infrared spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz on a Varian Mercury 300 spectrometer using TMS as an internal standard. Elemental analyses were performed by a PE-2400 instrument. Optical rotations were measured using WZZ-T1 polarimeter.

(2S,3S)-*N*-Benzoyl-3-phenylisoserine (3)

To a refluxing solution of erythro-*N*-benzoyl-3-phenylisoserine (2.9 g, 10.0 mmol) in ethanol (20 ml) was added S-(−)-α-methylbenzylamine (1.2 g, 10.0 mmol). The resulting solution was cooled to room temperature and

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allowed to stand at room temperature overnight. It was then filtered and S-(−)-α-methylbenzylamine salt of the desired product (1.7 g) was obtained after drying. The resulting salt was dissolved in water (45 ml). The resulting solution was acidified to pH = 2 and then was extracted with diethyl ether (3 × 50 ml), dried over $MgSO_4$. The solvent was removed. The residue was dissolved in acetone (10 ml) and petroleum ether (400 ml) was added subsequently. The desired product (1.1 g, 39%) was obtained by filtration. Mp 160–162°C. $[\alpha]_D^{25}$ - 35.0 (C 0.9, EtOH). IR (KBr) ν: 3600, 3500–2600, 1750, 1640, 1520, 700 cm^{-1}. ^1H NMR (acetone-d_6) δ: 4.75 (d, J = 4.5 Hz, 1H), 5.65 (dd, J = 4.5 Hz, 1H), 7.20–7.70 (m, 10H), 7.80–8.00 (d, J = 4.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 57.2, 74.6, 128.8, 129.1, 129.5, 129.9, 130.0, 136.1, 141.6, 167.4, 175.4. Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.31; H, 5.26; N, 4.87.

Threo-3-chloro-2-hydroxy-3-phenylisoserine Ethyl Ester (6)

Dry HCl gas was bubbled into a solution of **5** (38.4 g, 0.2 mol) in dry benzene (400 ml) for 3 h and the excess HCl was removed under partial vacuo. The solvent was evaporated and the residue was recrystallized from benzene-petroleum ether (1 : 3) to furnish pure crystalline product **6** (31.9 g, 70%). Mp 74–75°C. IR (KBr) ν: 3400, 1740 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.32 (t, J = 7.0 Hz, 3H), 3.30 (d, J = 7.5 Hz, 1H), 4.30 (q, J = 7.0 Hz, 2H), 4.49 (dd, J = 2.3 Hz, 1H), 5.27 (d, J = 2.3 Hz, 1H), 7.30–7.54 (m, 5H). Anal. Calcd. for $C_{11}H_{13}ClO_3$: C, 57.78; H, 5.73. Found: C, 57.67; H, 5.78.

cis-Ethyl-3-phenylglycidate (7)

A suspension of chlorohydrin **6** (9.8 g, 43 mmol) and Amberlite IRA-420(HO^-) resin (80 g) in dry THF (180 ml) was stirred at room temperature for 3 h under N_2 atmosphere. The resin was filtered and washed with THF (3 × 200 ml). The solvent was evaporated and the oily residue was dried under high vacuo to provide the *cis*-epoxide **7** (5.0 g, 61%) which was pure enough for the subsequent step. IR (neat) ν: 1755 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.02 (t, J = 7.2 Hz, 3H), 3.83 (d, J = 4.8 Hz, 1H), 3.9–4.1 (m, 2H), 4.27 (d, J = 4.8 Hz, 1H), 7.2–7.5 (aromatic, 5H). ^{13}C NMR ($CDCl_3$) δ: 13.8, 55.7, 57.3, 126.6, 127.9, 128.3, 132.8, 166.5. Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.63; H, 6.37.

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Threo-3-phenylisoserineamide (8)

A solution of **7**(20.0 g, 104 mmol) in methanol saturated with ammonia (prepared by passing anhydrous NH_3 through methanol at $-15^{\circ}C$) was sealed in a steel bomb and heated at 100°C for 22 h. The solution was cooled to room temperature. The solvent was evaporated and the residue was triturated with ethanol to provide a yellowish solid which was recrystallized from methanol to furnish pure crystalline product (12.2 g, 65%). Mp 193–194°C. IR (KBr) ν: 3400, 3360, 3306, 1660 cm^{-1}. ^1H NMR (DMSO-d_6/D_2O) δ: 3.87 (d, $J = 3.3$ Hz, 1H), 4.08 (d, $J = 3.3$ Hz, 1H), 7.0–7.5(aromatic, 5H). ^{13}C NMR (DMSO-d_6/D_2O) δ: 57.1, 75.5, 127.1, 128.1, 142.7, 175.9. Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.91; H, 6.67; N, 15.25.

Threo-3-phenylisoserine (9)

Threo-3-phenylisoserineamide (1.63 g, 9.05 mmol) was combined with 2.88 g (9.1 mmol) of $Ba(OH)_2 \cdot 8H_2O$ and water (16 ml). The resulting suspension was heated to reflux under nitrogen for 8 h. The reaction mixture was then cooled to 80°C, and water (120 ml) was added. The temperature of the solution was maintained at 80°C for 20 min before a solution of 0.91 g H_2SO_4 in 8 ml of water was added. The temperature of the mixture was maintained at 80°C for another 10 min, and then the mixture was cooled to room temperature. The resulting precipitate ($BaSO_4$) was removed by filtration, and the solvent of the filtrate was removed under vacuum to provide the product as a white solid (1.44 g, 88%). Mp 263–264°C. IR (KBr) ν: 3500, 1710, 1580, 1140, 700 cm^{-1}. ^1H NMR (D_2O/NaOD) δ: 3.94 (d, $J = 3.9$ Hz, 1H), 4.01 (d, $J = 3.9$ Hz, 1H), 7.0–7.5 (aromatic, 5H). Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.07; N, 7.73. Found: C, 59.21; H, 6.09; N, 7.58.

Threo-*N*-benzoyl-3-phenylisoserine ((±)– 2)

Threo-3-phenylisoserine (0.40 g, 2.2 mmol) was dissolved in 10% aqueous $NaHCO_3$ (55 ml) with stirring. The solution was cooled to 4°C and benzoyl chloride (0.89 g, 6.25 mmol) was added. This mixture was stirred at 4°C for 6 h and then acidified to pH = 1 by addition of aqueous HCl solution (18%). The mixture was extracted with THF/CH_2Cl_2 (4:1,3 × 60 ml), and the organic phases were combined, dried over $MgSO_4$. The solvent was removed under reduce pressure and the residue was dissolved in acetone (10 ml), then hexane (200 ml) was added subsequently.

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The desired product was isolated as a white solid by filtration (0.43 g, 69%). Mp 199–200°C. IR (KBr) ν: 3500, 3350, 1700, 1640, 1515, 1360, 1110 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 4.36 (d, $J = 4.2$ Hz, 1H), 4.00–4.60 (br, 1H), 5.45 (dd, $J = 8.7$, 4.2 Hz, 1H), 7.22–7.54 (m, 9H), 7.83 (d, $J = 6.6$ Hz, 1H), 8.55 (d, $J = 9.3$ Hz, 1H). ^{13}C NMR (acetone-d_6) δ: 56.3, 74.1, 127.9, 128.1, 129.0, 129.1, 131.9, 135.7, 141.1, 167.0, 173.8. Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.31; H, 5.26; N, 4.87.

(2R,3S)-*N*-benzoyl-3-phenylisoserine (2)

To a suspension of (±)− 2 (400 mg) in ethyl acetate (4.4 ml) was added *R*-(+)-α-methyl benzylamine (190 ml). The resulting solution was allowed to stand at room temperature for 2 h. It was then filtered and 536 mg of the salt was obtained after drying. The salt (200 mg) was dissolved in hot ethanol (1.8 ml). The solution was set aside at room temperature for 16 h. The resulting crystals were filtered and washed with cold ethanol, and dried in vacuum to furnish 90 mg of the R-(+)-α-methyl benzylamine salt of title product. The salt obtained was stirred in ethyl acetate (8.0 ml) and 5% aqueous $KHSO_4$ (8.0 ml). The aqueous layer was separated and extracted with ethyl acetate (3 × 8 ml). The combined organic layer was washed with brine (8 ml), dried over $MgSO_4$, filtered and concentrated to dryness to afford **2** (64 mg). $[\alpha]_D^{25}$ - 31.7 (C 1.0, EtOH) (Lit.,[13] $[\alpha]_D^{25}$ − 37.78, C 0.9, EtOH). Mp 166–168°C (Lit.,[13] 167–169°C). IR and NMR are consistent with those of the corresponding racemic acid.

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