cis-(-)-Menthyl phenylglycidates in the asymmetric synthesis of taxol side chain

Mustafa Er[1]* and Necdet Coşkun[2]

[1]*Muş Alparslan University, Department of Chemistry, 49100 Muş, Turkey*
[2]*Uludağ University, Department of Chemistry, 16059 Görükle-Bursa, Turkey*
E-mail: m.er@alparslan.edu.tr

Abstract

The one-pot azidation and benzoylation of a mixture of cis (-)-menthyl phenylglycidates provide quantitatively the corresponding (2R,3S)-, and (2S,3R)-3-azido-1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-1-oxo-3-phenylpropan-2-yl benzoate. Enantiopure (2R,3S)-3-azido-1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-1-oxo-3-phenylpropan-2-yl benzoate crystallize from MeOH at room temperature in high yields. The reduction of the latter with Zn-TMSCl produces (-)-menthyl 3-benzamido-3-phenyl-2-(trimethylsilyloxy)propanoate which upon simultanious desilylation and hydrolysis provide the taxol side chain N-benzoyl-(2R,3S)-3-phenylisoserine.

Keywords: *N*-Benzoyl-(2R,3S)-3-phenylisoserine, Taxol side chain, phenylglycidate, Zn-TMSCl reduction, azides

Introduction

The natural product Taxol,[1] isolated from *Taxus brevifolia,* is considered the most promising anticancer drug.[2] Because of the limited content in the bark of *Taxus brevifolia*, and the uneconomical production by total synthesis,[3] extensive efforts have been focused on semi-synthesis[4] of taxol by the condensation of commercially available 10-deacetylbaccatin III with a side chain such as *N*-benzoyl-(2R,3S)-3-phenylisoserine (-)-**5** (Figure 1). Therefore, the efficient synthesis of enantiopure side chain has attracted much attention from academic community as well as industry.[5]

Enantiomerically enriched phenylglycidates, are the most frequently used precursors of the taxol C-13 phenylisoserine side chain and diltiazem.[5a,e,f,i] Asymmetric epoxidation and asymmetric dihydroxylation are the main methods used in the preparation of optically active *cis* and *trans* phenylglycidates.[6] An alternative way to prepare enantiopure epoxides is the asymmetric applications of the Darzen's reaction.[7]

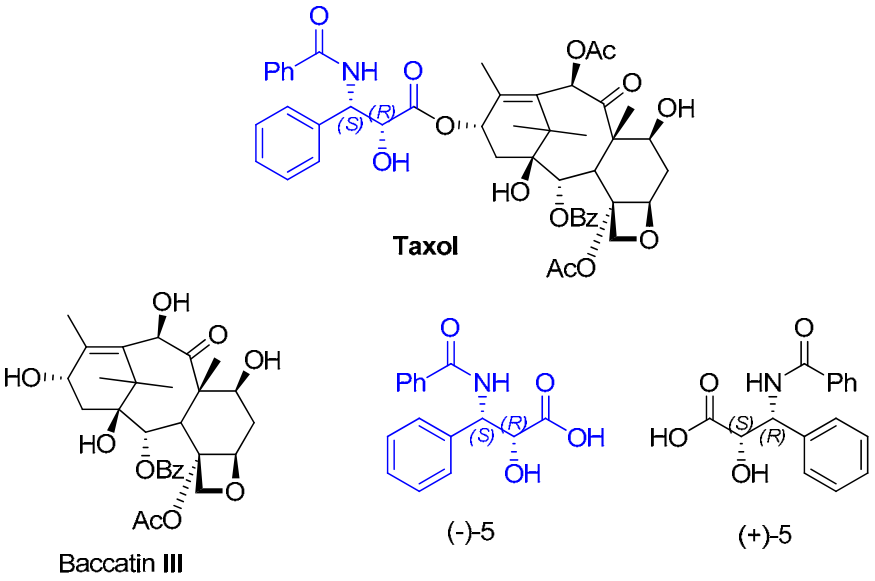
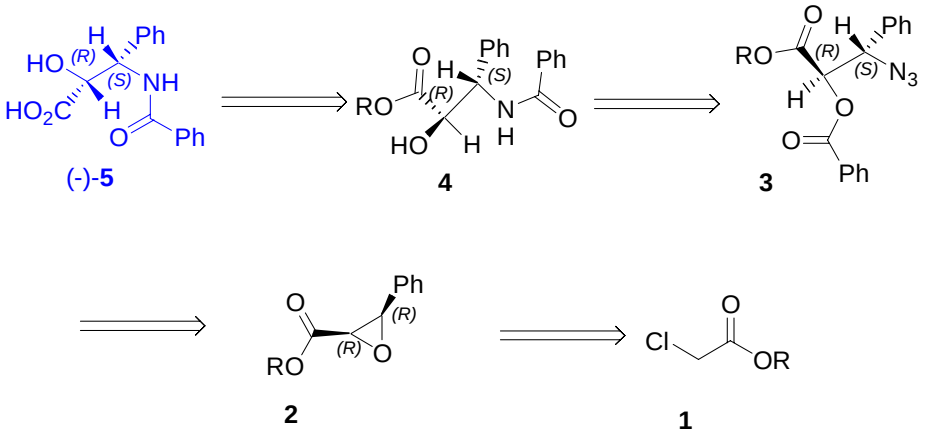


Figure 1. Structure of taxol, baccatin III and taxol side chain enantiomers.

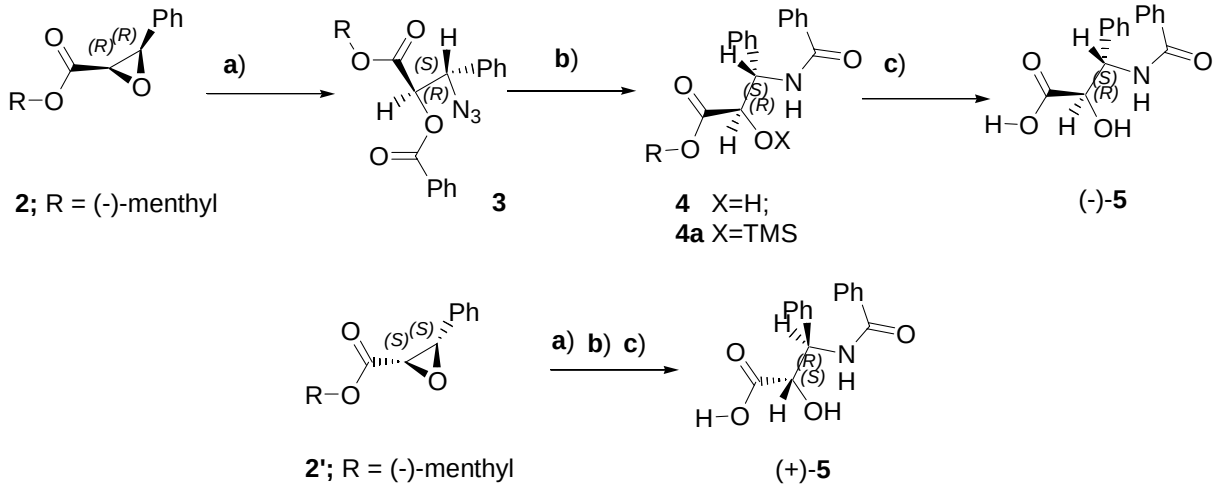
Here we report on the use of (2R,3R)- and (2S,3S)-(-)-menthyl 3-phenyloxirane-2-carboxylates[8] **2-2'** (Scheme 2) in the asymmetric syntheses of (2R,3S)- (-)-**5** and (2S,3R)-3-benzoylamino-2-hydroxy-3-phenylpropionic acid (+)-**5** (Scheme 2).

Results and Discussions

Our retrosynthetic plan for the synthesis of taxol side chain is depicted in Scheme 1. Taxol side chain **5** can be prepared from the hydrolysis of menthyl ester **4** which in turn could be prepared by the reduction of azide **3**. One-pot reaction of menthyl glycidate **2** involving azidation and benzoylation will provide azide **3**. The mixture (65/35) of phenylglycidates **2** and **2'** were converted to **3** and **3'** in one-pot by direct treatment with NaN_3 and following benzoylation (Sheme 2). Compound **3** crystallize in high yield from methanol at room temperature.

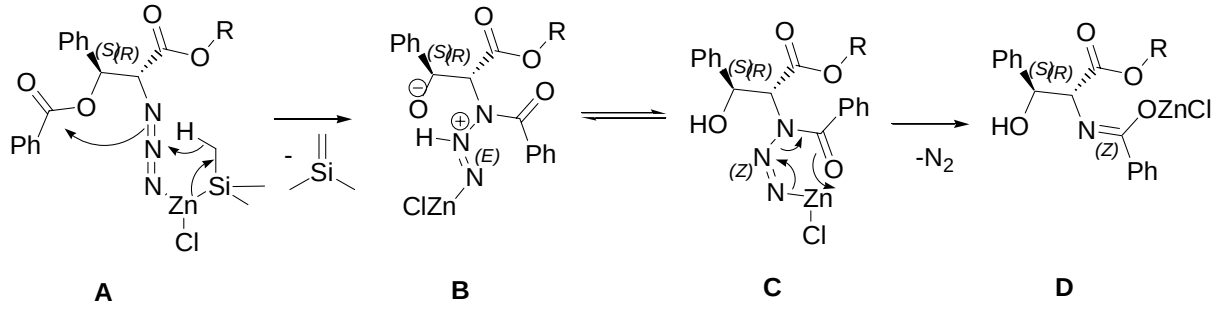


Scheme 1. Retrosynthetic analysis of the taxol side chain. **1-4**; R= (-)-menthyl.



Scheme 2. Reagents and conditions: (**a**) i) NaN_3, DMF-ethylformate, 60 ^oC, 90 h ii) DMAP, benzoyl chloride, CH_2Cl_2, rt; 2 h, lit[5i] (**b**) 5eq Zn-TMSCl, THF, reflux, 24 h (**c**) KOH, TBAHS, THF, rt, 24 h.

Compound **3** was treated with 5 eq. Zn and Me_3SiCl heating at reflux in THF for 24 h to give the mixtures of (-)-menthyl 3-benzamido-2-hydroxy-3-phenylpropanoates **4** and menthyl 3-benzamido-3-phenyl-2-(trimethylsilyloxy)propanoates **4a**. The treatment of **4**,**4a** with KOH in THF in the presence of a phase transfer catalyst gave the corresponding pure enantiomer (2R,3S)-3-benzamido-2-hydroxy-3-phenylpropanoic acid (-)-**5**. At similar conditions compound **2'** (Scheme 2) was converted in one-pot into the taxol side chain enantiomer (2S,3R)-3-benzamido-2-hydroxy-3-phenylpropanoic acid (+)-**5**.



Scheme 3. Probable mechanism for the reduction of azides **3** with Zn-TMSCl.

The probable mechanism for the conversion of azide **3** to **4** is depicted in Scheme 3. We assume that single electron transfer from Zn to the Si in TMSCl can give $ClZnSiMe_3$. The coordination of azide **3** to the metal centre of the latter through the terminal nitrogen would give intermediate **A** which synchronously abstracts dimethyl(methylene)silane to produce **B**. The later is probably in equilibrium with **C** which eliminates N_2 to give **D**. The silylation of the latter give **4a** or its hydrolysis produce the minor nonsilylated **4**.

Conclusions

Thus, the products from the *cis* diastereoselective asymmetric Darzen condensation of benzaldehyde with (-)-menthyl haloacetate were demonstrated to be useful in the syntheses of the taxol side chain enantiomers. For the first time Zn-TMSCl system was employed in the reduction of the azide[9] functionality of compounds **3-3'** to give the corresponding silylated **4-4'**. The latter were hydrolysed with KOH in the presence of a phase transfer catalyst such as tetrabutylammonium hydrogensulphate (TBAHS) to give the corresponding enantiopure taxol side chain enantiomers in high overall yields.

Experimental Section

General. Melting points were taken on an Electrothermal Digital melting point apparatus. Infrared spectra were recorded on a Thermo-Nicolet 6700 FTIR. 1D and 2D NMR spectra were recorded on a Varian Mercury Plus 400 MHz spectrometer. Elemental analyses were performed on a EuroEA 3000 CHNS analyser.
TBAHS (97% pure) were purchased from Aldrich. DMAP (≥99% GC), were Merck quality products. The THF (99% GC) was Riedel-de Haën product.

Synthesis of (2R,3S)-3-benzamido-2-hydroxy-3-phenylpropanoic acid (Taxol side chain) (-)-5
Synthesis of (2R,3S)-3-azido-1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-1-oxo-3-phenyl- propan-2-yl benzoate (3). To a solution of menthyl phenylglycidate **2/2'** (1 mmol, 302 mg) in MeOH (9 mL), H_2O (1 mL) and ethylformate (1.5 mL) mixture NaN_3 (10 mmol, 650 mg) was added and the reaction mixture stirred at 60 ^oC for 90 h.[5i] The mixture was cooled to room temperature and ethyl acetate (25 mL) was added and extracted with water (3X10 mL). The organic phase was separated and dried over Na_2SO_4. The solvent was evaporated and the residue dissolved in CH_2Cl_2 (10 mL). DMAP (1 mmol, 122 mg) was added and the mixture cooled to 0 ^oC then benzoyl chloride (1.24 mmol, 174 mg) was added drop-wise and the reaction mixture stirred at room temperature for 2 h.The mixture was washed with water (3X10 mL) and the organic phase dried over anhydrous Na_2SO_4, filtered and the solvent evaporated to produce an oily residue. Yield, 434 mg, 92%. The latter product was dissolved in methanol (20 mL) and left to crystallize in a refrigerator. The crystalline product was filtered and dried under vacuum to yield 368 mg, mixture of **3**/**3'** (The ratio determined by ^1H NMR is 65/35). The latter mixture (368 mg) was dissolved in MeOH (35 mL) and left to crystallize overnight at room temperature. The formed crystalline **3** was filtered and dried under vacuum. White needles, mp 134-135 ^oC; Yield 220 mg, 49%. $[\alpha]^{23}_D = +102$ (c, 1.8, $CHCl_3$). FTIR (KBr); ν_{N3} 2103, $\nu_{C=O}$ 1737, 1723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.63 (3H, d, J = 6.8 Hz), 0.73 (3H, d, J = 6.8 Hz), 0.79-0.88 (1H, m), 0.90 (3H, d, J = 6.4 Hz), 0.94-1.07 (2H, m), 1.28-1.35 (1H, m), 1.40-1.53 (2H, m) 1.59-1.67 (2H, m) 2.02-2.07 (1H, m), 4.69 (1H, dt, J = 10.8, 4.4 Hz), 5.15 (1H, d, J = 5.2 Hz), 5.45 (1H, d, J = 5.2 Hz), 7.35-7.41 (3H, m), 7.43-7.49 (4H, m), 7.57-7.61 (1H, m), 8.07-8.09 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.6;

20.8; 21.9; 22.8; 25.5; 31.4; 34.1; 40.4; 46.6; 65.6; 75.6; 76.6; 127.7; 128.5; 128.9; 129.0; 129.1; 130.0; 133.6; 134.6; 165.6; 166.9. Anal Calc for $C_{26}H_{31}N_3O_4$ (449.23) C, 69.47; H, 6.95; N, 9.35; Found C, 69.46; H, 6.97; N, 9.38.

(2S,3R)-3-azido-1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-1-oxo-3-phenylpropan-2-yl benzoate 3'. FTIR (ν cm^{-1}): 2103, 1738, 1723 ^{1}H NMR (400 MHz, $CDCl_3$) (The spectrum is elicited from the spectrum of a mixture containing 90% **3'**.) δ ppm 0.76 (3H, d, *J* = 7.2), 0.84 (3H, d, *J* = 6.8), 0.88 (3H, d, *J* = 6.4), 0.80-0.88 (1H, m), 0.94-1.08 (2H, m), 1.27-1.36 (1H, m), 1.41-1.54 (2H, m) 1.60-1.68 (2H, m) 2.01-2.07 (1H, m), 4.70 (1H, dt, *J* = 10.8, 4.4), 5.13 (1H, d, *J* = 5.2), 5.47 (1H, d, *J* = 5.2), 7.34-7.41 (3H, m), 7.43-7.49 (4H, m), 7.58-7.62 (1H, m), 8.07-8.10 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.2; 20.7; 21.9; 23.2; 26.1; 31.3; 34.0; 40.0; 46.8; 65.7; 75.5; 76.3; 127.8; 128.5; 128.9; 129.0; 129.1; 130.0; 133.5; 134.7; 165.5; 167.0
Anal Calc for $C_{26}H_{31}N_3O_4$ (449.23) C, 69.47; H, 6.95; N, 9.35; Found C, 69.42; H, 6.92; N, 9.42.

Reduction of compound 3. General procedure

The mixture of zinc powder (5 mmol, 325 mg) and Me_3SiCl (5 mmol, 540 mg) in THF (10 mL) was stirred for 5 minutes at room temperature. Benzoylated azide **3** (1 mmol) was added to the mixture and heated at reflux for 24 h. The unreacted zinc powder was filtered and water (10 mL) was added to the cooled mixture and extracted with ethyl acetate (3X10 mL). The organic phase was dried over anhydrous Na_2SO_4 filtered and the solvent evaporated. The residue was subjected to silica packed column and eluted with ethyl acetate and petroleum ether.

(2R,3S)-((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl) 3-benzamido-2-hydroxy-3-phenylpropanoate (4). Oil. Yield 102 mg, 24%. $[\alpha]^{22}_D$ = -78 (c, 0.5, $CHCl_3$). FTIR (neat): ν_{OH} 3520, ν_{NH} 3345, $\nu_{C=O}$ 1725, 1645 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.52 (3H, d, *J* = 7.2 Hz), 0.76 (3H, d, *J* = 7.2 Hz), 0.91 (3H, d, *J* = 6.4 Hz), 0.82-0.92 (1H, m), 0.94-1.10 (2H, m), 1.39-1.50 (2H, m), 1.63-1.71 (2H, m), 1.76-1.83 (1H, m), 1.94-1.99 (1H, m), 3.33 (1H, d, *J* = 3.2 Hz, C2-OH), 4.57 (1H, dd, *J* = 3.2, 2.0 Hz, C2-H), 4.84 (1H, dt, *J* = 10.8, 4.4 Hz, C1-H), 5.69 (1H, dd, *J* = 8.98, 2.0 Hz, C3-H), 7.11 (1H, d, *J* = 8.98 Hz, NH), 7.27-7.31 (1H, m), 7.33-7.37 (2H, m), 7.42-7.46 (4H, m), 7.49-7.53 (1H, m), 7.76-7.79 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.4; 20.8; 21.9; 22.7; 25.6; 29.7; 31.5; 34.0; 40.7; 46.7; 54.7; 73.8; 126.8; 127.1; 127.8; 128.5; 128.6; 131.7; 133.9; 138.9; 166.4; 172.5. Anal Calc for $C_{26}H_{33}NO_4$ (423.24) C, 73.73; H, 7.85; N, 3.31; Found C, 73.78; H, 7.81; N, 3.35.

(2R,3S)-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl) 3-benzamido-3-phenyl-2-(trimethylsilyloxy) propanoate (4a). Oil. Yield 287 mg, 58%. $[\alpha]^{22}_D$ = -76 (c, 0.3, $CHCl_3$). FTIR (KBr): $_{NH}$ 3346, $\nu_{C=O}$ 1728, 1645 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm -0.13 (9H, s, TMS), 0.57 (3H, d, *J* = 7.2 Hz), 0.80 (3H, d, *J* = 7.2 Hz), 0.87 (3H, d, *J* = 6.8 Hz), 0.84-0.90 (1H, m), 0.95-1.04 (2H, m), 1.38-1.48 (2H, m), 1.63-1.68 (2H, m), 1.79-1.93 (2H, m), 4.41 (1H, d, *J* = 1.56 Hz, C2-H), 4.80 (1H, dt, *J* = 10.8, 4.4 Hz, C1-H), 5.57 (1H, dd, *J* = 8.19, 1.56 Hz, C3-H), 7.20 (1H, d, *J* = 8.19 Hz, NH), 7.23-7.28 (1H, m), 7.30-7.38 (4H, m), 7.42-7.46 (2H, m), 7.49-7.53 (1H, m), 7.80-7.82 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -0.7; 15.6; 20.9; 22.0; 22.8; 25.7; 31.4; 34.1; 40.9; 46.9; 56.3; 75.3; 75.6; 126.7; 127.2; 127.5; 128.3; 128.5; 131.6; 134.3; 139.4; 166.4; 170.9. Anal Calc for $C_{29}H_{41}NO_4Si$ (495.28) C, 70.26; H, 8.34; N, 2.83; Found C, 70.35; H, 8.38; N, 2.91.

(2R,3S)-3-Benzamido-2-hydroxy-3-phenylpropanoic acid (Taxol side chain) (-)-5. General procedure

To a solution of **4** or **4a** (1 mmol) in THF (10 mL) TBAHS (0.1 mmol, 33.9 mg) and KOH (1 mmol, 56 mg) were added successively and the reaction mixture stirred at room temperature for 24 h. Water was added (15 mL) to the mixture and extracted with ethyl acetate (3X10 mL). The water phase was acidified with 1 N HCl to pH 2 and the precipitated solid filtered. From **4**, yield 193 mg, 68%. Mp 176-178 ^{o}C; $[\alpha]^{22}_{D}$ = -33.3 (c, 0.32, EtOH). Lit[10] mp 175.5–177.8 ^{o}C and $[a]_{D}^{22}$ = -35.5 (*c* 1.07, EtOH). From **4a**, yield 0.185, 65%, $[\alpha]^{22}_{D}$ = -33.3 (c, 0.32, EtOH). Mp 176-178 ^{o}C. FTIR (KBr); ν_{OH} 3523, ν_{NH} 3350, $\nu_{C=O}$ 1707, 1641 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-$_{d6}$) δ ppm 3.31 (2H, brs), 4.36 (1H, d, *J* = 4.3 Hz), 5.45 (1H, dd, *J* = 9.0, 4.3 Hz), 7.21-7.24 (1H, m), 7.30 (2H, t, *J* = 7.2 Hz), 7.38-7.39 (2H, m), 7.46-7.54 (3H, m), 7.81-7.84 (2H, m), 8.56 (1H, d, *J* = 9.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 56.3; 74.0; 127.4; 127.6; 127.8; 128.5; 128.8; 131.8; 134.8; 140.7; 166.5; 173.9 Anal Calc for $C_{16}H_{15}NO_4$ (285.10) C, 67.36; H, 5.30; N, 4.91; Found C, 67.38; H, 5.32; N, 4.98.

Synthesis of (2R,3S)-3-azido-2-hydroxy-3-phenylpropionic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester

To a solution of (-)-menthyl phenylglycidate **2** (1 mmol, 302 mg) in MeOH (9 mL), H_2O (1 mL) and ethylformate (1.5 mL) mixture NaN_3 (10 mmol, 650 mg) was added and the reaction mixture stirred at 60 ^{o}C for 90 h. The mixture was cooled to room temperature and ethyl acetate (25 mL) was added and extracted with water (3X10 mL). The organic phase was separated and dried over Na_2SO_4. The solvent was evaporated and the formed intermediate, 317 mg 92%, was analysed: The purity was controlled by ^{1}H NMR and shown to be 100%. FTIR (KBr); ν_{OH} 3483, ν_{N3} 2106, $\nu_{C=O}$ 1731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.79 (3H, d, *J* = 6.8 Hz), 0.93 (6H, d, *J* = 6.8 Hz), 0.87-0.91 (1H, m), 0.97-1.13 (2H, m), 1.42-1.54 (2H, m), 1.69-1.74 (2H, m), 1.79-1.86 (1H, m), 2.02-2.07 (1H, m), 3.12 (1H, d, *J* = 6.8 Hz, C2-OH), 4.33 (1H, dd, *J* = 6.8, 2.8 Hz, C2-H), 4.86 (1H, d, *J* = 2.8 Hz, C3-H), 4.84 (1H, dt, *J* = 10.8, 4.4 Hz, C1-H), 7.35-7.44 (3H, m), 7.47-7.50 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.6; 20.9; 22.0; 22.9; 26.1; 31.4; 34.1; 40.7; 46.9; 67.1; 73.8; 77.1; 128.0; 128.7; 128.8; 135.6; 171.6. Anal Calc for $C_{19}H_{27}N_3O_3$ (345.21) C, 66.06; H, 7.88; N, 12.16; Found C, 66.08; H, 7.92; N, 12.20.

The product obtained from the benzoylation of the latter was identical with those of **3**.

One-pot procedure for the synthesis of (2S,3R)-3-benzamido-2-hydroxy-3-phenylpropanoic acid (+)-5 (Taxol side chain enantiomer)

Menthyl phenylglycidate **2'** (3 mmol, 906 mg) was dissolved in a mixture containing MeOH (27 mL), H_2O (3 mL) and ethylformate (5 mL). NaN_3 (30 mmol, 1950 mg) was added and the reaction mixture was stirred at 60 ^{o}C for 90 h. The work up procedure is as described above. To a cooled to 0 ^{o}C solution of the nearly pure azidoalcohol (2.72 mmol, 940 mg) in CH_2Cl_2 (15 mL) and DMAP (2.72 mmol, 332 mg), benzoyl chloride (3.41 mmol, 479 mg) was added drop-wise and the reaction mixture stirred at room temperature for 2 h. The mixture was washed with water (3X15 mL) and the organic phase dried over anhydrous Na_2SO_4, filtered and the oily residue, 1060 mg, was dissolved

in methanol. The crystalline product was filtered and dried under vacuum to yield 950 mg **3'**. To the mixture of zinc powder (10.5 mmol, 687 mg) and Me_3SiCl (10.5 mmol, 1134 mg) in THF (20 mL) benzoylated azide **3'** was added and the mixture refluxed for 24 h. The unreacted zinc powder was filtered and water (15 mL) was added to the cooled mixture and extracted with ethyl acetate (3X15 mL). The organic phase was dried over anhydrous Na_2SO_4 filtered and the solvent evaporated. To the residue containing the **4**' and **4'a** (1000 mg, 68/32 by ^{1}H NMR spectroscopy) dissolved in THF (20 mL) TBAHS (0.21 mmol, 71 mg) and KOH (2.68 mmol, 156 mg) were added successively and the reaction mixture stirred at room temperature for 24 h. Water was added (15 mL) to the mixture and extracted with ethyl acetate (3X10 mL). The layers were separated and the water phase was acidified with 1 N HCl to pH 2 and the precipitated solid filtered to give 371 mg, 69.5% (+)-**5**. Mp 179-181 ^{o}C. $[\alpha]^{20}_D$ = +38.8 (c, 0.73, EtOH). FTIR (KBr); ν_{OH} 3523, ν_{NH} 3350, $\nu_{C=O}$ 1707, 1641 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-$_{d6}$) δ ppm 3.31 (2H, brs), 4.36 (1H, d, *J* = 4.3 Hz), 5.45 (1H, dd, *J* = 9.0; 4.3 Hz) , 7.21-7.24 (1H, m), 7.30 (2H, t, *J* = 7.2 Hz), 7.38-7.39 (2H, m), 7.46-7.54 (3H, m), 7.81-7.84 (2H, m) , 8.56 (1H, d, *J* = 9.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 56.3; 74.0; 127.4; 127.6; 127.8; 128.5; 128.8; 131.8; 134.8; 140.7; 166.5; 173.9 Anal Calc for $C_{16}H_{15}NO_4$ (285.10) C, 67.36; H, 5.30; N, 4.91; Found C, 67.40; H, 5.35; N, 4.93.

Acknowledgements

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