Large-Scale and Highly Enantioselective Synthesis of the Taxol C-13 Side Chain through Asymmetric Dihydroxylation

ARTICLE *in* CHEMINFORM · AUGUST 1994

Impact Factor: 0.74 · DOI: 10.1021/jo00096a072

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Large-Scale and Highly Enantioselective Synthesis of the Taxol C-13 Side Chain through Asymmetric Dihydroxylation

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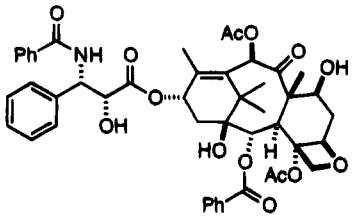
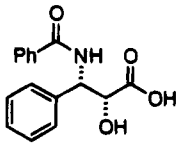
Received March 23, 1994

Taxol,[1] isolated from the bark of several yew species, is considered the most promising cancer chemotherapeutic agent and has recently been approved for the treatment of metastatic carcinoma of the ovary.[2] Taxol possesses unusually potent antileukemic and tumor inhibitory properties.[3] The scarcity[4] and highly challenging structure have stimulated interest in its synthesis.[5] Central to all synthetic strategies for taxol is the attachment[5e,6] of the C-13 side chain to the baccatin III[7] nucleus. Since the presence of this side chain has proven to be essential for the biological activity[1,4a,b] of taxol, the development of short and practical synthetic routes for phenylisoserine derivatives, which are adaptable for industrial-scale production, has become very important.

The numerous papers devoted to the preparation of enantiomerically enriched **1** include research on semisynthesis drawing from the chiral pool,[5d,8] enzymatic

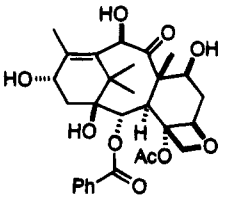


Taxol



1

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



Baccatin III

kinetic resolution of racemic esters of **1**,[9] diastereoselective reactions with covalently-bound chiral auxiliaries,[5c,6a,10] and asymmetric catalysis.[5a,b,f] Herein we present a large-scale, highly enantioselective synthesis of the taxol C-13 side chain proceeding through the asymmetric dihydroxylation (AD) reaction.[11] The concentration of the reaction mixtures, the low cost of all reagents, the absence of chromatographic separations, and the minimal extraction processes required may make our methodology the most practical and efficient for the large-scale production of enantiomerically pure *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine.

As outlined in Scheme 1, the procedure is carried out on a mole scale. First, commercial methyl cinnamate was subjected to the NMO-based AD process at room temperature.[12] The amount of ligand, $(DHQ)_2PHAL$, was reduced to 50% of the ligand present in AD-mix to further lower the cost of this procedure. *N*-Methylmorpholine *N*-oxide (NMO) was used as the cooxidant instead of $K_3Fe(CN)_6$, since this allows the reaction to be run at a very high concentration (2 M). Although this led to a slight decrease in enantioselectivity, the ee of the product could be increased to 99% by one recrystallization from toluene, affording enantiopure (2*R*,3*S*)-diol (**2**) as colorless needles in a yield of 72%.

The diol (**2**) was converted to the acetoxy bromo ester (**3**)[13] by reaction with trimethyl orthoacetate in the presence of a catalytic amount of *p*-TsOH at rt (5 h) followed by treatment with acetyl bromide at −15 °C (2 h). The latter step was regioselective (6:1 mixture of the two acetoxy bromo esters) favoring the desired product. As the unwanted isomer is an oil, it was easily removed in the subsequent filtration while **3** was obtained directly

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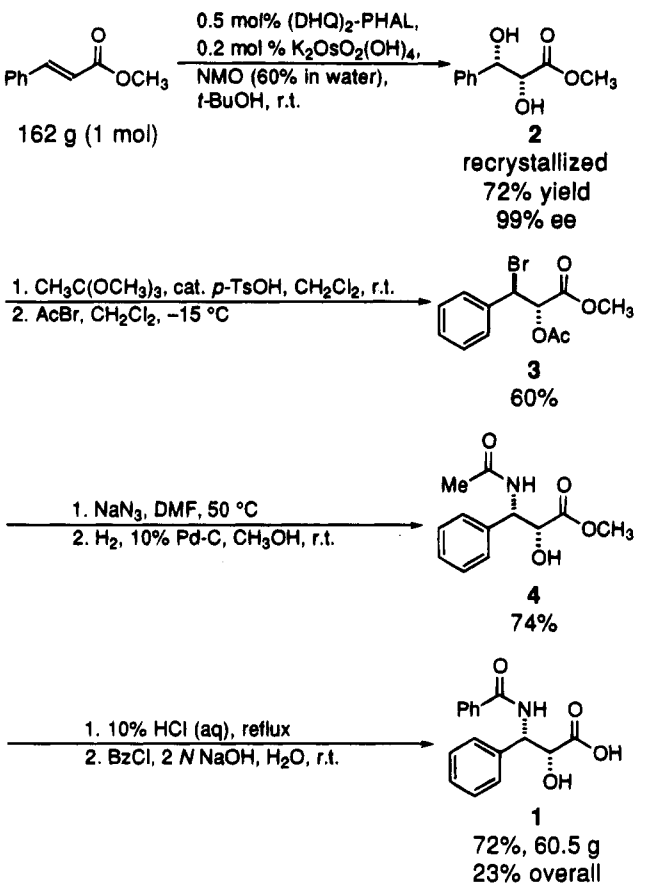
Scheme 1



by crystallization from a mixed solvent of hexane and ethyl ether (6:4) in 60% yield.

After reaction of the acetoxy bromo ester **3** with sodium azide in DMF at 50 °C, the crude acetoxyazide ester was subjected to hydrogenation with 10% Pd–C under 1 atm of hydrogen at rt, giving *N*-acetyl-3-phenylisoserine (**4**) in 74% yield (two steps). Amide ester **4** was then hydrolyzed by refluxing in 10% aqueous HCl for 2 h, and the crude HCl salt of the amino acid was converted to the taxol side chain (**1**) by benzoylation under Schotten–Baumann conditions. The crude product (**1**) was collected from the aqueous suspension by filtration and purified by recrystallization from ethyl acetate.

In conclusion, a simple and efficient six-step synthesis of the enantiopure taxol side chain has been effected through AD.

Experimental Section

Methyl (2*R*,3*S*)-2,3-Dihydroxy-3-phenylpropionate (2). A 1-L round-bottomed flask was charged with 3.89 g (0.5 mol %) of $(DHQ)_2PHAL$, 162 g (1 mol) of methyl cinnamate, 250 mL of NMO (60% in water), and 500 mL of *t*-BuOH. Under stirring 737 mg (0.2 mol %) of potassium osmate(VI) dihydrate was added. The reaction mixture was stirred at room temperature until the reaction finished (about 23 h) and then poured into a solution of 150 g of sodium sulfite in 500 mL of water. The mixture was stirred at rt for 2 h. The organic phase was separated and evaporated. The residue was dissolved in 600 mL of ethyl acetate. The aqueous phase was extracted once with 500 mL of ethyl acetate. The organic phases were combined and washed with 5% aqueous HCl (50 mL × 5) and dried over $MgSO_4$. After the solvent was removed, the crude diol was recrystallized from toluene (300 mL), and 140 g of pure diol (**2**) was obtained as colorless needles (71% yield and 99% ee). The ee was determined by GLC on β-cyclodextrin, J & W CDX-B column, 165 °C: mp 84–86 °C; $[\alpha]_D$ +3.4° (*c* 1.19, EtOH); ^1H NMR ($CDCl_3$ 400 MHz) δ_H 2.89 (br, 1H), 3.21 (br, 1H), 3.80 (s, 3H), 4.36 (d, J = 2.8 Hz, 1H), 5.01 (d, J = 2.8 Hz, 1H), 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 173.1, 139.9, 128.4, 128.1, 126.2, 74.7, 74.4, 52.8.

Methyl (2*R*,3*S*)-2-Acetoxy-3-bromo-3-phenylpropionate (3). A solution of 140 g of the diol ester **2**, 2.0 g of *p*-TsOH, and 250 mL of trimethyl orthoacetate in 500 mL of methylene chloride was stirred at rt for 5 h. The volatiles were evaporated, and the residue was taken up in 500 mL of methylene chloride. The resulting solution was cooled to −15 °C (ice–NaCl bath), 53 mL of acetyl bromide was added dropwise over 2 h, and stirring was continued at −15 °C for a further 2 h. The solvent was evaporated, and 500 mL of a mixture of hexane and ethyl ether (6:4) was added and then stirred for 30 min. The crystals (pure product) were isolated by filtration and washed with the same solvent mixture. The acetoxy bromide (**3**) (127 g, 60%) was thus obtained as colorless crystals: mp 86–87 °C; $[\alpha]_D$ −113.1° (*c* 1.28, EtOH); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 2.09 (s, 3H), 3.70 (s, 3H), 5.35 (d, J = 6.3 Hz, 1H), 5.65 (d, J = 6.3 Hz, 1H), 7.34 (m, 2H), 7.46 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 169.5, 167.3, 136.7, 129.1, 128.63, 128.57, 75.2, 52.7, 49.1, 20.4; FABMS m/z 323/325 (M^+ + Na) FABHRMS calcd for $C_{12}H_{14}BrO_4$ 301.0075, obsd 301.0070.

Methyl *N*-Acetyl-(2*R*,3*S*)-2-amino-3-hydroxy-3-phenylpropionate (4). A reaction mixture of 127 g of the acetoxy bromo ester **3** and 41.7 g of sodium azide in 500 mL of DMF was stirred at 50 °C overnight. When the reaction finished (TLC), the solvent was evaporated, 500 mL of ethyl ether was added, and the resulting suspension was stirred for 30 min. The NaBr was removed by filtration through a short pad of silica gel followed by washes with ethyl ether, and the filtrate and washing liquid were concentrated *in vacuo*. The resulting crude acetoxy azide ester was dissolved in 500 mL of methanol and hydrogenated in the presence of 2.0 g of 10% Pd–C under 1 atm of hydrogen at rt for 2 days. The catalyst was filtered off and washed with methanol. After the filtrate was concentrated, the crude product was recrystallized from toluene (100 mL), giving 73.4 g of the hydroxy amide (**4**) as colorless crystals in 74% yield: mp 148–149 °C $[\alpha]_D$ +6.1° (*c* 1.27, EtOH); ^1H NMR (DMSO-d_6, 400 MHz) δ_H 2.00 (s, 3H), 3.43 (br, 1H), 3.82 (s, 3H), 4.51 (br, 1H), 5.53 (d, J = 8.8 Hz, 1H), 6.41 (dd, J = 8.8 Hz, 1H), 7.37 (m, 5H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 173.4, 169.2, 138.8, 128.7, 127.9, 126.9, 73.2 54.5, 53.2, 23.2; FABMS m/z 260 (M^+ + Na); FABHRMS calcd for $C_{12}H_{16}NO_4$ 238.1079; obsd 238.1070. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.59; H, 6.19; N, 5.60.

***N*-Benzoyl-(2*R*,3*S*)-2-amino-3-hydroxy-3-phenylpropionic Acid (1).** A mixture of 70 g (0.295 mol) of *N*-acetyl-3-phenylisoserine (**4**) in 500 mL of 10% aqueous HCl was refluxed for 2 h, and then the water was removed *in vacuo*. The crude amino acid HCl salt was dissolved in 250 mL of water, and 600 mL of 2 N aqueous NaOH was added. Then 58 g of benzoyl chloride was added slowly dropwise at rt over 2 h, and stirring was continued for another hour. The reaction mixture was cooled to 0 °C, and concentrated hydrochloric acid was added dropwise until a pH of 2 was reached. The crude product was collected by filtration, washed with water (50 mL × 3), and stirred in refluxing toluene (150 mL) for 1 h. After the mixture cooled to room temperature, the solid was isolated by filtration and washed with toluene. Recrystallization from ethyl acetate (1 g/15 mL; *note: the mother liquor was concentrated and recrystallized again) gave 60.5 g (72%) of *N*-benzoyl-3-phenylisoserine (**1**) as colorless fine needles: mp 175.5–177 °C; $[\alpha]_D$ −35.5° (*c* 1.07, EtOH); ^1H NMR (DMSO-d_6, 400 MHz) δ_H 4.37 (d, J = 4.4 Hz, 1H), 5.46 (dd, J = 8.8, 4.4 Hz, 1H), 5.6 (br, 1H), 7.21–7.57 (m, 8H), 7.84 (d, J = 7.2 Hz, 1H), 8.56 (d, J = 8.9 Hz, 1H), 12.73 (br, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.5, 166.0, 140.3, 134.3, 131.4, 128.3, 128.3, 128.0, 127.4, 127.2, 126.9, 73.6, 55.8; MS FABHRMS calcd for $C_{16}H_{16}NO_4$ 286.1079, obsd 286.1070. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.19; H, 5.45; N, 4.83.

Acknowledgment. Financial support was provided by the National Institutes of Health (GM-28384). H.C.K. thanks the Deutsche Forschungsgemeinschaft (DFG) for providing a fellowship.