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One-step synthesis of paclitaxel side-chain precursor: benzamide-based asymmetric aminohydroxylation of isopropyl *trans*-cinnamate

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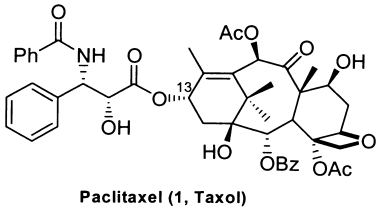
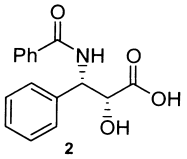
Abstract

A highly enantioselective (up to 97% ee) one-step synthesis of paclitaxel side chain precursor, (2*R*,3*S*)-isopropyl 3-benzamido-2-hydroxy-3-phenylpropionate, has been achieved by osmium-catalyzed asymmetric aminohydroxylation of isopropyl *trans*-cinnamate with *N*-bromobenzamide as an oxidant/nitrogen source in the presence of $(DHQ)_2PHAL$ as a chiral ligand. Simple recrystallization of crude product (containing regioisomer and diol) from ethyl acetate gave the enantiomerically pure product. © 1999 Elsevier Science Ltd. All rights reserved.

Paclitaxel (**1**, Taxol®), isolated from the bark of the Pacific yew (*Taxus brevifolia*), is currently regarded as one of the most promising new drugs in cancer chemotherapy and has recently been approved for treating both metastatic ovarian and breast cancer.[1] Other researchers have revealed its effects against non-small-cell lung cancer, head and neck cancer, and glioblastoma and oesophageal cancer. The C-13 side chain of (2*R*,3*S*)-configuration, *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine (**2**), is crucial for the anticancer activity of paclitaxel.



Paclitaxel (1, Taxol)



2

Thus, the development of short and practical synthetic routes to the taxol side chain, which are adaptable for industrial-scale production, have become very important. Much effort has been made in the preparation of enantiomerically enriched (2*R*,3*S*)-phenylisoserine derivatives.[2] Among these numerous

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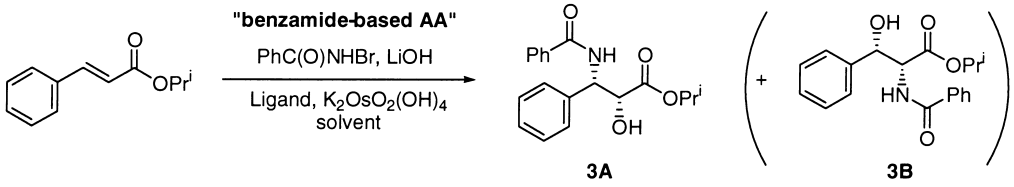
methods, the three-step synthesis of **2** by Sharpless's osmium-catalyzed asymmetric aminohydroxylation (AA) of *trans*-cinnamates using TsNClNa (Chloramine-T)[3a] or *N*-bromoacetamide–LiOH[3b] as the nitrogen source/oxidant, followed by hydrolysis of the *N*-toluene sulfonyl or *N*-acetyl group of the AA product, and subsequent *N*-benzoylation appears to be one of the most practical routes. These results intrigued us enough to warrant an examination of the efficiency of benzamide-based AA reactions of isopropyl *trans*-cinnamate, which could provide a direct route to the synthesis of the paclitaxel side chain precursor **3A** as shown in Scheme 1. Careful optimization (chiral ligands, solvent, molar ratio of reactants etc.) of the benzamide-based AA reaction of isopropyl *trans*-cinnamate gave the desired product **3A** in 46% yield with up to 97% ee in one step.



Scheme 1.

As shown in Table 1, the regio- and enantioselectivity were highly dependent on the choice of ligand, solvent, ligand–solvent combination, and the amounts of ligand and *N*-bromobenzamide. For the screening of chiral ligands, we first carried out an AA reaction using 4 mol% of $K_2OsO_2(OH)_4$ and 5 mol% of $(DHQ)_2PHAL$, $(DHQ)_2PYR$ or $(DHQ)_2AQN$ at 0°C with PhCONHBr/LiOH as the oxidant/nitrogen source in CH_3CN–H_2O solvent under reaction conditions similar to those reported by Bruncko et al.[3b] (entries 1–3). Phthalazine ligand ($(DHQ)_2PHAL$) exhibited the best result (entry 1). Using other ligands, ($(DHQ)_2PYR$ or $(DHQ)_2AQN$), the ratio of **3A** to **3B** was reversed and only poor enantioselectivities were observed (entries 2 and 3). Based on this result, the phthalazine ligand was selected as a standard ligand for the next experiment. We then investigated the effects of solvent and molar ratio of ligand to osmium on the regio- and enantioselectivity (entries 1, 4–10). In both solvent systems (CH_3CN–H_2O, *n*-PrOH–H_2O) the regioselectivity increased when the amounts of ligand increased. Whereas, in *n*-PrOH–H_2O, the molar ratio of ligand to osmium did not affect the enantioselectivity (entries 8–10), in CH_3CN–H_2O solvent (entries 1, 4–6), the enantioselectivity was highly dependent on the molar ratio of ligand to osmium. The ees increased from 79% to 91% by increasing the amount of ligand. The enantioselectivity also seems to be affected by the amount of *N*-bromobenzamide (entry 7). By using 2 equiv. of *N*-bromobenzamide, the ee value was improved up to 97%. Moreover, in the preparative scale experiment, the desired AA product **3A** was simply isolated by crystallization of the crude mixture (**3A**, **3B** and diol product) from ethyl acetate in 40% yield and >99% ee.

In summary, a direct and practical synthesis of the paclitaxel side chain precursor **3A** in 46% yield with up to 97% ee has been achieved by an AA reaction of a *trans*-cinnamate derivative in the presence of $(DHQ)_2PHAL$ as a chiral ligand using *N*-bromobenzamide as an oxidant/nitrogen source.

1. Experimental section

Chiral ligands, $(DHQ)_2PHAL$, $(DHQ)_2PYR$ and $(DHQ)_2AQN$, were purchased from Aldrich. *N*-Bromobenzamide was prepared from benzamide by the known procedure.[4]

Table 1
Benzamide-based catalytic AA reaction of isopropyl *trans*-cinnamate[a]

Entry	Ligand	Molar ratio of ligand to Os	Solvent (1:1, v/v)	Yield (%) [b] (**3A** + **3B**)	% ee [c] of **3A**	Regioselectivity [d] (**3A** : **3B**)
1	$(DHQ)_2PHAL$	1.25 : 1	CH_3CN-H_2O	44	79	2.3 : 1
2	$(DHQ)_2PYR$	1.25 : 1	CH_3CN-H_2O	47	37	1 : 1.3
3	$(DHQ)_2AQN$	1.25 : 1	CH_3CN-H_2O	46	14	1 : 2.1
4	$(DHQ)_2PHAL$	2.5 : 1	CH_3CN-H_2O	44	88	2.5 : 1
5	$(DHQ)_2PHAL$	3.75 : 1	CH_3CN-H_2O	45	90	3.2 : 1
6	$(DHQ)_2PHAL$	5 : 1	CH_3CN-H_2O	43	91	5.2 : 1
7 [e]	$(DHQ)_2PHAL$	5 : 1	CH_3CN-H_2O	60	97	3.3 : 1
8	$(DHQ)_2PHAL$	1.25 : 1	*n*-PrOH- H_2O	52	74	2.3 : 1
9	$(DHQ)_2PHAL$	2.5 : 1	*n*-PrOH- H_2O	45	79	3.2 : 1
10	$(DHQ)_2PHAL$	3.75 : 1	*n*-PrOH- H_2O	44	79	3.8 : 1

[a] Unless otherwise indicated, the reactions were carried out on 1 mmol scale using 4 mol% $K_2OsO_2(OH)_4$ and 1.1 equivalent of *N*-bromobenzamide at 0°C for 10 h. [b] Isolated yields by column chromatography. [c] % ees of **3A** were determined by chiral HPLC analysis and its absolute configuration was determined by comparison of physical data with those of authentic compound which was prepared from *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine. [d] Ratio of **3A** to **3B** was determined by ^1H NMR. [e] 2 equivalent of *N*-bromobenzamide was used.

1.1. General procedure for benzamide-based catalytic AA reaction of isopropyl trans*-cinnamate*

In 30 mL of an aqueous solution of $LiOH \cdot H_2O$ (806 mg, 10.2 mmol), $K_2OsO_2(OH)_4$ (147 mg, 0.4 mmol, 4 mol%) was dissolved by stirring. After addition of CH_3CN (120 mL), $(DHQ)_2PHAL$ (1.558 g, 2.0 mmol, 20 mol%) was added, and the mixture stirred for 10 min to give a clear solution. Water (30 mL) was subsequently added, and the mixture cooled to 0°C. After addition of isopropyl *trans*-cinnamate (1.902 g, 10 mmol), *N*-bromobenzamide (4.001 g, 20 mmol) was added in one portion, and the mixture then vigorously stirred at the same temperature. Progress of the reaction was monitored by TLC. Over the course of the reaction, the color changed from a deep green to yellow color. The reaction was quenched by addition of saturated aqueous Na_2SO_3 (5 g) and the mixture stirred for an additional hour. The two phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with 3 N HCl (to recover the ligand), water and brine, dried over anhydrous $MgSO_4$, then concentrated to afford the crude product contaminated by regioisomer **3B**, diol, and benzamide. The crude product was purified by chromatography on silica gel (ethyl acetate:*n*-hexane=1:1) to give 1.34 g (40%) of isopropyl (2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropionate **3A**. Product purification can also be accomplished by simple recrystallization of the crude product from ethyl acetate.

(2*R*,3*S*)-Isopropyl 3-benzamido-2-hydroxy-3-phenylpropionate (**3A**): mp 151–152°C (ethyl acetate); $[\alpha]_D^{16}$ −24.7 (*c* 0.618, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (d, *J*=6.2 Hz, 3H), 1.31 (d, *J*=6.2 Hz, 3H), 4.60 (d, *J*=2.1 Hz, 1H), 5.12 (sym.m, 1H), 5.77 (dd, *J*=2.1 Hz, *J*=9.2 Hz, 1H), 7.00 (d, *J*=9.2 Hz, 1H), 7.6–7.2 (m, 8H), 7.77 (d, *J*=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.99, 22.09, 55.02, 71.43, 73.77, 127.30, 127.43, 128.24, 129.07, 132.12, 134.64, 139.16, 167.14, 172.87; IR (KBr) 3344, 1713, 1636, 1535, 1373, 1310, 1238, 1096, 705 cm^{-1}. Anal. calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.46; N, 4.28. Found: C, 69.9; H, 6.54; N, 4.28. HPLC (Chiralcel AD, *i*-PrOH:*n*-hexane=20:80) 8.20 min (2*R*,3*S*), 17.05 min (2*S*,3*R*).

(2*R*,3*S*)-Isopropyl 3-hydroxy-2-benzamido-3-phenylpropionate (**3B**): mp 95°C (diethyl ether); $[\alpha]_D^{16}$

+28.02 (*c* 0.760, $CHCl_3$) (62% ee); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (d, *J*=6.2 Hz, 3H), 1.25 (d, *J*=6.2 Hz, 3H), 5.10–4.95 (m, 2H), 5.28 (d, *J*=3.6 Hz, 1H), 7.02 (d, *J*=8.4 Hz, 1H), 7.6–7.2 (m, 8H), 7.66 (d, *J*=7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.95, 22.13, 59.18, 70.13, 74.52, 126.40, 127.50, 128.49, 128.77, 128.90, 132.12, 134.16, 140.18, 168.21, 170.39. Anal. calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.46; N, 4.28. Found: C, 69.5; H, 6.68; N, 3.99. HPLC (Chiralcel AD, *i*-PrOH:*n*-hexane=20:80) 7.72 min (2*R*,3*S*), 12.73 min (2*S*,3*R*).

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