

Catalytic Asymmetric Aminohydroxylation Provides a Short Taxol Side-chain Synthesis[†]

Guigen Li and K. Barry Sharpless*

Department of Chemistry, The Scripps Research Institute, 10666 N. Torrey Pines Road, La Jolla, CA 92037, USA

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The *p*-toluenesulfonamide derivative of the C-13 side-chain of taxol was prepared on a one third mole scale in a single step from methyl cinnamate. The process employed is catalytic asymmetric aminohydroxylation (*catalytic* AA). In the present case, there is no work-up other than filtration of the pure product which is insoluble in the reaction mixture. The sulfonamide protecting group is removed by acidic hydrolysis.

The C-13 side-chain of taxol is known to be essential for its biological activity.¹ Hence synthesis of the side-chain and its analogs is a subject of significant recent interest. Modifications of the taxol side-chain are an important aspect of the structure–activity relationship (SAR).² Among numerous synthetic approaches, the asymmetric catalytic methods hold special interest for us. The catalytic asymmetric dihydroxylation (AD) and asymmetric epoxidation (AE) have been successfully applied in syntheses of the C-13 side-chain.^{3a–d} Very recently, a practical catalytic asymmetric aminohydroxylation (AA) process was developed,⁴ and we now report its use for the asymmetric synthesis of a side-chain precursor on a multigram scale.

The commercially available methyl cinnamate (**1**) was subjected to the catalytic AA process using somewhat reduced amounts of (DHQ)₂-PHAL ligand (2.5%) and potassium osmate(VI) (2%) from those described in our original procedure.^{4a} The experimental operation was modified by adding methyl cinnamate in three sequential portions. Each portion of olefin was completely consumed before the next portion was added.

The process was monitored by TLC (EtOAc–hexane, v/v=4/6) or by observing the color changes during the reaction (yellow to green, then back to yellow after each portion of the olefin was consumed). The desired hydroxysulfonamide (**2**) crystallizes directly from the reaction mixture and, after the yellow color returns following the final olefin addition step, the mixture is cooled to 0 °C to ensure that any product remaining in solution also precipitates.

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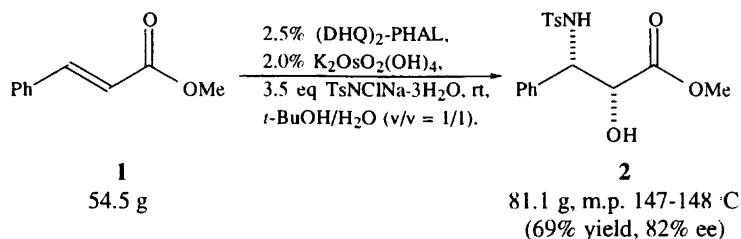
* To whom correspondence should be addressed.

Work-up involves only filtration and washing of the filtrate with cold *t*-BuOH–H₂O (v/v=1/1) to yield 81.1 g of product (**2**) (69% yield, 82% ee) which is almost pure by NMR and HPLC analysis. This crude **2** is raised to 92 % ee by trituration with ethyl acetate, and it is this 92% ee material which is carried on to the enantiomerically pure Taxol side-chain **4** (*vide infra*). It is important to note that the above trituration preferentially leaves the racemate behind, so that it is the triturate that contains the enriched **2**. If one desires enantiomerically pure **2**, it is obtained by recrystallization of the 92 % ee material from methanol, and this time it is the crystalline phase which is of high enantiopurity.

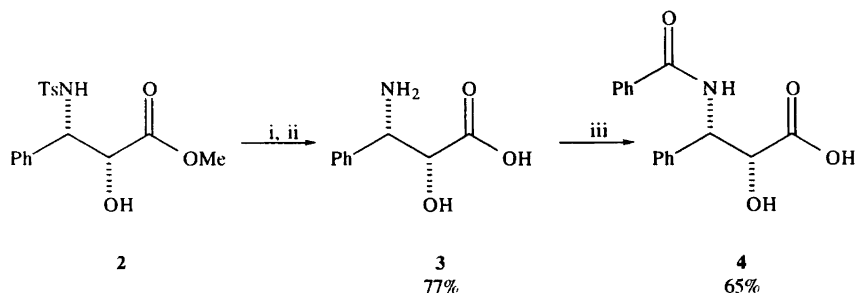
Removal of the *N*-toluenesulfonyl group from the resulting α -hydroxy-*p*-toluenesulfonamide (**2**) was achieved by a modified literature procedure.^{5a,b} The crude AA product was treated with 33% HBr in acetic acid for 10 h at 75 °C using phenol as a bromine scavenger. Of course, this treatment also hydrolyzes the methyl ester to the carboxylic acid. Surprisingly, no epimerized side-products were detected in spite of the harsh conditions. The bromide salt of the crude deprotected product was purified through ion-exchange chromatography on Amberlite IR-120 (plus) resin. The free α -hydroxy- β -amino acid was converted into the benzamide (**4**) under Schotten–Baumann conditions as already described for this identical conversion in the literature.^{3c,d}

Experimental

General. All commercial chemicals were used without purification and their stoichiometries were calculated based on the reported purities from the manufacturer. Melting points were measured without correction with a Thomas–Hoover capillary apparatus. Optical rotations were recorded on an Autopol III polarimeter (Rudolph



Scheme 1. A solution-to-solid catalytic AA. Product **2** crystallizes as it is formed, hence, isolation includes only filtration of the crude mixture.



Scheme 2. Removal of protecting groups and conversion into the Taxol side-chain.

Research, Fairfield, NJ). ¹H and ¹³C NMR spectra were recorded on a Bruker AMX 400 instrument.

(2*R*,3*S*)-(+)-Methyl 3-(*p*-toluenesulfonamido)-2-hydroxy-3-phenylpropionate (**2**). To a 2 l round-bottom flask, equipped with a mechanical stirrer and a thermometer, was added (DHQ)₂-PHAL (6.6 g, 2.5 mol%), *t*-BuOH (600 ml) and H₂O (600 ml). The flask was immersed in a room-temperature water bath. To the resulting homogeneous solution was added, in order, 290.4 g (1.01 mol) of Chloramine-T trihydrate (ca. 4/5 of the total added which is 338 g, 1.18 mol), methyl cinnamate (27.2 g, 167.6 mmol, half of the total amount of olefin, which is 54.4 g, 0.33 mol) and potassium osmate(VI) (2.5 g, 2.0 mol%). As the reaction was stirred, the color changed from yellow to green in 15 min and then back to yellow after 90 min; TLC (EtOAc–Hexane, v/v=4/6) revealed that the disappearance of olefin coincided with the return of the yellow color. The flask was then immersed in an ice bath (0 °C) for 20 min. (During this cooling, the crystals of precipitated product made their first appearance.) To this cold, stirred suspension the remainder of the Chloramine-T trihydrate (48.4 g, 0.168 mol) and the second portion of methyl cinnamate (13.6 g, 84 mmol) was added. The ice bath was replaced by the room temperature water bath, and the new olefin charge was consumed in about 45 min during which time the color changed as before from yellow to green and back to yellow again. The resulting mixture was cooled back to 0 °C for over 15 min and the third and last portion of methyl cinnamate (13.6 g, 84 mmol) was added. The reaction was returned to the room-temperature water bath and the remaining olefin was consumed in about 45 min with the above noted sequence of color changes. The flask was again immersed in an ice bath (0 °C) for

about 20 min. Essentially all of the product precipitated out of solution and was isolated by filtration, washed twice with cold (ca. 0 °C) 100 ml portions of *t*-BuOH–H₂O (v/v=1/1) to yield 81.1 g of (2*R*,3*S*)-(+)-methyl 3-(*p*-toluenesulfonamido)-2-hydroxy-3-phenylpropionate (**2**) (69% yield, 82% ee, m.p. 147–148 °C; for racemic: m.p. 125–126 °C^{4c}).

A 6.3 g portion of this crude **2** was triturated with EtOAc at room temperature (1 × 75 ml, 1 × 35 ml and 2 × 20 ml). The solid triturand of **2** remaining after these triturations was of low ee and was discarded. Concentration of the combined triturates afforded 5.3 g of enantiomerically enriched **2** (58 % yield, 92% ee), three recrystallizations from MeOH gave 3.2 g of enantiomerically pure product **2** (35% yield based on **1**), m.p. 154–155 °C; [α]_D²⁵ = +19.8° (c 0.5, 95% EtOH); ¹H NMR (400 MHz; DMSO–D₂O): δ 2.23 (s, 3 H), 3.45 (s, 3 H), 4.17 (d, *J*=4.0 Hz, 1 H), 4.65 (d, *J*=4.0 Hz, 1 H), 7.08–7.19 (m, 8 H), 7.40 (d, *J*=8.2 Hz, 2 H); ¹³C NMR (100 MHz; DMSO) δ 171.8, 141.9, 138.4, 138.7, 128.9, 127.6, 127.3, 126.9, 126.4, 74.4, 60.1, 51.6, 20.9.

(2*R*,3*S*)-2-Hydroxy-3-amino-3-phenylpropionic acid (**3**). A heavy-walled borosilicate pressure bottle was charged with the enantiomerically enriched (92% ee) **2** [i.e., the triturated but not recrystallized material (*vide supra*)] (1.25 g, 3.6 mmol), phenol (1.04 g, 11.1 mmol) and excess 33% hydrogen bromide in acetic acid (20 ml, 0.117 mol, Acros). The bottle was sealed with a bushing, having a Teflon-lined cap, before being immersed completely in an oil bath. The bath was maintained at 75 °C for 10–12 h. Water (20 ml) was then added and stirring was continued for 20 min with the bath at 50 °C. (This step effects hydrolysis of the 3-acetamido moiety, which otherwise is isolated as a major side-product). The

reaction mixture is then concentrated *in vacuo* to about 10 ml (water pump followed by an oil pump which was protected by a 0 °C aqueous KOH bubbler). The crude solution was purified by ion-exchange chromatography [Amberlite IR-120 (plus) resin, 35 g], eluting with 80 ml of water (to remove impurities), then with 80 ml of 5% ammonium hydroxide (starting with a dilute solution due the heat generated in the ion exchange process) followed by 80 ml of 15% ammonium hydroxide. Collection of the ammonium hydroxide eluate gave a solution of the ammonium salt of **3** which upon lyophilization yielded pure (2*R*,3*S*)-2-hydroxy-3-amino-3-phenylpropionic acid (**3**,⁷ 0.51 g, 77%). m.p. 235 °C (decomp.) [lit.^{3c} m.p. 238 °C, (decomp.)]; rotation after conversion into the hydrochloride salt is $[\alpha]_D^{25} = -14.5^\circ$ (*c* 0.37, MeOH; lit.⁶ $[\alpha]_D^{25} = -15.1^\circ$ *c* 0.365, MeOH). ¹H NMR (400 MHz; D₂O): δ 4.09 (d, *J*=6.0 Hz, 1 H), 4.32 (d, *J*=6.0 Hz, 1 H), 7.21–7.41 (m, 5 H); ¹³C NMR (100 MHz; D₂O–DMSO): δ 177.7, 135.4, 130.9, 130.7, 128.9, 75.0, 59.0.

(2*R*,3*S*)-3-Benzamido-2-hydroxy-3-phenylpropionic acid (**4**). The enantiomerically enriched **3**⁷ (0.43 g, 2.37 mmol) was converted into (2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropionic acid (**4**, 0.44 g, 65%) according to our earlier Schotten–Baumann-based procedure for this same transformation.^{3d} Chemically and enantiomerically pure **4** was isolated by simple filtration of the solid which appeared when the pH of the reaction mixture was adjusted to ca. 2 by addition of aqueous HCl,⁸ m.p. 166–167 °C (lit.^{3e} 167–169 °C); $[\alpha]_D^{25} = -34.0^\circ$ (*c* 0.50, EtOH) (lit.^{3c} $[\alpha]_D^{25} = -35.9^\circ$ *c* 0.565, EtOH); lit.^{3d} $[\alpha]_D^{25} = -35.5^\circ$ (*c* 1.07, EtOH); ¹H NMR (400 MHz; DMSO): δ 4.37 (d, *J*=4.3 Hz, 1 H), 5.46 (dd, *J*=8.8, 4.2 Hz, 1 H), 7.22–7.55 (m, 9 H), 7.84 (d, *J*=7.2 Hz, 1 H), 8.60 (d, *J*=8.9 Hz, 1 H), 12.73 (br, 1 H); ¹³C NMR (100 MHz; DMSO): δ 173.5, 166.0, 140.3, 134.4, 131.4, 128.4, 128.0, 127.4, 127.2, 126.9, 73.6, 55.8.

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