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A highly efficient synthesis of the C-13 side-chain of taxol using Shibasaki's asymmetric Henry reaction

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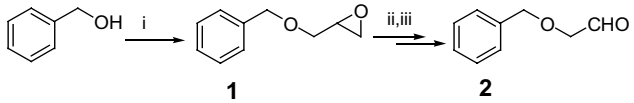
Abstract—The synthesis of the C-13 side-chain of taxol has been achieved using Shibasaki's asymmetric Henry reaction catalyzed by an optically active rare earth lanthanum-(*R*)-binaphthol complex.

Taxol,[1] an antimicrotubule agent isolated from *Taxus brevifolia*[2] has attracted much attention in recent years because of its efficacy in the treatment of various types of cancer. However, the major drawbacks in using taxol in cancer chemotherapy are its extremely limited availability from the natural source as well as the complexity involved in its total synthesis. The most attractive way of obtaining taxol at present is its partial synthesis from 10-DAB III, a diterpene analogous to taxol but devoid of the C-13 side-chain, which co-occurs with taxol in fairly high yield (1 g/kg) in the leaves of the European yew (*Taxus baccata*). Thus, by synthesizing the C-13 side-chain and linking it to 10-DAB III, taxol could be synthesized. Several syntheses of this moiety have been reported in recent years.[3]

The Henry reaction (nitro-aldol)[4] is one of the most powerful C–C bond-forming reactions in organic synthesis. The resulting nitro-aldol products can be easily transformed into various useful derivatives such as β-amino alcohols and α-hydroxy carbonyl compounds. β-Amino alcohols are found as important partial structures of many bioactive compounds such as α/β-adrenergic agonists or antagonists,[5] HIV protease inhibitors[6] and antifungal or antibacterial peptides.[7] The classical Henry reaction has been given a new dimension by Shibasaki and co-workers[8] who demonstrated that by using an appropriate optically active La complex, the reaction can be performed in an enantioselective manner giving 2-nitroalcohols with the desired stereochemistry. In continuation of our interest on the chemistry of aliphatic nitro compounds and their application in the synthesis of bioactive natural products,[9] we report here a significantly improved preparation of the taxol side-chain that is not only considerably shorter and higher in yield, but also experimentally much simpler involving Shibasaki's asymmetric Henry reaction as the key step.

The requisite aldehyde **2** was first prepared from epichlorohydrin in three steps (Scheme 1). Treatment of benzyl alcohol with epichlorohydrin and 50% aq NaOH solution in the presence of tetrabutylammonium bromide (TBAB) at <25 °C gave compound **1** in 80% yield. Transformation to its diol using 30% $HClO_4$ in Et_2O at room temperature and subsequent treatment of this diol with $Pb(OAc)_4$ in CH_2Cl_2 at 0 °C for 30 min[10] gave the aldehyde **2** in 52% overall yield.

Treatment of aldehyde **2** with phenylnitromethane as per the procedure described by Shibasaki and co-workers[11] at −50 °C in the presence of the asymmetric La-(*R*)-BINOL catalyst[12] (10 mol%) prepared from



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Scheme 1. Reagents and conditions: (i) epichlorohydrin, 50% aq NaOH, TBAB, <25 °C (80%); (ii) 30% $HClO_4$, Et_2O, rt (77%); (iii) $Pb(OAc)_4$, CH_2Cl_2, 0 °C (84%).

Keywords: Taxol; C-13 side chain of taxol; Asymmetric Henry reaction; La-(*R*)-binaphthol.

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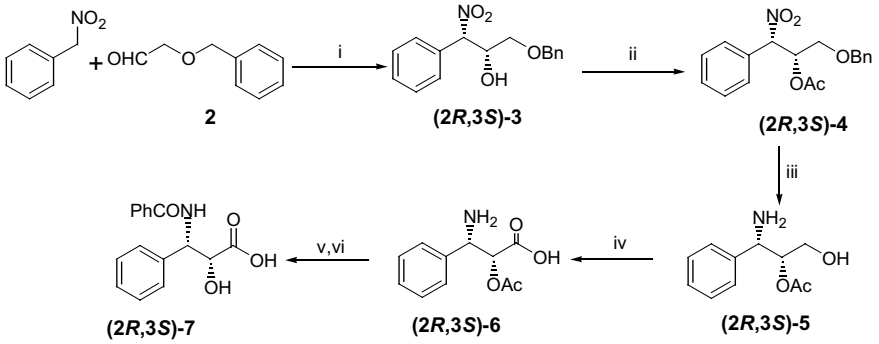

Scheme 2. Reagents and conditions: (i) La-(*R*)-BINOL (10 mol %), THF, −50 °C (80%); (ii) Ac_2O/Py (93%); (iii) 10% Pd/C, Et_2OH, H_2, rt (80%); (iv) CrO_3, glacial acetic acid, water, 5 °C (82%); (v) benzoyl chloride, Et_3N, 0 °C (80%); (vi) Et_2NMe–H_2O (85%).

$LaCl_3{\cdot}7H_2O$, dilithium (*R*)-(+)-binaphthoxide (1 mol equiv), NaO-*t*-Bu (1 mol equiv) and H_2O (4 mol equiv) in THF gave the nitro-aldol product (2*R*,3*S*)-**3** in 90% ee[13] and in 80% yield (Scheme 2).

The nitro-aldol product (2*R*,3*S*)-**3** was transformed into its acetate using acetic anhydride and pyridine in 93% yield and the resulting nitro-acetate (2*R*,3*S*)-**4** on hydrogenation with 10% Pd/C gave (2*R*,3*S*)-**5** in 80% yield and 98% ee. Treatment of (2*R*,3*S*)-**5** with CrO_3 in glacial acetic acid at 5 °C gave (2*R*,3*S*)-**6** in 82% yield and in 96% ee. Reaction of (2*R*,3*S*)-**6** with benzoyl chloride in the presence of triethylamine in an aqueous acetone mixture[14] and subsequent hydrolysis of the acetate group with Et_2NMe–H_2O[15] gave the C-13 taxol side chain[16] (2*R*,3*S*)-**7** in an overall yield of 33% from (2*R*,3*S*)-**3**.

In summary, a novel approach to the C-13 side-chain of taxol has been achieved with excellent optical purity using Shibasaki's asymmetric catalyst, La-BINOL complex.

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13. The enantiomeric excess (ee) was measured by HPLC analysis carried out using a Waters 510 HPLC system. Chiracel OD packed in a SS column of 4.6 mm i.d. × 250 m was used. Isocratic elution was applied with a mobile phase consisting of *n*-hexane 90% and isopropanol 10% at a flow rate of 0.8 mL/min and a pressure of 125 psi. UV detection at 243 nm.
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16. (2*R*,3*S*)-**3**: gum; $[\alpha]_D^{20}$ −40.3 (*c* 1, $CHCl_3$); ee: 90%. IR ($CHCl_3$): 3422, 2922, 2868, 1632, 1554, 1496, 1453, 1365, 1114, 736 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.82$ (10H, aromatic), 5.61 (d, $J = 9.4$ Hz, 1H, C*H*NO_2), 4.51 (m, 1H, C*H*OH), 4.25 (s, 2H, OCH_2Ph), 3.45 (d, $J = 4$ Hz, 1H, CH_aO–), 3.17 (d, $J = 4$ Hz, 1H, CH_bO–), 2.80 (br, 1H, OH). MS(ESI) $m/z = 310$ (M^++Na). Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.95; N, 4.88. Found: C, 66.94; H, 5.89; N, 4.91.

(2*R*,3*S*)-**5**: $[\alpha]_D^{20}$ +36.7 (*c* 0.4, $CHCl_3$); ee: 98%. IR ($CHCl_3$): 3400, 2926, 1722, 1602, 1454, 1237, 1037, 1072, 751, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.42$ (5H, aromatic), 4.8 (m, 1H, C*H*OAc), 3.52 (d, $J = 4$ Hz, 1H, C*H*NH_2), 3.5 (br, 2H, N*H*$_2$), 2.80 (d, $J = 6$ Hz, 2H, C*H*$_2$OH), 2.01 (s, 3H, OAc). MS(ESI) $m/z = 232$ (M^++Na). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.26; H, 7.28; N, 6.72.

(2*R*,3*S*)-**6**: Yield: 82%, ee: 96%. IR ($CHCl_3$): 3026, 1740, 1690, 1520, 1445, 1364, 1237, 1037 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.44$ (5H, aromatic), 5.3 (d, $J = 4$ Hz, 1H, C*H*OAc), 4. 0 (d, $J = 4$ Hz, H, C*H*NH_2), 3.5 (br, 2H, N*H*$_2$), 1.98 (s, 3H, OAc). MS(ESI) $m/z = 246$ (M^++Na). Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.22; H, 5.93; N, 6.35.

(2*R*,3*S*)-**7**: Benzoyl chloride (0.41 g, 2.9 mmol) in acetone (3 mL) was added dropwise to a stirred solution of (2*R*,3*S*)-**6** (0.5 g, 2.2 mmol) and Et_3N (0.54 g, 5.4 mmol) in water (5 mL) and acetone (3 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C and then for 3 h at rt. After precipitation, the acetone was removed under reduced pressure and the residue was extracted with ethyl acetate, dried over Na_2SO_4 and concentrated. The crude product was purified by preparative TLC using ethyl acetate/hexane (1:10) to give the benzoylated product (0.76 g, 2.3 mmol) which was hydrolyzed using a pH 9.0 solution of Et_2NMe (0.21 g, 2.3 mmol) in water. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was extracted with ethyl acetate, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by preparative TLC using ethyl acetate/hexane (1:7), to give the final product (2*R*, 3*S*)-**7** in 85% yield (0.56 g, 1.9 mmol). Spectral data of (2*R*,3*S*)-**7** were identical with those of an authentic sample.[3f]