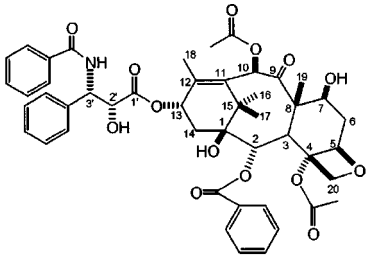
Synthesis of New Taxol Side Chain Precursor from L-Tartaric Ester

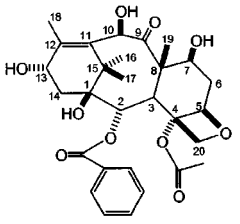
Seok-Chan Kim* and Hyon-Kyong Kim

Department of Chemistry, Kookmin University, Seoul 136-702, Korea
Received July 19, 2000

Paclitaxel (Taxol®, **1**),[1] highly functionalized diterpene isolated primarily from the inner bark of the western yew (*Taxus brevifolia*),[2] is a new anticancer drug with particular efficacy against refractory breast and ovarian cancers.[3,4] Because western yew is relatively rare and very slowly growing tree in old growth forests, the supply of taxol is solely dependent on the extraction from the bark of pacific yew in the early 1980. The harvest of those western yews endangers not only the old growth forests in the northwest of the United States, but also the future supply of taxol.



Taxol (1)



10-Deacetylbaccatin III (2)

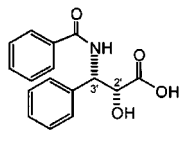
However, it has been found that 10-deacetylbaccatin III (**2**), the abundant constituent of the needles of the European yew tree species *Taxus baccata*, is more readily obtained.[5] With 10-deacetylbaccatin III (**2**) in hand, it appears that sufficient supplies of taxol can now be produced in a semisynthetic fashion.

It is known that C-13 side chain, *i.e.*, *N*-benzoyl-(2R,3S)-3-phenylisoserine (**3**) moiety, is crucial for the activity of taxol.[6] Semisynthetic taxol work[7] has generated a demand for new stereoselective preparations of isoserine type structure. So far, β-lactam **4** to reduce steric bulk derived from isoserine moiety is an excellent C-13 side chain precursor of taxol. In fact, Holton[8] and Ojima[9] have prepared β-lactam **4** for the side chain precursor from [2+2] cycloaddition and ester enolate-imine cyclocondensation reaction, respectively.

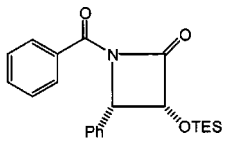
We report herein our new results regarding the stereoselective semisynthesis of taxol from optically active L-tartaric ester as our taxol side chain precursor.

Results and Discussion

L-Tartaric ester was converted to optically pure (R)-2-O-benzylglyceraldehyde (**6**) *via* the known procedure[10] (three steps, *ca.* 80%), as shown in Scheme 1.

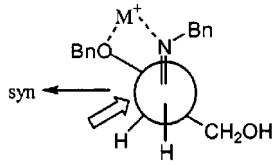


Taxol C-13 side chain (3)



β-lactam (4)

Imine **7** derived from benzylamine and (R)-2-O-benzylglyceraldehyde (**6**) was chosen as promising substrate that would allow for straightforward transformation at other terminus by adding C-nucleophiles to the C=N bond. Addition of phenylmagnesium bromide to imine **7** proceeded at a moderate pace and gave satisfactory yield with an isomer ratio greater than 9 : 1. The successful outcome of this diastereofacial selectivity has been attributed to prior formation of a five-membered chelation between the 2-benzyloxy group and imine nitrogen atom.[11]

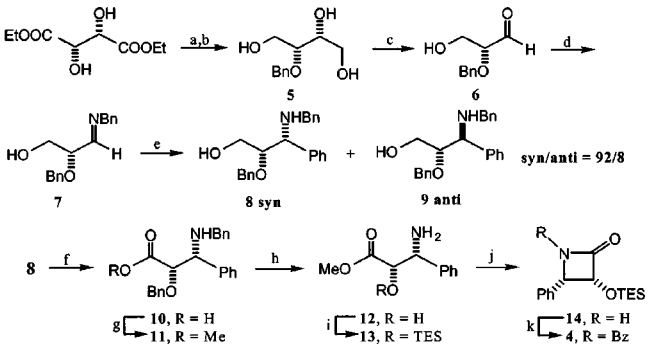


With **8** in hand, our next effort was directed toward the formation of β-lactam **4** shown in Scheme 1. Oxidation of primary alcohol with CrO_3/H_2SO_4 followed by methylation of resulting acid **10** afforded **11** in *ca.* 90% yield. Hydrogenolysis (Pd/C, HCOOH) of N,O-dibenzyl group in **11** furnished **12** in 85% yield. The resulting 2-hydroxy group was then selectively protected by using TESCl.[9,10] In order to obtain β-lactam **4**, cyclization was conducted with LHMDS in THF at 0 °C. Finally *N*-benzoyl group was introduced by standard procedure (BzCl, TEA). This fully functionalized β-lactam **4** is coupled with 7,10-ditriethylsilyl baccatin(III) (**15**) according to Holton[9] and Ojima protocols[10] shown in Scheme 2. Fluorine-induced removal of silyl protecting groups afforded 10-deacetyl taxol (**16**). Finally, the stereochemistry of **8** was reconfirmed by comparing 10-deacetyl taxol (**16**) with authentic sample obtained from other academic groups.[12]

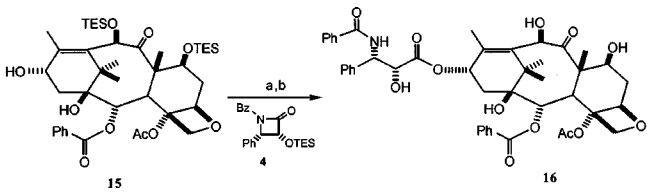
In conclusion, a facile synthetic route to optically active β-lactam **4** from L-tartaric ester has been developed. This highly useful protocol will provide an efficient stereoselective synthesis of β-lactam **4** which was important side chain precursor of taxol. Also we are now exploring the other β-lactams bearing the different alkyl substituents.

Experimental Section

Preparation of 8 and 9. To a solution of imine **7** (1.40 g, 5.0 mmol) in dry ether (20.0 mL) at 0 °C under N_2 was added dropwise over 30 min 3.0 M phenylmagnesium bromide in ether (4.2 mL, 12.5 mmol). This resulting mixture was stirred at room temperature for 20 h and quenched with saturated aqueous NH_4Cl (30 mL) at 0 °C. Organic layer was separated and aqueous layer was extracted with ether (3 ×



Scheme 1. [a]Reagents and conditions: (a) PhCHO, *p*-TsOH (cat.), PhH, reflux, 20 h; (b) $LiAlH_4$, $AlCl_3$, MC, -40 °C to reflux, two steps 85%; (c) $NaIO_4$, H_2O, 95%; (d) $PhCH_2NH_2$, $MgSO_4$, ether, 0 °C; (e) PhMgBr, ether; two steps 73% (f) CrO_3, H_2SO_4, acetone; (g) TMSCl, MeOH, reflux, two steps 80%; (h) Pd/C, HCOOH, reflux, 85%; (i) TESCl, TEA, ether/THF (1 : 1), 94% (j) LHMDS, THF, 0 °C, 85%; (k) BzCl, TEA, MC, rt, 96%.



Scheme 2. [a]Reagents and conditions: (a) LHMDS, -45 °C, then **4**; (b) HF/Py., CH_3CN 0 °C, two steps 77%.

20 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified with column chromatograph with 15% EtOAc in hexane to give major compound **8** (1.2 g, 67.0%) and minor **9** (0.10 g, 5.6%) as pale yellow syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) for **8** δ 7.20 (m, 15H, aromatics), 4.49 (d, 1H, J = 11.5 Hz, -OC$\underline{H}_2$Ph), 4.30 (d, 1H, J = 11.5 Hz, -OC$\underline{H}_2$Ph), 3.81 (d, 1H, J = 4.4 Hz, -C$\underline{H}$NBn), 3.75 (dd, 1H, J = 12.0, 3.4 Hz, -C$\underline{H}_2$OH), 3.54 (d, 1H, J = 12.9 Hz, -NC$\underline{H}_2$Ph), 3.49 (dd, 1H, J = 12.0, 2.5 Hz, -C$\underline{H}_2$OH), 3.41 (m, 1H, -C$\underline{H}$OBn), 3.36 (d, 1H, J = 12.9 Hz, -NC$\underline{H}_2$Ph), 3.0 (brs, 1H, -$\underline{H}$NBn). ^{1}H NMR ($CDCl_3$, 300 MHz) for **9** δ 7.20 (m, 15H, aromatics), 4.38 (d, 1H, J = 11.3 Hz, -OC$\underline{H}_2$Ph), 4.22 (d, 1H, J = 11.3 Hz, -OC$\underline{H}_2$Ph), 3.91 (d, 1H, J = 6.1 Hz, -C$\underline{H}$NBn), 3.65 (dd, 1H, J = 11.7, 3.0 Hz, -C$\underline{H}_2$OH), 3.64 (d, 1H, J = 12.9 Hz, -NC$\underline{H}_2$Ph), 3.55 (dd, 1H, J = 11.7, 4.8 Hz, -C$\underline{H}_2$OH), 3.45 (m, 1H, -C$\underline{H}$OBn), 3.36 (d, 1H, J = 12.9 Hz, -NC$\underline{H}_2$Ph), 2.9 (brs, 1H, -$\underline{H}$NBn).

10-Deacetyl taxol (**16**). To a solution of 7,10-bis-O-triethylsilyl baccatin III (**15**) (115 mg, 0.149 mmol) in dry THF (5.0 mL) at -45 °C was added dropwise 1.0 M LHMDS (1.08 mL, 7.2 eq) in THF. After 0.5 h at -45 °C, a solution of β-lactam **4** (285 mg, 0.7 mmol) in THF (5.0 mL) was added dropwise to this mixture. After 30 min stirring at -45 °C, the solution was quenched with saturated $NaHCO_3$ (3.0 mL) at this temperature. The mixture was extracted with EtOAc (50.0 mL), rinsed with brine, and dried over anhydrous $MgSO_4$. Evaporation of the organic layer gave a residue which was purified by column chromatography with 10% EtOAc in hexane to give a crude solid (155 mg). To a solution of this solid (155 mg) in CH_3CN (8.2 mL) and pyridine (410 μL) at 0 °C in polyethylene vial was added to 48% aqueous HF (1.25 mL). The mixture was stirred at 0 °C for 2 h, then at 25 °C for 4 h, and partitioned between saturated aqueous $NaHCO_3$ and EtOAc (30.0 mL). Evaporation of the EtOAc solution gave a crude solid which was purified by column chromatography with 50% EtOAc in hexane to give a white coupled 10-deacetyl taxol **16** (93.2 mg, two steps 77.0%): mp 205-207 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J = 7.3 Hz, 2H, aromatics), 7.70 (d, J = 7.1 Hz, 2H, aromatics), 7.58 (m, 1H, aromatic), 7.38 (m, 11H, aromatics, NH), 6.12 (t, J = 8.1 Hz, 1H, H13), 5.71 (dd, J = 8.8, 2.5 Hz, 1H, H3'), 5.61 (d, J = 6.4 Hz, 1H, H2), 5.18 (s, 1H, H10), 4.86 (dd, J = 9.0, 1.2 Hz, 1H, H5), 4.74 (d, J = 2.5 Hz, 1H, H2'), 4.19 (m, 3H, H7, H20), 3.81 (d, J = 6.4 Hz, 1H, H3), 2.44 (m, 1H, H6α), 2.31 (s, 3H, 4Ac), 2.19 (m, 2H, H14), 1.78 (m, 1H, H6β), 1.69 (s, 3H, Me18), 1.67 (s, 3H, Me19), 1.13 (s, 3H, Me17), 1.04 (s, 3H, Me16); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.63, 170.49, 167.33, 166.82, 138.19, 137.91, 135.86, 133.66, 133.55, 131.87, 130.09, 129.12, 128.84, 128.66, 128.58, 128.15, 127.08, 126.96, 84.18, 80.99, 78.56, 77.20, 74.76, 74.39, 73.21, 72.07, 71.83, 57.58, 55.14, 46.37, 42.94, 36.63, 35.70, 29.64, 26.44, 22.47, 20.57, 14.20, 9.80.

Acknowledgment. We would like to thank Hanmi Pharm. Co. Ltd. for free donation of 10-deacetylbaccatin (III) and financial support of this work.

References

1. Paclitaxel is the generic name for Taxol, which is now a registered trademark.
2. Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.
3. Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Nat. Cancer Inst.* **1990**, *82*, 1247.
4. Holmes, F. A.; Walters, R. S.; Theriault, R. L.; Forman, A. D.; Newton, L. K.; Raber, M. N.; Buzdar, A. U.; Frye, D. K.; Hortobagyi, G. N. *J. Nat. Cancer Inst.* **1991**, *83*, 1797.
5. Suffness, M. In *Ann. Repts. Med. Chem.*; Bristol, J. A., Ed.; Academic Press: San Diego, CA., 1993; pp 305-314.
6. (a) Swindell, C.; Krauss, N. E.; Horwitz, S. B.; Ringel, I. *J. Med. Chem.* **1991**, *34*, 1176. (b) Guéritte-Voegelein, F.; Guénard, D.; Lavelle, F.; Le Goff, M.-T.; Mangatal, L.; Potier, P. *J. Med. Chem.* **1991**, *34*, 992.
7. (a) Hart, D.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. (b) Georg, G. I. *Tetrahedron Lett.* **1984**, *25*, 3779.
8. Holton, R. A. *Eur. Pat. Appl. EP 400,971*, **1990**.
9. Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985.
10. (a) Jäger, V.; Wehner, V. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 469. (b) Schubert, T.; Kunisch, F.; Welzel, P. *Tetrahedron* **1983**, *39*, 2211.
11. (a) Cainelli, G.; Giacomini, D.; Mezzina, E.; Panunzio, M.; Zarantonello, P. *Tetrahedron Lett.* **1991**, *32*, 2967. (b) Cainelli, G.; Giacomini, D.; Panunzio, M.; Zarantonello, P. *Tetrahedron Lett.* **1992**, *33*, 7783. (c) Yamamoto, Y. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 947. (d) Cainelli, G.; Giacomini, D. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2150.
12. (a) Georg, G. I.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2467. (b) Chaudhary, A. G.; Kingston, D. G. I. *Tetrahedron Lett.* **1993**, *34*, 4921. (c) Margraff, R.; Bézard, D.; Bourzat, J-D.; Commercon, A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 233.