Total Synthesis of (±)-Taxusin

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The taxane diterpenes (Figure 1) isolated from various yew trees continue to be of extreme interest as synthetic targets[1] because of the challenging, complex molecular structure coupled with the important biological activities. Taxol (**3**) and its synthetic analogs are well-known to exhibit promising antitumor activities[2] and several other natural taxanes such as taxinine (**2**) were recently revealed to be inhibitors against the P-glycoprotein.[3] Remarkable contribution of both of these properties to development of new fields of cancer chemotherapy is expected. We now report a concise total synthesis of (±)-taxusin (**1**).[4]

In the synthetic plan, we envisioned two key transformations: (1) construction of the tricyclic taxane skeleton via cyclization of the eight-membered B ring between C9 and C10 and (2) subsequent installation of the C19 methyl group onto the ring system.[5] We have already established a powerful method for the eight-membered B ring cyclization by means of intramolecular vinylogous aldol reaction, using aromatic C ring derivatives as substrates.[6] It was essential for success of this total synthesis that the methodology could be extended to non-aromatic, allyl ester-type C ring derivatives such as **12**. The C ring allyl ester moiety was incorporated to serve as a flag for installation of the C19 methyl group.

Our first task was preparation of cyclization precursor **12** (Scheme 1). We chose vinyl bromide **4**[7] as the starting material, which corresponds to the C ring of taxusin. Successive

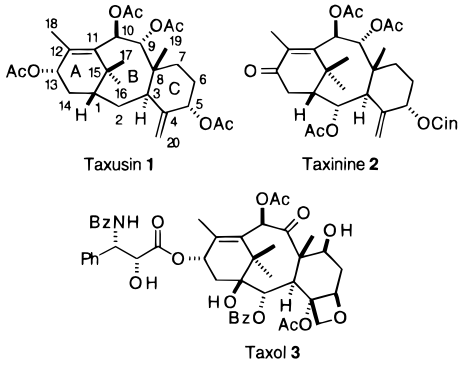
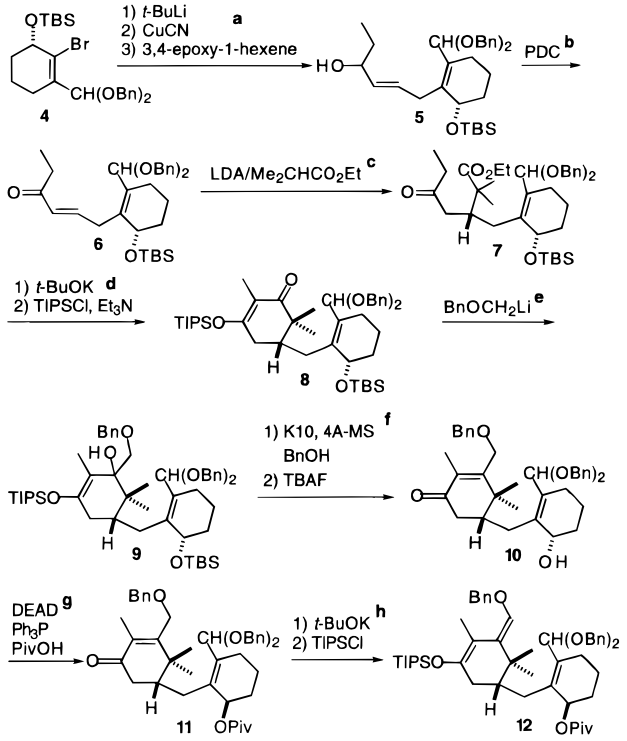


Figure 1. Structure of natural taxanes.

Scheme 1[a]



[a] (a) (1) Et_2O, −78 °C, 1.5 h; (2) −45 °C, 1 h; (3) −23 °C, 2 h. (b) 4A-MS, CH_2Cl_2, rt, 1.5 h, 66% from **4**. (c) THF, −78 to 5 °C, 7 h, quantitative. (d) (1) THF, 0 °C, 1 h; (2) 0 °C, 4 h, 60%. (e) THF, −78 °C, 2.5 h, 86%. (f) (1) CH_2Cl_2, −45 °C, 1 h, 79%; (2) THF, rt, overnight, 83%. (g) THF, rt, 1 week, 67%. (h) (1) THF, 0 °C, 1 h; (2) −78 °C, 1 h, quantitative.

treatment of **4** with *t*-BuLi and CuCN produced the corresponding cyanocuprate, and its reaction with 3,4-epoxy-1-hexene[8] gave rise to the S_N2' coupling product **5**. Pyridinium dichromate (PDC) oxidation[9] of the resulting allyl alcohol **5** afforded enone **6** in 66% yield (2 steps). Conjugate addition of the lithium enolate of ethyl isobutyrate to **6** proceeded with fairly high 1,4-asymmetric induction (4:1) to yield **7** as the major isomer.[10]

(1) There have been reported four total syntheses of natural taxanes. For taxusin, see: (a) Holton, R. A.; Juo, R. R.; Kim, H.-B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558. For taxol, see: (b) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597, 1599. (c) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630. Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624 and following papers. (d) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723.

(2) For reviews, see: (a) Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M. *Taxane Anticancer Agents*; American Cancer Society: San Diego, CA, 1995. (b) Kingston, D. G. I.; Molinero, A. A.; Rimoldo, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1. (c) Rowinsky, E. K.; Onetto, N.; Canetta, R. M.; Arbuck, S. G. *Semin. Oncol.* **1992**, *19*, 646.

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(5) The taxane numbering system, as illustrated in **1**, is used throughout.

(6) (a) Horiguchi, Y.; Furukawa, T.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 8277. (b) Furukawa, T.; Morihira, K.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron* **1992**, *48*, 6975. (c) Seto, M.; Morihira, K.; Katagiri, S.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *Chem. Lett.* **1993**, 133. (d) Morihira, K.; Seto, M.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 345. (f) Nakamura, T.; Waizumi, N.; Tsuruta, K.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1994**, 584. (g) Seto, M.; Morihira, K.; Horiguchi, Y.; Kuwajima, I. *J. Org. Chem.* **1994**, *59*, 3165.

(7) The starting material can be prepared in large scale from 3-isobutoxy-2-cyclohexen-1-one in 5 steps (58% overall yield) by means of the method developed in our laboratory[16] via (1) bromination with NBS, (2) 1,2-addition of (benzyloxy)(phenylthio)methyllithium and acidic workup, (3) acetal exchange with $CuCl_2$, CuO, and BnOH, (4) DIBAL reduction, and (5) protection with TBS group.

(8) Sauleau, J.; Bouget, H.; Huet, J. *C. R. Acad. Sci., Ser. C* **1971**, *273*, 829.

(9) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(10) The relative stereochemistry was inferred on the analogy of a closely related compound of which stereochemistry was confirmed by the X-ray analysis of its derivative, see: Takenaka, Y.; Sakai, Y.; Ohashi, Y.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *Anal. Sci.* **1993**, 883. The origin of the 1,4-asymmetric induction will be discussed in detail in the full paper.

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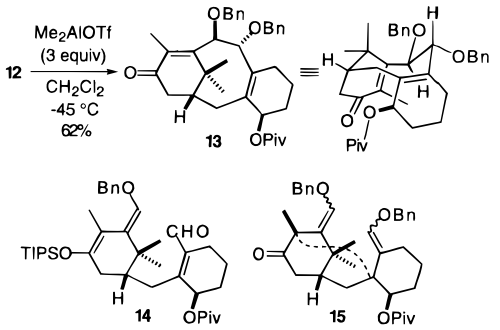
Scheme 2



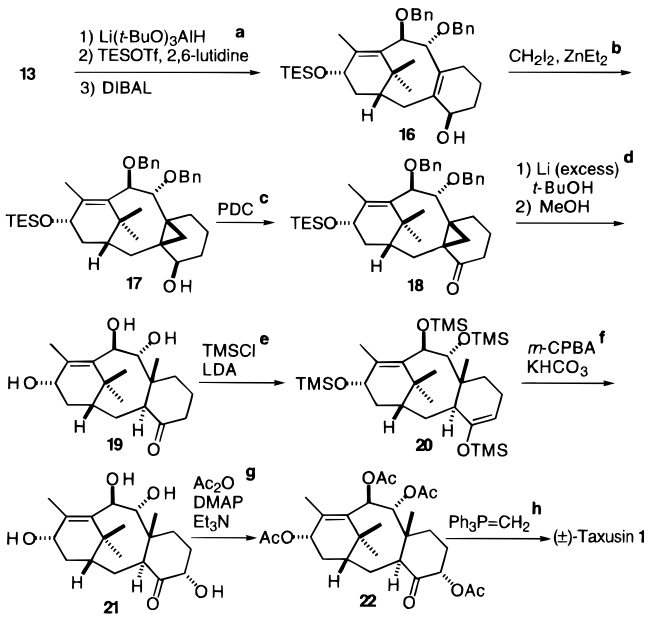
The Dieckmann-type cyclization of **7** upon treatment with *t*-BuOK and *in situ* silylation with triisopropylsilyl chloride (TIPSCl) afforded *β*-siloxyenone **8** in 60% yield (2 steps). Then, 1,2-addition of (benzyloxy)methyllithium[11] to **8**, followed by successive treatment with Montmorillonite K 10 (K10) and BnOH in the presence of molecular sieves 4 Å (4A-MS) and then with TBAF, furnished **10** in 56% yield (3 steps). Because the opposite relative 1,4-stereochemistry was supposed to be advantageous at the later stages (cyclopropanation, *vide infra*), the stereochemistry of C4 was inverted at this stage by the Mitsunobu reaction (DEAD, Ph_3P, PivOH) to give **11**.[12] Enolization of **11** under thermodynamic control and subsequent silylation with TIPSCl afforded **12**, the cyclization precursor with allyl ester-type C ring in 67% yield (2 steps).

With the cyclization precursor in hand, the crucial eight-membered B ring cyclization was examined (Scheme 2). Initial attempts using Lewis acids such as $TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, and TMSOTf were fruitless. Thus, aldehyde **14** and spirocyclization product **15** were obtained in considerable amounts. After investigating various Lewis acids and reaction conditions, Me_2-AlOTf was found to induce the desired eight-membered ring cyclization to give **13** in 62% yield. The stereochemistry of **13**, namely conformation of the B ring and configuration of C9 and C10, was determined by ^{1}H NMR.

Then, reduction of the C13 keto group of **13** (Li(*t*-BuO)$_3$-AlH), followed by silylation of the resultant hydroxyl group (TESOTf) and reductive removal of pivalate group (DIBAL), gave allyl alcohol **16** in 87% yield (3 steps, Scheme 3). Exclusive formation of the C13α alcohol could be attributed to the concave nature of the α face.[1c,6a,6c] The stage was set for investigation of the C19 methyl group installation according to the Dauben protocol,[13] utilizing the C ring allyl alcohol moiety. Introduction of the C19 carbon as a methylene group by the hydroxyl-group-directed cyclopropanation (Et_2Zn, CH_2I_2)[14] proceeded to give **17** quantitatively. Subsequent PDC oxidation,[9] then, afforded cyclopropyl ketone **18** in 85% yield (2 steps). The Birch reduction[13] of **18** induced cleavage of cyclopropane ring with the correct stereochemistry at C3 and concomitant removal of two benzyl groups and TES group in one operation to afford exclusively the desired product **19** (91%). Formation of the desired C3α protonation product should be a result of equilibration catalyzed by MeOLi presumably during evaporation of ammonia. We believe that the C13 hydroxyl group liberated *in situ* would play an important role to direct the protonation from the highly congested concave face.

After the C19 methyl group was successfully installed, sequential operations for completion of the total synthesis of taxusin paralleled that previously reported by Holton.[1a] Treatment of **19** with excess LDA and TMSCl resulted in regioselective enol silyl ether formation at C5, accompanied with silylation of hydroxyl groups. Oxidation of the resulting tetrasilyl ether **20** with *m*-CPBA, followed by acidic workup produced tetrol **21**, of which acetylation gave rise to tetraacetate **22** (80%, 3 steps from **19**). Finally, methylenation of C4 carbonyl ($Ph_3P{=}CH_2$, toluene, hexane, room temperature (rt)) furnished (±)-taxusin[15] identical to natural taxusin in respects of ^{1}H NMR, ^{13}C NMR and IR spectra and TLC mobility.

Scheme 3[a]



[a] (a) (1) THF, rt, overnight; (2) CH_2Cl_2, −23 °C, 1 h; (3) CH_2Cl_2, −78 °C, 1 h, 87% from **13**. (b) Et_2O, rt, 6 h, quantitative. (c) 4A-MS, CH_2Cl_2, rt, 1.5 h, 85%. (d) (1) NH_3(l), THF, −78 °C, 1 h; (2) rt, 1 h, 91%. (e) THF, −78 °C, 10 min, then 0 °C, 30 min. (f) CH_2Cl_2, 0 °C, 10 min. (g) CH_2Cl_2, rt, 1.5 h, 80% from **19**. (h) $Ph_3P{=}CH_2$, benzene, hexane, 0 °C, 1.5 h, 53% based on 32% conversion.

In conclusion, we have achieved a concise total synthesis of (±)-taxusin (2% overall yield through 25 steps from readily available 3-isobutoxy-2-cyclohexen-1-one). The synthetic route is highlighted by (1) remarkably effective eight-membered B ring cyclization leading to the C ring allyl ester-type tricyclic taxane skeleton with the desired B ring conformation and C9, C10 stereochemistry and (2) subsequent installation of the C19 methyl group via the Birch reduction of the cyclopropyl ketone. Because of failure to introduce C19 methyl group via conjugate addition,[16] this approach is one of the most reasonable solutions for such purpose.

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Supporting Information Available: Experimental details and characterization (^{1}H, ^{13}C, IR, and elemental analyses) for **4**, **6**, **8**, **10**−**13**, **16**, **18**, **19**, **22**, and **1** (15 pages). See any current masthead page for ordering and Internet access instructions.

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(12) Mitsunobu, O. *Synthesis* **1981**, 1.
(13) For angular methyl group introduction via reductive cleavage of cyclopropyl ketones, see: Dauben, W. G.; Deviny, E. J. *J. Org. Chem.* **1966**, *31*, 3794.
(14) Nishimura, J.; Kawabata, N.; Furukawa, J. *Tetrahedron* **1969**, *25*, 3353.
(15) Although Holton reported 70% yield for the olefination, we faced rather lower yield (53% yield on 32% conversion) as long as we examined the reaction a few times in small scale. As Holton stated, **22** is susceptible to deacetylation during the olefination reaction, see: Holton, R. B. In *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press, Inc.: San Diego, CA, 1991; Vol. 3, pp 165−197.
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