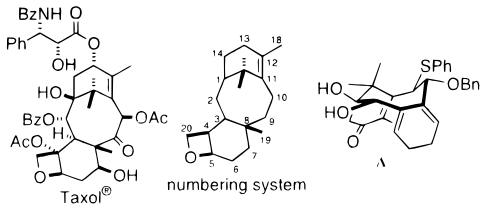
Enantioselective Total Synthesis of Taxol

Koichiro Morihira, Ryoma Hara, Shigeru Kawahara, Toshiyuki Nishimori, Nobuhito Nakamura, Hiroyuki Kusama,* and Isao Kuwajima*,†

Department of Chemistry, Tokyo Institute of Technology O-okayama, Meguro-ku, Tokyo 152-8551, Japan

Received July 15, 1998



Taxol isolated from pacific yew trees[1] continues to be of extreme interest as a synthetic target[2] because of the challenging and complex molecular structure coupled with important biological activities.[3] The major problems in taxol synthesis seem to be focused on the following: (1) construction of a taxane tricarbocycle and (2) stereocontrol of nine asymmetric centers. This paper describes an enantioselective total synthesis of (−)-taxol.

Our strategy for taxol synthesis was based on initial construction of an endo tricarbocyclic intermediate **A** with the correct stereochemistry at the C1 and C2 sites[4] followed by an appropriate functional group elaboration on the B- and C-rings. The structural feature of **A** may allow us to introduce the C19-methyl from the upper site of the C-ring. The use of a C-ring fragment **2** serves as a clue for installation of C4- and C7-oxygen functionalities from the convex β-face. We also envisioned that the present approach would lead to an enantioselective synthesis of taxol by using aldehyde **1** which has a chiral center at C1 site. Thus, chelation-controlled coupling of the enantiomerically pure hydroxyaldehyde[5] with the C-ring fragment **2** would confirm the stereochemical outcome at the C1 and C2 sites, and a subsequent B-ring cyclization between the C9 and C10 atoms[6] would lead to the enantioselective formation of the key intermediate **A** for taxol.

In the presence of Mg(II) ion, the reaction of **1** with the lithiated **2** gave the corresponding coupling product with complete stereocontrol in the desired fashion (Scheme 1). Protection of vicinal diol[6b] as a boronate gave the cyclization precursor **3**, and then the crucial B-ring cyclization was examined. Among several Lewis acids examined, $TiCl_2(O^iPr)_2$ proved to be the most efficient one to induce the cyclization. Subsequent removal of boronate produced the corresponding C9α,C10β-disubstituted tricarbocycle **4**.

For the introduction of C19-methyl, we adopted a similar strategy to that of taxusin synthesis,[7] namely, the cyclopropanation on the $\Delta^{3,8}$-double bond followed by ring cleavage of cyclopropyl ketone. Thus, **4** was treated successively with BuLi and ^{t}Bu$_2$Si(H)Cl[8] at low temperature. On warming up the reaction temperature, hydrogen evolved to give the dioxasilapentane.[9] Reduction of the C13-keto group followed by silylation afforded **5**. Singlet oxygen oxygenation of the diene moiety took place selectively from the β-face of the C-ring. A subsequent treatment with Bu_3SnH and AIBN induced both peroxide bond cleavage and removal of the phenylthio group, giving a diol. Removal of the benzyl group followed by the C7,C9-diol protection yielded **6** as a mixture of diastereomers (α:β = ca. 1:4). Of the two diastereomers of **6**, the major β-isomer underwent the expected methylenation by treating with $Et_2Zn/ClCH_2I$,[10] whereas the methylene transfer could not be effected with the α-isomer. Dess−Martin oxidation[11] of the C4-hydroxy group afforded the cyclopropyl ketone **7**.

During the synthetic studies of taxusin, it was revealed that the role of C13-OH is critical in converting an enol produced via the cyclopropane ring cleavage to the desired ketone: Conversion of the C13-OH-protected enol to the C3α-protonated ketone via intermolecular protonation was exceedingly difficult because the protonation to the C3 had to occur from the highly congested concave face. To overcome this difficulty, we achieved the enol/keto isomerization by utilizing the closely situated C13-OH to direct the protonation from the α-face.[7] Based on this observation, we initially removed the C13- as well as the C1,C2-silicon protecting groups of **7**, and the resulting triol was used for ring cleavage. Under the influence of SmI_2, the cyclopropane ring cleavage took place readily, but the resulting enol was exceptionally unstable, and in the presence of air, it quickly decomposed to form a complex mixture of unidentified products. At this stage, enol/keto isomerization was examined by using the protected C1,C2-diol substrate. Replacement of the C7,C9-protecting group of **7** with the carbonate followed by treatment with TBAF/AcOH gave a diol. Then the vicinal diol was protected with a benzylidene group and the carbonate was removed to give **8**. On exposure to SmI_2-HMPA-methanol,[12] **8** was smoothly converted to an enol stable enough to allow further manipulation under various reaction conditions. After several attempts, it was found that the removal of the TBS group followed by treatment under basic conditions

† Present address: The Kitasato Institute, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan.

(1) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhali, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

(2) (a) 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. Holton, R. A.; Kim, H.-B.; Somoza, C.; 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*, 1599. (b) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624. Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634. Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645. Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653. (c) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843. (d) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Gränicher, C.; Houze, J. B.; Jänichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Mühlebach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.; Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2755. Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 2757. (e) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Sakoh, H.; Tani, Y.; Hasegawa, M.; Saitoh, K. *Proc. Jpn. Acad., Ser. B* **1997**, *73*, 95. Shiina, I.; Iwadare, H.; Sakoh, H.; Hasegawa, M.; Tani, Y.; Mukaiyama, T. *Chem. Lett.* **1998**, 1. Shiina, I.; Saitoh, K.; Fréchard-Ortuno, I.; Mukaiyama, T. *Chem. Lett.* **1998**, 3.

(3) (a) *Taxol: Science and Applications*; Suffness, M., Ed.; CRC, Boca Raton, FL, 1995. (b) *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995.

(4) The taxane numbering system is used throughout.

(5) Nakamura, T.; Waizumi, N.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1994**, *35*, 7813.

(6) (a) Horiguchi, Y.; Furukawa, T.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 8277. (b) Nakamura, T.; Waizumi, N.; Tsuruta, K.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1994**, 584 and references therein.

(7) Hara, R.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1996**, *118*, 9186.

(8) At first, a synthetic route using a benzylidene protecting group for the C1,C2-diol moiety was examined. However, cyclopropanation of the $\Delta^{3,8}$-double bond did not proceed at all.

(9) Tanino, K.; Shimizu, T.; Kuwahara, M.; Kuwajima, I. *J. Org. Chem.* **1998**, *63*, 2422.

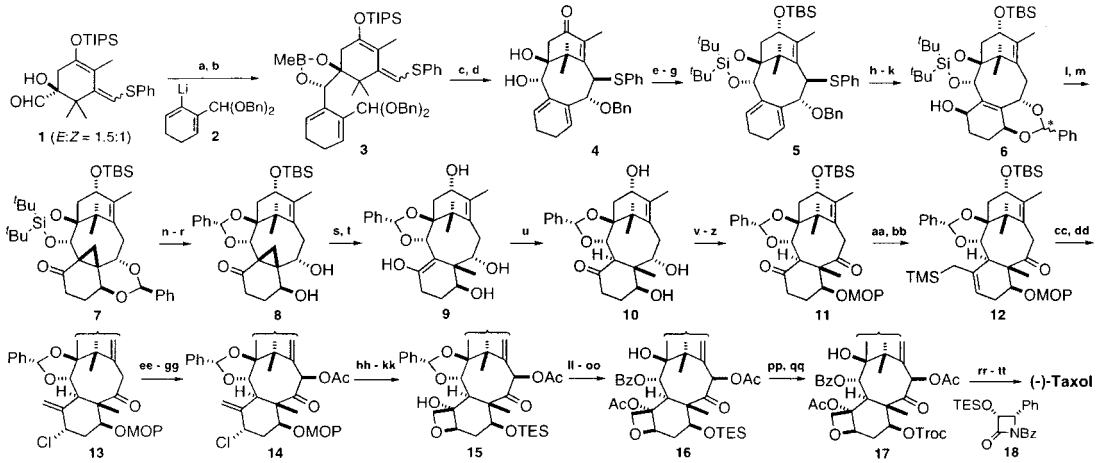
(10) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974.

(11) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(12) Batey, R. A.; Motherwell, W. B. *Tetrahedron Lett.* **1991**, *32*, 6211.

10.1021/ja9824932 CCC: $15.00
Published on Web 12/01/1998

Scheme 1[a]



[a] ^{t}BuMgCl, THF, −78 °C; then **2**, −78 °C, 68%. (b) $(MeBO)_3$, pyr, benzene, 77%. (c) $TiCl_2(O^iPr)_2$, CH_2Cl_2, −78−0 °C. (d) Pinacol, DMAP, benzene, 59% from **3**. (e) BuLi, $^t Bu_2Si(H)Cl$, THF, −78−0 °C. (f) DIBAL, CH_2Cl_2, −78 °C. (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, −23 °C, 62% from **4**; (h) O_2, TPP, hv, CH_2Cl_2. (i) Bu_3SnH, AlBN, benzene, reflux, 80% from **5**. (j) Pd/C, H_2, EtOH. (k) $PhCH(OMe)_2$, CSA, CH_2Cl_2, −23 °C, 79% in 2 steps (α:β = ca. 1:4). (l) Et_2Zn, $ClCH_2I$, toluene, 0 °C, 66%. (m) Dess−Martin, CH_2Cl_2, 77%. (n) $Pd(OH)_2$, H_2, EtOH, 84%. (o) Triphosgene, pyr, CH_2Cl_2, −45 °C. (p) TBAF, AcOH, THF, 95% in 2 steps. (q) $PhCH(OMe)_2$, PPTS, benzene, reflux, 86%. (r) K_2CO_3, MeOH-THF, quant. (s) SmI_2, THF−MeOH−HMPA, quant. (t) TBAF, BHT, THF. (u) NaOMe, BHT, degassed MeOH, 45% in 2 steps (ca 50% of **9** was recovered); 65% by repeating this isomerization procedure twice. (v) $PhB(OH)_2$, CH_2Cl_2; (w) TBSOTf, 2,6-lutidine, CH_2Cl_2, −45 °C; (x) H_2O_2, $NaHCO_3$, AcOEt, 70% from **10**. (y) Dess−Martin, CH_2Cl_2, 92%. (z) 2-Methoxypropene, PPTS, CH_2Cl_2, 97%. (aa) KHMDS, $PhNTf_2$, −78 °C, 89%; (bb) $Pd(PPh_3)_4$, $TMSCH_2MgCl$, Et_2O, 91%; (cc) NCS, MeOH, 88%; (dd) 2-methoxypropene, PPTS, CH_2Cl_2, 89%. (ee) LDA, MoOPH, THF, −23 °C, 80%. (ff) Ac_2O, DMAP, CH_2Cl_2, 92%. (gg) DBN, toluene, reflux, 68% at 92% conversion. (hh) OsO_4, pyr, Et_2O, 86%. (ii) DBU, toluene, reflux, 86%. (jj) PPTS, MeOH. (kk) TESCl, imidazole, DMF, 97% in 2 steps. (ll) $Pd(OH)_2$, H_2, EtOH, 97%. (mm) triphosgene, pyr, CH_2Cl_2, −78−0 °C, 94%. (nn) Ac_2O, DMAP, CH_2Cl_2, 66%. (oo) PhLi, THF, −78 °C, 83%. (pp) HF·pyr, THF, 88%. (qq) trocCl, pyr, CH_2Cl_2, 94%. (rr) TASF, THF, 80%. (ss) LHMDS, **18**, THF, −78−0 °C, 77% at 90% conversion. (tt) Zn, AcOH-H_2O, 84%.

of the resulting enol **9** induced the isomerization to give an almost 1:1 equilibrium mixture of **9** and **10**. Finally, the C3α-protonated ketone **10** was obtained in 65% yield by repeating this enol/keto isomerization procedure twice.

With the crucial synthetic intermediate **10** in hand, the C7,-C9-diol of **10** was initially protected as a boronate, and then the C13-OH was silylated with TBSOTf. After removal of the boron protecting group, selective oxidation of the C9-OH was achieved by Dess−Martin oxidation[11] and the remaining C7-OH was protected as a 2-methoxy-2-propyl ether (MOP),[13] giving **11**. Our next task was to introduce an exomethylene moiety on the C4 site. For such purpose, we explored an original methodology which may also serve as an introduction of the C5 functionality to construct the D-ring at a later stage. Regioselective generation of the $\Delta^{4,5}$-enolate by treating with KHMDS and quenching with $PhNTf_2$ gave the enol triflate in good yield. Cross-coupling reaction with $TMSCH_2MgCl$ in the presence of $Pd(Ph_3P)_4$ gave the corresponding allylsilane **12**, and chlorination of **12** with NCS in MeOH gave the corresponding C5α-chloride **13** in good yield.

For construction of the D-ring, introduction of a diol moiety on the $\Delta^{4,20}$-double bond of **13** was examined.[2] However, OsO_4 oxidation unexpectedly took place at the $\Delta^{11,12}$-double bond on the A-ring, yielding the C11,12-diol exclusively. At this stage, we decided to functionalize the C10 site to render the environment around the $\Delta^{11,12}$-double bond much more crowded. Functionalization of the C10 site was performed by generation of a $\Delta^{9,10}$-enolate with LDA followed by oxidation with MoO_5·pyr·HMPA (MoOPH),[14] giving the C10α-alcohol exclusively. Although the stereochemical result was the opposite, inversion of the C10α-oxygen functionality to the thermodynamically more favored C10β configuration was achieved as follows. Acetylation of the C10-hydroxy group (Ac_2O/DMAP) followed by treatment with DBN afforded the desired C10β-acetate **14** in good yield.

On applying OsO_4 oxidation to **14**, dihydroxylation took place selectively on the $\Delta^{4,20}$-site to afford the desired diol in good yield. By heating with DBU in toluene, oxetane formation[2a] proceeded to give the tetracyclic intermediate. Then, we examined acetylation of the C4α-OH, but the reaction did not take place under the usual conditions. Considering that the phenyl group might prevent the C4α-OH from undergoing acetylation, replacement of the benzylidene group with a carbonate group was examined. Since the MOP group on C7-OH was also eliminated under the conditions to remove the benzylidene group, it was initially replaced by a TES group and then the 1,2-diol protecting group was converted from the benzylidene to the carbonate. Acetylation of the C4α-OH took place smoothly, and then the carbonate group was converted to the C2-benzoyl group[2] to afford **16**. The TES group on C7-OH was replaced by a Troc group, and the TBS group was removed by treatment with TASF.[2a,15] Finally, attachment of the side chain using the β-lactam **18**[2a,16] followed by removal of the protecting groups gave (−)-taxol.

In conclusion, we have achieved an enantioselective total synthesis of taxol. The synthetic route is highlighted by (1) originally developed B-ring cyclization, (2) introduction of the C19-methyl via reductive cleavage of the cyclopropyl ketone, and (3) isomerization of the resulting enol to the ketone.

Acknowledgment. This work was financially supported by Grant-in-Aids from the Ministry of Education, Science, Sports, and Culture of the Japanese Government.

Supporting Information Available: Spectroscopic data and experimental procedures for the reported compounds and the fully detailed synthetic scheme (35 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA9824932

(13) We initially chose a TES group as a protecting group on the C7-OH. However, in the case of the introduction of a C10 functionality, migration of the TES group to a $\Delta^{9,10}$-enolate oxygen occurred to give an enol silyl ether.

(14) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

(15) Removal of the two silyl groups on **16** with TASF caused partial epimerization at the C7 stereocenter.

(16) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985.