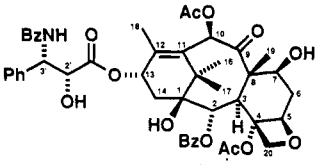
Synthesis of Novel Taxoids

K. C. Nicolaou,* Christopher F. Claiborne, Philippe G. Nantermet, Elias A. Couladouros, and Erik J. Sorensen

Department of Chemistry, The Scripps Research Institute 10666 North Torrey Pines Road, La Jolla, California 92037 Department of Chemistry, University of California San Diego, 9500 Gilman Drive, La Jolla, California 92093

Received November 30, 1993

Taxol (**1**), a naturally occurring substance isolated from the Pacific yew tree (*Taxus brevifolia*),[1] has recently been approved for clinical treatment of cancer patients. Its chemical synthesis and the synthesis of taxoid model systems have been the focus of extensive research efforts.[2] Recent publications[2-5] from these

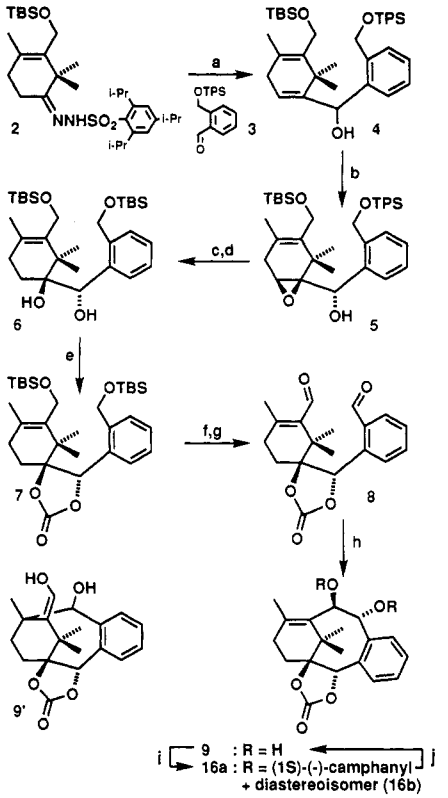


1: Taxol

laboratories disclosed a convergent approach to the taxoid family of compounds in which a Shapiro-type coupling[5] is used as a means of joining rings A and C.[6] In this communication we describe the application of this strategy to the synthesis of advanced taxoid systems containing the intact AB ring framework of taxol, including the side chain, and in which the CD ring system is replaced with an aromatic moiety.

According to this strategy, compound **9** (Scheme 1) was targeted as the initial key precursor to the designed molecules. Its construction is outlined in Scheme 1. Hydrazone **2** was coupled with aldehyde **3** as previously described with similar systems[5] leading to racemic **4** in 86% yield. Directed epoxidation of **4** using the Sharpless protocol[7] gave hydroxy epoxide **5** in 90% yield. Regioselective opening of the oxirane ring in **5** using $LiAlH_4$ was accompanied by desilylation, leading to the corresponding tetraol, which was selectively silylated with *tert*-butyldimethylsilyl chloride, furnishing diol **6** in 75% overall yield. The molecular framework of the intermediates was then rigidified in preparation for the ring closure by carbonate formation through exposure to carbonyldiimidazole (95%) affording compound **7**, which was then desilylated and oxidized[8] to give dialdehyde **8** (89% overall yield). McMurry coupling[9] of the aldehyde groups in **8** produced compound **9** in 53% yield, together with a mixture of three other isomeric diols of gross structure **9** (*ca.* 20% total yield) and product **9'**, resulting from a 1,4-participation of the enone functionality in **8** (15% yield). The major isomer **9**, mp 251 °C dec (methylene chloride–hexane), was subjected to X-ray crystallographic analysis, revealing the indicated stereochemistry (see ORTEP drawing, Figure 1).[10]

Scheme 1. Synthesis of Key Intermediate **9**[a]



[a] Reagents and conditions: (a) **2** (1 equiv), *n*-BuLi (2.1 equiv), THF, −78 → 25 °C; cool to 0 °C and add **3** (1.1 equiv), 30 min, 86%; (b) *t*-BuOOH (1.5 equiv), $VO(acac)_2$ (0.05 equiv), benzene, 25 °C, 5 h, 90%; (c) $LiAlH_4$ (5 equiv), Et_2O, reflux, 4 h, 75%; (d) TBS-Cl (2.1 equiv), imidazole (2.5 equiv), CH_2Cl_2, 25 °C, 1 h, 100%; (e) carbonyldiimidazole (10 equiv), acetonitrile, reflux, 2 h, 95%; (f) TBAF (4 equiv), THF, 25 °C, 2 h, 100%; (g) TPAP (0.05 equiv), NMO (5 equiv), CH_2Cl_2, 25 °C, 89%; (h) $TiCl_3(DME)_{1.5}$ (20 equiv), Zn–Cu (40 equiv), DME, reflux, 3 h, then add **8** at 55 °C via syringe pump, 1-h addition, then heat for additional 2 h, 53% of **9**, plus 20% total of two unassigned stereoisomers, plus 15% of **9'**; (i) (1*S*)-(−)-camphanic chloride (6 equiv), Et_3N (10 equiv), DMAP (0.05 equiv), CH_2Cl_2, 25 °C, 2 h, 100% (1:1, **16a**:**16b**); (j) K_2CO_3 (0.05 equiv), MeOH, 25 °C, 2 h, 100% (enantiomerically pure **9**).

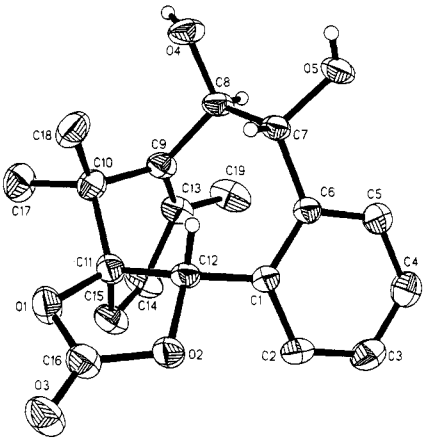


Figure 1. ORTEP drawing of **9**.

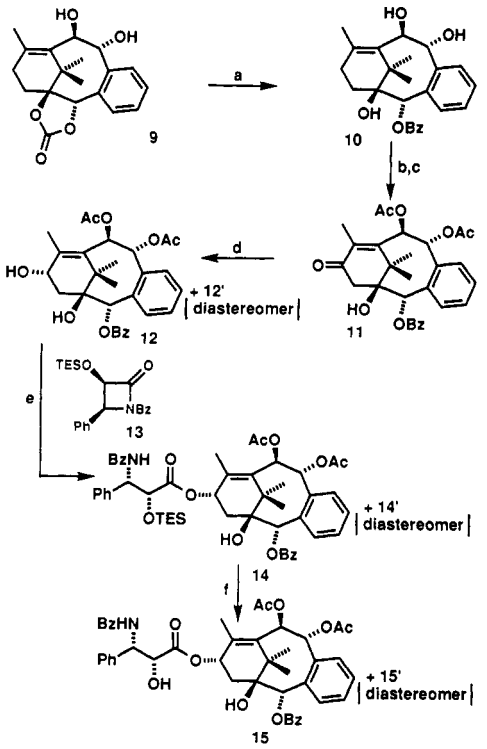
Carbonate **9** reacted with excess PhLi at low temperature to form, in a remarkably clean and regioselective fashion, the

(1) Wani, M. C.; Taylor, M. E.; Coggan, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.
(2) For a review, see: Nicolaou, K. C.; Guy, R. K.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15 and references cited therein.
(3) Nicolaou, K. C.; Hwang, C.-K.; Sorensen, E. J.; Claiborne, C. F. *J. Chem. Soc., Chem. Commun.* **1993**, 1017.
(4) Nicolaou, K. C.; Liu, J.-J.; Hwang, C.-K.; Dai, W.-M.; Guy, R. K. *J. Chem. Soc., Chem. Commun.* **1993**, 1118.
(5) Nicolaou, K. C.; Yang, Z.; Sorensen, E. J.; Nakada, N. *J. Chem. Soc., Chem. Commun.* **1993**, 1024.
(6) This strategy was later used by others to accomplish similar couplings: Di Grandi, M. J.; Jung, D. K.; Krol, W. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 4989. Maskers, J. J.; Jung, D. K.; Bornmann, W. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1993**, *34*, 7253.
(7) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.
(8) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.
(9) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. McMurry, J. E.; Rico, J. G.; Leckta, T. C. *J. Org. Chem.* **1989**, *54*, 3748. McMurry, J. E.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 1169. See also: Kende, A. S.; Johnson, S.; San Filippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513.

(10) This X-ray crystallographic analysis was carried out by Dr. Raj Chadha of The Scripps Research Institute.

0002-7863/94/1516-1591$04.50/0

Scheme 2. Synthesis of Taxoid **15** and Its Diastereomer **15'**[a]



[a] Reagents and conditions: (a) PhLi (10 equiv), THF, −78 °C, 30 min, 80%; (b) Ac_2O (2.5 equiv), Et_3N (2.8 equiv), DMAP (0.05 equiv), CH_2Cl_2, 25 °C, 1 h, 100%; (c) PCC (30 equiv), Celite, NaOAc (20 equiv), benzene, reflux, 2 h, 55%; (d) $NaBH_4$ (20 equiv), MeOH, 0 °C, 20 min, 90% (8:1 mixture α to β isomers); (e) **12** (1 equiv), **13** (2.0 equiv), $NaN(SiMe_3)_2$ (3 equiv), THF, −78 °C, 30 min, 33% of **14**, plus 33% of **14'**, plus 10% recovered starting material (73% combined yield based on 90% conversion); (f) HF·pyr (2.0 equiv), THF, 25 °C, 2 h, 90%.

secondary benzoate **10** in 80% yield (Scheme 2) (see Note Added in Proof). The later compound was selectively and quantitatively acetylated by exposure to Ac_2O–Et_3N, furnishing the corresponding diacetate, which was then oxidized with PCC–NaOAc–Celite to enone **11** (55% yield). Reduction of enone **11** with $NaBH_4$ in methanol resulted in the formation of two isomeric alcohols in *ca.* 8:1 ratio and 90% total yield. The two isomers were separated chromatographically (silica, benzene: EtOAc mixtures) leading to pure isomers **12** and **12'** (**12**, major, R_f = 0.4; **12'**, minor, R_f = 0.35). The major compound (**12**) was assigned the indicated α-stereochemistry on the basis of NMR spectroscopic data.[11] Finally, attachment of the taxol side chain onto the α-isomer **12** was accomplished using the Holton–Ojima method.[12,13] Thus, reaction of **12** with β-lactam **13**[13] at −78 °C in the presence of $NaN(SiMe_3)_2$ resulted in the formation of two diastereoisomers **14** (R_f = 0.45, silica, 80% ether in petroleum ether; $[\alpha]_D^{22}$ = 26.67°, *c* 1.5, $CHCl_3$) and **14'** (R_f = 0.32, silica, 80% ether in petroleum ether; $[\alpha]_D^{22}$ = −24.43°, *c* 1.4, $CHCl_3$) in a combined yield of 73% (*ca.* 1:1 ratio) at *ca.* 90% conversion. Chromatographic separation of the two diastereoisomers, followed by desilylation, resulted in the formation of taxoid **15** (R_f = 0.43, silica, ether; $[\alpha]_D^{22}$ = 52.33°, *c* 0.3, $CHCl_3$) and its diastereoisomer **15'** (R_f = 0.32, silica, ether; $[\alpha]_D^{22}$ = −16.00°, *c* 0.5, $CHCl_3$) in 90% yield. In order to secure stereochemical assignments, diol **9** was resolved through its diastereomeric dicamphanyl esters[14] **16a** and **16b**, which were separated chromatographically (**16a**, R_f = 0.58, silica, 15% EtOAc in benzene; **16b**, R_f = 0.50, silica, 15% EtOAc in benzene). The less polar isomer (**16a**) was hydrolyzed under basic conditions to afford optically active diol **9** ($[\alpha]_D^{22}$ = 92.00°, *c* 0.4, $CHCl_3$), whose X-ray crystallographic analysis (see ORTEP drawing, Figure 1) confirmed its absolute stereochemistry. This diol was then taken through the described sequence to enantiomerically pure **14**.

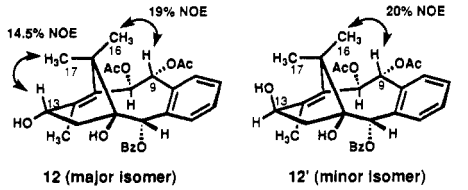
Interestingly, compound **15** exhibited significant cytotoxicity against a variety of tumor cell lines,[15] whereas its diastereoisomer (**15'**) showed essentially no cytotoxicity under the same conditions. These results define further structural parameters for the design of bioactive taxoids and provide a synthetic entry to such compounds.[16]

Note Added in Proof: For a total synthesis of taxol from these laboratories, see: Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulyannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630. For the use of PhLi to form the C-2 benzoate of taxol, see: Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K. *J. Chem. Soc., Chem. Commun.* **1994**, 295.

Acknowledgment. We thank Professor Ojima for useful discussions relating to taxol side chain attachment, Dr. Raj Chadha for the X-ray crystallographic analysis, and Dr. Wolfgang Wrasidlo for the cytotoxicity data. C.F.C. thanks Mr. Richard Staley for a generous graduate student fellowship (1992–1993) and Glaxo for a graduate student fellowship (1993–1994), P.G.N. thanks Rhone-Poulenc Rorer for a postdoctoral fellowship (1993), and E.J.S. thanks the Organic Division of the American Chemical Society for a graduate student fellowship (1992–1993). This work was supported by The Scripps Research Institute.

Supplementary Material Available: Schemes for synthesis of compounds **2** and **3** and listings of selected physical data for compounds **4**, **5**, **8–10**, **12**, **14**, **14'**, **15**, and **15'** (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) The indicated assignments were made on the basis of the following observations. **12** (major isomer): Irradiation at δ 1.09 (16-CH_3) resulted in 20% NOE enhancement at δ 5.81 (9-H), suggesting that **12** adopts a conformation wherein the 16-CH_3 and the 9-H are in close proximity as shown in the illustration. Irradiation at δ 1.03 (17-CH_3) resulted in 14.5% NOE enhancement at δ 4.33 (13-H), suggesting a β orientation for 13-H as indicated. **12'** (minor isomer): Irradiation at δ 1.0 (16-CH_3) resulted in 19% NOE enhancement at δ 5.73 (9-H), supporting the conformation shown. Irradiation at δ 1.25 (17-CH_3) resulted in no NOE with 13-H as expected for **12'**.



(12) Holton, R. A. Eur. Pat. Appl. EP 400,971, 1990; *Chem. Abstr.* **1990**, *114*, 164568q.

(13) Ojima, I.; Sun, C. M.; Zucco, M.; Park, Y. H.; Duclos, O.; Kuduk, S. *Tetrahedron Lett.* **1993**, *34*, 4149. Ojima, I.; Habus, I.; Zucco, M.; Park, Y. M.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985. We thank Professor Ojima for a generous gift of β-lactam **13**.

(14) Gerlach, H. *Helv. Chim. Acta* **1978**, *61*, 2773.

(15) Cell line (IC_{50} M value): HT-29 (1.29×10^{-7}); Ovcar 3 (2.80×10^{-7}); UCLA-P3 (2.96×10^{-7}); A-549 (6.45×10^{-7}); L-1210 (1.11×10^{-6}); SIH-A (1.29×10^{-6}); 786-0 (1.93×10^{-6}); SK-Mel-28 (2.71×10^{-6}); SK-NH-SH (4.91×10^{-6}); BT-549 (5.30×10^{-6}). The corresponding values for taxol are as follows: HT-29 ($5,1 \times 10^{-8}$); Ovcar 3 (6.2×10^{-10}); UCPLA-P3 (6.4×10^{-9}); A-549 (1×10^{-12}); L-1210 (7.0×10^{-9}); SIH-A (1×10^{-12}); 786-0 (2.2×10^{-6}); SK-Mel-28 (1.2×10^{-7}); SK-NH-SH (6.2×10^{-10}); BT-549 (5.0×10^{-10}).

(16) All new compounds exhibited satisfactory spectral and mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.