A Straightforward Approach to the Synthesis of the Tricyclic Core of Taxol

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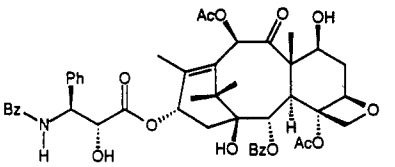
Summary: The tricyclic skeleton of taxol has been synthesized. The most challenging eight-membered ring was constructed through an intramolecular nucleophilic allylic bromide–aldehyde addition reaction promoted by Zn–Cu couple.

The promising anticancer activity[1] of the diterpenoid taxol[2] (1; Scheme I) combined with its structural complexity and limited availability have engendered worldwide intensive studies toward its total synthesis.[3-5] The synthetic studies may play a very important role in the search for taxol analogs or second-round drug candidates. We describe here a novel synthetic approach to the tricyclic framework 2 of taxol.

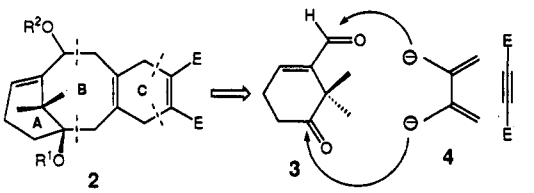
According to our synthetic strategy (Scheme I), the eight-membered ring is envisioned to be assembled by either a one-step annulation reaction or sequential addition and ring-closure reactions of keto aldehyde 3 with a dianionic 2,3-dimethylenebutadiene species 4. The product obtained by this type of ring closure conserves the feature of an exocyclic cis fixed 1,3-diene and may thus be further used in a subsequent Diels–Alder reaction to form the C-ring system of taxol.

The synthesis began with the preparation of the keto aldehyde 3 (Scheme II). Heating the readily available mono-protected 1,3-diketone 5[6] with *p*-toluenesulfonohydrazide in ethanol resulted in the formation of hydrazone 6 in quantitative yield. Treatment of 6 with 4 equiv of *n*-butyllithium, followed by trapping of the resulting alkenyllithium intermediate with excess *N,N*-dimethylformamide, provided α,β-unsaturated aldehyde 7 in excellent yield.[7] Acidic hydrolysis of 7 furnished the corresponding keto aldehyde 3.

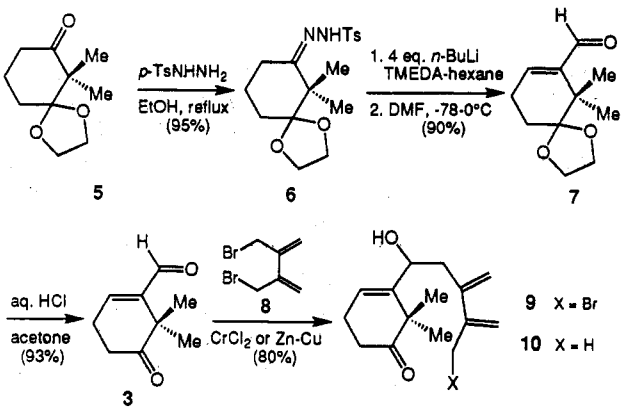
Scheme I



Taxol (1)



Scheme II



Having completed the synthesis of 3, we first explored the possibility of direct annulation of 3 with the dianionic species 4 generated in situ from dibromide 8[8] upon treatment with excess reducing metal or low-valent metal halides.[9] Unfortunately, the only observed products are the monoaddition compound 9 and its debrominated form 10 under the conditions we employed, such as Zn–Cu couple,[10] $CrCl_2$,[11] or SmI_2.[12] These results might be due to the steric hindrance surrounding the keto group of 3 or

(1) For a review of the biology of taxol, see: Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247.

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

(3) For a review on synthetic approaches to taxol and related compounds, see: Swindell, C. S. *Org. Prep. Proc. Intl.* **1991**, *23*, 465.

(4) For chemistry of taxol and its structure–activity relationships, see: Kingston, D. G. I. *Pharmac. Ther.* **1991**, *52*, 1.

(5) (a) For recent synthetic studies toward taxol, see: Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878. (b) Magee, T. V.; Bornmann, W. G.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 3274. (c) Queneau, Y.; Krol, W. J.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 4043. (d) Blechert, S.; Muller, R.; Beitzel, M. *Tetrahedron* **1992**, *34*, 6953. (e) Wahl, A.; Gueritte-Veogelein, F.; Guenard, D.; Le Goff, M.-T.; Potier, P. *Tetrahedron* **1992**, *34*, 6965. (f) Furukawa, T.; Morihira, I.; Zhoa, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *34*, 6985. (g) Jackson, R. W.; Higby, R. G.; Gilman, J. W.; Shea, K. J. *Tetrahedron* **1992**, *34*, 7013. (h) Wender, P. A.; Rawlins, D. B. *Tetrahedron* **1992**, *34*, 7033. (i) Winkler, J. D.; Subrahmanyam, D. *Tetrahedron* **1992**, *34*, 7049. (j) Nicolaou, K. C.; Hwang, C.-K., Sorensen, E. J.; Clairborne, C. F. *J. Chem. Soc., Chem. Commun.* **1992**, 1117. (k) Nicolaou, K. C.; Liu, J. J.; Hwang, C.-K.; Dai, W.-M.; Guy, R. K. *J. Chem. Soc., Chem. Commun.* **1992**, 1120. (l) Elmore, S. W.; Combrink, K. D.; Paquette, L. A. *Tetrahedron Lett.* **1991**, *32*, 6679.

(6) (a) Stetter, H.; Sandhagen, H.-J. *Chem. Ber.* **1967**, *100*, 2837. (b) Mori, K.; Mori, H. *Org. Synth.* **1989**, *68*, 56.

(7) (a) Shapiro, R. H.; Hornamoan, E. C. *J. Org. Chem.* **1974**, *39*, 2302. (b) Stemke, J. E.; Chamberlin, A. R.; Bond, F. T. *Tetrahedron Lett.* **1976**, 2947. (c) Traas, P. C.; Boelens, H.; Takken, H. J. *Tetrahedron Lett.* **1976**, 2287.

(8) Gaoni, Y.; Shoshana, S. *J. Org. Chem.* **1980**, *45*, 870.

(9) This type of dianions has been generated from the corresponding 1,3-dienes by direct metalation: Bahl, J. J.; Bates, R. B.; Gordon, B., III. *J. Org. Chem.* **1979**, *44*, 2290.

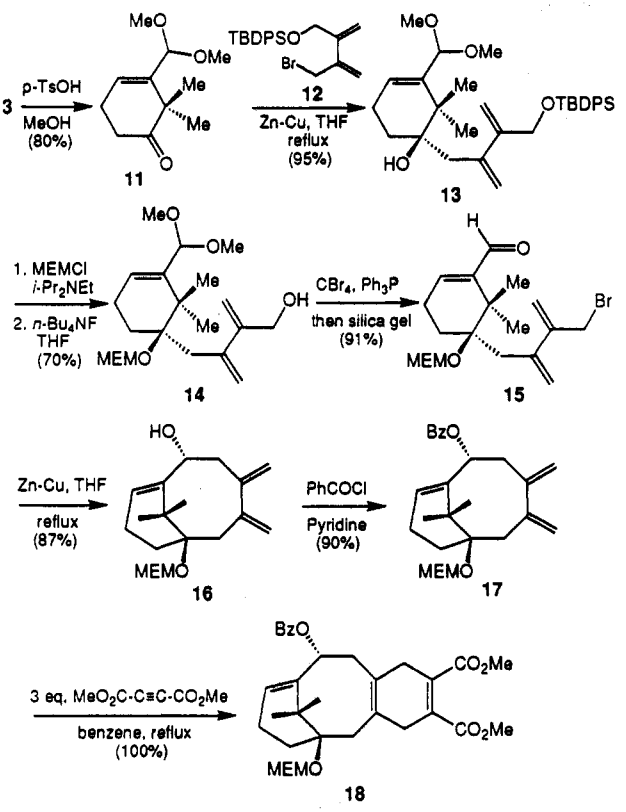
(10) Lambert, J. B.; Koeng, F. R.; Hamersma, J. W. *J. Org. Chem.* **1971**, *36*, 2941.

(11) For recent examples of $CrCl_2$-promoted macrocyclization, see: Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 3926.

(12) For a review on application of lanthanide reagents in organic synthesis see: Molander, G. A. *Chem. Rew.* **1992**, *92*, 29.

0022-3263/93/1958-2931$04.00/0

Scheme III



the unfavored conformation of the initial adduct **9** for further ring closure.

To overcome this problem, we decided to reverse the order of bond formation. It was reasoned that the only feasible way for the ring closure is through an intramolecular cycloaddition onto the aldehyde group after bond formation at the keto group of **3**. Thus, the aldehyde group of **3** was selectively protected as a dimethyl acetal group to give **11** (Scheme III). Treatment of **11** with **12**[13] and freshly prepared Zn–Cu couple in THF under refluxing conditions afforded tertiary alcohol **13** in 95% yield. The tertiary alcohol of **13** was protected as the MEM ether, and subsequent desilylation provided allylic alcohol **14**. Bromination of **14**, followed by silica gel chromatography, gave rise to **15** in a single step. After several unsuccessful attempts to promote the ring closure of **15** under a variety of conditions with $CrCl_2$ or SmI_2, we were delighted to find that, upon treatment with Zn–Cu couple in refluxing THF, **15** smoothly cyclized to provide the bicyclo[5.3.1] ring system **16** as a single stereoisomer in 87% yield. This represents one of the few examples of macrocyclization mediated by a zinc species.[14] Apparently, the unusually high reactivity of the allylzinc intermediate prevailed over the steric hindrance and the unfavored entropy involved in the eight-membered ring closure. The stereochemistry of **16** was determined by NOE experiments and subsequent X-ray crystallographic analysis of its benzoate derivative **17**.[15] Finally, the feasibility of constructing the C ring was demonstrated by a Diels–Alder reaction employing the diene unit of **17**. Heating **17** with dimethyl acetylenedicarboxylate resulted in the formation of the tricyclic skeleton **18** of taxol in quantitative yield. In analogy to the observations of others,[5a,16] tricycle **18** appears in the 300-MHz NMR spectrum at 25 °C as a 3:2 mixture of two slowly interconverting conformational isomers. Fast exchange on the ^1H NMR time scale at 300 MHz is achieved at 105 °C for the material dissolved in toluene-d_8.

In summary, a new strategy has been describerd for the synthesis of tricyclic skeleton of taxol. The high-yielding direct formation of the eight-membered ring is specially noteworthy. Progress directed toward the total synthesis of taxol and potentially useful analogs will be reported in due course.

Acknowledgment. We thank Ms. C. Li for mass spectra.

Supplementary Material Available: Experimental procedures and spectral data for compounds **3**, **11**, and **13–18** (23 pages). This material is contained in 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.

(13) Hamon, D. P. G.; Spurr, P. R. *Synthesis* **1981**, 873.

(14) For macrocyclization by intramolecular Reformatsky-type reactions, see: (a) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, Y.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705. (b) Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889.

(15) The author has deposited atomic coordinates for **17** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(16) Shea, K. J.; Gilman, J. W.; Haffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 4953.