# *Communications*

## Synthesis of Cyclopropyl Taxane Analogs via Sequential Diels−Alder Reactions

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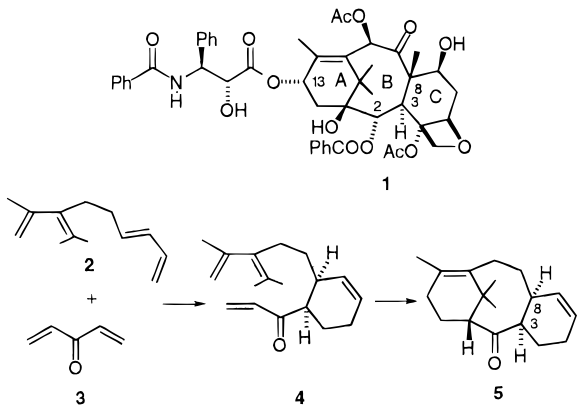
The tandem Diels−Alder cycloaddition is a valuable method for the construction of linearly fused tricyclic ring systems[1] as well as the tricyclic framework of taxol, **1** (Scheme 1). We have recently demonstrated that cycloaddition of bis-diene **2** and bis-dienophile **3** leads to the formation of **5**, via **4**, in excellent yield.[2] While the synthesis of the taxane ring system in two chemical steps from simple acyclic precursors underscores the utility of this methodology in organic synthesis, this construction does not address several critical issues in taxane synthesis, including the establishment of the angularly methylated *trans*-B/C ring fusion of the taxane ring system.

While our previously reported approach to the synthesis of taxanes couples bis-diene **2** with bis-diene **3**, a "homo" tandem cycloaddition, we have now examined the complementary coupling in which two diene−dienophile hybrids are combined, i.e., **9** and **10** (Scheme 2), a "hetero" tandem cycloaddition.[3] We report herein that this strategy leads to the stereoselective synthesis of the *trans*-B/C 7,8-methanotaxane ring system, a noteworthy result in light of the recent disclosure by groups at both Upjohn[4] and Bristol-Myers Squibb[5] that 7,8-methanotaxol is equipotent with taxol in cytotoxic and tubulin binding/polymerization assays.

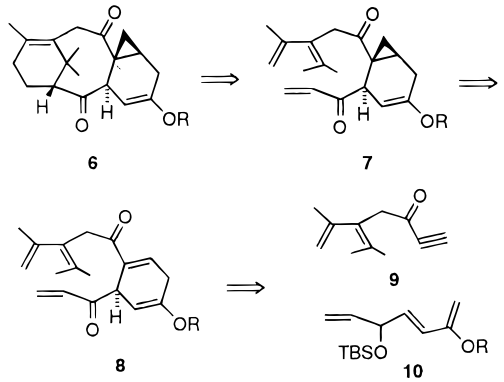
As outlined in the retrosynthetic analysis in Scheme 2, the tetracyclic cyclopropyl taxane ring system could be derived via intramolecular cycloaddition of **7**, which could in turn be prepared by diastereoselective cyclopropanation of **8**. The intermediacy of the dihydrobenzene **8**, which should result from the intermolecular cycloaddition of **9** and **10**, precludes the establishment of the undesired cis C-3/C-8 stereochemistry in the endo-selective intermolecular cycloaddition (as shown in **5**, Scheme 1).

The preparation of the acetylenic dienophile **9** was achieved on the basis of work of Shea[6] as outlined in Scheme 3. Addition of ethynyl Grignard to **11**[7] led to the formation of **12**, which on Jones oxidation gave **9**. The

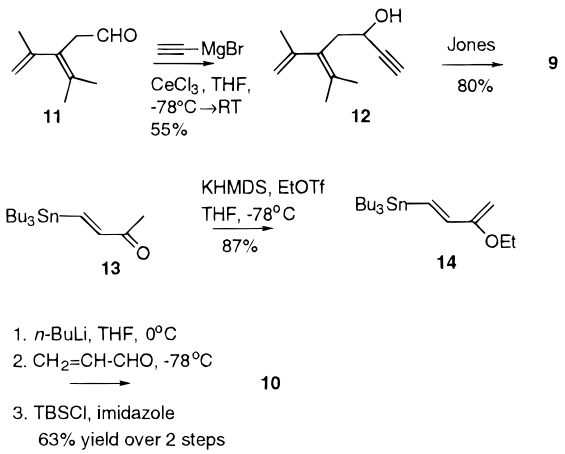
**Scheme 1**




**Scheme 2**




**Scheme 3**




oxy diene moiety **10** was prepared from **13**[8] by O-alkylation to give **14**, which, on reaction with *n*-BuLi, acrolein, and silylation of the pro-C-2 alcohol, gave the silyl ether **10**.

Cycloaddition of **9** and **10** under high-pressure conditions (10 kbar, 48 h, dichloromethane) led to the formation of **15** in 55% yield as a 2.9:1 ratio of diastereomers, as shown in Scheme 4. On the basis of the work of

(1) Winkler, J. D.; Kim, S.; Condroski, K. R.; Asensio, A.; Houk, K. N. *J. Org. Chem.* **1994,** *59,* 6879.
(2) Winkler, J. D.; Kim, H. S.; Kim, S. *Tetrahedron Lett.* **1995**, *36*, 687.
(3) The sequence outlined in Scheme 2 formally involves sequential and not tandem cycloadditions, as the cyclopropanation and unleashing of the second dienophile intercede between the two cycloadditions.
(4) Johnson, R. A.; Nidy, E. G.; Dobrowolski, P. J.; Gebhard, I.; Qualls, S. J.; Wicnienski, N. A.; Kelly, R. C. *Tetrahedron Lett.* **1994**, *35*, 7893.
(5) Chen, S.; Huang, S.; Wei, J.; Farina, V. *J. Org. Chem.* **1993**, *58*, 4520.
(6) Shea, K. J.; Haffner, C. D. *Tetrahedron Lett.* **1988**, *29*, 1367.
(7) Tjepkema, M. W.; Wilson, P. D.; Wong, T.; Romero, M. A.; Audrain, H.; Fallis, A. G. *Tetrahedron Lett.* **1995**, *36*, 6039.
(8) Compound **13** was obtained by hydrostannylation of 3-butyn-2-ol, based on the work of Zhang et al. (Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857), followed by oxidation using PDC.

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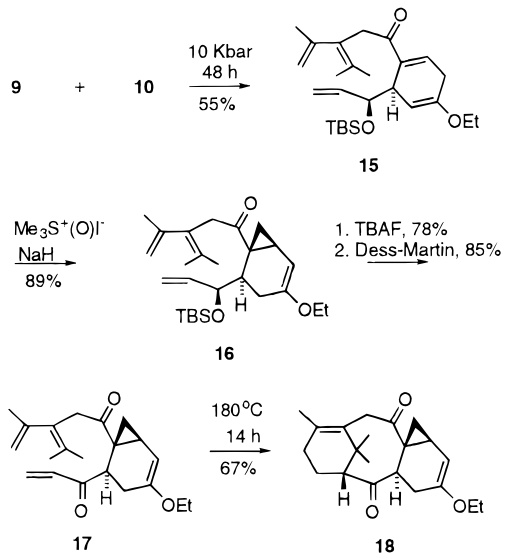
**Scheme 4**




Franck[9] and Trost,[10] the stereochemistry of the major diastereomer is assigned as shown in **15**, due to allylic strain considerations in the cycloaddition. We were delighted to find that exposure of **15** to dimethylsulfoxonium methylide[11] gave an 89% yield of a single cyclopropane, **16**, resulting from migration of the $\Delta^{4,5}$ alkene of **15** to the conjugated dienone, followed by addition of sulfoxonium methylide from the $\beta$-face of the derived enone. The stereochemistry of the addition can be explained by axial addition of the ylide to the dienone, in which the C-3 substituent occupies a pseudoaxial orientation due to allylic strain.

Desilylation and oxidation of **16** provided the intramolecular Diels–Alder cycloaddition substrate **17**, which on heating to 180 °C in toluene for 13 h gave a 67% yield of **18**, the structure and stereochemistry of which were established by X-ray crystallographic analysis. In analogy to the work of Jenkins[12] and Danishefsky,[13] we observe the efficient communication of stereochemical information from the C-3/C-8 stereochemistry of **17** to the newly formed C-1 stereocenter in **18**.

We have demonstrated that this sequential strategy can be used for the rapid and efficient stereoselective construction of the taxane ring system with the requisite *trans*-B/C ring fusion, in which the longest linear sequence to **18** is 11 steps.[14] Further studies on the application of this methodology to the synthesis of more highly functionalized taxane congeners are currently underway, and our results will be reported in due course.

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**Supporting Information Available:** Experimental procedures and compound characterization data (8 pages).

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(9) Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257.
(10) Trost, B. M.; Lee, D. C. *J. Org. Chem.* **1989**, *54*, 2271.
(11) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(12) Bonnert, R. V.; Jenkins, P. R. *J. Chem. Soc., Perkin Trans. 1* **1989,** 413.
(13) Park, T. K.; Kim, I. J.; Danishefsky, S. J.; de Gala, S. *Tetrahedron Lett.* **1995**, *36*, 1019.
(14) **Note Added in Proof**: Wender and co-workers have recently reported the synthesis of cyclopropyl taxanes, albeit without establishment of the *trans*-B/C ring fusion. We congratulate Professor Wender on his elegant study (Wender, P. A.; Glass, T. E.; Krauss, N. E.; Muhlebach, M.; Peschke, B.; Rawlins, D. *J. Org. Chem.* **1996**, *61*, 7662–7663.