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Construction of A and C Ring Intermediates for Taxol by Using (3+2)-Cycloaddition of Nitrile Oxide

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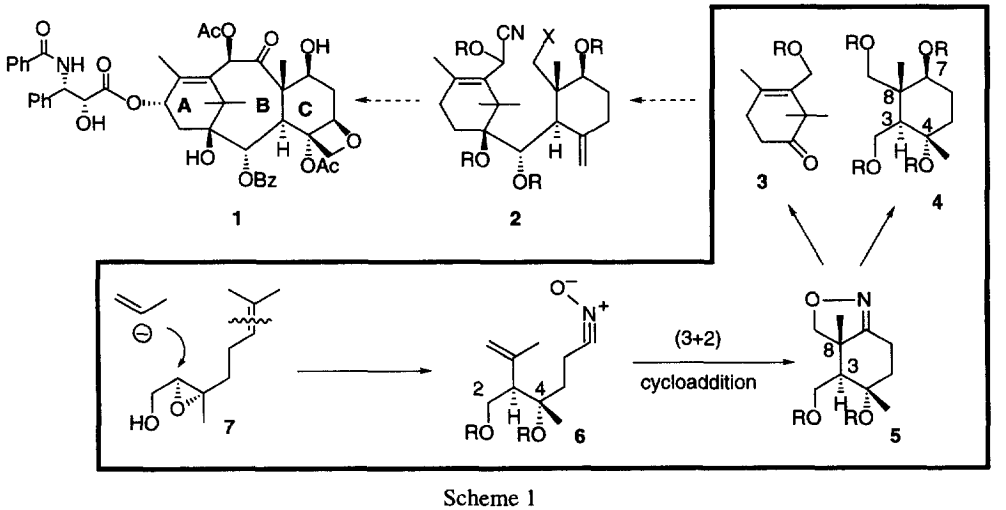
Abstract: Syntheses of the A-ring and the chiral C-ring model of taxol by using the intramolecular nitrile oxide cycloaddition and its diastereoselectivity based on MM2 transition state model are described. © 1997 Elsevier Science Ltd.

The unique diterpenoid taxol (**1**), isolated from the western yew *Taxus brevifolia,*[1] has potent anticancer and antileukemic properties, showing very promising activity in clinical trials, particularly against ovarian cancer and breast cancer.[2] Moreover, taxol can bind to a polymerized tubulin and can stabilize it to disassembly.[3] These properties have stimulated significant efforts toward syntheses of taxol and its various analogues.[4] Recently, four groups in the U.S.A. (Holton,[5] Nicolaou,[6] Danishfesky[7] and Wender[8]) have accomplished the total synthesis of taxol. In our synthetic plan for **1** (Scheme 1), the eight-membered B-ring is constructed by an intramolecular alkylation of the protected cyanohydrin **2**, derived from the A-ring **3** and the C-ring **4**. In this communication, we report the results of our initial efforts towards a total synthesis of **1**, the stereoselective syntheses of the A-ring **3** and the chiral C-ring **4** as a synthetic intermediate for taxol.



Scheme 1

In our synthesis, isoxazoline **5** is the key intermediate for both **3** and **4**, and its 6-membered ring including the *trans*-relative stereochemistry between the C(8)-methyl and C(3)-proton is constructed by the (3+2)-cycloaddition[9] of the nitrile oxide **6**. The MM2 transition state models based on *ab-initio* calculations[10] (Fig. 1) suggest that the (3+2)-cycloaddition of **6a** (R=isopropylidene group) should provide the *trans*-relative chemistry (C(8)-Me/C(3)-H), while the reaction of **6b** (R =Me) should give the *cis*-stereochemistry. Thus,

selection of the protecting group of the diol in **6** is essential to lead to the desired *trans*-stereochemistry (C(8)-Me/C(3)-H). The absolute configurations at C(3*R*) and C(4*S*) in **6** are introduced by the epoxide opening of **7**, prepared from geraniol by the Sharpless epoxidation, with isopropenyl magnesium bromide.

Molecular mechanics calculations[11] and MM2 transition state models[12] have proven useful for molecular modelings[13], e.g., stereochemical predictions (or analyses), and designing the synthetic key intermediate. Here, MM2 transition state model calculations (flexible model)[14] for the (3+2)-cycloaddition of acetonide **6a** were performed. In these calculations, was used the MM2* force field on MacroModel (ver. 4.5)[15], including a set of additional parameters reproducing the *ab initio* transition structure of the nitrile oxide cycloaddition of 6-heptenenitrile oxide and 5-hexenenitrile oxide. The Monte Carlo (MC) random-search method[16] was used to find the lower-energy "transition-state structures" of the (3+2)-cycloaddition of **6a**. The structures generated by the MC search were energy minimized by using extended MM2 parameters.[11] Three unique transition-state structures were found within 3.0 kcal/mol of the global minimum for the reaction of **6a**. Figure 1 shows the lowest energy transition state structures **A** and **B** leading to the *trans*-**5a** and the *cis*-**8**, respectively. These calculations and a Boltzmann distribution based on the energy difference among the three transition state structures predict the exclusive formation of **5a**, having the desired C(3*R*) and C(8*S*) configurations with the *trans*-stereochemistry (C(8)-Me/C(3)-H). Similar calculations for the dimethoxy derivative **6b** (five unique transition-state structures were found within 3.0 kcal/mol of the global minimum) predict that the ratio of the *trans*-**5b** and the *cis*-**9** would be 3:97. Thus, the cyclic protecting group of the diol in **6** is a prerequisite to obtain the desired *trans* -stereochemistry (C(8)-Me/C(3)-H).

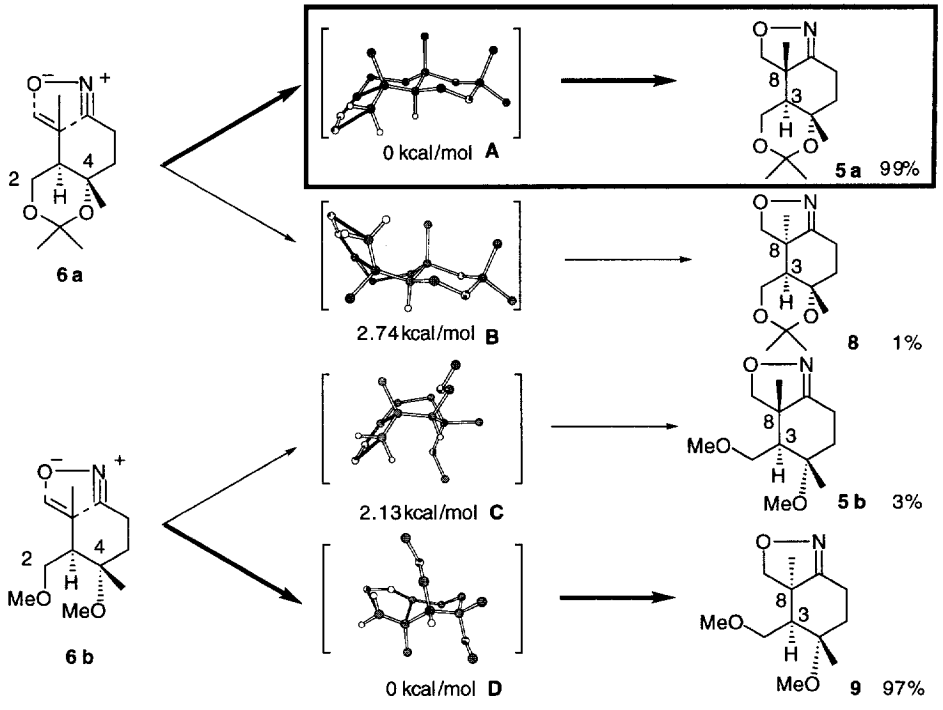
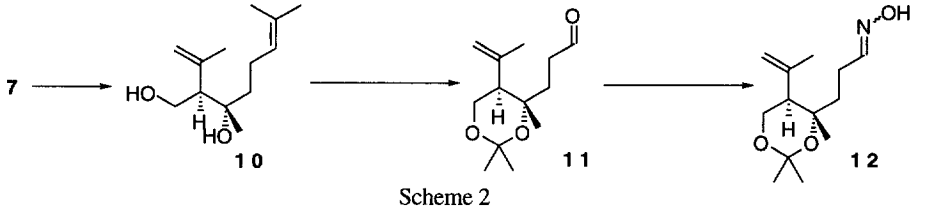


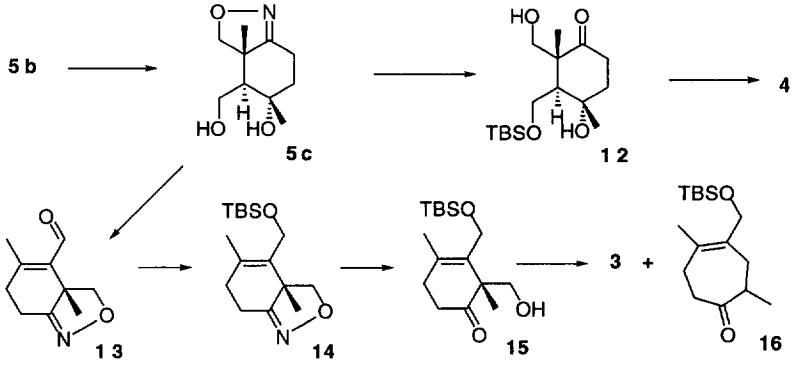
Fig. 1

The oxime **12** was prepared in the following way (Scheme 2). The Sharpless epoxidation of geraniol (t-BuOOH, MS4A, Ti(O^{i}Pr)4, L-(+)-DET at -20°C; 94% yield) and the epoxide opening of **7** ($[\alpha]_D^{25}$ –4.96 (c 3.79, $CHCl_3$)) with isopropenyl magnesium bromide in the presence of CuI at –20 °C gave diol **10** in 97% yield. Protection of the diol in **10** with 2-methoxypropene (86% yield) and the selective oxidation of the tri-substituted olefin to the diol (OsO_4/4-methylmorpholin N-oxide; 83% yield) followed by the oxidative cleavage ($NaIO_4$) of the diol gave aldehyde **11** in 79% yield. Treatment of **11** with hydroxylamine hydrochloride in pyridine gave oxime **12** in 95% yield. The (3+2)-cycloaddition of **12** was carried out by the Kozikowski method[17] (Fig. 1). The oxidation of **12** to the nitrile oxide **6a** with aq. NaOCl followed by spontaneous cycloaddition gave isoxazoline **5a** in 65% yield.[18] None of the *cis*-isomer **8** was detected by HPLC analysis. This high *trans*-stereoselectivity can be explained as follows. The overlapping of the dipole/dipolarophile orbitals (paralled plane approach of dipole and dipolarophile) in the chair-chair like transition state **A** requires less distortion of the forming cyclohexane and dioxane rings than in the chair-boat like transition state **B**.



Scheme 2

Transformation of the isoxazoline **5b** to the C-ring **4** was carried out in the following way (Scheme 3). Hydrolysis of the acetonide in **5b** (1M-HCl/THF at 25 °C) gave diol **5c** in 83% yield. The selective protection of the primary alcohol in **5c** (*tert*-butyldimethylsilyl (TBS) chloride/NEt_3, DMAP) and reductive hydrolysis of the isoxazoline ring with Raney Ni (W-2) in the presence of $B(OH)_3$ under a hydrogen atmosphere in aq MeOH gave the β-hydroxy ketone **12** in 72% overall yield. Reduction of the ketone in **12** with $NaBH_4$ gave the C-ring **4** in 83% yield. The A-ring **3** was then constructed from diol **5c** in the following way. The Swern oxidation of **5c**



Scheme 3

and simultaneous β-elimination of the tertiary alcohol gave the α,β-unsaturated aldehyde **13** in 95% yield. Reduction of the aldehyde in **13** ($LiAlH_4$) and protection of the resulting allylic alcohol (*tert*-butyldimethylsilyl (TBS) chloride/NEt_3, DMAP) gave the isoxazoline **14** in 83% yield. Reductive hydrolysis of the isoxazoline ring under the same reaction conditions as above gave the β-hydroxy ketone **15** in 65% yield. Iodination of the

alcohol in **15** (I_2 / PPh_3 / Im) and removal of the iodide (Bu_3SnH / AIBN at toluene reflux) gave the A-ring **3** in 60% yield and the 7-membered ketone **16** was also formed in 20% yield.

Thus, the chiral C-ring synthon **4** and the A-ring synthon **3** were synthesized from the (3+2)-cycloaddition product **5c**. Moreover, the described MM2 transition state models would be of potential value in designing the synthetic intermediate.

References and Notes

1. Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggen, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325-2327.
2. a) Caldas, C.; McGuire, W. P. III. *Semin. Oncol.* **1993**, *20* (4 Suppl. 3), 50-55. b) Holmes, F. A.; Walters, R. S.; Theriault, R. L.; Forman, A. D.; Newton, L. K.; Raber, M. N.; Buzdar, A. U.; Frye, D. K.; Hortobagyi, G. N. *J. Natl. Cancer Inst.* **1991**, *83*, 1797-1805.
3. Schiff, P. B.; Fant, J.; Horuritz, S. B. *Nature* **1979**, *277*, 665-667.
4. For recent reviews on the synthesis of taxanes, see a) Swindell, C. S. *Org. Prep. Procedures Intl.* **1991**, *23*, 465-543. b) Nicolaou K. C.; Dai, W.-D.; Guy, R. *Angew. Chem., Intl. Ed. Engl.* **1994**, *33*, 15-44.
5. 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*, 1597-1598. and 1599-1600.
6. a) 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*, 630-634. b) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624-633. c) 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*, 634-644. d) 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*, 645-652. e) 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*, 653-659.
7. a) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Intl. Ed. Engl.* **1995**, *34*, 1723-1726. b) 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*, 2843-2859.
8. Wender, P. A. This work was presented at the 20th IUPAC Symposium on THE Chemistry on NATURAL PRODUCTS. September 15-20, 1996.
9. Brown, F. K.; Raimondi, L.; Wu, Y.-D.; Houk, K. N. *Tetrahedron Lett.* **1992**, *33*, 4405-4408.
11. Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127-8134. QCPE#395.
12. Houk, K. N.; Paddon-Row, M. N.; Roundan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Scinece* **1986**, *231*, 1108-1117.
13. a) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315-4316. b) Takahashi, T.; Kanda, Y.; Nemoto, H.; Kitamura, K.; Tsuji, J.; Fukazawa, Y.; *J. Org. Chem.* **1986**, *51*, 3393-3394. c) Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J.; Fukazawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 2674-2676. d) Takahashi, T.; Yamashita, Y.; Doi, T.; Tsuji, J. *J. Org. Chem.* **1989**, *54*, 4273-4275. e) Takahashi, T.; Yokoyama, H.; Haino, T.; Yamada, H. *J. Org. Chem.* **1992**, *57*, 3521-3523.
14. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959-974.
15. All modeling calculations reported in this article were carried out by using the MacroModel/BATCHMIN V.4.5 software. We are grateful to Professor W. C. Still for providing a copy of this program.
    Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, T.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440-467.
16. Chang, G.; Guida, W. C.; Still, W. C. *J. Am Chem. Soc.* **1989**,*111*, 4379-4386.
17. a) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023-4024. b) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024-4026.
18. Satisfactory NMR and IR properties were obtained.

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