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Synthesis of Taxane A/B Ring by Intramolecular Nitrile Oxide Cyclization Reaction[1]

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Abstract: The reaction of nitro olefin **9** with *p*-chlorophenyl isocyanate and triethyl amine produced tricyclic compound **10** having the taxane A/B ring system with an aromatized C ring.

The synthesis of Taxol® (paclitaxel), a typical taxane diterpene, has been a topic in synthetic chemistry during the past decade because of its unique structural features, its potent anti-cancer activity and limited availability.[2] Recently, three groups succeeded in the total synthesis of Taxol®,[3] however, the efforts for developing an efficient synthetic method of taxanes are continuously being made.[4] One of the important problems during the synthesis of the taxane skeleton is construction of the A/B ring system bearing suitable functional groups. For this problem, we have devised the formation of a taxane carbon framework utilizing the intramolecular 1,3-dipolar cycloaddition of nitrile oxide[5] as depicted in Figure 1. To confirm the viability of this method, we chose the model system having a simplified C ring synthon. In this communication, we wish to describe a capable cyclization reaction for taxane synthesis.

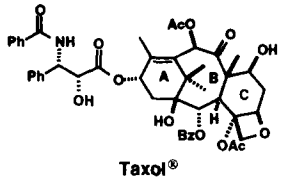
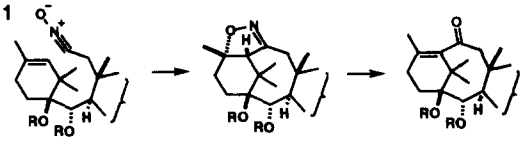
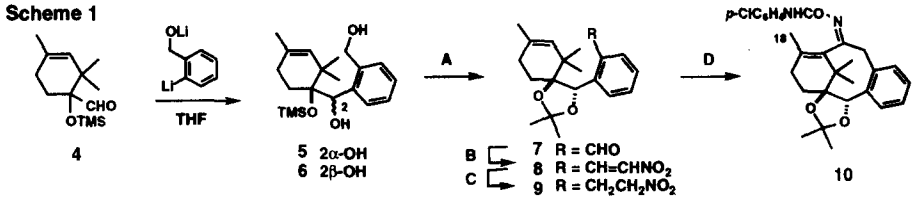


Figure 1

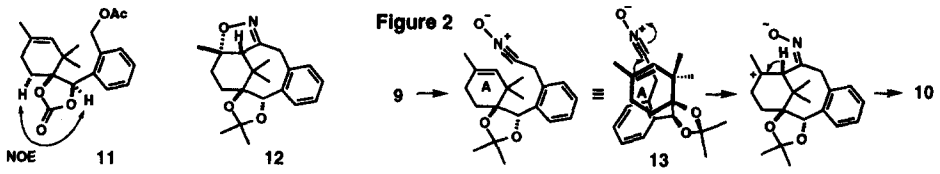


The reaction of the ring A precursor **4**[6] with aryllithium reagent,[8] prepared from 2-bromobenzyl alcohol by reductive metalation of BuLi, afforded a separable 1.7:1.0 epimeric mixture of **5** and **6** in 98 % yield (Scheme 1). The configuration of C2 in these isomers was determined by Phase sensitive NOESY experiment with **11**, obtained from **6**.[9] Conversion of the major isomer **5** into aldehyde **7** was carried out using a five-step sequence in 80 % overall yield. Subsequent treatment of **7** with the sodium carbanion of nitromethane gave a 2.3:1.0 mixture of the diastereomeric β-nitroalcohol, without separation, which was treated with methane-

Scheme 1



Reagents: **A.** 1) *t*-BuCOCl, Pyridine, 2) Bu_4NF, 3) CSA, $Me_2C(OMe)_2$, 4) $LiAlH_4$, THF, 5) PDC, 4AMS (80% 5 steps); **B.** 1) CH_3NO_2, NaOEt, EtOH, 2) MsCl, Et_3N (76% 2 steps); **C.** $NaBH_4$, THF-H_2O (4-1), 92%; **D.** *p*-ClC_6H_4N=C=O, Et_3N, PhH, 70°C, 10 h, 94%.



sulfonyl chloride to give **8**. The reduction of **8** with $NaBH_4$ in THF-H_2O (4:1) resulted in the formation of **9**[10] as a precursor of the cyclization reaction. The cyclization of **9** promoted by excess *p*-chlorophenyl isocyanate[11] and a catalytic amount of triethylamine at 70 °C in benzene was completed within 10 hr. This reaction directly gave the oxime derivatives **10**[12] corresponding to ketone **3** as a single isomer in 94 % yield. The expected isoxazoline **12** was not detected in the reaction mixture. The configuration of the oxime moiety in **10** was determined by NOESY experiments. The NOESY crosspeak was observed between the methyl proton (C-18) and the aromatic proton of the carbamoyl group in **10**. We propose this stepwise process for this cyclization reaction as shown Figure 2 rather than the process of 1,3-dipolar cycloaddition-cleavage of isoxazoline ring (**9**→**12**→**10**), since conformational analyses based on MM2 calculations[13] showed the nitrile oxide unit in the conformer **13** allowed for cyclization to be vertically oriented to the double bond of the A ring. To our knowledge, this is the first intramolecular Friedel-Crafts type cyclization of a nitrile oxide.

The application of this cyclization reaction to the taxane class of natural products is currently under investigation in our laboratories.[14]

REFERENCES AND NOTES

1. This paper is dedicated to Prof. Yoshito Kishi on the occasion of his 60th birthday.
2. (a) For a recent review on the preclinical and clinical development of Taxol®. Rothenbery, M. *Curr. Opin. Invest. Drugs.* **1993**, *2*, 1269-1277. (b) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15-44. (c) Swindell, C. S. *Org. Prep. Proced. Int.* **1991**, *23*, 465-543.
3. (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. *Narure.* **1994**, *367*, 630-634. (b) 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*, 1599-1560. (c) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1723-1726.
4. (a) Hara, R.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1996**, *118*, 9186-9187. (b) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, K.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Saitoh, K. *Chem. Lett.* **1996**, 483-484. (c) Wender, P. A.; Glass, T. E.; Krauss, N. E.; Mühlebach, M.; Peschke, B.; Rawlins, D. B. *J. Org. Chem.* **1996**, *61*, 7662-7663.
5. For a review on applications of the 1,3-dipolar cycloaddition of nitrile oxide for the synthesis of natural products, see: Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410-416.
6. The ring A precursor was synthesized from 1,5-dioxaspiro[5.5]-3,3,7,7-tetramethylundecan-8-one[7] in 7 steps. 1) Lithium diisopropylamide/MeI/THF(95%); 2) L-selectride/THF; 3) MsCl/DMAP; 4) DBU/toluene (87% 3 steps); 5. TsOH/acetone-H_2O; 6) TMSCN/CH_2Cl_2; 7) DIBAL/hexane (75% 3 steps).
7. Kress, M. H.; Ruel, R.; Miller, W. H.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 5999-6002.
8. (a) Nakamura, T.; Waizumi, N.; Tsuruta, K.; Horiguchi, Y.; Kuwajima, I. *STNLETT* **1994**, 584-586. (b) Young, W. B.; Masters, J. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5228-5234.
9. 1) Ac_2O/pyridine; 2) Bu_4NF/THF; 3) CDI, NaH/THF-DMF (50% overall yield from **6**)
10. Spectoscopic data for compound **9**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (1H, m), 7.27-7.30 (2H, m), 7.19 (1H, m), 5.35 (1H, s), 5.06 (1H, s), 4.56 (2H, t, *J*=7.7 Hz), 3.64 (1H, dt, *J*=14.1, 7.7 Hz), 3.38 (1H, dt, *J*=14.1, 7.7 Hz), 2.04-2.15 (2H, m) 1.80 (1H, m), 1.60 (3H, s), 1.49 (3H, s), 1.48 (3H, s), 1.39 (1H, m), 1.22 (3H, s), 0.92 (3H, s).
11. Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339-5342.
12. Spectroscopic data for compound **10**. IR (film) 3267,1728, 1600 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.99 (1H, bs), 7.68 (1H, d, *J*=7.7 Hz), 7.47 (2H, d, *J*=8.2 Hz), 7.31 (1H, t, *J*=7.7 Hz), 7.31 (2H, d, *J*=8.2 Hz), 7.21 (1H, d, *J*=7.7 Hz), 7.15 (1H, t, *J*=7.7 Hz), 5.06 (s, 1H), 3.88 (1H, d, *J*=16.5 Hz), 3.74 (1H, d, *J*=16.5 Hz), 2.17-2.35 (2H, m), 1.74 (1H, m), 1.59 (3H, s), 1.43 (3H, s), 1.33 (3H, s), 1.26 (3H, s), 1.22 (1H, m), 0.62 (3H, s). FAB-MS m/z 495(M^++H).
13. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440-467. MM2 calculation of **13** was carried out using the acetylene unit for the nitrile oxide unit.

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