Pergamon

*Tetrahedron Letters*, Vol. 35, No. 42, pp. 7813-7816, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01685-2

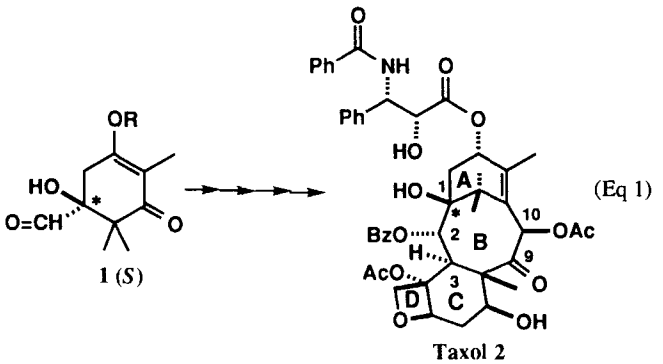
# An Enantioselective Synthesis of the A-Ring Fragment of Taxol

**Takashi Nakamura, Nobuaki Waizumi, Yoshiaki Horiguchi, and Isao Kuwajima***

Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

*Abstract:* A-Ring fragment of taxol (**2**), α-hydroxy aldehyde **1**, was enantioselectively prepared by using asymmetric dihydroxylation of enol silyl ether of the parent aldehyde.

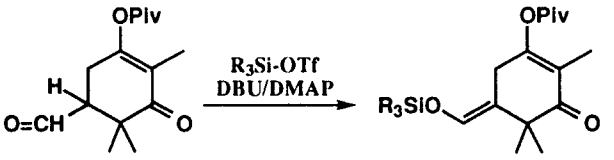
Due to important biological activities as well as unique carbon framework, synthetic studies on taxane diterpenoids,[1] especially taxol (**2**)[2] derivatives, have attracted much attention in organic chemistry. For such purpose we recently developed an efficient methodology for construction of taxane carbon frameworks, namely to connect C-9 and C-10 for B-ring closure.[3), 4] Our strategy for taxol synthesis is based on an initial connection between C-2 and C-3, followed by B-ring cyclization already established. To precede further studies on enantioselective synthesis of taxol, the most important fragment was α-hydroxy aldehyde **1**. According to our synthetic scheme, it seems possible to synthesize taxol in enantioselective manner by utilizing chirality of **1**. This paper describes a convenient method for an enantioselective synthetic pathway to **1** and its derivatives.




(Eq 1)

An obvious candidate for enantioselective synthesis of **1** was asymmetric oxidation of the α-position of the parent aldehyde **3**, which could be prepared from THP ether of propargyl alcohol in eight steps (ca. 40% overall yield) in multi-gram scale by the method developed by us.[4] The Sharpless osmium catalyzed asymmetric dihydroxylation[5] of the enol silyl ether derived from **3** was chosen for investigation.

The requisite enol silyl ethers **4a** and **4b** were prepared in high yield by treatment of **3** with TBSOTf or TIPSOTf in the presence of DBU and DMAP. Owing to the sterically demanding dimethyl substituent, preferential formation of the (*E*) isomer[6] has been achieved in each case as shown in Eq 2. Thus, situation to test efficacy of enantioselective functionalization has ideally been set up.




(Eq 2)

**3**

**4a** ($R_3Si$ = TBS) : 89% (95% *E*)
**4b** ($R_3Si$ = TIPS): 95% (98% *E*)

The Sharpless asymmetric dihydroxylation[5] of **4** proved to proceed with a reasonable rate, but the resulting α-hydroxy aldehyde **1a** (R = Piv) was found to readily dimerize under the basic conditions employed.[7] Usual workup gave **1a** in less than 30% yield, and it was very difficult to handle and convert the dimer to the desired **1a**. To circumvent such difficulty, various efforts have been made to obtain good recovery of **1a**. Among several attempts, isolation as the aminal derivative **5** followed by removal of the protecting group gave the most satisfactory result. Thus, the crude reaction product was heated with *N,N'*-dimethylethylenediamine in benzene to convert the dimeric product as well as **1a** to lead to **5** (Scheme 1). Chromatographic purification of the crude aminal **5** on silica gel (Merck Kieselgel 60) using 20% AcOEt-hexane induced hydrolysis of the aminal group and afforded α-hydroxy aldehyde **1a** in good overall yield. The enantiomeric excesses were determined by NMR analysis of the mono-(*R*)-MTPA ester of diol formed by selective reduction of the aldehyde moiety of **1a** with $LiAlH(O^tBu)_3$ in THF at -78 °C. As shown in the table, the steric hindrance of the silyl group profoundly affects the enantioselectivity. Namely with the same chiral ligand, DHQD-PHN, bulkier TIPS ether **4b** lead to much higher enantiomeric excess (94% ee) than TBS ether **4a** (78% ee) (entry 1 and 2). Absolute configuration of **1a** was determined on the basis of X ray crystallographic analysis[8] of C-aromatic taxol[7] derived from (*R*)-**1a**. As a result, (*S*)-**1a** required for taxol synthesis was obtained from **4b** in 90% ee[9] (96% yield) with DHQ-PHN as the chiral ligand (entry 3).

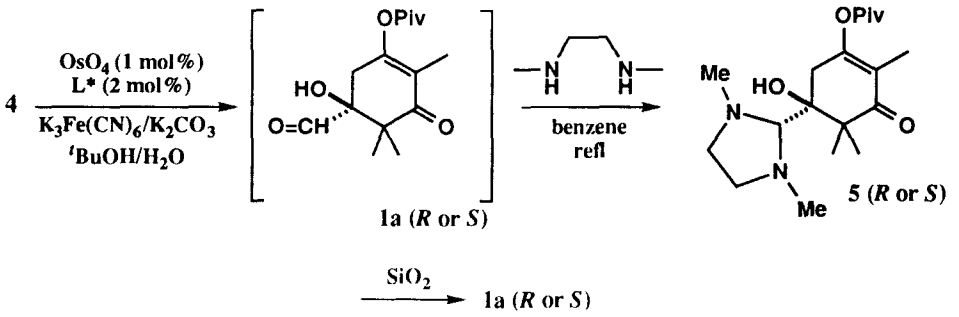
From synthetic points of view, use of the aminal **5** as an alternative of **1a** has provided several advantages for further manipulation. For example, replacement of O-Piv of **1a** with O-TIPS group could be readily performed to give **1b** in a high yield (Eq 3).

Further, application of Peterson olefination with lithiated trimethylsilylmethylsulfide before deprotection gave α-hydroxy aldehyde **6** containing phenylthiomethylene group, which has been proved a versatile building unit for construction of taxol framework.[10]

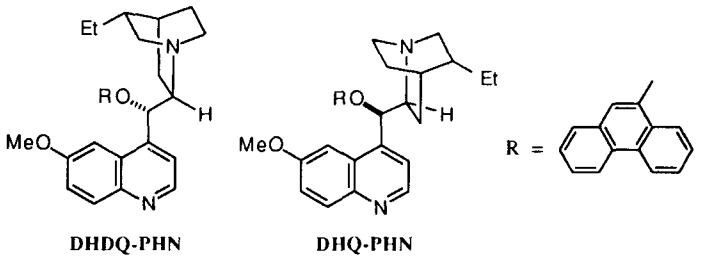
We are currently studying an enantioselective synthesis of taxol and its derivatives by using **1b** and **6** as starting materials.

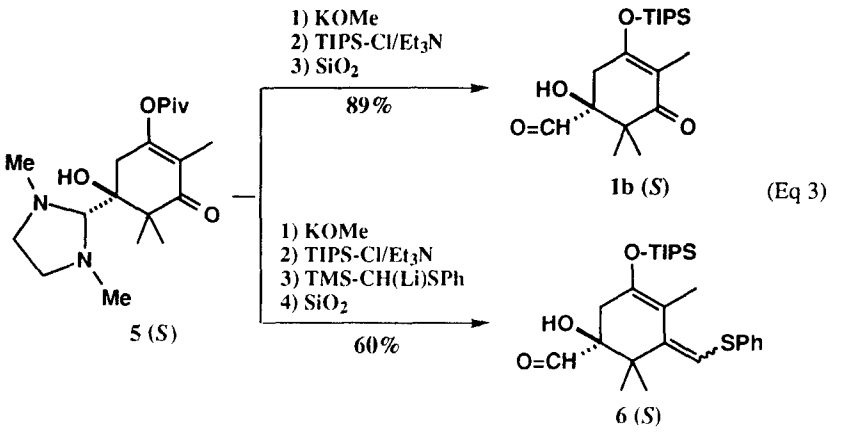
**Acknowledgment.** This work was partially supported by Grants from the Ministry of Education, Science, and Culture of the Japanese Government.

## Scheme 1




| entry | substrate | L* | conditions | % yield | % ee |
|---|---|---|---|---|---|
| 1 | **4a** | DHQD-PHN | 0 °C, 3 h | 78 | 78 (*R*) |
| 2 | **4b** | DHQD-PHN | 0 °C, 4 h | 88 | 94 (*R*) |
| 3 | **4b** | DHQ-PHN | 0 °C, 6 h | 96 | 90 (*S*) |




(Eq 3)

## References and Notes


1) For review, C. S. Swindell, *Organic Preparation and Procedures, Int.*, **23**, 465 (1991). N. A. Petasis and M. A. Patane, *Tetrahedron*, **48**, 5757 (1992). K. C. Nicolaou, W.-M. Dai, and R. K. Guy, *Angew. Chem. Int.. Ed. Engl.*, **33**, 15 (1994).

2) For recent total synthesis of taxol, K. C. Nicolaou, Z. Yang, J. J. Liu, H. Ueno, P. G. Nantermet, R. G. Guy, C. F. Cialborne, J. Renaud, E. A. Couladouros, K. Paulvannan, and E. J. Sorensen, *Nature*, **367**, 630 (1994). R. A. Holton, C. Somoza, H.-B. Kim, F. Liang, R. J. Biediger, P. D. Boatman, M. Sindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, and J. H. Liu, *J. Am. Chem. Soc.*, **116**, 1597 (1994), and the subsequent paper.

3) Y. Horiguchi, T. Furukawa, and I. Kuwajima, *J. Am. Chem. Soc.*, **111**, 8277 (1989). T. Furukawa, K. Morihira, Y. Horiguchi, and I. Kuwajima, *Tetrahedron*, **48**, 6975 (1992). M. Seto, K. Morihira, S. Katagiri, T. Furukawa, Y. Horiguchi, and I. Kuwajima, *Chem. Lett.*, 133 (1993).

4) M. Seto, K. Morihira, Y. Horiguchi, and I. Kuwajima, *J. Org. Chem.*, **59**, 3165 (1994).

5) K. B. Sharpless, W. Amberg, M. Beller, H. Chen, J. Hartung, Y. Kawanami, D. Lubben, E. Maunoury, Y. Ogino, T. Shibata, and T. Ukita, *J. Org. Chem.*, **56**, 4585 (1991). K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, and X.-L. Zhang, *ibid.*, **57**, 2768 (1992). T. Hashiyama, K. Morikawa, and K. B. Sharpless, *ibid.*, **57**, 5967 (1992).

6) The geometry of the double bond was determined based on the observed NOE from the *gem*-dimethyl group to the olefinic proton.

7) T. Nakamura, N. Waizumi, K. Tsuruta, Y. Horiguchi, and I. Kuwajima, *Synlett*, *in press*.

8) Y. Takenaka, S. Kubo, Y. Ohashi, T. Nakamura, Y. Horiguchi, and I. Kuwajima, *Acta Cryst.* C, *in press*.

9) We regard 90% ee for (*S*)-**1a** as satisfactory in practice to carry out asymmetric synthesis of taxol because presumed synthetic intermediates in the later stage possessing the taxane-like tricyclic skeleton are supposed to crystallize so as to enable us to obtain enantiomerically pure substrates. General tendency that DHQ-PHN gives somewhat lower enantioselectivities than DHQD-PHN was reported by Sharpless *et al.* see ref. 5).

10) The details will be reported elsewhere.


(*Received in Japan* 20 *May* 1994; *accepted* 29 *July* 1994)