Synthesis of the Chiral CD Rings of Paclitaxel from 2-Deoxy-D-ribose: Novel 1,2-Addition of a Dienolate to a Chiral Ketone

Takashi Takahashi,* Yoichiro Hirose, Hajime Iwamoto, and Takayuki Doi

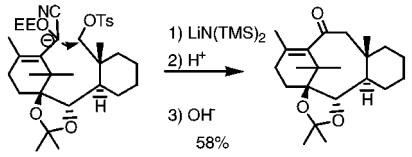
Tokyo Institute of Technology, Department of Chemical Engineering, 2-12-1 Ookayama, Meguro, Tokyo 152-8552, Japan

Received June 3, 1998

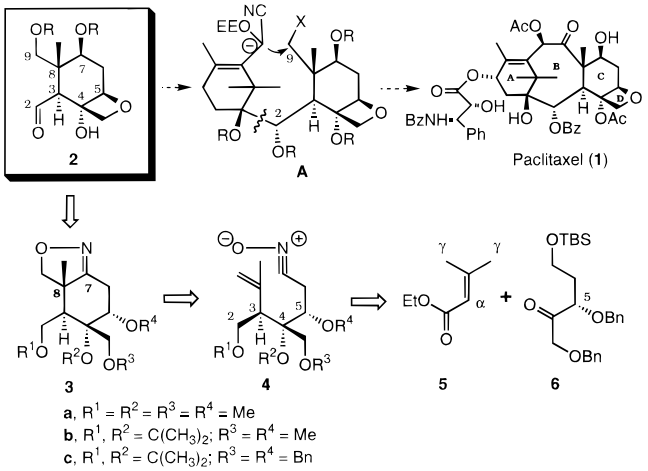
Paclitaxel (**1**, Scheme 2) is an antitumor agent that has a 6−8−6−4 ring system containing a fully functionalized carbon skeleton.[1] There have been numerous reports on approaches to the synthesis of paclitaxel, and we previously reported an efficient method for constructing the B ring of taxoids (AC → ABC) by way of an intramolecular alkylation of the protected cyanohydrin ether (Scheme 1).[2] Although many approaches have been reported for the synthesis of CD rings, only two approaches have accomplished complete formation of the CD rings.[3] We have previously disclosed a novel approach to the C-ring formation using a (3 + 2) cycloaddition of a nitrile oxide, thereby constructing the (3,8)-trans configuration on the C ring.[4] We now report the synthesis of the fully functionalized taxane CD ring system.

The synthetic plan is shown in Scheme 2. Our target CD ring is **2**, which possesses not only a fully functionalized CD ring but also an aldehyde at the C-2 position and an alkoxy group at the C-9 position corresponding to paclitaxel. The former can be used for the coupling reaction with an A-ring moiety, and the latter can be converted to a leaving group for the intramolecular alkylation of **A** in the formation of the B ring. The diol at the C-7 and C-9 positions in **2** can be prepared from **3** by reductive cleavage of an isoxazoline ring followed by the stereoselective reduction of the resulting ketone at the C-7 position. The isoxazoline **3** can be constructed from the nitrile oxide **4** via (3 + 2) cycloaddition,[4,5] which creates a six-membered ring C and a stereogenic center at the C-8 position. MM2 transition-structure model calculations[6,7] suggested that protective groups on the tetraol of **4** should control the stereochemistry at the C-8 position. Interestingly, **4b** with an acetonide protective group for the diol at the C-2 and C-4 positions (R^3, R^4 = Me) will give rise to a β-methyl group at the C-8 position with complete stereoselection.[8] On the other hand, acyclic protected compounds, such as **4a** (R^1, R^2, R^3, R^4 = Me), are predicted to give an α-methyl group at the C-8 position with 67% stereoselectivity.[8] All carbon units and the stereogenic centers at C3, C4, and C5 in **4** can be prepared by the 1,2-addition of ester **5** to chiral ketone **6**. However, few examples of the aldol reaction of dienolates and ketones have been reported. To achieve success in this strategy, we must consider the following points: (i) the addition occurs at the α-position of the dienolate of **5** rather than the γ-position,[9] (ii) the 1,2-addition should be faster than the enolization of the ketone (proton transfer), (iii) stereocontrol occurs from the ketone **6** to the newly formed stereogenic centers at the C-3 and C-4 positions in **4**.[10,11]

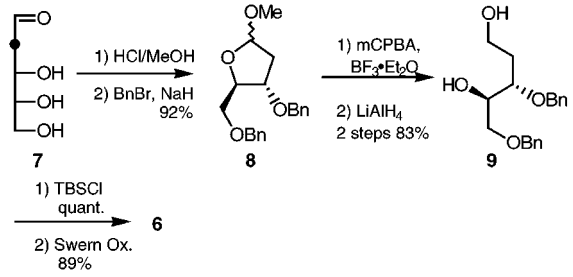
Scheme 1



Scheme 2



Scheme 3



The ketone **6** was prepared from 2-deoxy-D-ribose (**7**)[12] as shown in Scheme 3. Acetal formation of **7** (0.05% HCl in MeOH) followed by protection of the resulting diol as the corresponding benzyl ether (BnBr/NaH) gave **8** in 92% yield. Oxidation of acetal **8** (BF_3·Et_2O/*m*-CPBA)[13,14] to the lactone was followed by reduction ($LiAlH_4$), affording diol **9** in 83%

(1) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325−2327.

(2) Takahashi, T.; Iwamoto, H.; Nagashima. K.; Okabe, T.; Doi, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1319 and references therein.

(3) Magee, T. V.; Bornmann, W. G.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 3274. Nicolaou, K. C.; Hwang, C.-K.; Sorensen, E. J.; Clairborne, C. F. *J. Chem. Soc., Chem. Commun.* **1992**, 1117.

(4) Takahashi, T.; Iwamoto, H. *Tetrahedron Lett.* **1997**, *38*, 2483.

(5) For a review, see: Kanemasa, S.; Tsuge, O. *Heterocycles* **1990**, *30*, 719.

(6) Brown F. K.; Raimondi, L.; Wu, Y.-D.; Houk, K. N. *Tetrahedron Lett.* **1992**, *33*, 4405. Takahashi, T.; Nakazawa, M.; Sakamoto, Y.; Houk, K. N. *Tetrahedron Lett.* **1993**, *34*, 4075.

(7) All calculations were performed on MacroModel/BATCHMIN (ver 4.5). Initial coordinations generated by 1000 Monte Carlo steps were energy minimized by MM2 and Transition State Model. 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. Comput. Chem.* **1990**, *11*, 440.

(8) Details of the calculations and those of other candidates are presented in the Supporting Information.

(9) The α-preference regioselectivity observed in the aldol reaction of the dienolate of 3-methylcrotonate with a steroidal aldehyde has been reported. Kajikawa, A.; Morisaki, M.; Ikekawa, N. *Tetrahedron Lett.* **1975**, *47*, 4135.

(10) Preliminary stereochemical studies on the reactions of the dienolate of 3-methylcrotonate with aldehydes have been reported. Dugger, R. W.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1181. Majewski, M.; Mpango, G. B.; Thomas, M. T.; Snieckus, V. *J. Org. Chem.* **1981**, *46*, 2029.

(11) For recent examples of stereocontrolled aldol reactions of a dienolate bearing a chiral auxiliary to aldehydes, see: Black, W. C.; Giroux, A.; Greidanus, G. *Tetrahedron Lett.* **1996**, *37*, 4471. Tomooka, K.; Nagasawa, A.; Wei, S.-Y.; Nakai, T. *Tetrahedron Lett.* **1996**, *37*, 8899.

(12) 2-Deoxy-D-ribose was a gift from Kobayashi Koryo Kagaku.

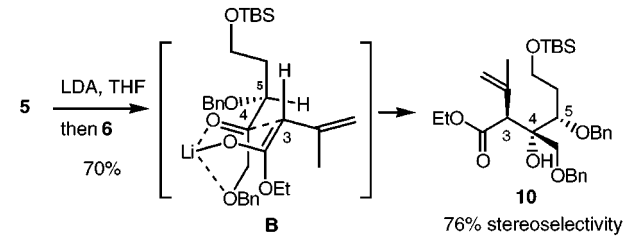
(13) Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, 419.

(14) Acid hydrolysis, followed by reduction, gave the desired diol **9** in rather low yield because of β-elimination of the lactol.

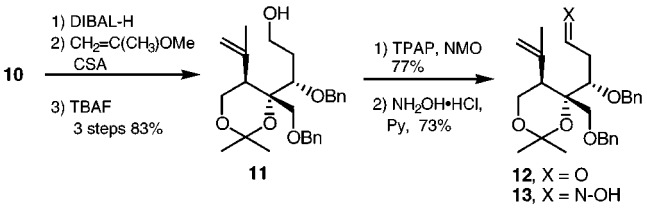
(15) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

S0022-3263(98)01056-1 CCC: $15.00
Published on Web 08/05/1998

Scheme 4



Scheme 5



yield. Selective protection of the primary alcohol of **9** (TBSCl, imidazole) and subsequent Swern oxidation[15] of the secondary alcohol provided ketone **6** in 89% overall yield.

The 1,2-addition of **5** to **6** was carried out as follows (Scheme 4): A THF solution of ketone **6** was added to 3 equiv of the lithium dienolate of ester **5** prepared with LDA at −78 °C. The reaction was complete within 10 min, providing only the α-adducts in 70% yield. HPLC analysis of the adducts showed four diastereomers in a ratio of 76:9:8:7. None of the γ-adduct was observed. The stereochemistry of the major diastereomer **10** was determined at a later stage in the synthesis. As the lithium enolate of ester **5** is known to be prepared as a 1:1 mixture of (*E*)- and (*Z*)-isomers,[16] it is conceivable that the (*E*)-enolate selectively reacted with ketone **6** via transition state **B** where the primary benzyloxy group of **6** could coordinate to a lithium cation through a chairlike six-membered transition state. It is noteworthy that the kinetic resolution of the (*E*)- and (*Z*)-enolates was observed in the 1,2-addition to the chiral ketone, producing two new stereogenic centers with high stereocontrol.[17]

DIBAL reduction of ester **10** followed by protection of the resulting diol (isopropenyl methyl ether, CSA) gave the acetonide whose TBS group was deprotected (TBAF, THF), leading to alcohol **11** in 83% overall yield (Scheme 5). Oxidation of **11** (TPAP, NMO, 77%)[18] followed by treatment of the resulting aldehyde **12** with hydroxylamine furnished oxime **13** as a mixture of (*E*)- and (*Z*)-isomers in 73% yield. The key (3 + 2) cycloaddition of **4c** was carried out as follows: Treatment of **13** with an excess of aqueous NaOCl solution at 0 °C for 15 min produced **4c**, which underwent cycloaddition upon addition of triethylamine at room temperature for 3 h.[19] As the MM2 transition-structure model calculations had suggested, the reaction proceeded stereoselectively via transition state **4c**‡ (Figure 1) giving **3c** in 56% yield.[20] The structure of **3c** was determined by NOE measurement as shown in the Supporting Information.

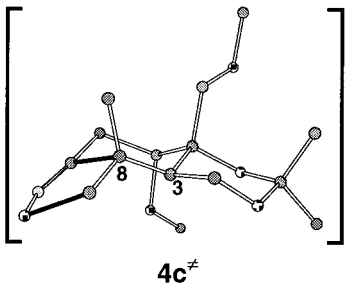
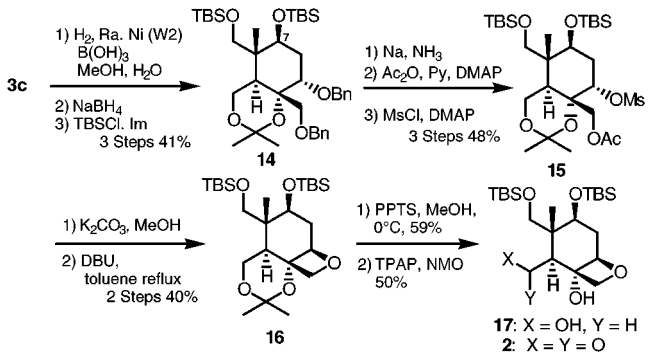


Figure 1. MM2 transition-state models.

Scheme 6



Reductive cleavage of the isoxazoline **3c** (Raney-Ni, H_2; $B(OH)_3$, MeOH, H_2O)[21] followed by stereoselective reduction ($NaBH_4$) of the resulting ketone at the C-7 position afforded the diol, which was protected as its diTBS ether **14** (TBSCl, imidazole, three steps, 41% yield, Scheme 6). Removal of the dibenzyl ether of **14** under Birch reduction conditions gave the diol. Subsequent acetylation of the primary alcohol followed by mesylation led to **15** in 48% overall yield. Deacetylation of **15** (K_2CO_3, MeOH) followed by treatment with DBU provided oxetane **16** in 40% overall yield.[22,23] Deprotection of the acetonide of **16** (PPTS, MeOH, 0 °C, 59%) followed by TPAP oxidation of the resulting diol **17** furnished the desired aldehyde **2** in 50% yield.

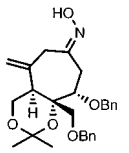
We have demonstrated that the novel stereocontrolled 1,2-addition of ester **5** to chiral ketone **6**, easily prepared from 2-deoxy-D-ribose (**7**), generated all of the carbon units required for the synthesis of paclitaxel's CD rings, and the (3 + 2) cycloaddition of the nitrile oxide proceeds stereoselectively to provide the 8β-methyl group during C-ring formation. Five consecutive chiral centers on the fully functionalized taxane CD ring system were successfully generated from only the one chiral center of ketone **6** in this synthesis.

Acknowledgment. We thank the Ministry of Education, Science, Sports, and Culture, Japan for supports of this work (Grant-in-aid No. 08245103). We also thank Professors Takeshi Nakai and Katsuhiko Tomooka (Tokyo Institute of Technology) for helpful discussions about aldol reactions of the dienolate.

Supporting Information Available: Synthetic procedures, spectral data, and MM2 transition-structure model calculations (41 pages).

JO9810563

(16) Casey, C. P.; Jones, C. R.; Tukada, H. *J. Org. Chem.* **1981**, *46*, 2089.
(17) Addition of 1 equiv of the ester enolate of **5** gave a low yield (30%). This also suggests that the (*E*)-enolate is less reactive in the 1,2-addition.
(18) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13.
(19) Lee, G. A. *Synthesis* **1982**, 508.
(20) Compound **i** was also formed in 33% yield, probably from the regioisomeric product in the (3 + 2) cycloaddition. This regioselectivity has previously observed in the intramolecular (3 + 2) cycloaddition of N-substituted nitrones. Majumdar, S.; Bhattacharjya, A.; Patra, A. *Tetrahedron Lett.* **1997**, *38*, 8581.



(21) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023. Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.
(22) Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1991**, *47*, 9823.
(23) 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.