Stereocontrolled Synthesis of the BC Ring System of Taxol

Isamu Shiina, Hayato Iwadare, Hiroki Sakoh, Yu-ichirou Tani, Masatoshi Hasegawa, Katsuyuki Saitoh, and Teruaki Mukaiyama
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162

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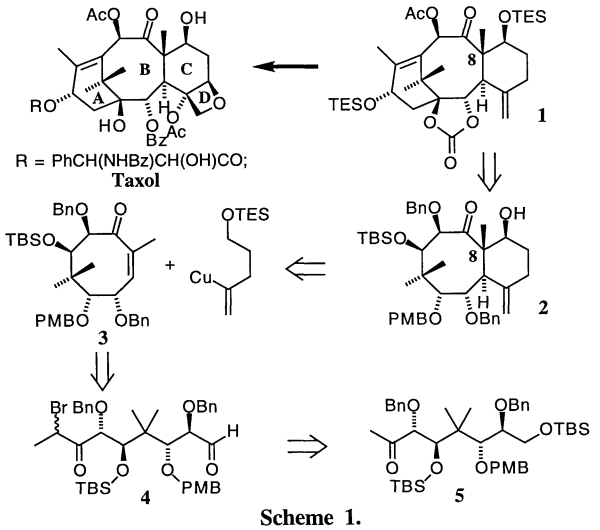
Optically active 2α,10β-dibenzyloxy-11β-(*t*-butyldimethylsiloxy)-7β-hydroxy-1α-(4-methoxybenzyloxy)-8β,15,15-trimethyl-4-methylene-*trans*-bicyclo[6.4.0]dodecan-9-one **2** that corresponds to BC ring system of Taxol was prepared from 8-membered ring enone **3** in high yield *via* stereoselective Michael addition and successive intramolecular aldol cyclization. The above 8-membered ring enone **3** was synthesized from the linear optically active polyoxy-compound **4** by SmI_2-mediated intramolecular aldol cyclization.

Taxol, a substance isolated from the Pacific yew tree, has been found to have an anti-cancer effect, and the synthesis of its complex structure has been a tempting challenge for synthetic chemists over the past decades.[1]

In 1994, two groups succeeded in chemical total synthesis of Taxol. In Holton's strategy, (-)-camphor was used as a starting material and the synthesis was achieved by a sequence of effective synthetic reactions whereas the key step of B ring closure reaction was carried out after connecting the A and C rings in Nicolaou's convergent approach.[2,3] Further, Danishefsky reported the total synthesis according to a convergent strategy by way of intramolecular Heck cyclization in 1995.[4] Recently, Wender accomplished it by a linear strategy which involved fragmentation of an epoxy-alcohol derived from α-pinene.[5]

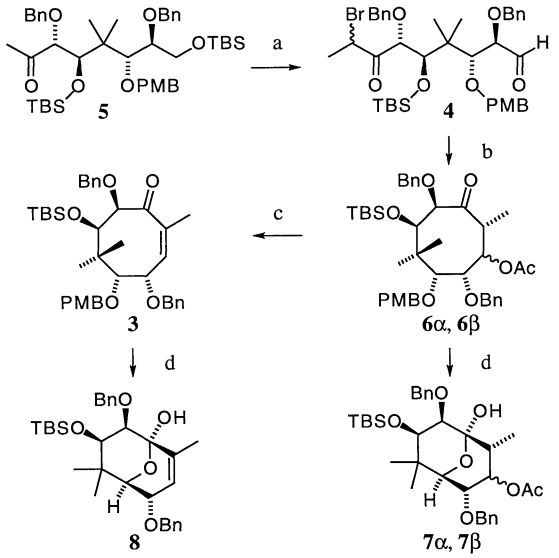
In our strategy, the synthesis of taxane's basic skeleton **1** was planned to start from B ring of Taxol, prepared from optically active polyoxy-unit **5**, and to proceed by constructing A and C ring systems onto this framework.[6] This novel strategy offers flexible pathways for the syntheses of Taxol and its analogues from their respective chiral linear precursors.

We would like to demonstrate here an effective method for the synthesis of BC ring system of Taxol by the following processes: a) an initial formation of 8-membered cyclic enone **3** from the optically active linear compound **4** using SmI_2, b) a stereoselective Michael addition of cuprate reagent to the 8-membered ring compound **3**, and c) a formation of BC ring system **2** by intramolecular aldol cyclization of the Michael adduct with NaOMe.



Scheme 1.

The desired α-bromoketoaldehyde **4** was obtained by bromination of methyl ketone **5** with NBS and successive methylation of the α-position of the brominated intermediate.[6] Further, deprotection of the *t*-butyldimethylsilyl group and Swern oxidation followed. Then, synthesis of 8-membered cyclic enone **3** from the optically active polyoxy-unit **4** that contained all the functionalities necessary for the construction of Taxol was attempted. In the presence of an excess amount of SmI_2, the intramolecular aldol cyclization reaction of **4** proceeded smoothly to give a mixture of β-hydroxycyclooctanones in high yield with good stereoselectivity (83 / 17 / 0 / 0). Acetylation of this mixture of isomeric alcohols and successive treatment with DBU gave the desired 8-membered ring enone **3** in high yield. The relative stereochemistries of major product **6α**, minor product **6β** and 8-membered ring enone **3** were assigned by 1H NMR measurements of the transformed products **7α**, **7β** and **8**.

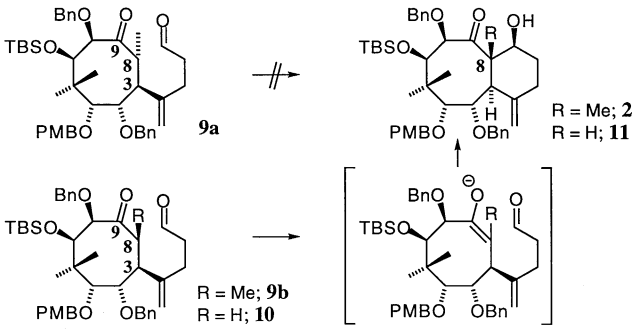


a) LHMDS, TMSCl, THF, -78 °C to 0 °C; NBS, THF, 0 °C (2steps 100%); LHMDS, MeI, HMPA, THF, -78 °C (100%); 1N HCl, THF, rt (84%); $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to rt (98%); b) SmI_2, THF, -78 °C (70%); Ac_2O, DMAP, pyridine, rt (85%, **6α** / **6β** = 83 / 17); c) DBU, benzene, 60 °C (91%); d) DDQ, H_2O, CH_2Cl_2, rt (43% for **6α**, 53% for **6β**, 44% for **3**)

Scheme 2.

The synthesis of BC ring system of 8-demethyltaxoid **11** having no C-19 methyl group from the corresponding ketoaldehyde **10**, which was prepared according to the procedure mentioned in the previous communication, was already shown to

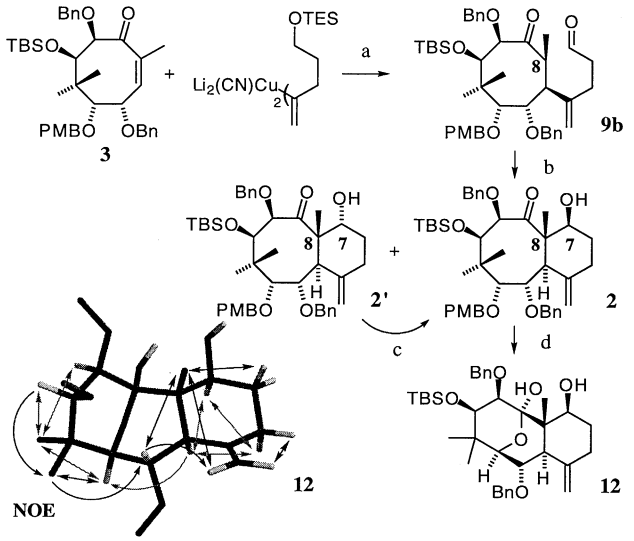
proceed smoothly by intramolecular aldol cyclization with NaOMe (Scheme 3). On the other hand, intramolecular aldol reaction did not proceed at all when the ketoaldehyde **9a** having C-19 methyl group on C-8 position was treated with NaOMe under the same reaction conditions.[6] These experimental results and a conformational search with MM2 force field of the precursors **9a** and **10** indicated that the generation of enolate anion by deprotonation from a ketoaldehyde **9a** having C-3,8 *trans* configuration hardly took place under the standard conditions because the dihedral angle of H-C8-C9=O bond was nearly antiperiplanar. This suggested that a ketoaldehyde **9b** having C-3,8 *cis* configuration is able to generate the key enolate anion. The enolate anion thus formed easily reacted with aldehyde to form the BC ring system of Taxol by intramolecular aldol cyclization. It was assumed that the desired ketoaldehyde **9b** having C-3,8 *cis* configuration would be produced on α-face selective hydrolysis of the intermediate Michael adduct, formed from 8-membered ring enone **3** and cuprate reagent (Scheme 4).



Scheme 3.

Michael addition of the cuprate reagent generated in situ from 7 mol of 2-bromo-5-triethylsiloxypentene, 14 mol of *t*-BuLi and 3.6 mol of copper cyanide to the enone **3** gave the 8-membered ring ketone having C-3,8 *cis* configuration in high yield with high diastereoselectivity by α-face selective hydrolysis of the enolate anion. Ketoaldehyde **9b**, a precursor of BC ring system of Taxol, was obtained in good yield by deprotection of the above Michael adduct with 0.5N HCl, followed by oxidation with TPAP and NMO. On treatment with a base, a precursor **9b** having C-3,8 *cis* configuration was expected to generate the enolate anion, which would form the desired bicyclic compound **2** as mentioned above. Actually, the reaction proceeded smoothly to afford a mixture of bicyclic compounds in nearly quantitative yield with good diastereoselectivity (92 / 8 / 0 / 0) when intramolecular aldol reaction of the precursor **9b** was carried out in the presence of NaOMe at 0 °C. The diastereomer **2'** that has α-hydroxyl group at C-7 position could be epimerized to the desired β-alcohol **2** in good yield on treatment with NaOMe. Finally, the NOE relationship and conformational analysis by MM2 calculation of a transannulated compound **12** derived from the BC ring compound **2** confirmed the structure as illustrated in Scheme 4. Both C-8 methyl and C-7 hydroxyl groups have the same β-configuration as in Taxol.

Thus, an asymmetric synthesis of the BC ring system of Taxol was accomplished *via* three successive reactions: namely, SmI_2-mediated intramolecular aldol cyclization of optically active linear ketoaldehyde **4**; stereoselective Michael addition on 8-membered ring enone **3**; and intramolecular aldol cyclization of



a) Et_2O, -23 °C (92%); 0.5N HCl, THF, 0 °C (100%); TPAP, NMO, MS 4Å, CH_2Cl_2, 0 °C (92%); b) NaOMe, MeOH, THF, 0 °C (98%, **2** / **2'** = 92 / 8); c) NaOMe, THF, 0 °C (90% based on 70% conversion); d) DDQ, H_2O, CH_2Cl_2, rt (44%)

Scheme 4.

thus formed ketoaldehyde **9b** having C-3,8 *cis* configuration with NaOMe.

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References

1 K. C. Nicolaou, W-M. Dai, and R. K. Guy, *Angew. Chem., Int. Ed. Engl.*, **33**, 15 (1994).

2 R. A. Holton, C. Somoza, H.-B. Kim, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, 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); R. A. Holton, H.-B. Kim, C. Somoza, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, 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**, 1599 (1994).

3 K. C. Nicolaou, Z. Yang, J.-J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladouros, K. Paulvannan, and E. J. Sorensen, *Nature*, **367**, 630 (1994).

4 J. J. Masters, J. T. Link, L. B. Snyder, W. B. Young, and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, **34**, 1723 (1995).

5 P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, C. Gränicher, J. B. Houze, J. Jänichen, D. Lee, D. G. Marquess, P. L. McGrane, W. Meng, T. P. Mucciaro, M. Mühlebach, M. G. Natchus, H. Paulsen, D. B. Rawlins, J. Satkofsky, A. J. Shuker, J. C. Sutton, R. E. Taylor, and K. Tomooka, *J. Am. Chem. Soc.*, **119**, 2755 (1997); P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, J. B. Houze, N. E. Krauss, D. Lee, D. G. Marquess, P. L. McGrane, W. Meng, M. G. Natchus, A. J. Shuker, J. C. Sutton, and R. E. Taylor, *J. Am. Chem. Soc.*, **119**, 2757 (1997).

6 T. Mukaiyama, I. Shiina, K. Sakata, T. Emura, K. Seto, and M. Saitoh, *Chem. Lett.*, **1995**, 179; I. Shiina, K. Uoto, N. Mori, T. Kosugi, and T. Mukaiyama, *Chem. Lett.*, **1995**, 181; T. Mukaiyama, I. Shiina, K. Kimura, Y. Akiyama, and H. Iwadare, *Chem. Lett.*, **1995**, 229; I. Shiina, H. Iwadare, M. Saitoh, N. Ohkawa, T. Nishimura, and T. Mukaiyama, *Chem. Lett.*, **1995**, 781; I. Shiina, M. Saitoh, K. Nishimura, K. Saitoh, and T. Mukaiyama., *Chem. Lett.*, **1996**, 223; T. Mukaiyama, I. Shiina, H. Iwadare, M. Saitoh, K. Nishimura, T. Nishimura, N. Ohkawa, H. Sakoh, and K. Saitoh, *Chem. Lett.*, **1996**, 483; I. Shiina, T. Nishimura, N. Ohkawa, H. Sakoh, K. Nishimura, K. Saitoh, and T. Mukaiyama, *Chem. Lett.*, **1997**, 419.