Asymmetric Total Synthesis of Taxol®

By Teruaki MUKAIYAMA, M. J. A., Isamu SHIINA, Hayato IWADARE, Hiroki SAKOH, Yu-ichirou TANI, Masatoshi HASEGAWA, and Katsuyuki SAITOH

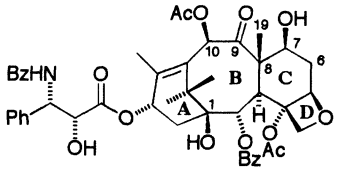
Department of Applied Chemistry, Faculty of Science, University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162

(Communicated June 12, 1997)

Abstract: Asymmetric total syntheses of Taxol and of 8-demethyltaxoids **24–27** from the 8-membered ring compounds **29** and **12** respectively were completed *via* successive formation of the BC ring system by intramolecular aldol reaction, then the ABC ring system utilizing an intramolecular pinacol cyclization. The conversion of the tricyclic compound **43** to 7-TES baccatin III (**49**) was carried out by way of a newly devised method of constructing the oxetane ring. The dehydration condensation between a derivative of *N*-benzoylphenylisoserine and **49**, followed by deprotection afforded the antitumor agent Taxol.

Key words: Taxol; 8-demethyltaxoids; 8-membered ring compounds; intramolecular aldol reaction; intramolecular pinacol cyclization; oxetane formation; dehydration.

Taxol, 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]



Taxol

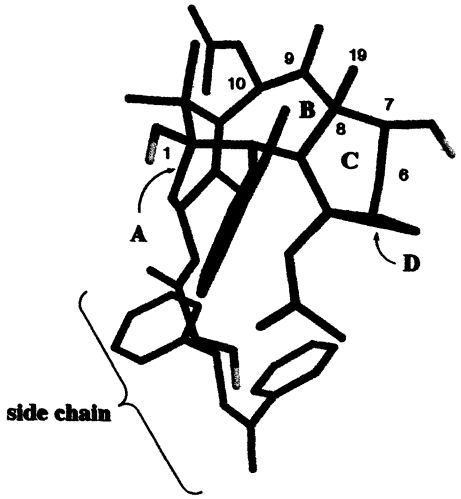


Fig. 1. Antitumor agent Taxol.

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

In our strategy, the synthesis of the basic skeleton of Taxol was planned to start from the chiral B ring intermediate **29**, prepared *via* optically active polyoxy-unit **8**, and to proceed by constructing the A and C ring systems onto this framework (Fig. 2). This novel strategy offers a flexible synthesis of the B ring system of Taxol and its analogues from chiral linear precursors.[6),7]

Commercially available neopentyl glycol (**1**) was converted to aldehyde **2** *via* its benzylideneacetal. An asymmetric aldol reaction between **2** and the requisite ketene silyl acetal promoted by $Sn(OTf)_2$ coordinated with chiral diamine gave the desired optically active ester **3** in good selectivity (anti/syn=79/21, anti aldol; 93% ee). The ester **3** was converted to aldehyde **4** as shown in Fig. 3.

The chiral aldehyde **4** was also prepared by the

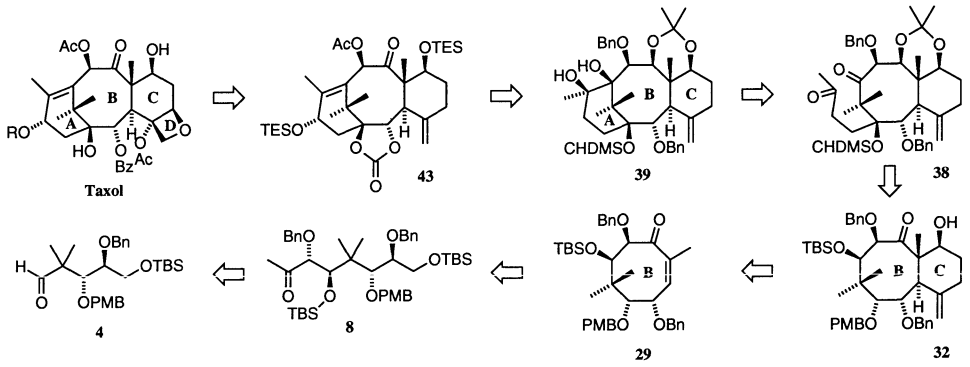


Fig. 2. Retrosynthesis of Taxol.

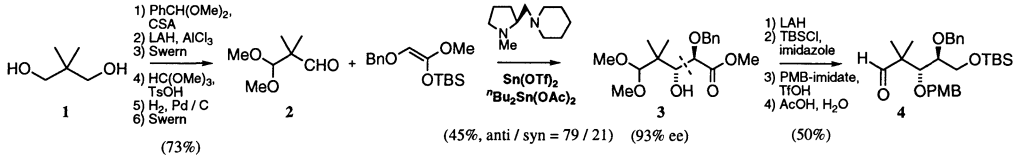


Fig. 3. Synthesis of optically active trialkoxy aldehyde **4** (Route 1).

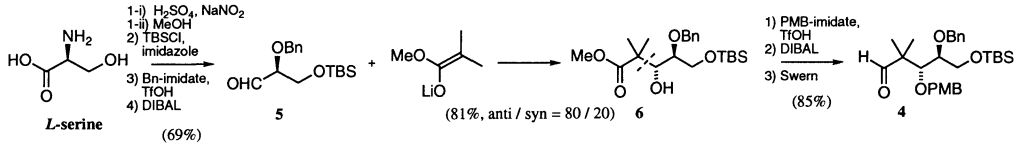


Fig. 4. Synthesis of optically active trialkoxy aldehyde **4** (Route 2).

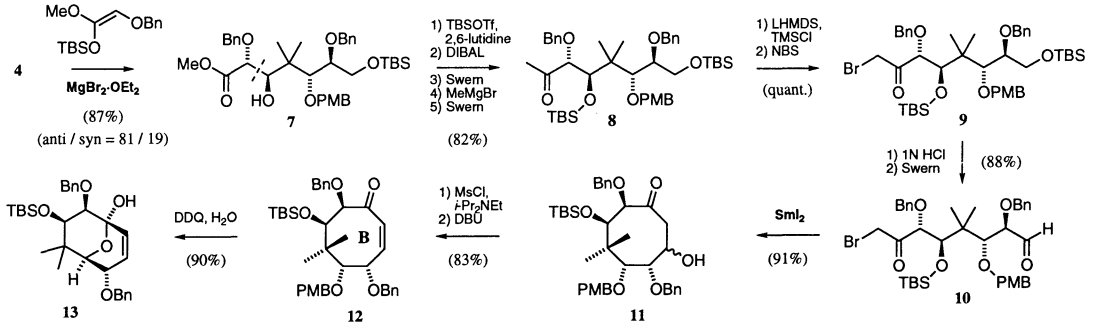


Fig. 5. Synthesis of 8-membered ring enone **12**.

following alternative route (Fig. 4): optically active dialkoxyaldehyde **5** was prepared from *L*-serine. A stereoselective aldol reaction between **5** and the lithium enolate derived from methyl isobutyrate smoothly proceeded to afford the aldol product **6** (anti/syn=80/20), which was then converted to the above aldehyde **4**.

The aldol reaction between **4** and the appropriate ketene silyl acetal took place rapidly in the presence of $MgBr_2 \cdot OEt_2$ to yield the desired ester **7** in good stereoselectivity (2,3,5-anti,anti/three diastereomers= 81/19/0/0). Methyl ketone **8** was prepared by successive reactions of methylation of aldehyde derived from **7** with MeMgBr and of Swern oxidation. A single recrystalization of **8** thus gave optically pure methyl ketone .[6] The relative stereochemistry of **8** was determined by X-ray crystallography (Fig. 7). Bromination of the α-position of synthetic intermediate **8**, followed by deprotection of the *t*-butyldimethylsilyl group and Swern oxiation gave the desired α-bromoketoaldehyde **10**, a precursor of the 8-membered ring compound **11**. In the presence of an excess amount of SmI_2 (ca. 3 eq.), the aldol cyclization of this α-bromoketoaldehyde **10** proceeded quite smoothly to give a mixture of β-hydroxycyclooctanones **11** in high yield (diastereomeric ratio 77/23). Successive mesylation

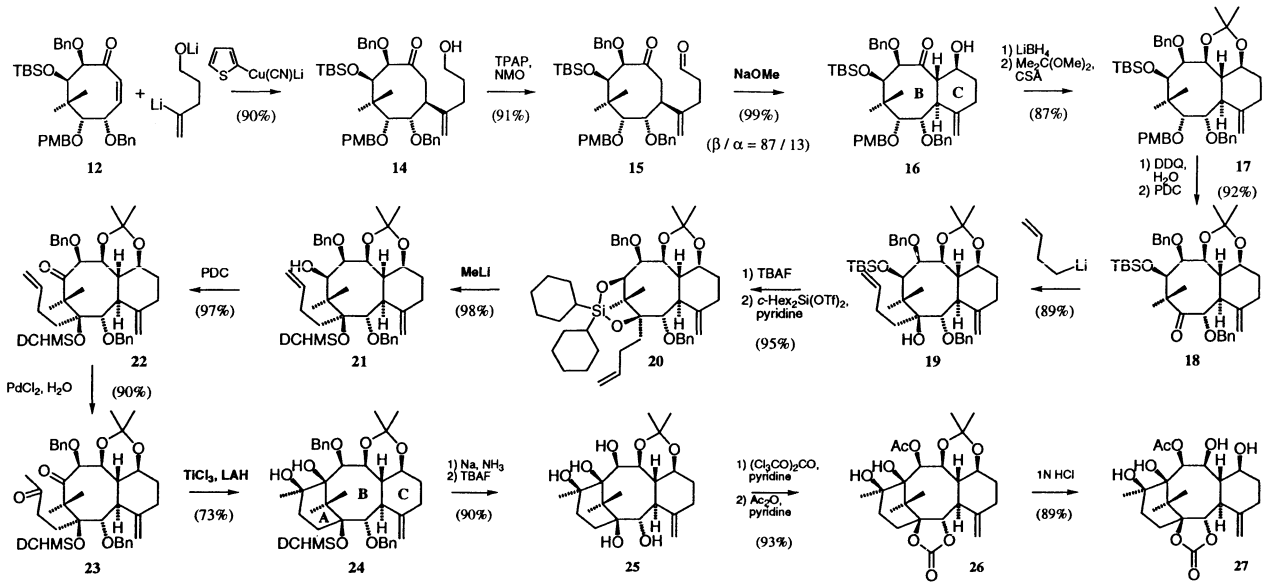


Fig. 6. Synthesis of 8-demethyltaxoid **24**.

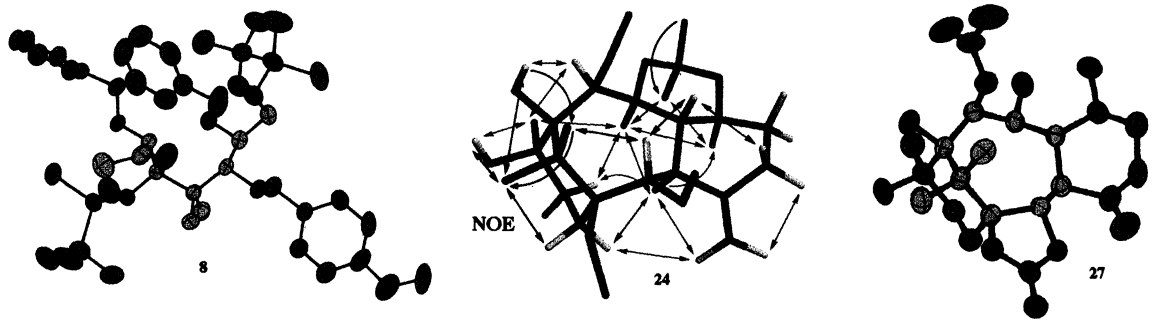


Fig. 7. Synthesis of 8-demethyltaxoid **27**.

of the alcohols **11** and treatment with DBU gave the desired 8-membered enone **12** in good yield (Fig. 5). 8-Membered ring compounds are known to have many conformational variationistics and the enone **12** formed in this way actually has, as expected, a unique structural character.[7] For example, the ^{1}H NMR of **12** shows that it is a mixture of two slowly interconverting conformational isomers corresponding to the broadened peaks in its spectra (in $CDCl_3$ at 25°C). Fast exchange of atropisomers on the ^{1}H NMR time scale at 270 MHz occurs at 100°C in toluene-d_8, whereas the two isomers did not interconvert at −30°C, as demonstrated by the sharp signals detected in the ^{1}H NMR (57/43 in $CDCl_3$). In order to clarify and confirm the structure of the compound **12**, it was transformed into a bicylic derivative **13** by transannulation, and the structure of the rigid bicyclic skeleton formed was confirmed by ^{1}H NMR.

Next, the synthesis of the ABC ring system of 8-demethyltaxoid was attempted as a model for the synthesis of the skeleton of taxane diterpenoids (Fig. 6).[8)–11)] Firstly, bicylic compound **16**, containing the BC ring system of 8-demethyltaxoid, was prepared easily from the 8-membered ring compound **12**.[10)] Michael addition to enone **12** using a higher-order cuprate reagent generated in situ from 1 mol of 4-bromo-4-penten-1-ol, 3 mol of *t*-BuLi and 1.1 mol of lithium 2-thienylcyanocuprate gave the β-substituted 8-membered ring ketone **14** in high yield with perfect diastereoselectivity. Ketoaldehyde **15**, a precursor of the BC ring system of 8-demethyltaxoid, was obtained directly by oxidation of this alcohol **14** with the TPAP and NMO combination. When the intramolecular aldol reaction of the precursor **15** was examined in the presence of NaOMe at room temperature, the desired reaction proceeded smoothly to afford the BC ring system of 8-demethyltaxoid **16** in high yield with good diastereoselectivity (87/13/0/0).

Secondly, synthesis of tricyclic compound **24** containing the ABC ring system of 8-demethyltaxoid was

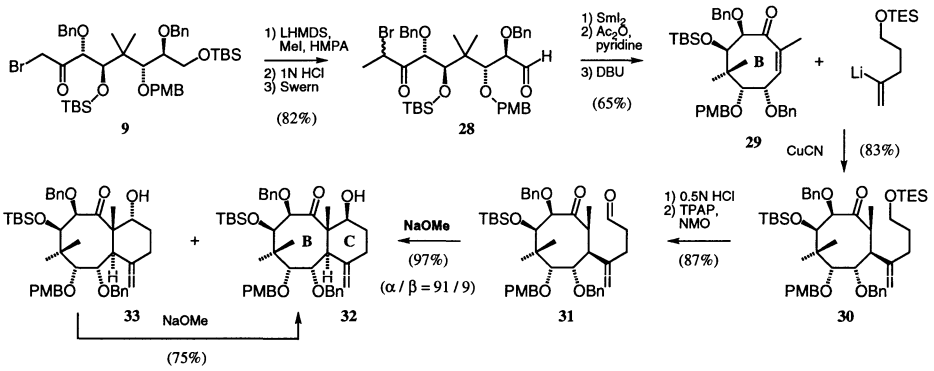


Fig. 8. Synthesis of BC ring system of Taxol **32**.

studied by constructing the A ring system onto the BC ring system.[11] Diastereoselective reduction of aldol **16** with $LiBH_4$ in THF afforded the *cis*-diol which in turn was treated with 2,2-dimethoxypropane to give tricyclic compound **17**. This was converted to the 8-membered ring ketone **18**, then alkylation of the C-1 position of **18** with homoallyllithium reagent produced the desired bishomoallyl alcohol **19** in high yield with good diastereoselectivity. The *cis*-diol derived from **19** was subsequently converted to silylene compound **20** in high yield. Similar to the synthesis of an AB ring model system,[8] alkylation of the silylene compound **20** with methyllithium furnished silyl ether **21** having the desired C-1 protected hydroxyl group. Oxygenation of the C-12 position of ketone **22** proceeded smoothly to yield the desired diketone **23** under forced Wacker oxidation conditions. By the above sequence of manipulations, the ABC ring system precursor **23** was efficiently synthesized from optically active 8-membered ring enone **12**. The ABC ring system of 8-demethyltaxoid **24** was obtained by an intramolecular pinacol coupling reaction of diketone **23** using the low-valent titanium reagent prepared from $TiCl_3$ and $LiAlH_4$ as shown in Fig. 6. In this reaction, the desired pinacol **24** was obtained as the main product along with a small amount of by-products such as rearranged pinacolone type derivatives. The NOE relationships and a conformational analysis by MM2 calculation of **24** confirmed the all stereochemistry and conformation as described in Fig. 7. Deprotection of benzyl and dicyclohexylmethylsilyl groups of **24** afforded C-1, C-2, C-10, C-11, C-12 pentaol **25** in high yield. Successive regioselective protections of this pentaol **25** gave the C-10 acetoxy and C-1, C-2 carbonate **26** with high selectivity. X-Ray crystallography of tetraol **27** derived from the carbonate **26** showed that it possessed the stereochemistry of the ABC ring system of 8-demethyltaxoid as depicted in Fig. 7. Thus, a method for the synthesis of the basic skeleton of 8-demethyltaxoid *via* intramolecular aldol and pinacol coupling reactions has been established.

Next, preparation of the ABC ring system of Taxol itself by way of Michael addition of a C ring fragment onto 8-membered ring enone **29** possessing a methyl group at the C-8 position was planned (Figs. 8, 9). The desired α-bromoketoaldehyde **28** was obtained by methylation of the α-position of synthetic intermediate **9** followed by deprotection of the *t*-butyldimethylsilyl group and Swern oxidation. Then, synthesis of 8-membered ring compound **29** from the optically active polyoxy-unit **28** containing all the functional groups necessary for the construction of Taxol was attempted. In the presence of an excess amount of SmI_2, the intramolecular aldol cyclization reaction of **28** proceeded quite smoothly to give a mixture of β-hydroxycyclooctanones in high yield. Successive acetylation of this mixture of isomeric alcohols and treatment with DBU gave the desired 8-membered enone **29** in good yield. Michael addition of the cuprate reagent generated in situ from 1 mol of 2-bromo-5-triethylsiloxypentene, 2 mol of *t*-BuLi and 1.1 mol of cuppercyanide to enone **29** gave the β-substituted 8-membered ring ketone **30** in high yield. Intramolecular aldol reaction of the precursor **31** derived from **30** using NaOMe at 0°C gave the bicylic compound **32** containing the BC skeleton of Taxol in excellent yield. Conformational analysis and NOE relationships of a transannulated compound derived from the BC ring system confirmed the structure of **32**. Both C-8 methyl and C-7 hydroxyl groups have the β-configuration as in Taxol.

Diastereoselective reduction of aldol **32** with DIBAL in hexane at low temperature, followed by treatment with isopropylidene acetal provided tricylic compound **34**. This was then converted to 8-membered ring ketone **35** and the subsequent C-1 alkylation of which with homoallyllithium reagent produced the desired bishomoallyl alcohol **36** with perfect stereoselectivity. Treatment of *cis*-diol derived from **36** with dichlorocyclohexylmethylsilane yielded the

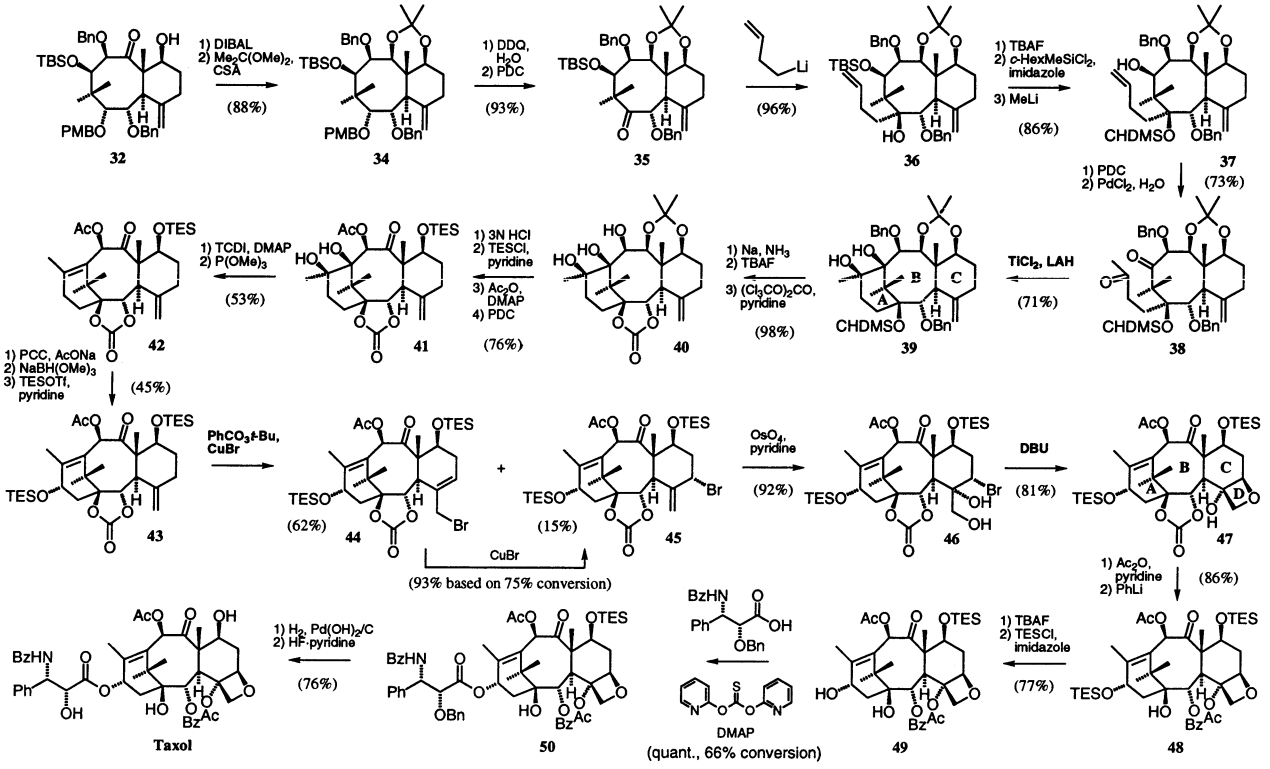


Fig. 9. Total Synthesis of Taxol.

silylene derivative in high yield. Alkylation of this with methyllithium furnished compound **37** having the desired C-1 protected hydroxyl group.[8] The desired diketone **38**, precursor of ABC ring system of Taxol, was obtained from the alcohol **37** by successive oxidation with PDC and Wacker-type oxygenation. Next, the intramolecular pinacol coupling reaction of **38** using the low-valent titanium reagent, prepared from $TiCl_2$ and $LiAlH_4$, gave the novel taxoid **39** containing the ABC ring system of Taxol. After the regioselective conversion of **39** to 8-membered ring ketone **41** *via* triol **40**, a novel taxoid **42** was formed by deoxygenation of the thionocarbonate using trimethylphosphite. Successive regioselective oxygenation with PCC, stereoselective reduction with $NaBH(OMe)_3$ at the C-13 position and protection of thus formed alcohol afforded tetracyclic compound **43** possessing all the functional groups necessary for conversion to Taxol.[12] Next, a new and efficient method was developed for formation of the oxetane ring required for Taxol.[13] Allylic oxygenation at the C-5 position of **43** using SeO_2 with or without TBHP did not take place at all, while PCC oxidation gave a mixture of undesirable oxygenated products. On the other hand, allylic bromides **44** and **45** were unexpectedly produced in 62% and 15% yields, respectively, when **43** was allowed to react with excess amounts of CuBr and $PhCO_3t$-Bu (1:1 molar ratio) under literature conditions for the allylic oxyacylation.[14] Further, the desired allylic bromide **45** was obtained on treating the allylic bromide **44** with CuBr in CH_3CN at 55°C. Dihydroxylation of this allylic bromide **45** with OsO_4 in pyridine gave a dihydroxy bromide **46** in 92% yield as a single stereosomer. The desired oxetanol **47** was obtained in good yield when this dihydroxy bromide was treated with DBU at 50°C in toluene.[13] The corresponding acetate was prepared by acetylation of the tertiary alcohol **47** using acetic anhydride in pyridine. 7,13-Bistriethylsilylbaccatin III (**48**) was synthesized in high yield by benzoylation at the C-2 position of C1-C2 carbonate.[13] Desilylation of **48** followed by monosilylation of the intermediate triol afforded 7-triethylsilylbaccatin III (**49**) in good yield. Finally, dehydration condensation between **49** and a derivative of *N*-benzoylphenylisoserine proceeded smoothly by the use of di-2-pyridinylthionocarbonate in toluene at 73°C to afford the desired coupling product **50** in quantitative yield at 66% conversion. Deprotection of the protected Taxol **50** thus formed gave the final target molecule Taxol in good yield.

In conclusion, a new method for the syntheses of Taxol and 8-demethyltaxoids was explored using optically active 8-membered ring compound intermediates as precursors of the B ring system of Taxol and of 8-

demethyltaxoids. This method could be widely applied to the syntheses of Taxol derivatives and various taxoids.

Acknowledgments. We would like to express our hearty thanks to Dr. Kouichi Uoto, Messrs. Kaku Sakata, Kaname Kimura, Takayuki Emura, Keitarou Seto, Yuji Akiyama, Nobuaki Mori, So Miyoshi, Masahiro Saitoh, Tomomi Kosugi, Toshihiro Nishimura, Naoto Ohkawa, Koji Nishimura and Koji Yamada for their cooperation, and also to Dr. Nobuharu Iwasawa (the University of Tokyo) for measurement of NOESY spectra and to Dr. Katsumi Fujimoto (Sankyo Co., Ltd.) for X-ray crystallographic analysis. This work was supported by a Research Grant of Japan Academy, SUT Grant for Research Promotion and Grant-in-Aids for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

References

1) Nicolaou, K. C., Dai, W-M., and Guy, R. K. (1994) Angew. Chem. Int. Ed. Engl. **33**, 15–44.
2) 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., and Liu, J. H. (1994) J. Am. Chem. Soc. **116**, 1597–1598: 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., and Liu, J. H. (1994) J. Am. Chem. Soc. **116**, 1599–1600.
3) 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., and Sorensen, E. J. (1994) Nature **367**, 630–634; Nicolaou, K. C., Nantermet, P. G., Ueno, H., Guy, R. K., Couladouros, E. A., and Sorensen, E. J. (1995) J. Am. Chem. Soc. **117**, 624–633; Nicolaou, K. C., Liu, J.-J., Yang, Z., Ueno, H., Sorensen, E. J., Claiborne, C. F., Guy, R. K., Hwang, C.-K., Nakada, M., and Nantermet, P. G. (1995) J. Am. Chem. Soc. **117**, 634–644; Nicolaou, K. C., Yang, Z., Liu, J.-J., Nantermet, P. G., Caiborne, C. F., Renaud, J., Guy, R. K., and Shibayama, K. (1995) J. Am. Chem. Soc. **117**, 645–652; Nicolaou, K. C., Ueno, H., Liu, J.-J., Nantermet, P. G., Yang, Z., Renaud, J., Paulvannan, K., and Chadha, R. (1995) J. Am. Chem. Soc. **117**, 653–659.
4) Masters, J. J., Link, J. T., Snyder, L. B., Young, W. B., and Danishefsky, S. J. (1995) Angew. Chem. Int. Ed. Engl. **34**, 1723–1726; 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., and Di Grandi, M. J. (1996) J. Am. Chem. Soc. **118**, 2843–2859.
5) Wender, P. A., Badham, N. F., Conway, S. P., Floreancig, P. E., Glass, T. E., Gränicher, C., Houze, J. B., Jänichen, J., Lee, D., Marquess, D. G., McGrane, P. L., Meng, W., Mucciaro, T. P., Mühlebach, M., Natchus, M. G., Paulsen, H., Rawlins, D. B., Satkofsky, J., Shuker, A. J., Sutton, J. C., Taylor, R. E., and Tomooka, K. (1997) J. Am. Chem. Soc. **119**, 2755–2756; Wender, P. A., Badham, N. F., Conway, S. P., Floreancig, P. E., Glass, T. E., Houze, J. B., Krauss, N. E., Lee, D., Marquess, D. G., McGrane, P. L., Meng, W., Natchus, M., Shuker, A. J., Sutton, J. C., and Taylor, R. E. (1997) J. Am. Chem. Soc. **119**, 2757–2758.
6) Mukaiyama, T., Shiina, I., Sakata, K., Emura, T., Seto, K., and Saitoh, M. (1995) Chem. Lett. **1995**, 179–180.
7) Shiina, I., Uoto, K., Mori, N., Kosugi, T., and Mukaiyama, T. (1995) Chem. Lett. **1995**, 181–182.
8) Mukaiyama, T., Shiina, I., Kimura, K., Akiyama, Y., and Iwadare, H. (1995) Chem. Lett. **1995**, 229–230.
9) Shiina, I., Iwadare, H., Saitoh, M., Ohkawa, N., Nishimura, T., and Mukaiyama, T. (1995) Chem. Lett. **1995**, 781–782.
10) Mukaiyama, T., Shiina, I., Iwadare, H., Saitoh, M., Nishimura, K., Nishimura, T., Ohkawa, N., Sakoh, H., and Saitoh, K. (1996) Chem. Lett. **1996**, 483–484.
11) Shiina, I., Nishimura, T., Ohkawa, N., Sakoh, H., Nishimura, K., Saitoh, K., and Mukaiyama, T. (1997) Chem. Lett. **1997**, 419–420.
12) **43**; $[\alpha]_D^{29} = -89.6°$ (c 1.086, benzene); IR (neat) 1812, 1749, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ =6.54 (s, 1H, 10-H), 5.41 (s, 1H, 20-H), 5.00 (s, 1H, 20-H), 4.79 (ddd, 1H, J=9.6, 4.2, 1.1 Hz, 13-H), 4.27 (d, 1H, J=5.4 Hz, 2-H), 4.14 (dd, 1H, J=11.1, 4.8 Hz, 7-H), 3.26 (d, 1H, J=5.4 Hz, 3-H), 2.56 (dd, 1H, J=15.3, 9.6 Hz, 14-H), 2.29–2.22 (m, 1H, 5-H), 2.21 (d, 3H, J=1.1 Hz, 18-Me), 2.17 (s, 3H, Ac), 2.14 (dd, 1H, J=15.3, 4.2 Hz, 14-H), 2.12–1.88 (m, 2H, 5-H, 6-H), 1.57–1.48 (m, 1H, 6-H), 1.19 (s, 3H, 19-Me), 1.13 (s, 6H, 16-Me, 17-Me), 0.98 (t, 9H, J=7.9 Hz, TES), 0.89 (t, 9H, J=7.9 Hz, TES), 0.65 (q, 6H, J=7.9 Hz, TES), 0.51 (q, 6H, J=7.9 Hz, TES); ^{13}C NMR ($CDCl_3$) δ =203.7 (9), 169.2 (10-Ac), 153.3 (carbonate), 146.4 (4), 140.0 (12), 130.7 (11), 114.5 (20), 90.2 (1), 82.1 (2), 76.5 (10), 73.7 (7), 62.6 (8), 48.8 (3), 40.3 (15), 38.0 (14), 32.1 (6), 27.5 (17), 20.9 (10-Ac), 19.0 (19), 17.9 (18), 11.2 (16), 6.7 (TES), 6.7 (TES), 5.2 (TES), 4.8 (TES); MS calcd for $C_{35}H_{59}O_8Si_2$, m/z 663, found 663 ($M+H^+$).
13) Shiina, I., Saitoh, M., Nishimura, K., Saitoh, K., and Mukaiyama, T. (1996) Chem. Lett. **1996**, 223–224.
14) Kharasch, M. S., Sosnovsky, G., and Yang, N. C. (1959) J. Am. Chem. Soc. **81**, 5819–5824.
15) Identical in all respects with an authentic sample of natural Taxol purchased from Aldrich Chemical Co., Inc.