

A Novel Approach to the Synthesis of Taxol. A Synthesis of Optically Active 3,7-dibenzyloxy-4,8-di-*t*-butyl-dimethylsiloxy-5,5-dimethyl-6-*p*-methoxybenzyloxy-2-octanone by Way of Stereoselective Aldol Reactions

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Optically active 3,7-dibenzyloxy-4,8-di-*t*-butyldimethylsiloxy-5,5-dimethyl-6-*p*-methoxybenzyloxy-2-octanone (**2**) has been synthesized by way of diastereoselective aldol reaction between 4-benzyloxy-5-*t*-butyldimethylsiloxy-2,2-dimethyl-3-*p*-methoxybenzyloxypentanal (**3**) and ketene silyl acetal **4** using $\text{MgBr}_2 \cdot \text{OEt}_2$ as a catalyst. The chiral pentanal **3** was synthesized either by asymmetric aldol reaction of both prochiral aldehyde **5** and ketene silyl acetal **4** using a chiral Lewis acid or by diastereoselective aldol reaction between the chiral aldehyde **6** derived from L-serine and the lithium enolate derived from methyl isobutyrate.

Taxol, a substance isolated from the Pacific yew tree, was found to have anti-cancer effects, and the synthesis of complex structure of taxol has been a tempting topic for synthetic chemists during past decades.¹

Quite recently, two groups succeeded in the chemical total synthesis of taxol; in Holton's strategy, (-)-camphor was used as a starting material and the synthesis of complex structure of taxol was achieved via multi-steps using a lot of highly effective synthetic reactions,² whereas in Nicolaou's convergent methodology, 8-ring closure reaction was carried out after constructing A and C ring systems.³ Our strategy in mean time is to synthesize the basic skeleton of taxol by making chiral B ring system **1** via optically active polyoxy-unit **2** first, and then to

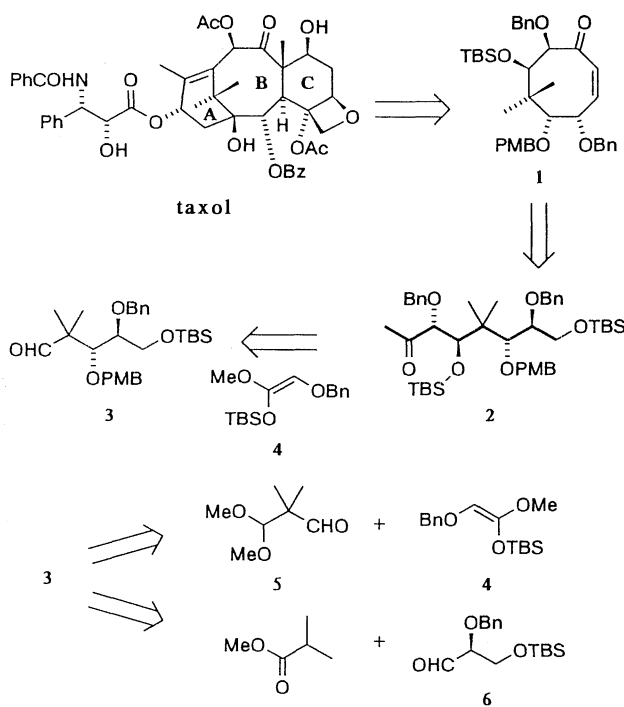
combine A and C ring systems. The above plan should be a flexible one for the synthesis of B ring system of taxol since it is possible to treat the synthetic intermediate of B ring system of taxol as a chiral linear compound according to this strategy.

Optically active polyoxy-unit **2** was synthesized by diastereoselective aldol reaction between chiral pentanal **3** and ketene silyl acetal **4** using $\text{MgBr}_2 \cdot \text{OEt}_2$ as a catalyst. The chiral pentanal **3** was synthesized by stereoselective aldol reactions; namely a) asymmetric aldol reaction of both prochiral aldehyde **5** and ketene silyl acetal **4** using a chiral Lewis acid developed in our laboratory,⁴ or b) diastereoselective aldol reaction between the chiral aldehyde **6** derived from L-serine and the lithium enolate derived from methyl isobutyrate as illustrated in the following scheme.

The treatment of benzylidene acetal of commercially available neopentyl glycol **7** with LiAlH_4 and AlCl_3 gave the corresponding alcohol, which in turn was oxidized to yield benzyloxyaldehyde **8**. After protecting aldehyde, the benzyl group was cleaved and thus-formed alcohol was oxidized to give the desired aldehyde **5**. Next, asymmetric aldol reaction between **5** and ketene silyl acetal **4** using chiral Sn(II) Lewis acid was tried under several reaction conditions. At last, the desired optically active ester **10** was obtained in good selectivity (anti / syn = 79 / 21, anti aldol; 93% ee) by use of $\text{Sn}(\text{OTf})_2$ coordinated with chiral diamine **9**. The relative configuration of **10** was determined by measuring the coupling constant of its derivative (Scheme 3). Reduction of **10** gave the corresponding diol which eventually led to monosilylether on treatment with *t*-butyldimethylsilyl chloride and imidazole. Then the secondary alcohol was protected by imide method using TfOH, which was followed by deprotection of acetal giving aldehyde **3**.

The chiral aldehyde **3** was also prepared by the following alternative route: optically active dihydroxyester **11** was prepared from L-serine by literature method⁵ and successive protection of primary alcohol with *t*-butyldimethylsilyl chloride and secondary alcohol with benzylimide gave dialkoxyester **12**, which in turn was reduced with L-selectride and followed by Swern oxidation to produce aldehyde **6**. Stereoselective aldol reaction between **6** and the lithium enolate derived from methyl isobutyrate smoothly proceeded to afford aldol product (anti / syn = 80 / 20). Successive treatments of the hydroxy group by imide method, reduction of ester function with diisobutylaluminum hydride (DIBAL) and Swern oxidation gave the aldehyde **3**.

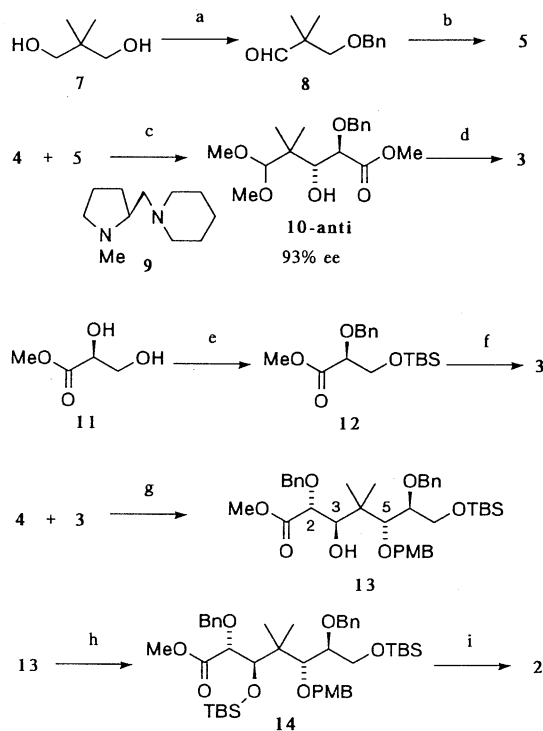
Though the aldol reaction between **3** and the lithium enolate derived from methyl 2-benzyloxyacetate gave the corresponding adduct with poor stereoselectivity, the aldol reaction between **3** and ketene silyl acetal **4** took place rapidly in the presence of $\text{MgBr}_2 \cdot \text{OEt}_2$ to yield the desired ester **13** in good stereoselectivity (2,3,5-anti, anti / three diastereomers = 81 / 19 / 0 / 0).⁶ The treatment of the alcohol with *t*-butyldimethylsilyl triflate and 2,6-lutidine afforded disiloxyester **14** in high yield. Reduction of ester function of **14** with DIBAL and Swern oxidation gave the



Scheme 1.

corresponding aldehyde, and the following alkylation by MeMgBr and Swern oxidation produced methyl ketone 2. First recrystallization of thus formed 2 gave optically pure methyl ketone 2.⁷ The pseudo-C₂ symmetrical structure of 2 was determined by measuring ¹H NMR of a derivative of 14 (Scheme 3).

Thus, an efficient and practical method for the synthesis of optically active polyoxy-unit 2, the synthetic intermediate of B ring system of taxol, was established by way of stereoselective aldol reactions.

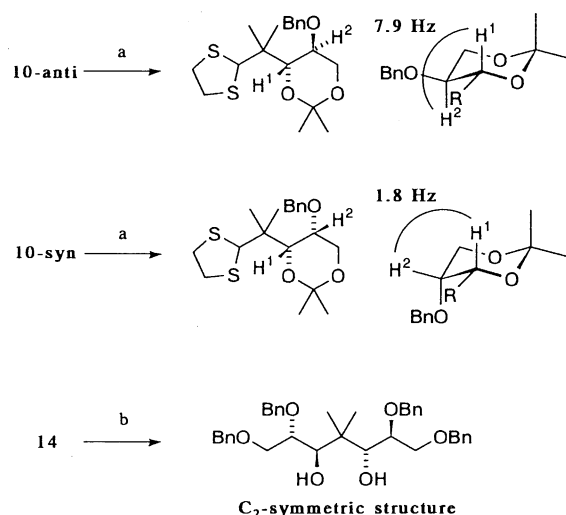


a) PhCH(OMe)₂, CSA, CH₂Cl₂, r.t. (97%); LiAlH₄, AlCl₃, CH₂Cl₂: Et₂O = 1 : 1, reflux (95%); (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C to r.t. (98%); b) HC(OMe)₃, TsOH, MeOH, r.t. (95%); H₂, Pd/C, EtOH, r.t., (99%); (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C to r.t. (86%); c) Sn(OTf)₂, chiral diamine 9, Bu₂Sn(OAc)₂, CH₂Cl₂, -23 °C, (45%, anti / syn = 79 / 21, anti aldol; 93% ee); d) LiAlH₄, THF, 0 °C; TBSCl, imidazole, CH₂Cl₂, 0 °C (2 steps 62%); PMBOC(CCl₃)=NH, TfOH, Et₂O, r.t.; AcOH, H₂O, THF, r.t. (2 steps 80%). e) TBSCl, imidazole, DMF, 0 °C (82%); BnOC(CCl₃)=NH, TfOH, Et₂O, reflux (quant.); f) L-selectride, THF, 0 °C (quant.); (COCl)₂, DMSO, N-methylmorpholine, CH₂Cl₂, -78 °C to r.t.; LDA, methyl isobutyrate, Et₂O, -78 °C (2 steps 75%, anti / syn = 80 / 20); PMBO-C(CCl₃)=NH, TfOH, Et₂O, 0 °C (98% based on 76% conversion); DIBAL, CH₂Cl₂, -78 °C (89%); (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C to r.t. (97%). g) MgBr₂·OEt₂, toluene, -15 °C (87% based on 88% conversion, anti, anti / three diastereomers = 81 / 19 / 0 / 0); h) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C (95%); i) DIBAL, toluene, -78 °C (96%); (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C to r.t. (98%); MeMgBr, THF, -78 °C (98%); (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C to 0 °C (89%).

Scheme 2.

References and Notes

- 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.



a) HSCH₂CH₂SH, BF₃·OEt₂, CH₂Cl₂, r.t. (94%); LiAlH₄, THF, 0 °C (90%); Me₂C(OMe)₂, CSA, CH₂Cl₂, r.t. (83%).
b) DIBAL, toluene, -78 °C (92%); TBAF, THF, r.t. (67%); BnBr, NaH, THF, r.t. (84%); DDQ, CH₂Cl₂, r.t. (76%); 1N HCl, THF, r.t. (31%).

Scheme 3.

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, *ibid.*, **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), and references cited therein. See, review; L. Wessjohann, *Angew. Chem., Int. Ed. Engl.*, **33**, 959 (1994).
- 4 T. Mukaiyama, I. Shiina, H. Uchiro, and S. Kobayashi, *Bull. Chem. Soc. Jpn.*, **67**, 1708 (1994), and references cited therein.
- 5 G. Hirth and W. Walther, *Helv. Chim. Acta.*, **68**, 1863 (1985).
- 6 Ether free MgBr₂ did not promote this aldol reaction.
- 7 2 (>99% ee); mp. 114 °C; [α]_D³⁰ +12.3° (c 1.00, PhH); IR (KBr) 1707 cm⁻¹; ¹H NMR (CDCl₃) δ = -0.05 (6H, s), 0.08 (3H, s), 0.09 (3H, s), 0.89 (9H, s), 0.94 (9H, s), 0.97 (3H, s), 0.99 (3H, s), 2.23 (3H, s), 3.55 (1H, ddd, J = 1.7, 4.0, 6.9 Hz), 3.79 (3H, s), 3.84 (1H, dd, J = 4.0, 11.5 Hz), 3.99 (1H, dd, J = 1.7, 11.5 Hz), 4.08 (1H, d, J = 6.9 Hz), 4.09 (1H, d, J = 2.3 Hz), 4.20 (2H, s), 4.32 (1H, d, J = 2.3 Hz), 4.40 (1H, d, J = 10.9 Hz), 4.54 (1H, d, J = 10.9 Hz), 4.62 (1H, d, J = 10.9 Hz), 4.73 (1H, d, J = 10.9 Hz), 6.86 (2H, d, J = 8.6 Hz), 7.10 - 7.37 (12H, m); HPLC (Daicel Chiralcel OD, hexane / iPrOH = 500 / 1, flow rate = 0.5 mL min⁻¹): t_R = 16.2 min (major enantiomer), t_R = 18.8 min (minor enantiomer).