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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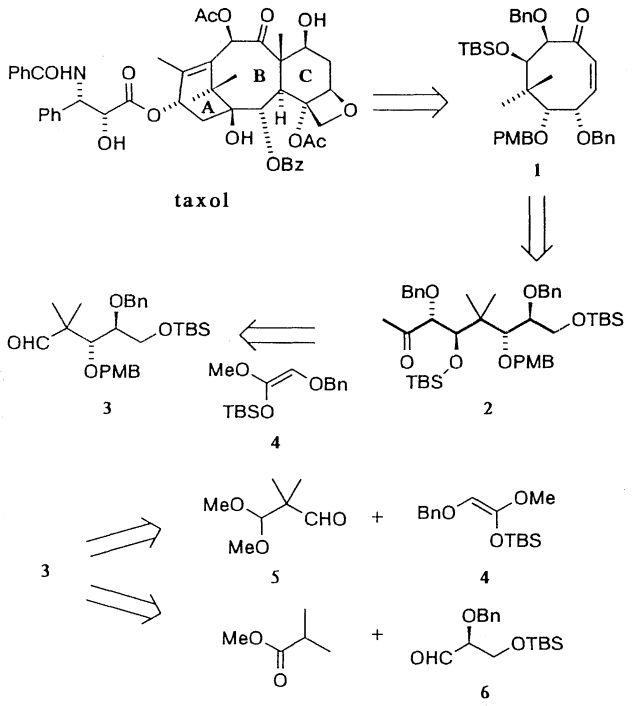
Optically active 3,7-dibenzyloxy-4,8-di-*t*-butyldimethylsiloxy-5,5-dimethyl-6-*p*-methoxybenzyloxy-2-octanone (**2**) has been synthesized by way of diastereoselective aldol reaction between 4-benzyloxy-5-*t*-butyldimethylsiloxy-2,2-dimethyl-3-*p*-methoxybenzyloxypentanal (**3**) and ketene silyl acetal **4** using $MgBr_2 \cdot OEt_2$ 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.



Scheme 1.

Optically active polyoxy-unit **2** was synthesized by diastereoselective aldol reaction between chiral pentanal **3** and ketene silyl acetal **4** using $MgBr_2 \cdot OEt_2$ 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.

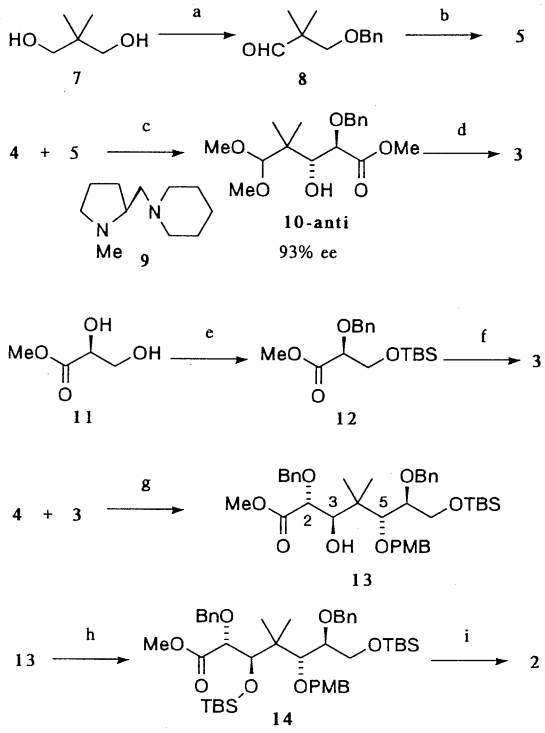
The treatment of benzylidene acetal of commercially available neopentyl glycol **7** with $LiAlH_4$ and $AlCl_3$ gave the corresponding alcohol, which in turn was oxidized to yield benzyloxyaldehyde **8**. After protecting aldehyde, the benzyl group was cleaved and thus-formed alcohol was oxidized to 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 $Sn(OTf)_2$ 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 imidate 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 method[5] and successive protection of primary alcohol with *t*-butyldimethylsilyl chloride and secondary alcohol with benzylimidate 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 imidate 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 $MgBr_2 \cdot OEt_2$ 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

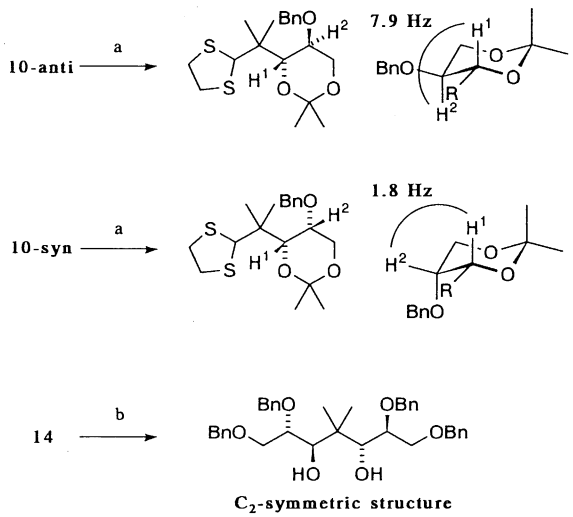
corresponding aldehyde, and the following alkylation by MeMgBr and Swern oxidation produced methyl ketone **2**. First recrystarization of thus formed **2** gave optically pure methyl ketone **2**.[7] The pseudo-C_2 symmetrical structure of **2** was determined by measuring ^{1}H NMR of a derivative 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, CH_2Cl_2, r.t. (97%); $LiAlH_4$, $AlCl_3$, CH_2Cl_2 : Et_2O = 1 : 1, reflux (95%); $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to r.t. (98%); b) $HC(OMe)_3$, TsOH, MeOH, r.t. (95%); H_2, Pd/C, EtOH, r.t., (99%); $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to r.t. (86%); c) $Sn(OTf)_2$, chiral diamine **9**, $Bu_2Sn(OAc)_2$, CH_2Cl_2, -23 °C, (45%, anti / syn = 79 / 21, anti aldol; 93% ee); d) $LiAlH_4$, THF, 0 °C; TBSCl, imidazole, CH_2Cl_2, 0 °C (2 steps 62%); $PMBOC(CCl_3)$=NH, TfOH, Et_2O, r.t.; AcOH, H_2O, THF, r.t. (2 ateps 80%).
e) TBSCl, imidazole, DMF, 0 °C (82%); $BnOC(CCl_3)$=NH, TfOH, Et_2O, reflux (quant.); f) L-selectride, THF, 0 °C (quant.); $(COCl)_2$, DMSO, N-methylmorpholine, CH_2Cl_2, -78 °C to r.t.; LDA, methyl isobutyrate, Et_2O, -78 °C (2 steps 75%, anti / syn = 80 / 20); PMBO-$C(CCl)_3$=NH, TfOH, Et_2O, 0 °C (98% based on 76% conversion); DIBAL, CH_2Cl_2, -78 °C (89%); $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to r.t. (97%).
g) $MgBr_2$·OEt_2, toluene, -15 °C (87% based on 88% conversion, anti, anti / three diastereomers = 81 / 19 / 0 / 0); h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (95%); i) DIBAL, toluene, -78 °C (96%); $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to r.t. (98%); MeMgBr, THF, -78 °C (98%); $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to 0 °C (89%).

Scheme 2.



a) $HSCH_2CH_2SH$, BF_3·OEt_2, CH_2Cl_2, r.t. (94%); $LiAlH_4$, THF, 0 °C (90%); $Me_2C(OMe)_2$, CSA, CH_2Cl_2, r.t. (83%).
b) DIBAL, toluene, -78 °C (92%); TBAF, THF, r.t. (67%); BnBr, NaH, THF, r.t. (84%); DDQ, CH_2Cl_2, r.t. (76%); 1N HCl, THF, r.t. (31%).

Scheme 3.

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. 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).

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6 Ether free $MgBr_2$ did not promote this aldol reaction.

7 **2** (>99% ee); mp. 114 °C; $[\alpha]_D^{30}$ +12.3° (c 1.00, PhH); IR (KBr) 1707 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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 / ^{i}PrOH = 500 / 1, flow rate = 0.5 mL min^{-1}): t_R = 16.2 min (major enantiomer), t_R = 18.8 min (minor enantiomer).