An Asymmetric Synthesis of Fully Functionalized B Ring System of Taxol

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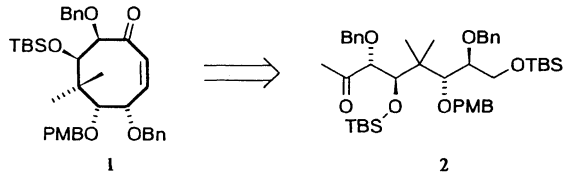
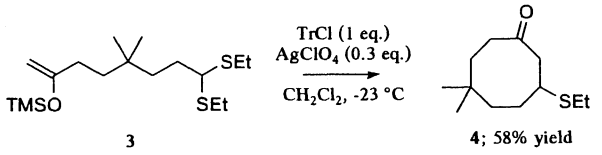
Optically active 7-*t*-butyldimethylsiloxy-4,8-dibenzyloxy-6,6-dimethyl-5-*p*-methoxybenzyloxy-2-cycloocten-1-one (**1**) was synthesized from 3,7-dibenzyloxy-4,8-di-*t*-butyldimethylsiloxy-5,5-dimethyl-6-*p*-methoxybenzyloxy-2-octanone (**2**) by way of intramolecular Reformatsky-type reaction using SmI_2.

In the preceding communication, our strategy for the synthesis of taxol via optically active fully functionalized 8-membered ring compound **1** was outlined and the synthesis of optically active polyoxy-unit **2**, a synthetic intermediate of **1**, by utilizing stereoselective aldol reactions was experimentally described.[1] Here, we would like to report an efficient method for the preparation of the optically active **1** by intramolecular Reformatsky-type reaction using SmI_2, and an attempted synthesis of **1** by intramolecular aldol reactions using Lewis acids.



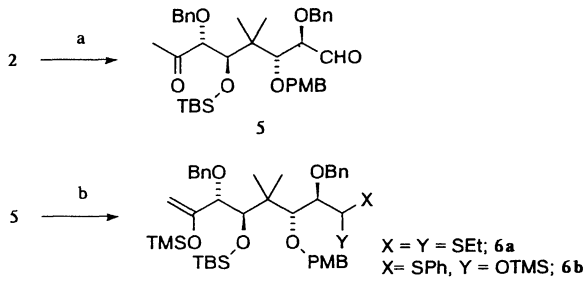
Scheme 1.

Kocienski reported on 8-membered ring cyclization between an acetal and an enol silyl ether by intramolecular aldol-type reaction using Lewis acid such as $TiCl_4$, $TiCl_2(OiPr)_2$, $BF_3{\cdot}OEt_2$, $SnCl_4$, TMSOTf, etc., in 1985.[2] Furthermore, it is well known that α,β-unsaturated ketone is formed from β-alkylthioketone by oxidation and successive elimination. Then, intramolecular aldol reaction between a dithioacetal and an enol silyl ether was tried in the presence of $TrClO_4$ using a model substrate that have no oxygen-containing functionalities at first.[3] Actually, in the presence of 100 mol% of TrCl and 30 mol% of $AgClO_4$, intramolecular aldol reaction of **3** smoothly proceeded at -23 °C to produce desired β-alkylthiocyclooctanone **4** in good yield (58%).

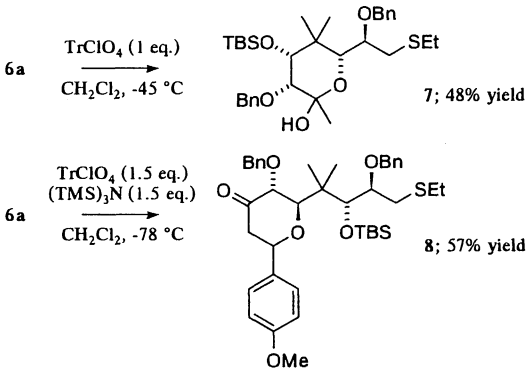


Next, syntheses of **6a** and **6b** were tried using optically active polyoxy-unit **2** which contains all functionalities for the construction of taxol. Selective cleavage of primary silyl ether and following Swern oxidation afforded keto aldehyde **5** in good yield. The aldehyde was protected by dithioacetal or O-trimethylsilyl monothioacetal, and was in turn transformed to the corresponding enol silyl ether **6a** or **6b**. Then, intramolecular aldol reaction of **6a** or **6b** was tried in the presence of $TrClO_4$ under several reaction conditions.

However, cyclic hemiketal **7** was produced exclusively via deprotection of *p*-methoxybenzylether of **6a**. On the other hand, when the same reaction was carried out in the coexistence of tris(trimethylsilyl)amine, cyclic ether **8** resulted unexpectedly. The reaction was considered to proceed via *p*-methoxybenzylic hydride reduction of dithioacetal, followed by aldol reaction between mixed acetal of *p*-methoxybenzaldehyde and enol silyl ether. Subsequent rearrangement of silyl ether and cyclization resulted in the formation of this undesired product. Also, 8-membered ring compound was not formed at all when the mixed acetal **6b** was used in place of **6a** in the above cyclization reaction.



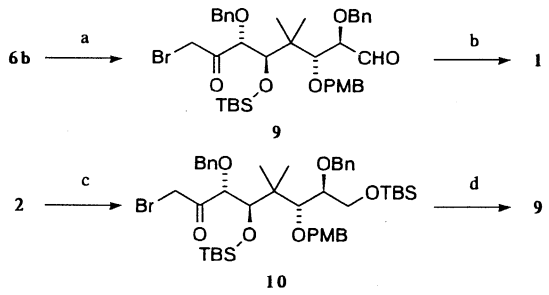
a) 1N HCl, THF, r.t. (98%); $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to r.t. (97%); b) (**6a**) $AgClO_4$, TMSCl, EtSTMS, toluene, -78 °C (80%); LDA, TMSCl, THF, -78 °C to r.t. (90%); (**6b**) $AgClO_4$, TMSCl, PhSTMS, toluene, -78 °C (87%); LHMDS, TMSCl, THF, -78 °C to r.t. (78%)



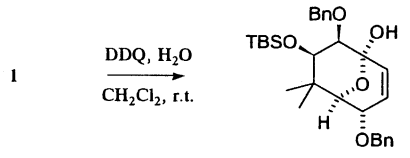
Scheme 2.

In the second place, utilization of intramolecular Reformatsky-type reaction using SmI_2 was planned for constructing 8-membered ring compound because there have been a few reports concerning SmI_2 mediated cyclization reactions for syntheses of medium and large membered ring compounds.[4] α-Bromoketo aldehyde **9** was obtained in high yield from mixed acetal **6b**. In the presence of an excess amount of SmI_2 (ca. 3 eq.), the cyclization reaction of **9** proceeded quite smoothly to give the β-hydroxycyclooctanone in high yield (diastereomers ratio 77 / 23).

The alcohols were mesylated and successive treatment with DBU gave the desired α,β-unsaturated cyclooctanone **1**[5] in good yield. The alternative and convenient synthesis for α-bromoketo aldehyde **9** was carried out by bromination of α-position of synthetic intermediate **2**, followed by deprotection of silyl ether **10**[6] and Swern oxidation. It is reported that 8-membered ring compounds have many conformational variations;[7] thus formed **1** has also unique structural character expectedly. For example, ^{1}H NMR of **1** shows that **1** is a mixture of two slowly interconverting conformational isomers for these broadening peaks in spectra (in $CDCl_3$ at 25 °C). Fast exchange of atropisomers on the ^{1}H NMR time scale at 270 MHz was attained at 100 °C in toluene-d_8, whereas the two isomers did not interconvert at -30 °C because sharp signals were detected on the ^{1}H NMR (57 / 43 in $CDCl_3$). In order to make clear the structure of the compound **1**, it was transformed into bicyclic compound **11** by DDQ oxidation, and rigid bicyclic skeleton of thus formed **11** was confirmed by its ^{1}H NMR.[8]



a) NBS, THF, r.t.; 1N HCl, THF, r.t. (2 steps 94%); b) SmI_2, THF, 0 °C (91%, 77 / 23); MsCl, ^{i}Pr$_2$NEt, CH_2Cl_2, r.t., then DBU, r.t. (81%); c) LHMDS, TMSCl, THF, -78 °C to r.t.; NBS, THF, r.t.(2 steps 97%); d) 1N HCl, THF, r.t. (90%); $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to r.t. (98%)



11; 90% yield

Scheme 3.

It is noted that an efficient and practical method for the synthesis of optically active fully functionalized B ring system of taxol was established by way of intramolecular Reformatsky-type reaction using SmI_2.

Further studies on constructing A and C ring systems onto 8-membered ring compound **1** are now in progress.

References and Notes

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4 T. Tabuchi, K. Kawamura, J. Inanaga, and M. Yamaguchi, *Tetrahedron Lett.*, **27**, 3889 (1986); E. Vedejs and S. Ahmad, *ibid.*, **29**, 2291 (1988); T. Moriya, Y. Hanada, J. Inanaga, and M. Yamaguchi, *ibid.*, **29**, 6947 (1988); J. Inanaga, Y. Yokoyama, Y. Hanada, and M. Yamaguchi, *ibid.*, **32**, 6371 (1991). See also; G. A. Molander and J. A. McKie, *J. Org. Chem.*, **57**, 3132 (1992); G. A. Molander and J. A. McKie, *ibid.*, **59**, 3186 (1994).

5 **1** (>99% ee); $[\alpha]_D^{29}$ +66.8° (c 0.733, PhH); IR (neat) 1676 cm^{-1}; HPLC (Daicel Chiralcel AD, hexane / ^{i}PrOH = 50 / 1, flow rate = 1.0 mL min^{-1}): t_R = 5.4 min (minor enantiomer), t_R = 7.6 min (major enantiomer).

6 **10** ; mp. 123 °C; $[\alpha]_D^{28}$ +4.7° (c 1.00, PhH); IR (KBr) 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = -0.09 (3H, s), -0.04 (3H, s), 0.15 (3H, s), 0.14 (3H, s), 0.90 (9H, s), 0.95 (3H, s), 0.98 (9H, s), 1.02 (3H, s), 3.53 (1H, ddd, *J* = 1.7, 3.0, 8.3 Hz), 3.80 (3H, s), 3.86 (1H, dd, *J* = 3.0, 11.5 Hz), 4.07 (1H, dd, *J* = 1.7, 11.5 Hz), 4.09 (1H, d, *J* = 8.3 Hz), 4.13 (1H, d, *J* = 10.9 Hz), 4.17 (1H, d, *J* = 10.9 Hz), 4.33 (1H, d, *J* = 2.6 Hz), 4.35 (2H, s), 4.35 (1H, d, *J* = 10.6 Hz), 4.39 (1H, d, *J* = 2.6 Hz), 4.55 (1H, d, *J* = 10.9 Hz), 4.60 (1H, d, *J* = 10.9 Hz), 4.72 (1H, d, *J* = 10.6 Hz), 7.05 (2H, d, *J* = 2.3 Hz), 7.06 - 7.08 (2H, m), 7.21 - 7.37 (10H, m).

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8 **11**; $[\alpha]_D^{29}$ +146.7° (c 0.61, PhH); IR (neat) 3380 cm^{-1}; ^{1}H NMR (C_6D_6) δ = 0.00 (3H, s), 0.05 (3H, s), 0.89 (9H, s), 0.91 (3H, s), 1.14 (3H, s), 2.78 (1H, br s), 3.62 (1H, br d, *J* = 4.0 Hz), 3.69 (1H, d, *J* = 4.0 Hz), 3.96 (1H, br s), 4.10 (1H, dd, *J* = 1.6, 3.3 Hz), 4.51 (1H, d, *J* = 12.2 Hz), 4.61 (1H, d, *J* = 12.2 Hz), 4.61 (1H, d, *J* = 10.9 Hz), 4.99 (1H, d, *J* = 10.9 Hz), 5.94 (1H, dd, *J* = 3.3, 10.2 Hz), 6.17 (1H, dd, *J* = 1.6, 10.2 Hz), 7.14 - 7.32 (10H, m); ^{13}C NMR ($CDCl_3$) δ = -5.20 (CH_3, TBS), -3.77 (CH_3, TBS), 18.60 (C, ^{t}Bu), 22.86 (CH_3), 25.95 (CH_3*3, TBS), 26.87 (CH_3), 39.75 (C), 67.94 (CH), 70.08 (CH_2), 74.02 (CH_2), 77.31 (CH), 78.26 (CH), 83.09 (CH), 94.23 (C, hemiketal), 127.60 (CH), 127.64 (CH), 127.75 (CH), 127.87 (CH*2), 128.14 (CH*2), 128.37 (CH*2), 128.66 (CH*2), 134.09 (CH), 138.22 (C), 138.29 (C); MS (EI) 453 (M^+-^{t}Bu).