

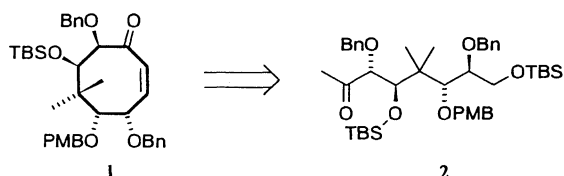
## An Asymmetric Synthesis of Fully Functionalized B Ring System of Taxol

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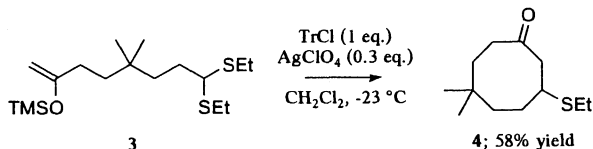
Optically active 7-*t*-butyldimethylsiloxy-4,8-dibenzyloxy-6,6-dimethyl-5-*p*-methoxybenzyloxy-2-cycloocten-1-one (**1**) was synthesized from 3,7-dibenzyloxy-4,8-di-*t*-butyldimethylsiloxy-5,5-dimethyl-6-*p*-methoxybenzyloxy-2-octanone (**2**) by way of intramolecular Reformatsky-type reaction using  $\text{SmI}_2$ .

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.<sup>1</sup> Here, we would like to report an efficient method for the preparation of the optically active **1** by intramolecular Reformatsky-type reaction using  $\text{SmI}_2$ , and an attempted synthesis of **1** by intramolecular aldol reactions using Lewis acids.



Scheme 1.

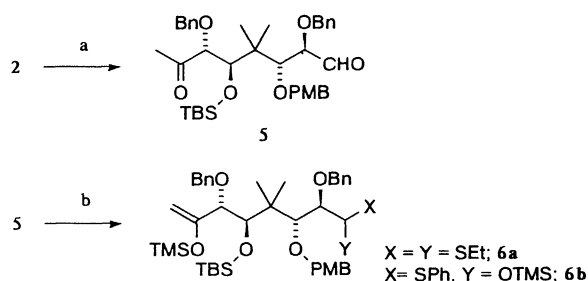
Kocienski reported on 8-membered ring cyclization between an acetal and an enol silyl ether by intramolecular aldol-type reaction using Lewis acid such as  $\text{TiCl}_4$ ,  $\text{TiCl}_2(\text{OiPr})_2$ ,  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{SnCl}_4$ ,  $\text{TMSOTf}$ , etc., in 1985.<sup>2</sup> Furthermore, it is well known that  $\alpha,\beta$ -unsaturated ketone is formed from  $\beta$ -alkylthio ketone by oxidation and successive elimination. Then, intramolecular aldol reaction between a dithioacetal and an enol silyl ether was tried in the presence of  $\text{TrClO}_4$  using a model substrate that have no oxygen-containing functionalities at first.<sup>3</sup> Actually, in the presence of 100 mol% of  $\text{TrCl}$  and 30 mol% of  $\text{AgClO}_4$ , intramolecular aldol reaction of **3** smoothly proceeded at  $-23^\circ\text{C}$  to produce desired  $\beta$ -alkylthiocyclooctanone **4** in good yield (58%).



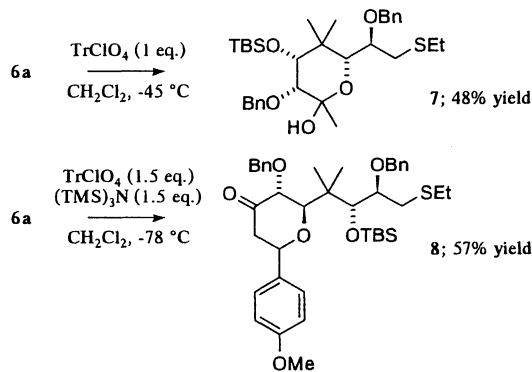
Next, syntheses of **6a** and **6b** were tried using optically active polyoxy-unit **2** which contains all functionalities for the construction of taxol. Selective cleavage of primary silyl ether and following Swern oxidation afforded keto aldehyde **5** in good yield. The aldehyde was protected by 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  $\text{TrClO}_4$

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.



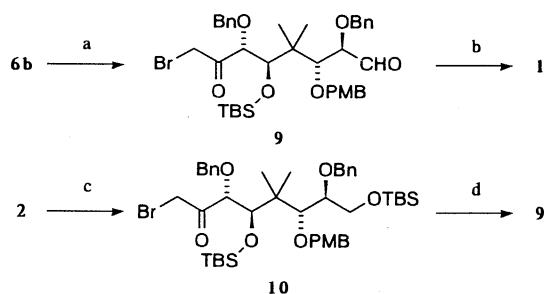
a) 1N HCl, THF, r.t. (98%);  $(\text{COCl})_2$ , DMSO,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$  to r.t. (97%); b) (**6a**)  $\text{AgClO}_4$ ,  $\text{TMSCl}$ ,  $\text{Et}_3\text{N}$ , toluene,  $-78^\circ\text{C}$  (80%);  $\text{LDA}$ ,  $\text{TMSCl}$ , THF,  $-78^\circ\text{C}$  to r.t. (90%); (**6b**)  $\text{AgClO}_4$ ,  $\text{TMSCl}$ ,  $\text{PhSTMS}$ , toluene,  $-78^\circ\text{C}$  (87%);  $\text{LHMDS}$ ,  $\text{TMSCl}$ , THF,  $-78^\circ\text{C}$  to r.t. (78%)



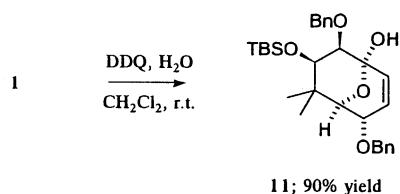
Scheme 2.

In the second place, utilization of intramolecular Reformatsky-type reaction using  $\text{SmI}_2$  was planned for constructing 8-membered ring compound because there have been a few reports concerning  $\text{SmI}_2$  mediated cyclization reactions for syntheses of medium and large membered ring compounds.<sup>4</sup>  $\alpha$ -Bromoketo aldehyde **9** was obtained in high yield from mixed acetal **6b**. In the presence of an excess amount of  $\text{SmI}_2$  (ca. 3 eq.), the cyclization reaction of **9** proceeded quite smoothly to give the  $\beta$ -hydroxycyclooctanone in high yield (diastereomers ratio 77 / 23).

The alcohols were mesylated and successive treatment with DBU gave the desired  $\alpha,\beta$ -unsaturated cyclooctanone **1**<sup>5</sup> in good yield. The alternative and convenient synthesis for  $\alpha$ -bromoketo aldehyde **9** was carried out by bromination of  $\alpha$ -position of synthetic intermediate **2**, followed by deprotection of silyl ether **10**<sup>6</sup> and Swern oxidation. It is reported that 8-membered ring compounds have many conformational variations;<sup>7</sup> thus formed **1** has also unique structural character expectedly. For example, <sup>1</sup>H NMR of **1** shows that **1** is a mixture of two slowly interconverting conformational isomers for these broadening peaks in spectra (in CDCl<sub>3</sub> at 25 °C). Fast exchange of atropisomers on the <sup>1</sup>H NMR time scale at 270 MHz was attained at 100 °C in toluene-*d*<sub>8</sub>, whereas the two isomers did not interconvert at -30 °C because sharp signals were detected on the <sup>1</sup>H NMR (57/43 in CDCl<sub>3</sub>). 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 <sup>1</sup>H NMR.<sup>8</sup>



a) NBS, THF, r.t.; 1N HCl, THF, r.t. (2 steps 94%); b) SmI<sub>2</sub>, THF, 0 °C (91%, 77/23); MsCl, <sup>1</sup>Pr<sub>3</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, 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)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C to r.t. (98%)



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<sub>2</sub>.

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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communication.

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- 5 **1** (>99% ee); [ $\alpha$ ]<sub>D</sub><sup>29</sup> +66.8° (c 0.733, PhH); IR (neat) 1676 cm<sup>-1</sup>; HPLC (Daicel Chiralcel AD, hexane/<sup>i</sup>PrOH = 50/1, flow rate = 1.0 mL min<sup>-1</sup>): *t*<sub>R</sub> = 5.4 min (minor enantiomer), *t*<sub>R</sub> = 7.6 min (major enantiomer).
- 6 **10**; mp. 123 °C; [ $\alpha$ ]<sub>D</sub><sup>28</sup> +4.7° (c 1.00, PhH); IR (KBr) 1728 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = -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).
- 7 D. Nasipuri, "Stereochemistry of Organic Compounds," Wiley, New York (1991), p. 278; F. A. L. Anet and V. J. Basus, *J. Am. Chem. Soc.*, 95, 4424 (1973); K. J. Shea, J. W. Gilman, C. D. Haffner, and T. K. Dougherty, *ibid.*, 108, 4953 (1986); P. A. Wender and T. P. Mucciari, *ibid.*, 114, 5878 (1992); Z. Wang, S. E. Warder, H. Perrier, E. L. Grimm, M. A. Bernstein, and R. G. Ball, *J. Org. Chem.*, 58, 2931 (1993).
- 8 **11**; [ $\alpha$ ]<sub>D</sub><sup>29</sup> +146.7° (c 0.61, PhH); IR (neat) 3380 cm<sup>-1</sup>; <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>)  $\delta$  = 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = -5.20 (CH<sub>3</sub>, TBS), -3.77 (CH<sub>3</sub>, TBS), 18.60 (C, <sup>t</sup>Bu), 22.86 (CH<sub>3</sub>), 25.95 (CH<sub>3</sub>\*3, TBS), 26.87 (CH<sub>3</sub>), 39.75 (C), 67.94 (CH), 70.08 (CH<sub>2</sub>), 74.02 (CH<sub>2</sub>), 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<sup>+</sup>-<sup>t</sup>Bu).