A New and Convenient Method for the Preparation of Cyclooctanone Containing Bis-Aldol Skeleton by Samarium(II) Iodide-mediated Intramolecular Aldol Cyclization of ω-Oxiranyl Keto Octanal

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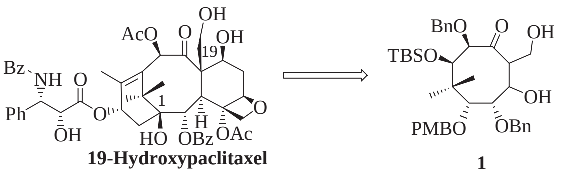
A polyoxy eight-membered ring compound containing a bis-aldol skeleton, 2,6-dibenzyloxy-3-(*t*-butyldimethylsiloxy)-7-hydroxy-8-hydroxymethyl-5-(*p*-methoxybenzyloxy)-4,4-dimethylcyclooctanone **1**, a key synthetic intermediate of 19-hydroxypaclitaxel, was prepared in high yield from 2,6-dibenzyloxy-5-(*t*-buthyldimethylsilyloxy)-3-(*p*-methoxybenzyloxy)-4,4-dimethyl-8,9-oxiranyl-7-oxononanal **6** by the samarium(II) iodide-mediated intramolecular aldol cyclization.

Taxane diterpenes, including antineoplastic agent Taxol, have a highly oxidized tricyclic carbon framework consists of a central eight-membered ring and two peripheral six-membered rings.[1] In the course of our synthetic studies on Taxol and its derivatives, fully substituted cyclooctanone which corresponds to the eight-membered ring structure of Taxol was first prepared in good yield by samarium(II) iodide-mediated aldol-type cyclization of a linear optically active acyclic ω-(α-bromoketo)octanal.[2–6] Further, asymmetric total synthesis of Taxol has been completed according to the synthetic strategy that started from the above eight-membered ring ketone.[3]

In order to improve pharmacological profile of Taxol, particularly to improve its solubility in water, synthesis of 19-hydroxypaclitaxel, a new Taxol derivative, was planned.

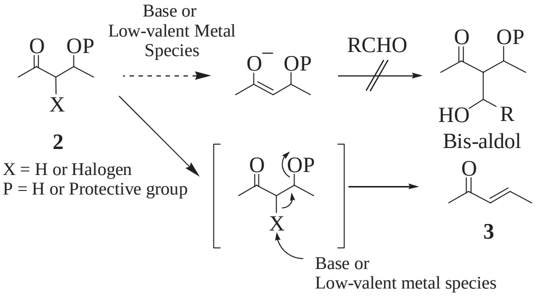


Scheme 1.

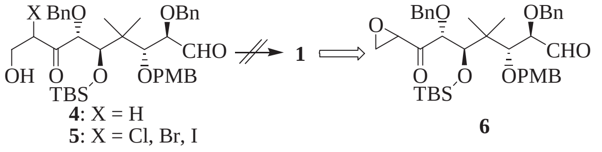
It was then thought that the construction of polyoxy eight-membered ring intermediate **1** containing bis-aldol skeleton should be the first thing to be done; however, it was previously noted that the bis-aldol was hardly obtained by base-promoted aldol reaction between β-hydroxyketone and aldehyde or by Reformatsky type aldol reaction between α-halo-β-hydroxyketone and aldehyde: that is, when β-alkoxyketone **2** was treated with strong bases such as LDA or reductants such as low-valent metal species, a dehydrated product, α, β-unsaturated ketone **3**, was formed as shown in Scheme 2.[7]

It thus seemed difficult to prepare eight-membered ring compound **1** from **4** (mono-aldol) or **5** (α-halo-β-hydroxyketone) on treatment with bases or reductants. On the other hand, it was recently reported from our laboratory that a new and useful method for the synthesis of unsymmetrical bis-aldols was established by SmI$_2$-mediated aldol reaction of aldehydes with aryl or alkyl oxiranyl ketones.[8] Therefore, it was considered that the synthesis of intermediate **1** would be performed according to this method using ω-oxiranyl keto aldehyde **6** as sketched in Scheme 3.

In this communication, we would like to describe an effective method for the preparation of the above key intermediate **1**, polyoxy eight-membered ring that contains bis-aldol skeleton, from ω-oxiranyloxononanal. The SmI$_2$-mediated aldol reaction of model compound **8** was investigated first and was further applied to the synthesis of an optically active fully oxidized cyclooctanone, a precursor for the synthesis of 19-hydroxypaclitaxel.

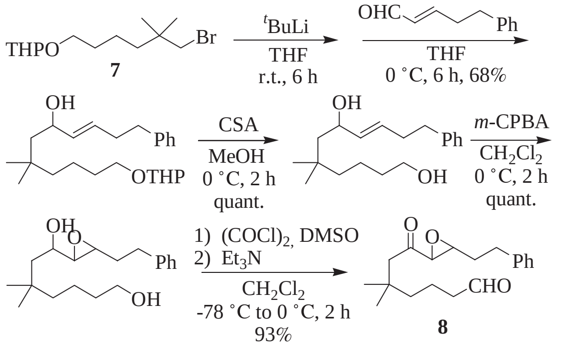


Scheme 2.



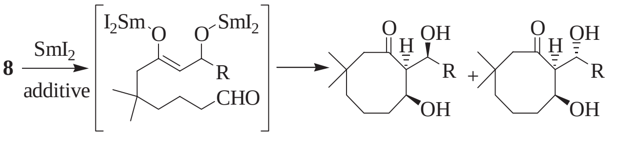
Scheme 3.

The ω-oxiranyl keto aldehyde **8** was prepared simply by four steps: namely, alkylation of 5-phenyl-2-pentenal with lithium reagent generated from ω-bromo-1-tetrahydropyranyl ether **7** and *t*-butyllithium, and deprotection of THP group, successive epoxidation with *m*-CPBA, and Swern oxidation (Scheme 4).



Scheme 4.

In the first place, formation of the eight-membered ring compound was tried by treating **8** with SmI$_2$ and the desired product **10** was obtained in 30% yield. The reducing ability of low-valent samarium species was generally known to be increased by the coordination of electron rich ligands such as H$_2$O to the metal ions. Kamochi and Kudo reported their interesting observations on the reduction of carboxylic acids, esters, amides and nitriles using SmI$_2$-H$_2$O to support the above.[9] Based on the above results, the cyclization reaction was carried out by adding water and a mixture of the cyclized product was obtained in 78% yield. Of possible four stereoisomers, *cis-syn* and *cis-anti*, determined by their conversion to the corresponding dimethyl acetonides, were isolated (Table 1, Entry 2).



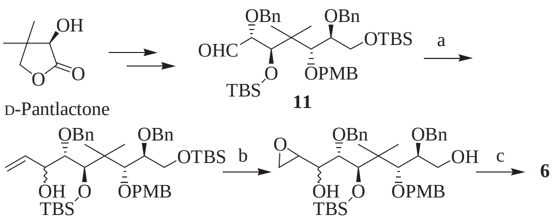
9: R = (CH$_2$)$_2$Ph *cis-syn* (**10a**) *cis-anti* (**10b**)

Table 1. Yields of cyclooctaneones **10**

Entry	Additive / eq	Yield / % (*cis-syn* / *cis-anti*)[a]
1	none	30 (nd)[b]
2	Water / 3	78 (50 / 50)

[a]The ratio of the possible four isomers was determined by integration of the ^{1}H NMR spectrum of a mixture of the corresponding dimethyl acetonide derivatives. [b]Not determined.

Next, the present method was applied to the synthesis of key intermediate **1**, a polyoxy eight-membered ring compound corresponding to the B ring of 19-hydroxypaclitaxel. The ω-oxiranyl keto aldehyde **6** was prepared from aldehyde **11** which prepared from D-pantolactone according to the original procedure of our laboratory (Scheme 5).[3]



Scheme 5. Reagent and conditions: a) vinylMgBr, THF, 0 °C (98%); b) 1 M HCl, THF, r.t. (88%); *m*-CPBA, CH$_2$Cl$_2$, 50 °C (96%); c) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, −78 °C to 0 °C (95%).

The SmI$_2$-mediated intramolecular aldol reaction of **6** proceeded to give the cyclized product **1** in 83% yield along with 2-debenzyloxygenation compound **12** in 10% yield in the absence of H$_2$O (Table 2, Entry 1). This debenzyloxygenation occurred by further SmI$_2$-reduction of **1** whose benzyloxy group was activated with Sm^{III} species generated by the reductive aldol reaction. Thus, it was considered that the addition of water would reduce Lewis acidity of the Sm^{III} species to inhibit the reductive elimination of the benzyloxy group with excess SmI$_2$. When water was added to the reaction mixture, the aldol reaction of **6** proceeded smoothly to give the cyclized products, **1a** and **1b**, in 30% and 46% yields, respectively, without forming **12** (Entry 2). A small amount of **4** was formed by ring opening of epoxide of **6** because hydrolysis of β-metalloxyketo samarium enolate took place competitively with the desired cyclization. It was further found that the yield of the cyclized product increased up to 91% when ^{i}PrOH was added (Entry 3). In order to clarify the structure of these eight-membered ring compounds, **1a** and **1b** were transformed into bicyclic derivatives **13a** and **13b** on treatment with DDQ and the structures of the formed rigid bicyclic skeletons were confirmed by ^{1}H NMR spectroscopy.

Thus, the synthesis of 8-membered ring compound containing bis-aldol skeleton, the key intermediate of the synthesis of 19-hydroxypaclitaxel, was efficiently performed by using an excess amount of SmI$_2$ *via* intramolecular aldol cyclization of the disamarium alkoxy enolate.

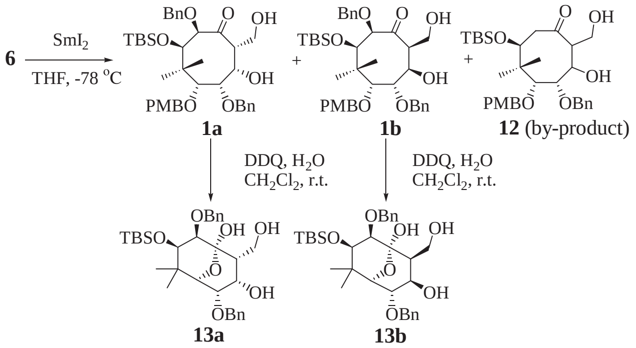


Table 2. Yields of cyclooctaneone **1**

Entry	Additive / eq	Yield / % (**1a**/**1b**)
1	None	83[a] (50/50)
2	Water / 3	76 (39/61)
3	^{i}PrOH / 2	91 (49/51)

[a]The deoxygenated product **12** was also detected in about 10%.

A typical procedure for the SmI$_2$-mediated cyclization (Table 2, Entry 3) is as follows: to a solution of ω-oxiranyl keto aldehyde **6** (1.54 g, 2.38 mmol) in THF (100 mL) was added a solution of SmI$_2$ in THF (0.1 M, 71.4 mL, 7.14 mmol) and ^{i}PrOH (300 mg, 4.76 mmol) immediately in succession at −78 °C under argon. The reaction mixture was kept stirring for 30 min at the same temperature and then saturated aqueous ammonium chloride was added. The mixture was filtered through a short pad of Celite and the filtrate was extracted with diethyl ether. The organic layer was washed with water and brine, and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (hexane/AcOEt = 3/1) to afford the cyclized products, **1a** (0.72 g, 45%) and **1b** (0.75 g, 46%) as colorless oil.

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