Fluoride Ion-Mediated Intramolecular Aldol Cyclization of 7-(*t*-Butyldimethylsiloxy)-7-octenal

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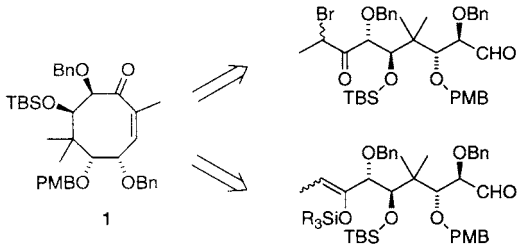
Polyoxy 8-membered ring compound was synthesized in moderate to good yields by intramolecular aldol cyclization of 7-(*t*-butyldimethylsiloxy)-7-octenal using tetrabutylammonium fluoride (TBAF).

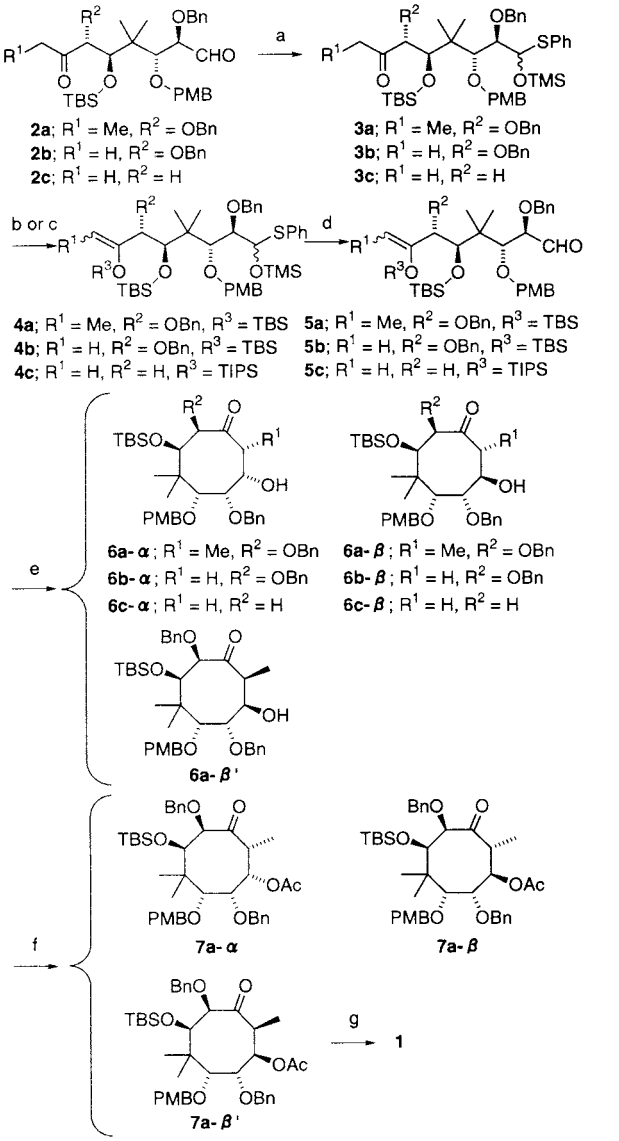
Several useful methods are known for the syntheses of macrocyclic compounds: e.g., conventional macrolactonizations of the corresponding active ω-hydroxyl carboxylic esters,[1] and carbon–carbon bond forming cyclizations using Heck[2] and Stille[3] coupling reactions. Recently, a ring closure by olefin metathesis using Grubbs' catalyst is often employed as a powerful method for carbon–carbon bond forming cyclization because of its applicability to macrocyclic compounds of various ring sizes.[4] On the other hand, it is well-known that the intramolecular aldol reactions are convenient tools for the syntheses of various cyclic compounds.[5] Most of these reactions were applied to the formations of five or six membered ring compounds under thermodynamic conditions by using such bases as alkali hydroxides and so on. Danishefsky demonstrated a ring closure in the total syntheses of the 16-membered macrolides, epothilones A and B, by macroaldolizations of potassium enolates of the corresponding ω-formyl esters having no α-proton in the aldehyde part under kinetic conditions.[6] Further, the usefulness of SmI_2-mediated intramolecular Reformatsky reactions was shown in the syntheses of medium-membered ring compounds by Yamaguchi and Inanaga.[7] In our total synthesis of Taxol, SmI_2-mediated intramolecular aldol reaction of ω-(α-bromoketo)aldehyde was successfully applied to the synthesis of a key intermediate **1**, polyoxy 8-membered ring compound corresponding to the B ring of Taxol (Scheme 1).[8–10]



Scheme 1.

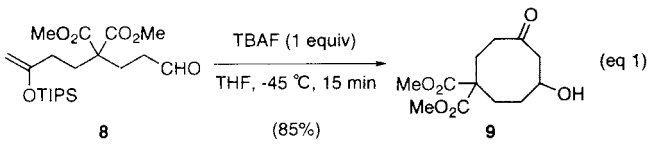
In the present experiment, the fluoride ion-mediated intramolecular aldol-type cyclization of 7-(*t*-butyldimethylsiloxy)-7-octenal was investigated in order to develop an alternative method for the efficient preparation of the above key intermediate **1** (Scheme 1). It is known that a silyl enol ether of a ketone or an ester having an aldehyde group with α-proton in the same molecule can hardly be prepared because the enolization of aldehyde part takes place faster than those of ketones and esters. Then, two possible ways for the preparation of silyl enol ethers having an enolizable aldehyde in the same molecule were considered: that is, 1) transformation of an alcohol or an ester group to the corresponding aldehyde after its ketone part was converted to silyl enol ether; 2) protection of the aldehyde group before the silyl enol ether was formed and then to regenerate the aldehyde group by deprotection. It was already shown that transformation of the ketoaldehyde to ω-(α-bromoketo)-aldehyde via a silyl enol ether proceeded smoothly after protection of the aldehyde as its *O*,*S*-acetal.[8,11] Based on these results, silyl enol ether, a precursor of cyclization, was regioselectively formed by treating *O*,*S*-acetal with a base and a trialkylsilyl trifluoromethanesulfonate. In this communication, we would like to report a successful method for the preparation of 8-membered ring compounds by fluoride ion-mediated intramolecular aldol cyclization of 7-(*t*-butyldimethylsiloxy)-7-octenal under mild conditions.[12]

O-Trimethylsilyl monothiophenyl acetal **3a** was prepared by treating ketoaldehyde **2a** with phenylthiosilane in the presence of a catalytic amount of trimethylsilyl perchlorate. The acetal **3a** was transformed to the corresponding silyl enol ether **4a** by using lithium hexamethyldisilazide and *t*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf). Although the deprotection of **4a** in 1 M citric acid methanol solution gave the desired aldehyde **5a** in 83% yield, it still needed a long reaction time before completing the deprotection in a large scale experiment. It is probably due to low solubility of **4a** in methanol. The desired deprotection proceeded to afford **5a** in 95% yield when anhydrous TBAF was used in THF solution at –78 °C for 2 h. The effect of Lewis acids such as $SnCl_2$, $Sn(OTf)_2$, $FeCl_3$, $MgBr_2{\cdot}OEt_2$, $InCl_3$, $InCl_3$–TBSCl, TrCl–$SnCl_2$, and ZnI_2 was examined in the intramolecular aldol cyclization of **5a**; however, no desired aldol adducts were obtained and several side reactions such as decomposition of **5a** including deprotection of TBS and PMB groups took place and a small amount of **5a** was recovered. Then, the synthetic plan was changed to generating a reactive enolate anion by treating **5a** with fluoride ion. When the TBAF-mediated intramolecular aldol cyclization of **5a** was tried in THF at –45 °C for 1 h, a mixture of **6a**-α and **6a**-β was obtained together with **6a**-β**'**. Acetylation of these aldol adducts gave **7a**-α (6.7%), **7a**-β (33.4%), and **7a**-β**'** (38.6%), respectively, in two steps from **5a**.[13] Configurations of **6a**-β**'** and **7a**-β**'** were determined by the transformation to the corresponding enone **1**.[9] This transformation shows **7a**-β**'** to be a new diastereomer which had not been obtained by SmI_2-mediated intramolecular aldol reaction.[9] Next, the present method was applied to the synthesis of other 8-membered ring compound, a precursor of the synthesis of Taxol derivatives. The aldehydes **5b** and **5c** were also prepared according to the procedure depicted in Scheme 2. Tetrabutylammonium fluoride-mediated intramolecular aldol reaction of **5b** proceeded smoothly to give **6b**-α (8%) and **6b**-β (62%). In the case of **5c**, a mixture of **6c**-α and **6c**-β was obtained in 45% yield.[14] Furthermore, the aldehyde **8** also worked well to afford **9** in 85% yield (eq 1).



a) $AgClO_4$, TMSCl, PhSTMS, toluene, -78 °C (81% of **3a**, 87% of **3b**, 61% of **3c**); b) LHMDS, TBSOTf, 0 °C (92% of **4a**, quant of **4b**); c) TIPSOTf, $^{i}Pr_2NEt$, 0 °C to rt (66% of **4c** and 34% of recovered **3c**); d) $CuCl_2$, TBAF, THF, -78 °C (95% of **5a**, 76% of **5b**, 64% of **5c** and 25% of recovered **4c**); e) TBAF, THF, -45 °C (8% of **6b**-α and 62% of **6b**-β, 45% of **6c**-α+**6c**-β, diastereomeric ratio = 90/10); f) Ac_2O, DMAP, pyridine, 0 °C (6.7% of **7a**-α, 33.4% of **7a**-β, and 38.6% of **7a**-β', 2 steps from **5a**); g) DBU, benzene, 60 °C (53% from **7a**-β' and 33% of recovered **7a**-β').

Scheme 2.



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13 To a solution of **5a** (206.7 mg, 0.2660 mmol) in THF (1.3 mL) was added slowly anhydrous TBAF in THF (0.5 M, 0.54 mL, 0.27 mmol) at –45 °C and then the mixture was stirred for 1 h. Aqueous saturated sodium hydrogencarbonate (2 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4. The organic solvents were evaporated under reduced pressure and the crude product was purified by thin-layer chromatography on silica gel (hexane/ethyl acetate = 5/1) to afford the mixture of **6a**-α and **6a**-β (73.1 mg) and **6a**-β' (78.9 mg), respectively. To a solution of the mixture of **6a**-α and **6a**-β (73.1 mg) and DMAP (1.3 mg, 0.011 mmol) in pyridine (2.5 mL) was added acetic anhydride (0.39 mL, 4.10 mmol) at 0 °C and then the mixture was stirred for 1 h at rt. Phosphate buffer (3 mL, pH = 7) was added to quench the reaction. The mixture was extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with saturated aqueous copper(II) sulfate (10 mL), saturated aqueous sodium hydrogencarbonate (10 mL), water (10 mL) and brine (10 mL), dried over Na_2SO_4. The organic solvents were evaporated under reduced pressure and the crude product was purified by thin-layer chromatography on silica gel (hexane/ethyl acetate = 6/1) to afford **7a**-α (12.6 mg, 6.7%), **7a**-β (62.7 mg, 33.4%) in two steps from **5a**. **6a**-β' was acetylated according to the above method to afford **7a**-β' (72.4 mg, 38.6%) in two steps from **5a**.
14 No attempts have been made to optimize this reaction. Configuration assignment was not made.