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# Further study on $SmI_2$-induced reductive intramolecular cyclization: synthesis of polycyclic ethers having an angular methyl group

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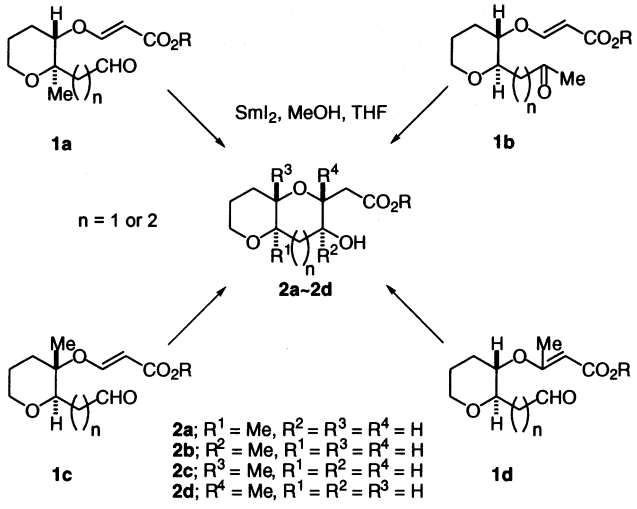
**Abstract**—The $SmI_2$-induced reductive intramolecular cyclization of an aldehyde and β-alkoxy acrylate was further investigated for the synthesis of polycyclic ethers having an angular methyl group. The cyclization produced 6,6- and 6,7-membered bicyclic ethers having a methyl group at C2 or C6 and C2 or C7 position, respectively. 

Marine polycyclic ethers,[1] exemplified by brevetoxins, have attracted the attention of synthetic organic chemists due to their unique structural framework and potent biological activities. The most characteristic structural feature of this family is a *trans*-fused polycyclic ether ring system, in which angular methyl groups are often found. Thus, the construction of four kinds of cyclic ethers **2a**–**d** having a methyl group ($R^1$, $R^2$, $R^3$, and $R^4$) is a very important step for the synthesis of various polycyclic ethers. We have already reported a facile and highly efficient strategy for the iterative synthesis of a *trans*-fused polycyclic ether ring system based on $SmI_2$-induced reductive intramolecular cyclization.[2] This method was successfully applied to the synthesis of cyclic ethers having an angular methyl group; i.e. reaction of **1a** and **1b** ($n=1$ or 2) with $SmI_2$ stereoselectively afforded *trans*-fused cyclic ethers **2a** ($R^1=Me$) and **2b** ($R^2=Me$), respectively (Scheme 1).[3] However, the $SmI_2$-induced cyclization of **1c** and **1d** ($n=1$ or 2) toward **2c** ($R^3=Me$) and **2d** ($R^4=Me$), has not yet been investigated as the remaining step, because the preparation of the requisite substrates **1c** and **1d** was difficult. We now report the results of $SmI_2$-induced cyclization of **1c** and **1d**.

First, the $SmI_2$-induced reductive cyclization of **1c** to **2c** was studied. The starting substrate **5** having a tertiary alcohol for the synthesis of **1c** was efficiently synthesized from commercially available 4-oxo-1-pentanol (**3**) (Scheme 2). The hetero-Michael reaction of **3** with ethyl propiolate in the presence of *N*-methylmorpholine[4] afforded β-alkoxy acrylate **4**. The $SmI_2$-induced reductive cyclization of **4** stereoselectively afforded *trans*-tetrahydropyran **5** in quantitative yield.

Then, construction of the requisite substrate **10**, corresponding to **1c**, from **5** was carried out (Scheme 3). After preparing acetate **6** and thioacetal **7** from the




**Scheme 1.** $SmI_2$-induced cyclization of **1** for the synthesis of polycyclic ethers having an angular methyl group.

*Keywords*: samarium diiodide; cyclizations; cyclic ethers; angular methyl.

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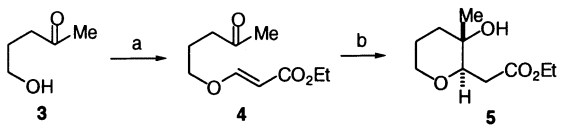
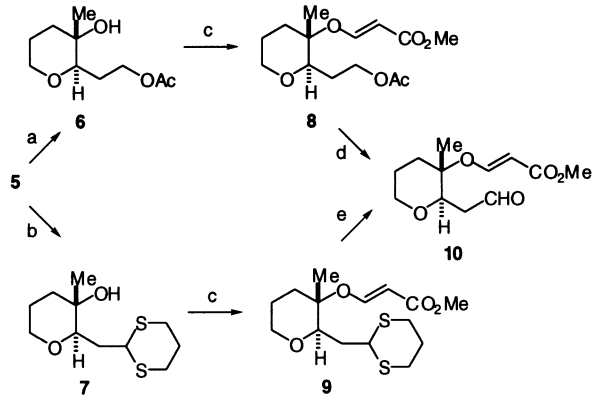


**Scheme 2.** *Reagents and conditions*: (a) ethyl propiolate, *N*-methylmorpholine, $CH_2Cl_2$, rt (63%); (b) $SmI_2$ (3 equiv), MeOH (3 equiv.), THF, rt (100%).

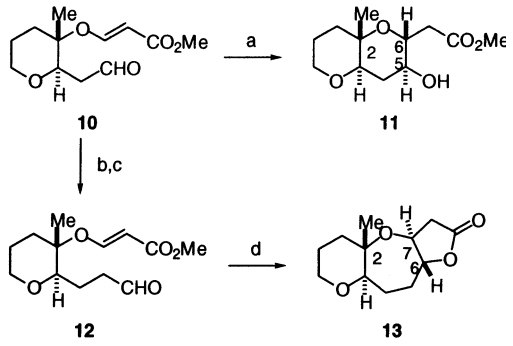


**Scheme 3.** *Reagents and conditions*: (a) i) $LiAlH_4$, $Et_2O$, rt, ii) $Ac_2O$, pyridine, rt (90%, 2 steps); (b) i) DIBAH, toluene, −78°C, ii) 1,3-propanedithiol, $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, 0°C (87%, 2 steps); (c) methyl 3-methoxyacrylate, PPTS, toluene, reflux (87% for **8**, 72% for **9**); (d) i) $K_2CO_3$, MeOH, rt, ii) Dess–Martin periodinane, $CH_2Cl_2$, rt (82%, 2 steps); (e) MeI, $NaHCO_3$, MeCN–$H_2O$, rt (91%).

ester **5**, respectively, we examined preparation of the desired β-alkoxy acrylate from these tertiary alcohols. The usual reaction conditions used for primary or secondary alcohol (i.e. treatment with ethyl propiolate in the presence of *N*-methylmorpholine) were ineffective, and after many trials, good results were finally obtained. Upon treatment of **6** and **7** with methyl 3-methoxyacrylate in the presence of PPTS under reflux with azeotropic removal of MeOH, the hetero-Michael addition and elimination of MeOH took place to give β-alkoxy acrylates **8** and **9**, respectively, in satisfactory yield. With the desired **8** and **9** in hand, we proceeded to the synthesis of aldehyde **10**. Deprotection of acetate **8** followed by Dess–Martin oxidation gave aldehyde **10** in 82% yield. On the other hand, dethioacetalization of **9** with MeI[5] also gave aldehyde **10** in 91% yield.

The stage was then set for examination of $SmI_2$-induced cyclization of **10** (Scheme 4). To our delight, upon treatment of **10** with $SmI_2$ in THF in the presence of MeOH, reductive cyclization proceeded smoothly to give a single product **11** in 83% yield. The product **11** was determined to have our desired 2,6-*syn*-5,6-*trans*-configuration by NMR analysis.

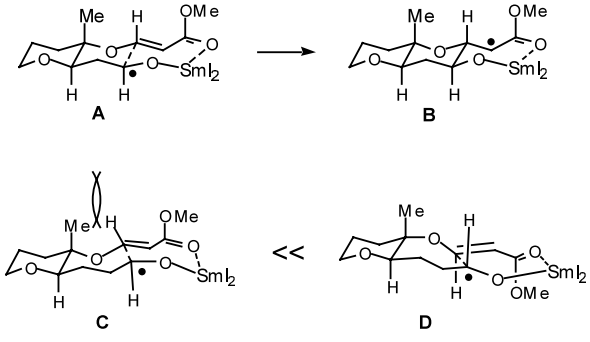
In addition, construction of the corresponding oxepane was investigated (Scheme 4). The Wittig reaction of aldehyde **10** with $Ph_3P{=}CHOMe$ followed by hydrolysis with CSA in aqueous MeCN provided the required aldehyde **12**. The reaction of **12** with $SmI_2$ also stereoselectively proceeded to give oxepane **13** as a single



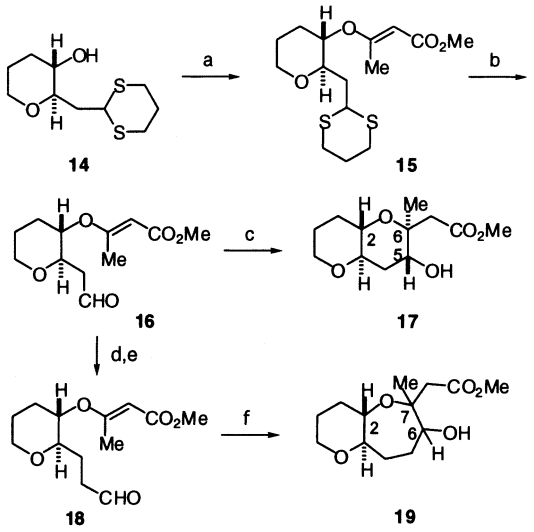
**Scheme 4.** *Reagents and conditions*: (a) $SmI_2$ (2.4 equiv.), MeOH (3 equiv.), THF, rt (83%); (b) $MeOCH_2P^+Ph_3Cl^-$, NaHMDS, THF, 0°C (74%); (c) CSA, MeCN–$H_2O$, rt (89%); (d) $SmI_2$ (4 equiv), MeOH (3 equiv.), THF, rt (75%).

product in 75% yield. However, contrary to our expectation, **13** has 2,7-*anti*-6,7-*trans* configuration.

These results would be explained as follows. The reaction of **10** would proceed through a chelated intermediate **A**.[2a] The C–C bond formation in **A** took place with complete stereoselectivity to give **B**, which is reduced to an anion by a second equiv of $SmI_2$ and then protonated by MeOH to give 2,6-*syn*-5,6-*trans*-tetrahydropyran **11**. On the other hand, in the reaction of **12**, the chelated intermediate **C** would have more severe steric repulsion between Me and H than that of **A**. Thus, the reaction of **12** giving **13** would proceed through intermediate **D**, which should be a more favorable intermediate than **C**.

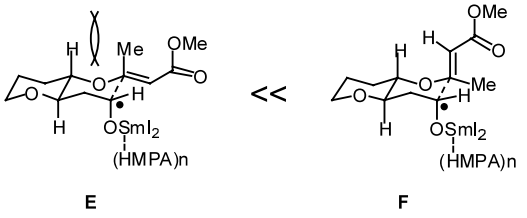


Next, the $SmI_2$-induced reductive cyclization of **1d** to **2d** was studied (Scheme 5). Although the hetero-Michael reaction of **14**[2a] with methyl 2-butynoate did not proceed under the usual conditions using *N*-methylmorpholine, the reaction was effected in the presence of $PBu_3$[6] to give β-alkoxy-β-methyl-acrylate **15** in 71% yield. Dethioacetalization of **15** with MeI gave aldehyde **16** in 90% yield. Treatment of **16** under the usual conditions ($SmI_2$, MeOH, THF, rt) resulted in recovery of the starting material **16**. Then, HMPA was added to accelerate the reaction, although the cyclization would proceed through a non-chelation mechanism.[2c] In fact, addition of HMPA effected the reductive cyclization, but the product was 2,6-*anti*-5,6-*trans*-tetrahydropyran **17** in 69% yield.




**Scheme 5.** *Reagents and conditions*: (a) methyl 2-butynoate, $PBu_3$, $CH_2Cl_2$, rt (71%); (b) MeI, $NaHCO_3$, $MeCN–H_2O$, rt (90%); (c) $SmI_2$ (6 equiv.), MeOH (3 equiv.), THF–HMPA, rt (69%); (d) $MeOCH_2P^+Ph_3Cl^-$, NaHMDS, THF, 0°C (76%); (e) CSA, wet $CH_2Cl_2$, rt (60%,); (f) $SmI_2$ (6 equiv), MeOH (3 equiv.), THF–HMPA, rt.

A plausible mechanism for the stereoselectivity would be explained as follows. The reaction in the presence of HMPA would proceed via non-chelated intermediates **E** and/or **F**,[2c] in which HMPA tightly coordinates to Sm(III). Because of steric repulsion between Me and H in **E**, the cyclization would proceed through intermediate **F** to produce **17** stereoselectively.




Aldehyde **16** was then converted into aldehyde **18** by following the same procedure used for **10** (Scheme 5). The reaction of **18** with $SmI_2$ in THF–HMPA afforded many spots, among which 2,7-*anti*-6,7-*trans*- and 2,7-*syn*-6,7-*trans*-oxepanes**19** were included.

The stereostructures of products **11**, **13**, and **17** were determined by NOE and coupling constants as shown in Fig. 1.

In summary, $SmI_2$-induced reductive cyclization of **10** gave 2,6-*syn*-5,6-*trans*-tetrahydropyran **11**, while that

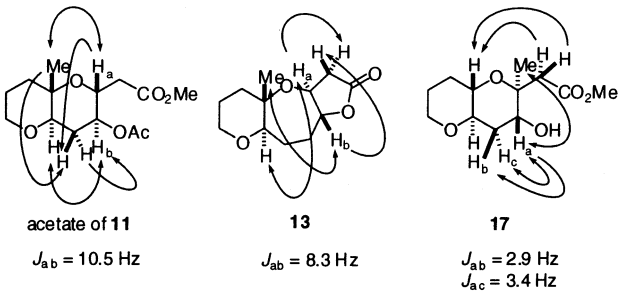



**Figure 1.**

of **12** gave 2,7-*anti*-6,7-*trans*-oxepane **13**. Reaction of **16** with $SmI_2$ proceeded only in the presence of HMPA, which effected reductive cyclization through a non-chelated intermediate to give 2,6-*anti*-5,6-*trans*-tetrahydropyran **17**, while that of **18** under the same conditions resulted in giving many products. Observation of these reactions would be useful for the construction of polycyclic ether ring systems bearing an angular methyl. Further studies on the synthesis of polycyclic ether ring systems and total synthesis of natural products based on the present $SmI_2$-induced cyclization are now in progress in this laboratory.

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