



A new method for the stereoselective construction of angular methyl group of fused cyclic ethers

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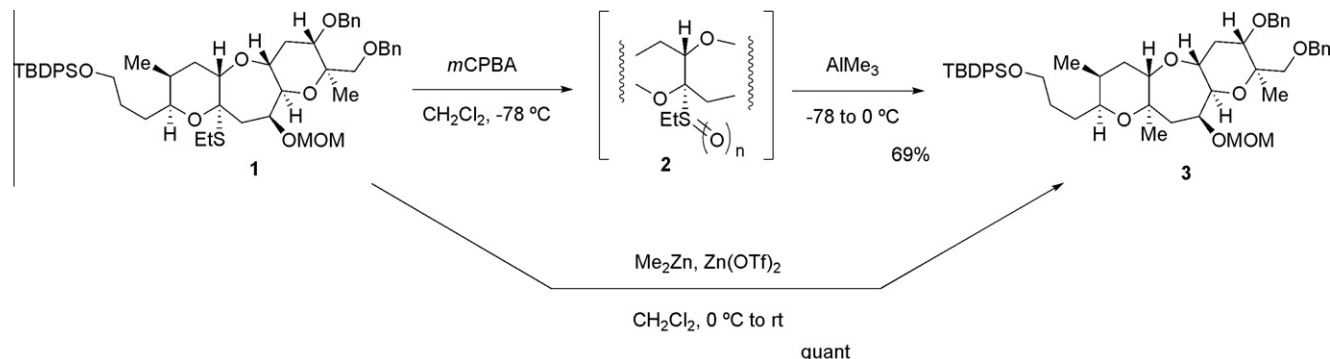
ABSTRACT

A convenient method for the stereoselective construction of angular methyl group of fused cyclic ethers is described. Reactions of mixed thioacetals with $\text{Me}_2\text{Zn}/\text{Zn}(\text{OTf})_2$ afforded the corresponding methylated products in good yields. Various protective groups such as MOM ether, benzylidene acetal, TBS ether, and pivaloyl group were stable under the reaction conditions.

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In recent years there has been an explosion of interest in biologically active natural products of marine origin.¹ Due to their structural novelty and toxicity, these compounds are particularly attractive targets for synthetic chemists.² In the synthesis of polycyclic ethers, the insertion of angular methyl groups as well as the construction of the fused ring system is an important task. Recently, we have achieved a total synthesis of brevenal.³ The synthesis included the insertion of an angular methyl group to **1** (Scheme 1). According to the reported procedure, the mixed thioacetal **1** was oxidized with *m*CPBA, and the resulting sulfoxide

or sulfone **2** was treated with Me_3Al in one-pot.⁴ Although the desired product **3** was obtained in a reasonable yield, the formation of significant amount of unidentified by-products was observed. Furthermore, the reproducibility of this reaction was not satisfactory in large-scale experiments, presumably, because of the low stability of the intermediate **2**. After several attempts, we found that the reaction of **1** with $\text{Me}_2\text{Zn}/\text{Zn}(\text{OTf})_2$ afforded **3**, directly, in quantitative yield.⁵ The reaction conditions did not affect the MOM protection of **1**. This result prompted us to investigate the generality of this reaction. In this Letter, we wish to report a new



Scheme 1.

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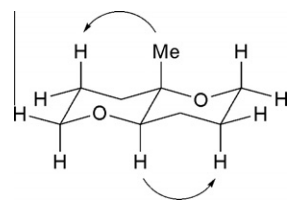
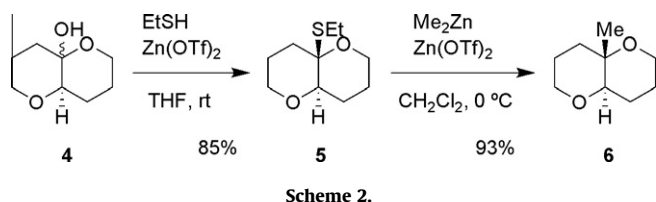


Figure 1. Observed NOEs are shown by arrows.

Table 1
Reactions of mixed thioacetals^a

Entry	Substrate	Product	Yield ^b (%)
1			93
2			81
3			93
4			88
5 ^c			88

^a Reactions were carried out with Me₂Zn (5 equiv) and Zn(OTf)₂ (2 equiv) in CH₂Cl₂ at 0 °C for 0.5–3 h.

^b Isolated yield.

^c The reaction was carried in ClCH₂CH₂Cl at 80 °C for 54 h.

method for the stereoselective construction of angular methyl group of fused cyclic ethers.

In an initial experiment, the synthesis of a 6-6 ring system was examined (Scheme 2). Treatment of the hemiacetal **4** with EtSH/

Zn(OTf)₂ gave the mixed thioacetal **5** in 85% yield.^{4b} The reaction of **5** with Me₂Zn/Zn(OTf)₂ proceeded smoothly to furnish the bicyclic ether **6** as a single stereoisomer in 93% yield.⁶ The stereochemistry of **6** was determined by ¹H NMR analysis and NOE experiments as shown in Figure 1.

On the basis of the results described above, we next examined the reaction of substrates **7–11** having various ring system and protective groups.⁷ The results are summarized in Table 1. The reaction of **7** gave the corresponding 6-7 ring ether **12** in 93% yield (entry 1). The benzylidene acetal was stable under the reaction conditions. Similarly, the mixed thioacetal **8** was converted to the 6-6-7 ring system **13** in 81% yield (entry 2). On the other hand, the reaction of **8** under the reported procedure, *m*CPBA oxidation followed by treatment with Me₃Al,⁴ gave a complex mixture. Formation of **13** was not observed. The substrate **9** having primary and secondary TBS ethers could be used for the reaction (entry 3). The product **14** was obtained in 93% yield. The reaction conditions did not affect the pivaloyl (Piv) group of **10**. The product **15** was obtained in 88% yield (entry 4). Furthermore, the methodology was successfully applied to the reaction of **11** to provide the 6-8-7 ring ether **16** in 88% yield, although prolonged reaction time was required (entry 5).

In conclusion, we have demonstrated a simple and convenient method for the insertion of angular methyl group to fused cyclic ethers via the reaction of mixed thioacetals with Me₂Zn/Zn(OTf)₂. Various protective groups such as MOM ether, benzylidene acetal, TBS ether, and pivaloyl group can survive under the reaction conditions. We anticipate that the present method will be useful in the total synthesis of polycyclic ethers and other natural products.

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- Experimental procedure is as follows:* To a mixture of **5** (57 mg, 0.28 mmol) in CH₂Cl₂ (2.7 mL) at 0 °C were added Me₂Zn (1.4 mL, 1.0 M in hexane, 1.4 mmol) and Zn(OTf)₂ (200 mg, 0.56 mmol). After stirring the reaction mixture for 5 h at the same temperature, the reaction was quenched with a 1:1 mixture of MeOH/Et₃N. The mixture was filtered through a Celite pad with ether as an eluent, and the filtrate was concentrated. The residue was purified by column chromatography to give **6** (41 mg, 93%): ¹H NMR (400 MHz, CDCl₃) δ 4.00–3.92 (m, 1H), 3.76 (ddd, *J* = 11.5, 11.5, 2.5 Hz, 1H), 3.75–3.70 (m, 1H), 3.36 (ddd, *J* = 12.4, 11.2, 2.2 Hz, 1H), 3.21–3.19 (m, 1H), 2.04–1.66 (m, 5H), 1.45–1.23 (m, 3H), 1.16 (s, 3H).
- The substrates **7–10** were prepared from the corresponding hemiacetals by the same procedure described in the Scheme 2. The mixed thioacetal **11** was synthesized from a hydroxy dithioacetal by using the Nicolaou's protocol, see Ref. 4a.