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Synthesis of methyl-substituted *trans*-fused tetrahydropyrans via 6-*endo* cyclization

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Abstract

A stereocontrolled synthesis of methyl-substituted *trans*-fused tetrahydropyrans having methyl groups adjacent to the ring oxygen is described. The strategy involves the coupling reaction of sulfonyl-stabilized oxiranyl anions with triflates and 6-*endo* cyclization of their products.

Keywords: epoxides; cyclization; tetrahydropyrans; oxiranyl anion.

Polycyclic ether marine toxins such as brevetoxins, maitotoxin, and yessotoxin constitute a structurally unique family of marine natural products and have been of great interest due to their potent biological activities and structural complexity characterized by *trans*-fused polycyclic ether units whose ring size ranges from six to nine members.[1] The polytetrahydropyran ring systems constitute the rigid backbone of these marine toxins and, frequently, tetrahydropyrans containing quaternary methyl groups adjacent to ring oxygen are incorporated in the ring systems (Fig. 1). In many cases, most of the methyl groups are located at the same side of the polyether skeleton and form a hydrophobic face which is considered to interact with lipid bilayers.[2] Although many iterative and convergent methods for polytetrahydropyran synthesis have been developed,[3] only a few methods have been reported for the synthesis of methyl-substituted polytetrahydropyran systems.[4] Recently, we reported the preparation of *trans*-fused polytetrahydropyrans based on an oxiranyl anion strategy.[5] The potential of this methodology for the synthesis of the methylated cyclic ethers is obvious by the introduction of methyl groups into cyclization precursors. In this paper, we wish to present a general and efficient approach to the construction of methyl-substituted tetrahydropyrans via 6-*endo* cyclization.

The cyclization precursor **3** (Scheme 1) was prepared by the reaction of the monocyclic triflate **1** and the optically active oxiranyl anion generated from epoxy sulfone **2** in THF at −100°C in the presence of 3 equiv. of HMPA in more than 90% yields, except for the reaction of **1** (R_1=Me) and **2** (R_2=Me) which required 7.5 equiv. of HMPA to afford a 71% yield of **3**. The results of the 6-*endo* cyclization of monomethylated **3** (R_1 or R_2=Me) are summarized in Table 1. Entry 1 demonstrates the originally

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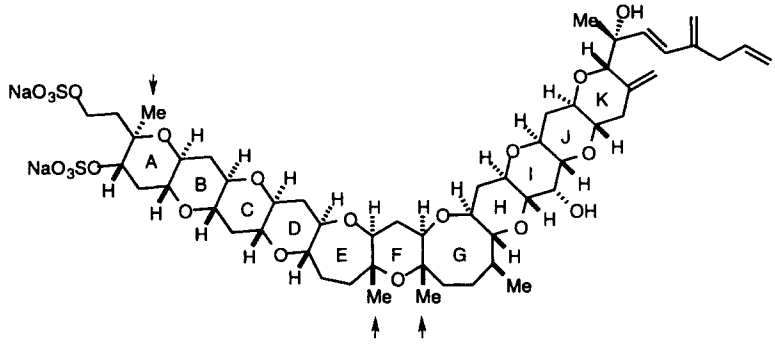
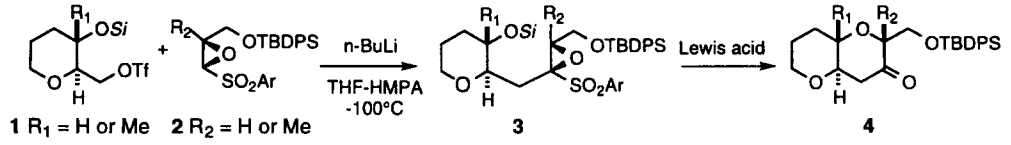


Figure 1. Structure of yessotoxin. The arrows indicate the angular methyl groups adjacent to the ring oxygens



Scheme 1.

reported cyclization conditions of the non-substituted epoxy sulfone **5**, where the reaction proceeded with complete stereochemical inversion, giving **6** as a single isomer.[5] At first, the methyl-substituted epoxy sulfone **7** was examined. Treatment of **7** with the same conditions as entry 1 gave an unexpected rearranged product **8a** in 52% yield instead of the desired product **10** which was isolated in less than 5% yield (entry 2). A similar result was observed in the reaction with $BF_3 \cdot OEt_2$ (entry 3). These results indicated that the presence of the methyl group on an epoxide ring activated this position and induced the 1,2-rearrangement of the sulfonyl group rather than 6-*endo* cyclization. The elevated temperature to deprotect the *t*-butyldimethylsilyl (TBS) group also favored the rearrangement. Then, the TBS group of **7** was replaced to the more labile triethylsilyl group in order to carry out the cyclization at a lower temperature. Exposure of **9** with $TsOH \cdot H_2O$ at 0°C led to detriethylsilylation within 30 min and the following cyclization proceeded smoothly to give **10** in high yield after 16 h (entry 4). These reaction conditions were also effective for the cyclization of the silylene derivative **11** to afford **12** which can serve as a precursor of higher polytetrahydropyrans (entry 5). On the other hand, cyclization of **13**, in which a tertiary alcohol and a trisubstituted epoxy sulfone participate, was achieved by heating with $TsOH \cdot H_2O$ to give **14** in moderate yield (entry 6). When $BF_3 \cdot OEt_2$ was employed, the reaction proceeded rapidly and gave **14** in excellent yield (entry 7).

Next, we turned our attention to the cyclization of **15** to the dimethyl-substituted terahydropyran **16** which has 1,3-diaxial methyl groups adjacent to the ring oxygen (Table 2). As suggested by the cyclization of **7** (Table 1, entry 2), the rearrangement of epoxy sulfone **15** to sulfonyl ketone **17** was a serious problem because of the reaction between the unreactive tertiary alcohol and reactive tetrasubstituted epoxy sulfone. However, reaction with $BF_3 \cdot OEt_2$ at room temperature gave the cyclization product **16**, albeit in low yield, along with serious amounts of **17** (entry 3), but increasing the amount of $BF_3 \cdot OEt_2$ at 0°C slightly suppressed the formation of **17** and increased the yield of **16** (entry 4). In order to prevent the rearrangement of the sulfonyl group, addition of a metal salt which traps the liberating *p*-toluenesulfinic acid was examined. After many attempts with various metal salts, Tl $(TFA)_3$ was found to be effective to quench the sulfinic acid, and **16** was obtained in 52% yield (entry 5). Moreover, exposure with $BF_3 \cdot OEt_2$ in the presence of $Tl(TFA)_3$ improved the yield of cyclization up to 62% (entry 6).

Finally, we explored the synthesis of the DEF ring system **22** of yessotoxin,[6] which was isolated

Table 1
Cyclization of monomethyl-substituted epoxy sulfones

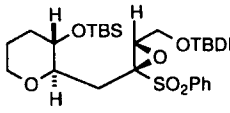
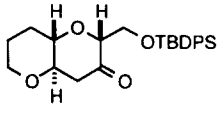
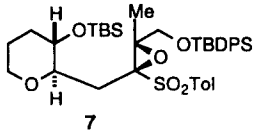
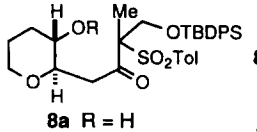
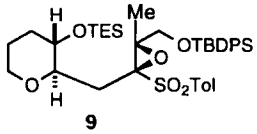
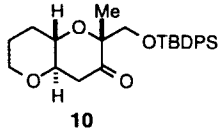
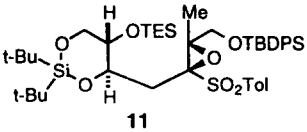
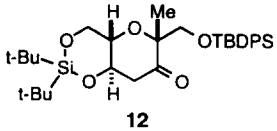
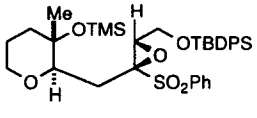
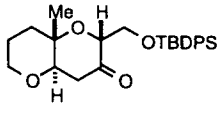
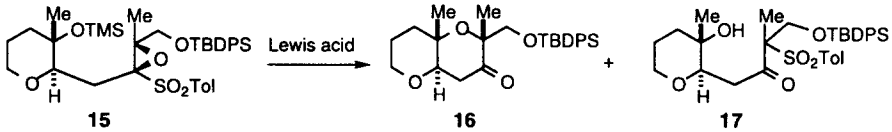
entry	epoxy sulfone	cyclization conditions	product	yield
1	 **5**	$TsOH•H_2O$ (1.3 eq) $CHCl_3$, 55°C, 3 h	 **6**	80%
2	 **7**	$TsOH•H_2O$ (1.3 eq) $CHCl_3$, 55°C, 4 h	 **8a** R = H **8b** R = TBS	**8a** 52%
3		$BF_3•OEt_2$ (2.0 eq) $CHCl_3$, rt, 4.5 h		**8b** 58%
4	 **9**	$TsOH•H_2O$ (1.5 eq) $CHCl_3$, 0°C, 16 h	 **10**	90%
5	 **11**	$TsOH•H_2O$ (1.5 eq) $CHCl_3$, 0°C, 13 h	 **12**	89%
6	 **13**	$TsOH•H_2O$ (1.3 eq) $CHCl_3$, 55°C, 8 h	 **14**	48%
7		$BF_3•OEt_2$ (5.0 eq) $CHCl_3$, 0°C, 30 min, rt, 30 min		89%

Table 2
Cyclization of dimethyl-substituted epoxy sulfone **15** in CH_2Cl_2

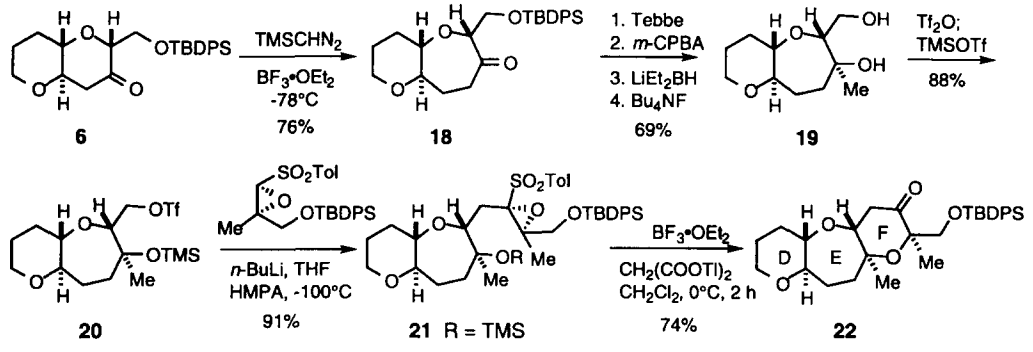


15 **16** **17**

entry	cyclization conditions				yield (%)	
	acid	eq.	temp (°C)	time (h)	**16**	**17**
1	TsOH	1.5	rt	72	-	28[a]
2	CSA	5.0	rt	60	-	59
3	$BF_3•OEt_2$	5.0	rt	72	25	51
4	$BF_3•OEt_2$	7.5	0	1	47	30
5	$Tl(TFA)_3$	4.0	rt	4	52	-[b]
6	$BF_3•OEt_2/Tl(TFA)_3$	1.0/3.0	0	2	62	-[b]

a) Detrimethylsilylated **15** was obtained in 31% yield.
b) Trace amounts (<5%)

as one of the causative toxins of diarrhetic shellfish poisoning, utilizing the conditions which were successful in the cyclization of **15**. The bicyclic ketone **6** was transformed into **18** by ring expansion with trimethylsilyldiazomethane (Scheme 2).[7] Attempts to introduce a methyl group directly into **18** with MeMgBr, MeLi, and Me_3Al were not successful, and the undesired β-methyl isomer of **19** was obtained as the major isomer. Thus, the required α-isomer **19** was prepared by the four-step manipulation in 69% overall yield. Triflation and silylation gave **20** which was coupled with the oxiranyl anion generated from a methyl-substituted epoxy sulfone to give the cyclization precursor **21** in 91%. Treatment of **21** with $BF_3 \cdot OEt_2$ (1 equiv.)/$Tl(TFA)_3$ (3 equiv.) at room temperature gave **22** only in 45% yield. Then, other thallium salts were reexamined in order to increase the yield, and a substantial improvement was achieved by employing dithallium malonate (3 equiv.) with $BF_3 \cdot OEt_2$ (5 equiv.) to provide **22** having 1,3-diaxial methyl groups on the F ring in 74% yield.



Scheme 2.

In summary, the synthesis of the methyl- and dimethyl-substituted tetrahydropyrans at the angular position adjacent to the ring oxygen was achieved via 6-*endo* cyclzation reaction by the proper choice of the cyclization conditions. Applications of this reaction are now in progress in our laboratory.

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