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Synthesis of *trans*-fused polycyclic ethers with angular methyl groups using sulfonyl-stabilized oxiranyl anions

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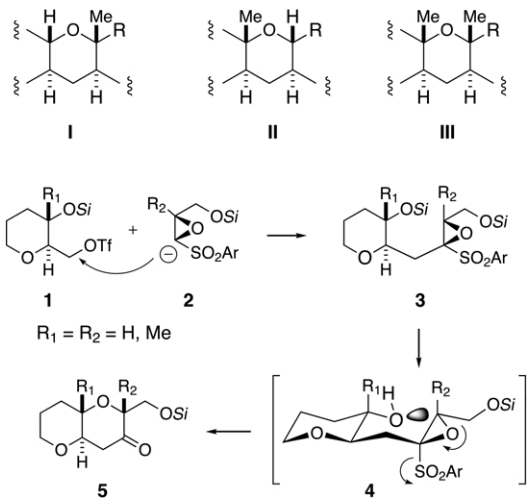
Abstract—An efficient method has been developed for the synthesis of *trans*-fused tetrahydropyrans with angular methyl groups adjacent to the ring oxygen. The procedure involves the coupling reaction of a sulfonyl-stabilized oxiranyl anion with an appropriate triflate followed by 6-*endo* cyclization, and is effective for the construction of 6/6- and 6/7/6-cyclic ether ring systems with sterically congested 1,3-diaxial methyl groups.

1. Introduction

Metalated oxiranes, considered as fleeting unstable intermediates, are emerging as useful synthons.[1] Their potential was first demonstrated by Eisch and Galle, who found that epoxides with anion-stabilizing groups can be metalated with strong bases at low temperatures and trapped by electrophiles.[2] Among them, the generation of sulfonyl-stabilized oxiranyl anions and their synthetic utility as a functionalized acyl anion equivalent have been extensively studied by Jackson and co-workers.[3] As a part of our program directed to the synthesis of polycyclic ether natural products, we have developed a general and iterative procedure for the synthesis of polytetrahydropyrans based on an oxiranyl anion strategy, in which alkylation of a sulfonyl-stabilized oxiranyl anion and the subsequent 6-*endo* cyclization were employed as key reactions.[4] The 6-*endo* cyclization directed by the electron-withdrawing ability of a sulfonyl group is complementary to that of the p-orbital-assisted cyclization developed by Nicolaou.[5] Taking advantage of our methodology, we envisioned a way to synthesize the 6-membered ether ring systems, **I-III**, containing angular methyl groups adjacent to the ring oxygen. Such ring systems are often encountered as structural units of polycyclic ether marine toxins,[6] and several synthetic efforts have been reported.[7] A particularly attractive feature of our approach is that the methyl-substituted keto tetrahydropyran **5** could be easily accessed by assembling triflate **1** and epoxy sulfone **2** followed by 6-*endo* cyclization of **3** via hydroxy epoxy sulfone **4** (Scheme 1). We report herein the details of the synthesis of 6/6- and 6/7/6-cyclic ether ring systems having angular methyl groups based on an oxiranyl anion strategy.[8]



Scheme 1.

2. Results and discussion

Since oxiranyl anions stabilized by a sulfonyl group are unstable even at low temperatures, the reaction of triflate **1** and oxiranyl anion **2** was carried out by an in situ trapping method in order to minimize decomposition of the transient lithiated epoxides prior to electrophile trapping.[9] Thus, a mixture of a triflate and an epoxy sulfone in THF at −100°C in the presence of DMPU or HMPA was treated with *n*-BuLi to afford a cyclization precursor in high yield (Table 1). The

Keywords: tetrahydropyrans; oxiranes; oxiranyl anions; 6-*endo* cyclization.
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Table 1. Reaction of triflate **1** with the oxiranyl anion generated from epoxy sulfone **2**

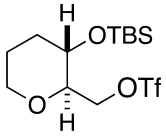
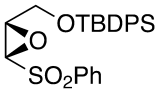
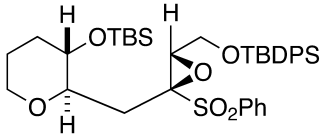
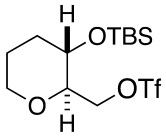
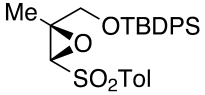
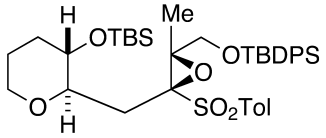
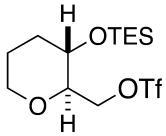
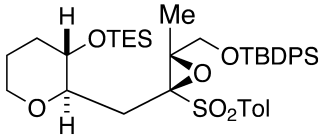
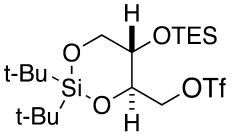
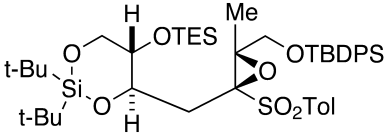
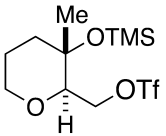
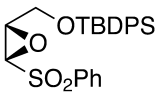
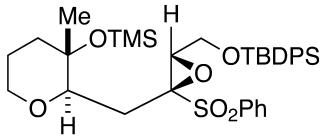
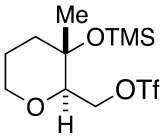
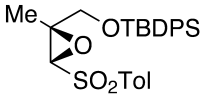
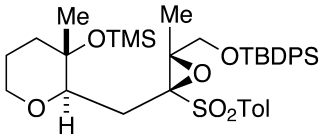
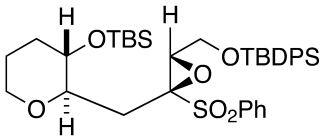
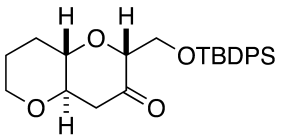
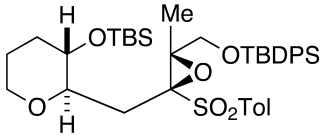
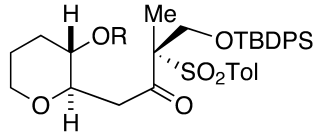
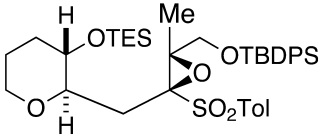
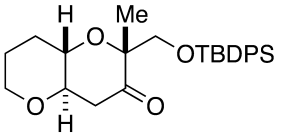
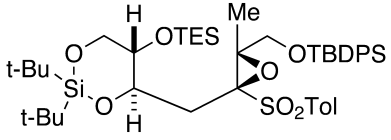
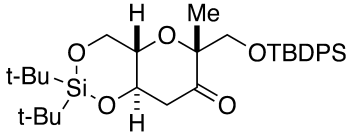
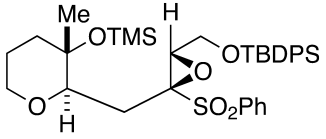
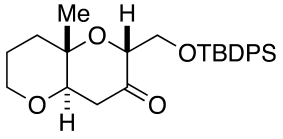
Entry	Triflate	Epoxy sulfone	Reaction conditions	Product	Yield (%)
1	**1a** 	**2a** 	*n*-BuLi, THF-DMPU, −100°C, 30 min	**3a** 	90
2	**1a** 	**2b** 	*n*-BuLi, THF-DMPU, −100°C, 40 min	**3b** 	90
3	**1b** 	**2b**	*n*-BuLi, THF-HMPA, −100°C, 25 min	**3c** 	94
5	**6** 	**2b**	*n*-BuLi, THF-HMPA, −100°C, 30 min	**7** 	95
6	**1c** 	**2a** 	*n*-BuLi, THF-HMPA, −100°C, 45 min	**3d** 	97
7	**1c** 	**2b** 	*n*-BuLi, THF-HMPA, −100°C, 90 min	**3e** 	71

Table 2. 6-*endo* Cyclization of monomethyl-substituted silyloxy epoxy sulfones

Entry	Epoxy sulfone	Cyclization conditions	Product	Yield (%)
1	**3a** 	$TsOH{\cdot}H_2O$ (1.3 equiv.), $CHCl_3$, 55°C, 3 h	**5a** 	80
2	**3b** 	$TsOH{\cdot}H_2O$ (1.3 equiv.), $CHCl_3$, 55°C, 4 h	**9a** R=H 	52
3		$BF_3{\cdot}OEt_2$ (2.0 equiv.), $CHCl_3$, rt, 4.5 h	**9b** R=TBS	58
4	**3c** 	$TsOH{\cdot}H_2O$ (1.5 equiv.), $CHCl_3$, 0°C, 16 h	**5c** 	90
5	**7** 	$TsOH{\cdot}H_2O$ (1.5 equiv.), $CHCl_3$, 0°C, 13 h	**8** 	89
6	**3d** 	$TsOH{\cdot}H_2O$ (1.3 equiv.), $CHCl_3$, 55°C, 8 h	**5d** 	48
7		$BF_3{\cdot}OEt_2$ (5.0 equiv.), $CHCl_3$, 0°C, 30 min, rt, 30 min		89

oxiranyl anions generated from epoxy sulfones **2a** and **2b** are configurationally stable under these conditions. In the case of the reaction of **1c** and **2b**, HMPA was necessary rather than DMPU as a co-solvent to obtain **3e** in good yield (entry 7). The monocyclic triflates **1a-c** and **6** were prepared from the corresponding diols by regioselective *O*-triflation and *O*-silylation by a one-pot procedure.[4] The optically active epoxy sulfones **2a** and **2b** were synthesized from (*S*)-*O*-pentylideneglyceraldehyde[10] and (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide,[11] respectively.

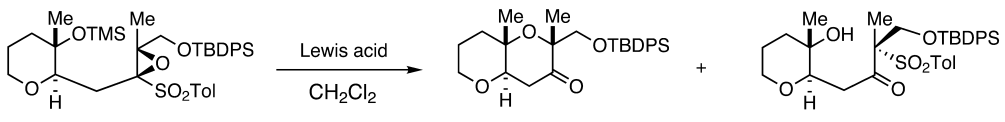
Construction of a new ether ring by 6-*endo* cyclization requires the conversion of the coupling product **3** to hydroxy epoxide **4** before the 6-*endo* cyclization reaction. We explored the reaction conditions that induce both desilylation of a secondary or a tertiary alcohol and 6-*endo* cyclization (Table 2). Entry 1 demonstrates the originally reported cyclization conditions employed for the non-methyl-substituted precursor **3a**.[4,10] Initial attempts to cyclize epoxy sulfone **3a** were conducted with $TsOH{\cdot}H_2O$ in CH_2Cl_2 at various temperatures. These conditions, however, were unable to deprotect the TBS group and then **3a** was heated with $TsOH{\cdot}H_2O$ in $CHCl_3$ at 55°C. We were pleased to find that deprotection of the TBS group and the following 6-*endo* cyclization proceeded simultaneously to give, after 3 h, the bicyclic ketone **5a** in 80% yield (entry 1). It is worthy to note that treatments with Lewis acids containing halogens such as $MgBr_2{\cdot}OEt_2$, $ZnCl_2$, and $AlCl_3$ caused the formation of the corresponding α-halo ketones by the nucleophilic attack of a halogen to the epoxy sulfone moiety as previously reported.[12]

In the case of the 6-*endo* cyclization of the substrates having a methyl group on an oxirane ring, reaction temperature was found to be critical. Reaction of the TBS-protected epoxy sulfone **3b** with $TsOH{\cdot}H_2O$ in $CHCl_3$ at 55°C induced a 1,2-shift of the sulfonyl group,[13] rather than 6-*endo* cyclization, to give α-sulfonyl ketone **9a** in 52% yield as a single isomer (entry 2). The stereochemistry of the sulfone-attached carbon was tentatively assigned based on the migration of the sulfonyl group to the back side of the cleaved epoxide center, but no further proof was carried out. In order to achieve the cyclization at or below room temperature to avoid the migration of the sulfonyl group, the TES-protected epoxy sulfone **3c** was prepared and subjected to the cyclization reaction. Exposure of **3c** to $TsOH{\cdot}H_2O$ in $CHCl_3$ at 0°C led to detriethylsilylation within 30 min and the following cyclization proceeded smoothly to give the bicyclic ketone **5c** in 90% yield (entry 4). Under these reaction conditions the silylene derivative **7** could be transformed to the keto tetrahydropyran **8** without any deprotection of the silylene group (entry 5).

Cyclization of **3d** was then examined, where a tertiary alcohol and a trisubstituted epoxy sulfone participate. In this case, a TMS group was employed for the protection of the tertiary alcohol because of its easier deprotection than that of the TES group. Heating a solution of **3d** with $TsOH{\cdot}H_2O$ in $CHCl_3$ at 55°C for 8 h resulted in the formation of the bicyclic ketone **5d** in moderate yield (entry 6). In order to improve the yield, several Lewis acids which are not potential sources of nucleophilic halide ions were examined as a stronger activator for cyclization. Among them, $BF_3{\cdot}OEt_2$ was found to be an excellent activator and the cyclization proceeded rapidly to afford the ketone **5d** in high yield (entry 7).

Construction of a tetrahydropyran of type **III** is a challenging synthetic issue because it contains sterically congested 1,3-diaxial methyl groups adjacent to the ring oxygen. Considering the 1,2-migration of the sulfonyl group observed in the case of the methyl-substituted epoxy sulfone **3b** (Table 2, entries 2 and 3), the cyclization of **3e** that requires reaction between a less reactive tertiary alcohol and a more reactive methyl-substituted epoxy sulfone would be difficult. It is, however, very interesting to construct such ring system by the 6-*endo* cyclization methodology. In fact, treatments of **3e** with $TsOH{\cdot}H_2O$ and camphorsulfonic acid at room temperature caused only the rearrangement of the epoxy sulfone to α-sulfonyl ketone **10** as a single isomer (Table 3, entries 1 and 2). Deprotection of the TMS group was rapid but the subsequent cyclization reaction was very slow under the conditions. However, $BF_3{\cdot}OEt_2$ did promote the cyclization of **3e** to the bicyclic ketone **5e**, albeit in low yield (entry 3). This result encouraged us to carry out the reaction with a larger amount of $BF_3{\cdot}OEt_2$ at below room temperature to suppress the 1,2-sulfonyl shift and to accelerate the cyclization. Thus, cyclization with 7.5 equiv

Table 3. 6-*endo* Cyclization of dimethyl-substituted silyloxy epoxy sulfone **3e**



3e **5e** **10**

Entry	Cyclization conditions				Yield (%)	
	Acid	Equiv.	Temperature	Time (h)	**5e**	**10**
1	TsOH	1.5	rt	72	–	28[a]
2	CSA	5.0	rt	60	–	59
3	$BF_3{\cdot}OEt_2$	5.0	rt	72	25	51
4	$BF_3{\cdot}OEt_2$	7.5	0°C	1	47	30
5	$Tl(TFA)_3$	4.0	rt	4	52	–[b]
6	$BF_3{\cdot}OEt_2/Tl(TFA)_3$	1.0/3.0	0°C	2	62	–[b]

[a] Detrimethylsilylated **3e** was obtained in 31% yield.
[b] Trace amount (<5%).

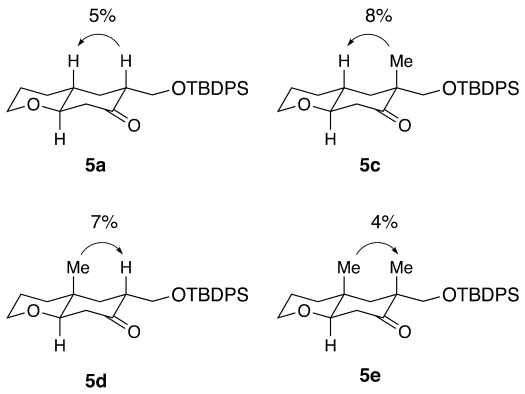
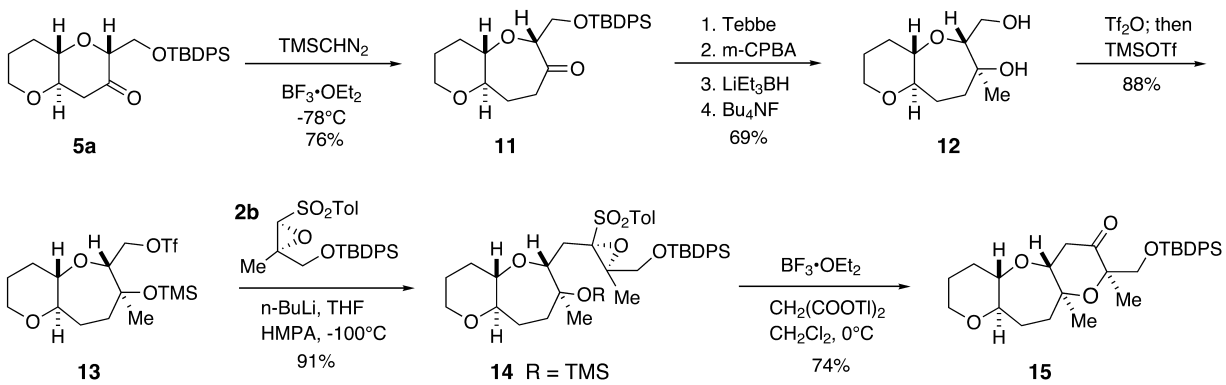


Figure 1. NOE in bicyclic ketones **5a** and **5c**-**e**.

of $BF_3{\cdot}OEt_2$ at 0°C increased the yield of **5e** up to 47% yield, but the formation of a considerable amount of **10** was still problematic. It is likely that addition of a metal ion which traps the sulfonyl group as a sulfinate salt would prevent the 1,2-sulfonyl shift and hence the cyclization would become a major reaction pathway. After many attempts with various metal compounds, a thallium ion was found to be effective to quench the sulfinate by forming insoluble salts in the reaction medium. Thus, treatment of **3e** with $Tl(TFA)_3$ gave a 52% yield of cyclization product **5e** along with a trace amount of the rearranged product. A combination of $BF_3{\cdot}OEt_2$ and $Tl(TFA)_3$ was more effective and the yield of **5e** was improved up to 62%.

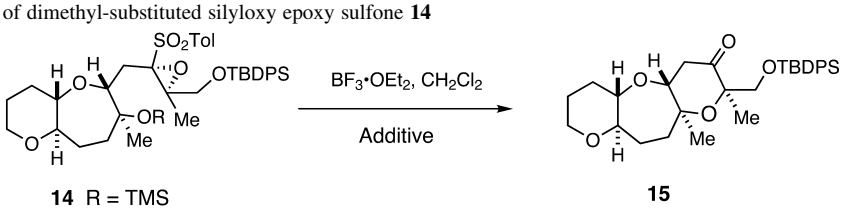
Now, stereocontrolled synthesis of the three types of methyl-substituted tetrahydropyrans **I**-**III** was accomplished by choosing suitable cyclization conditions depending upon the type of methyl-substitution. The stereochemistry of the cyclization products **5a** and **5c**-**e** was equivocally assigned on the basis of ^1H NMR NOE experiments as shown in Figure 1. These results indicate that the cyclization proceeded stereoselectively with inversion of the stereogenic center of the epoxide through the chair-like transition state **4** shown in Scheme 1.

In an effort to extend the 6-*endo* cyclization reaction to a 7-membered ring alcohol, the bicyclic ketone **11** was prepared from the keto tetrahydropyran **5a** by ring expansion reaction with trimethylsilyldiazomethane (Scheme 2).[10] Attempts to direct installation of an α-oriented methyl group to the ketone **11** with MeMgBr, MeLi, or Me_3Al were unsuccessful, resulting in the formation of the undesired β-methyl isomer as a major product. Then, the required α-methyl isomer **12** was prepared by a four-step manipulation in 69% overall yield: methylenation with Tebbe reagent, epoxidation with *m*-CPBA (α/β=3:1), reduction with $LiEt_3BH$, and desilylation with TBAF. Subsequent *O*-triflation and *O*-triethylsilylation in one pot gave triflate **13** in 88% yield. Reaction of **13** with the oxiranyllithium generated from **2b** gave the cyclization precursor **14** in 91% yield.



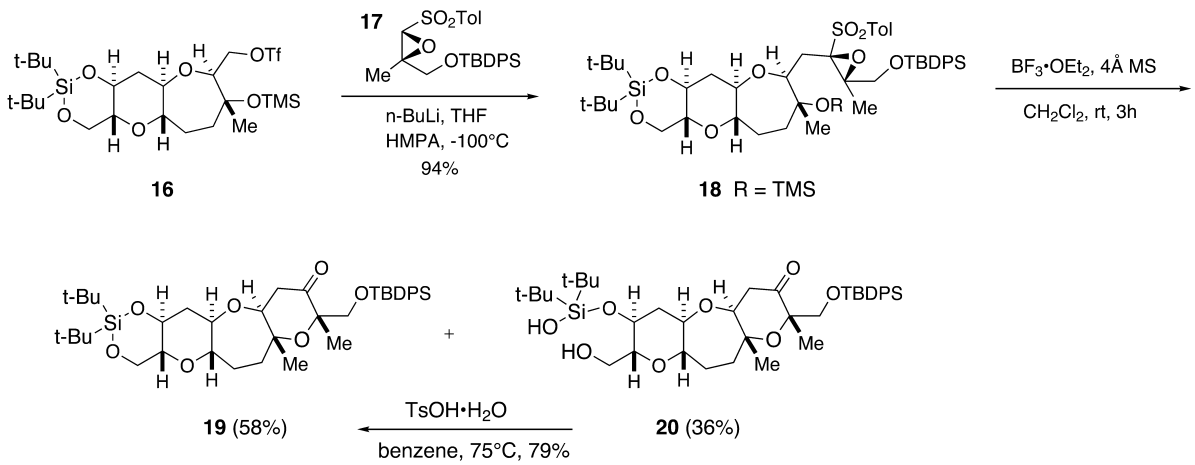
Scheme 2.

Table 4. 6-*endo* Cyclization of dimethyl-substituted silyloxy epoxy sulfone **14**



Entry	$BF_3{\cdot}OEt_2$ (equiv.)	Additive (equiv.)[a]	Temperature	Time (h)	Yield (%)
1	1.0	$Tl(TFA)_3$ (3.0), 4 Å MS	0°C	18	30
2	1.0	$Tl(TFA)_3$ (3.0), 4 Å MS	rt	20	45
3	3.0	$CH_2(COOTl)_2$ (3.0), 4 Å MS	rt	7.5	60
4	5.0	$CH_2(COOTl)_2$ (3.0), 4 Å MS	rt	3.5	74
5	5.0	–	rt	17	59
6	7.0	–	rt	1	64

[a] Molecular sieves were added to remove a trace amount of water in a reaction media.



Scheme 3.

Exposure of **14** to $BF_3{\cdot}OEt_2$ in the presence of $Tl(TFA)_3$ at 0°C and at room temperature gave **15** only in 30 and 45% yields, respectively (Table 4, entries 1 and 2). As the oxidative and acidic nature of $Tl(TFA)_3$ might be causative of the low yields of cyclization, Tl(I) salts were then reexamined. A substantial improvement was achieved by employing a combination of dithallium malonate and $BF_3{\cdot}OEt_2$, providing the tricyclic ketone **15** in 74% yield (entries 3 and 4). Moreover, we found that the cyclization occurred only with $BF_3{\cdot}OEt_2$ in good yields (entries 5 and 6). This is an interesting result compared with the case of the 6/6-membered ether ring formation in which a thallium ion was indispensable to prevent 1,2-shift of the sulfonyl group (Table 3). The different reactivity between **3e** and **14** could be explained by the flexibility of the existing rings of the cyclization precursors. The seven-membered ring is more flexible than the 6-membered ring and, therefore, the steric repulsion of two methyl groups in a 6-membered chair-like transition state would be reduced in the case of **14**.

Finally, we applied the BF_3-promoted cyclization conditions to epoxy sulfone **18**, which has a silylene protective group and was prepared by the reaction of triflate **16**[14] and the oxiranyl anion generated from epoxy sulfone **17** (Scheme 3).[15] Treatment of **18** with $BF_3{\cdot}OEt_2$ in the presence of 4 Å MS led to the formation of the 6/6/7/6-tetracyclic ketone **19** in 58% yield and the partially deprotected tricyclic ketone **20** in 36% yields, respectively. Although the silylene protective group was not compatible under these reaction conditions, the total yield of the cyclization was very high. Fortunately, the by-product **20** could be transformed into the desired ketone **19** in 79% yield by heating with $TsOH{\cdot}H_2O$ in benzene.

3. Conclusion

Our results demonstrated that alkylation of an oxiranyl anion and the following 6-*endo* cyclization provide a powerful method to construct *trans*-fused 6/6- and 6/7/6-cyclic systems having angular methyl groups adjacent to the ring oxygen. The cyclization precursors were synthesized by coupling reaction of a suitable triflate and an oxiranyl anion stabilized with a sulfonyl group. The stereocontrolled 6-*endo* cyclization was accomplished by choosing suitable cyclization conditions depending upon the substituted positions of the methyl groups of silyloxy epoxy sulfones. The present method was proved very efficient to construct a tetrahydropyran that has sterically congested 1,3-diaxial angular methyl groups.

4. Experimental

4.1. General

IR spectra were recorded in $CHCl_3$ solution on a JASCO FTIR-420 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL A-400 or A-600 spectrometer in $CDCl_3$ solution using TMS and $CDCl_3$ (77.00 ppm) as internal standards, respectively. Mass spectra were obtained on JEOL JMS-700 and HX-110 mass spectrometers. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. All air- and moisture-sensitive reactions were carried out under an argon atmosphere in dry, freshly distilled solvents under anhydrous conditions. Flash chromatography was carried out with E. Merck silica gel 60 (230–400 mesh). The term 'dried' refers to the drying of an organic solution over $MgSO_4$ followed by filtration.

4.1.1. 2-[(2*R*,3*R*)-3-(*tert*-Butyldiphenylsilyloxymethyl)-3-methyl-2-(toluene-4-sulfonyl)-oxiranylmethyl]-3-(triethylsilyloxy)-tetrahydropyran (3c). A solution of triflate **1b** (260 mg, 0.688 mmol) and epoxy sulfone **2b** (495 mg 1.032 mmol) in HMPA (0.480 mL, 2.752 mmol) and THF (7 mL) was cooled to −100°C and *n*-BuLi (0.645 mL of a 1.6 M solution in hexane, 1.032 mmol) was added dropwise. After stirring at −100°C for 30 min, the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was warmed to room temperature and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated in vacuo. Purification by flash chromatography (8% EtOAc in hexane) gave **3c** (459 mg, 94%) as a colorless oil. $[\alpha]_D^{24}$=+32.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1597, 1319, 1151, 1103, 813, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.59 (6H, q, *J*=7.8 Hz), 0.95 (9H, t, *J*=7.8 Hz), 1.08 (9H, s), 1.28 (1H, m), 1.57 (2H, m), 1.58 (3H, s), 1.99 (1H, br d, *J*=12.7 Hz), 2.12 (1H, dd, *J*=15.6, 9.3 Hz), 2.38 (3H, s), 2.59 (1H, dd, *J*=15.6, 2.0 Hz), 2.99 (1H, ddd, *J*=9.3, 8.3, 2.0 Hz), 3.09

(1H, ddd, J=11.7, 11.2, 4.4 Hz), 3.16 (1H, ddd, J=10.3, 8.3, 4.4 Hz), 3.76 (1H, br d, J=11.2 Hz), 4.24 (1H, d, J=11.7 Hz), 4.30 (1H, d, J=11.7 Hz), 7.17–7.71 (14H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.10 (3×C), 6.84 (3×C), 17.16, 19.38, 21.66, 25.83, 26.88 (3×C), 31.41, 33.48, 64.77, 67.36, 69.10, 71.32, 79.86, 81.05, 127.63, 127.68, 129.18, 129.31, 129.60, 129.69, 133.21, 133.36, 135.64, 135.68, 135.97, 144.08; HRFABMS calcd for $C_{39}H_{57}O_6SSi_2$ (MH^+) 709.3411, found 709.3425.

4.1.2. (4*R*,5*S*)-2,2-Di-*tert*-butyl-4-[(2*R*,3*R*)-3-(*tert*-butyldiphenylsilyloxymethyl)-3-methyl-2-(toluene-4-sulfonyl)-oxiranylmethyl]-5-(triethylsilyloxy)-1,3,2-dioxasilinane (7). According to the procedure for the preparation of **3c**, the reaction of **6** (127 mg, 0.250 mmol) and **2b** (180 mg, 0.375 mmol) gave **7** (200 mg, 95%) as a colorless oil after flash chromatography (5% EtOAc/hexane). $[\alpha]_D^{24}$=+67.1 (c 0.85, $CHCl_3$); IR ($CHCl_3$) 1599, 1473, 1313, 1219, 1105, 825, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.62 (6H, q, J=7.8 Hz), 0.94 (9H, s), 0.96 (9H, s), 0.97 (9H, t, J=7.8 Hz), 1.08 (9H, s), 1.61 (3H, s), 2.20 (1H, dd, J=15.6, 9.8 Hz), 2.38 (3H, s), 2.70 (1H, dd, J=15.6, 2.0 Hz), 3.36 (1H, ddd, J=13.2, 9.8, 4.4 Hz), 3.45 (1H, t, J=10.2 Hz), 3.47 (1H, ddd, J=13.2, 9.8, 2.0 Hz), 3.92 (1H, dd, J=10.2, 4.4 Hz), 4.31 (1H, d, J=11.7 Hz), 4.35 (1H, d, J=11.7 Hz), 7.17–7.79 (14H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.95 (3×C), 6.77 (3×C), 17.09, 19.81, 21.58, 22.57, 26.88 (3×C), 26.93, 27.37, 31.98, 64.82, 69.37, 70.02, 70.98, 75.72, 80.44, 127.60, 127.68, 129.31, 129.39, 129.59, 129.67, 133.04, 133.39, 135.64, 135.69, 144.24; HRFABMS calcd for $C_{45}H_{71}O_7SSi_3$ (MH^+) 839.4224, found 839.4220.

4.1.3. (2*R*,3*S*)-2-[(2*R*,3*R*)-3-(*tert*-Butyldiphenylsilyloxymethyl)-2-(toluene-4-sulfonyl)-oxiranylmethyl]-3-methyl-3-(triethylsilyloxy)-tetrahydropyran (3d). According to the procedure for the preparation of **3c**, the reaction of **1c** (111 mg, 0.317 mmol) and **2a** (244 mg, 0.540 mmol) gave **3d** (201 mg, 97%) as a colorless oil after flash chromatography (10% EtOAc/hexane). $[\alpha]_D^{25}$=+44.8 (c 0.79, $CHCl_3$); IR ($CHCl_3$) 1427, 1324, 1220, 1113, 840, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.09 (9H, s), 1.10 (9H, s), 1.10 (3H, s), 1.46–1.68 (3H, m), 1.80 (1H, m), 2.02 (1H, dd, J=15.1, 0.9 Hz), 2.08 (1H, dd, J=15.1, 9.3 Hz), 2.76 (1H, dd, J=9.3, 0.9 Hz), 3.17 (1H, ddd, J=11.7, 11.7, 2.4 Hz), 3.69 (1H, dd, J=6.3, 2.4 Hz), 3.79 (1H, dd, J=11.7, 5.4 Hz), 4.38 (1H, dd, J=13.2, 2.4 Hz), 4.51 (1H, dd, J=13.2, 6.3 Hz), 7.36–7.85 (15H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.41(3×C), 19.26, 20.48, 24.61, 26.82 (3×C), 28.28, 39.87, 61.47, 66.14, 67.56, 71.83, 75.44, 77.31, 78.79, 127.71, 129.06, 129.69, 133.31, 133.49, 133.95, 135.59, 137.37; HRFABMS calcd for $C_{35}H_{49}O_6SSi_2$ (MH^+) 653.2786, found 653.2769.

4.1.4. (2*R*,3*S*)-2-[(2*R*,3*R*)-3-(*tert*-Butyldiphenylsilyloxymethyl)-3-methyl-2-(toluene-4-sulfonyl)-oxiranylmethyl]-3-methyl-3-(triethylsilyloxy)-tetrahydropyran (3e). According to the procedure for the preparation of **3c**, the reaction of **1c** (55 mg, 0.157 mmol) and **2b** (128 mg, 0.540 mmol) gave **3e** (76 mg, 71%) as a colorless oil after flash chromatography (10% EtOAc/hexane). $[\alpha]_D^{25}$=+17.2 (c 0.75, $CHCl_3$); IR ($CHCl_3$) 1569, 1427, 1319, 1149, 1106, 840, 779 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (9H, s), 1.09 (9H, s), 1.12 (3H, s), 1.55 (1H, m), 1.57 (3H, s), 1.61 (2H, m), 1.87 (1H, m), 2.04 (1H, dd, J=15.6, 9.8 Hz), 2.33 (1H, dd, J=15.6, 1.0 Hz), 2.38 (3H, s), 3.18 (1H, br d, J=9.8 Hz), 3.21 (1H, ddd, J=10.2, 10.2, 2.0 Hz), 3.82 (1H, dd, J=10.2, 4.4 Hz), 4.23 (1H, d, J=11.7 Hz), 4.30 (1H, d, J=11.7 Hz), 7.17–7.71 (14H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.66 (3×C), 17.29, 19.34, 20.05, 21.62, 24.68, 26.88 (3×C), 28.97, 40.13, 64.69, 67.92, 68.86, 72.79, 81.38, 83.12, 127.63, 127.68, 129.11, 129.24, 129.62, 129.70, 133.18, 133.31, 135.64, 135.68, 136.07, 144.13; HRFABMS calcd for $C_{37}H_{53}O_6SSi_2$ (MH^+) 681.3098, found 681.3062.

4.1.5. 4-(*tert*-Butyldiphenylsilyloxy)-1-[(2*R*,3*S*)-3-hydroxy-tetrahydropyran-2-yl]-3-methyl-3-(toluene-4-sulfonyl)-butan-2-one (9a). A solution of **3b** (6.2 mg, 0.009 mmol) and $TsOH{\cdot}H_2O$ (2.6 mg, 0.0137 mmol) in $CHCl_3$ (0.3 mL) was stirred at 55°C for 4 h. After cooling to room temperature, Et_3N (0.05 mL) was added to the solution and the reaction mixture was concentrated in vacuo. Purification by flash chromatography (30% EtOAc in hexane) gave **9a** (3.5 mg, 52%) as a colorless oil. IR ($CHCl_3$) 3525, 1712, 1427, 1302, 1146, 818 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (9H, s), 1.37 (1H, m), 1.55 (3H, s), 1.63 (2H, m), 1.70 (1H, br, OH), 2.10 (1H, br d, J=11.7 Hz), 2.45 (3H, s), 3.04 (1H, dd, J=18.3, 7.4 Hz), 3.16 (1H, dd, J=18.3, 3.7 Hz), 3.24–3.33 (2H, m), 3.51 (1H, ddd, J=17.1, 11.0, 6.6 Hz), 3.76 (1H, br d, J=11.7 Hz), 3.91 (1H, d, J=10.3 Hz), 4.40 (1H, d, J=10.3 Hz), 7.22–7.61 (14H, Ar); HRFABMS calcd for $C_{33}H_{43}O_6SSi$ (MH^+) 595.2547, found 595.2521.

4.1.6. (2*R*,4a*R*,8a*S*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-2-methyl-hexahydro-pyrano[3,2-*b*]pyran-3-one (5c). A solution of **3c** (219 mg, 0.309 mmol) and $TsOH{\cdot}H_2O$ (88 mg, 0.463 mmol) in $CHCl_3$ (3.0 mL) was stirred at 0°C for 16 h. The reaction mixture was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried and concentrated in vacuo. Purification by flash chromatography (6% EtOAc in hexane) gave ketone **5c** (122 mg, 90%) as colorless crystals. Mp 73–74°C. $[\alpha]_D^{25}$=+3.95 (c 0.78, $CHCl_3$); IR ($CHCl_3$) 1718, 1464, 1427, 1093, 823, 706 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (9H, s), 1.17 (3H, s), 1.58 (1H, m), 1.80 (2H, m), 2.18 (1H, br d, J=12.2 Hz), 2.41 (1H, dd, J=18.1, 10.3 Hz), 2.96 (1H, dd, J=18.1, 6.3 Hz), 3.42 (1H, ddd, J=10.7, 9.3, 4.4 Hz), 3.43 (1H, ddd, J=11.2, 11.2, 4.4 Hz), 3.51 (1H, ddd, J=10.3, 9.3, 6.3 Hz), 3.58 (1H, d, J=10.4 Hz), 3.91 (1H, d, J=10.4 Hz), 3.93 (1H, br d, J=11.2 Hz), 7.35–7.76 (10H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.70, 19.23, 25.24, 26.63 (3×C), 29.60, 43.83, 67.39, 69.69, 71.06, 75.68, 85.28, 127.56, 127.63, 129.56, 129.64, 133.16, 133.34, 135.64, 135.69, 210.46; HRFABMS calcd for $C_{26}H_{35}O_4Si$ (MH^+) 439.2303, found 439.2315.

4.1.7. (4a*R*,8a*S*,6*R*)-2,2-Di-*tert*-butyl-6-(*tert*-butyldiphenylsilyloxymethyl)-6-methyl-tetrahydro-1,3,5-trioxa-2-sila-naphthalen-7-one (8). According to the procedure for the preparation of **5c**, treatment of epoxy sulfone **7** (164 mg, 0.196 mmol) with $TsOH{\cdot}H_2O$ (56 mg, 0.293 mmol) in $CHCl_3$ (2.0 mL) at 0°C for 13 h and purification by flash chromatography (5% EtOAc in hexane)

gave ketone **8** (99 mg, 89%). $[\alpha]_D^{25}$=+15.3 (*c* 0.53, $CHCl_3$); IR ($CHCl_3$) 1720, 1471, 1223, 1113, 825, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (9H, s), 1.01 (9H, s), 1.05 (9H, s), 1.17 (3H, s), 2.42 (1H, dd, *J*=18.1, 10.2 Hz), 3.08 (1H, dd, *J*=18.1, 6.3 Hz), 3.54 (1H, d, *J*=9.8 Hz), 3.67 (1H, ddd, *J*=10.2, 10.2, 4.9 Hz), 3.89 (1H, d, *J*=9.8 Hz), 3.96 (1H, dd, *J*=10.2, 10.2 Hz), 4.24 (1H, dd, *J*=10.2, 4.9 Hz), 4.32 (1H, ddd, *J*=10.2, 10.2, 4.9 Hz), 7.35–7.70 (10H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.51, 19.85, 26.60 (3×C), 27.00 (3×C), 27.44 (3×C), 46.81, 67.13, 69.48, 70.85, 71.67, 127.60, 127.65, 129.64, 129.69, 135.61, 210.10; HRFABMS calcd for $C_{32}H_{49}O_5Si_2$ (MH^+) 569.3116, found 569.3110.

4.1.8. (2*R*,4a*R*,8a*S*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-8a-methyl-hexahydro-pyrano[3,2-*b*]pyran-3-one (5d). To a stirred solution of **3d** (142 mg, 0.218 mmol) in CH_2Cl_2 (4.4 mL) at 0°C was added $BF_3{\cdot}OEt_2$ (134 μL, 1.091 mmol), and the reaction mixture was stirred at 0°C for 30 min and then at room temperature for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated in vacuo. Purification by flash chromatography (12% EtOAc in hexane) gave ketone **5d** (85 mg, 89%). $[\alpha]_D^{25}$=+50.2 (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 1720, 1211, 1113, 779, 769, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (9H, s), 1.27 (3H, s), 1.71 (2H, m), 1.89 (1H, m), 1.99 (1H, m), 2.40 (1H, dd, *J*=18.5, 11.7 Hz), 2.82 (1H, dd, *J*=18.5, 6.8 Hz), 3.47 (1H, ddd, *J*=11.7, 11.7, 2.0 Hz), 3.68 (1H, dd, *J*=11.7, 6.8 Hz), 3.85 (1H, dd, *J*=12.9, 2.9 Hz), 3.99 (1H, dd, *J*=11.7, 5.4 Hz), 4.06 (1H, dd, *J*=9.8, 2.9 Hz), 4.07 (1H, dd, *J*=12.7, 9.8 Hz), 7.36–7.76 (10H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.25, 19.20, 24.13, 26.67 (3×C), 37.00, 41.31, 65.15, 68.35, 71.50, 76.59, 79.75, 127.61, 127.66, 129.60, 129.69, 135.63, 135.66, 208.63; HRFABMS calcd for $C_{26}H_{35}O_4Si$ (MH^+) 439.2303, found 439.2348.

4.1.9. 4-(*tert*-Butyldiphenylsilyloxy)-1-[(2*R*,3*S*)-3-hydroxy-3-methyl-tetrahydropyran-2-yl]-3-methyl-3-(toluene-4-sulfonyl)-butan-2-one (10) (Table 3, entry 2). To a stirred solution of **3e** (6.3 mg, 0.0093 mmol) in CH_2Cl_2 (0.1 mL) at 0°C was added CSA (5.4 mg, 0.023 mmol), and the mixture was stirred at room temperature for 60 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated in vacuo. Purification by flash chromatography (12% EtOAc in hexane) gave ketone **10** (3.3 mg, 59%). $[\alpha]_D^{25}$=+10.0 (*c* 0.23, $CHCl_3$); IR ($CHCl_3$) 1718, 1597, 1220, 1105, 779, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (9H, s), 1.22 (3H, s), 1.54 (1H, m), 1.56 (3H, s), 1.58 (1H, m), 1.70 (1H, br s, OH), 1.72 (1H, m), 1.89 (1H, m), 2.42 (3H, s), 3.04 (1H, dd, *J*=18.1, 7.8 Hz), 3.19 (1H, dd, *J*=18.1, 2.9 Hz), 3.39 (1H. ddd, *J*=11.7, 11.2, 2.9 Hz), 3.69 (1H, dd, *J*=7.8, 2.9 Hz), 3.86 (1H, ddd, *J*=11.7, 3.4, 2.0 Hz), 3.91 (1H, d, *J*=10.3 Hz), 4.40 (1H, d, *J*=10.3 Hz), 7.22–7.61 (14H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.38, 19.28, 20.28, 21.65, 24.92, 26.77 (3×C), 39.95, 40.97, 64.36, 67.93, 69.38, 77.08, 79.49, 127.78, 129.36, 129.90, 130.08, 132.34, 132.48, 132.55, 132.64, 135.71, 145.22, 202.00; HRFABMS calcd for $C_{34}H_{43}O_5SSi$ (MH^+-H_2O) 591.2598, found 591.2591.

4.1.10. (2*R*,4a*R*,8a*S*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-2,8a-dimethyl-hexahydro-pyrano[3,2-*b*]pyran-3-one (5e) (Table 3, entry 6). To a stirred mixture of **3e** (29 mg, 0.0428 mmol) and 4 Å MS (60 mg) in CH_2Cl_2 (0.9 mL) at 0°C were added $Tl(TFA)_3$ (70 mg, 0.1284 mmol) and $BF_3{\cdot}OEt_2$ (5.3 μL, 0.0428 mmol), and the reaction mixture was stirred at 0°C for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated in vacuo. Purification by flash chromatography (12→30% EtOAc in hexane) gave ketone **5e** (12 mg, 62%). $[\alpha]_D^{25}$=+28.8 (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) 1714, 1222, 1088, 788, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (9H, s), 1.19 (3H, s), 1.23 (3H, s), 1.66 (1H, m), 1.76 (1H, ddd, *J*=12.7, 11.7, 3.9 Hz), 1.86 (1H, m), 2.00 (1H, br d, *J*=12.7 Hz), 2.36 (1H, dd, *J*=19.0, 11.2 Hz), 2.86 (1H, dd, *J*=19.0, 7.3 Hz), 3.41 (1H, ddd, *J*=12.2, 11.7, 2.4 Hz), 3.53 (1H. d, *J*=9.8 Hz), 3.64 (1H, d, *J*=9.8 Hz), 3.95 (1H, m), 3.96 (1H, dd, *J*=11.2, 7.3 Hz), 7.36–7.64 (10H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.40, 19.10, 23.34, 24.15, 26.73 (3×C), 37.31, 40.78, 68.25, 71.69, 72.38, 76.28, 83.98, 127.75, 127.79, 129.72, 129.84, 132.57, 132.83, 135.59, 135.63, 212.48; HRFABMS calcd for $C_{27}H_{37}O_4Si$ (MH^+) 453.2459, found 453.2481

4.1.11. (4a*S*,6*R*,7*S*,9a*R*)-6-Hydroxymethyl-7-methyl-octahydro-1,5-dioxa-benzocyclohepten-7-ol (12). (i) *Methylenation*. To a stirred solution of **11** (668 mg, 1.525 mmol) in THF (15 mL) at 0°C was added the Tebbe reagent (3.11 mL of a 0.5 M solution in toluene, 1.55 mmol), and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with Et_2O (20 mL) and treated with 0.1N NaOH (1.0 mL) until orange-yellow precipitates were formed. The mixture was extracted with Et_2O and the extract was washed with water and brine, dried, and concentrated in vacuo. Flash chromatography (7% EtOAc in hexane) gave an exocyclic methylene (633 mg, 95%) as an oil. $[\alpha]_D^{25}$=+53.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1471, 1427, 1219, 1093, 1030, 904, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.27 (1H, m), 1.44 (1H. m), 1.62 (2H, m), 2.06 (1H, m), 2.10–2.19 (3H, m), 3.04 (1H, ddd, *J*=9.3, 9.3, 4.9 Hz), 3.08 (1H, ddd, *J*=9.3, 9.3, 4.9 Hz), 3.29 (1H, ddd, *J*=10.7, 10.7, 2.9 Hz), 3.51 (1H, dd, *J*=10.7, 5.4 Hz), 3.70 (1H, d, *J*=10.7, 6.8 Hz), 3.83 (1H, ddd, *J*=10.7, 3.9, 2.0 Hz), 4.16 (1H, dd, *J*=6.4, 5.4 Hz), 4.74 and 4.97 (each 1H, s), 7.34–7.70 (10H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.23, 25.61, 26.82 (3×C), 28.00, 31.21, 36.61, 66.91, 67.31, 76.80, 81.21, 83.76, 112.84, 127.52, 129.52, 133.70, 133.83, 135.74, 150.63; HRFABMS calcd for $C_{27}H_{37}O_3Si$ (MH^+) 437.2510, found 437.2527.

(ii) *Epoxidation*. To a stirred solution of the exocyclic methylene (655 mg, 1.502 mmol) in CH_2Cl_2 (12 mL) and pH 7 phosphate buffer (12 mL) was added *m*-CPBA (80%, 972 mg, 4.506 mmol). The reaction mixture was stirred at room temperature for 6 h and then extracted with EtOAc. The extract was washed successively with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried and concentrated in vacuo. Purification by flash chromatography (10→15% EtOAc in hexane) gave a β-epoxide (475 mg, 70%) and an α-epoxide

(175 mg, 26%). β-Epoxide: $[\alpha]_D^{25}$=+52.1 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1471, 1427, 1306, 1182, 1093, 1028, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.22 (1H, ddd, *J*=14.2, 4.9, 2.9 Hz), 1.40 (1H, m), 1.64 (2H, m), 1.74 (1H, dddd, *J*=13.6, 13.6, 11.2, 2.9 Hz), 1.89 (1H, dddd, *J*=13.6, 4.9, 4.9, 2.9 Hz), 2.05 (1H, m), 2.09 (1H, ddd, *J*=14.2, 14.2, 2.9 Hz), 2.68 and 2.88 (each 1H, d, *J*=4.4 Hz), 3.07 (1H, ddd, *J*=10.7, 9.3, 5.4 Hz), 3.29 (1H, m), 3.32 (1H, t, *J*=5.4 Hz), 3.38 (1H, ddd, *J*=11.2, 9.3, 5.4 Hz), 3.63 (1H, dd, *J*=10.7, 5.9 Hz), 3.68 (1H, dd, *J*=10.7, 4.9 Hz), 3.85 (1H, m), 7.36–7.68 (10H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.13, 25.40, 25.75, 26.80 (3×C), 29.71, 31.22, 52.09, 60.43, 62.25, 67.23, 75.90, 80.92, 83.48, 127.65, 129.72, 133.21, 135.63; HRFABMS calcd for $C_{27}H_{37}O_4Si$ (MH^+) 453.2459, found 453.2443.

(iii) *Reduction*. To a stirred solution of the β-epoxide (1.52 g, 3.36 mmol) in THF (37 mL) at 0°C was added lithium triethylborohydride (6.72 mL of a 1.0 M solution in THF, 6.72 mmol), and the reaction mixture was stirred at 0°C for 30 min. The reaction was quenched with water and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (30% EtOAc in hexane) gave a tertiary alcohol (1.51 g, 99%). $[\alpha]_D^{25}$=−18.5 (*c* 0.15, $CHCl_3$); IR ($CHCl_3$) 3500, 1469, 1427, 1221, 1209, 1088, 791, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (9H, s), 1.22 (3H, s), 1.36 (1H, m), 1.60–1.68 (3H, m), 1.75–1.83 (3H, m), 2.87 (1H, ddd, *J*=9.8, 9.8, 3.9 Hz), 3.07 (1H, br s, OH), 3.08 (1H, m), 3.30 (1H, ddd, *J*=11.2, 7.8, 4.4 Hz), 3.64 (1H, t, *J*=6.8 Hz), 3.72 (1H, dd, *J*=9.8, 6.8 Hz), 3.76 (1H, dd, *J*=10.3, 6.8 Hz), 3.87 (1H, m), 7.38–7.70 (10H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.03, 24.36, 25.60, 26.88 (3×C), 27.85, 31.22, 38.83, 64.10, 68.02, 74.57, 84.32, 84.60, 84.64, 127.86, 129.95, 130.05, 135.51, 135.63; HRFABMS calcd for $C_{27}H_{39}O_4Si$ (MH^+) 455.2615, found 455.2641.

(iv) *Deprotection of the TBDPS group*. To a stirred solution of the tertiary alcohol (1.95 g, 4.295 mmol) in THF (42 mL) was added Bu_4NF (6.44 mL of a 1.0 M solution in THF, 6.44 mmol), and the solution was stirred at room temperature for 1.5 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (4% MeOH in EtOAc) to give **12** (926 mg, 100%). $[\alpha]_D^{25}$=+9.28 (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) 3600, 3473, 1454, 1439, 1221, 1209, 1088, 791, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, s), 1.46 (1H, m), 1.69 (2H, m), 1.74–1.94 (6H, m), 2.08 (1H, m), 2.94 (1H, ddd, *J*=8.8, 8.8, 3.9 Hz), 3.19 (1H, ddd, *J*=11.2, 9.3, 3.9 Hz), 3.32 (1H, ddd, *J*=11.2, 9.3, 6.8 Hz), 3.55 (1H, dd, *J*=7.8, 5.4 Hz), 3.66 (1H, dd, *J*=10.7, 7.8 Hz), 3.75 (1H, dd, *J*=10.7, 5.4 Hz), 3.89 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.45, 25.91, 27.84, 31.24, 39.45, 62.39, 67.95, 74.29, 84.08, 84.13, 86.82; HRFABMS calcd for $C_{11}H_{21}O_4$ (MH^+) 217.1439, found 217.1430.

4.1.12. (4a*S*,6*R*,7*S*,9a*R*)-Trifluoromethanesulfonic acid 7-methyl-7-(trimethylsilyloxy)-octahydro-1,5-dioxa-benzocyclohepten-6-ylmethyl ester (13). To a stirred solution of **12** (850 mg, 3.935 mmol) in CH_2Cl_2 (39 mL) and 2,6-lutidine (1.82 mL, 15.74 mmol) at −78°C was added Tf_2O (0.675 mL, 4.013 mmol). After stirring at −78°C for 30 min, TMSOTf (1.06 mL, 5.902 mmol) was added and the reaction mixture was stirred for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated in vacuo. Purification by flash chromatography (3% EtOAc in hexane) gave triflate **13** (1.46 g, 88%) as a pale yellow oil. $[\alpha]_D^{25}$=+19.6 (*c* 0.53, $CHCl_3$); IR ($CHCl_3$) 1413, 1245, 1223, 1145, 1083, 955, 842 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (9H, s), 1.13 (3H, s), 1.44 (1H, ddd, *J*=11.2, 8.8, 6.8 Hz), 1.68 (3H, m), 1.80 (2H, m), 1.99 (1H, m), 2.15 (1H, m), 2.92 (1H, ddd, *J*=8.8, 8.8, 4.4 Hz), 3.12 (1H, ddd, *J*=11.2, 9.3, 4.4 Hz), 3.31 (1H, ddd, *J*=11.2, 8.8, 5.9 Hz), 3.69 (1H, dd, *J*=9.3, 2.0 Hz), 3.88 (1H, m), 4.45 (1H, t, *J*=9.3 Hz), 4.63 (1H, dd, *J*=10.3, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.30 (3×C), 24.63, 25.91, 27.72, 30.68, 38.50, 68.10, 76.39, 83.96, 84.49, 84.68, 85.94; FABMS *m/z* 421 (MH^+).

4.1.13. (4a*S*,6*R*,7*S*,9a*R*)-6-[(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxymethyl)-3-methyl-2-(toluene-4-sulfonyl)-oxiranylmethyl]-7-methyl-7-(trimethylsilyloxy)-octahydro-1,5-dioxa-benzocycloheptene (14). A solution of triflate **13** (1.46 g, 3.476 mmol) and epoxy sulfone **2b** (2.0 g, 4.166 mmol) in THF (69 mL) and HMPA (6.21 mL) was cooled to −100°C, and *n*-BuLi (2.6 mL of a 1.6 M solution in hexane, 4.166 mmol) was added dropwise. After stirring at −100°C for 30 min, the reaction was quenched with saturated aqueous NH_4Cl and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated in vacuo. Purification by flash chromatography (10% acetone in hexane) gave epoxy sulfone **14** (2.38 g, 91%) as a colorless oil. $[\alpha]_D^{25}$=+41.8 (*c* 0.79, $CHCl_3$); IR ($CHCl_3$) 1427, 1319, 1151, 1111, 1078, 842, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.13 (9H, s), 1.07 (3H, s), 1.09 (9H, s), 1.27 (1H, m), 1.57 (3H, s), 1.62 (5H, m), 1.91 (1H, m), 2.10 (1H, dd, *J*=15.6, 10.2 Hz), 2.21 (1H, m), 2.37 (1H, d, *J*=14.2 Hz), 2.40 (3H, s), 2.79 (1H, m), 2.94 (1H, ddd, *J*=10.7, 9.3, 3.9 Hz), 3.27 (1H, m), 3.30 (1H, d, *J*=10.2 Hz), 3.85 (1H, m), 4.27 (1H, d, *J*=11.7 Hz), 4.34 (1H, d, *J*=11.7 Hz), 7.20–7.70 (14H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.30 (3×C), 17.16, 19.38, 21.66, 24.36, 26.06, 26.90 (3×C), 27.46, 28.49, 30.60, 38.58, 64.89, 68.28, 70.12, 77.63, 81.05, 83.91, 84.52, 84.64, 127.63, 127.71, 129.19, 129.49, 129.65, 129.74, 133.26, 135.69, 135.81, 144.46; HRFABMS calcd for $C_{34}H_{51}O_5Si_2$ ($MH^+-TolSO_2H$) 595.3272, found 595.3287.

4.1.14. (2*R*,4a*R*.5a*S*,9a*R*,11a*S*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-2,11a-dimethyl-decahydro-1,5,9-trioxa-dibenzo[*a*,*d*]cyclohepten-3-one (15). To a mixture of **14** (100 mg, 0.133 mmol) and 4 Å MS (190 mg) in CH_2Cl_2 (2.7 mL) was added dithallium malonate (204 mg, 0.400 mmol) at 0°C. After stirring at 0°C for 30 min, $BF_3{\cdot}OEt_2$ (82 μL, 0.666 mmol) was added. The reaction mixture was stirred at 0°C for 30 min and then at room temperature for 3.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated in vacuo. Purification by flash chromatography (6% acetone in hexane) gave ketone **15** (52 mg, 74%) as a colorless oil. $[\alpha]_D^{25}$=+32.9 (*c* 0.89, $CHCl_3$); IR ($CHCl_3$) 1714, 1429, 1211, 1088, 706 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.98 (3H, s), 1.07 (3H, s), 1.11

(9H, s), 1.16 (1H, m), 1.35 (2H, m), 1.70 (1H, ddd, J=15.1, 10.7, 2.4 Hz), 1.92 (1H, m), 1.99 (1H, m), 2.18 (1H, m), 2.27 (1H, ddd, J=15.1, 8.3, 2.4 Hz), 2.54 (1H, dd, J=19.0, 11.2 Hz), 2.85 (1H, ddd, J=8.8, 8.8, 4.4 Hz), 2.98 (1H, ddd, J=11.2, 11.2, 2.0 Hz), 3.04 (1H, dd, J=19.0, 6.8 Hz), 3.16 (1H, ddd, J=10.7, 9.3, 4.4 Hz), 3.63 (1H, d, J=9.3 Hz), 3.67 (1H, m), 3.81 (1H, d, J=9.3 Hz), 4.42 (1H, dd, J=11.2, 6.8 Hz), 7.17–7.86 (10H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.20, 20.66, 23.47, 25.84, 26.86 (3×C), 28.90, 31.26, 38.60, 42.18, 67.85, 72.46, 76.69, 78.17, 81.53, 83.48, 83.63, 127.76, 127.83, 129.75, 129.87, 132.48, 132.94, 135.53, 135.61, 213.16; HRFABMS calcd for $C_{31}H_{43}O_5Si$ (MH^+) 523.2877, found 523.2886.

4.1.15. (4a*R*,5a*S*,8*R*,9*S*,10a*R*,11a*S*)-2,2-Di-*tert*-butyl-9-[(2*S*,3*R*)-3-(*tert*-butyldiphenylsilyloxymethyl)-3-methyl-2-(toluene-4-sulfonyl)-oxiranylmethyl]-8-methyl-8-(trimethylsilyloxy)-decahydro-1,3,5,10-tetraoxa-2-sila-cyclohepta[*b*]naphthalene (18). According to the procedure for the preparation of **14**, treatment of triflate **16** (438 mg, 0.724 mmol) and epoxy sulfone **17** (521 mg, 1.090 mmol) in HMPA (1.3 mL) and THF (14.4 mL) with *n*-BuLi (0.68 mL of a 1.58 M solution in hexane, 1.074 mmol) and purification by flash chromatography (6% EtOAc in hexane) gave **18** (635 mg, 94%) as a colorless oil. $[\alpha]_D^{25}$=−36.8 (*c* 2.45, $CHCl_3$); IR ($CHCl_3$) 1472, 1318, 1252, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (9H, s), 0.97 (9H, s), 1.03 (9H, s), 1.05 (3H, s), 1.11 (9H, s), 1.39 (1H, q, J=11.2 Hz), 1.57–1.73 (3H, m), 1.58 (3H, s), 1.93 (1H, m), 1.98 (1H, dd, J=15.6, 10.3 Hz), 2.40 (3H, s), 2.41 (1H, d, J=15.6 Hz), 2.59 (1H, ddd, J=11.2, 4.4, 4.4 Hz), 2.93 (1H, ddd, J=9.3, 9.3, 3.9 Hz), 2.99 (1H, m), 3.24 (1H, ddd, J=10.2, 9.3, 4.9 Hz), 3.35 (1H, d, J=10.3 Hz), 3.75 (1H, m), 3.78 (1H, dd, J=10.2, 10.2 Hz), 4.11 (1H, dd, J=10.2, 4.9 Hz), 4.29 (1H, d, J=11.2 Hz), 4.42 (1H, d, J=11.2 Hz), 7.21–7.72 (14H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.46 (3×C), 17.39, 19.39, 19.92, 21.66, 22.62, 24.38, 26.72, 26.96 (3×C), 27.09 (3×C), 27.42 (3×C), 28.07, 38.49, 39.50, 64.77, 67.03, 70.01, 73.13, 77.63, 77.79, 80.72, 81.94, 84.26, 84.85, 127.68, 127.71, 129.21, 129.52, 129.72, 133.19, 133.32, 135.66, 135.74, 144.55; HRFABMS calcd for $C_{50}H_{77}O_9SSi_3$ (MH^+) 937.4663, found 937.4641.

4.1.16. (2*S*,4a*S*,5a*R*,6a*S*,10a*R*,11a*S*,13a*R*)-8,8-Di-*tert*-butyl-2-(*tert*-butyldiphenylsilyloxymethyl)-2,13a-dimethyl-decahydro-1,5,7,9,11-pentaoxa-8-sila-benzo[4,5]cyclohepta[1,2-*b*]naphthalen-3-one (19) and (2*S*,4a*S*,5a*R*,7*S*,8*R*,9a*S*,11a*R*)-2-(*tert*-butyldiphenylsilyl-oxymethyl)-7-(di-*tert*-butyl-hydroxy-silyloxy)-8-hydroxymethyl-2,11a-dimethyl-decahydro-1,5,9-trioxa-dibenzo[*a*,*d*]cyclohepten-3-one (20). To a stirred mixture of **18** (414 mg, 0.443 mmol) and 4 Å MS (700 mg) in CH_2Cl_2 (8.9 mL) at 0°C was added BF_3·OEt_2 (272 μL, 2.214 mmol), and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated in vacuo. Purification by flash chromatography (10→25% EtOAc in hexane) gave ketone **19** (183 mg, 58%) and ketone **20** (115 mg, 36%). **19**: mp 173–174°C; $[\alpha]_D^{25}$=+22.5 (*c* 0.48, $CHCl_3$); IR ($CHCl_3$) 1716, 1472, 1428, 1089 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (9H, s), 1.04 (9H, s), 1.05 (9H, s), 1.14 (6H, s), 1.48 (1H, q, J=11.2 Hz), 1.77–1.98 (3H, m), 2.20 (1H, m), 2.35 (1H, ddd, J=11.2, 3.9, 3.9 Hz), 2.40 (1H, dd, J=19.5, 10.7 Hz), 2.85 (1H, dd, J=19.5, 6.8 Hz), 3.01 (1H, ddd, J=11.2, 9.3, 3.9 Hz), 3.11 (1H, m), 3.22 (1H, ddd, J=10.2, 10.2, 4.9 Hz), 3.56 (1H, d, J=9.8 Hz), 3.64 (1H, m), 3.66 (1H, d, J=9.8 Hz), 3.75 (1H, dd, J=10.2, 10.2 Hz), 4.10 (1H, dd, J=10.2, 4.9 Hz), 4.17 (1H, dd, J=10.7, 6.8 Hz), 7.36–7.71 (10H, Ar); ^{13}C NMR (100 MHz, C_6H_6) δ 19.45, 20.14, 20.55, 22.79, 23.52, 26.97 (3×C), 27.37 (3×C), 27.63 (3×C), 28.55, 38.85, 40.73, 42.37, 67.38, 72.88, 73.34, 76.89, 77.78, 78.87, 80.02, 83.34, 83.59, 127.89, 128.13, 130.07, 130.24, 132.95, 133.69, 135.88, 136.00; HRFABMS calcd for $C_{40}H_{61}O_7Si_2$ (MH^+) 709.3952, found 709.3935. **20**: colorless oil. IR ($CHCl_3$) 3686, 3425, 1724, 1472, 1208, 1113 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (9H, s), 1.03 (9H, s), 1.04 (9H, s), 1.15 (6H, s), 1.55 (1H, q, J=11.3 Hz), 1.80 (1H, m), 1.87 (1H, m), 1.94 (1H, m), 2.18 (1H, br s, OH), 2.22 (1H, m), 2.40 (1H, dd, J=19.0, 11.2 Hz), 2.43 (1H, ddd, J=11.3, 4.1, 4.1 Hz), 2.86 (1H, dd, J=19.0, 6.8 Hz), 2.99 (1H, ddd, J=11.7, 9.7, 4.4 Hz), 3.06 (1H, t, J=2.9 Hz, OH), 3.08 (2H, m), 3.52 (1H, d, J=9.8 Hz), 3.66 (1H, d, J=9.8 Hz), 3.82 (2H, br s), 3.88 (1H, ddd, J=11.2, 9.3, 4.9 Hz), 4.20 (1H, dd, J=11.2, 6.8 Hz), 7.36–7.70 (10H, Ar); FABMS *m*/*z* 727 (MH^+).

4.2. Transformation of 20 to 19

A solution of **20** (35 mg, 0.048 mmol) and TsOH·H_2O (18.3 mg, 0.096 mmol) in benzene (0.5 mL) was heated at 75°C for 3 h. After cooling to room temperature, the reaction was quenched with triethylamine (0.1 mL) and the reaction mixture was concentrated in vacuo. Purification by flash chromatography (10% EtOAc in hexane) gave **19** (27 mg, 79%).

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References

1. For recent reviews, see: (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303–3325. (b) Mori, Y. *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; MYU: Tokyo, 1997; Vol. 17, pp 183–211. (c) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625–1642.
2. (a) Eisch, J. J.; Galle, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 4646–4648. (b) Eisch, J. J.; Galle, J. E. *J. Organomet. Chem.* **1976**, *121*, C10–C14. (c) Eisch, J. J.; Galle, J. E. *J. Organomet. Chem.* **1988**, *341*, 293–313. (d) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, *55*, 4835–4840.
3. (a) Ashwell, M.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. 1* **1989**, 835–837. (b) Ashwell, M.; Clegg, W.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 897–908.
4. Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158–8159.
5. Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330–5334.

6. (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909. (b) Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3–18. (c) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, 293–314.
7. (a) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517–4552. (b) Kadota, I.; Matsukawa, Y.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1993**, 1368–1641. (c) Matsuo, G.; Hori, N.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8859–8862. (d) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380–1386. (e) Sakamoto, Y.; Matsuo, G.; Matsukura, H.; Nakata, T. *Org. Lett.* **2001**, *3*, 2749–2752. (f) Tokiwano, T.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 335–338. (g) McDonald, F. K.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917–2919. (h) Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron* **2002**, *58*, 2027–2040.
8. Some of this work has been reported in a preliminary communication, see: Mori, Y.; Furuta, H.; Takase, T.; Mitsuoka, S.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 8019–8022.
9. Mori, Y.; Yaegashi, K.; Iwase, K.; Yamamori, Y.; Furukawa, H. *Tetrahedron Lett.* **1996**, *37*, 2605–2608.
10. Mori, Y.; Yaegashi, K.; Furukawa, H. *Tetrahedron* **1997**, *53*, 12917–12932.
11. Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3130–3136.
12. Mori, Y.; Yaegashi, K.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 7239–7242.
13. (a) Durst, T.; Tin, K.-C. *Tetrahedron Lett.* **1970**, 2369–2372. (b) Tavares, D. F.; Estep, R. E.; Blezard, M. *Tetrahedron Lett.* **1970**, 2373–2376. (c) Durst, T.; Tin, K.-C.; De Reinach-Hirtzbach, F.; Decesare, J. M. *Can. J. Chem.* **1979**, *57*, 258–266.
14. Compound **16** was prepared from (1*S*,6*R*,8*S*)-8-(benzyloxy)-methyl-3,3-di-*tert*-butyl-2,4,7-trioxa-3-silabicyclo[4.4.0]-deca-9-one. See: Mori, Y.; Hayashi, H. *J. Org. Chem.* **2001**, *66*, 8666–8668.
15. Epoxy sulfone **17** was prepared from (*R*)-*O*-isopropylidene-glyceraldehyde. See Ref. 10.