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New synthetic method for 2,3-*trans*-2-methyl-tetrahydropyran-3-ol and oxepan-3-ol by unique insertion of a methyl group

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ABSTRACT

Treatment of tetrahydropyran-3-ol and oxepan-3-ol derivatives, which have a 1′-mesyloxy group at the C-2 side chain, with Me_3Al effected removal of the mesyloxy group, 1,2-hydride shift, and stereoselective insertion of a methyl group into the resulting oxonium ion, giving 2,3-*trans*-2-methyl-tetrahydropyran-3-ol and oxepan-3-ol derivatives, respectively.

Since the isolation of brevetoxin-B as a red tide toxin, a large number of marine polycyclic ethers have been reported.[1] They have a unique *trans*-fused polycyclic ether ring system and exhibit potent biological activities, such as neurotoxicity, cytotoxicity, and antiviral and antifungal activities. Their synthetically challenging, complex structures and potent bioactivities have attracted the attention of numerous synthetic organic chemists. The marine natural products often contain cyclic ethers having a C-2 methyl group as an angular methyl group, such as 2-methyl-tetrahydropyran **i** and 2-methyl-oxepane **ii** (Fig. 1). Therefore, several methods for the synthesis of polycyclic ethers having a C-2 methyl group have been developed; for example, *endo*-cyclization of hydroxy-vinylepoxide,[2] methylepoxide,[3] and β-sulfonylepoxide,[4] and insertion of a methyl group into *O,S*-acetal[5] and 2,3-epoxy-tetrahydropyran.[6] We now report a new synthetic method for 2-methyl-tetrahydropyran and oxepane by unique insertion of a methyl group at the C-2 position.

In the course of synthetic studies on marine polycyclic ethers, we have recently examined the reaction of α-epoxide **1** with Me_3Al[7] in order to obtain 1′β-methyl diol **4a**. However, the reaction inserted a methyl group at the C-2 position besides the expected C-1′ position; that is, 2α- and 2β-methyl-tetrahydropyrans, **2b** (6%) and **3b** (9%), and 1′β-methyl- and 2′β-methyl-diacetates, **4b** (11%) and **5b** (12%), were produced after acetylation (Scheme 1).[8] This unique methyl-insertion reaction for **2a** and **3a** presumably proceeds via opening of the epoxide ring, 1,2-hydride shift, and insertion of a methyl group into the resulting oxonium ion **iv**

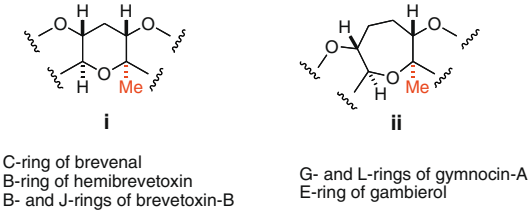
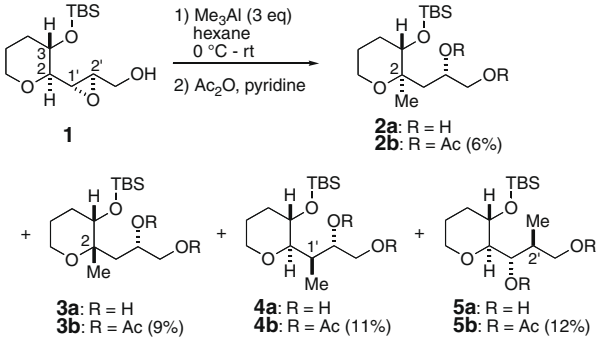


Figure 1. Cyclic ethers having a C-2 methyl group.



Scheme 1.

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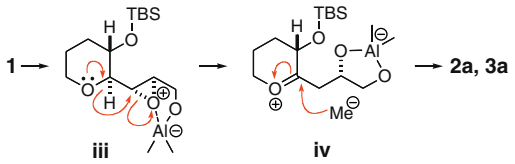


Figure 2. Plausible mechanism for C-2 methyl-insertion reaction.

(Fig. 2). We took a great interest in this methyl-insertion reaction to give **2a** because of the possibility that it would provide the basis for a new synthetic method for 2,3-*trans*-2-methyl-tetrahydropyran-3-ol derivatives, which are important segments for polycyclic ether synthesis. We expected that a substrate having a more active leaving group instead of epoxide would efficiently afford the desired 2-methyl-insertion product.

For more efficient synthesis of 2-methyl cyclic ethers, we anticipated that treatment of the mesylate **v** with Me_3Al would effect insertion of a methyl group at the C-2 position to give 2-methyl ether **vi** (Fig. 3). This synthetic strategy would be expected by a similar hydroxyl-insertion reaction in related systems developed by us.[9] During our studies using tetrahydropyran and oxepane derivatives, Donohoe and co-workers recently reported the same type of reaction using tetrahydrofuran derivatives.[10] Here, we present our results on reaction of the cyclic ethers **v** having a 1′-mesyloxy group with Me_3Al.

First, we examined the reactions using two stereoisomeric tetrahydropyrans, 1′,2-*syn*-**6** and 1′,2-*anti*-**7**, with Me_3Al (Scheme 2). Upon treatment of 1′,2-*syn*-tetrahydropyran **6** with 1.5 equiv of Me_3Al in hexane, the expected insertion of a methyl group at the C-2 position smoothly took place at 0 °C to give a ca. 9:1 mixture of 2,3-*trans*- and 2,3-*cis*-2-methyl-tetrahydropyrans, **8** and **9**, in 95% yield. On the other hand, treatment of the 1′,2-*anti*-isomer **7** with Me_3Al (3.0 equiv) at 0 °C gave a mixture of **8**, **9**, **10**, and **11** in the ratio of ca. 9:1:4:16 (82% combined yield). From these

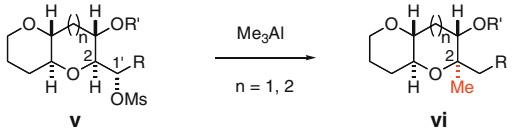
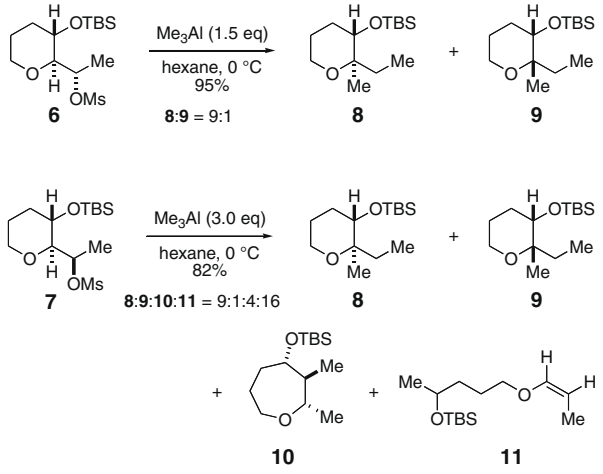


Figure 3. Synthetic plan for 2-methyl cyclic ether **vi**.



Scheme 2.

results, a substrate having 1′,2-*syn*-configuration appears to be suitable for the insertion of a methyl group at the C-2 position.

The reaction of **7** with Me_3Al is expected to proceed concertedly, starting with removal of the mesyloxy group, through three routes a–c (Fig. 4); (a) 1,2-hydride shift and insertion of a methyl group into oxonium ion **vii** to give methyl-inserted ethers **8** and **9**, (b) C–C bond migration and insertion of a methyl group into oxonium ion **viii** to give the ring-expanded ether **10**,[11] and (c) C–C bond cleavage and insertion of a methyl group into oxonium ion **ix** to give the ring-opened compound **11**.

Next, we examined the reactions using the 1′,2-*syn*-substrates **12** and **13** having a hydroxyl functional group on the side chain (Scheme 3). Treatment of the mesylate **12**, prepared from the corresponding 1,2-diol, with Me_3Al produced a complex mixture of compounds, which was not further characterized. On the other hand, reaction of **13**, prepared from 1,3-diol, efficiently afforded a 4:1 mixture of the desired 2,3-*trans*-2-methyl-tetrahydropyran **14** and 2,3-*cis*-isomer **15** in 88% yield.

Then, the present reaction was applied to bicyclic ethers, aiming toward the synthesis of polycyclic ethers (Scheme 4). Treatment of 6,6-membered bicyclic ether **16** with Me_3Al effected the insertion of a methyl group to give 2,6-*syn*-2,3-*trans*-2-methyl-tetrahydropyran **17** as a single product in 95% yield. Thus, the present methyl insertion reaction should be applicable to the construction of polycyclic ethers having a methyl group at the C-2 position. In addition,

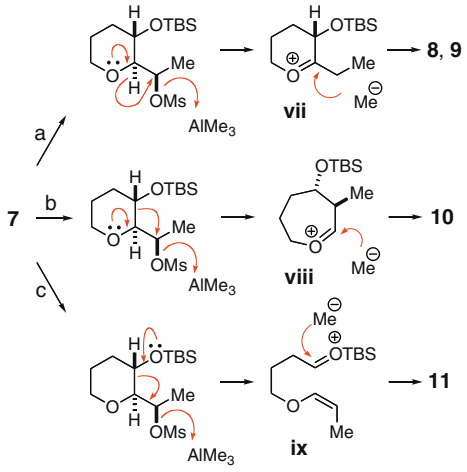
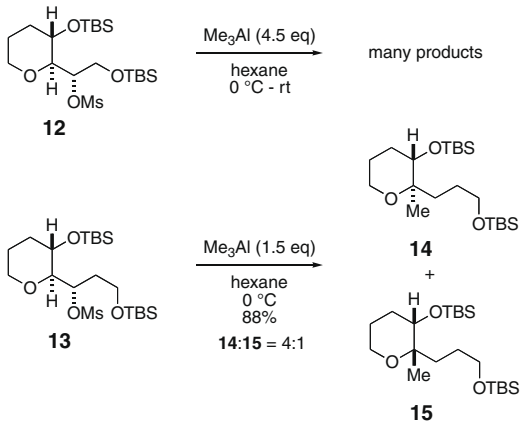
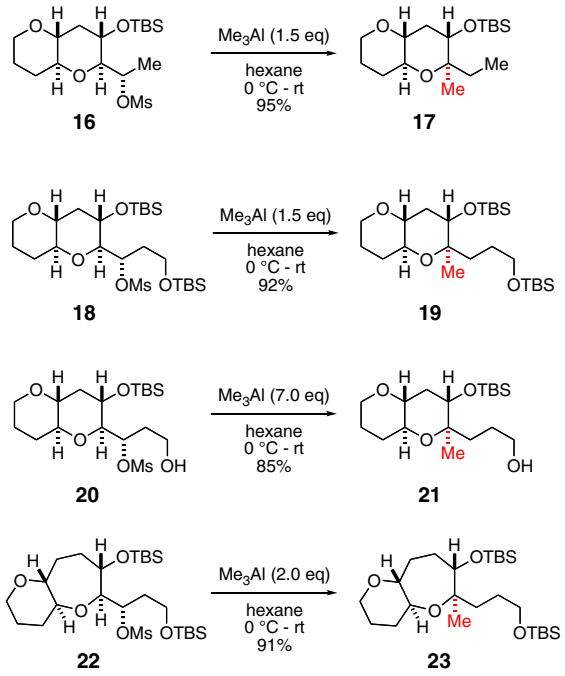


Figure 4. Plausible mechanisms for reaction of **7** with Me_3Al.



Scheme 3.



Scheme 4.

reaction of bicyclic ether **18** having TBS ether on the side chain afforded the desired product **19**[12] in 92% yield. The compound **20**, having a hydroxyl group on the side chain, also afforded the methyl-insertion product **21** in 85% yield. Silylation of the alcohol **21** with TBSCl gave TBS ether **19** in 86% yield. Insertion of a methyl group at the C-2 position of oxepane is interesting, because the position is slightly hindered compared with the corresponding position of tetrahydropyran. Upon treatment of 6,7-membered bicyclic ether **22** with Me_3Al, methyl insertion efficiently took place to give the desired 2,7-*syn*-2,3-*trans*-2-methyl-oxepane **23**[13] as a single product in 91% yield. Thus, the present reaction should be very useful for the stereoselective construction of *syn*-*trans*-polycyclic ethers having a methyl group at the C-2 position.

The structures of the products **17**, **19**, and **23** were confirmed by ^1H and ^{13}C NMR, and NOE measurements (Fig. 5).

These results can be explained as follows, using **16** (Fig. 6). Treatment of **16** with Me_3Al concertedly effected removal of the mesyloxy group, 1,2-hydride shift, and formation of oxonium ion **xi**. Then, methyl insertion into the oxonium ion **xi** would take place from the α-axial side to yield a chair-form transition state, giving the methyl-insertion product **17**.

In summary, we have developed an efficient synthesis of 2,3-*trans*-2-methyl-tetrahydropyran-3-ol and oxepan-3-ol by unique insertion reaction of a methyl group. The key feature of this method is that it is possible to insert a methyl group at the C-2 position after construction of the cyclic ether rings. This method should

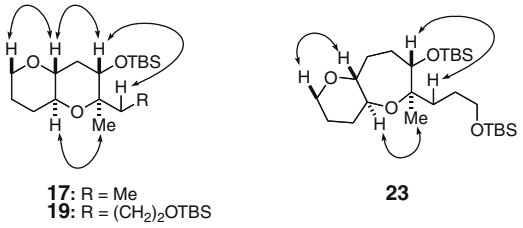


Figure 5. Observed NOEs of **17**, **19**, and **23**.

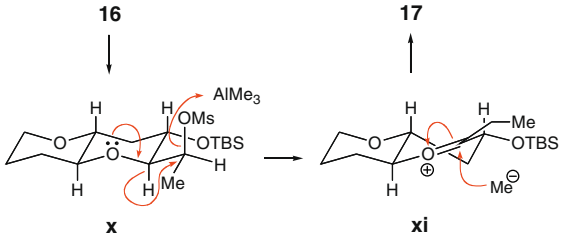


Figure 6. Plausible mechanism for reaction of **16** with Me_3Al.

work very efficiently for the stereoselective synthesis of cyclic ethers having a C-2 methyl group.

Acknowledgments

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8. Treatment of the corresponding β-epoxy isomer of **1** with Me_3Al effected a methyl insertion at the expected C-1′ position to give 1′α-methyl-2′,3′-diol, predominantly. Cf.: Sasaki, M.; Matsumori, N.; Maruyama, T.; Nonomura, T.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem., Int. Ed.* **1996**, *35*, 1672.
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11. This route was supported by the reaction using 1′-deuterated **7**; that is, the product was 3-deuterated oxepane **10**.
12. *Data for* **19**: $[\alpha]_D^{25}$ +12.9 (*c* 0.79, $CHCl_3$); IR (neat) 2955, 2857, 1472, 1361, 1255, 1100, 1034, 939, 836, 774, 669, 418 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.89 (br d, *J* = 11.3 Hz, 1H), 3.64–3.56 (m, 2H), 3.56 (dd, *J* = 11.3, 4.6 Hz, 1H), 3.35 (ddd, *J* = 11.3, 11.3, 3.4 Hz, 1H), 3.16 (ddd, *J* = 10.6, 9.1, 4.2 Hz, 1H), 2.88 (ddd, *J* = 12.1, 9.5, 4.1 Hz, 1H), 2.00 (ddd, *J* = 11.7, 4.5, 4.5 Hz, 1 H), 1.92–1.90 (m, 1H), 1.75–1.59 (m, 4H), 1.41–1.28 (m, 4H), 1.13 (s, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.7, 72.1, 70.1, 67.9, 64.0, 36.4, 35.4, 29.7, 26.1, 26.0 (3C), 25.72 (3C), 25.67, 18.4, 17.8, 15.7, −3.9, −4.9, −5.26, −5.30; HRMS (ESI) calcd for $C_{24}H_{50}O_4Si_2Na$ (M+Na$^+$) 481.3140, found 481.3129.
13. *Data for* **23**: $[\alpha]_D^{25}$ +5.67 (*c* 0.97, $CHCl_3$); IR (neat) 2931, 2857, 1472, 1361, 1254, 1100, 993, 938, 913, 835, 773, 418 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.82 (br d, *J* = 10.6 Hz, 1H), 3.74 (d, *J* = 7.1 Hz, 1H), 3.62 (ddd, *J* = 9.8, 6.4, 6.4 Hz, 1H), 3.55 (ddd, *J* = 9.8, 6.4, 6.4 Hz, 1H), 3.45 (ddd, *J* = 10.9, 9.1, 5.3 Hz, 1H), 3.26 (ddd, *J* = 10.2, 7.1, 7.1 Hz, 1H), 2.99 (ddd, *J* = 9.5, 9.5, 5.6 Hz, 1H), 1.90–1.78 (m, 3H), 1.73–1.57 (m, 4H), 1.50–1.42 (m, 1H), 1.37 (ddd, *J* = 13.2, 13.2, 4.9 Hz, 1H), 1.32 (ddd, *J* = 12.5, 12.5, 4.9 Hz, 1H), 1.28–1.24 (m, 2H), 1.10 (s, 3H), 0.94 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H), 0.04 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.5, 79.9, 75.4, 70.2, 67.1, 63.6, 37.1, 32.2, 27.9, 26.7, 26.03 (3C), 25.96 (3C), 25.6, 25.5, 19.3, 18.3, 18.2, −4.4, −5.26 (2C), −5.30 (2C); HRMS (ESI) calcd for $C_{25}H_{52}O_4Si_2Na$ (M+Na$^+$) 495.3296, found 495.3297.