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Stereoselective Synthesis of 2,6-*syn*-Dimethyl-tetrahydropyran Derivatives, Important Segments of Marine Polycyclic Ethers, by Unique Insertion of the Methyl Group

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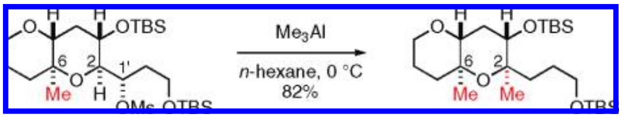
ABSTRACT



Treatment of 6-methyl-tetrahydropyran derivatives, which have a 1′-mesyloxy group at the C2-side chain, with Me$_3$Al effected stereoselective insertion of a methyl group at the C2-position to give 2,6-*syn*-dimethyl-tetrahydropyran derivatives. This reaction proceeds via removal of the mesyloxy group, 1,2-hydride shift, and stereoselective insertion of a methyl group into the resulting oxonium ion.

Since the isolation of brevetoxin-B as a red tide toxin, many marine polycyclic ethers, such as gambierol and maitotoxin, have been reported.[1] They have a unique *trans*-fused polycyclic ether ring system and exhibit potent biological activities, including neurotoxicity, cytotoxicity, and antiviral activities. Their synthetically challenging structures and potent bioactivities have attracted the attention of numerous synthetic organic chemists.[2] The marine natural products often contain cyclic ethers having a C2-methyl group as an angular methyl group, such as 2-methyl-tetrahydropyran. Thus, synthetic methods for cyclic ethers including 2-methyl-tetrahydropyran structures have been extensively investigated.[3] Furthermore, 2,6-*syn*-dimethyl-tetrahydropyran derivatives are also important segments, being present, for example, in the F-ring of brevetoxin-B, the B-ring of gambierol, and the W-, Z-, and E′-rings of maitotoxin (Figure 1). However, there are only a few reports on synthetic methods applicable to 2,6-*syn*-dimethyl-tetrahydropyran derivatives, that is, 6-*endo*-cyclization of hydroxy vinyl epoxide by Nicolaou et al.,[3c] Claisen rearrangement of allyl enol ether

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(1) For reviews on polycyclic ethers, see: (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (b) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685. (c) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293. (d) Yasumoto, T. *Chem. Rec.* **2001**, *1*, 228. (e) Deranas, A, H.; Norte, M.; Fernández, J. *J. Toxicon* **2001**, *39*, 1101.

(2) For reviews on synthetic methods and total syntheses, see: (a) Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953. (b) Fujiwara, K.; Hayashi, N.; Tokiwano, T.; Murai, A. *Heterocycles* **1999**, *50*, 561. (c) Mori, Y. *Chem.—Eur. J.* **1997**, *3*, 849. (d) Marmsäter, F. P.; West, F. G. *Chem.—Eur. J.* **2002**, *8*, 4347. (e) Inoue, M. *Org. Biomol. Chem.* **2004**, *2*, 1811. (f) Fujiwara, K.; Murai, A. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 2129. (g) Sasaki, M.; Fuwa, H. *Synlett* **2004**, *2*, 1811. (h) Kadota, I.; Yamamoto, Y. *Acc. Chem. Res.* **2005**, *38*, 423. (i) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379. (j) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314. (k) Clark, J. S. *Chem. Commun.* **2006**, 3571. (l) Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7182.

(3) Selected papers: (a) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (c) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517. (d) Mori, Y.; Furuta, H.; Takase, T.; Mitsuoka, S.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 8019. (e) Rainier, J. D.; Allwein, S. P. *J. Org. Chem.* **1998**, *63*, 5310. (f) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *Org. Lett.* **2000**, *2*, 231. (g) Majumder, U.; Cox, J. M.; Johnson, H. W. B.; Rainier, J. D. *Chem.—Eur. J.* **2006**, *12*, 1736. (h) Matsuo, G.; Matsukura, H.; Hori, N.; Nakata, T. *Tetrahedron Lett.* **2000**, *41*, 7673. (i) Suzuki, K.; Matsukura, H.; Matsuo, G.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **2002**, *43*, 8653. See also ref 2.

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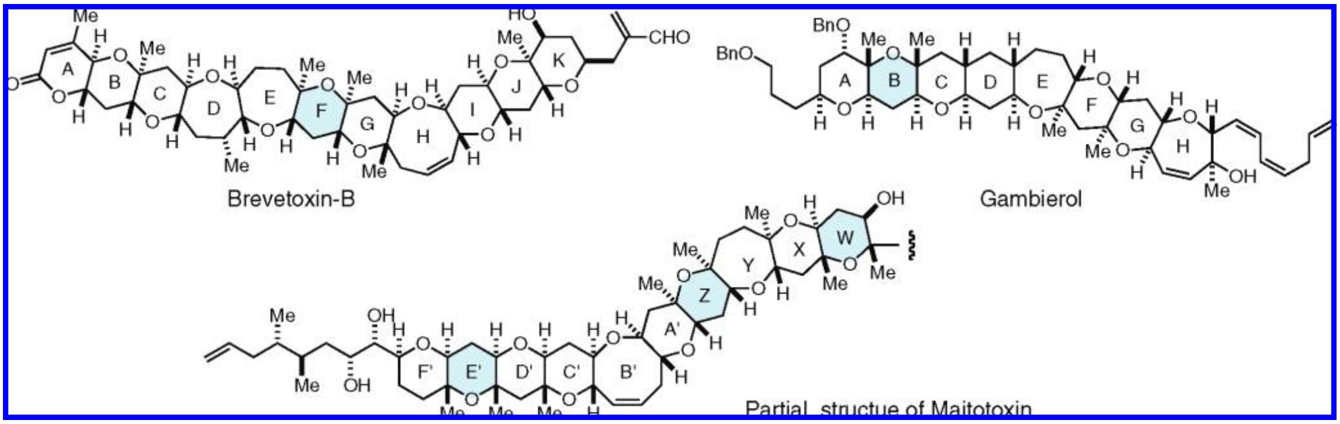

Figure 1. Structures of brevetoxin B and gambierol and partial structure of maitotoxin.

by Rainier et al.,[3g] and 6-*endo*-cyclization of hydroxy epoxy sulfone by Mori et al.[3d] Among them, Nicolaou's method[3c] has been frequently used in synthetic studies on marine polycyclic ethers.[2]

We have recently developed a stereoselective synthesis of 2-methyl-tetrahydropyran derivative **2** via unique insertion of a methyl group by treatment of the mesylate **1** with Me_3Al (Figure 2).[4,5] We now report a new synthetic method for 2,6-*syn*-dimethyl-tetrahydropyran derivatives, **i** and **ii**, by application of this insertion reaction of a methyl group in mono- and bicyclic ether ring systems (Figure 3).

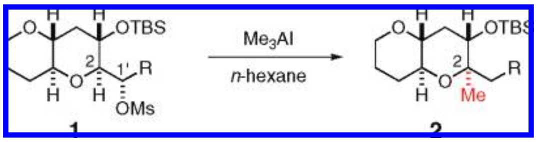

Figure 2. Insertion reaction of a methyl group.

Figure 3. 2,6-*syn*-Dimethyl-tetrahydropyran derivatives.

First, insertion of a methyl group in a monocyclic ether system was investigated. The synthesis of the required 6-methyl-tetrahydropyran-1′-mesylate **8**, a substrate for insertion of a C2-methyl group, was started with the known alcohol **3**,[6] prepared from 2-deoxy-D-ribose (Scheme 1). Oxidation of **3** with SO_3•pyridine afforded aldehyde **4**. We first examined the route via Sharpless asymmetric epoxidation[7] to give C1′-α-alcohol **7**. The Wittig reaction of **4** with $Ph_3P=CHCO_2Et$ and DIBAH reduction gave allyl alcohol **5** in 70% yield (three steps). The Sharpless epoxidation of **5** using (−)-DET afforded a 2:1 mixture of α- and *β*-epoxides, which was reduced with Red-Al to give the desired α-alcohol **7** in 39% yield (two steps, after separation). To find a more efficient route to the diol **7**, stereoselective allylations were next examined. Brown's asymmetric allylation[8] of **4** by treatment with (−)-IPC_2B(allyl) at −78 °C afforded the desired α-alcohol **6** in 82% yield (two steps from **3**) with 10:1 diastereomeric ratio. After several attempts, reaction of **4** with allylTMS in the presence of $MgBr_2$•OEt_2 afforded the desired α-alcohol **6** as a single product in 90% yield (two steps from **3**).[9] The alcohol **6** was converted into the corresponding acetonide **10** by deprotection of TBS and acetonization to determine the stereochemistry (Figure 4). Observed NOE and the coupling constant of Ha and Hb (J = 6.8 Hz) suggested that **10** should have the conformation **10a**, which supports the configuration of C1′-α-alcohol **6**. Oxidative cleavage of the olefin **6** with OsO_4-NaIO_4 followed by $NaBH_4$ reduction in one pot afforded diol **7** in 86% yield. Selective TBS protection of the diol and mesylation of the secondary alcohol in one pot quantitatively afforded the required mesylate **8**. Treatment of **8** with Me_3Al (3.0 equiv) in *n*- hexane at 0 °C effected methyl insertion to give the desired 2,6-*syn*-dimethyl-tetrahydropyran **9** in 90% yield. The stereoselectivity was ca. 30:1. The stereostructure of **9** was confirmed by observed NOE between C2-Me and C6-Me of the corresponding alcohol **9′**.

We next investigated insertion of a methyl group in a bicyclic ether system. By employing the effective allylation route shown in Scheme 1, the required mesylate **15** was

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[4] Kimishima, A.; Nakata, T. *Tetrahedron Lett.* **2008**, *49*, 6563.

[5] The same type of reaction using tetrahydrofuran derivatives was reported. Donohoe, T. J.; Williams, O.; Churchill, G. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2869.

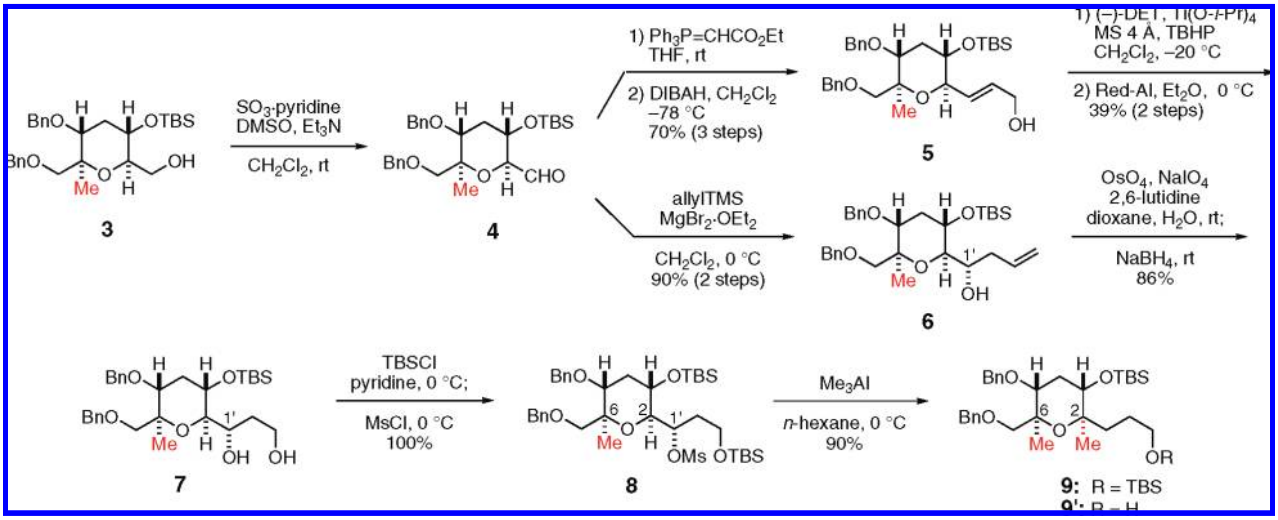
[6] Satoh, M.; Koshino, H.; Nakata, T. *Org. Lett.* **2008**, *10*, 1683.

[7] (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1–300.

[8] Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

[9] (a) Keum, G.; Kang, S. B.; Kim, Y.; Lee, E. *Org. Lett.* **2004**, *6*, 1895. (b) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265.

Scheme 1



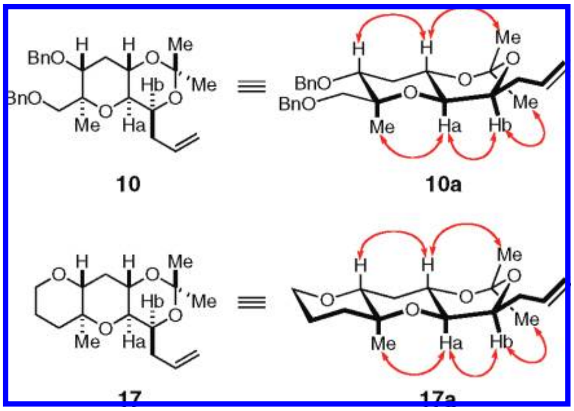
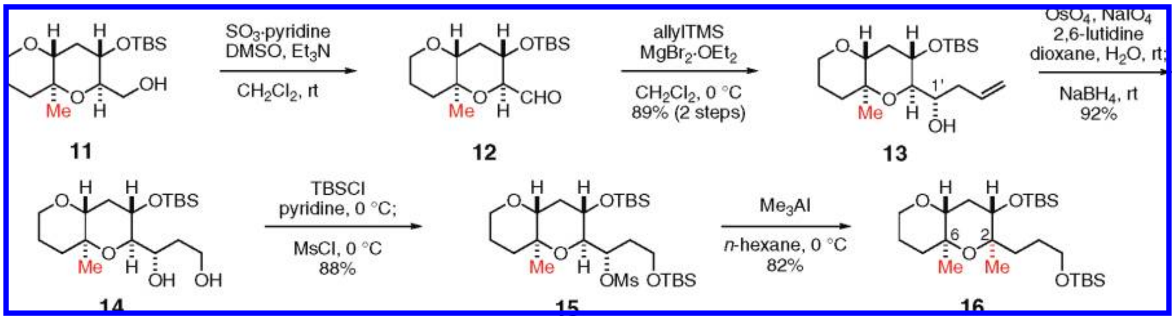


Figure 4. Observed NOEs of **10** and **17**.

obtained (Scheme 2). The reaction started with bicyclic alcohol **11**,[10] which was prepared from 2-deoxy-D-ribose. Oxidation of **11** with SO$_3$·pyridine gave aldehyde **12**, which was treated with allylTMS in the presence of MgBr$_2$·OEt$_2$ to give α-alcohol **13** as a single product in 89% yield (two steps from **11**). The configuration of the C1′-α-alcohol **13** was also determined based on observed NOE and the coupling constant of Ha and Hb (J = 7.0 Hz) of the corresponding acetonide **17** (Figure 4). Oxidative cleavage of the olefin **13** with OsO$_4$−NaIO$_4$ followed by NaBH$_4$ reduction in one pot afforded diol **14** in 92% yield. One-pot TBS protection−mesylation afforded the mesylate **15** in 88% yield. Upon treatment of **15** with Me$_3$Al (3.0 equiv) in *n*-hexane at 0 °C, methyl insertion took place smoothly with ca. 17:1 stereoselection to give 2,6-*syn*-dimethyl-tetrahydropyran **16** in 82% yield. The stereostructure of **16** was confirmed by observed NOE between C2-Me and C6-Me. Thus, the present methyl insertion reaction was also effective to give 2,6-*syn*-dimethyl-tetrahydropyran in a bicyclic ether system. Stereoselective insertion of the methyl group can be explained as shown in Figure 5. The reaction would proceed concertedly via removal of the mesylate, 1,2-hydride shift, and methyl insertion into the resulting oxonium ion **iii**. The methyl group should attack from the α-axial side, in spite of the steric hindrance of the C6-α-methyl group, to take a chair-form transition state, providing 2,6-*syn*-dimethyl-tetrahydropyran **16**.

Scheme 2



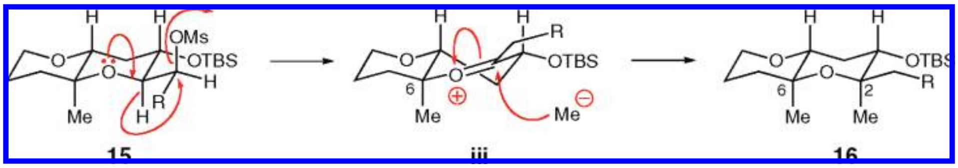


Figure 5. Reaction mechanism of **15** with Me_3Al.

In summary, we have developed an efficient and reliable synthetic method for 2,6-*syn*-dimethyl-tetrahydropyran derivatives through a unique methyl insertion reaction by treatment with Me_3Al. The present method should be useful for construction of 2,6-*syn*-dimethyl-tetrahydropyran segments as starting materials or key intermediates for the synthesis of marine polycyclic ethers.

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Supporting Information Available: Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Synthesis of **11**, see Supporting Information.