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METHYL INSERTION REACTIONS OF TETRAHYDROPYRANS HAVING A C1'-MESYLOXY GROUP ON THE C2-SIDE CHAIN WITH TRIMETHYLALUMINUM[†]

Keigo Nakamura, Atsushi Kimishima, and Tadashi Nakata*

Department of Chemistry, Faculty of Science, Tokyo University of Science, 1-3
Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan
E-mail: nakata@rs.kagu.tus.ac.jp

[†]Dedicated to Professor Emeritus Akira Suzuki on the occasion of his 80th birthday.

Abstract – Methyl insertion reactions of tetrahydropyrans having a C1'-mesyloxy group on the C2-side chain, mediated by trimethylaluminum, were investigated. Removal of the mesyloxy group, 1,2-hydride shift and/or ring-expansion, and methyl insertion took place concertedly, depending on the stereostructure of the substrate, to give 2-methylated tetrahydropyran and/or 2- or 3-methylated oxepane.

Since brevetoxin B was isolated as a red tide toxin, many 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. The marine natural products often contain cyclic ethers having a C2-methyl group as an angular methyl group, such as 2-methyl-tetrahydropyran. In connection with synthetic studies on marine polycyclic ethers, we have recently developed a new synthetic method for 2,3-*trans*-2-methyl-tetrahydropyran-3-ol and oxepan-3-ol derivatives through a unique methyl insertion reaction of cyclic ethers (**1**) having mesylate on the C2-side chain.[2,3] Thus, upon treatment of cyclic ethers (**1**) having a C1'-mesyloxy (OMs) group with trimethylaluminum (Me_3Al), methyl insertion took place to give the C2-methylated compound (**2**) as the sole product (Figure 1). The present reaction is considered to take place concertedly via removal of the mesyloxy group, 1,2-hydride shift, and methyl insertion into the resulting oxonium ion.

We now report further studies on the present reaction using the four possible stereoisomers of 2-(1'-mesyloxy)ethyl-5-hexyl-tetrahydropyrans (**3**–**6**) (Figure 2).[4,5]

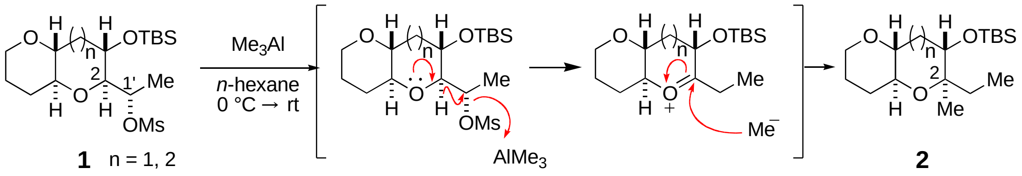
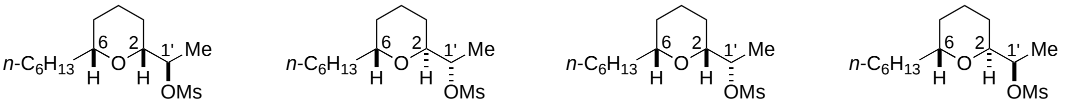


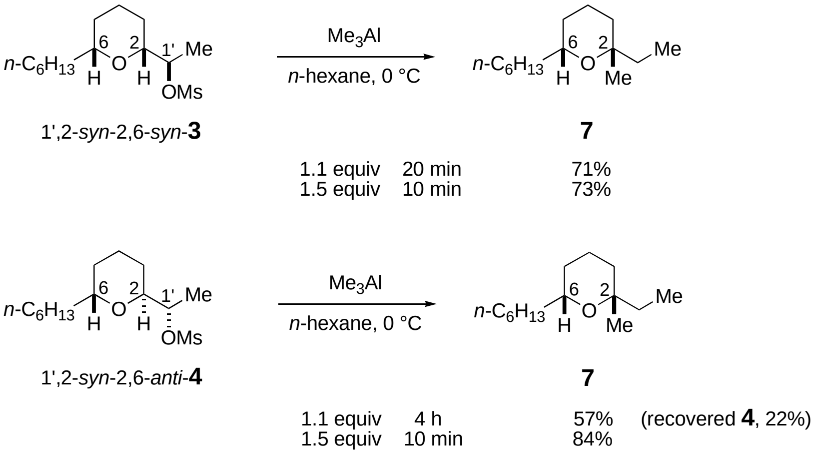
Figure 1. Methyl insertion reaction of **1** with Me_3Al.



1',2-*syn*-2,6-*syn*-**3** 1',2-*syn*-2,6-*anti*-**4** 1',2-*anti*-2,6-*syn*-**5** 1',2-*anti*-2,6-*anti*-**6**

Figure 2. Four possible stereoisomers (**3**–**6**).

First, the reactions of two stereoisomers (**3** and **4**) having 1',2-*syn*-configuration with Me_3Al were examined in *n*-hexane at 0 °C (Scheme 1).[6] Upon treatment of 1',2-*syn*-2,6-*syn*-tetrahydropyran (**3**) with 1.1 equiv of Me_3Al for 20 min, methyl insertion took place stereoselectively to give 2,6-*syn*-2-methyl-tetrahydropyran[7] (**7**) in 71% yield (Scheme 1). The same reaction using 1.5 equiv of Me_3Al afforded **7** in 73% yield within 10 min. On the other hand, reaction of the 1',2-*syn*-2,6-*anti*-isomer (**4**) with 1.1 equiv of Me_3Al also stereoselectively afforded the same product (**7**) in 57% yield, along with recovered starting material (**4**, 22%). The reaction of **4** using 1.5 equiv of Me_3Al increased the yield to give **7** as the sole product in 84% yield.



1',2-*syn*-2,6-*syn*-**3** → **7**

1.1 equiv 20 min 71%
1.5 equiv 10 min 73%

1',2-*syn*-2,6-*anti*-**4** → **7**

1.1 equiv 4 h 57% (recovered **4**, 22%)
1.5 equiv 10 min 84%

Scheme 1

The present methyl insertion reactions of **3** and **4** with Me_3Al can be explained as follows (Figure 3). Treatment of **3** and **4** with Me_3Al concertedly effected removal of the mesyloxy group and 1,2-hydride shift through the conformers (**3-i** and **4-i**),[8] respectively, which have an antiperiplanar relationship between C2-H and C1'-OMs, to produce the same oxonium ion intermediate (**A**). Then, the methyl group would attack from the β-axial side into this oxonium ion (**A**) to take a chair-form transition state, giving 2,6-*syn*-2- methyl-tetrahydropyran (**7**).

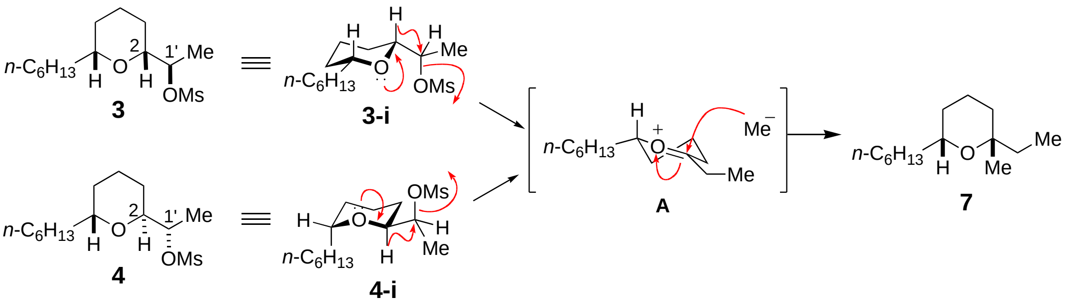
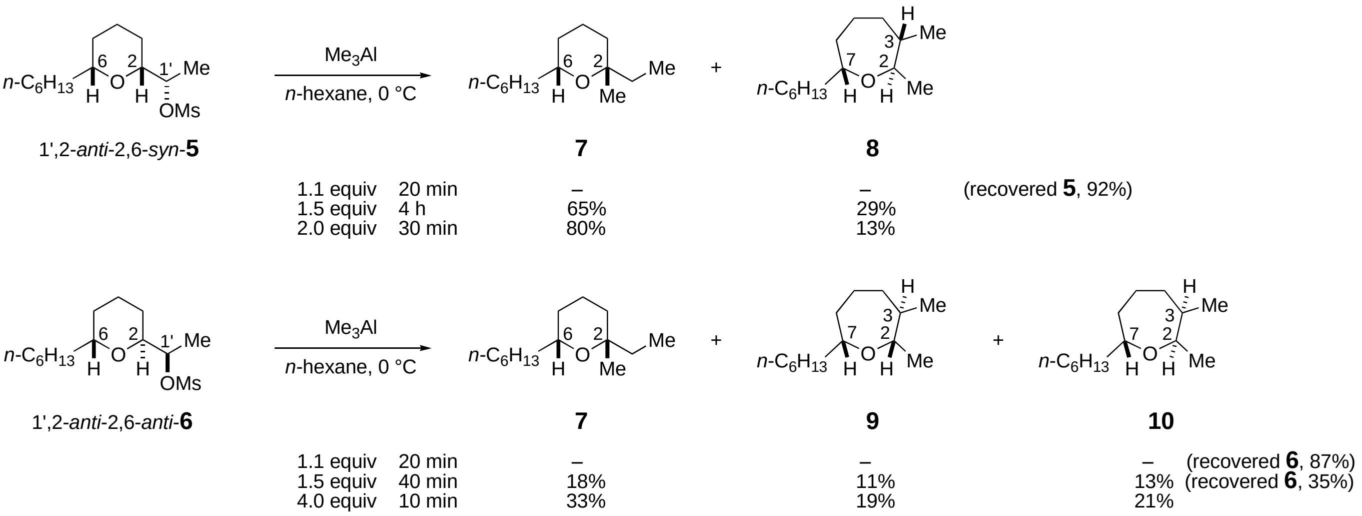


Figure 3. Plausible mechanisms for reaction of **3** and **4** with Me_3Al.

Next, the reactions of the other stereoisomers (**5** and **6**), having 1',2-*anti*-configuration, were examined (Scheme 2). Reaction of 1',2-*anti*-2,6-*syn*-**5** with 1.1 equiv of Me_3Al for 20 min resulted only in recovery of the starting material (**5**) in 92% yield. But, treatment with 1.5 equiv of Me_3Al for 4 h afforded 2,6-*syn*-2-methyl-tetrahydropyran (**7**) (65%) and ring-expanded 2,7-*anti*-2,3-*trans*-2,3-dimethyl-oxepane[9] (**8**) (29%). Furthermore, the reaction using 2.0 equiv of Me_3Al afforded **7** (80%) and **8** (13%). Reaction of 1',2-*anti*-2,6-*anti*-**6** with 1.1 equiv of Me_3Al for 20 min also resulted in recovery of the starting material



		7	**8**	
1.1 equiv	20 min	–	–	(recovered **5**, 92%)
1.5 equiv	4 h	65%	29%	
2.0 equiv	30 min	80%	13%	

		7	**9**	**10**	
1.1 equiv	20 min	–	–	–	(recovered **6**, 87%)
1.5 equiv	40 min	18%	11%	13%	(recovered **6**, 35%)
4.0 equiv	10 min	33%	19%	21%	

Scheme 2

(**6**) in 87% yield. The reaction using 1.5 equiv of Me_3Al gave three products, i.e., 2,6-*syn*-2-methyl-tetrahydropyran (**7**) (18%), 2,7-*syn*-2,3-*trans*-2,3-dimethyl-oxepane[10,11] (**9**) (11%), and 2,7-*anti*-2,3-*cis*-2,3- dimethyl-oxepane[10,11] (**10**) (13%), along with recovered **6** (35%). Use of 4.0 equiv of Me_3Al resulted in completion of the reaction within 10 min to give **7** (33%), **9** (19%), and **10** (21%).

In order to examine the reaction mechanism for **5** and **6**, we employed C1'-deuterated compounds (**d-5** and **d-6**), which were prepared from the corresponding alcohols by oxidation with TPAP-NMO, followed by $NaBD_4$ reduction. Reaction of the C1'-deuterated 1',2-*anti*-2,6-*syn*-tetrahyropyran (**d-5**) with Me_3Al afforded C1'-deuterated 2,6-*syn*-2-methyl-tetrahydropyran (**d-7**) and C3-deuterated 2,7-*anti*-2,3-*trans*-2,3-dimethyl-oxepane (**d-8**). Thus, the reaction would proceed as shown in Figure 4. The C1'-deuterated 2-methyl-tetrahydropyran (**d-7**) would be produced through the conformer (**d-5-i**) via methyl insertion into the resulting oxonium ion (**d-A**). From the conformer (**d-5-ii**), removal of the mesyloxy group, antiperiplanar C2-C3 bond migration, and methyl insertion into the oxonium ion (**d-B**) would take place from the β-side to give the C3-deuterated 2-methylated oxepane (**d-8**).

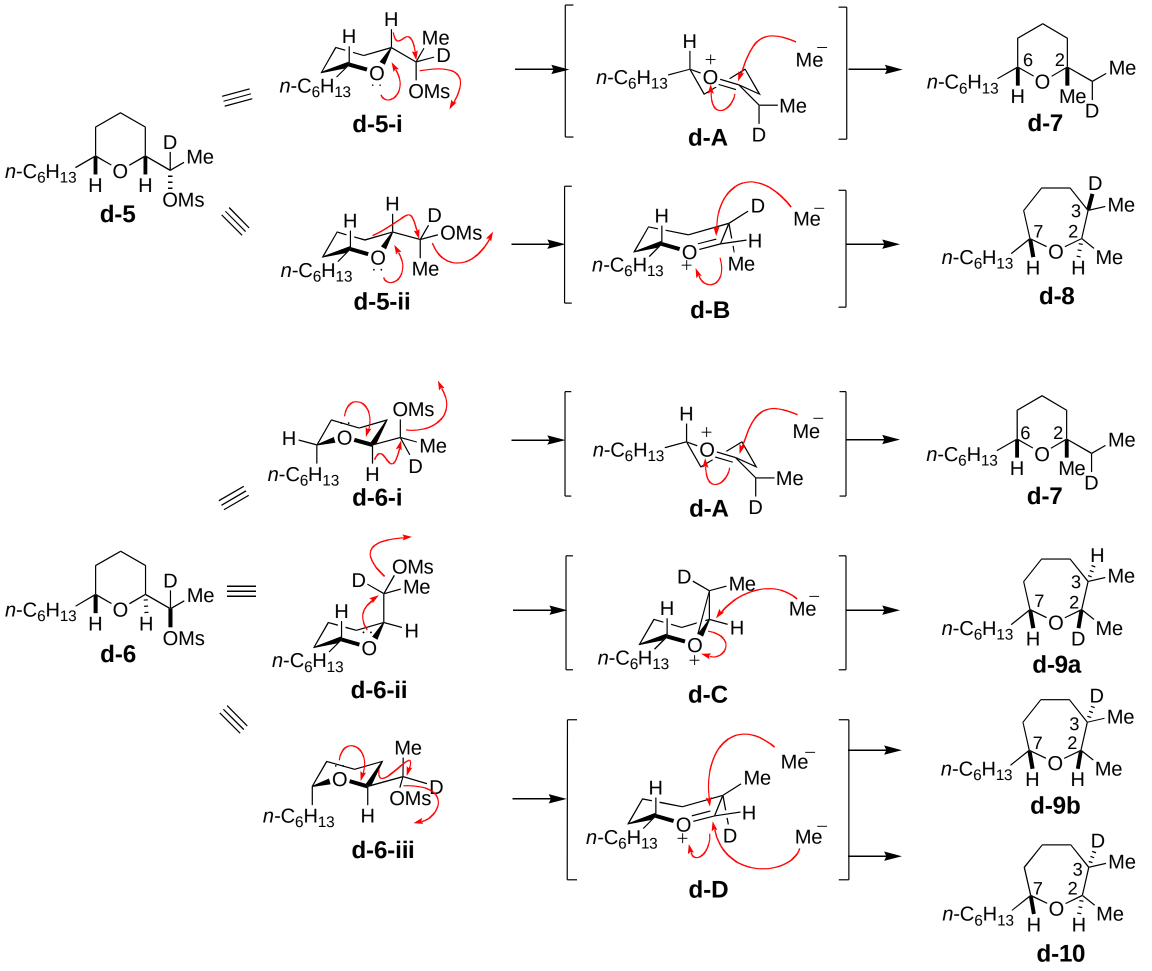


Figure 4. Plausible mechanisms for reaction of **5** and **6** with Me_3Al using C1'-deuterated substrates.

Next, reaction of the C1'-deuterated 2,6-*anti*-1',2-*anti*-tetrahydropyran (**d-6**) with Me_3Al produced C1'-deuterated 2-methyl-tetrahydropyran (**d-7**), C2-deuterated 2,7-*syn*-2,3-*trans*-2,3-dimethyl-oxepane (**d-9a**), and C3-deuterated 2,7-*syn*-2,3-*trans*- and 2,7-*anti*-2,3-*cis*-2,3-dimethyl-oxepanes (**d-9b** and **d-10**). The ratio of **d-9a** and **d-9b** was ca. 91:9. The 2-methylated tetrahydropyran (**d-7**) would also be produced via methyl insertion into the oxonium ion (**d-A**) through the conformer (**d-6-i**).[12] Ring-expanded C2-deuterated 3-methylated oxepane (**d-9a**) should be produced through the conformer (**d-6-ii**), which has an antiperiplanar relationship between the C1'-MsO group and C2-O bond, via methyl insertion at the C3-position into the oxonium ion (**d-C**). The other C3-deuterated 2-methylated products (**d-9b** and **d-10**) would be produced through the conformer (**d-6-iii**) via methyl insertion at the C2-position into the oxonium ion (**d-D**) from the α-side and β-side, respectively. Thus, it was found that 2,7-*syn*-2,3-*tran*s-oxepane (**9**) in Scheme 2 was produced via two routes through transition states corresponding to **d-C** and **d-D**.

In conclusion, the reactions of 2-(1'-mesyloxy)ethyl-5-hexyl-tetrahydropyrans with Me_3Al proceed via removal of the mesyloxy group, 1,2-hydride shift and/or ring-expansion, and methyl insertion, depending on the stereostructure of the substrate, to give 2-methylated tetrahydropyran and/or 2- or 3-methylated oxepane.

ACKNOWLEDGEMENTS

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2. A. Kimishima and T. Nakata, *Tetrahedron Lett.*, 2008, **49**, 6563.
3. The same type of reaction using tetrahydrofuran derivatives was reported. T. J. Donohoe, O. Williams, and D. H. Churchill, *Angew. Chem. Int. Ed.*, 2008, **47**, 2869.
4. We have already reported the rearrangement reaction of the same stereoisomers (**3**-**6**) with zinc acetate; K. Nagasawa, N. Hori, H. Koshino, and T. Nakata, *Heterocycles*, 1999, **50**, 919.
5. Only one enantiomer of the racemate is drawn for the sake of simplicity.
6. A typical procedure for methyl-insertion reaction: To a solution of **3** (74.0 mg, 0.25 mmol) in *n*-hexane (1.5 mL) was added Me_3Al (1.08 M solution in *n*-hexane, 250 μL, 0.27 mmol) at 0 °C under argon atmosphere. After stirring at 0 °C for 20 min, the mixture was quenched with sat. aq.

$NaHCO_3$ solution and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (Silica gel 60N, *n*-hexane:EtOAc= 100:1) to give **7** (37.8 mg; 71 % yield) as a colorless oil.

7. Data for **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46 (m, 1H), 1.67-1.60 (m, 2H), 1.57–1.49 (m, 2H), 1.47-1.25 (m, 13H), 1.11 (s, 3H), 1.10–1.00 (m, 1H), 0.89 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.3, 69.9, 37.4, 37.0, 34.4, 31.94, 31.89, 29.4, 25.5, 22.6, 20.0, 19.2, 14.1, 7.6. HRMS (EI) calcd for $C_{14}H_{28}ONa$ [M+Na$^+$] 212.2140, found 212.2144.
8. The coupling constants ($J_{2,3\text{-}syn}$ = 3.3 Hz and $J_{2,3\text{-}anti}$ = 9.9 Hz) and ROE observation between C2-H and methylene protons of the C6-hexyl group in **4** suggested that **4** would mainly take the conformation having an equatorial C2-side chain, although **4** is a mixture of ring-flipped conformers.[4]
9. Data for **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (m, 1H), 3.35 (dq, J = 9.1, 6.3 Hz, 1H), 1.78–1.67 (m, 2H), 1.57–1.54 (m, 2H), 1.49–1.34 (m, 6H), 1.32–1.24 (m, 7H), 1.15 (d, J = 6.3 Hz, 3H), 0.88 (t, J = 7.0 Hz, H), 0.85 (t, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz,) δ 76.3, 73.5. 42.3, 36.8, 36.23, 36.15, 31.9, 29.4, 27.4, 26.4, 22.6, 20.4, 19.9, 14.1. HRMS (EI) calcd for $C_{14}H_{28}ONa$ [M+Na$^+$] 212.2140, found 212.2144.
10. Yields of **9** and **10** were calculated from the ^{1}H NMR analysis, because the products could not be isolated.
11. Selected ^{1}H-NMR data (600 MHz, $CDCl_3$): for **9** d 3.37 (m, 1H), 3.04 (dq, J = 9.5, 6.4 Hz, 1H), 1.10 (d, J = 6.4 Hz, 3H), 0. 84 (d, J = 6.8 Hz, 3H); for **10** δ 3.80 (dd, J = 6.8, 6.4 Hz, 1H), 3.60 (m, 1H), 1.20 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H). HRMS (EI) calcd for $C_{14}H_{28}ONa$ [M+Na$^+$] 212.2140, found 212.2137.
12. The observed ROEs between the C1'- and C6-H_2, and C2-H and methylene protons of the C6-hexyl group in **6** support the presence of ring-flipped conformers.[4]