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Cu(II)-MEDIATED STEREOSELECTIVE MICHAEL ADDITION OF A METHYL GROUP TO AN α,β -UNSATURATED ESTER AS THE C2-SIDE CHAIN IN 3-(*t*-BUTYLDIMETHYLSILOXY)TETRAHYDROPYRANS

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Abstract – Stereoselective Michael addition of a methyl group to an α,β -unsaturated ester as the C2-side chain in 3-(*t*-butyldimethylsilyloxy)tetrahydropyrans was accomplished under the conditions using MeMgBr and TMSCl in the presence of a catalytic amount of Cu(*N*-*i*-Pr-Sal)₂.

Marine polycyclic ethers, exemplified by brevetoxins, ciguatoxins, yessotoxins, etc.,¹ have attracted the attention of numerous synthetic organic chemists due to their unique and complex structure, and potent biological activities. Among these polycyclic ethers, an α - or a β -methyl group is often found on the six- to nine-membered ether rings; for example, the α -methyl group on the D-ring of brevetoxin-B (BTX-B) and the β -methyl group on the G-ring of yessotoxin (YTX) (Figure 1). Thus, stereoselective construction of a methyl group on the ether ring should be an important task for the synthesis of these natural products. Although there are several reports of stereoselective introduction of a methyl group to the cyclic ether ring,² few methods for stereoselective methylation to an acyclic side chain in the ether ring have been

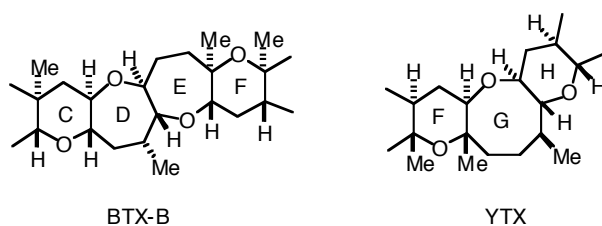
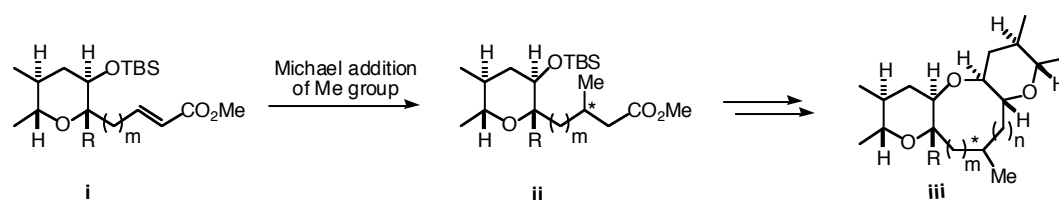


Figure 1. Partial structure of brevetoxin-B and yessotoxin

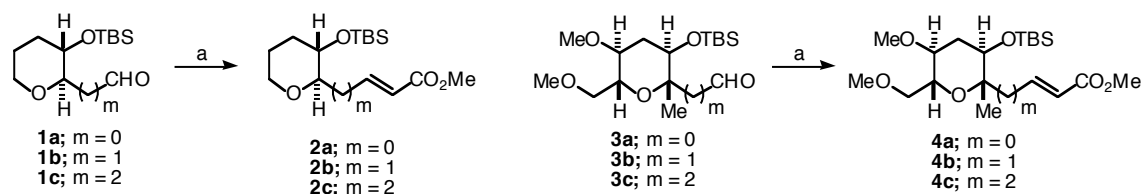
reported.³ We now report an efficient method for Cu(II)-mediated stereoselective addition of a methyl group to an α,β -unsaturated ester as the C2-side chain in the ether ring.

Our strategy for the stereoselective introduction of a methyl group to the acyclic side chain on the ether ring is outlined in Scheme 1. We chose tetrahydropyran derivative (**i**) as the substrate, which has an *equatorial* TBS ether at the C3 position and an *equatorial* side chain bearing an α,β -unsaturated ester at the C2 position. We expected that a methyl group might be stereoselectively introduced under the influence of the bulky TBSO group to give a methyl adduct (**ii**). The product (**ii**) could be applied to the synthesis of polycyclic ether (**iii**) having an α - or a β -methyl group.



Scheme 1.

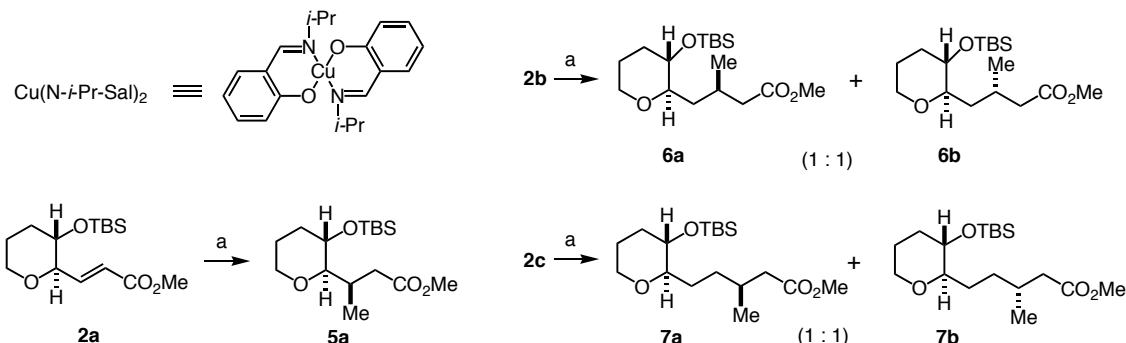
With this prospect, our studies began with the synthesis of 3-(*t*-butyldimethylsilyloxy)tetrahydropyrans (**2a-c**) and (**4a-c**), which have a side chain of various lengths at the C2 position (Scheme 2). The Wittig reaction of aldehydes (**1a-c**)⁴ or (**3a-c**)⁵ furnished the α,β -unsaturated esters (**2a-c**)⁶ or (**4a-c**), respectively, corresponding to the required substrate (**i**).



Scheme 2. Reagents and conditions: (a) $Ph_3P=CHCO_2Me$, toluene, reflux, 89% for **2a**, 85% for **2b**, 71% for **2c**, 97% for **4a**, 98% for **4b**, 94% for **4c**.

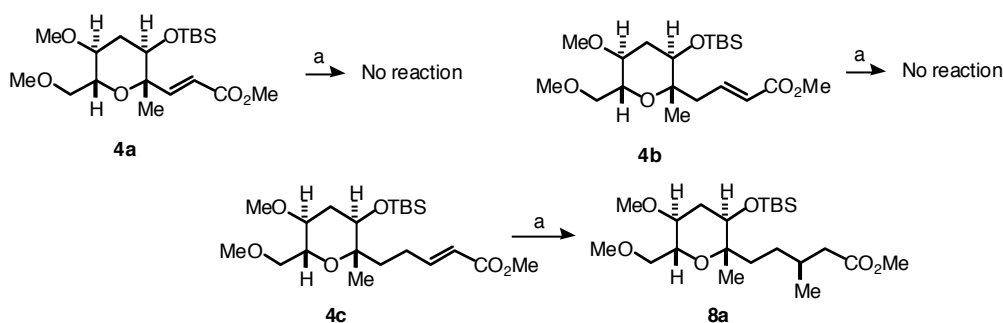
With the α,β -unsaturated esters (**2a-c**) and (**4a-c**) in hand, we investigated the Michael addition of a methyl group. First, we examined the α,β -unsaturated ester (**2a**) bearing a hydrogen atom at the C2 position. Cu-mediated Michael addition was attempted by treatment with Me_2CuLi , $Me_2Cu(CN)Li_2$, etc., but only the starting material (**2a**) was recovered. After several experiments, we found that the desired Michael addition efficiently proceeded under Kuwajima's conditions.⁷ Namely, upon treatment of **2a** with 2 equiv. of $MeMgBr$ and 3 equiv. of $TMSCl$ in the presence of a catalytic amount of $Cu(N\text{-}i\text{-}Pr\text{-}Sal)_2$ in THF, addition of a methyl group smoothly and effectively proceeded at $-78^\circ C$ for 1 h to give β -methyl adduct (**5a**) as a single product⁸ in 95% yield (Scheme 3).⁹ Thus, in this reaction, not only high reactivity but also perfect stereoselectivity were observed. We further investigated other substrates (**2b**) and (**2c**) with a longer side chain. In contrast to **2a**, the Michael addition of **2b** and **2c** under the same conditions

did not show high stereoselectivity to give a 1:1 mixture of the products (**6a** and **6b**, **7a** and **7b**), respectively, although the reaction proceeded in high yield.



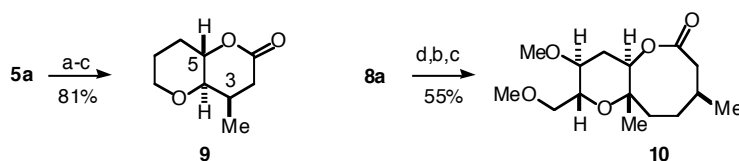
Scheme 3. Reagents and conditions: (a) MeMgBr , TMSCl , $\text{Cu}(\text{N-}i\text{-Pr-Sal})_2$, THF , -78°C , 95% for **5a**, 87% for **6a** and **6b** (1:1), 94% for **7a** and **7b** (1:1).

Next, Michael addition to the α,β -unsaturated esters (**4a-c**) bearing a methyl group at the C2 position was investigated (Scheme 4). Reaction of **4a** or **4b** under the same conditions as those for **2** did not proceed at all. The result would be caused by steric hindrance of the C2-methyl group. We then examined the reaction of **4c**, whose side chain is longer than that of **4a** and **4b**. Addition of a methyl group to **4c** smoothly and stereoselectively proceeded to give β -methyl adduct (**8a**) as a single product⁸ in 94% yield; this reaction also gave complete stereoselection.

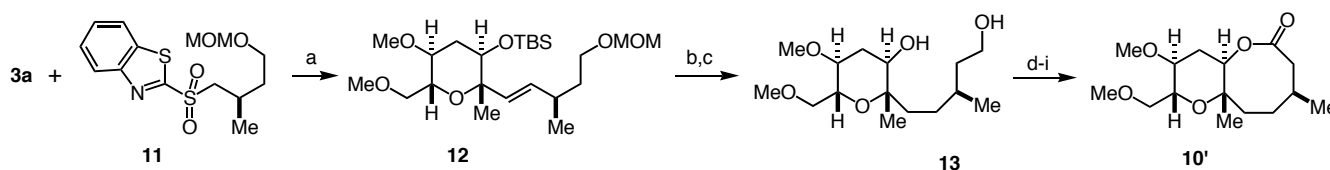


Scheme 4. Reagents and conditions: (a) MeMgBr , TMSCl , $\text{Cu}(\text{N-}i\text{-Pr-Sal})_2$, THF , -78°C , 94% for **8a**.

In order to determine the stereostructures of the products, **5a** and **8a** were converted into lactones (**9**)¹⁰ and (**10**)¹¹, respectively, as shown in Scheme 5. NOE between C3- CH_3 and C5-H of **9** was observed. On the other hand, an authentic sample (**10'**) for **10** was synthesized *via* Julia coupling¹² of aldehyde (**3a**) and sulfone (**11**)¹³ as shown in Scheme 6. The NMR spectral data of **10'** were identical with those of **10**. Thus, the configuration of the introduced methyl group of **5a** and **8a** was unequivocally confirmed. The configurations of the introduced methyl group in the products (**5a**) and (**8a**) correspond to those of the α -methyl group on the D-ring of BTX-B and the β -methyl group on the G-ring of YTX, respectively.



Scheme 5. Reagents and conditions: (a) CSA, MeOH, rt; (b) LiOH, MeOH, THF, H₂O, rt; (c) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, 0°C, then DMAP, benzene, 80°C; (d) TBAF, THF, rt.



Scheme 6. Reagents and conditions: (a) LHMDs, THF, $-78^{\circ}\text{C} \rightarrow \text{rt}$, 79%; (b) conc. HCl, MeOH, rt, 39%; (c) H₂, PtO₂, MeOH, 50°C; (d) TBSCl, imidazole, DMF, rt; (e) CSA, MeOH, rt, 84%, 3 steps; (f) (COCl)₂, DMSO, CH₂Cl₂, -78°C , then Et₃N $-78^{\circ}\text{C} \rightarrow \text{rt}$; (g) NaClO₂, 2-methyl-2-butene, NaH₂PO₄, *t*-BuOH, H₂O, rt; (h) TBAF, THF, rt, 42%, 3 steps; (i) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, 0°C, then DMAP, benzene, 80°C, 85%.

The stereoselectivity in the Michael addition of **2** would be explained as follows. The ¹H NMR spectrum of **2a** was measured under various temperatures with or without reagents in *d*-THF (Table 1). The *J* value between Ha and Hb in the presence of reagents showed 2.9 Hz at -78°C and 4.1 Hz at 24°C , while that in the absence of reagents was also almost the same (3.2 Hz at -78°C and 3.9 Hz at 24°C). These results suggest that the side chain should be fixed as **2a-A** in Figure 2; the conformer (**2a-B**) should be

Table 1. *J* value between Ha and Hb of **2a**

Temperature	with TMSCl, Cu(<i>N</i> - <i>i</i> -Pr-Sal) ₂	without TMSCl, Cu(<i>N</i> - <i>i</i> -Pr-Sal) ₂
24°C	<i>J</i> = 4.1 Hz	<i>J</i> = 3.9 Hz
-40°C	— ^a	<i>J</i> = 3.4 Hz
-78°C	<i>J</i> = 2.9 Hz	<i>J</i> = 3.2 Hz

a) not measured.

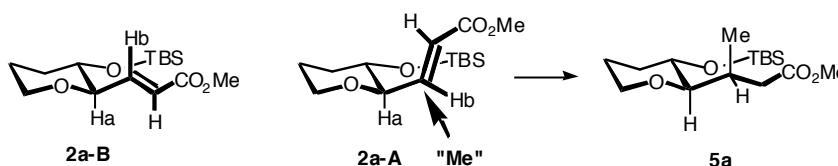


Figure 2.

eliminated. Thus, the addition of the methyl group would proceed from the less hindered β -side, *i.e.* the opposite side of the TBSO group, to give the β -methyl adduct (**5a**) stereoselectively. In the case of **2b** and

2c, the side chain would not be fixed as one predominant conformation because of the longer distance between the olefin and the ether ring. Thus, addition of a methyl group would not proceed stereoselectively.

On the other hand, in the case of **4c**, the C2-methyl and TBSO groups might fix the conformation of the side chain as **4c-A** in Figure 3. Thus, addition of a methyl group would proceed from the less hindered β -side, due to the bulkiness of the TBSO group, to give β -methyl adduct (**8a**) stereoselectively.

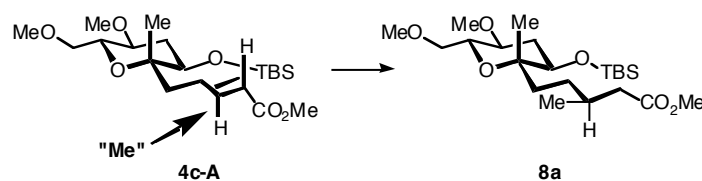


Figure 3.

In conclusion, the present Cu(II)-mediated Michael addition is effective for stereoselective introduction of a methyl group to acyclic α,β -unsaturated esters (**2a**) and (**4c**). This method would be useful for the construction of polycyclic ethers having a methyl group on the ether ring. In fact, these methods (**2a** $\rightarrow$ **5a** and **4c** $\rightarrow$ **8a**) were successfully applied in total synthesis of BTX-B¹⁴ and synthesis of the F'GHIJ-ring system of yessotoxin,¹⁵ respectively.

ACKNOWLEDGEMENTS

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5. (a) **3a**: K. Suzuki and T. Nakata, *T. Org. Lett.*, 2002, **4**, 2739. (b) Compound (**3b**) was synthesized from **3a** in three steps by the following procedure: (a) $\text{Ph}_3\text{P}^+\text{MeBr}^-$, NaHMDS, THF, 84%; (b) $\text{BH}_3\cdot\text{THF}$, THF, then NaOH, H_2O_2 , 67%; (c) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78°C , then Et_3N , $-78^\circ\text{C} \rightarrow \text{rt}$; (c) Compound (**3c**) was synthesized from **3b** following the same procedure as above.
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11. **10**. ^1H NMR (500 MHz, CDCl_3) δ 4.33 (d, $J = 11.9, 4.6$ Hz, 1H), 3.57-3.52 (m, 2H), 3.39 (s, 3H), 3.37 (s, 3H), 3.28-3.23 (m, 1H), 3.02 (dd, $J = 12.4, 6.0$ Hz, 1H), 2.38 (dd, $J = 11.9, 4.6$ Hz, 1H), 2.25 (dd, $J = 12.4, 3.2$ Hz, 1H), 2.18-2.13 (m, 1H), 1.85-1.81 (m, 1H), 1.77 (ddd, $J = 11.9, 11.9, 11.9$ Hz, 1H), 1.62-1.57 (m, 1H), 1.25-1.15 (m, 2H), 1.25 (s, 3H), 1.09 (d, $J = 6.9$ Hz, 3H).
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13. The sulfone (**11**) was synthesized from (*R*)-2-methylsuccinic acid 4-*t*-butyl ester as follows: (a) $\text{BH}_3\cdot\text{Me}_2\text{S}$, THF, rt; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2 , 0°C ; (c) LiAlH_4 , THF, 0°C ; (d) MOMCl, *i*-Pr₂NEt, DMAP, CH_2Cl_2 , rt; (e) TBAF, THF, rt, 71%, 5 steps; (f) 2-mercaptobenzothiazole, Ph_3P ,

DEAD, THF, rt; (g) MCPBA, NaHCO₃, CH₂Cl₂, rt, 34%, 2 steps.

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