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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*-BUTYLDIMETHYLSILYLOXY)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

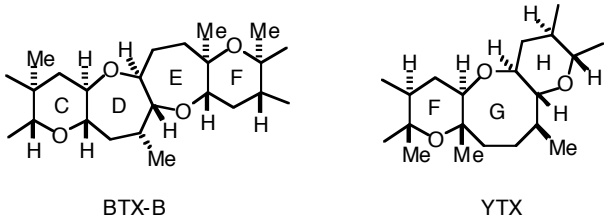
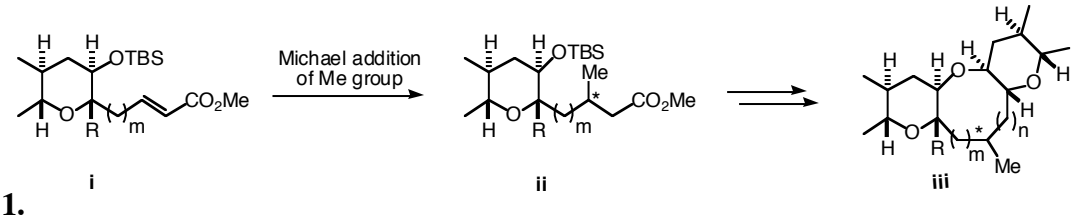



**Figure 1.** Partial structure of brevetoxin-B and yessotoxin

This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

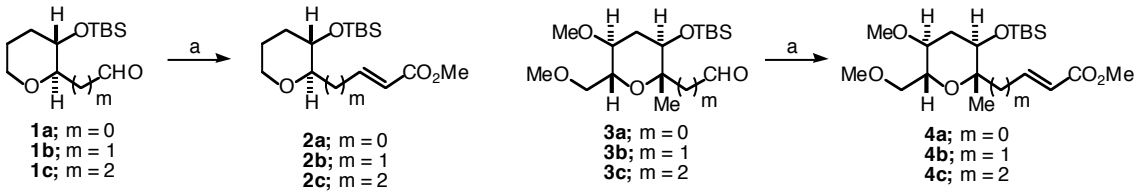
reported.[3] We now report an efficient method for Cu(II)-mediated stereoselective addition of a methyl group to an α,β-unsaturated ester as the C2-side chain in the ether ring.

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.**

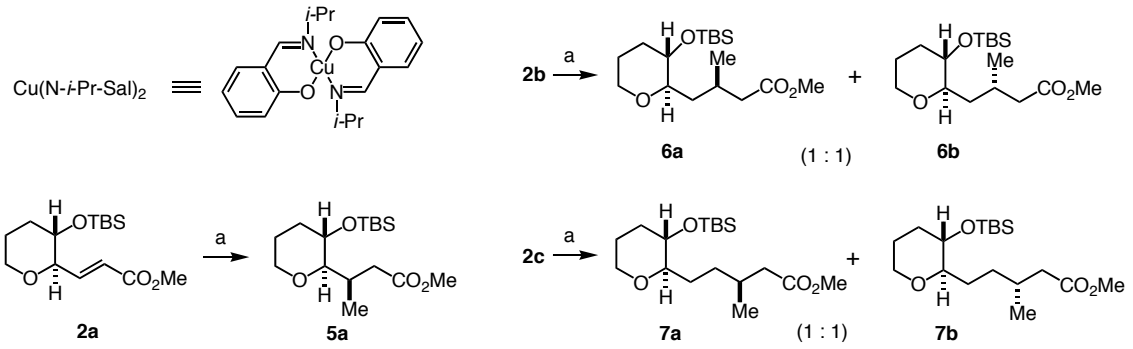
With this prospect, our studies began with the synthesis of 3-(*t*-butyldimethylsilyloxy)tetrahydopyrans (**2a-c**) and (**4a-c**), which have a side chain of various lengths at the C2 position (Scheme 2). The Wittig reaction of aldehydes (**1a-c**)[4] or (**3a-c**)[5] furnished the α,β-unsaturated esters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

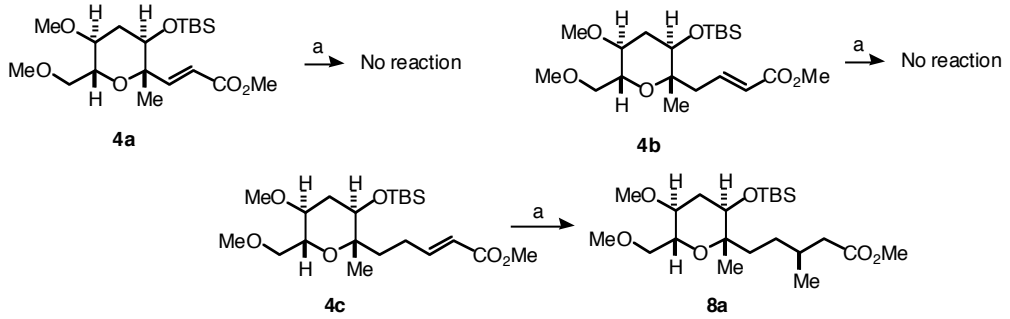
With the α,β-unsaturated esters (**2a-c**) and (**4a-c**) in hand, we investigated the Michael addition of a methyl group. First, we examined the α,β-unsaturated ester (**2a**) bearing a hydrogen atom at the C2 position. Cu–mediated Michael addition was attempted by treatment with $Me_2CuLi$, $Me_2Cu(CN)Li_2$, 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-*i*-Pr-Sal)$_2$ in THF, addition of a methyl group smoothly and effectively proceeded at –78°C for 1 h to give β-methyl adduct (**5a**) as a single product[8] 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.



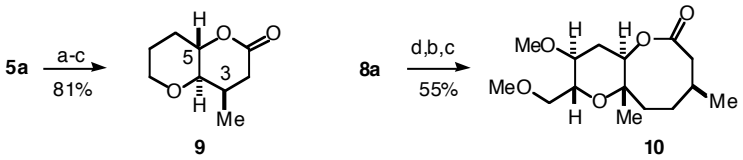

**Scheme 3.** *Reagents and conditions*: (a) MeMgBr, TMSCl, Cu(N-*i*-Pr-Sal)$_2$, THF, –78°C, 95% for **5a**, 87% for **6a** and **6b** (1:1), 94% for **7a** and **7b** (1:1).

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 product[8] in 94% yield; this reaction also gave complete stereoselection.

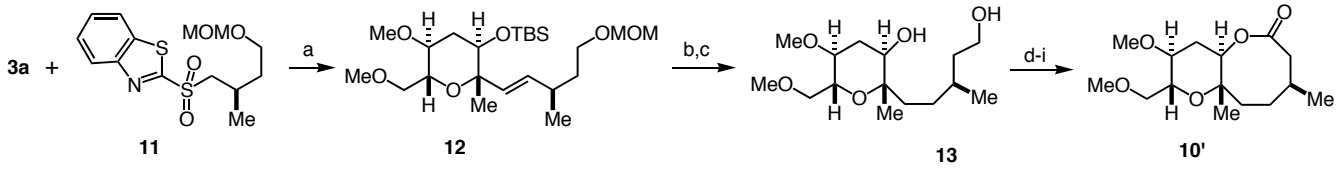



**Scheme 4.** *Reagents and conditions*: (a) MeMgBr, TMSCl, Cu(N-*i*-Pr-Sal)$_2$, THF, –78°C, 94% for **8a**.

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 coupling[12] 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, $H_2O$, rt; (c) 2,4,6-trichlorobenzoyl chloride, $Et_3N$, THF, 0°C, then DMAP, benzene, 80°C; (d) TBAF, THF, rt.




**Scheme 6.** *Reagents and conditions*: (a) LHMDS, THF, –78°C→rt, 79%; (b) conc. HCl, MeOH, rt, 39%; (c) $H_2$, $PtO_2$, MeOH, 50°C; (d) TBSCl, imidazole, DMF, rt; (e) CSA, MeOH, rt, 84%, 3 steps; (f) $(COCl)_2$, DMSO, $CH_2Cl_2$, –78°C, then $Et_3N$ –78°C→ rt; (g) $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4$, *t*-BuOH, $H_2O$, rt ; (h)TBAF, THF, rt, 42%, 3 steps; (i) 2,4,6-trichlorobenzoyl chloride, $Et_3N$, 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 bewteen Ha and Hb of **2a**

| Temperature | with TMSCl, Cu(N-*i*-Pr-Sal)$_2$ | without TMSCl, Cu(N-*i*-Pr-Sal)$_2$ |
|---|---|---|
| 24°C | $J$ = 4.1 Hz | $J$ = 3.9 Hz |
| –40°C | –[a] | $J$ = 3.4 Hz |
| –78°C | $J$ = 2.9 Hz | $J$ = 3.2 Hz |

a) not measured.

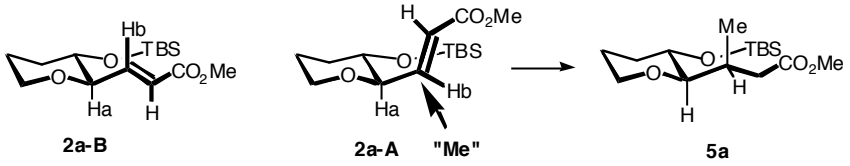



**Figure 2.**

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.

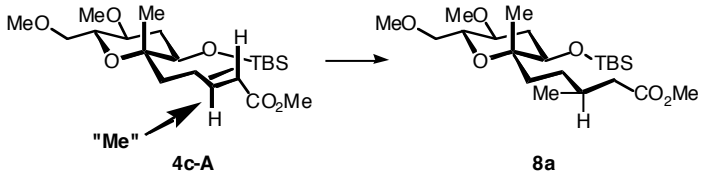



**Figure 3.**

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** → **5a** and **4c** → **8a**) were successfully applied in total synthesis of BTX-B[14] 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) $Ph_3P^+MeBr^-$, NaHMDS, THF, 84%; (b) $BH_3$·THF, THF, then NaOH, $H_2O_2$, 67%; (b) $(COCl)_2$, DMSO, $CH_2Cl_2$, –78°C, then $Et_3N$, –78°C→rt; (c) Compound (**3c**) was synthesized from **3b** following the same procedure as above.
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10. **9**. $^1$H NMR (500 MHz, $CDCl_3$) δ 4.14 (ddd, *J* = 10.1, 10.1, 4.3 Hz, 1H), 4.01-3.96 (m, 1H), 3.45 (dt, *J* = 11.0, 4.1 Hz, 1H), 3.38 (dd, *J* = 9.5, 5.6 Hz, 1H), 2.77 (dd, *J* = 17.6, 6.8 Hz, 1H), 2.47 (dd, *J* = 17.6, 3.9 Hz, 1H), 2.36 (ddd, *J* = 12.7, 7.1, 3.7 Hz, 1H), 2.29-2.25 (m, 1H), 1.77-1.57 (m, 3H), 1.09 (d, *J* = 6.8 Hz, 3H).
11. **10**. $^1$H 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) $BH_3$·$Me_2S$, THF, rt; (b) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0°C; (c) $LiAlH_4$, THF, 0°C; (d) MOMCl, *i*-$Pr_2NEt$, DMAP, $CH_2Cl_2$, rt; (e) TBAF, THF, rt, 71%, 5 steps; (f) 2-mercaptobenzothiazole, $Ph_3P$,

DEAD, THF, rt; (g) MCPBA, $NaHCO_3$, $CH_2Cl_2$, rt, 34%, 2 steps.

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