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SYNTHESIS OF 6/6/6-TRICYCLIC ETHER SYSTEM VIA ACHMATOWICZ AND INTRAMOLECULAR OXA-MICHAEL REACTIONS

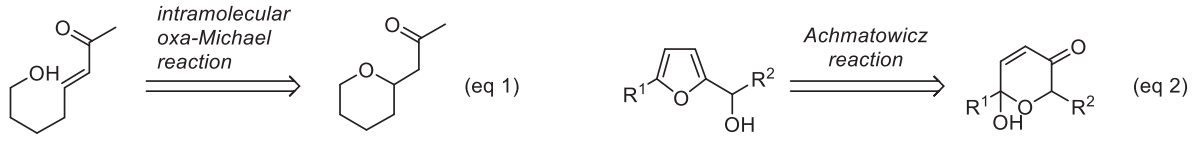
Hiroki Yamamoto, Kohei Torikai, Makoto Ebine, and Tohru Oishi*

Department of Chemistry, Faculty and Graduate School of Science, Kyushu University, 744 Motooka, Nishi-ku, Fukuoka 819-0395, Japan. e-mail: oishi@chem.kyushu-univ.jp

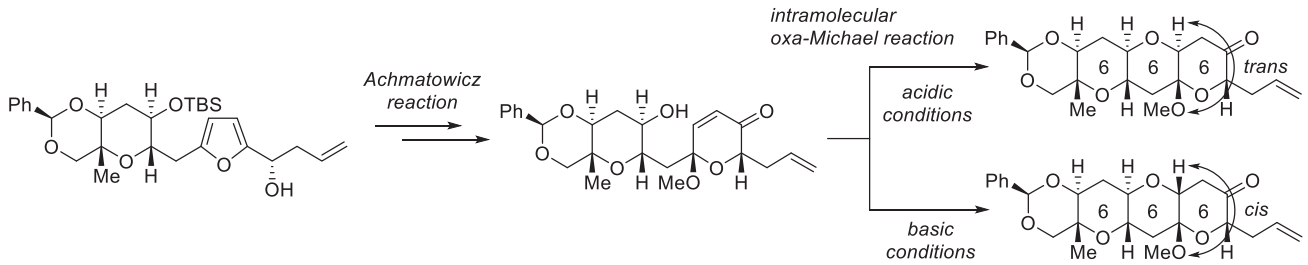
Dedicated to Professor Kiyoshi Tomioka on the occasion of his 70th birthday

Abstract – Synthesis of 6/6/6-tricyclic ethers possessing 1,3-diaxial methyl groups was examined via Achmatowicz reaction and intramolecular oxa-Michael reaction. A key precursor was prepared via coupling of an aldehyde with a furyllithium derivative followed by radical deoxygenation of the resulting secondary alcohol. The intramolecular oxa-Michael reaction proceeded in a stereoselective manner to afford *cis*-fused product as a single isomer.

Trans- and *cis*-fused pyranopyran systems are found as partial structures in ladder-shaped polyethers. Although a number of synthetic methodologies to synthesize polycyclic ethers have been reported, intramolecular oxa-Michael reaction is one of the powerful tool to construct tetrahyropyran system (Scheme 1, eq 1).[1,2] On the other hand, Achmatowicz reaction is a versatile method to construct dihydropyranone derivatives from furfuryl alcohols via oxidation of the furan rings (eq 2).[3,4] During the course of our synthetic studies of ladder-shaped polyethers, we have developed a strategy to synthesize 6/6/6-tricyclic system by combining these reactions (Scheme 2),[5] and found that intramolecular oxa-Michael reaction under the acidic conditions afforded *trans*-fused system while that under the basic conditions resulted in the formation of *cis*-fused system.

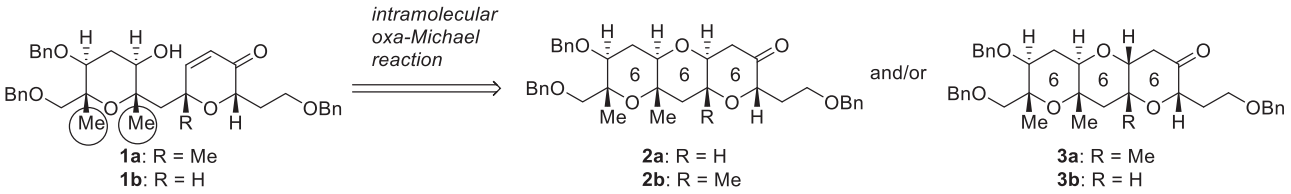


Scheme 1. Intramolecular oxa-Michael reaction (eq 1) and Achmatowicz reaction (eq 2)



Scheme 2. Synthesis of 6/6/6-tricyclic ether system via Achmatowicz and intramolecular oxa-Michael reactions

To elucidate the scope and limitation of this strategy, we planned to examine intramolecular oxa-Michael reaction by using precursors **1a** and **1b** having 1,3-diaxial methyl groups on the tetrahydropyran ring which would be synthesized via Achmatowicz reaction (Scheme 3).

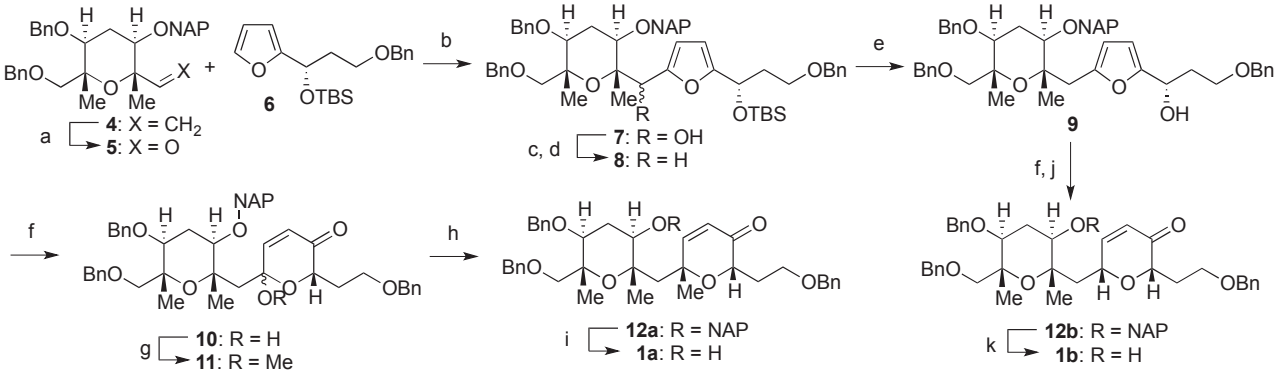


Scheme 3. Strategy to synthesize 6/6/6-tricyclic ether system possessing 1,3-diaxial methyl groups

Syntheses of **1a** and **1b** are shown in Scheme 4. Aldehyde **5** derived from terminal olefin **4**[6] by ozonolysis (86%) was coupled with furyllithium derivative generated from **6**[6] by treatment with *sec*-BuLi to afford coupled product **7** as a mixture of diastereomers in a 2 : 1 ratio. Removal of the resulting hydroxy group was achieved by radical deoxygenation via xanthate formation (65%, two steps) followed by reduction with Bu_3SnH to afford **8** (88%).[7] After removing TBS group, Achmatowicz reaction of the secondary alcohol **9** with $MeReO_3$ in the presence of urea hydrogen peroxide complex[8] resulted in the formation of dihydropyranone derivative **10**, which was followed by methyl acetal formation to furnish **11**. Chemo- and stereoselective methylation of the methyl acetal was achieved by treatment with Me_2Zn in the presence of $BF_3{\cdot}OEt_2$[9] to afford **12a** (62%), and removal of the NAP group with DDQ furnished **1a** (84%). On the other hand, reductive etherification of **10** with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ furnished **12b** (42%, two steps from **9**), and removal of the NAP group gave **1b** (80%).

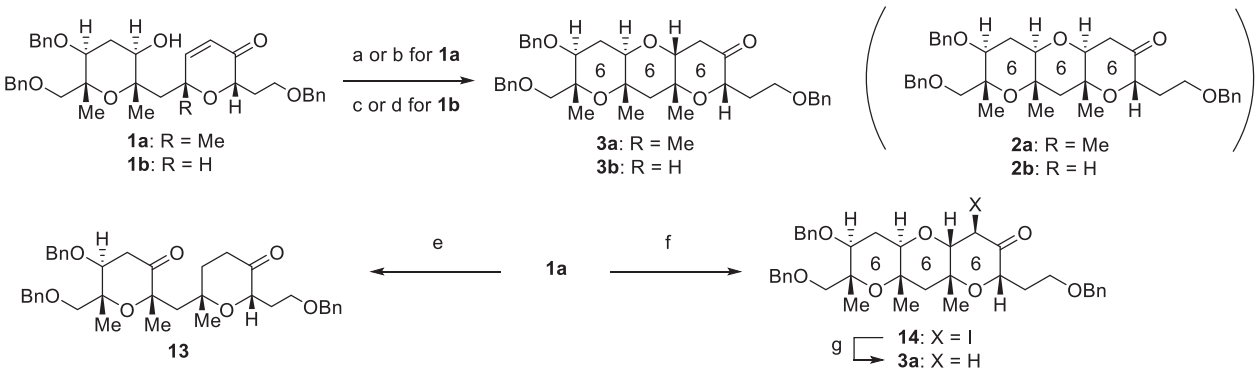
Having synthesized **1a** and **1b**, intramolecular oxa-Michael reaction was examined (Scheme 5). In the previous results (Scheme 2), *trans*-fused product was obtained under the acidic conditions. However, when **1a** (R = Me) was treated with $TsOH{\cdot}H_2O$ in CH_2Cl_2, the reaction was sluggish and *cis*-fused **3a** was obtained in 57% yield with recovery of **1a** (RSM 21%), and *trans*-fused **2a** was not detected. The structure of **3a** was determined by NOESY experiments.[6] On the other hand, oxa-Michael reaction of **1a**

under the basic conditions by treatment with NaH in THF afforded *cis*-fused **3a** (37%) as expected, but the reaction was also sluggish (RSM 32%).



Scheme 4. Reagents and conditions: (a) O_3, CH_2Cl_2, MeOH, −78 °C, 20 min; PPh_3, −78 °C to rt, 6 h, 86%; (b) **6**, *sec*-BuLi, THF, −78 °C, 10 min; **5**, THF, −78 °C, 30 min; (c) NaH, THF, 0 °C to rt, 20 min; CS_2, rt, 40 min; MeI, rt, 20 min, 65% (2 steps); (d) Bu_3SnH, AIBN, toluene, 110 °C, 3 h, 88%; (e) TBAF, THF, 0 °C to rt, 7 h, 88%; (f) $MeReO_3$, $CO(NH)_2{\cdot}H_2O_2$, CH_2Cl_2, 0 °C, 0 °C, 1 h; (g) $BF_3{\cdot}OEt_2$, MeOH, $(MeO)_3CH$, MS3A, Et_2O, 0 °C, 25 min, 84% (2 steps); (h) Me_2Zn, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to rt, 2 h, 62%; (i) DDQ, pH7 buffer, CH_2Cl_2, 0 °C, 1.5 h, 84%; (j) $BF_3{\cdot}OEt_2$, Et_3SiH, MS4A, CH_2Cl_2, −78 °C, 30 min, 42% (2 steps); (k) DDQ, pH7 buffer, CH_2Cl_2, 0 °C, 1.5 h, 80%.

Then, oxa-Michael reaction of **1a** was examined by using Lewis acids, i. e. $TiCl_4$ or $Ti(O\textit{i}\text{-Pr})_4$ in CH_2Cl_2, $ZnBr_2$ or $MgBr_2{\cdot}OEt_2$ in Et_2O, and $Zn(OTf)_2$ or $Ag(OTf)_2$ in THF. However, the reaction did not occur



Scheme 5. Reagents and conditions: (a) $TsOH{\cdot}H_2O$, CH_2Cl_2, rt, 1.5 h, 57% (RSM 21%); (b) NaH, THF, 0 °C to rt, 2.1 h, 37% (RSM 32%); (c) $TsOH{\cdot}H_2O$, CH_2Cl_2, rt, 24 h, 50% (RSM 24%); (d) NaH, THF, 0 °C to rt, 2 h, decomposition; (e) $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 40 min, 63%; (f) $Fe(acac)_3$ (20 mol%), NIS, CH_2Cl_2, rt, 27 h, 67%; (g) Bu_3SnH, AIBN, benzene, 80 °C, 25 min, 56%.

and/or decomposition of **1a** was observed. When $BF_3{\cdot}OEt_2$ was used as a Lewis acid, diketone **13** was obtained (63%) by intramolecular hydride shift from the secondary alcohol to the enone via 1,4-addition. Although iodoetherification of **1a** was also examined by using NIS in the presence of Fe catalyst,[10] *cis*-fused compound **14** (67%) was obtained, which was reduced with Bu_3SnH to furnish **3a** (56%). Next,

oxa-Michael reaction of **1b** (R = H) was examined. Treatment of **1b** with $TsOH \cdot H_2O$ in CH_2Cl_2 resulted in the formation of *cis*-fused **3b** (50%, RSM 24%), but that with NaH in THF caused decomposition of **1b**. The reason for obtaining *cis*-isomer in the case of **1a** and **1b** possessing 1,3-diaxial groups is presumably due to avoiding the severe 1,3-diaxial interactions in the transition state of intramolecular oxa-Michael reaction (Figure 1).

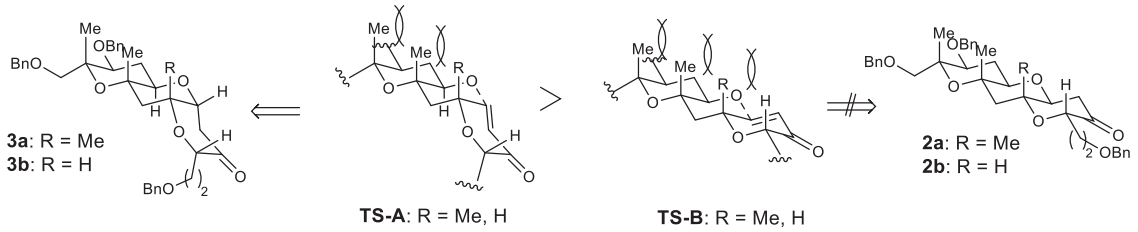


Figure 1. Explanation for stereochemical outcome of the intramolecular oxa-Michael reaction

In conclusion, 6/6/6-tricyclic ethers possessing 1,3-diaxial methyl groups were synthesized via the intramolecular oxa-Michael reaction to afford *cis*-fused products, respectively. These results indicate that presence of the 1,3-diaxial angular methyl groups highly affect the stereoselectivity of the intramolecular oxa-Mchael reaction, and might be useful guidance to design synthetic strategy of polycyclic ether system.

ACKNOWLEDGEMENTS

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