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SYNTHESIS OF CYCLIC ETHER *VIA* AN INTRAMOLECULAR BARBIER REACTION OF IODO ESTER WITH BUTYLLITHIUM

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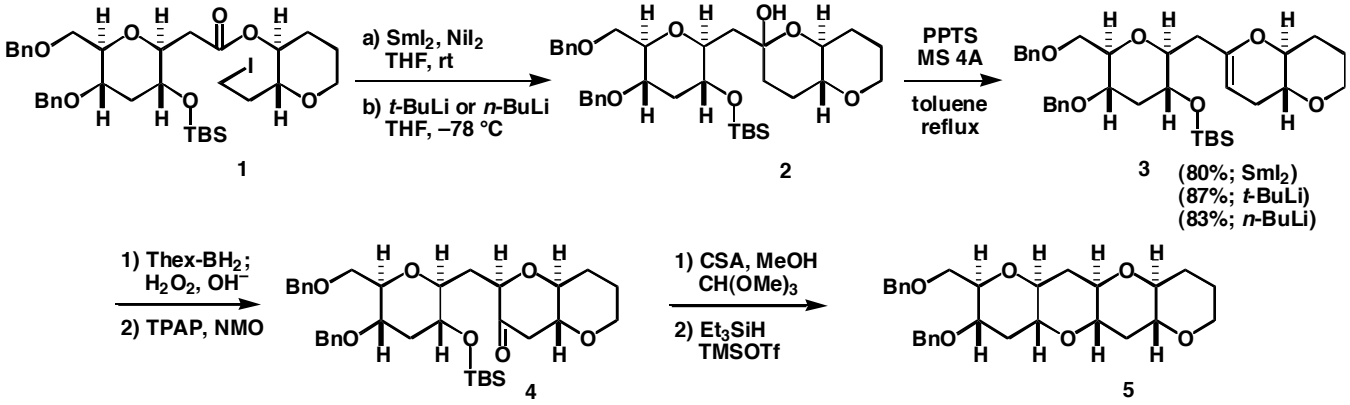
Abstract – Intramolecular Barbier reaction of 2-(2-iodoethyl)-3-tetrahydropyranyl esters or acyclic 4-iodobutyl ester with *t*-BuLi or *n*-BuLi effected cyclization to give six-membered hemiacetals. Based on the present reaction, the synthesis of 2,6-*syn*-tetrahydropyran and *trans*-fused polycyclic ethers, and coupling of the AB- and E'FG-rings of gambierol were accomplished.

Many marine polycyclic ethers, exemplified by brevetoxins, gambierol, and maitotoxin,[1] have attracted the attention of numerous synthetic organic chemists due to their synthetically challenging complex structures and their potent bioactivities. The structural feature of these natural products is a *trans*-fused polycyclic ether ring system. Thus, various methods for construction of a cyclic ether ring system have been extensively studied toward the total synthesis of marine polycyclic ethers;[2] convergent methods for construction of polycyclic ethers are particularly important. We have already developed an efficient strategy for convergent synthesis of a *trans*-fused polycyclic ether based on an intramolecular Barbier reaction of 2-(2-iodoethyl)-3-tetrahydropyranyl ester (**1**) with SmI_2-NiI_2 to give hemiacetal (**2**) (Scheme 1).[3] Dehydration of **2** by treatment with PPTS afforded dihydropyran (**3**) (80% yield, two steps), which was then converted to *trans*-fused tetracyclic ether (**5**). However, the key step, i.e., SmI_2-promoted cyclization of iodo ester, might cause problems in some cases; for example, in the case of α-hydroxy esters, reductive removal of the hydroxy group should take place.[4] Thus, alternative conditions to overcome these problems are required. Our attention turned to use of alkyl lithium as reagent for the desired cyclization; there are very few reports for intramolecular Barbier reaction of iodo ester with *t*-BuLi.[5] We now report the synthesis of cyclic ether via an intramolecular Barbier reaction of iodo ester with *t*-BuLi or *n*-BuLi as a key step.

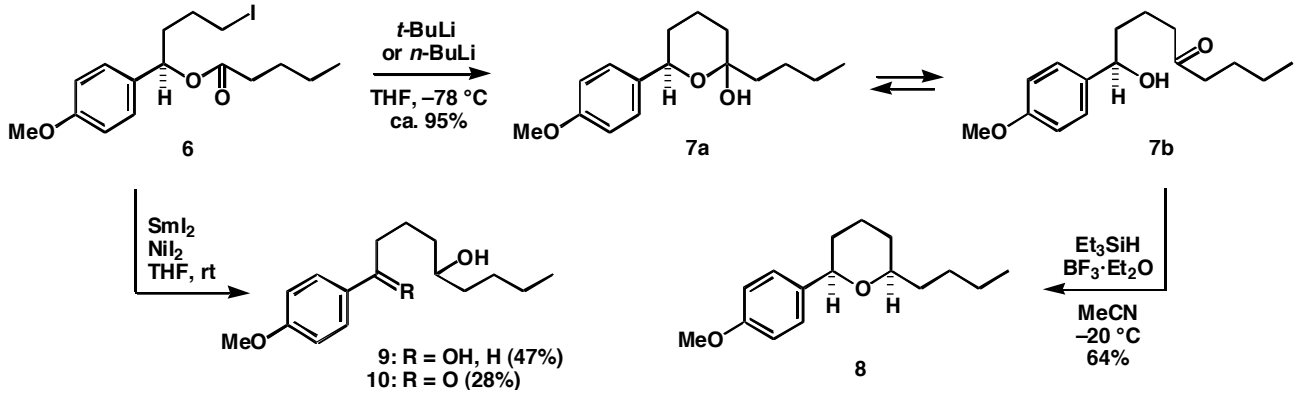
This paper is dedicated to Prof. Yoshito Kishi (Harvard University) on the occasion of his 70th birthday.

First, the key cyclization of iodo ester (**1**),[3] was examined by using *t*-BuLi or *n*-BuLi instead of SmI_2 (Scheme 1). Upon treatment of **1** with *t*-BuLi (2.2 equiv) in THF, the desired cyclization smoothly took place at –78 °C to give hemiacetal (**2**), which was dehydrated by PPTS and MS 4A in refluxing toluene to give dihydropyran (**3**) in 87% yield (two steps). Moreover, treatment of **1** with *n*-BuLi (1.2 equiv) under the same conditions followed by dehydration with PPTS also afforded **3** in 83% yield (two steps). Thus, *t*-BuLi or *n*-BuLi efficiently served for the intramolecular Barbier reaction of iodo ester to give cyclic hemiacetal in high yield. Hemiacetal (**3**) was already converted to *trans*-fused tetracyclic ether (**5**) via hydroboration, oxidation, formation of cyclic acetal, and Lewis acid-promoted silane reduction.[3]



Scheme 1.

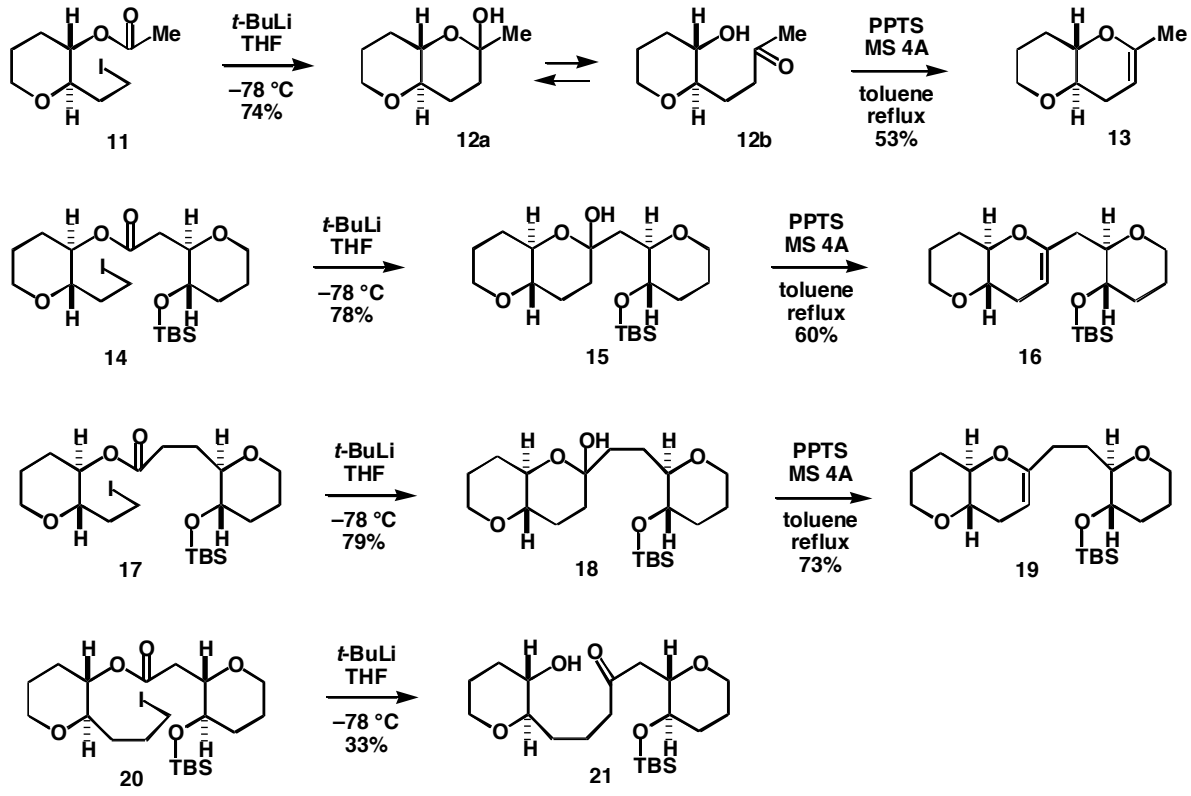
Next, the present reaction was applied to cyclization of an acyclic 4-iodobutyl ester (**6**) (Scheme 2). Upon treatment of **6** with 2~3 equiv of *t*-BuLi or *n*-BuLi, the reaction smoothly took place, giving cyclized product (**7**) in high yields. The product (**7**) mostly exists in acyclic ketone form (**7b**). Reduction of hydroxy ketone (**7b**) with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ afforded 2,6-*syn*-tetrahydropyran (**8**) in 64% yield. On the other hand, SmI_2-promoted reaction of **6** did not give the desired product (**7**), but afforded diol (**9**; 47%) and keto alcohol (**10**; 28%). Thus, the intramolecular Barbier reaction using



Scheme 2.

t-BuLi or *n*-BuLi is very effective and useful for acyclic iodo ester.

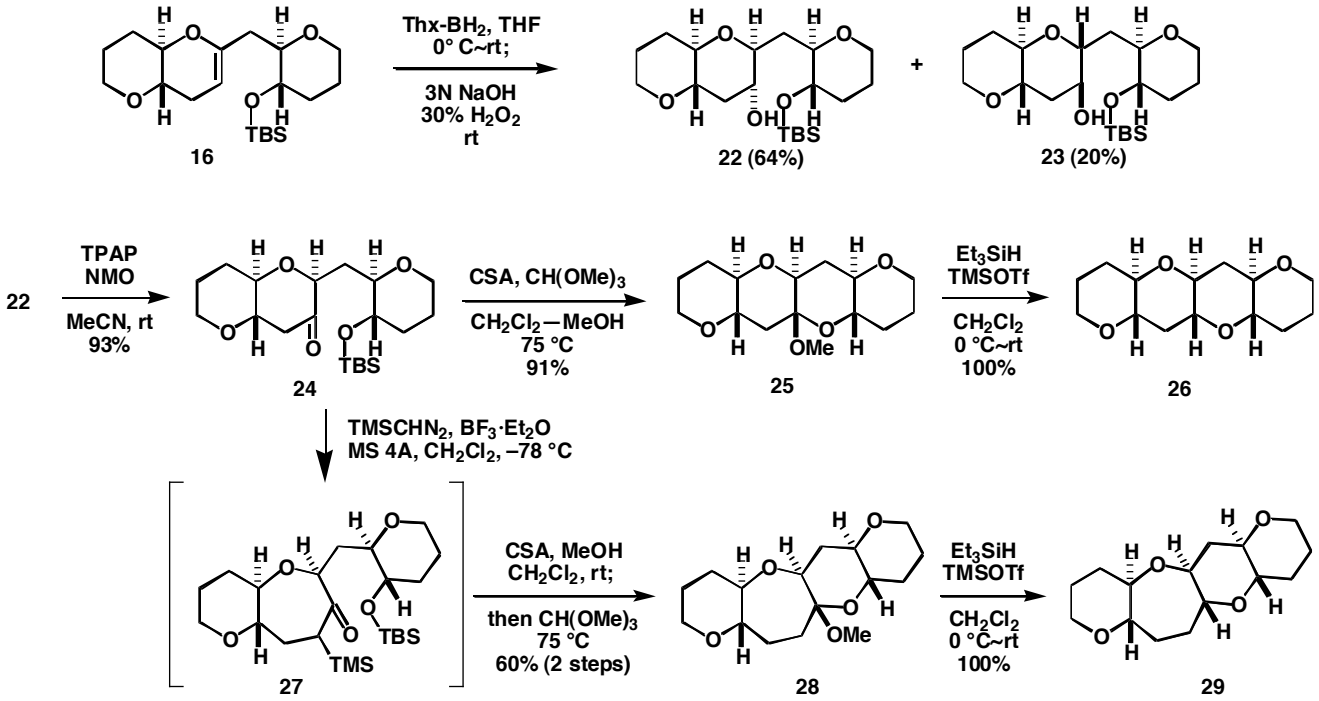
Then, these reaction conditions were examined for cyclization of several tetrahydropyran derivatives using *t*-BuLi (Scheme 3). Reaction of tetrahydropyran (**11**) having an acetate and iodoethyl group with *t*-BuLi (3 equiv) gave cyclized product (**12**) in 74% yield, which is a ca. 3:2 mixture of hemiacetal (**12a**) and ketone (**12b**). Dehydration of **12** by PPTS treatment afforded dihydropyran (**13**) in 53% yield.[6] Treatment of esters (**14** and **17**) with *t*-BuLi (3 equiv) afforded hemiacetals (**15**; 78% and **18**; 79%), which were treated with PPTS to give dihydropyrans (**16**; 60% and **19**; 73%), respectively. Upon treatment with *t*-BuLi (3 equiv), cyclization of **20** having an iodopropyl group took place to give ketone (**21**) in 33% yield. Thus, in the intramolecular Barbier reaction of iodo esters with *t*-BuLi, cyclization to a six-membered ring gave good yield, while that to a seven-membered ring gave a rather low yield.



Scheme 3.

Several polycyclic ethers were synthesized from **16** (Scheme 4). Hydroboration of **16** with thexylborane afforded **22** (64%) and **23** (20%). TPAP oxidation of **22** gave ketone (**24**) in 93% yield, which was treated with CSA and $CH(OMe)_3$ in MeOH–CH_2Cl_2 at 75 °C to give acetal (**25**) in 91% yield. Reduction of **25** with Et_3SiH and TMSOTf afforded *trans*-fused 6-6-6-6-membered tetracyclic ether (**26**),[7] quantitatively. Ring-expansion of ketone (**24**) with $TMSCHN_2$ with $BF_3{\cdot}Et_2O$[8] afforded seven-membered ketone (**27**), which was treated in one-pot with CSA in MeOH-CH_2Cl_2 at room temperature and then

$CH(OMe)_3$ at 75 °C to give acetal (**28**) in 60% yield (two steps). TMSOTf-mediated Et_3SiH reduction of **28** afforded *trans*-fused 6-7-6-6-membered tetracyclic ether (**29**) in quantitative yield.



Scheme 4.

Finally, intramolecular Barbier reaction using *t*-BuLi was successfully applied to coupling of the AB-ring and the E'FG-ring[9] in a synthetic study of gambierol (Figure 1) (Scheme 5). Esterification of AB-ring alcohol (**30**) and E'FG-ring carboxylic acid (**31**) was performed by Shiina's procedure[10] using 2-methyl-6-nitrobenzoic anhydride (MNBA) and DMAP to give ester (**32**) in 75% yield. Upon treatment with *t*-BuLi (2.2 equiv) at –78 °C, the desired intramolecular cyclization smoothly took place to give hemiacetal (**33**), which was dehydrated with PPTS and MS 4A in refluxing toluene to give C-ring dihydropyran (**34**) in 86% yield (two steps). Thus, the present reaction was also effective for cyclization of the large molecule.

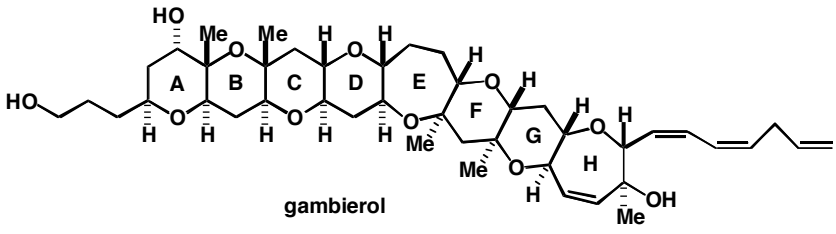
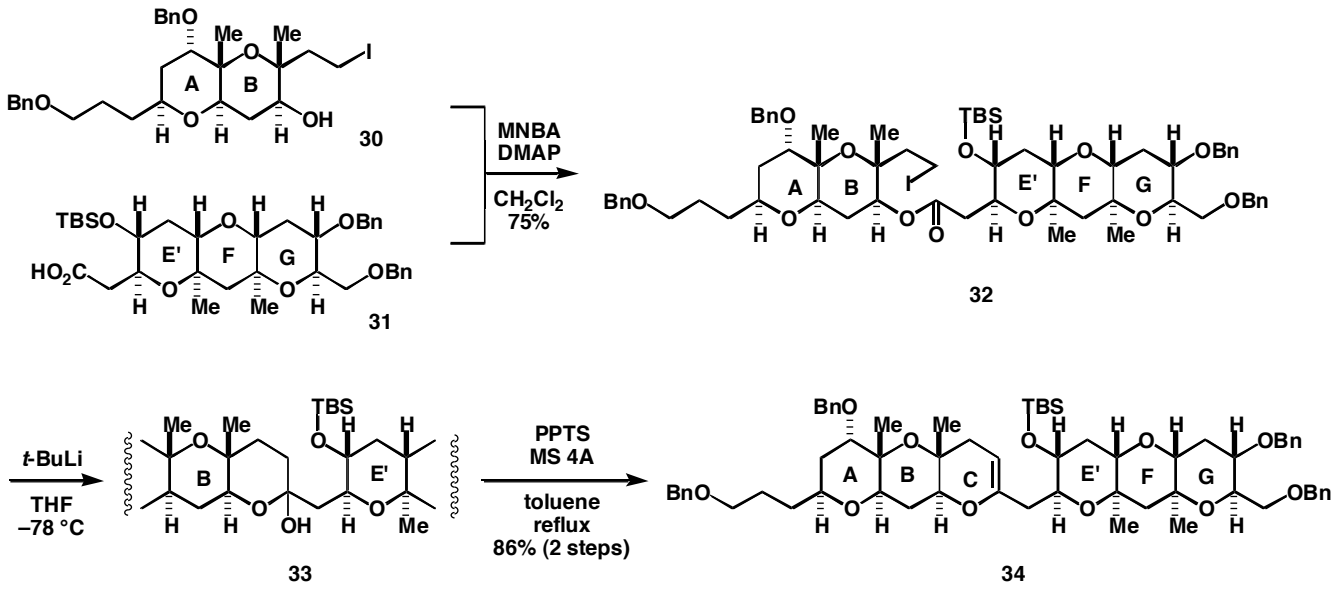


Figure 1.

In summary, intramolecular Barbier reaction of 2-(2-iodoethyl)-3-tetrahydropyranyl esters or acyclic 4-iodobutyl ester with *t*-BuLi or *n*-BuLi effected cyclization to give hemiacetals. The present method

should work as a reliable key reaction for the synthesis of tetrahydopyran derivatives and convergent synthesis of *trans*-fused polycyclic ethers.



Scheme 5.

ACKNOWLEDGEMENTS

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