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A simple convergent synthesis of *trans*-fused six-membered polycyclic ethers

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Abstract

A highly convergent method for the synthesis of *trans*-fused polytetrahydropyrans was developed, which involves: (i) coupling of cyclic triflate with an acetylene unit; (ii) oxidation of acetylene to 1,2-diketone; (iii) formation of a *trans*-fused cyclic dihemiacetal; (iv) *O*-methylation of the dihemiacetal; and (v) stereoselective reduction of the diacetal to *trans*-fused oxane rings. © 2000 Elsevier Science Ltd. All rights reserved.

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Polytetrahydropyran ring systems are the most frequently encountered cyclic units and they form the rigid backbone of marine toxins such as brevetoxins, maitotoxin, and yessotoxin.[1] The synthesis of such fused systems is currently receiving a great deal of attention, and diverse approaches have been developed with increasing emphasis on convergent strategies.[2] During the course of our synthetic studies on polycyclic ethers,[3] the finding that the hydroxy ketone **1**[4] existed in a keto form and no five-membered hemiacetal was observed, suggested to us an efficient convergent approach to polytetrahydropyrans via 1,2-diketone **IV** (Scheme 1). Simultaneous two acetal ring formation of **IV** would be expected to take place to form six-membered diacetal **V**, which would provide the *trans*-fused ring system **VI** by reductive etherification. In turn, the 1,2-diketone **IV** would be generated by the oxidation of acetylene **III** which could be prepared by the coupling of two segments **I** and **II**. Very recently, the same strategy has been reported by Murai's[5] and Nakata's[6] groups, but the tetracyclic oxane prepared contained no functionalities for further elaboration. In this paper we disclose our own results where oxygenated building blocks **II** containing silylene, benzylidene, and benzyl protective groups were employed.

The coupling reactions of the lithium acetylide of **2** with triflates **3**, **4**, and **5** were carried out in the presence of HMPA in THF[7] to give the products (Table 1). The moderate yields are mainly attributed to the instability of the TES-protected lithium acetylide, which was confirmed by deuteration experiments at −20°C in THF. The degree of deuterium incorporation of the product (>97% recovery) was 76% after 2 min, 71% after 5 min, 69% after 15 min, 66% after 30 min, and 47% after 60 min. Although replacement

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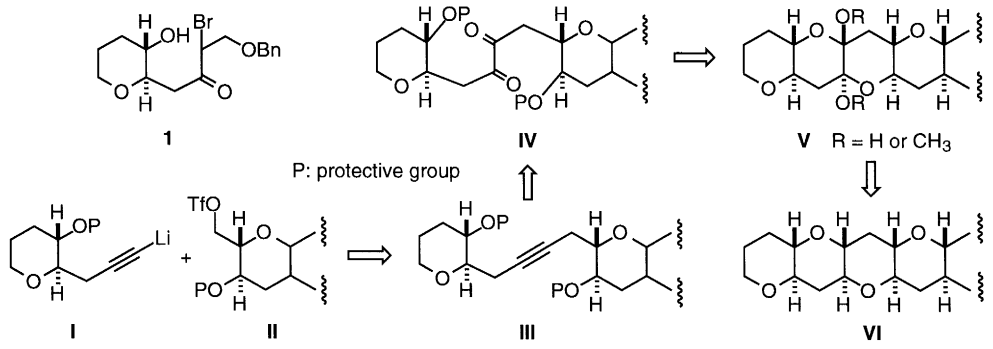
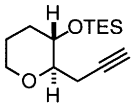
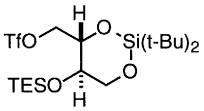
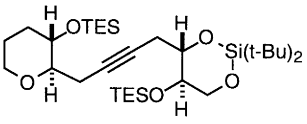
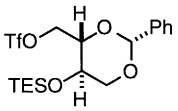
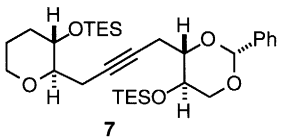
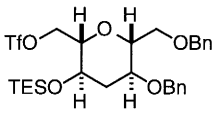
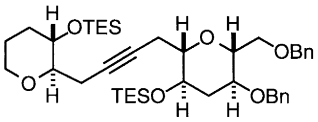


Scheme 1.

of the TES to a TBS group could improve the yield of the coupling reaction,[5,6] deprotection of TBS group at a later stage requires acidic conditions or a fluoride ion; under those conditions a silylene or benzylidene group is intolerable.

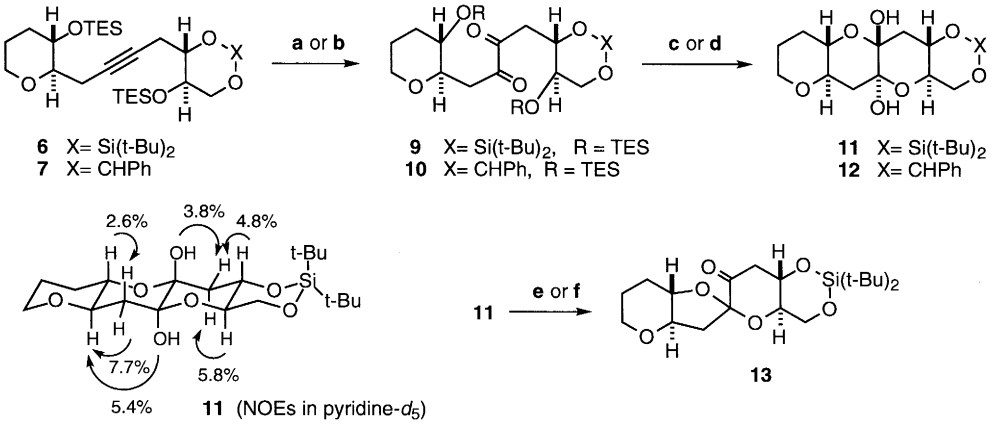
Table 1
Coupling reaction of lithium acetylide of **2** with triflates

Acetylene	Triflate (1.0 eq)	Product	Yield
 **2** (1.2 eq)	 **3**	 **6**	64%
2 (1.0 eq)	 **4**	 **7**	45%
2 (1.5 eq)	 **5**	 **8**	67%

Reaction conditions: **2**, BuLi, THF-HMPA (10:1), -78°C, 2 min, then triflate (1.0 eq), -78 → -20°C, 1~2 h.

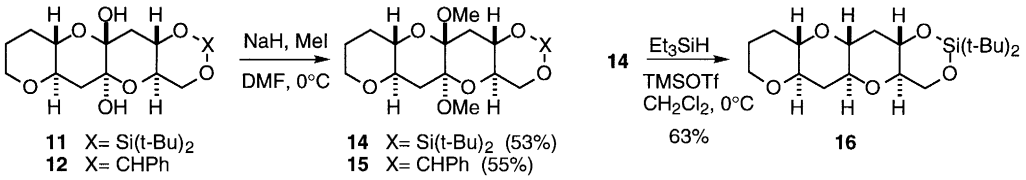
Oxidation of acetylene **6** with $RuO_2 \cdot H_2O$–$NaIO_4$[8] afforded 1,2-diketone **9** in 71% yield (Scheme 2). In the case of benzylidene derivative **7**, OsO_4–$KClO_3$ oxidation[9] was found to be better than RuO_4 oxidation, giving **10** in 72% yield. The expected six-membered dihemiacetal formation proceeded uneventfully by treatment of the diketone **9** with $TsOH \cdot H_2O$ in chloroform[3c] to give **11** in 97% yield as the sole product, while benzylidene derivative **12** was obtained in 93% yield by the reaction of **10** with Bu_4NF. The stereochemistry of dihemiacetal **11** was unambiguously determined by the NOE experiments as shown in Scheme 2. Then, we envisioned the reductive etherification of dihemiacetals to *trans*-fused oxane ring systems. Reduction of **11** with Et_3SiH in the presence of $BF_3 \cdot OEt_2$ or TMSOTf resulted in the formation of a complex mixture. Treatment with Ph_2MeSiH–$BF_3 \cdot OEt_2$[2b] caused an unexpected skeletal rearrangement to spiroketal **13** in 74% yield as a single isomer, which was also obtained in 77% yield only by treating **11** with TMSOTf in THF.

The results stated above suggested that the two hydroxyl groups of dihemiacetals should be



Scheme 2. Reaction conditions: (a) **6**, $RuO_2 \cdot H_2O$ (cat.), $NaIO_4$ (2.4 equiv.), CCl_4–MeCN pH 7 buffer, rt, 30 min, 71%; (b) **7**, OsO_4 (cat), $KClO_3$ (2.5 equiv.), ether–H_2O, rt, 17 h, 72%; (c) **9**, $TsOH \cdot H_2O$ (2 equiv.), $CHCl_3$, 0°C, 1 h, 97%; (d) **10**, Bu_4NF (2 equiv.), THF, 0°C, 30 min, 93%; (e) Ph_2MeSiH (10 equiv.), TMSOTf (5 equiv.) THF, 0°C, 2.5 h, 74%; (f) TMSOTf (4 equiv.), THF, 0°C, 40 min, 77%

protected as methyl ethers. However, commonly employed procedures such as TsOH/MeOH and TsOH–$CH(OMe)_3$/MeOH are not suitable for the substrates containing acid-sensitive silyl and acetal protective groups. We then examined *O*-methylation of hemiacetals under basic conditions. In fact, it was possible to introduce methyl groups onto the acetalic hydroxyl groups of **11** and **12** by treatment with MeI–NaH in THF, and the methyl diacetals **14** and **15** were obtained in good yields (Scheme 3). It is noteworthy that the dihemiacetal ring structure is retained to a considerable extent in spite of the basic reaction conditions. Other reaction conditions such as MeI–Ag_2O/DMF, rt (38% for **11**, 42% for **12**) and MeI–$CsCO_3$/DMF, rt (44% for **11**) were also effective albeit that the yields were lower.

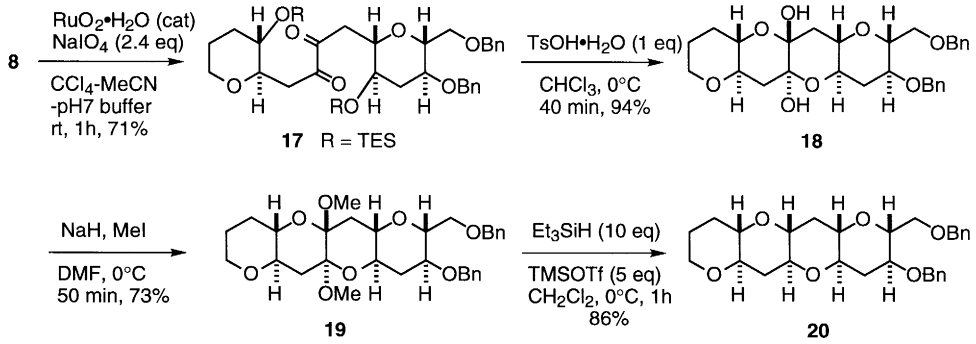


Scheme 3.

Reductive etherification of the methyl diacetal **14** with Et_3SiH (10 equiv.) in the presence of TMSOTf (4 equiv.) in CH_2Cl_2 at 0°C afforded the tricyclic oxane **16** in 63% yield. Usage of $BF_3 \cdot OEt_2$ instead of TMSOTf caused decrease of the yield (<20%) due to the cleavage of the protective group. In the case of benzylidene derivative **15**, it was expected that both the stereoselective reduction of the diacetal and the regioselective reductive cleavage of the benzylidene group could take place, but the product obtained was a mixture of products.

Finally, the above method was applied to the synthesis of the tetracyclic compound **20** as an advanced model system (Scheme 4). The acetylene **8** was transformed into 1,2-diketone **17** by catalytic oxidation with RuO_2–$NaIO_4$ in 71% yield. Acidic treatment of **17** produced dihemiacetal **18** (94%) as the sole product, which was *O*-methylated by NaH–MeI in DMF to give **19** in 73% yield. Reduction of diacetal **19** with Et_3SiH–TMSOTf in CH_2Cl_2 produced the *trans*-fused tetracyclic ether **20** in 86% yield.

In conclusion, we have developed a convergent method for the synthesis of *trans*-fused polytetrahydropyrans containing functionalities useful for further elaboration. Application of the present method to the synthesis of marine polycyclic ethers is now in progress.



Scheme 4.

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