syn-trans Fused Bicyclic Ether Formation *via* Acetylene-biscobalthexacarbonyl Complex

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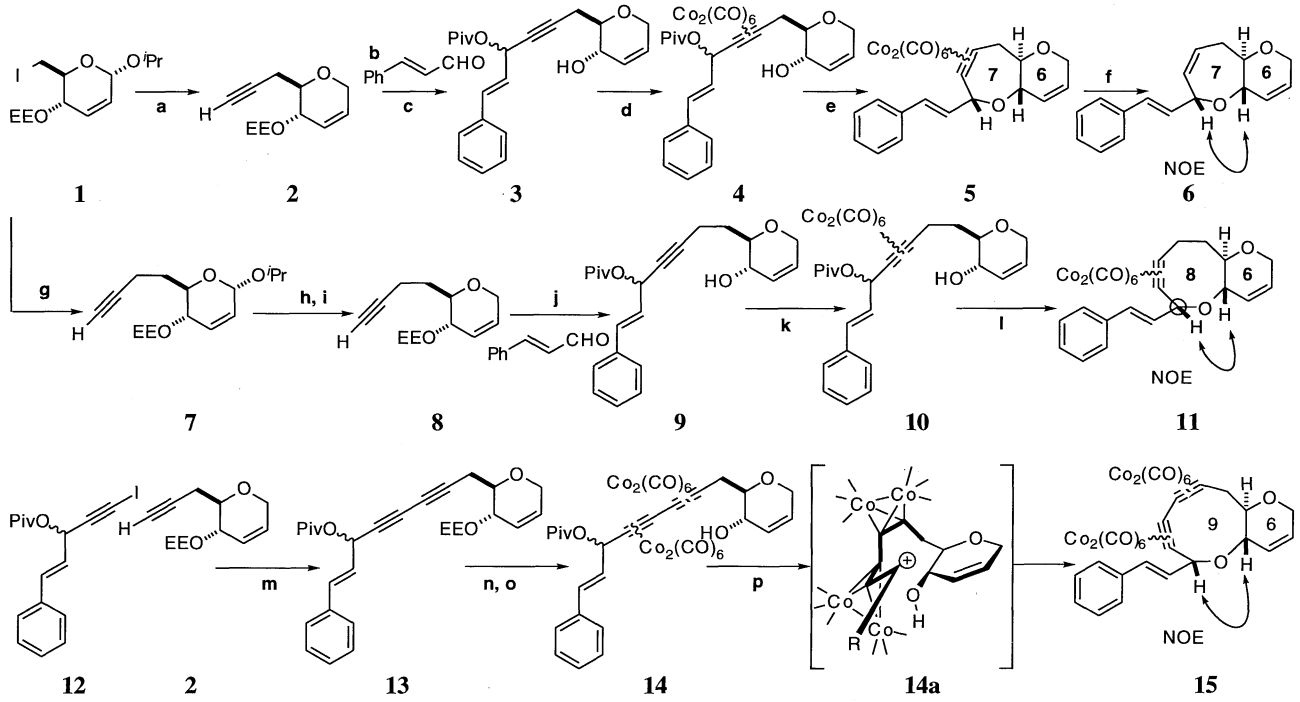
Medium size bicyclic ethers of 7-, 8-, and 9-membered rings were synthesized by connection between a hydroxy group on dihydropyranyl ring and a propargylic cation that was stabilized as an acetylene biscobalthexacarbonyl complex under acidic conditions. This cyclization selectively afforded the *syn-trans* bicyclic ring system often seen in marine toxins such as ciguatoxin.

We became interested in the synthesis of a marine toxin, ciguatoxin, having many polyether rings of *syn-trans* ladders.[1] As one of the synthetic methodologies useful toward this natural product, we have been studying ether bond formation by means of acetylene biscobalthexacarbonyl complexes. Namely, the cation stabilization by Nicholas reaction of the complexes would allow to generate stable cations,[2] which could be trapped intramolecularly by a hydroxy group. We have recently reported some of our successful results along this line in the single ether ring formation[3] as well as partial synthesis of ciguatoxin.[4] In this communication, we describe improved cyclization to form 6-7, 6-8, and 6-9 bicyclic system as extention of this line. Recently, Palazoa and Martin reported similar ether bond formation chemistry.[5]

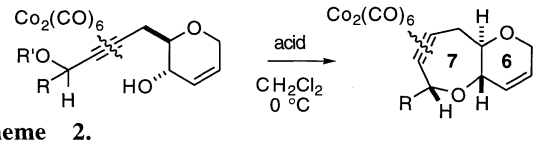
In our previous papers, we have reported synthesis of the 6-iodide (**1**) from glucal triacetate as an intermediate for the synthesis of AB-fragment of ciguatoxin.[4] This iodide **1** was converted into the acetylene **2** in 6 steps as similar route as reported.[4,6] The lithium salt of **2** was added to cinnamaldehyde to form an alkoxide, which was successively trapped by pivaloyl chloride to give the propargylic pivaloate (**3**). Formation of the acetylene biscobalthexacarbonyl complex (**4**) and treatment with BF_3•OEt_2 in CH_2Cl_2 gave the cyclization product of 7-membered ring (**5**) as a single stereoisomer in 89% yield. The decomplexation of this cobalt complex was achieved by the high pressure hydrogenation condition using Wilkinson's catalyst[4] in a sealed reactor at 75 °C. The product **6** was assigned as *syn-trans* stereochemistry by arrows from the NOESY data between the two juncture protons as indicated in Scheme 1. In this case, 6-7 ring system was only the product, and no 6-9 ring system was detected.



Scheme 1. a) TMS-C≡C-H *n*-BuLi THF-HMPA (5:1); MeOH PPTS; Ac_2O Py; BF_3•OEt_2 Et_3SiH CH_2Cl_2; K_2CO_3 MeOH; $EtOCH{=}CH_2$ PPTS (74%); b) *n*-BuLi then PivCl; c) PPTS MeOH (59% in 2 steps); d) $Co_2(CO)_8$, CH_2Cl_2 (78%); e) BF_3•OEt_2 CH_2Cl_2 (single isomer, 89%); f) H_2 (100 kg/cm^2) cat. $RhCl(PPh_3)_3$ PhH, 75 °C (73%); g) TMS-C≡C-Me *n*-BuLi THF-HMPA 5:1 0 °C then 30% NaOMe/MeOH (86%); h) BF_3•OEt_2 $HSiEt_3$ CH_2Cl_2-CH_3CN 1:1 (74%); i) EVE cat. PPTS CH_2Cl_2 (97%); j) *n*-BuLi PivCl then cat. PPTS MeOH (70%); k) $Co_2(CO)_8$ CH_2Cl_2 (91%) l) TsOH•H_2O CH_2Cl_2 0 °C (89%); m) $Pd_2(dba)_3$•$CHCl_3$ CuI (furyl)$_3$P *i*-Pr_2NH PhH (51%); n) cat. PPTS MeOH (97%); o) $Co_2(CO)_8$ CH_2Cl_2 (70%); p) BF_3•OEt_2 CH_2Cl_2 (79%).

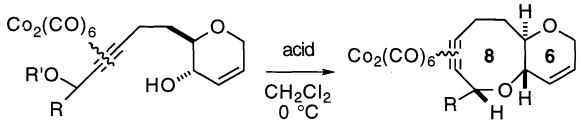
The same iodide **1** was displaced by a homologous carbanion generated from trimethylsilylpropyne, and the silyl group in the product was removed by sodium methoxide to afford **7**. The isopropyl glucosidic group was reduced by triethylsilane in the presence of BF_3•OEt_2, and the alcohol was reprotected as ethoxy ethyl ether **8**. Similar treatment with cinnamaldehyde as the above case provided **9** (a higher homolog of **4**), and the following cyclization was repeated via **10** with BF_3•OEt_2 to afford 8-6 bicyclic compound **11**. No 10-membered product was found in this case either.

A bishomo precursor should provide 9-6 bicyclic compound **15**. This was indeed synthesized in a few more steps started by a coupling between **2** and iodoacetylene **12** in the presence of a palladium catalyst.[7] The 1,3-butadiyne derivative (**13**) was converted into the di-(biscobalthexacarbonyl) derivative **14**, and then subjected to acid conditions to give the cyclized 9-6 product **15**. A 79% yield was best achieved by high-dilution conditions as 0.1 mM (or 0.01 w/v%) in dichloromethane. This cyclization would go through the possible intermediate **14a** that may have the bulky di-(biscobalthexacarbonyl) moieties sticking outside to result in bringing the two reaction sites close enough, though the dihedral angle between the two complex moieties was not yet known. Similar NOE experiments proved the stereochemistry of **15**.



Scheme 2.

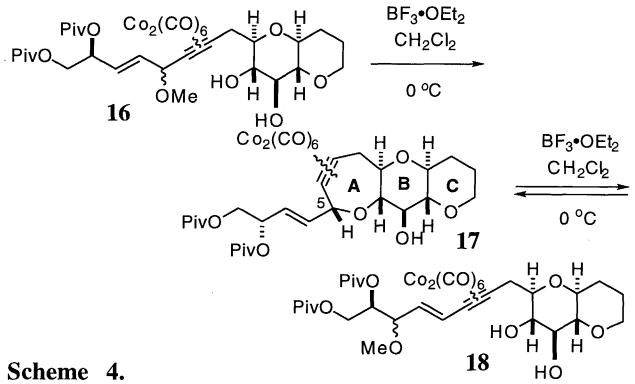
R'	R	acid	yield
CH_3	H	TfOH	trace
C(=O)CMe_3	CH=CH-Me	CSA	74 %
C(=O)CMe_3	CH=CH-Ph	BF_3•OEt_2	89 %
CH_3	CH=CH-CH(*S*-OPiv)CH_2OPiv	BF_3•OEt_2	67 %
CH_3	CH=CH-CH(*R*-OPiv)CH_2OPiv	BF_3•OEt_2	79 %



Scheme 3.

R'	R	acid	yield	*syn:anti*
CH_3	H	TfOH	40 %	-
C(=O)CMe_3	CH=CH-Ph	TsOH•H_2O	79 %	4.3 : 1
C(=O)CMe_3	CH=CH-Ph	BF_3•OEt_2	66 %	3.3 : 1

The critical step in Scheme 1 as above was the cyclization; thus, formation of the cationic intermediates, which were stabilized at the propargylic position by the effects of the acetylene biscobalthexacarbonyl complex known as Nicholas reaction.[2] Each of these cations was further stabilized as an allylic position by an additional double bond on the other side. Several examples of such cyclization forming 7-6 (Scheme 2) and 8-6 (Scheme 3) bis-ether rings are shown above. Most of the cyclization proceeded under moderately acidic conditions due to the presence of an additional double bond. In case of the primary propargylic ethers (Scheme 2, 3 R=H), the reaction did not proceed with BF_3•OEt_2 nor TsOH•H_2O, but proceeded only with trifluoromethanesulfonic acid (TfOH). On the other hand, in the most stabilized case worked even BF_3•OEt_2.



Scheme 4.

Table 1. Reaction profile of the cyclization of **16**

entry	acid	temp (° C)	conc (mM)	time (min)	yield % **17** : **18**
1	TsOH•H_2O	0	6.3	40	27 : 43
2	TfOH	0	3.4	40	10 : 48
3	TMSOTf	0	6.9	30	15 : 45
4	BF_3•OEt_2	-20	5.4	20	0 : 0
5	BF_3•OEt_2	0	5.8	20	42 : 42
6	BF_3•OEt_2	0	5.4	60	24 : 42
7	BF_3•OEt_2	0	2.6	20	63 : 37
8	BF_3•OEt_2	0	1.0	20	71 : 23

Comparing the 7-membered ring cyclization in Scheme 2 and the case with **16**, the reaction course was somewhat different; thus, the reaction of the latter was not as smooth as the formers. Treatment of **16** with BF_3•OEt_2 under the same conditions gave the cyclization product **17** (as a single stereoisomer about the C-5 position) together with the open-chain compound **18** (as a more stable product). Attempted cyclization of **18** took longer time than its allylic isomer **16**. These results are summarized in Table 1. In this cyclization, BF_3•OEt_2 was the best catalyst. The reaction made progress at 0 °C rather than -20 °C (entries 4 and 5). When the reaction time was elongated, we obtained the cyclic product **17** in poorer yields and **18** became the major product (entries 5 and 6). Finally, this cyclization was strongly affected by the concentration because the by-product **18** was formed intermolecularly. The best result was realised in entry 8, where the yield of **17** was 71%.

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References and Notes

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6 These involved (i) lithium trimethylsilylacetylide addition, (ii) hydrolysis of the ethoxyethyl protective group, (iii) protection as acetate, (iv) reduction of C-1 position, (v) hydrolysis of the acetate and trimethylsilyl group and (vi) formation of the ethoxyethyl ether with ethyl vinyl ether and PPTS.
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