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# Opening of Dihydropyran and Recyclizing to Dehydrooxepane through C-1 Alkynyl Cobalt Complex----A New Method toward Marine Polyether Toxins

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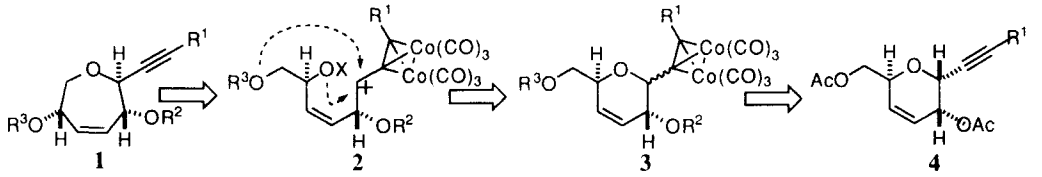
*Abstract: Ring opening of dihydropyran having alkynyl group as dicobalt hexacarbonyl complex was achieved with acylinium ion to furnish the corresponding linear molecule. A recyclization using same Nicholas-type cation intermediate afforded an oxepane derivative.*

Oxepane rings often occur in marine polyether toxins as partial structures of brevetoxin, ciguatoxin, yessotoxin, gambierol, gambieric acids or maitotoxin, which has *trans*-fused ring system to other cyclic ethers varying from 6 to 9 members with two *syn*-substituents neighboring to the oxygen atom of cyclic ether.[1] New method of stereoselective synthesis toward such a ring in **1** is currently collecting much attention.[2] Recently, we have reported an approach to enantiomeric synthesis of pyran subunits of marine toxins by epimerization of dicobalt hexacarbonyl complexes of **4** obtainable from 2,3,4,6-tetraacetyl D-glucal under carbohydrate synthon.[3] This epimerization [from the alpha into the beta C-1 alkynyl sugar (**3**) ] would involve a ring-opening intermediate such as **2**. Trapping of this intermediate **2** with the cobalt complex of alkynyl glycosides had become extremely interesting as a promising new intermediate for the synthesis of those marine polyether toxins. Recyclization, on the other hand, would afford oxepane ring (**1**). This idea, in principle, is illustrated in Scheme 1, which may be realized by taking advantage of the stabilization of the cationic intermediate (**2**) at the propargylic position that has been well known as Nicholas reaction.[4]

**Scheme 1**

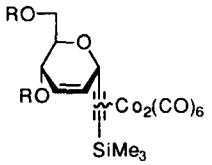
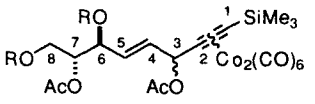
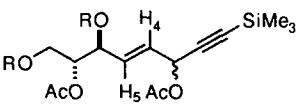
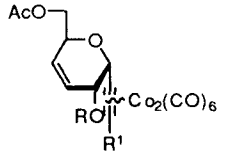
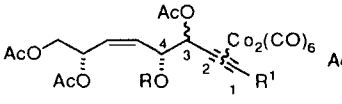
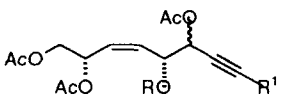



Attempted ring-opening of the cobalt complex **3** did not take place at all during the epimerization using protonic acid. This might be due to thermodynamic nature of the cationic intermediate (**2**, OX= OH) to recyclize to 6-membered ring. Trapping of the hydroxy group should prompt the ring-opening by acylation (**2**, OX= OAc) using acetic anhydride and trifluoromethanesulfonic acid (TfOH).[5] In fact, those dicobalt hexacarbonyl complexes of two kinds of alkynyl glycoside (**5**, **8**)[3] in Table 1 gave the corresponding ring opening products by treatment with TfOH in acetic anhydride at various temperatures followed by quenching with triethylamine.

The complex **5a**, for example, was subjected to the trapping condition; thus, the complex (0.16 mmol) was stirred in a mixture of acetic anhydride (5 ml) containing TfOH (0.17 mmol) at -20 °C for 1 hr, and then quenched with triethylamine (2.2 mmol) before work-up. The yield of **6a** in Table 1 is the isolated one by silica gel chromatography. Both the products **6a** and **6b** had *trans*-double bonds that were assigned from the coupling constants in $^1$H NMR spectra of the decomplexed propargyl acetates (**7a**, **7b**) with iodine,[3] which showed the olefinic protons at δ 5.82 ($H_4$, $J_{4,5}$= 15.0 Hz) and δ 5.26 ($H_4$, $J_{4,5}$= 15.5 Hz), respectively. Although this olefinic isomerization was slower at lower temperatures (e.g. -40 °C, 3.5 hrs), the main product was always isolated as *trans*-isomer. This olefinic isomerization clearly indicated significant participation of the π-electorons in stabilizing the intermediate cation as well as the cobalt complex at propargyl position. Although the details are omitted from the table, the complexes **5a** and **5b** with $\Delta_{2,3}$-double bond did react faster than those **8a-c** with 2-protected hydroxy group.

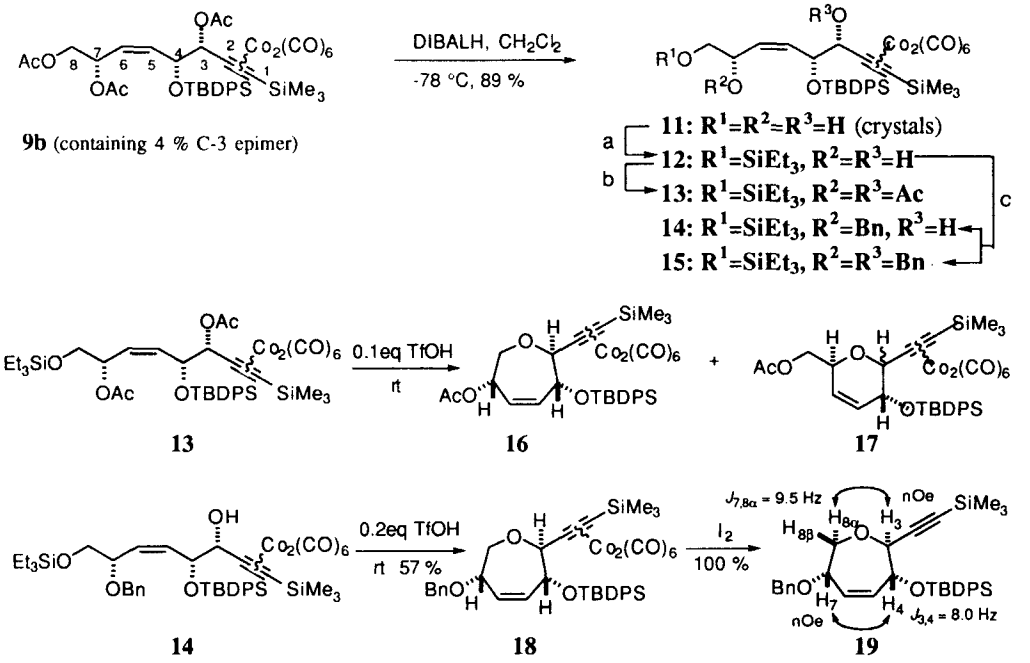
The other acetylene dicobalt hexacarbonyl complexes **8a**, **8b** and **8c** with other unsaturated ($\Delta_{3,4}$) system required 3~6 times as much amount of TfOH and longer time for completion of the ring-opening reaction. This was merely because no π-electron stabilization to the intermediate cation as the above cases. All products were obtained as diastereoisomeric mixtures at the original anomeric position, but the ratios of **9b** and **9c** were very high. Since the diastereoisomeric ratio of **9a** was extremely low (53:47), the interaction between C-1 and C-4 substituents ($R^1$ and OR) was presumably responsible for this selectivity.[6]

**Table 1**. Ring opening of cobalt-complexed alkynyl glycosides with TfOH in acetic anhydride

| Entry | Substrate | conc. TfOH (M) | (equiv.) | temp. (°C) | time (h) | Product (yield % diastereomer ratio) | Propargyl acetate (%) |
|---|---|---|---|---|---|---|---|
| |  | | | | |  |  |
| 1 | **5a R=Ac** | 0.03 | 1 | -20 | 1.0 | **6a** ( 95 %, 50:50) | **7a** (90 %) |
| 2 | **5b R=TBDPS** | 0.03 | 1 | 0 | 0.2 | **6b** ( 70 %, 70:30) | **7b** (96 %) |
| |  | | | | |  |  |
| 3 | **8a R=Ac** **$R^1$=SiMe$_3$** | 0.13 | 5.5 | -40 | 2.0 | **9a** ( 54 %, 53:47) | **10a** (66 %) |
| 4 | **8b R=TBDPS** **$R^1$=SiMe$_3$** | 0.20 | 3.0 | -40 | 1.5 | **9b** ( 84 %, 94: 6) | - |
| 5 | **8c R=TBDPS** **$R^1$=H** | 0.13 | 4.4 | -40 | 2.0 | **9c** ( 71 %, 88:12) | **10c** (87%) |

Two cobalt complexes, **9a** and **9c** were decomplexed with iodine[3] in good yields giving **10a** and **10c** and characterized by instrumental analyses. The cobalt complex **9b** was used for further cyclization to 7 membered ring (dehydrooxepane) because it preserved the *cis*-olefin. Reduction of **9b** with excess DIBALH at -78 °C gave the corresponding triol **11** as reddish brown crystals (recrystallized from *n*-hexane) in 89 % yield. Selective silylation of the primary alcohol using chlorotriethylsilane and 1,2,2,6,6-pentamethylpiperidine[7] afforded the triethylsilyl ether diol compound **12** in 96 % yield.[8] In order to conduct intramolecular Nicholas reaction[4] between carbon atom at 3-position (new numbering as in figure) and oxygen atom at 8-position, the remaining two hydroxy groups were acetylated with acetic anhydride, triethylamine and DMAP (**13** in 86 % yield).

**Scheme 2**




**Reagents**; (a) $Et_3SiCl$, 1,2,2,6,6-pentamethylpiperidine[7] (96 %); (b) $Ac_2O$, $Et_3N$, N,N-dimethylaminopyridine (86 %); (c) benzyl trichloroacetimidate, TfOH; **14** (63 %) and **15** (9 %).

Attempted cyclization from **13** to the dehydrooxepane **16** under various acidic conditions at various temperatures only occurred in 12 % yield (0.1 equiv. TfOH, at rt) since migration of the C-7 acetoxy group to the C-8 position before the cyclization yielded the diastereoisomeric pyran **17** as a main product (62 % yield). Non-migratory protective group for the C-7 hydroxy as benzylether **14** was necessary to prevent from this acyl migration. Treatment of the diol **12** with benzyltrichloroacetimidate[9] in the presence of catalytic amount of TfOH gave a mixture of monobenzylether **14**[10] (63 %) and dibenzylether **15** (9 %). Treatment of **14** with 0.2 equiv. of TfOH at rt afforded dehydrooxepane **18** as only the cyclization product in 57 % isolated yield. The cobalt complex in **18** was removed by oxidation with iodine to obtain **19** {$[\alpha]_D^{23}$=+19.0° (*c* 0.78 $CHCl_3$)} in quantitative yield. The trans-configuration of C-3 and C-4 substituents in **19** was determined by the coupling

constants $J_{3,4}$= 8.0 Hz and $J_{7,8\alpha}$= 9.5 Hz, which were consistent with the value reported by Nicolaou.[2a] The stereochemistry of **19** was also confirmed by observing two nOe's between $H_3$-$H_{8\alpha}$ and $H_4$-$H_7$. Apparently this highly selective cyclization was thermodynamically controlled. The thermodynamic stability difference between **18** and its isomer would be due to 1,2-torsional strain between the two bulky substituents at C-3 and C-4.[11] Dehydrooxepane **19** is of extreme interests as a candidate of precursor not only for D or E ring of ciguatoxin but also other marine toxins as an attractive synthetic intermediate.

To the best of our knowledge the stabilization[12] of propargyl cation by acetylene-dicobalt hexacarbonyl complex made it first possible to cleave pyranose ring of C-glycosides and recyclize in other sized ring. Basically the current method could be applied to other medium sized rings. Besides the linear cobalt complexes obtained by the ring opening reaction could also be used for synthesizing a variety of natural products because of those asymmetric carbons and easily manipulated acetylene moiety.

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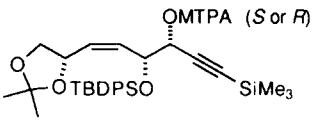

**20**

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11. The vicinal coupling constant between H-3 and H-4 of **18** was almost zero. This would be due to the two bulky substituents being in +anti-clinal position each other to diminish the 1,2-torsional strain.
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