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A Stereoselective Synthesis of Medium-Sized Cyclic Ethers by the Intramolecular Cyclization of Linear Hydroxyalkyl-Propargylic Alcohols Assisted by $Co_2(CO)_8$

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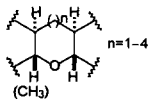
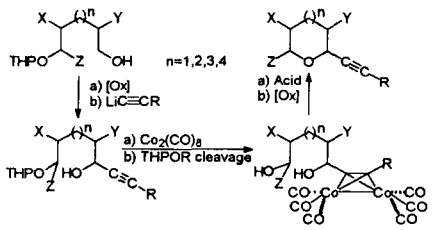
Abstract: A highly efficient, mild and general cyclization reaction of hydroxy *exo*-(propargyl)$Co_2(CO)_6$ cations leading to medium-sized (6 to 9 membered) cyclic ethers is described. The reaction is highly stereoselective when defined stereocenters are encountered in the linear precursor, providing a way to obtain fused cyclic ethers in their enantiomeric forms.

Marine toxins such as maitotoxin,[1] brevetoxins,[2] ciguatoxin,[3] yessotoxin,[4] gambierol[5] and gambieric acids[6] have been described as substances interacting with the cation channels of cellular membranes.[7] These highly complex molecules are characterized by having fused cyclic ether units whose size oscillates from 6 to 9 members and with a well-defined stereochemistry, usually with a *trans*-relationship between the two substituents (H or CH_3) in the fusion of rings and a *cis*-stereochemistry in the substituents (H or CH_3) close to the oxygen atom of the cyclic ether (n = 1→4). Polyfunctionalized cyclic ethers are also the main structural feature of a wide group of substances isolated from different species of *Laurencia*.[8]



A challenging aspect of the synthesis of such molecules is the proper construction of the cyclic units.[9] Four major strategies have been used in the synthesis of medium-sized cyclic ethers: conversion of lactones to cyclic ethers,[10] fragmentation of oxabicyclo systems,[9,11] carbocyclization of linear ethers[12] and intramolecular nucleophilic attack of a hydroxy group to an activated functional group in a chain.[13] We have focused our attention on the last approach.[14] In general, to achieve rings with more than 6-members an entropic activation is necessary in the chain to aproximate the nucleophilic hydroxy group to the center to be attacked.[15]

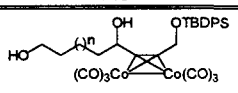
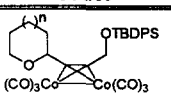
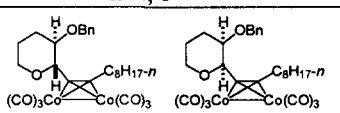
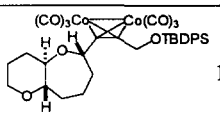
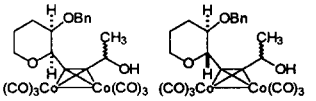
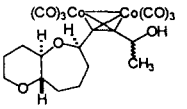
In this communication we report on a new and general method to obtain medium-sized cyclic ethers (6 to 9 members) involving the intramolecular attack of a hydroxy group located in a saturated chain to a carbocation generated by acid treatment of *exo*-(propargyl)$Co_2(CO)_6$ complexes (intramolecular Nicholas' reaction.[16]



The starting point for these investigations was our observation that the acid treatment of the free diol **1** afforded the tetrahydropyrane **2** in good yield which, under oxidative treatment [$Ce(NH_4)_2(NO_3)_6$] to remove

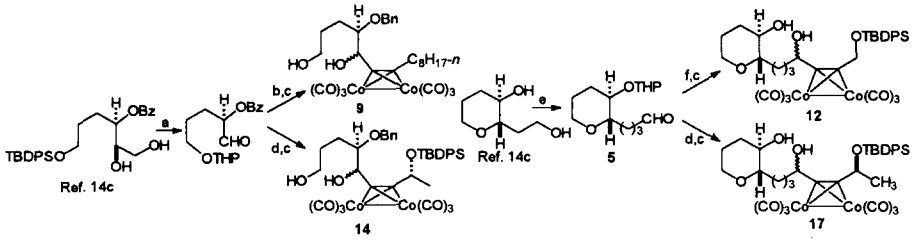
the cobalt complex, yielded almost quantitatively the free acetylene product with the silyl protected primary hydroxy group unaffected under the reaction conditions. Our expectations that the method could be applied to larger rings were gratifyingly fulfilled when additional methylene groups were introduced in the saturated chain in the starting diol. As indicated in **Table I**, the procedure works smoothly forming 6 throughout 9 membered rings (entries 1-4) using 1 equivalent of acid (HBF_4 or $BF_3.OEt_2$). Although the reaction can also be performed in a catalytic manner (entry 1) we found that in general the best yields were obtained when 1 equivalent amount of acid was used. The maximum rate was achieved for the oxepane formation being a roughly order of cyclization to 7>6>8>9 membered rings. The reaction is regiospecific in that we had not observed any competition between the two propargylic alcohols, the cyclic ethers being obtained in all cases by attack on the carbon with the free alcohol.

Table I. Cyclization of hydroxy *exo*-(propargyl)$Co_2(CO)_6$ cations

Entry	Diol[a]	Product[a,b]	Yield[c]
1.	 n=1, **1**	 n=1, **2**	85 78[d]
2.	n=2, **3**	n=2, **4**	78
3.	n=3, **5**	n=3, **6**	72
4.	n=4, **7**	n=4, **8**	55
5.	**9**	 **10** 3 : 1 **11**	82
6.	**12**	 **13**	73
7.	**14**	 **15** 3 : 1 **16**	80
8.	**17**	 **18**	71

a) All Co_2CO_6-complexes have been prepared treating the propargylic alcohols with Co_2CO_8 in CH_2Cl_2 at rt. b) The cyclizations have been performed at -30 °C using 1 equiv of $BF_3.OEt_2$, following the reaction by TLC (1 to 9 h) and quenching the reaction with saturated aqueous $NaHCO_3$ solution. c) Isolated yields. d) The reaction has been performed in a catalytic manner (0.1 equiv of HBF_4).

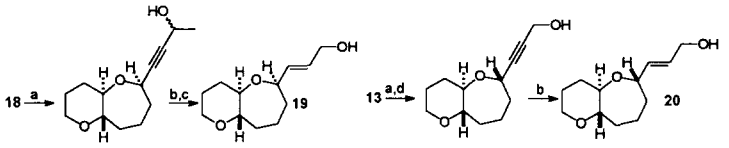
One additional and very important feature of the presented methodology is that the stereochemistry of the cyclization is sensitive to other stereocenters located in the product to be cycled. Thus, when the acidic cyclization of **9** (**Scheme 1**) was performed an inseparable 3:1 mixture (NMR analysis) of diastereoisomers *trans*-**10** and *cis*-**11** was obtained. Such selectivity was the basis for the synthesis of fused cyclic ethers in a stereoselective manner, since the acidic treatment of **12** led to the bicyclic oxane-oxepane **13** (entry 6) as the only isolated stereoisomer. [17]



a) i) $PhCH(OMe)_2$, CSA (cat), CH_2Cl_2, rt, ii) NaOMe, THF, rt, iii) $PhCH_2Cl$, NaH, *n*-Bu_4NI, THF, rt, iv) CSA (cat), MeOH, v) Ac_2O, DMAP, CH_2Cl_2, 0°C, vi) *n*-Bu_4NF, THF, rt, vii) DHP, PPTS (cat), CH_2Cl_2, rt, viii) K_2CO_3, MeOH, rt, ix) $NaIO_4$, THF-H_2O, rt; b) $LiC{\equiv}CC_8H_{17}$-*n*, THF, -50 °C, c) i) $Co_2(CO)_8$, CH_2Cl_2, rt, ii) CSA (cat), MeOH, rt; d) (R)- or (S)-$C{\equiv}CCH(CH_3)OTBDPS$, THF, -50 °C;[18] e) i) BzCl (1 equiv), Et_3N, CH_2Cl_2, 0 °C, ii) DHP, PPTS (cat), CH_2Cl_2, rt, iii) NaOMe, CH_2Cl_2, rt, iv) SO_3.Py, DMSO, Et_3N, CH_2Cl_2, rt, v) $(MeO)_2P(O)CH_2CO_2Me$, NaH, benzene, 0 °C, vi) DIBAL, ether, 0 °C, vii) H_2, PtO_2, EtOAc, rt; viii) SO_3.Py, DMSO, Et_3N, CH_2Cl_2, rt; f) $LiC{\equiv}CCH_2OTBDPS$, THF, -50 °C.

Scheme 1

In order to test the influence of an additional stereocenter we prepared **14** which after acid treatment yielded the mixture of **15** and **16**. Interestingly, the newly created stereocenter in the more abundant **15** was reverted relative to **10**. Although this is a very promising result, the removal of the silyl protecting group under the reaction conditions made us suspect a possible modification of the absolute configuration of the *exo*-propargylic stereocenter[19] presumably by a C-O bond cleavage and further reaction with water of the cation formed.[17a] In order to confirm such a possibility and additionally to study the stereochemical course with a different system we prepared **17**. We found that although such racemization occurred a complete stereoselection was reached in the newly created stereocenter in the oxepane formation yielding **18**. It is noteworthy that the cyclization of **17** to **18** yielded the complementary stereochemistry to that obtained in the cyclization of **12** to **13**. Although the racemization in the carbinol center is not a desired reaction, by itself it is not a serious limitation of the reported method since the acetylenic portion can be easily removed to a suitable functionality for homologation of the chain.



a) $Ce(NH_4)_2(NO_3)_6$, acetone, rt; b) $LiAlH_4$, THF, 0 °C; c) i) O_3, CH_2Cl_2-MeOH, -78 °C, then Me_2S, -78 °C → rt, ii) $MeO)_2P(O)CH_2CO_2Me$, NaH, benzene, 0 °C, iii) DIBAL, ether, 0 °C; d) *n*-Bu_4NF, THF, rt.

Scheme 2

In conclusion, we present here a powerful method to obtain medium-sized rings without any entropic activation in the linear precursor. The high degree of stereocontrol reached when defined stereocenters are present and the mildness of the method predictably render it very useful in the synthesis of functionalized polycyclic ethers.[20] Additional applications and mechanistic studies of this new and effective approach are under way in our laboratory and will be reported in due course.

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19. Although we have further evidence that both **15** and **16** are actually an approximately 1 : 1 mixture of diastereoisomers in the stereocenter where the free alcohol is located, NMR (^1H and ^{13}C) studies (^1H-400 Mhz) were completely inefficient to differentiate such mixtures.
20. Satisfactory spectroscopic data were obtained for the new compounds. The stereochemistry in all chiral products has been determined by ROESY and NOEDIFF experiments (BRUKER AMX400).

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