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Stereoselective Intramolecular Nicholas Reaction Using Epoxides as Nucleophiles

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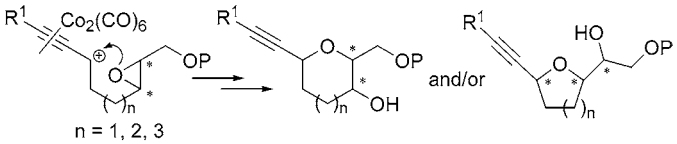
ABSTRACT



The intramolecular nucleophilic attack of the epoxides on the *exo*-$Co_2(CO)_6$-propargylic cations provided cyclic ethers in good yields. The use of substrates with stereochemically defined oxiranes provided polysubstituted tetrahydropyrans and oxepanes with a high degree of stereocontrol. The cyclization is sensitive to the nature of the protecting group used at the primary alcohol, the use of *tert*-butyl carbonates being highly effective in terms of regioselectivity and yields.

A series of compounds, many of them showing strong biological activities, have been isolated from marine organisms.[1] This class of compounds includes the so-called ladder ether toxins, which exhibit a high degree of structural complexity in regard to stereochemistry, molecular dimension, and ring size.[2,3] On the other hand, polyfunctionalized cyclic ethers are also the main structural features of a wide range of substances isolated from different species of *Laurencia* red algae.[1] These synthetically challenging structures and potent biological activities have attracted the attention of numerous synthetic chemists, and a variety of approaches have been explored.[4]

Considering the biological origin of the above-mentioned molecules involving a cascade poly-oxacyclization,[5] the two most attractive basic strategies include the intramolecular opening of epoxides[6] and the trapping of electron-deficient carbons,[7] in both cases using alcohols as nucleophiles. In this context, the Nicholas reaction[8] has proved to be an excellent way to achieve both the activation of epoxides[9]

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(5) (a) Nakanishi, K. *Toxicon* **1985**, *23*, 473−9. (b) Chou, H.-N.; Shimizu, Y. *J. Am. Chem. Soc.* **1987**, *109*, 2184−2185. (c) Lee, M. S.; Qin, G.-W.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1989**, *111*, 6234−6241.

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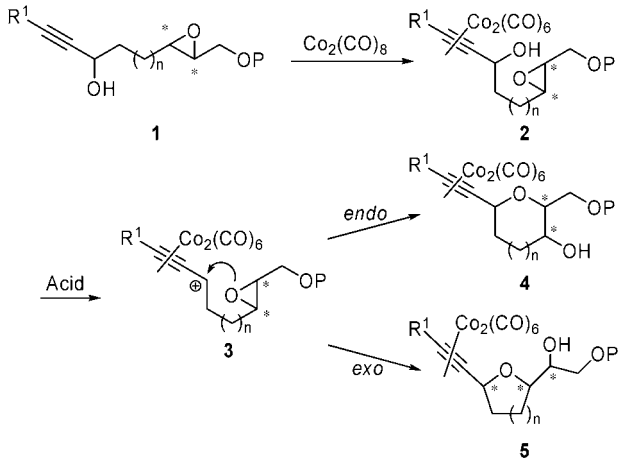
and the generation of cations that could be transformed into cyclic ethers.[10] On the other hand, methodologies making use of epoxides as nucleophiles in the synthesis of cyclic ethers have also been reported.[11]

Within our program directed toward the development of strategies for the stereoselective construction of cyclic ether metabolites, we wish to report on a new methodology based of the use of the Nicholas reaction, making use of epoxides as nucleophiles (Scheme 1). To the best of our knowledge,

Scheme 1. Use of Epoxides as Nucleophiles in the Intramolecular Nicholas Reaction

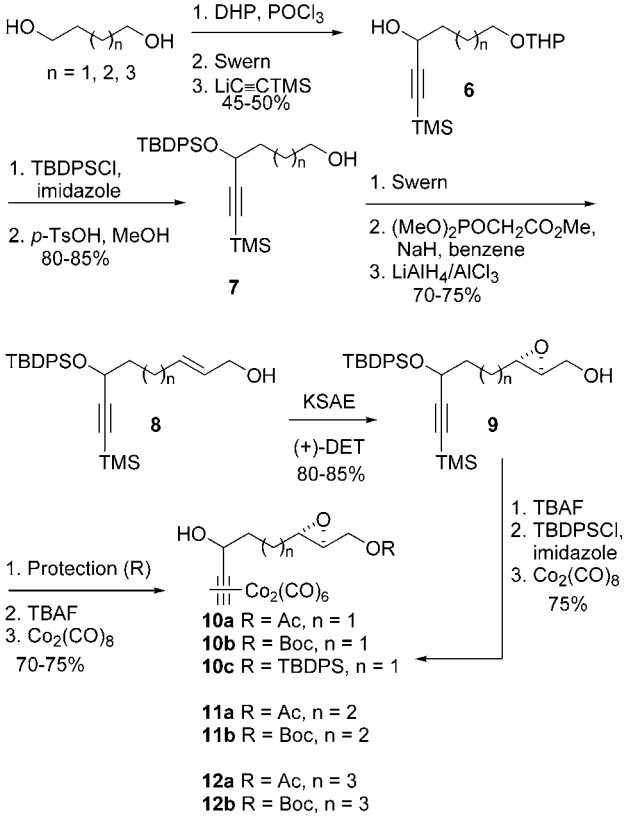


this is the first report on the use of an epoxide as a nucleophile to trap dicobalt hexacarbonyl-stabilized propargylic cations. Here we describe the scope and limitations of this reaction as an alternative method to synthesize oxacycles in a stereocontrolled manner.

To study the cyclization process, the synthesis of a series of linear precursors was achieved, in which propargylic alcohol and an epoxi-alcohol were linked through an alkyl chain with a variable length (Scheme 2). We were also interested in verifying the influence that exerted the protecting groups (P) of the primary alcohol on the process of cyclization.

To perform the synthesis of the necessary lineal precursors, we used as starting material the suitable diols, that after monoprotection as THP derivatives were oxidated and treated with the lithium salt of trimethylsilyl acetylene yielding the corresponding propargylic alcohols **6**. Protection of the secondary alcohol as a silyl ether, followed by cleavage of the tetrahydropyranyl ether afforded compounds **7**. Oxidation of the primary alcohol to the aldehyde followed by a Horner−Wadsworth−Emmons homologation provided the corresponding α,β-unsaturated esters that after reduction of the ester yielded the allylic alcohols **8**. These were converted to the corresponding diastereomeric 2,3-epoxy alcohols **9** via the Katsuki−Sharpless asymmetric epoxidation using (*R*,*R*)-(+)-diethyl tartrate as the chiral auxiliary.[12] Protection of the free alcohol, as a *tert*-butyl carbonate, acetate or silyl ether, and cleavage of the secondary silyl groups and further

Scheme 2. Preparation of $Co_2(CO)_6$-propargylic Alcohols Bearing Remote Protected Epoxy Alcohols



complexation of the acetylene moiety by direct reaction with $Co_2(CO)_8$, in CH_2Cl_2, afforded the complexed epoxides **10, 11** and **12**. Compound **10c** was obtained by a slightly different sequence (Scheme 2).

Gratifyingly, we found that cyclization took place under treatment with $BF_3{\cdot}OEt_2$ providing the corresponding complexed oxacycles.[13] However, the products were different, depending on the protection, length of the chain and reaction conditions (Table 1). To better analyze the resulting cyclic products, we performed a sequence of processes, namely cyclization, acetylation and further oxidative removal of the cobalt complex. Thus, the *endo*-tetrahydropyran diacetate **13** was obtained as the main product when **10a** (n = 1, R = Ac) was submitted to the cyclization conditions at room temperature for 24 h (entry 2). However, the amount of tetrahydrofurans **14** and **15** increased substantially when a shorter reaction time was applied (entry 1). The influence

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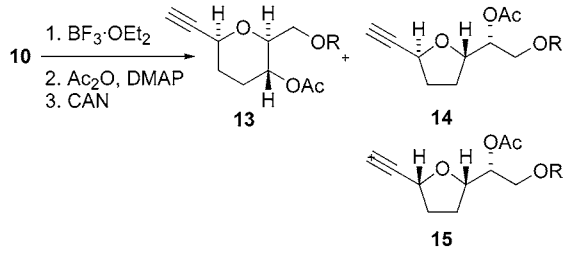
Table 1. Intramolecular Trapping of *exo*-$Co_2(CO)_6$-propargylic Cations by Epoxides Leading to Oxacycles



entry	**10**	*T* (°C)	time[a] (h)	yield (%)	**13/14/15**
1	**10a**	rt	1	91	R = Ac, 50:25:25
2			24	95	R = Ac, 80:11:9
3	**10b**	−20	4	70	R = Boc, 100:0:0
4		rt	24	93	R = Ac, 92:4:4
5	**10c**		1	65	R = TBDPS, 56:44:0
6			4	73	R = TBDPS, 56:44:0
7			24	25	R = TBDPS, 0:100:0

[a] Time refers to the cyclization step.

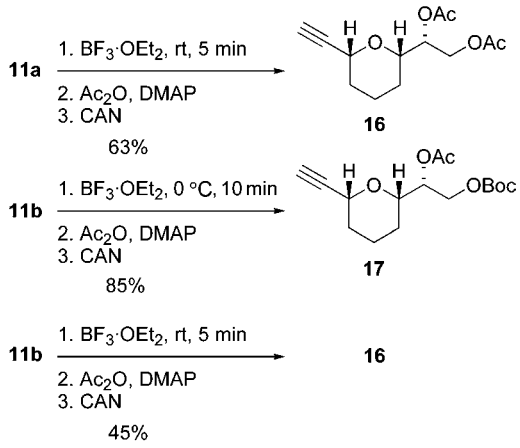
of the nature of the protecting group at the primary alcohol was clearly established when the cyclization of **10c** was performed forcing thermodynamic conditions (entry 7), affording **14** as the only cyclic product, albeit in a poor yield. The best results in terms of selectivity to afford the six-membered rings were achieved when the carbonate **10b** was treated under similar acidic conditions at −20 °C, the tetrahydropyran **13** being obtained as the sole product.[14] At temperatures lower than −20 °C the reaction is impractical in terms of conversion. The configuration was established by NOE studies, coinciding with that present in the ladder toxins.[3]

(13) **Typical Procedure (Preparation of 13, R = Ac).** To a stirred solution of the hexacarbonyldicobalt complex of **10a** (100 mg, 0.21 mmol) in dry CH_2Cl_2 (10.5 mL) was added $BF_3{\cdot}OEt_2$ (31 μL, 0.21 mmol) at room temperature. The reaction mixture was stirred for 24 h. The mixture was poured with vigorous stirring into a saturated solution of $NaHCO_3$ at 0 °C and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The crude complex was dissolved under argon atmosphere in dry CH_2Cl_2 (2.1 mL) at room temperature, and acetic anhydride (30 μL, 0.32 mmol) and DMAP (39 mg, 0.32 mmol) were added. The resulting mixture was stirred for 30 min. The reaction was diluted with CH_2Cl_2 and washed with HCl aqueous solution (5% w/v), a saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The crude mixture was dissolved in acetone (2.1 mL) at 0 °C. Ceric ammonium nitrate (323 mg, 0.84 mmol) was added in portions with stirring until evolution of CO ceased and the CAN color persisted (10 min). The solvent was removed under vacuum, and the pink solid residue was then partitioned between Et_2O and H_2O. The aqueous phase was extracted additionally twice with Et_2O. The combined organic extracts were dried, filtered, concentrated, and subjected to silica gel flash chromatography yielding **13**, R = Ac, as an oil (38 mg, 76% yield): $[\alpha]^{25}_D = -44.2$ (*c* 0.52, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 1.07 (m, 1H), 1.50 (m, 1H), 1.69 (s, 3H), 1.69 (m, 1H), 1.75 (s, 3H), 1.95 (m, 1H), 2.10 (d, *J* = 2.1 Hz, 1H), 3.27 (ddd, *J* = 2.1, 5.1, 9.8 Hz, 1H), 3.77 (ddd, *J* = 2.3, 2.3, 11.5 Hz, 1H), 4.23 (dd, *J* = 2.1, 12.1 Hz, 1H), 4.4 (dd, *J* = 5.2, 12.0 Hz, 1H), 4.84 (ddd, *J* = 4.9, 10.2, 10.6 Hz, 1H); ^{13}C (75 MHz, C_6D_6) δ 20.0 (q), 20.1 (q), 28.7 (t), 31.3 (t), 62.8 (t), 66.8 (d), 67.5 (d), 72.9 (d), 77.7 (d), 81.9 (s), 168.8 (s), 169.9 (s); IR (cm^{-1}) 3240, 2930, 1736, 1231; MS *m/z* (relative intensity) 167 (35), 138 (40), 95 (100), 67 (70). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.98; H, 7.19.

(14) For the influence of temperature to control the stereochemistry in cobalt induced cyclizations, see: (a) Liu, T.-Z.; Isobe, M. *Tetrahedron* **2000**, *56*, 5391−5404. (b) Takase, M.; Morikawa, T.; Abe, H.; Inouye, M. *Org. Lett.* **2003**, *5*, 625−628. (c) Reference 10b.

To extend the use of the reaction to larger rings we performed the cyclization over **11a** (Scheme 3). However,

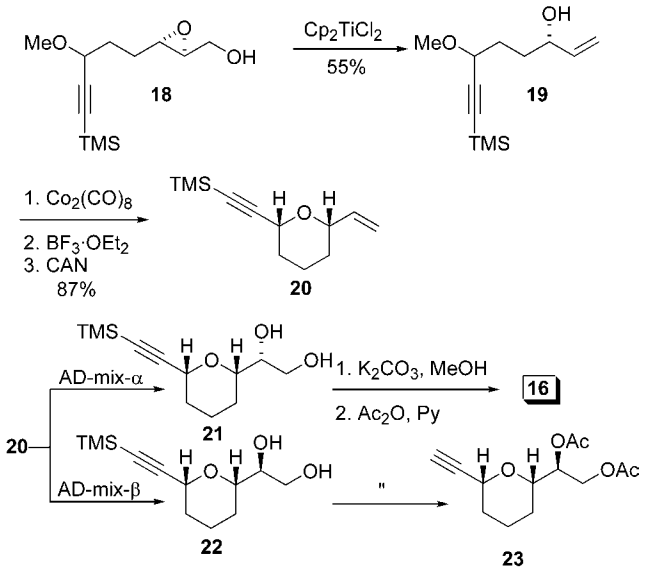
Scheme 3. Synthesis of *Exo*-Substituted *syn*-Tetrahydropyrans



in this case the sequence of reactions yielded stereoselectively the *exo*-substituted tetrahydropyran **16**. The influence of the protecting group was also significant since the use of the carbonate **11b**, at 0 °C, provided cleanly **17** in excellent yield as the only detected product.[15] Resulting from the cleavage of the primary carbonate, when the reaction was ran at room temperature, the process yielded **16**.

Although by NOE studies of **16** we verified the *syn*-relationship between the two hydrogens vicinal to the heterocyclic oxygen, we could not clarify the configuration of the secondary alcohol of the chain. Thus, we decided to prepare this compound by an alternative way, guaranteeing the configuration at the carbinol center (Scheme 4). The epoxy alcohol **18**[16] was directly converted into the vinyl

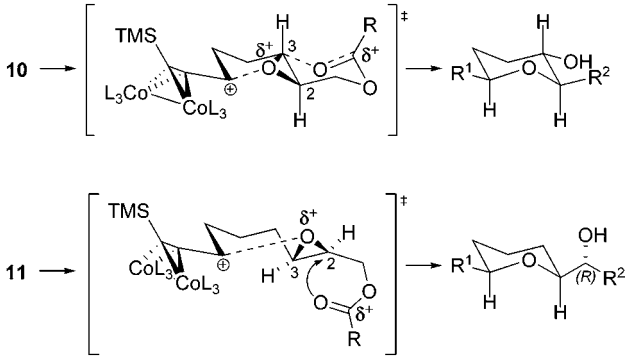
Scheme 4. Alternative Synthesis of *Exo*-Substituted *syn*-Tetrahydropyrans



carbinol **19** by treatment with bis(cyclopentadienyl)titanium-(III) chloride.[17] Then complexation of the acetylene with $Co_2(CO)_8$ and cyclization induced by Lewis acid yielded the corresponding *syn*-tetrahydropyran **20** as recognized by NOE analysis.[10b,18] Stereoselective dihydroxylation using both AD-mix-α and AD-mix-*β* afforded the respective diols **21** and **22**.[19] Removal of the TMS group and full acetylation established the equivalence of **16** with the diacetate of **21**.

Considering the different behavior in the opening reactions regarding the length of the chain and the nature of the protecting group at the primary alcohol, we propose a vicinal participation of this functionality in the ring formation (Scheme 5).[20] Thus, for the smaller chain the concomitant

Scheme 5. Mechanistic Proposal in the Cyclization of Epoxy Propargylic Cations Depending on the Carbon Chain Length



attack of the carbonyl group of the protecting group on the C3 carbon and the oxygen of the epoxide to the propargylic cation, produce the *endo*-tetrahydropyran with inversion at the configuration of the C3 center. However for larger chains such carbonyl attack takes place at the C2 carbon, opening the epoxide and yielding the ring by nucleophilic attack of the resulting alcohol.

We observed the same influence of the protecting group at the primary alcohol when the carbon chain was elongated

(15) For the use of electronically enriched carbonyl derivatives in cyclization reactions using 2,3-epoxy alcohols, see ref 11c.

(16) Obtained by a similar sequence to that shown in Scheme 1 using a methyl ether as the protecting group at the secondary carbinol.

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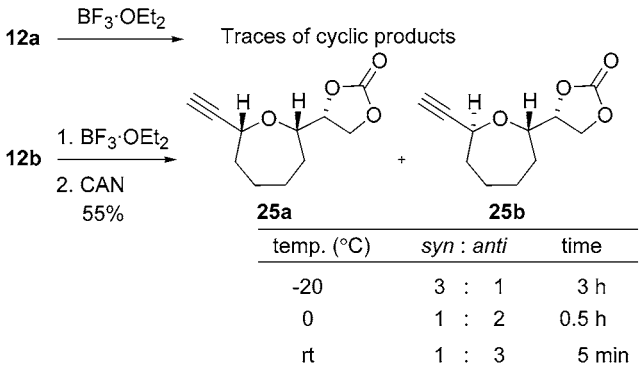
(20) To clarify the scheme the enantiomers of reactants and products were drawn.

Scheme 6. Temperature dependence in the stereoselective ynthesis of substituted oxepanes



temp. (°C)	*syn* : *anti*	time
-20	3 : 1	3 h
0	1 : 2	0.5 h
rt	1 : 3	5 min

(Scheme 6). Thus, the treatment of the acetate **12a** at different temperatures yielded tiny amounts of *exo*-cyclic products. Much better results were obtained when the corresponding carbonate **12b** was submitted to the cyclization conditions. In this case, a significant amount of the oxepanes **25** was produced. Also in this case the stereochemistry was highly sensitive to the temperature, almost exchanging the *syn*-*anti* ratio from −20 °C to room temperature.

In summary, we present a new, highly stereoselective use of the intramolecular Nicholas reaction using epoxides as nucleophiles leading to substituted 6 and seven-membered oxacycles in good yield. Regioselectivity in the cyclization relies on the distance between the epoxide and the propargylic cation, nature of the protecting group at the primary alcohol and reaction conditions. The stereochemistry of the reaction is controlled by the temperature and reaction time. Further application of the developed methodology addressed to the synthesis of marine natural products is currently underway.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for the new compounds and NOE studies of compounds **13**−**15**, **17**, **20**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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