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Synthesis of Hydroxymethyl Lactones and Spiroketals *via* Cyclization of Epoxy Oxacarbene Complexes

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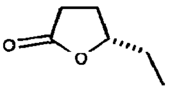
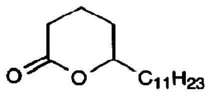
Abstract: Metal acyls containing a terminal epoxide unit undergo cyclization with $SnCl_4$ to give oxacarbene complexes that can be cleaved to hydroxymethyl lactones using pyridine *N*-oxide.

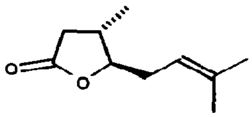
Five- and six-membered lactones are important features of many natural products, in particular insect pheromones.[1] For example, γ-caprolactone[2] and 5-hexadecanolide[3] are pheromones of the *Trogoderma* beetle and the oriental hornet, respectively. Eldanolide is the wing gland pheromone of the male African sugar cane borer.[4]



caprolactone

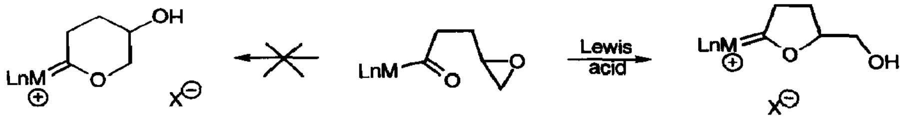


5-hexadecanolide



eldanolide

We reasoned that a general approach to precursors of lactones could be provided by an intramolecular ring closure of a nucleophilic metallo-carbene moiety onto an epoxide. The regiocontrol for a cationic cyclization depicted in Scheme 1 was anticipated to lead to the five-membered ring, given that a 5-*Exo-Tet* cyclization is favoured and a 6-*Endo-Tet* ring closure is disfavoured,[5] and assuming the absence of other factors which could be capable of inducing a preference for the 6-*Endo-Tet* process.[6,7] The preference for attack at the more substituted epoxide carbon atom during a cationic cyclization[6] would also lead to the same sense of regiocontrol.



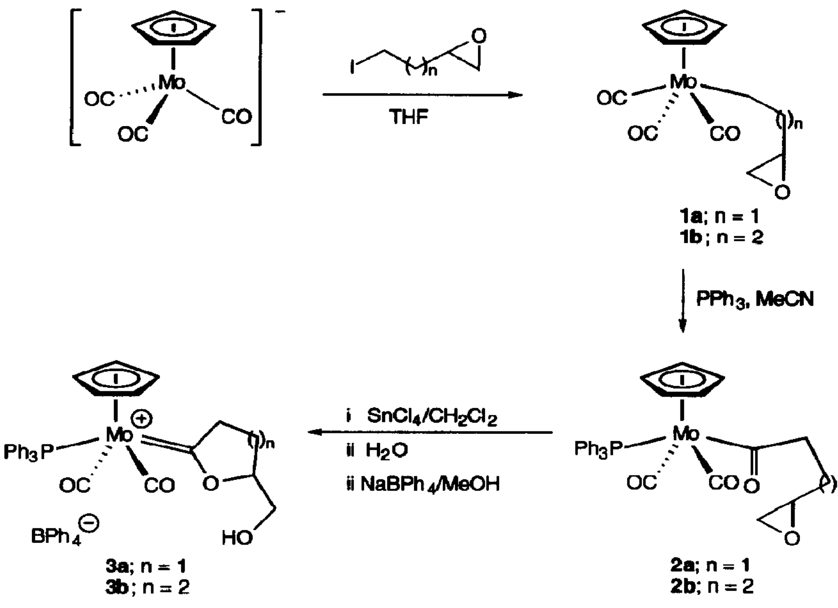
Scheme 1

The γ-hydroxymethyl-γ-butyrolactone **4a** (Scheme 3) is an intermediate in a number of syntheses of natural products[1-4,8-11] including the pheromones caprolactone,[2] eldanolide,[4] and sulcatol,[10] and was selected as an initial test of the methodology. The desired oxidative cleavage of the carbene cation complexes, an essential final step in the liberation of the lactones, was known to be viable.[12]

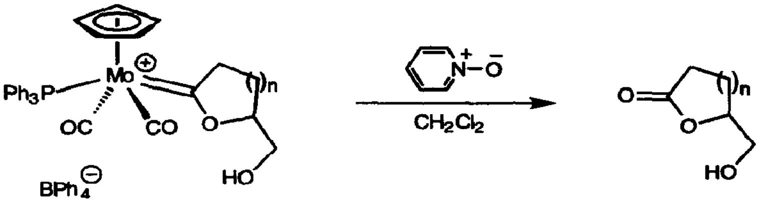
The requisite terminal iodo-epoxides were prepared from the corresponding terminal bromoalkenes by epoxidation with *m*CPBA in CH_2Cl_2 at 0°C, followed by a Finkelstein reaction. Thus, 4-bromo-1-butene was epoxidized to give 2-bromoethyloxirane (64%) which with NaI afforded 2-iodoethyloxirane (94%). Similarly, 3-bromopropyloxirane was prepared in 64% yield from 5-bromo-1-pentene, and afforded 3-iodopropyloxirane (98%) with NaI (1.5 eq.) in acetone.[13]

Reaction of those epoxides with $[Mo(CO)_3(\eta\text{-}C_5H_5)]^-$ (available through treatment of $Mo_2(CO)_6(\eta\text{-}C_5H_5)_2$ with $NaC_{10}H_8$/THF][14] proceeded as for α,ω-diiodoalkanes,[15] to give the corresponding molybdenum alkyls **1a** and **1b**, in which the epoxide function remains intact. The IR spectra of the reaction mixtures suggest clean conversion into **1a** and **1b**. However, epoxides **1** proved too unstable to isolate; they are stable in solution and were used *in situ*. Alkyl to carbonyl migrations for **1a** and **1b** were induced by PPh_3 in MeCN,[16] giving the corresponding molybdenum acyls **2a** and **2b** (46%). Complex **2a** decomposes upon workup but **2b** is isolable and fully characterized. This is notable for being an isolable metal acyl incorporating an epoxide function into the alkyl chain. In practice, solutions of both **2a** and **2b** are best prepared and used as required without isolation.

The extensive literature on cationic cyclizations using epoxide terminators[17] suggested $SnCl_4$ could be a suitable Lewis acid for the ring closures in complexes **2** to *O*-heterocycles. Reaction of the metal acyls **2a** and **2b** with $SnCl_4$ (5 eq.) in CH_2Cl_2 (0°C, 0.5 h) followed by anion exchange ($NaBPh_4$/MeOH) afforded the



Scheme 2



3a; n = 1
3b; n = 2

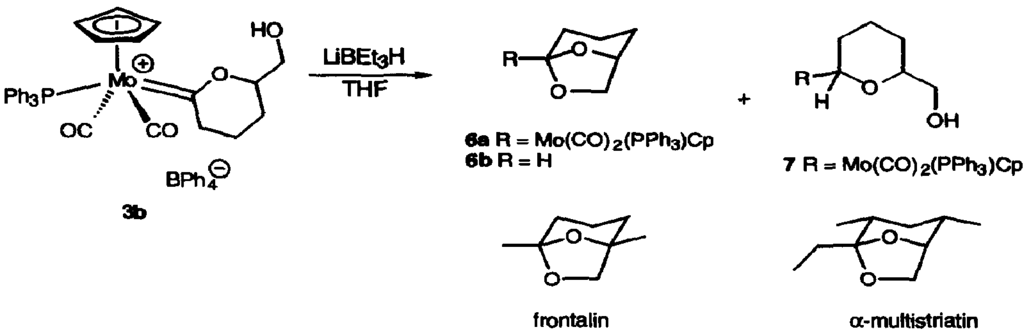
4a; n = 1
4b; n = 2

Scheme 3

oxacyclopentylidene complex **3a** [51% based upon $Mo_2(CO)_6(\eta\text{-}C_5H_5)_2$] and the oxacyclohexylidene **3b** [46% based upon $Mo_2(CO)_6(\eta\text{-}C_5H_5)_2$] respectively. Those results are consistent with a requirement of the development of positive charge in the transition state, a feature of cationic cyclizations in which nucleophilic attack occurs at the more substituted carbon atom of the epoxide ring.[6] Thus, these examples represent the first realizations of Scheme 1.

The oxoniacarbenes **3a** and **3b** were reacted with pyridine *N*-oxide (15 eq.) in CH_2Cl_2 (25°C, 4h). This smoothly effected oxidative cleavage of the molybdenum carbene bond, giving the corresponding hydroxymethyl lactones **4a** (82%) and **4b** (86%) (Scheme 3). Their solution IR spectra in CH_2Cl_2 exhibited lactonic carbonyl bands at 1775 and 1730 cm^{-1}, respectively. The corresponding reaction of cerium(IV) ammonium nitrate (2eq.) with complex **3b** in acetone provides a lesser yield of **4b** (75%) and only after 24h.

The tolerance of the functionality of **3b** to reduction was investigated by addition of $Li[BEt_3H]$[18] to a solution of **3b** in THF. This afforded the spiroketal metal complex **6a** (36%) together with the expected heteroalkyl derivative **7** (48%). Complex **6a** was also obtained (46%) by reaction of **3b** with BuLi (1.3 equiv.) in THF (-78°C, 10 min.). Complex **6a** contains the 6,8-dioxabicyclo[3.2.1]octane system which is also present in frontalin[19] and α-multistriatin,[20] pheromones of the pine beetle and the European elm bark beetle repectively. When complex **6a** was subjected to GC-mass spectrometry, a volatile component (*m/z* 114) was identified. This is consistent with formation of 6,8-dioxabicyclo[3.2.1]octane **6b** by protonolysis of the Mo—C bond in **6a**.



3b

6a R = $Mo(CO)_2(PPh_3)Cp$
6b R = H

7 R = $Mo(CO)_2(PPh_3)Cp$

frontalin

α-multistriatin

Scheme 4

The scope of cyclizations involving a transition metal acyl moiety and an epoxide is under investigation. The applicability of such cyclizations to the synthesis of natural products containing lactone or ketal units has been demonstrated and further studies are in progress.

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