giving 1.46 g of pure hendecanal (86% overall yield from the iodide).

Acknowledgment. The authors wish to express appreciation to Jenny Adams and Alice Fukushima for technical assistance.

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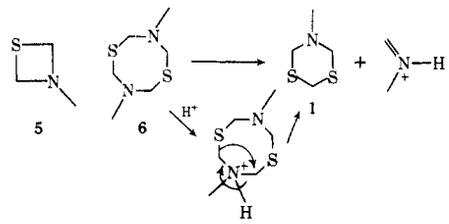
(4) The literature preparation of **1** indicates that cyclobutane **5** is formed by



reaction of formaldehyde, methylamine, and hydrogen sulfide.[3] On close examination by NMR and mass spectroscopy, this intermediate was shown to be cyclooctane **6**. This explains the facile conversion of **6** to **1**.
(5) A. I. Meyers and co-workers have noted similar problems in the alkylation of α-lithio imino esters; cf. *J. Am. Chem. Soc.*, **91**, 763 (1969).
(6) Very low yields of aldehydes were obtained using the following dithiane hydrolysis procedures: refluxing in 20% sulfuric acid [D. Collins and J. Graymore, *J. Chem. Soc.*, 9 (1957)]; Cu(I) triflate [T. Cohen et al., *J. Org. Chem.*, **40**, 812 (1975)]; and CuCl/CuO [K. Narasaka et al., *Bull. Soc. Chem. Jpn.*, **45**, 3724 (1972)].
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(8) Crystalline methiodides of **3** are easily obtained by reaction with a molar excess of clean methyl iodide in peroxide free ether.

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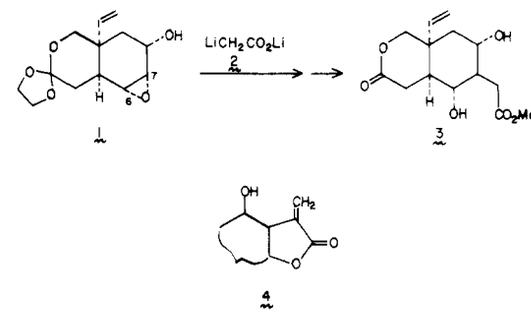
Specific Directing Effects in the Opening of Vicinal Hydroxy Epoxides

Summary: Important directing effects in the ring opening of α-hydroxy epoxides and α-trimethylsilyloxy epoxides are observed in their reactions with dilithioacetate. In reactions of the same substrates with diethylethoxyethynylalane, the key factor determining the sense of ring opening is the stereochemical relationship of the oxy function with the epoxide.

Sir: The decisive step in our recent syntheses of vernolepin and vernomenin involved the reaction of hydroxy epoxide **1** with dilithioacetate (**2**), to give, after suitable treatment, the crucial methyl ester **3**.[1-3] Within the limits of our detection, we were unable to find any product arising from attack at C_6. We thought this result to be surprising since compound **1** would be expected to exist in a preferred conformation, wherein trans diaxial opening would dictate reaction at C_6. We considered the possibility that the ortho ester linkage in **1** effectively shields axial entry at C_6, clearing the way for unencumbered attack at C_7 through a higher energy conformer (Curtin–Hammett principle).[4] Another interesting feature of the process is that the O tetrahydropyranyl derivative of **1** is not attacked by **2**, even under relatively forcing conditions.

In view of the rather wide occurrence of systems such as **4** in both cis- and trans-lactonic arrangements in natural products,[5] many of which have antitumor properties of varying degrees of promise, it was of interest to investigate a potentially straightforward method of synthesis, involving the opening of vicinal, oxygen-substituted epoxides with **2**. Surprisingly, there has been no recorded study, using compound **2**,[6] which is addressed to the attractive possibility of synthesizing systems such as **4** by a direct method of this sort.[7]



As substrates for this investigation, we have studied compounds **5**, **6**, **7**, and **8**. Compound **5** was, of course, well known from the work of Henbest.[8] Silylation of **5** with trimethylchlorosilane–triethylamine–ether at room temperature gives **6** in 81% yield.

The entry to the trans-oxy epoxide series was much facilitated by a recent disclosure of Heathcock, wherein epoxidation of 3-trimethylsilyloxycyclohexene affords **8** as virtually the sole product.[9] Cleavage of **8** with ammonium chloride gives **7**.[9] The reactions of **5**–**8** with **2** are described below.

Lithium diisopropylamide (from 20 mequiv of *n*-butyllithium and an equivalent amount of diisopropylamine) in dimethoxyethane reacted with 10 mequiv of dry acetic acid at −40 °C to generate a solution of **2**. To this solution, was added 1 mequiv of **5**. The system was heated at 55 °C for 15 h. The reaction was quenched with water. After separation of the neutral fraction (starting material) by extraction, the acids were isolated by acidification and extraction. The total acid fraction was heated with *p*-TsOH in benzene and the resultant lactones were readily purified by chromatography on silica gel, using 1:1 ethyl acetate–hexane for elution. There was thus obtained, in 66% combined yield,[10] the homogeneous lactones **9** and **10** in a 3:1 ratio (Scheme I).

When the same reaction was conducted on silyl ether **6**, compounds **9** and **10** were obtained in a ratio of 1:3.2. The structures of the lactones were supported by C and H analysis and infrared and mass spectra: for **9** $\bar{\nu}$ ($CHCl_3$) 1770 cm^{-1}, *m/e* 156 (parent); for **10** $\bar{\nu}$ ($CHCl_3$) 1795 cm^{-1}, *m/e* 156 (parent). Each compound gave a monoacetate (*m/e* 198) with pyridine–acetic anhydride. The NMR spectra ($CHCl_3$) of the two acetates, **9a** and **10a**, readily allowed for their decisive differentiation.[11] In **9a**, both the acetoxy and *O*-lactonic methine protons give rise to a doublet of triplets [δ 3.85 (lactonic methine, J_d = 4.0 Hz, J_t = 11.0 Hz), 4.75 (acetoxymethine J_d = 3.8 Hz, J_t = 11.5 Hz)]. This reflects two virtually equal axial–axial couplings and one axial–equatorial coupling for each proton. Accordingly, the three hydrogens at the asymmetric carbons must be axial—a situation embraced in **9a**. In the isomeric acetoxylactone, the lactonic methine (δ 3.88) is seen as a doublet of doublets (J_1 = 2.8 Hz, J_2 = 11.0 Hz) while the acetoxy-bound methine proton gives rise to a multiplet ($h_{1/2} \sim 7$ Hz). It may be safely concluded that his proton is predominantly equatorially disposed, while the lactonic methine hydrogen is axial. Thus, compounds **9** and **10** both arise from inversion of configuration of the epoxide by anion

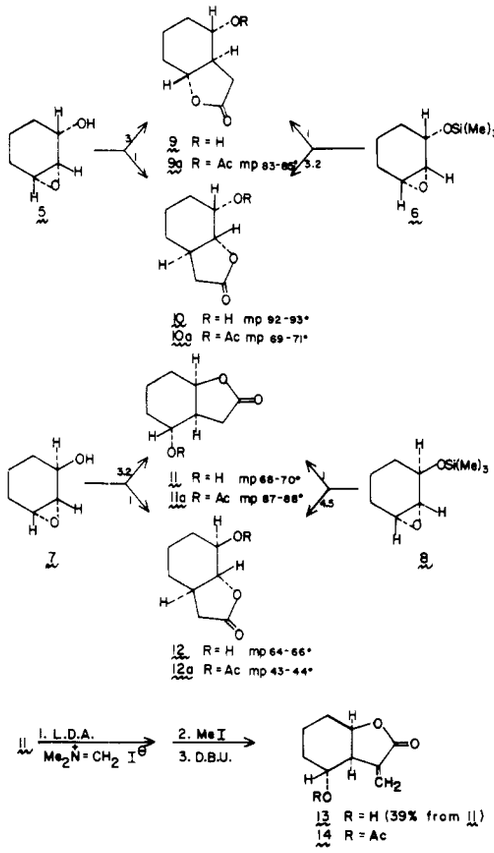
2, but differ in the site of attack and hence the relationship of the hydroxyl and lactonic groups.

Similar reactions were conducted on the trans-hydroxy epoxide **7** and its silyl ether **8**. Compound **7** afforded a 61% yield of a 3.2:1 ratio of homogeneous lactones **11** and **12**, whereas **8** afforded a 50% yield of the same lactones, now in a 1:4.5 ratio. The gross formulae of **11** and **12** were supported by their carbon–hydrogen combustion analyses, in addition to their infrared and mass spectra. The structures of **11** and **12** were, as before, most convincingly established from the NMR spectra of their respective acetylation products, **11a** and **12a**.[11]

In compound **11a**, the lactonic and the acetoxy-bound proton signals overlap, giving a 2 H multiplet centered at δ 4.68 ($H_{1/2}$ 16 Hz). The displacement to lower field, of methine hydrogens bound to the oxygen of a cis-γ-lactone, relative to that found in the corresponding trans system, has been noted in a variety of stereoisomeric γ-lactones.[12] In compound **12a**, the oxygen-bound proton of the trans-fused γ-lactone gives rise to a triplet (J = 10.0 Hz), centered at δ 3.83 ppm, while the acetoxy-bound proton is seen as a doublet of triplets at δ 4.75 (J_d = 5.2 Hz, J_t = 12. 0 Hz). Thus, the two critical methine hydrogens are primarily axial and the stereochemistry is fully defined. Again, compounds **11** and **12** are thus positional isomers, each arising from inversion of configuration in the epoxide opening step.

Structural corroboration was achieved for compound **11**. This compound was converted to its α-methylene derivative, **13**, mp 46–48 °C, without protection of the hydroxyl group, using our new method of α-methylenation.[2] Compound **12**, upon acetylation gave **13**, mp 86–87 °C. The 270-MHz NMR spectrum of **13**, thus produced, was identical with that of authentic sample (mp 87–88 °C) previously prepared by Ziegler and associates by their elegant solvolysis reaction.[13a]

Scheme I. Reactions of α-Oxygenated Epoxides with Dilithioacetate



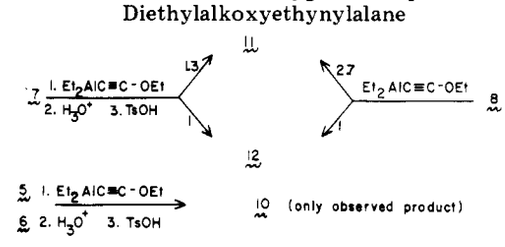
The major products in the cases of silyl ether **6** and hydroxy epoxide **7** may be rationalized in terms of trans-diaxial opening of a conformer in which the bulky substituents are disposed equatorially. However, such an analysis leads to formulations contrary to observation in the cases of **5** and **8**, and is apparently of little predictive value. What emerges from these dianion reactions is that the stereochemistry of the epoxide relative to the adjacent oxygen is not of decisive influence. The key factor seems to be the nature of the α oxygen. When this is originally hydroxyl, the nearest bond of the epoxide is displaced. When this is an trimethylsilyl ether, the remote epoxide bond is preferentially severed.

Recently we have developed a mild method for the conversion of cyclohexane oxides into trans-fused γ-lactones using diethylethoxyalkynylalane.[13b] It was therefore of interest to determine the course of this reaction in the presence of neighboring oxygen functionality. Toward this end, we studied the opening of epoxides **5**–**8** with the alane reagent. Reactions were conducted in toluene, from −40 °C to room temperature as previously described. For purposes of analysis, the resultant trans ethoxyalkynylcarbinols were directly converted to the corresponding ethyl esters by treatment with aqueous HCl–THF.[13b] These suffered lactonization with p-TsOH–benzene under reflux for 16 h. The results are shown in Scheme II. The yields of the final lactones were in the range of 50 to 60%.

It will be noted that the reaction course in the alane opening depends largely on the stereochemical relationship of the oxy function and the epoxide, and only to an insignificant extent on whether the oxygen is initially in the form of a hydroxyl or a trimethylsilyl ether. *These results are opposite to those in the dianion case, wherein the nature of the oxygen, rather than its stereochemical relationship with the epoxide, appears to be decisive.*

The openings of **5** and **6** by the alane reagent may be interpreted in terms of trans-diaxial opening of the epoxide, assuming a preferred equatorial conformation of the neighboring oxygen substituent. In these cases, the alane is not reacting under a directing influence by the neighboring oxygen, since attack occurs trans to the oxygen. The reaction course in the case of **7** and **8** may be interpreted in terms of competing forces. Attack nearest the oxygen would be favored on conformational (trans diaxial) considerations, while remote attack would possibly be favored on the grounds of steric hindrance. There is no clear evidence for a directing influence from the proximate oxygen, though this can not be ruled out.

Scheme II. Reactions of α-Oxygenated Epoxides with Diethylalkoxyethynylalane



In the dianion reactions, it would appear that the neighboring hydroxyl, now undoubtedly present as an alkoxide, provides a guidance for ring opening at the adjacent epoxide center in both the cis and trans series. This may well be the consequence of energy lowering solvation possibilities between the metal alkoxide and the attacking dianion.

It should be emphasized that, although the ability of a hydroxyl group to participate in, and direct, the course of epoxide openings has been documented in some recent studies,[14–16] these pertain only to the free hydroxyl which is cis to

the epoxide. The specificity in the case of **2**[17] undoubtedly involves the alkoxide, rather than the free alcohol, and is operative in both the cis and trans series. A pertinent analogy is seen in the work of Fried, wherein a remote hydroxyl (presumably as the alkoxide) is efficacious in directing epoxide opening by an organoalane.[18,19] In the cases studied here (**7** and **8**), one can not clearly discern such an effect, though it may be operative as one of several competing forces.

There emerges from our data an empirically based approach for the construction of variations of system **4** with complete stereospecificity and acceptable regioselectivity by utilization of suitable organometallic equivalents of $^{-}CH_2CO_2H$. The feasibility of using this methodology in total synthesis contexts is receiving continuing attention.

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(10) In our experience, the yields of epoxide openings using the Creger method[6] do not exceed 70% even with very simple substrates. The virtue of the method is that the reagent is quite stable to temperatures up to 60–70 °C where this becomes necessary. However, for reasons not yet understood, substantial starting material is recovered even with copious excesses of reagent and long reaction times.
(11) NMR analysis of the parent alcohols gives the same conclusions. However, in the three compounds which have trans-fused γ-lactones, the carbinol methine proton signal overlaps with that arising from the oxygen-bound lactonic methine.
(12) This trend has been noted in a variety of cis- and trans-fused γ-lactones with and without α-hydroxyl groups. The oxygen-bound lactonic methine proton absorbs in the region δ 4.6–5.0 ppm while that of the trans series absorbs in the region 3.8–4.1 ppm. This is the case in seven sets of isomers which we have prepared.
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(17) In the case of compound **1** the total regiospecificity must involve factors in addition to alkoxy participation. The shielding effect of the axial bond of the ortho ester would appear to be a reasonable explanation. This would account for the failure of **1** tetrahydropyranyl ether to react at all, since the expected mode, based on compound **6**, would occur at carbon **6**. For a possibly related case, in the synthesis of luciduline, see W. L. Scott and D. A. Evans, *J. Am. Chem. Soc.*, **94**, 4780 (1972).
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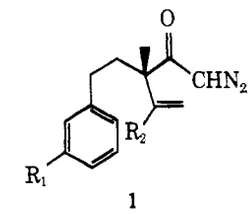
β,γ-Unsaturated Diazo Ketones. A New Initiator for Polyolefinic Cationic Cyclization

Summary: The synthetic utility of β,γ-unsaturated diazo ketones as initiators for polyolefinic cationic cyclization is described.

Sir: Recently, we have demonstrated that β,γ-unsaturated diazo ketones are synthetically useful precursors of both simple and annulated cyclopentenone derivatives when subjected to acid-catalyzed decomposition.[1] We now wish to report that such species hold considerable potential for the initiation of polyolefinic cyclizations.[2] To our knowledge unsaturated diazo ketones have not previously been employed in this manner.[3]

In order to investigate this question, we selected diazo ketones **1a–c** which would not be expected to become involved



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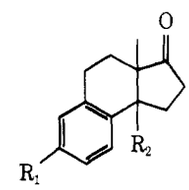

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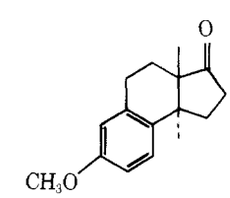

3

a, $R_1 = OCH_3$; $R_2 = CH_3$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = H$; $R_2 = H$
d, $R_1 = OH$; $R_2 = CH_3$

in complex structural rearrangements. In addition, diazo ketone **1a** appeared ideally suited for our initial study since two of the four possible tricyclic products (**2a** and **3**) have recently been prepared and their stereochemistry established rigorously by Jeger and co-workers.[4]

The required diazo ketones **1a–c** were prepared in the usual manner (oxalyl chloride, CH_2N_2) from the corresponding β,γ-unsaturated acid derivatives **4a–c**[5] readily available via alkylation of the ethyl esters of either 2,3,3-trimethylacrylic acid or tiglic acid with the tosylate ester of phenethyl or *m*-methoxyphenethyl alcohol, employing as base the lithium diisopropylamide–hexamethylphosphoramide complex in THF described recently by Rathke[6] and Schlessinger.[7] Subsequent hydrolyses of the resultant esters (5% aqueous NaOH, 14 h) yielded **4a**[5] and **4b**[5] as crystalline solids (mp 73.5–74.5 °C and 67–68 °C, respectively), whereas **4c**[5] was obtained as a viscous oil. The overall yields based on the tosylate were 43–48%.