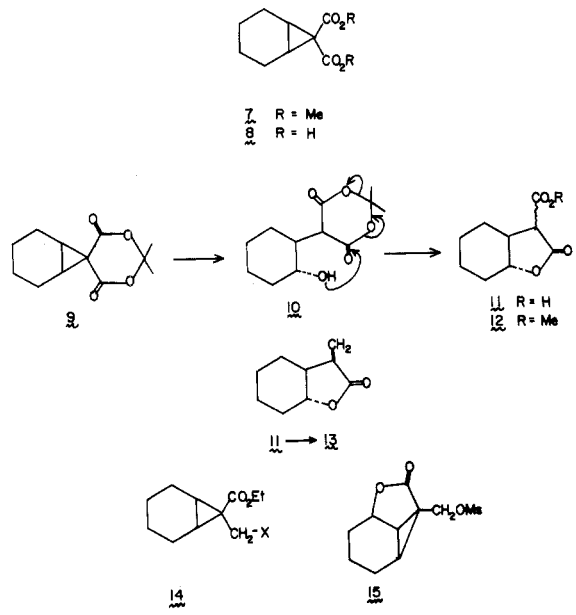


molecular capture of the electron-deficient homoallylic carbon by the proximate ester oxygen.

Ziegler[15] was the first to demonstrate inversion of configuration in the course of acetolysis of the cyclopropylcarbinyl system, **15**. While this result is potentially of considerable interest in the control of stereochemistry of oxygen functionality adjacent to α-methylenelactones,[16] we believe that the transformation of **9** → **11** represents the first instance of using activated cyclopropanes for the de novo synthesis of a γ-lactone in the trans series.

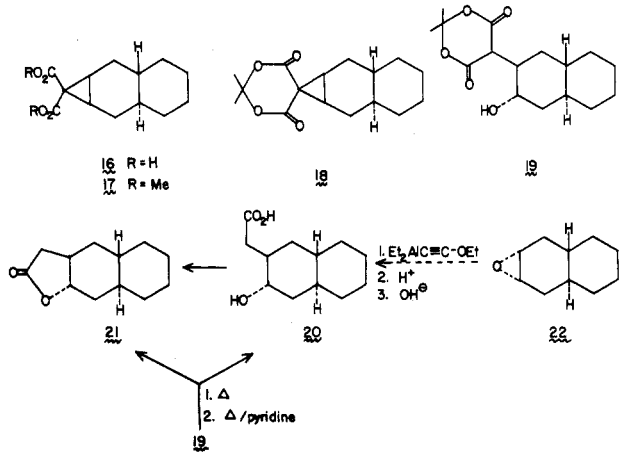
Parenthetically it will be noted that the cyclization of **10** → **11** is apparently[17] uncatalyzed and is occurring under conditions which must be regarded as quite mild for the closure of a trans-fused γ-lactone.[2] Again this is suggestive of particularly strong acylating powers of the cyclic acylal linkage.

A finer understanding of the stereochemical pathway of the solvolytic opening of spiroactivated cyclopropanes was possible in the context of the conformationally defined *trans*-decalin system, **18**. *trans*-Δ^2-Octalin was converted to the cyclopropane derivative **16**[12] (76%) by the action of dimethyl diazomalonate under the influence of copper bronze (3 equiv of diazo compound to 1 equiv of olefin, 150 °C). This was hydrolyzed to give diacid **17**, mp 195–197 °C,[12a] in 83% yield, which was converted to **18**,[12] mp 145–148 °C, in 82% yield via isopropenyl acetate.[4]

Compound **18** was heated in 1:1 acetone–water for 24 h under reflux. NMR analysis indicated the presence of two or more acidic components. Accordingly, the total reaction mixture was heated in pyridine[2] under reflux for 0.5 h thereby achieving decarboxylation. At this stage, an acidic product, identified as **20**, mp 117–120 °C (lit.[2] mp 116–117 °C), was isolated in 60% yield. A neutral product, mp 52–53 °C, shown to be Johnson's boat lactone **21** (lit.[2] 49.6 °C) was isolated in 30% yield. Although an authentic sample of **21** by the original method of synthesis[2] was not available, the lactone so produced was identical with the same compound obtained from the opening of the epoxide, **22**,[2] with diethyl ethoxyethynylalane.[18] Furthermore, **21** was also obtained by the cyclization of **20** by the method of Johnson (tosyl acid–xylene, reflux 30 min).

It is seen that a minimum of 90% of the solvolysis of **18** can be accounted for in terms of stereospecific opening of the activated cyclopropane to give trans-diaxial substitution. This is followed primarily by decarboxylation of the diacid produced by hydrolysis of the resultant acylal, **19**. To a small (but remarkable) extent, the acylal undergoes lactonization prior to the decarboxylation step with pyridine.

Application of this stereoelectronically specific conversion of fused spiroactivated cyclopropanes to trans-fused γ-lactones will be studied.



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References and Notes

(1) M. S. Newman and C. A. Vander Werf, *J. Am. Chem. Soc.*, **67**, 233 (1945).
(2) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dryer, and W. R. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).
(3) S. Danishefsky and R. K. Singh, *J. Am. Chem. Soc.*, **97**, 3239 (1975).
(4) R. K. Singh and S. Danishefsky, *J. Org. Chem.*, **40**, 2969 (1975).
(5) S. Danihsefsky and R. K. Singh, *J. Org. Chem.*, **40**, 3807 (1975).
(6) K. Nakanishi, T. Goto, S. Ito, S. Nortori, and S. Nozoe, "Natural Products Chemistry", Vol. 1, Academic Press, New York, N.Y., 1974, Chapter 3, p 39.
(7) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971).
(8) For a review of this area of synthesis, see (a) P. A. Grieco, *Synthesis*, 67 (1976); (b) R. B. Gamill, C. A. Wilson, and T. A. Bryson, *Synth. Commun.*, **5**, 245 (1975).
(9) J. Martin, P. Watts, and F. Johnson, *Chem. Commun.*, 27 (1970).
(10) B. W. Peace and D. S. Wulfman, *Synthesis*, 137 (1973).
(11) H. Musso, *Chem. Ber.*, **101**, 3710 (1968).
(12) The structure of this compound is in accord with (a) its ir, NMR, and mass spectra; (b) its C and H combustion within 0.3% of theory.
(13) E. S. Behare and R. B. Miller, *Chem. Commun.*, 402 (1970).
(14) P. F. Hudrlik, L. R. Rudnick, and S. H. Korzeniowski, *J. Am. Chem. Soc.*, **95**, 6848 (1973).
(15) F. E. Ziegler, A. F. Marino, O. A. C. Petroff, and W. L. Studt, *Tetrahedron Lett.*, 2035 (1974).
(16) For another application, see R. D. Clark and C. H. Heathcock, *Tetrahedron Lett.*, 529 (1975).
(17) Since malonic acids are almost certainly generated in this reaction these may function as acid catalysts.
(18) S. Danishefsky, T. Kitahara, M. Tsai, and J. Dynak, *J. Org. Chem.*, following paper.

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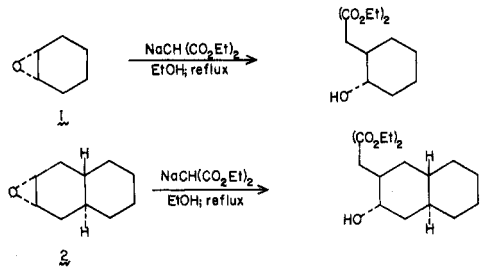
Functionalized Alanes for the Conversion of Epoxides to Trans-Fused γ-Lactones

Summary: Aluminum derivatives of *tert*-butylacetate and ethoxyacetylene have been shown to be useful for the opening of oxidocycloalkanes.

Sir: In view of the large number of biologically active natural products containing trans-fused γ-lactones,[1,2] a general method of reaching such systems via oxidocycloalkanes could be useful. The traditional route involves the opening of an

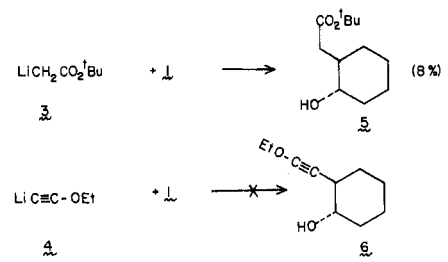
epoxide with an equivalent of carbanionic acetate and lactonization after suitable unravelling.

The usual nucleophile employed in such epoxide openings is malonic ester enolate.[3,4] Such ring openings [cf. cyclohexane oxides (1)] proceed with inversion of configuration, eventually furnishing the trans relationship of OH and CH_2CO_2R required for generation of a trans-fused γ-lactone. Johnson's elegant demonstration of trans-diaxial opening of the conformationally definable 2,3-oxido-*trans*-decalin[4] (2) provides further stereochemical insight into this reaction. However, a major weakness of the malonic ester enolate method of epoxide openings is the rather harsh conditions required even with unencumbered substrates such as **1** and **2**. Thus, it is not surprising that this method has not been successfully employed with more complicated epoxides.



Other carbanionic acetate equivalents have been employed in epoxide openings. Dilithio trimethylsilylacetate reacts with simple epoxides but appears to fail to open compound **1**.[5] Dilithio thiophenylacetate does open compound **1** but in rather modest yield.[6] Dilithio acetate itself may have potential with more hindered epoxides, though the yield of opening of compound **1**, even under relatively forcing conditions, is somewhat discouraging.[7,8]

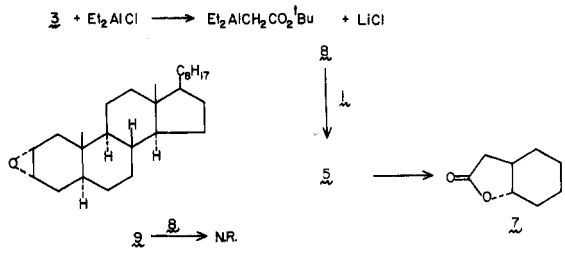
The first phase of our study involved the attempted reaction of lithium *tert*-butylacetate (Rathke's salt **3**)[9] and lithium ethoxyacetylide (**4**) with compound **1**. In our hands, the reaction of **3** + **1** afforded compound **5** in a maximum of 8% yield (toluene, room temperature, 12 h). The use of the more polar solvent, dimethoxyethane (DME), furnished only a 5% yield. The results of the reaction of **1** and **4** were even more discouraging in that no detectable amounts of **6** were noted.[10]



In view of the impressive success recorded by the Fried school in the opening of hindered epoxides with dialkylalkynylalanes,[11,12] it was of interest to study the application of this technology to the problem at hand. Treatment of 2.5 equiv of **3** with 2.5 equiv of diethylaluminum chloride in toluene (3 ml/mmol of lithium salt) at −40 °C led to the instantaneous deposition of lithium chloride. Reaction of this system, maintained at −30–40 °C for 6 h, with **1** gave a 34% yield of **5**.[13] The stereochemistry of **5** was demonstrated by its transformation to the known[3] **7** in 85% yield upon reaction with tosyl acid/benzene under reflux for 15 h.

Since there is no reaction between **1** and **3** under these conditions, and, in view of the method of formation,[11] it seems reasonable to conclude that the active specie is, in fact, diethylcarbo-*tert*-butoxymethylalane (**8**). The yield of **5** was raised to 68% by allowing the reaction mixture containing **1** and **8** to warm to ambience where it was maintained for 6 h.

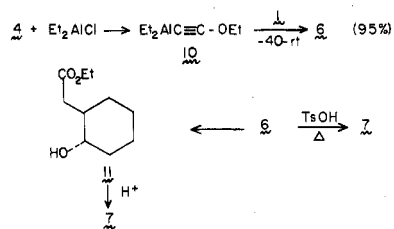
Although the chemistry of this interesting aluminum enolate[14] remains to be explored, this reagent does not constitute a satisfactory general acetic acid equivalent for opening hindered epoxides. For instance, attempted reaction of **8** with 2,3-oxido-α-cholestane (**9**) fails, leading to 86% recovered epoxy steroid. Attempts to increase reactivity by heating led to apparently rapid decomposition of the organometallic system.



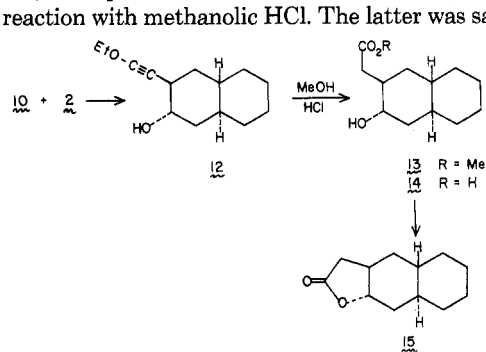
Treatment of lithium ethoxyacetylide (2.5 equiv, generated from the reaction of 2.5 equiv of *n*-butyllithium in hexane with 2.5 equiv of ethoxyacetylene) with 2.5 equiv of diethylchloroalane in toluene at −40 °C (2 ml/mmol of lithium salt) again led to the deposition of lithium chloride. Treatment of **10**, so produced, with **1**, from −40 to −30 °C for 6 h, followed by quenching with aqueous sodium bicarbonate at that temperature, gave, after chromatography on silica gel, a 66% yield of *trans*-2-ethoxyethynylcyclohexanol[13] (**6**) and 5% *trans*-2-carbethoxymethylcyclohexanol (**11**).[13a,15] The yield of the process was substantially improved (80% **6** and 10% **11**) by allowing the temperature of the reaction of **10** and **1** to warm from −40 °C to ambience, where it was maintained for 6 h. If analytically pure **6** is not needed, the crude yield of essentially pure compound is 95%.

The stereochemistry of **6** was demonstrated by its conversion (88%) to **7** upon reaction with tosyl acid toluene under reflux. The mechanism of this transformation has not been determined. There may be enough water present to effect the conversion of **6** → **11** and the latter may be the active acylating specie. Alternatively, cyclization of **6** may give a cyclic ketene acetal which is cleaved by aventitious water. Finally, **6** may suffer protonation followed by de-ethylation to give a ketene. The latter could well cyclize to give the observed **7**.

Alternatively, treatment of **6** with ethanolic HCl afforded a quantitative yield of **11**. The latter was converted in 90% yield to **7** by the action of tosyl acid–benzene under reflux.

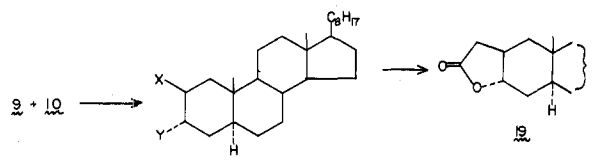


A clear trans-diaxial pathway was demonstrated in the reaction of **10** with **2**. There was produced an 80% yield of ethoxyethynylcarbinol **12** after 15 h (−40 °C to room temperature). Compound **12** was converted to *methyl* ester **13**[16] upon reaction with methanolic HCl. The latter was saponified



with methanolic KOH to give the known acid,[4] **14**, mp 114–116 °C which was converted to the known[4] boat lactone system **15**, mp 49–51 °C (lit.[4] 49.6 °C). No evidence for the formation of stereoisomers of **13** could be detected.

Reaction of **10** with 2,3-oxido-α-cholestane (**9**) under these conditions gave a 63% yield of **16**,[13] mp 92–93 °C, $[\alpha]$D ($CHCl_3$) +4.7°. The epoxide was recovered to the extent of 15%. The diaxial nature of **16** was confirmed through the NMR spectrum[17] of its derived acetate, **17**,[13a] mp 112–114 °C. Treatment of **17** with methanolic HCl gave the methyl ester **18**,[13,16] mp 163–164 °C, $[\alpha]$D ($CHCl_3$) +32.0°, in 85% yield. The latter was converted to the pentacyclic steroidal lactone **19**,[13a] mp 165–167 °C, $[\alpha]$D ($CHCl_3$) +31.7°, in 73% yield by the forcing conditions of Johnson[4] (tosyl acid–xylene, reflux).



9 + 10 → 19

16 X = C≡C-OEt; Y = OH
17 X = C≡C-OEt; Y = OAc
18 X = CH_2CO_2Me; Y = OH

It is thus seen that this method of cleavage occurs in a stereoelectronically specific trans-diaxial fashion. The efficacy and stereoelectronic specificity of the method are not seriously disrupted by a 1,3-diaxial interaction with an angular methyl group. Other applications of these aluminum bound synthetic equivalents of acetic acid carbanion are currently under investigation.

Acknowledgments. This research was supported by PHS Grant CA-12107-12. NMR services were maintained on instrumentation supported by RR-00292-06. Support from the Hoffmann-La Roche Company is gratefully acknowledged.

Supplementary Material Available. Experimental procedures for these reactions (6 pages). Ordering information is given on any current masthead page.

References and Notes

(1) K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nozoe, "Natural Products", Vol. 1, Academic Press, New York, N.Y.–Tokyo, 1974, Chapter 3.
(2) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971).
(3) M. S. Newman and C. A. Vander Werf, *J. Am. Chem. Soc.*, **67**, 233 (1945).
(4) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dryer, and W. R. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).
(5) P. A. Grieco and C. L. Wang, *J. Chem. Soc., Chem. Commun.*, 714 (1975).
(6) K. Iwai, M. Kawai, H. Kosugi, and H. Uda, *Chem. Lett.*, 385 (1974).
(7) P. L. Creger, *J. Org. Chem.*, **37**, 1907 (1972).
(8) T. Fujita, S. Watanabe, and K. Suga, *Aust. J. Chem.*, **27**, 2205 (1974).
(9) M. W. Rathke and D. F. Sullivan, *J. Am. Chem. Soc.*, **95**, 3050 (1972).
(10) For the successful reaction of lithium ethoxyacetylide with simple terminal epoxides, see J. Link, P. Vermeer, J. G. Kooiman, J. Meijer, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **93**, 92 (1974).
(11) (a) J. Fried, C. H. Lin, and S. H. Ford, *Tetrahedron Lett.*, 1379 (1969); (b) J. Fried and J. C. Sih, *ibid.*, 3899 (1973).
(12) The first preparation of an alane derivative of ethoxyacetylene was achieved in the laboratories of Professor Fried. The reagent was used in a successful opening of cyclopentane oxide. This successful reaction was described by J. Fried, M. Mehra, C. Lin, W. Kao, and P. Dalven in the *Ann. N.Y. Acad. Sci.*, **180**, 38 (1971). The resultant *trans*-ethoxyethynyl functions was converted to CH_2CHO by partial reduction of the triple bond followed by hydrolysis of the resultant enol ether. We thank Professor Fried for apprising us of his experimental procedures.
(13) The structure and homogeneity of this compound was established by (a) its *ir*, NMR, and mass spectra; (b) C and H combustion analysis was within 0.4% of theory.
(14) For the generation of aluminum enolates by the $Ni(acac)_2$-catalyzed conjugate addition of trimethyl aluminum to enones, see E. A. Jeffrey, A. Meisters, and T. Mole, *J. Organometal. Chem.*, **74**, 365 (1974).
(15) Compound **11** is an artifact produced on chromatography of the labile ethynyl ether **6**.
(16) We have found that treatment of the *trans*-2-hydroxyethynyl ethers **12** and **16** with ostensibly anhydrous HCl–methanol gives cleanly the methyl esters. We are, at present, unable to define the mechanism of this transformation. It may involve the presence of adventitious water, leading to a mixing of methyl and ethyl esters followed by transesterification of the latter in favor of the former. Alternatively, it may be the consequence of protonation followed by demethylation giving rise to a ketone intermediate. The latter is then captured by the solvent, methanol, to give the observed methyl ester. In any case, it is a useful method for transforming ethoxyethynyl ethers, arising from the commercially available ethoxyacetylene, into methyl esters which tend to be more easily crystalline and more readily amenable to NMR analysis.
(17) The resonance of the methine proton at C_3 in compound **16** is obscured by overlap with the methylene protons of the ethoxy group. However, in the derived acetate **17** the resonance ($CDCl_3$) is seen as a multiplet centered at δ 5 ppm with a line width at half-height of 5 Hz, clearly indicative of an equatorial proton. The β stereochemistry of the X group in compounds **16–18** follows from inversion of the α stereochemistry of the epoxide.

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Carbon-13 Magnetic Resonance. Downfield Shifts Induced by $M(CH_3)_3$ (M = Si, Ge, Sn, Pb) at the γ Position and Antiperiplanar to the Carbon-13 Center

Summary: Carbon-13 NMR spectra of certain cycloalkyl derivatives of group 4B have been obtained, and the chemical shifts of γ carbons are discussed in terms of geometrical array and possible electronic interactions.

Sir: The γ effect (the usually *upfield* shift of a resonance for a carbon-13 nucleus gauche to another carbon or heteroatom at the γ position) is generally ascribed to steric compression which polarizes the C–H bonds causing shielding of the carbon nucleus.[1] When heteroatoms are incorporated, it was recognized[2–4] some years ago that significant upfield γ shifts may occur when such heteroatoms are anti to the carbon nucleus. More recently, Eliel and co-workers[5] established that a carbon nucleus anti to a second row heteroatom (N, O, F) in the γ positions generally resonates at higher field than when anti to methyl or methylene. The nature of this shielding mechanism is not established, but Eliel[5] favored interaction of free electron pairs (on N, O, F) with the C_α–C_β bond, resulting in a type of "conjugative" transfer of electron density to the C_γ region. On the other hand, Heumann and Kolshorn,[6] from their studies of 2-substituted bicyclo[3.3.1]nonan-9-ones, suggested that "electronically induced" anti γ effects were associated with back-lobe overlap, as originally outlined by Grutzner and Roberts.[2] Our studies of the ^{13}C spectra of geometrically well-defined cycloalkyl derivatives of group 4B elements have provided values for the γ effects of $M(CH_3)_3$ (M = Si, Ge, Sn, Pb) in gauche and antiperiplanar arrays. These data are particularly pertinent to the mechanism of the anti γ effect, but also make available a further assignment criterion for the spectra of the group 4B derived systems.

The chemical shift data for cyclohexyl[7] and certain norbornyltin compounds[8] are assembled in Table I, together with relevant information on the bicyclo[2.2.2]octyltin system.[9] The values in parentheses are the substituent chemical shifts and the γ effects are italicized. For the tin compounds, the γ effects are substantially downfield in anti arrangements (where steric compression cannot be important) and largest at C_6 in the *exo*-2-norbornyl compound (+3.9 ppm). Where steric compression is operative, e.g., in the axial conformer[7] of cyclohexyl trimethylstannane, the γ effect is upfield, perhaps as expected. The γ effect of $Sn(CH_3)_3$ attached to a bridgehead position (in the bicyclo[2.2.2]octyl system) is still significantly downfield (+2.4 ppm), in contrast to the observation[5] that the normally upfield anti γ effect of fluorine becomes downfield in such a situation.[10]

The equatorial cyclohexyl derivatives[11] of group 4B exhibit anti γ effects that are significantly downfield, i.e., from +0.8 ppm for $C(CH_3)_3$[4] to +3.06 ppm for $Pb(CH_3)_3$. It is instructive