The pathway to the 1,3-diazepines **7** from the 1,2-diazepine **5** must involve the bicyclic valence isomers **8** and **10** (Scheme I). Analogous steps have been postulated[8,12] for the formation of 2-arylbenz[*d*]-1,3-oxazepines with the photoisomerization of 2-arylquinoline 1-oxides; however, benzo[*d*]-1,3-diazepines are not observed in the analogous reactions of quinoline-1-acylimides.[13,14] The fact that products of type **6** or **7** have not been observed in thermal reactions of other 1-benzoyldiazepines suggests that the acetoxy group of **5** is an important factor in the mechanism. A possible role is stabilization of a dipolar intermediate such as **9**, which could give rise to **6** and **10** by well precedented steps.

Experimental. A solution of **5** in toluene was kept at 110 °C for 40 min. After removal of solvent, the NMR spectrum of the solid residue indicated a mixture of two products in a 6:4 ratio. Fractional crystallization of the mixture from CH_2Cl_2–ether gave the main product (50% yield) as white crystals: mp 169–170 °C; IR ν (KBr) 3300, 1755, 1650; NMR δ ($CDCl_3$) 1.97 (s, 3), 2.38 (s, 3), 7.2–7.7 (m, 10), 7.82 (br, 1), 8.33 (s, 1); anal.[9] This compound was identified as the 6-benzamido-3-acetoxypyridine **6** by mild alkaline hydrolysis to the known 6-benzamido-3-hydroxypyridine.[10] The more soluble fractions were recrystallized several times from ether and benzene to give the 1,3-diazepine **7** as large, faceted prisms: mp 146–147 °C; IR ν (KBr) 1760, 1670, 1635; NMR δ ($CDCl_3$) 1.75 (s, 3), 2.28 (s, 3), 6.7–7.7 (m, 12); anal.[9]

Crystallography. Crystals of **7** were orthorhombic, space group *Pbca*, with $a = 25.029$ (9), $b = 10.123$ (6), and $c = 14.191$ (6) Å; $d_{calcd} = 1.28$ g cm^{-3} for $Z = 8$.

Intensity data were obtained with Mo Kα radiation with scan rate of 1°/min over a range of 1.75° plus Kα_1 – Kα_2. A total of 2345 reflections were measured, with 2093 observed. No absorption correction was made. The structure was solved by tangent refinement techniques using the ORTEP program to find a possible molecule from several *E* maps. Subsequent cycles of least-squares refinement located all nonhydrogen atoms with anisotropic temperature factors.[11] Hydrogen positions were calculated and were not refined. Further refinement led to a final $R = 0.083$ and $R_w = 0.071$ where $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_w = [\Sigma_w(|F_o| - |F_c|)^2/\Sigma_w|F_o|^2]^{1/2}$. A final difference map encompassing the atoms of the seven-membered ring showed no electron density greater than 0.5 e/Å^3. A stereoscopic view of **7** is shown in Figure 1.

Acknowledgment. We are most grateful to Dr. Lloyd Guggenberger, E. I. du Pont de Nemours and Co., for providing the diffractometer data used in the crystallographic analysis.

Supplementary Material Available: Table of positional and thermal parameters for the structure of **7** (2 pages). Ordering information is given on any current masthead page.

References and Notes

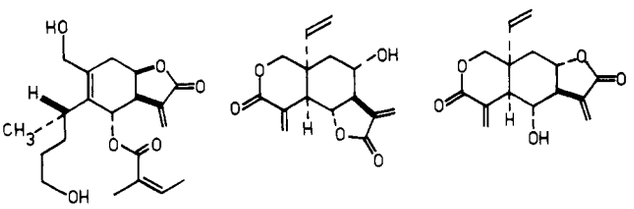
(1) For a recent review of the preparation and reactions of 1,2-diazepines (140 references), see M. Nastasi, *Heterocycles*, **4**, 1509 (1976).
(2) J. Streith and J. M. Cassal, *Bull. Soc. Chim. Fr.*, 2175 (1969).
(3) G. Kan, M. T. Thomas, and V. Snieckus, *Chem. Commun.*, 1022 (1971).
(4) J. Streith, J. P.Luttringer, and M. Nastasi, *J. Org. Chem.*, **36**, 2962 (1971).
(5) M. Nastasi and J. Streith, *Bull. Soc. Chim. Fr.*, 635 (1973).
(6) J. A. Moore, W. J. Freeman, K. Kurita, and M. G. Pleiss, *J. Org. Chem.*, **38**, 2939 (1973).
(7) T. Mukai and H. Sukawa, *Tetrahedron Lett.*, 1835 (1973).
(8) O. Buchardt, B. Jensen, and I. K. Larsen, *Acta Chem. Scand.*, **21**, 1841 (1967).
(9) Satisfactory analytical values (±0.4% for C, H, N) were obtained.
(10) J. A. Moore, R. L. Wineholt, F. J. Marascia, R. W. Medeiros, and F. J. Creegan, *J. Org. Chem.*, **32**, 1353 (1967).
(11) Structural refinements were carried out with the "X-ray '70" programs of J. M. Stewart, F. A. Kundell, and J. C. Baldwin, University of Maryland.
(12) G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **70**, 257 (1970).
(13) Y. Tamura, S. Matsugashita, H. Ishibashi, and M. Ikeda, *Tetrahedron*, **29**, 2359 (1973).
(14) T. Tsuchiya, J. Kurita, and V. Snieckus, *J. Org. Chem.*, **42**, 1856 (1977).

James A. Moore,* Walter J. Freeman
Richard C. Gearhart, Howard B. Yokelson
Department of Chemistry, University of Delaware
Newark, Delaware 19711
Received October 28, 1977

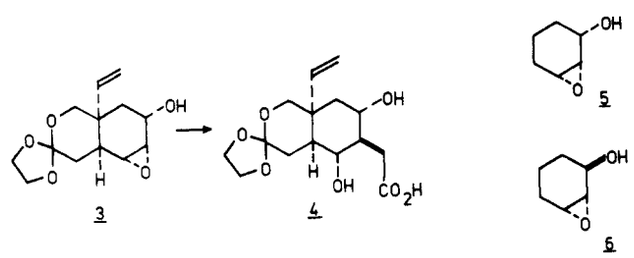
Ring-Opening Reactions of α-Oxy Epoxides with *tert*-Butyl Dilithioacetoacetate

Summary: tert-Butyl dilithioacetoacetate has been employed in ring-opening reactions of certain α-hydroxy epoxides and α-methoxymethyloxy epoxides. The regiochemical nature of ring opening for this dinanion is essentially the same as that previously observed for dilithioacetate. A notable exception, however, was observed with an α-methoxymethyloxy epoxide bearing a geminal dialkyl substituent at the α′ position. This substance was found to regiospecifically open to the corresponding 1,3-dioxy system.

Sir: The occurrence in nature of antitumor agents such as eriolangin (**1**) and vernolepin (**2**) which contain either cis- or trans-lactone arrays bearing an α-hydroxy group has prompted the experimental consideration of elaborating such systems by the vehicle of ring opening of α-oxygen substituted epoxides with an appropriate nucleophile. In a brilliant series of investigations, Danishefsky and co-workers succeeded in this regard with the ring opening of the α-hydroxy epoxide **3** with dilithioacetate to realize formation of the acid diol **4**, subsequently converted into both vernolepin and vernomenin.[1] In addition, these authors have also studied the dilithioacetate induced ring opening of the simple α-hydroxy epoxides **5** and **6** together with their trimethylsilyloxy analogues.[2]

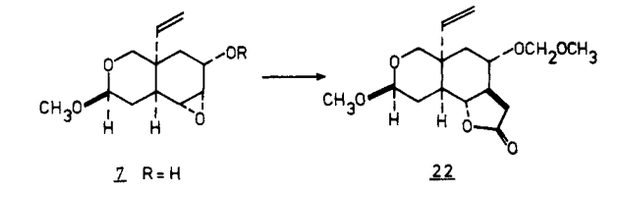


1 Eriolangin **2** Vernolepin **8** Vernomenin



3 **4** **5** **6**

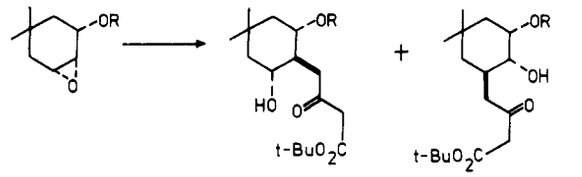
Recently, we attained the same synthetic juncture in our synthesis of vernolepin which required regiospecific ring opening of the α-hydroxy epoxide **7**. We were, however, interested in using an alcohol-protected form of **7** to realize the exclusive formation of vernolepin as opposed to the concurrent construction of both vernolepin and its biologically less active isomer vernomenin (**8**). Taking cognizance of Danishefsky's results, which indicated that α-trimethylsilyloxy epoxides would either not react or would open predominantly in the undesired manner,[1,2] we nevertheless examine the feasibility of preparing vernolepin by ring opening of the α-methoxy-



7 R = H **22**
9 R = CH_2OCH_3

0022-3263/78/1943-0788$01.00/0

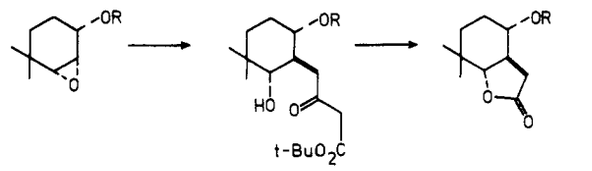
methyloxy epoxide **9**. Compound **9** was obtained from **7** by reaction of the latter with chloromethyl methyl ether.[3] Not surprisingly, reaction of **9** with dilithioacetate gave only unreacted epoxide even under forcing conditions. This result brought us to the conclusion that use of **9** in a vernolepin synthesis would require a more energetic nucleophile for epoxide ring opening. We thus set out to examine the ring opening of the model α-hydroxy epoxides **10**[4] and **11**[4] as well as their α-methoxymethyloxy analogues with *tert*-butyl dilithioacetoacetate.[5] Compound **10**, on reaction with 3 equiv of *tert*-butyl dilithioacetoacetate[6] for 2 h at 22 °C, gave in 90% yield a 3:1 mixture of compounds **12** and **13**, respectively.[7] The



10 R=H **12** R = H **13** R = H
14 R=CH_2OCH_3 **15** R = CH_2OCH_3 **16** R = CH_2OCH_3

α-methoxymethyloxy epoxide **14** gave a 1:5 mixture of compounds **15** and **16** under the same conditions.[7] These results parallel those obtained by Danishefsky.[2]

The α-hydroxy epoxide **11**, on the other hand, gave a 70% yield of the adduct **17** with no detectable regioisomeric product when treated with 5 equiv of *tert*-butyl dilithioacetoacetate for 24 h at 22 °C. Even more gratifying was the finding that the α-methoxymethyloxy epoxide **18**, on reaction



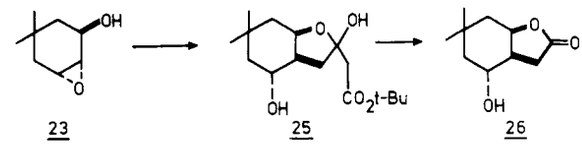
11 R=H **17** R = H **20** R=CH_2OCH_3
18 R=CH_2OCH_3 **19** R = CH_2OCH_3 **21** R = H

with 7 equiv of *tert*-butyl dilithioacetoacetate for 7 h at 22 °C, gave a 97% yield of the desired adduct **19**. The steric buttressing effect of the geminal dimethyl group adjacent to the epoxide clearly enhances the desired regiospecificity of this reaction and completely overwhelms the counter directive effect anticipated from the α-methoxymethyloxy moiety.

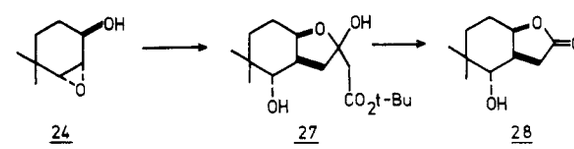
Use of *tert*-butyl dilithioacetoacetate for these ring-opening reactions introduces four carbon atoms instead of the desired two atoms; thus, it was imperative for us to develop a means of transforming products such as **19** into the desired lactonic substances. To this end, a second-order Beckmann rearrangement was applied to **19** in which the β-keto ester was treated first with isoamyl nitrite and potassium *tert*-butoxide in *tert*-butyl alcohol and second with acetic acid, sodium acetate, and acetic anhydride to afford, after chromatography and crystallization, the lactone **20** (mp 55–56 °C) in 62% yield.[8] Treatment of **20** with perchloric acid in acetonitrile gave the corresponding lactone alcohol **21** (mp 95–97 °C) in 65% yield.[9] This reaction sequence constitutes a regiospecific synthesis of an unsymmetrically substituted lactone system of this type by an epoxide ring-opening process.

Encouraged by these results, which we felt represented a reasonable model for our vernolepin intermediate, we then reacted **9** with *tert*-butyl dilithioacetoacetate. The resulting adduct subjected to the Beckmann degradation sequence gave the lactone **22** (mp 158–160.5 °C) in 65% overall yield.[10]

At this point we were curious as to the course of reaction between *tert*-butyl dilithioacetoacetate and the *trans*-α-hydroxy epoxides **23** and **24**, since successful reaction in these instances could serve as model studies for a synthesis of eriolangin (**1**). Compounds **23** and **24** were readily available using the recently developed method of Heathcock.[11] Reaction of **23** with *tert*-butyl dilithioacetoacetate (8 equiv) for 4 h at 22 °C afforded a waxy solid, spectroscopically identified as the *cis*-lactol **25** (81% yield). Treatment of **25** with 1 equiv of



23 **25** **26**



24 **27** **28**

potassium *tert*-butoxide in *tert*-butyl alcohol for 24 h at 50 °C gave in 55% yield the *cis*-lactone **26** (mp 64–65.5. °C). Similarly, the epoxide **24** on reaction with 8 equiv of *tert*-butyl dilithioacetoacetate at 50 °C for 3 h gave the lactol **27** in 80% yield, again as a waxy solid. Subsequent base treatment of this lactol using the same conditions as previously described gave the *cis*-lactone **28** (mp 93.5–95 °C) in 60% yield. In neither the preparation of lactone **26** nor in the preparation of lactone **28** could any other regioisomeric lactone component be detected. It thus appears that ring opening of *trans*-α-hydroxy epoxide systems with *tert*-butyl dilithioacetoacetate is more regioselective than comparable reactions carried out with dilithioacetate.

Acknowledgments. This research was supported by PHS Grant CA-18485-02. Support from the Hoffmann-LaRoche Foundation is gratefully acknowledged.

References and Notes

(1) S. Danishefsky, T. Kitahara, P. F. Schuda, and S. J. Etheredge, *J. Am. Chem. Soc.*, **98**, 3028 (1976).
(2) S. Danishefsky, M. Y. Tsai, and T. Kitahara, *J. Org. Chem.*, **42**, 394 (1977).
(3) The details of this work will be published shortly.
(4) Prepared following the work of H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).
(5) The dianion derived from methyl acetoacetate has been reported to ring open epoxides by T. A. Bryson, *J. Org. Chem.*, **38**, 3428 (1973).
(6) The procedure used for generation of this dianion follows that described by S. N. Huckin and L. Weiler, *J. Am. Chem. Soc.*, **96**, 1082 (1974).
(7) This mixture of compounds was separated by chromatography. The NMR spectra of these compounds confirm their assigned structures. The geminal dimethyl group present in these materials greatly simplifies their proton pattern in the NMR.
(8) The degradation of **19** into **20** is reminiscent of the conversion of strychnine into Weiland–Gumlich aldehyde. For a recent and extensive discussion of the latter transformation, see: J. R. Hymon, H. Schmid, P. Karrer, A. Boller, H. Els, P. Fahrni, and A. Furst, *Helv. Chim. Acta*, **52**, 1564 (1969). We thank Professor D. Cane of Brown University for bringing this reference to our attention.
(9) No attempt was made to optimize the yields for any of the reactions reported herein. The lactone **21** and all other lactones described here gave satisfactory physical data with the infrared and NMR spectra of these materials corresponding to similar compounds reported in ref 2.
(10) S. Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheredge, *J. Am. Chem. Soc.*, **99**, 6066 (1977) have found that the THP derivative of compound **3** does not undergo ring opening with dilithioacetate. As stated earlier in the text, compound **9** also does not undergo reaction with this nucleophile.
(11) C. G. Chavdarian and C. H. Heathcock, *Synth. Commun.*, **6**, 277 (1976).
(12) Holder of Uniroyal, Hooker, and Sherman-Clarke fellowships.

Gerard R. Kieczykowski,[12] Michael R. Roberts
Richard H. Schlessinger*
Department of Chemistry, University of Rochester
Rochester, New York 14627
Received November 25, 1977