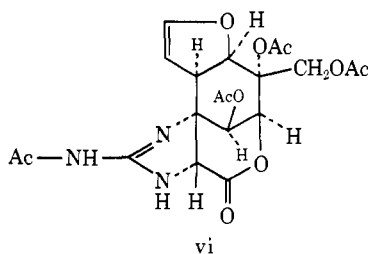


of **14** in THF at -20° gave the monoacetylguanidine diol **15** [λ_{uv} (MeOH) 240 nm]. The monoacetylguanidine diol **15** thus obtained was rather unstable; namely it isomerizes to the diacetylguanidine diol **16** [λ_{uv} (MeOH) 256 nm] on silica gel tlc or under basic conditions.²⁰ Sodium periodate oxidation of **15** in aqueous THF at 0° for 30 min, followed by quenching the oxidant with ethylene glycol, and then ammonium hydroxide hydrolysis in aqueous methanol,¹³ afforded crystalline DL-tetrodotoxin **1**, which was identified with natural tetrodotoxin by comparison of spectroscopic data (nmr and ir¹⁴) and toxicity.¹⁵ The overall yield from **13** to **1** by this route was around 25%.

Compared with the first route, the second one was better both in the overall yield from **2** and in reproducibility.

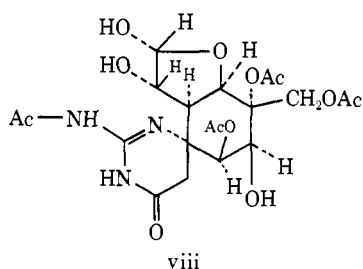
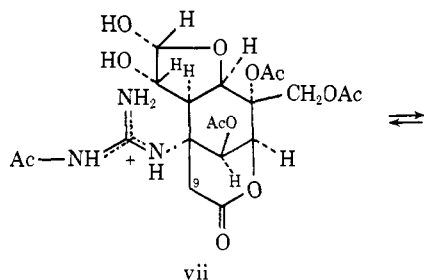
Acknowledgment. Financial support from Matsunaga Science Foundation, Yamaji Foundation, and Asahi Foundation is gratefully acknowledged.

(18) One of the by-products of this step was the cyclic monoacetylguanidine vi^{3b} [nmr (CDCl₃) 2.02 (6 H, s), 2.04 (3 H, s), and 2.12 (3 H, s)].



(19) Ozonolysis of **14** under neutral or acidic conditions was not promising.

(20) In the 9-deoxy series (lacking acetoxy group at C-9), the compound vii corresponding to **15** was present under acidic conditions and the compound viii corresponding to **16** was present under neutral and basic conditions.



Y. Kishi,* T. Fukuyama, M. Aratani
F. Nakatsubo, T. Goto

Department of Agricultural Chemistry, Nagoya University
Chikusa, Nagoya 464, Japan

S. Inoue, H. Tanino, S. Sugiura, H. Kakoi
Faculty of Pharmacy, Meijo University
Showa, Nagoya 468, Japan

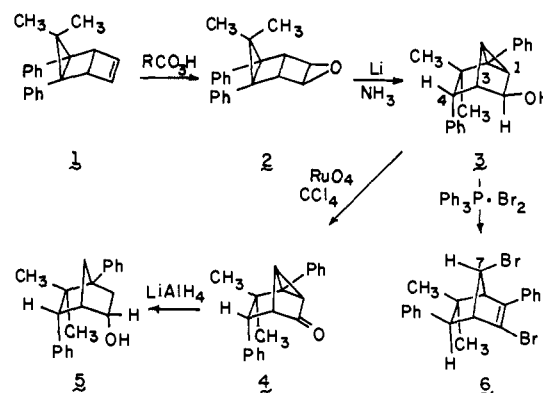
Received September 5, 1972

Intramolecular Epoxide Cleavage by Dissolving Metal Reduction of Proximal Cyclopropane Rings

Sir:

Recent research has revealed that phenyl substitution of cyclopropane rings is sufficient to promote their ready cleavage under conditions of alkali metal reduction.^{1,2} The chief mechanistic question at issue has been evaluation of the extent to which stereoelectronic and steric factors control the stereospecificity of the observed ring openings. The latent chemical reactivity of the radical anions or dianions produced under these conditions has not heretofore been explored. The present work illustrates a synthetic application of this reduction which provides a novel synthetic entry to functionalized derivatives of strained tricyclic hydrocarbons.

When epoxide **2**, mp $71-72.5^{\circ}$,³ readily available from *m*-chloroperbenzoic acid oxidation of tricycloheptene **1**,⁴ was allowed to react with 2 equiv of lithium in liquid ammonia, alcohol **3** (mp $121-123^{\circ}$; $\nu_{\text{max}}^{\text{KBr}}$ 3300 cm^{-1})³ was obtained in 90% yield. Its nmr spectrum (CDCl₃, 60 MHz) includes singlets at δ 1.02 and 0.88 (3 H each, methyls), multiplets at 7.2 (10 H), 3.13 (2 H), 2.58 (2 H), and 1.88 (1 H), and a particularly revealing doublet ($J = 3.7 \text{ Hz}$) for the $>\text{CHOH}$ proton at 4.55. The tricyclic structural assignment to **3** fol-



lows convincingly from appropriate $\text{Eu}(\text{fod})_3$ shifting of the above spectrum,⁵ high-yield (96%) ruthenium tetroxide oxidation⁷ to ketone **4**, mp $117-118^{\circ}$,^{3,8} and subsequent hydride reduction of **4** to *endo*-norbornanol **5**, mp $142.5-144.5^{\circ}$.^{3,9}

(1) H. M. Walborsky, M. S. Aronoff, and M. S. Schulman, *J. Org. Chem.*, **36**, 1036 (1971), and relevant references cited therein.

(2) For an excellent comprehensive review of this field, see S. M. Staley, *Selec. Org. Transform.*, **2**, 309 (1972).

(3) Satisfactory ($\pm 0.3\%$) combustion data and mass spectral results were obtained for all new compounds. In those cases where the nmr spectra are not explicitly given, full agreement with the structural assignment was evidenced.

(4) L. A. Paquette and L. M. Leichter, *J. Amer. Chem. Soc.*, **92**, 1765 (1970); **93**, 5128 (1971).

(5) The relevant ΔEu values⁶ are: H₁, -4.26 ; H₂, -11.53 ; H₃, -7.93 ; H₄, -2.37 ; H₇, -5.97 .

(6) P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, **92**, 5734 (1970).

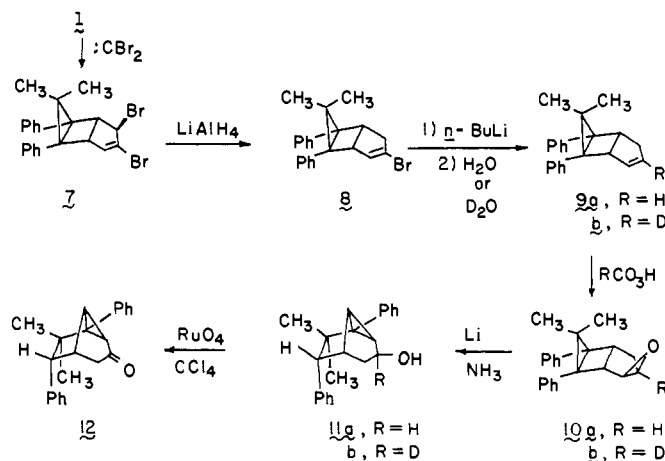
(7) H. Nakata, *Tetrahedron*, **19**, 1959 (1963); R. M. Moriarty, H. Gopal, and T. Adams, *Tetrahedron Lett.*, 4003 (1970); H. Gopal, T. Adams, and R. M. Moriarty, *Tetrahedron*, **28**, 4259 (1972).

(8) $\lambda_{\text{max}}^{\text{CH}_2\text{CN}}$ 228 (ϵ 1740), 252 (350), 258 (435), and 265 nm (340); $\delta_{\text{TM}^{\text{S}}}^{\text{CDCl}_3}$ 7.32 (s, 10, aryl), 3.42 (m, 3), 3.1 (m, 1), 0.94 (s, 3), and 0.70 (s, 3). For a leading reference to conjugative effects in cyclopropyl carbonyl compounds, consult: A. Padwa, L. Hamilton, and L. Norling, *J. Org. Chem.*, **31**, 1244 (1966).

(9) $\delta_{\text{TM}^{\text{S}}}^{\text{CDCl}_3}$ 7.2-7.6 (m, 10, aryl), 4.48 (m, 1), 3.2 (m, 1), 2.9 (m, 1), 1.55-2.25 (m, 5), 1.15 (s, 3), and 0.88 (s, 3). This reduction may be considered analogous to that of the double bond in α,β -unsaturated

The hydroxyl group in **3** has been assigned the exo orientation on the strength of the multiplicity and coupling constant of the α -hydroxyl proton.^{10a} The endo stereochemistry of the 4-phenyl substituent was deduced from the coupling constant of H₄ with H₃ ($J = 3.6$ Hz) characteristic of an *exo*-norbornyl proton^{10b} and this assignment was supported by the finding that **3** reacts with triphenylphosphine dibromide¹¹ to give dibromide **6**, mp 142.5–143.5°,³ whose detailed structure was established by three-dimensional X-ray analysis.¹²

Further insight into the generality and mechanism of the title reaction was gained from examination of the behavior of unsymmetrical epoxides **10a** and **10b**. These were available by conversion of **1** to dibromide **7** by reaction with dibromocarbene, followed by lithium aluminum hydride reduction, metal-halogen interconversion, and addition of water or deuterium oxide. The nmr spectrum (CDCl₃, 60 MHz) of hydrocarbon **9a** exhibits singlet resonances at δ 7.22 (10 H, aryl), 1.57 (3 H, methyl), and 0.73 (3 H, methyl), multiplets of area 1 at 5.8, 5.55, 3.3, and 2.85, and a two-proton multiplet at 2.35.¹⁴ When derived epoxide **10a** was subjected to the action of lithium in liquid ammonia, **11a**, mp 131–132°,³ was obtained in 95% yield. The nmr spectrum of the latter compound shows the presence of ten aryl protons (s, δ 7.3) and two methyl groups (s, 1.19 and 0.73) in addition to an endo α -hydroxyl proton adjacent to a methylene group (t, $J = 5.5$ Hz, 5.06). The methylene and methine protons appear together with the OH peak as two groups of multiplets centered at 2.85 (4 H) and 1.72 (3 H). In like fashion, **10b** led uniquely to **11b** (nmr analysis). Ruthenium tetroxide oxidation gave ketone **12**, mp 151–152.5°.³



The nonindiscriminant deuterium labeling pattern in **11b** reveals that the epoxide ring does not experience initial reduction in this reaction since highly regio-

ketones. This subject has recently been surveyed briefly by M. N. Reick in "Reduction," R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1968, Chapter 1.

(10) (a) J. J. Tufariello and D. W. Rowe, *J. Org. Chem.*, **36**, 2057 (1971); (b) P. Laszlo and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964), and pertinent references cited therein.

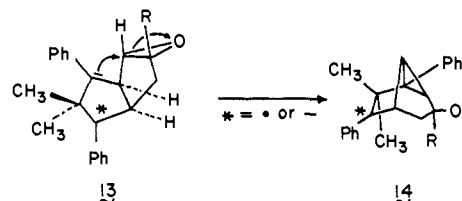
(11) G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *ibid.*, **86**, 964 (1964).

(12) J. Clardy, personal communication. Details of this analysis and a mechanism for this reaction will be elaborated upon in the full paper. Suffice it to say at this time, however, that the replacement of hydroxyl by bromine is proposed to proceed chiefly with retention¹³ and that C₂ in **3** becomes C₇ in **6**.

(13) J. P. Schaefer and D. W. Weinberg, *J. Org. Chem.*, **30**, 2635, 2639 (1965).

(14) In the spectrum of **9b**, the peak at δ 5.8 was seen to be lacking.

cific C–O bond cleavage is not expected.¹⁵ It must be concluded, therefore, that the cyclopropyl bond common to the two phenyl substituents is ruptured with overwhelming kinetic preference. The generation of radical anion **13** (or its dianion equivalent)² is followed by backside attack on the proximate C–O bond with formation of a cyclopropane ring. The ultimate protonation of anion **14** to position the phenyl substituent



in an endo stereodisposition presumably stems from control by kinetic factors.¹⁶ The cyclopropane ring in **14** presumably is protected from further reduction because of electrostatic factors.

While this study relates specifically to the preparation of tricyclic alcohols having exo stereochemistry, the utilitarian nature of intramolecular reactions triggered by the reductive cleavage of cyclopropane rings is conceivably multifarious. Other aspects of this new synthetic method are receiving attention in these laboratories.

Acknowledgment. The authors thank the National Science Foundation for their financial support of this research.

(15) H. C. Brown, S. Ikegami, and J. Kawakami, *J. Org. Chem.*, **35**, 3243 (1970).

(16) A. F. Thomas, R. A. Schneider, and J. Meinwald, *J. Amer. Chem. Soc.*, **89**, 68 (1967).

Leo A. Paquette,* Kenneth H. Fuhr

Department of Chemistry, The Ohio State University
Columbus, Ohio 43210

Received August 15, 1972

Evidence for Autocatalysis in the Silver(I)-Promoted Reactions of Bicyclobutanes with Methanol¹

Sir:

It is presently recognized that the interaction of bicyclobutanes with silver(I) salts in anhydrous nonprotic media (e.g., benzene) promotes interesting structural bond reorganizations, whereas similar reaction in protic solvents (e.g., methanol) leads instead to ready solvent incorporation.^{2–4} In those examples where the same bond is initially cleaved under both sets of conditions, interception of appropriate organosilver intermediates has been claimed.³ When a different bond experiences initial rupture, the transition metal has been given the role of catalyzing a different rearrangement process.⁴ We now wish to report several pieces of evidence which demonstrate collectively the previously unrecognized but fundamental fact that *silver(I) promoted reactions of*

(1) Silver(I) Ion Catalyzed Rearrangements of Strained σ Bonds. XVII. For the previous paper, see L. A. Paquette, R. S. Beckley, D. Truesdell, and J. Clardy, *Tetrahedron Lett.*, in press.

(2) (a) L. A. Paquette, *Accounts Chem. Res.*, **4**, 280 (1971); (b) L. A. Paquette and S. E. Wilson, *J. Amer. Chem. Soc.*, **93**, 5934 (1971); (c) L. A. Paquette, R. P. Henzel, and S. E. Wilson, *ibid.*, **93**, 2335 (1971).

(3) M. Sakai, H. H. Westberg, H. Yamaguchi, and S. Masamune, *ibid.*, **93**, 4611 (1971), and earlier papers by the Alberta group.

(4) P. G. Gassman and T. Nakai, *ibid.*, **94**, 5497 (1972).