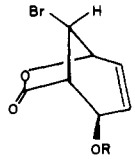
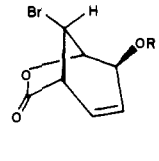


10 R=H
11 R=Ms



12 R=H
13 R=THP, TBDMS, CH_3

clean bimolecular kinetics with a second-order k = 0.875 L mol^{-1} min^{-1}. No other product is formed within the limits of experimental detection (1–2%). We feel these data are best explained by a synchronous S_N2' process and note in particular that this compact ring network, bearing electron-withdrawing substituents at both allylic termini, meets the criteria suggested by Bordwell[9,10] for observing such authentic, four-bond, concerted bimolecular processes. Moreover, by recycling **9** → **8** in this way, the overall yield of **2** from dihydrobenzoic acid becomes 17%.

As with **9**, hydrolysis of acetate **8** in H_2SO_4 also produces its allylic alcohol **12** (86%, mp 83–84 °C, NMR δ 4.69 (s, 1 H, bridging H)). Reaction of **12** with dihydropyran, *tert*-butyldimethylchlorosilane, or diazomethane yields **13** whose saponification provides access to monoprotected diols **3.** Elaboration of such substances into chorismic acid is presently under study.

Acknowledgment. We wish to thank Professor Glenn A. Berchtold of M.I.T. for kindly providing spectra of racemic **2**, and Eli Lilly & Co. for partial support of this research.

References and Notes

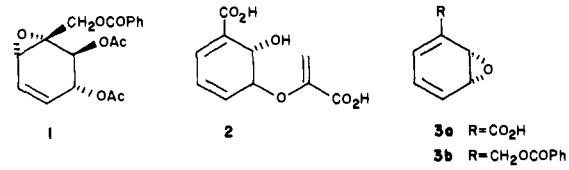
(1) For part I see B. Ganem and G. W. Holbert, *Bioorg. Chem.*, **6**, 393 (1977).
(2) (a) F. Gibson and J. Pittard, *Bacteriol. Rev.*, **32**, 465 (1968); (b) E. Haslam, "The Shikimate Pathway", Butterworths, London, 1974.
(3) B. A. Chiasson and G. A. Berchtold, *J. Am. Chem. Soc.*, **96**, 2898 (1974).
(4) (a) I. G. Young, F. Gibson, and C. G. MacDonald, *Biochem. Biophys. Acta*, **192**, 62 (1969); (b) I. G. Young and F. Gibson, *ibid.*, 177, 182 (1969).
(5) For recent results on this subject, see G. Stork and A. F. Kreft, III, *J. Am. Chem. Soc.*, **99**, 3850, 3851 (1977), and references cited therein.
(6) H. Plieninger and G. Ege, *Chem. Ber.*, **94**, 2088 (1961).
(7) Satisfactory spectral data and elementary analyses were obtained for this and all other new compounds.
(8) In support of our stereochemical assignment, the bridging hydrogens in **8** (δ 4.57) and **9** (4.85) are also deshielded by the β-allylic substituent. The corresponding α-allylic acetates have been synthesized by reducing the enones derived from alcohols **12** and **10.** These α-acetates exhibit no downfield shift in the bridging hydrogen absorptions (δ 4.48, 4.47, respectively) relative to **5.**
(9) F. G. Bordwell, *Acc. Chem. Res.*, **3**, 281 (1970).
(10) Surprisingly, Professor Bordwell seems to have overlooked in his review the first unambiguous S_N2' reactions described over 20 years ago by Stork and Clarke in the family of α and β-halocodides. These workers were also aware of the particular combination of factors permitting the observation of such concerted rearrangements: G. Stork and F. H. Clarke, *J. Am. Chem. Soc.*, **78**, 4619 (1956).

Nobuo Ikota, Bruce Ganem*
Department of Chemistry, Cornell University
Ithaca, New York 14853
Received August 8, 1977

Shikimate-Derived Metabolites. 3.[1] Total Synthesis of Senepoxide and Seneol According to a Biogenetic Proposal

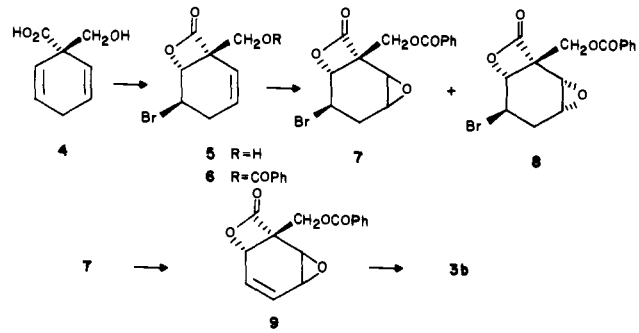
Sir:

Senepoxide **1** is one of a number of highly oxygenated cyclohexane epoxides which display tumor-inhibitory, antileukemic, or antibiotic activity.[2] Although this family of natural products was first discovered nearly 10 years ago, only two of its members, senepoxide and crotepoxide, have been prepared synthetically.[3] Almost nothing is known about their biosynthesis. Recently we advanced a scheme postulating (−)-(2*S*,3*S*)-isochorismic acid (**2**) as the precursor in nature of senepoxide, crotepoxide, and pipoxide through the intermediacy of arene oxides **3a** and/or **3b.**[4] Herein we disclose the stereospecific synthesis of senepoxide from **3b** in accordance with our biogenetic plan.



1 2 3a R=CO_2H 3b R=CH_2OCOPh

Alkylation of the dianion[5] of 1,4-dihydrobenzoic acid (LDA, THF, −10 °C) with gaseous formaldehyde produces hydroxymethyl acid **4** in 80–90% yield. Reaction of **4** dissolved in aqueous $NaHCO_3$ with 1 equiv of Br_2 in CCl_4 affords hydroxymethyl-β-lactone **5:** 90%; mp 50–55 °C; ν_{max} 1818, 3470 cm^{-1}; ^{1}H NMR δ 2.75 (m, 2 H, -CH_2-), 3.78, 4.10 (AB quartet, 2 H, J = 11 Hz, -CH_2OH), 4.56 (m, 1 H, -CHBr), 5.14 (d, 1 H, J = 3 Hz, -CHO-), 5.62 (d, 1 H, J = 10 Hz, vinyl), 6.10 (m, 1 H, vinyl).[6-8] After benzoylation of **5** (PhCOCl, pyridine, CH_2Cl_2, 98%), the very hindered olefin **6** (mp 103–104 °C) can be epoxidized (CF_3CO_3H, Na_2HPO_4,



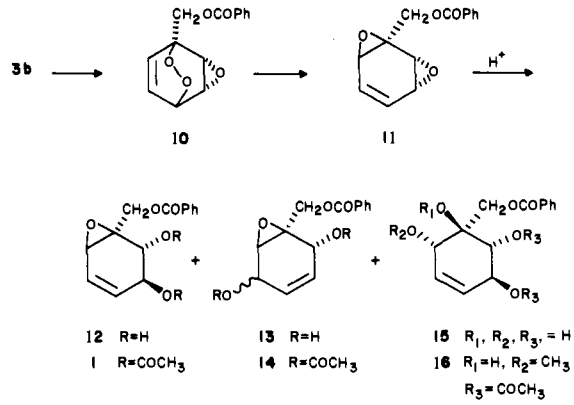
4 5 R=H 6 R=COPh 7 8 9

CH_2Cl_2, 85–90%) so as to furnish a 7:3 mixture of isomeric epoxylactones. This ratio reflects the syn-directing influence of the nearby benzoate ester carbonyl during oxidation.[9] While it is unnecessary for the continuation of the synthesis, these stereoisomers can be separated by silica gel column chromatography to give the major, more polar trans epoxylactone **7** (mp 118–120 °C) and the minor, cis product **8** (oil).

Both isomers **7** and **8** undergo smooth dehydrobromination when treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) and, as might be predicted, the rate of HBr loss from **7** is slightly faster (10 °C, 4 h, C_6H_6). Olefinic epoxylactone **9** can be isolated by careful workup but is usually not purified: NMR (C_6D_6) δ 5.66 (dd, 1 H, J = 10.5, 4.5 Hz, vinyl), 5.96 (dd, 1 H, J = 10.5, 3 Hz, vinyl). When heated in dry, ammonia-washed glassware (C_6H_6, reflux), **9** spontaneously decarboxylates to form **3b.** This substance is an exceptionally stable arene oxide–oxepin and can be prepared from **7** in yields exceeding 90%.

In keeping with our proposed biosynthesis, cycloaddition of **3b** with photochemically generated singlet oxygen (EtOH–$CHCl_3$, chlorophyll, 0 °C, 2 h) leads only to the crystalline trans endoperoxyepoxide **10** (80%, mp 85–87 °C).[10] When exposed to trimethyl phosphite (C_6H_6, room temperature, 2 h), **10** is reduced regiospecifically to dioxide **11:** 88%; mp 67–69 °C; ν_{max} 1724 cm^{-1}; NMR δ 3.18 (m, 2 H, epoxide), 3.88 (d, 1 H, J = 4.5 Hz, epoxide), 4.38, 4.75 (AB quartet, 2 H, J = 13.5 Hz, -CH_2OCOPh), 6.09 (m, 2 H, vinyl), 7.51, 8.09 (2 m, 5 H, benzoate). No trace of the corresponding positional isomer can be detected.[11] On the basis of published experiments with crotepoxide[2c] we expected that mild acid would selectively open the less stable disubstituted epoxide in **11.** Our expectations were fulfilled in the event, although the desired hydrolysis

0002-7863/78/1500-0352$01.00/0

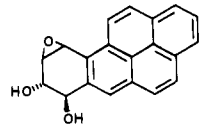


generates both 1,2- and 1,4-diols in a ratio which is highly dependent on solvent and acid. Under thus-far optimum conditions (1:1 THF:10% HOAc, room temperature, 20 h), trans-1,2-diol **12** is produced in 30% yield along with **13** (30%) and **15** (30%). Additional experiments have shown that tetraol **15** arises from **12,** a fact which has important mechanistic consequences.[12] Diol **12,** obtained pure by chromatography, can be acetylated (94%) and thereby produces *dl*-senepoxide, mp 97–98 °C, whose IR, NMR, and TLC characteristics are identical with those of an authentic sample. The methanolysis of **1** catalyzed by perchloric acid additionally confirms its structure by producing seneol **16,** a metabolite of senepoxide in *Uvaria catocarpa*.[2a]

Acknowledgment. Financial support from the National Institutes of Health and Eli Lilly & Co. is gratefully acknowledged. We also thank Mme Judith Polonsky (CNRS, Gif-sur-Yvette, France) for an authentic sample of senepoxide.

References and Notes

(1) For part II see N. Ikota and B. Ganem, *J. Am. Chem. Soc.*, preceding paper in this issue.
(2) Senepoxide: (a) R. Hollands, D. Becher, A. Gaudemer, and J. Polonsky, *Tetrahedron*, **24,** 1633 (1968); (b) A. Ducruix, C. Pascard, and J. Polonsky, *Acta Crystallogr., Sect. B,* **32,** 1589 (1976). Crotepoxide: (c) S. M. Kupchan, R. J. Hemingway, and R. M.Smith, *J. Org. Chem.*, **34,** 3898 (1969). LL-Z1220: (d) D. B. Borders and J. E. Lancaster, *ibid.*, **39,** 435 (1974). Pipoxide: (e) J. Singh, K. L. Dhar, and C. K. Atal, *Tetrahedron*, **26,** 4403 (1970). Triptolide: (f) S. M. Kupchan, W. A. Court, R. G. Dailey, C. J. Gilmore, and R. F. Bryan, *J. Am. Chem. Soc.*, **94,** 7194 (1972).
(3) Senepoxide: (a) A. Ichihara, K. Oda, M. Kobayashi, and S. Sakamura, *Tetrahedron Lett.*, 4235 (1974). Crotepoxide: (b) K. Oda, A. Ichihara, and S. Sakamura, *ibid.*, 3187 (1975); (c) M. R. Demuth, P. E. Garrett, and J. D. White, *J. Am. Chem. Soc.*, **98,** 634 (1976).
(4) All drawings except for structures 1 and **2** are meant to connote racemic mixtures. The fact that arene oxides **3a** and **3b** can racemize via their respective oxepin tautomers has interesting biosynthetic consequences: B. Ganem and G. W. Holbert, *Bioorg. Chem.*, **6,** 393 (1977).
(5) H. Plieninger and G. Ege, *Chem. Ber.*, **94,** 2095 (1961).
(6) W. E. Barnett and L. L. Needham, *J. Org. Chem.*, **40,** 2843 (1975).
(7) Satisfactory elemental analyses were obtained for all new compounds.
(8) G. W. Holbert, L. B. Weiss, and B. Ganem, *Tetrahedron Lett.*, 4435 (1976).
(9) Epoxidation of the corresponding alcohol **5** is a considerably slower reaction and produces a 1:1 mixture of stereoisomers. Carboxyl groups have been shown to exert specific syn-directing effects by S. A. Cerefice and E. K. Fields, *J. Org. Chem.*, **41,** 355 (1976).
(10) A similar result has been obtained with benzene epoxide using chemically generated singlet oxygen: C. H. Foster and G. A. Berchtold, *J. Org. Chem.*, **40,** 3743 (1975).
(11) For related examples see (a) G. O. Pierson and O. A. Runquist, *J. Org. Chem.*, **34,** 3654 (1969); (b) J. E. Baldwin and O. W. Lever, *J. Chem. Soc., Chem. Commun.*, 344 (1973).
(12) The trisubstituted oxirane ring is much more readily hydrolyzed in **12** than it is in **11.** We point out in this regard that **12** is remarkably similar in



i

structure to acid-labile diolepoxide i, produced by metabolism of benzo[*a*]pyrene in hepatic tissue. The epoxide's pronounced electrophilicity in i, presumably due to anchimeric assistance from the benzylic hydroxyl, is thought to be responsible for the potent activity of benzpyrene as an environmental carcinogen: D. L. Whalen, J. A. Montemarano, D. R. Thakkar, H. Yagi, and D. M. Jerina, *J. Am. Chem. Soc.*, **99,** 5523 (1977), and references cited therein.

Gene W. Holbert, Bruce Ganem*
Department of Chemistry, Cornell University
Ithaca, New York 14853
Received September 12, 1977

Production of Hydrogen from Interaction of an Anion Radical and Water

Sir:

Solvated hydrocarbon anion radicals and dianions have been known to be rapidly protonated (without exception) upon the addition of protic solvents such as water or alcohols for over 30 years (Birch reduction).[1] In fact, there exists a vast number of reports including those that elucidate the kinetics and mechanisms involved in these protonation reactions.[2] Even solid anion radical and dianion salts are rapidly protonated upon water addition.[3] However, we wish to report here the cleavage of water to yield hydrogen gas via anion radical reduction as opposed to anion radical protonation.

During our investigation into the heats of formation of organic anion radicals,[3] the reactions of the solid sodium salts of the polyacene series (pentacene, tetracene, anthracene, and naphthalene) were studied. The anion radicals were generated from a 1.5- to 2-fold excess of neutral hydrocarbon to sodium metal in tetrahydrofuran (THF). After complete dissolution of the sodium mirror, the anion radical solution was passed through a sintered-glass frit and the solvent (THF) distilled off under high vacuum (10^{-6} Torr).[4] A large excess (~2 mL) of degassed water was then added to the solid salt. The noncondensable gasses resulting form the reaction of the water with the salt (NaA) were allowed to pass into a vacuum system connected with a Toepler pump fitted with a gas buret.[5]

From 1 mmol of NaA, 0.5 mmol of hydrogen would be expected if eq 1 rather than eq 2 describes the reaction. The 0.5 mmol of H_2 would generate about half of an atmosphere of pressure in the 10-mL bulb of the gas buret. For A = pentacene, tetracene, and anthracene no gas was detected indicating that at least 99.9% of the reaction procedes via eq 2. However, for the reaction of water with the naphthalene anion radical, large quantities of H_2 are evolved.[6]

$$2A^{-}\cdot_{cryst} + 2H_2O \rightarrow 2A + H_2 + 2OH^{-} \quad (1)$$

$$2A^{-}\cdot_{cryst} + 2H_2O \rightarrow AH_2 + 2OH^{-} + A \quad (2)$$

After pumping all of the H_2 into the gas buret, the remaining reaction mixture was titrated with HCl to yield the initial amount of anion radical. From 10 such reactions 42 ± 8% of the reaction procedes via eq 1 rather than eq 2. The large standard deviation in this percent may be due to the fact that the pathway may vary with the crystal size of the $NaC_{10}H_8$. NMR analysis of the reaction mixture substantiates these conclusions as to the reaction pathway, in that ~80% of the organic material is naphthalene and 20% is dihydronaphthalene. When eq 2 describes the reaction pathway, a 50:50 mixture of A and AH_2 is obtained.

The possibility existed that the H_2 production could be explained by a partial microscopic reversal of the sodium reduction back to naphthalene and sodium metal upon solvent removal. If this were the case, the added water would simply react with the Na^0. This is not the situation, however, as naphthalene cannot be sublimed from the salt after solvent evaporation when an excess of sodium is used to ensure com-

0002-7863/78/1500-0353$01.00/0