$$(C_5H_5)_2NbCl(C_3H_4) \xrightarrow{HCl} \text{(>90 \%)} \quad (7)$$

metal-coordinated cyclopropene is feasible, the formation of propene by a similar initial metal coordination has not yet been verified. Further examples of the reduction of cyclopropene by metal centers are being investigated to demonstrate the conditions necessary for both cyclopropane and propene formation. In addition, the seemingly extraordinarily rich chemistry of bis(cyclopentadienyl)niobium species is being more fully investigated.

Acknowledgments. The authors are grateful to Professor Charles McKenna and Ms. Marie-Claire McKenna for helpful discussions and assistance with the analysis of hydrocarbon gas samples, and to Dr. Leo Manzer for helpful discussions in the early stages of this work. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to Research Corporation for a Cottrell Research Grant which provided financial support of this project. Exceptional contributions to our work by the professional glass blowing efforts of Mr. Jörg Meyer are also gratefully acknowledged.

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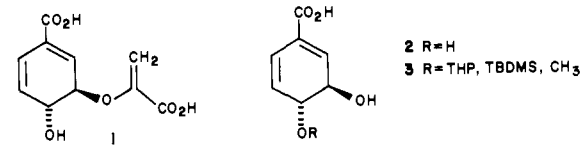
Shikimate-Derived Metabolites. 2.[1] Synthesis of a Bacterial Natural Product Illustrating a Concerted Syn-S_N2' Reaction

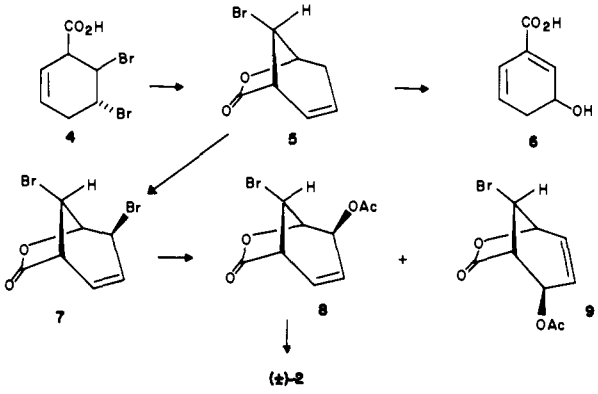
Sir:

Chorismic acid (**1**) occupies a central position in the shikimate metabolic pathway since it is the first branch point intermediate governing the biosynthesis of aromatic amino acids, bacterial growth promoters, and the isoprenoid quinones essential to respiratory chain phosphorylation.[2] We have been interested in the chemistry of chorismic acid and in processes which regulate metabolism at this juncture, specifically the partnership of chorismate mutase and complementary prephenate dehydratase/dehydrogenase enzymes. Among the many in vivo transformations of **1** in *Aerobacter aerogenes* is the cleavage of its enolpyruvyl side chain to produce *trans*-3,4-dihydroxy-3,4-dihydrobenzoic acid (**2**). This substance,



previously synthesized by Chiasson and Berchtold,[3] may have some biochemical function directly or indirectly in controlling metal ion consumption, or as a weak growth promoter.[4] This communication describes a five-step stereospecific synthesis of **2** and brings new information to bear on the mechanism and stereochemistry of the controversial S_N2' reaction.[5]

Bromination of 1,4-dihydrobenzoic acid in CH_2Cl_2 furnishes a mixture of dibromo acids from which the major isomer **4** can be crystallized (62%, mp 98–102 °C). Cyclization of **4** in aqueous $NaHCO_3$ affords **5** (65%, mp 52 °C, IR λ_{max} 5.61 μ).[6,7] This olefinic bromolactone contains the requisite diene system for **1** and **2** in masked form; saponification of **5** ($Ba(OH)_2$, EtOH) leads to **6** in good yield. Compound **5** is resistant to most allylic oxidizing agents but a slow reaction ensues with NBS (CCl_4, $(C_6H_5CO_2)_2$, reflux, 18 h) which generates enedibromide **7** stereospecifically in 70% yield (mp 69–70 °C) along with ~10% of an unidentified tribromide (mp 114 °C). The structure of **7** was assigned on the basis of ^{13}C and ^1H magnetic resonance data, particularly the sharp singlet for the bridging hydrogen at δ 4.84 ($CDCl_3$), shifted 22 Hz downfield from the corresponding singlet in **5** (4.47). Dibromide **7** can be converted (4 equiv of NaOAc, HMPA) to a 1:1 mixture of allylic acetates **8** and **9** (86%) which are readily



separated by column chromatography.[8] Saponification of **8** (mp 74–75 °C) using aqueous KOH (3.0 equiv) furnishes (±)-**2** in 77% yield. After recrystallization from acetone–pentane, pure **2** (56%) has mp 150–151 °C, UV λ_{max} 273 nm as well as IR, NMR, and mass spectral data fully in accord with literature values.[3]

We have noticed during this work a remarkable preference for reactions to occur on the β face of these bicyclic lactones which suggests an efficient way to use allylic ester **9**, coproduced with **8** during the acetolysis of **7**. Acidic hydrolysis of **9** (1:2 10% H_2SO_4–THF, reflux, 80%) affords the corresponding allylic alcohol **10** (mp 121–23 °C, NMR (acetone-d_6) δ 4.94 (s, 1 H, bridging H)) with no trace of rearrangement product. Treatment of this alcohol with methanesulfonyl chloride (1.1 equiv, C_5H_5N, 0 °C) furnishes mesylate **11** (85%, mp 155–156 °C) which when stirred with LiOAc in HMPA is quantitatively converted to the rearranged syn-allylic acetate **8**. Under these homogeneous conditions, which cause no isomerization in the starting mesylate, the reaction follows

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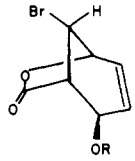
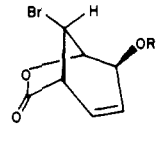


10 R=H
11 R=Ms



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.

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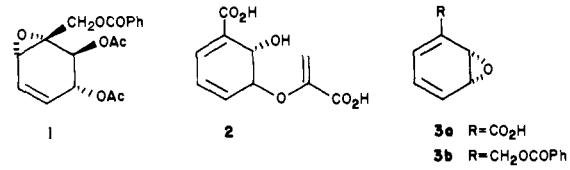
Shikimate-Derived Metabolites. 3.[1] Total Synthesis of Senepoxide and Seneol According to a Biogenetic Proposal

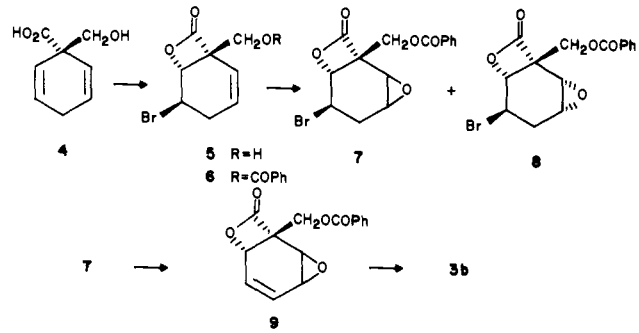
Sir:

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

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