that the k_{-1} steps could be slower than this (k_2) step. Murdoch estimates the rate constant for separation of molecules in solution as $\leq 10^{12}$ s^{-1} and suggests that values of 10^8–10^{10} may not be uncommon, with even slower rates (10^5–10^8) for hydrogen-bonded complexes.[12] The figure 10^8 s^{-1} corresponds to $\Delta G^{\ddagger} \approx 6.6$ kcal mol^{-1}, comparable to $\Delta G^{\ddagger}$ for the k_2 step.

Another question is whether discrete complexes such as **4** and **5** are credible species. Direct evidence is lacking. Chemical shifts of ketones in the presence of europium shift reagents have been explained by analogous complexes,[13] but a more sophisticated NMR analysis favors a linear complex (>C=O···M) for symmetrical ketones and a single, only slightly nonlinear one for unsymmetrical ketones.[14] In the absence of experimental information on species more directly related to **4** and **5**, however, we continue to regard Scheme II, or some mechanism with analogous intermediates, as a viable explanation of our results.

We are now testing the mechanism of Scheme II and exploring its implications.

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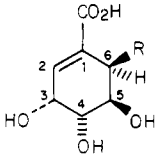
Shikimate-Derived Metabolites. 12.[1] Stereocontrolled Total Synthesis of Shikimic Acid and 6β-Deuterioshikimate

Summary: A short total synthesis of shikimic acid and related derivatives is described in which an unusual, stereoselective Bu_3SnD debromination conveniently furnishes 6β-deuterioshikimate for biosynthetic studies.

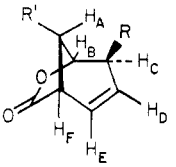
Sir: Shikimic acid (**1a**) figures prominently in microbial and plant metabolism as a key intermediate in the biosynthesis of aromatic amino acids, isoprenoid quinones, bacterial growth promoters, and other vital compounds.[2] Commensurate with its biochemical significance, **1a** has



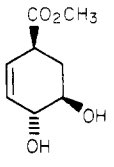
1a, R = H
b, R = D

become a popular target for total synthesis, and many successful approaches have been described.[2a,3] We now report a new shikimic acid synthesis that permits selective operations at C-3 and thus access to other metabolites of the main biosynthetic pathway.[4] Moreover, a remarkable, stannane-mediated bromide reduction occurring with a high degree of stereocontrol has led to the synthesis of 6β-deuterioshikimic acid (**1b**).

The synthesis of shikimic acid was achieved as follows. Alcohol **3**, readily available by acid hydrolysis of the known allylic acetate **2**,[5] was stereoselectively epoxidized using



2, R = OAc; R′ = Br
3, R = OH; R′ = Br
4, R = OAc; R′ = $H_{A'}$
5, R = OAc; R′ = D
6, R = $H_{C'}$; R′ = Br



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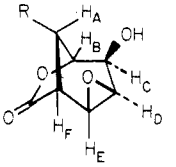

8, R = Br
9, R = $H_{A'}$
10, R = D

CF_3CO_3H ($ClCH_2CH_2Cl$, reflux, 23 h, 84%) to furnish β-oxide **8** (mp 137–140 °C) as the only product.[6] This bicyclic lactone underwent smooth debromination (Bu_3SnH, AIBN, toluene, reflux, 2 h, 72%) to give the corresponding reduced epoxyol **9** (mp 123–125 °C).[7] Upon saponification with KOH (1.25 equiv, 4:1 CH_3OH/H_2O, 24 h), **9** was transformed into *dl*-shikimic acid (**1a**: 90%; mp and lit.[2a] mp 191–192 °C). This seven-step synthesis of **1a** in 13% overall yield from 1,4-dihydrobenzoic acid demonstrated that both shikimate as well as chorismate[1] ring systems could be fashioned from the same bicyclic framework.

In related experiments, allylic acetate **2** was likewise reduced with Bu_3SnH (toluene, reflux, 3 h) to afford **4** in 82% yield.[8] Lactone **4** could then be opened either in base ($NaOCH_3$–CH_3OH) or in acid (concentrated HCl–CH_3OH) to afford methyl 3-deoxyshikimate [90%; mp 94–95 °C (lit.[9] mp 97 °C)] or its unconjugated isomer **7**[10] (100% yield, colorless oil), respectively.

According to the generally accepted radical mechanism of Bu_3SnH reductions, most dehalogenations occur with stereochemical randomization.[11] Exceptions include bridgehead bromides[12] and certain *gem*-fluorohalocyclopropanes which afford fluorocarbons, both with retention of configuration.[13] Net inversion has also been observed in the Ph_3SnH reduction of two chiral cyclopropyl bromides.[14] These conflicting reports notwithstanding, the

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(6) **8**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.64 (br s, 2 H, H_A, H_B), 4.21 (m, 1 H, H_C), 3.67 (dd, 1 H, J = 5.0, 3.1 Hz; H_E), 3.42 (d, 1 H, J = 5.0 Hz; H_D); IR (KBr) 3330, 1795 cm^{-1}; CIMS, *m/e* (relative intensity) 235, 237 (M + 1, M + 3, 100).
(7) **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.47 (m, 1 H, H_B), 4.04 (br s, 1 H, H_C), 3.65 (dd, 1 H, J = 4.0, 4.3 Hz, H_E), 3.52 (m, 1 H, H_D), 3.04 (dd, 1 H, J = 4.6, 4.3 Hz, H_F), 2.38 (d, 1 H, 12.5 Hz, H_A), 2.06 (m, 1 H, $H_{A'}$); IR ($CHCl_3$) 3425, 1805, 1785 cm^{-1}; CIMS, *m/e* (relative intensity) 157 (M + 1, 5).
(8) **4**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.33 (dd, 1 H, J = 7.4, 9.4 Hz, H_E), 5.78 (ddd, 1 H, J = 1.6, 3.1, 9.4 Hz, H_D), 5.23 (dd, 1 H, J = 3.0, 3.1 Hz, H_C), 4.72 (m, 1 H, H_B), 3.02 (dd, 1 H, J = 3.4, 7.4 Hz, H_F), 2.34 (m, 1 H, $H_{A'}$), 2.12 (d, 1 H, 11.6 Hz, H_A), 2.08 (s, 3 H, acetate); IR ($CHCl_3$) 1785, 1733 cm^{-1}; CIMS, *m/e* (relative intensity) 183 (M + 1, 100).
(9) R. Grewe and I. Hinrichs, *Chem. Ber.*, *97*, 443 (1964).
(10) Partial methanolysis of **4** in acid was also possible and gave the C-4 monoacetate of **7** in high yield.
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(12) T.-Y. Luh and L. M. Stock, *J. Org. Chem.*, **42**, 2790 (1977).
(13) (a) T. Ando, F. Namigata, H. Yamanaka, and W. Funasaka, *J. Am. Chem. Soc.*, **89**, 5719 (1967), and references cited therein; (b) T. Ando, T. Ishihara, E. Ohtani, and H. Sausaka, *J. Org. Chem.*, **46**, 4446 (1981).

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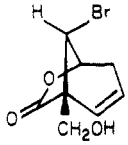
reduction of lactones 2 and 8 was repeated with Bu_3SnD to test whether a deuterium label might be introduced selectively at the pro-C-6 position of shikimate. In fact, both 2 and 8 were cleanly transformed to monodeuterio lactones 5 and 10, respectively. NMR spectroscopy (including decoupling experiments at 300 MHz) proved especially powerful in assigning these structures: H_A which conveniently appeared as a singlet in 2 (δ 4.53) and 8 (δ 4.64) became a doublet in 4 (δ 2.12, J = 11.6 Hz) and 9 (δ 2.38, J = 12.5 Hz). However, after Bu_3SnD reduction, H_A appeared as a slightly broadened singlet in 5 (δ 2.12) and 10 (δ 2.35). Moreover, the extent of deuterium in place of H_A was judged in each case to be no greater than 5% by NMR.[15] This stereochemical outcome could be the result of steric approach control[16] in delivering a hydrogen donor to the radical; alternatively, it may indicate some difference in the thermodynamic stability of the two isomeric radicals. The former seems unlikely since unsubstituted bromo lactone 6 gave results identical with those for 2 and 8 with Bu_3SnD. However, we also observed that the known *anti*-bromo lactone 11[17] was cleanly reduced by Bu_3SnD to 12 with complete inversion of configuration.



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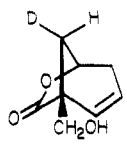

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As further proof of its structure, deuterated epoxy alcohol 10 [CIMS, m/e (relative intensity) 158 (M + 1), 100%)] was saponified to 6β-deuterioshikimic acid (1b) whose NMR spectrum matched that of an authentic sample prepared by Hill and Newkome.[18] These studies should now facilitate the synthesis of specifically labeled shikimate and dihydrochorismate[10] analogues for biochemical experiments.

Acknowledgment. We thank the National Institutes of Health for generous financial assistance and Mr. Richard Wood for help in performing numerous NMR experiments. NSF support of the Cornell Nuclear Magnetic Resonance Facility is gratefully acknowledged.

Supplementary Material Available: Listings of experimental details, physical, and spectral data for key intermediates (4 pages). Ordering information is given on any current masthead page.

(14) L. J. Altman and B. W. Nelson, *J. Am. Chem. Soc.*, 91, 5163 (1969).
(15) Structures 5 and 10 were fully supported by additional NMR, IR, and CIMS data.
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(17) B. Ganem, G. W. Holbert, L. B. Weiss, and K. Ishizumi, *J. Am. Chem. Soc.*, 100, 6483 (1978).
(18) R. K. Hill and G. R. Newkome, *J. Am. Chem. Soc.*, 91, 5893 (1969); ^1H NMR (D_2O, 300 MHz) δ 6.63 (dd, 1 H, J = 4, 1.5 Hz), 4.60 (s, HOD), 4.26 (m, 1 H), 3.84 (dd, 1 H, J = 8, 5 Hz), 3.59 (dd, 1 H, J = 8, 4 Hz), 2.53 (br s, 1 H).

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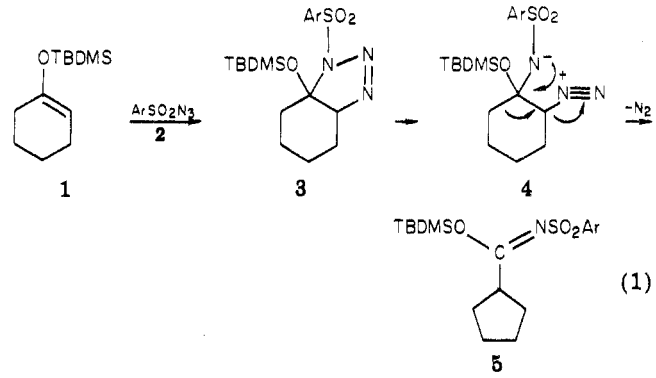
Organic Reactions at High Pressure. Dipolar Cycloaddition-Ring Contraction Reactions of Hindered Silyl Enol Ethers and Arylsulfonyl Azides[1,2]

Summary: Dipolar cycloaddition of arylsulfonyl azides with sterically congested silyl enol ethers at 15 kbar (1.5 GPa) in acetonitrile/methylene chloride cleanly affords good yields of one-carbon ring-contracted products.

Sir: In 1973, a ring contraction[3] was reported involving dipolar cycloaddition of arylsulfonyl azides with unsubstituted cyclic enol ethers to afford good yields of sulfonamide products. Subsequent work in our laboratories directed toward construction of the ophiobolin nucleus[4] demonstrated that the method is sensitive to the steric environment surrounding the electron-rich double bond. Since dipolar cycloadditions are known to exhibit a negative $\Delta V^{\ddagger}$,[5] a rate enhancement is anticipated under elevated pressure conditions. The present study describes the successful application of high-pressure chemistry to the ring contraction of a variety of silyl enol ethers possessing varying degrees of substitution.

The reaction, formulated in eq 1, reportedly involves



1 3 4 5 (1)

regioselective 1,3-dipolar azide addition to the electron-rich double bond to give a Δ^2-1,2,3-triazoline 3[6] which fragments stepwise via a diazonium betaine 4 to give the water-sensitive imidate ester 5. The regioselectivity of the addition to the polarized enol π bond assures that ring contraction occurs predictably with σ bond migration from the α to the β enol carbon. This constitutes an advantage of this procedure over Favorskii-type rearrangements.[7]

The reaction was performed on the *tert*-butyldimethylsilyl (TBDMS) enol ethers[8] which exhibited greater stability than the corresponding trimethylsilyl (Me_3Si) enol ethers in cases where prolonged heating was required. In contrast to enamines,[9] known to undergo this ring contraction without pressure, silyl enol ethers allow for greater control of regiospecificity in enol formation and afford cleaner products. It was observed that the thermodynamic

(1) This work was supported in part by National Science Foundation Grant No. CHE-810-2938.
(2) NIH Postdoctoral Fellow, 1981 to present.
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(6) (a) The first report of Δ^2-1,2,3-triazoline formation was in: Wolff, L. *Justus Liebigs Ann. Chem.* 1912, *394*, 23. (b) For a review of this reaction see: L'Abbé, G. *Chem. Rev.* 1969, *69*, 345. (c) See also: Sheradsky, T. In "The Chemistry of the Azido Group"; Patai, S., Ed.; Wiley-Interscience: New York; pp 359, 373. (d) Lwowski, W. *Ibid.*, pp 529–31.
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