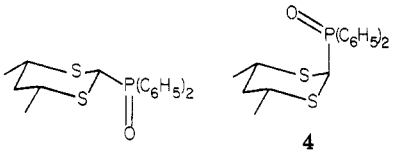
Scheme III



3 4

Idealized hydrogen positions were calculated and tied to the associated non-hydrogen positions through a riding model for the remainder of the refinement. Final refinement of 20 non-hydrogen atoms using anisotropic thermal parameters and 17 hydrogen atoms using isotropic thermal parameters gave residual values of $R_1 = 0.049$ and $R_2 = 0.067$ where $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$ and $R_2 = [\sum\omega(|F_o| - |F_c|)^2/\sum\omega|F_o|^2]^{1/2}$.

A perspective view of the molecular structure is shown in Figure 1 (supplementary material). The heterocyclic six-membered ring exists in a chair conformation with the substituent at C(1) being axial. The plane containing S(1), S(2), C(2), and C(4) bisects that passing through C(2), C(3), and C(4) at 58.1° and the S(1), C(1), S(2) plane at 54.1°. The two latter planes are almost parallel, forming an angle of 4.1°. The oxygen atom is centered above the heterocyclic ring and the two phenyl ring planes bisect at 85.8°. Bond distances and bond angles (supplementary material) within the molecule are consistent with those expected from the molecular geometry.

In an attempt to quantitate this conformational effect, the anancomeric derivatives 3 and 4 (Scheme III) were prepared,[11] and their proton NMR spectra were compared with that for 2. Most interestingly, the coupling constant of H_2 to phosphorus in 2, 3, and 4 varies considerably: 6, 15, and 4.2 Hz, respectively. On the assumption that $^2J_{H(2)/P}$ in the mobile dithiane (2) is the weighed average of those for the model diastereomers 3 and 4,[12] then $K = (J_{ax} - J)/(J - J_{eq}) = 5.0$, which affords $\Delta G^\circ \simeq 1.0$ kcal/mol, for the free energy difference favoring 2-ax over 2-eq.

Most commonly, the anomeric effect has been rationalized in terms of stabilization by (1) dipole–dipole interaction[13] and (2) delocalization of the lone pair on the endocyclic heteroatom into the antiperiplanar (axial) adjacent polar bond[15] (Scheme II). So far, we have not found supporting evidence for either mechanism.[16] On the one hand, if dipole–dipole interactions were operative here, it would be expected that the contribution of 2-eq should increase with increasing dielectric constant of the medium.[18] However, little change was observed for the proton NMR spectra of 2 [e.g., fairly similar $\Delta\delta_{ax/eq}(H_{4,6})$] in solvents of different polarity[19] (Table I).

Table I. Solvent Effect on the Chemical Shift Difference ($\Delta\delta_{ax/eq}$) for the C(4,6) Methylene Protons

solvent	ϵ[a]	$\Delta\delta$, ppm
$CDCl_3$	4.7	1.19
CD_3CO_2D[b]	6.2	1.05
CD_3COCD_3[b]	20.7	1.36
CD_3OD[b]	32.6	0.94
DMF-d_7	36.7	1.22
CD_3CN	37.5	1.04

[a] Dielectric constant for protiated solvents. [b] Due to low solubility in this solvent, the measurement was performed by pulse FT NMR at 100.1 MHz, using a (PD, 180°, τ, 90°, AT)$_n$ sequence to eliminate the solvent signal.

On the other hand, n_S/σ^*_{C-P} interaction (Scheme II) in 2-ax should result in a shorter than normal sulfur–anomeric carbon bond and a longer than normal axial carbon–phosphorus bond.[15] This is not the case, though. Both the sulfur–anomeric carbon (1.809 ± 0.012 Å) and the carbon–phosphorus (1.825 ± 0.003 Å) bond distances appear normal.

Registry No. 1, 505-23-7; 2, 83476-36-2; 3, 83463-92-7; 4, 83509-98-2; $ClP(C_6H_5)_2$, 1079-66-9.

Supplementary Material Available: Listings of atomic coordinates, anisotropic thermal parameters for all non-hydrogen atoms, isotropic thermal parameters for hydrogen atoms, observed and calculated structure factors, bond distances and bond angles, and an ORTEP drawing (15 pages). Ordering information is given on any current masthead page.

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(19) The possibility exists that alternative C(2)–P rotamers, which in relation to the dominant conformer are on steric and/or dipolar grounds slightly more destabilized and which may become only modestly populated over the polarity range studied, are responsible for the small variations observed in Table I.[20]
(20) We thank one of the reviewers for this suggestion.

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Deuterium Isotope Effects and the Mechanism of Kinetic Enolate Formation[1]

Summary: The reaction of lithium diisopropylamide with 2-methyl-3-pentanone in tetrahydrofuran at 0 °C occurs with a deuterium isotope effect of 5.1 at the 2-position but only of 0.9 at the 4-position, suggesting a mechanism of at least two steps in which the proton transfer need not always be the slow step.

Sir: We present evidence that the mechanism of kinetic enolate formation involves at least two steps and that the proton-transfer step is not always rate determining. By "kinetic enolate" we mean the product of irreversible attack

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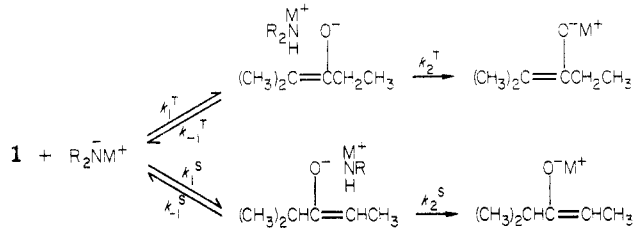
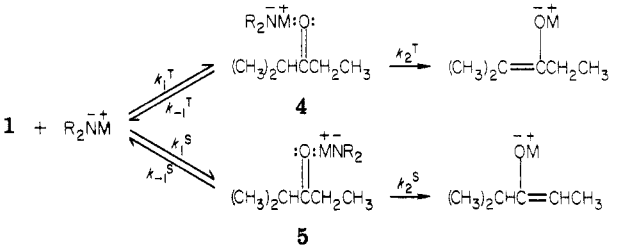
Table I. Arrhenius Parameters for the Temperature Dependence of the Isotope Effect from 0 to −50 °C for the Deprotonation of 2-Methyl-3-pentanone with Lithium Diisopropylamide in Tetrahydrofuran

parameter	product 2	(E)-3 + (Z)-3	(E)-3	(Z)-3
A_H/A_D	0.399 ± 0.184	0.876 ± 0.282	1.089 ± 0.386	0.742 ± 0.358
$E_D - E_H$, kcal mol^{-1}	1.38 ± 0.22	0.024 ± 0.157	−0.019 ± 0.173	−0.173 ± 0.235
k_H/k_D, 0 °C	5.06 ± 0.81	0.92 ± 0.12	1.05 ± 0.13	0.78 ± 0.13

Scheme I



Scheme II

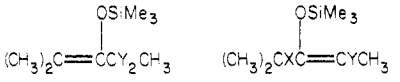


by a very strong base on a ketone, which usually gives the less stable regioisomer.[3-5]

The ketones **1a–c** were prepared by standard methods

$(CH_3)_2CXC(O)CY_2CH_3$
1a, X = Y = H
1b, X = D; Y = H
1c, X = H; Y = D

and added to at least a threefold excess of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) over a temperature range of 0 to −50 °C. The resulting solution (ca. 0.04 M in enolate) was treated with trimethylsilyl chloride, and the mixture of trimethylsilyl ethers (**2** and **3**) was analyzed by gas chromatography. The product



2 **3**

compositions did not change over a 24-h period at room temperature when the reaction mixture was protected from moisture, and yields, determined by use of an internal standard, were 92–96%. The deuterated ketones **1b** and **1c** contained no protium in the labeled positions (NMR), and the trimethylsilyl ethers **2** and **3** from **1b** and **1c** were shown (NMR) to have suffered no exchange of deuterium.

The ratios of [(E)-3 + (Z)-3]/2, (E)-3/2, and (Z)-3/2 were fitted to the Arrhenius equation. The resulting parameters were used to calculate the Arrhenius parameters of the isotope effects, assuming that deprotonation at the undeuterated α positions of **1b** and **1c** occurs at the same rate as at the corresponding positions of **1a**, an assumption probably good to within a few percent.

The most striking aspect of the results (Table I) is the large difference in k_H/k_D for the formation of **2** and **3**: for the former, k_H/k_D has a normal value for a rate-determining proton transfer, while for **3** (and for (E)-3 and (Z)-3 treated separately) k_H/k_D is near unity or perhaps slightly inverse. We consider it quite unreasonable to suppose that a single methyl group on the α-carbon could make so much difference in k_H/k_D for a simple rate-determining proton transfer. Consequently, we are compelled to assume that proton removal is preceded or followed by one or more other steps that can be partially or wholly rate determining.

An immediately obvious formulation is an internal return mechanism such as that in Scheme I. If $k^T_2 \gg k^T_{-1}$ or k^T_{-1D}, then the observed isotope effect is simply k^T_1/k^T_{1D}, a normal primary isotope effect. If, on the other hand, $k^S_2 \ll k^S_{-1}$ or k^S_{-1D}, the observed isotope effect is $k^S_1k^S_{-1D}/k^S_{1D}k^S_{-1}$, which is the *equilibrium* isotope effect for the proton-transfer step, expected to be within about 20% of unity. The mechanism has, however, a serious flaw: the highly exothermic proton transfer (the estimated pK_a for a secondary amine is ≥44,[6] and the measured pK_a for diethyl ketone = 27[7]) means that $\Delta G^\ddagger$ for the k_{-1} steps must be at least 20 kcal mol^{-1}, far larger than is reasonable for the diffusion steps (k_2) that the k_{-1} steps compete with.

Another mechanism consistent with the facts is shown in Scheme II. Although formally of the same type as the mechanism in Scheme I, the first step now is complex formation, and the second is the actual proton transfer. If $k^T_{-1} \gg k^T_2$ or k^T_{2D}, the observed isotope effect is k^T_2/k^T_{2D}, while if $k^S_{-1} \ll k^S_2$ or k^S_{2D}, the observed isotope effect is k^S_1/k^S_{1D}, which should be close to unity. Such a relationship of the rate constants is plausible, since $k^T_{-1} > k^S_{-1}$ is expected for steric reasons and $k^S_2 > k^T_2$ for both steric and electronic reasons.

To estimate $\Delta G^\ddagger$ for the k_2 step of Scheme II, we utilize Marcus theory.[8] Data on the nearly thermoneutral proton transfer from 9-methylfluorene to fluorenyllithium[9] suggests that $\Delta G^\ddagger_0$ (the intrinsic barrier[8]) for carbon-to-carbon proton transfers may be just below 80% of $\Delta G°$ for ionization[7] in polar aprotic media. This gives $\Delta G^\ddagger_0 \approx 29$ kcal mol^{-1} for the identity reaction diethyl ketone enolate + diethyl ketone. The other relevant identity reaction, R_2N^- + R_2NH, must be close to diffusion controlled,[10,11] giving $\Delta G^\ddagger_0 \approx 3$ kcal mol^{-1}. Following Marcus,[8] we take $\Delta G^\ddagger_0$ for R_2N^- + $RCOCH_2CH_3$ as the mean of those for the two identity reactions, or 16 kcal mol^{-1}. From the Marcus equation

$$\Delta G^\ddagger = \Delta G^\ddagger_0 (1 + \Delta G°/4\Delta G^\ddagger_0)^2$$

and the known (from pK_a values[6,7]) $\Delta G°$ of −23 kcal mol^{-1}, $\Delta G^\ddagger \approx 6.6$ kcal mol^{-1}. It is not unreasonable to suppose

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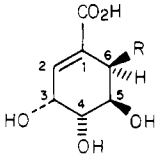
Shikimate-Derived Metabolites. 12.[1] Stereocontrolled Total Synthesis of Shikimic Acid and 6β-Deuterioshikimate

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.

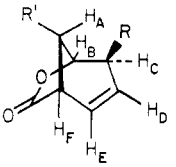
Sir: Shikimic acid (**1a**) figures prominently in microbial and plant metabolism as a key intermediate in the biosynthesis of aromatic amino acids, isoprenoid quinones, bacterial growth promoters, and other vital compounds.[2] Commensurate with its biochemical significance, **1a** has



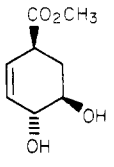
1a, R = H
b, R = D

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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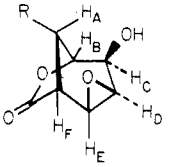

8, R = Br
9, R = $H_{A'}$
10, R = D

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).
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