cords well with theoretical expectation for a partial change in hybridization of the C_2 carbon from sp^2 to sp^3 in the transition state for disrotatory closure to **2**.[8] The near identity of the other three values in the upper right quadrant of Table I suggests that valence tautomerism is likewise rate limiting in these examples.

The deuterium isotope effects which are evidenced in the cycloaddition of MA to **1a** and **1b** are substantially larger and arise because of reduced dienophilic reactivity which causes the k_2[DP] and k_{-1} terms to approach each other in magnitude. The same progression toward case II behavior is witnessed in the DCMI reactions with **1c** and **1d** but for a different reason. In these examples, the diminished concentration gradient of **2c** and **2d** (relative to the methyl and phenyl derivatives) arising from an increase in k_{-1} is the responsible factor.

The enormous k_H/k_D values for the **1c**– and **1d**–MA examples, utterly unprecedented in their magnitude, can be understood if the kinetic profile has progressed well into the case I manifold (eq 2). Under these circumstnces, a multiplicative isotope effect ($k_1^H k_{-1}^D / k_1^D k_{-1}^H$) obtains. Consequently, limiting case I behavior is merely a preequilibrium situation where $\mathbf{2}^H$ and $\mathbf{2}^D$ are of necessity in complete equilibrium with each other. Accordingly, these large isotope effects duly reflect the full difference in heats of formation of the isomeric species $\mathbf{2}^H$ and $\mathbf{2}^D$. One should recognize that k_2 could be the source of a small fraction of this isotope effect and that it would tend to amplify matters in the observed direction. As concerns eq 2, the assumption has been made that the k_2^H and k_2^D terms are essentially identical (thus cancelling) and therefore noncontributory to the isotopic fractionation due to the low level of discrimination anticipated for capture of $\mathbf{2}^H$ and $\mathbf{2}^D$ by dienophile. To our knowledge, however, experiments designed to assess this specific question remain to be addressed and our assumption must be viewed as presently untested.

To the extent that the isotope effect in case I is indeed wholly derived from an equilibrium isotope effect, then these are unusually large values which reflect the equilibrium isotope effect difference for tetrahedral *vs.* trigonal deuterium. Notwithstanding, the observed K_{eq}'s (Table I) are in essential agreement with the best estimates available from consideration of appropriate vibrational frequencies,[9] although this level of magnitude has never been attained in SN1 solvolysis reactions.

Thus we have demonstrated that the kinetic deuterium isotope effect at the transition state of a cycloaddition reaction which is preceded by electrocyclic rearrangement is substantially less than that which constitutes equilibrium. The study takes advantage of the correlatibility of a predictable mechanistic trend (kinetic order) with a relatively unpredictable but mechanistically sensitive probe (secondary deuterium isotope effects). This method may serve as a simple experimental device to derive useful conclusions concerning the kinetic order of these cycloadditions without resorting to tedious dilatometric rate measurements.[1]

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(5) In the case of DCMI, this general mode of positional regioselectivity has also been observed for R = F, OCH_3, and Br.
(6) Very careful measurement of signal intensities in the labeled 1c–MA adduct showed $(H_4 + H_2)/2$ >CHC(O)– = 0.51 (theory 0.50), while the unlabeled 1c–DCMI adduct integrated for $(H_9 + H_{10})/H_4 = 1.95 \pm 0.05$ (theory 2.00).
(7) We thank Dr. S. V. Ley for this experiment.
(8) In the cyclooctatetraene–MA adduct, the C_4–H and C_2–H coupling constants are seen to be 172.1 and 141.6 Hz, respectively, corresponding to 34.4% s ($sp^{1.90}$) and 28.3% s ($sp^{2.53}$) character at these sites: [L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N.Y., 1969, p 345. It follows from these data that the extent of hybridization perturbation in C_4–H during conversion of 1 to **2** is minimal by comparison.
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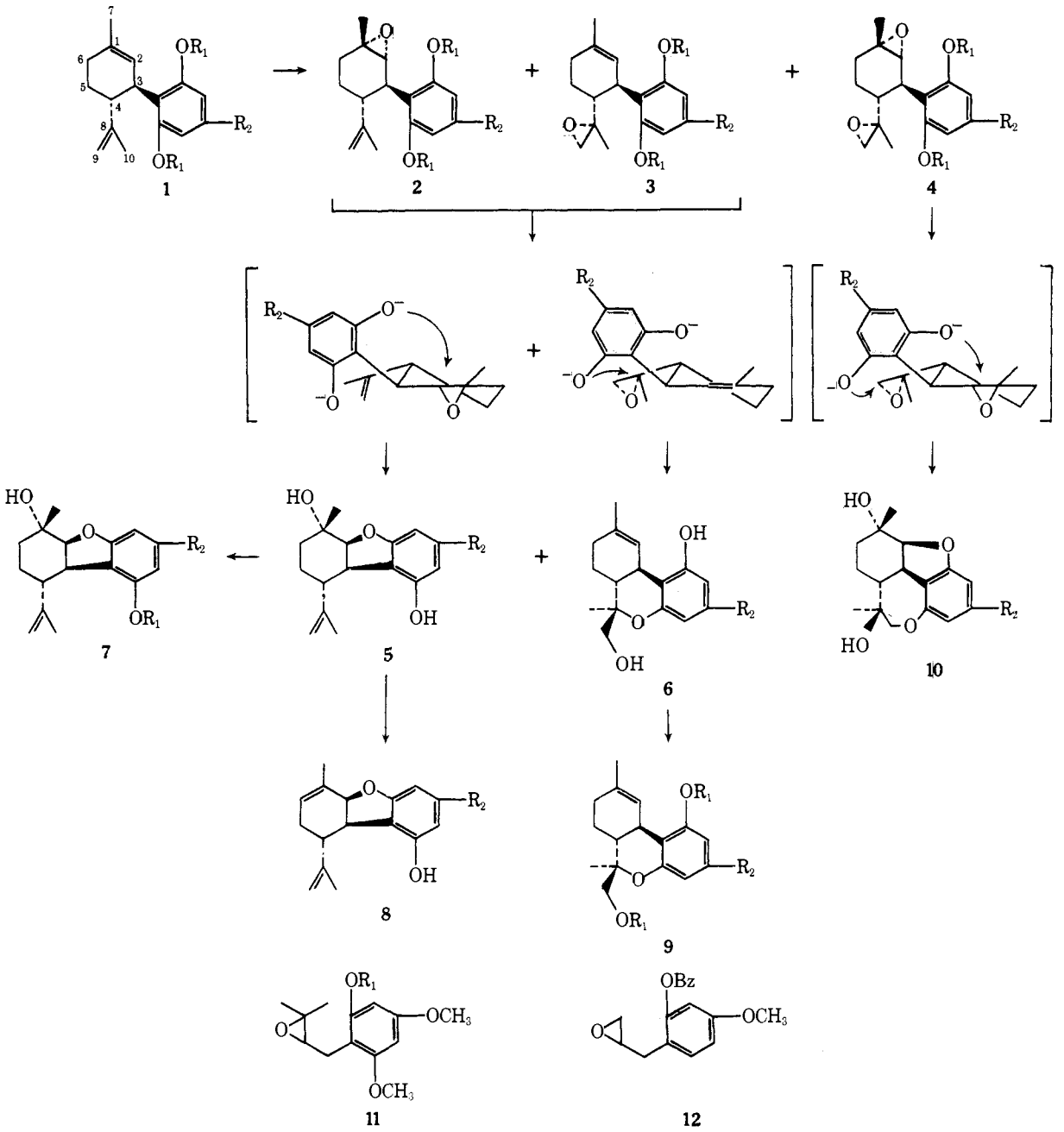
Stereospecific Intramolecular Epoxide Cleavage by Phenolate Anion. Synthesis of Novel and Biologically Active Cannabinoids

Sir:

As part of a program initiated to further our understanding of the chemical and biological activity of Hashish constituents,[1] we wish to report a stereospecific intramolecular epoxide cleavage by phenolate anion leading to the dihydrobenzofuran,[2] dihydrobenzopyran, and tetrahydrobenzoxepin ring systems. Utilizing this transformation we have effected: (a) the first stereochemically unambiguous synthesis of cannabielsoin[3] (**5**), (b) the preparation of a new biologically potent derivative of Δ^1-tetrahydrocannabinol (THC) (**6**); and (c) the synthesis of a novel tetracyclic cannabinoid (**10**) (Scheme I).

Cannabidiol diacetate (**1**), prepared from (−)-cannabidiol[1c,4] (pyridine, acetic anhydride, room temperature, quantitative), gave a mixture of epoxides **2**, **3**, and **4** when allowed to react at room temperature with *m*-chloroperbenzoic acid in chloroform. Gradient elution from Florisil with an ether-petroleum ether solvent system furnished pure diepoxide **4** (40% isolated yield) (δ (CCl_4) 6.73 (s, 2, aromatics), 3.05 (d, 1, J = 11 Hz, C_3–H), 2.73 (s, 1, C_2–H, 2 Hz band width at half-height), 2.30 (s, 3, acetate), 2.23 (s, 3, acetate), 2.00, 1.67 (AB, 2 J = 5 Hz, C_9–2H), 1.30 (s, 3, CH_3), 1.10 (s, 3, CH_3), 0.88 (t, 3, ω-CH_3)) and a mixture of **2** and **3** (40% isolated yield, in a ratio of 4:1) which shows similar absorptions at 3.10 (d, 1 J = 11 Hz, C_3–H) and 2.80 (s, 1, C_2–H, 2 Hz band width at half-height). The lack of observable coupling between the C_2- and C_3-protons, the presence of significant steric hindrance on the β-face, and the ease of opening these epoxides (see below) make the assignment of an α-configuration to the endocyclic epoxides[5] in **2** and **4** secure.

Scheme I



The mixture of epoxides **2** and **3**, in the presence of 2% NaOH in MeOH-H_2O (1:1) at room temperature afforded cannabinoids **5** and **6** *via* ester hydrolysis and phenolate anion attack at the oxirane. Separation by preparative tlc on silica gel using an ether–petroleum ether (1:1) solvent system gave pure **5** and **6** in 75% isolated yield in a ratio of 4:1. The nmr of **5** (δ (CCl_4) 6.15 (s, 2, aromatics), 5.50 (br, 1, O*H*), 4.90 (br, 2, vinylics), 3.92 (d, 1, J = 6 Hz, C_2-*H*), 3.23 (m, 1, C_3-*H*), 2.10 (br, 1, O*H*), 1.78 (s, 3, C_8-CH_3), 1.38 (s, 3, C_1-CH_3), 0.88 (t, 3, ω-CH_3)) as well as the mass spectrum and glc retention time are virtually identical with those reported[3b] for cannabielsoin obtained by decarboxylation of cannabielsoic acid.[3] Acetylation of **5** provided a monoacetate (**7**): δ (CCl_4) 6.43, 6.33 (AB, 2, J = 2 Hz, aromatics), 4.63 (br, 1, vinylic), 4.58 (br, 1, vinylic), 3.95 (d, 1, J = 5 Hz, C_2-*H*), 3.13 (m, 1, C_3-*H*), 2.23 (br, 1, O*H*), 2.13 (s, 3, acetate), 1.72 (s, 3, C_8-CH_3), 1.33 (s, 3, C_1-CH_3), 0.88 (t, 3, ω-CH_3). Dehydration of **5** (pyridine, $SOCl_2$, room temperature, 80%) gave **8**: δ (CCl_4) 6.13 (s, 2, aromatics), 5.72 (br, 1, C_6-*H*, vinylic), 5.40 (s, 1, O*H*), 5.03 (br, 2, C_9-2*H*, vinylic), 4.60 (d, 1, J = 8 Hz, C_2-*H*), 3.17 (dd, $J_{2,3}$ = 8 Hz, $J_{3,4}$ = 12 Hz, C_3-*H*), 1.87 (s, 3, CH_3), 1.80 (s, 3, CH_3), 0.88 (t, 3, ω-CH_3); mass spectrum (70 eV) *m/e* 312 ($M^{\cdot+}$), 297, 257, 244, 231, and 193. The transformation of **2** to **5** involves an intramolecular trans diaxial[6] cleavage of the α-epoxide[7] at its less hindered site which fixes the stereochemistry of the fused furan ring at C_2 and C_3 as cis and the configuration of the C_1-hydroxyl group as α (axial). In view of this we wish to revise the reported[3b] stereochemistry of cannabielsoin at C_1 so as to conform to structure **5**.[8]

In epoxide **3** generation of the phenolate anion resulted in

cleavage of the oxirane at the *more* hindered site[9] to form dihydrobenzopyran **6:** mp 146–147°; $[\alpha]^{25}D$ −166° (*c* 0.97, EtOH); δ (CCl_4) 6.37 (br, 1, vinylic), 6.20, 6.08 (AB, 2, *J* = 2 Hz, aromatics), 4.90 (br, 1, O*H*), 3.65 (s, 2, CH_2OH, 3 Hz band width at half-height), 3.23 (m, 1, C_3–*H*), 2.05 (br, 1, O*H*), 1.67 (br, 3, CH_3, vinylic), 1.00 (s, 3, C_8–CH_3), 0.90 (t, 3, ω-CH_3); mass spectrum (70 eV) *m/e* 330 ($M^{\cdot+}$), 299 ($[M - CH_2{=}OH]^+$, base peak), 231 and 193. Acetylation of **6** resulted in the facile formation of a diacetate (**9**) (δ (CCl_4) 6.48, 6.30 (AB, 2, *J* = 2 Hz, aromatics), 5.95 (br, 1, vinylic), 4.15 (s, 2, CH_2–OAc, 3 Hz band width at half-height), 3.03 (m, 1, C_3–*H*), 2.20 (s, 3, acetate), 2.03 (s, 3, acetate), 1.66 (br, 3, CH_3, vinylic), 1.06 (s, 3, C_8–CH_3), 0.88 (t, 3, ω-methyl); mass spectrum (70 eV) *m/e* 414 ($M^{\cdot+}$), 371, 355, 295, and 231), which caused the expected downfield shift of the methylene adjacent to the asymmetric C_8. Although this methylene appears as a singlet, the nonequivalence of its protons can be demonstrated using benzene-d_6 as solvent: δ (C_6D_6) 4.17, 4.32 (AB, 2, *J* = 12 Hz). The assignment of the β-configuration to the C_8-hydroxymethyl substituent in **6** is based on the presence of a methyl signal at δ 1.00 and the absence of the lower field signal (δ 1.35–1.41) exhibited by the C_8-β-methyl group in various THC derivatives.[10] Since no β-methyl isomers were isolated, the precursor epoxide **3** probably consisted of a single isomer indicating stereoselectivity during epoxidation of the 8,9-double bond.[11] This same selectivity would be expected in the formation of diepoxide **4.**

When **4** was treated with aqueous NaOH in MeOH the compound isolated in 60% yield showed: δ (CCl_4) 6.22 (s, 2, aromatics), 4.34 (d, 1, *J* = 9 Hz, C_2–*H*), 4.04, 3.38 (AB, 2, *J* = 13 Hz, CH_2–O), 3.3 (m, 1, C_3–*H*), 2.17 (br, 2, 2-O*H*), 1.30 (s, 3, CH_3), 1.22 (s, 3, CH_3), 0.88 (t, 3, ω-CH_3); mass spectrum (70 eV) *m/e* 346 ($M^{\cdot+}$), 290, 285, 218, and 214. The same material (by glc) could be obtained from **7** *via* epoxidation and alkaline hydrolysis. Although two exchangeable protons are apparent in the nmr, silylation could not be achieved. The structure in concert with the data is the novel tetracyclic ether **10** comprising the dihydrobenzoxepin ring system. Compound **10** is formed by dual phenolate anion attack at the less highly substituted oxirane sites.

The selectivity of these cyclizations indicates that in the intramolecular base-induced cleavage of epoxides ring size is more important than substitution. While both ring size and steric factors favor furan ring formation in **5,** ring size prevails in the cyclization of **3,** in spite of an adverse substitution pattern, to give a pyran (**6**) rather than an oxepin. Formation of the oxepin ring in **10** probably occurs only after initial closure to the furan ring. Furan formation places severe steric constraints on the subsequent cyclization, thus effectively eliminating the possibility of pyran formation. These findings, together with the observation that both compounds **11**[2a] and **12**[2b] give dihydrobenzofurans under basic conditions, suggest that the entropy of ring formation is the major factor in determining the product of an intramolecular epoxide cleavage.[12]

(−)-8β-Hydroxymethyl-Δ^1-THC (**6**) exhibited THC-like overt CNS symptomatology in rodents at 1.0 mg/kg iv (equivalent to that of Δ^1-THC) and is of interest as a possible metabolite of Δ^1-THC. Cannabielsoin (**5**) and the tetracyclic ether (**10**) showed no CNS activity up to 10 mg/kg iv.

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Paramagnetic Hydride and Alkyl Complexes of Niobium(IV) and Tantalum(IV)

Sir:

Transition metal hydrides are recognized as important intermediates and catalysts in a variety of reactions including hydroformylation, hydrogenation, olefin isomerization, and hydrogen exchange.[1] Electron spin resonance (esr) spectroscopy represents one of the best available techniques for the study of paramagnetic hydrides; however, only a few are extant.[2] The recent synthesis[3] of the early transition metal hydrides of niobium and tantalum, which are involved in H–D exchanges,[4] coupled with the development of esr techniques for the study of transient paramagnetic species,[5] provide an excellent opportunity to generate and to study metal-centered radicals, particularly those with nuclear magnetic moments, *e.g.*, ^{93}Nb with $I = 9/2$ and ^{181}Ta with $I = 7/2$, both present in 100% natural abundances.

We wish to report the observation by esr of dicyclopentadienylniobium(IV) dihydride produced in solution by abstraction of a single hydrogen from the diamagnetic dicyclopentadienylniobium trihydride (π-$C_5H_5)_2NbH_3$ (I).[3] Thus, a rigorously degassed solution of I in a mixture of benzene and cyclopropane containing di-*tert*-butyl peroxide (DTBP) on photolysis at −80° in the cavity of an esr spec-