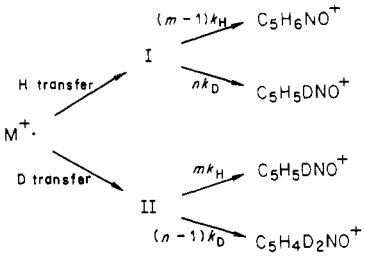
Scheme I

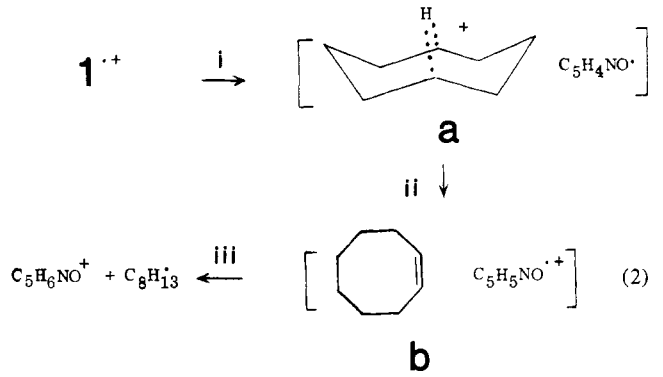


serves, therefore, as a diagnostic for reaction 1. Intervention of the cation renders positions 2 and 8 equivalent to positions 4 and 6.

The photoionization mass spectrometer has been previously described,[13] and it has the advantage that intensity ratios of adjacent peaks in the mass spectrum can be measured precisely. Low-energy ionization gives rise to fragmentation patterns in which simple bond fissions contribute only a small fraction of the total ionization.[14] At 130 nm (9.5 eV),[15] protonated hydroxypyridine ($C_5H_6NO^+$) constitutes nearly half of the total ionization (Σ), and the other prominent fragments (the M - 1, C_8H_{15}, and C_8H_{14} ions) constitute only 7%, 6%, and 3% of Σ, respectively. At this low ionizing energy, further fragmentation of the base peak is not observed.

The pathway by which protonated hydroxypyridine arises from photoionization of **1** is revealed by examination of the deuterated analogues **2** and **3**.[16] From the data summarized in Table I, it can be seen that simple vicinal elimination cannot be a major step in transferring two hydrogens to the aromatic moiety, since the perprotio daughter ion still predominates even when all of the β positions are deuterated (**2**). The isomeric deuterated ether **3** gives very nearly the same peak ratios as does **2**,[17] and the $C_5H_5DNO^+/C_5H_4D_2NO^+$ ratio is the same (2.85) for both d_4 analogues. Can this be explained by hydrogen scrambling? If n deuterium atoms become completely scrambled with m protons in the molecular ion prior to its decomposition, then the pertinent kinetic expressions can be derived from Scheme I.[18] A kinetic analysis based on the relative abundance in Table I reveals that there is no kinetic isotope effect k_H/k_D that can account for the data. Therefore, Scheme I can be ruled out as representing the major pathway.

A mechanism based on reaction 1 provides an explanation for the experimental results. The specific pathway is proposed in reaction 2 and is corroborated by examination of the d_1 and d_2 analogues listed in Table I. Ion–molecule complex a is formed by a simple bond cleavage (step i). Proton transfer (step ii) yields



(2)

ion–molecule complex b, and the nitrogen-containing radical cation subsequently abstracts a hydrogen atom (step iii). In step iii, abstraction of an allylic hydrogen is preferred but not exclusive. Thus, a negligible proportion of $C_5H_4D_2NO^+$ results from the 5,5-d_2 analogue, and levels of $C_5H_5DNO^+$ from the 1-d_1 and 5,5-d_2 analogues are low.

The experiments illustrate the utility of photoionization measurements above threshold in probing fragmentation mechanisms of gaseous ions. The scope of reaction 1 has been widened to include a new class of double hydrogen transfers. A more detailed kinetic analysis of these data will be presented in a full paper.

Acknowledgment. We are grateful to Professor J. N. Pitts and Dr. G. W. Harris, in whose laboratory the photoionization experiments were conducted. This work was supported by the NIH (Grant NS 17109), the donors of the Petroleum Research Fund, administered by the Americal Chemical Society (Grant 10840-AC4), and the NSF (Grant CHE 81 27133).

Registry No. 1, 37054-59-4; **2**, 80906-63-4; **3**, 80906-64-5; [5,5-$^2H_2$]-cyclooctyl 4-pyridyl ether, 80906-65-6; [1-^{2}H]-cyclooctyl 4-pyridyl ether, 80906-66-7; 5-oxocyclooctyl tetrahydropyranyl ether, 2616-83-3.

Supplementary Material Available: 130-nm photoionization mass spectra of compounds **1–3** (1 page). Ordering information is given on any current masthead page.

(13) Biermann, H. W.; Harris, G. W.; Pitts, J. N., Jr. *J Phys. Chem.*, in press.

(14) Morton, T. H.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1975**, *97*, 2355–2362; **1977**, *99*, 1288.

(15) The light source used for these studies was an oxygen resonance lamp, with a microwave discharge through 1% oxygen in helium [Davis, D.; Braun, W. *Appl. Opt.* **1968**, *7*, 2071–2074] and a calcium fluoride window.

(16) Compound **2** was prepared from the corresponding ketone-d_4,[11] while the alcohol corresponding to compound **3** was prepared from the monotetrahydropyranyl ether of *cis*-cyclooctane-1,5-diol[12] as follows: Oxidation with pyridinium chlorochromate to 5-oxocyclooctyl tetrahydropyranyl ether [bp 108–119 °C/(0.3 torr)] was followed by repetitive exchange with basic D_2O, and the labeled ketone was reduced with lithium aluminum hydride and then converted to the labeled cyclooctanol by a procedure analogous to that described in ref 12. The 5,5-d_2 compound was prepared by a similar procedure. The 4-pyridyl ethers were purified by distillation at 0.2 torr, followed by extraction from a CCl_4 solution with 10% aqueous HCl, basification, and reextraction of the aqueous layer with CCl_4. Approximate isotopic purities, as estimated from corrected molecular ion intensities, are as follows: **2**, 96 atom % D; **3**, 92 atom % D; the 5,5-d_2 ether, 75–80 atom % D; the 1-d_1 ether, 94 atom % D.

(17) The proportions of $C_5H_6NO^+$ differ by a slight amount, which we attribute to the lower level of deuteration of compound **3**.

(18) The steady-state approximation gives the following expressions, where $a = [I]/[II]$ and $b = k_H/k_D$: $[C_5H_5DNO^+]/[C_5H_6NO^+] = (na + mb)/(m - 1)ab$; $[C_5H_4D_2NO^+]/[C_5H_6NO^+] = (n - 1)/(m - 1)ab$. Solution of these formulas for b gives a quadratic equation for which there are no real roots when experimental values for the isotopic ratios are substituted. An exact solution for Scheme I gives an identical result.

Natural Product Synthesis via Allylsilanes. 1. Synthesis and Reactions of (1*E*,3*E*)-4-Acetoxy-1-(trimethylsilyl)-1,3-butadiene and Its Use in the Total Synthesis of (±)-Shikimic Acid

Masato Koreeda* and Marco A. Ciufolini

Department of Chemistry, The University of Michigan Ann Arbor, Michigan 48109

Received December 14, 1981

The structural moiety **2** and its epoxidized derivatives are frequently found in biologically active natural products such as the antitumor agent crotepoxide and its congeners[1] and in most of the active metabolites of carcinogenic polycyclic aromatic hydrocarbons.[2] In addition, the extreme lability associated with the presence of this moiety renders synthetic endeavors highly challenging. Here, we describe the synthesis and Diels–Alder reactions of the novel diene (1*E*,3*E*)-4-acetoxy-1-(trimethylsilyl)-1,3-butadiene (**1**) and its application to the efficient total synthesis of (±)-shikimic acid (**11**).

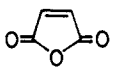
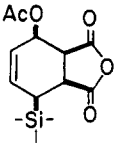
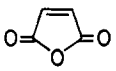
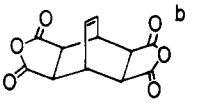
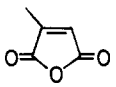
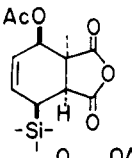
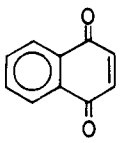
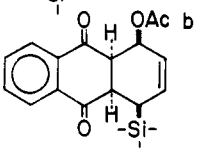
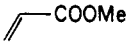
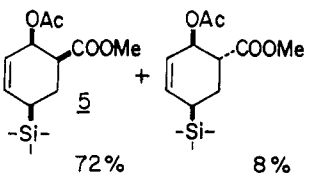
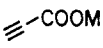
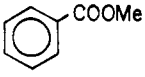
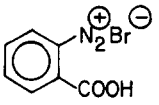
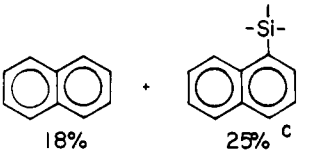
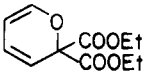
The *trans*-enediol **2** could be envisaged as being derived from **3** through a stereospecific oxidative allylic desilylation (Scheme I).[3] The allylsilane **3** in turn may be obtained via the Diels–Alder

(1) (a) Holbert, G. W.; Ganem, B. *J. Am. Chem. Soc.* **1978**, *100*, 352 and references cited therein. (b) Ganem, B. *Tetrahedron* **1978**, *34*, 3353.

(2) (a) Gelboin, H. V., Ts'o, P. O. P., Eds. "Polycyclic Hydrocarbons and Cancer"; Academic Press: New York, 1978; Vols. 1 and 2. (b) Harvey, R. G. *Acc. Chem. Res.* **1981**, *14*, 218.

0002-7863/82/1504-2308$01.25/0

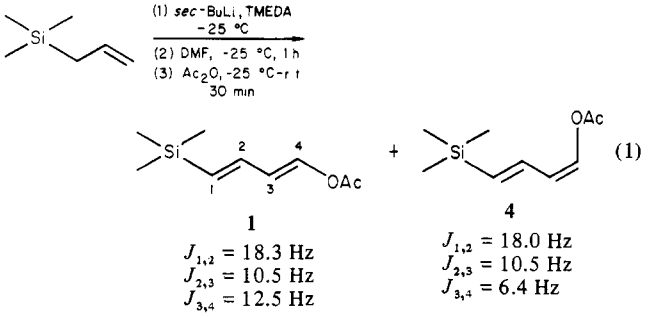
Table I. Diels-Alder Reactions of the Diene **1**

entry	dienophile	molar ratio of dienophile/diene	conditions	products and yields[a]
1		0.5	neat, 70°C 40 min	 b 74%
2		2.2	neat, 100°C 1h	 b 95%
3		0.5	neat, 100°C 20h	 b 76%
4		0.5	neat, 70°C 12h	 b 55%
5		5.0	xylenes reflux 40h	 72% 8%
6		5.0	neat, 100°C 20h	 5%[c]
7		0.5	$CHCl_3$, propylene oxide, reflux 1h[d]	 18% 25%[c]
8	$(EtOOC)_2CO$	1.0	xylenes, reflux 20h	 12%[c]

[a] Isolated yields of chromatographically pure products. Yields are based on the dienophile, except for entries 2, 5, and 6 where excess dienophile is used and yields are based on the diene. [b] No other regio- and/or stereoisomers detected. [c] The balance of the diene is recovered unchanged. [d] Schmidt, R.; Angerbauer, R. *Angew. Chem., Int. Ed. Engl.* 1979, *18*, 304.

reaction between the hitherto unknown diene **1** and an appropriate dienophile.

The synthesis of the requisite novel diene **1** is effected via a convenient one-pot procedure from allyltrimethylsilane (eq 1).



(1)

1: $J_{1,2}$ = 18.3 Hz, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 12.5 Hz

4: $J_{1,2}$ = 18.0 Hz, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 6.4 Hz

Thus, the allylic carbanion generated with *sec*-BuLi in the presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA)[4] is treated with DMF and then with excess acetic anhydride, to afford a stereoisomeric mixture (4:1) of the dienes **1**[5-7] and **4** in 60% yield. While these stereoisomers can be separated by silica gel flash chromatography,[8] the marked difference in reactivity between the

(3) For reviews of allylsilane chemistry, see: (a) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761. (b) Fleming, I. *Chem. Soc. Rev.* **1981**, *10*, 83.

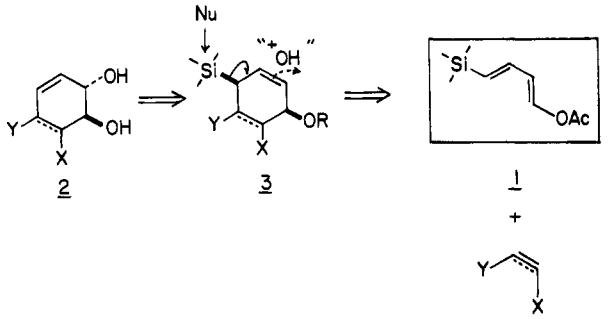
(4) (a) Ayalon-Chass, D.; Ehlinger, E.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1977**, 772. (b) Magnus, P. *Aldrichimica Acta* **1980**, *3*, 43.

(5) Satisfactory spectral and/or elemental analyses have been obtained for this and all other new compounds described in this communication.

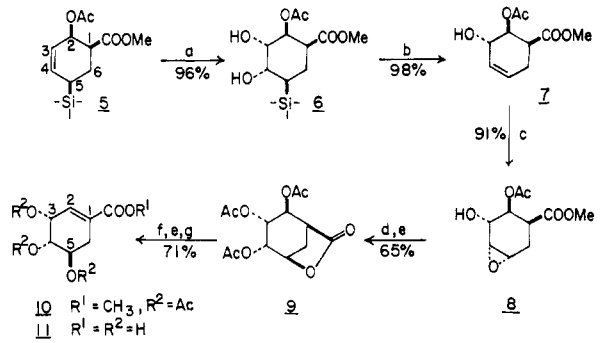
(6) **1**: bp 54 °C (0.2 mmHg); IR (neat) 1772, 1652, 1206 cm^{-1}; UV (MeOH) λ_{max} 231 nm; mass spectrum (EI), *m/z* 184 (M^+), 127 (base peak), 73; ^1H NMR (360 MHz, $CDCl_3$) δ 0.058 (s, 9 H, Me_3Si), 2.130 (s, 3 H, OAc), 5.80 (dd, 1 H, $J_{1,2}$ = 18.3 Hz, $J_{1,3}$ = 0.7 Hz, 1-H), 6.016 (ddd, 1 H, $J_{2,3}$ = 10.7 Hz, $J_{3,4}$ = 12.5 Hz, $J_{1,3}$ = 0.7 Hz, 3-H), 6.418 (ddd, 1 H, $J_{1,2}$ = 18.3 Hz, $J_{2,3}$ = 10.7 Hz, $J_{2,4}$ = 0.5 Hz, 2-H) and 7.392 ppm (dd, 1 H, $J_{2,4}$ = 0.5 Hz, $J_{3,4}$ = 12.5 Hz, 4-H); ^{13}C NMR (90 MHz, $CDCl_3$) δ -1.33, 20.67, 118.29, 134.42, 138.60, 138.94, 167.66.

(7) Dr. M. E. Jung of UCLA has recently informed us of his five-step synthesis of **1** from propargyl alcohol.

Scheme I



Scheme II[a]



[a] Conditions: (a) OsO_4 (catalytic), *N*-methylmorpholine *N*-oxide, *t*-BuOH/acetone/H_2O (30/6/5), room temperature, 10 h,[12] (b) *p*-TsOH (5 mole %), benzene, reflux, 20 min; (c) MCPBA, CH_2Cl_2, room temperature, 20 h; (d) LiOH, THF/H_2O, room temperature, 6 h; (e) Ac_2O, pyridine, room temperature, 20 h; (f) HCl gas, MeOH, room temperature, 3 h; (g) DBU, THF, room temperature, 6 h.

two dienes in the described Diels–Alder reactions makes their separation unnecessary. The less reactive 1*E*,3*Z* isomer **4** is recovered unchanged after the reaction.

The results of Diels–Alder reactions of the diene **1** with various symmetric and unsymmetric dienophiles are summarized in Table I.[9] As evident from the table, the diene undergoes facile cycloaddition to activated dienophiles with remarkably high regio- and stereoselectivity, thus indicating its potential as a versatile synthon toward a number of oxygenated cyclohexane compounds. Under forcing conditions, cyclic dienes are generated through the 1,4 elimination of the initially produced cycloadducts. In the presence of excess dienophile, a second addition to the cyclic diene thus generated takes place (entry 2).

The versatility of the novel diene **1** in the synthesis of the *trans*-enediol **2** or its equivalent is apparent from the following regio- and stereocontrolled synthesis of (±)-shikimic acid (**11**) (Scheme II). The synthesis utilizes the cycloadduct **5**, arising as the major product from the reaction of the diene **1** with methyl acrylate (entry 5) as the key intermediate. The most crucial step in this synthesis involves oxidative desilylation of the allylsilane **5**. The direct epoxidation–desilylation of **5** with a number of peracids under various conditions was found to be unsuccessful.[9d,10,11] However, the facile, stereospecific conversion of **5** into the allylic alcohol **7** can be achieved by a two-step sequence in 94% overall yield. Thus, refluxing the *cis*-diol **6** (obtained from **5** by using the Upjohn procedure[12]) in benzene for 20 min in the presence of a catalytic amount of *p*-TsOH results in the smooth elimination of the trimethylsilyl–hydroxy unit to furnish the olefin **7**.[13] Remarkably, the potentially labile β-acetoxy ester moiety remains intact under these conditions. Introduction of the 3β,4α-diol system turned out not to be trivial. Acidic hydrolysis of the epoxide ring of **8**, prepared stereoselectively from **7** with *m*-chloroperoxybenzoic acid (MCPBA), invariably leads to the formation of three triols. In contrast, treatment of **8** with LiOH followed by acetylation affords the γ-lactone triacetate **9** directly. Lactone ring opening with dry HCl in MeOH followed by acetylation generates the required 3β,4β,5α-triacetoxy compound, which upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provides (±)-methyl triacetylshikimate (**10**), whose spectroscopic (360-MHz ^1H NMR and IR) and TLC characteristics are identical with those of an authentic sample. This ester can be hydrolyzed under alkaline conditions[14] to free shikimic acid (~80%).[15] The present efficient synthesis of (±)-shikimic acid, overall yield 23% from the diene **1**, should provide a convenient means for introducing a C-13 label at C-2 of shikimic acid, a key biosynthetic intermediate to a number of natural products, when C-13 labeled DMF is used in the synthesis of the diene **1**.

Further applications using the diene **1** in the synthesis of natural products possessing the highly oxygenated cyclohexane ring are currently under investigation in our lab.

Acknowledgment. We are grateful to the National Cancer Institute, NIH (CA-25185) for the support of this research, and to the National Science Foundation for its contribution to the purchase of both a Bruker 360 MHz NMR and a Finnigan 4000 GC/MS instruments. M.A.C. is grateful for a Knoller Fellowship and for an Ethyl Corp. Fellowship during the course of this work.

Registry No. 1, 81158-99-8; **4**, 81159-00-4; (±)-**5**, 81159-01-5; (±)-**6**, 81159-02-6; (±)-**7**, 81159-03-7; (±)-**8**, 81159-04-8; (±)-**9**, 81159-05-9; (±)-**10**, 16613-45-9; (±)-**11**, 15271-51-9; 2,5-furandione, 108-31-6; 3-methyl-2,5-furandione, 616-02-4; 1,4-naphthalenedione, 130-15-4; 2-propenoic acid methyl ester, 96-33-3; 2-propynoic acid methyl ester, 922-67-8; 2-carboxybenzenediazonium bromide, 56024-26-1; 2-oxopropanedioic acid diethyl ester, 609-09-6; (±)-4-acetoxy-7-trimethylsilyl-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione, 81159-06-0; (±)-2,3,5,6-tetramethoxycarbonyl[2.2.2]bicyclooct-7-ene, 81203-29-4; (±)-1-acetoxy-4-trimethylsilyl-1,4,4a,9a-tetrahydroanthracene-9,10-dione, 81159-07-1; (±)-2-acetoxy-5-trimethylsilylcyclohex-3-enecarboxylic acid methyl ester, 81159-08-2; benzoic acid methyl ester, 93-58-3; naphthalene, 91-20-3; 1-trimethylsilylnaphthalene, 18052-80-7; 2,2-bis(ethoxycarbonyl)pyran, 81159-09-3; allyltrimethylsilane, 762-72-1; (±)-4-acetoxy-3a-methyl-7-trimethylsilyl-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione, 81159-10-6.

Supplementary Material Available: The experimental details of the synthesis of the diene **1** and spectroscopic data of the Diels–Alder adducts in Table I, as well as the synthetic intermediates **5–9**, are available (6 pages). Ordering information is given on any current masthead page.

(8) Still, C. W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(9) For Diels–Alder reactions of trimethylsilylated butadienes see: (a) Bock, H.; Seidl, H. *J. Am. Chem. Soc.* **1968**, *90*, 5694. (b) Fleming, I.; Percival, A. *J. Chem. Soc., Chem. Commun.* **1976**, 681. (c) Jung, M. E.; Gaede, B. *Tetrahedron* **1979**, *35*, 621. (d) Fleming, I.; Percival, A. *J. Chem. Soc., Chem. Commun.* **1978**, 178. (e) Batt, D. G.; Ganem, B. *Tetrahedron Lett.* **1978**, 3323. (f) Oppolzer, W.; Burford, S. C.; Marazza, F. *Helv. Chim. Acta* **1980**, *63*, 555. (g) Carter, M. J.; Fleming, I.; Percival, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2415. For a review on the preparation and Diels–Alder reactions of hetero-substituted 1,3-butadienes, see: Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753.

(10) (a) Carter, M. J.; Fleming, I. *J. Chem. Soc., Chem. Commun.* **1976**, 679. (b) Au-Yeung, B.-W.; Fleming, I. *Tetrahedron* **1981**, *37* (supplement 1), 13.

(11) Both buffered and unbuffered conditions with peracetic acid and MCPBA were employed. Interestingly, in a recent report, Fleming[9g] emphasizes that the peracid reaction of allylsilanes is effective only with unbuffered peracid, indicating the significance of the acidic conditions required for this reaction. See also ref 10b and footnote 1 in Hudrlik, P. F.; Withers, G. P. *Tetrahedron Lett.* **1976**, 29.

(12) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

(13) For the Lewis acid catalyzed elimination of β-hydroxysilanes to olefins, see: (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780. (b) Hudrlik, P. F.; Peterson, D. *Tetrahedron Lett.* **1974**, 1133 and references cited therein. (c) Chan, T. H. *Acc. Chem. Res.* **1977**, *10*, 442. (d) Hudrlik, P. F.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1981**, *103*, 6251.

(14) Doshi, M. M. *Diss. Abstr.* **1964**, *24*, 3998.

(15) For previous syntheses of shikimic acid, see ref 1b and: Bohm, B. A. *Chem. Rev.* **1965**, *65*, 435.