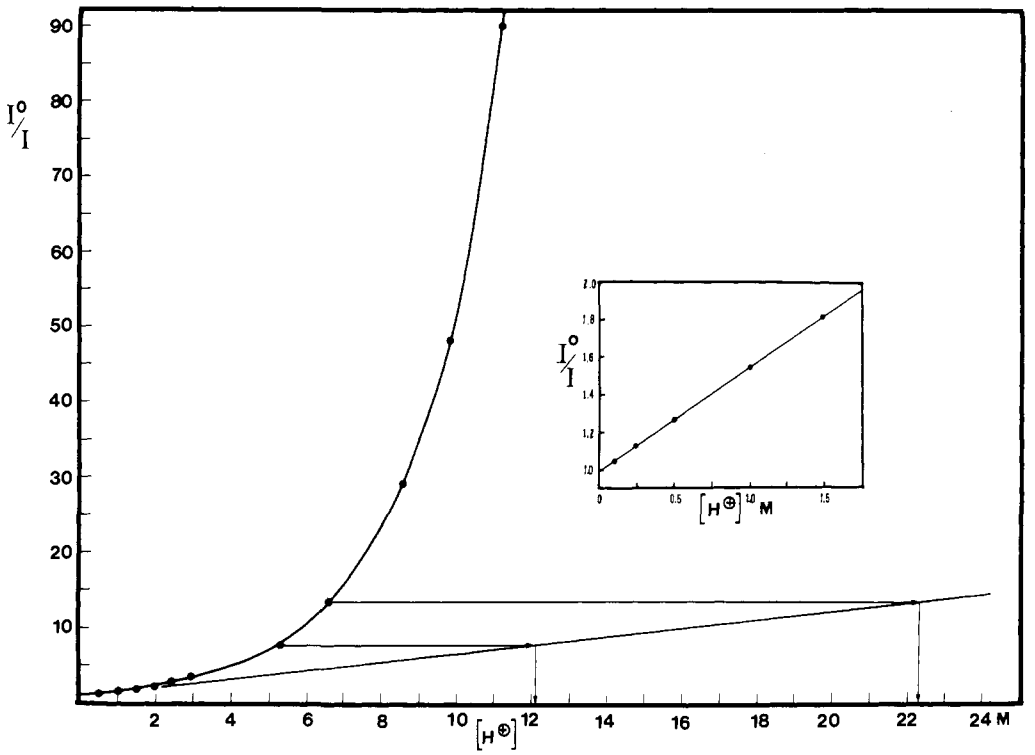

Figure 1. Stern-Volmer plot for the quenching of 1-cyanonaphthalene fluorescence vs. [H+]. The inset shows the region of 0-1.5 M expanded.

Table I. Singlet Lifetimes and Stern-Volmer Results for the Naphthalene Derivatives **2-7**

compd	τ,[a] ns	$k_q\tau$,[b,c] M^{-1}	$10^{-9}k_q$, M^{-1} s^{-1}	$k_q\tau$,[c,d] M^{-1}	$10^{-7}k_q$, M^{-1} s^{-1}
2[e]	9.28	11.4 ± 0.2 0.9996 (8)	1.22		
3	9.88	26.0 ± 0.1 0.99995 (8)	2.63		
4	8.96	12.0 ± 0.07 0.9996 (8)	1.36		
5[f]	10.5	<0.1[g]	<0.01	0.072 ± 0.001 0.9991 (6)	0.68
6	14.5	0.28 ± 0.02[g] 0.98 (7)	0.019	0.292 ± 0.002 0.9998 (5)	2.0
7	9.86	0.22 ± 0.01[g] 0.98 (5)	0.017	0.216 ± 0.005 0.998 (6)	2.2

[a] By single photon counting. [b] Using [H+] by titration. [c] Errors are standard deviation of the least-squares slope with correlation coefficient and number of points given below. [d] Using $[H^+]^{h\nu}$. [e] Values of 8.9 ns, 9.6 M^{-1}, and 1.08×10^9 M^{-1} s^{-1} have been reported for 20% acetonitrile/80% water.[9] [f] Values of 10 ns, <0.03 M^{-1}, and $<3 \times 10^6$ M^{-1} s^{-1} have been reported.[9] [g] Calculated from points up to [H+] = 2.0 M only.

Finally, some comment about the proton quenching of these substrates is required. The singlet lifetimes for the compounds allow calculations of the k_q values shown in the table. Compounds **4** and **7** are the naphthalene analogues of the benzyl alcohols studied by Wan and Turro.[2] There is clearly no meta effect. However, the reason is obvious. The 1-methoxy compounds all have similar reactivity with protons and it is well-established that the pathway for quenching of the excited state of 1-methoxynaphthalene (**2**) is via ring protonation.[9] Likely, the others are similarly quenched by protons. Since the 2-methoxy compounds are also all quenched at similar rates (about a factor of 10^2 slower than the 1-methoxy isomers) the most likely process is, again, ring protonation.[17] MO calculations[9] of the excited state of 1- and 2-methoxynaphthalene support the idea that electron density increases in the ring are greater for the 1-isomer. Clearly, substrates that have several basic centers must be examined quite carefully to determine what the k_q value obtained from fluorescence quenching means in terms of the reactivity of any given functional group. To have ascribed the k_q solely to benzylic cleavage in this case would have been wrong.

Acknowledgment. The financial assistance of NSERC of Canada is gratefully acknowledged.

(17) Note that 1-cyanonaphthalene and 2-cyanonaphthalene have very similar k_q values,[9] suggesting that quenching by protons occurs at nitrogen. The methoxynaphthalenes, in contrast, protonate at ring carbons. This suggests that $[H^+]^{h\nu}$ may be a fundamental property of the medium and not just a method of linearizing Stern-Volmer plots.

Acrolein Acetals as Allyl Cation Precursors in the Ionic Diels-Alder Reaction

Paul G. Gassman,* Daniel A. Singleton,[1]
James J. Wilwerding,[2] and Subhash P. Chavan

Department of Chemistry, University of Minnesota
Minneapolis, Minnesota 55455

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Diels-Alder reactions that employ acrolein as the dienophile often give undesirable results due to the ease of polymerization of acrolein. In order to circumvent this problem, a variety of Lewis acids[3] and high pressures[4] have been employed. Even under these conditions yields are often less than 50%. Our experience with the ionic Diels-Alder reaction of allyl cations[5] suggested that acetals of acrolein[6] (**1**) should be convenient precursors of the alkoxy-substituted allyl cations **2**, which, in turn, should be ex-

(1) National Science Foundation Fellow, 1983-1986.
(2) Petroleum Research Fund Undergraduate Summer Fellow, 1986.
(3) For typical examples, see: Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595. Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1985**, *26*, 2507. Laszlo, P.; Lucchetti, J. *Ibid.* **1984**, *25*, 2147.
(4) Dauben, W. G.; Krabbenhoft, H. O. *J. Org. Chem.* **1977**, *42*, 282.
(5) Gassman, P. G.; Singleton, D. A. *J. Am. Chem. Soc.* **1984**, *106*, 6085, 7993. Gassman, P. G.; Singleton, D. A. *J. Org. Chem.* **1986**, *51*, 3075.
(6) 3,3-Diethoxypropene (acrolein diethyl acetal) was purchased from Aldrich Chemical Co. and used without purification. 2-Vinyl-1,3-dioxolane was prepared according to the literature procedure (Piasecki, A.; Burczyk, B. *J. Prakt. Chem.* **1985**, *327*, 543).

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Scheme I

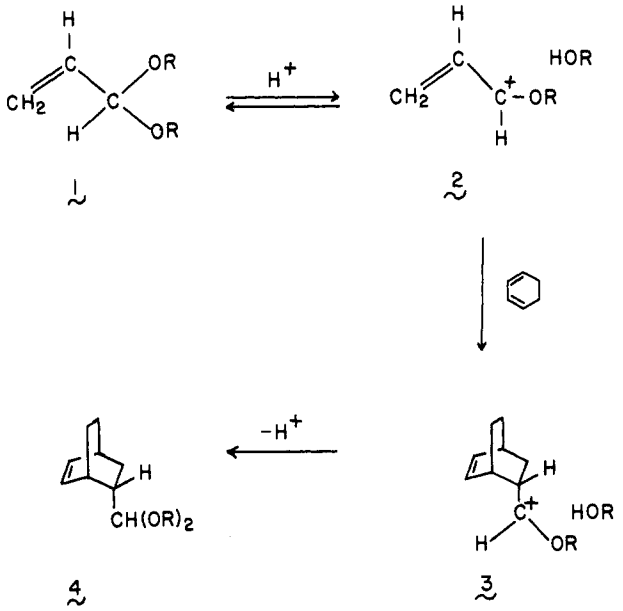
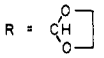


Table I. Yields Obtained in the Reactions of Acrolein Acetals with 1,3-Dienes

diene	product	R = $CH(OC_2H_5)_2$ **1a** isolated yield, %	R =  **1b** isolated yield, %	GLC yield, %
		57	94	100
		31	63[a]	72[a]
		48	58[b]	72[b]
		52	65	69
		27	62	63
		61	56	77

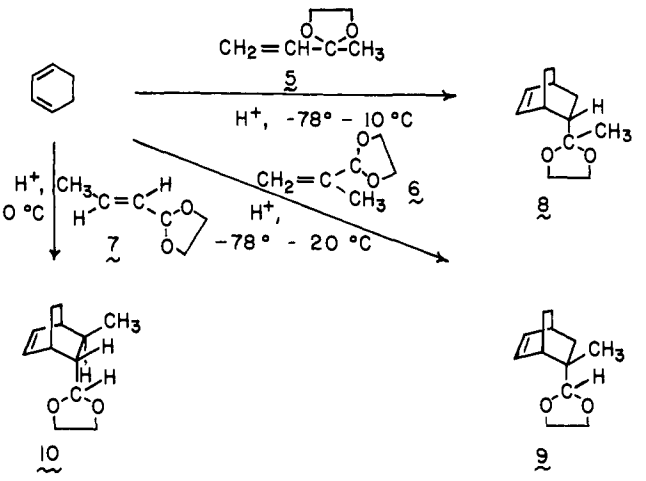
[a] This material is a 12:1 mixture of stereoisomers as determined by NMR analysis. [b] This material is an 8:1 mixture of stereoisomers as determined by NMR analysis. None of the regioisomer was detected. [c] A 4:1 ratio of isoprene to **1b** was used due to the ease of polymerization of isoprene.

cellent dienophiles (Scheme I). We now wish to report studies that confirm this hypothesis.

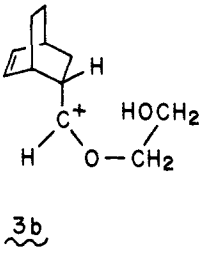
In a typical procedure utilizing 3,3-diethoxypropene[6] (**1a**, R = C_2H_5), 10 mmol of the appropriate diene and 5 mmol of **1a** in 50 mL of methylene chloride were cooled to −78 °C and 0.1 mmol (2 mol %) of triflic acid in 1,1,2-trichloro-1,2,2-trifluoroethane was added. The reaction was allowed to warm slowly while the presence of **1a** was monitored by GLC. When **1a** was no longer detected, 0.1 mL of triethylamine was added, the solvent was removed, and the product was isolated by column chromatography or by medium-pressure liquid chromatography. Table I lists the yields of Diels–Alder adducts obtained with a series of six common dienes.[7]

(7) Satisfactory elemental analyses and/or exact mass molecular weights were obtained on all new compounds. All new compounds had ^1H NMR, ^{13}C NMR, and IR spectra consistent with the assigned structures.

Scheme II



The cycloaddition of **1a** to a series of dienes via the intermediacy of **2a** is an attractive reaction because it occurs readily below 0 °C. This can be contrasted with the related Diels–Alder reactions of the intact acetals of α,β-unsaturated ketones and aldehydes, which require long reaction times at high temperature.[8] As can be noted from Table I, the yields obtained in the addition of 3,3-diethoxypropene were not attractive from a synthetic point of view. We reasoned that a possible cause of these mediocre yields was the diffusion of the alcohol away from the cation **3a** with resultant failure to recombine to yield **4a**. In order to circumvent this problem, we chose to use 2-vinyl-1,3-dioxolane[6] (**1b**, R = $-CH_2CH_2-$) as the precursor of **2b** and **3b**.[9] In this case, **3b** would



3b

have the alcohol moiety tethered and held in the proximity of the resulting carbocation. The data shown in Table I illustrate that in most cases this provided a dramatic increase in the yields of the cycloadducts. Because the isolated yields of products from 2-vinyl-1,3-dioxolane were based on reactions run on a 0.5-g scale, GLC yields were also obtained. These ranged from 63% to 100%.

In order to demonstrate the general scope of this cycloaddition reaction, we examined the effect of methyl substitution on 2-vinyl-1,3-dioxolane. Treatment of 1,3-cyclohexadiene with 2-methyl-2-vinyl-1,3-dioxolane (**5**; ethylene glycol acetal of methyl vinyl ketone[10]), 2-(2-propenyl)-1,3-dioxolane (**6**),[11] and 2-(1-propenyl)-1,3-dioxolane (**7**),[11] gave **8**[12] (78% yield; isolated from an 11:1 mixture[13] of **8** and its anti isomer), **9** (57% yield of a 6.5:1.0

(8) For examples of intramolecular Diels–Alder reactions of acetals of α,β-unsaturated ketones at temperatures of 170–200 °C for 24–15 h, see: Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1981**, *22*, 3929. Bal, S. A.; Helquist, P. *Ibid.* **1981**, *22*, 3933.

(9) For **1b**, the volume of solvent was reduced to 25 mL.

(10) Hahn, E. *J. Org. Chem.* **1973**, *38*, 2092.

(11) Acetals **6** and **7** were prepared according to a modification of the published procedure (Piasecki, A.; Burczyk, B. *J. Prakt. Chem.* **1985**, *327*, 543).

(12) The stereochemistry of **8** was established by both chemical and spectroscopic means. The Diels–Alder adduct of 1,3-cyclohexadiene and methyl vinyl ketone was prepared according to the literature procedure (Kozlov, N. S.; Raikova, T. S.; Aramo, A. P. *Vestsi Akad. Navuk BSSR, Ser. Khim. Navuk* (2) **1974**, 78). Acetal formation using this adduct and ethylene glycol gave **8**. Hydrolysis of **8** with aqueous 10% hydrochloric acid gave material identical with the adduct formed by the literature procedure. Eu(fod)$_3$ shift-reagent studies on **8** and on its epimer showed the acetal moiety to be syn to the double bond in **8** and anti to the double bond in the epimer of **8**.

mixture[14] of **9**[15] and its anti isomer), and **10** (67% yield of a 27:1 mixture of **10**[15] and its anti[16] isomer), respectively (Scheme II). The formation of **8-10** demonstrates that a variety of substitution patterns can be tolerated by **1b** without major inhibition of the formal 2 + 4 cycloaddition[17] of the corresponding allyl cation to 1,3-cyclohexadiene. This bodes well for the broad generality of this reaction.

In summary, we have developed a very low temperature process for the addition of acetals of acrolein and its derivatives to 1,3-dienes. We believe that the underlying mechanistic concept associated with this facile cycloaddition reaction will find widespread usage. We are currently exploring a variety of applications of these principles to other systems.

Acknowledgment. We are indebted to the National Science Foundation and to the General Medical Institute of the National Institutes of Health for grants that supported this investigation.

(13) The two components of the mixture were separated by chromatography and the isomer ratio was based on the isolated yields of 78% for **8** and 7% for the epimer of **8**.

(14) The isomer ratio was determined by the use of ^{1}H NMR studies.

(15) The stereochemistries of **9** and **10** were assigned on the basis of difference NOE studies and shift-reagent studies, respectively.

(16) Trace amounts (3-4%) of an impurity could be detected in **10** by ^{1}H NMR. The peak positions that could be determined for this impurity were consistent with it having the structure of the anti isomer.

(17) It is interesting to note that the structure of **10** establishes the formal suprafacial nature of our cycloaddition reaction.

Biosynthesis of Brevetoxins. Evidence for the Mixed Origin of the Backbone Carbon Chain and the Possible Involvement of Dicarboxylic Acids

Hong-Nong Chou and Yuzuru Shimizu*

Department of Pharmacognosy and Environmental Health Sciences, College of Pharmacy The University of Rhode Island Kingston, Rhode Island 02881

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The toxins found in the extremely deleterious red tide organism *Gymnodinium breve* (=*Ptychodiscus brevis*) possess unusual polycyclic ether structures examplified by brevetoxin A (**1**)[1] and brevetoxin B (**2**).[2] Although the ring systems of the two toxins differ significantly, the resemblance of the terminal four rings suggests their closely related biosynthesis. The methyl-substituted carbon chain backbone appeared to be biosynthesized by the straightforward elongation of acetate units and the introduction of methyl groups from methionine and/or propionate as seen with the biosynthesis of most polyketides and fatty acid derivatives. However, the feeding experiments conducted by the authors' group[3] and Nakanishi's group[4] using carbon-13-labeled acetates and methionine resulted in inexplicable labeling patterns in brevetoxin B (**2**), as summarized in Figure 1A. The puzzling finding prompted us to reexamine the entire ^{13}C NMR signal assignment[5] and repeat the experiments. Now we are able to present experimental data to explain what initially appeared to be irrational results.

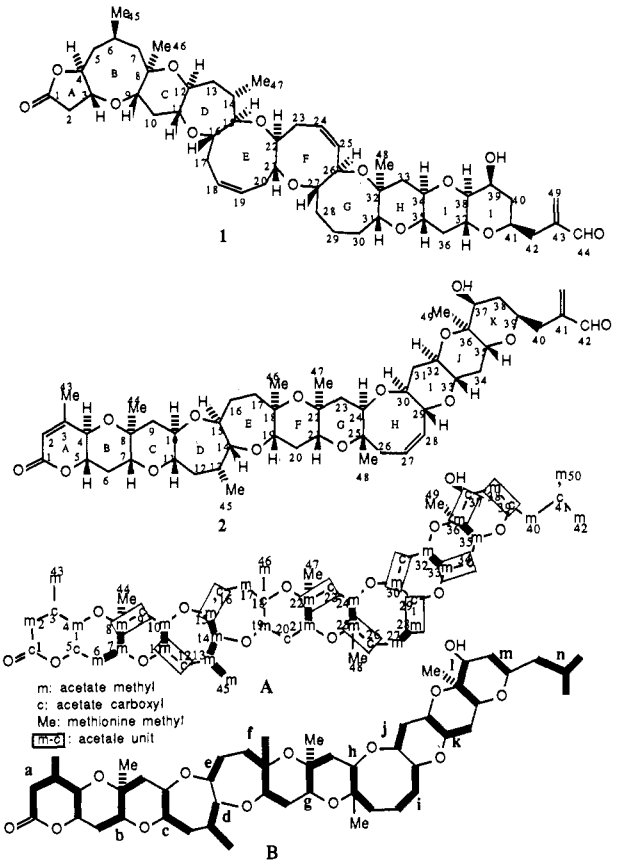

Figure 1. Structures of brevetoxin A (**1**) and brevetoxin B (**2**), the labeling patterns resulted from feeding experiments with carbon-13-labeled precursors (A) and assumed building blocks of **1** (B). The solid lines in (A) indicate the presence of couplings.

First we observed that the prolonged incubation with carbon-13-labeled acetate led to the random but differential labeling of carbons in **2**. In attempts to pulse feed acetate by a brief exposure of the organism to a large dose of methyl-^{13}C-labeled acetate, we isolated **2**, whose ^{13}C NMR spectrum shows carbon-carbon spin-spin couplings with only selected carbons.

In a typical experiment, the organism was grown in NH-15 medium[6] in Fernbach flasks (2 L × 10) under 4000-5000-lux illumination. Eleven days after inoculation, each flask was fed with [2-$^{13}C_1$]CH_3COONa (100 mg), chloramphenicol (5 mg), and streptomycin (10 mg). After 48 h, the culture was harvested, and a total of 1.1 mg of pure **2** was isolated according to the previously established procedure.[7] The ^{13}C NMR spectrum of the isolated toxin[8] showed enrichment with all the carbons which were found to be of acetate methyl origin in the previous experiments, but most significantly, the signals for the carbon fragments C6-C7-C8, C10-C11, C45-C13-C14-C15, C21-C22, C24-C25, C27-C28, C32-C33, and C35-C36 showed distinct splittings due to spin-spin couplings between the adjacent carbons. No such randomization was observed when carboxyl-labeled acetate was fed under a similar condition.[8] *The observed couplings indicate that those carbon fragments were constructed by rather confined carbon-carbon linkage formation between methyl originated carbons during the concentrated pulse feeding.* Furthermore, feeding experiments with [1,2-$^{13}C_2$]acetate indicate that

(1) Shimizu, Y.; Chou, H. N.; Bando, H.; Van Duyne, G. D.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514-515.

(2) Lin, Y. Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773-6775.

(3) [1-^{13}C]Acetate, [2-^{13}C]acetate, [1,2-$^{13}C_2$]acetate, and [*methyl*-^{13}C]-methionine were used in a number of feeding experiments. The details of the experiments will be published elsewhere.

(4) Lee, M. S.; Repeta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855-7856.

(5) The carbon signal assignment was made by a combination of hetero-COSY and exhaustive proton-decoupling experiments. The total proton and carbon assignment of signals in CD_2Cl_2 can be found in the supplementary material.

(6) Wilson, W. B.; Collier, A. *Science* (*Washington, D.C.*) **1955**, *121*, 394-395.

(7) Chou, H. N.; Shimizu, Y.; Van Duyne, G. D.; Clardy, J. C. In *Toxic Dinoflagellates*; Anderson, D. M., White, A. W., Baden, D. G., Eds.; Elsevier/North Holland: New York, 1985, pp 305-308.

(8) The ^{13}C NMR sppctra were obtained in CD_2Cl_2 on a Bruker WM500 instrument at 125 MHz with SW-29 500 Hz, AQ = 0.5 s, and PW = 5 μs. The numbers of scans (NS) are 45 816 and 12 404 for the samples from the methyl- and carboxyl-^{13}C acetate feedings, respectively. The spectra are provided in the supplementary material along with the assignment.

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