approximately equally between 10 1-L Erlenmeyer flasks, each of which contained 200 mL of sterile replacement medium. The replacement medium was identical to the "normal" fermentation medium described by Kusaka et al.[2a] except that it lacked both glucose and soluble starch. After replacement, the fermentation was carried out in the usual fashion. Labeled precursors were administered at ca. 40 and 48 h after the start of the original fermentation. The fermentation was usually terminated at about 115 h. The yield of aristeromycin under replacement conditions was typically less than half that produced under "normal" fermentation conditions.

Acknowledgment. We are pleased to acknowledge the support of this work by the National Institutes of Health (Grant No. GM 26569), The Robert A. Welch Foundation (Grant No. C-729), N.I.H. Institutional Funds, and an M. M. Hasselmann Fellowship (to V.B.). Thanks are also due to Dr. T. Kusaka for information concerning *S. citricolor*, to Dr. H. Floss for experimental details regarding the preparation of chirally tritiated glucose, to Drs. S. Yaginuma and M. Suffness for samples of neplanocin A, to Dr. T. L. Nagabhushan for a sample of aristeromycin, and to Dr. A. Kook for NMR spectra.

Registry No. 1, 19186-33-5; **2**, 72877-50-0; sodium formate, 141-53-7; glycine, 56-40-6; sodium bicarbonate, 144-55-8; adenosine, 58-61-7; D-ribose, 50-69-1; D-glucose, 50-99-7; D-fructose, 57-48-7.

Mechanism and Synthetic Applications of the Photochemical Generation and X–H Insertion Reactions of Oxacarbenes

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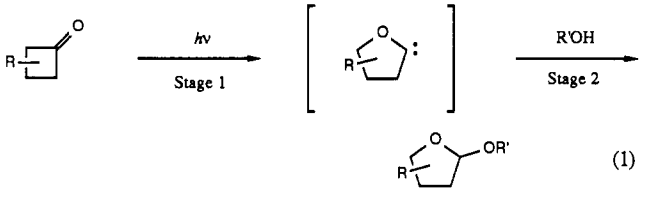
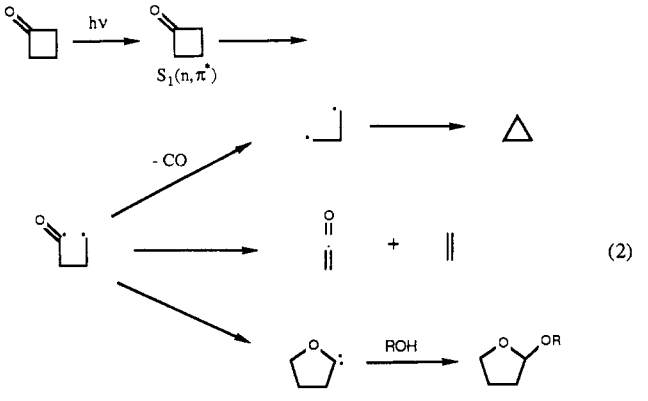
Abstract: A kinetic study of the photochemical ring expansion of cyclobutanones to oxacarbenes has shown that, in the presence of alcohol, the oxacarbene is generated irreversibly. Substrates for the intramolecular versions of the oxacarbene generation–insertion sequence (heteroalkylcyclobutanones) were prepared by an intramolecular [2 + 2]-Baeyer–Villiger sequence. These have been used to form 5-, 6-, 7-, and 8-membered nitrogen, oxygen, and sulfur bicyclic ring systems.

The production of tetrahydrofuryl ethers via irradiation of cyclobutanones in the presence of alcohols has been postulated to proceed as a two-stage process: the first is generation of a 2-tetrahydrofuranylidene; the second is insertion into the O–H bond (eq 1). Much of the previous work on this reaction has



(1)

focused on stage 1. The mechanistic postulate of Yates[2] for the first reported oxacarbene[3] generation, namely α-cleavage to a biradical followed by rebonding on oxygen (eq 2), has been adopted



(2)

widely.[4] This mechanistic view is strongly supported by the following factors: that ring expansion is highly regioselective in unsymmetrical cyclobutanones, that byproducts include cyclopropanes from decarbonylation and ketene-derived esters from β-cleavage, and that alkyl substitution enhances the yield of ring expansion products.[5] This latter point reflects the requirement for a nucleophilic alkyl radical for attack at the oxygen of the acyl radical.[6] One impediment to acceptance of the hypothesis is the retention of stereochemistry observed when the cyclobutanone possesses an α-stereogenic center.[7,8] This has led Quinkert to propose, based on qualitative and quantitative MO arguments, that conversion of S_1 (n,π*) cyclobutanone to the oxacarbene may be a concerted process.[9] However, stereospecific reactions (β-cleavage or ring formation) involving 1,4-biradicals are well-known.[10] This seeming conflict was resolved by Miller,[11] who independently generated 1,4-acylalkyl biradicals from the corresponding 1,1-diazenes. When the biradicals are produced in methanol, the tetrahydrofuryl ethers derived from them show retention of configuration. Thus, the α-cleavage mechanism has

(1) Research Fellow of the Alfred P. Sloan Foundation, 1986–1988. Presidential Young Investigator, 1985–1990.
(2) Yates, P.; Kilmurry, L. *Tetrahedron Lett.* **1964**, 1739. Yates, P.; Kilmurry, L. *J. Am. Chem. Soc.* **1966**, *88*, 1563.
(3) This term is used specifically to refer to cyclic α-alkoxycarbenes.
(4) (a) Yates, P.; Loutfy, R. O. *Acc. Chem. Res.* **1975**, *8*, 209. (b) Yates, P. *J. Photochem.* **1976**, *5*, 91. (c) Turro, N. J.; Morton, D. R. *J. Am. Chem. Soc.* **1973**, *95*, 3947. (d) Yates, P. *Pure Appl. Chem.* **1968**, *16*, 93. The mechanistic similarity to the Brook rearrangement of acylsilanes is also noted: Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77. Dalton, J. C. *Org. Photochem.* **1985**, *7*, 149.
(5) Turro, N. J.; Morton, D. R. *Adv. Photochem.* **1974**, *9*, 197.
(6) Turro, N. J.; Morton, D. R. *J. Am. Chem. Soc.* **1971**, *93*, 2569.
(7) (a) Turro, N. J.; McDaniel, D. M. *J. Am. Chem. Soc.* **1970**, *92*, 5727. (b) Quinkert, G.; Cimbollek, G.; Buhr, G. *Tetrahedron Lett.* **1966**, 4573. (c) Turro, N. J.; McDaniel, D. M. *Ibid.* **1972**, 3035.
(8) Pirrung, M. C.; DeAmicis, C. V. *Tetrahedron Lett.* **1988**, *29*, 159.
(9) (a) Quinkert, G.; Wiech, G.; Stohrer, W. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 199, 200. (b) Quinkert, G.; Jacobs, P.; Stohrer, W. D. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 197. (c) Quinkert, G.; Jacobs, P. *Chem. Ber.* **1974**, *107*, 2473.
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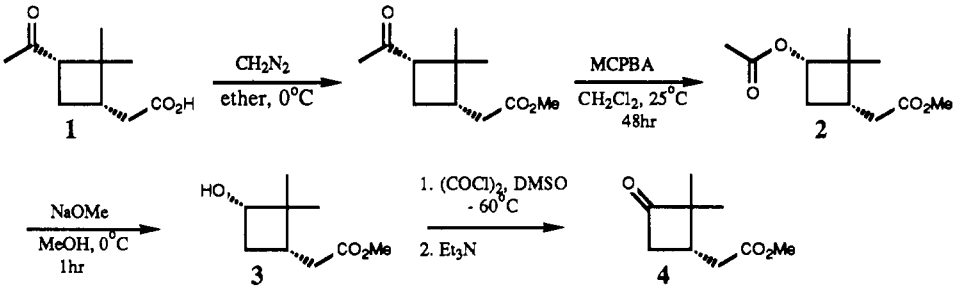
Scheme I. Synthesis of Cyclobutanone **4**



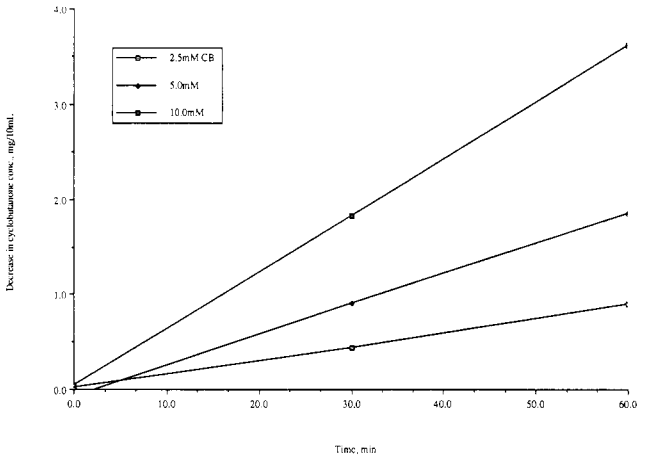


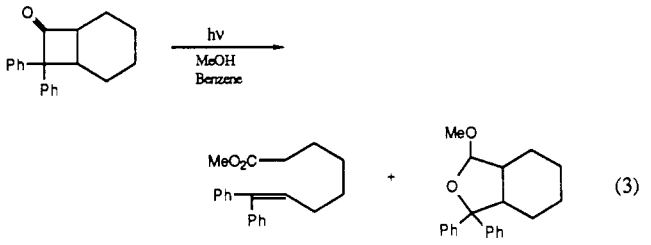
Figure 1. Irradiation of cyclobutanone **4** in 0.5 M methanol at varying concentrations.

both theoretical[12] and experimental support.

The existence of oxacarbenes in the ring-expansion process has received further support from Sheridan's study of the photochemistry of nortricyclanone in matrix isolation.[13] Both the observation of a UV spectrum consistent with theoretical predictions[14] and methanol-trapping experiments give strong evidence for the oxacarbene.

The insertion of a photochemically generated oxacarbene into the O–H bond of methanol was demonstrated by Turro in a deuterium-labeling experiment.[15] Subsequently, insertion into OH bonds of other alcohols[16] as solvent or in inert solvents[17] has been conducted. Intramolecular versions of the insertion reaction conducted in inert solvents have also been fruitfully applied toward various synthetic goals.[18]

One important issue concerns the reversibility of formation of oxacarbenes. Turro showed that the quantum yield for cyclobutanone disappearance drops substantially when the solvent is changed from methanol to cyclohexane.[5] Also, on the basis of Agosta's work[19] in which oxacarbenes were independently generated from tosylhydrazones and shown to revert to cyclobutanones, it was postulated that an equilibrium exists between oxacarbenes and cyclobutanones.[5,20] Lee-Ruff's results[21] on the effect of alcohol on the ring-expansion process in benzene also support this conclusion (eq 3).

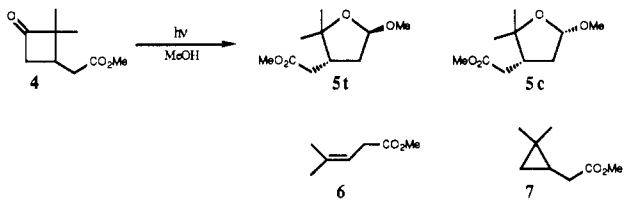


(3)

We have been involved in defining the uses of photochemically generated oxacarbenes for several synthetic goals.[8,18,22] It was therefore of interest to examine the mechanism of the oxacarbene-insertion reaction and investigate the breadth of its intramolecular version.

Results

A typical cyclobutanone was required for a kinetic study of the ring expansion–insertion reaction. As previously reported,[22a] detailed in the Experimental Section, and summarized in Scheme I, racemic *cis*-pinonic acid is converted to cyclobutanone **4** in 82% overall yield. It is transformed by irradiation in methanol solvent into the expected four products, **5c**, **5t**, **6**, and **7**. Neither the



β-cleavage products methyl acetate and **6** nor the decarbonylation product **7** are isolated due to volatility, but they were identified by GC/MS. The isolated yield of **5** is 60%. Stereochemical assignments are made based on DNOE studies of the trans isomer.[23] In the solvents methylene chloride, acetonitrile, and hexane, containing 0.25 M methanol, the yields of **5** are 65, 65, and 53%, respectively. The reaction rates in all four cases are comparable.

The photochemistry of **4** in the absence of trapping agents was also investigated. Irradiation in methylene chloride containing

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(19) (a) Agosta, W. C.; Ayral-Kaloustian, S. *J. Org. Chem.* **1982**, *47*, 284. (b) Agosta, W. C.; Foster, A. M. *J. Am. Chem. Soc.* **1972**, *94*, 5777. (c) *Ibid.* **1973**, *95*, 608. (d) Agosta, W. C.; Smith, A. B.; Foster, A. M. *Ibid.* **1972**, *94*, 5100.

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(22) (a) Pirrung, M. C.; DeAmicis, C. V. *Heterocycles* **1987**, *25*, 189. (b) Pirrung, M. C.; Kenney, P. M. *J. Org. Chem.* **1987**, *52*, 1635.

(23) DeAmicis, C. V. Ph.D. Thesis, Stanford University, 1987.

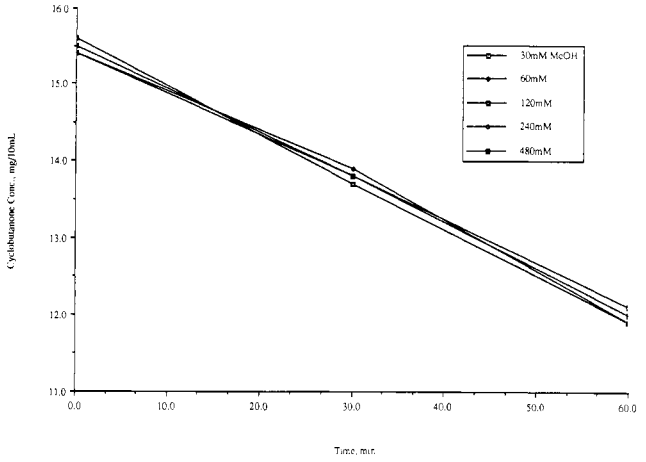
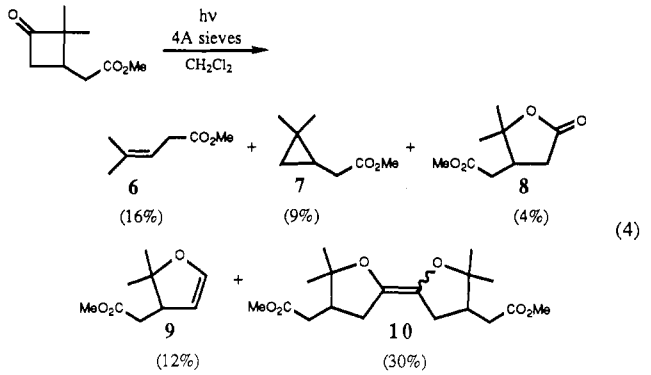


Figure 2. Irradiation of 10 mM cyclobutanone **4**, varying the methanol concentration.

molecular sieves produces three ring-expansion products **8–10** as well as **6** and **7** in the yields indicated (eq 4). The three new



(4)

products arise via reaction with oxygen[4] (**8**), 1,2-hydrogen shift (**9**), and dimerization (**10**). The products of 1,2-shift have not been previously reported in the cyclobutanone ring expansion (though Agosta did report such products from tosylhydrazones[19]) and Turro's labeling experiment rules out their intermediacy in acetal formation.[15] The only reports of oxacarbene dimerization have involved propellane systems.[24] The yields in eq 4 were determined by GC because of the difficulty in isolating the volatile compounds **6** and **7**. After flash chromatography, dihydrofuran **9** is obtained in 12% yield, and the oxacarbene dimer **10** is obtained in 22% yield.

The kinetics of the ring expansion–insertion of **4** were investigated to address the question of oxacarbene reversibility. At constant light intensity in the limit of low absorption, the rate law for loss of substrate should be first order in cyclobutanone and alcohol if the oxacarbene is formed reversibly (and must return to starting material) and zero order in alcohol if it is formed irreversibly. The rate of loss of cyclobutanone **4** was studied under optically thin conditions (OD $\leq$ 0.1) at low conversion ($\leq$20%) in methylene chloride containing methanol. Under pseudo-first-order conditions ([MeOH] = 0.5 M, [**4**] = 2.5–10 mM), the rate is linearly dependent on [**4**] (Figure 1) as expected. The converse pseudo-first-order study ([**4**] = 10 mM, [MeOH] = 30–480 mM) demonstrates that the rate is independent of methanol in this regime (Figure 2).

The time course of the irradiation of **4** in the absence and presence of methanol ([MeOH] = 0.25 M) under optically thick conditions (OD > 1.0) shows that over the first 10% of reaction (0.5 h) the rate is independent of methanol (data not shown). The rate of cyclobutanone loss does slow substantially after this period in the absence of methanol (Figure 3). Further, after 10 h of

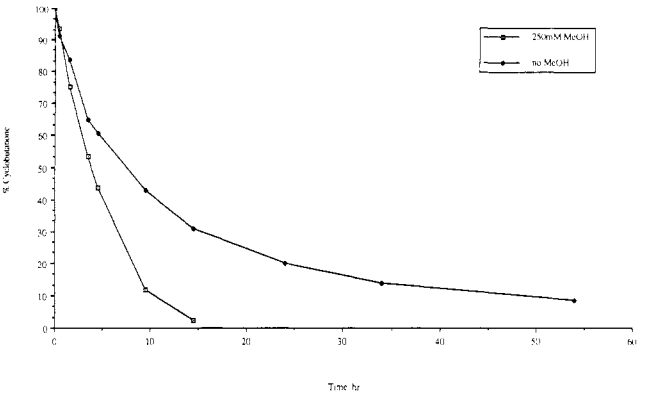
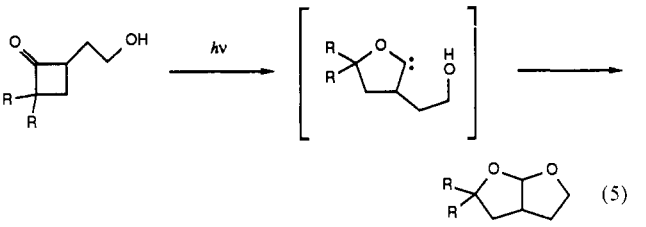


Figure 3. Irradiation of 41 mM cyclobutanone **4** in the presence and absence of methanol.

irradiation without a trap, the addition of methanol does not lead to a revival in rate. These data suggest that the photochemical ring expansion of **4** to the oxacarbene is inhibited after an initial period of irradiation in the absence of a trap. Reaction mixtures of this type show large increases in absorption at 280 nm. Thus, interfering absorbers generated during irradiation in the absence of trap must inhibit the reaction. If this idea is correct, irradiation under optically thin conditions should show no rate dependence on the presence of methanol. This is indeed observed (data not shown).

The formation of polyheterocyclic systems has achieved importance in synthetic organic chemistry in part because of the diverse array of biologically active natural products containing heterocyclic substructures.[25] Because of the common occurrence of the dioxabicyclo[*n*.3.0] ring system in such materials, it constituted the initial focus in an examination of the intramolecular version of the X–H insertion of oxacarbenes (eq 5). One example



(5)

of a known 2-(hydroxyethyl)cyclobutanone is the mixture **16**/**17**, obtained via the route shown in Scheme II.[26] Note that in **14**,

(24) (a) Fukuda, Y.; Toshihiko, N.; Kimura, K.; Odaira, Y. *J. Org. Chem.* **1980**, *45*, 177. (b) Fukuda, Y.; Odaira, Y.; Sakai, Y.; Negoro, T.; Fumiaki, H.; Tobe, Y.; Kumura, K. *J. Org. Chem.* **1981**, *46*, 2977.

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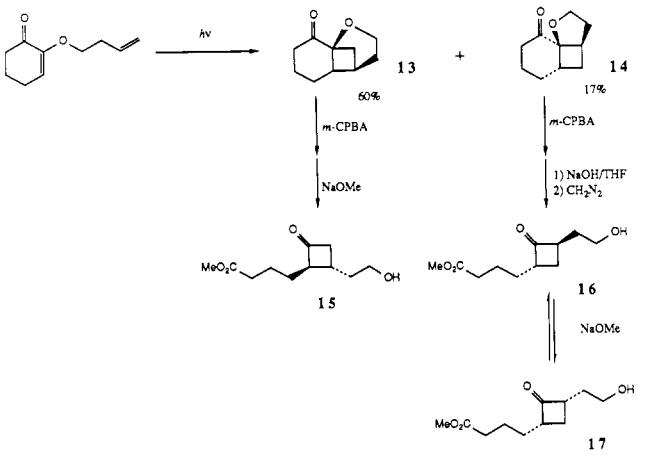
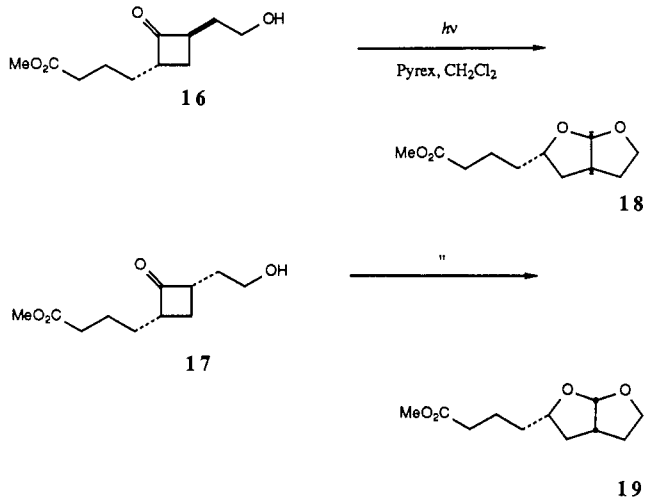
Scheme II. Ikeda's Preparation of Cyclobutanones **15–17**

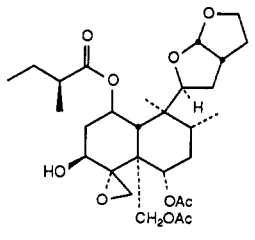


the trans relative stereochemistry is in place on the cyclobutane ring. In the course of methanolysis, this relationship is lost; however, by hydrolysis to the carboxylate salt and diazomethane esterification, the extent of epimerization (=production of **17**) can be minimized (15%).

The irradiation of **16**/**17** might be expected a priori to provide a regioisomeric mixture of products, since either α-cleavage pathway yields a secondary alkyl radical. However, **18**/**19** are



produced exclusively. They are assigned cis ring junction stereochemistries on the basis of the coupling constant and thermodynamic expectations about the [3.3.0] ring system. The relative sterochemistry of the butyric acid side chain is assigned by analysis of ^{1}H NMR data for **18** and related compounds such as ajugareptansin (**20**);[27] in particular, **18** has a doublet at 5.61 ppm (J



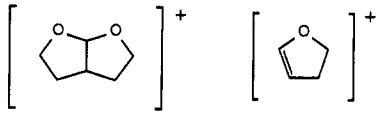
20

= 6 Hz) coupled to a complex 2.82 ppm signal, the bridgehead methine. In **20**, these signals are at 5.62 (6 Hz) and 2.75 ppm.

(26) Ikeda, M.; Takahashi, M.; Uchino, T.; Ohno, K.; Tamura, Y.; Kido, M. *J. Org. Chem.* **1983**, *48*, 4241.

(27) Camps, F.; Coll, J.; Cortel, A.; Messeguer, A. *Tetrahedron Lett.* **1979**, 1709.

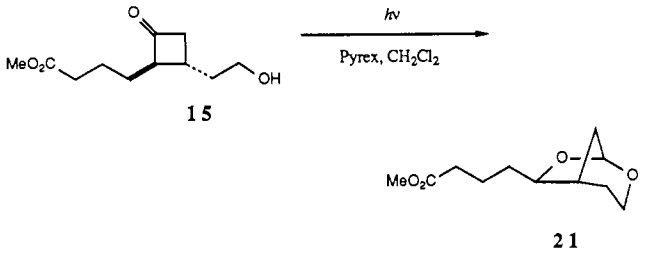
Additionally, a CH_2O absorption at 3.80 ppm corresponds to one at 3.84 ppm in **20**. In diastereomer **19**, obtained from irradiation of the minor isomer, the acetal resonance is at 5.72 ppm, and the CH_2O group is at 3.90 ppm. The gross structural characteristics of the ring-expansion products are also corroborated by comparison with **20**. In particular, mass spectral fragments of m/z 113 and 69 are prominent in all.



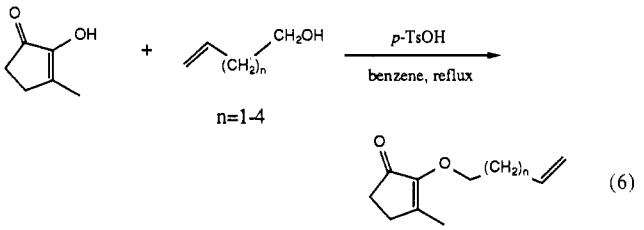
113 (base) 69

Solvent effects were examined via the irradiation of **16** and its derived acetate in methanol. In both cases, complex mixtures of at least 5 methyl acetals are produced. Temperature effects were consistent with literature reports that ring expansion is favored at lower temperature (50% yield at −60 °C);[11] however, no products of decarbonylation or β-cleavage could be identified.

Compound **15** is produced by Ikeda's route as a single stereoisomer under thermodynamic control; on irradiation the dioxabicyclo[3.2.1] system **21** is obtained in 45% yield. This skeleton represents a homothromboxane structure previously prepared only once.[28]



It was expected that α,α-disubstitution of the cyclobutanone would increase the yields in ring-expansion reactions. Enol ethers of 3-methyl-2-hydroxycyclopentenone with unsaturated alcohols were obtained in 88–99% yield as shown in eq 6. They were used

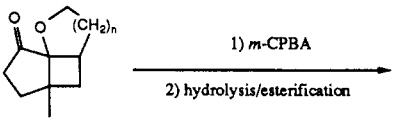


(6)

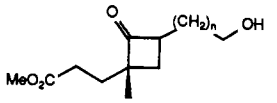
in a sequence similar to Ikeda's in Scheme II. The intramolecular photocycloaddition (5 mM, 350 nm) of compounds **22**–**25** (Scheme III) provides exclusively the head-to-head products. In all cases a single stereoisomer is obtained. The stereochemistry was not assigned for **28** or **29**, while **26** and **27** were assumed based on thermodynamics. The regiochemistry was best analyzed after conversion to the cyclobutanones, which was accomplished by Ikeda's procedure. Listed in eq 7 are the cyclobutanone products. In general, they can be obtained as stereochemically enriched mixtures at a sacrifice in yield (see the Experimental Section) by hydrolysis/methylation as reported above. Quantitative yields of 1:1 mixtures are obtained by methanolysis.

From compound **30** (1:1 mixture), four additional cyclobutanone derivatives were prepared (Scheme IV). PDC oxidation and cyanohydrin formation yield **36**. Mesylation produces **34**, which on treatment with sodium azide gives **35**. These reaction conditions cause equilibration of the hydroxyethyl side chain when stereochemically enriched **30** is used, so the use of a 1:1 mixture is suitable. Reduction of the azide by hydrogenation suffered

(28) Schaaf, T. K.; Busolotti, D. L.; Parray, M. J.; Corey, E. J. *J. Am. Chem. Soc.* **1981**, *103*, 6502.



26 n=1
27 n=2
28 n=3
29 n=4



(7)

30 n=1	4:1
31 n=2	7.5:1
32 n=3	8:1
33 n=4	1:1

problems connected with imine formation, so a recently reported reductive acylation method was used.[29] Treatment of **35** with thioacetic acid provides acetamide **37** in 65% yield and thioacetamide **38**, a product type not observed by Rosen and coworkers, in 15% yield. The acetamide can also be obtained by hydrogenation in the presence of acetic anhydride (98%). The mesylate, on treatment with potassium thioacetate,[30] forms an intermediate thioester which on methanolysis generates the bicyclic system **39**.

The ring expansion–insertion reactions of cyclobutanones **30–33** and **36–39** are summarized in Chart I. Irradiation of these cyclobutanones with a Hanovia-Pyrex source or in a Rayonet photoreactor at 350 nm is conducted in methylene chloride. Conversion to bicyclic acetals **40–47** requires 16–40 h. Assignment of ring-fusion stereochemistry is based on the coupling constant of the readily discernible acetal proton and force field calculations.[31] For compound **40**, a 5.2 Hz coupling constant is observed, and the cis fusion is expected to be >5 kcal/mol more stable. In the dioxabicyclo[4.3.0] system **41**, the cis fusion is predicted to be 1.4 kcal/mol more stable; the coupling constant is 3.5 Hz. For **42** and **43**, the number of conformations of comparable energy with both cis and trans fusions made structural assignment with the aid of calculation impossible. For **42**, the coupling constant is 5.4 Hz; in the case of **43**, the two diastereomers are separable by crystallization, and coupling constants are 4.6 and 4.4 Hz.

Irradiation of **31** and **32** gives products **41** and **42** in which the diastereomeric ratio in the starting material is *not* reflected in the product. For example, **31** (2.5:1 mixture) is converted to a 1.5:1 mixture of **41**. On irradiation of an 8:1 mixture of diastereomers of **32**, a 1:1 mixture of **42** is obtained. By carrying the reaction to 50% conversion and isolating both product and starting material, it was shown that these observations reflect equilibration of the cyclobutanone. A 1.5:1 mixture of **32** and 1.5:1 mixture of **42** were obtained.

On the basis of previous observations on the intermolecular reaction,[22] it is not surprising that insertion into an amide NH to produce **45** and **46** proceeds successfully. Coupling constants for the acetal protons in these amides are 6.0–6.4 Hz. Thiols are also expected to successfully participate in this reaction sequence. However, the formation of the hemithioacetal **39** posed a new problem. It was circumvented by irradiation in the presence of a catalytic amount of triethylamine, which does in fact lead to the sulfur-oxygen bicyclic **47** in respectable yield. Presumably, the base serves as catalyst for ring–chain tautomerism, allowing the cyclobutanone to absorb a photon and enter the by now well-appreciated reaction manifold.

Discussion

The kinetic data reported above have shown that for the simple cyclobutanone **4**, *the photochemical generation of the oxacarbene is irreversible.* Presuming, on the basis of theoretical studies,[12,14] that a dissociative mechanism via the biradical would apply to

Scheme III. Intramolecular [2+2] Photocycloaddition of Cyclopentenone Enol Ethers **22–25**

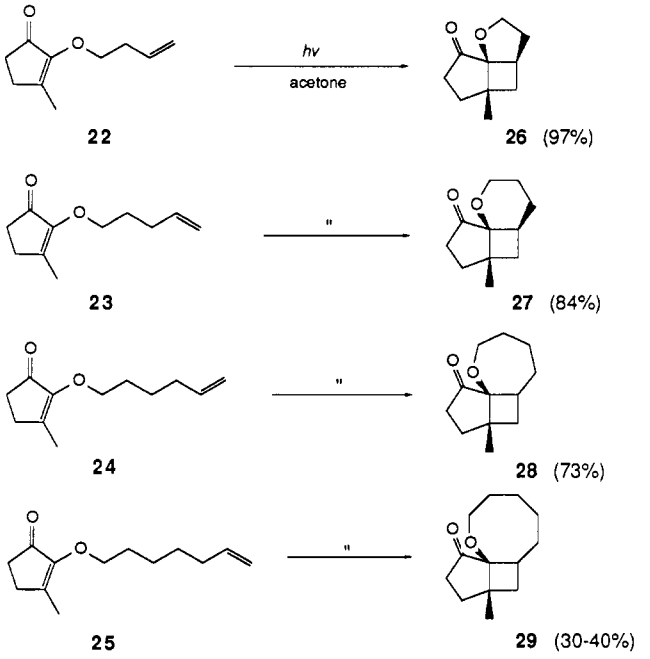
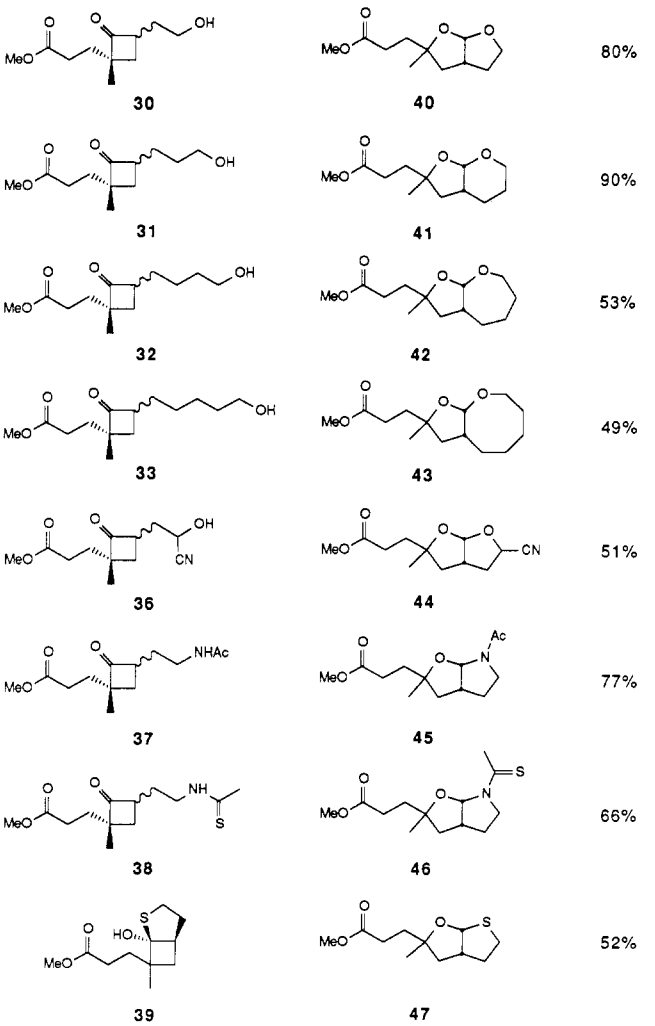
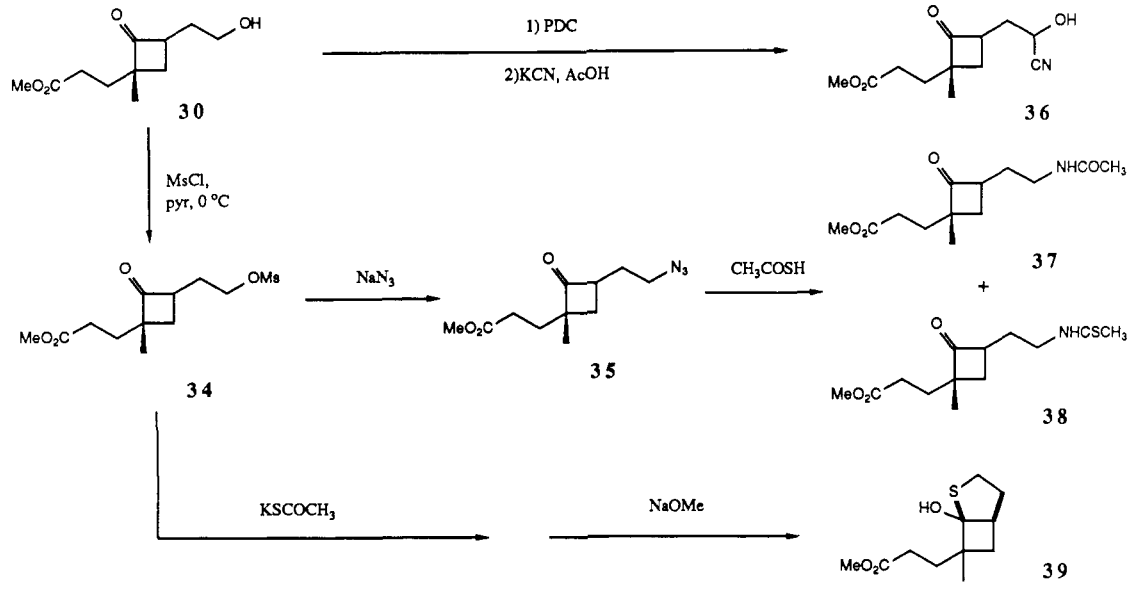


Chart I



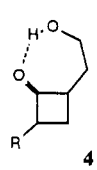
(29) Rosen, T.; Lico, I. M.; Chu, D. *J. Org. Chem.* **1988**, *53*, 1580.
(30) Chapman, J. H.; Owen, L. N. *J. Chem. Soc.* **1950**, 579.
(31) The Serena IBM PC version of MM2 was used.

Scheme IV. Preparation of Cyclobutanones **36–39**

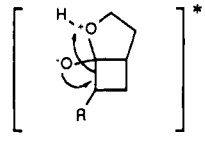


the reversion of oxacarbene to cyclobutanone, the difference of these results compared to previous studies of reversibility can be readily explained. Radical stabilizing groups such as phenyl or vinyl may promote reversion by lowering the barrier to C–O bond cleavage. In the absence of such stabilizing groups, alternative modes of reaction compete. This explains the high yields of oxacarbene dimers obtained on irradiation of propellane cyclobutanones, where no other channels are available. The kinetic data also show that, in previous studies where starting materials were recovered after long irradiations, the large increase of optical density in the absence of sufficiently active traps, rather than oxacarbene reversion, is responsible. Assuming diffusion-controlled reaction of the oxacarbene with trapping agent, its lifetime in the regime of our kinetic experiments is $>10^{-8}$ s. As we previously reported[22a] without kinetic data, reduced yields of ring-expansion products result when the trap is less than 3-fold in excess.

In the case of the 2,4-disubstituted cyclobutanone **16**/**17**, the high regiochemical control over the α-cleavage process requires explanation, since this substrate does not benefit from any factors previously shown to exert such control. Solvent is critically important in this reaction, and it was hypothesized[18b] that the key may lie in a directed, intramolecular hydrogen bond (cf. **48**).



48



49

Unlike most ketones, these (hydroxyethyl)cyclobutanones show little solvent effect on the (n,π^*) absorption. More bizarre alternative mechanisms for the intramolecular oxacarbene insertion, such as nucleophilic attack of the alcohol on the excited state of the cyclobutanone to give **49** followed by diotopic rearrangement, remain untested. It is clear that, in the ground state, cyclic forms of **48** can contribute nothing to the observed reactivity, since they lack a chromophore. The favored formation of **39** due to sulfur substitution shows the fairly delicate balance between open and closed forms, however, which is dependent on the preferred bond lengths and angles of the atoms involved. This compound's successful participation in photochemical ring expansion demonstrates a facile equilibrium between the two forms.

The preparation of the disubstituted cyclobutanones relies on the intramolecular photochemical [2 + 2] cycloaddition of **22–25**. This path is extremely successful for ring sizes five through seven and is serviceable for the 8-membered ring **29**. Only one previous report concerns an intramolecular [2 + 2] photocycloaddition to produce a cyclooctane derivative.[32]

The intramolecular insertion of photochemically generated oxacarbenes is an efficient method for generation of oxabicyclic systems as evidenced in Chart I. Even in situations where 7- and 8-membered rings are being formed, respectable yields are obtained. This is in contrast to previous reports on the synthesis of medium-ring heterocycles via metal-mediated carbene-insertion reactions.[33] The most vexing problem with applications of the reaction in the synthetic context is the facile equilibration of the starting cyclobutanones.

Experimental Section

Methyl 2,2-Dimethyl-3-oxocyclobutaneacetate (4). A solution of 1.3 mL (1.9 g, 15 mmol) of oxalyl chloride in 25 mL of dichloromethane was cooled to −60 °C and 1.8 mL (2.0 g, 25 mmol) of DMSO was added dropwise over 5 min. After stirring of the mixture for 10 min, a solution of 1.72 g (10.0 mmol) of **4** in 10 mL of dichloromethane was added over 5 min. The reaction was allowed to warm to room temperature and 30 mL of H_2O added. After stirring for 10 min, the phases were separated, and the aqueous phase was extracted with 2 × 25 mL dichloromethane. The dichloromethane extracts were combined, washed with 1 N HCl, 5% sodium bicarbonate, and brine solution, dried ($MgSO_4$), and filtered. Rotary evaporation of the solvent gave 1.6 g (97%) of crude product. Purification by HPLC (ethyl acetate/hexanes, 20:80) gave 1.4 g (84%) of cyclobutanone **3** as a colorless oil. GC: t_R 3.13. ^{1}H NMR ($CDCl_3$): δ 3.70 (s, 3 H), 3.24 (dd, J = 8.4, 17.8 Hz, 1 H), 2.78 (dd, J = 6.7, 18.0 Hz, 1 H), 2.62–2.50 (m, 3 H), 1.24 (s, 3 H), 1.08 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 208, 172, 77, 60, 48, 34, 32, 22, 16. IR (film): 2960, 1780, 1735, 1440, 1380, 1320, 1270, 1200, 1190, 1070, 1020 cm^{-1}. UV (CH_2Cl_2): λ_{max} 295 (ϵ 20). MS: 142.1 (10), 128.1 (11), 111.0 (6), 96.0 (25), 70.0 (33), 69.1 (59), 68.1 (27), 67.0 (11), 59.0 (15), 41.1 (100). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.27; H, 8.39.

Methyl (3*R,5*R**)- and (3*R**,5*S**)-5-Methoxy-2,2-dimethyltetrahydro-3-furanacetate (5c and 5t).** A solution of 63.2 mg (0.371 mmol) of cyclobutanone **4** in 8 mL of degassed methanol was placed into a stoppered 13 mm × 100 mm Pyrex tube and irradiated for 16 h. Rotary evaporation gave 56.3 mg (75%) of crude product. Purification by flash chromatography (ethyl acetate/hexanes, 10:90) gave 44.7 mg (60%) of **5c** and **5t** as a 1:1.5 mixture (by ^{1}H NMR). The mixture was separated by HPLC (ethyl acetate/hexanes, 15:85). **5c**: HPLC: t_R 26.71. ^{1}H NMR ($CDCl_3$): δ 4.97 (dd, J = 4.0, 6.2 Hz, 1 H), 3.69 (s, 3 H), 3.35 (s, 3 H), 2.53 (ddd, J = 6 Hz, 8, 13, 1 H), 2.44–2.28 (m, 3 H), 1.68 (ddd, J = 4, 9, 13, 1 H), 1.25 (s, 3 H), 1.17 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 173.1, 104.3, 82.6, 55.2, 51.7, 43.9, 39.1, 35.2, 28.1, 23.4. IR (film): 2980, 1740, 1440, 1380, 1310, 1210, 1160, 1110, 1040, 990, 960, 850 cm^{-1}. MS: 187.1 (5), 171.1 (13), 155.0 (31), 139.0 (21), 97.0 (30), 84.0 (56), 71.1 (70), 55.1 (54), 43.1 (89), 41.1 (100). Anal. Calcd for

(32) Winkler, J. D.; Hey, J. P.; Hannon, F. J. *Heterocycles* **1987**, *25*, 55.
(33) Heslin, J. C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1417.

$C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 58.78; H, 8.73. **5t**: HPLC: t_R 31.32. ^{1}H NMR ($CDCl_3$): δ 4.90 (d, J = 4.9 Hz, 1 H), 3.68 (s, 3 H), 3.33 (s, 3 H), 2.60 (m, 1 H), 2.40 (dd, J = 5.5, 14.9 Hz, 1 H), 2.23 (dd, J = 9.7, 14.9 Hz, 1 H), 2.16 (dd, J = 6.7, 12.8 Hz, 1 H), 1.78 (ddd, J = 5.4, 11.6, 12.8 Hz, 1 H), 1.35 (s, 3 H), 1.05 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 172.8, 103.0, 83.2, 54.2, 51.7, 42.0, 39.0, 35.1, 29.5, 23.7. IR (film): 2980, 1740, 1440, 1370, 1310, 1265, 1200, 1165, 1140, 1100, 1040, 980 cm^{-1}. MS: 187.1 (4), 171.1 (14), 155.1 (28), 139.1 (21), 97.1 (25), 84.1 (49), 71.1 (60), 55.0 (53), 43.1 (89), 41.1 (100). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 59.15; H, 9.18.

Methanol Trapping in Inert Solvents. Into three 13 mm × 100 mm Pyrex tubes were placed 72 mg (0.42 mmol) of cyclobutanone **4**, 67 mg (2.0 mmol) of methanol, and 8 mg of *n*-decane (used as an internal standard for GC analysis). To tubes 1, 2, and 3 were added 8 mL of degassed dichloromethane, hexanes, and acetonitrile, respectively. Each tube was sealed with a serum stopper and irradiated for 20 h. The solvents were removed by rotary evaporation, and the crude product was purified by flash chromatography. This gave 54.5 mg (65%), 41.0 mg (53%), and 54.5 mg (65%) of a 1:1.5 mixture of **5c** and **5t** for tubes 1, 2, and 3, respectively.

Irradiation of Cyclobutanone 4 in the Absence of a Trapping Agent. A solution of 92 mg (0.54 mmol) of cyclobutanone **4** in 7 mL of degassed dichloromethane containing 4-Å molecular sieves was irradiated for 3 days. The solvent was removed by rotary evaporation and the product was purified by gradient flash chromatography (ethyl acetate/hexanes, 5:95 (100 mL), 20:80 (150 mL), 30:70 (100 mL)). This gave 12 mg (16%) of methyl 4-methyl-pent-3-enoate, **6**, 11 mg (12%) of methyl 2,2-dimethyl-4,5-dihydro-3-furanacetate, **9**, 1 mg of **8**, and 20 mg (22%) of methyl 2,2-dimethyl-5-(2,2-dimethyltetrahydro-3-(methoxycarbonyl)furan-5-ylidene)tetrahydro-3-furanacetate, **10**. **9**: GC: t_R 2.03. ^{1}H NMR ($CDCl_3$): δ 6.23 (t, J = 2.3 Hz, 1 H), 4.83 (t, J = 2.6 Hz, 1 H), 3.69 (s, 3 H), 3.01 (m, 1 H), 2.46 (dd, J = 6.8, 15.8 Hz, 1 H), 2.28 (dd, J = 8.5, 15.8 Hz, 1 H), 1.37 (s, 3 H), 1.25 (s, 3 H). IR (film): 2935, 1740, 1440, 1370, 1270, 1175, 1130, 1050 cm^{-1}. MS: 170 (16), 142 (4), 138 (13), 110 (19), 97 (88), 82 (37), 69 (23), 55 (30), 41 (100). HRMS: m/e calcd for $C_9H_{14}O_3$ 170.0942, found 170.0941. **10** (mixture of four isomers): GC: t_R 6.72 and 6.77. ^{1}H NMR ($CDCl_3$): (two isomers) δ 3.69 (s, 3 H), [2.81 (m), 2.72 (dd, J = 9, 19 Hz), 1 H], [1.00 (s), 0.61 (s), 3 H]. ^{1}H NMR ($CDCl_3$): (two isomers) δ 3.69 (s, 3 H), [2.76 (dd, J = 9, 19 Hz), 2.67 (m), 1 H], [1.22 (s), 1.04 (s), 3 H], [0.95 (s), 0.61 (s), 3 H]. IR (film): (four isomers) 2980, 2960, 1740, 1440, 1375, 1310, 1250, 1210, 1165, 975 cm^{-1}. MS: 340.1 (4), 309.1 (3), 267.1 (3), 212.1 (100), 180.1 (20), 162.1 (14), 109.1 (14), 95.1 (13), 69.1 (29), 55.1 (20). HRMS: m/e calcd for $C_{18}H_{28}O_6$ 340.1885, found 340.1880.

Methyl 4-[(1*S,5*S**,6*R**)-2,7-Dioxabicyclo[3.2.1]oct-6-yl]butyrate (21).** A solution of **15** (23 mg, 0.11 mmol) in 5 mL of CH_2Cl_2 was irradiated in a quartz test tube by a Pyrex-filtered Hanovia lamp. After 3 h, the solvent was evaporated and the residue was purified by flash chromatography to afford 10.1 mg (45%) of **21**. ^{1}H NMR ($CDCl_3$): δ 5.34 (d, J = 1.6 Hz, 1 H), 4.12 (t, J = 6.3 Hz, 2 H), 3.91 (td, J = 12.1, 4.8 Hz, 1 H), 3.72 (dd, J = 6.8, 4.4 Hz, 1 H), 3.68 (s, 3 H), 2.37 (td, J = 7.4, 3.0 Hz, 2 H), 2.0–1.4 (m). IR (film): 2950, 1740, 1470, 1190, 1120 cm^{-1}. HRMS: m/e calcd for $C_{11}H_{18}O_4$ 214.1203, found 214.1193.

3-Methyl-2-(3-butenyloxy)cyclopent-2-enone (22). A solution of 25.00 g (0.22 mol) of 3-methyl-1,2-cyclopentanedione, 21.1 mL (17.68 g, 0.25 mol) of 3-buten-1-ol, and 2.60 g (0.01 mol) of *p*-toluenesulfonic acid monohydrate in 625 mL of benzene was refluxed through a Soxhlet extractor filled with molecular sieves (4 Å) for 24 h. The reaction was monitored by thin-layer chromatography and gas chromatography. The reaction mixture was cooled to room temperature and washed with 1 N sodium hydroxide and brine. The organic layer was dried (magnesium sulfate) and concentrated by rotary evaporation. Kugelrohr distillation afforded 32.4 g (88%) of a clear, colorless liquid, bp 82–85 °C (0.4 Torr). IR (neat): 3080, 2920, 1700, 1645, 1335, 1205, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.85 (ddt, J = 17.0, 10.3, 6.8 Hz, 1 H), 5.10–5.15 (ddd, J = 17.2, 3.4, 1.6 Hz, 1 H), 5.05–5.09 (ddt, J = 10.3, 2.2, 1.1 Hz, 1 H), 4.18 (t, J = 6.7 Hz, 2 H), 2.42–2.45 (m, 2 H), 2.39–2.41 (dt, J = 6.4, 1.4 Hz, 2 H), 2.34–2.38 (m, 2 H), 1.98 (s, 3 H). HRMS: m/e calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.1002.

(1*R,5*S**,7*R**)-7-Methyl-2-oxatricyclo[5.3.0.0^{1,5}]decan-10-one (26).** A solution of 1.80 g (10.8 mmol) of **22** in 100 mL of acetone was degassed with nitrogen for 15 min. The solution was irradiated at 350 nm for 7 h. Concentration by rotary evaporation gave 1.74 g (97%) of a yellow oil, bp 68 °C (0.3 Torr). IR (neat): 2955, 2870, 1740, 1450, 1165, 1068, 1023 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.38 (ddd, J = 9.0, 7.8, 2.5 Hz, 1 H), 4.17 (ddd, J = 10.1, 8.9, 6.0 Hz, 1 H), 2.91 (tdd, J = 8.1, 6.3, 1.7 Hz, 1 H), 2.66 (dt, J = 18.2, 9.1 Hz, 1 H), 2.33 (ddd, J = 18.0, 9.6, 5.1 Hz, 1 H), 2.14 (dd, J = 12.6, 8.3 Hz, 1 H), 1.86–2.06 (m, 3 H), 1.78 (ddt, J = 12.5, 6.0, 2.1 Hz, 1 H), 1.68 (dd, J = 12.6, 6.3 Hz, 1 H), 1.11 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 216.18, 91.07, 71.43, 41.14, 39.60, 36.14, 35.15, 34.45, 31.80, 21.41. HRMS: m/e calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0990.

(1*R,6*S**,8*R**)-6-Methyl-2,11-dioxatricyclo[6.3.0.0^{1,6}]undecan-3-one.** To a solution of 0.51 g (3.08 mmol) of **26** in 25 mL of methylene chloride was added 2.00 g (9–10 mmol) of *m*-chloroperoxybenzoic acid. The reaction mixture was stirred at reflux for 1 h and then concentrated by rotary evaporation. The residue was taken up in ether and washed twice with 10% sodium sulfite, twice with sodium bicarbonate, and twice with brine. The organic layer was dried (magnesium sulfate) and concentrated by rotary evaporation to afford 0.39 g (70%) of a pale yellow oil. Recrystallization from ether afforded a white solid, mp 35–36 °C. IR (neat): 2940, 2880, 1745, 1450, 1250, 1175, 1088, 1050, 1000 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.34 (ddd, J = 8.9, 7.7, 5.5 Hz, 1 H), 4.15 (dt, J = 8.7, 7.2 Hz, 1 H), 2.85–2.91 (m, 1 H), 2.50 (dd, J = 7.2, 6.0 Hz, 2 H), 2.21 (dtd, J = 12.7, 8.0, 6.8 Hz, 1 H), 1.97–2.03 (dd, J = 12.1, 9.8 Hz, 1 H), 1.90–1.97 (m, 1 H), 1.82–1.87 (m, 1 H), 1.76–1.83 (dddd, J = 12.8, 7.6, 5.3, 2.2 Hz, 1 H), 1.26 (dd, J = 12.1, 6.9 Hz, 1 H), 1.16 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 170.13, 112.21, 71.24, 42.19, 39.53, 32.72, 31.47, 30.60, 27.72, 19.48. HRMS: m/e calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0941.

Hydrolysis of Lactones to Cyclobutanones. Method A. A solution of the lactone in THF/water was cooled to 0 °C in an ice/brine bath. Sodium hydroxide (0.95 equiv) was added dropwise and the reaction mixture was stirred an additional 5 min. The THF was removed by rotary evaporation. The remaining aqueous layer was extracted with ether to remove residual lactone and then acidified with hydrochloric acid and extracted with ether. The organic layer was dried (magnesium sulfate) and concentrated by rotary evaporation to yield the crude acid. Esterification was accomplished by reaction with a solution of diazomethane in ether at 0 °C. The reaction mixture was concentrated by rotary evaporation to yield the crude ester.

Method B. To a solution of the lactone in dry methanol under nitrogen was added approximately 1 equiv of sodium. The reaction mixture was stirred until complete conversion to the methyl ester as evidenced by thin-layer chromatography and gas chromatography. The reaction mixture was quenched with hydrochloric acid and extracted with methylene chloride. The organic layer was washed with brine, dried (magnesium sulfate), and concentrated by rotary evaporation to yield the desired cyclobutanone derivative.

Methyl 3-[4-(2-Hydroxyethyl)-2-methyl-1-oxocyclobut-2-yl]propionate (30). Method A. To a solution of 5.00 g (27.47 mmol) of **26′** in THF/water at 0 °C was added 24.70 mL (26.06 mmol) of 1.055 N sodium hydroxide. In accord with the above described procedure, the crude ester was obtained. Purification by flash chromatography with 1:1 hexanes/ethyl acetate yielded 1.72 g (30%) of a pale yellow oil as a 4:1 mixture of diastereomers. Purification was also achieved by Kugelrohr distillation, bp 105–115 °C (0.05 Torr). Unreacted **26′** (0.54 g, 11%) was recovered. IR (neat): 3470, 2960, 2880, 1770, 1740, 1205, 1185 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.63–3.78 (m, 2 H), 3.68 (s, 3 H), 3.41–3.50 (m, 1 H), 2.57 (br s, 1 H), 2.27–2.46 (m, 2 H), 2.19 (t, J = 11.0 Hz, 1 H, major), 2.05 (t, J = 11.0 Hz, 1 H, minor), 1.75–2.02 (m, 4 H), 1.63 (dd, J = 11.3, 8.1 Hz, 1 H, minor), 1.52 (dd, J = 11.3, 8.1 Hz, 1 H, major), 1.28 (s, 3 H, minor), 1.17 (s, 3 H, major). HRMS: m/e calcd for [M^+ – OH] $C_{11}H_{17}O_3$ 197.1177, found 197.1169. m/e calcd for [M^+ – OCH_3] $C_{10}H_{15}O_3$ 183.1021, found 183.1015.

Method B. To a solution of 169 mg (0.93 mmol) of **26′** in methanol under nitrogen was added 23 mg (1.00 mmol) of sodium. After workup, 170 mg (85%) of **30** was obtained as a 1:1 mixture of diastereomers.

Methyl 3-[4-(2-Acetamidoethyl)-2-methyl-1-oxocyclobut-2-yl]-propionate (37). Methyl 3-[4-[2-(Thioacetamido)ethyl]-2-methyl-1-oxocyclobut-2-yl]propionate (38). To 173 mg (0.72 mmol) of **35**, a 1:1 mixture of diastereomers, was added 210 μL (0.22 g, 2.94 mmol) of thioacetic acid. The reaction mixture was stirred for 4 h under nitrogen and concentrated by rotary evaporation. The residue was purified by flash chromatography through Florisil with a solvent gradient from 1:1 hexanes/ethyl acetate to 100% ethyl acetate to afford 0.12 g (65%) of **37** and 0.03 g (15%) of **38**, both as 1:1 mixtures of diastereomers. **37**: IR (neat): 3300, 2960, 2940, 2880, 1765, 1735, 1655, 1555, 1440, 1380, 1300, 1205, 1185 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.42 (br s, 1 H), 3.679 (s, $^3/_2$ H), 3.675 (s, $^3/_2$ H), 3.34–3.49 (m, 2 H), 3.09–3.17 (m, 1 H), 2.26–2.48 (m, 2 H), 2.20 (t, J = 11.0 Hz, $^1/_2$ H), 1.99 (s, 3 H), 1.75–2.09 (m, $4^1/_2$ H), 1.59 (dd, J = 11.1, 8.1 Hz, $^1/_2$ H), 1.49 (dd, J = 11.2, 8.1 Hz, $^1/_2$ H), 1.27 (s, $^3/_2$ H), 1.16 (s, $^3/_2$ H). ^{13}C NMR ($CDCl_3$): δ 217.30, 217.19, 173.46, 173.34, 170.27, 59.94, 59.62, 54.21, 53.47, 51.70, 38.09, 31.87, 31.40, 30.71, 30.56, 29.56, 29.36, 29.14, 23.23, 21.34, 19.66. HRMS: m/e calcd for [M^+ – OCH_3], $C_{12}H_{18}NO_3$ 224.1287, found 224.1297. **38**: IR (neat): 3330–3260, 2950, 2930, 1760, 1730, 1540, 1440, 1200, 1180 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.70 (br s, 1 H), 3.86–3.96 (m, 1 H), 3.684 (s, $^3/_2$ H), 3.675 (s, $^3/_2$ H), 3.34–3.50 (m, 2 H), 2.59 (s, 3 H), 2.26–2.48 (m, 2 H), 2.25 (t, J = 11.1 Hz, $^1/_2$ H), 2.12 (t, J =

11.0, 1/2 H), 1.82–2.05 (m, 4 H), 1.62 (dd, J = 11.2, 8.3 Hz, 1/2 H), 1.51 (dd, J = 11.2, 8.3 Hz, 1/2 H), 1.30 (s, 3/2 H), 1.17 (s, 3/2 H). ^{13}C NMR ($CDCl_3$): δ 218.07, 218.00, 200.92, 173.34, 173.20, 59.79, 59.43, 54.62, 53.85, 51.73, 45.30, 33.85, 31.87, 31.22, 30.45, 30.38, 29.61, 29.51, 29.28, 28.01, 27.61, 21.34, 19.48. HRMS: *m/e* calcd for $C_{13}H_{21}NO_3S$ 271.1242, found 271.1243.

Methyl 3-[4-[2-(Thioacetoxy)ethyl]-2-methyl-1-oxocyclobut-2-yl]-propionate. To a solution of 110 mg (0.38 mmol) of **34**, a 4:1 mixture of diastereomers, in 15 mL of acetone was added 88 mg (0.77 mmol) of potassium thioacetate. The reaction mixture was stirred at reflux for 1 h and cooled to room temperature. The mixture was filtered, and the salts were washed with cold acetone. The acetone filtrate and washings were concentrated by rotary evaporation. The crude residue was taken up in water and extracted with ether. The ether fractions were combined, washed with water, dried (magnesium sulfate), and concentrated by rotary evaporation. Purification by flash chromatography through silica gel using 2:1 hexanes/ethyl acetate afforded 82 mg (80%) as a 4:1 mixture of diastereomers. IR (neat): 2960, 2880, 1765, 1735, 1690, 1440, 1140 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.67 (s, 3 H), 3.39 (dddd, J = 10.6, 8.9, 7.9, 6.4 Hz, 1 H), 2.91 (dd, J = 8.0, 6.9 Hz, 2 H), 2.23–2.45 (m, 2 H), 2.33 (s, 3 H), 2.16 (t, J = 10.9 Hz, 1 H, major), 1.84–2.05 (m, 3 H + 1 H, minor), 1.70–1.80 (m, 1 H), 1.61 (dd, J = 11.1, 7.8 Hz, 1 H, minor), 1.51 (dd, J = 11.4, 7.9 Hz, 1 H, major), 1.24 (s, 3 H, minor), 1.15 (s, 3 H, major). HRMS: *m/e* calcd for [M^+ – OCH_3] $C_{12}H_{17}O_3S$ 241.0898, found 241.0893.

Methyl 3-[(1*R,5*S**)-1-Hydroxy-7-methyl-2-thiabicyclo[3.2.0]hept-7-yl]propionate (39).** To a solution of 79 mg (0.29 mmol) of the above thioacetate, a 4:1 mixture of diastereomers, in 10 mL of dry methanol was added 8 mg (0.35 mmol) of sodium. The reaction mixture was stirred for 30 min and quenched with hydrochloric acid. The aqueous solution was extracted with methylene chloride. The combined methylene chloride fractions were washed with brine, dried (magnesium sulfate), and concentrated by rotary evaporation. Purification by flash chromatography using 2:1 hexanes/ethyl acetate afforded 54 mg (81%) of **39** as a 2.5:1 mixture of diastereomers. IR (neat): 3460, 2960, 2880, 1740, 1442, 1275, 1210, 1180 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.69 (s, 3 H, major), 3.68 (s, 3 H, minor), 3.11–3.19 (m, 1 H), 3.01–3.09 (m, 1 H), 2.89–2.96 (m, 1 H), 2.48–2.64 (m, 1 H), 2.24–2.43 (m, 2 H), 1.85–2.19 (m, 3 H), 1.75–1.82 (ddd, J = 13.6, 9.7, 6.0 Hz, 1 H), 1.62 (dd, J = 11.6, 9.3 Hz, 1 H, minor), 1.57 (dd, J = 11.1, 9.0 Hz, 1 H, major), 1.28 (s, 3 H, major), 1.17 (s, 3 H, minor), 1.08 (dd, J = 11.2, 9.1 Hz, 1 H, major), 1.01 (dd, J = 11.7, 8.9 Hz, 1 H, minor). HRMS: *m/e* calcd for [M^+ – H] $C_{11}H_{17}O_3S$ 229.0893, found 229.0896.

Methyl 3-[(1*R,5*S**)-3-Methyl-2,8-dioxabicyclo[3.3.0]oct-3-yl]-propionate (40).** A solution of 0.50 g (2.34 mmol) of **30**, a 3:1 mixture of diastereomers, in 500 mL of methylene chloride was degassed with nitrogen for 15 min. The solution was irradiated at 350 nm for 40 h. The reaction mixture was concentrated by rotary evaporation. Purification by flash chromatography using 1:1 hexanes/ethyl acetate afforded 0.40 g (80%) of a yellow oil as a 3:1 mixture of diastereomers. Further purification was achieved by Kugelrohr distillation, bp 90–95 °C (0.2 Torr). IR (neat): 2970, 2880, 2740, 1440, 1205, 1175, 1020 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.67 (d, J = 5.2 Hz, 1 H, minor), 5.63 (d, J = 5.2 Hz, 1 H, major), 3.85–3.97 (m, 2 H), 3.68 (s, 3 H), 2.95–2.99 (m, 1 H), 2.30–2.49 (m, 2 H), 2.11 (dd, J = 12.9, 9.8 Hz, 1 H, major), 1.62–2.08 (m, 4 H + 1 H, minor), 1.46 (dd, J = 13.0, 8.2 Hz, 1 H), 1.31, (s, 3 H, major), 1.15 (s, 3 H, minor). HRMS: *m/e* calcd for [M^+ – CH_3] $C_{10}H_{15}O_4$ 199.0971, found 199.0970.

Methyl 3-[(1*R,5*S**)-3-Methyl-2-oxa-8-thiabicyclo[3.3.0]oct-3-yl]-propionate (47).** A solution of 50 mg (0.22 mmol) of **39**, a 2.5:1 mixture of diastereomers, in 22 mL of methylene chloride was degassed with nitrogen for 15 min. Triethylamine (2 μL, 6 mol %) was added by syringe. The reaction mixture was irradiated at 350 nm for 33 h and concentrated by rotary evaporation. The residue was purified by flash chromatography with 3:1 hexanes/ethyl acetate to yield 26 mg (52%) of a clear, colorless oil as a 2:1 mixture of diastereomers. IR (neat): 2950, 2870, 1735, 1440, 1175, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.86 (d, J = 6.5 Hz, 1 H, major), 5.78 (d, J = 6.5 Hz, 1 H, minor), 3.68 (s, 3 H, major), 3.67 (s, 3 H, minor), 3.18–3.31 (m, 1 H), 2.99–3.10 (m, 1 H), 2.75–2.82 (m, 1 H), 2.45–2.49 (m, 1 H), 2.33–2.42 (m, 1 H), 2.06–2.13 (m, 1 H), 1.96–2.02 (m, 2 H), 1.88–1.98 (m, 1 H, major), 1.81–1.86 (ddd, J = 12.5, 8.7, 1.3 Hz, 1 H), 1.63–1.71 (ddd, J = 14.0, 9.8, 5.9 Hz, 1 H, minor), 1.50 (dd, J = 12.5, 10.4 Hz, 1 H), 1.34 (s, 3 H, minor), 1.17 (s, 3 H, major). HRMS: *m/e* calcd for $C_{11}H_{18}O_3S$ 230.0976, found 230.0983.

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Supplementary Material Available: Experimental procedures for compounds **3**, **8**, **18/19**, **23–25**, **27–29**, **31–36**, and **41–46** and a description of kinetic experiments (14 pages). Ordering information is given on any current masthead page.

Kalmanol, a Pharmacologically Active Diterpenoid with a New Ring Skeleton from *Kalmia angustifolia* L.

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Abstract: Kalmanol (**4**), $C_{20}H_{34}O_6$, a hexahydroxy B-homo-C-nor grayanoid isolated from *Kalmia angustifolia* L. represents a new diterpenoid ring system and possesses cardiotoxic properties like those of the grayanotoxins. Its structure was determined by spectral methods: IR, MS, and ^{1}H and ^{13}C NMR, including 2D CH-correlation and COLOC. NOE difference established all stereochemical centers except for C-8 and C-16. Single-crystal X-ray analysis confirmed the derived structure and fixed the stereochemistry at the unknown centers.

The grayanoids, or grayanotoxins, such as grayanotoxin I (**1**), are a unique class of toxic diterpenoids with an A-nor-B-homo *ent*-kaurane skeleton that occur in the heath family (Ericaceae).[2] Alterations in that basic skeleton are also known as in the example leucothol A (**2**)[3] with the A-homo-B-nor grayanoid ring system and grayanol B (**3**)[4] with the 1,5-seco grayanoid system. We wish to report a third modification of that system as found in kalmanol

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