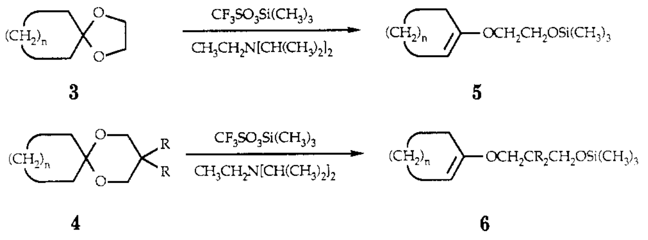
The conversion of cyclic ethers (1,3-dioxolanes, **3**, and 1,3-dioxanes, **4**) into enol ethers (**5** and **6**, respectively) was also investigated. In a general procedure, the cyclic acetal (1.00 equiv), *N,N*-diisopropylethylamine (1.35 equiv for **3**, 1.90 equiv for **4**), and dichloromethane (1.67 mL/mM of acetal) were combined and cooled to 0 °C under nitrogen, and trimethylsilyl triflate (1.20 equiv for **3**, 1.70 equiv for **4**) was added dropwise. The reaction was allowed to warm to ambient temperature and stirred for the time indicated in Table I. The reaction mixture was diluted with pentane (2–3 volumes) and cooled overnight to precipitate the *N,N*-diisopropylethylammonium triflate. The liquid phase was decanted, the precipitate was washed with pentane, the liquid phases were combined, and the solvent was removed under reduced pressure. Distillation of the residue gave the yields of enol ethers (**5** and **6**)[6] listed in Table I.

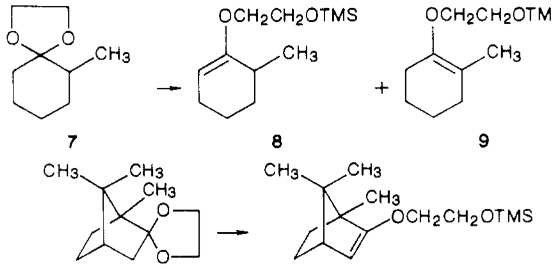


3 **5** **4** **6**

(a) R = H; (b) R = CH_3

In general, the yields of enol ethers were excellent. While the dimethyl acetals reacted rapidly, the dioxolanes were slightly less reactive, and the dioxanes were much less reactive. Thus, a larger molar ratio of trimethylsilyl triflate and a longer reaction period were used for the dioxanes. The dialkyl-substituted dioxanes were significantly less reactive than the simple dioxanes. For simple dimethyl acetals, the procedure described herein appears to give the best average yields of any available procedure.[7] For the dioxolanes and dioxanes, the previously published procedures either failed to give satisfactory yields in our hands[3a] or required experimental conditions that did not readily lend themselves to the preparation of large quantities of enol ethers in a simple laboratory procedure.

Two unsymmetrically substituted acetals were examined. When **7** was treated with trimethylsilyl triflate under the general procedure described above, a 96% yield of an 89:11 mixture of **8**:**9** was obtained based on 89% conversion of **7** after 5 h. This indicated that our procedure was more regioselective than procedures described earlier,[3] which tended to give ratios of **8** to **9** that approached the thermodynamic equilibrium mixture (63:37, respectively, for the methyl ethers).[8] When **10** was allowed to react under our general conditions for 18 h, except in refluxing methylene dichloride, a 91% yield of **11** was obtained. No rearrangement of the bornane skeleton was expected or observed. Thus, the procedure is applicable to molecules that tend to rearrange under cationic conditions.



7 **8** **9** **10** **11**

In conclusion, we have developed a simple, general, high-yield method for the preparation of enol ethers from acetals.

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[6] Satisfactory elemental analyses and/or exact mass molecular weights were obtained on all new compounds. All products had IR, ^1H NMR, and ^{13}C NMR spectral data consistent with the assigned structures.

[7] Our yields are generally superior to those obtained by the procedure of Miller and McKean,[3a] which offers good yields of methyl vinyl ethers from dimethyl acetals.

(8) For the dimethyl acetal of 2-methylcyclohexanone, we obtained an 88:12 ratio of 1-methoxy-6-methylcyclohexene to 1-methoxy-2-methylcyclohexene.

Ring Expansions via Photoinduced Single Electron Transfer Promoted Opening of Cyclopropyl Ethers

Summary: A general method of ring expansion involving acetal to ring-homologated acetal is described. The key steps in the overall process involve (a) acetal to enol ether conversion, (b) cyclopropane formation, and (c) photoinduced single electron transfer promoted opening of the cyclopropane.

Sir: Recently, we have described a series of synthetically useful transformations of nonconjugated olefins, which were promoted by photoinduced single electron transfer reactions.[1-3] In principle, any molecule with an $E_{1/2}^{ox}$ less than 2.2 V vs a saturated calomel electrode (SCE) can be oxidized via single-electron transfer to an appropriate excited-state photosensitizer. The ease with which cyclopropyl ethers are oxidized (1.6–2.0 V vs SCE) suggested that a general process for acetal to acetal ring expansion might be possible involving (a) acetal to enol ether conversion,[4] (b) methylene addition to the enol ether to form a cyclopropyl ether, and (c) photochemical single electron transfer promoted cleavage of the cyclopropane and nucleophile capture by the intermediate cation radical to regenerate an acetal with a one-carbon homologation. We now report a series of examples of such homologations through, what we believe to be, the first examples of photoinduced single electron transfer promoted cleavages of simple nonconjugated cyclopropanes.

Our initial studies started with cyclic methyl enol ethers, **1**.[4] Cyclopropane formation from **1** was achieved with methylene iodide and zinc–copper couple in a standard Simmons–Smith reaction[5] to give **2** in yields ranging from 14 to 78%.[6] Irradiation of a methanolic solution that was

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(1) Gassman, P. G.; Bottorff, K. *J. Am. Chem. Soc.* **1987**, *109*, 7547.

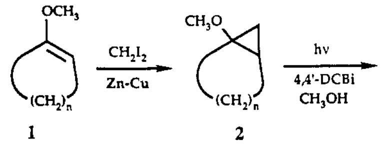
(2) Gassman, P. G.; Bottorff, K. *Tetrahedron Lett.* **1987**, *28*, 5449.

(3) Gassman, P. B.; Bottorff, K. *J. Org. Chem.* **1988**, *53*, 1097.

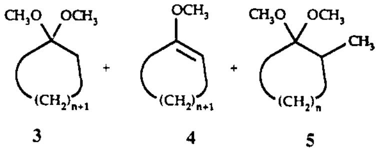
(4) For a general procedure for the conversion of acetals to enol ethers, see: Gassman, P. G.; Burns, S. J. *J. Org. Chem.*, preceding paper in this issue.

(5) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1.

0.10 M in **2** and 0.06 M in 4,4′-dicyanobiphenyl (4,4′-DCBi)[7,8] gave 22–45% yields of the ring-expanded products, **3**, in which methanol was added across the C1–C(n + 2) ring-fusion bond of **2** in a photoinduced single electron transfer (SET) process. Because the yields were unattractive from a synthetic point of view, we turned our attention to a system containing an internal nucleophile.



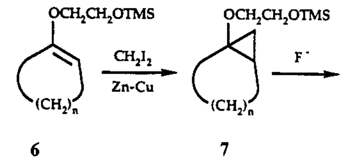
1a	n = 3	14%[a] (1.55 V)[b]
1b	n = 4	64%[a] (1.86 V)[b]
1c	n = 5	78%[a] (1.75 V)[b]
1d	n = 6	60%[a] (1.79 V)[b]



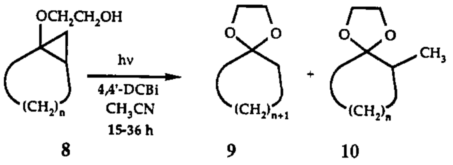
3	4	5
45%[c]	-	-
22%[c]	6%[c,d]	5%[c,d]
31%[c]	-	-
31%[c]	-	-

[a] Yields of cyclopropyl ether from methyl vinyl ether. [b] Nonreversible oxidation potential ($E_{1/2}^{\text{ox}}$) for **2** vs ferrocene–ferrocenium couple at 0.31 V. [c] GLC yields vs an internal standard. [d] Analogues of **4** and **5** were not found in the reactions of **1a**, **1c**, and **1d**.

Treatment of the ethylene glycol derived ether, **6**,[4] with methylene iodide and zinc–copper couple gave 75–81% yields of **7**. Fluoride ion desilylation of **7** with potassium fluoride in methanol gave 85–96% yields of **8**. Irradiation of a 0.10 M solution of **8** in acetonitrile containing 0.06 M 4,4′-DCBi[8] produced 19–54% isolated yields of **9**. Comparison of the GLC yields of **9** (26–67%) showed that these were generally superior to the GLC yields of **3** from **2**. Thus, the use of a tethered nucleophile provided obvious improvements in the overall procedure. The overall synthetic utility of our procedure is marginal for ring expansion of the five- and six-membered ring systems, **8a** and **8b**, due to the limiting yields in the photoinduced ring expansion step. For ring expansion in the seven- and eight-membered ring systems, **8c** and **8d**, the method should prove useful.



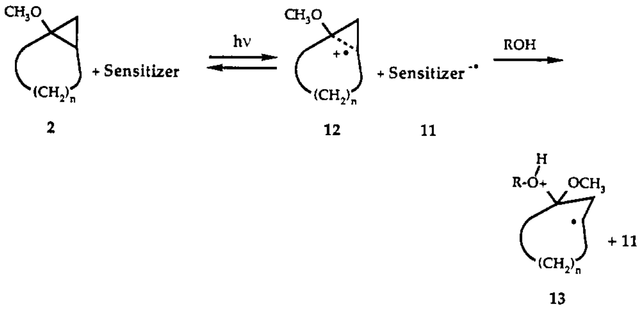
6a	n = 3	75%[a]
6b	n = 4	81%[a]
6c	n = 5	80%[a]
6d	n = 6	78%[a]



8	9	10
85%[b] (1.60 V)[c]	37%[d] (43%)[e]	-
89%[b] (1.80 V)[c]	19%[d] (26%)[e]	22%[d] (32%)[e]
90%[b] (1.71 V)[c]	42%[d] (60%)[e]	-
96%[b] (1.76 V)[c]	54%[d] (67%)[e]	-

[a] Yields of cyclopropyl ether from **6**. [b] Yields of desilylated ether from **7**. [c] Nonreversible oxidation potential ($E_{1/2}^{\text{ox}}$) for **8** vs ferrocene–ferrocenium couple at 0.31 V. [d] Isolated yields of pure **9** (or pure **10**). [e] GLC yields of **9** (or **10**) vs an internal standard.

Although the procedures described above will be of limited synthtic utility, the results are of considerable mechanistic interest. Significant evidence exists for a single electron transfer mechanism in the cleavage of **2** to **3** and of **8** to **9**. The reaction is photoinduced since control reactions showed that the starting reaction mixture was unchanged in the absence of irradiation. The strength of the excited state photosensitizer as an oxidant was crucial. Whereas 4,4′-DCBi was a very effective photosensitizer, biphenyl, which had an excited state $E_{1/2}^{\text{red}*}$ = 1.25 V, was ineffective. Sensitizers of intermediate excited state $E_{1/2}^{\text{red}*}$ such as 1-cyanonaphthalene ($E_{1/2}^{\text{red}*}$ = 1.84 V) and 1,4-dicyanonaphthalene ($E_{1/2}^{\text{red}*}$ = 2.17 V) gave no photoconversion and slow photoconversion, respectively. The fluorescence of both 1-cyanonaphthalene and 1,4-dicyanonaphthalene was efficiently quenched by **2b**. Thus, it is thought that rapid back electron transfer from the resultant anion radical **11** to the paired cation radical **12** occurred with these sensitizers. With 4,4′-DCBi, where back electron transfer was less pronounced, product formation occurred through reaction of **12** with the nucleophilic solvent to produce the intermediate distonic[9] cation radical **13**. The details of the reaction of **13** with **11** to regenerate the photosensitizer and yield the product of the addition of solvent across the carbon–carbon single bond of the cyclopropane[10] are not well defined at this time.



In summary, we have developed a new, mechanistically interesting method for ring expansion.[11]

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

(7) 4,4′-Dicyanobiphenyl was prepared according to the literature procedure: Friedman, L.; Shechter, H. *J. Org. Chem.* **1961**, *26*, 2522. We are unaware of any prior use of this compound as a single electron transfer photosensitizer. In its excited state, 4,4′-DCBi has an $E_{1/2}^{\text{red}*}$ = 2.34 V.

(8) The irradiations were carried out in quartz reaction vessels at 254 nm with a bank of sixteen 21-W lamps, or at 313 nm with a medium-pressure 450-W Hanovia light source.

(9) Yates, B. F.; Bouma, W. J.; Radom, L. *Tetrahedron* **1986**, *42*, 6225. Radom, L.; Bouma, W. J.; Nobes, R. H.; Yates, B. F. *Pure Appl. Chem.* **1984**, *56*, 1831. Golding, B. T.; Radom, L. *J. Am. Chem. Soc.* **1976**, *98*, 6331.

(10) For examples of the photoinduced single electron transfer promoted addition of alcohols across the central bond of bicyclo[1.1.0]butane derivatives, see: Gassman, P. G.; Olson, K. D.; Walter, L.; Yamaguchi, R. *J. Am. Chem. Soc.* **1981**, *103*, 4977. Gassman, P. G.; Olson, K. D. *J. Am. Chem. Soc.* **1982**, *104*, 3740. Gassman, P. G.; Carroll, G. T. *Tetrahedron* **1986**, *42*, 6201.

(11) The overall yields from the ethylene glycol acetals (1,3-dioxolanes) of cyclopentanone, cyclohexanone, cycloheptanone, and cyclooctanone to the ethylene glycol acetals of cyclohexanone, cycloheptanone, cyclooctanone, and cyclononanone, respectively, were 27%, 18%, 42%, and 50%, respectively.

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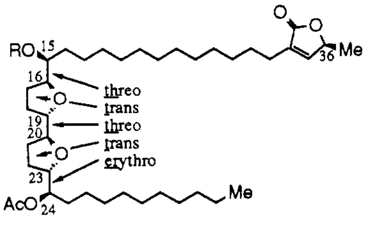
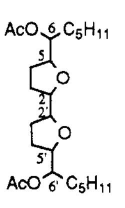
Validation of the ^1H NMR Chemical Shift Method for Determination of Stereochemistry in the Bis(tetrahydrofuranyl) Moiety of Uvaricin-Related Acetogenins from Annonaceae: Rolliniastatin 1 (and Asimicin)

Summary: A valuable new method for quantitative correlation of the ^1H NMR chemical shift data from the appropriate members (**a**, **g**) of a set of model diastereomeric bis(tetrahydrofurans) (**2a–l**) with those from the triacetate derivative of rolliniastatin 1 (**5**) was developed.

Sir: Unique methodology for determining the relative stereochemical relationship among the six stereogenic carbon atoms in the bis(tetrahydrofuranyl) portion [i.e., C(15)-C(24)] of the antitumor agent uvaricin (**1**)[2] was recently described by us.[3] That process involved, first, the synthesis of 12 diastereomers of the model bis(acetates) **2** having known stereorelationships (because of the methods used in their synthesis)[3,4] and, second, a careful comparison of the chemical shifts observed in the ^1H NMR spectra of **2** with those of the acetate derivative of uvaricin (**3**). While we are quite confident in the conclusions we could draw, i.e., the relative stereochemistry indicated in **1**, we recognized that "it is difficult to decide what constitutes a *proof* of stereochemistry by [this class] of arguments".[2] Given that this emerging family of natural products shows potential of having substantial biological significance; given that, with the important exception noted below, it has not been possible to effect X-ray crystallographic analysis of any of these "waxy", "microcrystalline", or "amorphous" natural materials or their derivatives; and given the natural skepticism in our methodology that has been expressed to us by some who are not experienced in chemical shift analysis within series of diastereomeric components, we sought an opportunity to further validate our methodology.



1 R = H or C(15)-C(24)
3 R = Ac hexepimer



2

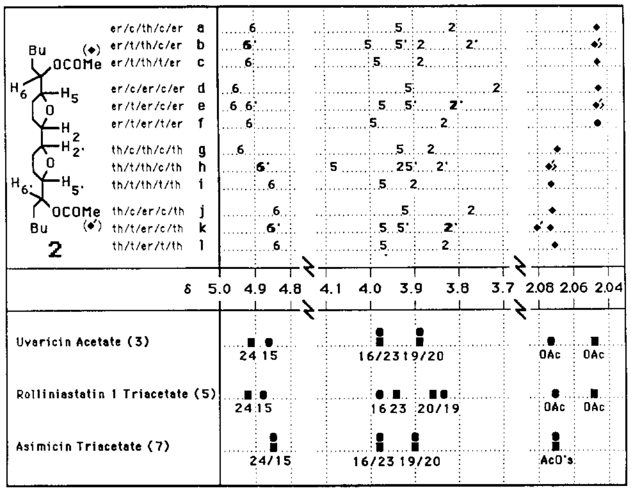
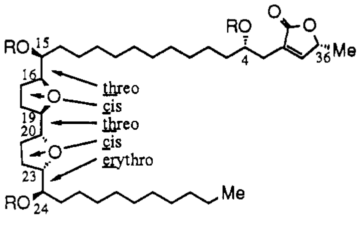
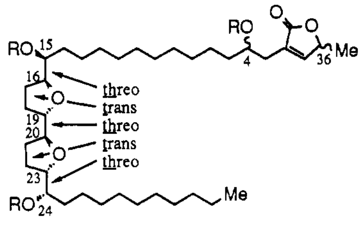


Figure 1. Proton NMR chemical shifts of diagnostic protons in the 12 isomeric dibutylated diacetates (**2**) and of uvaricin acetate (**3**), rolliniastatin triacetate (**5**), and asimicin triacetate (**7**).[11]

Prior to our work the only stereochemical feature reported for any of the 10 or so known compounds of this class was the absolute configuration of the methyl-bearing C(36) in uvaricin and desacetyluvaricin, which was determined as *S* by degradation to lactic acid.[5] Recently, Pettit and co-workers have described their success in determining the first X-ray crystallographic analysis of a derivative of a natural product from this class, rolliniastatin 1 (**4**).[6] The availability of this first family member of known relative configuration prompted us to use it as a test case for our method. Rolliniastatin 1 (**4**)[7] was converted to its triacetate derivative **5** by simple treatment with Ac_2O in pyridine at room temperature.



4 R = H or
5 R = Ac enantiomer



6 R = H or C(15)-C(24)
7 R = Ac hexepimer

Asimicin (**6**) is yet another member of this family whose constitution (but not stereochemistry) and cytotoxic and pesticidal[8] activities were described by the McLaughlin

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[1] Fellow of the Alfred P. Sloan Foundation, 1985–89.

[2] Jolad, S. D.; Hoffmann, J. J.; Schram, K. H.; Cole, J. R.; Tempesta, M. S.; Kriek, G. R.; Bates, R. B. *J. Org. Chem.* **1982**, *47*, 3151.

[3] Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 4402.

[4] (a) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5312. (b) Hoye, T. R.; Suhadolnik, J. C. *Tetrahedron* **1986**, *42*, 2855.

[5] Jolad, S. D.; Hoffmann, J. J.; Cole, J. R.; Barry, C. E. III; Bates, R. B.; Linz, G. S. *J. Nat. Prod.* **1985**, *48*, 644.

[6] The X-ray analysis was performed on the 15-*O*-(*p*-bromophenyl)urethane derivative of **4**: Pettit, G. R.; Cragg, G. M.; Polonsky, J.; Herald, D. L.; Goswami, A.; Smith, C. R.; Meretti, C.; Schmidt, J. M.; Weisleder, D. *Can. J. Chem.* **1987**, *65*, 1433.

[7] A generous sample of rolliniastatin 1 (**4**) was kindly provided to us by Dr. Cecil R. Smith from Professor Pettit's laboratory. We are indebted for their assistance.

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