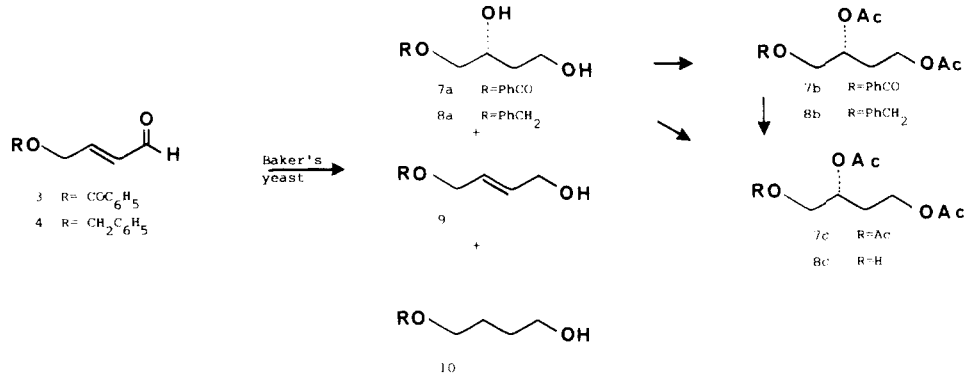
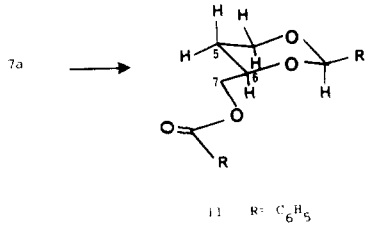
Scheme I



aldehyde from the monobenzoate of butyne-1,4-diol in two steps: (a) D_2/Lindlar catalyst/AcOEt; (b) pyridinium chlorochromate oxidation. While the intermediate monobenzoate contained over 95% deuterium at positions 2 and 3, the resulting *E* aldehyde (**3**) contained over 95% deuterium at position 3 but only 55–60% deuterium at position 2. Incubation of the latter material at pH 5.2 as above yielded unreacted **3** and products **7a**, **9**, and **10** each containing >95% deuterium at the position corresponding to position 3 of the precursor. In contrast, considerable variation was found in the amount of deuterium label retained at the 2 position: recovered **3** (ca. 5–10% ^2H), **9** and **10** (40%), and **7a** (ca. 20%). Diol **7a** was converted (C_6H_5CHO, TsOH, toluene, reflux) into the 1,3-dioxane (**11**). ^1H NMR analysis allowed the assignment of the



stereochemistry of the ring protons.[7] ^2H NMR spectroscopy indicated that the retained deuterium is equally distributed into the axial (δ 1.59) and equatorial (δ 0.84) positions at C-5. The deuterium labeling experiments thus indicate (i) almost complete loss of ^2H at position 2 of the recovered aldehyde **3**, (ii) consistent retention at the same positions in alcohols **9** and **10**, and (iii) retention of less than 50% of the deuterium (equally in both configurations) in **7a**.

A reasonable interpretation of these results might be the following. A reversible water addition across the double bond gives rise to (3*R*)-3-hydroxy-4-(benzoyloxy)butyraldehyde. The deuterium at position 2 of the latter is subsequently lost by enolization prior to enzymic reduction to **7a**, thus causing scrambling of the remaining deuterium.

Consideration of the mechanism and the nature of the enzyme(s) involved in the above processes is outside the scope of the present paper. However, it is worthwhile to note the dramatic difference in reactivity observed between **2** (acyloin condensation) and **3** (water addition and reduction) as a consequence of the additional methyl group in the former. Also the present process extends the scope of enzymic transformations of nonconventional substrates in organic synthesis.[8] The regioselectively protected 1,2,4-butanetriols **7a** and **8a** are formally derivatives of the unnatural (*R*)-malic acid, a starting material of current interest in the synthesis of enantiomerically pure compounds.[9]

Supplementary Material Available: Experimental procedures for **4**, **7a**, **8a**, **7b**, **8b**, **7c**, and **11** (2 pages). Ordering information is given on any current masthead page.

(7) ^1H NMR (C_6D_6): 5.31 (s, 1 H, H-2), 4.31 (dd, 1 H, H-7a, *J*(7a,7b) = 11.1, *J*(7a,6) = 5.7 Hz), 4.25 (dd, 1 H, H-7b, *J*(7b,6) = 4.0 Hz), 3.88 (ddd, 1 H, H-4e, *J*(4e,5a) = 5.0, *J*(4e,5e) = 1.5, *J*(4e,4a) = 11.5 Hz), 3.75 (m, 1 H-6a, *J*(6a,7a) = 11.5, *J*(6a,7e) = 2.5 Hz), 3.40 (ddd, 1H, H-4a, *J*(4a,5a) = 12.5, *J*(4a,5e) = 2.5 Hz), 1.59 (m, 1 H, H-5a, *J*(5a,5e) = 13.0 Hz), 0.84 (m, 1 H, H-5e).

(8) Seebach, D.; Kalinowski, H. O. *Nachr. Chem. Techn.* **1976**, *24*, 415.
(9) Tanner, D.; Somfai, P. *Tetrahedron Lett.* **1988**, *29*, 2373.

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Intramolecular 4 + 3 Cycloadditions of 2-Alkoxyallylic Cations Derived from 2-Alkoxyallylic Sulfones

Summary: Certain 2-alkoxyallylic sulfones lead to 2-alkoxyallylic cations, which can be intramolecularly trapped by a furan ring via a 4 + 3 cycloaddition.

Sir: Notwithstanding the many advances made in the synthesis of carbocyclic compounds, there is a continuing need to develop new synthetic methodology for the purposes of versatility, expediency, and practicality. Seven-membered rings fall into that class of substructures particularly significant because of their occurrence in a wide variety of structurally intriguing or biologically active natural products. Specific examples include tumor-promoting diterpenes such as phorbol,[1] antiviral agents such as reiswigin A,[2] the fenestrane laurenene,[3] and the myriad of guiane and pseudoguiane sesquiterpenes.[4] In ap-

(1) For the first synthesis of the phorbol skeleton and leading references, see: Wender, P. A.; Keenan, R. M.; Lee, H. Y. *J. Am. Chem. Soc.* **1987**, *109*, 4390.
(2) Kashman, Y.; Hirsch, S.; Koehn, F.; Cross, S. *Tetrahedron Lett.* **1987**, *28*, 5461.
(3) For leading references, see: Paquette, L. A.; Okazaki, M. E.; Caille, J. C. *J. Org. Chem.* **1988**, *53*, 477.
(4) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1983; Vol. 5, pp 347–377.

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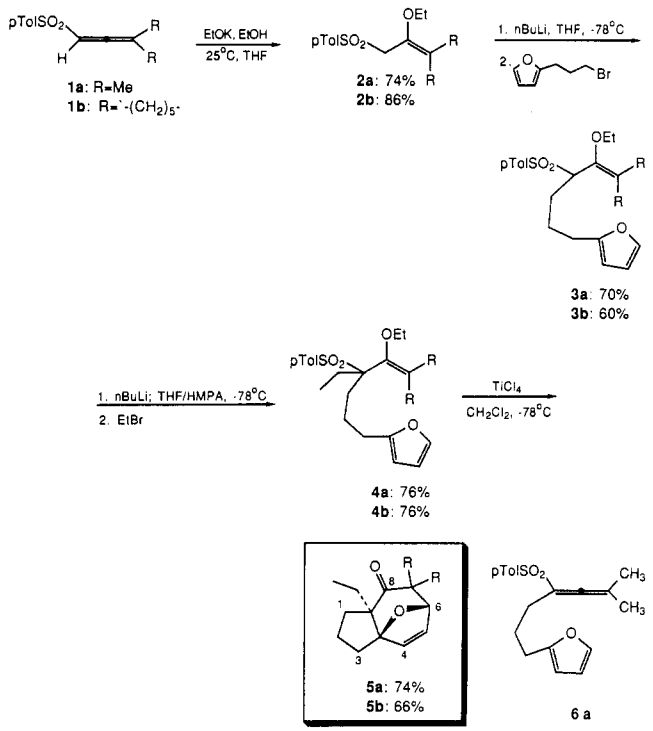
Scheme I



proaching the synthetic challenges posed by these structures, we have developed a new route to 2-alkoxyallylic cations and have studied their 4 + 3 cycloaddition reactions with furans to produce seven-membered rings.

The formation of seven-membered rings via 4 + 3 cycloaddition is well known.[5] A number of methods exist for the generation of the appropriate alkoxyallylic cations or their equivalents. Quite often, however, the precursors to the allylic cations, such as polyhalo ketones or tertiary allylic halides, are difficult to make and not easily handled. We sought to develop an alkoxyallylic cation precursor that was easily prepared, stable, and adaptable to a variety of chemical processes such as asymmetric synthesis.

Recently Trost and co-workers have demonstrated that allylic sulfones can behave as "chemical chameleons" and that the sulfone group can be converted to a good leaving by Lewis acid activation.[6] The resulting intermediates show reactivity anticipated for allylic cations. This observation served as the impetus for our work.

2-Alkoxyallylic sulfones are easily prepared by the nucleophilic addition of alcohols to the corresponding allene.[7] The latter are readily available by the 2,3-sigmatropic rearrangement of the corresponding sulfinate esters.[8] Most importantly, 2-alkoxyallylic sulfones can be deprotonated and alkylated without elimination of the alkoxy groups.[9] This allows for the rapid construction of structurally complex intermediates suitable for intramolecular 4 + 3 cycloaddition chemistry.

Our results are summarized in Scheme I. The systems prepared were designed to facilitate carbocation formation

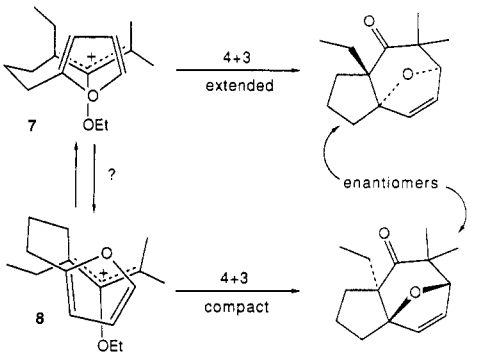


Figure 1.

by maximizing alkyl substitution at the requisite positions. Reaction of 3-methyl-1-((4-methylphenyl)sulfonyl)-1,2-butadiene (**1a**) with catalytic potassium ethoxide in ethanol/THF at 0 °C proceeded smoothly to give a 74% yield of **2a**. Treatment of **2a** with *n*-BuLi in THF at −78 °C followed by alkylation with 2-(3-bromopropyl)furan gave **3a** in 70% yield after chromatographic purification. A second metalation and trapping with bromoethane gave **4a** in 76% yield. It is important to note that HMPA as a cosolvent was critical to the success of the second alkylation sequence. Without it, significant amounts of allene **6a** were formed as a side product. We believe that the HMPA serves to decrease association between the carbanion and the lithium cation. This keeps the carbanion orthogonal to the carbon–oxygen bond due to resonance delocalization and inhibits elimination.

With **4a** in hand, a number of Lewis acids were screened to assess the viability of the cycloaddition sequence. We were particularly concerned with the enol ether functional group and its potential lability in the presence of strong Lewis acids. Our fears were allayed when we found that treatment of **4a** with 1.1 equiv of $TiCl_4$ at −78 °C in methylene chloride (0.2 M) produced cycloadduct **5a**[10] in 74% yield after chromatographic purification, apparently as a single isomer. The facility with which this highly substituted system was prepared is noteworthy. We had considered it possible that steric problems would lead to low yields of **5a**.

The entire sequence in Scheme I could be successfully executed beginning with allene **1b**, providing a second example of the cycloaddition. As for **5a**, **5b** was apparently produced as a single stereoisomer.

The relative stereochemical relationships in **5b** were determined by X-ray analysis.[11] Attempts to correlate the stereochemistry of **5b** with **5a** by using ^1H NMR spectroscopy in the presence of a shift reagent were unsuccessful. Use of NOE was also not effective in providing support for the stereochemical assignments in **5a**. Irradiation of the ethyl group's methylene hydrogens produced an insignificant NOE in the signal of the proton attached to carbon 4 in **5b**. We are currently engaged in attempts

(5) (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (b) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (c) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163.

(6) (a) Trost, B. M.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 7260. (b) Trost, B. M.; Ghadiri, M. R. *Ibid.* **1986**, *108*, 1098.

(7) (a) Stirling, C. J. M. *J. Chem. Soc.* **1964**, 5856. (b) Denmark, S. E.; Harmata, M. A.; White, K. S. *J. Org. Chem.* **1987**, *52*, 4031.

(8) (a) Braverman, S.; Mechoulam, H. *Tetrahedron* **1974**, *30*, 3883. (b) Smith, G.; Stirling, C. J. M. *J. Chem. Soc. C* **1971**, 1530.

(9) (a) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972. (b) Padwa, A.; Billock, W. H.; Dyszlewski, A. D. *Tetrahedron Lett.* **1987**, *28*, 3193.

(10) The structural assignment of **5a** proceeded in a straightforward fashion from spectroscopic analysis. The infrared spectrum indicated the presence of a ketone (1700 cm^{-1}). The 300-MHz ^1H NMR spectrum showed the loss of the tolylsulfonyl and ethoxy groups and the complete disappearance of the furan ring. The high-field region of the spectrum showed two methyl groups at 0.91 and 1.34 ppm, suggesting that these groups were no longer allylic. A one-proton doublet (J = 1.9 Hz) at 4.43 ppm suggested an ether functionality as expected for **5a**. In the olefinic region, two single-proton resonances occurred as a doublet at 6.25 ppm (J = 6 Hz) and a doublet of doublets at 6.33 ppm (J = 1.9, 6 Hz) and are assigned to the hydrogens on carbons 4 and 5 (azulene numbering) of **5a**, respectively. Finally, spectral data for **5a** correlated extremely well with known compounds of similar structure.[11]

(11) Fohlisch, B.; Herter, R. *Chem. Ber.* **1984**, *117*, 2580.

to assign stereochemistry in **5a** by chemical means.

It is interesting to speculate about the origin of the apparent stereoselectivity in this reaction. For a concerted process, two possibilities are allowed based on the configuration of the intermediate alkoxyallylic cation and the mode of cycloaddition: extended (exo) or compact (endo). These possibilities are illustrated in Figure 1. Inspection of molecular models suggests that **7** represents the best transition state structure for the reaction. The incipient five-membered ring in **8** is in a boatlike conformation, resulting in a severe transannular interaction between hydrogens on the methylene group next to the furan ring and on the angular ethyl group. While the high stereoselectivity supports a concerted process, a stepwise mechanism has not been ruled out. Moreover, the configurational stability of the heavily substituted allylic cations, the probable intermediates in the work, is open to some question, leading to further uncertainties regarding the specific course of the reaction.[12] Experiments designed to deal with these uncertainties are in progress.[13]

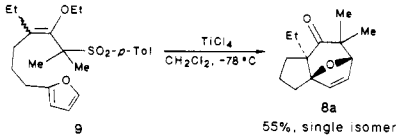
In summary, we have found that certain 2-alkoxyallylic sulfones serve as efficient precursors to 2-alkoxyallylic cations or their functional equivalents. These intermediates undergo intramolecular 4 + 3 cycloaddition with furans in high yield. Quaternary centers are formed with impressive ease. The cycloadducts are formed stereoselectively and bear alkyl and oxygen functionality in locations shared by various guiane and pseudoguiane sesquiterpenes. This methodology may therefore be of use in the total synthesis of these and other natural products. Further progress will be reported in due course.[14,15]

Acknowledgment. We are grateful to the National Science Foundation for partial support of the NMR (Grant PCM-8115599) and MS (Grant PCM-8117116) facilities at the University of Missouri. Thanks to Professor Elmer O. Schlemper for acquisition of the X-ray data and to Dr. Hanna Gracz and Dale Sanson for high-field NMR data.

Supplementary Material Available: Tables of positional parameters, thermal parameters, interatomic distances, interatomic angles, and dihedral angles for non-hydrogen atoms (9 pages). Ordering information is given on any current masthead page.

(12) (a) Schleyer, P. v. R.; Su, T. M.; Saunders, M.; Rosenfeld, J. C. *J. Am. Chem. Soc.* **1969**, *91*, 5174. (b) Deno, N. C.; Hadden, R. C.; Nowak, E. N. *Ibid.* **1970**, *92*, 6691. (c) Bolinger, J. M.; Brinich, J. M.; Olah, G. A. *Ibid.* **1970**, *92*, 4025.

(13) We have recently found that treatment of **9** as a mixture of isomers with $TiCl_4$ results in the formation of **5a** in 55% yield as the only cycloaddition adduct. However, we have not yet succeeded in separating the isomers of **9**.



9 8a

55%, single isomer

(14) All new compounds exhibited acceptable ^1H NMR and IR spectra as well as satisfactory combustion or HRMS data. All yields are for chromatographically purified materials.

(15) This work was presented in part at the 196th National Meeting of the American Chemical Society, Los Angeles, CA; ORGN 158.

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Another Challenge to the Validity of the Use of Cyclizable Probes as Evidence for Single-Electron Transfer in Nucleophilic Aliphatic Substitution. The Reaction of $LiAlH_4$ with Alkyl Iodides

Summary: It has been found that a recent report challenging the use of cyclizable radical probes as evidence for single-electron transfer in the reaction of $LiAlH_4$ with alkyl iodides is itself based on an invalid model system.

Sir: We[1] and others[2] have used cyclizable radical probes in a number of studies to obtain evidence for the intermediacy of radicals in nucleophilic aliphatic substitution. The mechanism that we proposed in 1984 for this reaction is shown in Scheme I.[1d,4,5]

Recently Newcomb et al.[6,7] have reported that the lack of cyclization of **1b** (Scheme I) on reaction with $LiAlH_4$ "indicates that SET from the reducing agent to the halide to give a free radical is not an important process" and that "these reductions are best explained as conventional nucleophilic displacements of halide by hydride." The reason given for the lack of cyclization product (**7**, **8**) is that radical **6b**, because of its stability, does not participate in rapid halogen exchange with **1b** to produce **9b**, therefore eliminating what he claims to be the only route to cyclized product. It was concluded that when halogen atom exchange (**6** $\xrightarrow{\perp}$ **9**) does not take place, cyclized product is not produced, and hence when other probes used by ourselves and others resulted in cyclization, all cyclized product was a result of reduction of **9**. It was also suggested that the initial radical (**3**) originates from impurities,[5] hence eliminating our suggestion that $LiAlH_4$ is the one-electron donor that initiates the process (**1** → **2** → **3**). Three years prior to the Newcomb report, we had already reported that the formation of **8** via the process **6** $\xrightarrow{\perp}$ **9** → **8** is important in the reaction of $LiAlH_4$ with alkyl iodides but that some of **8** is also formed directly from **6**.[1d,7] More recently, we have provided even more convincing evidence to support this point.[1i] It is important to note that we have never reported the formation of cyclized product when $LiAlH_4$ is allowed to react with an unhindered primary alkyl iodide probe in THF, but only with a hindered one (neopentyl type). Therefore, the lack of formation of cyclized product in the reaction of $LiAlH_4$ with **1b** in THF was not a surprise to us.

(1) (a) Ashby, E. C.; DePriest, R. N.; Pham, T. N. *Tetrahedron Lett.* **1983**, *24*, 2825. (b) Ashby, E. C.; DePriest, R. N.; Su, Wei-yang *Organometallics* **1984**, *3*, 1718. (c) Ashby, E. C.; Wenderoth, B.; Pham, T. N.; Park, Won-suh *J. Org. Chem.* **1984**, *49*, 4505. (d) Ashby, E. C.; DePriest, R. N.; Goel, A. B.; Wenderoth, B.; Pham, T. N. *J. Org. Chem.* **1984**, *49*, 3545. (e) Ashby, E. C.; Argyropoulas, J. N. *J. Org. Chem.* **1985**, *50*, 3274. (f) Ashby, E. C.; Su, Wei-Yang; Pham, T. N. *Organometallics* **1985**, *4*, 1493. (g) Ashby, E. C.; Pham, T. N. *J. Org. Chem.* **1986**, *51*, 3598. (h) Ashby, E. C.; Pham, T. N. *J. Org. Chem.* **1987**, *52*, 1291. (i) Ashby, E. C.; Pham, T. N. *Tetrahedron Lett.* **1987**, *28*, 3197.

(2) (a) Chung, S. J. *J. Org. Chem.* **1980**, *45*, 3513. (b) Singh, P. R.; Nigam, A.; Kurona, J. M. *Tetrahedron Lett.* **1980**, *21*, 4753. (c) Lee, K. W.; Flippo, J. *Organometallics* **1983**, *2*, 906. (d) Bailey, W. F.; Gagnier, R. P.; Patricia, J. J. *J. Org. Chem.* **1984**, *49*, 2098.

(3) Ashby, E. C.; Goel, A. B.; DePriest, R. N. *Tetrahedron Lett.* **1981**, *22*, 3729.

(4) The mechanism reported in 1984[1d] was for a sterically hindered primary alkyl iodide and for secondary alkyl iodides. The same mechanistic pathway is described in Scheme I except that a non-sterically hindered primary alkyl iodide is used for the purpose of this discussion.

(5) It has been suggest by a referee that conversion of **6** → **8** and **3** → **5** might take place by reaction of **6** and **3** with $LiAlH_4$ rather than $LiAlH_4^{\cdot+}$ in a radical chain hydrogen atom abstraction process. We agree and present evidence to support this suggestion.

(6) Park, Seung-Un; Chung, Sung Kee; Newcomb, M. *J. Org. Chem.* **1987**, *52*, 3275.

(7) A summary of Newcomb's position was published after submission of this manuscript. Newcomb, Martin; Curran, Dennis P. *Acc. Chem. Res.* **1988**, *21*, 206.

0022-3263/88/1953-6156$01.50/0