Stereocontrolled Preparation of Tetrahydrofurans by Acid-Catalyzed Rearrangement of Allylic Acetals

Mark H. Hopkins and Larry E. Overman*

Department of Chemistry, University of California Irvine, California 92717

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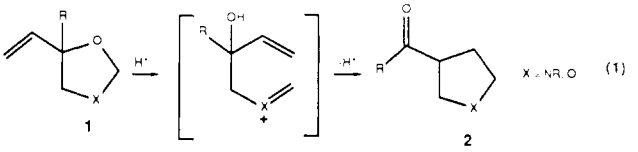
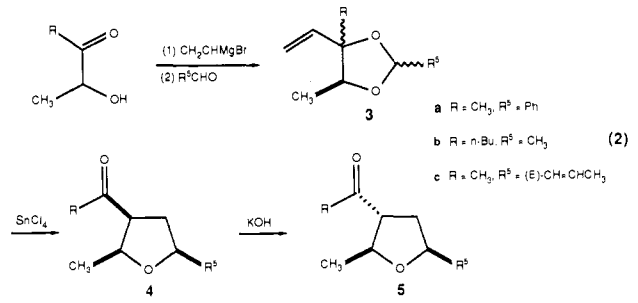
Previous investigations in our laboratories have shown that acid-catalyzed rearrangements of 5-alkenyloxazolidines **1** (X = NR) and similar precursors can be profitably employed to prepare substituted pyrrolidines and complex alkaloids.[1] In this communication we report that a related rearrangement of allylic acetals (eq 1, X = O) allows highly substituted tetrahydrofurans to be



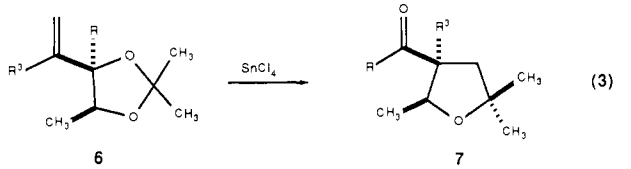
readily assembled in a stereo- and enantioselective fashion. A key feature of this new tetrahydrofuran synthesis is the use of a carbon–carbon bond-forming reaction to establish the stereochemistry of the cyclic ether product. This approach differs markedly from most other syntheses of complex tetrahydrofurans which typically involve carbon–oxygen bond formation.[2]

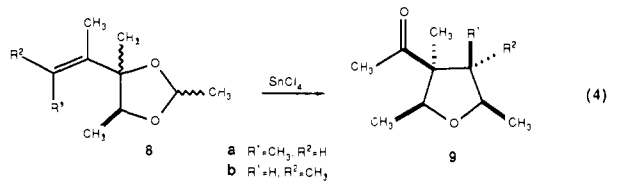
The method can be illustrated by the reaction of acetoin (3-hydroxy-2-butanone) with vinylmagnesium bromide (2.5 equiv, 25 °C, THF) to give a mixture of allylic diols (~1:1) that was subsequently converted (catalytic HCl, $MgSO_4$, 25 °C) to the benzylidene acetal **3a** in 72% overall yield. Exposure of this mixture of stereoisomeric acetals to 1.1 equiv of $SnCl_4$ in CH_2Cl_2 (−70 °C → −10 °C, 2 h, quench at −70 °C with 5–10 equiv of Et_3N) gave tetrahydrofuran **4a**[3,4] in 58% yield after rapid pu-



rification on silica gel. The stereostructure of **4a** followed from its rapid epimerization in methanolic KOH (1 N, 25 °C) to **5a**[3] and from the strong NOE observed between the *cis*-methine hydrogens at C-2 and C-5 of both acetyl epimers. If the rearrangement of **3a** was allowed to warm to room temperature before quenching with excess Et_3N, the trans epimer **5a** could be isolated directly in 85% yield. Allylic acetals derived from aliphatic aldehydes and aliphatic enals rearranged similarly under identical conditions: e.g., **3b** → **4b** (73%), **3c** → **4c** (70%).[3,4] To obtain the all cis kinetic product it was again necessary to not allow the reaction mixture to warm above −10 °C prior to quenching at −70 °C with excess Et_3N. In the case of **3b**, the allylic diol stereoisomers were separated, and the derived acetaldehyde acetals were individually rearranged to afford, after epimerization of the acyl group, **5b** as the sole tetrahydrofuran product (73% from the 4*R**,5*R** diastereomer, 82% from the 4*R**,5*S** diastereomer).[5]

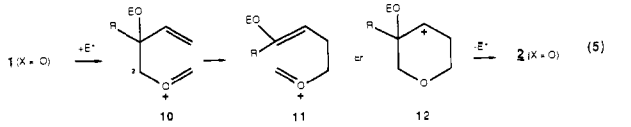
The scope of this new tetrahydrofuran synthesis is illustrated further by the conversions summarized in eq 3 and 4. Ketals **6a**[6] and **6b** rearranged cleanly in the presence of $SnCl_4$ (1 equiv, −78 °C → room temperature) to give tetrahydrofurans **7a**[3] (77%) and **7b**[3] (94%) as the only detectable cyclic products. When a ketal is employed as the rearrangement "initiator", the alkene must be more nucleophilic than a simple terminal vinyl group. For example, attempted rearrangement of **6c**[6] in the presence of a variety of acid catalysts resulted in predominant fragmentation to produce (*E*)-3-butyl-3-penten-2-one (vide infra). The stereospecific (>97%) conversions of acetals **8a** and **8b** to tetrahydrofurans **9a**[3] and **9b**[3] (1.0 equiv of $SnCl_4$, −78 °C → 0 °C; 90% and 73% yields, respectively) demonstrates that polysubstituted tetrahydrofurans





containing a substituent at each ring carbon can be stereoselectively prepared in this way. Chiral nonracemic tetrahydrofurans can be accessed also in high enantiomeric purity from the rearrangement of optically active allylic acetals. For example, rearrangement of optically active **6b** (prepared[7] from ethyl L-lactate, >95% ee) gave **7b**,[3] $[\alpha]_D^{25}$ −25 °C (*c* 1.0, $CHCl_3$), in 90% yield.[8] Reduction of this ketone with *i*-Bu_2AlH and analysis of the major alcohol product by the method of Mosher[9] confirmed that there had been *no* loss of enantiomeric purity in the conversion of **6b** to **7b**.

Two mechanisms for the allylic diol → 3-acyltetrahydrofuran conversion can be envisaged (see eq 5): 2-oxonia[3,3]sigmatropic



rearrangement[10] (**10** → **11**) followed by intramolecular aldol cyclization of **11** or cationic (Prins-type) cyclization of **10** followed by pinacolic rearrangement of the resulting tetrahydropyranyl cation **12**. The fact that chiral nonracemic tetrahydrofurans can be prepared from optically active allylic acetals *without* loss of enantiomeric purity is consistent with a cyclization–pinacol mechanism.[11] The high stereoselectivity observed in the tetrahydrofuran syntheses reported here follows in each case from

(1) Overman, L. E.; Kakimoto, M.; Okazaki, M.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622. Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745. and other papers in this series.

(2) (a) For reviews, see: Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D.; Ed.; Academic: New York, 1984; Vol. 3, Chapter 6. Semple, J. E.; Joullie, M. M. *Heterocycles* **1980**, *14*, 1825. (b) Recent examples include the following: Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105. Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106. Williams, D. R.; White, F. H. *Tetrahedron Lett.* **1986**, *27*, 2195. Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691.

(3) The stereostructure for this material was assigned on the basis of ^1H NMR DNOE experiments. New compounds showed ^1H NMR, IR, and high resolution mass spectra in accord with their assigned structures.

(4) Minor amounts (~5%) of the acetyl epimer **5** were also formed.

(5) Other Lewis acids can be employed also, e.g., $EtAlCl_2$.

(6) This intermediate was an ~1:1 mixture of stereoisomers.

(7) Prepared by a sequence related to the one described in Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355.

(8) The *R**,*R** diastereomer of **6a** rearranged in an identical fashion to optically active **7a**.

(9) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. The corresponding ester prepared from a racemic sample of this tetrahydrofuran showed well-separated signals for the C-2 methine hydrogens of both diastereomers.

(10) To our knowledge, no examples of this hetero-Cope rearrangement have been described.

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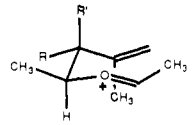
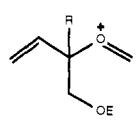
a preference for cyclization to occur in the most stable chair conformation[12] via an *E* oxonium ion[13,14] intermediate (e.g., see **13**). The fact that both allylic diol stereoisomers rearrange to



13 R, R = OH or CH_3



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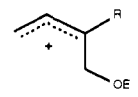

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give the same tetrahydrofuran product is rationalized also by this model. Success of this tetrahydrofuran synthesis requires that ring opening of the starting acetal to form **14** is readily reversible and that oxonium ion **10** is "trapped" by the intramolecular alkene group more rapidly than the starting acetal undergoes ionization at the tertiary allylic oxygen to afford an allyl cation (e.g., **15**).[15]

In summary, polyfunctional tetrahydrofurans can be prepared stereoselectively in three steps from readily available α-hydroxy ketone precursors. The key rearrangement demonstrates, moreover, that simple acetals can be employed in a rational fashion to "trigger" complex reorganizations. New opportunities in the area of stereocontrolled synthesis of oxygenated materials are opened up by these observations.

Acknowledgment. This research was supported by NIH Grant NS-12389. The high field (500 and 300 MHz) NMR and high resolution mass spectrometers used in this research were purchased with the assistance of NSF Shared Instrumentation Grants.

Supplementary Material Available: Typical experimental procedures and characterization data (preparation of **7b**) (2 pages). Ordering information is given on any current masthead page.

(11) This experiment does not rule out the rather unlikely sequence in which initially formed **11** undergoes intramolecular aldol cyclization more rapidly than it relaxes (by C–C bond rotation) to an achiral conformation. This possibility arises since intermediate **11** (produced from **10** containing a substituent at C-2), although devoid of stereogenic centers, would likely be formed in a chiral chairlike conformation.

(12) A preference for chair reaction topographies has been seen in cyclization of acetals to form hydropyran products, see: e.g., Kay, I. T.; Williams, E. G. *Tetrahedron Lett.* **1983**, *24*, 5915. Melany, M. L.; Lock, G. A.; Thompson, D. W. *J. Org. Chem.* **1985**, *50*, 3925. Overman, L. E.; Castaneda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303.

(13) Inversion and rotation barriers for oxonium ions are sufficiently low[14] that reaction via only the more stable oxonium ion stereoisomer is expected.

(14) Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am Chem. Soc.* **1985**, *107*, 2435.

(15) (*E*)-3-Butyl-3-penten-2-one, the major product formed from attempted rearrangement of **6c**, is presumed to result from pinacolic (or semipinacolic) rearrangement of an intermediate related to **15**, followed by conjugation of the enone product.

The Molecular Structure of a Substituted 2-Norbornyl Cation, 2-Methoxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylium Fluoroborate

Lawrence K. Montgomery,* Martin P. Grendze, and John C. Huffman

Department of Chemistry, Indiana University Bloomington, Indiana 47405

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The structure, bonding, and chemistry of the 2-norbornyl cation have been focal points of physical-organic research for almost 4 decades.[1,2] In spite of unparalleled effort, a universally accepted picture of this fascinating carbocation system has not been achieved.[2] Rapidly equilibrating classical, symmetrical nonclassical, and rapidly equilibrating unsymmetrical nonclassical intermediates have been invoked to accommodate the results of numerous experimental and theoretical findings.[2] Further complicating the situation is the concern that gas-phase, stable-ion, and solvolytic experiments may involve different species.[2] Since a central issue in the norbornyl controversy is the precise geometry of the cation, it is astonishing that there has been so little published research devoted to acquiring its absolute structure.[3] On the other hand, the dearth of information may be understandable; securing X-ray crystallographic data for all but the most stable carbocations is difficult.[3-5] Our own experience confirms that the experimental problems are formidable. We have been able to isolate a stable salt[3] of the 2-norbornyl cation from 2-fluoronorbornane and antimony pentafluoride, but we have not succeeded in obtaining a single-crystal X-ray structure. Although our work along these lines is continuing, we have also undertaken studies of substituted analogues. Our first successful attempt is related in this communication.

One point on which norbornyl cation researchers seem to agree is that placing electron-releasing substituents at the 2-position tips the balance toward the classical end of the spectrum.[1,2] In fact, it has been asserted that a methyl group provides sufficient stabilization to ensure that 2-methyl derivatives are essentially classical.[6,1f] In light of accumulating evidence, it is probably more prudent to conclude that methyl substitution produces an unsymmetrical species (classical or nonclassical).[7,1f,2d] The carbocation reported here, 2-methoxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylium fluoroborate, has the more strongly electron-releasing methoxy group in the 2-position. On the basis of methoxyl exchange studies of camphor dimethyl ketal in methanol-d_4, Traylor and Perrin[8] have argued cogently that 2-methoxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylium is a classical ion. Our X-ray results indicate that it does, indeed, have a structure with a distinct classical bias. A careful look at the molecular parameters reveals some unusual features, however.

The fluoroborate salt was prepared[8] by the reaction of triphenylmethyl fluoroborate with the dimethyl ketal of (1*R*)-(+)-camphor (inert-atmosphere techniques). The X-ray crystallographic data were collected[9,10] in a dry-nitrogen atmosphere at −155 °C. Selected bond lengths and angles for 2-methoxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylium are given in Table I (atom-numbering scheme, Figure 1). The structure of the fluoroborate anion is normal[11] (average B–F = 1.376 (8) Å). The

(1) (a) Winstein, S.; Trifan, D. S. *J. Am. Chem. Soc.* **1949**, *71*, 2953; **1952**, *74*, 1147, 1154. (b) Brown, H. C. *Spec. Publ.-Chem. Soc.* **1962**, *16*, 140. (c) Bartlett, P. D. *Nonclassical Ions*; W. A. Benjamin: New York, 1965. (d) Brown, H. C. *Acc. Chem. Res.* **1973**, *6*, 377. (e) Olah, G. A. *Acc. Chem. Res.* **1976**, *9*, 41. (f) Brown, H. C. (with comments by Schleyer, P. v. R.) *The Nonclassical Ion Problem*; Plenum Press: New York, 1977.

(2) (a) Grob, C. A. *Acc. Chem. Res.* **1983**, *16*, 426. (b) Brown, H. C. *Acc. Chem. Res.* **1983**, *16*, 432. (c) Olah, G. A.; Prakash, G. K. S.; Saunders, M. *Acc. Chem. Res.* **1983**, *16*, 440. (d) Walling, C. *Acc. Chem. Res.* **1983**, *16*, 448. (e) See, also the letters to the editor by Olah and Brown: Olah, G. A., Brown, H. C. *Chem. Eng. News* **1983**, *61*, May 23.

(3) (a) Dinnocenzo, J. P. Ph.D. Thesis, Cornell University, 1985. See, also: (b) Olah, G. A. *Aldrichim. Acta* **1979**, *12*, 43. (c) Yannoni, C. S.; Macho, V.; Myhre, P. C. *J. Am. Chem. Soc.* **1982**, *104*, 907.

(4) Childs, R. F.; Mahendran, M.; Zweep, S. D.; Shaw, G. S.; Chadda, S. K.; Burke, N. A. D.; George, R. E.; Faggiani, R.; Lock, C. J. L. *Pure Appl. Chem.* **1986**, *58*, 111.

(5) Sundaralingam, M.; Chwang, A. K. In *Carbonium Ions*; Olah, G. A.; Schleyer, P. v. R., Eds.; Wiley: New York, 1976; Vol. V, Chapter 39.

(6) Two early examples are the following: (a) Bunton, C. A. *Nucleophilic Substitution at a Saturated Carbon*; Elsevier Publishing Co.: New York, 1963; p 62. (b) Brown, H. C.; Chloupek, F. J.; Rei, M.-H. *J. Am. Chem. Soc.* **1964**, *86*, 1247.

(7) (a) Saunders, M.; Telkowski, L.; Kates, M. R. *J. Am. Chem. Soc.* **1977**, *99*, 8070. (b) Olah, G. A.; DeMember, J. R.; Lui, C. Y.; Porter, R. D. *J. Am. Chem. Soc.* **1971**, *93*, 1442. (c) Haseltine, R.; Wong, N.; Sorensen, T. S. *Can. J. Chem.* **1975**, *53*, 1891. (d) Myhre, P. C.; McLaren, K. L.; Yannoni, C. S. *J. Am. Chem. Soc.* **1985**, *107*, 5294.

(8) Traylor, T. G.; Perrin, C. L. *J. Am. Chem. Soc.* **1966**, *88*, 4934.

(9) $[C_{11}H_{19}O^+][BF_4^-]$: $P2_1$, a = 8.015 (4) Å, b = 7.246 (3) Å, c = 11.285 (6) Å, β = 104.30 (4)°, Mo Kα radiation, $6 < 2\theta < 65°$, MULTAN78, Fourier, non-hydrogens anisotropic, 1297 reflections (5954 total), $|F_o| > 3\sigma(|F_o|)$, R = 0.061 and R_w = 0.064.

(10) Experimental procedures: Huffman, J. C.; Lewis, L. N.; Caulton, K. G. *Inorg. Chem.* **1980**, *19*, 2755.

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