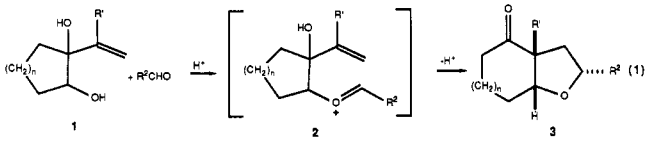
Ring-Enlarging Furan Annulations

Summary: Substituted cycloheptatetrahydrofurans and octahydrobenzofurans are formed with high levels of stereocontrol by acid-promoted rearrangement of acetals derived from 1-alkenyl-2-hydroxycyclohexanols and 1-alkenyl-2-hydroxycyclopentanols, respectively. In some cases, these bicyclics can be prepared by the direct reaction of an allylic diol precursor and an aldehyde.

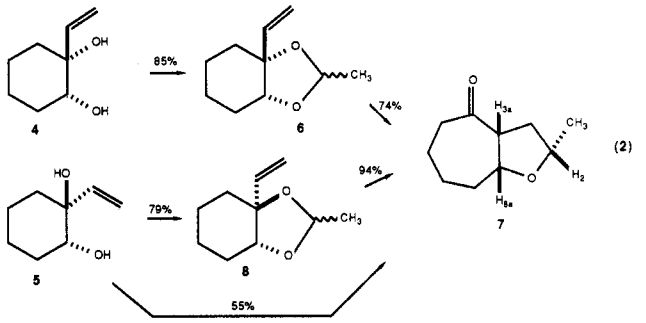
Sir: We have reported that stereochemically complex tetrahydrofurans can be prepared in useful yields by acid-catalyzed rearrangement of allylic acetals.[2] In order to extend this new tetrahydrofuran synthesis to more complex ring systems, we recently investigated the related rearrangement of cyclic allylic diols and acetals. Our expectation was that rearrangement in cyclic systems would result in an unusual annulation reaction in which elaboration of a new tetrahydrofuran ring would be coupled with a one-carbon ring-enlargement of the starting carbocyclic ring (see eq 1). Conceptually related "ring-enlarging"



(1)

pyrrolidine annulation reactions had been developed earlier in our laboratories for the synthesis of pyrrolidine-containing heterocycles and complex alkaloids.[3] In this paper, we report that a variety of substituted cis-fused octahydrobenzofurans **3** (n = 1) and cycloheptatetrahydrofuans **3** (n = 2) can be prepared in a stereocontrolled fashion as outline in eq 1.

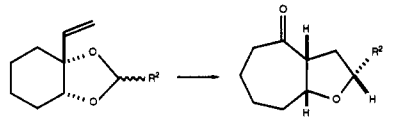
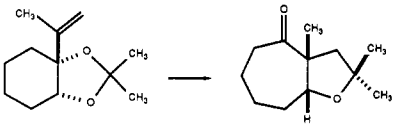
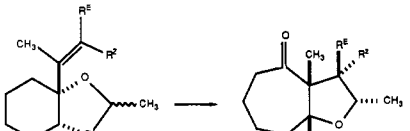
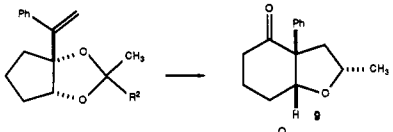
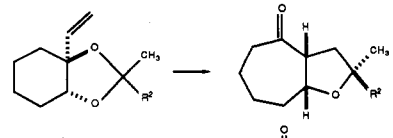
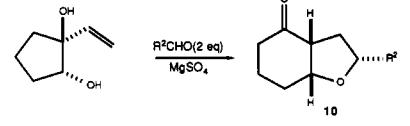
In order to investigate the rearrangement in both stereochemical series, the cis and trans allylic diols **4** (35%) and **5** (34%) were prepared (CH_2=$CHMgBr$, 25 °C, THF) from α-hydroxycyclohexanone and separated on silica gel (eq 2). Conversion of **4** to acetal **6** (2 equiv of CH_3CHO,



(2)

0.2 equiv of p-TsOH, 25 °C), followed by rearrangement of the latter at −70 °C in the presence of 1 equiv of $SnCl_4$ (CH_2Cl_2, 1 h), gave cycloheptatetrahydrofuran **7** [4] as the sole bicyclic product in 63% overall yield from **4**. The cis ring fusion of **7** followed from the strong (23%) NOE observed between the angular hydrogens H_{3a} (apparent q at δ 3.40, J = ~9 Hz, in $CDCl_3$) and H_{8a} (apparent ddd at δ 4.19, J = 3.0, 9.3, 10.7 Hz) and the weaker (6%) NOE observed between H_{3a} and H_2 (m, δ 3.8–4.0).[5] Oxabicyclic **7** could also be prepared from the trans diol **5** by direct treatment at room temperature with acetaldehyde (2 equiv) and p-toluenesulfonic acid (0.3 equiv). Since this rearrangement was accompanied by partial epimerization of **7** at H_{3a}, it was preferable to carefully convert **5** to acetal **8**[6] (2 equiv of CH_3CHO, 0.01 mol % HCl, 23 °C) and then rearrange this intermediate in the presence of $SnCl_4$ (−70

Table I. Ring-Enlarging Tetrahydrofuran Annulations of Diol and Acetal Precursors

entry	conversion[a]		conditions	yield, %
1		R^2 = CH_3	$SnCl_4$ (1 equiv), −70 °C, 1 h	74
2		R^2 = n-Pr	$SnCl_4$ (1 equiv), −70 °C, 1 h	76
3		R^2 = Ph	$SnCl_4$ (1 equiv), −70 °C, 2 h	63
4		R^2 = (E)-CH=CHPh	$MgBr_2$ (2 equiv), 23 °C, 2 h	53
5		R^2 = CH_2OCH_3	BF_3·OEt_2 (2 equiv), 23 °C, 8 h	48
6			$SnCl_4$ (1 equiv), −70 → 23 °C	94
7		R^E = CH_3, R^Z = H	$SnCl_4$ (1 equiv), −70 → 23 °C, 5 h	81
8		R^E = H, R^Z = CH_3	$SnCl_4$ (1 equiv), −70 → 23 °C, 6 h	56
9			$SnCl_4$ (1 equiv), −70 → 23 °C, 2 h	80
10		R^2 = H	$SnCl_4$ (1 equiv), −70 → 23 °C, 2 h	94[c]
11		R^2 = CH_3	$SnCl_4$ (1 equiv), −70 → 23 °C, 2 h	~10[c]
12		R^2 = Ph	RSO_3H (0.3 equiv), 23 °C, 1 h	47
13		R^2 = CH=CH_2	RSO_3H (0.3 equiv), 23 °C, 1 h	63[b]
14		R^2 = CH_2OBu-t	RSO_3H (0.3 equiv), 23 °C, 1 h	56

[a] Reference 4. [b] 1.1 equiv of acrolein was employed. [c] A crude sample of the starting acetal was employed.

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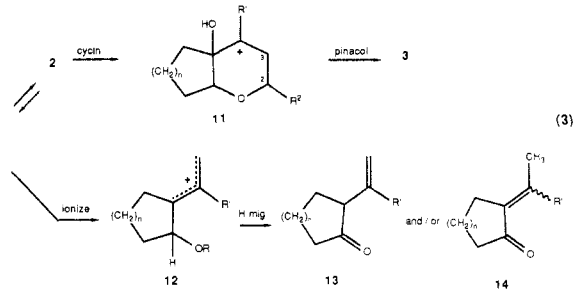
°C → 23 °C, 2 h) to provide[4] **7** as the *sole* bicyclic product.

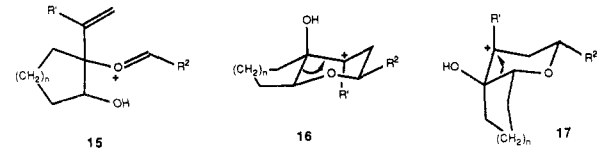
A variety of cycloheptatetrahydrofurans and octahydrobenzofurans can be prepared in this simple fashion from 2-hydroxy-1-alkenylcyclohexanol or 2-hydroxy-1-alkenylcyclopentanol precursors, and some representative examples are collected in Table I.[4] In all cases, only a *single* bicyclic product was isolated.[4a] Several Lewis acids were examined for the rearrangement reported in entry 2: BF_3 etherate (−70 → 23 °C), $TiCl_4$ (−70 °C), $EtAlCl_2$ (−70 → 23 °C) and $MgBr_2$ (23 °C) can be successfully employed, while Me_2AlCl (23 °C) was ineffective. In most cases only one Lewis acid was examined so the yields reported may not be optimum. Entries 7 and 8 demonstrate that the stereochemistry of a terminal alkene substituent is faithfully[7] transmitted to the C-3 position of the bicyclic product. The successful rearrangement of ketal derivatives requires that the alkene substituent contain an electron-releasing substituent at the internal alkene carbon (compare entries 6 and 11).[8] When this substituent was lacking a fragmentation process dominated, which in the case of entry 11 gave (*E*)-2-ethylidenecyclohexanone (**14**, R′ = H, n = 2) as the major product.

Our earlier mechanistic investigations[2] suggest that the transformations reported in eq 2 and Table I likely occur by a Prins cyclization–pinacol rearrangement sequence as outlined in eq 3. Two oxonium ions can be formed from



(3)

1 and an aldehyde (or the corresponding acetal) in the presence of an acid. It is a key element of the annulation sequence reported here that only **2**, and *not* **15**, can undergo oxonium ion–alkene cyclization (i.e. **2** → **11**) in a stereoelectronically favorable fashion.[9] When the C_2–C_3 bond that would be formed in the oxonium ion–alkene cyclization is heavily substituted, ionization of **1** to allyl cation **12** apparently becomes competitive with cyclization and fragmentation products **13** and **14** result. The stereochemistry of the bicyclic product produced in the ring-enlarging furan annulation follows in each case from a preference for the cyclization reaction to occur via a chair topography with the more stable (*E*)-oxonium ion[2,10] to form intermediate bicyclic cations **16** or **17**. It is significant in the trans diol series, where cyclization could occur in a chair sense to give two cis-fused bicyclic intermediates, that only products derived from **17** are observed.[11]



In summary, this study shows that a variety of stereochemically complex bicyclic ethers can be prepared in 2–3 steps from simple α-hydroxycycloalkanones. Although this sequence has been specifically demonstrated with cyclopentanone and cyclohexanone precursors only, it is likely not limited to these ring systems. The increase in molecular and stereochemical complexity realized in the conversions reported here suggests potential applications of this chemistry for the synthesis of complex cyclic ethers. As one example, Baeyer–Villiger oxidation of bicycles **7** and **10** provides a short stereocontrolled synthesis of all cis 2,5-disubstituted-3-hydroxytetrahydrofurans.[12]

Acknowledgment. This research was supported by NIH Grant NS-12389. The high field (500 and 300 MHz) NMR and medium 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 **7**, **9**, and **10** (R^2 = Ph)] (3 pages). Ordering information is given on any current masthead page.

(1) NSERC Postdoctoral Fellow of the National Research Council of Canada, 1985–86.

(2) Hopkins, M. H.; Overman, L. E. *J. Am. Chem. Soc.*, in press.

(3) See, inter alia: Overman, L. E.; Mendelson, L.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629. Overman, L. E.; Jacobsen, E. J.; Doedens, R. J. *J. Org. Chem.* **1983**, *48*, 3393. Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745. Overman, L. E.; Angle, S. R. *J. Org. Chem.* **1985**, *50*, 4021.

(4) (a) It was essential to quench the rearrangement reaction with excess Et_3N at −70 °C, *prior* to aqueous workup, to avoid partial epimerization to the trans-fused stereoisomer in the cases where the C_{3a} substituent was H. (b) The stereostructure for this (these) intermediate(s) was (were) assigned on the basis of ^1H NMR DNOE experiments. (c) Yields refer to materials obtained after purification by chromatography and/or distillation.

(5) This hydrogen is observed as a dd (J = 8.7, 7.8 Hz) when the CH_3 group is decoupled.

(6) This compound, which was a mixture of acetal stereoisomers, could not be isolated in pure form. The crude acetal was used directly in the rearrangement step.

(7) Capillary GC analysis showed that there was <0.1% crossover in these conversions.

(8) A similar limitation is also observed in the synthesis of bicyclic products containing substituents at *both* C-2 and C-3. Thus, rearrangements related to those shown in entries 7 and 8 were unsuccessful if the 1-methyl group was not present on the alkene substituent.

(9) See, e.g.: Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

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

(11) The origin of this selectivity is currently being investigated and will be discussed in our full account of this work.

(12) This is a substitution pattern found in many tetrahydrofuran-containing marine natural products.[13]

(13) See, e.g.: Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1, and earlier reviews in this series.

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