$SnCl_4$ (0.1 mL, 0.9 mmol) to give, after purification by flash chromatography (1:2 EtOAc–hexane), 249 mg (58%) of the tetrahydrofuran (2*S*)-**25e**, which was contaminated to the extent of 10% by the acetyl epimer. This mixture was used without further purification in the following reaction.

(−)-(2*S*,3*R*,5*S*)-1-[Tetrahydro-2-methyl-5-(hydroxymethyl)-3-furanyl]ethanone ((−)-33). A solution of KOH (183 mg, 3.26 mmol), a 569-mg (2.17-mmol) sample of the optically active mixture of 3-acetyltetrahydrofurans described in the previous procedure, and MeOH (5 mL) was maintained at 23 °C for 3 h. Saturated aqueous NH_4Cl (20 mL) was then added, and the mixture was concentrated to remove MeOH. The resulting aqueous suspension was saturated with NaCl and extracted with CH_2Cl_2 (5 × 20 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (1:50 MeOH–CH_2Cl_2) to provide 210 mg (61%) of the tetrahydrofuran (−)-**33** (95% pure by ^1H NMR analysis) as a colorless oil: $[\alpha]_D$ −21.1 (*c* 1.1, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 4.11–4.08 (m, 2 H, 2 CH), 3.77–3.74 (m, 1 H, CH32OH), 3.53–3.51 (m, 1 H, CH_2OH), 2.79 (ddd, J = 7.5, 2.3, 5.3 Hz, H(3)), 2.20 (s, 3 H, CH_3CO), 2.21–2.00 (m, 2 H, CH_2), 1.92 (br s, 1 H, OH), 1.34 (d, J = 6.1 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 78.77, 77.6, 64.5, 58.8, 31.2, 30.1, 20.5; IR (film) 3411, 2875, 1708, 1702, 1096, 1040 cm^{-1}; MS (CI) *m/z* 159.1040 (159.1021 calcd for $C_8H_{14}O_3$, MH).

(−)-2,5-Anhydro-1,4-dideoxy-D-*ribo*-hexitol ((−)-34). A mixture of the ketone (−)-**33** (73 mg, 0.46 mmol), 3,4-dinitroperoxybenzoic acid (630 mg, 2.77 mmol), 2.0 mg of *tert*-butyl 4-hydroxy-5-methylphenyl sulfide, and CH_2Cl_2 (10 mL) was heated at reflux for 3 h. The mixture was then poured into saturated aqueous Na_2SO_3 (20 mL) and extracted with CH_2Cl_2 (20 mL). The CH_2Cl_2 extract was washed with saturated aqueous $NaHCO_3$ (20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (1:1 EtOAc–hexane) to provide 51 mg (64%) of the 3-acetate (95% pure by ^1H NMR analysis) as a colorless oil: $[\alpha]_D$ −11.8 (*c* 1.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.88–4.86 (m, 1 H, $CHOCOCH_3$), 4.22–4.20 (m, 1 H, CH), 4.04–4.03 (m, 1 H, CH), 3.80 (d, J = 11.7 Hz, 1 H, CH_2OH), 3.54 (d, J = 11.7 Hz, 1 H, CH_2OH), 2.47 (br s, 1 H, OH), 2.13–2.08 (m, 1 H, CH_2), 2.07 (s, 3 H, CH_3CO), 1.90–1.86 (m, 1 H, CH_2), 1.27 (d, J = 8.7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 80.5, 79.8, 78.9, 63.8, 32.9, 21.0, 19.7; IR (film) 3421, 1739, 1737, 1728, 1249, 1105, 1086, 1079 cm^{-1}; MS (CI) *m/z* 175.0969 (175.0970 calcd for $C_8H_{14}O_4$, MH).

Sodium metal (7 mg, 0.3 mmol) dissolved in MeOH (1 mL) was added to a solution of a 36.0-mg (0.21-mmol) sample of the 3-acetate and MeOH (3 mL), and the resultant solution was maintained at 23 °C for 30 min. The solution was then poured into saturated aqueous NH_4Cl (20 mL), and the mixture was concentrated to remove MeOH. The resulting aqueous suspension was saturated with NaCl and extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (EtOAc) to provide 26 mg (97%) of the diol (−)-**34** (90% pure by ^1H NMR) as a colorless oil: $[\alpha]_D$ −17.2 (*c* 1.29, EtOAc) (lit.[32] $[\alpha]_D$ −16.9 (*c* 1.14, EtOAc)); ^1H NMR (300 MHz, CD_3OD) δ 4.20–4.09 (m, 1 H, H(5)), 3.92–3.88 (m, 1 H), 3.84–3.76 (m, 1 H), 3.58 (dd, J = 11.6, 3.9 Hz, 1 H, H(6)), 3.49 (dd, J = 11.6, 5.3 Hz, 1 H, H(6)), 1.94 (ddd, J = 13.0, 8.6, 6.5 Hz, 1 H, H(4)), 1.82 (ddd, J = 13.0, 6.7, 3.5 Hz, 1 H, H(4)), 1.18 (d, J = 6.3 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.6, 78.3, 77.6, 64.4, 35.8, 19.6; IR (film) 3391, 2973, 2932, 1087, 1080, 1035, 736 cm^{-1}; MS (CI) *m/z* 133.0880 (133.0885 calcd for $C_6H_{12}O_3$, MH).

(+)-Muscarine Tosylate (35). Following the procedures of Mubarak and Brown,[33] the diol (−)-**34** (26 mg, 0.20 mmol) was converted to the tosylate, $[\alpha]_D$ +1.62 (*c* 1.0, $CHCl_3$), and this intermediate was treated with NMe_3 and MeOH to provide (+)-muscarine tosylate (**35**) in 50% yield from diol (−)-**34** (90% pure by ^1H NMR analysis) as a colorless oil: $[\alpha]_D$ +3.9 (*c* 0.45, EtOH) (lit.[33] $[\alpha]_D$ +4.0 (*c* 4, EtOH)).

Muscarine tosylate (**35**) was subjected to ion-exchange chromatography on Amberlyst resin to give muscarine chloride, which was identical by ^1H NMR (500 MHz, D_2O) to authentic muscarine chloride purchased from Sigma Chemical Co.

Acknowledgment. The financial support of PHS Grant NS-12389 is gratefully acknowledged. NMR and mass spectra were determined at the University of California at Irvine with spectrometers purchased with the assistance of NSF Shared Instrumentation grants.

Supplementary Material Available: Experimental procedures and characterization data for the preparation of acetals **12a–d,f,g**, **15**, **16**, **18a,b**, **26a,b**, and **28** (7 pages). Ordering information is given on any current masthead page.

Acid-Promoted Reaction of Cyclic Allylic Diols with Carbonyl Compounds. Stereoselective Ring-Enlarging Tetrahydrofuran Annulations

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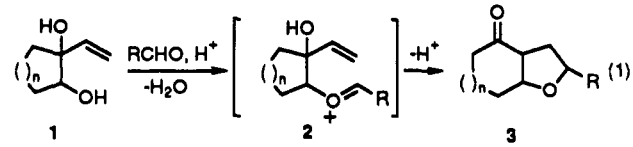
Abstract: A wide variety of cis-fused hexahydrocyclopenta[*b*]furan-4-ones (**3**, n = 0), hexahydro-4(2*H*)-benzofuranones (**3**, n = 1), and octahydrocyclohepta[*b*]furan-4-ones (**3**, n = 2) can be prepared with high levels of stereocontrol by the title reaction. The scope and limitations of this powerful new method for assembling polycyclic ethers are explored in detail. Conformational analysis of potential oxabicyclo[4.4.0]decanyl, oxabicyclo[4.3.0]nonanyl, and oxabicyclo[4.2.0]octanyl cation intermediates allows the stereochemical outcome of the title reaction to be predicted.

The preceding paper in this issue presented details of the preparation of stereochemically complex 3-acyltetrahydrofurans from the acid-promoted reaction of allylic diols with aldehydes and ketones.[2] In an effort to extend this powerful new tetrahydrofuran synthesis to more complex ring systems, we have investigated the related reaction of cyclic allylic diols (eq 1). This



(1)

transformation appends a tetrahydrofuran ring and expands by one carbon the ring of the starting cyclic diol. We have termed this unusual conversion a *ring-enlarging tetrahydrofuran annu-*

(1) NSERC Postdoctoral Fellow of the National Research Council of Canada, 1985–1986.

(2) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.*, preceding paper in this issue.

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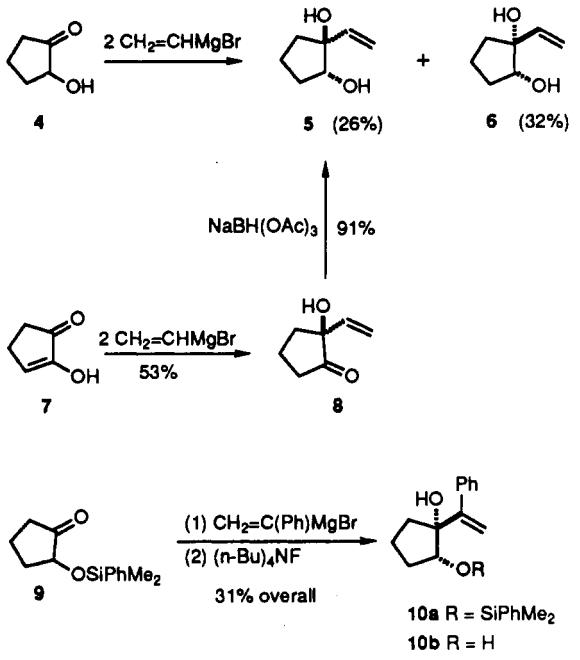
Table I. Preparation of 1-Alkenylcyclohexane-1,2-diols as Shown in Scheme II

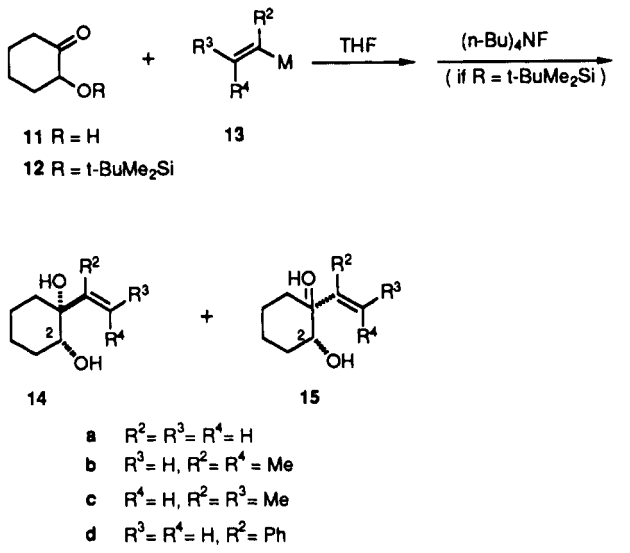
ketone	vinylorganometallic 13				temp,[a] °C	diol	yield,[b] %	
	R^2	R^3	R^4	M			14	15
11	H	H	H	MgBr	23	a	27	31
11	Me	H	Me	Li	−70 → +23	b	49 (1:6)[c]	
11	Me	Me	H	Li	−70 → +23	c	51 (1:4)[c]	
12	Ph	H	H	MgBr	23	d	e	34[d]

[a] In THF. [b] After isomer separation. [c] Yield of isomer mixture. [d] After desilylation with $(n\text{-Bu})_4NF$ and crystallization. [e] The amount of the minor isomer was not quantified.

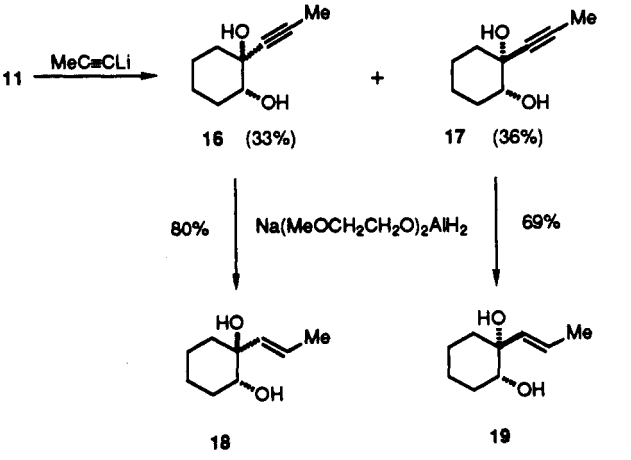
Scheme I



Scheme II



Scheme III



lation.[3] Conceptually related ring-enlarging pyrrolidine annulations, developed in our laboratories, have proven to be potent reactions for the synthesis of pyrrolidine-containing heterocycles and complex alkaloids.[4]

The studies reported here examine ring-enlarging tetrahydrofuran annulations with starting 1-alkenyl-1,2-cycloalkanediols of ring sizes four–six (eq 1; n = 0–2). These studies demonstrate that a wide variety of cis-fused hexahydrocyclopenta[*b*]furan-4-ones (**3**, n = 0), hexahydro-4(2*H*)-benzofuranones (**3**, n = 1), and octahydrocyclohepta[*b*]furan-4-ones (**3**, n = 2) can be prepared with high levels of stereocontrol by this experimentally convenient reaction.

Results

Preparation of Cyclic Allylic Diols. The 1-alkenyl-1,2-cycloalkanediol starting materials are readily prepared, although nonstereoselectively, from the reaction of an excess of a vinyllithium or vinyl Grignard reagent with a 2-hydroxycycloalkanone. The latter materials either are available commercially or are directly prepared from diesters by acyloin cyclization.[5] Alternatively, the trans-diol stereoisomers are expediently prepared with complete stereocontrol by (acyloxy)borohydride reduction[6] of 2-alkenyl-2-hydroxycycloalkanones.[7] In the cyclopentyl series, the cis-diol stereoisomers can be accessed also in stereoselective fashion by the face selective[8] addition of vinyl Grignard reagents to the 2-silyloxycyclopentanone **9**. These sequences are summarized for the preparation of three alkenylcyclopentanediols in Scheme I. It is noteworthy that the stereocontrolled preparation of the trans-diol **5** from 1,2-cyclopentadione has been conveniently carried out in 48% overall yield on a 40-g scale. Cyclopentane-1,2-dione is in turn procurable on a large scale by ozonolysis of commercially available 2-cyclopentylidenecyclopentanone.[9] The stereochemical assignments for **5**, **6**, and **10** followed directly from earlier studies of Conia[7] or strong mechanistic precedent.[6,8]

In a similar fashion, the *cis*- and *trans*-1-alkenylcyclohexane-1,2-diols **14** and **15** were accessed from commercially available

(3) (a) For our initial report, see: Herrinton, P. M.; Hopkins, M. H.; Mishra, P.; Brown, M. J.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 3711. (b) Part of this work is also briefly reported in: Overman, L. E. In *Selectivities in Lewis-Acid Promoted Reactions*; NATO ASI Series; Schinzer, D., Ed.; Kluwer: Dordrecht, The Netherlands, 1989; Vol. 289, p 1.

(4) For a brief review, see: Overman, L. E.; Ricca, D. J. *Compr. Org. Synth.* 1991, in press.

(5) Bloomfield, J. J.; Owsley, D. C.; Nelke, J. M. *Org. React.* **1976**, *23*, 259.

(6) (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (b) Gribble, G. W.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun.* **1975**, 535. (c) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(7) This basic approach was defined earlier: (a) Barnier, J.-P.; Conia, J.-M. *Bull. Soc. Chim. Fr.* **1975**, 1654. (b) Barnier, J.-P.; Conia, J.-M. *Ibid* **1975**, 1659.

(8) See, inter alia: Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355. Nakata, T.; Tanaka, T.; Oishi, T. *Ibid.* **1983**, *24*, 2653. Keck, G. E.; Boden, E. P. *Ibid.* **1984**, *25*, 265.

(9) Wrobel, J.; Cook, J. M. *Synth. Commun.* **1980**, *10*, 333.

Table II. Preparation of Octahydrocyclohepta[*b*]furan-4-ones **26** from Lewis Acid Promoted Rearrangements of Acetals **25** Derived from *cis*-Cyclohexanediol **14a** and Aldehydes

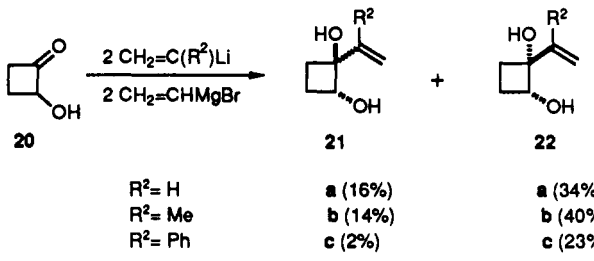
	diol **15**			aldehyde **24**	acetal		rearrangement conditions			hydrocycloheptafuranone	
entry	R^2	R^3	R^4	R^1	compd	yield, %	acid (equiv)	temp, °C	time, h	compd	yield, %
1	H	H	H	*n*-Pr	**25a**	76	$SnCl_4$ (1)	−70	1	**26a**	76
2							$BF_3{\cdot}OEt_2$ (1)	−70 → +23	2	**26a**	75
3							$EtAlCl_2$ (1)	−70 → +23	2	**26a**	67
4							$MgBr_2$ (2)	23	10	**26a**	61
5	H	H	H	Me	**25b**	85	$SnCl_4$ (1)	−70	1	**26b**	74
6	H	H	H	Ph	**25c**	68	$SnCl_4$ (1)	−70	2	**26c**	63
7	H	H	H	(*E*)-CH=CHPh	**25d**	52	$MgBr_2$ (2)	−70	2	**26d**	53
8	H	H	H	CH_2OMe	**25e**	70	$BF_3{\cdot}OEt_2$ (1)	23	8	**26e**	48

Table III. ^1H NMR Characterization Data for Octahydrocyclohepta[*b*]furan-4-ones

					^1H NMR,[a] δ			
compd	R^1	R^2	R^3	R^4	H(8a)	H(2)	H(3a)	other
26a	*n*-Pr				4.10 [ddd (10.8, 9.2, 2.8)]	3.7 [m]	3.35 [q (9)]	CH_3, 0.85 [t (5.5)]
26b	Me				4.19 [ddd (10.7, 9.3, 3.0)]	3.8 [m]	3.40 [q (9)]	CH_3, 1.30 [d (5.4)]
26c	Ph				4.37 [ddd (10.3, 9.5, 3.0)]	4.80 [dd (10.4, 5.9)]	3.57 [q (9)]	Ph, 7.3 [m]
26d	(*E*)-CH=CHPh				4.59 [ddd (10.4, 9.6, 2.8)]	4.76 [q (5.2)]	3.4–3.6 [m]	PhC*H*=, 6.6 [d (10.8)] PhCH=C*H*, 6.27 [dd (10.8, 4.7)]
26e	CH_2OMe				4.24 [ddd (10.3, 9.5, 3.0)]	4.0 [m]	3.5–3.4 [m]	CH_3O, 3.61 [s]
28a		Ph	H	H	4.70 [d (10.2)]	4.0 [m]		Ph, 7.4–7.2 [m] CH_3, 1.24 [d (6.5)]
28b		Me	Me	H	3.73 [dd (6.7, 4.6)]	3.56 [dq (9.8, 6.0)]		CH_3CHO, 1.27 [d (6.0)] CH_3, 1.15 [s] CH_3CH, 0.90 [d (6.9)]
28c		Me	H	Me	3.64 [d (7.7)]	4.19 [dq (8.8, 6.6)]		CH_3CHO, 1.20 [d (6.6)] CH_3, 1.0 8 [s] CH_3CH, 0.77 [d (7.8)]

[a] In $CDCl_3$. Most diagnostic signals only. Coupling constants in hertz are in parentheses.

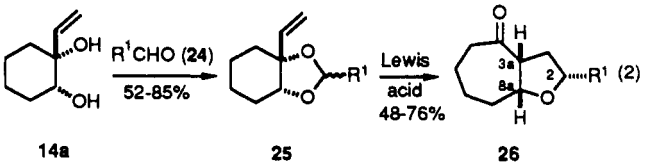
Scheme IV



2-hydroxycyclohexanone.[10] Details are reported in Scheme II and Table I. The 1(*E*)-propenylcyclohexanediol stereoisomers **18** and **19** were prepared by stereoselective reduction of the corresponding propargylic alcohol precursors (Scheme III). Structural assignments for cyclohexanediols **14–19** were readily secured by analysis of ^1H NMR spectra. The cis-diol stereoisomer is expected to exhibit the largest vicinal couplings for the diagnostic C(2) methine hydrogen, since this isomer should strongly prefer a single chair conformation with the 1-alkenyl (or 1-alkynyl) and 2-hydroxyl substituents equatorial.[11] The stereostructures of the epimer pair **14a**/**15a** have also been rigorously secured by chemical correlations.[7b,12]

Identical strategies were employed to prepare 1-alkenylcyclobutanediols from 1-hydroxycyclobutanone (Scheme IV).[13] In this case, the 2-alkenyl-2-hydroxycyclobutanone precursors of the trans-diol stereoisomers **21** were prepared by Parikh–Doering oxidation of the cis-diols **22b** and **22c**.[14] Stereochemical assignments for the cyclobutanediols followed unambiguously from the results of (acyloxy)borohydride reduction[6] of **23b,c** and the ready formation of cyclic acetals from the cis-diol stereoisomers **22**.

Preparation of Octahydrocyclohepta[*b*]furan-4-ones. Rearrangements in the cis-diol series were carried out by initial conversion to the acetal derivative **25**, which was typically isolated as a mixture of stereoisomers at the acetal carbon (eq 2). The



a R^1 = n-Pr; **b** R^1 = Me; **c** R^1 = Ph
d R^1 = (E)-CH=CHPh; **e** R^1 = CH_2OMe

rearrangement of the *n*-propyl acetal **25a** was examined in detail, and key findings are summarized in Table II. As detailed in entries 1–4, **25a** could be successfully converted to the cis-fused octahydrocycloheptafuranone **26a** when exposed to a variety of Lewis acids: $SnCl_4$, $BF_3{\cdot}OEt_2$, $EtAlCl_2$, and $MgBr_2$. The conversion of **25a** → **26a** was fastest with $SnCl_4$, and this Lewis acid was typically employed in subsequent experiments. Related rearrangements to prepare bicyclic keto ethers with methyl, phenyl, styrenyl, and methoxymethyl substitution at C(2) were similarly accomplished in preparatively useful yields (Table II, entries 5–8). In these latter cases, yields were not optimized and higher efficiencies may be possible.

To the extent of detection by ^1H NMR only a single stereoisomer of **26** was produced from the rearrangement of acetals **25**. To ensure that HCl-promoted epimerizatiion at C(3a) did not occur during workup, reaction mixtures were cooled to −70 °C and treated with excess Et_3N *prior* to aqueous quenching.

The stereostructures of **26** followed in each case from ^1H NMR homonuclear decoupling and ^1H NOE experiments. The data for **26b** are representative. The angular hydrogen adjacent to oxygen (H(8a)) is observed as a ddd (J = 3.0, 9.3, 10.7 Hz) at 4.19 ppm. Coupling constant data alone are not sufficient to assign the ring fusion stereochemistry, since minimum energy conformations of

(10) The commercial product is a mixture of the monomer and dimer. Both appear to react with an excess of a vinyl organometallic.
(11) For related examples, see: Battistini, C.; Crotti, P.; Macchia, F. *J. Org. Chem.* **1981**, *46*, 434.
(12) Jefferies, P. R.; Milligan, B. *J. Chem. Soc.* **1956**, 4384.
(13) Bloomfield, J. J.; Nelke, J. M. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. 6, p 167.
(14) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(15) 2-Hydroxy 2-substituted cyclobutanones are not generally available from the reaction of organometallics with cyclobutane-1,2-dione: Barnier, J. P.; Conia, J. M. *Bull. Soc. Chim. Fr.* **1976**, 281. Barnier, J. P.; Denis, J. M.; Salavn, J.; Conia, J. M. *Tetrahedron Lett.* **1974**, 1404.

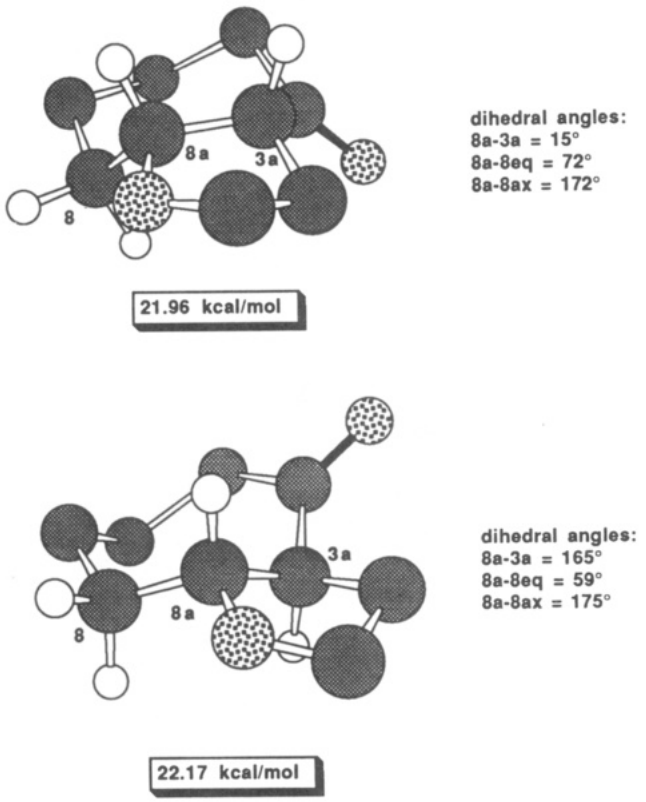
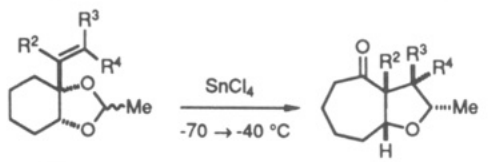


Figure 1. Minimum energy conformations for *cis*- and *trans*-octahydrocyclohepta[*b*]furan-4-ones (MMX force field, only hydrogens at C(3a), C(8a), and C(8) are shown).

both *cis*- and *trans*-octahydrocyclohepta[*b*]furan-4-ones would be characterized in their ^{1}H NMR spectra by one small and two large vicinal couplings for H(8a) (Figure 1).[16-18] However, the strong (20%) NOE observed between the angular hydrogen H(3a) (apparent q at δ 3.40, $J \approx 9$ Hz) and H(8a) and the NOE (6%) observed between H(3a) and H(2) (m, δ 3.8–4.0) establish both the cis ring fusion and the trans orientation of the methyl substituent. Diagnostic ^{1}H NMR data for the other 4-oxooctahydrocycloheptafurans are summarized in Table III.

Bicyclic acetals containing substituted alkene moieties can be successfully rearranged to afford hydrocycloheptafuranones adorned with substituents at each carbon of the tetrahydrofuran ring (eq 3). In the three cases illustrated in eq 3 *only a single*



27 28 (3)

a R^2 = Ph, R^3 = R^4 = H	93%
b R^2 = R^3 = Me, R^4 = H	75%
c R^2 = R^4 = Me, R^3 = H	81%

cis-fused product of ring-enlarging furan annulation was produced. The formation of **28b** and **28c** with no detectable stereochemical crossover (<0.5%) confirms that the rearrangement occurs with high stereochemical fidelity in a suprafacial sense with respect to the alkene participant. Stereochemical assignments again followed from ^{1}H NMR NOE studies; key observations defining the stereostructures of **28a–c** are summarized in Figure 2.

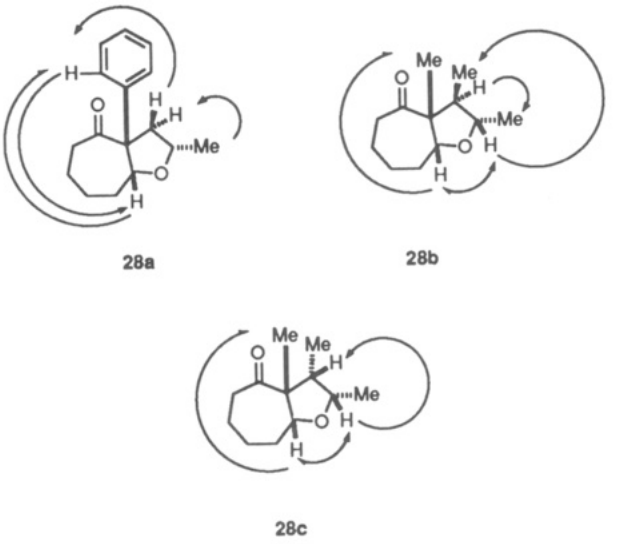
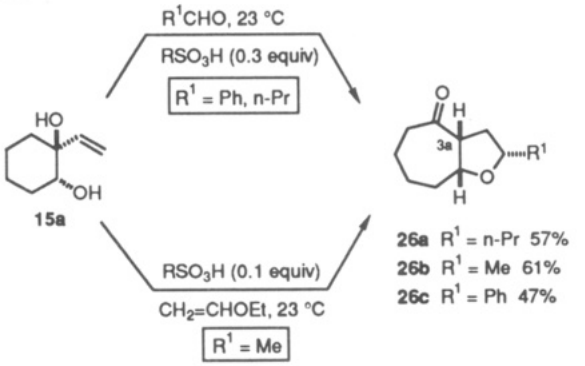
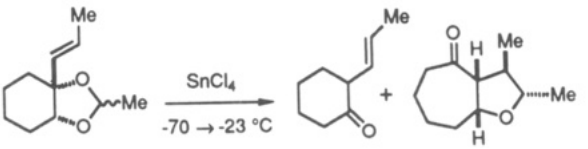


Figure 2. Key ^{1}H NOE enhancements for cycloheptafuranones **28**.

Scheme V



An important limitation to the formation of substituted cycloheptatetrahydrofuranones in this way is depicted in eq 4 and arises when the vinyl moiety is not biased toward addition of an electrophile to the distal vinylic carbon. Thus, attempted rearrangement in CH_2Cl_2 of acetal **29** with $SnCl_4$ afforded only traces of the desired octahydrocyclohepta[*b*]furan-4-one and provided as the major product (87% yield) the propenylcyclohexanone **30**.



29 30 <5% (4)

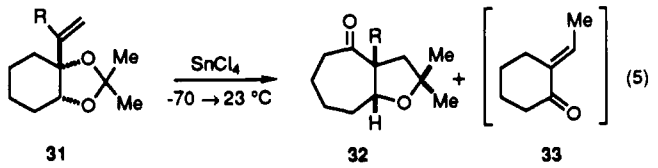
A second limitation, which was also observed in related preparations of monocyclic tetrahydrofurans,[2] arises when the carbonyl component is a ketone. Thus, while the rearrangement of acetonide **31a** containing a phenyl substituent at the internal alkene carbon occurs efficiently to afford **32a**, the related reaction of acetonide **31b**, containing a less nucleophilic terminal vinyl moiety, provided only trace amounts of **32b** (eq 5). The major product isolated in this latter case was the product of fragmentation, 2-ethylidenecyclohexanone (**33**).

Our investigations of related rearrangements in the *trans*-cyclohexanediol series focused solely on cyclohexanediol **15a**; these are summarized in Scheme V. Ring-enlarging furan annulation to afford hydrocycloheptafuranones **26** was most easily accomplished by the *direct* reaction (at room temperature) of **15a** with an aldehyde or enol ether under protic acid conditions typically

(16) PCMODEL Molecular Modeling Software for the Macintosh II, obtained from Serena Software, Bloomington, IN, was used for these calculations. For a discussion of the MMX enhanced version of MM2, see: Gajewski, J. J.; Gilbert, K. E.; McKelvey, J. *Advances in Molecular Modeling*; JAP Press: Greenwich, CT, Vol. 2, in press.

(17) The subroutine RANDOMIZ, which is based on Saunder's stochastic approach for exploring molecular mechanics energy surfaces,[18] was employed in our search for the global minimum.

(18) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150.



(5)

31 **32** **33**

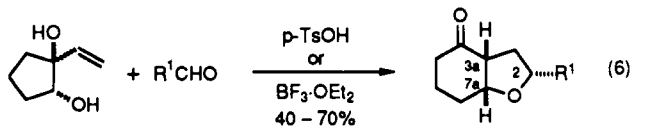
a R = Ph; b R = H

a 90% R = Ph
b <20% R = H

50% when R = H

employed to prepare acetals. Unless monitored with extreme care, this direct rearrangement is accompanied by partial epimerization (10–20%) of the kinetically favored cis-fused products **26** at C(3a). Of note is the fact that the ring-enlarging furan annulations of *both* vinylcyclohexane-1,2-diol stereoisomers (**14a** and **15a**) occur with complete stereoselectivity to afford the same products, the cis-fused bicyclic ethers **26**.

Preparation of Hexahydro-4(2*H*)-benzofuranones. As a result of our interest in exploiting cis hydrobenzofurans containing angular hydrogen substituents as precursors to oxacyclic marine natural products,[19] we have investigated in detail ring-enlarging furan annulations of 1,2-cyclopentanediols that carry an unsubstituted vinyl substituent at C(1). The desired molecular reorganization was successfully accomplished by the direct reaction of the trans-diol stereoisomer **5** with a wide variety of aliphatic, aromatic, and α-oxygenated aldehydes (eq 6). Both *p*-toluene-



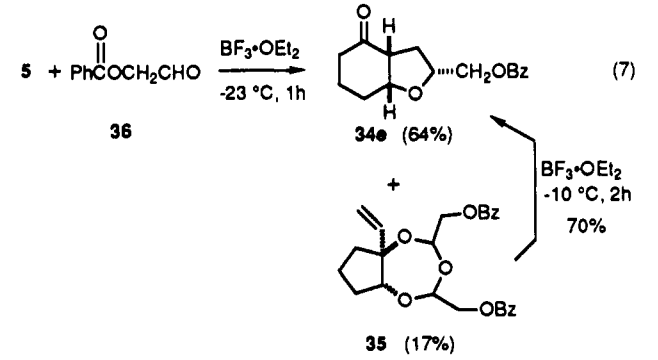
(6)

5 **34**

a R^1 = Me; b R^1 = n-Pr; c R^1 = Ph; d R^1 = CH_2OBn;
e R^1 = CH_2OBz; f R^1 = CH_2OBu^t

sulfonic acid and BF_3·OEt_2 can be utilized to promote this rearrangement; experimental details are summarized in Table IV. As in the six-membered ring series, only a single product of ring-enlarging furan annulation was observed: the cis stereoisomer with a trans-oriented side chain at C(2). A particularly important attribute of this transformation is its experimental simplicity (*mix and stir*!), which allows scale-up to be readily accomplished. For example, the rearrangement summarized in entry 5 of Table IV *provided 21 g of hydrobenzofuran* ***34d***.

Additional insight into the direct reaction of *trans*-cyclopentanediol **5** with aldehydes was provided by the experiments summarized in eq 7. Exposure of diol **5** to 1.05 equiv of (ben-



(7)

36 **34e** (64%)

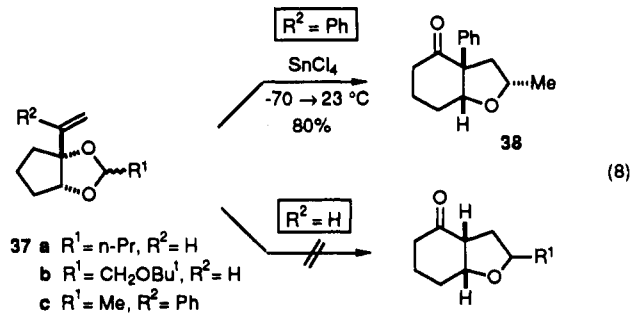
35 (17%)

zoyloxy)acetaldehyde (**36**) in the presence of 1.0 equiv of BF_3·OEt_2 resulted, within 1 h at −23 °C, in complete consumption of **5**. Quenching at this point with excess Et_3N and chromatographic purification provided 64% of the crystalline hydrobenzofuranone **34e** and 17% of **35**. This latter product, which is a 2:1 adduct of **5** and the starting aldehyde **36**, was isolated as a single stereoisomer, although its spatial constitution was not established.

It was readily shown that **35** was not an intermediate in the direct formation of **34e** from **5**, since **35** was converted in the presence of BF_3·OEt_2 to **34e** only very slowly at −23 °C. However, at −10 °C acetal **35** was converted within 2 h into a 1:1 mixture of **34e** and (benzoyloxy)acetaldehyde.

The stereochemical assignments for hexahydro-4(2*H*)-benzofuranones **34** were based initially on analyses of ^1H NMR spectra (see Table V). In most cases the cis ring fusion was readily defined by the appearance of the angular C(7a) hydrogen. This hydrogen ($\delta \approx 4.3$ ppm) appeared as an apparent quartet with $J \approx 4$ Hz, or alternatively as an unresolved multiplet whose outer line separation was 12–14 Hz. A narrow absorption of this type would not be observed for the trans stereoisomer for which H(7a) would have two large axial–axial couplings. The cis relationship of H(3a) and H(7a) was typically also apparent from the large (ca. 20%) NOE observed between these hydrogens. For **34a** and **34f** a strong NOE was also observed between H(2) and H(3a) defining a cis relationship for these hydrogens and, thus, the trans orientation of the side chain. The stereostructures of **34d** and **34e** were rigorously established: in the first case by conversion to the *Laurencia* metabolite, (*E*)-kumausyne,[19] and in the second by single-crystal X-ray analysis of a derivative.[20] The stereochemical assignments at C(2) for **34b** and **34c** were based on analogy with other members of this series.

The related rearrangement of bicyclic acetals derived from *cis*-1-vinylcyclopentane-1,2-diol (**6**) was not successful. For example, attempted rearrangements of acetals **37a** or **37b** in the presence of a wide variety of acids (inter alia, $SnCl_4$, BF_3·OEt_2, $TiCl(OPr^i)_3$, Me_3SiOTf, *p*-TsOH) did not engender ring-enlarging furan annulation (eq 8). In several of these cases, epimerization

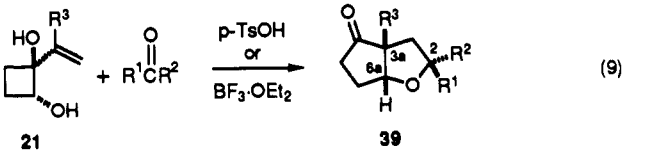


(8)

37 a R^1 = n-Pr, R^2 = H
b R^1 = CH_2OBu^t, R^2 = H
c R^1 = Me, R^2 = Ph

at the acetal carbon provided evidence for reversible acetal cleavage under these conditions. In marked contrast, acetal **37c**, which contains the more nucleophilic 1-phenylvinyl moiety, rearranged in good yield under the aegis of $SnCl_4$ to afford the 3a-phenyl-substituted cis hydrobenzofuranone **38** (eq 8).

Preparation of Hexahydrocyclopenta[*b*]furan-4-ones. As with their five-membered ring counterparts, bicyclic acetals derived from *cis*-1,2-cyclobutanediols **22** did not undergo ring-enlarging furan annulation when exposed to acidic reagents. However, the direct reaction of the trans-diol stereoisomers **21** with aldehydes and ketones was highly successful (eq 9). Both *p*-toluenesulfonic



(9)

21
a R^3 = H
b R^3 = Me
c R^3 = Ph

39
a R^1 = R^3 = H, R^2 = Me
b R^1 = R^3 = H, R^2 = Ph
c R^1 = H, R^2 = Ph, R^3 = Me
d R^1 = H, R^2 = R^3 = Me
e R^1 = H, R^2 = CH=CH_2, R^3 = Me
f R^1 = H, R^2 = Me, R^3 = Ph
g R^1, R^2 = $(CH_2)_5$, R^3 = Me
h R^1, R^2 = $(CH_2)_4$, R^3 = Me

(19) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.*, following paper in this issue.

(20) Hutchinson, K. D. Ph.D. Dissertation, University of California, Irvine, 1990.

Table IV. Preparation of Hexahydro-4(2*H*)-benzofuranones **34** from the Direct, Acid-Promoted Reaction of *trans*-Cyclopentanediol **5** with Aldehydes

	R^1CHO		rearrangement conditions[a]				
entry	R^1	equiv	acid (equiv)	temp, °C	time, h	hydrobenzofuranone	yield,[b] %
1	Me	2.2	TsOH (0.3)	23	1	**34a**	46
2	Me	3.0[c]	TsOH (0.1)	23	0.5	**34a**	42
3	*n*-Pr	2.0	TsOH (0.3)	23	1	**34b**	55
4	Ph	2.0	TsOH (0.3)	23	1	**34c**	47
5	CH_2OBn	0.9	TsOH (0.3)	23	1.5	**34d**	69[d]
6	CH_2OBn	1.0	$BF_3{\cdot}OEt_2$ (1.5)	−23	1.5	**34d**	50
7	CH_2OBz	1.0	$BF_3{\cdot}OEt_2$ (1.0)	−23	0.2	**34e**	64 (76)[e]
8	CH_2O-*t*-Bu	2.0	TsOH (0.4)	23	1	**34f**	41

[a] In CH_2Cl_2. [b] After chromatographic purification. [c] Ethyl vinyl ether was used instead of acetaldehyde. [d] Reaction conducted on a 20-g scale. [e] Yield after resubmission of acetal **35** (see eq 7).

Table V. Characterization Data for Hexahydro-4(2*H*)-benzofuranones **34**

		IR[a]	^1H NMR,[b] δ			
compd	R	$\nu_{C=O}$, cm^{-1}	H(7a)	H(2)	H(3a)	other
34a	Me	1710	4.23 [m][c]	3.97 [sept (5.2, 1.0)]	2.87 [m]	Me, 1.22 [d (5.0)]
34b	*n*-Pr	1708	4.23 [m][c]	3.82 [sept (5.6, 1.0)]	2.85 [m]	Me, 0.96 [t (6.4)]
34c	Ph	1710	4.40 [m][c]	4.81 [br t (7.3)]	2.93 [m]	Ph, 7.3 [m]
34d	CH_2OBn	1716[c]	4.31 [m][c]	4.09 [dddd (8.7, 6.1, 6.1, 4.2)]	2.74 [ddd (8.8, 5.5, 3.3)]	Ph, 7.3 [m] $PhCH_2$, 4.56 [AB q (12.2, $\Delta\vartheta$ = 25.5)] C*H*HOBn 3.45 [dd (10.1, 4.3)] CH*H*OBn 3.39 [dd (10.1, 7.0)]
34e[d]	CH_2OBz	1718	3.69 [m][c]	3.88 [app ddt (13.2, 6.6, 3.3)]	2.46 [app dt (5.6, 2.8)]	Ph, 8.2 [m], 7.1 [m]
34f	CH_2O-*t*-Bu	1712	4.31 [m][c]	3.99 [m]	2.71 [ddd (10.2, 5.9, 4.1)]	*t*-Bu, 1.20 [s]

[a] Thin film. [b] In $CDCl_3$. Coupling constants in hertz are shown in parentheses. [c] CCl_4 solution. [d] NMR in C_6D_6. [e] Narrow multiplet, outer line separation 10–12 Hz.

Table VI. Preparation of Hexahydrocyclopenta[*b*]furan-4-ones **39** from the Reaction of *trans*-Cyclopentanediols with Aldehydes and Ketones

					hydrocyclopentafurans **39**	
entry	R^1	R^2	R^3	rearrg cond[a]	compd	yield, %
1	H	Me	H	A	**39a**	low
2	H	Me	H	B	**39a**	50
3	H	Ph	H	B	**39b**	57
4	H	Ph	Me	A	**39c**	71
5	H	Ph	Me	B	**39c**	74
6	H	Me	Me	A	**39d**	56
7	H	$CH{=}CH_2$	Me	A	**39e**	45
8	H	Me	Ph	B	**39f**	53
9	Me	Me	H			b
10		$(CH_2)_5$	Me	B	**39h**	65
11		$(CH_2)_4$	Me	B	**39i**	45
12	H	Ph	Ph	B	**42**	90[c]

[a] Rearrangement conditions: A, *p*-TsOH (1 equiv), aldehyde (2 equiv), CH_2Cl_2, 23 °C; B, $BF_3{\cdot}OEt_2$ (1 equiv), aldehyde (2 equiv), CH_2Cl_2, −23 °C. [b] Not isolated. [c] A 2:1 mixture of stereoisomers at C(2).

acid and $BF_3{\cdot}OEt_2$ have been successfully employed to promote this conversion (Table VI). In accordance with the related reactions of five- and six-membered trans diols with aldehydes, the alkene participant can either be an unsubstituted vinyl substituent or carry an electron-donating substituent at the internal vinylic carbon (Table VI, entries 1–8). However, when the carbonyl component is a ketone, only substrates with alkene substituents more nucleophilic than terminal vinyl rearrange successfully (compare Table VI entries 9–11). The structurally interesting spiro tricyclic ethers **39g** and **39h** were readily assembled by the direct reaction of **21b** with cyclohexanone and cyclopentanone, respectively.

The gross structure of keto ethers **39** was signaled by the diagnostic cyclopentanone carbonyl absorption at ca. 1740 cm^{-1} in the infrared spectrum; other key characterization data are summarized in Table VII. With but a single exception (entry 12), the reactions summarized in Table VI provided, to the limits of detection by high-field ^1H NMR analysis, a single stereoisomeric product. The relative stereochemistry of these bicyclic

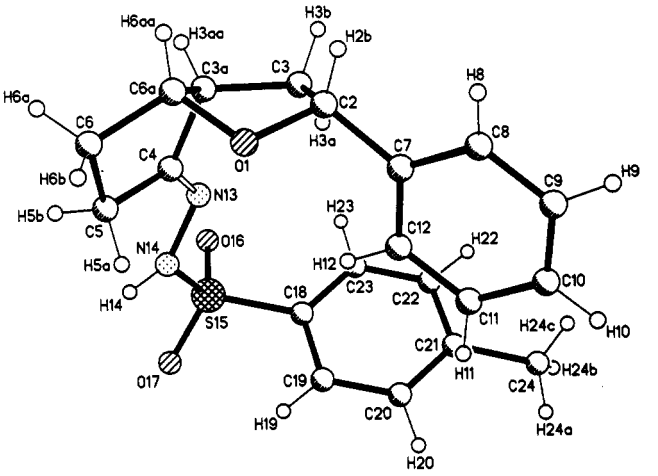
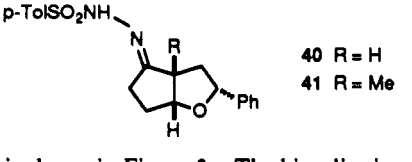


Figure 3. View of the crystallographic model of **40**.

tetrahydrofurans was typically elucidated by ^1H NMR NOE experiments (either 1D or 2D). Particularly diagnostic were the 1,3 NOE's observed between the ether methine hydrogens H(2) and H(6a) and the strong NOE's observed between the cis angular substituents H(6a) and H(3a) (or C(3) Me). A characteristic feature of the ^1H NMR spectra of **39** is the appearance of the angular 6a-hydrogen as a simple doublet (J = 4–5 Hz).

Stereochemical assignments were confirmed for cyclopentafuranones **39b** and **39c** by single-crystal X-ray analyses of the *p*-toluenesulfonylhydrazone derivatives **40** and **41**. The X-ray



40 R = H
41 R = Me

model of **40** is shown in Figure 3. The bicyclic rings of **40** and **41** adopt identical conformations in the solid state, and overlaps of the X-ray models showed deviations of <0.02 Å for all the ring atoms. The characteristic observation of H(6a) as a doublet in the ^1H NMR spectrum (Table VII) when $R^3 \neq H$ is readily

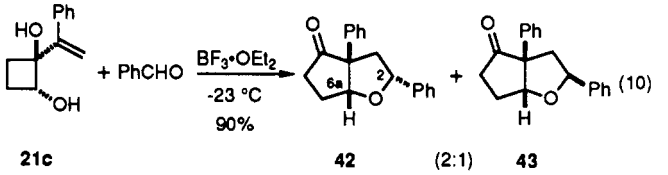
Table VII. Characterization Data for Hexahydrocyclopenta[b]furan-4-ones

compd	R^1	R^2	R^3	IR[a] $\nu_{C=O}$, cm^{-1}	^{1}H NMR,[b] δ H(2)	H(6a)	H(3a)	H(3β)	H(3α)	other
39a	H	Me	H	1744	3.96 (app sextet, J = 6.4 Hz)	4.53 (t, J = 4.9 Hz)	2.67 (dt, J = 4.4, 4.4, 9.8 Hz)	2.38 (ddd, J = 6.9, 9.9 12.9 Hz)	*c*	1.22 (d, J = 6.0 Hz, CH_3)
39b	H	Ph	H	1744	4.82 (t, J = 7.9 Hz)	4.71 (t, J = 4.9 Hz)	2.82 (dt, J = 4.8, 9.6 Hz)	2.69 (ddd, J = 7.4, 10.5, 13.0 Hz)	2.03 (ddd, J = 4.0, 8.5, 13.1 Hz)	
39c	H	Ph	Me	1739	4.90 (t, J = 7.9 Hz)	4.34 (d, J = 4.3 Hz)		*d*	2.02–2.11 (m)	1.24 (s, CH_3)
39d	H	Me	Me	1740	4.01 (app d quintets, J = 5.4, 6.8, 6.8, 6.8, 6.8 Hz)	4.13 (d, J = 4.3 Hz)		*d*	1.78 (dd, J = 8.1, 12.9 Hz)	1.18 (d, J = 6.0 Hz, C_2-CH_3)
39e	H	CH=CH_2	Me	1740	4.35 (qt, J = 1.0, 7.5, 7.5, 7.5 Hz)	4.22 (d, J = 4.3 Hz)		*d*	*d*	1.11 (s, C_{3a}-CH_3) 1.14 (s, CH_3) 5.75 (ddd, J = 6.8, 10.4, 17.1 Hz, CH=CH_2)
39f	H	Me	Ph	1750	4.18 (dq, J = 6.7, 6.7, 6.7, 13.6 Hz)	4.79 (d, J = 3.8 Hz)		*d*	*c*	1.26 (d, J = 6.0 Hz, CH_3)
39g		$(CH_2)_5$	Me	1750		4.28 (d, J = 3.7 Hz)		*c*	*c*	1.11 (s, CH_3)
39h		$(CH_2)_4$	Me	1750		4.22 (d, J = 3.9 Hz)		*c*	*c*	1.11 (s, CH_3)
43	Ph	H	Ph	1750	4.95 (dd, J = 6.4, 9.6 Hz)	5.13 (d, J = 3.8 Hz)		3.19 (dd, J = 6.4, 12.6 Hz)	*c*	
42	H	Ph	Ph	1750	5.05 (t, J = 8.0 Hz)	4.98 (d, J = 3.8 Hz)		*c*	*c*	

[a] Thin film. [b] 500 MHz in $CDCl_3$ unless otherwise noted. [c] Not determined. [d] Part of an unresolved multiplet.

understood from these X-ray models, since H(6a) and the trans-related hydrogen at C(6) have a dihedral relationship of 85° in **40** and 76° in **41**. The crystalline conformations of **40** and **41** also nicely rationalize the observation of H(2) as a triplet ($J \approx$ 8 Hz) in the ^{1}H NMR spectra of **39b** and **39c**. The dihedral angles found between H(2) and the cis and trans vicinal hydrogens at C(3) of **40** are 18° and 139°, respectively. These angles are perfectly consistent[21] with the 8-Hz vicinal couplings observed between H(2) and both C(3) hydrogens for the hydrazones **40** and **41** and the parent ketones **39b** and **39c**.

The reaction of the trans styrenyl diol **21c** with benzaldehyde was unique in providing two stereoisomeric products of ring-enlarging furan annulation (eq 10). These products, **42** and **43**,

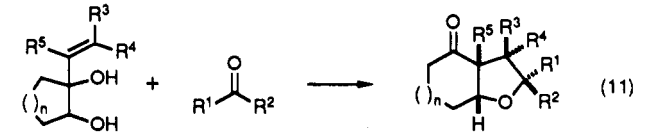


21c **42** (2:1) **43**

could be separated by preparative HPLC. That both bicyclic ethers have the cis ring fusion was indicated by the observation of H(6a) as a doublet in each case: **42**, δ 4.98 (J = 3.8 Hz); **43**, δ 5.13 (J = 3.8 Hz). Two lines of ^{1}H NMR evidence suggest that the major isomer, **42**, also has a trans relationship of the C(2) Ph and the angular substituents: (a) The ^{1}H NMR signals for H(2) of **42** (δ 5.04, t, J = 8.0 Hz) and H(2) of the crystallographically characterized C(3a) methyl analogue **39c** (δ 4.90, t, J = 7.9 Hz) are quite similar. In contrast, this signal of **43** appears as a doublet of doublets (J = 6.4, 9.6 Hz) at δ 4.95. (b) One of the H(3) hydrogens of **43** is observed at abnormally low field (δ 3.19, J = 6.4, 12.6 Hz). This chemical shift is plausible for H(3β) of **43**, since this hydrogen would be cis-related to two adjacent phenyl substituents.

Discussion

A wide variety of bicyclic ethers can be expediently prepared by ring-enlarging tetrahydrofuran annulations (eq 11). A hallmark of this experimentally simple sequence is the marked increase in



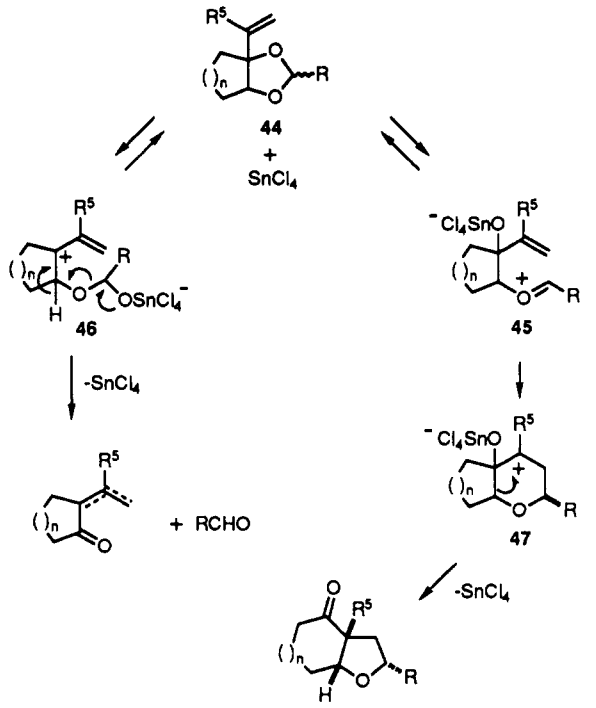
(11)

chemical complexity that is realized in the formation of the oxacyclic products from the cyclic allylic diol and carbonyl components. This unusual annulation has been specifically demonstrated with four-, five-, and six-membered cyclic allylic diol precursors (eq 11, n = 0–2). One would anticipate that cyclic allylic diols of larger ring size also would undergo this transformation to afford tetrahydrofurans fused to medium or large carbocyclic rings. The asymmetric construction of fused tetrahydrofurans is additionally readily realized from nonracemic allylic diol starting materials.[19]

The construction represented in eq 11 occurs with high stereochemical fidelity to afford exclusively cis-fused cyclic ether products. The alkene component is incorporated into the bicyclic product in a stereospecific suprafacial sense. In the cyclohexane series, either diol stereoisomer can be employed. In contrast, if the starting allylic diol is four- or five-membered, only the trans-diol stereoisomer generally undergoes ring-enlarging tetrahydrofuran annulation. Limitations are also seen in the nature of the alkene component, which must display a "Markovnikov bias" toward adding electrophiles at its terminal carbon. Thus, if R^5 = H, R^3 and R^4 must also be hydrogen; if R^3 or R^4 is an electron-donating group, R^5 must be also. A final limitation is seen in the condensation of cyclic allylic diols with ketones where the alkene participant must be more nucleophilic than terminal vinyl.

(21) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

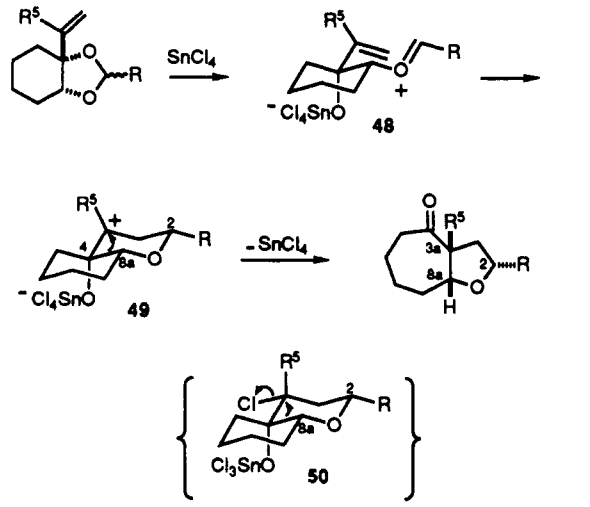
Scheme VI



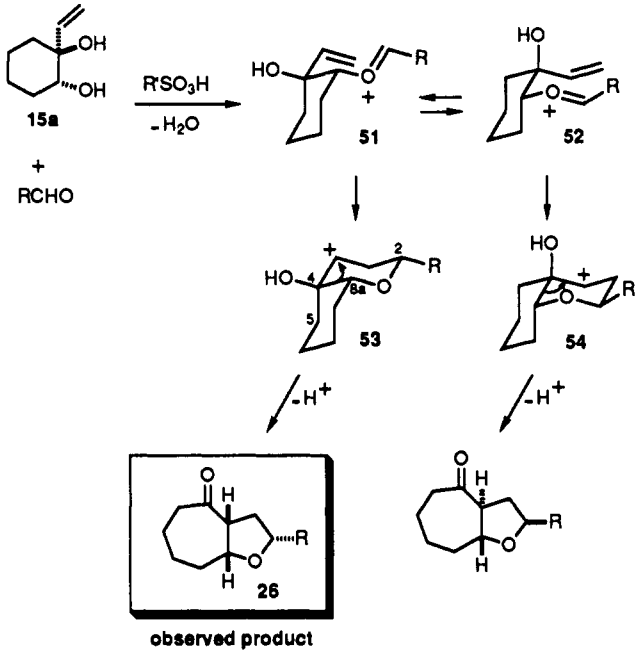
The scope and limitations of ring-enlarging tetrahydrofuran annulations are readily rationalized by the analysis developed in the preceding paper for reactions of acyclic allylic diols. Assuming that the tetrahydrofuran product arises from a Prins–pinacol sequence,[2] the key issue is the competition between ionization of the starting acetal **44** at the tertiary allylic carbon and Prins cyclization of the "productive" oxocarbenium ion **45** (Scheme VI). The former occurrence (**44** → **46**) results in fragmentation to regenerate the carbonyl component and form an enone product (see eqs 4 and 5), while kinetic dominance of the Prins cyclization step (**45** → **47**) results in the desired tetrahydrofuran annulation. With acetals derived from *cis*-1,2-cyclobutanediols, the concentration of the open oxocarbenium ion **45** is apparently so low that Prins cyclization is slow relative to acetal fragmentation. With similar acetals derived from *cis*-1,2-cyclopentanediols, the low concentration of the productive oxocarbenium ion **45** can be overcome by incorporation of an electron-releasing substituent R^5 to increase the rate constant for the **45** → **47** conversion. The limitations with regard to the alkene component are identical with those observed in the acyclic series and are readily rationalized in a similar manner.[2]

The stereochemical outcome of ring-enlarging tetrahydrofuran annulations was anticipated from the stereochemical analysis developed for the preparation of monocyclic 3-acyltetrahydrofurans.[2] The exclusive formation of the cis-fused octahydrocyclohepta[*b*]furan-4-ones **26** and **28** from acetal derivatives of *cis*-cyclohexanedioil precursors (eqs 2 and 3) is readily rationalized as rendered in Scheme VII. The relative orientation at C(2) and C(8a) is set in the cyclization step, and the observed outcome requires only preferential participation of the more stable *E* oxocarbenium ion **48**.[22] In a Prins–pinacol mechanism the stereochemistry at the angular carbon 3a evolves from the topography of the pinacol rearrangement step. The cis-fused bicycle would arise if this step takes place, as shown in Scheme VII, preferentially through a chairlike hydropyranyl cation intermediate. That the chair–chair oxadecalin **49** would be more stable than a related chair–boat conformer is reasonable. Although not ideal, the approximately 30° dihedral angle between the angular C(8a)–C(4) σ bond and the vacant p orbital is apparently sufficient to occasion Wagner–Meerwein reorganization.[23,24]

Scheme VII



Scheme VIII



The stereoelectronics for the pinacol step would be ideal if the chloride **50** was the operative intermediate rather than a "free" carbenium ion. The formation of 4-chlorohydropyrans from $SnCl_4$-promoted Prins cyclizations has much precedent.[25] Anti addition of the oxocarbenium ion and an external chloride nucleophile to the vinyl group of **48** would lead to **50**. Although the intermediacy of **50** cannot be rigorously excluded, the successful rearrangement of acetal **25a** with a variety of Lewis acids (including $BF_3 \cdot OEt_2$) provides some argument against the intervention of a nucleophile-trapped intermediate such as **50**.

The formation of the identical octahydrocycloheptafuranones **26** from the *trans*-cyclohexanediol **15a** is more complex to analyze,

(22) Inversion and rotation barriers for oxonium ions are sufficiently low that reaction via only the more stable *E* stereoisomer is expected: Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am. Chem. Soc.* **1985**, *107*, 2435.

(23) The ca. 30° dihedral angle estimate derives from the anticipated eclipsed orientation of a vicinal equatorial substituent and the substituent at the carbenium ion center.[24]

(24) The dihedral angle between C=O and C_2—H(eq) is 4° in cyclohexanone: Moffitt, W.; Woodward, R. B.; Moscowitz, A.; Klyne, W.; Djerassi, C. *J. Am. Chem. Soc.* **1961**, *83*, 4013.

(25) Bunnelle, W. H.; Seamon, D. W.; Mohler, D. L.; Ball, T. F.; Thompson, D. W. *Tetrahedron Lett.* **1984**, *25*, 2653. Melany, M. L.; Lock, G. A.; Thompson, D. W. *J. Org. Chem.* **1985**, *50*, 3925. Winstead, R. C.; Simpson, T. H.; Lock, G. A.; Schiavelli, M. D.; Thompson, D. W. *J. Org. Chem.* **1986**, *51*, 275. Lolkema, L. D. M.; Hiemstra, H.; Mooiweer, H. H.; Speckamp, W. N. *Tetrahedron Lett.* **1988**, *29*, 6365. Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911.

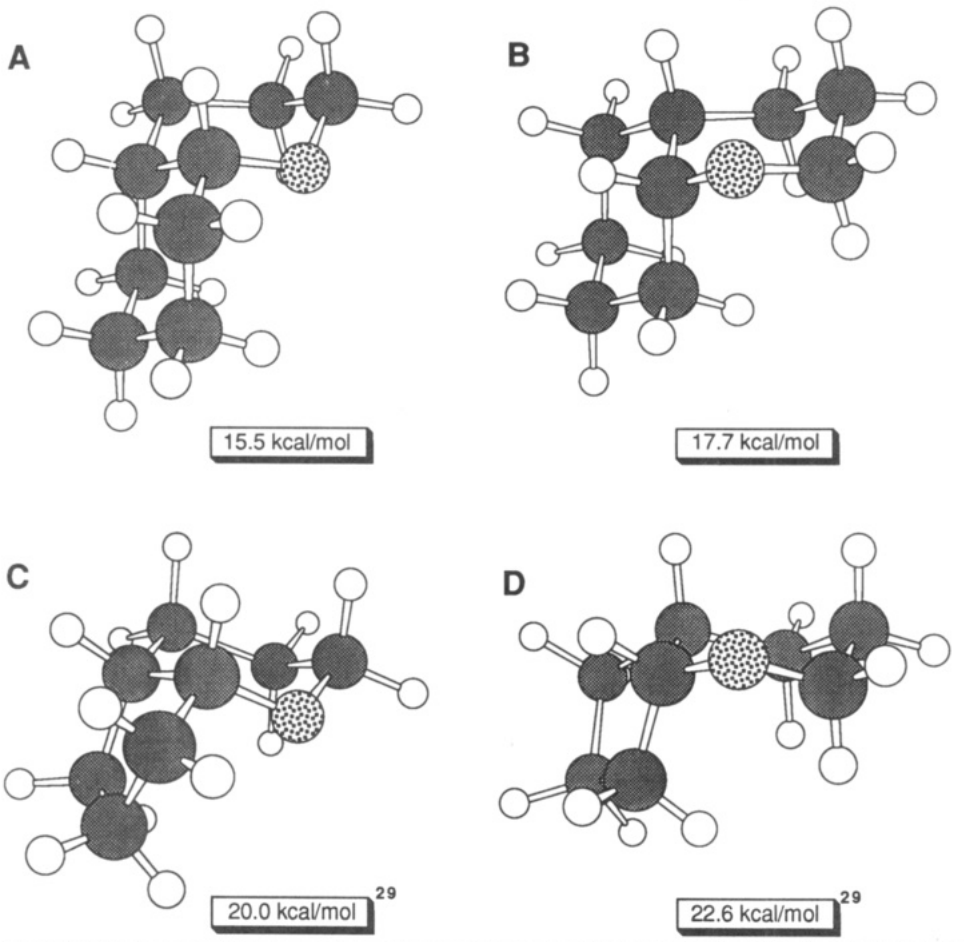
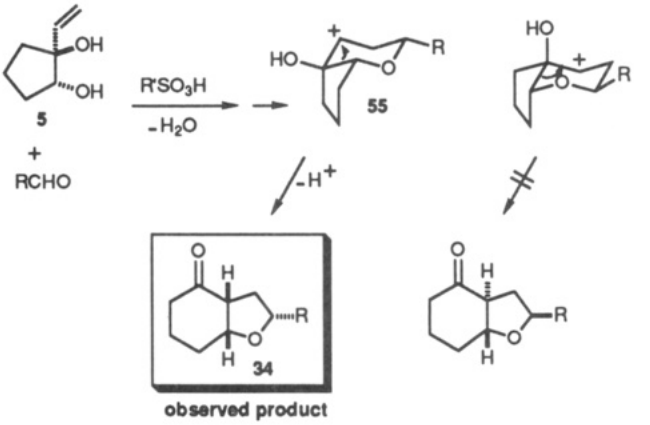


Figure 4. Lowest energy chair hydropyran conformations of *cis*-octahydro-2*H*-1-benzopyran (A and B) and *cis*-2-oxabicyclo[4.2.0]nonane (C and D) as determined by molecular mechanics calculations (MMX force field).

since the intervention of two chair–chair *cis*-octahydro-2*H*-benzopyranyl cation intermediates is possible. Invoking the same assumptions discussed in the context of Scheme VII, the observed product would evolve from the intermediacy of the chair–chair cation **53** (Scheme VIII). That **53** would be sufficiently lower in energy than **54** to occasion a highly stereoselective reaction is certainly plausible. Molecular mechanics calculations[16] show that the *cis*-octahydro-2*H*-1-benzopyran conformer related to **53** is slightly more stable (by 2.2 kcal/mol) than that related to **54** (Figure 4). Similar calculations using the MMX force field of the *cis*-octahydro-2*H*-1-benzopyran-4-yl cations also find that the conformer related to **53** is of lower energy (2.5 kcal/mol) than that related to **54**.[16,26] These energy differences are reasonable since two 1,3 diaxial interactions are removed when the oxygen atom occupies an axial orientation on the cyclohexane ring.[27] Moreover, electronic effects would also stabilize carbenium ion **53** relative to **54**. The C–OH σ bond in cation **53** is essentially orthogonal to the vacant p orbital,[24] while the same bond in cation **54** has good overlap with this orbital. Since a conjugatively interacting C–OH σ bond is less electron releasing than a C–C σ bond, intermediate **53** should be significantly stabilized relative to **54**.. The C(4)–C(5) and C(4)–C(8a) σ bonds have similar overlap (ca. 30° torsional angles)[23] with the vacant p orbital of carbenium ion **53**.. The preferential migration of C(8a) likely reflects the higher migratory aptitude of the more substituted carbon center.[29]

Scheme IX



The preferential formation of the cis-fused hydrobenzofurans **34** from the reaction of *trans*-cyclopentanediol **5** with aldehydes is readily rationalized in a related fashion. The two chair conformations of the 2-oxabicyclo[4.3.0]nonanyl cation arising from Prins cyclization of an *E* oxocarbenium ion intermediate are depicted in Scheme IX. Preferential intervention of cation **55**, which has oxygen oriented in an axial fashion with respect to the cyclopentane ring and the O–H σ bond oriented orthogonal to the vacant p orbital, would rationalize the formation of the observed cis hydrobenzofurans. A molecular mechanics study of the *cis*-2-oxabicyclo[4.3.0]nonane ring system again shows that

(26) To the best of our knowledge, the conformational preference of *cis*-octahydro-2*H*-[1]benzopyran has not received experimental study. The MMX force field[16] would not account for the electronic interaction of the C–O σ bond and the vacant p orbital.

(27) We note that $A^{1,3}$ allylic interactions[28] would also favor the preferential intervention of oxocarbenium ion **51** rather than **52**.

(28) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(29) The covalent analogue of **53** that would arise from antiperiplanar addition to the vinyl group of **51** of the oxocarbenium ion and an external nucleophile would preferentially undero migration of the angular C(4)–C(8a) σ bond.

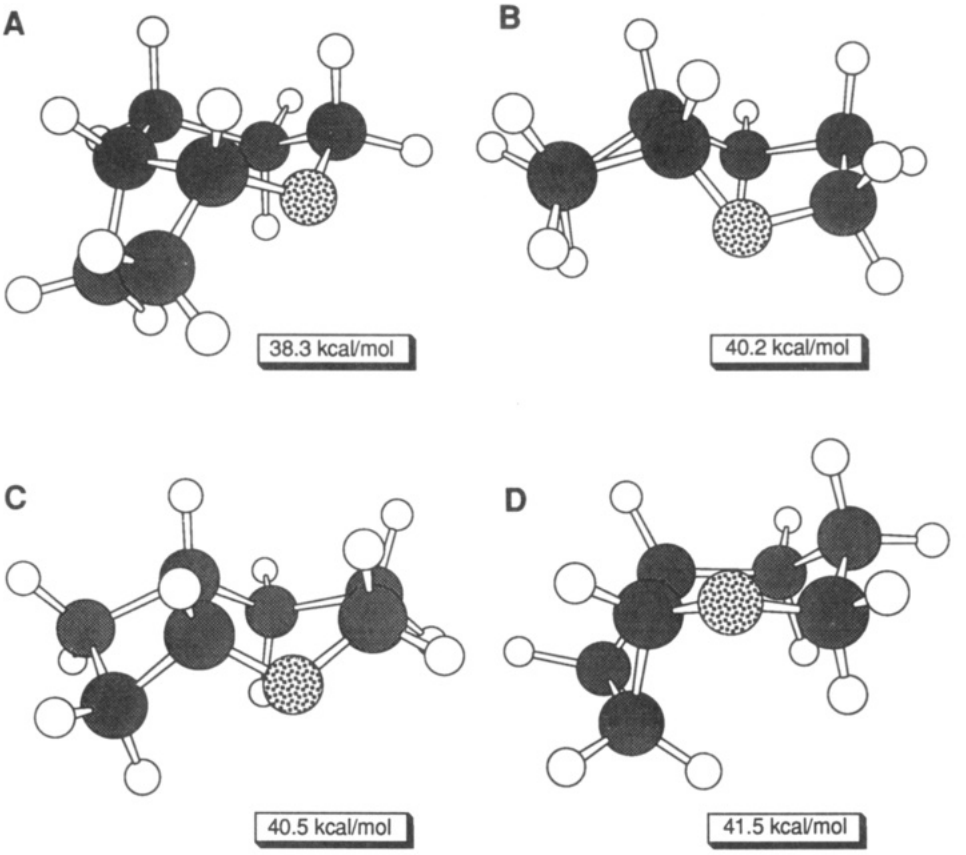


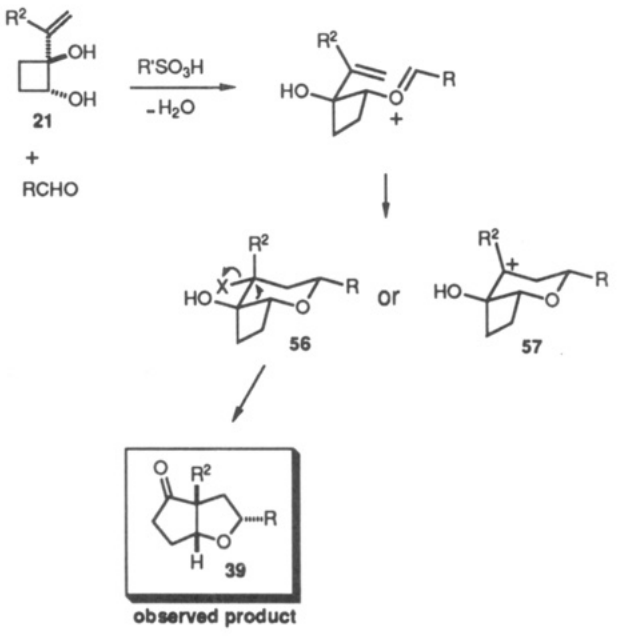
Figure 5. Four lowest energy conformations of *cis*-2-oxabicyclo[4.2.0]octane as determined by molecular mechanics calculations (MMX force field).

the parent ring system related to conformer **55** is slightly more stable than the alternate chair conformer (see Figure 4).[30]

The formation of the cis-fused hexahydrocyclopenta[*b*]furan-4-ones **39** from the reaction of *trans*-cyclobutanediols **21** with aldehydes and ketones (eq 9) can be rationalized also by the analysis developed for the larger ring homologues (Scheme X). Although **57** is the most likely bicyclic carbenium ion to be formed from Prins cyclization of an *E* oxocarbenium ion intermediate, it is not a plausible conformation for the pinacol rearrangement step. The constraints of the bicyclo[4.2.0]octane skeleton enforce poor overlap between the ring fusion bond and the vacant p orbital of such an intermediate. The pinacol rearrangement step may occur via a higher energy carbocation conformer or by way of a covalent intermediate such as **56** (e.g., X = OSO_2Ar). This latter intermediate would manifest good overlap between the two participating σ bonds.

The formation of both C(2) phenyl epimers of the bicyclic ether product (**42** and **43**) in the reaction of the styrenylcyclobutanediol **21c** with benzaldehyde (eq 10) is curious. No trace of a second epimer was seen in the closely related reaction of the propenylcyclobutanediol **21b** with benzaldehyde under nearly identical conditions. Assuming that a cyclization–pinacol mechanism operates also in the former case, the unexpected epimer **43** has its genesis in the Prins cyclization step, since it is in this step that the C(2)/C(6a) stereochemical relationship is set. Since reactions of benzaldehyde with all other 1-alkenylcycloalkanediol substrates afforded products reasonably derived from *E* oxocarbenium ion

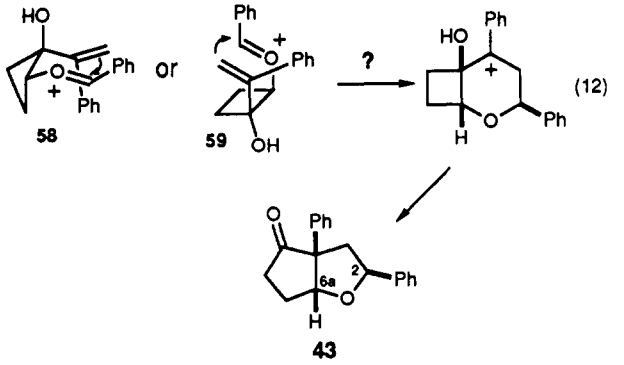
Scheme X



intermediates, the suggestion that the *Z* stereoisomer is the precursor of **43** appears unlikely.

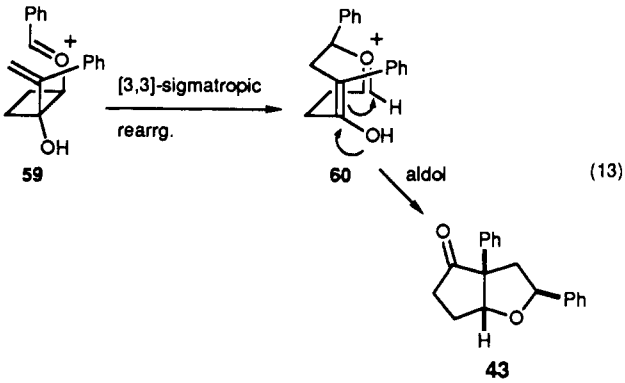
Two cyclization topographies, the chair **58** and boat **59**, would generate a 2-oxobicyclo[4.2.0]octane intermediate with the proper stereorelationship of the substituents flanking oxygen to conceivably lead to **43** (eq 12). Why these arguably higher energy processes would become significant is certainly unclear. The divergent stereochemical outcome observed in this single case suggests at least the possibility of a change in mechanism. It is worth bearing in mind that the stereochemical experiments that led to cyclization–pinacol mechanistic formulation for the acid-promoted reaction of allylic diols and aldehydes were accomplished with quite different substrates.[2] Notably dissimilar is the con-

(30) Although an exhaustive study was not undertaken, a large number of conformational minima in addition to C and D of Figure 4 were found which are interconverted by slight pseudorotations of the cyclopentane ring.[16-18] Three low-energy "clusters" of conformations were found: (a) Those clustered around an MMX energy of 20.1 kcal/mol in which the oxygen atom takes up an axial position on the cyclopentane ring and the hydropyran ring exists in a chair conformation. The lowest energy of these is C shown in Figure 4. (b) Those clustered around an MMX energy of 22.6 kcal/mol in which the oxygen atom takes up an equatorial position on the cyclopentane ring and the hydropyran exists in a chair conformation. The lowest energy of these we have found is D shown in Figure 4. (c) Conformations with MMX energies in the range 21.9–22.4 kcal/mol in which the hydropyran ring exists in a twist conformation.



(12)

siderable strain energy of the cyclobutanediol-derived oxocarbenium ions depicted in Scheme X and eq 12. This strain could arguably facilitate a 2-oxonia [3,3] sigmatropic rearrangement,[2] which would be expected to occur preferentially in a boat topography[31] via **59** to afford the oxacyclooctadiene intermediate **60**. Intramolecular aldol cyclization of **60** would lead to **43** (eq 13).



(13)

Conclusion

This study demonstrates that a wide variety of stereochemically complex bicyclic ethers can be prepared in two to three steps from simple α-hydroxycycloalkanone precursors. Although this sequence has been specifically demonstrated with cyclobutanone, cyclopentanone, and cyclohexanone precursors only, it is undoubtedly 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. One example of such an application is provided in the following paper in this issue.[19]

Experimental Section[32]

A. Preparation of Allylic Diols. 2-Hydroxy-2-vinylcyclopentanone (8). A slight modification of the procedure of Barnier and Conia was employed.[7] A solution of cyclopentane-1,2-dione (53.4 g, 0.545 mol) and dry THF (60 mL) was added dropwise during ca. 30 min to a cooled (ice bath) solution of vinylmagnesium bromide (1 M in THF, 1.2 L, 1.2 mol) maintaining the internal temperature below 30 °C. The reaction mixture was then quenched with 1 M HCl (1.3 L), while maintaining external cooling, the organic layer was separated, and the aqueous phase was extracted with EtOAc (2 × 300 mL). The combined organic extracts were washed with brine (1 × 300 mL), dried ($MgSO_4$), and concentrated to leave an orange-red oil. Purification by distillation at reduced pressure gave the hydroxy ketone (36.3 g, 53%) as a pale yellow oil: bp 49–50 °C, 0.5 mm (lit.[7] bp 40 °C, 0.03 mm); ^1H NMR (250 MHz, $CDCl_3$) δ 5.85 (dd, J = 15.5, 7.8 Hz, CH_2=C*H*), 5.26 (d, J = 15.5 Hz, CH*H*=CH), 5.22 (d, J = 7.8 Hz, C*H*H=CH), 3.15 (s, O*H*), 2.4–1.7 (m, 6 H).

Stereoselective Preparation of (1*R,2*S**)-1-Vinylcyclopentane-1,2-diol (5).** To a stirring solution of AcOH (78 mL) and CH_3CN (78 mL) at 5 °C was added portionwise $NaBH_4$ (7.4 g, 200 mmol), while the internal temperature was maintained below 20 °C. After complete addition, the cooling bath was removed and the reaction mixture was stirred at 23 °C until gas evolution had ceased (ca. 15 min). The resulting colorless solution was cooled to −20 °C, and a solution of **8** (9.8 g, 78 mmol) was added dropwise during 10 min. The solution was allowed to warm 23 °C and maintained at this temperature for 16 h, and then the volatiles were removed by short-path distillation (30–40 °C, 6 mm). Aqueous workup (saturated $KHCO_3$, EtOAc) followed by purification of the residue on silica gel (3:1 hexanes–ether) gave known[7] **5** (8.3 g, 91%) as a clear, viscous oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (dd, J = 17.5, 10.9 Hz, C*H*=CH_2), 5.40 (dd, J = 17.5, 1.3 Hz, CH=C*H*H), 5.29 (dd, J = 10.8, 1.4 Hz, CH=CH*H*), 3.86 (broad s, COH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 115.2, 83.8, 80.4, 35.7, 32.1, 20.2; IR (film) 3376, 2955, 1455, 1417, 1294, 1200, 1131, 1069, 970 cm^{-1}; MS (CI) m/z 129 (MH), 110.

Preparation of 1-Vinylcyclopentane-1,2-diols (5 and 6) from 2-Hydroxycyclopentanone. A solution of vinylmagnesium bromide was prepared in THF (90 mL) from vinyl bromide (2.1 g, 20 mmol) and an excess of Mg turnings. After being cooled to 23 °C, a solution of acyloin **4** (2.5 g, 25 mmol)[13] and THF (25 mL) was added dropwise over 30 min. After 1 h, THF was removed in vacuo. Aqueous workup (1 N HCl, EtOAc) provided 2.6 g of a yellow oil, which was purified on silica gel (1:1 ether–hexane) to give 1.03 g (32%) of the known[7] (1*R**,2*R**)-diol **6** as a light yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 5.90 (dd, J = 13.6, 8.2 Hz, C*H*=CH_2), 5.36 (dd, J = 13.6, 1.2 Hz, CH=CH*H*), 5.18 (dd, J = 8.2, 1.2 Hz, CH=C*H*H), 3.89 (broad m, 1 H, CHOH); MS (CI) m/z 129 (MH), 110, 95; IR (film) 3885, 2970, 2880, 1435, 1410, 1295, 1195, 1100, 1070, 1000, 970, 670 cm^{-1}. In later fractions, 0.83 g (26%) of the (1*R**,2*S**)-diol **5** was recovered.

Preparation of 1-Vinylcyclohexane-1,2-diols (14a and 15a) from 2-Hydroxycyclohexanone. Commercially available 2-hydroxycyclohexanone (2.2 g, 20 mmol)[10] was condensed with excess vinylmagnesium bromide as described for the preparation of **5** and **6**. Separation on silica gel gave 880 mg (31%) of the known[7b] crystalline (1*R**,2*S**)-diol **15a** as a colorless solid (mp 56–58 °C) and 770 mg (27%) of the (1*R**,2*R**)-diol **14a** as a viscous yellow oil.

(1*R,2*S**)- and (1*R**,2*R**)-1-((*Z*)-2-Butenyl)cyclohexane-1,2-diols (15b and 14b).** To a solution of 2-bromo-2-butene (2.6 mL, 26 mmol, an 85:15 mixture of *Z* and *E* stereoisomers) and ether (40 mL) at −70 °C was added *t*-BuLi (32.5 mL of a 1.6 M solution in pentane, 52 mmol). Following the addition, the solution was allowed to warm to 23 °C and then was recooled to −60 °C and a solution of 2-hydroxycyclohexanone (1.0 g, 8.8 mmol)[10] and ether (60 mL) was added dropwise. Aqueous workup ($CHCl_3$) and filtration of the residue through a short column of silica gel (6:1 hexane–EtOAc) gave 730 mg (49%) of a crude diol product, which capillary GC analysis showed to be a 5:1 mixture of the cis- and trans-diol stereoisomers. Careful chromatography on silica gel (6:1 hexane–EtOAc) provided the major 1*R**,2*S** isomer **15b** as a colorless solid and the minor 1*R**,2*R** isomer **14b** as a colorless oil. **15b**: mp 59–60 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 5.43 (qq, J = 1.2, 7.4 Hz, C=C*H*), 3.79 (dd, J = 3.5, 10.6 Hz, OCH), 2.3–2.4 (broad s, OH), 1.9–2.1 (broad s, OH), 1.84 (dd, J = 1.2, 7.4 Hz, CH_3CH=), 1.74 (d, J = 1.2 Hz, CH_3C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 123.6, 77.8, 72.8, 34.5, 29.4, 24.3, 23.1, 20.6, 15.2; IR (CCl_4) 3622, 3573, 3490, 2942, 1459, 1080, 1053, 1005, 981 cm^{-1}; MS (CI) m/z 171 (MH); 153; MS (EI) m/z 170.1291 (170.1307 calcd for $C_{10}H_{18}O_2$). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.27; H, 10.57. **14b**: ^1H NMR (300 MHz, $CDCl_3$) 5.55 (qq, J = 1.4, 7.4 Hz, C*H*=C), 3.9–4.1 (broad s, OCH), 2.0–2.2 (m, OH), 1.87 (dd, J = 1.4, 7.4 Hz, 3 H, CH_3CH=), 1.79 (d, J = 1.4, 1.4 Hz, CH_3C=C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 125.4, 75,8, 72.1, 32.6, 28.5, 23.9, 21.0, 19.2, 15.6; IR (CCl_4) 3617, 2481, 2936, 1462, 1068, 1042, 977, 867 cm^{-1}; MS (CI) m/z 171 (MH), 153; MS (EI) m/z 170.1315 (170.1307 calcd for $C_{10}H_{18}O_2$).

(1*R,2*S**)- and (1*R**,2*R**)-1-((*E*)-2-Butenyl)cyclohexane-1,2-diols (15c and 14c).** In a similar fashion to the preparation of **14b** and **15b**, the lithium reagent prepared from (*E*)-2-bromo-2-butene (92% *E* by GLC analysis) was added to 2-hydroxycyclohexanone[10] to give 760 mg (51%) of a mixture of diastereomeric diols (4:1 cis to trans by capillary GC analysis). Pure samples of the major 1*R**,2*S** isomer **15c** and the

(31) For the well-studied parent system, see: Hammond, G. S.; DeBoer, C. D. *J. Am. Chem. Soc.* **1964**, *86*, 899. Berson, J. A.; Dervan, P. B.; Malherbe, R.; Jenkins, J. A. *Ibid.* **1976**, *98*, 5937.

(32) General experimental details are described or cited in ref 2. Stannic chloride came from a freshly opened commercial bottle (Aldrich) or was purified by distillation from P_2O_5. The description "aqueous workup (aqueous phase, organic phase)" describes the routine sequence of diluting the reaction mixture with H_2O (not specified) or the specified aqueous solution, extraction two to three times with the specified organic solvent, and drying the combined organic phases over a desiccant (typically anhydrous $MgSO_4$). Filtration to remove the drying agent and concentration afforded the crude product whose purification is explicitly described. Since many of the new compounds reported in this paper were prepared by similar sequences, the Experimental Section contains only representative examples of each procedure. Details on the preparation and characterization of all other compounds can be found in the supplementary material.

(33) *Beilstein* 7, II, 62.

minor 1*R**,2*R** isomer **14c** were obtained by preparative GLC (10% SP2300, 135 °C). **15c**: colorless solid; mp 77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (qq, J = 1.5, 6.8 Hz, C*H*=C), 3.74 (broad dd, $J \approx 4$, 11 Hz, OCH), 2.1 (broad s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 119.7, 76.8, 71.1, 34.6, 29.1, 24.4, 20.9, 13.7, 12.8; IR (CCl_4) 3612, 3569, 3468, 2941, 1448, 1254, 1123, 1060, 1006, 984 cm^{-1}; MS (CI) m/z 171 (MH) 153; MS (EI) m/z 170.1302 (170.1307 calcd for $C_{10}H_{18}O_2$). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.70; H, 10.67. **14c**: colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (qq, J = 1.2, 6.6 Hz, C*H*=C), 3.73 (broad s, 1 H, OCH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 122.4, 75.6, 69.4, 30.6, 27.8, 21.5, 19.4, 13.9, 11.3; IR (film) 3420, 3027, 2931, 1655, 1447, 1153, 1035, 1006 cm^{-1}; MS (EI) m/z 170.1289 (170.1307 calcd for $C_{10}H_{18}O_2$).

(1*R,2*S**)-1-(1-Phenylethenyl)cyclohexane-1,2-diol (15d).** A solution of silyloxy ketone **12** (13.3 g, 62.0 mmol) and THF (20 mL) was added dropwise at 23 °C to freshly prepared 1-(bromomagnesio)-1-phenylethene (from 93 mmol of 1-bromo-1-phenylethene, excess Mg and 50 mL of THF). Aqueous workup (NH_4Cl–NH_4OH, ether) followed by purification on silica gel (hexane) gave 22.3 g (46%) of the pure major isomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.4–7.2 (m, 5 H, Ph), 5.58 (d, J = 1.4 Hz, *H*HC=), 5.22 (d, J = 1.4 Hz, H*H*C=), 3.86 (m, OCH), 0.91 (s, SiBu^t), 0.06 (s, SiMe), −0.4 (s, SiMe).

An 8.2-g (24.7-mmol) sample of this material was desilylated at 23 °C by treatment with 30 mmol of (n-Bu)$_4$NF in 60 mL of 1:1 THF–CH_2Cl_2. Aqueous workup (Na_2CO_3, hexane–EtOAc) and purification on silica gel (1:1 hexane–EtOAc) gave 4.0 g (74%) of chromatographically pure **15d** as a white solid: mp 95–96 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33–7.22 (m, 5 H, Ph), 5.61 (d, J = 1.7 Hz, =C*H*H), 5.11 (d, J = 1.7 Hz, =CH*H*), 3.69 (dd, J = 4.7, 10.1 Hz, OCH), 2.27 (broad s, 2 H, OH); MS (EI) m/z 218.1314 (218.1302 calcd for $C_{14}H_{18}O_2$, M, 3), 200 (36), 183 (49), 141 (52), 132 (37), 129 (51), 115 (56), 105 (67), 104 (59), 103 (100), 91 (70); IR ($CHCl_3$) 3420, 3040, 2940, 2840 cm^{-1}.

(1*R,2*R**)- and (1*R**,2*S**)-1-(1-Propynyl)cyclohexane-1,2-diols (17 and 16).** Propynyllithium (from excess propyne and 160 mmol of n-BuLi in 150 mL of 1:1 THF–hexane) was treated dropwise at −70 °C with a solution of 6.0 g (53 mmol) of 2-hydroxycyclohexanone[10] and 55 mL of THF. After 2 h the reaction was allowed to warm to 23 °C. Aqueous workup ($CHCl_3$) followed by careful chromatography on silica gel (1:1 hexane–ether) gave 2.9 g (36%) of the 1*R**,2*R** isomer **17** as a white solid: mp 70–72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (dd, J = 3.9, 7.9 Hz, C*H*OH), 2.5–2.9 (broad s, 2 H, OH) 1.83 (s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.0, 80.9, 74.4, 70.3, 35.9, 28.7, 22.0, 21.4, 3.7; IR (KBr) 3409, 3301, 2942, 2244, 1446, 1066, 1068, 998 cm^{-1}; IR (CCl_4) 3611, 3584, 3473 cm^{-1}; MS (CI) m/z 137 (MH − H_2O); MS (EI) m/z 154.0989 (154.0994 calcd for $C_9H_{14}O_2$). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.17; H, 9.19.

The slower eluting 1*R**,2*S** isomer **16** was obtained in 33% yield (2.7 g): mp 80–82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.36 (broad d, J = 10.3 Hz, C*H*OH), 3.2–3.3 (broad s, OH), 2.3–2.4 (broad s, OH), 1.87 (s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.5, 79.0, 77.2, 74.2, 38.1, 32.1, 24.3, 23.4, 3.8; IR (KBr) 3569, 3399, 3280, 2935, 2244, 1447, 1086, 1038 cm^{-1}; IR (CCl_4) 3611, 3583, 3462 cm^{-1}; MS (CI) m/z 137 (MH − H_2O); MS (EI) m/z 154.1001 (154.0994 calcd for $C_9H_{14}O_2$). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.11; H, 9.20.

(1*R,2*R**)-1-((*E*)-1-Propenyl)cyclohexane-1,2-diol (19).** A toluene solution of RedAl (8.4 mL, 28 mmol; Aldrich) was added dropwise at 23 °C to a stirred solution of the alkynyl diol **17** (1.1 g, 7.1 mmol) and THF (40 mL). A 24-h aqueous workup ($CHCl_3$) and purification on silica gel (1:1 hexane–ether) gave 760 mg (69%) of **19** as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (dq, J = 6.5, 15.4 Hz, CH_3C*H*=CH), 5.49 (dq, J = 1.5, 15.4 Hz, C*H*=CHCH$_3$), 3.4–3.5 (m, 1 H, C*H*OH), 2.2–2.3 (m, OH), 2.0–2.2 (m, OH), 1.72 (dd, J = 1.5, 6.5 Hz, CH_3CH=); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5, 125.4, 73.9, 73.8, 36.0, 29.2, 23.8, 21.0, 18.0; IR (KBr) 3373, 3034, 2937, 1673, 1451, 1080, 986 cm^{-1}; IR (CCl_4) 3615, 3570, 3470 cm^{-1}; MS (EI) m/z 156.1137 (156.1150 calcd for $C_9H_{16}O_2$). Anal. Calcd for $C_9H_{16}O_2$: C, 69.20, H, 10.32. Found: C, 69.28; H, 10.32.

(1*R,2*S**)-1-((*E*)-1-Propenyl)cyclohexane-1,2-diol (18)** was prepared in 80% yield from **16** following the procedure described for the preparation of **19**. **18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.8–5.9 (m, CH=CH), 3.4–3.6 (m, C*H*OH), 2.4–2.7 (broad s, OH), 2.2–2.5 (broad s, OH), 1.73 (d, J = 5.2 Hz, CH_3CH=); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.7, 127.4, 76.7, 75.1, 37.1, 31.0, 23.8, 22.9, 18.4; IR (film)) 3406, 3078, 2937, 1669, 1451, 1035 cm^{-1}; IR (CCl_4), 3610, 3584, 3439, cm^{-1}; MS (CI) 139 (MH-H_2O); MS (EI) m/z 156.1143 (156.1150 calcd for $C_9H_{16}O_2$).

(1*R,2*R**)- and (1*R**,2*S**)-1-(1-Methylethenyl)cyclobutane-1,2-diols (22b and 21b).** A solution of 2-hydroxycyclobutanone (**20**; 1.0 g, 1.2 mmol)[13] and THF (47 mL) was added at −70 °C to a freshly prepared solution of isopropenyllithium [from 2-bromopropene (2.8 g, 23 mmol), t-BuLi (47 mmol) and THF 47 mL)]. After the reaction was allowed to warm to 23 °C, aqueous workup (EtOAc) and purification on silica gel (3:2 hexane–EtOAc) gave 610 mg (40%) of the 1*R**,2*R** isomer **22b** and 210 mg (14%) of the 1*R**,2*S** isomer **21b**. Cis-diol **22b**: mp 56–58 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (broad s, CH*H*=C), 4.84 (d, J = 2.2 Hz, CH*H*=C), 4.16 (dd, J = 15.5, 7.4 Hz, C*H*OH), 2.87 (d, J = 8.8 Hz, OH) 2.62 (s, OH), 2.15–2.22 (m, 1 H), 1.81–2.00 (m, 3 H), 1.72 (s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 110.5, 81.0, 69.8, 27.5, 26.4, 17.8; IR (film) 3381, 2943, 2988, 1431, 1131 cm^{-1}; MS (EI) m/z 128.0837 (128.0837 calcd for $C_7H_{12}O_2$, M, 42). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.53; H, 9.43. Trans-diol **21b**: mp 59–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (broad d, J = 1.4 Hz, 1 H, C*H*H=), 5.04 (broad s, 1 H, CH*H*=C), 4.16 (app t, J = 8.1 Hz, 1 H, C*H*OH), 3.14 (s, OH), 2.90 (s, OH), 2.15–2.33 (m, 2 H), 1.92 (s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 112.1, 82.6, 76.1, 26.7, 23.9, 20.1; IR (film) 3340, 3331, 2987, 2950, 1087 cm^{-1}; MS (EI) m/z 128.0830 (128.0837 calcd for $C_7H_{12}O_2$). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.54; H, 9.49.

Preparation of 2-Hydroxy-2-(1-methylethenyl)cyclobutanone (23b). The general procedure of Doering and Parikh was followed.[14] To a solution of diol **22b** (180 mg, 0.948 mmol), Me_2SO (2.4 mL, 34 mmol), and Et_3N (1.2 mL, 8.6 mmol) was added a solution of pyridine–SO_3 complex (0.52 g, 3.3 mmol) and Me_2SO (2.40 mL), and the reaction was maintained at 23 °C for 2 h. Aqueous workup (CH_2Cl_2) followed by purification on silica gel (3:2 hexane–EtOAc) gave 117 mg (65%) of **23b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.01 (broad s, C=C*H*H), 4.98 (d, J = 2.4 Hz, C=CH*H*), 2.81–3.04 (m, 2 H), 2.39 (dt, J = 6.1, 5.4 Hz, 1 H), 2.01–2.12 (m, 1 H), 1.85 (s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 142.0, 113.2, 93.9, 40.8, 25.7, 17.7; IR (film) 3431, 2962, 1781, 1450, 1156 cm^{-1}; MS (EI) m/z 126.0667 (126.0681 calcd for $C_7H_{10}O_2$).

Preparation of (1*R,2*S**)-1-(2-Methylethenyl)cyclobutane-1,2-diol (21b) from (Acyloxy)borohydride Reduction of 23b.** Following the general procedure of Evans,[6c] $Me_4NBH(OAc)_3$ (1.46 g, 5.55 mmol) was added at 23 °C to a solution of **23b** (137 mg, 1.08 mmol), HOAc (4.0 mL), and MeCN (4.0 mL). After the reaction was maintained at 23 °C for 1 h, a solution of sodium/potassium tartrate (0.25 M, 4 mL) was added and the reaction was allowed to stir for 30 min. Solid $NaHCO_3$ was then added until the pH was ca. 6, and then sufficient H_2O was added to obtain a solution. Extraction with EtOAc and purification on silica gel (3:2 hexane–EtOAc) gave 109 mg (79%) of isomerically pure **21b**.

General Procedure for Preparing Cis-Fused Acetals. Preparation of (3a*R,7a*R**)-2-Propyl-3a-vinyl-3a,7a,4,5,6,7-hexahydro-1,3-benzodioxole (25a).** A mixture of diol **14a** (140 mg, 1.0 mmol), 1-butanal (140 mg, 2 mmol), $MgSO_4$ (1 g), p-toluenesulfonic acid (60 mg, 0.3 mmol), and CH_2Cl_2 (4 mL) was stirred at 23 °C for 1 h. Solid $NaHCO_3$ (0.5 g) was added, and after the mixture was stirred for 15 min, the suspension was filtered and the filter cake washed with ether (2 × 10 mL). Concentration and purification of the residue on silica gel (20:1 hexane–Et_2O) gave 140 mg (76%) of acetal **25a**, a nearly colorless oil, which was predominantly one epimer at C(2): ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.91 (dd, J = 14.0, 7.84 Hz, C*H*=CH$_2$), 5.34 (dd, J = 14.0, 1.3 Hz, *trans*-CH=C*H*H), 5.12 (dd, J = 7.8, 1.3 Hz, *cis*-CH=CH*H*), 4.99 (t, J = 4.8 Hz, OCHO), 3.77 (broad t, J = 2.8 Hz, OCH), 1.96–2.03 (m, 1 H), 1.2–1.8 (m, 11 H), 0.97 (t, J = 6.2 Hz, Me); MS (EI, 70 eV) m/z 196 (M, 1), 153 (40), 125 (29), 107 (45), 95 (20), 79 (34), 55 (100); IR (film) 2950, 2880, 1450, 1415, 1125, 990 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.47; H, 10.20. Found: C, 73.18; H, 10.17.

B. Rearrangements To Form Bicyclic Keto Ethers. General Procedure for Rearrangement of Acetals with $SnCl_4$. Preparation of (2*R,3a*S**,8a*S**)-Octahydro-2-propyl-4*H*-cyclohepta[*b*]furan-4-one (26a).** A solution of acetal **25a** (50 mg, 0.26 mmol) and CH_2Cl_2 (1.5 mL) was cooled in a dry ice–acetone bath, and $SnCl_4$ (30 μL, 0.26 mmol) was added dropwise. The resulting solution was maintained at ca. −70 °C for 1 h, and then Et_3N (0.5 mL) was added followed by MeOH (1 mL). After the reaction mixture was allowed to warm to 23 °C, aqueous workup ($NaHCO_3$, EtOAc) and purification on silica gel (5:1 hexane–ether) gave 38 mg (76%) of ketone **26a** as a clear colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.10 (ddd, J = 10.8, 9.2, 2.8 Hz, H(8a)) 3.70 (m, H(2)), 3.35 (app q, J = 9 Hz, H(3a)), 2.38 (broad t, J = 6.7 Hz, 2 H, H(5)), 1.97–1.23 (m, 12 H), 0.85 (t, J = 5.5 Hz, CH_3); MS (EI) m/z 196.1450 (196.1463 calcd for $C_{12}H_{20}O_2$) 153 (100); IR (film) 2940, 2880, 1710, 1500, 1380, 1250, 1160, 1100, 1050, 910 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.47; H, 10.20. Found: C, 73.80; H, 10.22.

Attempted Rearrangement of Acetal 29. Formation of 2-((*E*)-1-Propenyl)cyclohexanone (30). A solution of acetal **29** (100 mg, 0.55 mmol) and CH_2Cl_2 (5 mL) was cooled under Ar to −65 °C (internal thermometer), and then $SnCl_4$ (64 μL, 0.55 mmol) was added. The resulting solution was maintained at −50 to −40 °C for 4 h and then quenched with Et_3N (0.5 mL, 3 mmol). Aqueous workup ($CHCl_3$) and

purification on silica gel (1:1 hexane–ether) gave 60 mg (87%) of **30** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (dd, J = 7.1, 15.6 Hz, C*H*=CHCH$_3$), 5.46 (dq, J = 6.2, 15.6 Hz, C=C*H*CH$_3$), 2.9–3.1 (m, CHC=O), 2.2–2.5 (m, CH$_2$C=O), 1.70 (d, J = 6.2 Hz, 3 H, C*H*$_3$CH=C), 1.5–2.1 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.7, 128.8, 127.3, 54.1, 41.8, 34.6, 27.8, 24.5, 18.3; IR (film) 3016, 2937, 1712, 1675, 1449, 1129, 965 cm^{-1}; MS (CI) m/z 139 (MH); MS (EI) m/z 138.1055 (138.1045 calcd for $C_9H_{14}O$).

The nonconjugated enone **30** was isomerized to 2-propylidenecyclohexanone in the presence of Et_3N over 1 week at room temperature: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.5–6.7 (m, CH=C), 2.4–2.5 (m, 4 H), 1.7–1.9 (m, 4 H), 1.05 (t, J = 7.5 Hz, C*H*$_3$); IR (film) 2928, 1690, 1617, 1459, 1143 cm^{-1}.

Rearrangement of Ketal 31a with $SnCl_4$. Preparation of *cis*-Octahydro-2,2-dimethyl-3a-phenyl-4*H*-cyclohepta[*b*]furan-4-one (32a). A solution of ketal **31a** (200 mg, 0.77 mmol) and CH_2Cl_2 (2 mL) was cooled to −70 °C, and 90 μL of $SnCl_4$ (0.77 mmol) was added. The cooling bath was removed, and the resulting solution was allowed to warm to 23 °C. Aqueous workup ($NaHCO_3$, hexane), and purification on silica gel (5:1 hexane–EtOAc) afforded 180 mg (90%) of **32a** as a colorless liquid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.2–7.4 (m, 5 H, Ph), 4.84 (dd, J = 9.8, 1.3 Hz, H(8a)), 2.86 (d, J = 13.4 Hz, 1 H, H(3α)), 1.5–2.4 (m, 8 H), 2.02 (d, J = 13.4 Hz, 1 H, H(3β)), 1.31 (s, Me), 0.94 (s, Me); IR (film) 2930, 1705, 1601, 1440, 1050, 760, 690 cm^{-1}; MS (EI) m/z 258.1621 (256.1620 calcd for $C_{17}H_{22}O_2$, M, 90), 243 (35), 200 (60), 171 (100), 145 (65), 131 (60), 91 (55).

Preparation of (2*R,3a*S**,8a*S**)-Octahydro-2-methyl-4*H*-cyclohepta[*b*]furan (26b) by *p*-Toluenesulfonic Acid Catalyzed Reaction of *trans*-Cyclohexanediol 15a with Ethyl Vinyl Ether.** A solution of diol **15a** (71 mg, 0.50 mmol), ethyl vinyl ether (110 mg, 1.5 mmol), *p*-toluenesulfonic acid (10 mg, 0.05 mmol), and CH_2Cl_2 (1 mL) was maintained at 23 °C for 1 h and worked up (as described for the preparation of **34d** from **5**) to give, after purification on silica gel, 51 mg (61%) of **26b** as a colorless liquid. This material was contaminated with 10–20% of an isomer presumed to be the C(3a) epimer. **26b**: ^{1}H NMR (250 MHz, C_6D_6) δ 3.79 (ddd, J = 10.7, 9.3, 3.0 Hz, H(8a)), 3.61 (broad septet, J = 8 Hz, H(2)), 2.79 (q, J = 9.3 Hz, H(3a)), 2.2–1.8 (m, 4 H), 1.60 (m, 2 H), 1.43–1.25 (m, 4 H), 1.22 (d, J = 5.4 Hz, Me); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.19 (ddd, J = 10.7, 9.3, 3.0 Hz, H(8a)), 3.8 (m, H(2)), 3.40 (app q, J = 9 Hz, H(3a)), 2.42 (dd, J = 5.3, 4.6 Hz, 2 H), 1.97 (m, 2 H), 1.90–1.40 (m, 7 H), 1.30 (d, J = 5.4 Hz, Me); MS (EI) m/z 168.1144 (168.1140 calcd for $C_{10}H_{16}O_2$, M, 18), 153 (27), 126 (100); IR (film) 2990, 1715, 1500, 1370, 1140, 1070, 980, 760 cm^{-1}.

General Procedure for the *p*-Toluenesulfonic Acid Catalyzed Reaction of *trans*-Cyclopentanediol 5 with Aldehydes. Preparation of (2*R,3a*R**,7a*R**)-Hexahydro-2-[(benzyloxy)methyl]-4(2*H*)-benzofuranone (34d).** To a rapidly stirring mixture of diol **5** (15 g, 0.12 mol), $MgSO_4$ (60 g), and CH_2Cl_2 (300 mL) at 0 °C was added dropwise over 5 min a solution of (benzyloxy)acetaldehyde (16.8 g, 0.112 mol). *p*-Toluenesulfonic acid monohydrate (7.4 g, 39 mmol) was then added in one portion, and the mixture was allowed to warm to 23 °C and then stirred at 23 °C for 1.5 h. Solid Na_2CO_3 (18 g) was then added, and the dark red mixture was stirred for 15 min and then filtered through a pad of Celite. Concentration and purification of the residue on silica gel (4:1 and then 1:1 hexane–EtOAc) gave **34d** (21.0 g, 69%) as a pale yellow oil, which was homogeneous by TLC and capillary GLC analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.35 (m, Ph), 4.56 (AB q, J = 12.2 Hz, $\Delta\nu$ = 25.5 Hz, C*H*$_2$Ph), 4.29–4.33 (m, H(7a)), 4.09 (dddd, J = 4.2, 6.1, 6.1, 8.7 Hz, H(2)), 3.45 (dd, J = 4.3, 10.1 Hz, C*H*HOBn), 3.39 (dd, J = 7.0, 10.1 Hz, CH*H*OBn), 2.74 (ddd, J = 3.3, 5.5, 8.8 Hz, H(3a)), 2.40–2.49 (m, 1 H), 2.26–2.36 (m, 2 H), 1.80–2.17 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.6, 138.2, 128.3, 127.8, 127.5, 80.1, 77.0, 73.3, 72.8, 51.2, 40.8, 29.1, 27.7, 20.4; IR (CCl_4) 2949, 2909, 2875, 2862, 1716, 1455, 1117, 1083; MS (CI) m/z 261 (MH), 153, 91; MS (EI) m/z 260.1413 (260.1412 calcd for $C_{16}H_{20}O_3$).

General Procedure for the BF_3·OEt_2-Catalyzed Reaction of *trans*-Cyclopentanediol 5 with Aldehydes. Preparation of (2*R,3a*R**,7a*R**)-Hexahydro-2-[(benzoyloxy)methyl]-4(2*H*)-benzofuranone (34e).** To a cooled (−23 °C) solution of diol **5** (3.0 g, 0.23 mol), (benzoyloxy)acetaldehyde (4.0 g, 24.3 mmol), and dry CH_2Cl_2 (30 mL) was added neat BF_3·OEt_2 (3.0 mL, 0.024 mol). The resulting solution was maintained at −23 °C for 10 min and then quenched by the addition of Et_3N (13 mL). Aqueous workup (CH_2Cl_2) and crystallization from hexane–Et_2O (ca. 4:1) at 0 °C afforded 3.6 g (56%) of the bicyclic ketone **34e** as a colorless crystalline solid. Concentration and purification of the mother liquor on silica gel (2:1 hexane–ether) gave, in order of elution, 1.72 g (17%) of the bicyclic acetal **35** and an additional 515 mg (8%) of crystalline **34e** (total yield of **34e** 64%).

Hexahydrobenzofuranone 34e: mp 76–77 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 8.20 (m, 2 H, Ph), 7.05 (m, 3 H, Ph), 4.40 (dd, J = 3.7 Hz, 11.6 Hz, 1 H, C*H*$_2$OCOPh), 4.20 (dd, J = 6.6, 11.6 Hz, 1 H, CH$_2$OCOPh), 3.88 (app ddt, J = 3.3, 6.6, 13.2 Hz, H(2)), 3.69 (narrow m, H(7a)), 2.46 (app dt, J = 2.8, 5.6 Hz, H(3a)), 2.14–2.19 (m, 1 H), 1.96 (ddd, J = 8.6, 2.8, 5.6 Hz, 1 H, H(3)), 1.68–1.79 (m, 3 H), 1.49 (app dt, J = 12.9, 8.8 Hz, 1 H, H(3)); ^{13}C NMR (125 MHz, C_6D_6) δ 210.2, 166.4, 132.9, 130.0, 129.7, 128.3, 80.3, 75.7, 66.6, 51.2, 40.9, 28.9, 27.7, 20.4; IR (film) 2956, 1718, 1281 cm^{-1}; MS (CI) m/z 275 (MH); MS (EI, 70 eV) m/z 275.1290 (275.1283 calcd for $C_{16}H_{18}O_4$), 152 (50), 139 (100), 105 (62), 95 (42), 77 (72). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.04; H, 6.63; Found: C, 70.12; H, 6.66.

Bicyclic Acetal 35: mp 73–75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (m, 4 H, Ph), 7.49 (m, 2 H, Ph), 7.33 (m, 4 H, Ph), 6.24 (dd, J = 17.7, 11.1 Hz, C*H*=CH$_2$), 5.61 (app t, J = 5.3 Hz, OCHO), 5.57 (dd, J = 17.7, 1.3 Hz, =C*H*H), 5.43 (dd, J = 11.1, 1.3 Hz, C=CH*H*), 5.32 (app t, J = 4.5 Hz, OCHO), 4.39 (dd, J = 5.3, 0.8 Hz, CH$_2$O), 4.36 (d, J = 4.5 Hz, CH$_2$O), 4.26 (t, J = 9.4 Hz, OCH), 2.0 (m, 1 H), 1.9–1.6 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.96, 165.92, 135.8, 133.0, 132.9, 129.6, 129.5, 128.2, 118.3, 97.3, 91.3, 84.8, 84.2, 64.8, 64.3, 33.5, 25.1, 16.9; IR (film) 2961, 1725, 1451, 1272, 711 cm^{-1}; MS (CI) m/z 275, 165, 111. Anal. Calcd for $C_{25}H_{26}O_7$: C, 68.48; H, 5.98. Found: C, 68.25; H, 5.99.

Conversion of Bicyclic Acetal 35 to Hexahydrobenzofuranone 34e. A solution of acetal **35** (248 mg, 0.57 mmol), BF_3·Et_2O (140 μL, 1.1 mmol), and dry CH_2Cl_2 (5 mL) was maintained at −23 °C for 40 min, and then an additional 140 μL of BF_3·Et_2O was added. The temperature was allowed to warm to −10 °C during 2 h, and the mixture was quenched by the addition of Et_3N (1 mL). Aqueous workup (CH_2Cl_2) provided an oil, whose ^{1}H NMR spectrum showed the presence of **34e** and (benzoyloxy)acetaldehydye in a 1:1 ratio. Purification of this material on silica gel (2:1 hexanes–ether and then ether) gave 143 mg of a 1.5:1 mixture of **34e** and (benzoyloxy)acetaldehyde, respectively.

(2*R,3a*R**,7a*S**)-Hexahydro-2-methyl-3a-phenyl-4(2*H*)-benzofuranone (38).** Following the general procedure for the rearrangement of acetals with $SnCl_4$, 506 mg (2.17 mmol) of **37c** was treated in CH_2Cl_2 (5 mL) with 1 equiv of $SnCl_4$ at −70 °C and the reaction allowed to warm to 23 °C. Quenching with Et_3N at −70 °C followed by aqueous workup ($NaHCO_3$, CH_2Cl_2) and purification on silica gel (9:1 hexane–EtOAc) gave 396 mg (80%) of **38** as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.4–7.1 (m, Ph), 4.67 (broad d, J = 2.7, H(7a)), 4.15–4.05 (m, H(2)), 3.03 (dd, J = 12.7, 5.3 Hz, H(3α)), 2.35–2.06 (m, 5 H), 1.99 (dd, J = 12.7, 9.1 Hz, H(3β)), 1.92–1.83 (m, 2 H), 1.25 (d, J = 5.8 Hz, Me); MS (EI, 70 eV) m/z 230.1307 (230.1306 calcd for $C_{16}H_{20}O_2$, M, 27), 158 (100), 131 (40), 129 (24), 91 (21); IR (film) 2940, 2875, 1710, 1445, 1130, 1070 cm^{-1}. ^{1}H NOE enhancements between H(7a) and the Ph and H(2) signals were consistent with the assigned stereochemistry.

General Procedure for the Reaction of *trans*-Cyclobutanediols with Ketones or Aldehydes in the Presence of BF_3·OEt_2. Preparation of (2*R,3a*R**,6a*R**)-Hexahydro-2-phenyl-4*H*-cyclopenta[*b*]furan-4-one (39b).** A solution of trans-diol **21a** (97 mg, 0.85 mmol), benzaldehyde (0.17 mL, 1.7 mmol), BF_3·OEt_2 (0.10 mL, 1.7 mmol), and CH_2Cl_2 (3.5 mL) was maintained at −23 °C for 1 h, and then Et_3N (0.5 mL, 3.4 mmol) was added and the reaction allowed to warm to 23 °C. Aqueous workup (CH_2Cl_2) and purification on silica gel (5:1 hexane–EtOAc) gave 97 mg (57%) of **39b** as a colorless liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.42 (m, 5 H, Ph), 4.82 (app t, J = 7.9 Hz, H(2)), 4.71 (app t, J = 4.9 Hz, H(6a)), 2.82 (dt, J = 4.8, 9.6 Hz, H(3a)), 2.69 (ddd, J = 13.0, 10.5, 7.4 Hz, 1 H, H(3β)), 2.56–2.64 (m, 1 H), 2.31–2.44 (m, 2 H), 2.10–2.18 (m, 1 H), 2.03 (ddd, J = 13.1, 8.5, 4.0 Hz, H(3α)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.5, 140.7, 128.5, 127.8, 126.0, 82.4, 81.9, 52.6, 38.6, 35.0, 25.9; IR (film) 2950, 1744, 1056 cm^{-1}; MS (EI) m/z 202.0984 (202.0994 calcd for $C_{13}H_{14}O_2$, M, 98), 201 (100).

The (*p*-toluenesulfonyl)hydrazone derivative **40** was prepared in standard fashion (in refluxing EtOH containing one drop of HOAc). Recrystallization from EtOH provided, in 77% yield, X-ray-quality colorless crystals of **40**: MS (EI) m/z 370.1348 (370.135 calcd for $C_{20}H_{22}N_2O_3S$). Anal. Calcd for $C_{20}H_{22}N_2O_3S$: C, 64.83; H, 6.00; N, 7.56. Found: C, 64.89; H, 6.00; N, 7.59.

General Procedure for the Reaction of Aldehydes with *trans*-Cyclobutanediols in the Presence of *p*-Toluenesulfonic Acid. Preparation of (2*R,3a*R**,6a*R**)-Hexahydro-3a-methyl-2-phenyl-4*H*-cyclopenta[*b*]-furan-4-one (39c).** A mixture of diol **21b** (51 mg, 0.397 mmol), CH_2Cl_2 (1.6 mL), anhydrous $MgSO_4$ (0.15 g), benzaldehyde (80 μL, 0.79 mmol), and *p*-toluenesulfonic acid (22.4 mg, 0.119 mmol) was stirred at 23 °C for 1 h. Solid $NaHCO_3$ was then added, the reaction was stirred for an additional 30 min, filtered, and concentrated, and the residue was purified on silica gel (3:2 hexane–EtOAc) to give 61 mg (71%) of **39c** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.37 (m, Ph), 4.90 (app t, J = 7.9 Hz, H(2)), 4.34 (d, J = 4.3 Hz, H(6a)), 2.60–2.75 (m, 1 H), 2.18–2.42 (m, 4 H), 2.02–2.14 (m, 1 H), 1.24 (s, CH$_3$); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 222.0, 140.8, 128.4, 127.8, 126.0, 88.1, 80.8, 56.7, 46.3, 34.6, 24.2, 18.6; IR (film) 2962, 1739, 1455, 1083, 1070 cm^{-1}; MS (EI) *m/z* 216.1139 (216.1140 calcd for $C_{14}H_{16}O_2$, M, 70), 131 (100), 85 (75).

The (*p*-toluenesulfonyl)hydrazone **41** (73% yield) provided X-ray-quality crystals from hexane–EtOAc: mp 168–169 °C; MS (EI) *m/z* 384.1571 (384.1507 calcd for $C_{21}H_{24}N_2O_3S$). Anal. Calcd for $C_{21}H_{24}N_{20}O_3S$: C, 65.59; H, 6.30; N, 7.29. Found: C, 65.46; H, 6.38; N, 7.24.

Preparation of (2*R,3a*S**,6a*R**)- and (2*R**,3a*R**,6a*S**)-Hexahydro-2,3a-diphenyl-4*H*-cyclopenta[*b*]furan-4-ones (42 and 43).** Following the general procedure described for the preparation of **39b**, a solution of diol **21c** (10 mg, 0.05 mmol), benzaldehyde (11 μL, 0.10 mmol), and CH_2Cl_2 (0.25 mL) was maintained at −23 °C for 1 h to provide, after aqueous workup and chromatography (3:2 hexane–EtOAc), 13 mg (90%) of a 2:1 mixture of **42** and **43**, respectively. Separation of this mixture was achieved by preparative HPLC (Supelcosil, 25 cm × 10 mm, 5-μm particle size column (9:1 hexane–THF). Data for **43**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.24–7.37 (m, 10 H, Ph), 5.13 (d, *J* = 3.8 Hz, H(6a)), 4.95 (dd, *J* = 6.4, 9.6 Hz, H(2)), 3.19 (dd, *J* = 6.4, 12.6 Hz, 1 H, H(3)), 2.18–2.55 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.4, 140.6, 137.9, 128.9, 128.5, 127.8, 127.3, 126.7, 126.2, 87.0, 81.1, 65.5, 48.0, 34.4, 24.3; IR (film) 2925, 1750, 1050, 693 cm^{-1}; MS (EI) *m/z* 278.1293 (278.1307 calcd for $C_{19}H_{18}O_2$). Data for **42**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.27–7.35 (m, 10 H, Ph), 5.04 (t, *J* = 8.0 Hz, H(2)), 4.98 (d, *J* = 3.8 Hz, H(6a)), 2.64–2.85 (m, 3 H), 2.42–2.55 (m, 2 H), 2.25–2.35 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.4, 2.85 (m, 3 H), 2.42–2.55 (m, 2 H), 2.25–2.35 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.4, 128.9, 128.5, 127.6, 127.6, 127.4, 126.5, 125.4, 86.0, 80.7, 66.0, 47.5, 35.3, 26.5; IR (film) 3025, 2925, 1750, 1050, 694 cm^{-1}; MS (EI) *m/z* 278.1293 (278.1307 calcd for $C_{19}H_{18}O_2$, M, 19).

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Supplementary Material Available: Experimental procedures and characterization data for compounds **9**, **10a,b**, **12**, **16**, **17**, **19**, **21a,c**, **22a,c**, **23c**, **25b–e**, **26c–e**, **27a,b**, **28a–c**, **31a,b**, **34a–c,f**, **37a–c**, **39a,b,e–h** (20 pages). Ordering information is given on any current masthead page.

General Approach to Halogenated Tetrahydrofuran Natural Products from Red Algae of the Genus *Laurencia*. Total Synthesis of (±)-*trans*-Kumausyne and Demonstration of an Asymmetric Synthesis Strategy

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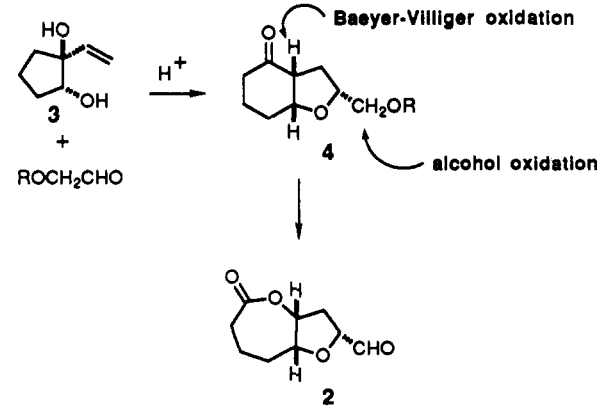
Abstract: A general strategy for the synthesis of C_{15} halogenated tetrahydrofuranoid lipids from red algae of the genus *Laurencia* has been developed. The central step is the convenient formation of hydrobenzofuranone (±)-**5** on a large scale, and with complete stereocontrol, from the acid-catalyzed condensation of 1-vinylcyclopentanediol (**3**) and α-(benzyloxy)acetaldehyde (Scheme II). Starting with the chiral, nonracemic (1*S*,2*R*)-diol **3**, hydrobenzofuranone (−)-**5** is also available in good enantiomeric purity (Scheme V). The total synthesis of (±)-*trans*-kumausyne from *rac*-**5** is accomplished in 13 steps and >5% overall yield.

A rich variety of halogenated, nonisoprenoid sesquiterpenes have been isolated from the widely distributed red algae of the genus *Laurencia*.[1] The majority of these metabolites can be envisaged to arise from the halocyclization of various 6,7-dihydroxypentadeca-3,9,12-trien-1-ynes (laurediols).[2] A large number of these *Laurencia* lipids contain at least one tetrahydrofuran ring. In many of these, the oxygen of the tetrahydrofuran ring is flanked by cis side chains which are also cis related to an oxygen substituent at C(3). A representative selection of metabolites of this common type is shown in Figure 1.[3-7] Also depicted in Figure 1 is a proposed approach for the assembly of members of this class

Scheme I



of marine natural products from a common bicyclic lactone aldehyde precursor **2**. This intermediate embodies the three stereogenic centers of the central tetrahydrofuran ring and also provides loci for the elaboration of the remaining six carbons of these halogenated lipid targets.

A central feature of this potentially widely applicable synthesis plan is the ready assembly of *cis*-hydrobenzofuranones of general structure **4** by ring enlarging tetrahydrofuran annulations of cy-

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