Stereocontrolled Preparation of Tetrahydrofurans from Acid-Promoted Rearrangements of Allylic Acetals

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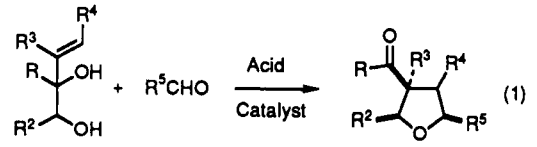
Abstract: A new method for constructing substituted tetrahydrofurans from readily available allylic diol and carbonyl components is reported (eq 1). This synthesis is highly stereocontrolled and allows carbon side chains to be incorporated at each carbon. Enantiomerically pure tetrahydrofurans are readily prepared from chiral, nonracemic allylic diol precursors. The asymmetric synthesis of (+)-muscarine tosylate from the lactate-derived allylic diol **6a** demonstrates that the key rearrangement step occurs with retention of configuration at the homoallylic stereogenic center (Scheme V). The complete preservation of optical activity in the assembly of acyltetrahydrofuran (−)-**27b** from the 5*R* ketal **26b** (Scheme IV) is consistent with the central rearrangement occurring by a two-step cyclization–pinacol sequence (Scheme VII). The utility of this new tetrahydrofuran synthesis for constructing more complex oxacyclics as well as for the asymmetric synthesis of marine *Laurencia* metabolites is disclosed in the two accompanying papers.

Tetrahydrofuran rings of rich stereochemical complexity are definitive structural features of a wide variety of natural products, exemplified by polyether antibiotics[1] and marine *Laurencia* metabolites.[2] Notable methods have been developed in recent years for accessing these heterocycles, the vast majority of which involve construction of the oxacyclic ring by carbon–oxygen bond formation.[3] In this[4] and the following two papers in this issue, we outline the scope[5] and provide a few applications[5,6] of a broadly useful new method for assembling substituted tetrahydrofurans from allylic diol and carbonyl components (eq 1). This unusual and highly stereocontrolled tetrahydrofuran construction involves the formation of three bonds: two carbon–carbon bonds, C-(2)–C(3) and C(4)–C(5), and one carbon–oxygen bond, O–C(5).

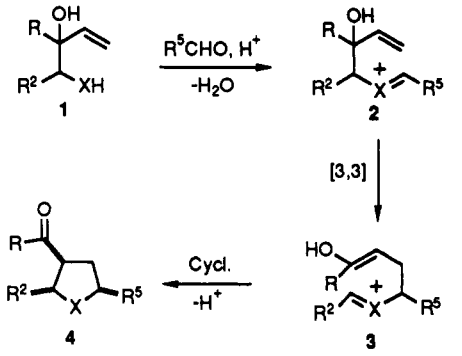


(1)

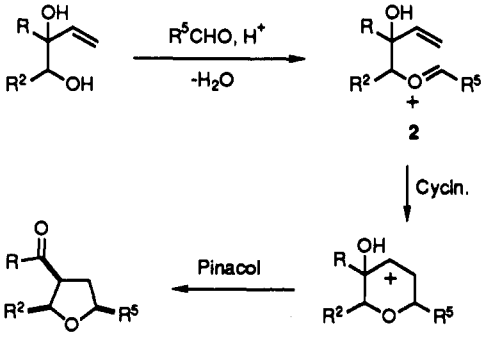
Our investigations in this area were an outgrowth of our earlier development of a general synthesis of pyrrolidines and related azacyclics from the acid-promoted reaction of carbonyl compounds with allylically oxygenated homoallylic amines (Scheme I, X = NR).[7,8] This earlier designed transformation involves in its key steps [3,3] sigmatropic rearrangement (aza-Cope rearrangement) of iminium ion **2** (X = NR) and the subsequent intramolecular Mannich cyclization of isomer **3** (X = NR) to yield the acylpyrrolidine **4** (X = NR).[8d] An exploration of the extension of this mechanistic paradigm to allylic diols (Scheme I, X = O) led to the general synthesis of 3-acyltetrahydrofurans,[9] which is the subject of this and the following accounts.

At the outset of our studies in this area, two issues were of some concern: (1) Although [3,3] sigmatropic rearrangements of a wide variety of hetero-1,5-dienes are known, to the best of our knowledge this reorganization of unsaturated oxocarbenium ions (a 2-oxonia [3,3] sigmatropic rearrangement) had not been documented.[10] (2) Ionization of the tertiary allylic alcohol functionality of **1** under acidic conditions would undermine the desired transformation. In the case at hand, such ionization would not be inhibited by an adjacent charged function as it is in the aza-Cope–Mannich transformation where the homoallylic substituent is an ammonium or iminium group. As will become apparent, the first concern was of little importance since the transformation depicted in eq 1 undoubtedly occurs in quite different mechanistic fashion, proceeding by a sequential Prins cyclization–pinacol rearrangement reaction sequence (Scheme II).[11,12]

Scheme I. [3,3] Sigmatropic Rearrangement–Cyclization Mechanistic Pathway (X = NR or O)



Scheme II. Cyclization–Pinacol Mechanistic Pathway



Several alternate methods for preparing 3-acyltetrahydrofurans have recently appeared. These methods involve assembling the

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(1) Westley, J. W. *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Marcel Dekker: New York, 1982; Vols. 1 and 2.
(2) For reviews, see: Faulkner, D. J. *Nat. Prod. Rep.* **1987**, *4*, 539; **1986**, *3*, 1; **1984**, *1*, 251, 551. Moore, R. E. *Marine Natural Products: Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 1.
(3) For recent reviews, see (a) Bolvin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D.; Ed., Academic: New York, 1984; Vol. 3, Chapter 6. (c) Semple, J. E.; Joullie, M. M. *Heterocycles* **1980**, *14*, 1825.
(4) A small part of this study was described in preliminary form: Hopkins, M. H.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 4748.
(5) Brown, M. J.; Harrison, T.; Herrinton, P. M.; Hopkins, M. H.; Oswell, K. N.; Overman, L. E.; Mishra, P. *J. Am. Chem. Soc.*, in press.
(6) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.*, in press.
(7) For a brief review, see: Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Ed.; Pergamon: Oxford, in press.

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Table I. Preparation of Allylic Acetals **12** and Stannic Chloride Promoted Rearrangement To Form 3-Acetyltetrahydrofurans **13**

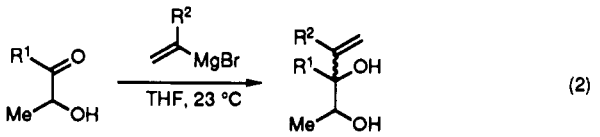
entry	aldehyde R^2	allylic acetal compd	allylic acetal yield,[a] %	rearrg conditions[b] $SnCl_4$ (equiv)	tetrahydrofuran compd	tetrahydrofuran yield, %	other products
1	Me	**12a**	64	A (2)	**13a**	77	
2	Et	**12b**	74	A (2)	**13b**	76	
3	*i*-Pr	**12c**	74	A (3)	**13c**	81	
4	CH_2CH_2Ph	**12d**	72	A (3)	**13d**	91	
5	$CH{=}CH_2$	**12e**	72	A (3)	**13e**	60	
6	Ph	**12f**	70	A (3)	**13f**	64–66[c,e]	PhCHO (~10%)
7	Ph	**12f**	70	−78 → +23 °C (3–4)[d]	**13f**	25–30[e]	PhCHO (~30%)
8	(*E*)-CH=CHPh	**12g**	70	A (3)			(*E*)-PhCH=CHCHO (95%)

[a] After purification by chromatography or distillation. [b] In CH_2Cl_2 (0.3–0.4 M) in the presence of 2–4 equiv of $SnCl_4$. [c] In condition A, $SnCl_4$ was added at −78 °C and the reaction was allowed to warm to −23 °C where it was maintained for 4 h before quenching. [d] The reaction was allowed to warm over ca. 1 h to room temperature. [e] Range of two to three experiments.

acyltetrahydrofuran by acid-catalyzed rearrangement of 4,5-dihydro-1,2-dioxepines[13] or from Prins cyclizations of oxocarbenium ions derived from 4-hydroxy-1-enol ethers.[14,15]

Results

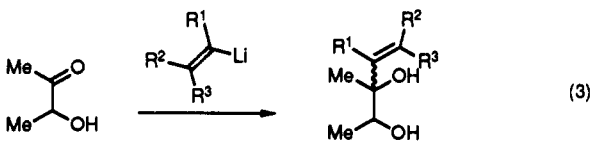
Preparation of Allylic Diols. Allylic diols **6a–d** are procurable on a large scale, although with low (2–5:1) stereoselectivity, by the direct reaction of α-hydroxy ketones with 2 equiv of vinyl Grignard (eq 2) or vinyllithium (eq 3) reagents.[16] Since both the syn and anti diol diastereomers react to form identical tetrahydrofuran products (vide infra), these diastereomers were typically not separated. For exploratory investigations, the syn and anti diastereomers of **6b** were obtained in pure form by careful separation on silica gel.



(2)

5 **a** R^1 = Me
b R^1 = n-Bu

6 **a** R^1 = Me, R^2 = H (60%)
b R^1 = n-Bu, R^2 = H (41%)
c R^1 = R^2 = Me (95%)
d R^1 = Me, R^2 = Ph (61%)



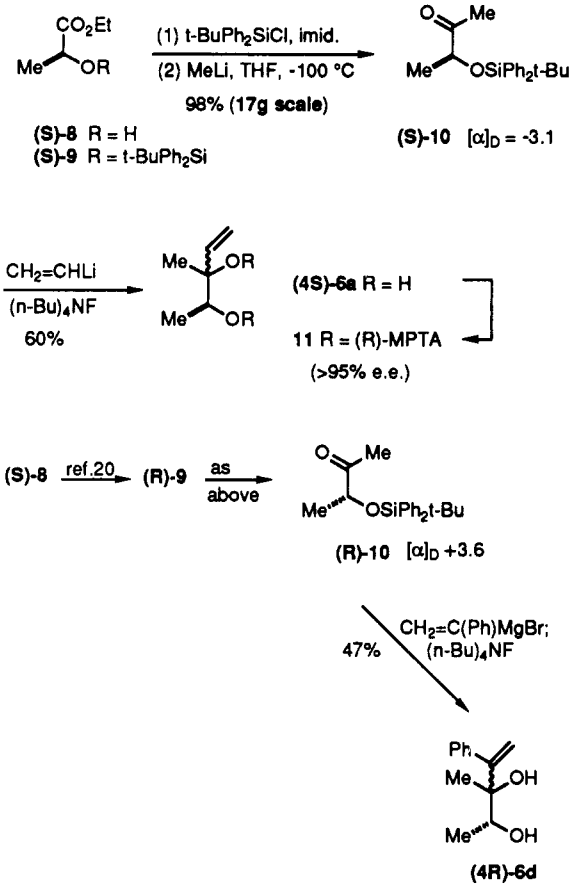
(3)

5a

7 **a** R^1 = R^3 = Me, R^2 = H (46%)
b R^1 = R^2 = Me, R^3 = H (38%)

Optically active allylic diols can be accessed in similar fashion from the reaction of vinyl organometallics with nonracemic α-oxygenated ketones. Numerous practical methods for the asymmetric synthesis of these latter intermediates are now available.[17] In the present study we have developed a quite convenient, large-scale synthesis of either enantiomer of 3-methyl-4-alkene-2,3-diols from inexpensive (*S*)-(−)ethyl lactate (Scheme III). The key development in implementing this sequence was our finding that MeLi is cleanly acylated at −100 °C with the *tert*-butyldiphenylsilyl ether[18] of ethyl lactate. This reaction can easily be carried out on preparative scales (10–20 g) to deliver (*S*)-**10** of high chemical purity, and essentially complete enantiomeric fidelity, in two steps and nearly quantitative yield from commercially available (*S*)-**8**. The use of the *tert*-butyldiphenylsilyl ether is essential. Similar reactions of MeLi with the triethylsilyl ether of ethyl lactate provided up to 20% of the undesired tertiary alcohol. The high enantiomeric purity of (*S*)-**10**, as well as the lack of racemization upon the reaction of this ketone with vinyllithium, was ascertained by analysis of the (*R*)-(+)-α-meth-

Scheme III



(8) See, inter alia: (a) Overman, L. E.; Mendelson, L.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629. (b) Overman, L. E.; Jacobsen, E. J.; Doedens, R. J. *J. Org. Chem.* **1983**, *48*, 3393. (c) Overman, L. E.; Okazaki, M.; Jacobsen, E. J. *Ibid.* **1985**, *50*, 2403. (d) Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2248.
(9) Named as [tetrahydro-3-furanyl]ethanones in *Chemical Abstracts*.
(10) For a recent review, see: Blechert, S. *Synthesis* **1989**, 71.
(11) For brief reviews of Prins cyclization reactions that form carbocycles, see: (a) Thieme, J. In *Methoden der Organishen Chemie*; Houben-Weyl, Ed.; Thieme: Stuttgart, 1980; Vol. VI/1a, Part 2, pp 793–799. (b) Snider, B. S. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon: New York; Vol. 5, in press.
(12) For a review of pinacol rearrangements, see: Bartok, M.; Molnar, A. In *Chemistry of Ethers, Crown Ethers, Hydroxyl Compounds and Their Sulfur Analogues*; Patai, S., Ed.; New York, 1980; Part 2, pp 722–733.
(13) (a) Suzuki, H.; Yashima, H.; Hirose, T.; Takahashi, M.; Moro-oka, U.; Ikawa, T. *Tetrahedron Lett.* **1980**, *21*, 4927. (b) Frauenrath, H.; Runsink, J. *J. Org. Chem.* **1987**, *52*, 2707.
(14) Linderman, R. J.; Godfrey, A. *J. Am. Chem. Soc.* **1988**, *110*, 6249.
(15) Hoppe, D.; Krämer, T.; Erdbrüger, C. F.; Egert, E. *Tetrahedron Lett.* **1989**, *30*, 1233.
(16) The major stereoisomer undoubtedly arises by "chelation-controlled" face selectivity and is assigned the anti 3*R**,4*R** stereochemistry: Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.
(17) Morrison, J. D., Ed. *Asymmetric Synthesis*; Academic Press: New York; 1983–1985; Vols. 2–5.
(18) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1977**, *55*, 562.

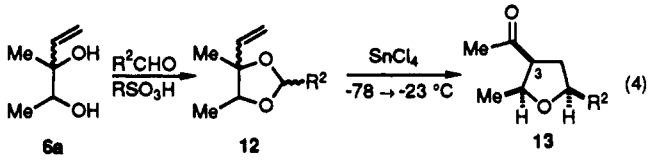
Table II. Characteristic Spectral Data for Acyltetrahydrofurans **13**, **17**, **19**, and **25**

compd	IR[a] $\nu_{C=O}$, cm^{-1}	^{1}H NMR[b] H(2)	H(3)	H(5)	MeC=O
13a	1711	4.23 (m)	3.29 (q, 6.2)	3.96 (m)	2.18 (s)
13b	1713	4.27 (m)	3.27 (q, 8.1)	3.75 (m)	2.17 (s)
13c	1712	4.30 (m)	3.32 (q, 8.3)	3.51 (q, 7.8)	2.17 (s)
13d	1712	4.20 (m)	3.20 (q, 8.1)	3.76 (m)	2.11 (s)
13e	1712	4.28 (m)	3.26 (q, 6.1)	4.28 (m)	2.13 (s)
13f	1710	4.47 (m)	3.45 (q, 8.4)	4.84 (dd, 6.3, 9.9)	2.19 (s)
17	1712	4.23 (m)	3.31 (q, 8.2)	3.96 (m)	
19a	1704	3.82 (q, 6.6)		5.17 (d, 9.2)	2.16 (s)
19b	1704	4.01 (q, 6.5)		4.42 (d, 10.1)	2.21 (s)
25a	1713	4.38 (m)	3.36 (q, 7.8)	4.15 (m)	2.19 (s)
25b	1711	4.40 (m)	3.39 (m)	4.14 (m)	2.19 (s)
25c	1712	4.38 (m)	3.37 (q, 8.1)	4.07 (m)	2.20 (s)
25d	1712	4.32 (m)	3.24 (q, 8.0)	4.31 (m)	2.16 (s)
25e	1713	4.30 (m)	3.37 (q, 8.0)	4.54 (m)	2.19 (s)

[a] Thin film. [b] In $CDCl_3$; multiplicities and coupling constants in hertz are in parentheses.

oxy-α-(trifluoromethyl)phenylacetate (MPTA) derivative (**11**)[19] of the major allylic diol formed from the sequential reaction of (*S*)-**10** with vinyllithium and $(n\text{-Bu})_4NF$. Comparison of the 500-MHz ^{1}H NMR of **11** with that of the same material prepared from racemic acetoin **5a** defined the enantiomeric excess of **11** to be greater than 95%. The opposite enantiomeric series, e.g., (4*R*)-**6d**, can be accessed similarly from (*R*)-**9**. This latter intermediate can be prepared in high enantiomeric purity through Mitsunobu inversion of ethyl (*S*)-lactate.[20,21]

Preparation of 3-Acyltetrahydrofurans by Lewis Acid Promoted Rearrangements of Allylic Acetals. The conversion of the diastereomeric mixture of allylic diols **6a** to 3-acyltetrahydrofurans is conveniently carried out by initial protic acid-catalyzed condensation of **6a** with the aldehyde component to form the 1,3-dioxolane derivatives **12** (eq 4). These latter intermediates, which



(4)

6a **12** **13**

a R^2 = Me, **b** R^2 = Et, **c** R^2 = i-Pr, **d** R^2 = CH_2CH_2Ph, **e** R^2 = $CH{=}CH_2$, **f** R^2 = Ph, **g** R^2 = (E)-CH=CHPh

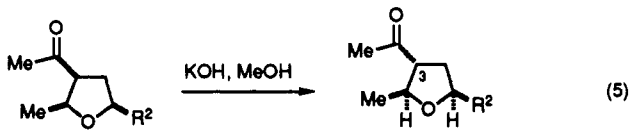
are a mixture of four stereoisomers, can be purified by either vacuum distillation or flash chromatography (Table I). Preliminary studies with **12a** and **12b** indicated that the conversion to the corresponding acyltetrahydrofuran could be realized with a variety of Lewis acids, inter alia, $EtAlCl_2$, $BF_3{\cdot}OEt_2$, and $SnCl_4$. Rearrangements of **12** with $SnCl_4$ occurred readily at temperatures between −70 and −20 °C; this Lewis acid was generally superior and was chosen for systematic study.

Addition of 2–3 equiv of $SnCl_4$ to a dry ice cooled CH_2Cl_2 solution of acetals **12a–f** followed by reaction at −23 °C for 4 h provided the *all-cis*-3-acyltetrahydrofurans **13a–f** in good yields (Table I). Aliphatic, α,β-unsaturated (vide infra) and aryl aldehydes can be employed. A notable aspect of this conversion is that only a single tetrahydrofuran isomer **13** is produced from the complex mixture of stereoisomeric acetals **12**. In some reactions allowed to warm to room temperature, partial epimerization of the acetyl group was observed. That the kinetic product had a cis relationship of vicinal substituents at C(2) and C(3) was demonstrated with **13b,d,f** by base-catalyzed epimerization to afford (at equilibrium) a ~10:1 mixture of the 2,3-trans (**14**) and 2,3-cis stereoisomers, respectively (eq 5). The cis relationship of the C(5) substituent was signaled by the strong NOE observed between the cis methine hydrogens at C(2) and C(5) of both acetyl

Table III. Diagnostic ^{1}H DNOE Results for Acyltetrahydrofurans **13**, **14**, and **19**

13b	H(2)/H(3)	H(2)/H(5)	
14a		H(2)/H(5)	
13f	H(2)/H(3)	H(2)/H(5)	
14c		H(2)/H(5)	
13d	H(2)/H(3)	H(2)/H(5)	
14b		H(2)/H(5)	
19a		H(2)/H(5)	H(4)/H(5)
19b		H(2)/H(5)	C(3)-Me/C(4)-Me

epimers. Key characterization data for the 3-acetyltetrahydrofurans **13** and **14** are summarized in Tables II and III.



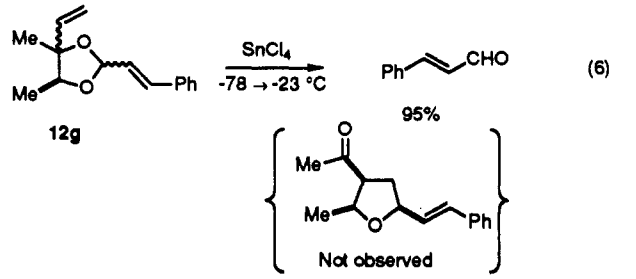
(5)

13b,d,f

14 a R = Et
b R = CH_2CH_2Ph
c R = Ph

Byproducts of the formation of acetyltetrahydrofurans **13** from acetals **12** are the starting aldehydes. For less volatile aldehydes, their presence (prior to aqueous quenching) can be detected by TLC or GLC analysis. To minimize the formation of benzaldehyde in the conversion of **12f** → **13f**, it was essential to prevent the reaction mixture from warming above −20 °C prior to aqueous quenching. Rearrangements of **12f**, that were allowed to rapidly warm to room temperature after $SnCl_4$ addition, gave significantly reduced yields of acetyltetrahydrofuran **13f** (entry 7, Table I). Although temperature control is not critical for all substrates, as a general rule we have conducted the $SnCl_4$-promoted rearrangements of allylic acetals at as low a temperature as possible.

In one case, the cinnamyl acetal **12g** fragmentation to reform cinnamaldehyde dominated even at low temperature (entry 8, Table I). Conducting the rearrangement of **12g** under standard conditions (−78 → −23 °C) provided cinnamaldehyde in 95% yield (eq 6). Rigorous evidence that the relative stereochemistry at



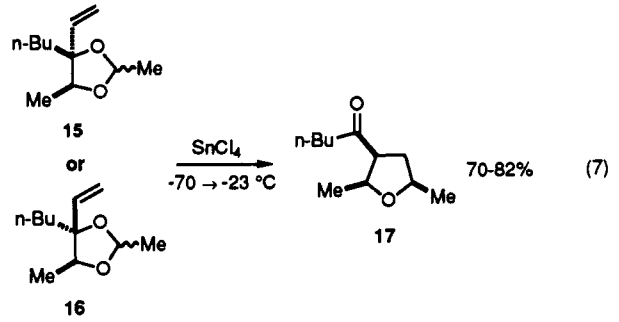
(6)

12g

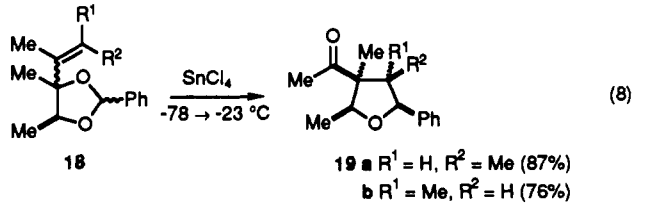
the tertiary allylic carbon of the starting acetal is inconsequential was obtained from the rearrangement of acetals **15** and **16**; these latter intermediates were prepared from isomerically pure samples of the syn and anti stereoisomers of diol **6b**.[22] For both **15** and

(19) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(20) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192.
(21) Mitsunobu, I. *Synthesis* **1981**, 1.

16 $SnCl_4$-promoted rearrangement afforded *a single product*: the *all-cis*-3-acyltetrahydrofuran **17**.

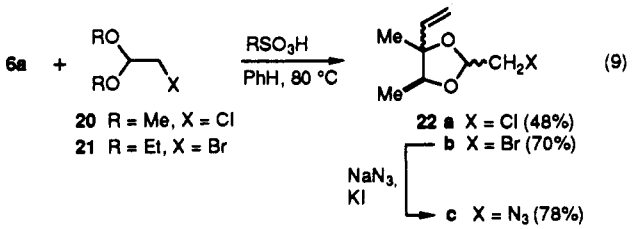


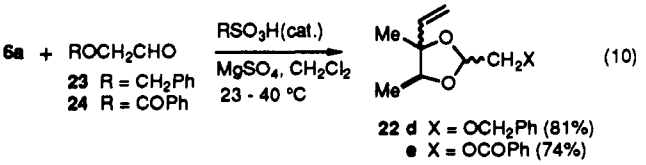
To investigate the preparation of tetrahydrofurans containing a side chain at each ring carbon, we investigated the rearrangements of acetals **18**, which contain (*Z*)- or (*E*)-1-methylpropenyl substituents (eq 8). The acetal samples studied were prepared



from benzaldehyde and samples of diols **7a** or **7b**, the latter of which were contaminated with 5% of the alternate double-bond geometrical isomer. The desired rearrangements of **18a** or **18b** took place cleanly in the presence of $SnCl_4$ to provide tetrahydrofurans **19a** or **19b**, respectively. The amount of crossover (ca. 5%) detected in the product acyltetrahydrofurans was consistent with the isomeric purity of the starting alkenes. These conversions affirm the high stereoselectivity of this new tetrahydrofuran synthesis and specifically demonstrate the stereospecific involvement of the alkene participant in a suprafacial sense. The stereostructures for **19a** and **19b** followed directly from ^1H NMR NOE studies (see Table III).

Since many tetrahydrofuran-containing natural products possess C(2) or C(5) side chains that contain oxygen or halogen at their origin carbon,[1,2] we have investigated rearrangements of allylic acetals derived from α-functionalized aldehydes. The 2-(halomethyl)-1,3-dioxolanes **22a** and **22b** were prepared from diol **6a** and the commercially available haloacetals **20** and **21** by protic acid catalyzed acetal exchange (eq 9). The azide derivative **22c** was accessed from **22b**. The related dioxolanes **22d** and **22e** bearing ether or ester side chains could be directly prepared from **6a** and the corresponding α-oxygenated acetaldehydes **23** or **24** (eq 10).





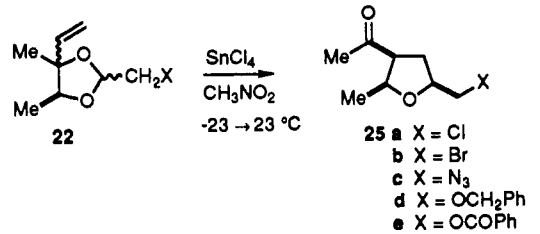
(22) The major isomer is assigned the syn 3*R**,4*S** diol stereochemistry on the expectation that the addition to an α-silyloxy ketone would occur preferentially with simple Cram (Felkin-Ahn) face selectivity: Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355. Nakata, T.; Tanaka, T.; Oishi, T. *Ibid.* **1983**, *24*, 2653. Keck, G. E.; Boden, E. P. *Ibid.* **1984**, *25*, 265.

Table IV. Stannic Chloride Promoted Rearrangements of Acetals **22** To Form Tetrahydrofurans **25** Containing Functionalized C(5) Side Chains

		rearrg conditions[a]	tetrahydrofuran	
entry	X	solvent	compd	yield, %
1	Cl	CH_2Cl_2	**25a**	*c*
2	Cl	CH_3NO_2	**25a**[b]	11 (35)[d]
3	Br	CH_2Cl_2	**25b**	*c*
4	Br	CH_3NO_2	**25b**[b]	32
5	N_3	CH_2Cl_2	**25c**	*c*
6	N_3	CH_3NO_2	**25c**[b]	40
7	OCH_2Ph	CH_2Cl_2	**25d**	10
8	OCH_2Ph	CH_3NO_2	**25d**[b]	59
9	OCOPh	CH_2Cl_2	**25e**	*c*
10	OCOPh	CH_3NO_2	**25e**[b]	58

[a] In reactions conducted in CH_3NO_2, $SnCl_4$ (3 equiv) was added at −23 °C and the reaction was allowed to warm over 3 h to room temperature prior to quenching. Reactions conducted in CH_2Cl_2 were similar, although $SnCl_4$ in this case was added at −78 °C. [b] Rearrangements in CH_3NO_2 resulted in ca. 10% epimerization of the 3-acetyl substituent. The yield reported is for this epimer mixture. [c] No acetyl methyl signal was seen in the crude reaction product. [d] Crude yield. Purification of **25a** was accompanied by significant loss of mass.

The heteromethyl-substituted 1,3-dioxolanes were considerably more resistant to Lewis acids than their hydrocarbon analogues. Thus, treatment of acetals **22** with $SnCl_4$ at −78 → −23 °C in CH_2Cl_2 resulted primarily in recovery of the starting acetal. Allowing the reaction temperature to rise to 23 °C afforded complex reaction mixtures, which only in the case of **22d** contained even small amounts of the desired acyltetrahydrofuran **25** (eq 11 and Table IV). The markedly reduced reactivity of this acetal



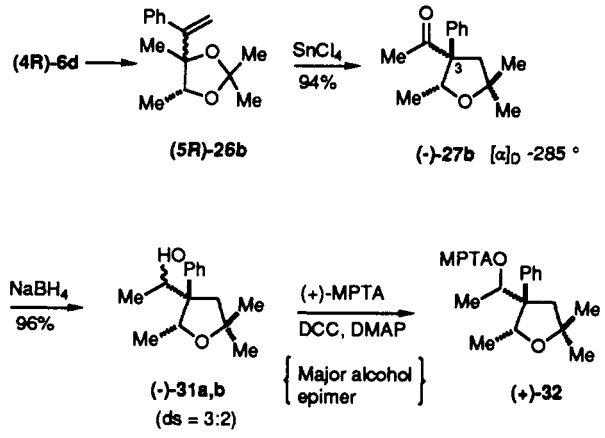
series is likely due to the electron-withdrawing nature of the hetero substituent, which inhibits oxocarbenium ion formation. With the aim of facilitating dioxolane opening, we examined solvents more highly ionizing than CH_2Cl_2.[23,24] Of these, nitromethane proved best, and in this solvent the desired conversion of **22** → **25** could be realized at room temperature in fair to moderate yield (Table IV). The formation of **25** in this way is accompanied by partial epimerization (ca. 10%) of the acetyl substituent, which is a natural result of having to conduct this rearrangement reaction at room temperature. In the two oxygenated cases, both acetyl epimers of **25** could be isolated by careful chromatography and were fully characterized (see Experimental Section). The *all-cis*-tetrahydrofurans **25** displayed diagnostic spectral characteristics similar to those of acyltetrahydrofurans **13**.

We also briefly examined the preparation of tetrahydrofurans with geminal substitution at C(5). As depicted in eq 12, acetonide derivatives **26** of diols **6a** or **6b** could be obtained in good yield by conventional ketalization. The desired rearrangement of these ketals to tetrahydrofurans **27a** and **27b** was readily accomplished in CH_2Cl_2 under the aegis of $SnCl_4$ (eq 12). In each case, only a single tetrahydrofuran stereoisomer was produced. The ste-

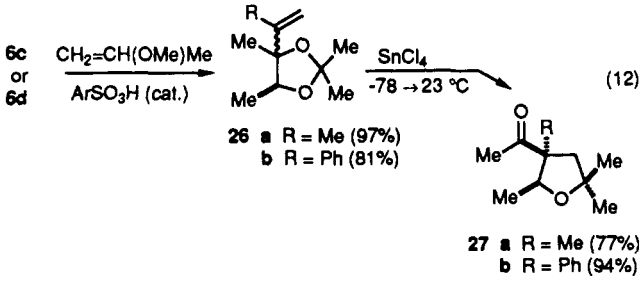
(23) Depending on stoichiometry, at −78 °C acetals form two hexacoordinate complexes, $R^1CH(OR)_2SnCl_4$ and $[R^1CH(OR)_2]_2SnCl_4$ with $SnCl_4$, rather than detectable amounts of oxocarbenium ions.[24] These complexes should be less polar than the products of their ionization to form an oxocarbenium ion.

(24) Denmark, S. E.; Wilson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258. Denmark, S. E.; Wilson, T. M. In *Selectivities in Lewis Acid-Promoted Reactions*; Schinzer, D., Ed.; NATO ASSI Series; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1989; Chapter 13.

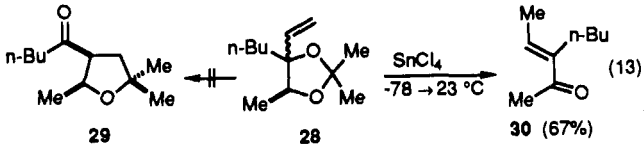
Scheme IV



reochemical assignments for **27** again followed from ^{1}H NMR NOE experiments



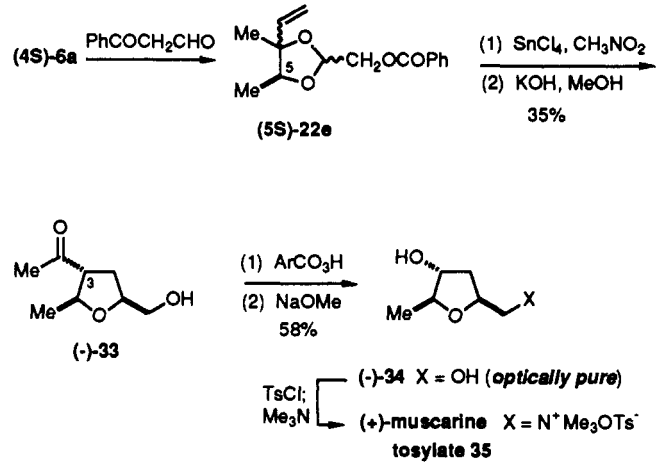
The rearrangement of ketal precursors was strictly limited to substrates that contain alkene substituents more nucleophilic than terminal vinyl. Thus, attempted rearrangement of acetonide **28** afforded at most trace amounts of tetrahydrofuran **29** (eq 13). The major product, isolated in 67% yield, was (*E*)-3-butyl-3-penten-2-one (**30**).



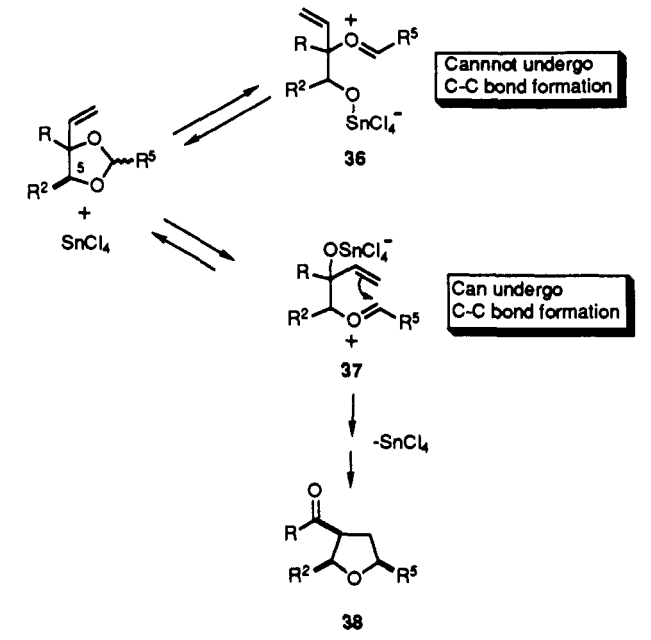
Asymmetric Synthesis of 3-Acyltetrahydrofurans. In part to probe the mechanism of tetrahydrofuran formation (vide infra), we investigated the reorganization of acetonide (5*R*)-**26b** derived from the 4*R* diol **6d** (Scheme IV). $SnCl_4$-promoted rearrangement of (5*R*)-**26b** provided the levorotatory ketone (-)-**27b** in 94% yield. To assay the enantiomeric purity of this product, (-)-**27b** was reduced with $NaBH_4$ to provide two levorotatory alcohols in a ratio of 3:2. Mosher analysis[19] of the major alcohol diastereomer ((-)-**31a**) established the enantiomeric purity of this intermediate to be >95%. The rearrangement of (5*R*)-**26b**, thus, occurred with no detectable degradation of enantiomeric purity.

Synthesis of (+)-Muscarine. To pursue whether or not the rearrangement of optically active allylic diols took place with retention of configuration at the homoallylic stereogenic center, we developed an asymmetric synthesis of the cholinergic agent (+)-muscarine.[25-27] The starting point for this undertaking was the 4*S* allylic diol **6a**, which is available on a large scale from natural (+)-ethyl lactate (vide supra). Conversion of (4*S*)-**6a** to

Scheme V



Scheme VI



the dioxolanes (5*S*)-**22e** was followed by $SnCl_4$-promoted Prins pinacol rearrangement in CH_3NO_2. Subsequent treatment of the crude tetrahydrofuran products with methanolic KOH resulted in both cleavage of the benzoate and essentially complete epimerization at C(3) to afford the levorotatory acetyltetrahydrofuranmethanol (-)-**33** in 35% overall yield from dioxolanes (5*S*)-**22e**, (Scheme V).

The acetyltetrahydrofuran (-)-**33** resisted Baeyer–Villiger oxidation with a variety of conventional and less conventional oxidants: e.g., *m*-chloroperoxybenzoic acid, HOOH, ROOH,[28] $Me_3SiOOSiMe_3$–Me_3SiOTf.[29] The desired conversion was finally accomplished at 40 °C with 3,5-dinitroperoxybenzoic acid[30] in the presence of a radical scavenger.[31] Deacetylation of the Baeyer–Villiger product then provided the known diol (-)-**34** in 58% overall yield from (-)-**33**. The optical rotation of (-)-**34**, $[\alpha]_D$ -17.2° (*c* 1.3, EtOAc) was, within experimental uncertainty, identical with the highest rotation previously reported for this intermediate ($[\alpha]_D$ -16.9° (*c* 1.1, EtOAc)).[32] This identity provides a second demonstration of the complete preservation of

(25) For a recent review of muscarine alkaloids, see: Wang, P.-C.; Joullié, M. M. *Alkaloids* **1984**, *23*, 327.

(26) For recently published enantioselective syntheses of (+)-muscarine, see: Mulzer, J.; Angermann, A.; Muench, W.; Schlichthoerl, G.; Hentzschel, A. *Liebigs Ann. Chem.* **1987**, 7. Bandzouzi, A.; Chapleur, Y. *J. Chem. Soc., Perkin Trans. 1* **1987**, 661. Adams, J.; Poupart, M.-A.; Grenier, L. *Tetrahedron Lett.* **1989**, *30*, 1753. Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1371.

(27) For a brief review of the current interest in muscarinic agonists for senile dementia therapy, see: Gray, J. A.; Enz, A.; Spiegel, R. *Trends Pharmacol. Sci Suppl.* **1989** (Dec), 85.

(28) For recent versions, see: Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649. Feldman, K. S.; Wu, M.-J.; Rotella, D. P. *J. Am. Chem. Soc.* **1989**, *111*, 6457.

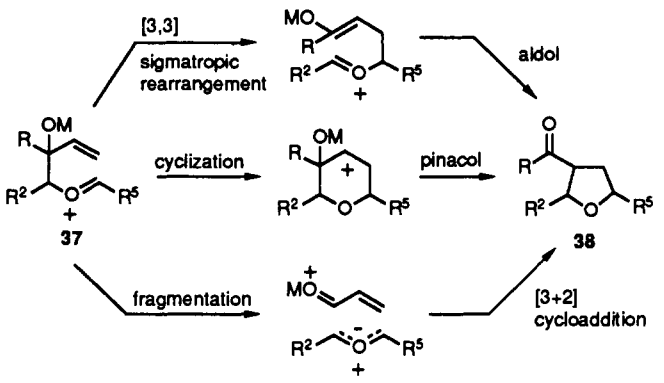
(29) Suzuki, M.; Takada, H.; Noyori, R. *J. Org. Chem.* **1982**, *47*, 902.

(30) Rastetter, W. H.; Richard, T. J.; Lewis, M. D. *J. Org. Chem.* **1978**, *43*, 3163.

(31) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T. *J. Chem. Soc., Chem. Commun.* **1972**, 64.

(32) Adams, J.; Poupart, M.; Grenier, L. *Tetrahedron Lett.* **1989**, *30*, 1753.

Scheme VII. Three Possible Mechanisms for the Conversion of **37** → **38** (M = $SnCl_4$)



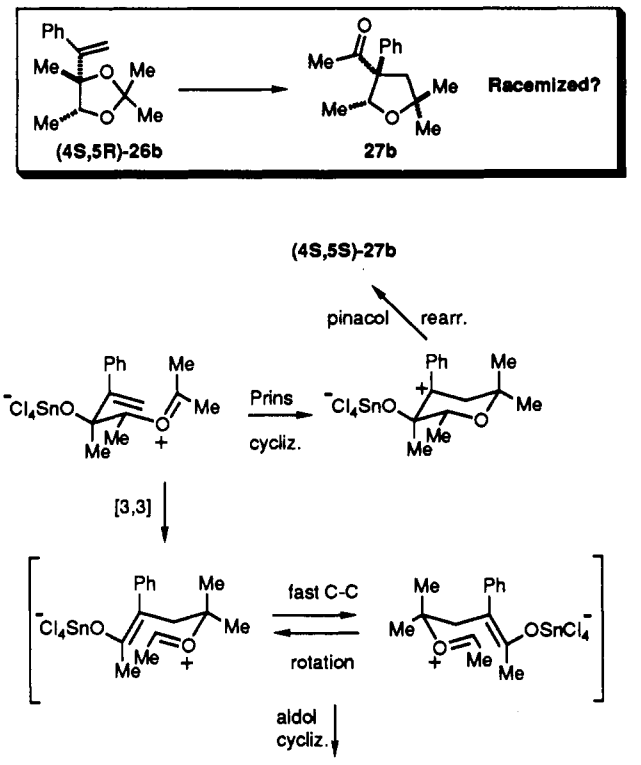
enantiomeric purity in the conversion of an allylic diol to a 3-acyltetrahydrofuran and rigorously establishes that this conversion occurs with retention of configuration at a homoallylic stereogenic center. Conventional tosylation and aminolysis of the primary tosylate derivative of diol (−)-**34** provided (+)-muscarine tosylate (**35**).[33]

Discussion

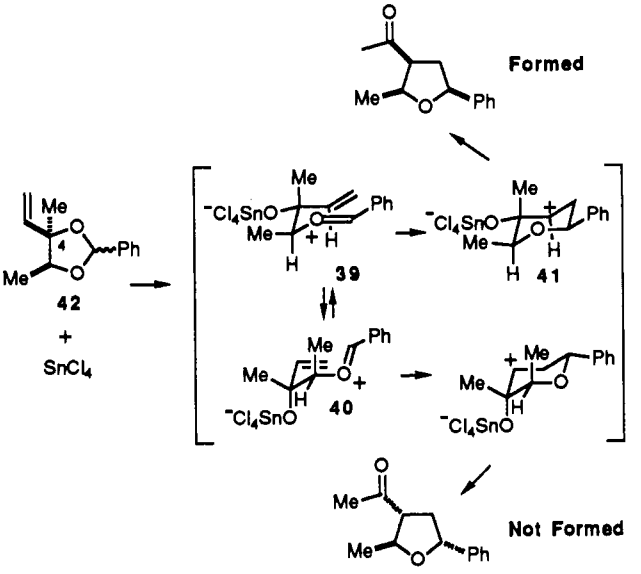
Mechanistic Aspects. A stereoelectronic consideration that was central to our design of this new tetrahydrofuran synthesis is illustrated in Scheme VI. Acid-promoted opening of the starting dioxolane can occur in two ways to provide oxocarbenium ions **36** and **37**. However, even though both intermediates should be readily accessible, only in oxocarbenium ion **37** can the terminal carbons readily engage in bond formation.[34] Because of poor overlap between the p orbitals of the alkene and the electron-deficient carbon of **36** (a carbon–carbon bond-forming cyclization of this intermediate would be a disfavored 5-endo-trigonal process[35]), the predominant pathway open to this intermediate is reversion to the starting dioxolane. Thus, nonproductive acetal cleavage in the "wrong" sense to afford **36** is of little consequence in the conversion of allylic acetals to 3-acyltetrahydrofurans.

Let us now consider the details of the conversion of the "productive" oxocarbenium ion **37** to the 3-acyltetrahydrofuran product **38**. Three possibilities for this conversion are presented in Scheme VII. These parallel mechanisms we recently considered[8d] for the formation of 3-acylpyrrolidines from acid-catalyzed condensation of allylic amino alcohols with carbonyl compounds (Scheme I, X = NR). The top two mechanistic scenarios depicted in Scheme VII appear most probable, and the approach that we have taken to probing these is outlined in Scheme VIII. To clarify the analysis, only one of the allylic diastereomers of this acetal is depicted in Scheme VIII. A cyclization–pinacol sequence for the conversion of (5*R*)-**26b** to tetrahydrofuran **27b** should proceed with retention of configuration at the homoallylic stereogenic center.[12] In contrast, a [3,3] sigmatropic rearrangement–aldol process would yield racemic products if the rearranged oxocarbenium ion (which contains no stereogenic centers) attained an achiral conformation prior to aldol cyclization. We are aware of no evidence to suggest that the barrier for the intramolecular aldol reaction would be nearly as low as the barrier

Scheme VIII



Scheme IX



for carbon–carbon single-bond rotation (~3–6 kcal/mol).[37] Thus, the complete preservation of enantiomeric purity in the conversion of (5*R*)-**26b** to the acyltetrahydrofuran (−)-**27b** provides strong evidence for a cyclization–pinacol pathway.[38]

In the context of a cyclization–pinacol mechanism, the kinetically controlled stereoselectivity in forming the *all-cis*-2,5-disubstituted-3-acyltetrahydrofuran stereoisomer is readily explained, *and more importantly anticipated*, as outlined in Scheme IX. Since inversion and rotation barriers for oxonium ions are small

(33) Mubarek, A. M.; Brown, D. M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 809.

(34) In fact, kinetically one would expect **36** to be produced most rapidly, since Lewis acid coordination to the less hindered acetal oxygen is involved.

(35) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, *734*, 736.

(36) Complete racemization was observed in the related rearrangement of chiral, nonracemic 5-vinyloxazolidines, which ruled out a cyclization–pinacol pathway for the related rearrangement that forms 3-acylpyrrolidines.[8d] The observation of high relative diastereoselectivity in forming the 3-acyltetrahydrofuran product does not provide a tool for distinguishing between [3,3] sigmatropic rearrangement–cyclization and cyclization–pinacol pathways, since the aforementioned conversion in the azacyclic series (which was attended with racemization) occurred with high levels of relative diastereoselectivity.

(37) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; American Chemical Society: Washington, DC, 1965; Chapters 2–3.

(38) We take the demonstration of retention of configuration in the related rearrangement to afford (+)-muscarine as persuasive evidence that the sense of enantiomeric preservation in the conversion of (5*R*)-**26b** → (−)-**27b** is, as we have depicted in Schemes V and VIII, retention.

(~10–14 kcal/mol),[39] cyclization should proceed via the more stable *E* oxonium ion stereoisomer. Of the two possible chair conformations of this intermediate (**39** and **40**), **39** should be favored since the methyl group at the secondary carbon occupies an equatorial orientation.[40] Pinacol rearrangement of the tetrahydropyranyl cation **41**, produced from cyclization of **39**, would lead to the observed product. That the relative stereochemistry at the allylic stereogenic center is of little significance (vide supra) arises from the similar sizes of CH_3 and the Lewis acid coordinated oxygen substituents. Thus, the stereoselective rearrangement of the 4-epimer of **42** would be rationalized by an identical scheme with only the spatial orientation of the CH_3 and $OSnCl_4$ substituents reversed in Scheme IX. Although not explicitly indicated, the sequence shown in Scheme IX would also rationalize the suprafacial participation of the alkene group, which was demonstrated in rearrangements of acetals **18** (eq 8).

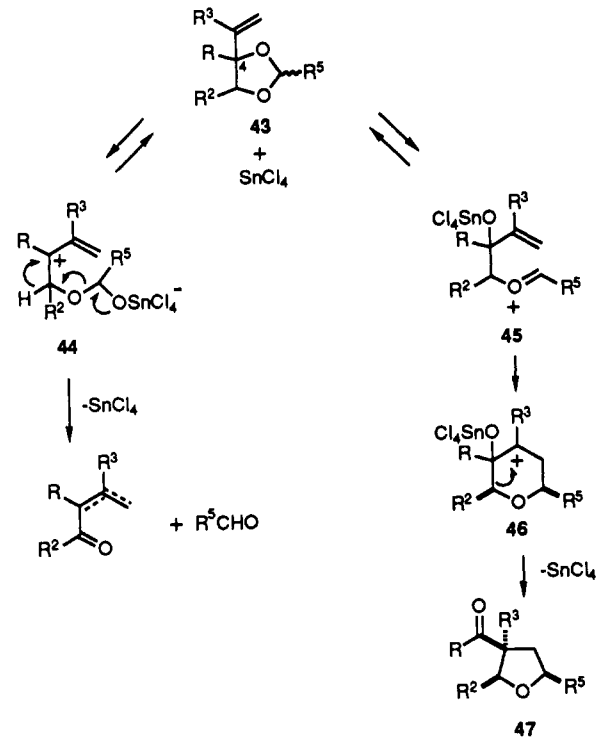
Synthetic Aspects. A wide variety of highly substituted 3-acyltetrahydrofurans can be conveniently assembled from readily available allylic diol and carbonyl components (eq 1). In most cases only three steps are required for assembly of the substituted tetrahydrofurans from commercially available starting materials. High cis stereoselectivity (at least 20:1)[41] is observed in the preparation of tetrahydrofurans containing side chains at carbons 2 and 5. The kinetically controlled product also has a cis relationship of these side chains and the 3-acyl substituent (e.g., see eqs 4 and 11). The trans acyl epimer can also be accessed in a number of cases by thermodynamic equilibration (see eq 5). The ability to stereospecifically introduce carbon side chains at C(3) and C(4) was specifically demonstrated in two cases.

A definitive feature of this highly stereoselective new route to substituted tetrahydrofurans is that *both* syn and anti allylic diol stereoisomers are expected (in most cases) to afford identical tetrahydrofuran products. Thus, there is typically no need for stereoselective construction of the allylic diol reaction partner. The construction of substituted tetrahydrofurans in high enantiomeric purity from nonracemic allylic diol precursors has also been established. Although the asymmetric synthesis of (+)-muscarine in this way is somewhat too protracted to be of practical utility, this asymmetric route to nonnatural muscarinic agonists has proven quite expeditious.[42]

Three major limitations emerge from our exploratory studies to date: (1) When the tetrahydrofuran construction involves the formation of a quaternary center at C(5), only allylic diols with alkene substituents more nucleophilic than terminal vinyl rearrange successfully. (2) Allylic acetals such as the heteromethyl-substituted acetals **22**, which are reluctant to ring open in the presence of acid catalysts to oxocarbenium ions, are converted in moderate yield only to acyltetrahydrofuran products. (3) Acetals that form highly stabilized oxocarbeniums (e.g., cinnamyl-derived acetals) also do not undergo conversion to 3-acyltetrahydrofurans. In the three cases enumerated, fragmentation to the starting carbonyl component (prior to any aqueous quench) is the predominant alternate reaction pathway.

Fragmentation to regenerate the starting carbonyl component and produce, from the diol component, an enone product (see eq 13) likely arises by ionization of the allylic acetal at C(4) to form allylcarbenium ion intermediate **44** (Scheme X). When the rate of the cyclization of oxocarbenium ion **45** to the tetrahydropyranyl cation **46** is high, the fragmentation process is apparently not competitive and high yields of tetrahydrofurans **47** are realized. However, when this step is slow, resulting either from a decrease in the concentration of **45** or from lowered reactivity of either the alkene or oxocarbenium ion components, ionization of **43** to **44** becomes competitive.

Scheme X



Conclusion

A fundamentally new approach for the stereocontrolled preparation of substituted tetrahydrofurans has been developed. This practical method assembles the tetrahydrofuran ring from allylic diol and carbonyl components and in the process forms three ring bonds: C(2)–C(3), C(4)–C(5), and O–C(5). The scope and mechanism of the reaction have been investigated in sufficient detail to provide clear guidance for using this new tetrahydrofuran construction in more complex synthesis contexts. The two accompanying papers in this issue[5,6] provide some indication of the rich applications of this chemistry that are possible. The current study also reveals, for the first time, the potential of reaction designs in which a pinacol rearrangement is employed to terminate a cationic cyclization. The development of further useful conversions based upon this concept is the object of ongoing studies in our[43] and other[44] laboratories.

Experimental Section[45]

A. Preparation of Racemic Allylic Diols. (±)-3-Methyl-1-pentene-3,4-diol (6a). Acetoin (**5a**; 20.0 g, 227 mmol) was dissolved in THF (50 mL) by heating at reflux for 1 h. Vinylmagnesium bromide (1.0 M in THF, 500 mL, 500 mmol) was then added dropwise at 0 °C over 20 min. The resulting solution was warmed to 23 °C, maintained there for 1 h, and then poured into saturated aqueous NH_4Cl (300 mL). This mixture was concentrated to remove THF, the resulting aqueous suspension was saturated with NaCl and extracted with CH_2Cl_2 (5 × 100 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (1:1 EtOAc–hexane) and the fractions containing the polar product were distilled (89 °C, 4 mm) to give 15.9 g (60%) of a colorless oil, which was a 5:1 mixture of the

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

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

(41) We estimate that no more than 5% of the trans stereoisomer could have been undetectable in 500-MHz ^1H NMR analysis of the crude cyclization products.

(42) Overman, L. E.; Rishton, G. M. Manuscript in preparation.

(43) (a) Hirst, G. C.; Howard, P. N.; Overman, L. E. *J. Am. Chem. Soc.* **1989**, *111*, 1514. (b) Overman, L. E. In *Selectivities in Lewis Acid-Promoted Reactions*; Schinzer, D., Ed.; NATO ASSI Series; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1989; Chapter 1.

(44) Sworin, M.; Neumann, W. L. *J. Org. Chem.* **1988**, *53*, 4894. Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 6556.

(45) General experimental details were recently described.[46] Tin(IV) chloride was purchased from Aldrich Chemical Co. and stored under argon. Anhydrous nitromethane was prepared by heating a 10:1 mixture of nitromethane and trifluoroacetic anhydride followed by distillation and collection of the fraction distilling at 100 °C.

diastereomeric diols **6a** by ^{1}H NMR analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98–5.88 (m, 1 H, C=CH), 5.37–5.17 (m, 2 H, C=CH_2), 3.68–3.63 (m, 1 H, CH), 2.48–2.28 (m, 2 H, 2 OH), 1.28 and 1.22 (s, 3 H, CH_3), 1.16–1.42 (m, 3 H, CH_3); IR (film) 3409, 3242, 2983, 1416, 1375, 1094, 989, 826 cm^{-1}; MS (CI) *m/z* 99.0805 (99.0810 calcd for $C_6H_{12}O_2$, MH – H_2O). Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 61.80; H, 10.33.

(±)-3-Butyl-1-pentene-3,4-diol (6b). Vinylmagnesium bromide (1.0 M in THF, 39 mL, 39 mmol) was added dropwise over 10 min to a solution of **5b** (2.5 g, 19 mmol) and THF (20 mL). The solution was maintained at 23 °C for 2 h and then poured into saturated aqueous NH_4Cl (100 mL). The mixture was then concentrated to remove THF, the resulting aqueous suspension was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated to afford 1.24 g (41%) of a yellow oil, which was a 2:1 mixture of the diastereomeric diols **6b** by ^{1}H NMR analysis. Separation by flash chromatography (1:3 EtOAc–hexane) provided pure samples of each diastereomer.

Major diastereomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.81 (dd, *J* = 10.7, 17.3 Hz, 1 H, CH=C), 5.33 (dd, *J* = 1.5, 7.3 Hz, 1 H, C=C*H*H), 5.24 (dd, *J* = 1.5, 10.7 Hz, 1 H, C=C*H*H), 3.64 (q, *J* = 6.4 Hz, 1 H, CH), 2.26 (bs, 1 H, OH), 1.59–1.20 (m, 6 H), 1.16 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.88 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2); IR (film) 3417, 2958, 1083, 923 cm^{-1}; MS (CI) *m/z* 158.1298 (158.1302 calcd for $C_9H_{18}O_2$, M).

Minor diastereomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.76 (dd, *J* = 10.8, 17.3 Hz, 1 H), 5.28 (dd, *J* = 1.6, 7.4 Hz, 1 H), 5.21 (dd, *J* = 1.6, 10.8 Hz, 1 H), 3.62 (1, *J* = 6.5 Hz, 1 H), 2.60 (s, 1 H, O*H*), 1.52–1.15 (m, 6 H), 1.11 (d, *J* = 6.5 Hz, 3 H), 0.86 (t, *J* = 6.8 Hz, 3 H); IR (film) 3433, 2958 cm^{-1}; MS (EI) *m/z* 158.1283 (158.1302 calcd for $C_9H_{18}O_2$, M).

(±)-2,3-Dimethyl-1-pentene-3,4-diol (6c). 2-Bromopropene (5.01 g, 41.4 mmol) was added dropwise over 3 min to magnesium metal (2.02 g, 33.2 mmol), THF (50 mL), and a crystal of I_2. The mixture was heated at reflux until all the magnesium metal was used (1 h) and was then cooled to –20 °C. A solution of acetoin (1.46 g, 16.6 mmol) and THF (50 mL) was added dropwise over 1 min, and the mixture was warmed to 23 °C and maintained for 2 h. Saturated aqueous NH_4Cl (50 mL) was added, and the mixture was concentrated to remove THF. The resulting aqueous suspension was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), and evaporated to give 2.04 g (95%) of a yellow oil, which was a 2:1 mixture of diastereomeric diols **6c** by ^{1}H NMR analysis. This mixture was resolved by preparative GC (60 °C, SP 2330). The first fraction contained the major diastereomer as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.06 (s, 1 H, CH=C), 4.89 (d, *J* = 3.9 Hz, 1 H, CH=C), 3.81–3.73 (m, 1 H, CH), 2.42–2.17 (m, 2 H, 2 OH), 1.76 (s, 3 H, CH_3C=C), 1.37 (s, 3 H, CH_3), 1.10 (d, *J* = 6.5 Hz, CH_3CH); IR (film) 3411, 2961, 1450, 1375, 1088, 902 cm^{-1}; MS (CI) *m/z* 113.0936 (113.0966 calcd for $C_7H_{14}O_2$, MH – H_2O).

(±)-3-Methyl-2-phenyl-1-pentene-3,4-diol (6d). Freshly distilled α-bromostyrene (6.4 mL, 50 mmol) in THF (10 mL) was added to magnesium (1.21 g, 49.9 mmol), THF (30 mL), and a crystal of I_2. The mixture was heated briefly at reflux (30 s) and removed from the heat, and the reaction proceeded exothermically for 1 h. At this time, acetoin **5a** (2.00 g, 22.7 mmol) in THF (25 mL) was added and the mixture was maintained at 23 °C for 2 h. Concentrated aqueous NH_4Cl (30 mL) was added, and the mixture was concentrated to remove THF. The resulting aqueous suspension was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography (1:20 MeOH–CH_2Cl_2) to give 2.67 g (61%) of a colorless oil, which was a 2:1 mixture of diastereomeric diols **6d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.18 (m, 5 H, Ph), 5.48 and 5.46 (d, *J* = 1 Hz, 1 H, C=C*H*H), 5.07 and 5.05 (d, *J* = 1 Hz, 1 H, C=C*H*H), 3.81–3.68 (m, 1 H, CH), 3.20–2.85 (m, 2 H, OH), 1.41 and 1.30 (s, 3 H, CH_3), 1.19 and 1.08 (d, *J* = 6 Hz, 3 H, CH_3CH); IR (film) 3455, 3432, 3348, 2983, 1073, 918 cm^{-1}; MS (CI) *m/z* 193.1205 (193.1288 calcd for $C_{12}H_{16}O_2$, MH). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.04; H, 8.43.

(±)-(*Z*)-3,4-Dimethyl-2-hexene-4,5-diol (7a). *tert*-Butyllithium (1.7 M in pentane, 58 mL, 98.7 mmol) was added over 10 min to (*Z*)-2-bromo-2-butene[46] (6.66 g, 49.3 mmol, a 10:1 mixture of *Z* and *E* isomers by 500-MHz ^{1}H NMR analysis) and THF (20 mL) at –78 °C. The resulting suspension was warmed to 0 °C over 20 min and was added to a solution of acetoin (**5a**; 2.17 g, 24.6 mmol) and THF (20 mL) at –78 °C. The resulting solution was warmed to 23 °C over 20 min. Saturated aqueous NH_4Cl (20 mL) was added, the mixture was concentrated to remove THF, and the resulting aqueous suspension was saturated with NaCl and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (20:1 CH_2Cl_2–CH_3OH) to give 1.60 g (46%) of **7a** as a colorless oil, which was contaminated to the extent of 10% with the diastereomeric (*E*)-alkene stereoisomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.48–5.43 (m, 1 H, CH=CH_3), 4.12 (q, *J* = 7.0 Hz, CH), 2.46–2.44 (m, 2 H, 2 OH), 1.84 (d, *J* = 1.5 Hz, 3 H, CH_3CH=C), 1.74 (s, CH_3C=C), 1.27 (s, 3 H, CH_3), 1.15 (d, *J* = 6.38 Hz, 3 H, CH_3CH); IR (film) 3442, 2980, 2844, 1093, 1057 cm^{-1}; MS (CI) *m/z* 127.1117 (127.1123 calcd for $C_8H_{16}O_2$, MH – H_2O).

(±)-(*E*)-3,4-Dimethyl-2-hexene-4,5-diol (7b). *sec*-Butyllithium (1.3 M in cyclohexane, 23 mL, 31 mmol) was added over 10 min to a solution of (*E*)- and (*Z*)-2-bromo-2-butene[47] (8.31 g, 61.5 mmol, a 3:2 mixture of *E* and *Z* isomers by 500-MHz ^{1}H NMR analysis) and THF (10 mL) at –78 °C. To the resulting solution was added acetoin (1.35 g, 15.3 mmol) in THF (10 mL) at –78 °C over 10 min. The resulting mixture was maintained at –78 °C for 30 min, aqueous NH_4Cl (20 mL) was then added, the mixture was concentrated to remove THF, and the resulting aqueous suspension was saturated with NaCl and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (1:1 EtOAc–hexane) to give 825 mg (38%) of a colorless oil, which was a mixture of the diastereomeric diols **7b** contaminated to the extent of 30% with the diastereomeric (*Z*)-alkene isomers. Repeated chromatography gave 429 mg (20%) of a colorless oil, which was a 10:1 mixture of the diastereomeric diols **7b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69–5.62 (m, 1 H, CH=C), 3.85 and 3.75 (m, 1 H, CH), 2.80–2.39 (m, 2 H, 2 OH), 1.73–1.60 (m, 6 H, 2 CH_3C=C), 1.33–1.21 (s, 3 H, CH_3), 1.14 and 1.12 (d, 3 H, CH_3CH); MS (CI) *m/z* 127.1120 (127.1123 calcd for $C_8H_{16}O_2$, MH – H_2O).

B. Preparation of Enantiomerically Pure Allylic Diols. (*S*)-Ethyl 2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]propanoate ((*S*)-9). A mixture of (*S*)-(–)-ethyl lactate (**8**; 10.0 g, 84.6 mmol), *tert*-butyldiphenylsilyl chloride (23.3 g, 84.6 mmol), imidazole (14.4 g, 211 mmol), and THF (100 mL) was stirred at 23 °C for 2 h. The mixture was filtered through a glass wool plug into water (400 mL) and concentrated to remove THF, and the resulting aqueous suspension was extracted with EtOAc (400 mL). The organic layer was washed with water (2 × 400 mL), dried (Na_2SO_4), and concentrated to give 30.0 g (99%) of the silyl ester (*S*)-**9** (96% pure by GLC analysis) as a colorless oil: $[\alpha]_D$ –45.1 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.65 (m, 4 H, Ph), 7.41–7.36 (m, 6 H, Ph), 4.27 (q, *J* = 6.7 Hz, 1 H, CH), 4.04–3.99 (m, 2 H, OCH_2), 1.37 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.14 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.09 (s, 9 H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 135.8, 135.7, 133.5, 133.1, 129.7, 127.6, 68.9, 60.5, 26.8, 21.2, 19.2, 14.0; IR (film) 2980, 2933, 2859, 1753, 1735, 1429, 1198, 1139, 1112, 1081, 823, 739, 702, 690, 611 cm^{-1}. Anal. Calcd for $C_{21}H_{28}O_3Si$: C, 70.74; H, 7.92. Found: C, 70.94; H, 7.89.

(*S*)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-butanone ((*S*)-10). MeLi (1.4 M in Et_2O, 52 mL, 73 mmol) was added dropwise over 20 min to a mechanically stirred solution of the silyl ester (*S*)-**9** (20.0 g, 56.2 mmol) and THF (200 mL) at –105 °C (internal temperature). The internal reaction temperature was not allowed to rise above 100 °C during the addition. The resulting mixture was maintained at –105 to –100 °C for an additional 10 min, Me_3SiCl (20 mL) was then added, and the reaction was warmed to 23 °C and maintained there for 20 min. To this clear solution was added 1 N HCl (200 mL), and the two-phase mixture was stirred vigorously for 1 h. The mixture was slowly poured onto solid $NaHCO_3$ (30 g) and concentrated to remove THF, and the resulting aqueous suspension was extracted with EtOAc (400 mL). The organic layer was washed with water (2 × 400 mL), dried (Na_2SO_4), and evaporated to give 16.8 g (99%) of the silyl ketone (*S*)-**10** (95% pure by GLC analysis) as a colorless oil: $[\alpha]_D$ –3.1 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66–7.60 (m, 4 H, Ph), 7.40–7.36 (m, 6 H, Ph), 4.17 (q, *J* = 6.8 Hz, 1 H, CH), 2.16 (s, 3 H, $COCH_3$), 1.19 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.10 (s, 9 H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 135.7, 129.9, 127.8, 127.6, 75.7, 26.9, 24.9, 20.6, 19.2; IR (film) 2961, 2933, 2859, 1719, 1428, 1114, 823, 741, 703, 691 cm^{-1}; MS (CI) *m/z* 327.1760 (327.1780 calcd for $C_{20}H_{26}O_2Si$, MH). Anal. Calcd for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03. Found: C, 73.52; H, 8.07.

For the purpose of measuring optical purity, the ketone (*S*)-**10** was treated sequentially with MeLi (2.1 equiv, THF, –78 °C) and tetrabutylammonium fluoride (2.1 equiv, THF, RT) (RT = room temperature), the resulting diol was converted to its MPTA diester (2.5 equiv of (*R*)-(+)-MPTA, 3.0 equiv of DCC, 0.2 equiv of DMAP, CH_2Cl_2), and the reaction mixture was analyzed by 500-MHz ^{1}H NMR and shown to contain essentially one diastereomer, which exhibited a characteristic resonance at δ 5.03. This was compared directly to the diester mixture

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(47) Bordwell, F. G.; Landis, P. S. *J. Am. Chem. Soc.* **1957**, *79*, 1593.

derived in a similar fashion from racemic acetoin (**5a**), which exhibited an additional diagnostic resonance at δ 5.18.

(*R*)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-butanone ((*R*)-10). The title compound was similarly derived from (*S*)-(−)-ethyl lactate;[20] $[\alpha]_D$ +3.6 (*c* 1.0, MeOH).

(3*R*,4*S*)-3-Methyl-1-pentene-3,4-diol and (3*S*,4*S*)-3-Methyl-1-pentene-3,4-diol ((4*S*)-6a). A solution of vinyllithium (prepared from 25.0 g of tetravinyltin[48]) and THF (200 mL) was added dropwise over 20 min to a solution of the ketone (*S*)-**10** (17.4 g, 53.4 mmol) and THF (150 mL) at −78 °C. The resulting solution was maintained at −78 °C for an additional 10 min, saturated aqueous NH_4Cl (200 mL) was added dropwise, and the temperature was increased to 23 °C over 20 min. The mixture was concentrated to remove THF, the resulting aqueous suspension was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated to give 26.8 g of a yellow oil. A solution of this crude material, 50 mL of THF, and tetrabutylammonium fluoride (1.0 M in THF, 107 mL, 107 mmol) was maintained at 23 °C for 4 h and then poured into saturated aqueous NH_4Cl (200 mL). This mixture was concentrated to remove THF, the resulting aqueous suspension was saturated with NaCl and extracted with CH_2Cl_2 (5 × 100 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (1:1 EtOAc–hexane) to give 3.72 g (60% from ketone **10**) of a colorless oil, which was a 6:1 mixture of syn and anti diastereomers of (4*S*)-**6a** (by ^1H NMR analysis). For spectral data, see the preparation of (±)-**6a**.

(3*R*,4*R*)-3-Methyl-2-phenyl-1-pentene-3,4-diol and (3*S*,4*R*)-3-Methyl-2-phenyl-1-pentene-3,4-diol ((4*R*)-6d). Following the general procedure described for the preparation of racemic **6d**, (1-phenylethenyl)magnesium bromide (1.7 mmol in 5 mL THF) was condensed with ketone (*R*)-**10** (500 mg, 1.53 mmol) to afford after deprotection with (*n*-Bu)$_4$NF and purification by flash chromatography (20:1 CH_2Cl_2–CH_3OH) 138 mg (47% from ketone (*R*)-**10**) of (4*R*)-**6d** as a colorless oil, which was a 6:1 mixture of the diastereomeric diols. For spectral data, see the preparation of (±)-**6d**.

C. Preparation of Racemic 3-Acyltetrahydrofurans. General Procedure for Preparing Acetals from Allylic Diols and Aldehydes. Preparation of (±)-2,4-Diethenyl-4,5-dimethyl-1,3-dioxolane (12e). A solution of the diol **6a** (2.83 g, 24.4 mmol), acrolein (3.3 mL, 48 mmol), *p*-toluenesulfonic acid (50 mg), and CH_2Cl_2 (10 mL) over $MgSO_4$ (4.0 g) was maintained at 23 °C for 15 h. The solution was then poured into saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL), the combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (1:4 EtOAc–hexane). The product was distilled (70 °C, 4 mm) to provide 2.70 g (72%) of a colorless oil, which was a mixture of the diastereomeric acetals **12e**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.00–5.24 (m, 6 H, 2 CH=CH_2), 5.20–5.16 (m, 1 H, ROCHOR), 3.91–3.80 (m, 1 H, CHOR), 1.35 and 1.23 (s, 3 H, 2 CH_3), 1.21–1.17 (m, 3 H, CH_3); IR (film) 2983, 1104, 980, 930 cm^{-1}; MS (CI) *m/z* 155 (MH). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.11; H, 9.17.

Unless indicated otherwise, all other allylic acetals were prepared in this way in yields of 60–85% (Table I). Complete experimental details and characterization data can be found in the supplementary material.

Formation of Halomethyl Acetals by Acetal Exchange. Preparation of (±)-4-Ethenyl-2-(chloromethyl)-4,5-dimethyl-1,3-dioxolane (22a). A solution of the diol **6a** (427 mg, 3.67 mmol), chloroacetaldehyde dimethyl acetal (**20**; 0.4 mL, 3.7 mmol), *p*-toluenesulfonic acid (50 mg), and benzene (25 mL) was heated at reflux with Dean–Stark distillation for 1.5 h. The solution was then poured into saturated aqueous $NaHCO_3$ (30 mL). The organic phase was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (hexane). The product was distilled (122 °C, 4 mm) to provide 313 mg (48%) of a yellow oil, which was a mixture of the diastereomeric acetals **22a**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.93–5.76 (m, 1 H, C=CH), 5.40–5.24 (m, 2 H, C=CH_2), 5.23–5.14 (m, 1 H, ROCHOR), 3.96–3.87 (m, 1 H, CHOR), 3.62–3.49 (m, 2 H, CH_2Cl), 1.39 and 1.21 (s, 3 H, CH_3), 1.22 and 1.18 (d, *J* = 3.0 Hz, CH_3); IR (film) 2983, 1382, 1138, 1117, 1101, 1034, 1009 cm^{-1}; MS (CI) *m/z* 177.0678 (177.0682 calcd for $C_8H_{13}O_2Cl$, MH). Anal. Calcd for $C_8H_{13}O_2Cl$: C, 54.40; H, 7.42. Found: C, 54.40; H, 7.47.

(±)-4-Ethenyl-2-(bromomethyl)-4,5-dimethyl-1,3-dioxolane (22b). A solution of the diol **6a** (346 mg, 2.98 mmol), bromoacetaldehyde diethyl acetal (**21**; 0.45 mL, 2.98 mmol), *p*-toluenesulfonic acid (50 mg), and benzene (20 mL) was heated at reflux with Dean–Stark distillation for 1.5 h. The solution was then poured into saturated aqueous $NaHCO_3$ (30 mL). The organic phase was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (hexane) to provide 461 mg (70%) of a brown oil, which was a mixture of the diastereomeric acetals **22b**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.95–5.75 (m, 1 H, C=CH), 5.40–5.35 (m, 2 H, C=CH_2), 5.22–5.18 (m, 1 H, ROCHOR), 4.00–3.87 (m, 1 H, CHOR), 3.49–3.32 (m, 2 H, CH_2Br), 1.40–1.10 (m, 6 H, 2 CH_3); IR (film) 2981, 1425, 1381, 1131, 1112, 1034, 1009, 993, 930 cm^{-1}; MS (CI) *m/z* 221.0164 (221.0177 calcd for $C_8H_{13}O_2Br$, MH). Anal. Calcd for $C_8H_{13}O_2Br$: C, 43.42; H, 5.93. Found: C, 43.28; H, 5.94.

(±)-4-Ethenyl-2-[(benzyloxy)methyl]-4,5-dimethyl-1,3-dioxolane (22d). A solution of the diol **6a** (759 mg, 6.55 mmol), (benzyloxy)-acetaldehyde[49] (980 mg, 6.55 mmol), *p*-toluenesulfonic acid (50 mg), and CH_2Cl_2 (20 mL) over $MgSO_4$ (2.0 g) was heated at reflux for 3 h. The solution was then poured into saturated aqueous $NaHCO_3$ (40 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (1:5 EtOAc–hexane) to provide 1.31 g (81%) of a yellow oil, which was a mixture of the diastereomeric acetals **22d**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.19 (m, 5 H, Ph), 5.85–5.70 (m, 1 H, C=CH), 5.38–5.20 (m, 2 H, C=CH_2), 5.19–5.12 (m, 1 H, ROCHOR), 4.67–4.58 (m, 2 H, CH_2Ph), 3.89–3.78 (m, 1 H, CHOR), 3.63–3.47 (m, 2 H, CH_2), 1.37–1.15 (m, 6 H, 2 CH_3); IR (film) 2982, 2866, 1455, 1376, 1106, 1029, 996, 929, 737 cm^{-1}; MS (CI) *m/z* 249 (MH). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.52; H, 8.13.

(±)-4-Ethenyl-2-[(benzoyloxy)methyl]-4,5-dimethyl-1,3-dioxolane (22e). A solution of the diol **6a** (1.80 g, 15.5 mmol), *O*-benzoylglycoaldehyde (1.96 g, 11.9 mmol),[50] *p*-toluenesulfonic acid (50 mg), and CH_2Cl_2 (20 mL) over $MgSO_4$ (3.0 g) was maintained at 23 °C for 20 h. The solution was then poured into saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (1:4 EtOAc–hexane) to provide 2.32 g (74%) of a colorless oil, which was a mixture of the diastereomeric acetals **22e**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8 Hz, 2 H, ArH), 7.60–7.51 (m, 1 H, ArH), 7.48–7.39 (m, 2 H, ArH), 5.95–5.74 (m, 1 H, C=CH), 5.40–5.15 (m, 2 H, C=CH_2), 5.39–5.31 (m, 1 H, ROCHOR), 4.53–4.36 (m, 2 H, CH_2OCOPh), 3.94–3.83 (m, 1 H, CHOR), 1.39 and 1.22 (s, 3 H, CH_3), 1.24 and 1.18 (d, *J* = 6 Hz, 3 H, CH_3); IR (film) 1728, 1725, 1720, 1282, 1276, 1147, 1110, 1071, 1028, 939 cm^{-1}; MS (CI) *m/z* 263.1270 (263.1283 calcd for $C_{15}H_{18}O_4$, MH).

(4*R*,5*S*)- and (4*S*,5*S*)-4-Ethenyl-2-[(benzoyloxy)methyl]-4,5-dimethyl-1,3-dioxolane ((5*S*)-22e) was prepared as above from the optically active diol (4*S*)-**6a**.

(±)-4-Ethenyl-2-(azidomethyl)-4,5-dimethyl-1,3-dioxolane (22c). A solution of the acetal **22b** (160 mg, 0.49 mmol), sodium azide (100 mg, 1.46 mmol), KI (1 mg), and 4 mL of DMF was heated at 70 °C for 24 h. The solution was then poured into benzene (20 mL) and washed with water (3 × 20 mL). The benzene layer was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (CH_2Cl_2) to give 52 mg (78%) of a colorless oil, which was a mixture of the diastereomeric acetals **22c**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.92–5.76 (m, 1 H, CH=C), 5.37–5.25 (m, 2 H, C=CH_2), 5.15 (m, 1 H, CH), 3.90 (m, 1 H, CH), 3.38 (m, 2 H, CH_2N_3), 1.42–1.12 (m, 5 H, 2 CH_3); IR (NaCl) 2984, 2106, 2103 (intense), 1382, 1292, 1272, 1136, 1099, 1072, 930.

General Procedure for the Rearrangement of Allylic Acetals with $SnCl_4$ in CH_2Cl_2. Preparation of (±)-(2α,3α,5α)-1-(Tetrahydro-2,5-dimethyl-3-furanyl)ethanone (13a). $SnCl_4$ (0.8 mL, 7 mmol) was added to a solution of the acetals **12a** (478 mg, 3.37 mmol) and CH_2Cl_2 (10 mL) at −78 °C. The solution was warmed to −23 °C and maintained for 4 h. Saturated aqueous NaCl (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (1:2 EtOAc–hexane) to provide 362 mg (77%) of the tetrahydrofuran **13a** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.28–4.19 (m, 1 H, H(2)), 4.02–3.90 (m, 1 H, H(5)), 3.29 (q, *J* = 6.2 Hz, 1 H, H(3)), 2.18 (s, 3 H, CH_3), 2.11–2.02 (m, 1 H), 1.91–1.81 (m, 1 H), 1.33 (d, *J* = 4.2 Hz, 3 H, CH_3), 1.15 (d, *J* = 4.1 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 75.3, 74.7, 55.6, 35.2, 30.6, 20.3, 17.2; IR (film) 2977, 1711, 1381, 1356, 1168, 1093, 918, 733 cm^{-1}; MS (CI) *m/z* 143.1066 (143.1080 calcd for $C_8H_{14}O_2$, MH). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found; C, 67.45; H, 9.97.

Prepared in similar fashion were the 3-acyltetrahydrofurans **13** shown in Table I.

(±)-(2α,3α,5α)-1-(Tetrahydro-5-ethyl-2-methyl-3-furanyl)ethanone (13b): 203 mg 76% as a colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ

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4.27 (p, J = 6.7 Hz, 1 H, H(2)), 3.75 (m, 1 H, H(5)), 3.27 (q, J = 8.1 Hz, H(3)), 2.17 (s, 3 H, CH_3CO), 2.10–1.50 (m, 4 H, 2 CH_2), 1.13 (d, J = 6.4 Hz, CH_3), 0.96 (t, J = 7.4 Hz, 3 H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 80.2, 75.0, 55.2, 32.9, 30.5, 28.1, 17.3, 10.1; IR (film) 2971, 1713, 1350, 1130 cm^{-1}; MS (CI) m/z 157.1231 (157.1227 calcd for $C_9H_{16}O_2$, MH).

(±)-(2α,3α,5α)-1-[Tetrahydro-2-methyl-5-(1-methylethyl)-3-furanyl]ethanone (13c): 142 mg (81%) as a colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 4.33–4.27 (m, 1 H, H(2)), 3.51 (q, J = 7.8 Hz, 1 H, H(5)), 3.32 (q, J = 8.3 Hz, 1 H, H(3)), 2.17 (s, 3 H, CH_3CO), 1.95 (t, J = 8.1 Hz, 2 H, CH_2), 1.79–1.73 (m, 1 H, $CHMe_2$), 1.10 (d, J = 6.5 Hz, 3 H, CH_3CH), 0.99 (d, J = 6.6 Hz, 3 H, CH_3), 0.90 (d, J = 6.8 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 84.6, 74.9, 55.5, 33.1, 31.0, 30.6, 19.5, 18.3, 17.7; IR (film) 2962, 2941, 2913, 2874, 1712, 1384, 1365, 911 cm^{-1}; MS (CI) m/z 171.1395 (171.1385 calcd for $C_{10}H_{18}O_2$, MH). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.43; H, 10.62.

(±)-(2α,3α,5α)-1-[Tetrahydro-2-methyl-5-(2-phenylethyl)-3-furanyl]ethanone (13d): 681 mg (91%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.12 (m, 5 H, Ph), 4.20 (m, 1 H, H(2)), 3.73–3.80 (m, 1 H, H(5)), 3.20 (q, J = 8.1 Hz, 1 H, H-3), 2.80–2.61 (m, 2 H, 2 CH_2), 2.11 (s, 3 H, CH_3CO), 2.03–1.78 (m, 2 H, CH_2), 1.12 (d, J = 6.4 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 141.5, 128.0, 127.9, 125.4, 78.0, 75.0, 55.2, 36.9, 33.2, 32.2, 30.6, 17.4; IR (film) 2940, 1712, 1455, 1380, 1354, 1163, 1111, 1099, 1087, 750 cm^{-1}; MS (CI) m/z 233.1525 (233.1541 calcd for $C_{15}H_{20}O_2$, MH).

(±)-(2α,3α,5α)-1-(Tetrahydro-5-ethenyl-2-methyl-3-furanyl)ethanone (13e): 289 mg (60%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97–5.83 (m, 1 H, CH=C), 5.35–5.13 (m, 2 H, $C=CH_2$), 4.36–4.20 (m, 2 H, H(2) and H(5)), 3.26 (q, J = 6.1 Hz, 1 H, H(3)), 2.13 (s, 3 H, CH_3CO), 2.07 (m, 2 H, H(4)), 1.51 (d, J = 5.2 Hz, 3 H, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 138.3, 116.4, 80.1, 75.6, 55.8, 33.8, 30.8, 17.7; IR (film) 2979, 1712, 1383, 1369, 1356, 1164, 1100, 1074, 991, 923 cm^{-1}; MS (CI) m/z 155.1063 (155.1072 calcd for $C_9H_{14}O_2$, MH).

(±)-(2α,3α,5α)-1-(Tetrahydro-2-methyl-5-phenyl-3-furanyl)ethanone (13f): 432 mg (66%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.20 (m, 5 H, Ph), 4.84 (dd, J = 6.3, 9.9 Hz, 1 H, H(5)), 4.47 (m, 1 H, H(2)), 3.45 (q, J = 8.4 Hz, 1 H, H(3)), 2.28 (m, 2 H, H(4)), 2.19 (s, 3 H, CH_3CO), 1.24 (d, J = 6.6 Hz, 3 H, CH_3CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.4, 142.1, 128.3, 127.5, 126.0, 80.7, 75.7, 55.8, 36.4, 31.0, 17.7; IR (film) 2977, 1710, 1456, 1376, 1355, 1190, 1163, 1105, 1083, 1067, 1051, 1033, 759 cm^{-1}; MS (CI) m/z 205.1210 (205.1230 calcd for $C_{13}H_{16}O_2$, MH).

(±)-(2α,3α,5α)-1-(Tetrahydro-2,5-dimethyl-3-furanyl)pentanone (17): from acetal **15** (213 mg, 1.20 mmol, prepared from the major diastereomer of allylic diol **6b**) 150 mg (70%) as a colorless oil; ^1H NMR (250 MHz, $CDCl_3$) δ 4.23 (m, 1 H, H(2)), 3.96 (m, 1 H, H(5)), 3.31 (app q, J = 8.2 Hz, 1 H, H(3)), 2.43 (t, J = 7.2 Hz, 2 H, CH_2CO), 2.14–1.36 (m, 6 H), 1.34 (d, J = 5.8 Hz, 3 H, CH_3), 1.11 (d, J = 6.5 Hz, 3 H, CH_3), 0.91 (t, J = 7.2 Hz, 3 H, CH_3CH_2); IR (film) 2965, 1712, 1458, 1381, 1102 cm^{-1}; MS (CI) m/z 185 (MH, 100), 141, 99, 83.

(±)-(2α,3α,4α,5α)-1-(Tetrahydro-2,3,4-trimethyl-5-phenyl-3-furanyl)ethanone (19a). Following the procedure described for the preparation of tetrahydrofuran **13a**, a solution of the acetals **18a** (305 mg, 1.32 mmol) was treated with $SnCl_4$ (0.6 mL, 5.3 mmol) to give, after purification by flash chromatography (1:2 EtOAc–hexane), 265 mg (87%) of the tetrahydrofuran **19a** as a colorless oil, which was contaminated to the extent of 5% with the epimeric isomer **19b**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.22 (m, 5 H, Ph), 5.17 (d, J = 9.2 Hz, 1 H, H(5)), 3.82 (q, J = 66 Hz, 1 H, H(2)), 2.59–2.52 (m, 1 H, H(4)), 2.16 (s, 3 H, CH_3CO), 1.36 (d, J = 6.6 Hz, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 0.57 (d, J = 7.7 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.7, 138.9, 127.6, 126.8, 126.7, 82.5, 81.6, 61.0, 48.8, 30.8, 22.0, 14.7, 12.6. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.31; H, 8.70.

(±)-(2α,3α,4β,5α)-1-(Tetrahydro-2,3,4-trimethyl-5-phenyl-3-furanyl)ethanone (19b). Following the procedure described for the preparation of tetrahydrofuran **13a**, a solution of the acetals **18b** (174 mg, 0.75 mmol, contaminated to the extent of 5% with the isomeric acetal **18a**) was treated with $SnCl_4$ (0.4 mL, 3.0 mmol) to give, after purification by flash chromatography (1:2 EtOAc–hexane), 132 mg (76%) of the tetrahydrofuran **19b** as a colorless oil, contaminated to the extent of 5% with the epimeric isomer **19a**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.24 (m, 5 H, Ph), 4.42 (d, J = 10.1 Hz, 1 H, H(5)), 4.01 (q, J = 6.5 Hz, 1 H, H(2)), 2.65 (m, 1 H, H(4)), 2.21 (s, 3 H, CH_3CO), 1.31 (s, 3 H, CH_3), 1.23 (d, J = 6.5 Hz, 3 H, CH_3), 0.85 (d, J = 6.9 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 140.7, 128.4, 127.8, 126.5, 86.7, 83.1, 60.8, 45.5, 28.4, 18.4, 17.8, 10.6; IR (film) 2974, 1704, 1455, 1111, 1070, 1027, 759, 701 cm^{-1}; MS (CI) m/z 233.1536 (233.1540 calcd for $C_{15}H_{20}O_2$, MH).

Epimerization of 3-Acyltetrahydrofurans. Preparation of (±)-(2α,3β,5α)-1-(Tetrahydro-2-methyl-5-phenyl-3-furanyl)ethanone (14c). A solution of the tetrahydrofuran **13f** (224 mg, 1.10 mmol), 1 N methanolic KOH (1.0 mL), and MeOH (3 mL) was maintained at 23 °C for 16 h. The solution was then poured into saturated aqueous NH_4Cl (50 mL), and the mixture was concentrated to remove MeOH. The resulting aqueous suspension was extracted with CH_2Cl_2 (3 × 20 mL), and the combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated. Remaining starting material (ca. 10%) was removed by careful flash chromatography (1:2 EtOAc–hexane) to provide 136 mg (61%) of tetrahydrofuran **14c** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.19 (m, 5 H, Ph), 4.91 (t, J = 7.0 Hz, 1 H, H(5)), 4.17–4.23 (m, 1 H, H(2)), 2.92–2.84 (m, 1 H, H(3)), 2.59–2.48 and 2.10–1.99 (m, 2 H, H(4)), 2.17 (s, 3 H, CH_3CO), 1.44 (d, J = 6.1 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 141.9, 128.2, 127.3, 125.6, 80.0, 77.3, 58.4, 38.0, 29.8, 20.6; IR (film) 2974, 1710, 1452, 1371, 1365, 1360, 1173, 1133, 1099, 1058, 1028, 757 cm^{-1}; MS (CI) m/z 205.1219 (205.1228 calcd for $C_{13}H_{16}O_2$, MH).

(±)-(2α,3β,5α)-1-[Tetrahydro-2-methyl-5-(2-phenylethyl)-3-furanyl]ethanone (14b). Following the procedure described for the preparation of tetrahydrofuran **14c**, a solution of the tetrahydrofuran **13d** (129 mg, 0.56 mmol) was treated with 1 N methanolic KOH (1 mL). Remaining starting material (ca. 10%) was removed by careful flash chromatography (1:2 EtOAc–hexane) to give tetrahydrofuran **14b** (90 mg, 70%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.16 (m, 5 H, Ph), 4.05–3.96 (m, 1 H, H(2)), 3.94–3.85 (m, 1 H, H(5)), 2.82–2.71 (m, 1 H, H(3)), 2.71–2.60 (m, 2 H, CH_2Ph), 2.23–2.19 (m, 1 H), 2.18 (s, 3 H, CH_3CO), 2.00–1.68 (m, 3 H), 1.36 (d, 3 H, J = 6.1 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.3, 141.8, 128.3, 125.8, 78.2, 58.7, 37.3, 35.2, 32.3, 29.8, 20.8; IR (film) 2973, 2931, 1709, 1455, 1375, 1383, 1357, 1173, 1107 cm^{-1}.

(±)-(2α,3β,5α)-1-(Tetrahydro-2-methyl-5-ethylfuranyl)ethanone (14a). Following the procedure described for the preparation of tetrahydrofuran **14c**, a solution of **13b** (90 mg, 0.60 mmol) was treated with 1 N methanolic KOH (1 mL). Purification by flash chromatography (5:95 MeOH–CH_2Cl_2) gave a mixture (71 mg, 79%) of tetrahydrofuran **14a** and starting material (ca. 10%) as a colorless oil. Data for **14a**: ^1H NMR ($CDCl_3$, 300 MHz) δ 4.05–4.00 (m, 1 H, OC*H*CH_3), 3.84–3.77 (m, 1 H, OC*H*CH_2), 2.79–2.71 (m, 1 H, C*H*$COCH_3$), 2.20 (s, 3 H, CH_3CO), 2.23–2.17 (m, 2 H, CH_2), 1.82–1.43 (m, 2 H), 1.34 (d, J = 6.8 Hz, 3 H, CH_3), 0.93 (t, J = 7.1 Hz, 3 H, CH_3CH_2); MS (CI) m/z 157.1218 (157.1228 calcd for $C_9H_{16}O_2$, MH).

Rearrangement of 4-Ethenyl-2-heteromethyl-4,5-dimethyl-1,3-dioxolanes with $SnCl_4$ in CH_3NO_2. Preparation of (±)-(2α,3α,5α)-1-[Tetrahydro-2-methyl-5-(bromomethyl)-3-furanyl]ethanone (25b). $SnCl_4$ (0.8 mL, 6.4 mmol) was added to a solution of the acetals **22b** (475 mg, 2.15 mmol) and $MeNO_2$ (8 mL) at −23 °C. The solution was warmed to 23 °C and maintained for 3 h. Saturated aqueous NaCl (10 mL) was then added, and the mixture was concentrated to remove $MeNO_2$. The resulting aqueous suspension was extracted with CH_2Cl_2 (3 × 20 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (1:1 EtOAc–hexane) to provide 156 mg (33%) of the crude tetrahydrofuran **25b** (90% pure by ^1H NMR analysis) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.45–4.36 (m, 1 H, H(2)), 4.19–4.10 (m, 1 H, H(5)), 3.56–3.46 (m, 2 H, CH_2Br), 3.44–3.34 (m, 1 H, H(3)), 2.22–2.07 (m, 2 H, CH_2), 2.19 (s, 3 H, CH_3CO), 1.15 (d, J = 6.5 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 206.7, 78.1, 76.1, 55.0, 34.6, 30.9, 17.6; IR (film) 2977, 1711, 1702, 1380, 1374, 1357, 1187, 1113, 1090, 1071, 1037 cm^{-1}; MS (CI) m/z 221.0167 (221.0177 calcd for $C_8H_{13}O_2Br$, MH).

The other acetyltetrahydrofurans **25** were prepared in a similar fashion as summarized in Table IV.

(±)-(2α,3α,5α)-1-[Tetrahydro-2-methyl-5-(chloromethyl)-3-furanyl]ethanone (25a): 29 mg (35% recovered mass) of the crude tetrahydrofuran **25a**; repeated flash chromatography (1:1 ethyl acetate–hexane) provided 9 mg (11%) of the tetrahydrofuran **25a** (90% pure by ^1H NMR analysis) as a brown oil; ^1H NMR (300 MHz, $CDCl_3$) δ 4.43–4.34 (m, 1 H, H(2)), 4.22–4.09 (m, 1 H, H(5)), 3.73–3.56 (m, 2 H, CH_2Cl), 3.36 (q, J = 7.8 Hz, 1 H, H(3)), 2.19 (s, 3 H, CH_3CO), 2.12 (app t, J = 7.9 Hz, 2 H, CH_2), 1.16 (d, J = 6.5 Hz, 3 H, CH_3CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.1, 78.6, 77.4, 76.3, 55.2, 46.5, 31.5, 31.1, 17.8; IR (film) 2974, 1713, 1375, 1113, 1095, 1074 cm^{-1}; MS (CI) m/z 177.0660 (177.0682 calcd for $C_8H_{13}O_2Cl$, MH).

(±)-(2α,3α,5α)-1-[Tetrahydro-2-methyl-5-[(benzyloxy)methyl]-3-furanyl]ethanone (25d): 44 mg (59%) of the tetrahydrofuran **25d**, which was contaminated to the extent of 10% by the acetyl epimer. These could be separated by careful flash chromatography (1:1 EtOAc–hexane).

Tetrahydrofuran 25d: ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.23 (m, 5 H, Ph), 4.59 (dd, J = 12.1, 14.4 Hz, 2 H, OCH_2Ph), 4.36–4.27 (m, 1 H, H(2)), 4.17–4.05 (m, 1 H, CH), 3.61 (m, 2 H, CH_2), 3.24 (q, J =

8.0 Hz, 1 H, H(3)), 2.16 (s, 3 H, CH_3CO), 2.06–1.96 (m, 2 H, CH_2), 1.15 (d, J = 6.4 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7, 138.1, 128.3, 127.7, 127.5, 78.0, 76.1, 73.4, 72.7, 55.2, 30.9, 30.3, 17.6; IR (film) 2922, 2896, 2892, 2864, 1712, 1382, 1167, 1101, 1093, 736 cm^{-1}; MS (CI) m/z 249.1485 (249.1490 calcd for $C_{15}H_{20}O_3$, MH).

Acetyl epimer of 25d: ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.21 (m, 5 H, Ph), 4.58 (dd, J = 12.2, 16.2 Hz, 2 H, OCH_2Ph), 4.18–4.13 (m, 1 H), 4.08–4.03 (m, 2 H), 3.50 (app d, J = 4.9 Hz, CH_2OBn), 2.80–2.76 (m, 1 H, H(3)), 2.19 (s, 3 H, CH_3CO), 2.20–2.00 (m, 2 H, CH_2), 1.15 (d, J = 6.4 Hz, 3 H, CH_3).

(±)-(2α,3α,5α)-1-[Tetrahydro-2-methyl-5-[(benzoyloxy)methyl]-3-furanyl]ethanone (25e). Following the procedure described for the preparation of tetrahydrofuran **25b**, a solution of the acetals **22e** (431 mg, 1.64 mmol) was treated with $SnCl_4$ (0.1 mL, 0.9 mmol) to give, after purification by flash chromatography (1:2 EtOAc–hexane), 249 mg (58%) of the tetrahydrofuran **25e**, which was contaminated to the extent of 10% by the acetyl epimer. These could be separated by careful flash chromatography (1:1 EtOAc–hexane).

Tetrahydrofuran 25e: ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, J = 1.0, 7.1 Hz, 2 H, Ph), 7.58–7.53 (m, 1 H, Ph), 7.46–7.26 (m, 2 H, Ph), 4.54 (dd, J = 3.6, 8.0 Hz, 1 H), 4.43–4.38 (m, 2 H), 4.35–4.25 (m, 1 H), 3.37 (q, J = 8.0 Hz, 1 H, H(3)), 2.18–2.07 (m, 2 H, CH_2), 2.19 (s, 3 H, CH_3CO), 1.16 (d, J = 6.5 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 166.4, 133.0, 130.0, 129.9, 128.3, 76.1, 66.6, 55.2, 31.5, 31.0, 29.8, 22.6, 17.8, 14.1; IR (film) 1717, 1713, 1452, 1315, 1274, 1169, 1114, 1093, 1071 cm^{-1}; MS (CI) m/z 263.1262 (263.1283 calcd for $C_{15}H_{18}O_4$, MH).

Acetyl epimer of 25e: ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, J = 1.1, 7.0 Hz, 2 H, Ph), 7.58–7.52 (m, 1 H, Ph), 7.51–7.26 (m, 2 H, Ph), 4.43–4.30 (m, 3 H), 4.16–4.08 (m, 1 H), 2.81–2.89 (m, 1 H, H(3)), 2.39–2.00 (m, 2 H, CH_2), 2.22 (s, 3 H, CH_3CO), 1.37 (d, J = 6.0 Hz, 3 H, CH_3).

(±)-(2α,3α,5α)-1-[Tetrahydro-2-methyl-5-(azidomethyl)-3-furanyl]ethanone (25c): 20 mg (40%) of the tetrahydrofuran **25c** (85% pure by ^1H NMR analysis) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 4.38 (m, 1 H, H(2)), 4.07 (m, 1 H, H(5)), 3.44 (m, 2 H, CH_2N_3), 3.37 (q, J = 8.1 Hz, 1 H, H(3)), 2.20 (s, 3 H, CH_3CO), 2.07 (m, 2 H, CH_2), 1.10 (d, J = 6.1 Hz, 3 H, CH_3); IR (film) 2979, 2101 (intense), 1712, 1381, 1355, 1280, 1243, 1166, 1114, 1090 cm^{-1}.

Rearrangement of Ketals. Preparation of (±)-1-(Tetrahydro-2,3,5,5-tetramethyl-3-furanyl)ethanone (27a). $SnCl_4$ (0.5 mL, 4.3 mmol) was added to a solution of the ketals **26a** (720 mg, 4.28 mmol) and CH_2Cl_2 (10 mL) at −78 °C. The mixture was warmed to 23 °C over 1 h, then recooled to −78 °C, quenched with Et_3N (1.0 mL, 5 mmol), diluted with saturated aqueous $NaHCO_3$, (5 mL), and warmed to 23 °C over 30 min. The mixture was extracted with CH_2Cl_2 (2 × 5 mL), the combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (1:1 EtOAc–hexane) to provide 554 mg (77%) of the tetrahydrofuran **27a** as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 3.87 (q, J = 6.6 Hz, 1 H, H(2)), 2.33 (d, J = 6.6 Hz, 3 H, CH_3), 2.15 (s, 3 H, $COCH_3$), 1.59 (d, J = 13.5 Hz, 1 H, H(4)), 1.38 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.10 (d, J = 6.6 Hz, 3 H, CH_3); IR (film) 2974, 1704, 1383, 1106; MS (EI) m/z 170 (M).

(*E*)-3-Butyl-3-penten-2-one (30) from Attempted Rearrangement of (±)-4-Ethenyl-4-butyl-2,2,5-trimethyl-1,3-dioxolane (28). Following the procedure described for the preparation of tetrahydrofuran **27a**, a solution of the ketals **28** (1.00 g, 5.10 mmol) was treated with $SnCl_4$ (0.6 mL, 5.1 mmol) to give, after purification by flash chromatography (1:4 EtOAc–hexane), 458 mg (67%) of the enone **30** (95% pure by ^1H NMR analysis) as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 6.72 (q, J = 6.9 Hz, 1 H, CH=C), 2.31–2.26 (m, 5 H, CH_3CO and CH_2C=C), 1.87 (d, J = 7.0 Hz, 3 H, CH_3), 1.33–1.24 (m, 4 H), 0.90 (t, J = 6.9 Hz, 3 H, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 144.1, 137.9, 31.4, 25.7, 25.1, 23.1, 14.7, 14.0; IR (film) 2958, 1669, 1267 cm^{-1}; MS (CI) m/z 141 (MH, 100), 140, 139, 125, 99, 83.

D. Preparation of Optically Active 3-Acyltetrahydrofurans. (4*R*,5*R*)- and (4*S*,5*R*)-4-(1-Phenylethenyl)-2,2,4,5-tetramethyl-1,3-dioxolane ((5*R*)-26b). A mixture of the diol (2*R*)-**6d** (1.35 g, 7.02 mmol), 2-methoxypropene (2.0 mL, 21 mmol), *p*-toluenesulfonic acid (50 mg), and CH_2Cl_2 (20 mL) and $MgSO_4$ (2.0 g) was stirred at 23 °C for 15 h. The solution was then poured into saturated aqueous $NaHCO_3$ (40 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (CH_2Cl_2) to provide 1.32 g (81%) of a yellow oil, which was a 2:1 mixture of the diastereomeric ketals (5*R*)-**26b**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.20 (m, 5 H, Ph), 5.46 and 5.43 (d, J = 1.5 Hz, 1 H, C=CHH), 5.26 and 5.05 (d, J = 1.5 Hz, 1 H, C=CH*H*), 4.26 and 4.08 (q, J = 6.4 Hz, 1 H, CHOR), 1.52 and 1.43 (s, 3 H, CH_3), 1.46 and 1.28 (s, 3 H, CH_3), 1.40–1.10 (m, 6 H, 2 CH_3); IR (film) 2987, 1379, 1253, 1217, 1189, 1103 cm^{-1}; MS (CI) m/z 233.1576 (233.1541 calcd for $C_{15}H_{20}O_2$, MH). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.62; H, 8.67.

The racemic acetonides **26a** and **26b** were prepared in 92–97% yield in a similar fashion. Experimental details and characterization data can be found in the supplementary material.

(−)-1-(Tetrahydro-2,5,5-trimethyl-3-phenyl-3-furanyl)ethanone ((−)-27b). Following the procedure described for the preparation of tetrahydrofuran **13a**, a solution of the ketals (5*R*)-**26b** (521 mg, 2.25 mmol) was treated with $SnCl_4$ (0.8 mL, 6.7 mmol) to give, after purification by flash chromatography (1:2 EtOAc–hexane), 488 mg (94%) of the tetrahydrofuran (−)-**27b** (95% pure by ^1H NMR analysis) as a colorless oil: $[\alpha]_D$ −284.9 (*c* 1.2, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.23 (m, 5 H, Ph), 4.81 (q, J = 6.5 Hz, 1 H, H(2)), 2.98 (d, J = 13.0 Hz, 1 H, CH_2), 1.93 (d, J = 13.0 Hz, 1 H, CH_2), 1.83 (s, 3 H, CH_3CO), 1.39 (s, 3 H, CH_3), 1.35 (d, J = 6.5 Hz, 3 H, CH_3), 1.00 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 142.3, 129.0, 127.1, 126.8, 79.8, 76.5, 68.8, 48.1, 30.1, 29.1, 29.0, 18.5; IR (film) 2974, 1709, 1354, 1111, 702 cm^{-1}; MS (CI) m/z 233.1560 (233.1540 calcd for $C_{14}H_{20}O_2$, MH). Anal. Calcd for $C_{14}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.66; H, 8.68.

(−)-1-(Tetrahydro-2,5,5-trimethyl-3-phenyl-3-furanyl)ethanols ((−)-31a and (−)-31b). Sodium borohydride (500 mg) was added to a solution of the ketone (−)-**27b** (439 mg, 1.89 mmol) and MeOH (5 mL), and the mixture was maintained at 23 °C for 1 h. Saturated aqueous NH_4Cl (20 mL) was then added, and the mixture was concentrated to remove MeOH. The resulting aqueous suspension was extracted with CH_2Cl_2 (3 20 mL). The combined CH_2Cl_2 extracts were dried and concentrated to give 441 mg (99%) of a colorless oil, which was a 3:2 mixture of the diastereomeric alcohols. The diastereomers were separated by flash chromatography (1:4 EtOAc–hexane), and the less polar fraction provided 112 mg (26%) of the minor diastereomer (−)-**31b** (95% pure by ^1H NMR analysis) as a colorless oil: $[\alpha]_D$ −42.9 (*c* 0.66, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.20 (m, 5 H, Ph), 4.37 (q, J = 6.1 Hz, 1 H, CH), 4.18 (q, J = 6.4 Hz, 1 H, CH), 3.03 (br s, 1 H, OH), 2.50 (d, J = 13.4 Hz, 1 H, CH_2), 2.32 (d, J = 13.4 Hz, 1 H, CH_2), 1.59 (d, J = 6.4 Hz, 3 H, CH_3CH), 1.45 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 0.89 (d, J = 6.1 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.0, 128.2, 126.9, 126.3, 81.1, 78.7, 70.3, 57.5, 43.5, 28.3, 27.9, 18.6, 15.6; IR (film) 3494, 2975, 1388, 1371, 1267, 1115, 1092, 1081, 758 cm^{-1}; MS (CI) m/z 235.1699 (235.1700 calcd for $C_{15}H_{22}O_2$, MH).

The more polar fraction provided 308 mg (70%) of the major diastereomer (−)-**31a** as a colorless oil: $[\alpha]_D$ −29.8 (*c* 1.65, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5 H, Ph), 4.48 (q, J = 6.5 Hz, 1 H, CH), 4.10–4.05 (m, 1 H, CH), 2.36 (d, J = 13.4 Hz, 1 H, CH_2), 2.10 (d, J = 13.4 Hz, 1 H, CH_2), 1.56 (d, J = 6.5 Hz, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.09 (d, J = 6.3 Hz, 3 H, CH_3), 1.08 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 128.1, 127.8, 126.4, 80.6, 78.0, 69.8, 58.3, 46.8, 29.7, 28.1, 19.9, 18.0; IR (film) 3442, 3433, 3427, 3423, 2977, 1267, 1114, 737 cm^{-1}; MS (CI) m/z 235.1705 (235.1700 calcd for $C_{15}H_{22}O_2$, MH).

Mosher Esterification of the Major Alcohol Diastereomer (−)-31a. A mixture of alcohol (−)-**31a** (33 mg, 0.14 mmol), DCC (116 mg, 0.544 mmol), (*R*)-(+)-MPTA (99 mg, 0.42 mmol), DMAP (3 mg, 0.03 mmol), and CH_2Cl_2 (1 mL) was maintained at 23 °C for 20 h. The mixture was then poured into 1 N HCl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined 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 to provide 55 mg (87%) of the ester (+)-**32**, a single diastereomer, as a colorless oil; $[\alpha]_D$ +6.10 (*c* 1.0, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.04 (m, 10 H, 2 Ph), 5.64 (q, J = 6.1 Hz, 1 H, CH), 4.21 (q, J = 6.6 Hz, 1 H, CH), 3.20 (s, 3 H, OCH_3), 2.47 (d, J = 14.1 Hz, 1 H, CH_2), 2.20 (d, J = 14.1 Hz, 1 H, CH_2), 1.36 (d, J = 8.4 Hz, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 142.3, 131.7, 129.3, 128.3, 127.4, 127.2, 126.6, 80.6, 87.5, 76.4, 56.9, 54.9, 44.6, 29.1, 27.9, 17.0, 15.9; IR (film) 2979, 1744, 1740, 1265, 1241, 1182, 1170, 1115, 1018, 735 cm^{-1}; MS (CI) m/z 451.2073 (451.2095 calcd for $C_{25}H_{29}O_4F_3$, MH).

Analysis of diastereomeric purity was performed with use of 500-MHz ^1H NMR by comparison to the MPTA ester diastereomer mixture derived from racemic **31a**. This mixture of MPTA esters exhibited additional well-resolved resonances diagnostic of the alternate diastereomer at δ 5.43 (q, J = 6.2 Hz, 1 H, CH), 4.28 (q, J = 6.5 Hz, 1 H, CH), and 3.25 (s, 3 H, OCH_3). Integration of these regions in the 500-MHz NMR spectrum of (−)-**31a** indicated diastereomeric purity to be at least 95%.

E. Asymmetric Synthesis of (+)-Muscarine. Preparation of the (2*S*,3*S*,5*S*)- and (2*S*,3*R*,5*S*)-1-[Tetrahydro-2-methyl-5-[(benzoyloxy)methyl]-3-furanyl]ethanones ((2*S*)-25e) from Acetal (5*S*)-22e. Following the procedure described for the preparation of tetrahydrofuran **25a** a solution of the acetals (5*S*)-**22e** (431 mg, 1.64 mmol) was treated with

$SnCl_4$ (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.

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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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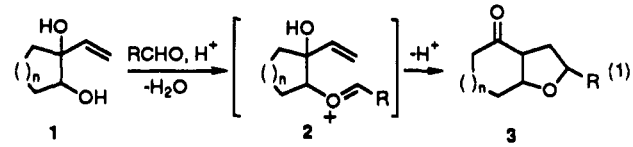
Abstract: A wide variety of cis-fused hexahydrocyclopenta[*b*]furan-4-ones (**3**, n = 0), hexahydro-4(2*H*)-benzofuranones (**3**, n = 1), and octahydrocyclohepta[*b*]furan-4-ones (**3**, n = 2) can be prepared with high levels of stereocontrol by the title reaction. The scope and limitations of this 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



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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-*

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

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