6 as a white, crystalline solid (590 mg, 59%). Crystallization from ether–dichloromethane gave colorless rectangular prisms: mp 104–105 °C; IR (KBr) ν 3027, 2940, 2866, 1715, 1424, 1194, 1172, 878, 789, 723, 700 cm^{-1}; ^{1}H NMR δ 5.75 (m, 1 H), 5.50 (m, 1 H), 2.60 (m, 1 H), 2.54 (m, 1 H), 2.46 (br, 1 H), 2.39 (m, 1 H), 2.30 (m, 2 H), 2.23 (m, 1 H), 2.11 (m, 2 H), 2.06 (m, 1 H), 1.7–1.4 ppm (complex, 4 H); ^{13}C NMR δ 217.7 (s), 129.7 (d, J = 158 J Hz), 127.1 (d, J = 156 Hz), 53.2 (d, J = 145 Hz), 49.9 (d, J = 141 Hz), 47.8 (d, J = 144 Hz), 46.6 (d, J = 138 Hz), 45.3 (d, J = 144 Hz), 45.1 (d, J = 138 Hz), 43.1 (d, J = 132 Hz), 33.9 (d, J = 137 Hz), 27.9 (t, J = 130 Hz), 27.4 (t, J = 131 Hz), 23.1 ppm (t, J = 131 Hz); m/e 200 (P$^+$, 100). Anal. Calcd for $C_{14}H_{16}O$: C, 83.95; H, 8.05. Found: C, 84.19; H, 7.96.

Single-crystal X-ray diffraction analysis of (±)-pentacyclo[6.6.0.0^{5,14}.0^{7,12}.0^{9,13}]tetradec-2-en-6-one (6): $C_{14}H_{16}O$, FW = 200.3, tetragonal space group $I4$, a = 17.708 (3), c = 6.360 (1) Å, V = 1994.5 (6) Å^3, Z = 8, ρ_{calc} = 1.334 mg mm^{-3}, λ(Mo Kα) = 0.710 73 Å, μ = 0.076 mm^{-1}, F(000) = 864, T = 223 K. A clear, colorless, 0.16 × 0.27 × 0.48 mm crystal in the shape of a lath was used for data collection on an automated Siemens R3m/V diffractometer equipped with an incident beam monochromator. Lattice parameters were determined from 25 centered reflections within 20.8 ≤ 2θ ≤ 30.2°. The lattice parameters were determined from 25 centered reflections within 20.8 ≤ 2θ ≤ 30.2°. The data collection range of hkl was: $-1 \le h \le 19$, $0 \le k \le 19$, $0 \le l \le 6$ with $[(\sin\theta)/\lambda]_{max}$ = 0.538. Three standards, monitored after every 97 reflections, exhibited random variations with deviations up to ±2.0% during the data collection. A set of 863 reflections was collected in the $\theta/2\theta$ scan mode, with scan width $[2\theta(K_{\alpha1}) - 0.45]$ to $[2\theta(K_{\alpha2}) + 0.45]$° and ω scan rate (a function of count rate) from 5.0°/min to 30.0°/min. There were 813 *unique* reflections, and 777 were observed with $F_o > 3\sigma(F_o)$. The structure was solved and refined with the aid of the SHELXTL system of programs.[10] The full-matrix least-squares refinement varied 201 parameters namely atom coordinates and anisotropic thermal parameters for all non-H atoms, atom coordinates, and isotropic thermal parameters for the hydrogen atoms. Final residuals were R = 0.024 and R_w = 0.029 with final difference Fourier excursions of 0.13 and −0.14 e Å^{-3}.

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Registry No. 1, 13002-57-8; 4, 130011-60-8; 4 (acetate isomer), 129986-79-4; 5, 130011-61-9; 6, 129986-80-7.

Supplementary Material Available: Tables of atomic coordinates, bond distances and angles, and anisotropic thermal parameters (4 pages). Ordering information is given on any current masthead page.

(10) Sheldrick, G. M. *SHELXTL80. An Integrated System for Solving, Refining, and Displaying Crystal Structures from Diffraction Data*; Univ. of Gottingen: Federal Republic of Germany, 1980.

On the Mechanism of Lewis Acid Mediated Nucleophilic Substitution Reactions of Acetals[1]

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Lewis acid mediated nucleophilic substitution of acetals can occur by direct displacement (S_N2) or oxocarbenium ion (S_N1) mechanisms. With acyclic acetals, stereoselectivity increases with increasing steric bulk of the alkoxy group and with increasing polarity of the reaction medium. The enhanced stereoselectivity observed with acetals of secondary and tertiary alcohols is explained by perturbation of the approach trajectory of the nucleophilic alkene as it attacks the oxocarbenium ion. Highest stereoselectivity is seen in the reaction of 2-(1-phenylethyl)-4,4,5,5-tetramethyl-1,3-dioxolane (**4**) with enol silane **5**; only one diastereomeric product (**9s**) is obtained, even in the relatively nonpolar solvent CH_2Cl_2. The $TiCl_4$-mediated reactions of cyclic acetals **18c**, **18t**, **25**, and **28** with silyl enol ether **5** show that in these systems the substitution does not occur by the S_N2 mechanism.

Introduction

The Lewis acid mediated reaction of acetals with nucleophiles such as silyl enol ethers and allylsilanes is a powerful method for carbon–carbon bond formation[3] and has proven to be highly stereoselective in many cases.[4] Detailed mechanistic studies are scarce, although some mechanistic rationales have been put forward for these and related reactions.[3o,4a,c,5-9] Recent communications from Denmark and co-workers provide strong evidence for a mechanistic divergence in an intramolecular version of the reaction[10] and give information pertaining to the structures

(1) Paper 52 in the series Acyclic Stereoselection. For paper 51, see: Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5966.

(2) (a) Berkeley. (b) Nagoya. (c) San Francisco.

(3) For example, see: (a) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941. (b) Tsunoda, T.; Suzuki, M.; Noyori, R. *Ibid.* **1980**, *21*, 71. (c) Sakurai, H.; Sasaki, K.; Hosomi, A. *Tetrahedron Lett.* **1981**, *22*, 745. (d) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899. (e) Sakurai, H. *Pure. Appl. Chem.* **1982**, *54*, 1. (f) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4876. (g) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1982**, *23*, 2281. (h) Danishefsky, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *37*, 3803. (i) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383. (j) Keck, G. E.; Enholm, E. J.; Kachensky, D. F. *Ibid.* **1984**, *25*, 1867. (k) Mukaiyama, T.; Nagaoka, H.; Murakami, M.; Oshima, M. *Chem. Lett.* **1985**, 977. (l) Hosomi, A.; Ando, M.; Sakurai, H. *Tetrahedron Lett.* **1986**, 365. (m) Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082. (n) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *Ibid.* **1987**, *109*, 8117. (o) Murata, S.; Suzuki, M.; Noyori, R. *Ibid.* **1988**, *44*, 4259.

(4) (a) Bartlett, P. A.; Johnson, W. S.; Elliot, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. (b) Choi, V. M. F.; Elliot, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 591. (c) Maruoka, K.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 668; *Angew. Chem.* **1985**, *97*, 670. (d) Berlan, J.; Besace, J.; Prat, D.; Pourcelot, G. *J. Organomet. Chem.* **1984**, *264*, 399.

(5) Silverman, R.; Edington, C.; Elliott, J. D.; Johnson, W. S. *J. Am. Chem. Soc.* **1987**, *52*, 180 and references therein.

(6) Mori, A.; Fujiwara, J.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581.

(7) (a) Imwinkelried, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 765. (b) Seebach, D. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: New York, 1986; p 191.

(8) Mukaiyama, T.; Ohshima, M.; Miyoshi, N. *Chem. Lett.* **1987**, 1121.

(9) Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116.

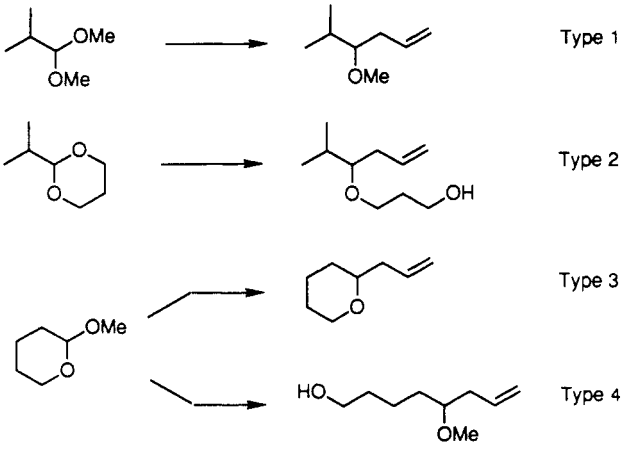
(10) Denmark, S. E.; Wilson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475.

0022-3263/90/1955-6107$02.50/0

Table I. Stereochemistry of Acetal Substitution Reactions

entry	acetal	concn, M	solvent	temp, °C	syn/anti	products	yield, %
1	1	0.2	CH_3CN	−40 to 0	4.4:1	**6s:6a**	92
2	1	0.2	CH_3CN	0	2.9:1	**6s:6a**	100
3	1	0.2	CH_2Cl_2	−78	2.5:1	**6s:6a**	84
4	1	0.02	CH_2Cl_2	−78	2.6:1	**6s:6a**	89
5	1	0.2	toluene	−78	1.3:1	**6s:6a**	83
6	1	0.2	hexane	−78	1.3:1	**6s:6a**	31
7	2	0.2	CH_2Cl_2	−78	3.6:1	**7s:7a**	90
8	3	0.2	CH_2Cl_2	−78	7.3:1	**8s:8a**	82
9	3	0.2	toluene	−78	2.2:1	**8s:8a**	82
10	4	0.2	CH_2Cl_2	−78	>50:1	**9s**	94

Scheme I

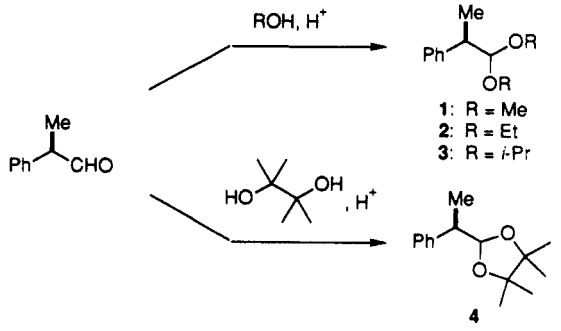


of complexes of cyclic acetals with BF_3 in various solvents.[11] In this paper, we report two sets of experiments that provide information about the mechanism of the intermolecular reaction.[12]

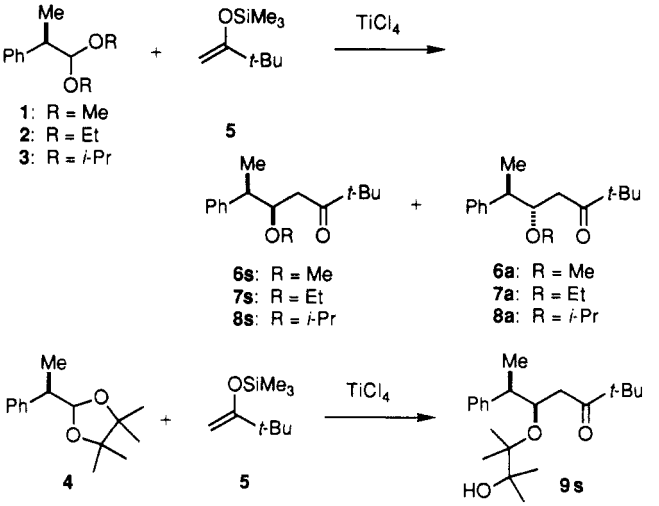
Intermolecular substitution reactions of acetals can be classified in four groups, depending on the structure of the acetal and which alkoxy group is replaced. These are illustrated in Scheme I for hypothetical reactions with allyltrimethylsilane. In this study, we have examined reactions of type 1 and type 2. Our results also indicate a mechanistic divergence; acetal substitution can occur by S_N1 (oxocarbenium ion) or S_N2 mechanisms. The operative mechanism depends on the size of the acetal alkoxy group and the polarity of the solvent. Greater steric bulk in the acetal alkoxy group and more polar solvent promote ionization to the oxocarbenium ion.

Results

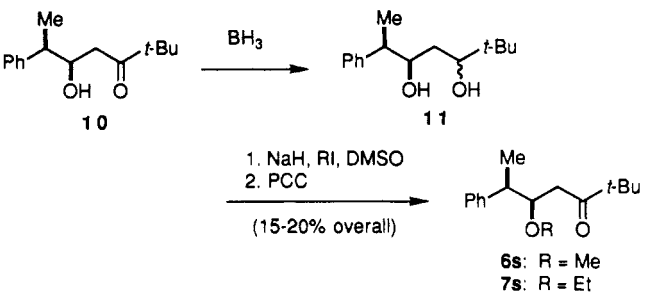
A. Effect of Alkoxy Group on Stereochemistry of Type 1 Acetal Reactions. Acetals 1–3 were prepared by reaction of 2-phenylpropanal with methanol, ethanol, and 2-propanol, respectively. The *tert*-butyl acetal cannot be prepared by this method because of elimination to give an enol ether. However, 2-phenylpropanal reacts with pinacol to give acetal 4, a reasonable substitute for the di-*tert*-butyl acetal.



Reactions of acetals 1–4 were carried out with the trimethylsilyl enol ether derived from pinacolone. Reactions were carried out in methylene chloride with $TiCl_4$ as catalyst. Results are summarized in Table I.



The major isomers from reaction of acetals 1 and 2 with 5 were shown to be the syn isomers **6s** and **7s** by independent synthesis from aldol **10**. An attempt to prepare alkoxy ether **8s** by this method failed, so the structure of the major isomer from reaction of acetal 3 with 5 is assigned by analogy.



The stereochemistry of the sole isomer from the reaction of acetal 4 with 5 is inferred to be syn on the basis of the following. As shown in Scheme II, 4 reacts with 12 to give a mixture of diastereomeric products in a ratio of 10:1. This mixture was reduced to a diol, which was treated with trimethylsilyl bromide to remove the pinacol group. The major product of this mixture was identical with the diol (15) produced from authentic syn β-hydroxy thioester 16, obtained by the $TiCl_4$-mediated reaction of 12 with 2-phenylpropanal.

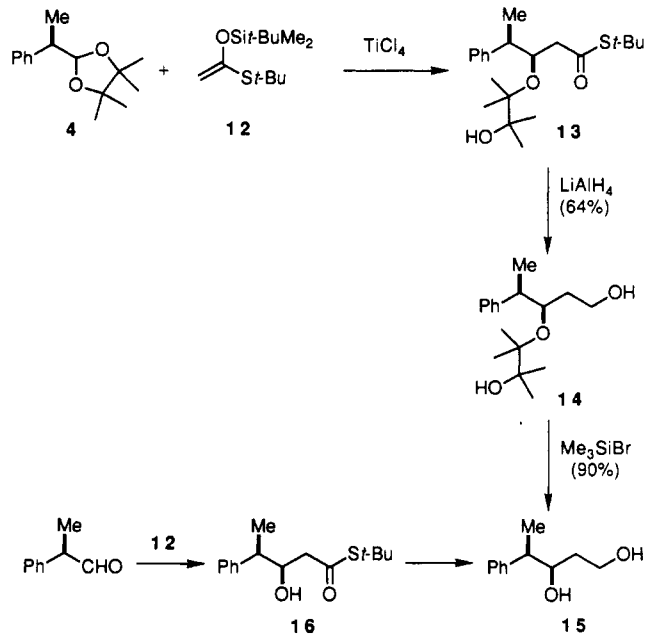
(11) Denmark, S. E.; Wilson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258.

(12) In the course of the review and revision of this manuscript, we became aware that Denmark and co-workers have carried out similar experiments and reached essentially the same mechanistic conclusions as are set forth in this paper. Professor Denmark's results will be published separately.

Table II. Stereochemistry of Acetal Substitution Reactions (Scheme IV)

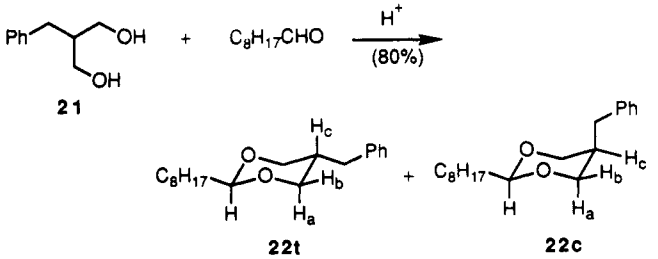
entry	acetal	26:27	29:30	36:37	39:40	yield, %	31:32	33:34	yield, %
1	**25**	83:17	–	–	–	69	82:18	–	97
2	**28**	–	70:30	–	–	86	–	71:29	86
3	**35**	–	–	95:5	–	94	95:5	–	>99
4	**38**	–	–	–	89:11	>99	–	89:11	84

Scheme II



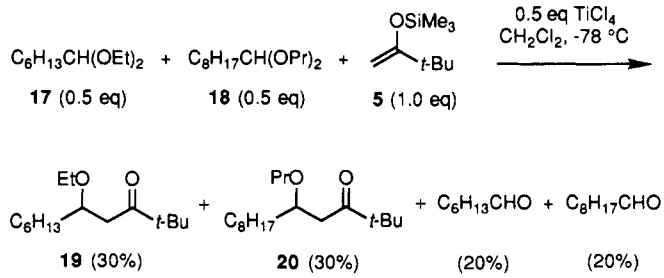
One further experiment was carried out. As shown in Scheme III, an equimolar mixture of acetals **17** and **18** was treated with silyl enol ether **5** and $TiCl_4$ in methylene chloride. Under these conditions, β-alkoxy ketones **19** and **20** were each obtained in 30% yield; heptanal and nonanal were each obtained in 20% yield. Crossover products in which ethoxy is associated with C_6H_{13} or propoxy with C_8H_{17} were not observed.

B. Stereochemistry of Type 2 Acetal Reactions. Acetals **22t** and **22c** were prepared by reaction of diol **21** with nonanal. The configurations of the two acetals were readily established by the vicinal ^1H NMR coupling constants; J_{ac} is 10.5 Hz in **22t** and <1.0 in **22c**.

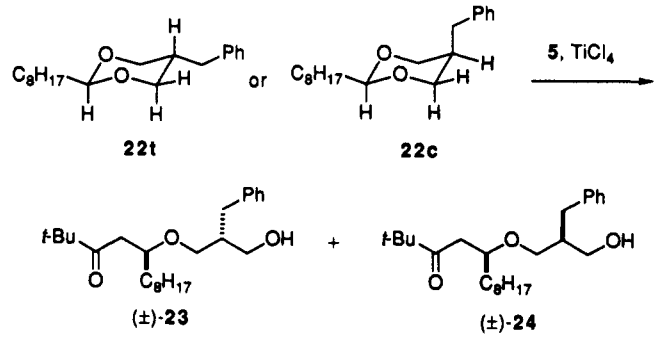


The $TiCl_4$-promoted reactions of both **22t** and **22c** with silyl enol ether **5** occurred in good yield to give 1:1 mixtures of diastereomers (±)-**23** and (±)-**24**. To fully interpret this result, it was necessary to carry out control experiments to show that the observed 1:1 ratio of products was not the result of acetal equilibration. In fact, reaction of **22c** with $TiCl_4$ in CH_2Cl_2 at −78 °C for 15 min followed by $NaHCO_3$ quench at the same temperature gave rise to a 1:1 mixture of **22c** and **22t**. When **22t** was treated with 2 equiv of **5** and 0.2 equiv of $TiCl_4$ under the same conditions, there was obtained in 50% yield a 1:1 mixture of the *R*,S** and *S*,S** diastereomeric products [(±)-**23** and (±)-**24**] along with 50% of unchanged **22t**. Similar treatment of **22c** afforded in 33% yield a 1:1 mixture of (±)-**23** and (±)-**24**

Scheme III



along with 67% yield of unchanged **22c**. These controls show that, although **22t** and **22c** *are* equilibrated under the reaction conditions (presumably *via* the oxocarbenium ion), the equilibration is slower than reaction with **5**.[13]



Similar experiments were carried out with acetals **25** and **28**, derived from *meso*-2,4-pentanediol (Scheme IV). For comparison, identical experiments were carried out with acetals **35** and **38**, derived from (*R*,R**)-2,4-pentanediol and the same two aldehydes. In all four experiments the initial hydroxy ketones were oxidized to diketones. Mixtures **26**/**27** and **36**/**37** each gave diketones **31** and **32**, whereas mixtures **29**/**30** and **39**/**40** gave diketones **33** and **34**. For each of the four experiments, diastereomer ratios were determined by ^1H NMR and GC. Results are summarized in Table II.

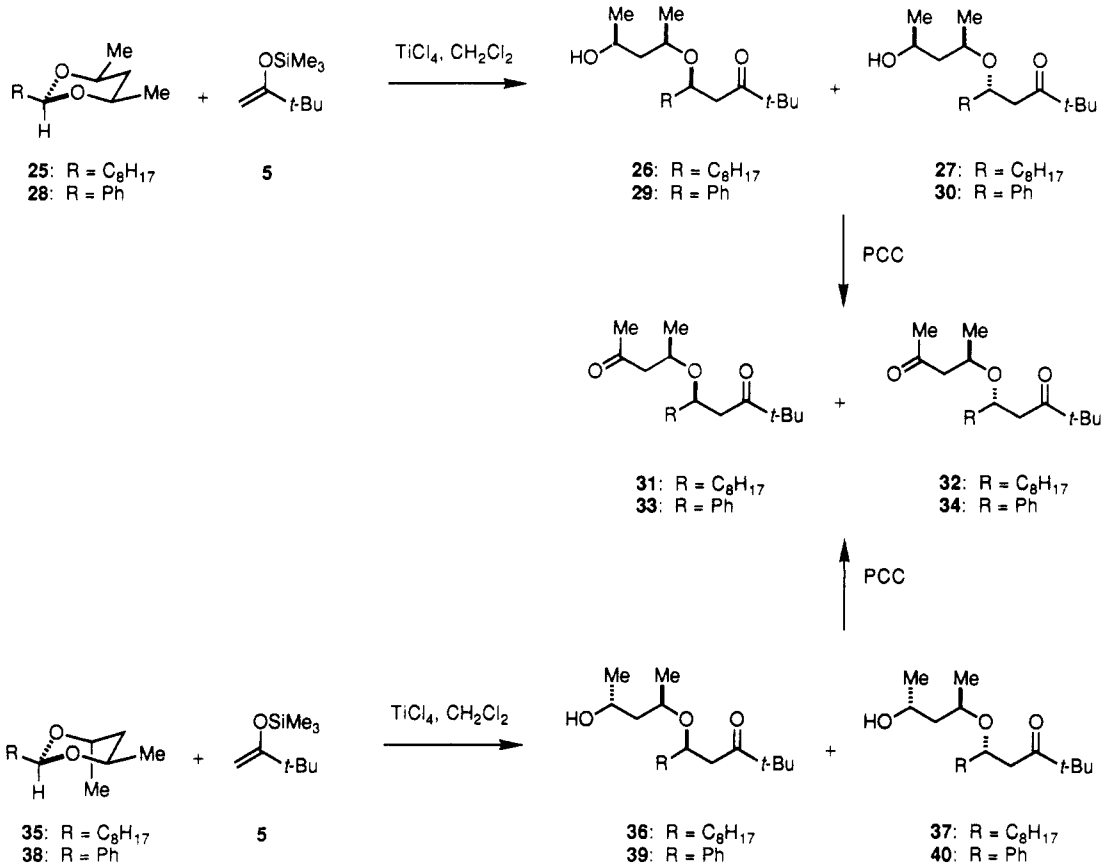
Discussion

A general mechanistic scheme for type 1 acetal reactions is put forth in Scheme V for acetals for 2-phenylpropanal (A). If products D and E result from S_N1 attack on an oxocarbenium ion, our previous work suggests that the diastereofacial preference of F should increase with increasing steric bulk of R.[14] If D and E arise from B and C by the S_N2 mechanism, the effect of R on the stereochemistry of the substitution reaction is harder to predict. If the decomplexation of B and C is slower than substitution, the D/E ratio would depend on the relative rates of complexation of the diastereotopic alkoxy groups, and it is likely that the stereoisomer ratio would be approximately 1:1 and independent of the nature of R. If the equilibrium between A and B is fast, the D/E ratio would depend on the relative heats of formation of the diaste-

(13) Identical results were obtained in the reactions of **18t** and **18c** with allyltrimethylsilane.

(14) (a) Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667. (b) Lodge, E. P.; Heathcock, *Ibid.* **1987**, *109*, 2819. (c) Mori, I.; Bartlett, P. A.; Heathcock, *Ibid.* **1987**, *109*, 7199. (d) Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5966.

Scheme IV



25: R = C_8H_{17}
28: R = Ph

5

26: R = C_8H_{17}
29: R = Ph

27: R = C_8H_{17}
30: R = Ph

31: R = C_8H_{17}
33: R = Ph

32: R = C_8H_{17}
34: R = Ph

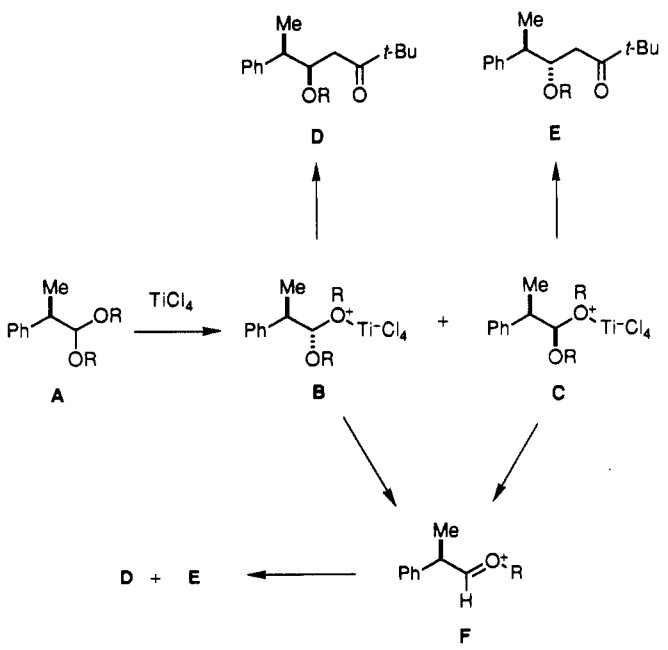
35: R = C_8H_{17}
38: R = Ph

5

36: R = C_8H_{17}
39: R = Ph

37: R = C_8H_{17}
40: R = Ph

Scheme V



A B C D E F

reomeric complexes and on their rates of reaction to give D and E.

The experiment summarized in Scheme III rules out reversible formation of free oxocarbenium ions under the reaction conditions. Substitution could occur by the S_N2 mechanism or by the S_N1 mechanism by way of free oxocarbenium ions provided reaction of the intermediate oxocarbenium ions with **5** are faster than reaction with Cl_4Ti^-OR. Reaction via oxocarbenium ion pairs are also not ruled out by this experiment.

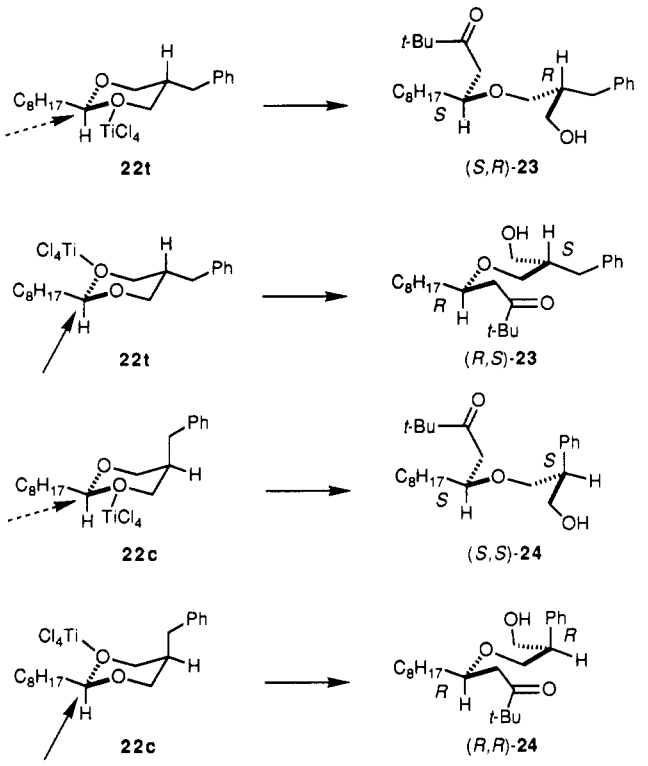
The results in Table I (cf. entries 3, 7, 8, 10) show that there *is* an effect of the steric bulk of the alkoxy group on the stereochemistry of the acetal substitution reaction in the direction expected for the S_N1 mechanism. There is also a solvent effect; with methyl acetal **1** and isopropyl acetal **3** the product syn/anti ratio increases with increasing solvent polarity (cf. entries 1, 3, 5, 6 and entries 8, 9). The 4:1 ratio of isomers obtained in the reaction of acetal **1** with **5** in acetonitrile is a normal Cram/anti-Cram ratio for 2-phenylpropanal and may represent the intrinsic diastereofacial preference of the oxocarbenium ion (Scheme V, F, R = Me). The nearly 1:1 ratio of stereoisomers resulting from this reaction in the nonpolar solvents hexane and toluene suggests that **1** reacts by the S_N2 mechanism or via oxocarbenium ion pairs in these solvents. The 2.5:1 ratio observed in CH_2Cl_2 is most consistent with a mixture of S_N2 and oxocarbenium ion pair mechanisms. The absence of an effect of concentration on stereochemistry (Table I, entried 3 and 4) would seem to rule out S_N1 reaction through dissociated ions in this solvent.[15]

The simplest explanation of the data is that acetals **3** and **4** react essentially completely by the S_N1 mechanism in CH_2Cl_2 and acetal **2** reacts partly by this mechanism. It is reasonable that dissociation to an oxocarbenium ion would be favored by steric repulsion of the alkoxy groups in complexes B and C (Scheme V).

The experimental design for the type 2 acetal study is shown in Schemes VI and VII. The acetal oxygens in acetals **22t** and **22c** are enantiotopic. Thus, as shown in Scheme VI, if substitution occurs by the S_N2 mechanism, **22t** would give the *R**,*S** diastereomer (±)-**23** and **22c**

(15) If the reaction of acetal **1** is carried out by premixing the acetal with $TiCl_4$ in CH_2Cl_2 prior to addition of silyl enol ether **5**, the **6s**:**6a** ratio is 1.4:1. Although we have not studied this reaction in detail, it is possible that **1** reacts with $TiCl_4$ under these conditions to form an α-chloro ether.

Scheme VI

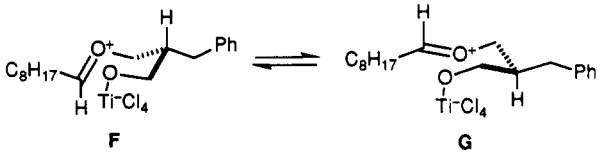


would give the S^*,S^* diastereomer (±)-**24**. On the other hand, if substitution occurs by the S_N1 mechanism both acetals should give both diastereomeric products (Scheme VII). Although the faces of the oxocarbenium ion are diastereotopic, little 1,4-asymmetric induction is expected and a nearly 1:1 mixture of R^*,S^* and S^*,S^* diastereomers is expected by this mechanism.

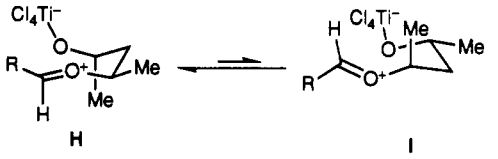
The results of the study of cyclic acetals **22c** and **22t** are quite definitive and only consistent with acetal replacement by the S_N1 (oxocarbenium ion) mechanism. With the meso acetals **25** and **28** the situation is identical to that described for **22t** and **22c**. Thus, if reaction occurs by the S_N2 mechanism, both **25** and **28** should give a 1:1 mixture of the S^*,R^*,S^* and R^*,S^*,R^* enantiomers. On the other hand, if substitution occurs by the S_N1 mechanism both acetals should give a mixture of diastereomeric products. The results in Table II indicate that the reaction mechanism must be completely or largely S_N1.

The results of this study, particularly those obtained from **25** and **28**, raise an interesting question about the origin of stereoselectivity in Johnson's chiral acetal substitutions, which have been explained by invoking the S_N2 mechanism.[4,5] It was for this reason that acetals **35** and **38** were examined. As seen in Table II, the results obtained with these two acetals were qualitatively similar to those obtained with **25** and **28**. In both the nonanal and benzaldehyde series, the meso acetal gives slightly lower diastereomer ratios than does the chiral acetal.

In summary, the bulk of our evidence, especially the behavior of cyclic acetals **22t**, **22c**, **25**, and **28**, points to the S_N1 mechanism for acetal substitution. How, then, do we account for the results observed for acetals **35** and **38**, and for high stereoselectivity seen in substitution reactions of Johnson-type acetals in general? The answer to this question may be that the reactions, at least of the type 2 acetals in CH_2Cl_2, occur through oxocarbenium ion pairs, and that in some cases, these tight ion pairs behave very much as though the six-membered ring is still intact. Under the acidic conditions of their formation, acetals **22c** and **22t** exist in an equilibrium ratio of 1:1 and it is not likely that complexation with $TiCl_4$ would perturb this ratio. If the geometries of the two ion pairs G and F closely resemble those of **22c** and **22t**, it is expected that attack on the oxocarbenium ion would be stereorandom.

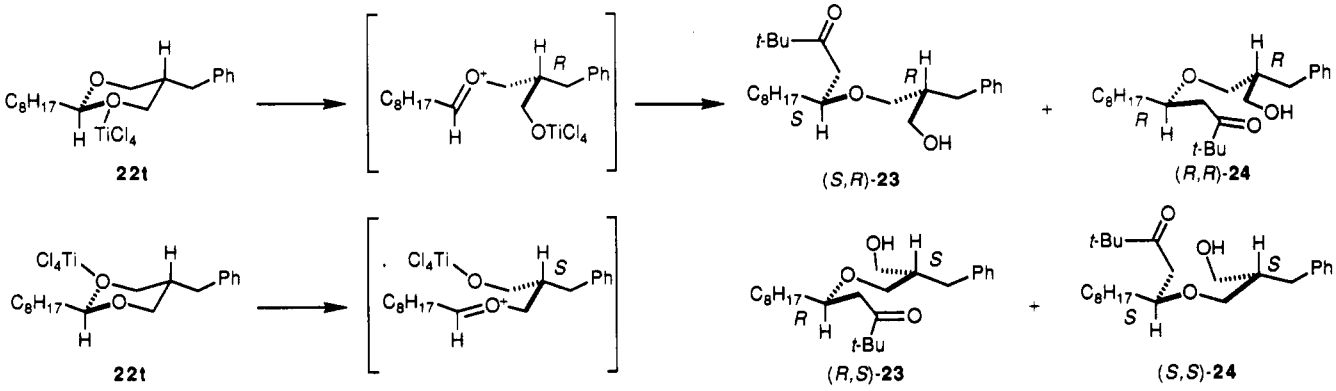


On the other hand, the comparable ion pairs H and I derived from chiral acetals **35** and **38** are likely to differ significantly in energy, since it has been shown that there is a strong preference for complexation of the dioxane oxygen next to the axial methyl group.[11] In these cases, attack of nucleophile on the more exposed *si* face of H would be quite reasonable and would approximate the results expected from the S_N2 mechanism. The slightly lower stereoselectivity seen with the benzaldehyde acetal **38** would be consistent with some reaction through an extended conformer of H/I.



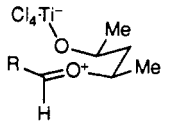
With meso acetals **25** and **28** the Lewis acid has no choice but to complex an oxygen next to an equatorial methyl group. As a result, the pseudocyclic ion pair J might be sufficiently disfavored that some reaction occurs through some extended, non-ion-paired conformer. Again,

Scheme VII[a]



[a] The same situation holds for **22c**; an approximate 1:1 mixture of diastereomers should result.

the lower stereoselectivity seen with the benzaldehyde-derived acetal **28** is consistent with this notion.



J

Thus, the stereochemistry observed in substitutions of type 2 acetals in CH_2Cl_2 under $TiCl_4$ catalysis can be adequately understood in terms of a predominate oxocarbenium ion pair mechanism. With type 1 acetals of tertiary and secondary alcohols the stereochemical trends observed argue strongly for a substitution mechanism involving either free oxocarbenium ions or ion pairs. For type 1 acetals of methanol and primary alcohols the evidence is not quite so definitive, and substitutions may occur partly by the S_N2 mechanism.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial sources and used without further purification. All reactions were performed under a dry nitrogen atmosphere. Tetrahydrofuran (THF), diethyl ether, and benzene were distilled from sodium/benzophenone ketyl, CH_2Cl_2 and acetonitrile from CaH_2, and dimethylformamide from $CaSO_4$. Melting and boiling points are uncorrected. Chromatography was performed with silica gel 60 (E. Merk, Darmstadt), 100–120 mesh. Analytical thin-layer chromatography was performed on precoated glass plates (250 m, silica gel 60, E. Merk, Darmstadt). ^1H NMR spectra were acquired in $CDCl_3$, and coupling constants are given in hertz. IR spectra were measured as thin films on NaCl unless otherwise indicated. Capillary GC was performed on a 0.25 mm × 25 m 5% cross-linked phenylmethyl silicone column (GC-a) or a 0.2 mm × 25 m bonded PEG-HT capillary column (GC-b). Preparative GC was done on a 6 ft × 0.24 in. 3% Silicone OV-101 on 80–100-mesh Chromosorb W-HP column. High-performance liquid chromatography (HPLC) was done using a 4.6 mm × 25 cm JASCO Finepak Sil column.

2-Methyl-1,1-dimethoxy-2-phenylpropane (1). To a solution of 2-phenylpropanal (6.70 g, 50 mmol) and trimethyl orthoformate (6.6 mL, 60 mmol) in 50 mL of methanol was added 0.1 g of *p*-toluenesulfonic acid. The mixture was stirred at room temperature for 1 day, poured into 100 mL of water, and extracted with three 50-mL portions of ether. The combined organic layers were dried over Na_2SO_4 and concentrated to give 8.86 g of a crude oil. Distillation gave 6.34 g (70% yield) of acetal 1 as a colorless oil, bp 45–51 °C/Torr. IR: 1605, 760, 705 cm^{-1}. ^1H NMR (250 MHz): δ 1.28 (d, 3, J = 7.0), 3.01 (quintet, 1, J = 7.0), 3.24 (s, 3), 3.37 (s, 3), 4.36 (d, 1, J = 7.0), 7.27 (m, 5). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.34; H, 8.87.

2-Methyl-1,1-diethoxy-2-phenylpropane (2). A 250-mL round-bottomed flask fitted with a Soxhlet extractor containing activated 4-Å molecular sieves was charged with 3.54 g (0.0264 mol) of 2-phenylpropanal, 100 mL of absolute ethanol, and 0.3 g of *p*-toluenesulfonic acid. The mixture was refluxed for 5 h and cooled in an ice bath. Solid $NaHCO_3$ (1 g) was added, and the mixture was diluted with 300 mL of ice water and extracted with two 50-mL portions of ether. The combined ether layers were washed with three 100-mL portions of ice water, dried, and concentrated to obtain 3.61 g (66%) of acetal, 90% pure by ^1H and ^{13}C NMR analysis. An analytical sample was obtained by hplc (19:1 hexane–ether, μ-Porasil column). ^1H NMR (300 MHz): δ 1.03 (t, 3, J = 7.1), 1.20 (t, 3, J = 7.0), 1.30 (d, 3, J = 7.0), 3.00 (quintet, 1, J = 6.9), 3.32 (m, 1), 3.45 (m, 1), 3.55 (m, 1), 3.70 (m, 1), 4.45 (d, 1, J = 6.5), 7.15–7.35 (br s, 5). ^{13}C NMR (75 MHz): δ 15.1, 15.2, 16.5, 43.9, 62.67, 62.72, 106.9, 126.2, 128.0, 128.1, 148.6. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.92; H, 9.71.

2-Methyl-1,1-diisopropoxy-2-phenylpropane (3). A solution of 10.0 g (75 mmol) of 2-phenylpropanal and 0.3 g of *p*-toluenesulfonic acid in 250 mL of 2-propanal was heated at reflux for 4 h, during which time a mixture of 2-propanal–water was occasionally removed by distillation (total volume of solvent removed = 50 mL). The reaction mixture was diluted with 500 mL of cold water containing 0.5 g of $NaHCO_3$ and extracted with 3 × 50 mL of ether. The combined ether layers were washed with 2 × 100 mL of water, dried over $MgSO_4$, filtered, and concentrated to give 12.4 g of a yellow oil. Analysis of the crude product by NMR showed it to be primarily a 1:1 mixture of the desired acetal and 1-isopropoxy-2-phenyl-1-propene. The acetal was isolated from the 4 g of crude material by two cycles of MPLC purification. In the first cycle a 1:1 mixture of the acetal and the ether byproducts were separated from uncharacterized, slow-moving constituents with 3:1 hexane–ether (silica gel: 12 mL/min). In the second cycle the 1:1 mixture was resolved into its separate components by using 19:1 hexane–ether (silica gel: 12 mL/min) to give 0.72 g of pure acetal 3. ^1H NMR (300 MHz): δ 7.4–7.15 (m, 5), 4.46 (d, 1, J = 5.6), 3.73 (septet, 1, J = 6.2), 3.55 (septet, 1, J = 6.2), 2.86 (dq, 1, J = 1.1, 6.8), 1.24 (d, 3, J = 7.0), 1.13 (d, 3, J = 6.2), 1.01 (d, 3, J = 6.2), 0.97 (d, 3, J = 6.2), 0.83 (d, 3, J = 6.9). ^{13}C NMR (75 MHz): δ 15.7, 22.0, 22.3, 23.0, 23.4, 45.0, 68.6, 69.0, 103.6, 126.1, 127.9, 128.4, 143.4. Anal. Calcd for $C_{14}H_{24}O_2$: C, 76.27; H, 10.17. Found: C, 76.30; H, 10.28.

2-(1-Phenylethyl)-4,4,5,5-tetramethyl-1,3-dioxolane (4). A mixture of 2-phenylpropanal (5 mmol, 0.67 g) and pinacol (5 mmol, 1.13 g) in 25 mL of benzene was heated under reflux while water was continuously removed with a Dean–Stark trap for 1 h. $NaHCO_3$ (0.2 g) was added to the cooled reaction mixture, and the mixture was concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexane–ethyl acetate, 20:1) to give 1.02 g (87% yield) of acetal 4 as a colorless oil. IR: 1605, 980, 770, 700 cm^{-1}. ^1H NMR (250 MHz): δ 7.27 (m, 5), 5.08 (d, 1, J = 5.4), 2.87 (dq, 1, J = 5.4, 7.2), 1.32 (d, 3, J = 7.2), 1.18 (s, 3), 1.14 (s, 3), 1.08 (s, 6). ^{13}C NMR (50.78 MHz): δ 16.2, 22.1, 22.2, 24.06, 24.11, 45.1, 81.6, 81.7, 103.6, 126.4, 127.9, 128.5, 142.4. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.04; H, 9.34.

General Procedure for Reactions of Acetals 1–3 with Enol Silane 5: Reaction of 1 with 5. To a mixture of dimethyl acetal 1 (1 mmol, 180 mg) and the trimethylsilyl enol ether of pinacolone (**5**) (1.5 mmol, 0.24 mmol) in 5 mL of CH_2Cl_2 was added $TiCl_4$ (1 mmol, 0.11 mL) at −78 °C. After being stirred for 0.5 h, the reaction mixture was quenched with 20 mL of 1 N HCl. The organic layer was separated, washed with 20 mL of brine, dried over Na_2SO_4, and concentrated. A measured amount of acetophenone (117.4 mg) was added to the crude product. After the mixture was mixed well, a small portion was analyzed by ^1H NMR to obtain the yield (by comparing the methyl resonance of acetophenone with methoxy resonance of the product) and the ratio of diastereomers (84% yield, **6s**:**6a** = 2.45:1). An analytical sample was obtained by chromatography on silica gel (hexane–ethyl acetate, 20:1).

(5*R,6*R**)-5-Methoxy-2,2-dimethyl-6-phenyl-3-pentanone (6s) (Major Isomer).** Ir: 1700, 1600, 765, 700. ^1H NMR (250 MHz): δ 7.28 (m, 5), 3.90 (m, 1), 3.33 (s, 3), 2.85 (quintet, 1, J = 7.0), 2.65 (dd, 1, J = 17.2, 7.9), 2.33 (dd, 1, J = 17.2, 3.6), 1.33 (d, 3, J = 7.0), 1.03 (s, 9). ^{13}C NMR (50.78 MHz): δ 17.1, 30.0, 40.1, 41.1, 44.3, 59.0, 81.6, 126.2, 127.7, 128.2, 144.0, 214.1. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.33; H, 9.55.

(5*S,6*R**)-5-Methoxy-2,2-dimethyl-6-phenyl-3-pentanone (6a) (Minor Isomer).** This compound was not obtained free of the major (syn) diastereomer, but its NMR resonances were obtained from spectra of the mixture of isomers. ^1H NMR (250 MHz): δ 7.28 (m, 5), 3.90 (m, 1), 3.27 (s, 3), 3.30 (m, 1), 2.76 (dd, 1, J = 7.9, 17.2), 2.28 (dd, 1, J = 4.2, 17.2), 1.30 (d, 3, J = 6.9), 1.06 (s, 9). ^{13}C NMR (50.78 MHz): δ 16.0, 26.1, 38.4, 42.4, 44.2, 58.5, 81.5, 126.2, 128.0, 128.1, 143.1, 214.2.

The following β-alkoxy ketones were prepared by the foregoing general procedure:

(5*R,6*R**)-5-Ethoxy-2,2-dimethyl-6-phenyl-3-heptanone (7s).** ^1H NMR (300 MHz): δ 7.30–7.18 (m, 5), 3.99 (td, 1, J = 7.6, 3.6), 3.49 (m, 2), 2.83 (quintet, 1, J = 7.0), 2.69 (dd, 1, J = 17.1, 7.9), 2.30 (dd, 1, J = 17.1, 3.6), 1.33 (d, 3, J = 6.78), 1.10 (t, 3, J = 6.6), 1.03 (s, 9). ^{13}C NMR (75.1 MHz): δ 15.6, 17.4, 26.1, 40.9, 44.9, 66.9, 80.2, 126.3, 127.9, 128.3.

(5*S,6*R**)-5-Ethoxy-2,2-dimethyl-6-phenyl-3-pentanone (7a).** ^1H NMR (300 MHz): δ 7.30–7.18 (m, 5), 3.98 (dt, 1, J = 7.6, 5.0), 3.43 (quintet, 1, J = 7.6), 3.33 (quintet, 1, J = 7.4), 2.98 (quintet, 1, J = 7.2), 2.76 (dd, 1, J = 16.7, 8.3), 2.25 (dd, 1, J =

16.7, 4.8), 1.30 (d, 3, J = 7.6), 1.07 (s, 9), 1.04 (t, 3, J = 6.7). ^{13}C NMR (75.1 MHz): δ 15.5, 16.4, 26.2, 39.2, 43.1, 44.4, 66.4, 80.1, 126.3, 128.1, 128.4, 143.6, 214.6.

(5*R,6*R**)-5-Isopropoxy-2,2-dimethyl-6-phenyl-3-heptanone (8s).** ^{1}H NMR (300 MHz): δ 7.35–7.15 (m, 5), 4.1 (m, 1), 3.50 (septet, 1, J = 6.1), 2.85 (quintet, 1, J = 6.9), 2.60 (dd, 1, J = 17.4, 6.2), 2.45 (dd, 1, J = 17.3, 5.0), 1.30 (d, 3, J = 7.0), 1 06 (d, 3, J = 5.7), 1.04 (d, 3, J = 5.7), 1.00 (s, 9). ^{13}C NMR (75.1 MHz): δ 17.0, 22.4, 26.1, 41.5, 44.5, 70.9, 77.0, 126.2, 128.1, 144.4.

(5*S,6*R**)-5-Isopropoxy-2,2-dimethyl-6-phenyl-3-heptanone (8a).** ^{1}H NMR (300 MHz): δ 7.35–7.15 (m, 5), 4.08 (m, 1), 3.56 (septet, 1, J = 6.1), 3.0 (m, 1), 2.70 (dd, 1, J = 17.3, 7.0), 2.24 (dd, 1, J = 17.0, 5.0), 1.30 (d, 3, J = 7.1), 1.06 (s, 9), 1.05 (d, 3, J = 6.0), 1.04 (d, 3, J = 6.0). ^{13}C NMR (75.1 MHz): δ 16.1, 22.6, 22.8, 26.2, 29.7, 39.4, 43.1, 70.9, 77.3, 126.2, 128.4.

(5*R*,6*R)-5-(2-Hydroxy-1,1,2-trimethylpropoxy)-2,2-dimethyl-6-phenyl-3-heptanone (9s).** To a mixture of acetal **4** (0.5 mmol, 117 mg) and the trimethylsilyl enol ether of pinacolone (1.0 mmol, 0.16 mL) in 2.5 mL of CH_2Cl_2 was added $TiCl_4$ (0.75 mmol, 82 μL) at −78 °C to give a pale yellow solution. After being stirred for 0.5 h, the reaction mixture was diluted with 20 mL of 1 N HCl and was extracted with three 10-mL portions of CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give 200 mg of a crude product. Analysis by ^{1}H NMR of the crude product showed the ratio of diastereomers to be >98:2. The crude product was purified by flash chromatography on silica gel (hexane–ethyl acetate, 10:1) to give 158 mg (94% yield) of the title compound. IR: 3570, 1705, 1610 cm^{-1}. ^{1}H NMR (250 MHz): δ 7.25 (m, 5), 4.32 (m, 1), 2.90 (m, 1), 2.89 (dd, 1, J = 7.5, 18.5), 2.50 (dd, 1, J = 3.2, 18.5), 2.40 (br s, 1), 1.28 (d, 3, J = 7.2), 1.15 (s, 3), 1.10 (s, 3), 1.03 (s, 12), 0.75 (s, 3). ^{13}C NMR (50.78 MHz): δ 15.0, 20.0, 20.7, 24.5, 24.6, 26.2, 42.5, 44.1, 44.2, 71.2, 75.0, 126.3, 128.0, 128.3, 134.0, 213.9. Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.38; H, 10.30.

Confirmation of Stereochemistry of the Major β-Alkoxy Ketones. Preparation of an Authentic Sample of 6s. A solution of 1.066 g (4.6 mmol) of aldol **10**[12] in 15 mL of diethyl ether was cooled to 0 °C, and 0.46 mL (4.6 mmol) of BH_3-DMS was added under a nitrogen atmosphere. Very little gas evolution was noticed at 0 °C, so the solution was brought to room temperature (moderate gas evolution) and allowed to stand for 1.5 h. The reaction was carefully quenched by addition of 5 mL of 6 M KOH (reaction time = 1 h), and the mixture was transferred to a separatory funnel. The ether layer was washed several times with cold water, separated, dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to give 1.037 g (96% yield) of a white semisolid. ^{1}H NMR analysis of this product showed only the presence of two diols **11** in 60:40 mixture (the product distribution from this reduction is almost exactly reversed from that of $LiAlH_4$ reduction of the same ketone).

A mixture of 1.02 g (4.3 mmol) of diols **11** and 0.27 mL (4.4 mmol) of methyl iodide in 8 mL of dry DMSO was stirred under a stream of nitrogen while 0.11 g (4.4 mmol) of oil-free NaH was added. The reaction mixture was allowed to stand at room temperature for 3 h, quenched with dilute HCl, and extracted with several portions of ether. The combined ether layers were dried over $MgSO_4$, filtered, and concentrated to afford 0.82 g (77% yield) of a colorless oil. ^{1}H NMR analysis of the crude material indicated the presence of small amounts of starting material and dialkylated products as well as four monoalkylated products. Column chromatography on silica gel (hexane–ether, 19:1) furnished 0.381 g (35%) of a mixture of the four monoalkylated products. This mixture was dissolved in 10 mL of CH_2Cl_2 and oxidized with 0.62 g of pyridinium chlorochromate (PCC) at room temperature for 2 h. Routine workup of the reaction mixture provided 0.355 g of a yellow oil that contained two major components by thin-layer chromatography. Column chromatography of the mixture afforded two fractions weighing 0.083 and 0.218 g, respectively. The major component was identical with **6s** by ^{1}H NMR and ^{13}C NMR analyses.

Preparation of an Authentic Sample of 7s. Similar treatment of 0.174 g (0.74 mmol) of a 60:40 mixture of the diastereomeric diols **11** obtained via BH_3–DMF reduction of authentic aldol **10** provided 0.053 g (27% yield) of a 7:3:2 mixture of monoethylated products, which was oxidized with PCC to obtain 0.040 g (76% yield) of **7s**, identified by its ^{1}H NMR and ^{13}C NMR spectra.

***S*-*tert*-Butyl (3*R**,4*R**)-3-(2-Hydroxy-1,1,2-trimethylpropoxy)-4-phenylthiopentanoate (13).** The procedure used for the reaction of acetal **4** and enol silane **5** was followed, except that 3 equiv of $TiCl_4$ and 2 equiv of silyl ketene acetal **12** were used. Analysis of the crude product by ^{1}H NMR showed that the ratio of diastereomers was about 10:1. The crude product was purified by flash chromatography on silica gel (hexane–ethyl acetate, 10:1) to give 142 mg (94%) of ester **13** as a colorless oil. IR: 3560, 2980, 1670, 1605 cm^{-1}. ^{1}H NMR (250 MHz): δ 7.08 (m, 5), 4.02 (dt, 1, J = 5.0, 6.1), 2.98 (dq, 1, J = 7.2, 5.0), 2.63 (br s, 1), 2.59 (dd, 1, J = 14.9, 6.4), 2.47 (dd, 1, J = 14.9, 5.0), 1.35 (s, 9), 1.22 (d, 3, J = 7.2), 1.08 (s, 3), 1.05 (s, 3), 1.04 (s, 3), 0.80 (s, 3). ^{13}C NMR (50.78 MHz): δ 15.5, 20.4, 20.6, 24.5, 29.6, 43.8, 48.1, 48.9, 72.8, 75.1, 80.9, 126.3, 128.0, 128.2, 143.2, 198.3. Anal. Calcd for $C_{12}H_{34}O_3S$: C, 68.81; H, 9.35; S, 8.75. Found: C, 68.84; H, 9.51; S, 8.55.

(3*R,4*R**)-3-(2-Hydroxy-1,1,2-trimethylpropoxy)-4-phenyl-1-pentanol (14).** To a solution of 101 mg of ester **13** (0.29 mmol) in 5 mL of ether was added 20 mg of $LiAlH_4$ (0.58 mmol) in one portion at 0 °C. After being stirred for 1 h, the reaction mixture was quenched with 0.5 mL of aqueous saturated Na_2SO_4 and extracted with ether. The combined organic layers were concentrated and purified by flash chromatography on silica gel (hexane–2-propanol–CH_2Cl_2, 70:10:1) to give 52 mg (64%) of diol **14** as a white solid. An analytical sample, mp 92–94 °C (needles), was obtained by recrystallization from hexane. IR ($CHCl_3$): 3450, 1605 cm^{-1}. ^{1}H NMR (250 MHz): δ 7.25 (m, 5), 3.78 (q, 1, J = 5.5), 3.82–2.53 (m, 2), 3.06 (quintet, 1, J = 6.8), 2.96 (br s, 2), 1.81 (m, 1), 1.44 (m, 1), 1.33 (d, 3, J = 7.1), 1.25 (s, 3), 1.23 (s, 3), 1.19 (s, 3), 1.06 (s, 3). ^{13}C NMR (50.78 MHz): δ 17.5, 20.8, 24.5, 24.9, 35.1, 43.4, 59.1, 73.6, 75.3, 80.5, 126.1, 128.1, 144.1. Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.73; H, 9.99.

***S*-*tert*-Butyl (3*R**,4*R**)-3-Hydroxy-4-phenylthiopentanoate (16).** To a mixture of 268 mg of 2-phenylpropanal (2.0 mmol) and 689 mg of enol silane **12** (4 mmol) in 10 mL of CH_2Cl_2 was added 0.23 mL (2 mmol) of BF_3-OEt_2 at −78 °C. After being stirred for 1 h, the mixture was diluted with 20 mL of water. The organic layer was dried over Na_2SO_4 and concentrated to obtain 880 mg of a crude product, which was purified by flash chromatography on silica gel (hexane–ethyl acetate, 20:1) to give 384 mg (72%) of thiol ester **16** as a white solid. An analytical sample, mp 68.5–69.5 °C, was obtained by recrystallization from hexane. IR: 3460, 1680, 775, 710 cm^{-1}. ^{1}H NMR (250 MHz): δ 7.24 (m, 5), 4.11 (dt, 1, J = 4.3, 7.6), 2.92 (br s, 1), 2.75 (quintet, 1, J = 7.1), 2.51 (dd, 1, J = 15.8, 4.2), 2.44 (dd, 1, J = 15.8, 7.8), 1.43 (s, 9), 1.35 (d, 3, J = 7.0). ^{13}C NMR (50.78 MHz): δ 17.1, 29.1, 45.5, 48.3, 48.9, 73.1, 126.6, 127.6, 128.5, 143.6, 200.6. Anal. Calcd for $C_{15}H_{22}O_2S$: C, 67.63; H, 8.32; S, 12.03. Found: C, 67.77; H, 8.21; S, 11.98.

(3*R,4*R**)-4-Phenyl-1,3-pentanediol (15). Method a.** To a solution of 249 mg (0.94 mmol) of ester **16** in 5 mL of ether was added 160 mg (4 mmol) of $LiAlH_4$ in two portions at 0 °C. After being stirred for 0.5 h, the reaction mixture was quenched with 0.5 mL of saturated Na_2SO_4 and extracted with ether. The combined organic layers were concentrated and purified by flash chromatography on silica gel (hexane–2-propanol–CH_2Cl_2, 7:1:0.07) to give 145 mg (86%) of the title compound as a colorless oil. IR: 3350, 1605 cm^{-1}. ^{1}H NMR (250 MHz): δ. 7.21 (m, 5), 3.84 (dt, 1, J = 5.8, 6.8), 3.69 (m, 2), 3.44 (s, 1), 2.73 (quintet, 1, J = 7.0), 1.51 (m, 3), 1.31 (d, 3, J = 7.0): ^{13}C NMR (50.78 MHz): δ 16.7, 36.0, 46.2, 61.2, 75.9, 126.3, 127.6, 128.3, 144.2. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.98; H, 8.80.

Method b. To a solution of 37 mg (0.13 mmol) of diol **14** in 1 mL of CH_2Cl_2 was added 55 μL (0.42 mmol) of trimethylsilyl bromide at room temperature. After the mixture was stirred for 3 days, 200 mg of $NaHCO_3$ was added. The mixture was concentrated and purified by flash chromatography on silica gel (hexane–ethyl acetate, 1:1) to give 21 mg (90%) of a colorless oil. The major isomer of the crude product was identical with diol **15** by ^{1}H NMR and ^{13}C NMR analyses.

1,1-Diethoxyheptane (17). A mixture of 1.4 mL (10 mmol) of heptanal, 2.49 mL (15 mmol) of triethyl orthoformate, and 10 mg of NH_4NO_3 in 1 mL of ethanol was stirred for 10 h at 0 °C. The mixture was poured into 20 mL of $NaHCO_3$ solution, and

the resulting mixture was extracted with three 20-mL portions of ether. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with 50:1 hexane–ethyl acetate. The combined product fractions were distilled with a Kugelrohr apparatus (bath temperature 90 °C, 8 Torr) to give 1.32 g (70%) of **17** as a clear, colorless oil. The product was more than 98% pure by GC-b (130 °C, t_R = 2.9 min). ^1H NMR (200 MHz): δ 0.90 (t, 3, J = 6), 1.20–1.40 (m, 8), 1.21 (t, 6, J = 7.1), 1.53–1.70 (m, 2), 3.50 (dq, 2, J = 9.4, 7.1), 3.65 (dq, 2, J = 9.4, 7.1), 4.49 (t, 1, J = 5.7). Anal. Calcd for $C_{11}H_{24}O_2$: C, 70.16; H, 12.85. Found: C, 70.02; H, 13.20.

1,1-Dipropoxynonane (18). A mixture of 1.72 mL (10 mmol) of nonanal, 1.87 mL (25 mmol) of propanol, and 10 mg of pyridinium *p*-toluenesulfonate in 50 mL of benzene was refluxed with continuous azeotropic removal of water for 2 h. After being cooled to room temperature the mixture was poured into 20 mL of a $NaHCO_3$ solution. The benzene layer was dried and evaporated, and the resulting crude product was purified first by flash chromatography on silica gel, eluting with 25:1 hexane–ethyl acetate, and then by distillation using a Kugelrohr apparatus (bath temperature 150 °C, 7 Torr). There was obtained 1.78 g (73%) of acetal as a colorless oil, more than 98% pure by GC-b (130 °C, t_R = 6.2 min). ^1H NMR (200 MHz): δ 0.89 (t, 3, J = 6.5), 0.95 (t, 6, J = 7.3), 1.20–1.40 (m, 12), 1.50–1.70 (m, 6), 3.39 (dt, 2, J = 9.2, 6.8), 3.55 (dt, 2, J = 9.2, 6.8), 4.49 (t, 1, J = 5.8). Anal. Calcd for $C_{15}H_{32}O_2$: C, 73.71; H, 13.20. Found: C, 73.71; H, 13.57.

Reaction of Acetals 17 and 18 with Silyl Enol Ether 5. To a mixture of 94.2 mg (0.50 mmol) of acetal **17**, 122 mg (0.5 mmol) of acetal **18**, and 172 mg (1.00 mmol) of silyl enol ether **5** in 8.0 mL of CH_2Cl_2 was added $TiCl_4$ (0.50 mL of a 1.00 M CH_2Cl_2 solution, 0.50 mmol) dropwise at −78 °C. After being stirred for 30 min at −78 °C the resulting yellow solution was poured into 20 mL of $NaHCO_3$ solution and extracted with three 10-mL portions of ether. The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed on silica gel, eluting with 40:1 hexane/ethyl acetate. Keto ethers **19** and **20** (159 mg, 60%) were obtained as a colorless oil. ^1H NMR and capillary GC analysis of the crude product showed the presence of **19**, **20**, heptanal, and nonanal in a ratio of 3:3:2:2. Neither starting acetals nor other keto ethers were present by GC-b (130 °C). Authentic samples of **19** and **20** were obtained from the reactions of silyl enol ether **5** with acetals **17** and **18**, respectively.

2,2-Dimethyl-5-ethoxyundecan-3-one (19). GC-b, 130 °C, t_R = 7.6 min. IR: 1720 cm^{-1}. ^1H NMR (200 MHz): δ 0.89 (t, 3, J = 6.4), 1.10–1.18 (m, 3), 1.14 (s, 9), 1.20–1.54 (m, 10), 2.44 (dd, 1, J = 5.4, 16.8), 2.83 (dd, 1, J = 7.0, 16.8), 3.49 (dq, 2, J = 2.2, 7.0), 3.76–3.90 (m, 1). Anal. Calcd for $C_{15}H_{30}O_2$: C, 74.33; H, 12.47. Found: C, 74.21; H, 12.63.

2,2-Dimethyl-5-propoxytridecan-3-one (20). GC-b: 130 °C, t_R = 22.1 min. IR: 1720 cm^{-1}. ^1H NMR (200 MHz): δ 0.89 (t, 6, J = 7.4), 1.14 (s, 9), 1.20–1.62 (m, 14), 2.43 (dd, 1, J = 5.4, 16.8, 2.83 (dd, 1, J = 6.9, 16.8), 3.30–3.47 (m, 2), 3.75–3.88 (m, 1). Anal. Calcd for $C_{18}H_{36}O_2$: C, 76.00; H, 12.75. Found: C, 75.98; H, 12.93.

Heptanal. GC-b: 130 °C, t_R = 2.5 min.

Nonanal. GC-b: 130 °C, t_R = 3.2 min.

2-Benzyl-1,3-propanediol (21). To a solution of 4.3 g (0.12 mol) of $LiAlH_4$ in 200 mL of ether was added dropwise 25 g (0.1 mol) of diethyl benzylmalonate in 200 mL of ether. Addition with stirring required 1.5 h, and the mixture was heated at reflux for 3.5 h. The reaction mixture was then cooled, and 50 mL of aqueous saturated Na_2SO_4 was added. The ether layer was decanted, and the residue was washed with four 50-mL portions of ether. The combined ether layers were dried over $MgSO_4$, concentrated, and distilled to give 10.0 g (60%) of the diol as a colorless oil, bp 143–152 °C (0.4 Torr). IR: 3450, 1610, 750, 705 cm^{-1}. ^1H NMR (250 MHz): δ 7.20 (m, 5), 4.18 (br s, 2), 3.57 (m, 4), 2.52 (d, 2, J = 6.3), 1.92 (m, 1). ^{13}C NMR (50.78 MHz): δ 34.2, 44.0, 64.1, 126.0, 128.4, 128.9, 139.9. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.33; H, 8.27.

***trans*- and *cis*-5-Benzyl-2-octyl-1,3-dioxane (22t and 22c).** A mixture of 3.3 g (20 mmol) of diol **21**, 3.4 mL (20 mmol) of nonanal, and a small portion of *p*-toluenesulfonic acid in 40 mL of benzene was heated at reflux, and water was continuously removed with a Dean–Stark trap. After the theoretical amount of water had been collected in the trap, the reaction mixture was cooled to room temperature, washed with 1 M KOH and brine, dried over Na_2SO_4, concentrated, and distilled to give 4.52 g (80%) of acetals **22t** and **22c** in the ratio of 1:1 as a colorless oil, bp 162–166 °C (0.4 Torr). IR: 1610, 760, 710. Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.71; H, 10.52.

The isomers were separated by flash chromatography (hexane–CH_2Cl_2, 2:1) on silica gel.

Acetal 22t: R_f = 0.16. ^1H NMR (250 MHz): δ 7.19, (m, 5), 4.42 (t, 1, J = 5.1), 3.99 (dd, 2, J = 4.3, 12.1), 3.41 (dd, 2, J = 10.5, 12.1), 2.32 (br s, 2), 1.59 (m, 2), 1.25 (m, 13), 0.87 (t, 3, J = 6.9). ^{13}C NMR (50.78 MHz): δ 14.1, 22.6, 24.0, 29.2, 29.4, 31.8, 34.87, 34.83, 35.8, 71.7, 102.2, 126.2, 128.3, 128.5, 138.1.

Acetal 22c: R_f = 0.27. ^1H NMR (250 MHz): δ 7.27 (m, 5), 4.53 (t, 1, J = 5.0), 3.84 (br s, 4), 3.01 (d, 2, J = 7.8), 1.75–1.20 (m, 15), 0.88 (t, 3, J = 6.1). ^{13}C NMR (50.78 MHz): δ 14.1, 22.6, 23.8, 29.2, 29.50, 29.54, 31.8, 35.1, 35.7, 36.3, 69.4, 102.7, 125.9, 128.3, 129.2, 140.5.

(5*S)-2,2-Dimethyl-5-[(2*S**)-2-benzyl-3-hydroxy-1-propoxy]-3-tridecanone (23) and (5*S**)-2,2-Dimethyl-5-[(2*R**)-2-benzyl-3-hydroxy-1-propoxy]-3-tridecanone (24). Method a.** To a mixture of acetal **22c** (145 mg, 0.5 mmol) and the trimethylsilyl enol ether of pinacolone (0.16 mL, 1.0 mmol) in 2.5 mL of CH_2Cl_2 was added $TiCl_4$ (82 μL, 0.75 mmol) dropwise at −78 °C. After being stirred for 0.5 h, the resulting yellow solution was poured into 20 mL of 1 N HCl and extracted with three 10-mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed on silica gel (hexane–ethyl acetate, 10:1) to give 152 mg (78%) of 1:1 mixture (determined by ^{13}C NMR) of diastereomers as colorless oil. An identical experiment with acetal **22t** gave the same mixture of diastereomeric hydroxy ketones. The following data were obtained on the mixture. IR: 3480, 1710, 1605 cm^{-1}. ^1H NMR (250 MHz): δ 7.22 (m, 5), 3.81 (m, 1), 3.72–3.38 (m, 4), 2.82 (m, 1), 2.58 (m, 2), 2.43 (m, 1), 2.02 (m, 1), 1.48 (m, 2), 1.27 (m, 13), 1.14 (s, 9) and 1.12 (s, 9) in a 1:1 ratio, 0.88 (t, 3, J = 6.7). ^{13}C NMR (50.78 MHz): δ 14.0, 22.6, 25.1, 26.1, 29.2, 29.45, 29.47, 29.6, 29.7, 31.8, 34.0, 34.36, 34.39, 41.4, 42.6, 42.8, 44.3, 64.3, 64.8, 71.1, 71.8, 75.9, 76.0, 125.8, 128.2, 128.9, 140.0, 140.1, 214.7, and 214.6 in a 1:1 ratio. Anal. Calcd for $C_{25}H_{42}O_3$: C, 76.87; H, 10.84. Found: C, 76.74; H, 10.71.

Method b. To a mixture of acetal **22c** (45 mg, 0.16 mmol) and the trimethylsilyl enol ether of pinacolone (0.25 mL, 1.6 mmol) in 0.15 mL of CH_2Cl_2 was added $TiCl_4$ (26 μL, 0.23 mmol) at −78 °C. Most of the $TiCl_4$ stuck to the bottom of the flask and the solution was a light yellow color. After stirring for 15 min, the mixture was poured into 5 mL of saturated $NaHCO_3$ and extracted with three 5-mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed on silica gel (hexane–ethyl acetate, 10:1) to give 34 mg (75%) of recovered **22c** and 13 mg (22%) of a colorless oil shown by ^1H NMR spectrometry to be a 2:1 mixture of diastereomers, presumably **24** and **23**. An identical experiment with acetal **22t** gave 35 mg (76%) of recovered **22t** and 12 mg (20%) of a colorless oil shown by ^1H NMR spectrometry to be a 2:1 mixture of diastereomers, presumably **23** and **24**.

Control Experiments: (a) Treatment of Acetal 22c with $TiCl_4$. To a solution of acetal **22c** (30 mg, 0.1 mmol) in 1 mL of CH_2Cl_2 was added $TiCl_4$ (11 mL, 0.1 mmol) at −78 °C. After being stirred for 5 min, the resulting yellow solution was quenched with saturated $NaHCO_3$. The organic layer was separated, dried over Na_2SO_4, and concentrated. Analysis of the crude product indicated a 1:1 mixture of acetals **22t** and **22c**.

(b) Reaction of Acetals 22t and 22c with Enol Silane 5 in the Presence of 0.2 Equiv of $TiCl_4$. To a mixture of acetal **22t** (68 mg, 0.23 mmol) and enol silane **5** (74 μL, 0.46 mmol) in 1.2 mL of CH_2Cl_2 was added $TiCl_4$ (5 mL, 0.05 mmol) at −78 °C. After being stirred for 15 min, the reaction mixture was quenched with saturated $NaHCO_3$. The organic layer was separated, dried over Na_2SO_4, and concentrated. Analysis of the crude product by ^1H NMR indicated that acetal **22t** and ketones **23** and **24** were present in a ratio of 66:17:17. An identical experiment with acetal **22c** gave recovered, unchanged **22c** and the two diastereomeric hydroxy ketones in a ratio of 50:25:25.

General Procedure for the Preparation of Acetals 25, 28, 35, and 38. A mixture of 10.0 mmol of the appropriate aldehyde, 1.15 g (11.0 mmol) of 2,4-pentanediol (mixture of meso and chiral

isomers), and a small amount of pyridinium *p*-toluenesulfonate in 25 mL of benzene was refluxed under a Dean–Stark trap for 4 h. To the cooled solution was added 50 mL of $NaHCO_3$ solution, and the resulting mixture was extracted with three 20-mL portions of hexane. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The diastereomeric acetals were separated by flash chromatography on silica gel, eluting with hexane/ether. The products were obtained as colorless oils in a total yield that was nearly quantitative.

(4*R,6*S**)-4,6-Dimethyl-2-octyl-1,3-dioxane (25).** TLC: R_f = 0.44, 10:1 hexane–ethyl acetate. ^1H NMR (200 MHz): 0.88 (t, 3, J = 6.4), 1.20–1.68 (m, 16), 1.22 (d, 6, J = 6.2), 3.71 (ddq, 2, J = 2.6, 12.4, 6.2), 4.52 (t, 1, J = 5.2). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.98; H, 8.39.

(2*S,4*R**,6*R**)-4,6-Dimethyl-2-octyl-1,3-dioxane (35).** TLC: R_f = 0.35, 10:1 hexane–ethyl acetate. ^1H NMR (200 MHz): δ 0.89 (t, 3, J = 6.5), 1.18–1.64 (m, 15), 1.22 (d, 3, J = 6.2, equatorial Me), 1.36 (d, 3, J = 7.0, axial Me), 1.84 (ddd, 1, J = 6.2, 11.6, 13.2), 3.95 (ddq, 2, J = 2.4, 12.2, 6.2), 4.31 (dq, 1, J = 6.2, 7.0). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.97; H, 8.33.

(4*R,6*S**)-4,6-Dimethyl-2-phenyl-1,3-dioxane (28).** TLC: R_f = 0.31, 10:1 hexane–ether. ^1H NMR (200 MHz): δ 1.29 (d, 6, J = 6.2), 1.30–1.50 (m, 1), 1.60 (dt, 1, J = 13.0, 2.7), 3.93 (ddq, 2, J = 2.7, 12.6, 6.2), 5.51 (s, 1), 7.25–7.40 (m, 3), 7.45–7.55 (m, 2). Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.63; H, 12.70.

(2*S,4*R**,6*R**)-4,6-Dimethyl-2-phenyl-1,3-dioxane (38).** TLC: R_f = 0.22, 10:1 hexane/ether. ^1H NMR (200 MHz): δ 1.29 (d, 3, J = 6.0, equatorial Me), 1.44 (ddd, 1, J = 1.0, 2.4, 13.2), 1.49 (d, 3, J = 7.0, axial Me), 2.00 (ddd, 1, J = 6.0, 11.7, 13.2), 4.20 (ddq, 1, J = 2.4, 11.7, 6.0), 4.74 (dq, 1, J = 6.0, 7.0), 5.84 (s, 1), 7.25–7.40 (m, 3), 7.45–7.55 (m, 2). Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.63; H, 12.68.

General Procedure for the Reactions of Acetals 25, 28, 35, and 38 with Silyl Enol Ether 5. To a mixture of 0.50 mmol of the acetal and 129 mg (0.75 mmol) of silyl enol ether **5** in 8.5 mL of CH_2Cl_2 was added $TiCl_4$ (0.50 mL of a 1.00 M CH_2Cl_2 solution, 0.50 mmol) dropwise at −78 °C. After being stirred for 30 min at −78 °C, the resulting yellow solution was poured into 20 mL of a $NaHCO_3$ solution and extracted with three 20-mL portions of ether. The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed on silica gel with hexane–ethyl acetate as eluent. The resulting diastereomeric mixture of hydroxy ketones was analyzed by HPLC or GC; individual isomers were not separated.

(5*R,1′*R**,3′*S**)-2,2-Dimethyl-5-(3′-hydroxy-1′-methylbutoxy)tridecan-3-one (26).** GC-b: 190 °C, t_R = 16.6 min. TLC: R_f = 0.46, 5:2 hexane–ethyl acetate. ^1H NMR (200 MHz): δ 0.89 (t, 3, J = 6.5), 1.08 (d, 3, J = 6.0), 1.12 (s, 9), 1.14 (d, 3, J = 6.2), 1.20–1.70 (m, 17), 2.38 (dd, 1, J = 4.5, 16.5), 2.80 (dd, 1, J = 7.9, 16.5), 3.70–4.08 (m, 3). Anal. Calcd for $C_{20}H_{40}O_3$: C, 73.12; H, 12.27. Found: C, 72.97; H, 12.48.

(5*S,1′*R**,3′*S**)-2,2-Dimethyl-5-(3′-hydroxy-1′-methylbutoxy)tridecan-3-one (27).** GC-b: 190 °C, t_R = 15.0 min. TLC: R_f = 0.41, 5:2 hexane–ethyl acetate. ^1H NMR (200 MHz): δ 1.15 (s, 3), 2.62 (dd, 1, J = 6.6, 17.6). Other resonances could not be discerned for this minor isomer.

(5*S,1′*R**,3′*S**)-2,2-Dimethyl-5-(3′-hydroxy-1′-methylbutoxy)-5-phenylpentan-3-one (29).** HPLC: t_R = 13.4 min, 2.0 mL/min 15:2 hexane–ethyl acetate. TLC: R_f = 0.28, 5:2 hexane/ethyl acetate. ^1H NMR (200 MHz): δ 1.03 (d, 3, J = 5.2), 1.04 (s, 9), 1.12 (d, 3, J = 6.0), 1.30–1.75 (m, 2), 2.54 (dd, 1, J = 4.5, 16.5), 3.11 (dd, 1, J = 8.5, 16.5), 3.40–3.60 (m, 1), 3.60–4.00 (m, 2), 5.05 (dd, 1, J = 4.6, 8.4), 7.20–7.40 (m, 5). Anal. Calcd for $C_{18}H_{28}O_3$; C, 73.93; H, 9.65. Found: C, 73.93; H, 9.97.

(5*S,1′*S**,3′*R**)-2,2-Dimethyl-5-(3′-hydroxy-1′-methylbutoxy)-5-phenylpentan-3-one (30).** HPLC: t_R = 16.3 min, 2.0 mL/min 15:2 hexane–ethyl acetate. ^1H NMR (200 MHz): δ 0.89 (d, 3, J – 6.2), 1.05 (s, 9), 1.14 (d, 3, J = 6.2), 2.63 (dd, 1, J = 4.6, 17.6), 3.04 (dd, 1, J = 8.4, 17.6), 4.94 (dd, 1, J = 4.5, 8.5). Other resonances could not be discerned for this minor isomer.

(5*R,1′*R**,3′*R**)-2,2-Dimethyl-5-(3′-hydroxy-1′-methylbutoxy)tridecan-3-one (36).** GC-b: 190 °C, t_R = 16.0 min. TLC: R_f = 0.43, 5:2 hexane–ethyl acetate. ^1H NMR (200 MHz): δ 0.89 (t, 3, J = 6.4), 1.13 (s, 9), 1.14 (d, 3, J = 6.2), 1.18 (d, 3, J = 6.2), 1.20–1.74 (m, 17), 2.41 (dd, 1, J = 4.8, 16.8), 2.79 (dd, 1, J = 7.6, 16.8), 3.78–4.18 (m, 3). Anal. Calcd for $C_{20}H_{40}O_3$: C, 73.12; H, 12.27. Found: C, 73.13; H, 12.50.

(5*S,1′*R**,3′*R**)-2,2-Dimethyl-5-(3′-hydroxy-1′-methylbutoxy)tridecan-3-one (37).** GC-b: 190 °C, t_R = 14.3 min.

(5*S,1′*R**,3′*R**)-2,2-Dimethyl-5-(3′-hydroxy-1′-methylbutoxy)-5-phenylpentan-3-one (39).** HPLC: t_R = 12.3 min, 2.0 mL/min 15:2 hexane–ethyl acetate. TLC: R_f = 0.29, 5:2 hexane–ethyl acetate. ^1H NMR (200 MHz): δ 1.04 (s, 9), 1.06 (d, 3, J = 6.2), 1.17 (d, 3, J = 6.2), 1.38–1.53 (m, 2), 2.55 (dd, 1, J = 4.6, 16.7), 2.63 (s, 1), 3.09 (dd, 1, J = 8.4, 16.7), 3.47–3.63 (m, 1), 3.93–4.10 (m, 1), 4.96 (dd, 1, J = 4.6, 8.4), 7.20–7.40 (m, 5). Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.93; H, 9.95.

(5*R,1′*R**,3′*R**)-2,2-Dimethyl-5-(3′-hydroxy-1′-methylbutoxy)-5-phenylpentan-3-one (40).** HPLC: t_R = 11.8 min, 2.0 mL/min 15:2 hexane–ethyl acetate. ^1H NMR (200 MHz): 4.88 (dd, 1, J = 3.4, 9.4). Other resonances could not be discerned for this minor isomer.

General Procedure for the Oxidation of Hydroxy Ketones 26/27, 29/30, 36/37, and 39/40. A solution of 0.40 mmol of the hydroxy ketone and 172 mg (0.80 mmol) of pyridinium chlorochromate in 2.0 mL of CH_2Cl_2 was kept at room temperature for 12 h. After the addition of 10 mL of $NaHSO_3$ solution the mixture was extracted with three 10-mL portions of ether. The combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed on silica gel using hexane/ethyl acetate as eluant to give a mixture of the hydroxy ketones as a colorless oil. The diastereomeric ratio was determined by HPLC or GC.

(5*R,1′*R**)-2,2-Dimethyl-5-(1′-methyl-3′-oxobutoxy)-5-phenylpentan-3-one (33).** HPLC: t_R = 10.3 min, 2.0 mL/min 10:1 hexane–ethyl acetate. TLC: R_f = 0.35, hexane–ethyl acetate. ^1H NMR (200 MHz): δ 1.07 (s, 9), 1.16 (d, 3, J = 6.0), 1.98 (s, 3), 2.33 (dd, 1, J = 5.6, 15.0), 2.50 (dd, 1, J = 4.5, 16.4), 2.56 (dd, 1, J = 7.2, 15.0), 3.09 (dd, 1, J = 8.8, 16.4), 3.70–3.87 (m, 1), 4.97 (dd, 1, J = 4.5, 8.8), 7.20–7.40 (m, 5). Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.44; H, 9.21.

(5*S,1′*R**)-2,2-Dimethyl-5-(1′-methyl-3′-oxobutoxy)-5-phenylpentan-3-one (34).** HPLC: t_R = 9.8 min, 2.0 mL/min 10:1 hexane–ethyl acetate. ^1H NMR (200 MHz): δ 1.07 (s, 9), 1.01 (d, 3, J = 6.2), 2.17 (s, 3), 4.90 (dd, 1, J = 4.0, 8.6). Other resonances coud not be discerned for this minor isomer.

(5*R,1′*R**)-2,2-Dimethyl-5-(1′-methyl-3′-oxobutoxy)-5-tridecan-3-one (31).** GC-b: 190 °C, t_R = 13.0 min. TLC: R_f = 0.50, 5:2 hexane–ethyl acetate. ^1H NMR (200 MHz): δ 0.89 (t, 3, J = 6.5), 1.10 (d, 3, J = 6.2), 1.14 (s, 9), 1.20–1.50 (m, 14), 2.38 (dd, 1, J = 5.7, 15.4), 2.41 (dd, 1, J = 5.2, 16.6), 2.68 (dd, 1, J = 7.0, 15.4), 2.77 (dd, 1, J = 7.0, 16.6), 3.84–4.04 (m, 2). Anal. Calcd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73. Found: C, 73.55; H, 12.01.

(5*S,1′*R**)-2,2-Dimethyl-5-(1′-methyl-3′-oxobutoxy)-5-tridecan-3-one (32).** GC-b: 190 °C, t_R = 11.4 min. ^1H NMR (200 MHz): δ 1.15 (s, 9). Other resonances could not be discerned for this minor isomer.

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