Asymmetric Synthesis via Acetal Templates. 3.[1] On the Stereochemistry Observed in the Cyclization of Chiral Acetals of Polyolefinic Aldehydes: Formation of Optically Active Homoallylic Alcohols

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A number of years ago, in connection with the early phases of development of biomimetic polyolefin cyclizations, we investigated the Lewis acid catalyzed cyclization of the chiral dienic acetal 1, derived from (−)-2,3-butanediol (*R,R* configuration).[1] Upon
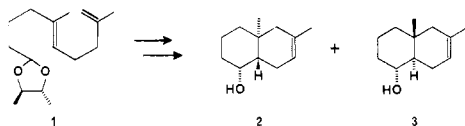
treatment of **1** with stannic chloride in benzene at room temperature, followed by cleavage of the ether side chain, the octalin alcohols **2** and **3** were isolated in high yield. These alcohols were separately oxidized to the corresponding ketones, giving products of strikingly high optical purity (83–84% ee). While the axial (**2**) and equatorial (**3**) alcohols are of *opposite* chirality at the bridgehead centers, they have, ipso facto, the *same* predominant configuration (*R*) at the carbinol center. The chiral auxiliary therefore exerts a strong influence only on the direction of attack by the olefinic bond on the cationic acetal, favoring the *R* chirality at this new center irrespective of the stereochemical sequelae.[2]

In seeking to explain the asymmetric induction produced by the chiral acetal, we take as a lead the reasonable suggestion proposed earlier[1b] and postulate that the acetal is only partially cleaved in the transition state. As the acetal opens, the configuration of the oxocarbonium ion must approach a planar, sp^2-hybridized geometry, with the departing oxygen leaving in a roughly perpendicular direction. On the assumption that attack of the participating double bond takes place at some point along this sequence, the four diastereomeric structures **4–7** can be
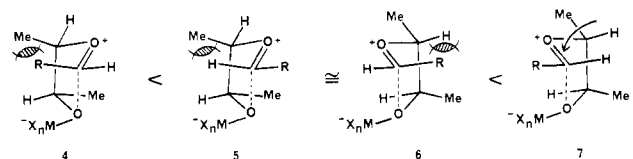
considered. The least sterically congested of these four would appear to be **7**, in which the *pro-R* oxygen of the acetal is the leaving group. Attack of the double bond from the direction anti to this departing oxygen would lead to the *R* configuration at the resulting ether carbon, as observed.[3]

An important implication of this analysis is that the *intermolecular* version of this reaction might be a useful method for enantioselective generation of secondary alcohols.[4] Since the

Scheme I

a (R = *n*-C$_8$H$_{17}$, n = 0)
b (R = *n*-C$_8$H$_{17}$, n = 1)
c (R = CH$_2$=CHCH$_2$CH$_2$, n = 1)
d (R = Cyclohexyl, n = 1)
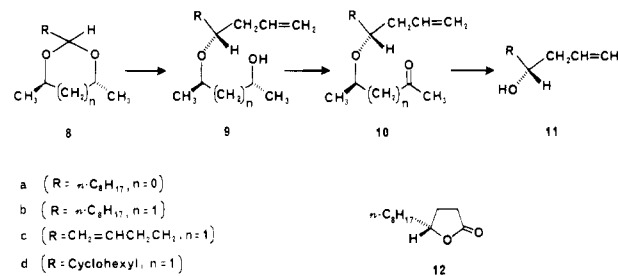
Lewis acid catalyzed reaction of acetals with allyltrimethylsilane is a well-established, high-yield process,[5] we decided first to examine the reaction of the acetal **8a** of nonaldehyde and (2*R*,3*R*)-butanediol[6] with allyltrimethylsilane (Scheme I).[6b] This particular case was attractive since the anticipated product promised to be readily convertible into the insect pheromone γ-dodecanolactone, which is known to have the *R* configuration in its natural form.[7]

Our initial attempts to couple acetal **8a** with allyltrimethylsilane under conditions previously employed in acetal-initiated cyclizations[1] were unpromising. However, when conditions such as those generally recommended[5] for coupling acetals with allyltrimethyl silane (TiCl$_4$ in CH$_2$Cl$_2$ as described below) were employed, product **9a**[8b,9] was obtained in 91% yield (see series a, Table I). GC analysis of the *tert*-butyldimethylsilyl ether showed two peaks in the ratio of 88:12,[10] corresponding to the two diastereomeric forms of **9a**.

Substance **9a** was oxidized[11] to the ketone **10a**[8a,9] and then cleaved by using sodium in ether[12] to give the *R*-alcohol **11a**,[8b,9a] [α]$_D^{25}$ +8.4° (*c* 2.5, CCl$_4$), which was indentical (GC, ^{1}H NMR, IR, MS) with the alcohol **11b**, the optical purity of which was confirmed as described below.

Although the result obtained on coupling the five-membered acetal **8a** with allyltrimethylsilane is consistent with theory, the difficulty encountered in removing the chiral auxiliary from the product **9a** reduced the utility of this process in synthesis.

Fortunately, recent cyclization studies[13] related to earlier work[1b] have revealed that acetals from either of the chiral 2,4-pentanediols possess a number of advantages over their five-membered-ring counterparts: (a) the diol is very readily available in both the *R,R* and *S,S* forms via the asymmetric hydrogenation of acetylacetone;[14] (b) the diastereoselectivity of the cyclization is improved; (c) removal of the chiral auxiliary (after cyclization) is a facile high-yield process involving β-elimination of the derived keto compound (e.g., **9 → 10 → 11**). Therefore the reactions of acetals **8b–d** with allyltrimethylsilane were examined, along with conversion of the products **9b–d** into the homoallylic alcohols **11b–d**. The results are summarized in Table I.

(1) Previous papers in this series: (a) Johnson, W. S.; Harbert, C. A.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1968**, *90*, 5279–5280. (b) Johnson, W. S.; Harbert, C.A.; Ratcliffe, B. E.; Stipanovic, R. O. *Ibid.* **1976**, *98*, 6188–6193.

(2) A related correlation has been observed in a polyolefin cyclization initiated by an optically active immonium ion: Demailly, G.; Solladié, G. *J. Org. Chem.* **1981**, *46*, 3102–3108.

(3) Solvent effects and the nature of the Lewis acid clearly play a role as well in determining the stereoselectivity of the process.

(4) After submission of the original version of this communication, McNamara and Kishi (McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7371–7372) reported, along with a series of related diastereoselective aldol coupling processes, the reaction of acetal **8** (R = C$_6$H$_5$, *n* = 0) with allyltrimethylsilane (83:17 ratio of diastereomers). This product was not, however, transformed into the homoallylic alcohol.

(5) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941; **1978**, 499–502.

(6) (a) A generous sample of (2*R*,3*R*)-butanediol was kindly donated by Dr. Karl L. Smiley, U.S. Department of Agriculture, Peoria, IL. (b) Available from Aldrich Chemical Co.

(7) (a) Wheeler, J. W.; Happ, G. M.; Araujo, J.; Pasteels, J. M. *Tetrahedron Lett.* **1972**, 4635–4638. (b) Solladié, G.; Matloubi-Moghadam, F. *J. Org. Chem.* **1982**, *47*, 91–94.

(8) (a) The crude product was homogeneous with respect to GC and TLC. (b) The product was purified by low-pressure column chromatography using Merck silica gel 60 H for thin-layer chromatography.

(9) (a) The ^{1}H NMR, IR, and mass spectra were consistent with the assigned structure. (b) A satisfactory combustion analysis was obtained for an appropriately purified specimen of this compound.

(10) The diastereomeric ratio was determined by GC on a 12-m SE-54 capillary column. The alkylation products **9** were also converted into the *tert*-butyldimethylsilyl ethers, which gave clean base-line separation on GC.

(11) Pyridinium chlorochromate (1.5 mol equiv), CH$_2$Cl$_2$, 25 °C, 18 h: Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2650.

(12) Excess Na, ether, 25 °C, stir 22 h (72% yield); this procedure was developed by G. Hanson of our laboratories (Stanford University).

(13) Johnson, W. S.; Elliott, J. D.; Hanson, G. unpublished observations.

(14) Ito, K.; Harada, T.; Tai, A. *Bull. chem. Soc. Jpn.* **1980**, *53*, 3367–3368.

Table I. Results of Transformations Shown in Scheme I

series	acetal 8, % yield[8b,9]	ether 9		ketone 10, % yield[8a,9]	alcohol 11	
		% yield[9]	ratio[10]		% yield[8b]	$[\alpha]^{25}_D$, deg (c), CCl$_4$
a	96	90[8b]	88:12	91	72[9a]	+8.4 (2.5)
b	95	98[8a]	87:13	98	98[9]	+7.9 (2.5)
c	95	92[8b]	82:18	98	73[9]	+8.3 (4.1)
d	94	96[8b]	82:18	98	88[9a]	−0.5 (4.3)

The procedure is typified by the following example. Equimolar amounts of *n*-nonaldehyde and (2*R*,4*R*)-pentanediol[6b] were condensed (C$_6$H$_6$, trace of *p*-TsOH, reflux 2 h) to give the acetal **8b**[8b,9] in 95% yield. Titanium tetrachloride (0.19 mL, 1.7 mmol) was added rapidly to a stirred solution of 273 mg (1.2 mmol) of acetal **8b** and 0.7 mL (4.4 mmol) of allyltrimethylsilane in 25 mL of dichloromethane at −78 °C under argon. After 20 min, 1 mL of methanol was added, and then the mixture was warmed to above 0 °C and partitioned between 1 M hydrochloric acid and dichloromethane. The crude product, which amounted to 318 mg (98% yield), was homogeneous by TLC, and the ^{1}H NMR spectrum was consistent with the formula **9b**. GC analysis[10] showed two cleanly separated peaks in the ratio of 87:13 corresponding to the two diastereomeric forms of **9b**. It is noteworthy that in this case a single rapid chromatography on silica gel[8b] gave a 78% yield of **9b** with a diastereomeric ratio of 94:6. Crude **9b** was oxidized[11] to the ketone **10b** (98% yield), which underwent base-catalyzed[15] β-elimination to give the homoallylic alcohol **11b**[8b,9] (98% yield) $[\alpha]^{25}_D$ +7.9° (*c* 2.5, CCl$_4$).

Proof of Constitution of the Homoallylic Alcohols. The constitution of **11b** was confirmed by its transformation[16] into the natural product γ-dodecanolactone (**12**), which has been shown by a stereorational synthesis[7] to have the *R* configuration. The structure and *R* configuration of the dienol **11c**, which has been used as an intermediate in the synthesis of nonactic acid,[19] were confirmed by comparison with an authentic specimen of (4*S*)-octa-1,7-dien-4-ol (enantio-**11c**) derived from (*S*)-(−)-malic acid.[20] The GC (co-injection) and spectral properties (^{1}H NMR, IR, MS) of the two specimens were identical. The $[\alpha]^{25}_D$ (*c* 4.1, CCl$_4$) for the *S* isomer was −12.6° while that of our specimen was +8.3°, corresponding to 65% ee, which is in agreement with the diastereomeric composition of the precursor **9c**.

The product **11d** exhibited a very low $[\alpha]_D$ in carbon tetrachloride solution; however, in ethanol the value was −7°. The configuration of this alcohol is presumed to be as shown in **11d** by analogy to the established cases (see above).

Conclusions. The diastereoselectivity of the Lewis acid catalyzed reaction of the chiral acetals **8a–d** is consistent with the hypothesis outlined at the outset, which may be reasonably extended to include six-membered-ring acetals. This process, coupled with removal of the chiral auxiliary, provides a facile enantioselective synthesis of some homoallylic alcohols (65–74% ee), which

promises to be generally useful for either the *R* or *S* forms.[21]

(21) **Note Added in Proof**: Recently S. Natarajan of our laboratory (Stanford) showed that the diastereoselectivity of the reaction **8** → **9** is dramatically improved by the use of a premixed solution of TiCl$_4$ and Ti(O-*i*-Pr)$_4$ (4 mol equiv of each) in CH$_2$Cl$_2$ (cf. Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817–826). Thus the diastereomeric ratio[10] was 96:4 for **9b** (90% yield after 4 h, −78 °C), 97:3 for **9c** (92%, 3.5 h, −78 °C), and 95.5:4.5 for **9d** (>85%, 3 h, −40 °C), corresponding to >90% ee for each of the homoallylic alcohols **11**.

Simplest Magnesium Cluster Grignard. Theoretical Evidence for Strong Metal–Metal Stabilization of RMg$_2$X Species

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Grignard reagents, RMgX, have a long history of study,[1] yet clearly there is certain knowledge about these molecules that is still lacking. In part, this is a consequence of the fact that Grignards are generally formed and used synthetically in solution. The characterization of an isolated RMgX molecule then is not so forthcoming. However, recent experimental studies[2–4] where magnesium atoms and alkyl halides are codeposited in a matrix have provided some fascinating insights into the process of forming Grignards. In particular, Klabunde and co-workers[4] have suggested that it is clusters of magnesium atoms that may be necessary for reaction with alkyl halides.

We have carried out ab initio electronic structure calculations that support Klabunde's contention because they show at least comparable stability of CH$_3$MgX and CH$_3$(Mg)$_2$X (X = F, Cl). The existence of these dimagnesium Grignards is predicted not only by these stabilities but also by what we find to be a strong magnesium–magnesium bond that places an activation barrier in the way of unimolecular dissociation to a monomagnesium Grignard.

Formation of an RMg$_2$X molecule in a matrix deposition experiment would seem possible in several ways. Mg$_2$ is a fleeting, van der Waals molecule[5] in the gas phase, but deposition of

(15) Except for the case **10a** → **11a**, the side-chain-elimination procedure involved stirring with 4:2:1 THF/MeOH/7.5 M KOH at 26 °C for 5 h.
(16) Conversion of **11b** (74% ee) into the silyl ether[8b,9] (99% yield) followed by hydroboration[17] (2.5 mol equiv of 9-BBN,[6b] THF, reflux, 5 h) and oxidation (0.5:2:1, 6 M KOH, EtOH, 30% H$_2$O$_2$) gave the alcohol i[8b,9] (81% yield). Further oxidation[18] of i (3.8 mol equiv of pyridinium dichromate,[6b] DMF, 26 °C, 10 h), followed by desilylation (*n*-Bu$_4$NF, THF, 25 °C, 12 h), and then lactonization (trace of *p*-TsOH, C$_6$H$_6$, reflux, 1 h) of the acid ii afforded the lactone **12**[8b,9] (60% yield from i), $[\alpha]^{25}_D$ +29° (*c* 1.1, MeOH) corresponding to an optical purity of 70% on the basis of the reported value of $[\alpha]^{25}_D$ +41.1° (*c* 5, MeOH).[7] The overall yield from nonaldehyde was 43%.

i   ii
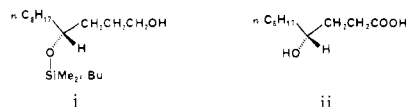
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