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CHELATION AND NON-CHELATION DIRECTED CLEAVAGE OF ACETALS

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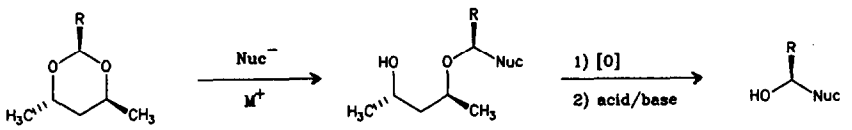
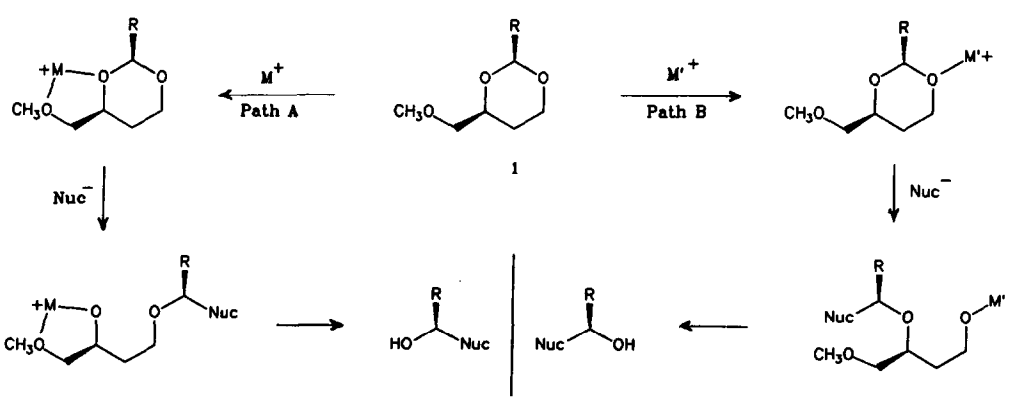
Abstract: *Regioselectivity in the cleavage of chiral 2-substituted-3-methoxymethyl-1,3-dioxanes can be controlled to a high degree by choice of an appropriate activating Lewis acid. However, the diastereoselectivity of the cleavage reactions is uniformly poor.*

In recent years, chiral acetals derived from either (R,R)- or (S,S)-2,4-pentanediol have been shown to have considerable utility for the synthesis of secondary alcohols of high optical purity[1]. Reaction of these acetals with a wide variety of carbon nucleophiles in the presence of a Lewis acid results in a highly diastereoselective cleavage of the acetal C-O bond to give a β-hydroxy ether. Subsequent degradation by a simple oxidation - elimination sequence yields the desired alcohol.



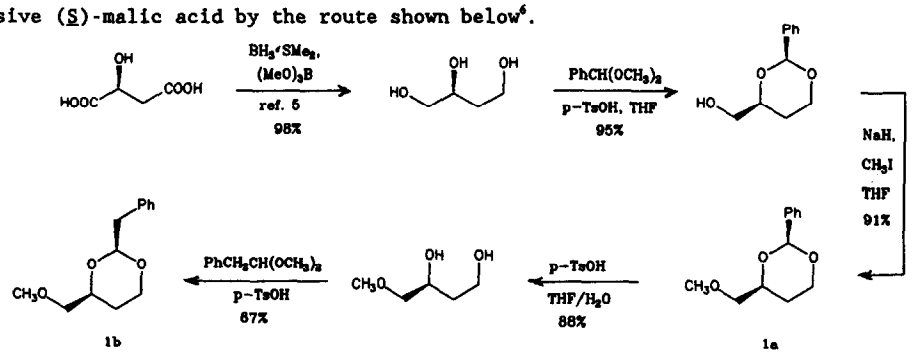
On the basis of recent results of cleavage reactions of related acetals,[2] it seems likely that the origin of the diastereoselectivity in the above reactions is a result of steric hindrance to Lewis acid activation of the acetal oxygen flanked by the R- group and the equatorial methyl group.[3] It occurred to us that the cleavage of compounds such as 1 by carbon nucleophiles might be directed towards *either* of the two acetal C-O bonds by judicious choice of the activating Lewis acid (Scheme 1).

Scheme 1

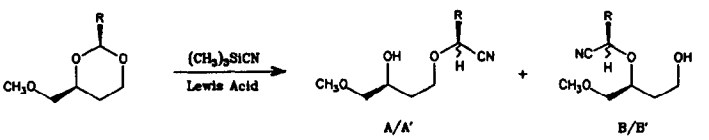


A Lewis acid subject to chelation should be directed towards activation of the acetal oxygen adjacent to the methoxymethyl group (path A). On the other hand, a Lewis acid not subject to chelation should be forced by steric hindrance towards the distal acetal oxygen[4]. Ultimately, this strategy offers the possibility of selectively obtaining *either* enantiomer of a secondary alcohol from the *same* chiral acetal template. We report here our studies on the Lewis acid mediated cleavage of compound 1 with $(CH_3)_3SiCN$.

The compounds used in these studies were synthesized in an efficient manner from inexpensive (S)-malic acid by the route shown below[6].



The bulk of our investigations on these systems have focussed on the reactions of the phenyl acetal 1a with $(CH_3)_3SiCN$. Four products are possible in these reactions: the two diastereomers resulting from chelation directed activation of the acetal (A/A'), and the two diastereomers resulting from cleavage of the acetal C-O bond distal to the methoxymethyl group (B/B'). The relative proportions of the various products were easily determined by integration of the cyanohydrin methine singlets of the products[6,7]. The results of cleavage reactions under a number of different conditions are summarized in Table 1.



There are a number of features of note in these results. Use of $TiCl_4$ as the activating Lewis acid results in an extremely high level of selectivity for the cleavage product expected on the basis of a chelation directed activation of the acetal; from >250: 1 under "optimum" conditions (entry 1) to *ca.* 22:1 under conditions designed to give minimal selectivity (entry 3). However, even under the optimum conditions of entry 1 the diastereoselectivity of the reaction is modest, at best.

TABLE 1: Cleavage of acetal **1a** with $(CH_3)_3SiCN$*

	Lewis Acid	Solvent	Temp. (°C)/ Time	A/A':B/B'	Diastereoselectivity (major regioisomer)
1	$TiCl_4$	CH_2Cl_2	-78°/2.5 hr.	≥250 : 1	1.6 : 1
2		CH_2Cl_2#	-78°/2.5 hr.	≥180 : 1	1.6 : 1
3		CH_2Cl_2	+37°/0.5 min.	22 : 1	1.2 : 1
4		1:1 CH_2Cl_2/ hexanes	-78°/2.5 hr.	≥250 : 1	1.3 : 1
5		1.6% THF/ CH_2Cl_2	0°/0.33 hr.	17 : 1	2.2 : 1
6		5% THF/ CH_2Cl_2	0°/2 hr.	11 : 1	2.4 : 1
7		8.9% THF/ CH_2Cl_2	0°/1 hr.	9.5 : 1	2.4 : 1
8		20% THF/ CH_2Cl_2	0°/6 hr.	6.2 : 1	1.6 : 1
9		5% CH_3CN/ CH_2Cl_2	-20°/2 hr.	150 : 1	1.3 : 1
10	$SnCl_4$	CH_2Cl_2	-78°/4 hr.	1 : 2.2	2.2 : 1
11	$BF_3 \cdot Et_2O$	CH_2Cl_2	0°/0.33 hr.	1 : 3	3 : 1
12	$ZnBr_2$	CH_2Cl_2	25°/20 hr.	≤1 : 250	2.1 : 1

* Unless otherwise indicated, all reactions were run at ca. 0.04 M substrate and 0.4 M $(CH_3)_3SiCN$ in the indicated solvent. $TiCl_4$ and $SnCl_4$ (1.1 equiv. relative to substrate) were added as 1.0 M CH_2Cl_2 solutions *via* syringe pump over 30 minutes. Substrate and $(CH_3)_3SiCN$ were added to a suspension of $ZnBr_2$ in CH_2Cl_2. Isolated yields of products ranged from 82 - 98%. Ratios of regio- and diastereomers were obtained from the crude products. Use of $Mg(CF_3SO_3)_2$, $MgBr_2$-etherate or $ZnCl_2$ gave no reaction within a 24 hour period.
# Inverse addition: $TiCl_4$ added *via* syringe pump to substrate, followed by syringe pump addition of $(CH_3)_3SiCN$.

On the assumption that the reaction was proceeding by a combination of S_N1 and S_N2 pathways we attempted to favor the latter by decreasing the solvent polarity; in fact, this led to a *decrease* in the diastereoselectivity (entry 4). On the other hand, increasing the solvent polarity through the addition of THF gave an initial increase in diastereoselectivity, followed by a decrease (entries 5 - 8). Both the regioselectivity and reaction rates in these latter experiments showed marked decreases with higher concentrations of THF. Within experimental error, cleavage of the acetal **1b** (R = CH_2Ph) under the conditions of entry 1 proceeded with the same regio- and diastereoselectivity found with **1a**, although the reaction was considerably slower.

A second striking feature in the reactions of 1a is the dependence of the regioselectivity of the cleavage reaction on the identity of the activating Lewis acid. In particular, use of $ZnBr_2$ (entry 12) results in a complete reversal of the regioselectivity of the cleavage reaction as compared to $TiCl_4$. Similar chelation/non-chelation control by $TiCl_4$, $SnCl_4$, BF_3 and $ZnBr_2$ have been observed by Reetz in the addition of $(CH_3)_3SiCN$ to α-amino aldehydes, although the degree of control in our system seems significantly greater[8].

With the acetal template presently in hand we are able to control the regioselectivity of the cleavage reaction with $(CH_3)_3SiCN$ with essentially complete fidelity. Efforts directed towards controlling the diastereoselectivity of these cleavage reactions are currently in progress.

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Other, related work:
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e) Schreiber, S. L.; Reagan, J., *Tetrahedron Lett.*, 1986, 27, 2945.

2. a) cleavage of acetals derived from chiral 1,3-butanediols: Johnson, W. S.; Kelson, A. B.; Elliott, J. D., *Tetrahedron Lett.*, 1988, 29, 3757.
b) relative cleavage rates of a number of substituted cyclic acetals: ref. 1c.

3. Selective Lewis acid complexation was first proposed for this system by Yamamoto and co-workers (ref. 1b). The same argument for selective cleavage of a related ketal was given by Mallory et al., *J. Org. Chem.*, 1967, 32, 1417. After the initial submission of this manuscript, a report by Denmark and co-workers appeared concerning the solution structures of complexes between BF_3 and number of substituted and unsubstituted cyclic acetals (Denmark, S. E.; Willson, T. M.; Almstead, N. G., J. Am. Chem. Soc., 1989, 111, 9258). Their findings offer convincing support for the preferential coordination of BF_3 to sterically less hindered acetal oxygens.

4. For a review of chelation and non-chelation controlled reactions see Reetz, M. T., *Angew. Chem., Int. Ed. Eng.*, 1984, 23, 556.

5. Hanessian, S.; Ugolini, A.; Dube, D.; Glamyan, A., *Can. J. Chem.*, 1984, 62, 2146.

6. All new compounds had spectral data (^1H NMR, ^{13}C NMR, IR, MS) entirely consistent with the assigned structures. In addition, structural assignments were supported by subsequent chemical transformations (to be communicated elsewhere).

7. Chemical shifts of the benzylic cyanohydrin methine protons (in C_6D_6) are δ4.56/4.54 (A/A') and δ5.43/5.16 (B/B').

8. Reetz, M. T.; Drewes, M. W.; Harms, K.; Reif, W., *Tetrahedron Lett.*, 1988, 29, 3295.

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