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ASYMMETRIC SYNTHESIS *VIA* CHIRAL ACETAL TEMPLATES. 7.[1] FURTHER STUDIES ON THE CYANATION REACTION. THE USE OF ACETALS DERIVED FROM DIOLS WITH ONE CHIRAL CENTER

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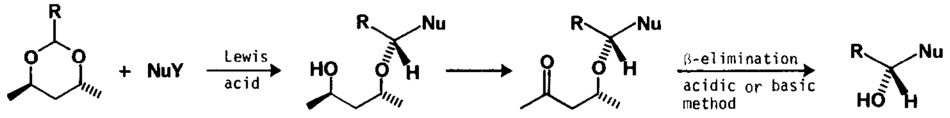
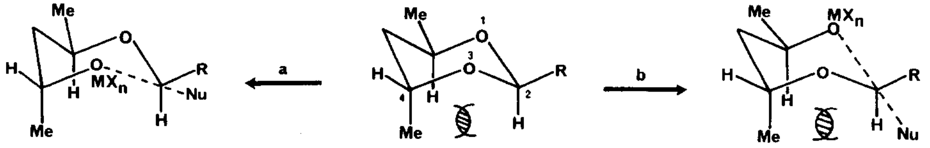
Abstract: *New examples of the cyanation reaction are described, including one that affords the cyanohydrin 8, an intermediate for synthesizing pyrethroid insecticides. Also the reaction with acetals derived from S-1,3-butanediol has been examined.*

Recently we have shown that the Lewis acid catalyzed reaction of acetals (1) derived from R,R-2,4-pentanediol,[2,3] with various nucleophilic partners (NuY) proceeds highly diastereoselectively to give adducts 2 in high yield. Removal of the chiral auxiliary from these adducts via the ketone 3 affords secondary hydroxy compounds 4 in high yield and generally in ee of 90% or over. Thus homoallylic alcohols have been produced from allyltrimethylsilane as the nucleophile;[4] propargylic alcohols from silylacetylenic compounds;[5] and cyanohydrins (as well as some derived α-hydroxy esters and β-amino alcohols) from cyanotrimethylsilane.[6] These products all have the same absolute configuration at the newly developed chiral center, shown in formula 4. The method also lends itself to preparation of products of the opposite stereochemical series by use of the acetals (enantio-1) derived from S,S-2,4-pentanediol.[2]



1 2 3 4

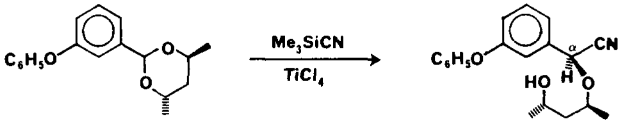
It is not so clear that the model suggested for the transition state of the reaction of 5-membered ring acetals with nucleophiles is applicable to the 6-membered counterparts.[4] We rather prefer the S_N2-like transition state A which is stabilized by a lengthening of the 2,3 bond (process "a") of the ground state B with consequential relief of the relatively large[7]



A B C

2,4-diaxial H/Me interaction. No such interaction is relieved in the alternative process "b" involving 1,2 bond lengthening in the transition state C, which is therefore less favored.

The use of cyanotrimethylsilane as the nucleophilic partner has now been extended to the coupling with the S,S acetal 5 derived from m-phenoxybenzaldehyde, which was chosen for examination because it promised to provide a route to (S)-α-cyano-3-phenoxybenzyl alcohol (8). Interest in this substance stems from the fact that most of the important pyrethroid insecticides, e.g., deltamethrin (9), are esters derived from alcohol 8 and certain complex chiral acids. The corresponding esters derived from the R-cyanohydrin (enantio-8) have relatively low activity as insecticides; hence it would be useful to have a practical source of 8 which, hitherto, has been available in high optical purity only via an impractical, classical type of resolution of racemic 8.[8]



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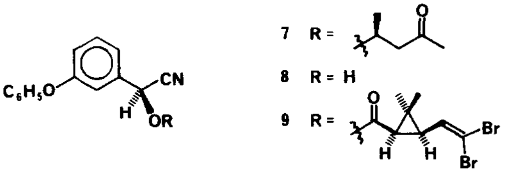
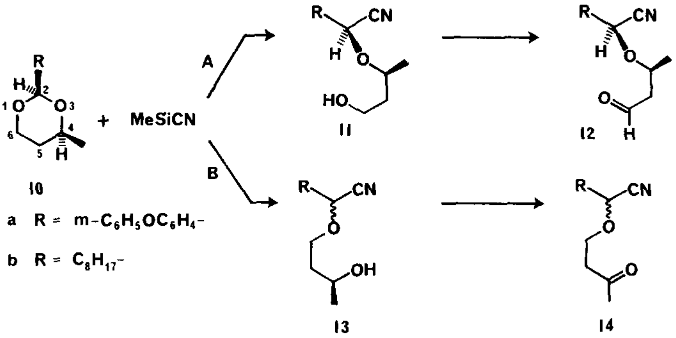


Acetal 5[9a,b,10] *was prepared in 99% yield from* m-phenoxybenzaldehyde[11] and S,S-2,4-pentanediol[2] (1.2 mol equiv) by the pyridinium tosylate method.[12] When the reaction of 5 with cyanotrimethylsilane[3] was performed at -78°C as described for the benzaldehyde acetal,[6] the product[9a,10] (100% *yield*) proved to be a 97.5:2.5 (de 95%) mixture of 6 and α-epi-6 as shown by GC[13] of the ketone mixture 7 + α-epi-7[9a,10] obtained (99% yield) on oxidation (PCC) of 6. (At 0°C the coupling reaction was less selective: 92:8.) Treatment of ketone 7 by the acid procedure[6] for effecting β-elimination gave cyanohydrin 8[9b,10a] (95% yield) $[\alpha]_D^{25}$ -24° (c. 1.0, CCl_4) having the S-configuration.[8] The ee of this product, determined by the Mosher method,[14] was 91%. A modification, which has potential of being more practical, is described below.

Acetals Derived from 1,3-Diols Having a Single Chiral Center. This type of acetal, e.g., 10 derived from S-1,3-butanediol,[3] presents an especially interesting situation, because the 2-position (derived from the aldehyde carbon) becomes chiral in the acetalization, and the product can exist in two diastereomeric forms, e.g., 10 (cis) and 2-epi-10 (trans). Moreover, in the coupling reaction the acetal has the option of opening either by pathway A to give the primary alcohol 11, or B to give the secondary alcohol 13. The reaction, therefore, has the potential of being quite non-selective.



From the conformational analysis of 1,3-dioxane systems[15] the diequatorial form of the 2(R),4(S)-cis-compound 10 should be the most stable of all possible forms of the acetal; hence under equilibrating acetalization conditions a single product would be expected. Indeed reactions[12] of S-1,3-butanediol with m-phenoxybenzaldehyde and with nonanal gave in 97% and 98% yields respectively what appeared by GC, TLC and NMR to be homogeneous products, presumably 6a[9a,c,10] and 6b.[9a,c,10] The stereochemical consequence of the cyanation of 10 (see below) *via* pathway A (presumably favored by preferential $TiCl_4$ complexation at the less hindered site) may be rationalized on the basis of an S_N2-like transition state evolving from an acetal complex in which the two chiral centers retain the same relationship as in the ground state 10.

When acetal 10a was treated, as above, with Me_3SiCN at -78°C, the product proved to be a 1:1 mixture of 11a and 13a as shown by oxidation (PCC) to the mixture of aldehyde 12a and ketone 14a which was clearly resolved by GC into a singlet (14a) and a 95:5 doublet corresponding to the diastereomeric mixture of 12a (de 90%) and α-epi-12a.[16] The 11a/13a ratio varied from 1:1 to 99:1 depending on rate of addition of reagents and temperature. Eventually the following procedure was developed to give high regio- as well as diastereoselectivity. Thus $TiCl_4$ (0.56 mmol) in CH_2Cl_2 (1 ml) was added over 40 min to a solution of acetal 10a (0.37 mmol) and Me_3SiCN (1.3 mmol) at 0°C under argon; then more Me_3SiCN (0.74 mmol) was added. After 1.5 h at 0°C the mixture was quenched with 1:1 $MeOH/CH_2Cl_2$ (0.2 ml). Preparative TLC (2:1 hexane) gave 101.5 mg (92% yield) of 11a, which on oxidation (PCC) gave 11a/13a 97:3; de of 11a, 88%. Removal of the chiral auxiliary from the oxidation product (as above) afforded cyanohydrin 8 (100% yield)[9a,10a] $[\alpha]_D^{25}$ -14°. The ee of this product proved[13] to be 71% which is the expected result considering that the optical purity of the S-1,3-butanediol was 80%.[14] Comparable results were obtained for the cyanation of 10b, but the de was lower, 81%. The obvious availability, in high optical purity, of 1,3-diols with one chiral center, *via* yeast reduction of β-keto esters,[17] offers real promise for refinement of the methodology disclosed here. Further preliminary studies with acetal 10b indicate that whether it reacts *via* pathway A or B depends also on the nature of the nucleophilic component; thus a generalized method of controlling this process is yet to be established.

Acknowledgement. We wish to thank the National Institutes of Health and the National Science Foundation for support of this research.

References and Notes

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7) Due to the short C-O-C link, the 2,4-diaxial H/Me distance in B is about 15% less than in the cyclohexane system, resulting in a 0.5-0.7 kcal/mol higher energy. Eliel, E. L. Accounts of Chem. Res., 1970, 3, 1-8.

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9) (a) The GC and TLC of the crude product showed no indication of extraneous components; (b) The product was evaporatively distilled (<1.0 mm); (c) The product was purified by low pressure column chromatography using "Merck silica-gel 60 H for thin layer chromatography."

(10) (a) The NMR, IR and mass spectra were consistent with the assigned structure. The identity of 8 was confirmed by comparison (above spectra and GC coinjection) with an authentic dl specimen. (b) A satisfactory combustion analysis was obtained for an appropriately purified specimen of this compound.

(11) We thank Dr. C. A. Henrick, Zoecon Corp., for a generous gift of this substance.

(12) Sterzycki, R. Synthesis, 1979, 724-725.

(13) The diastereomeric ratio was determined by GC on a 12-m SE-54 capillary column, which showed a base-line separation of the two peaks.

(14) Determined by GC analysis (base-line separation) of R-(+)-MTPA esters. Dale, J. A.; Dull, D. L.; Mosher, H. S. J. Org. Chem., 1969, 34, 2543-2549.

(15) Eliel, E. L. Accounts Chem. Res., 1970, 3, 1-8.

(16) 11a and 13a were separated by HPLC and they were separately oxidized to 12a[10a] and 14a[10a] respectively.

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