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1,2-ANTI DIASTEREOSELECTIVE REDUCTION OF 2-ALKYL-3-HYDROXY-KETONES VIA THEIR SILYL ETHERS.

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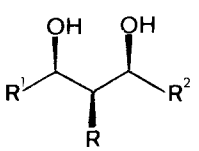
Abstract : T-butyldimethylsilyl ethers of a range of acyclic 2-alkyl-3-hydroxy-ketones are reduced with lithium aluminum hydride to give with a high 1,2-anti diastereoselective induction syn,anti or anti,anti 2-alkyl-1,3-diols.

The diastereoselective synthesis of 1,3-dioxygenated fragments is of current interest since these entities are frequently found in the structure of biologically active natural compounds. Several methods have for instance been very recently described in the literature for the stereoselective reduction of β-hydroxyketones either to 1,3-diols 1 through the reduction of an intermediate chelate (1) or to 1,3-diols 2 by an intramolecular reduction (2).



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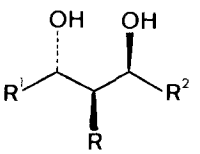

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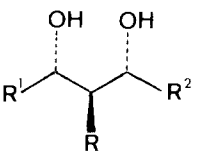

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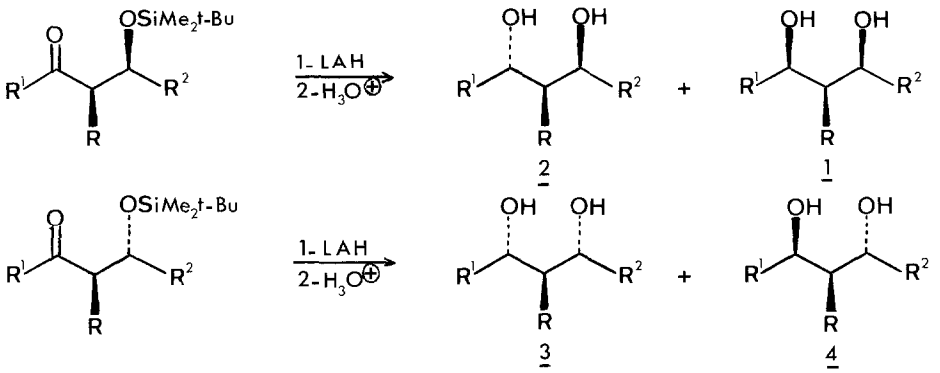
However, to our knowledge, the selective obtention of anti,anti 1,3-diols 3 through the reduction of 2-alkyl-3-hydroxy-ketones has not yet been mentioned.

In this communication we report a simple and general method for the selective formation of either anti,anti 1,3 diols 3 or syn,anti 1,3-diols 2. We examined the selectivity of the reduction of a range of t-butyldimethylsilyl ethers of anti-2,3 and syn-2,3 2-alkyl-3-hydroxy-ketones by lithium aluminum hydride (3).

The reductions were carried out in diethyl ether at -78°C with an excess (1,5 equivalents) of reducing agent. The mixture was then allowed to reach room temperature and was hydrolyzed with 10% aqueous HCl. In these conditions the hydroxyl protecting group was cleaved and the free 1,3-diols were very simply obtained.

The results of such reductions are listed in Table I. In all cases (entries 1 to 8) a high



degree of 1,2-anti asymmetric induction (>15:1) is achieved and is not affected by the relative stereochemistry of the C-2 and C-3 substituents of the starting silyloxy ketones (4).

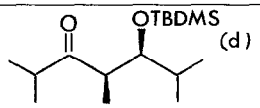
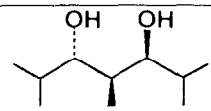
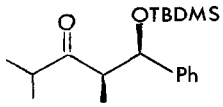
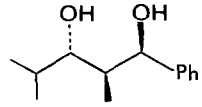
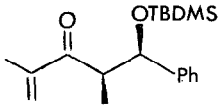
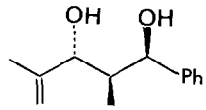
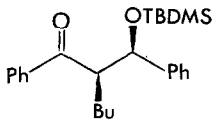
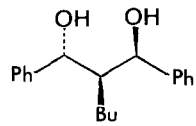
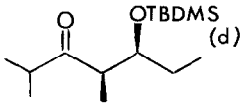
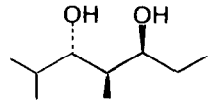
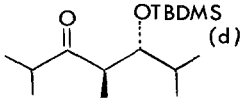
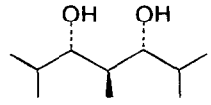
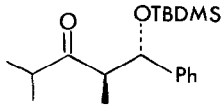
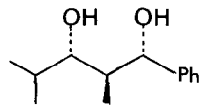
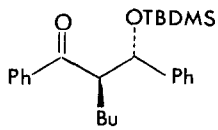
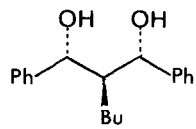
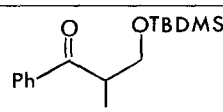
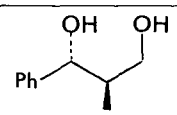
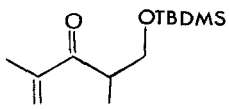
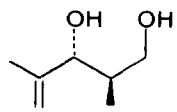
The bulky t-butyldimethylsilyl protecting group was chosen (6) in order to prevent intramolecular chelation, so that the reduction should proceed through the open-chain model A proposed by Felkin (7) and Anh (8).

A B

The stereochemical course of the reaction can be rationalized by considering the relative stabilities of the two conformers A and B. Conformer B must be destabilized by the steric interaction between the substituents R and R^1 and furthermore the non-perpendicular approach of the reducing agent is impeded by the presence of R in B. Therefore, the reduction should occur predominantly through conformer A, leading to 1,2-anti 1,3-diols 2 or 3. This assumption is supported by the poor selectivity (~60:40) observed during the LAH reduction of β-(t-butyldimethylsilyl)oxy ketones bearing no substituents in α-position (R = H). The high degree of generality shown by the reaction is of real interest compared to the results reported for the Vitride® reduction of α-(t-butyldiphenylsilyl) oxy ketones (9). In our case the reduction seems effectively quite independent of the nature of the substituents R, R^1 and R^2. However it must be noticed that in the absence of a substituent in the γ-position (R^2=H) the CH_2-$OSiMe_2$t-Bu group is not large enough to favor the conformers A or B and thus the selectivity of the reduction cannot be controlled (entries 9 and 10).

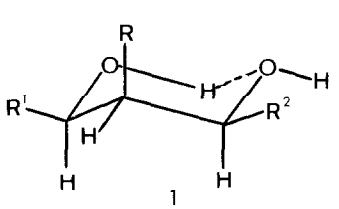
The relative configurations of diols 1-4 have been assigned by careful examination of their ^1H and ^{13}C N.M.R. spectra. It has been reported that 1,3-diols exist predominantly in an intramolecularly hydrogen-bonded form (1c,12). The vicinal coupling constants for the C-1/C-2 and C-2/C-3 protons can be rationalized in term of these structures (13) and we effectively observed J_{syn} (0-4Hz) $> J_{anti}$ (5-10 Hz). The relative 1,3-syn or 1,3-anti configurations of the two hydroxy groups were

Table I. Stereoselective reduction of 2-alkyl-3-(t-butyldimethylsilyl)oxy ketones by lithium aluminum hydride

Entry	Reactant [a]	Product	Ratio [b] 2/1	Ratio [b] 3/4	Yield % [c]
1	 (d)		98/2		73
2			96/4		90
3			> 98/2		74
4			97/3		81
5	 (d)		96/4		76
6	 (d)			94/6	85
7				98/2	91
8				97/3	71
				anti/syn	
9				30/70	87
10				38/62	92

a) The silyl ethers were prepared, unless otherwise stated, following the standard procedure (10).
b) Diastereomer ratios were estimated by ^{1}H NMR of the crude product.
c) Isolated yields of the major diastereomer isolated by column chromatography.
d) Prepared with t-butyldimethylsilyl trifluoromethanesulfonate (11).

confirmed by ^{13}C N.M.R. : the sums of the chemical shifts of the two oxygen bearing carbon atoms were in all cases numerically smaller for the 1,3-anti diols than for their 1,3-syn counterpart (12). Furthermore we found that if R = CH_3, the chemical shift of the carbon of the methyl group is characteristic and can be useful for structure assignment: δ = 4.1 - 4.5 ppm in 1 ; δ = 10.2 - 10.9 ppm in 2 ; δ = 13.1 - 13.4 ppm in 3 (14).



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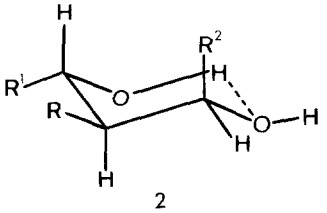

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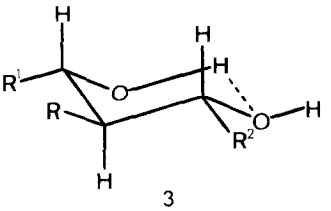

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In conclusion the method described in this note complements nicely the recently reported selective reductions of β-hydroxy-ketones.

References and Notes

1) a) T. NAKATA, Y. TANI, M. HATOZAKI and T. OISHI, Chem. Pharm. Bull., **1984**, 32, 1411.
b) K. NARASAKA and F.C. PAI, Tetrahedron, **1984**, 40, 2233.
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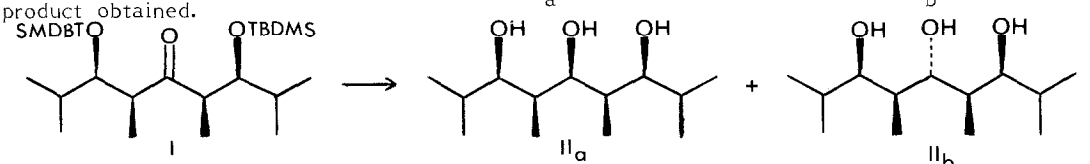
2) a) S. ANWAR and A.P. DAVIS, J. Chem. Soc. Chem. Comm., **1986**, 831.
b) D.A. EVANS and K.T. CHAPMAN, Tetrahedron Letters, **1986**, 27, 5939.

3) Two other metal hydrides were tested : Red-Al and DIBAL. But LAH was found to give the best selectivity.

4) While this manuscrit was in preparation the reduction I $\xrightarrow{LAH}$ II has been reported (5) to give a ratio II_a/II_b = 94/6. However considering the ^{13}C chemical shifts of the methyl groups observed by the authors (δ = 10.39 and 11.21 ppm for II_a) and in view of the results described here, we think that the configuration attributed to II_a is erroneous and that in fact II_b is the major product obtained.



I $\quad$ II_a $\quad$ II_b

5) P.A. McCARTHY and M. KAGEYAMA, J. Org. Chem., **1987**, 52, 4681.

6) The trimethylsilyl protecting group was not bulky enough to totally prevent chelation since the 1,2-anti selectivity of the reduction of α-alkyl-β-trimethylsilyloxy-ketones was found to be only around 5 to 1.

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11) Since in standard conditions (t-BuMe2Cl/Imidazole in DMF) the reaction was slow and led to partial isomerization of the reactant, we used t-butyldimethylsilyl trifluoromethanesulfonate, a very reactive silylating agent mentioned by R.F. STEWART and L.L. MILLER, J. Amer. Chem. Soc., **1980**, 102, 4999.

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14) These criteria seem quite general and, although not noticed by the authors, the different ^{13}C chemical shifts observed for the methyl groups (δ =4.58 and 4.64 ppm for syn-syn, δ =11.09 and 11.21 ppm for syn-anti and δ =13.63 and 13.76 ppm for the anti-anti diastereomers) can be used for the structure determination of the different 1,3-diols described in a recent publication: J. BARLUENGA, J.G. RESA, B. OLANO and S. FUSTERO, J. Org. Chem., **1987**, 52, 1425.

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