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STEREOSELECTIVE REDUCTION OF β-ALKOXY KETONES: A SYNTHESIS OF SYN-1,3-DIOLS

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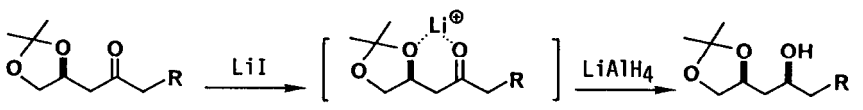
Abstract: The diastereoselective reduction of acyclic β-alkoxy ketones with lithium aluminum hydride in the presence of lithium iodide has been studied and found to provide syn-1,3-diol derivatives with high diastereoselection.

The stereocontrolled formation of 1,3-diols is of great interest to synthetic chemists since the 1,3-polyhydroxylated chain forms the basic skeleton of polyene and polyol macrolide antibiotics.[1] In connection with our stereochemical study of sporaviridin,[2] a polyol macrolide, we needed an efficient method for preparing syn-1,3-diols. Among the procedures developed for the synthesis of 1,3-diols, hydroxy-directed reduction of β-hydroxy ketones has proven to be highly valuable, with boron or zinc chelating intermediates playing an important role in determining the stereoselectivity.[3] On the other hand, aluminum complex hydride methods have been of less interest due to their low selectivity.[4] We have now developed a lithium aluminum hydride-lithium iodide reduction as a promising new method for our purposes. In this letter we report our results on the β-alkoxy-directed reduction of acyclic β-alkoxy ketones using $LiAlH_4$-LiI as the reducing agent (eq. 1).



A B C (eq 1)

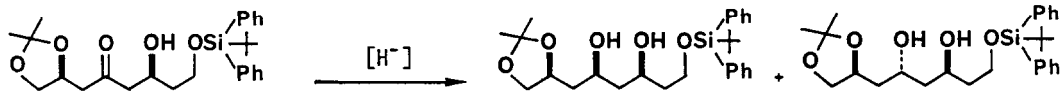
Diastereoselection 95:5

The β-alkoxy-β'-hydroxy ketone **1** is a useful precursor for 1,3-polyol synthesis.[5] Reduction of the ketone **1** with $NaBH_4$ and $LiAlH_4$ afforded 1,3-diols with moderate 1,3-syn selectivity in nearly quantitative yields (Table I, entries 1,3,4). Considering the typically low selectivity observed in $LiAlH_4$ reductions of β-hydroxy ketones,[4a] these results suggested that 1,3-asymmetric induction from the β-alkoxy group in **1** was operative.

In order to increase the asymmetric induction, the effect of additional inorganic salts on this reduction was examined.[4c] Eventually, the syn-stereoselectivity of the reduction was remarkably enhanced by the addition of LiI. Reduction of **1** with $LiAlH_4$ in the presence of LiI in ether at -100°C for 30 min resulted in the formation of the syn and anti-diols **2**[6] with excellent syn-selectivity (syn:anti = 95:5)(entry 8).

To examine the affect of the lithium cation on the syn-selectivity, the reductions of the β-alkoxy ketones **3**, **5**, and **7** with $LiAlH_4$ in the presence of LiI were examined. In all cases

the major reduction products were found to possess a syn-relationship between the newly formed hydroxy group and the β-alkoxy group of the 1,3-dioxolane ring. The $LiAlH_4$-LiI method again exhibited high levels of 1,3-syn-diastereoselection.



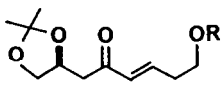
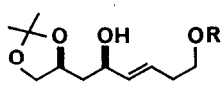
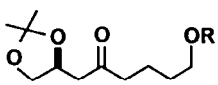
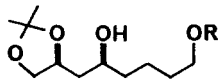
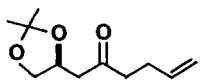
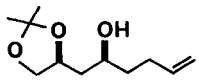
1 syn-2 anti-2

Table I Diastereoselective Reduction of β-Alkoxy-β'-hydroxy Ketone 1

	hydride	solvent	temp(°C)	syn : anti[a]	yield(%)
1	$NaBH_4$	MeOH	0	75 : 25	99
2	$NaBH_4$	MeOH	-78	63 : 37	90
3	$LiAlH_4$	Et_2O	0	75 : 25	97
4	$LiAlH_4$	Et_2O	-78	79 : 21	97
5	$LiAlH_4$	THF	-78	76 : 24	99
6	$LiAlH_4$-LiI	Et_2O	0	86 : 14	99
7	$LiAlH_4$-LiI	Et_2O	-78	89 : 11	96
8	$LiAlH_4$-LiI	Et_2O	-100	95 : 5	94
9	$LiAlH_4$-LiI	THF	-78	87 : 13	88
10	DIBAL-LiI	Et_2O	-78	66 : 34	95

a. Syn:anti ratios determined by NMR (400MHz, C_6D_6) analysis.

Table II Reduction of β-Alkoxy Ketones by $LiAlH_4$-LiI Method[a]

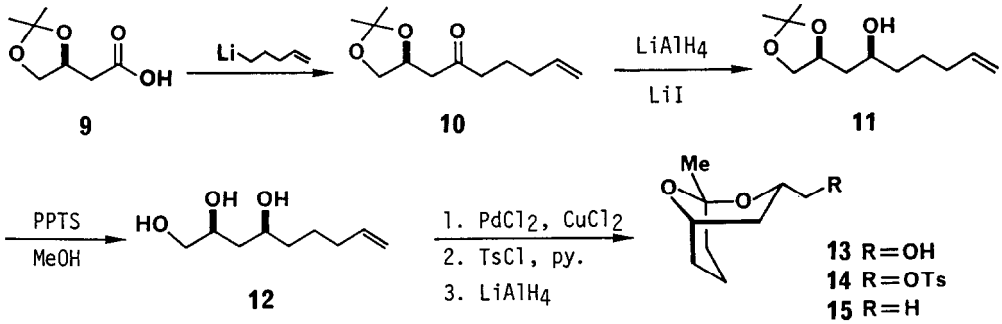
	β-alkoxy ketone[b]	product	temp(°C)	syn : anti[c]	yield(%)
1	 3	 4	-100	96 : 4	98
2	 5	 6	0 -78 (0	93 : 7 95 : 5 74 : 26	90 98 80)[d]
3	 7	 8	-78 (-78	95 : 5 82 : 18	98 98)[d]

a. Reductions were carried out in ether for 30 min.
b. R= t-Butyldiphenylsilyl
c. Syn:anti ratios determined by NMR (400MHz, C_6D_6) analysis.
d. Reductions were conducted in the absence of LiI.

The $LiAlH_4$-LiI reduction of β-alkoxy-β'-hydroxy and β-alkoxy ketones with terminal 1,3-dioxolane rings is a versatile and useful method for the diastereoselective formation of syn-1,3-diol derivatives. The highly syn-selectivity arises from β-chelation of both the ketone and ether oxygens with lithium cation to form an intermediate complex B (eq. 1). This locks the conformation of the β-alkoxy ketone chain and hydride then attacks from less hindered side, resulting in the formation of the syn-product C.

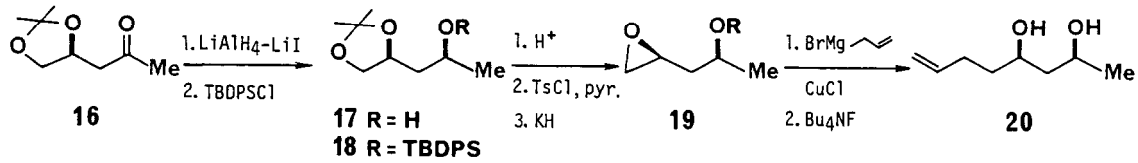
Applications of the $LiAlH_4$-LiI reduction were demonstrated in short and efficient syntheses of optically active (-)-endo-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane **15**, a host specific substance for the ambrosia beetle which infests the Norwegian spruce,[6] and a synthetic intermediate **20** of (+)-nonactic acid.[7]

The starting ketones **10** and **16** were prepared from the acid **9**, which was obtained from (S)-(-)-malic acid (95% ee),[8] by the treatments of 4-pentenyllithium and methyllithium, respectively, in good yield. A highly syn-selective reduction of **10** with $LiAlH_4$ in the presence of LiI in ether at -78°C gave the syn-alcohol **11**, $[\alpha]_D^{22}$+3.35° (c 1.0, $CHCl_3$), in 88% yield (syn:anti=95:5). Deprotection of the acetonide group in **11** gave the triol **12**, $[\alpha]_D^{22}$+7.84° (c 0.5, $CHCl_3$) in 95% yield. Direct bicyclic acetal formation was achieved



9 **10** **11** **12**

using palladium chloride catalyst with cupric chloride[9] in DMF-H_2O (95:5), giving **13**, $[\alpha]_D^{24}$ -17.4° (c 1.0, $CHCl_3$) in 60% yield. Tosylation of **13** followed by $LiAlH_4$ reduction of **14** yielded the bicyclic acetal **15** (84% overall yield), $[\alpha]_D^{24}$-35.9° (c 0.5, pentane), Lit.[6g] $[\alpha]_D^{22}$ -37.3°(pentane).



16 **17** R = H, **18** R = TBDPS **19** **20**

The synthesis of **20** started with the $LiAlH_4$-LiI reduction of **16** at -78°C, giving **17**, $[\alpha]_D^{23}$+14.7° (c 1.0, $CHCl_3$) in 87% yield (syn:anti=94:6). After protection of the hydroxy group **18** was converted to the epoxide **19**, $[\alpha]_D^{24}$-11.4° (c 0.67, $CHCl_3$) in 77% overall yield. Copper (I)-catalyzed oxirane ring opening with allylmagnesium bromide followed by deprotection gave the (+)-nonactic acid synthetic intermediate **20** (92% overall yield), $[\alpha]_D^{24}$+21.5° (c 0.37, CCl_4), Lit.[7b] $[\alpha]_D^{25}$+18.4° (c 1.0, CCl_4).

General procedure of $LiAlH_4$-LiI reduction: To a solution of an alkoxy ketone (1 mmol) in dry ether (20 ml) at room temperature under nitrogen was added LiI (10 mmol) and the mixture was stirred at -40°C for 5 min. The resulting mixture was then cooled to the

indicated temperature and $LiAlH_4$ (10 mmol) was added. The reaction mixture was stirred for 30 min. Workup in usual manner gave products. The reduction products may be purified by flash chromatography on silica gel.

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