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Regioselective reduction of keto groups in Michael adducts of levoglucosenone and cyclohexanone

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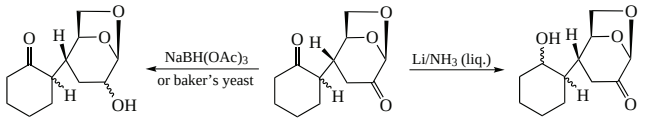
Conditions for the highly regioselective reduction of the specified keto groups in the Michael adduct of levoglucosenone and cyclohexanone have been developed. Selective reduction of the keto group in the cyclohexanone moiety was performed under the action of lithium metal in NH_3/THF system. Reduction of the keto group in the carbohydrate residue was accomplished microbiologically or by refluxing with $NaBH(OAc)_3$ in benzene.



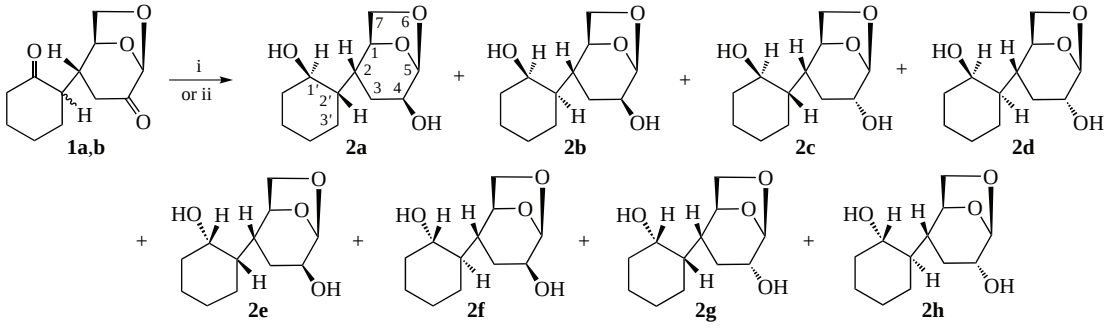
Keywords: levoglucosenone, cyclohexanone, Michael adduct, regioselective reduction, ketones.

Studies on the reactivity of Michael adduct of levoglucosenone with cyclohexanone[1] led us to the conclusion that the chemical behavior of its keto groups toward some reagents differs significantly. In fact, the keto group in the carbohydrate residue can be protected with high regioselectivity into a dioxolane, methoxylated, dichloromethylated as well as converted into tosylhydrazone or epoxide functions.[2] Assuming that the lower reactivity of the keto group in the cyclohexanone moiety is due to its shielding by the carbohydrate residue, the reverse removal of the dioxolane protective group from the cyclohexanone moiety should seem problematic. However, this reaction occurs quite readily, in contrast to the hard-to-remove dioxolane protection of the carbohydrate residue. These facts prompted us to study herein the possibility of regioselective reduction of keto groups in the Michael adduct of levoglucosenone and cyclohexanone being the diastereomeric mixture **1a**,**b**.

The reduction of diketone mixture **1a**,**b** with sodium borohydride was not selective and afforded a mixture of eight diastereomeric diols **2a**–**h** in total 94% yield (Scheme 1). A similar result was obtained upon application of Red-Al [sodium bis(2-methoxyethoxy)aluminum hydride] when the yield of diol mixture **2a**–**h** was 88%. Despite the difficulties in the spectral analysis of this mixture, we indicated in both cases noticeable selectivity towards diols **2a**,**c** with the 1′*R*-configuration. Most likely, this is a consequence of shielding of the keto group in the cyclohexanone moiety by the carbohydrate residue.

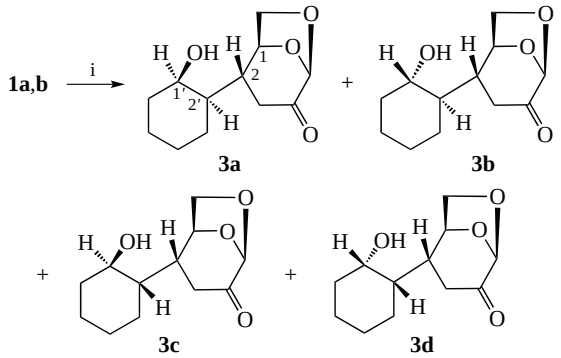
Taking into account the weak capability of cyrene, the dihydro derivative of levoglucosenone, to enolization in comparison with ordinary ketones, we studied the possibility of regioselective reduction of the keto group in the cyclohexene moiety in adducts **1a**,**b** with lithium in liquid ammonia.[3] The reaction resulted exclusively in the reduction of the keto group in the cyclohexanone moiety to give four diastereomeric keto alcohols **3a**–**d** in 10:9:5:3 ratio in a total yield of 92% (Scheme 2). To exclude the possible contribution of the cyclohexanone substituent to the reduction of the keto group in the carbohydrate residue, a control experiment with cyrene was performed. In fact, cyrene remained unchanged when treated with Li/NH_3 (liq.) under similar conditions. The attempt confirmed the inertness of the hard-to-enolyze cyrene to the action of Li/NH_3 (liq.).

Considering the selective reducing ability of sodium triacetoxyborohydride $NaBH(OAc)_3$ with respect to ketones, which strictly depends on the presence of a suitably arranged additional carbonyl group in substrates,[4] we studied the capability of this reagent to perform the regioselective reduction of diketones **1a**,**b**. Their prolonged reflux with $NaBH(OAc)_3$ in



2a/**2b**/**2c**/**2d**/**2e**/**2f**/**2g**/**2h** = 5.0:4.0:10.0:0.6:0.5:1.7:1.0:2.0

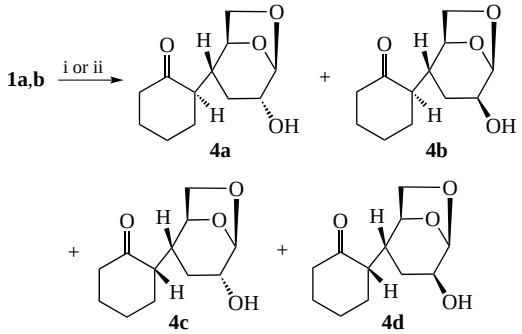
Scheme 1 *Reagents and conditions*: i, $NaBH_4$, EtOH, 25 °C, 30 min, 94%; ii, Red-Al, THF, 0 °C, 2 h, 88%.



Scheme 2 *Reagents and conditions*: i, Li/NH_3 (liq.), THF, –33 °C, 5 min, 92%.

benzene resulted in the selective reduction of only the keto group in the carbohydrate moiety with predominance of two 2′*R*,4*R*- and 2′*R*,4*S*-diastereomers **4a** and **4b** in 1 : 1 ratio, while 2′*S*,4*RS*-diastereomers **4c**,**d** were detected in trace amounts (Scheme 3). The formation of mostly diastereomers **4a**,**b** is presumably due to the complexation of $NaBH(OAc)_3$ through both oxygen atoms of the acetal center followed by hydride attack at the keto group. The reaction outcome is affected by the solvent. For example, treatment of adducts **1a**,**b** with $NaBH(OAc)_3$ in ethyl acetate gave diastereomeric diols **2a**–**h**. Thus, while in the former case the reduction of the keto group in the cyclohexanone moiety presumably occurred due to its enolyzing capability, its inertness towards $NaBH(OAc)_3$ can be explained by the formation of associates with the solvent rather than by the lack of anchimeric assistance.[4(c)]

Taking into account that enzymatic synthesis is more selective, the reduction of adducts **1a**,**b** with baker's yeast (*Saccharomyces cerevisiae*)[5] was studied. The reaction in water



Scheme 3 *Reagents and conditions*: i, $NaBH(OAc)_3$, C_6H_6, 25 °C, 24 h, 70%; ii, *S. cerevisiae*, D-glucose, H_2O, 30 °C, 11 days, 88%.

at 30 °C and with continuous stirring in the presence of D-glucose brought about a mixture of diastereomeric alcohols **4a**–**d**. The ratio of diastereomers 2′*R*,4*R*-**4a** and 2′*R*,4*S*-**4b** was 2 : 6331, unlike in the case of $NaBH(OAc)_3$. The 2′*S*,4*RS*-diastereomers were also formed in trace amounts (see Scheme 3).

In conclusion, if a molecule contains keto groups that differ in their enolyzing capability, their differentiation can be used for the direct conversion to keto alcohols or in some cases as an alternative to the use of protecting groups.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.09.021.

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