In this paper we describe the reduction by NaBH₄ of some cyclopentanones containing an oxygenated function at the side chain position β to the carbonyl group, both in the presence and in the absence of CeCl₃. Some suggestions for the rationalization of the results are discussed, considering the stereochemical course of the reactions.

Keywords: cyclopentanones; stereoselective reduction; sodium borohydride; ceric chloride.

In the course of our studies on the synthesis of natural products we came across the problem of stereoselectively reducing some cyclopentanones with a quaternary α-carbon atom and containing an oxygenated function at the side chain position β to the carbonyl group (general structure A, Figure 1).

\[
\begin{align*}
\text{R₁} & \quad \text{R₂} \\
\text{O} & \quad \text{R₃}
\end{align*}
\]

\[\text{R₃ = H or alkyl}\]

\text{Figure 1.}

As no simple solution to this problem could be found in the literature, we undertook a detailed study of the reduction of compounds 1, 2, 3 and 4 (see Scheme 1 and Table 1). This led to a number of useful results and conclusions which we now disclose.

Gallagher \textit{et al}. demonstrated that the reduction of a cyclopentanone bearing an α-side chain containing a hydroxyl group β to the ring carbonyl function (cf. structure A) can be effected with low stereoselectivity by NaBH₄ and with high stereoselectivity by NaBH(OAc)₃; both reagents gave the same main product, and the results can be rationalized by assuming a generally accepted mechanism of hydroxyl group complexation to the reagent followed by intramolecular delivery of hydride to the ketone.

Luche \textit{et al}. have used CeCl₃ as a catalyst for regioselective 1,2 - reductions of α-ones by NaBH₄. They proposed that the major effect of Ce⁺³ is to catalyse the formation of alkoxycarbonyloxyborohydrides, and they found low stereoselectivity in their reductions. However, Maycock \textit{et al}. have reduced a number of prostaglandin precursors, \textit{i.e.} substituted cyclopentenones, and obtained considerable stereoselectivity in some cases. There are also a few other examples of stereocontrol during reduction by the addition of CeCl₃ to NaBH₄. In this paper we describe the reduction of some cyclopentanones (see Table 1) with NaBH₄ in the absence (reaction conditions A) or in the presence (reaction conditions B) of CeCl₃. The oxygenated group β to the ring ketone function is either a hydroxyl group (compounds 2 and 3) or an alkoxyl group (compounds 1 and 4). A remarkable difference between these two cases can be noted in the results: when a β-hydroxyl group is present, the major product of the reaction is always the isomer a, the addition of CeCl₃ having the main effect of lowering the yield. However, when a β-alkoxy group is present, CeCl₃ has a pronounced effect on the ratio of isomers, roughly reversing it and giving isomer b as the major product. This selectivity is to be expected considering the near planar conformation of the five membered ring and the affinity between NaBH₄ (or any of its possible methoxyborohydrid derivatives) and the oxygenated functions. After complexation (and resultant activation), NaBH₄ should deliver the hydride from the same face as the OH or OR groups, thus producing isomer a. Compound 1 could give a slightly different result as a consequence of competition between steric hindrance and complexation. Further evidence supporting this conclusion is given by the LiAlH₄ reduction of compound 1, which produced a 3:1 ratio of isomers 5a:5b, presumably due to stronger complexation between the LiAlH₄ and the OMe groups.

The role of CeCl₃ can be rationalized in at least two different ways: it can be assumed either that the salt forms a complex with the oxygenated functions, thus reducing the importance of NaBH₄ complexation and introducing additional steric hindrance, or that the salt acts only as a catalyst for the formation of alkoxycarbonyloxyborohydrides from NaBH₄ and the solvent, enhancing the reactivity and the bulk of the reducing agent and lowering its tendency towards complexation with substrate oxygenated functions. However, the difference between the results obtained with hydroxyl and alkoxyl groups would be better explained by assuming that it is due to the unequal tendency for complex formation between these groups and NaBH₄; the hydroxyl group would form a strong complex with NaBH₄, while the complex formed with alkoxyl groups would be weak. It should be noted that Maycock \textit{et al}. considered, and discarded, the idea of chelation control to explain the stereochemistry of their reductions; however, their results are not really inconsistent with this interpretation, and it must be noted that they did not compare results obtained in the presence of Ce⁺³ to those obtained using only NaBH₄.
Table 1. Reduction of Cyclopentanones

<p>| starting | R₁  | R₂  | R₃  | reaction | product | yield | ratio a:b |</p>
<table>
<thead>
<tr>
<th>material</th>
<th></th>
<th></th>
<th></th>
<th>conditions</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe</td>
<td>H</td>
<td>OMe</td>
<td>A</td>
<td>5a + 5b</td>
<td>90</td>
<td>1:1</td>
</tr>
<tr>
<td>2</td>
<td>OH</td>
<td>H</td>
<td>CH₂CO₂Me</td>
<td>B</td>
<td>6a (+6b)</td>
<td>84</td>
<td>6a only</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>OH</td>
<td>CH₂CO₂Me</td>
<td>B</td>
<td>7a + 7b</td>
<td>75</td>
<td>7a only</td>
</tr>
<tr>
<td>4</td>
<td>OEt</td>
<td>H</td>
<td>CH₂CO₂Me</td>
<td>B</td>
<td>8a + (8b)</td>
<td>56</td>
<td>3:1</td>
</tr>
</tbody>
</table>

reaction conditions: A: NaBH₄/MeOH/-78°C, 2 h (in the case of compound 1, the reaction temperature was 0°C). B: NaBH₄/MeOH/CeCl₃·7H₂O/-78°C, 2 h.

§ compound 6b was not formed; compound 7b slowly lactonizes to form compound 12, but it could be isolated and characterized; compound 8b was never isolated, as it rapidly lactonizes to give compound 13, which was the actual indicator of the amount of 8b obtained in the reduction.

† yield of crude product, calculated as if it consisted only of the mentioned isomeric products.
‡ ratio determined by H NMR.
§ ratio determined by yields after column chromatography.

Compounds 1 - 4 were prepared from the keto-aldhyde 9 (Figure 2). Treatment of 9 with trimethyl orthoformate and PTSA gave compound 1 in 77% yield. We have already described the details for the preparation and analyses of compounds 2 - 4, a Reformatsky reaction on compound 9 with methyl bromoacetate and zinc in Et₂O/CH₂Cl₂ at reflux furnished a mixture of products 2 and 3 in a ratio of 2:1, and a yield of 60%; compound 4 was obtained in 56% yield by treating 2 with Et₂O·BF₃ and K₂CO₃ in CH₂Cl₂ at room temperature for 24 h.

Figure 2.

The relative stereochemistry of compounds 5a and 5b was determined with the aid of NOE experiments, which showed that the carbinolic proton of isomer 5b had a stronger signal enhancement by irradiation of the methyl group at the asymmetric carbon when compared to the carbinolic proton of isomer 5a.

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EXPERIMENTAL

Reaction Conditions A

Reduction of Compound 1. A solution of compound 1 (251 mg, 1.25 mmol) in CH₃OH (10 mL) was cooled to 0°C, NaBH₄ (472 mg, 1.25 mmol) was added and the mixture was stirred at 0°C for 2 h. Water was then added, and the resulting mixture was diluted with water and ether, the layers were separated, and the aqueous layer was extracted with ether (5 times). The organic phase was washed with saturated NaCl solution, dried with MgSO₄ and concentrated under vacuum. The residue (228 mg, 90%), a pale yellow oil, consisted of a 1:1 mixture (by H NMR) of compounds 5a and 5b. This mixture was separated by column chromatography (silica gel) eluting with hexane at the beginning and then adding gradually ethyl acetate to reach a maximum of 20% of ethyl acetate in hexane.

Note: Compounds 2, 3 and 4 were reduced in a similar manner, except that the reaction temperature was -78°C.

Reaction Conditions B

Reduction of Compound 1 in the Presence of CeCl₃. A solution of compound 1 (54.6 mg, 0.27 mmol) in CH₃OH (5 mL) was cooled to -78°C, CeCl₃·7H₂O (201 mg, 0.54 mmol) was added and the mixture was stirred at -78°C for 10 min, NaBH₄ (12.0 mg, 0.32 mmol) was added and stirring was continued at -78°C for another 2 h. The temperature was then raised to 0°C and the reaction was quenched and extracted as described under reaction conditions A. After evaporation of the solvent, a colorless oil (49.6 mg, 90%) was obtained, consisting of a 1:6 mixture of compounds 5a and 5b, as determined by the yields after column chromatography.

Note: Compounds 2, 3 and 4 were reduced in a similar manner.
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5. In the case of compound 1 it was not exactly a reversion, as NaBH₄ alone gave no stereoselectivity.⁶
6. It is also possible that the lack of stereoselectivity observed in the reduction of 1 with NaBH₄ is, at least partly, due to the comparatively high temperature (0°C) used in this case.
8. All compounds described in this text were fully characterized by ¹H and ¹³C NMR, IR and mass spectra.
10. Spectroscopic data for compounds 1, 5a and 5b: Compound 1: IR (liquid film) 1777, 1371, 1194, 1092, 1073 cm⁻¹; ¹H NMR (CDCl₃, 80 MHz) δ 4.01 (s, 1H), 3.38 (s, 3H), 3.34 (s, 3H), 2.29 (d, 1H, J=13.8 Hz), 2.10 (d, 1H, J=16 Hz), 1.99 (dd, 1H, J₁=16.0 Hz and J₂=1.5 Hz), 1.39 (dd, 1H, J₁=13.8 Hz and J₂=1.5 Hz), 1.16 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H); ¹³C NMR (CDCl₃, 20 MHz) δ 217.5, 110.1, 57.7, 56.5, 54.6, 53.7, 44.5, 32.7, 30.3, 22.2; MS m/z (rel. intensity) 169 (M⁺)¹ (10), 129 (20), 115 (21), 101 (8), 75 (100), 55 (9). Compound 5a: IR (liquid film) 3454, 1368, 1188, 1104, 1070 cm⁻¹; ¹H NMR (CDCl₃, 80 MHz) δ 4.04 (dd, 1H, J₁=7.7 Hz and J₂=10.1 Hz), 3.91 (s, 1H), 3.46 (s, 3H), 3.43 (s, 3H), 2.16 (br, s, 1H), 1.64 (dd, 1H, J₁=12.7 Hz and J₂=7.7 Hz), 1.53 (dd, 1H, J₁=12.7 Hz and J₂=10.1 Hz), 1.55 (d, 1H, J₁=13.9 Hz), 1.26 (d, 1H, J₁=13.9 Hz), 1.07 (s, 3H), 0.99 (s, 3H), 0.91 (s, 3H); ¹³C NMR (CDCl₃, 20 MHz) δ 113.4, 74.7, 58.0, 56.6, 50.4, 48.6, 46.3, 33.1, 32.6, 32.4, 16.1; MS m/z (rel. intensity) 202 (M⁺)² (8), 135 (40), 111 (12), 95 (16), 85 (29), 75 (100), 69 (17). Compound 5b: IR (liquid film) 3466, 1372, 1186, 1107, 1070 cm⁻¹; ¹H NMR (CDCl₃, 80 MHz) δ 4.27 (s, 1H), 3.92 (t, 1H, J=5.0 Hz), 3.52 (s, 3H), 3.50 (s, 3H), 2.98 (br, s, 1H), 1.85 (d, 1H, J₁=13.5 Hz), 1.25 (d, 1H, J₁=13.5 Hz), 1.82 (dd, 1H, J₁=13.0 Hz, J₂=5.0 Hz), 1.87 (dd, 1H, J₁=13.0 Hz, J₂=5.0 Hz), 1.13 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H), ¹³C NMR (CDCl₃, 20 MHz) δ 110.8, 81.1, 57.5, 56.7, 52.0, 48.9, 48.6, 36.4, 33.0, 32.7, 21.2.