

Reduction of Natural Enones in the Presence of Cerium Trichloride¹

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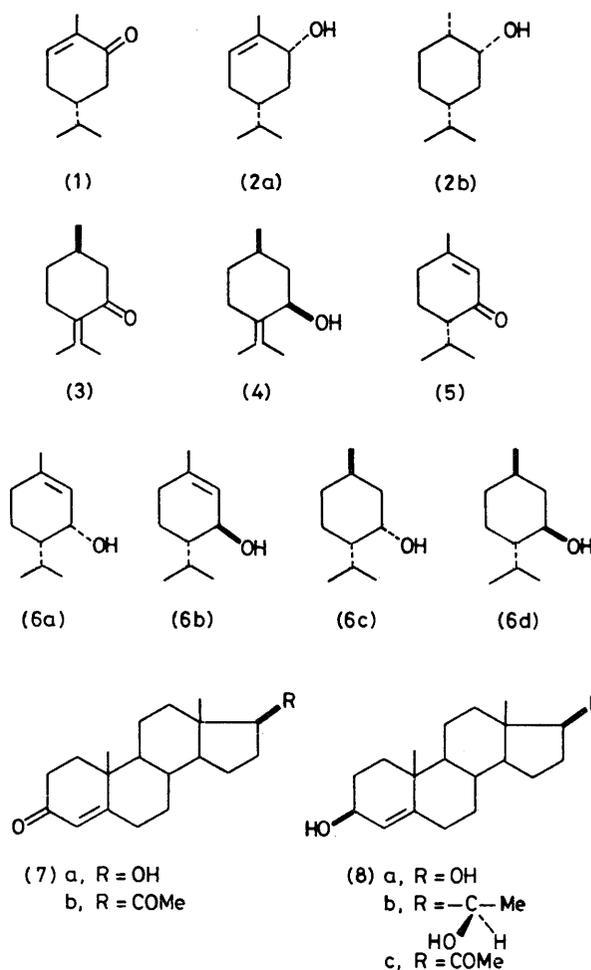
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Summary The reduction of $\alpha\beta$ -unsaturated ketones with sodium borohydride in methanol solution in the presence of cerium chloride gives almost exclusively the allylic alcohol, sometimes stereoselectively; the reduction of a variety of natural products containing a conjugated keto-group is described.

LANTHANIDES derivatives, which are widely used in n.m.r. spectroscopy,² have received only scarce attention from synthetic organic chemists.³ Their high co-ordinative ability with many functional groups should result in modifications of the steric and electronic environment of the reactive site of a molecule. Thus, regio- and/or stereoselective reactions are expected from the addition of a lanthanide derivative to a reactive species. It has been shown⁴ recently that addition of a lanthanide salt to an α -enone and NaBH_4 affords almost quantitatively 1,2 reduction compounds. It is well known that the regio-specific reduction of α -enones to allylic alcohols is difficult to perform. NaBH_4 and LiAlH_4 have been shown to give 1,2 and/or 1,4 addition products depending on the type and substituents of the substrate.⁵ A number of new hydride reducing agents have been investigated in recent years, which are claimed to give mainly⁶ 1,2 addition products, but the applicability of these reagents depends on the structure of a particular substrate.⁷ Conversely, the method using lanthanides salts seems to be of wide applicability, and we report here its application to the reduction of a number of natural products.

The reduction of the monoterpene ketones carvone (1), pulegone (3), and piperitone (5) to the corresponding allylic alcohols is known to yield mixtures.⁸ In contrast, reduction with NaBH_4 in methanol solution in the presence of $\text{CeCl}_3 \cdot 6\text{H}_2\text{O}$ almost completely prevents the formation of the saturated alcohol and the allylic alcohols (2a), (4), (6a), and (6b) are obtained in good yields by this procedure (see Table). Similar results were obtained for testosterone (7a) and progesterone (7b) (see Table). When the reaction with (7b) is carried out with half the stoichiometric amount of NaBH_4 (8c) is obtained in 45% yield, showing an inversion of the normal tendency⁹ of faster reduction of saturated ketones with NaBH_4 .

In all the cases investigated so far, no saturated alcohol could be detected in the reaction mixture, and a good stereoselectivity was observed.

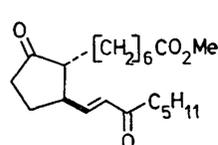


When this method is applied to enones of the prostanoid series, the regioselectivity is retained, but the reduction is no longer stereoselective. Thus, treatment of (9)¹⁰ with NaBH_4 (half the stoichiometric amount) in the presence of CeCl_3 , affords a mixture of the recovered diketone (9), the 15 α -hydroxy 9-keto derivative (10a), and its 15-epimer (10b), as well as the corresponding diol (10c) in a 1:1:1:1 ratio.

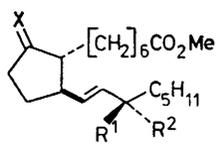
TABLE. Reduction of α -enones with NaBH_4 and $\text{CeCl}_3 \cdot 5\text{H}_2\text{O}$.^a

Starting material	Reducing agent	Recovered starting material/(%)	Allylic alcohol(%)	Saturated alcohol(%)
(-)-Carvone (1)	NaBH_4	16	(2a) (71)	(2b) (13)
	$\text{NaBH}_4 + \text{Ce}^{3+}$	—	(2a) (98)	(2b) (2)
Pulegone (3)	NaBH_4	28	(4) (70)	
	$\text{NaBH}_4, \text{Ce}^{3+}$	—	(4) (100)	
Piperitone (5)	LiAlH_4	—	(6a) (31)	
	NaBH_4	—	(6a) (22)	(6c) (14)
	$\text{NaBH}_4, \text{Ce}^{3+}$	—	(6b) (39)	(6d) (25)
Testosterone (7a)	NaBH_4	—	(8a) (90) ^{b,c}	
	$\text{NaBH}_4, \text{Ce}^{3+}$	—	(8a) (99)	
Progesterone (7b)	$\text{NaBH}_4, \text{Ce}^{3+}$	—	(8b) (65) ^c	
			(8c) (8) ^d	

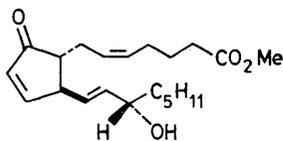
^a Typically the starting material (1 mmol) was dissolved in methanolic $\text{CeCl}_3 \cdot 6\text{H}_2\text{O}$ (2.5 ml, 0.4 M) and NaBH_4 (1 mmol) was slowly added (1–2 min) with stirring. The mixture was allowed to react for 3–5 min, then treated with water and extracted with ether. The products were identified and their stereochemistry was assigned by i.r. and n.m.r. spectroscopy, optical rotation, m.p., and/or comparison with authentic samples. The yields were estimated by g.l.c. (2 m \times 2 mm column 10% Carbowax 20 M on Chromosorb WAW, Carlo Erba Fractovap 1501, 15 ml N_2 min⁻¹) except for compounds derived from (3) where n.m.r. and optical rotation data were used. For (8a), (8b), and (8c) the yields were obtained from the isolated materials after column chromatography. ^b A. Butenandt and A. Heusner, *Ber.*, 1938, **71**, 198. ^c J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 1955, 426. ^d M. Stefanovic and S. Lajsic, *Tetrahedron Letters*, 1967, 1777.



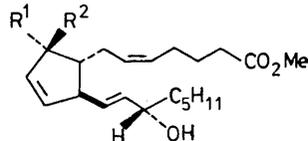
(9)



(10) a, X = O, R¹ = H, R² = OH
 b, X = O, R¹ = OH, R² = H
 c, X = H, OH, R¹, R² = H, OH



(11)



(12) a, R¹ = H, R² = OH
 b, R¹ = OH, R² = H

Reduction of PGA₂ methyl ester (11) provides an equimolar mixture of the diols (12a) and (12b), which were separated by preparative t.l.c. on silica gel. No dramatic change in stereoselectivity is observed by protection of

the 15-hydroxy group either as a tetrahydropyranyl ether or a trimethylsilyl ether derivative. There is no evidence of formation of a saturated alcohol.

The above results indicate that the reduction of conjugated ketones with NaBH_4 in methanol solution, in the presence of CeCl_3 , is a method of general applicability to various types of polyfunctional molecules and can be used in a wide pH range without substantial loss of regioselectivity. In an acidic solution (HCl, pH 1) (1) was reduced to (2a) in 95% yield. Even in the presence of pyridine, the same result was obtained, in spite of the well known tendency of pyridine to induce 1,4 reductions.¹¹ The same regioselectivity was also observed in diethyl ether solution, in the presence of $\text{Er}(\text{NO}_3)_2 \cdot 5\text{H}_2\text{O}$.

Although the governing factors of these reductions remain obscure, stereoselectivity is frequently observed. Usually, these reductions are very fast and can be performed within a few minutes. Anhydrous conditions and inert atmosphere are not necessary. These experimental advantages, along with the high yields usually obtained, clearly make this novel reduction procedure both simple and synthetically useful.

(Received, 29th March 1978; Com. 326.)

¹ For previous paper, see A. E. Greene, *Tetrahedron Letters*, 1978, 851.

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