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The Unexpected Reductive Products of δ– Alkoxyenal by Sodium Borohydride in Methanol with A Trace of Magnesium Methoxide

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Abstract: Reduction of δ-alkoxy enal **1** and **4** by sodium borohydride in methanol with a catalytic amount of magnesium methoxide gave unexpected methoxylated poducts **3** and **6** respectively.

Keywords: Sodium borohydride, Magnesium methoxide, Michael addition.

The selective 1,2-reduction of α, β-unsaturated carbonyl compounds such as enones and enals, has been achieved by $NaBH_4$[1]. In the course of our studies toward the total synthesis of macrolactin A, it was found that reduction of enal **1** by $NaBH_4$ in MeOH, which contained a trace of $Mg(OMe)_2$ from the preparation of absolute MeOH, formed an unexpected product **3** (**Table 1**).

According to the known procedues[2], allylic alcohol **2** was normally formed in 78% yield by reduction of enal **1** with $NaBH_4$ in MeOH at –78°C. However, when methanol contained a catalytic amount of $Mg(OMe)_2$, the reduction of **1** gave methoxy compound **3** instead of **2** in 54% yield. The structure of the unexpected reductive product **3**, which is a mixture of two diastereomers in a ratio of 1:1, was confirmed by ^1H NMR, ^1H-^1H COSY, MS and IR[3]. The acetate[4] of **3** was also prepared in order to assist the structure assignments of the product. To further understand this reaction, experiments were carried out with δ-silyloxy enal **4** and 7-alkoxy enal **7**. Enal **4** gave the 1,2-reduction product **5** in 92% yield *via* procedure i, while a saturated methoxy alcohol **6** was formed in 66% yield *via* procedure ii. However, enal **7** only gave allylic alcohol **8** by both procedures in a yield around 90% (**Table 1**).

In respect of the mechanism of the distinct reductive products of enal **1**, **4** and **7** *via* procedure i and ii, we suppose that a catalytic amount of $Mg(OMe)_2$ and the δ-alkoxy group of α, β-unsaturated aldehyde are requisite for the Michael addition of methoxy group. A possible mechanism is envisioned in **Scheme 1**, in which magnesium first coordinates with the oxygen of δ-alkoxy group, forming a six-member cyclic transition state, then one methoxy group of $Mg(OMe)_2$ adds to the β carbon atom of enal followed by the reduction of aldehyde group. This mechanism can explain well why the methoxy addition did not occur to enal **7**, considering the disfavor of forming an eight-member ring transition state.

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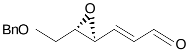
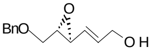
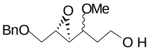
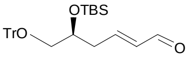
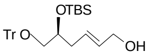
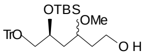
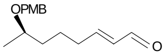
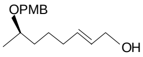
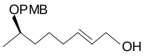
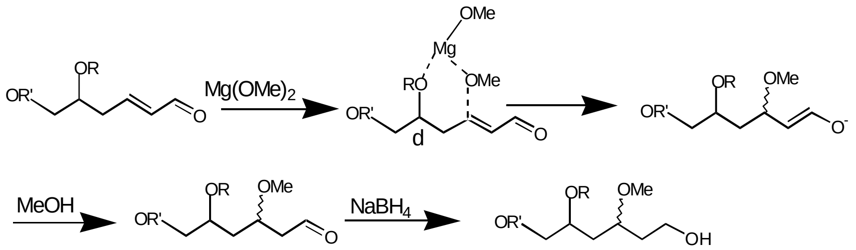
Table 1 Reduction of enal by $NaBH_4$ *via* procedure i or ii

	product and yield (%)	
substrate	procedure i	procedure ii
 **1**	 78 **2**	 54 **3**
 **4**	 92 **5**	 66 **6**
 **7**	 91 **8**	 90 **8**

Procedure i: 1.5 molar equiv. of $NaBH_4$ for each mole of enal in MeOH at –78°C, 0.5 h. ii: The same conditions as in i except the MeOH containing a catalytic amount of $Mg(OMe)_2$.

Scheme 1



In summary we found that reduction of δ-alkoxy α, β-unsaturated aldehyde by $NaBH_4$ / MeOH with a catalytic amount of $Mg(OMe)_2$, gave methoxy alcohol *via* Michael addition and reduction.

Acknowledgment

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References and Notes

1. S.W.Chaikin, W.G.Brown, *J. Am. Chem. Soc.*, **1949**, *71*, 122.
2. D.C.Whirtenour, S.Masamune, *J. Org. Chem.*, **1989**, *54*, 2817.
3. All products show satisfactory spectroscopic data. Selected data for compound 3. ^1H NMR (600MHz,$CDCl_3$) δ: 7.23-7.34 (m, 5H), 4.54 (s, 2H), 3.73-3.78 (m, 2H), 3.70 (dd, 1H J=3.4, 11.2 Hz,), 3.50 (dd, J=5.4, 1H 11.2 Hz,), 3.47 (s,1.5H), 3.40 (s, 1.5H), 3.25-3.30 (m,1H), 3.14-3.21 (m, 1H), 2.83-2.96 (m,1H), 2.36 (brs, 1H), 1,78-1.90 (m, 2H) ; MS(*m/z*, %): 252 (M^+ , 3.1), 149 (38), 91 (100).
4. Alcohol **3** was converted to the corresponding acetate under standard conditions (Ac_2O:pyr: DMAP=1.5:2.0: 0.1, CH_2Cl_2, 0-25°C, 1 h) in quantitative yield. ^1H NMR (400MHz,$CDCl_3$) δ: 7.26-7.37 (m, 5H), 4.58 (s, 2H), 4.16-4.22 (m, 2H), 3.64 (dd, 1H J=3.5, 11.3 Hz,), 3.51 (dd, 1H, J=5.9, 11.3 Hz), 3.47 (s, 1.5H), 3.40 (s, 1.5H), 3.16-3.22 (m,1H), 2.96-3.09 (m, 1H), 2.82-2.93 (m,1H), 2.04 (brs, 1H), 1,80-2.00 (m, 2H); MS(*m/z*, %): 294(M^+), 91(84), 71(100).

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