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HYDROFORMYLATION AS A SIMPLE AND EFFICIENT ONE CARBON HOMOLOGATION OF HOMOALLYLIC ALCOHOLS. SYNTHESIS OF PRELOG-DJERASSI LACTONE.

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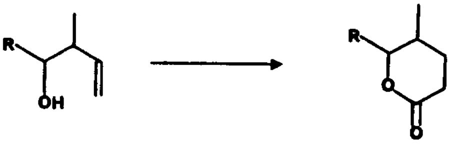
Summary: A hydroformylation oxidation sequence is described for the efficient conversion of homoallylic alcohols to δ-lactones. The methodology is applied to the synthesis of Prelog-Djerassi lactone.

During the course of some synthetic studies in our laboratory, we required a simple procedure for the conversion of homoallylic alcohols such as 1 to lactones 2. Although numerous methods to affect this transformation exist, these generally tend to be multi-step sequences and thus rather inefficient. As a result, we examined an alternative procedure based on the hydroformylation reaction which has seen extensive industrial importance in the conversion of alkenes to their homologous aldehydes[1] but has rarely been used for laboratory scale preparations.

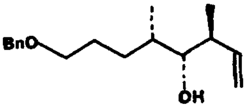
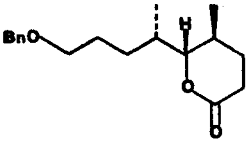
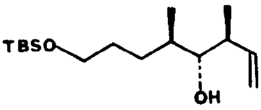
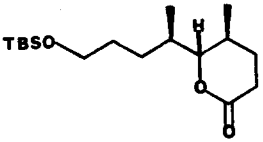
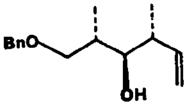
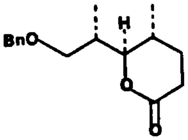
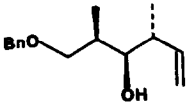
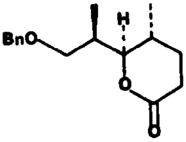
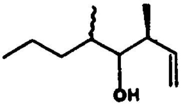
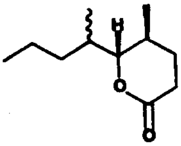


1 2

We now describe a simple and efficient procedure for the conversion of alcohols 1 to lactones 2 based on a rhodium catalyzed hydroformylation and its application to the synthesis of Prelog-Djerassi lactone 7.[2,3] Rhodium was chosen as the catalyst as opposed to cobalt, the other common catalyst, because it was known to result in higher selectivity for terminal olefin carbonylation versus branched chain carbonylation.[1] Furthermore, the use of rhodium allows the use of lower temperatures and pressures. Rhodium catalysts also tend to be air stable whereas $Co_2(CO)_8$, the common form of cobalt, is not.

Thus, each of the alcohols in Table I was subjected to hydroformylation in ethyl acetate with rhodium acetate dimer and the resulting hemiacetals directly oxidized with pyridinium chlorochromate[4] to give δ-lactones in excellent overall yield after purification by flash chromatography.

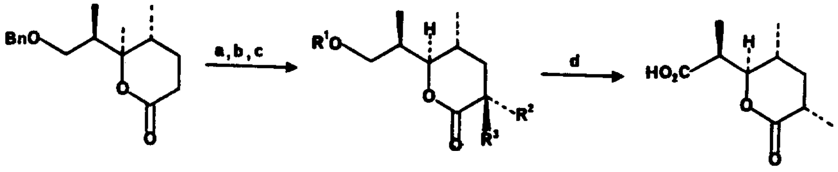
Table I

Entry	Alcohol	Lactone	% Yield
1			86
2			80
3			85
4			86[5]
5			81

The application of this methodology to the synthesis of Prelog-Djerassi lactone is illustrated in Scheme 1. The lactone 3 (Table I, entry 4) was alkylated with LDA and methyl iodide to give a 1:1 mixture of lactones 4 and 5 in 97% yield.[2j] Isomerization using the Grieco procedure, chromatographic separation of the isomers and hydrogenolysis of the benzyl group over Pd/C (97%) gave the known alcohol 6. Conversion to Prelog-Djerassi lactone

7 was readily accomplished by oxidation with $RuCl_3/NaIO_4$ under the Sharpless conditions.[6] The melting point (112-113°C) and spectral data were in accord with values reported in the literature.[7,8]

Scheme 1



3

4, R^1=Bn, R^2=CH_3, R^3=H
5, R^1=Bn, R^2=H, R^3=CH_3
6, R^1=H, R^2=H, R^3=CH_3

7

(a) LDA, HMPA, MeI, TFH, -78°C. (b) LDA, THF; H^+. (c) H_2, Pd/C. (d) $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4.

Sample Experimental Procedure. A steel bomb was charged with 3.0 g (12.8 mmol) of the alcohol (entry 4, Table I), 2.0 g (7.55 mmol) of triphenylphosphine and 40 mg $Rh_2(OAc)_4$ and 10 mL of ethyl acetate. The bomb was pressurized with a 1:1 mixture of CO/H_2 to 350 psi and heated to 100° for 6 h. After cooling, the contents were removed from the bomb, the ethyl acetate was removed under reduced pressure and the crude hemiacetal was dissolved in CH_2Cl_2 and treated with 5.40 g (25.0 mmol) of PCC. The mixture was stirred for 3 h and the product was isolated by filtration through silica gel with ether. Flash chromatography on silica with 20% EtOAc/hexane gave the pure lactone in 86% yield.

In conclusion, the methodology described herein for the conversion of homoallylic alcohols to δ-lactones coupled with the numberous methodologies for the synthesis of stereochemically defined homoallylic alcohols[9] should find broad application in the synthesis of a variety of propionate derived natural products.[10]

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