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A SHORT AND EFFICIENT SYNTHESIS OF 4-HYDROXY-5-(1-HYDROXYALKYL)-γ-BUTYROLACTONES

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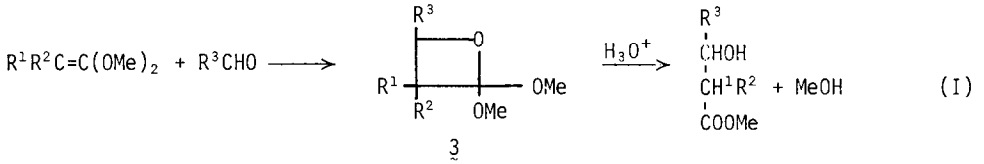
Abstract. The cycloaddition of α,β-epoxyaldehydes or ketones (2) with the ketene acetal $MeHC{=}C(OMe)_2$ (1) gives epoxyoxetanes (3) in high yields. Without isolation they can be transformed into 4-hydroxy-5-(1-hydroxyalkyl)-γ-butyrolactones (6) *via* the epoxy esters 4 and trihydroxy esters (5). The lactones 6 appear to be valuable precursors for the synthesis of 5-(1-hydroxyalkyl)-3-methyl-2-5*H*-furanones (7) and 3-methyl-5-ylidene-2-5*H*-furanones (8)

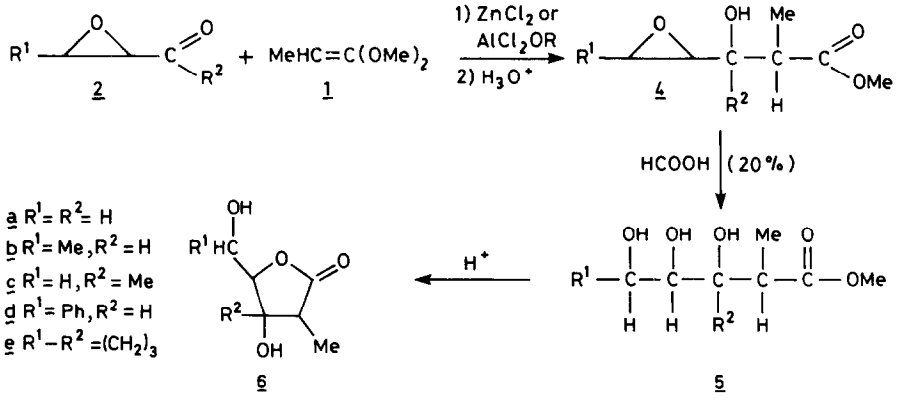
In preceeding papers we showed that ketene acetals $R^1R^2C{=}C(OMe)_2$ react with aldehydes in the presence of $ZnCl_2$ to yield 2,2-dimethoxyoxetanes[1] (3) which can be hydrolysed into β-hydroxy esters[2] according to Eqn I.



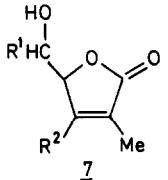
Ketones need an electron-withdrawing substituent at the α-position to be sufficient reactive in this oxetane formation. The use of α-acyloxyaldehydes or ketones in reaction sequence (I) has led to the synthesis of 4-hydroxybutyrolactones[3].

The easy access to α,β-epoxyaldehydes and ketones (2) from the corresponding unsaturated carbonyl compounds[4] did explore us their cycloaddition with a suitable ketene acetal as an entry to 5-(1-hydroxyalkyl)-γ-butyrolactones (6) as is outlined in Scheme 1.

Scheme 1



1,1-Dimethoxypropene (1) was used as the ketene acetal not only because it is easy available but also because the 3-methyl substituent in the resulting products (6) is also presented in many related natural products[3,5]. Lactones 6 may serve as precursors for 5-(1-hydroxyalkyl)-3-methyl-2-5*H*-furanones[6,7,8] (7) and 3-methyl-5-ylidene-2-5*H*-furanones (8)[9,10].



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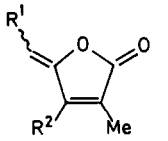

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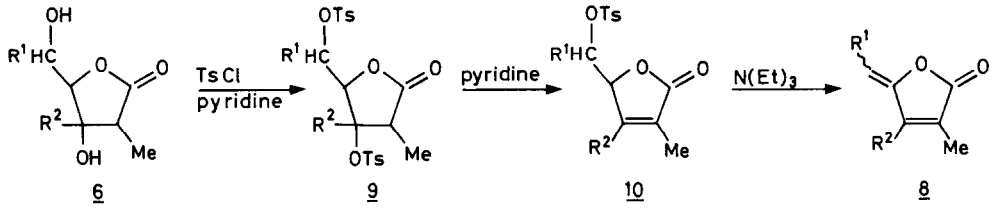
In the presence of $ZnCl_2$ or $AlCl_2OR$[11] and at temperatures below 0° the epoxycarbonyl compounds 2 were converted into oxetanes in almost quantitative yields. The formation of an oxetane appears easily from the characteristic NMR absorption for the H-C-CH_3 proton between 2.5 and 2.9 ppm[3]. The use of the catalyst $AlCl_2OR$ is preferred because $ZnCl_2$ causes more dimerisation and polymerisation of the ketene acetal. Without isolation the oxetanes are hydrolysed with 0.1 N HCl solution into the more stable epoxy esters (4a-e). After removal of the solvent *in vacuo*, 4 was obtained in about 90% yields. It contained dimerisation products from 1 (purity ca 90% by NMR) but could be purified by bulb to bulb distillation.

Hydrolysis of 4 with 20% formic acid solution at 40° yielded 6 (IR, $\nu_{C=O}$=1770-1780) as the sole product. Under these reaction circumstances the ring closure is so fast that the intermediate trihydroxy esters 5 could not be isolated. The resulting lactones 6 are stable compounds which could be purified by distillation *in vacuo*. These results given in the Table indicate that this synthesis has a wide scope with respect to variation of the substituents R^1 and R^2.

As our main goal was to use 6 in further transformations into 7 and 8, no special attention has been paid to the stereochemistry of the various reaction steps. The chirality is partly or completely lost during the formation of 7 and 8. However, in the case of 6b and 6e one of the diastereomers could be obtained pure by repeated crystallisation from ethyl acetate (sharp m.p. and sharp CH_3-C-H doublet in 90 MHz NMR). The configuration of these isomers has not been determined up to now.

The conversion of 6 into 8 was studied as described in Scheme 2.

Scheme 2



6 9 10 8

The dihydroxy lactones 6a, 6b and 6d (having no tertiary hydroxy groups) were tosylated in pyridine. By simple heating of the reaction mixture 6d converted into 8d in 65% yield. In the other cases only the tosyl group in the 4-position was eliminated under these circumstances. Elimination of the tosyl group from 10 could, however, be achieved by prolonged reflux in the presence of triethylamine.

Our further investigations are devoted to milder conversions of 6 into 8[12] and to the use of these reaction sequences in the synthesis of sesquiterpene lactones having the structural elements of 7 and 8.

Typical procedures

4-hydroxy-5-(1-hydroxyalkyl)-γ-butyrolactones (6)

A stirred solution of 0.1 mole of an epoxyaldehyde or ketone (2) and 0.11 moles of 1,1-dimethoxypropene (1) in dichloromethane is cooled down to -60°. Then 1.5 ml of a 0.55 molar solution of $AlCl_2$Obornyl is added[11]. It is also possible to use three drops of a concentrated solution of $ZnCl_2$ in acetonitrile but this leads to larger amounts of dimeric products of 1 so that 1 has to be used in larger excess. The temperature is allowed to rise slowly to room temperature, and the mixture is kept for one hour at this temperature. After cooling again to 0°, 50 ml of water containing 100 mg of p-toluenesulphonic acid are added, and the two phase system is stirred vigorously. The dichloromethane layer is separated and the water layer is extracted several times with dichloromethane. The dichloromethane layers are dried and evaporated *in vacuo* leaving the epoxy esters in a purity of at least 85% (NMR).

Before further use the epoxy esters (4) are purified by bulb to bulb distillation to separate 4 from the lower boiling dimeric products of 1. B.p.: 4a 80-85°/0.2; 4b 85-90°/0.3; 4c 95-100°/0.3; 4d 160-170°/0.4; 4e 140-150°/0.2. The yields were in all cases between 80 and 90%.

0.1 Mole of an epoxy ester 4 is treated with 80 ml of a 20% formic acid solution during 15 h at 40°. While stirring water and formic acid are removed at low pressure (0.2-0.5 mm). Finally the lactones 6 are isolated by bulb to bulb distillation. Repeated crystallisation of the oily products 6b and 6e from ethyl acetate leads to a single diastereomer. Yields based on 4 and boiling or melting points are given in the Table.

Z-5-benzylidene-3-methyl-2-5H-furanone (8d)

0.011 Moles of 6d (2.2 g) are added to a solution of 0.024 moles of tosylchloride (2.4 g) dissolved in 20 ml of pyridine. The mixture is stirred overnight at room temperature and then refluxed for an hour at 120°. After cooling to room temperature 20 ml of water are added, the mixture is stirred for 30 minutes, and then several times extracted with dichloromethane. The collected dichloromethane layers are dried and concentrated *in vacuo*. The residue is purified by crystallisation from diisopropyl ether. Yield: 65%; m.p. 120-122°; Mass 186 (M^+), 171 (M-CH_3), 158 (M-CO). IR (KBr) $\nu_{C=O}$, 1650 and 1770 (s). NMR δ ($CDCl_3$), 2.04 (d, J=0.9 Hz, C-CH_3); 5.89 (b.s., 1H, C=CH), 7.13 (d, J=1.5 Hz, 1H, C=CHPh); 7.18-7.81 (5H, aromatic). The Z-geometry is tentatively ascribed as the Z-isomer is expected to be the most stable and because of the shift[14] of the PhCH= C proton (δ, 7.13). The lactones 6a-e and compound 8d gave satisfactory microanalyses.

Table PREPARATION OF 6a-e ACCORDING TO SCHEME 1

R^1	R^2	compound	yield %	b.p./torr.	m.p.
H	H	6a	85	110-120°/0.1	
CH_3	H	6b	80	140-150Z/0.1	102-103°[b]
H	CH_3	6c	87	165-170°/0.4	86- 88°
C_6H_5	H	6d	90	160-170°/0.4	
$-(CH_2)_3-$		6e	80[a]		123-124°[b]

[a]Yield after evaporation of the solvents.
[b]Melting point of the diastereomer obtained by crystallisation from ethyl acetate.

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4. G.B. Payne, *J. Org. Chem.* 26, 250 (1961); O.L. Chapman and T.C. Hess, *J. Org. Chem.* 44, 962 (1979).
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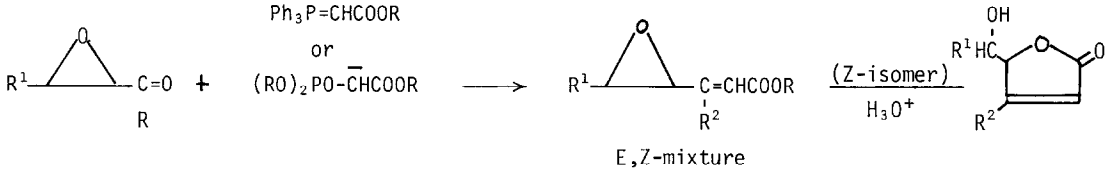
6. Recently other routes[7,8] to 7 have been described also starting with epoxyaldehydes *via* the reaction sequence.



A disadvantage of this method is, however, that the E-isomer of the intermediate does not yield 7.

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9. Many compounds 8 have been found in nature during the last 15 years. Several of them display interesting biological activities[10].
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11. For the preparation of this catalyst see R.W. Aben and J.W. Scheeren, *Synthesis* 1982, 779.
12. Several mild methods for the transformation of 7 into 8 have been published[13]. As the conversion of 6 into 7 is generally more easy than that of 7 into 8, these methods may also be valuable for the conversion of 6 into 8.
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