

## Reversal of Regioselectivity in the Reduction of *gem*-Disubstituted Cyclic Carboxylic Acid Anhydrides

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The regioselective partial reduction of *gem*-disubstituted cyclic carboxylic acid anhydrides to the corresponding  $\gamma$ -lactones with  $\text{LiAlH}_4$  or  $\text{NaBH}_4$  is almost completely reversed when potassium tri-*s*-butylborohydride is used as the reducing agent.

The partial reduction of *gem*-disubstituted cyclic anhydrides (**1**;  $\text{R}^3 = \text{R}^4 = \text{H}$ ) with sodium borohydride or lithium aluminium hydride occurs with a high degree of regioselectivity<sup>1</sup> at the carbonyl group adjacent to the substituted carbon atom to give the corresponding lactones (**2**). Although the isomeric lactones (**3**) can be obtained from the disubstituted anhydrides by hydrogenation catalysed with  $\text{RuCl}_2\text{-(Ph}_3\text{P)}_3$ , the reaction must be carried out under a pressure<sup>2</sup> of *ca.* 300 lb in<sup>-2</sup>. A much simpler route to these isomeric lactones has been achieved by partial reduction of *gem*-disubstituted cyclic anhydrides with K-Selectride (potassium tri-*s*-butylborohydride, Aldrich 18,014-9).

The results<sup>†</sup> of K-Selectride and sodium borohydride reductions of *gem*-disubstituted anhydrides are summarized in Table 1. Product ratios obtained with L-Selectride (Aldrich 17,849-7) as the reducing agent are similar to those observed in K-Selectride reductions.

Reductions were carried out in dry tetrahydrofuran, with a slight excess of K-Selectride. The temperature was maintained at  $-70^\circ\text{C}$  for 1.5–2 h in reduction of the methyl and ethyl substituted anhydrides. It should be stressed that this low

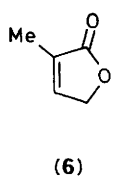
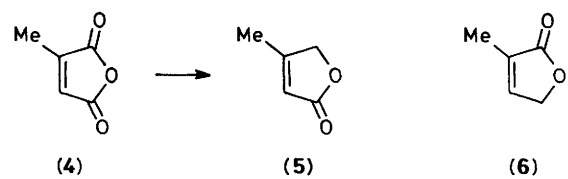
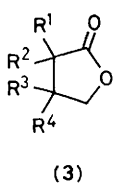
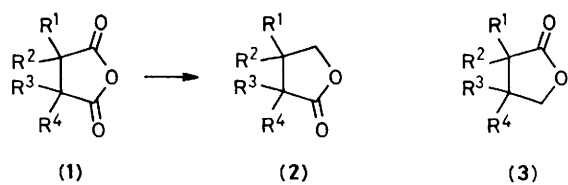
**Table 1.** Reduction of *gem*-disubstituted cyclic anhydrides.

Anhydride (1)	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Method	Yield (%) of isolated lactones	Ratio of (2) to (3)
Me Me H H	Me	Me	H	H	$\text{NaBH}_4^{1c}$	69	19:1
					K-Selectride	42	1:6
Me Et H H	Me	Et	H	H	$\text{NaBH}_4$	81	6.5:1
					K-Selectride	66	only (3)
Ph Ph H H	Ph	Ph	H	H	$\text{NaBH}_4^{1c}$	67	only (2)
					K-Selectride	90	1:6
Ph Ph Me Me	Ph	Ph	Me	Me	$\text{NaBH}_4^3$	95	only (2)
					K-Selectride	67	only (3)

temperature is essential in order to obtain a high degree of regioselectivity. For the anhydrides substituted with phenyl groups the reactants were initially stirred at  $-70^\circ\text{C}$  and the solution was gradually warmed to  $10^\circ\text{C}$  over a period of 2.5 h. After adding 6 M NaOH and  $\text{H}_2\text{O}_2$  to the reaction mixture and subsequent acidification with 6 M HCl, the products were isolated in the usual manner by extraction with methylene dichloride.

Since a certain degree of regioselectivity has been reported<sup>4</sup> for the L-Selectride reduction of a planar 4-methoxy-2,3-naphthoic anhydride we were interested to determine if the similar regioselective control is operating in other planar molecules such as citraconic anhydride (**4**).

<sup>†</sup> Analyses were carried out with a Varian Vista 6000 gas chromatograph and structures confirmed by n.m.r. and i.r. spectroscopy.



$\text{NaBH}_4$  reduction of (4) gives predominantly the lactone resulting from the reduction of the carbonyl group adjacent to the methyl substituent [(5):(6) 85:15].<sup>5</sup> It was found that with K-Selectride the isomeric lactone (6) was the principal product and only a trace of the other lactone (5) could be detected.

Received, 18th January 1982; Com. 050

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