Highly Regioselective Reduction of Ring B Seco-5α-steroid Anhydrides to afford the Lactone Grouping Characteristic of Brassinolide

Charles J. W. Brooks* and I. Victor Ekhato
Chemistry Department, University of Glasgow, Glasgow G12 8QQ, U.K.

B-Homo-7-oxa-5α-cholestan-6-ones are formed in high yield *via* sodium borohydride reduction of the corresponding cyclic anhydrides.

The ε-lactone grouping characteristic of the natural plant hormone brassinolide (**1**) is obtainable under suitable conditions as the major product of Baeyer–Villiger oxidation[1] of 6-oxo-5α-cholestane derivatives: the most satisfactory oxidant appears to be peroxytrifluoroacetic acid, which affords good yields of the desired lactones in conveniently short reaction times.[2] We describe an alternative approach based on selective reduction of the corresponding (5α) seco-steroid dioic acid anhydrides (**2**). The virtually complete regioselectivity observed is of both mechanistic and practical interest. The reduction of 3β-chloro-6,7-seco-5β-cholestane-6,7-dioic acid anhydride by $LiAlH_4$ has been reported to occur, in contrast, *via* attack at C-6, affording B-homo-7-oxa-5β-cholestan-7a-one (**3**) together with the acid (**4**).[3]

6,7-Seco-5α-cholestane-6,7-dioic anhydride and five substituted analogues (3β-Cl,[4] 3β-OMe, 3β-OAc, 3β-OCOPh, and 2α,3α-diOAc) were prepared essentially by standard methods *via* 6-oxo- and 7α-bromo-6-oxo-intermediates: displacement of the 7α-bromo-group by the hydroxide ion[5] was best achieved at room temperature in aqueous pyridine.[6] Conversion of the ketols into seco-dioic acids was effected by sequential oxidations with $NaIO_4$ in dioxan–water (10:3 v/v) and CrO_3 in acetic acid–water (10:3 v/v). Anhydrides were formed by treatment with acetic anhydride under reflux. Reduction of the anhydrides (0.2—0.5 mmol) with excess of sodium borohydride in tetrahydrofuran proceeded at room temperature, or more rapidly under reflux. Treatment of the acidified crude products with acetic anhydride and pyridine[7]

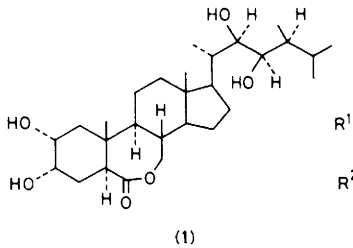
Table 1. Products from sodium borohydride reductions of anhydrides.

Substituents in ring A	Isolated yields (%) based on anhydride			M.p.s/°C	
	Method (i)[a]		Method (ii)[b]		
	Lactone	AcO-acid	Lactone	Anhydride[c]	Lactone[c]
None	61	*ca.* 25	88	106—107	110—112 [lit. 126[d]]
3β-Cl	93	*ca.* 6	94	121—122	140—141 [lit. 145[d]]
3β-OMe	83	*ca.* 9	90	84—85	103—104
3β-OAc	85	*ca.* 8	93	196—197	179—180 [lit. 181[d]]
3β-OCOPh	92	*ca.* 7	—	194—195	180
2α,3α-diOAc	75	*ca.* 16	82	169—170	192—194

[a] Reductions effected at room temperature for 5 h: products isolated after treatment with Ac_2O–pyridine, and chromatography. [b] Reductions effected at reflux temperature for 3 h; products isolated by vacuum sublimation (0.01 Torr) and trituration of the sublimate with methanol. [c] All new crystalline compounds gave satisfactory spectral data and elemental analyses. [d] Ref. 9: the discrepancy in the data for the unsubstituted lactone is as yet unexplained.

at 80—100 °C gave mixtures which were separated by chromatography on silica gel columns, yielding the crystalline lactones (**5**) with small proportions of the corresponding acetoxy-acids (**6**), obtained as oils. More satisfactorily, the products of reduction were isolated directly as lactones by vacuum sublimation.[8] Yields are shown in Table 1. The structures of three of the lactones (unsubstituted,[9] 3β-acetoxy,[9] and 2α,3α-diacetoxy) were verified by direct comparisons (mixed m.p.s and spectroscopic data) with samples prepared by established routes. The other assignments are based primarily on spectroscopic data.

With reference to 5- and 6-membered anhydrides, many examples are known of regioselective hydride reductions affording lactones (*inter alia*[10—16]). (The use of potassium or lithium tri-s-butylborohydride instead of sodium borohydride has, in several instances, markedly altered[16] or reversed[17] the regioselectivity.) We are unaware of any observations on the regioselective hydride reduction of 7-membered anhydrides, other than that in ref. 3 and those in this work. The apparently complete selectivity of reduction at the C-7a carbonyl group in the 5α-series does not seem to be adequately rationalised by the concept of steric hindrance along the preferred reaction path.[15]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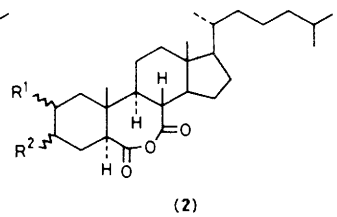
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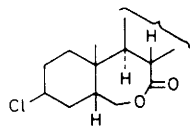
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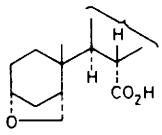
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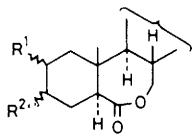
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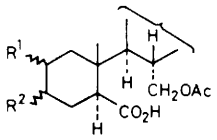
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