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STEROIDS. IX[1]. FACILE INVERSION OF UNHINDERED STEROL CONFIGURATION

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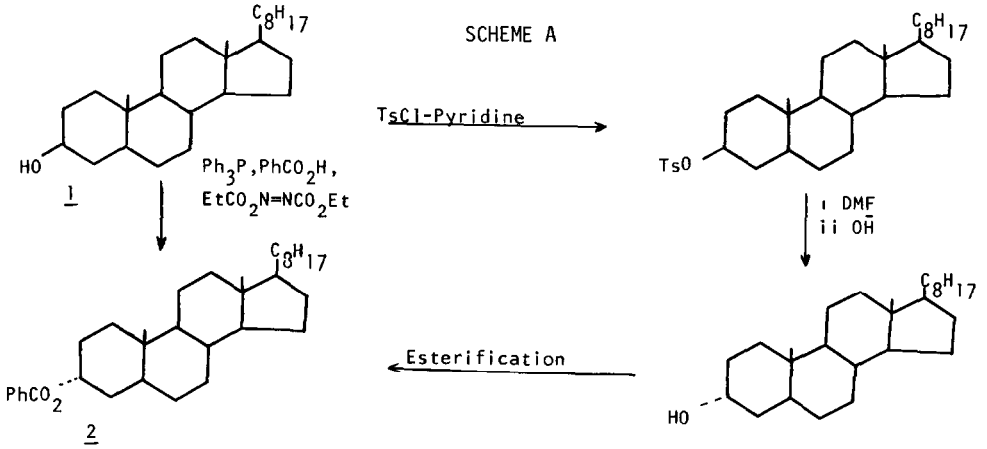
An important functional group in steroids is the hydroxy group the replacement of which in a stereospecific fashion generally requires a series of reactions. For example, the conversion of 5α-cholestan-3β-ol (1) to 5α-cholestan-3α-ol benzoate (2) by known methods would involve tosylation, inversion with saponification[2] and reesterification[7] (Scheme A).

SCHEME A



We have prepared (2) in one step from (1) using an adaptation of a published reaction[3,4,5]. This method consists in treating at room temperature a mixture of a steroid alcohol, triphenylphosphine, and diethyl azodicarboxylate in tetrahydrofuran solution with an acid such as benzoic acid or formic acid. In a few hours a sterically pure ester is formed in good yield that corresponds to inversion of configuration (see Table). Saponification of the ester then allows easy access to the epimer of the starting alcohol.

We find that steric requirements play an important role for the success of this synthesis. When methyl esters of cholic and deoxycholic acid were treated with formic acid under the standard conditions, esterification occurred only at C-3 with inversion of configuration while the hydroxy groups at C-7 and C-12 were unchanged. On the other hand, 5-androsten-3β, 16α-diol was converted to the 3α, 16β-diol dibenzoate. We have also observed that the 20β-hydroxy but not the 11β-hydroxy group is affected under these reaction conditions. It should therefore be possible to use this method for selective derivatization of polyhydroxy steroids.

Surprisingly, 5α-cholestan-3α-ol which is an axial alcohol was not esterified under the usual conditions while the axial hydroxy group of 4-t-butylcyclohexanol was easily formylated. Taking advantage of this observation we were able to react with formic acid a mixture of 3α- and 3β-cholestanol and obtain a product (consisting of the 3α-alcohol and its formate) which could be saponified to the pure 3α-alcohol. A typical experiment is described below.

Methyl 3β-formyloxy-12α-hydroxycholanate

A solution of methyl desoxycholate (2.03 g, 0.005 mole), triphenyl phosphine (2.62 g, 0.01 mole) and formic acid (0.46 g, 0.01 mole) in dry THF (60 ml) was stirred at room temperature. To this was added dropwise a solution of 1.74 g (0.01 mole) of diethyl azodicarboxylate in 10 ml THF. A moderately exothermic reaction took place. The contents were stirred for 14 hr. Removal of THF under reduced pressure afforded a syrupy product which was chromatographed over a Florisil column. First five fractions (50 ml each) using benzene-hexane mixture (60:40) as the eluant gave 2.1 g (97%) of the title compound[6], mp 160-161°, with satisfactory spectral data.

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TABLE †

Configurational inversion of sterols via esters

S.NO	Starting Alcohol	Acid Component	Product	Yield %	M.P. C°
1	5α-Cholestan-3β-ol	HCOOH	5α-Cholestan-3α-ol formate	97	110-112°
2	5α-Cholestan-3β-ol	$PhCH_2COOH$	5α-Cholestan-3α-ol phenyl-acetate	90	112
3	5α-Cholestan-3β-ol	PhCOOH	5α-Cholestan-3α-ol benzoate	100	100[7]
4	5α-Cholestan-3α-ol	PhCOOH	No reaction	--	----
5	4-Androsten-17β-ol-3-one	PhCOOH	No reaction	--	----
6	5-Androsten-3β,16α-diol	PhCOOH	5-Androsten-3α,16β-diol dibenzoate	75	187-190
7	5α-Androstan-3β-ol-17-one	HCOOH	3α-Formyloxy-5α-androstan-17-one	85	179-181[2]
8	Methyl 3α,12α-dihydroxy-cholanate	HCOOH	Methyl 3β-formyloxy-12α-hydroxycholanate	97	160-161[6]
9	Methyl 3α,7α,12α-tri-hydroxy cholanate	HCOOH	Methyl 3β-formyloxy-7α,12α-dihydroxycholanate	75	110-112
10	16α-Methyl-5α-pregnan-3β-ol-20-one	HCOOH	3α-Formyloxy-16α-methyl-5α-pregnan-20-one	75	148-151

† Known compounds were directly compared with literature data. New compounds gave satisfactory spectral and elemental analyses.

Thus, when 5α-cholestan-3β-ol was treated in the above reaction with benzoic acid, 5α-cholestan-3α-ol benzoate was obtained in nearly quantitative yield. Hydrolysis with methanolic potassium hydroxide gave 5α-cholestan-3α-ol[8] which was free from 5α-cholestan-3β-ol. Formic acid and phenylacetic acid under similar reaction conditions produced the corresponding 3α-esters exclusively as shown by their PMR spectra. Cholesterol was converted to its epimeric benzoate ester using the same reaction conditions; the presence of the homoallylic double bond at C-5 did not affect the progress or the stereochemistry of the reaction. The presence of an ester group did not significantly alter the effectiveness of this method. If a keto group is present it is necessary to add one extra mole of the phosphine: the reaction of 5α-androstan-3β-ol-17-one with formic acid using two moles of triphenylphosphine gave the 3α-alcohol formate in better than 70% yield without affecting the carbonyl function.

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