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INTRAMOLECULAR CONDENSATION OF STEROIDAL 17α-FORMYL-17β-ACETATES: SYNTHESIS OF 14-HYDROXYMETHYL-3-OXO-19-NOR-17α-PREGN-4-ENE-21,17-CARBOLACTONE[1]

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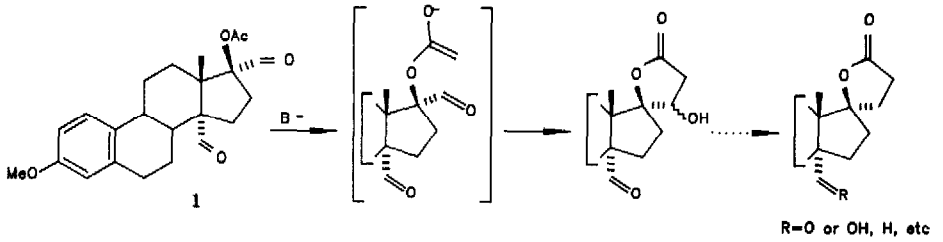
Abstract: Intramolecular condensation of steroidal 17β-acetoxy-17α-carbaldehydes offers a synthetic route to 19-nor-17,17-spirolactones.

A cycloaddition-mediated route to ring D modified 19-norsteroids has recently been described,[2] in which 17β-acetoxy-3-methoxyestra-1,3,5(10)-triene-14,17α-dicarbaldehyde(1) is readily prepared by oxidative cleavage of a ring D bridged intermediate. The stereochemically defined array of 14,17-functionality in (1) invited exploration of a novel approach to the synthesis of 14-functionalised 19-nor analogues of spironolactone.[3] It was reasoned that an enolate derived from the 17β-acetoxy group should condense selectively with the proximate 17α-formyl group, and that the resultant 17,17-spirolactone could readily be modified to the desired analogues (Scheme 1).

Scheme 1



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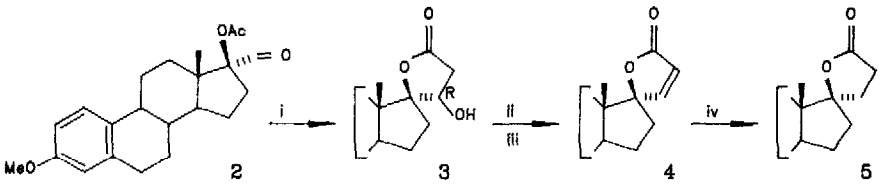
Intramolecular condensations of this nature have been encountered in 17α-acyloxy 17β-acetyl steroids,[4] and the principle has been applied to synthesis of γ-lactones from α-acyloxy ketones,[5] but the proposed approach to synthesis of a steroidal 21,17β-carbolactone, unadorned by alkyl residues on the spirolactone ring, has not been described.

Accordingly, a model study was first performed in order to establish conditions for intramolecular condensation of a geminal formyl acetate. For this purpose, 17β-acetoxy-3-methoxyestra-1,3,5(10)-triene-17α-carbaldehyde(2)[6] (prepared by forcing acetylation of the corresponding 17β-hydroxy-17α-carbaldehyde[7] with Ac_2O-Et_3N-DMAP) was treated with various amide bases at low temperature, to give variable amounts of condensation products. The most controlled conversion into a single product (89%) was

achieved in tetrahydrofuran at -100°C, in the presence of lithium 2,2,6,6-tetramethylpiperidide(LiTMP).

The product was formulated as (20*R*)-20-hydroxy-3-methoxy-19-nor-17α-pregna-1,3,5(10)-triene-21,17-carbolactone(3)[m.p. 181-184°C (from ethyl acetate-hexane); $[\alpha]_D$ + 19°(*c* 0.9; $CHCl_3$)]; the presence of a γ-lactone ring was evident from i.r. absorption at 1760cm^{-1}, and the n.m.r. spectrum revealed a distinctive downfield shift of the signal for 16α-H, consistent with the presence of a 20(*R*)-hydroxy group. The product(3) was readily converted into the known[8] spirolactone(5) through sequential β-elimination and catalytic hydrogenation (Scheme 2), and the overall efficiency of the procedure[(2) → (3) in *ca* 80% yield] encouraged the expectation that 14α-functionalised analogues could similarly be prepared from (1).

Scheme 2

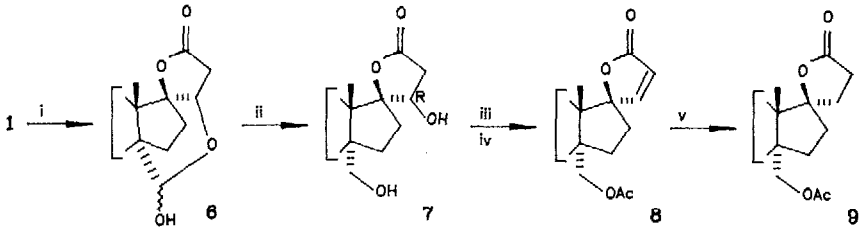


Reagents:(i) LiTMP-THF,-100°C (ii) MsCl-pyr,0°C (iii) SiO_2 (iv) Pd-$CaCO_3$,H_2

The 14α,17α-diformyl 17β-acetate(1), with LiTMP in tetrahydrofuran at -100°C, underwent rapid intramolecular condensation (15 min) to give, after chromatography, an inseparable mixture (ca 1:1) of spirolactone hemiacetals (6). A 500 MHz n.m.r. spectrum revealed the absence of a CHO proton; instead 'half-proton' signals were observed at δ 5.0 (d, *J* 3Hz) and 5.69(d, *J* 5Hz), which were assigned to diastereomeric 14^1-H's, together with doubled signals (each s, at δ 1.12 and 1.2) for 13β-CH_3 and for 20-H (each dd, *J* 11.6 and 7.7Hz, at δ 4.61 and 4.9). The correspondence of the latter multiplets suggested that (20*R*) configuration was present in both isomers.

Attempted conversion of (6) into (9) via direct or stepwise methods, intended to trap the open form of the hemiacetal, proceeded inefficiently. However, sodium borohydride reduction of (6) afforded the diol (7) cleanly, and the derived acetylation product underwent efficient β-elimination during slow chromatography on alumina, to give the unsaturated spirolactone (8). Hydrogenation of (8) over palladium on calcium carbonate completed the reaction sequence to the 14α-acetoxymethyl 17,17-spirolactone (9) in an overall yield of 44% from (1) (Scheme 3).

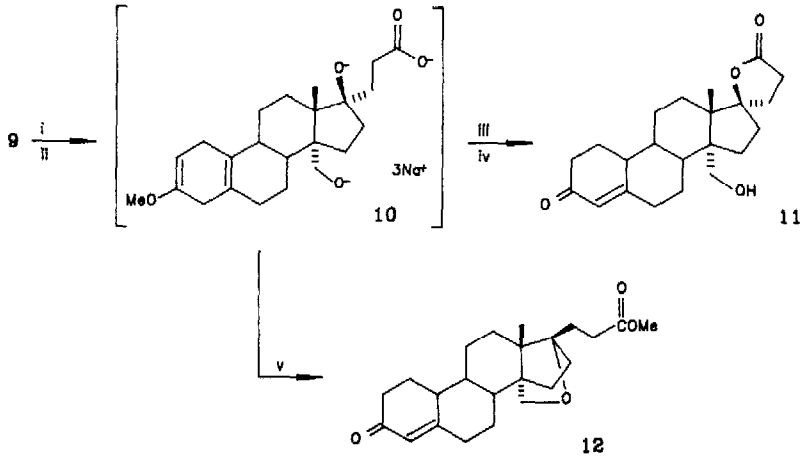
Scheme 3



Reagents: (i) LiTMP-THF,-100°C (ii) $NaBH_4$ (iii) Ac_2O-Et_3N-DMAP
(iv) Al_2O_3 (v) Pd-$CaCO_3$,H_2

The ring D functionality in (9) was protected as the trisodium salt, prior to Birch reduction, followed by sequential treatment of the presumed intermediate (10) with oxalic acid (to hydrolyse the enol ether and reconstitute the spirolactone) and sodium methoxide (to effect conjugation in ring A). These steps furnished 14-hydroxymethyl-3-oxo-19-nor-17α-pregn-4-ene-21,17-carbolactone(11)[m.p.204-206°C (from chloroform-ethyl acetate); $[\alpha]_D$ +56° (c 0.9; $CHCl_3$); μ_{max} 1760 and 1660 cm^{-1}; λ_{max} 238 nm (logϵ 4.21)] in an overall yield of 60% from (9) (Scheme 4).

Scheme 4



Reagents: (i) NaOH-MeOH (ii) Li-NH_3-tBuOH (iii) $(CO_2H)_2$-THF-H_2O
(iv) NaOEt-EtOH (v) HCl-MeOH.

If, instead of the foregoing stepwise process, the intermediate (10) was subjected to treatment with methanolic hydrochloric acid, the spirolactone(11) was isolated in

poor yield (*ca* 25%), and was accompanied by methyl 3-(17α,14-epoxymethano-3-oxo-estr-4-en-17β-yl)propanoate (12) (28%), [m.p. 141-143°C (from ethyl acetate); $[\alpha]_D$ +42° (*c* 0.9; $CHCl_3$)]. Evidence for the structure derived from 500 MHz n.m.r. signals for a closed AA'BB' spin system (δ 1.8-2.48)(17β-side chain) and a distinctive pair of signals at δ 3.31 (1H, d, *J* 7.3 Hz) and 3.88(1H, dd, *J* 7.3 and 4.1 Hz) for 14^1-H_2.[1] It is suggested that this product arose from intramolecular capture by the 14α-hydroxymethyl group of an incipient 17-carbocation generated by the strongly acidic conditions, in a process reminiscent of those observed[9] in acid-catalysed rearrangements of other 21,17-carbolactones.

Despite the need for exercising particular care with 14-functionalised systems, the option of synthesising 17,17-spirolactones from the corresponding 17-formyl acetates under the exceptionally mild conditions described here, adds to the methodology already available.

References

1. The experimental work described in the paper was carried out largely at the former National Chemical Research Laboratory in Pretoria, and is taken in part from the Ph.D thesis of L.M. Steer (University of South Africa,1987).

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5. See, for example, J.R. Bull and A. Tuinman, *J. Chem.Soc., Perkin Trans.* 1, 1976, 212, and refs. cited.

6. All new compounds described in this paper displayed the correct microanalytical and spectroscopic data.

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