Lewis Acid-mediated Isomerisation of (25*R*)-3β-Acetoxy-5α-spirostan-23-one, a C-22 Spiroacetal: an Approach to the Synthesis of C-23 Spiroacetal Steroidal Sapogenins

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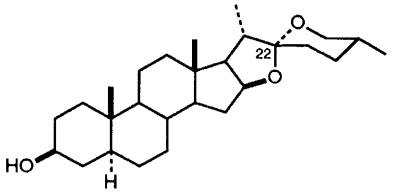
Treatment of (25*R*)-3β-acetoxy-5α-spirostan-23-one (23-oxo-tigogenin acetate) **3** with titanium tetrachloride afforded the 22-oxo-23-spiroacetal isomer **4** in excellent yield.

Spiroacetals enjoy widespread occurrence as the substructure of many compounds available from a diverse range of natural sources including insects, microbes, plants, fungi and marine organisms.[1] Among these natural products the spirostan sapogenins form a well-defined class and several reviews concerning them have been reported.[2] These compounds contain a spiroacetal moiety fused to the ring *D* of the steroidal nucleus (*e.g.* tigogenin, Scheme 1).

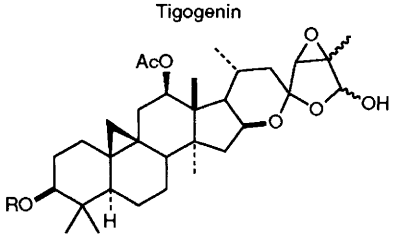
A similar spiroacetal assembly has also been found in a few triterpenoid saponins, for example: cimicifugoside and actein (Scheme 1), the former isolated from the roots of *Cimicifuga simplex*[3a] which exhibits potent immunosuppressive activity,[3b,c] and the latter from the rhizome of *Actea racemosa*.[4] In these compounds the spiroacetal unit is attached at C-23 in ring *D* (steroids numbering).

To the best of our knowledge no steroidal C-23 spiroacetal sapogenin has been isolated from a natural source. Since the chemistry of C-22 spiroacetal steroidal sapogenins (spirostan sapogenins) has been studied in some detail,[5] a comparative study of the chemical behaviour of their isomeric C-23 spiroacetal analogues would be of interest. Piancatelli *et al.*[6] have reported the synthesis of such a C-23 spiroacetal steroidal sapogenin **2** from **1** (Scheme 1). However, the multistep synthesis resulted in a low overall yield and provided material with a C-20 stereochemistry opposite to that of the natural steroids along with an unassigned configuration at C-25.

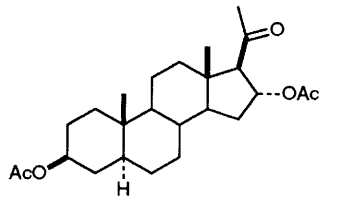
Herein we report an approach to the synthesis of steroidal C-23 spiroacetal sapogenins *via* a new, mild and efficient Lewis acid mediated isomerisation of a 23-oxo-22-spiroacetal. Thus, treatment of (25*R*)-3β-acetoxy-5α-spirostan-23-one



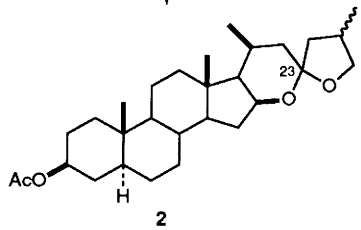
Tigogenin



Actein (R = β-D-xylose)
Cimicifugoside (Δ^7, R = β-D-xylose)



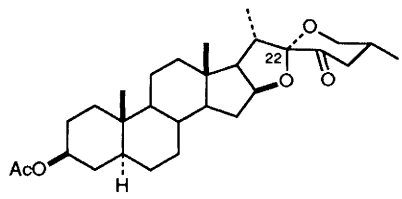
1



2

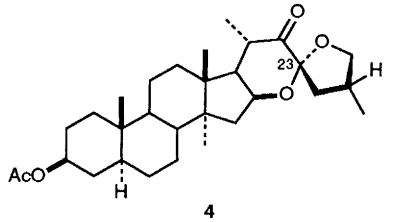
Scheme 1

(23-oxo-tigogenin acetate) **3**[7] with titanium tetrachloride (2.5 equiv.) in dichloromethane under argon atmosphere at room temperature for 30 min. provided the isomer 22-oxo-23-spiroacetal **4**† as a single product in excellent yield (99%) after radial chromatography (Scheme 2). If the amount of Lewis acid is decreased not only is a longer reaction time required but also side-products are observed.



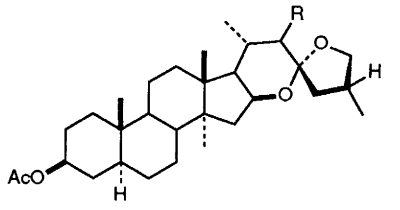
3

i



4

ii



5; R = 22β-OH
6; R = 22α-OH

Scheme 2 *Reagents and conditions*: i, $TiCl_4$ (2.5 equiv.), CH_2Cl_2, room temp., 30 min, 99%; ii, $NaBH_4$, EtOH, room temp., 5 min, 95%

Since the opening rings *E* and *F* were involved in the reaction, the stereochemistry of the new spiroacetal centre, C-23, was expected to be controlled by the anomeric effect,[8] resulting in the 23*R* epimer. However, X-ray diffraction analysis to confirm this was considered desirable. Since repeated attempts to obtain suitable crystals of the ketone **4** were unsuccessful we sought a derivative that would furnish quality crystals. Reduction of the ketone with sodium borohydride afforded the separable diastereoisomeric alcohols **5** and **6**† (2.2 : 1), in 95% yield. Suitable crystals of alcohol **6** were obtained and the X-ray crystal structure determined‡ (Fig. 1). This revealed an *R* configurated spiroacetal centre. As the spiroacetal centre is unaffected by reduction of the ketone, the Lewis acid isomerisation of **3** gave the product whose

† *Selected spectroscopic data* (^{1}H NMR at 200 MHz and ^{13}C NMR at 50.3 MHz in $CDCl_3$, δ in ppm to Me_4Si, W and *J* in Hz; IR in $CHCl_3$, ν_{max}/cm^{-1}) for **4**: IR, 1725, 1250, 1020; ^{1}H NMR, 0.79 (s, 18-H_3), 0.90 (s, 19-H_3), 0.99 (d, *J* 6.8, 21-H_3), 1.02 (d, *J* 6.5, 27-H_3), 1.95 (s, 3H, AcO), 2.35 (m, w 22, 25-H), 2.73 (m, w 16, 20-H), 3.47 (t, *J* 8.6, 26-H), 4.06 (t, *J* 7.6, 26-H), 4.30 (m, w 22, 16-H), 4.60 (m, w 25, 3-H); ^{13}C NMR, 72.82 (d), 73.53 (d), 75.23 (t), 107.96 (s), 170.59 (s), 213.46 (s); MS (15 e V) *m/z* (%) 472 (M^+, 1); MS (70 e V) 442 (M^+-2Me, 2), 344 (79), 122 (100); MS high resolution *m/z* (calc. for) 442.2850 (442.2717 = $C_{23}H_{38}O_5$), 344.2718 (344.2713 = $C_{23}H_{36}O_2$), 122.1085 (122.1076 = C_9H_{14}). For **5**: IR, 3590, 1720, 1250, 1020. ^{1}H NMR, 0.82 (s, 3H), 0.84 (s, 3H), 1.02 (d, *J* 6.6, 3H), 1.04 (d, *J* 6.6, 3H), 2.02 (s, 3H, AcO), 2.61 (dd, *J* 8.6, 8.5, 1H), 3.42 (AMX, J_{AM} 10.4, J_{AX} 8.2, 26-H), 3.52 (A′M′X′, $J_{A'M'}$ 11.7, $J_{A'X'}$ 4.0, 22-H), 3.92 (t, *J* 7.6, 26-H), 4.19 (m, w 20, 16-H), 4.67 (m, w 20, 3-H); ^{13}C NMR, 60.17 (d), 71.60 (d), 73.39 (t), 73.65 (d), 75.96 (d), 112.16 (s), 170.70 (s),; MS (70 e V) m/z (%) 474 (M^+, 1), 101 (100); MS high resolution *m/z* (calc. for) 474.3353 (474.3345 = $C_{29}H_{46}O_5$), 101.0590 (101.0603 = $C_5H_9O_2$). For **6**: IR, 3590, 1715, 1250, 1015; ^{1}H NMR, 0.76 (s, 3H), 0.83 (s, 3H), 1.03 (d, *J* 6.4, 3H), 1.13 (d, *J* 6.9, 3H), 2.01 (s, 3H, AcO), 3.01 (bs, w 4, O-H), 3.45 (d, *J* 1.7, 22-H), 3.55 (AMX, J_{AM} 10.1, J_{AX} 8.2, 26-H), 3.97 (t, *J* 7.3, 26-H), 4.31 (m, w 17, 16-H), 4.68 (m, w 20, 3-H); ^{13}C NMR, 73.19 (d), 73.70 (d), 74.06 (t), 76.35 (d), 108.31 (s), 170.53 (s); MS (70 e V) *m/z* (%) 474 (M^+, 1), 101 (100); MS high resolution *m/z* (calc. for) 474.3368 (474.3345 = $C_{29}H_{46}O_5$), 101.0634 (101.0603 = $C_5H_9O_2$).

‡ *Crystal data* for **6**: a crystal measuring 0.3 × 0.3 × 1.2 mm was mounted on an Enraf-Nonius CAD4-F diffractometer equipped with a Cu-Kα radiation source (λ = 1.54180 Å), $C_{29}H_{46}O_5$. Space group $P2_1$, monoclinic, *a* = 10.72(1), *b* = 7.64(1), *c* = 16.10(2) Å, β = 93.75(6)°, *Z* = 2, D_c = 1.191 g cm^{-3}, *U* = 1316 Å^3. The origin in $P2_1$ was fixed by the method of Flack and Schwarzenbach.[9] Data were collected in an ω-2θ scan mode from 1 to 70° to yield 2836 unique reflections of which 2574 were considered observed having $I > 3\sigma(I)$. The structure was solved by direct methods and refined using full-matrix least-squares analysis to give a final *R* = 0.081 (R_w = 0.096). SHELXS-86 (G. Sheldrick, SHELXS-86 User Guide, Göttingen, Germany, 1986) was used for direct methods and CRYSTALS (D. J. Watkin, J. R. Carruthers and P. W. Betteridge, CRYSTALS User Guide, Chemistry Crystallography Laboratory, Oxford University, Oxford, UK, 1985) for all other least-squares calculations. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

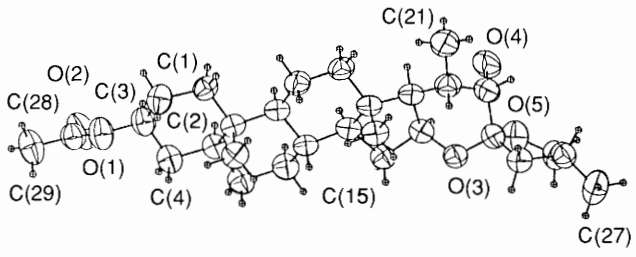


Fig. 1 The molecular structure of **6**

stereochemistry was controlled by the anomeric effect as expected.

In summary, we have shown that the new Lewis acid isomerisation of the oxo-spiroacetal **2** proceeds in excellent yield to the C-23 steroidal sapogenin **4**, whose stereochemistry is identical with that of naturally occurring analogues. Further investigations into the mechanism of this rearrangement and its scope and generality are underway.

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