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One-step axial acetoxylation at C-23. A new method for the functionalization of the side chain of steroid sapogenins

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Abstract—Treatment of steroid sapogenins with diacetoxyiodobenzene (DIB) and boron trifluoride ethyl etherate in acetic acid led to the introduction of an axial acetoxyl group at position C-23 of the side chain.

1. Introduction

For many years steroid sapogenins (SS) have served as starting materials for the synthesis of bioactive steroids. First, as a way to understand the reactivity of the side chain, and later as part of synthetic procedures, many reactions of the spiroketal moiety of SS were found and applied.[1] After a period of relative low activity in this field, new reactions of this structural fragment are being reported.[2]

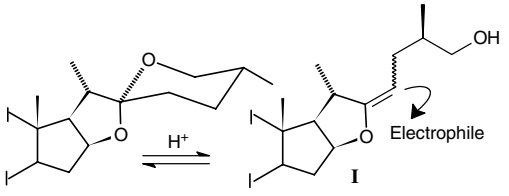
SS are involved in the synthesis of cephalostatins[3] and spirostanic analogues of brassinosteroids.[4] The available approaches for the synthesis of 23*R*-hydroxysapogenins imply the production and separation of diastereomeric mixtures. The first approach, that uses 23-bromosapogenins obtained from the parent sapogenins as an 1/1 mixture of the axial and equatorial diastereomers, suffers from the drawback that only the axial diastereomer dehydrohalogenates to the Δ^{23}-sapogenin, that on epoxidation leads to a mixture of the α and β oxiranes. Separation and reduction of the β-oxirane with $LiAlH_4$ leads to the 23*R*-alcohol in poor overall yield.[5]

A more convenient alternative involves the preparation of 23-oxosapogenins that can be obtained in 50–68% from the parent sapogenin.[4,6] Hydrogenation over PtO_2 or reduction with different metal hydrides lead to mixtures of the 23*S* and 23*R* alcohols in *S*/*R* ratios that range from 37/63 to 95/5.[2b,4,7] Despite all the cumulated work, the diastereoselective preparation of 23*R*-hydroxysapogenins has been an unsolved problem that hinders the synthesis of the natural 23*R* isomer of cephalostatins[7] or the application of stereospecific reactions of the *R* epimer.[2b]

In acid media SS undergo reversible F-ring opening to produce the enol ether **I** that has been claimed as the intermediate for the reactions of functionalization at C-23 (Scheme 1).[6] The capability of hypervalent iodine compounds to react with enols is well documented.[8] Considering that a hypervalent iodine moiety, after its electrophilic attack to an enol, can be displaced by a nucleophile, the reaction of SS with DIB in AcOH was envisaged as an alternative for functionalization of the spiroketal side chain.

Treatment of 3-epismilagenin and hecogenin acetates **1a** and **1b** with DIB and $BF_3{\cdot}Et_2O$ in AcOH produced the corresponding 23*R*-acetoxysapogenins in moderate to good yields (Scheme 2).

The ^1H and ^{13}C signals of the 23*R*-acetoxysapogenins **2a** and **2b** are in good agreement with the previously



Scheme 1.

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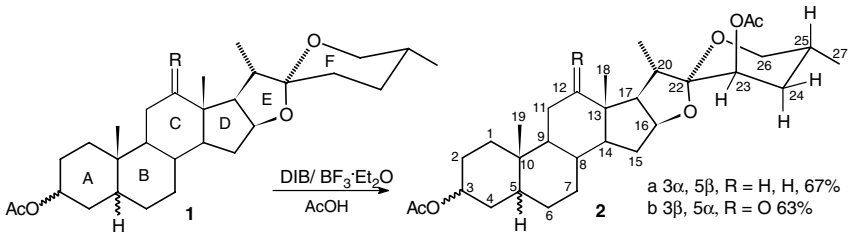


Scheme 2.

reported NMR data.[9] The axial orientation of the acetoxyl group at C-23 and hence the 23*R* configuration can be easily corroborated by the dd coupling pattern of the equatorial H-23 in which two small and similar coupling constants indicate equatorial–axial and equatorial–equatorial coupling of H-23 with both axial and equatorial H-24. Additionally, the nearly five ppm upfield shift of C-25 (from the normal 30.0 ppm in 25*R*-sapogenins with no functional group at C-23)[9a,b] indicates an 1,3 diaxial interaction between the acetoxyl group at C-23 and H-25 that accounts for the 23*R* configuration.

2. General procedure

To a stirred solution of the sapogenin acetate (2 mmol) in glacial AcOH (20 ml), DIB (644 mg, 2 mmol) and $BF_3{\cdot}Et_2O$ (1 ml) were added in this order and the mixture was stirred for 20 min. The additions of DIB (644 mg, 2 mmol) and $BF_3{\cdot}Et_2O$ (1 ml) were repeated and the resulting mixture was stirred for 20 min, poured into saturated NaCl solution (50 ml) and extracted with CH_2Cl_2 (2×30 ml). The combined extracts were washed with water (5×15 ml), 5% solution of Na_2CO_3 (until evolution of CO_2 ceased) and saturated NaCl solution (2×20 ml), dried (anhyd Na_2SO_4) and evaporated to afford a yellow syrup which was redissolved in a small amount of warm methanol, cooled and the resulting solid 23-acetoxysapogenin was filtered and washed with cool methanol. Evaporation of the mother liquor and purification by column chromatography (hexane/ethyl acetate 1/0–9/1) afforded an additional amount of the syrupy 23-acetoxysapogenin that was crystallized in methanol. Combined yields of crystallization and chromatography are reported.[10]

2.1. (23*R*,25*R*)-5β-Spirostan-3α,23-diol diacetate (2a)

Yield 67%. Mp 162–164 °C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$); 4.82 (dd, 1H, *J* 2.6, 2.6 Hz, H-23); 4.70 (m, 1H, H-3); 4.46 (ddd, 1H, *J* 5.5, 7.8 Hz, *J* 7.9 Hz, H-16); 3.54 (m, 1H, H-26 equiv); 3.43 (dd, 1H, *J* 11.2, 11.2 Hz, H-26 ax); 2.09 (s, 3H, CH_3 acetate); 2.01 (s, 3H, CH_3 acetate); 1.03 (d, 3H, *J* 7.0 Hz CH_3-21); 0.93 (s, 3H, CH_3-19); 0.77 (d, 3H, *J* 6.7 Hz, CH_3-27); 0.74 (s, 3H, CH_3-18). ^{13}C NMR (75.5 MHz) 35.0 C-1; 26.5* C-2; 74.3 C-3; 32.2 C-4; 41.7 C-5; 26.8* C-6; 26.5* C-7; 35.5 C-8; 40.5 C-9; 34.7 C-10; 20.4 C-11; 39.7 C-12; 41.0 C-13; 56.4 C-14; 31.8 C-15; 81.5 C-16; 64.0 C-17; 16.1 CH_3-18; 23.3 CH_3-19; 40.3 C-20; 16.1 CH_3-21; 107.0 C-22; 72.1 C-23; 33.6 C-24; 24.7 C-25; 66.4 C-26; 16.6 CH_3-27. 21.4 and 21.2 CH_3 acetate; 170.6 and 170.3 C=O acetate. (*Interchangeable.) MS (70 eV) 517 MH^+, 389 (M^+-127), 329, 315, 255, 197, 147, 107, 85, 43. Elemental analysis: calculated for $C_{31}H_{48}O_6$ C, 72.06; H, 9.36. Found C, 72.36; H, 9.40.

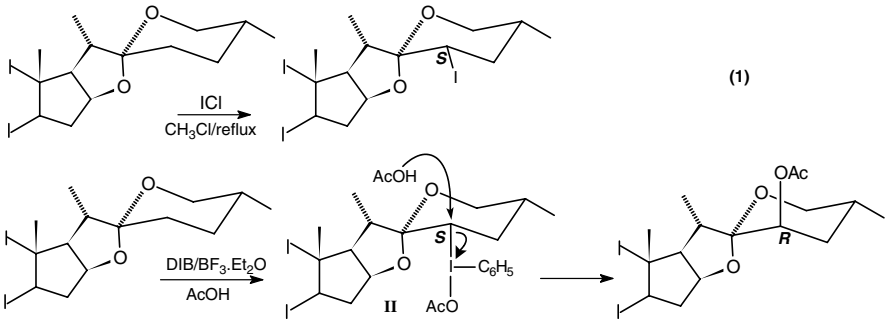
2.2. (23*R*,25*R*)-3β,23-Diacetoxy-5α-spirostan-12-one (2b)

Yield 63%. Mp 280–282 °C (from ethanol). ^{1}H NMR (400 MHz, $CDCl_3$); 4.80 (dd, 1H, *J* 2.8, 2.8 Hz, H-23); 4.65 (m, 1H, H-3); 4.41 (ddd, 1H, *J* 5.2, 7.7, 8.1 Hz, H-16); 3.55 (ddd, 1H, *J* 1.6, 4.7, 10.8 Hz, H-26 equiv); 3.41 (dd, 1H, *J* 11.3, 11.3 Hz, H-26 ax); 2.08 (s, 3H, CH_3 acetate); 2.01 (s, 3H, CH_3 acetate); 1.14 (d, 3H, *J* 7.0 Hz, CH_3-21); 1.04 (s, 3H, CH_3-18); 0.90 (s, 3H, CH_3-19); 0.77 (d, 3H, *J* 6.7 Hz, CH_3-27). ^{13}C NMR (100 MHz) 36.2 C-1; 27.2 C-2; 73.1 C-3; 33.7* C-4; 44.4 C-5; 28.1 C-6; 31.4# C-7; 34.9 C-8; 55.3& C-9; 36.0 C-10; 37.6 C-11; 213.3 C-12; 55.4 C-13; 55.4& C-14; 31.2# C-15; 79.8 C-16; 55.8& C-17; 15.8 CH_3-18; 11.8 CH_3-19; 41.0 C-20; 14.6 CH_3-21; 107.0 C-22; 71.8 C-23; 33.7 C-24; 24.6 C-25; 66.5 C-26; 16.6 CH_3-27. 21.4 and 21.2 CH_3 acetate; 170.6 and 170.3 C=O acetate. (*,&,#Interchangeable.) MS (70 eV). 530 M^+, 403 (M^+-127), 385, 357, 329, 315, 197, 147, 85. Elemental analysis: calculated for $C_{31}H_{46}O_7$ C, 70.16; H, 8.74. Found C, 70.25; H, 8.73.

It has been reported that treatment of SS with ICl in refluxing chloroform affords the corresponding 23*S*-iodosapogenin as the sole product (Scheme 3, Eq. 1).[11] In our particular cases it seems likely that the electrophilic attack of the hypervalent iodine reagent to enol **I** leads to the 23*S* isomer **II**, which on S_N2 displacement of the hypervalent iodine moiety attached to C-23 affords the observed 23*R*-acetoxysapogenins **2a** and **2b** (Scheme 3).

Another important observation is that in hecogenin acetate (**1b**), no product of reaction due to enolization of the carbonyl group at C-12 was observed. Previous reports indicate that meanwhile monobromination of **1b** proceeds rapidly at room temperature to afford the 23-brominated compound, dibromination to the 11,23-dibromo derivative requires stronger conditions (i.e., excess of bromine, warming and longer reaction times).[12] This is a clear indication of the higher reactivity of the spiroketal moiety that explains the chemoselective functionalization achieved in this reaction.

In summary, the diastereoselective introduction of an axial acetoxyl group at position C-23 can be effected in one step and with moderate to good yields by treatment



Scheme 3.

of the steroid sapogenin with DIB and $BF_3{\cdot}Et_2O$ in acetic acid. This new reaction provides a solution for the diastereoselective production of 23*R*-acetoxysapogenins useful in the synthesis of cephalostatins.[7b] Additionally, 23-acetoxysapogenins can be hydrolyzed to the corresponding 23-hydroxysapogenin[13] that may be easily converted into Δ^{23}-sapogenins, paving the way to the introduction of further functionality in the F ring.

Further experiments to extend this new reaction to other systems and to explore its compatibility with other functional groups are on development.

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