Steroids 77 (2012) 819–828

Contents lists available at SciVerse ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

$BF_3{\cdot}Et_2O$-induced stereoselective aldol reaction with benzaldehyde, and steroid sapogenins and its application to a convenient synthesis of dinorcholanic lactones

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ARTICLE INFO

Article history:
Received 29 April 2011
Received in revised form 21 February 2012
Accepted 22 February 2012
Available online 15 March 2012

Keywords:
Aldol reaction
Steroids sapogenins
E-23(23′)-benzylidenspirostanes
Spiroketals
Dinorcholanic lactones
X-ray diffraction

ABSTRACT

Treatment of steroid sapogenins with benzaldehyde and $BF_3{\cdot}Et_2O$ cleanly produces *E*-23(23′)-benzylidenspirostanes in good yields in a reaction pathway which consists on an aldol reaction followed by a dehydration step. The obtained *E*-23(23′)-benzylidenspirostanes can be easily converted to dinorcholanic lactones by treatment with CrO_3 in acetic acid. The synthetic sequence to dinorcholanic lactones is compatible with the presence of double bonds and carbonyl groups in the steroid framework.

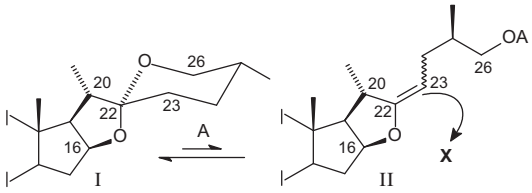
1. Introduction

The chemistry of steroid sapogenins (SS) has concentrated the attention of organic chemist for nearly a century. A wide variety of reactions of the spiroketal side chain discovered and initially considered mere curiosities have became useful tools for the transformation of SS into bioactive compounds that include sexual and adrenocortical hormones [1], ecdysteroids [2], plant growth stimulators [3–9], and cytotoxic steroids [10–16] among many others. The search for new reactions of the spiroketal side chain of SS stills an interesting task from both the mechanistic and synthetic point of views.

Meanwhile the chemical properties of the steroid nucleus of SS are similar to those of the steroids in general, the reactivity of the spiroketal side chain constitute the distinguishing characteristic of SS. It is well known that the presence of Brønsted or Lewis acids catalyzes the ketal ⇆ enol ether equilibrium associated to the side chain of SS, increasing the concentration of the exocyclic enol ether **II**. The reaction of the enol ether **II** with electrophiles gives place to a variety of methods for the introduction of substituents at position C-23 that allow the transformation of the side chain paving the way to the synthesis of a wide diversity of bioactive steroids [17–25].

Considering that in the case of steroid sapogenins, the concentration of the reactive enol ether **II** in the equilibrium is considerably low and can be slightly increased by the addition of a Lewis acid (see Scheme 1), we envisaged that in such conditions a controlled nucleophilic addition of the *in situ* produced enol ether **II** to a non-enolizable aldehyde could be achieved. This prompted us to employ benzaldehyde as a model to explore the possibility to produce aldol reactions in the side chain of readily available SS that are commonly employed as starting materials for the industrial production of steroids of medicinal interests.

Herein we report on the $BF_3{\cdot}Et_2O$-induced aldol condensation of different steroid sapogenins with benzaldehyde that cleanly effects the high yield and stereoselective introduction of an *E*-benzylidene



A= **Brønsted or Lewis acid**, X = **Electrophile** (D $^+$, Br^+, I^+, I^{3+}, NO^+, etc)

Scheme 1. Acid catalyzed ketal ⇆ enol ether of the side chain of steroid sapogenins.

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0039-128X/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.steroids.2012.02.016

group at position C-23 of the spiroketal side chain. A convenient alternative for the synthesis of diverse dinorcholanic lactones (including those containing carbonyl groups or double bonds) by treatment of the obtained *E*-23(23′)-benzylidenspirostanes with CrO_3 in acetic acid is also described.

2. Experimental section

2.1. General experimental procedures

Reactions were monitored by TLC on ALUGRAM® SIL G/UV254 plates from MACHEREY–NAGEL. Chromatographic plates were sprayed with a 1% solution of vanillin in 50% $HClO_4$ and heated until color developed. Melting points were measured on a Melt-Temp II equipment and are uncorrected. Electronic impact Mass spectra (70 eV) were registered in a Thermo-Electron spectrometer model DFS (Double Focus Sector). NMR spectra were recorded in $CDCl_3$ solutions in a Varian INOVA 400 spectrometer using the solvent signal 7.26 ppm for ^1H and 77.00 ppm for ^{13}C as references. NMR signals assignments were made with the aid of a combination of 2D homonuclear (^1H–^1H) and heteronuclear (^1H–^{13}C) correlation techniques, which included Correlation Spectroscopy (COSY), Nuclear Overhauser Effect Spectroscopy (NOESY), Heteronuclear Single Quantum Correlation (HSQC) and Heteronuclear Multiple Bond Correlation (HMBC). All 2D NMR spectra were recorded using the standard pulse sequences and parameters recommended by the manufacturer and processed employing the NMR processing program MestreNova. X-ray measurements were performed on an Oxford Diffraction Atlas (Gemini) diffractometer.

2.2. General procedure for the synthesis of E-23(23′)-benzylidenspirostanes

Freshly distilled $BF_3{\cdot}Et_2O$ (6 ml) was added to solution of the steroid sapogenin (1 mmol) and benzaldehyde (212 mg, 2 mmol) in dry CH_2Cl_2 (30 ml) and the mixture was stirred under argon at room temperature until the starting steroid sapogenin was consumed (TLC, see Table 1 for reaction times and yields). The reaction mixture was washed with water (8 × 50 ml), dried (anh. Na_2SO_4) and evaporated to produce a syrupy residue that was purified in a chromatographic column packed with silica gel to afford the corresponding *E*-23(23′)-benzylidenspirostane.

2.3. [23(23′)E,25R]-23(23′)-Benzylidene-5α-spirostan-3β-ol acetate (**2a**)

Yield: 502 mg (92%). Mp 215–216 °C (ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.37–7.30 (m, 2H, H-meta), 7.27–7.19 (m, 3H, H-ortho and H-para), 6.57 (s, 1H, H-23′), 4.69 (ddd, *J* = 16.2, 11.2, 4.9 Hz, 1H, H-3), 4.44 (dd, *J* = 16.0, 7.2 Hz, 1H, H-16), 3.61–3.49 (m, 2H, H-26 ax./eq.), 2.78 (dd, *J* = 13.3, 3.7 Hz, 1H, H-24, eq.), 2.59 (dq, *J* = 6.9 Hz, 1H, H-20), 2.14–2.06 (m, 1H, H-24 ax.), 2.02 (s, 3H, CH_3 acetyl), 1.90 (dd, *J* = 8.9, 7.2 Hz, 1H, H-17), 1.10 (d, *J* = 6.9 Hz, 3H, H-21), 0.85 (s, 3H, H-19), 0.83 (s, 3H, H-18), 0.80 (d, *J* = 6.6 Hz, 3H, H-27). ^{13}C NMR (100 MHz) δ ppm: δ 36.7 C-1; 27.4 C-2; 73.6 C-3, 34.0 C-4, 44.6 C-5, 28.5 C-6, 32.2 C-7, 35.0 C-8, 54.2 C-9, 35.6 C-10, 21.1 C-11, 40.2 C-12, 40.8 C-13, 56.2 C-14, 31.6 C-15, 80.4 C-16, 61.6 C-17, 16.7 C-18, 12.3 C-19, 37.3 C-20, 14.8 C-21, 110.5 C-22; 137.1 C-23*, 32.9 C-24, 33.1 C-25, 66.1 C-26, 17.2 C-27, 170.7 C=O acetyl, 21.4 CH_3 acetyl, 137.2 *ipso**, 129.1 *ortho*, 128.1 *meta*, 126.5 *para*, 122.8 C-23′. EIMS *m*/*z* 546 M^+ (25), 469(31), 468 (23), 466 (12), 456 (12), 453 (14), 428 (14), 416 (31), 415 (12), 325 (22), 315 (16), 269 (12), 256 (19), 255 (90), 254 (21), 253 (20), 252 (14), 251 (20), 239 (23), 238 (13), 227 (25), 226 (12), 215 (10), 214 (15), 213 (11), 212 (12), 211 (21), 204 (15), 203 (100), 201 (13), 199 (19), 198 (10), 197 (14), 185 (13), 183 (11), 174 (12), 173 (13), 171 (12), 165 (11), 161 (30), 159 (17), 157 (15), 155 (13), 149 (11), 147 (36), 146 (11), 145 (25), 143 (18), 142 (10), 141 (13), 135 (11), 133 (16), 131 (22), 129 (22), 128 (14), 121 (16), 119 (17), 117 (27), 115 (20), 109 (12), 107 (32) 106 (10), 105 (34), 95 (41), 93 (31) 91 (60), 81 (24), 79 (24), 77 (14), 69 (11), 55 (18). HREIMS *m*/*z* 546.3713 (calcd. for $C_{36}H_{50}O_4$, 546.3704).

Table 1
Results of the $BF_3{\cdot}Et_2O$-catalyzed reaction of steroid sapogenins with benzaldehyde.

Entry	Starting material	Reaction time (h)	Product	Yield[a] (%)
1	Tigogenin acetate (**1a**)	5.5	**2a**	92
2	Sarsasapogenin acetate (**1b**)	1.5	**2b**	87
3	Diosgenin acetate (**1c**)	6	**2c**	91
4	Hecogenin acetate (**1d**)	6	**2d**	53+[b]
5	Hecogenin acetate (**1d**)	24	**2d**	65+[b]

[a] Yields after purification in chromatographic column.
[b] Recovered starting material.

2.4. [23(23′)E, 25S]-23(23′)-Benzylidene-5β-spirostan-3β-ol acetate (**2b**)

Yield: 475 mg (87%). Mp 197–198 °C (ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.32 (m, 2H, H-meta), 7.21 (m, 3H, H-ortho and H-para), 6.72 (s, 1H, H-23′), 5.07 (m, 1H, H-3), 4.47 (dd, *J* = 16.0, 7.2 Hz, 1H, H-16), 4.05 (dd, *J* = 11.0, 4.2 Hz, 1H, H-26 ax.), 3.32 (d, *J* = 11.0 Hz, 1H, H-26 eq.), 2.72 (ddd, *J* = 13.6, 5.6, 1.2 Hz, 1H, H-24 eq.), 2.54–2.45 (m, 1H, H-20), 2.29 (dd, *J* = 13.6, 5.2 Hz, 1H, H-24 ax.), 1.92–1.84 (m, 1H, H-17) 2.04 (s, 1H, CH_3 acetyl), 1.11 (d, *J* = 6.9 Hz, 3H, H-21), 0.99 (s, 3H, H-19), 0.99 (d, *J* = 7.1 Hz, 3H, H-27), 0.85 (s, 3H, H-18). ^{13}C NMR (100 MHz) δ ppm: 30.6 C-1; 25.0 C-2; 70.7 C-3, 31.6 C-4, 39.3 C-5, 26.4 C-6, 26.4 C-7, 35.2 C-8, 40.0 C-9, 35.0 C-10, 20.9 C-11, 40.4 C-12, 40.9 C-13, 56.4 C-14, 30.7 C-15, 81.0 C-16, 61.8 C-17, 16.7 C-18, 23.9 C-19, 39.8 C-20, 14.7 C-21, 111.4 C-22; 136.8 C-23*, 30.9 C-24, 30.3 C-25, 65.1 C-26, 18.3 C-27, 170.7 C=O acetyl, 21.5 CH_3 acetyl, 137.2 *ipso**, 129.1 *ortho*, 128.0 *meta*, 126.5 *para*, 122.8 C-23′. EIMS *m*/*z* 546 M^+ (17), 486 (11), 469 (20), 468 (17), 429 (10), 417 (15), 416 (47), 415 (14), 395 (12), 269 (10), 256 (22), 255 (100), 253 (12), 251 (15), 239 (11), 227 (18), 211 (14), 204 (11), 203 (75), 201 (16), 199 (11), 173 (12), 161 (20), 159 (12), 149 (11), 147 (21), 145 (16), 143 (11), 133 (11), 131 (17), 129 (14), 119 (12), 117 (19), 115 (12), 107 (24), 105 (23), 95 (23), 93 (24) 91 (40), 81 (18), 79 (19), 55 (13). HREIMS *m*/*z* 546.3716, (calcd. for $C_{36}H_{50}O_4$, 546.3704).

2.5. [23(23′)E,25R]-23(23′)-Benzylidenspirost-5-en-3β-ol acetate (**2c**)

Yield: 495 mg (91%). Mp 190–191 °C (ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.37–7.29 (m, 2H, H-meta), 7.27–7.19 (m, 3H, H-ortho and H-para), 6.58 (s, 1H, H-23′), 5.38 (d, *J* = 4.9 Hz, 1H, H-6), 4.60 (ddd, *J* = 10.4, 8.6, 4.3 Hz, 1H, H-3), 4.46 (dd, *J* = 16.0, 7.2 Hz, 1H, H-16), 3.62–3.50 (m, 2H, H-26 ax./eq.), 2.78 (dd, *J* = 13.3, 3.9 Hz, 1H, H-24 eq.), 2.60 (m, 1H, H-20), 2.38–2.27 (m, 2H H-4 ax./eq.), 2.15–2.06 (m, 1H, H-24 ax.), 2.03 (s, 3H, CH_3 acetyl), 1.94–1.87 (m, 1H, H-17), 1.11 (d, *J* = 6.9 Hz, 3H, H-21), 1.05 (s, 3H, H-19), 0.86 (s, 3H, H-18), 0.80 (d, *J* = 6.6 Hz, 3H, H-27). ^{13}C NMR (100 MHz) δ ppm: 36.9 C-1; 27.7 C-2; 73.9 C-3, 38.1 C-4, 139.7 C-5, 122.3 C-6, 30.1 C-7, 31.3 C-8, 49.9 C-9, 36.7 C-10, 20.9 C-11, 39.9 C-12, 40.5 C-13, 56.4 C-14, 31.76 C-15, 80.4 C-16, 61.5 C-17, 16.5 C-18, 19.3 C-19, 37.3 C-20, 14.9 C-21, 110.6 C-22, 137.1 C-23*, 32.9 C-24, 33.2 C-25, 66.1 C-26, 17.2 C-27, 170.5 C=O acetyl, 21.4 CH_3 acetyl, 137.2 *ipso**, 129.1 *ortho*, 128.1 *meta*, 126.6 *para*, 122.8 C-23′. EIMS *m*/*z* 544 M^+ (12), 467 (20),