Pergamon

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Tetrahedron: *Asymmetry* 14 (2003) 2781–2785

TETRAHEDRON: *ASYMMETRY*

A convenient synthesis of oxandrolone through a regioselective *Candida antarctica* lipase-catalyzed transformation

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Received 30 June 2003; accepted 23 July 2003

Abstract—The use of a regioselective CAL-catalyzed transformation of a suitable intermediate allowed a convenient synthesis of oxandrolone, an anabolic hormone actually employed to improve the quality of life for patients with HIV-infections.

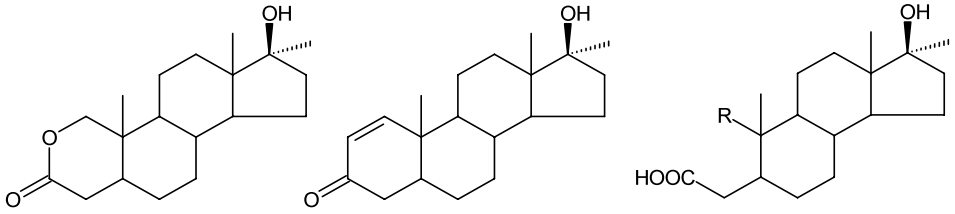
1. Introduction

Oxandrolone **1** (17β-hydroxy-17α-methyl-2-oxa-5α-androst-3-one) is a clinically useful, synthetic, anabolic steroid administered in conditions which included weight loss due to extensive surgery, chronic infections, trauma, etc. Actually,[1,2] for the activity in increasing skeletal muscle protein synthesis, oxandrolone is employed to mitigate weight loss associated with disease progression, reduced quality of life and increased mortality, in patients with HIV (human immunodeficiency virus)-infection.

In 1963 Pappo and Jung[3] prepared the appropriate intermediate, 17β-hydroxy-17α-methyl-1-oxo-1,3-seco-2-nor-5α-androstan-3-oic acid **3**, for the synthesis of lactone **1**, opening the A-ring of 17β-hydroxy-17α-methyl-1-androsten-3-one **2**[4] with osmium tetroxide and lead tetraacetate. The choice of these oxidants, although toxic and expensive, provided the advantage of a different functionalization of C-1 and C-3, necessary in the next steps of the synthesis. We followed a different approach, planning to open the 1,2-double bond of compound **2** with potassium permanganate and sodium periodate,[5] delaying to a later step the discrimination of C-1 and C-3 of the obtained 1,3-diacid **4**.

2. Results and discussion

Derivative **2** was prepared starting from 3β-hydroxy-5α-androstan-17-one **5** in 65% overall yield: in the first step the 17α-methyl group was introduced by reaction with methylmagnesium bromide;[3] then oxidation of 3-hydroxy group and selective halogenation with pyridinium tribromide[6] afforded the 2-bromo-3-keto derivative that, by elimination (lithium bromide and lithium carbonate in dimethylformamide[4]) furnished compound **2**. The best results for oxidative cleavage of ring A were achieved carrying out the reaction with potassium permanganate and sodium periodate in the presence of potassium carbonate in *tert*-butanol, at reflux;[7] the 17β-hydroxy-17α-methyl -1,3-seco-2-nor-5α-



1 **2** **3** R = CHO, **4** R = COOH

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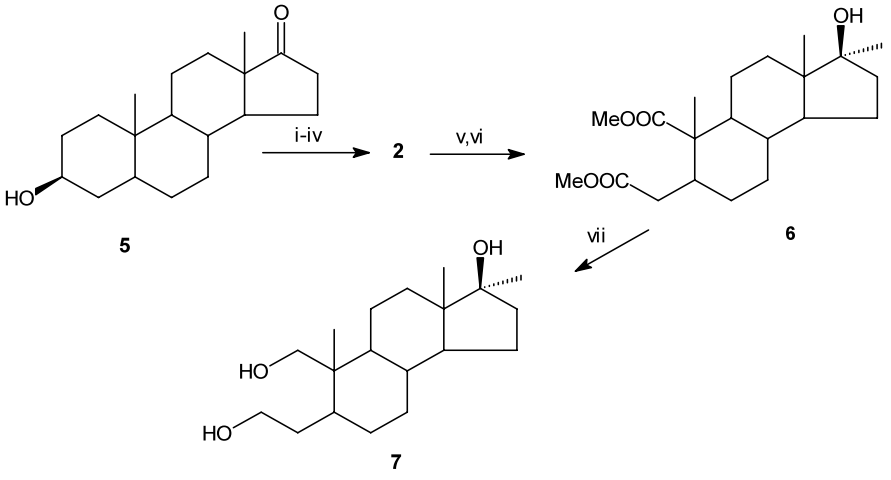
doi:10.1016/S0957-4166(03)00593-7

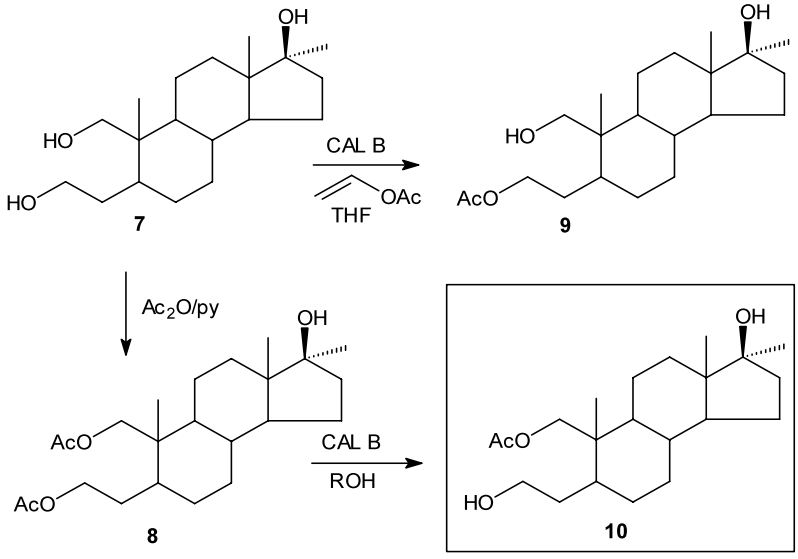
androstane-1,3-diacid **4** was treated with diazomethane and the obtained dimethylester **6** reduced to 1,3-seco-2-nor-1,3-diol **7**[8] with lithium aluminum hydride in tetrahydrofuran (78% yields from **2**) (Scheme 1).

The well documented hydrolytic enzymes regio- and stereoselectivity prompted us to investigate a biocatalytic method for a different functionalization of 1- and 3-hydroxy group of **7**. Considering the lypophylicity of substrate we tested some commercially available lipases, known for their activity in organic solvents and selective transformations of steroids.[9] Whereas 1,3-diol **7** was not substrate for the lipases from *Pseudomonas cepacia* and *Candida rugosa*, good results were observed with lipase from *Candida antarctica* (Novozym 435, type-B lipase from *C. antarctica* immobilized on an acrylic resin), already successfully applied with steroidal compounds, by others[10,11] as well as in our laboratory.[12] In fact by acylation of **7** and alcoholysis of diacetate **8** the two different regioisomers were obtained: under irreversible transesterification conditions[13,14] (vinyl acetate in tetrahydrofuran, 3 h) 1,3-diol **7** was completely converted into 3-monoacetate **9**, whereas diacetate **8**, on treatment with 1-octanol in tetrahydrofuran[15] (24 h, 70% conversion), afforded only 1-monoacetate **10**† (Scheme 2).

The identity of the novel monoacetates **9** and **10** was ascertained through ^{1}H NMR analyses. In particular, lower field shifts of the methylenic C-1 or C-3 protons with respect to the 1,3-diol **7**, accounted for the structure of compounds **10** or **9**, respectively. Complete ^{1}H and ^{13}C NMR characterisation of these new steroids was also obtained using a combination of 1D and 2D (COSY, HSQC) experiments recorded in pyridine at 338 K, as this solvent gave the best spread of proton resonances.



Scheme 1. *Reagents*: (i) CH_3MgBr; (ii) CrO_3/H_2SO_4; (iii) $Py{\cdot}HBr{\cdot}Br_2$; (iv) Li_2CO_3, LiBr; (v) $KMnO_4$, $NaIO_4$; (vi) CH_2N_2; (vii) $LiAlH_4$.



Scheme 2.

† The enzyme in both cases acts on the less hindered position 3.

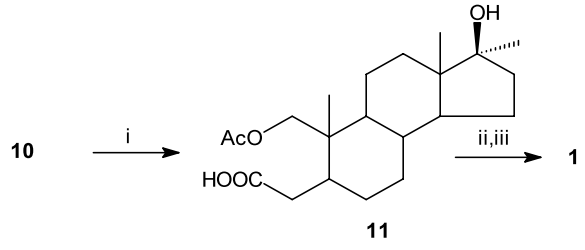
Since compound **10** is a suitable intermediate for oxandrolone synthesis we tested different CAL-catalyzed alcoholysis conditions of **8** with the aim of optimizing the results in terms of conversion and reaction times. Carrying out the transformation in pure 1-octanol a 90% conversion after 24 h was observed and similar results (80% conversion after 20 h) were furnished by 1-butanol. Best results were obtained in pure ethanol: in fact, a 95% conversion of 1,3-diacetate **8** was reached after only 3 h[‡] and the obtained **10**, after crystallization, could be transformed into oxandrolone **1** (70% yields) by oxidation (Jones conditions), hydrolysis of acetate **11** and acidic treatment of the intermediate hydroxyacid (Scheme 3).

3. Conclusion

In summary, a regioselective CAL-catalyzed transformation, avoiding use of highly toxic and very expensive reagents, allowed a simple and safe preparation of the anabolic steroid oxandrolone, actually the object of a renewed interest for its therapeutic application in AIDS patients; moreover chemoenzymatically prepared monoacetates **9** and **10** can be useful intermediates for the synthesis of other 2-etherosteroids.

4. Experimental

All solvents and reagents were purchased from Sigma–Aldrich. All reactions were monitored by TLC on silica gel 60 F_{254} plates (Merck) with detection by spraying with 10% phosphomolybdic acid in ethanol solution and heating at 110°C. Column chromatographies were performed on silica gel 60 (0.063–0.200 mm) (Merck). Uncorrected melting points were determined on a Büchi apparatus. Differential scanning calorimetry (DSC) were performed on a Perkin Elmer DSC-7 instrument. GLC analysis were performed on a Hewlett Packard HP5890 instrument at 260°C oven temperature, with an HP5-WB capillary column (25 m×0.32 mm i.d., 0.52 μm film thickness). Optical rotations were determined on a Perkin Elmer model 241 polarimeter in a 1 dm cell at 25°C. The NMR spectra were recorded with a Bruker AM-500 spectrometer operating at 500.13 and 125.76 MHz for ^1H and ^{13}C, respectively. Chemical shifts are reported as δ (ppm) relative to TMS as internal reference. Analytical samples were dissolved in $CDCl_3$, unless otherwise stated, and their spectra recorded at 298 or 338 K (compounds **9** and **10**). The assignments for compounds **9** and **10** were given by a combination of 1D and 2D COSY and HSQC experiments, using standard Bruker pulse programs. MS analyses were performed on a Varian Saturn Spectrometer (EI 70 eV).



Scheme 3. *Reagents*: (i) CrO_3/H_2SO_4; (ii) NaOH; (iii) HCl.

[‡] The enzyme, in these conditions, can be recycled showing an almost unaltered activity, whereas longer reaction times are required, if it is re-used after transesterification with vinyl acetate.

4.1. 17β-Hydroxy-17α-methyl-5α-androst-1-en-3-one 2

To a solution of methylmagnesium bromide (1.4 M in toluene/tetrahydrofuran 75/25, 84 mL), at room temperature, 3β-hydroxy-5α-androstan-17-one **5** (3 g, 10.33 mmol) in toluene (84 mL) was added. The reaction mixture was kept, under stirring, at 80°C for 5 h and at room temperature overnight. A solution of ammonium chloride (8.4 g) in water (60 mL) was added dropwise. The aqueous phase was further extracted with ethyl acetate (75 mL) and chloroform (75 mL). The combined organic fractions were washed with water and dried over sodium sulphate. After evaporation of the solvents at reduced pressure crude 17α-methyl-5α-androstan-3β,17β-diol (2.84 g, 90%) was recovered and used in the next step without any further purification. ^1H NMR (selected signals) δ 0.75 (3H, s, CH_3-18), 0.76 (3H, s, CH_3-19), 1.12 (3H, s, CH_3-20), 3.50 (1H, m, H-3). Jones reagent was added to the above 3β,17β-diol solution in acetone (60 mL) until orange colour persisted. Addition of 2-propanol, filtration through a Celite pad and evaporation of the solvent afforded 17β-hydroxy-17α-methyl-5α-androstan-3-one (2.55 g, 90%). ^1H NMR (selected signals) δ 0.85 (3H, s, CH_3-18), 1.01 (3H, s, CH_3-19), 1.19 (3H, s, CH_3-20). To the 3-ketone (2.53 g, 8.38 mmol), dissolved in a mixture of ethanol (40 mL) and methylene chloride (20 mL), pyridinium tribromide (2.69 g, 8.41 mmol) was added and the reaction mixture was kept under stirring at 40°C (2 h). Complete transformation of starting material (monitored by TLC, toluene/ethyl acetate, 7/3) was achieved by an additional amount of pyridinium tribromide (0.9 g) keeping the reaction mixture at 40°C (1 h). A saturated sodium hydrogen carbonate aqueous solution (15 mL) was added and, after removal of the organic solvents at reduced pressure and addition of water (30 mL), 2α-bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (3.0 g) was recovered by filtration and directly used in the next step. ^1H NMR (selected signals) δ 0.84 (3H, s, CH_3-18), 1.08 (3H, s, CH_3-19), 1.18 (s, CH_3-20) 1.79 (1H, dd, $J_{1a,1b}$ 13.0 Hz, $J_{1a,2}$13.6 Hz, H-1a), 2.38 (1H, dd, $J_{4a,4b}$ 14.7 Hz, $J_{4a,5}$ 5.0 Hz, H-4a), 2.41 (1H, dd, $J_{4b,5}$ 12.0 Hz, H-4b), 2.62 (1H, dd, $J_{1b,2}$ 6.4 Hz, H-1b), 4.72 (1H, dd, H-2). Mp 193–195°C (acetone/hexane).

Dehydrobromination was achieved by treatment of 2-bromo derivative (3.0 g, 7.85 mmol) with lithium bromide (4.5 g, 51.8 mmol) and lithium carbonate (3.9 g, 52.8 mmol) in dimethylformamide (70 mL) at reflux (2 h). The reaction progress was monitored by TLC (toluene/ethyl acetate, 7/3). The mixture was poured into cool water (200 mL) and the precipitate recovered by filtration. The crude Δ^1-derivative **2** was purified by

crystallization from acetone/hexane (2.04 g, 65% yields from **5**). ^{1}H NMR (selected signals) δ 0.86 (3H, s, CH_3-18, 1.00 (3H, s, CH_3-19), 1.20 (s, CH_3-20), 2.20 (1H, dd, $J_{4a,4b}$ 17.5 Hz, $J_{4a,5}$ 4.0 Hz, H-4a), 2.35 (1H, dd, $J_{4b,5}$ 14.0 Hz, H-4b), 5.83 (1H, d, $J_{2,1}$ 10.0 Hz, H-2), 7.12 (1H, d, H-1). Mp 140–142°C (acetone/hexane). $[\alpha]_D^{25}$ +25.6 (*c* 1, $CHCl_3$) (lit.[4] +25.8).

4.2. 17β-Hydroxy-17α-methyl-1,3-seco-2-nor-5α-androstane-1,3-diacid, 1,3-dimethylester 6

Compound **2** (1.5 g, 4.97 mmol) was dissolved in *t*-butanol (22 mL) and sodium carbonate (0.77 g, 7.27 mmol) in water (3 mL) was added. To the mixture, kept under vigorous stirring at reflux, a solution of sodium metaperiodate (6.0 g, 28 mmol) and potassium permanganate (0.045 g, 0.28 mmol) in warm water (50 mL) was added. The reaction progress was monitored by TLC (chloroform/methanol, 8/2) and additional amounts of permanganate were added after 5 and 15 h (0.020 and 0.040 g, respectively). When starting material disappeared, the precipitate was removed by filtration; the filtrate was concentrated at reduced pressure, acidified at pH 3 (1 M hydrochloric acid) and extracted with ethyl acetate (4×40 mL). Collected organic phase was dried over sodium sulphate and solvent removed at reduced pressure. The crude diacid (1.5 g, 90%), dissolved in methanol, was treated with an ethereal solution of diazomethane, affording the diester **6** (1.5 g, 92%). An analytical sample was purified by column chromatography (silica gel 1/10, elution by hexane/ethylacetate, 6/4). ^{1}H NMR (selected signals) δ 0.79 (3H, s, CH_3-18), 1.00 (3H, s, CH_3-19), 1.16 (s, CH_3-20), 3.60 (3H, s, CH_3O), 3.63 (3H, s, CH_3O). Mp 112–115°C (acetone/hexane).

4.3. 17α-Methyl-1,3-seco-2-nor-5α-androstane-1,3,17α-triol 7

A solution of **6** (1.5 g, 4.09 mmol) in anhydrous tetrahydrofuran (20 mL) was added dropwise to a suspension of lithium aluminium hydride (1.9 g, 5.1 mmol) in tetrahydrofuran (15 mL). The mixture was kept under stirring at room temperature (2 h). Then water (2 mL), 15% sodium hydroxide (2 mL) and water (6 mL) were added dropwise. The precipitate was removed by filtration through a Celite pad and the solvent evaporated at reduced pressure. Crude product was purified by crystallization (diisopropylether/hexane) affording pure diol **7** (1.21 g, 95%). ^{1}H NMR (selected signals, $CDCl_3$/CD_3OD) δ 0.68 (3H, s, CH_3-18), 0.80 (3H, s, CH_3-19), 1.15 (s, CH_3-20), 3.37 (1H, d, $J_{1a,1b}$ 12.0 Hz, H-1a), 3.39 (1H, d, H-1b), 3.51 (1H, ddd, $J_{3a,3b}$ 10.0 Hz, $J_{3a,4}$ 10.0 Hz, $J_{3a,4}$ 4.0 Hz, H-3a), 3.66 (1H, ddd, $J_{3b,4}$ 3.0 Hz, $J_{3b,4}$ 6.0 Hz, H-3b). Mp 146°C (lit.[8] 139–140°C). $[\alpha]_D^{25}$ −45.6 (*c* 1, $CHCl_3$).

4.4. 17α-Methyl-1,3-seco-2-nor-5α-androstane-1,3,17α-triol, 1,3-diacetate 8

A solution of **7** (0.5 g, 1.6 mmol) in pyridine (4 mL) was treated overnight with acetic anhydride (0.9 mL, 9.5 mmol) at room temperature. The mixture was poured into water (15 mL); after extraction with dichloromethane (3×10 mL), the collected organic phase was washed with 1 M hydrochloric acid and water. Usual work-up afforded crude diacetate that was purified by crystallization (acetone/water) (0.56 g, 90%). ^{1}H NMR (selected signals) δ 0.66 (3H, s, CH_3-18), 0.80 (3H, s, CH_3-19), 1.16 (3H, s, CH_3-20), 1.96 (3H, s, CH_3CO), 2.02 (3H, s, CH_3CO), 3.84–3.94 (3H, m, H-1a, H-1b and H-3a), 4.04 (1H, ddd, $J_{3a,3b}$ 10.0 Hz, $J_{3b,4}$ 5.0 Hz, $J_{3b,4}$ 8.0 Hz, H-3b). Mp 89°C (lit.[16] 90–91°C from benzene). $[\alpha]_D^{25}$ −36.7 (*c* 1, $CHCl_3$).

4.5. CAL-catalyzed transesterification of 1,3-diol 7

To a solution of **7** (0.15 g, 0.48 mmol) in tetrahydrofuran (30 mL) CAL B (Novozym 435, 0.53 g) and vinyl acetate (0.19 mL, 2.05 mmol) were sequentially added. The mixture was kept under stirring at 30°C, monitoring the reaction progress by TLC (chloroform/methanol, 9/1) until starting material disappearance (1 h). The enzyme was removed by filtration; evaporation at reduced pressure afforded a crude product (GLC T_R 16.99) that was purified by column chromatography (silica gel 1/10, elution with hexane/ethyl acetate, 6/4). To the obtained product (0.14 g, 82.5%) was assigned the structure of 3-monoacetate **9** in agreement with the observed chemico-physical data. ^{1}H NMR (Py-d_5) δ 0.70 (s, 3H, CH_3-18), 0.91 (m, 1H, H-7a), 1.1 (s, 3H, CH_3-19), 1.29 (m, 1H, H-14), 1.30 (m, 2H, H-4a and H-6b), 1.33 (m, 1H, H-15a), 1.34 (s, 3H, CH_3-20), 1.36 (m, 1H, H-12a), 1.45 (m, 1H, H-8), 1.41 (m, 1H, H-11a), 1.56 (m, 1H, H-9), 1.61 (m, 1H, H-15b), 1.63 (m, 1H, H-12b), 1.73 (m, 1H, H-7b), 1.77 (m, 1H, H-6b), 1.78 (m, 1H, H-16a), 1.84 (m, 1H, H-11b), 2.01 (m, 1H, H-5), 2.02 (s, 3H, CH_3C=O), 2.13 (m, 1H, H-4b), 2.13 (m, 1H, H-16b), 3.66 (dd, 1H, $J_{1a,OH}$ 4.2 Hz, $J_{1a,1b}$ 11.2 Hz, H-1a), 3.70 (dd, $J_{1b,OH}$ 3.5 Hz, 1H, H-1b), 4.24 (ddd, 1H, $J_{3a,3b}$ 10.5 Hz, $J_{3a,4a}$ 7.7 Hz, $J_{3a,4b}$ 7.7 Hz, H-3a), 4.31 (ddd, 1H, $J_{3b,4b}$ 8.4 Hz, $J_{3b,4a}$ 5.6 Hz, H-3b), 4.63 (br s, 1H, OH), 5.25 (br dd, 1H, OH). ^{13}C NMR (Py-d_5) δ 11.80 (C-18 or C-19), 14.60 (C-18 or C-19), 20.80 (CH_3C=O), 21.63 (C-11), 23.86 (C-15), 26.57 (C-20), 27.96 (C-6), 29.81 (C-4), 32.08 (C-7), 32.34 (C-12), 36.57 (C-8), 37.87 (C-5), 39.64 (C-16), 41.05 (C-10 or C-13), 45.98 (C-10 or C-13), 46.41 (C-9), 51.52 (C-14), 64.35 (C-1 and C-3), 80.72 (C-17), 170.67 (C=O). Mp 140–141°C. $[\alpha]_D^{25}$ −37.7 (*c* 1, $CHCl_3$). Endothermic peak fusion (DSC) at 140.17°C. EI-MS 317 (18%), 301 (7.8%), 275 (64%), 257 (100%), 243 (66%), 231 (12.5%), 217 (41). Found C, 71.42; H, 10.27; $C_{21}H_{36}O_4$ requires C, 71.55; H, 10.29.

4.6. CAL-catalyzed alcoholysis of 1,3-diacetate 8

Compound **8** (0.15 g, 0.38 mmol) was dissolved in ethanol (9 mL) and CAL B was added (0.72 g); the reaction mixture was kept at 30°C under stirring, monitoring the progress by GLC. After 3 h a 95% conversion of the starting material (GLC T_R 17.73) to a product with T_R 14.63 was observed. The oil recovered after filtration and evaporation of the solvents at reduced pressure was purified by column chromatography (silica gel 1/10); elution by hexane/ethyl acetate 6/4

afforded a product (0.114 g, 85%) that was identified as 1-monoacetate **10**. ^{1}H NMR (Py-d_5) δ 0.77 (s, 3H, CH_3-18), 0.88 (m, 1H, H-7a), 1.09 (s, 3H, CH_3-19), 1.28 (m, 1H, H-6a), 1.29 (m, 1H, H-14 or H-9), 1.31 (m, 1H, H-4a), 1.31 (m, 1H, H-15a), 1.33 (m, 1H, H-9 or H-14), 1.35 (s, 3H, 17α-CH_3), 1.42 (m, 2H, H-11a and H-12a), 1.43 (m, 1H, H-8), 1.61 (m, 1H, H-15b), 1.67 (m, 2H, H-11b and H-12b), 1.72 (m, 1H, H-7b), 1.77 (m, 1H, H-16a), 1.86 (m, 1H, H-5), 1.87 (m, 1H, H-6b), 2.03 (m, 4H, CH_3C=O and H-4b), 2.12 (m, 1H, H-16b), 3.84 (br ddd, 1H, $J_{3a,3b}$ 10.5 Hz, $J_{3a,4a}$ 7.7 Hz, $J_{3a,4b}$ 7.7 Hz, H-3a), 3.91 (br ddd, 1H, $J_{3b,4b}$ 7.7 Hz, $J_{3b,4a}$ 5.0 Hz, H-3b), 4.11 (d, 1H, $J_{1a,1b}$ 11.9 Hz, H-1a), 4.27 (d, 1H, H-1b), 4.70 (br s, 1H, OH), 5.22 (br s, 1H, OH). ^{13}C NMR (Py-d_5) δ 11.51 (C-18 or C-19), 14.57 (C-18 or C-19), 20.66 (CH$_3$C=O), 21.78 (C-11 or C-12), 23.82 (C-15), 26.56 (C-20), 27.90 (C-6), 31.93 (C-7), 32.17 (C-11 or C-12), 34.34 (C-4), 36.56 (C-8), 38.51 (C-5), 39.59 (C-16), 41.05 (C-10 or C-13), 45.98 (C-10 or C-13), 47.57 (C-9 or C-14), 51.37 (C-9 or C-14), 61.19 (C-3), 66.51 (C-1), 80.67 (C-17), 170.73 (C=O). Mp 123–125°C. $[\alpha]_D^{25}$ −26.2 (*c* 1, $CHCl_3$). Endothermic peak fusion (DSC) at 122.67°C. EI-MS 317 (12%), 289 (11%), 275 (36%), 257 (58%), 243 (100%), 231 (12%), 217 (57%). Found C, 71.45; H, 10.25; $C_{21}H_{36}O_4$ requires C, 71.55; H, 10.29.

4.7. Oxandrolone 1

1-Monoacetate **10** (0.1 g, 0.28 mmol) was dissolved in acetone and Jones reagent was added until orange colour persistent. 2-Propanol was added to destroy reagent excess and precipitated salts removed by filtration through a Celite pad. Crude product **11**, recovered after evaporation of solvents at reduced pressure, was dissolved in a 5% potassium hydroxide methanol/water (95/5) solution (2 mL). The mixture was heated at 50°C (3 h); after cooling at room temperature, 1 M hydrochloric acid was added to neutral pH; methanol was removed at reduced pressure and pH of the remaining mixture brought to 3. Extraction with ethyl acetate (3×5 mL) and usual work-up afforded pure **1** (0.06 g, 70%). ^{1}H NMR (selected signals) δ 0.84 (3H, s, CH_3-18, 0.98 (3H, s, CH_3-19 (3H, s, CH_3-20), 2.23 (1H, dd, $J_{4a,4b}$ 19.0 Hz, $J_{4a,5}$ 13.0 Hz, H-4a), 2.50 (1H, dd, $J_{4b,5}$ 6.0 Hz, H-4b), 3.90 (1H, d, $J_{1a,1b}$ 10.0 Hz, 1a), 4.2 (1H, d, 1b). Other chemico-physical properties are in agreement with the reported data.[4]

Acknowledgements

This work was financially supported by the Università degli Studi di Milano. We thank Professor Fiamma Ronchetti for helpful discussions.

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