Preparation of 3β-Acetoxy-5β-pregnan-20-one from 3α-Acetoxy-5β-cholan-24-oic Acid Aimed at the Isotopic Labelling of the Pregnane Side Chain

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Z. Naturforsch. **39b,** 1617–1621 (1984); received May 25, 1984

3β-Acetoxy-5β-pregnan-20-one, 3α-Acetoxy-5β-cholan-24-oic Acid, Synthesis, ^{1}H NMR Spectra, ^{13}C NMR Spectra

3α-Acetoxy-5β-cholan-24-oic acid was transformed into 3β-acetoxy-5β-pregnan-20-one by a sequence of reactions that involves inversion of the configuration at C-3 and degradation of the side chain of the bile acid. The procedure would allow the introduction of a label at C-21 of the final compound.

In connection with our research on the biosynthesis of cardiotonic steroids [1] it was required the preparation of 3β-hydroxy-5β-pregnan-20-one labelled at either C-20 or C-21. The unlabelled compound have been obtained by different methods such as reduction of pregnandione [2], or pregnenolone [3], and by degradation of smilagenin [4] but these procedures follow unappropriate routes for introducing a label at the side chain and produce the needed compound in very low yields.

We wish to report that using a low cost compound commercially available in large quantities as lithocholic acid, the title compound was prepared following a procedure that would allow the introduction of an isotopic carbon-atom at C-21.

Results and Discussion

As it is indicated in the Scheme, copper catalysed oxidative decarboxylation of 3α-acetoxy-5β-cholan-24-oic acid (**1**) with lead tetraacetate in pyridine-containing benzene gave 3α-acetoxy-24-nor-5β-chol-22-ene (**2**). Treatment of **2** with N-lithioethylendiamine afforded the $\Delta^{20,22}$ olefin **3a** as the sole reaction product [5] with no traces of the $\Delta^{17,20}$ isomer, the ^{13}C NMR spectrum of **3a** indicated the presence of just the Z isomer. Acetylation of **3a** afforded **3b** which was ozonised giving the ketone **4;** compound **4** had been previously obtained from lithocholic acid but following a different degradation approach [6]. Acetoxylation of compound **4** gave compound **5a** [7] which after hydrolysis [8] afforded the α-ketol **5b.** Treatment of **5b** with sodium periodate produced the cleavage of the side chain giving the etianic acid **6a** which was isolated as its methyl ester.

Inversion of C-3 configuration was performed by displacement of a tosyloxy group on the etianic ester **6b.** This classical method gave in this case better results than those obtained by the formic acid–ethyl azodicarboxylate procedure or by oxidation–reduction of the C-3 hydroxy group. Formylation of **6b** yielded the 3β-formyloxy derivative **7a** which was transformed into the acetyl derivative **7c** by usual methods.

For construction of the pregnane side chain, the acid **7c** was converted into the acyl chloride derivative **8** which was subjected to alkylation by an organometallic reagent. For this step, and considering the requirements of millimole scale that has to be used for the introduction of the labelled carbon, the usual procedures employing a large excess of a Grignard reagent were not suitable. The best results were obtained using dimethyl cadmium on the acyl chloride **8** adapting the original technique [9, 10] to microscale preparation.

Experimental

Melting points are uncorrected. IR spectra were determined as Nujol dispersions using a Perkin Elmer 421 spectrophotometer. ^{1}H and ^{13}C FT NMR spectra were recorded with a Varian XL-100-15, using TMS as internal standard and solvents indicated in each case. Mass spectra (MS) were performed at 70 eV (direct inlet) with a Varian-Mat CH7-A spectrometer interfased to a Varian-Mat Data System 166 computer.

3β-Acetoxy-24-nor-5β-chol-22-ene (**2**)

A mixture of 3β-acetoxy-5β-cholan-24-oic acid (800 mg, 1.90 mmoles), cupric acetate (80 mg,

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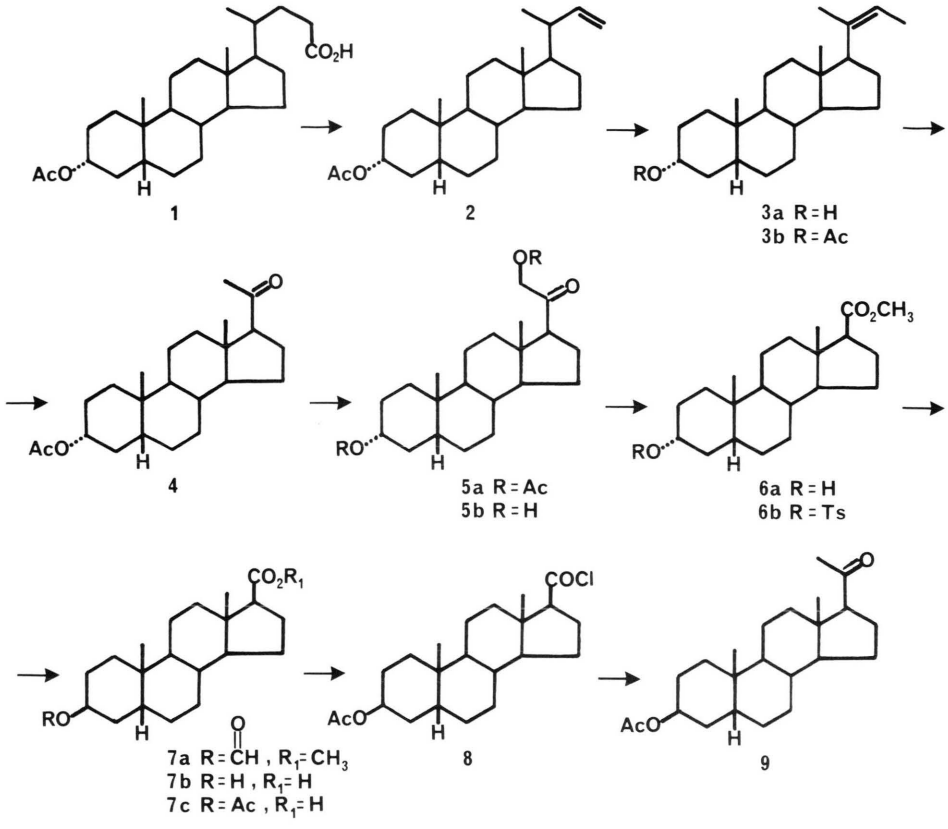
0340–5087/84/1100–1617/$ 01.00/0



0.44 mmoles) and anhydrous pyridine (0.01 ml, 0.12 mmoles) in dry benzene (30 ml) was refluxed under nitrogen for 4 h while lead tetraacetate (2.4 g, 5.40 mmoles) was added in portions. The solids were then collected and the filtrate was evaporated to dryness. The residue was dissolved in methylene chloride, washed with 5% hydrochloric acid, 5% sodium hydrogen carbonate solution and water, dried over magnesium sulphate and evaporated. The crude extract was chromatographed on silica gel G, elution with toluene afforded compound **2** (450 mg, 63%). It was crystallized from methanol, m.p. 84–85 °C. IR (cm^{-1}) 1730 (C=O), 1630 (C=C). ^1H NMR (Cl_3CD)(δ): 0.68 (s, 3H, 18-C$\underline{H}_3$), 0.94 (s, 3H, 19-C$\underline{H}_3$), 1.03 (d, 3H, J = 6 Hz, 21-C$\underline{H}_3$), 2.04 (s, 3H, C$\underline{H}_3$CO), 4.75 (m, 1H, 3β-H), 4.90 (m, 2H, 23-C$\underline{H}_2$), 5.70 (m, 1H, 22-C$\underline{H}$). ^{13}C NMR (Cl_3CD) (ppm): 35.10 (C-1), 26.39 (C-2), 74.39 (C-3), 32.31 (C-4), 41.94 (C-5), 27.08 (C-6), 26.68 (C-7), 35.85 (C-8), 40.51 (C-9), 35.10 (C-10), 20.90 (C-11), 40.10 (C-12), 42.71 (C-13), 56.55 (C-14 or C-17), 24.27 (C-15), 28.51 (C-16), 56.55 (C-17 or C-14), 12.28 (C-18), 23.40 (C-19), 41.22 (C-20), 20.15 (C-21), 145.14 (C-22), 111.43 (C-23), 21.54 (C$\underline{H}_3$CO), 170.47 ($CH_3\underline{C}O$). MS: *m/e* (%): 372 (M^+, 2.4), 357 (M^+-CH_3, 4.1), 317 (M^+–side chain, 2.9), 312 (M^+-CH_3COOH, 38.4), 297 ($M^+-CH_3COOH-CH_3$, 12.9), 257 (M^+-CH_3COOH–side chain, 100), 215 (28.6).

3α-Hydroxy-24-nor-5β-chol-20(22)-ene (**3a**) *and 3α-acetoxy-24-nor-5β-chol-20(22)-ene* (**3b**)

3α-Acetoxy-24-nor-5β-chol-22-ene (**2**) (3.5 g, 9.40 mmoles) was added in one lot to a stirred and heated solution (125–130 °C) of 7.8 equivalents of N-lithioethylene-diamine (234 mg Li added in portions to stirred dry ethylendiamine (7.9 ml) at 90–100 °C bath temperature, under nitrogen and heating for 2 h to complete the reaction) under nitrogen and the mixture refluxed for 15 min. After cooling, water was added and the solution extracted twice methylene chloride. The organic extracts were washed with water until neutral reaction, dried over magnesium sulphate and evaporated under reduced pressure to afford crude **3a** which crystallized from diluted ethanol; m.p. 114–115 °C (2.8 g, 90%). IR (cm^{-1}) 3300 (broad, OH), 1650 (C=C). ^1H NMR

(Cl_3CD) (δ): 0.52 (s, 3H, 18-C$\underline{H_3}$), 0.93 (s, 3H, 19-C$\underline{H_3}$), 1.58 (s, 3H, 23-C$\underline{H_3}$), 1.62 (s, 3H, 21-C$\underline{H_3}$), 3.65 (m, 1H, 3β-H), 5.25 (m, 1H, 22-C$\underline{H}$). ^{13}C NMR (Cl_3CD) (ppm): 35.42 (C-1), 30.48 (C-2), 71.62 (C-3), 36.42 (C-4), 42.16 (C-5), 27.20 (C-6), 26.44 (C-7), 36.16 (C-8), 40.74 (C-9), 34.63 (C-10), 20.82 (C-11), 39.05 (C-12), 43.71 (C-13), 55.98 (C-14), 24.21 (C-15), 27.20 (C-16), 59.02 (C-17), 13.40 (C-18), 23.36 (C-19), 135.15 (C-20), 24.78 (C-21), 118.72 (C-22), 17.51 (C-23). MS: *m/e* (%): 330 (M^+, 14.1), 312 (M^+-H_2O, 2.2), 257 (M^+-H_2O−side chain, 3.9), 215 (3.4).

Acetylation with pyridine−acetic anhydride (1:1) at room temperature for 18 h afforded **3b** as a solid which crystallized from ethanol; m.p. 104−105 °C. IR (cm^{-1}) 1740 (C=O), 1650 (C=C). ^{1}H NMR (Cl_3CD) (δ): 0.52 (s, 3H, 18-C$\underline{H_3}$), 0.94 (s, 3H, 19-C$\underline{H_3}$), 1.58 (s, 3H, 23-C$\underline{H_3}$), 1.62 (s, 3H, 21-C$\underline{H_3}$), 2.04 (s, 3H, C$\underline{H_3}$CO), 4.75 (m, 1H, 3β-H), 5.25 (m, 1H, 22-C$\underline{H}$). ^{13}C NMR (Cl_3CD) (ppm): 35.11 (C-1), 26.36 (C-2), 74.34 (C-3), 32.30 (C-4), 41.95 (C-5), 27.04 (C-6), 26.65 (C-7), 36.16 (C-8), 40.73 (C-9), 34.69 (C-10), 20.85 (C-11), 39.05 (C-12), 43.79 (C-13), 56.04 (C-14), 24.25 (C-15), 26.25 (C-16), 59.10 (C-17), 13.48 (C-18), 23.38 (C-19), 135.21 (C-20), 24.80 (C-21), 118.85 (C-22), 17.62 (C-23), 21.47 (C$\underline{H_3}$CO), 170.40 ($CH_3\underline{C}O$). MS: *m/e* (%): 372 (M^+, 76.5), 357 (M^+-CH_3, 3.1), 312 (M^+-CH_3COOH, 64.1), 297 ($M^+-CH_3-CH_3COOH$, 26.9), 257 (M^+-CH_3COOH−side chain, 21.3), 215 (43.1).

3α-Acetoxy-5β-pregnan-20-one (**4**)

Ozone was passed through a solution of 3α-acetoxy-24-nor-5β-chol-20(22)-ene (**3b**) (1.0 g, 2.70 mmoles) in methylene chloride (10 ml) at −10 °C, until the mixture was blue. The mixture was evaporated under reduced pressure. The residue was dissolved in acetone (10 ml) and treated with Jones reactive at 0 °C till the mixture was redish brown. It was poured onto ice-water and extracted twice with methylene chloride. The combined organic extracts were washed with water, dried over magnesium sulphate and evaporated under reduced pressure. The residue was chromatographed on silica gel G. Elution with toluene − ethyl acetate (90:10) afforded 3α-acetoxy-5β-pregnan-20-one (**4**) (770 mg, 80%) of m.p. 101−102 °C (Lit. [8] m.p. 101−102 °C). IR (cm^{-1}) 1720 (C=O, acetoxy group), 1705 (C=O). ^{1}H NMR (Cl_3CD) (δ): 0.61 (s, 3H, 18-C$\underline{H_3}$), 0.95 (s, 3H, 19-C$\underline{H_3}$), 2.04 (s, 3H, C$\underline{H_3}$CO), 2.12 (s, 3H, 21-C$\underline{H_3}$), 4.65 (m, 1H, 3β-H). MS: *m/e* (%): 360 (M^+, 1.2), 300 (M^+-CH_3COOH, 67.0), 285 ($M^+-CH_3COOH-CH_3$, 14.2), 257 (M^+-CH_3COOH−side chain, 10.6), 215 (33.0), 43 (100).

3α,21-Diacetoxy-5β-pregnan-20-one (**5a**) *and 3α,21-dihydroxy-5β-pregnan-20-one* (**5b**)

Treatment of 3α-acetoxy-5β-pregnan-20-one (**4**) in the conditions described by Cocker *et al.* [7] for 3β-acetoxy-pregn-5-en-20-one afforded 3α,21-diacetoxy-5β-pregnan-20-one (**5a**) (600 mg, 73%) of m.p. 95−96 °C (Lit. [8] m.p. 97−98 °C). IR (cm^{-1}) 1740 (C=O, acetoxy group), 1710 (C=O). ^{1}H NMR (Cl_3CD) (δ): 0.64 (s, 3H, 18-C$\underline{H_3}$), 0.94 (s, 3H, 19-C$\underline{H_3}$), 2.04 (s, 3H, 3-C$\underline{H_3}$CO), 2.18 (s, 3H, 21-C$\underline{H_3}$CO), 4.62 (q_{AB}, 2H, J = 6 Hz, 21-C$\underline{H_2}$), 4.70 (m, 1H, 3β-H). MS: *m/e* (%): 358 (M^+-CH_3COOH, 4.4) 345 ($M^+-CH_2OCOCH_3$, 70.4), 343 ($M^+-CH_3COOH-CH_3$, 1.4), 257 (M^+-CH_3COOH−side chain, 93.3), 75 (100).

Acetate **5a** (400 mg, 0.96 mmoles) was refluxed with sulphuric acid (0.6 ml) in ethanol (30 ml) for 24 h. The mixture was poured onto ice-water, extracted twice with ethyl acetate and the combined organic extracts were washed with water, dried over magnesium sulphate and evaporated. The crude extract was chromatographed on silica gel G with mixtures of increasing polarity of methylene chloride−methanol. Elution with 95:5 afforded **5b** (230 mg, 72%) of m.p. 130−131 °C (Lit. [8] m.p. 152.5−153.5 °C from acetone). IR (cm^{-1}) 3300 (broad, OH), 1705 (C=O). ^{1}H NMR (Cl_3CD) (δ): 0.62 (s, 3H, 18-C$\underline{H_3}$), 0.93 (s, 3H, 19-C$\underline{H_3}$), 3.65 (m, 1H, 3β-H), 4.18 (b.s., 2H, CH_2OH). MS: *m/e* (%): 334 (M^+, 0.9), 316 (M^+-H_2O, 0.8), 303 (M^+-OCH_3, 94.9), 301 ($M^+-H_2O-CH_3$, 2.2), 257 (M^+-H_2O−side chain, 100), 215 (5.8).

3α-Hydroxy-5β-androstan-17β-carboxylic acid methyl ester (**6a**) *and 3α-tosyloxy-5β-androstan-17β-carboxylic acid methyl ester* (**6b**)

To a solution of 3α,21-dihydroxy-5β-pregnan-20-one (**5b**) (1.0 g, 2.99 mmoles) in methanol (50 ml) a solution of sodium periodate (2.0 g, 9.30 mmoles) in water (20 ml) was added. The stirred mixture was maintained at room temperature for 4 h during which a white solid appeared. The mixture was poured into water and the precipitate formed was filtered off, washed with water and dried. The solid was dissolved in methanol and treated with diazomethane. Evaporation of the solvent afforded 3α-hydroxy-5β-androstan-17β-carboxylic acid methyl ester (**6a**) (913 mg, 91.3%) which crystallized from methanol; m.p. 142−146 °C (Lit. [11] m.p. 142−146 °C from ether − petroleum ether). IR (cm^{-1}) 3300 (broad, OH), 1740 (C=O). ^{1}H NMR (Cl_3CD) (δ): 0.65 (s, 3H, 18-C$\underline{H_3}$), 0.93 (s, 3H, 19-C$\underline{H_3}$), 3.60 (m, 1H, 3β-H), 3.68 (s, 3H, COOC$\underline{H_3}$). MS: *m/e* (%): 316 (M^+-H_2O, 1.5), 302

(M^+-CH_3OH, 100), 287 ($M^+-CH_3OH-CH_3$, 70), 275 (M^+−side chain, 4.1), 257 (M^+−side chain−H_2O, 3.6), 230 (21.1), 215 (59.3).

To a solution of **6a** (140 mg, 0.42 mmoles) in dry pyridine (5 ml) a solution of *p*-toluenesulphonyl chloride (280 mg, 1.47 mmoles) in dry pyridine (5 ml) was added. The mixture was maintained at room temperature for 20 h and poured into dilute hydrochloric acid−ice. It was extracted twice with methylene chloride and the combined organic extracts were washed with water, dried over magnesium sulphate and evaporated under reduced pressure. Crystallization from methanol afforded 3α-tosyloxy-5β-androstan-17β-carboxylic acid methyl ester (**6b**) (194 mg, 95%) of m.p. 120−121 °C. IR (cm^{-1}) 1735 (C=O), 1300, 1170 and 1000−750 (tosyloxy group). ^1H NMR (Cl_3CD) (δ): 0.64 (s, 3H, 18-C$\underline{H_3}$), 0.91 (s, 3H, 19-C$\underline{H_3}$), 2.46 (s, 3H, $\underline{H_3}C-C_6H_4-SO_2$), 3.68 (s, 3H, COOC$\underline{H_3}$), 4.45 (m, 1H, 3β-H), 7.55 (dd, 4H, $H_3C-C_6\underline{H_4}-SO_2$). MS: *m/e* (%): 316 ($M^+-H_3CC_6H_4SO_3H$, 100), 301 ($M^+-H_3CC_6H_4SO_3H-CH_3$, 87.6), 284 ($M^+-H_3CC_6H_4SO_3H-CH_3OH$, 4.1), 257 ($M^+-H_3CC_6H_4SO_3H$−side chain, 37.1), 230 (11.6), 215 (52.5), 172 (88.0).

3β-Formyloxy-5β-androstan-17β-carboxylic acid methyl ester (**7a**), *3β-hydroxy-5β-androstan-17β-carboxylic acid* (**7b**) *and 3β-acetoxy-5β-androstan-17β-carboxylic acid* (**7c**)

A solution of 3α-tosyloxy-5β-androstan-17β-carboxylic acid methyl ester (**6b**) (100 mg, 0.20 mmoles) in dry N,N-dimethylformamide (4.0 ml, 52.00 mmoles) was stirred under nitrogen at 80 °C for 50 h. It was then poured onto ice-water and the mixture extracted twice with methylene chloride. The combined organic extracts were washed with water several times, dried over magnesium sulphate and evaporated under reduced pressure. The crude extract was chromatographed on silica gel G. Elution with toluene afforded 5β-androst-3-en-17β-carboxylic acid methyl ester (22 mg, 34%). Further elution with toluene−ethyl acetate 95:5 afforded 3β-formyloxy-5β-androstan-17β-carboxylic acid methyl ester (**7a**) (45 mg, 61%) which crystallized from ethanol; m.p. 95−96 °C. ^1H NMR (Cl_3CD) (δ): 0.66 (s, 3H, 18-C$\underline{H_3}$), 0.99 (s, 3H, 19-C$\underline{H_3}$), 3.68 (s, 3H, COOC$\underline{H_3}$), 5.20 (m, 1H, 3α-H), 8.08 (s, 1H, $\underline{H}$COO). MS: *m/e* (%): 316 (M^+−HCOOH, 100), 303 (M^+−side chain, 4.1), 301 ($M^+-HCOOH-CH_3$, 40.5), 257 (M^+−HCOOH−side chain, 12.3), 215 (19.9).

A solution of **7a** (100 mg, 0.28 mmoles) in 2% sodium hydroxyde hydroalcoholic solution (10 ml) was refluxed for 2 h. The mixture was poured onto ice − water, acidified with hydrochloric acid and extracted twice with ethyl acetate. The combined organic extracts were washed with water until neutral reaction, dried over magnesium sulphate and evaporated under reduced pressure. Crystallization from ethanol afforded 3β-hydroxy-5β-androstan-17β-carboxylic acid (**7b**) (82 mg, 93%) m.p. 239−241 °C (Lit. [12] m.p. 226−228 °C). IR (cm^{-1}) 3350 (broad, OH), 3500−2700 (broad, COO$\underline{H}$), 1700 (C=O). ^1H NMR (Cl_3CD-CH_3OD 1:1) (δ): 0.88 (s, 3H, 18-C$\underline{H_3}$), 1.02 (s, 3H, 19-C$\underline{H_3}$), 4.30 (m, 1H, 3α-H). MS: *m/e* (%): 302 (M^+-H_2O, 4.7), 287 ($M^+-H_2O-CH_3$, 2.7), 215 (1.0), 45 (100).

Acetylation of **7b** (100 mg, 0.31 mmoles) with glacial acetic acid at reflux for 2 d afforded **7c** as a solid which was purified by column chromatography on silica gel G using methylene chloride as eluent and crystallized from ethanol; m.p. 170−172 °C. ^1H NMR (Cl_3CD) (δ): 0.73 (s, 3H, 18-C$\underline{H_3}$), 0.95 (s, 3H, 19-C$\underline{H_3}$), 2.07 (s, 3H, C$\underline{H_3}$CO), 5.10 (m, 1H, 3α-H).

3β-Acetoxy-5β-pregnan-20-one (**9**)

a) Preparation of 3β-acetoxy-5β-androstan-17β-carboxylic acid chloride (**8**): To a solution of 3β-acetoxy-5β-androstan-17β-carboxylic acid (**7c**) (100 mg, 0.28 mmoles) in dry benzene (1 ml), oxalyl chloride (1 ml) was added. The mixture was stirred and maintained at room temperature for 2 h after which the solvents were evaporated at reduced pressure to afford a crude product which was identified as 3β-acetoxy-5β-androstan-17β-carboxylic acid chloride (**8**) and used without further purification. IR (cm^{-1}) 1800 (ClC=O), 1730 (C=O, acetoxy group).

b) Preparation of dimethyl cadmium and reaction with acid chloride **8:** To magnesium turnings (8 mg) contained in an evacuated tube, dry ether (1 ml) and methyl iodide (0.018 ml) dried over phosphorous pentoxide were added. The mixture was stirred at room temperature until most of the magnesium disappeared (1 h). Then cadmium chloride (122 mg) was added under nitrogen atmosphere. The mixture was stirred at room temperature for 2 h followed by the addition of the solution of acid chloride **8** (105 mg) in benzene (2 ml). After 18 h in the same conditions the mixture was warmed to 50 °C and further stirred for 1 h. The reaction was quenched by addition of 1N hydrochloric acid, decanted and extracted twice with methylene chloride. The combined organic extracts were washed with water, dried over magnesium sulphate and the solvents evaporated under reduced pressure. Chromatography on

silica gel G using as solvent methylene chloride–methanol 98:2 afforded 3β-acetoxy-5β-pregnan-20-one (**9**) (37 mg, 38%) m.p. 120–121 °C (Lit. [2] m.p. 121 °C). IR (cm^{-1}) 1740 (C=O, acetoxy group), 1700 (C=O). ^1H NMR (Cl_3CD) (δ): 0.62 (s, 3H, 18-C$\underline{H}_3$), 0.98 (s, 3H, 19-C$\underline{H}_3$), 2.06 (s, 3H, C$\underline{H}_3$CO), 2.12 (s, 3H, 21-C$\underline{H}_3$), 5.10 (m, 1H, 3α-H). MS: *m/e* (%): 360 (M^+, 1.1), 300 (M^+-CH_3COOH, 100), 285 ($M^+-CH_3COOH-CH_3$, 21.9), 257 (M^+–side chain–CH_3COOH, 10.6), 215 (31.8).

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