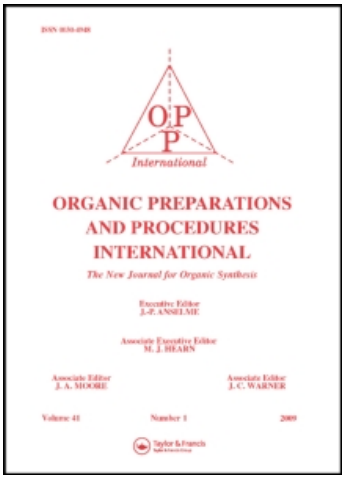

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SYNTHESIS OF 13-ETHYL-11-METHYLENE-18,19-DINOR-17α-PREGN-4-EN-20-YN-17-OL

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SYNTHESIS OF

13-ETHYL-11-METHYLENE-18,19-DINOR-17α-PREGN-4-EN-20-YN-17-OL

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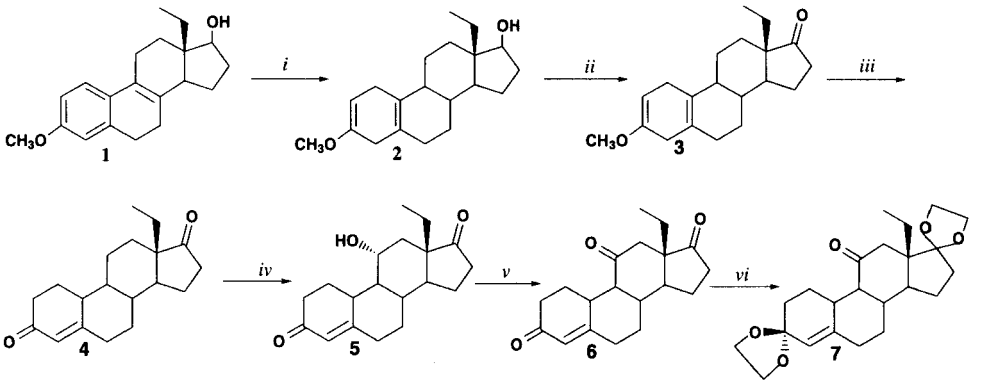
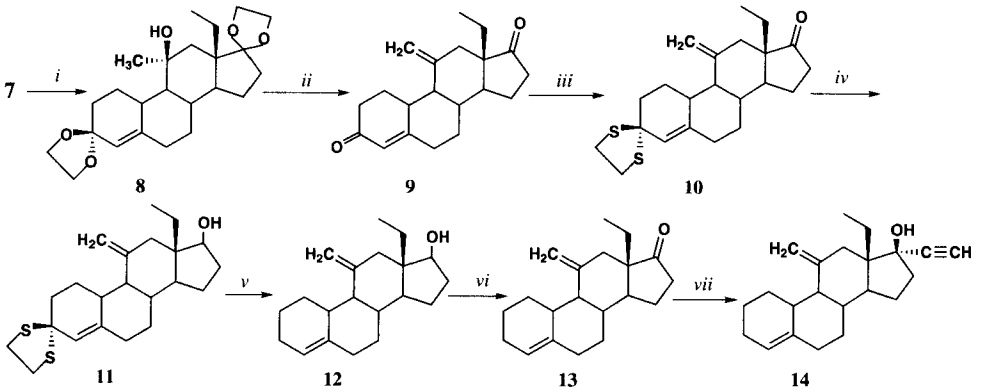
13-Ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol (desogestrel, **14**) is a powerful progestrogen and widely used in oral contraceptives.[1] Recently two synthetic routes have been described, the first starting by homologation of the 18-methyl group of an estrane derivative by intramolecular hypoiodite reaction.[2] The other route used the 11α-hydroxy steroid which was synthesized from the 1,3,5(10),9(11)-tetraene precursor by hydroboration/alkaline hydrogen peroxide oxidation.[3] We now report an efficient approach to the preparation of desogestrel from 13β-ethyl-11α-hydroxy-gon-4-ene-3,17-dione (**5**), readily available by microbial oxidation of 13β-ethyl-gon-4-ene-3,17-dione (**4**).[4]

The introduction of hydroxy group at C-11, a key step in the synthesis of desogestrel, may be accomplished by hydroboration/alkaline hydrogen peroxide oxidation of 9(11)-double bond of 1,3,5(10),9(11)-tetraene steroids.[3, 5] However, the by-products (11β-OH, 9α-H; 11α-OH, 9β-H; 9β-OH; 9α-OH; starting material) present in the hydroboration-oxidation mixture caused difficulty in purification. Recently, Liu[6] reported a oxygen-peroxidation method to introduce 11β-hydroxy. However, the subsequent selective hydrogenation of 9(10)-double bond in 17 substituted 13β-ethyl-11α-hydroxy-gona-4,9-dien-3-ones gave three configurational isomers.[7] In 1983, 13β-ethyl-gon-4-ene-3,17-dione (**4**)[8] was reported to be converted to 13β-ethyl-11α-hydroxy-gon-4-ene-3,17-dione (**5**) by microbial oxidation.[4] We successfully repeated this procedure to obtain **5** (41%). The 11-ketone **6** was obtained in 94% by oxidation of **5** with Jones' reagent[6] and converted, by treatment with ethylene glycol/triethyl orthoformate/*p*-toluenesulfonic acid in methylene chloride at reflux temperature, into the bisdiethylene ketal **7**.[9,10]



(i) Li, liq. NH_3, ethanol, THF, 63.2% (ii) $(i\text{-PrO})_3Al$, toluene, 85% (iii) HCl (conc.), acetone, 70%
(iv) Aspergillus ochraceus, 41% (v) Jones' reagent, 94% (vi) $HC(OEt)_3$, $(CH_2OH)_2$, *p*-TsOH, 79%

Treatment of 11-ketone **7** with methyl lithium in diethyl ether and benzene, as described by van den Broek *et al.*, produced the 11α-methyl-11β-hydroxy derivative **8**.[9] The configuration of the hydroxy group at C-11was unequivocally established by NMR.[9] The subsequent formation of the 11-methylene and the removal of the protecting acetal groups were accomplished simultaneously by heating in formic acid with *p*-TsOH as the catalyst; formic acid without *p*-TsOH gave *endo* ring elimination.[5] The A-ring conjugated enone **9** was then selectively converted into the cyclic 3-(1,2-ethanediyl dithioketal) **10**.[9] The subsequent reduction product of 17-oxo group of **10** was confirmed by IR ($\gamma_{17\alpha\text{-OH}}$ = 3432 cm^{-1}) and ^1H NMR ($\gamma_{17\alpha\text{-H}}$ = 3.79 ppm). Reductive removal of the cyclic 3-(1,2-ethanediyl dithioketal) followed by Jones' oxidation gave **13**, which was allowed to react with lithium acetylide/diethyl ether affording desogestrel **14** in 72% yield.



(i) CH_3Li, Et_2O, C_6H_6, 88% (ii) *p*-TsOH, HCOOH, 74% (iii) BF_3, $(CH_2SH)_2$, CH_3OH, 98%
(iv) $NaBH_4$, CH_3OH, quantitative yield (v) Na, liq. NH_3, THF, 94% (vi) Jones' reagent, 82%
(vii) Li, C_2H_2, *n*-C_4H_9Br, Et_2O, 72%

EXPERIMENTAL SECTION

^1H NMR spectra were recorded on a Varian 90 MHz in $CDCl_3$ and chemical shifts are reported as δ values in ppm downfield from TMS as internal standard. Melting points were measured on a X4 micro hot-stage mp. apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1320 infrared spectrophotometer as KBr discs. Mass spectra were recorded on a VG20-253 or VGZAB-HS Spectrometer. Optical rotations were measured with a polartronic-D-automatic Polarimeter, solvent chloroform, c = 1g/100mL, t = 20°. Column chromatography was performed on silica gel H (200-300 mesh, Qing Dao Chemical Co.). Work-up of the extract includes: the organic phase was washed with brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to give the crude products.

D-13β-ethyl-gon-4-ene-3,11,17-trione (6).- To a stirred solution of **5** (3.2g, 10.6 mmol) in acetone (150 mL) was added Jones' reagent (6 mL) between -15° and -10°. Stirring was continued at this temperature for 15 min. Methanol (5 mL) was added dropwise in order to decompose the excess of Jones' reagent. The solution was then neutralized with saturated sodium bicarbonate solution, acetone was distilled off *in vacuo*, and the resulting mixture was partitioned between brine and ether. The

ethereal phase was concentrated (1/4) and the precipitated product was collected as a colorless solid to give **6** (3.0g, 94%), mp. 187-189°, $[\alpha]_D$ +29°; lit.[6] mp. 185- 187 °, $[\alpha]_D$ +28°. IR (cm^{-1}): 1729 (s, C_{17}=O), 1698 (s, C_{11}=O), 1661(s, C_3=O), 1611 (s, C=C). ^1H NMR ($CDCl_3$): δ 0.75 (3H, t, 18-CH_3), 5.56 (1H, broad, H-4). MS (m/z): 300 $[M]^+$.

Anal. Calcd for $C_{19}H_{24}O_3$: C, 76.00; H, 8.00. Found: C, 76.22; H, 7.83

D-13β-ethyl-gon-5-ene-3,11,17-trione-3,17-diethylene Ketal (7).- To a solution of **6** (5g, 16.7 mmol) in methylene chloride (100 mL) was added ethylene glycol (10 mL, 0.2 mol), triethyl orthoformate (30 mL, 0.18 mol) and *p*-toluenesulfonic acid hydrate (0.5g, 2.7 mmol). The mixture was refluxed for 7 h under a nitrogen blanket and washed with saturated aqueous sodium hydrogen carbonate solution (50 mL). The organic layer was worked up to yield **7** (5.1g, 79%). An analytical sample was obtained by chromatography (ether/ cyclohexane, 1:20), mp. 173-175°, $[\alpha]_D$ +66°; lit.[2] mp. 175-177°, $[\alpha]_D$ +69°. IR (cm^{-1}): 1698 (s, C_{11}=O), 1257. ^1H NMR ($CDCl_3$): δ 0.80 (3H, t, 18-CH_3), 3.82 (4H, s, 17-ethylene ketal), 3.90 (4H, s, 3-ethylene ketal), 5.40 (1H, broad, H-6). MS (m/z): 388 $[M]^+$.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 71.30; H, 8.54

D-13β-ethyl-11β-hydroxy-11α-methylgon-5-ene-3,17-dione-3,17-diethylene Ketal (8).- To a solution of **7** (3.7g, 9.5mmol) in a mixture of benzene (100 mL) and ether (100 mL) was added methyl lithium (50 mL of a 1.2M solution). After 3 h of stirring at 10-15°, this solution was quenched with ice cold water and the mixture was extracted with ether. The work-up of the combined organic phase afforded a residue from which **8** (3.4g, 88%) was obtained by chromatography (ether/petroleum ether, 1:20), mp. 130-132°, $[\alpha]_D$+72.5°. IR (cm^{-1}): 3451 (s, OH), 1268. ^1H NMR ($CDCl_3$): δ 0.76 (3H, t, 18-CH_3), 1.38 (3H, s, 11α-CH_3), 3.80 (4H, s, 17- ethylene ketal), 3.87 (4H, s, 3-ethylene ketal), 5.44 (1H, broad, H-6). MS (m/z): 404 $[M]^+$.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.29; H, 8.91. Found: C, 71.50; H, 8.78

D-13β-ethyl-11-methylenegon-4-en-3,17-dione (9).- A mixture of **8** (1.65g, 4.08mmol), *p*-toluenesulfonic acid hydrate (0.12g, 0.63 mmol) and formic acid (30 mL, 95%) was stirred for 7 h at 50-60° and then diluted with water. The solution was extracted with methylene chloride (30 mL x 3) and the combined organic phase was worked up to give **9** (0.9g, 74%). To obtain a pure sample, the product was crystallized from ether, mp. 153-155°, $[\alpha]_D$ +223°; lit.[9] mp. 153-154 °, $[\alpha]_D$ +223°. IR (cm^{-1}): 1725 (s, C_{17}=O), 1662(s, C_3=O), 903 (m, =CH_2). ^1H NMR ($CDCl_3$): δ 0.78 (3H, t, 18-CH_3), 4.82 (1H, s, =CH_2), 4.97 (1H, s, =CH_2), 5.84 (1H, broad, H-4). MS (m/z): 298 $[M]^+$.

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.17; H, 9.00

D-13β-ethyl-3,3-ethylenedithio-11-methylenegon-4-ene-17-one (10).- Compound **9** (0.3g, 1.01 mmol) was dissolved in methanol (15 mL) and ethanedithiol (0.16 mL, 1.91 mmol). While this solution was stirred between 0° and 5°, boron trifluoride diethyl ether (0.1 mL, 0.8 mmol) was added dropwise. The mixture was stirred for additional 2.5 h at this temperature. The precipitated crystals were collected, washed with cold methanol and dried to yield 0.37g (98%) of **10** as a colorless solid. A pure sample was obtained by recrystallization from ether, mp. 191-193°, $[\alpha]_D$ +184°; lit.[9] mp. 185-187 °, $[\alpha]_D$ +188°. IR (cm^{-1}): 1727 (s, C_{17}=O), 1637(s, C=C), 905 (m, =CH_2). ^1H NMR ($CDCl_3$): δ

0.76 (3H, t, 18-CH_3), 3.31 (4H, m, -S-CH_2-CH_2-S-), 4.79 (1H, s, =CH_2), 4.91 (1H, s, =CH_2), 5.65 (1H, s, H-4). MS (m/z): 374 $[M]^+$.

Anal. Calcd for $C_{22}H_{30}OS_2$: C, 70.56; H, 8.08; O, 4.27. Found: C, 70.80; H, 7.92; O, 4.53

D-13β-ethyl-3,3-ethylenedithio-11-methylenegon-4-ene-17α-ol (11).- Compound **10** (0.37g, 0.98 mmol) was dissolved in methanol (15 mL). While this solution was stirred at room temperature, sodium borohydride (0.1g, 2.64 mmol) was added slowly. The mixture was stirred for another 2 h. The acetic acid was added dropwise in order to decompose the excess sodium borohydride. Methanol was distilled off as completely as possible, water was added and the precipitated crystals were filtered off, washed with water and dried. Yield: 0.37g, 100%. A pure sample of **11** was obtained by recrystallization from ether, mp. 152-154°, $[\alpha]_D$ +148°. IR (cm^{-1}): 3432 (s, OH), 1638(s, C=C), 894 (m, =CH_2). ^1H NMR ($CDCl_3$): δ 0.75 (3H, t, 18-CH_3), 3.32 (4H, m, -S-CH_2-CH_2-S-), 3.79 (1H, m, 17α-H), 4.70 (1H, s, =CH_2), 4.92 (1H, s, =CH_2), 5.59 (1H, s, H-4). MS (m/z): 376 $[M]^+$.

Anal. Calcd for $C_{22}H_{32}OS_2$: C, 70.21; H, 8.51; O, 4.25. Found: C, 69.97; H, 8.75; O, 4.57

D-13β-ethyl-11-methylenegon-4-en-17α-ol (12).- To liquid ammonia (30 mL) was added at - 50° a solution of **11** (0.6g, 1.59 mmol) in THF (10 mL) under a nitrogen blanket. Sodium (0.7g, 0.05g-atom) was added with stirring, while the temperature was maintained between -50° and - 45°. Stirring was continued at this temperature for an additional 0.5 h. Then ethanol was added carefully until the blue color disappeared. The ammonia was allowed to evaporate. The resulting solution was partitioned between water and ether. Work-up of ethereal layer afforded a residue from which **12** (0.43g, 94%) was obtained by chromatography (ether/petroleum, 1:20), mp. 56-58°, $[\alpha]_D$ +138°. IR (cm^{-1}): 3375 (s, OH), 1638(s, C=C), 893 (m, =CH_2). ^1H NMR ($CDCl_3$): δ 3.79 (1H, m, 17α-H), 4.66 (1H, s, =CH_2), 4.83 (1H, s, =CH_2), 5.46 (1H, broad, H-4). MS (m/z): 286 $[M]^+$.

Anal. Calcd for $C_{20}H_{30}O$: C, 83.91; H, 10.49. Found: C, 83.65; H, 10.62

D-13β-ethyl-11-methylenegon-4-en-17-one (13).- To a stirred solution of **12** (0.42g, 1.47 mmol) in acetone (20 mL) was added Jones' reagent (0.6 mL) between -15° and -10°. Stirring was continued at this temperature for 15 min. Methanol (5 mL) was added dropwise in order to decompose the excess of Jones' reagent. The solution was then neutralized with saturated sodium bicarbonate solution, acetone was distilled off *in vacuo*, and the resulting mixture was partitioned between brine and ether. Work-up of the ethereal phase afforded a residue from which **13** (0.34g, 82%) was obtained by chromatography (ether/petroleum, 1:20), mp. 97-99°, $[\alpha]_D$ +165°; lit.[9] mp. 96-99 °, $[\alpha]_D$ +166°. IR (cm^{-1}): 1729 (s, C_{17}=O), 1631 (s, C=C), 901 (m, =CH_2). ^1H NMR ($CDCl_3$): δ 0.75 (3H, t, 18-CH_3), 4.81 (1H, s, =CH_2), 4.89 (1H, s, =CH_2), 5.46 (1H, broad, H-4). MS (m/z): 284 $[M]^+$.

Anal. Calcd for $C_{20}H_{28}O$: C, 84.50; H, 9.86. Found: C, 84.51; H, 10.10

D-13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol (14).- A solution of *n*-C_4H_9Br (4 mL, 37.2 mmol) in anhydrous ether (10 mL) was added to a solution of lithium (0.75g, 0.03g-atom) in anhydrous ether (15 mL) under a nitrogen blanket, while the temperature was maintained between -10° and 0°. The reaction was continued at -10° for additional two hours. Ethyne was then passed into the solution for three hours at -5°. Then a solution of **13** (0.32g, 1.12 mmol) in THF (15 mL) was

added and the resulting reaction mixture was stirred for 3 h at -5°. The solution was diluted with ice water and neutralized to pH=3 with sulfuric acid (2N). Work-up of the organic phase gave **14**, which was subjected to chromatography (ether/petroleum, 1:20) and subsequently to crystallization from *n*-hexane (0.25g, 72%), mp. 108-110°, $[\alpha]_D$ +54°; lit.[9] mp. 109-110 °, lit.[3] $[\alpha]_D$ +55°. IR(cm^{-1}): 3425 (s, -OH), 3310 (s, C≡CH), 898 (m, $=CH_2$). ^1H NMR ($CDCl_3$): δ 1.06 (3H, t, 18-CH_3), 2.60 (1H, s, -C≡CH), 4.69 (1H, s, $=CH_2$), 4.88 (1H, s, $=CH_2$), 5.36 (1H, s, H-4). MS (m/z): 310 $[M]^+$.

Anal. Calcd for $C_{22}H_{30}O$: C, 85.11; H, 9.74. Found: C, 85.39; H, 9.58

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