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A NOVEL AND EFFICIENT PROCESS TO 13β-ETHYL-GON-4-ENE-3,11,17-TRIONE

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Abstract: A novel synthetic process to 13β-ethyl-gon-4-ene-3,11,17-trione with the total yield of 44% starting from 13β-ethyl-17β-hydroxy-3-methoxy-gona-2,5(10)-diene was described.

The 11-oxo 4-en-3-one 19-nor steroids are important intermediates to the synthesis of 11-functional steroid drugs such as desogestrel and its derivatives, the new generation of progestational contraceptives with high biological activities and low side-effects.[1,2] The previous methods always involved the microbial oxidation of the corresponding 4-en-3-one compounds to introduce 11α-hydroxy group, which was elaborated in the later steps.[2] Since 1964, it was found that 5(10),

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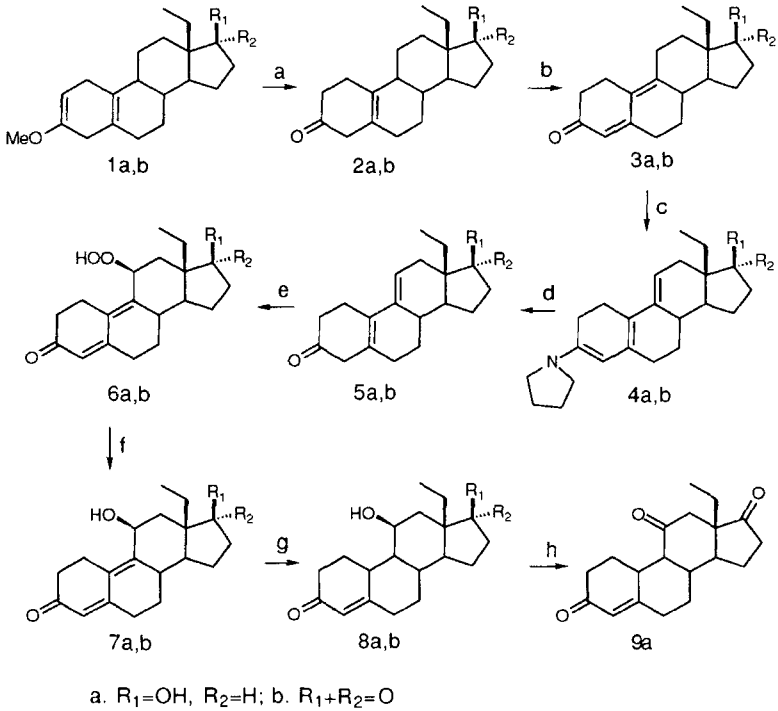
9(11)-dien-3-one steroids could be peroxidised to 11β-perhydroxy-4,9-dien-3-ones by molecule oxygen under the basic condition.[3] The peroxides were unstable and reduced to hydroxides consequently. We used this idea in the synthesis of the title compound, which was the most common intermediate in the synthesis of



a. R_1=OH, R_2=H; b. R_1+R_2=O

Scheme

a. oxalic acid on silica gel, CH_2Cl_2, r.t., 20min., yield 2a 94% 2b 87%; **b**. pyridinium hydrobromide perbromide (PBP), pyridine, r.t., overnight, yield 3a 92% 3b 57%; **c**. pyrrolidine, MeOH, 69°C, 2.5h, yield 4a 94% 4b 95%; **d**. 86% HCOOH, r.t., 10min.; **e**. O_2, MeOH (1% Et_3N), r.t., 52h; **f**. NaI, HoAc–dioxane, r.t., 8h, over-all yield of three steps d, e, f 7a 70% 7b 46%; **g**. H_2, 5% Pd/$SrCO_3$, pyridine, r.t., 2h, yield 8a 81% 8b 45%; **h**. Jones' reagent, -10°C, 35min., yield 95%.

desogestrel and its derivatives.[2] The novel process with the total yield of 44% starting from 13β-ethyl-3-methoxy-gona-2,5(10)-diene (1a)[4] included eight steps, i.e., selective hydrolysis with oxalic acid on silica gel, bromination–dehydrobromination with pyridinium hydrobromide perbromide, pyrrolidine enamination, selective hydrolysis with formic acid, oxygen–peroxidation, reduction with sodium iodide, regio- and stereo-selective hydrogenation with palladium on strontium carbonate catalyst and Jones' oxidation.(see **Scheme**) All of the steps were undertaken in the mild conditions, of which six steps were processed at room temperature. These were more suitable for industry.

Selective hydrolysis of 3-methoxy-2,5(10)-diene steroids (step a) could be accomplished by using acid catalysts, such as aliphatic acids — acetic,[5] oxalic and propanedioic acid[6] or mineral acids—perchloric[7] and sulphuric acid.[5] But the common problem of acid-catalysed isomerism of 5(10)-en-3-ones to the more stable conjugated 4-en-3-ones decreased the yield and made the control of the reaction difficult. Therefore we chose the heterogenous catalyst, oxalic acid supported on silica gel.[8] The reaction was easily controlled without any 4-en-3-ones (UV λ_{max}=~240nm, EtOH) observed after prolonging reaction time.

4,9-dien-3-ones (3) were formed in one step via bromination and dehydrobromination using pyridinium bromide perbromide (PBP) in pyridine[9]. The conversion of 4,9-dien-3-ones to 5(10),9(11)-isomers could be via selective hydrolysis of ketal,[10] enol ester,[11] or enamine[12] or via tetrachlorosilane ($SiCl_4$) catalysed isomerism.[13] Pyrrolidine enamination followed by formic acid-catalysed hydrolysis was found a simple way with high yield (step c and d). 5(10),9(11)-dien-3-ones were unstable and peroxidised on exposure to air. Therefore they were used directly without further purification.

Trace experiments demonstrated the conversion of 4,9-dien-3-one steroids without 11-functional groups to corresponding 4-en-3-ones via catalysed hydrogenation.[14] The stereochemistry of position 9, 10 were dependent on the direction of 17 substituents and reaction media. 17β-substituted reactant gave mainly (9α, 10α)-product only in benzene, which could be isomerised to natural configuration (9α, 10β) under mild acid or basic conditions.[14a] However, 17α-substituent gave mainly (9β, 10β)-isomer in ethanol, which was converted to 9β-5(10)-en-3-one or *retro*-configuration (9β, 10α) under more violent condition.[14b] We took the reaction in pyridine with $Pd/SrCO_3$ catalyst and only the required product with natural configuration (9α, 10β) was isolated (step g). This was believed via pyridine catalysed isomerism of the initial (9α, 10α)-product. Normally allylic hydroxy directed hydrogen approach double bond from the same side of hydroxy group in catalysed hydrogenation.[15] But in our reaction, the steric effects played more important role. The substitutes on β-side of steroid skeleton such as, 11β-hydroxy and 13β-ethyl groups, facilitated the formation of (9α, 10α) isomer. Especially 17β-hydroxy led to higher stereoselectivity and therefore higher yield than 17-one.

EXPERIMENTAL

General — Melting points were measured on a X4 micro hot-stage m.p. apparatus and were uncorrected. UV spectra were recorded in 95% ethanol on Shimadzu PU-8800 Spectrophotometer. Infrared spectra were measured on a Perkin Elmer 983G Spectrometer using a pressed potassium bromide disc (see **Table**). Optical rotations were measured with a polartronic-D-automatic Polarimeter. NMR spectra were recorded on a JEOL FX-90Q or VXR-300 Spectrometer in

Table. IR spectra of the products (KBr)

products	vibrations	
	$\nu_{C=O}$ and $\nu_{C=C}$	ν_{C-O}
2a	1721 (s, 3-one)	1070 (m, 17β-OH)
2b	1730 (s, 17-one) 1715 (s, 3-one)	
3a	1648, 1602 (s, $\Delta^{4,9}$-3-one)	1048 (m, 17β-OH)
3b	1730 (s, 17-one) 1648, 1599, 1576 (s, $\Delta^{4,9}$-3-one)	
4a	1616, 1597, 1551 (s,$\Delta^{3,5(10),9(11)}$-triene)	1033 (m, 17β-OH)
4b	1725 (s, 17-one) 1615, 1591, 1553 (s, $\Delta^{3,5(10),9(11)}$-triene)	
5a	1710 (s, 3-one) 1644 (s, $\Delta^{5(10),9(11)}$-diene)	1052 (m, 17β-OH)
6b	1732 (s, 17-one) 1636, 1596 (s, $\Delta^{4,9}$-3-one)	
7a	1647, 1604 (s, $\Delta^{4,9}$-3-one)	1066, 1030 (m, 11β, 17β-OH)
7b	1731 (s, 17-one) 1641, 1598 (s, $\Delta^{4,9}$-3-one)	
8a	1655, 1608 (s, Δ^{4}-3-one)	1052, 1029 (m, 11β, 17β-OH)
9a	1735 (s, 17-one) 1701 (s, 11-one) 1661, 1608 (s, Δ^{4}-3-one)	

deuteriochloroform with chemical shifts reported in δ units downfield from internal tetramethylsilane. Mass spectra were recorded on a VG20-253 or VGZAB-HS Spectrometer.[16] Column chromatography was performed on silica gel H (200~300 mesh, Qing Dao Chemical Co.) with petroleum ether (60~90^{0}C)/ethyl acetate as eluent. Oxalic acid on silica gel catalyst,[8] Pyridinium bromide perbromide (PBP),[9a] and 5% palladium on strontium carbonate catalyst[17] were prepared as reported methods.

D-13β-ethyl-17β-hydroxy-gon-5(10)-en-3-one (2a)

To the solution of. D-13β-ethyl-17β-hydroxy-3-methoxy-gona-2,5(10)-diene (1b, 11.2g, 37.1mmol) in dichloromethane (60ml) was added oxalic acid on silica gel (3.0g) and water (0.7ml). The mixture was stirred at room temperature for 20 min. and filtered on suction. The filtrate was concentrated under vacuum, and the residue crystallised from methanol to give colourless rods 2a (10.0g, 94% yield). m.p. (MeOH) 107~109^{0}C [lit.[18] 110^{0}C].

DL-13β-ethyl-gon-5(10)-ene-3,17-dione (2b)

Following the same procedure as the above, DL-13β-ethyl-3-methoxy-gona-2,5(10)-diene-3,17-dione (1b, 20.0g, 66.7mmol) gave colourless rods 2b (16.5g, 87% yield). m.p. (Et_2O) 128~129^{0}C [lit.[6b] 127~128^{0}C].

D-13β-ethyl-17β-hydroxy-gona-4,9-diene-3-one (3a)

To the solution of 8.9g (30.9mmol) of 2a in pyridine (40ml) was added dropwise the solution of pyridinium bromide perbromide (PBP, 9.8g, 30.6mmol) in pyridine (60ml). After stirred at room temperature overnight, the mixture was filtered, and the residue washed with pyridine (4x10ml). The combined filtrate

was concentrated under vacuum, and poured into cold water (50ml), which was extracted with ethyl acetate (3x100ml). The combined extracts was successively washed with water (50ml), 7% HCl (4x150ml), 5% NaOH (30ml), and NaCl (sat., 100ml) solution. The dry solution (anhydrous Na_2SO_4) was evaporated to dryness, and the residue crystallised from acetone to give colourless rods 3a (8.1g, 92% yield). m.p. (acetone) 149~151^{0}C [lit.[19] 152~153^{0}C]. UV: λ_{max}=305nm.

DL-13β-ethyl-gona-4,9-diene-3,17-dione (3b)

Following the same procedure as the above, 10.1g (35.3mmol) of 2b gave 5.7g of 3b (57% yield). m.p. (Et_2O) 125~127^{0}C [lit.[6a] 126~128^{0}C]. UV: λ_{max}=301nm. ^{1}H NMR (90MHz): 5.71(s, 1H, Δ^4-H), 0.86(t, 3H, 18-CH_3).

D-13β-ethyl-17β-hydroxy-3-(N-pyrrolidinyl)-gona-3,5(10),9(11)-triene (4a)

To the solution of 3a (6.6g, 23.2mmol) in methanol (70ml) was added dropwise pyrrolidine (4.8ml, 58mmol). The mixture was stirred at 69^{0}C under nitrogen for 2.5h, cooled, and then filtered on suction to give yellow crystalline solid 4a (7.4g, 94% yield). m.p. (MeOH) 116~120^{0}C (dec.). UV: λ_{max}=344nm.

DL-13β-ethyl-3-(N-pyrrolidinyl)-gona-3,5(10),9(11)-triene-17-one (4b)

Following the same procedure as the above, 2.0g (7.0mmol) of 3b gave yellow crystalline solid 4b (2.3g, 95% yield). m.p. (MeOH) 165.5~166.5^{0}C [lit.[12a] 175.5~178.5^{0}C]. UV: λ_{max}=346nm. ^{1}H NMR (90MHz): 5.33(dt, 1H, $\Delta^{9(11)}$-H), 4.40(s, 1H, Δ^4-H), 0.78(t, 3H, J=7.8Hz, 18-CH_3).

D-11β,17β-dihydroxy-13β--ethyl-3-gona-4,9-dien-3-one (7a)

4.0ml of 86% formic acid was added dropwise to 3.2g (9.4mmol) of 4a with stirring at room temperature. After stirred for 10 min., the mixture was

poured into ice-water (50ml), and then extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with $NaHCO_3$ (sat.) and NaCl (sat.), respectively, and then dried with anhydrous Na_2SO_4. Evaporation to dryness under vacuum yielded colourless solid 5a, which was used directly because of its liability on exposure to air.

The above product was dissolved in methanol (20ml, including 1% Et_3N) and a stream of oxygen bubbled into the solution at room temperature for 52h. Evaporation of the solvent under vacuum yielded colourless solid 6a, which was unstable and changed easily to 7a as indicated by TLC. UV: λ_{max}=298nm.

This product was dissolved in methanol (60ml) and acetic acid (40ml), and then NaI (6.5g, 35mmol) added. The mixture was stirred at room temperature for 8h. 0.5N $Na_2S_2O_3$ solution was added until the solution turned colourless, and then neutralised with $NaHCO_3$ powder until no bubble was produced. The mixture was filtered, and extracted with $CHCl_3$ (4x50ml). The combined chloroform was washed with 5% NaOH and NaCl (sat.), respectively, and dried with anhydrous Na_2SO_4. The solution was concentrated, and the residue purified by column chromatography to give colourless crystalline solid 7a (2.0g, 70% over-all yield of three steps). m.p. (EtOAc) 174~176^{0}C. $[\alpha]_D^{20}$ -18^0 (c. 0.55, $CHCl_3$). UV: λ_{max}=298nm. ^{1}H NMR (90MHz): 5.81(s, 1H, Δ^4-H), 5.03(bs, 1H, $W_{1/2}$=7.9Hz, 11α-H), 3.76(t, 1H, J=7.5Hz, 17α-H), 1.20(t, 3H, J=7.9Hz, 18-CH_3).

DL-13β--ethyl-11β-hydroxy-gona-4,9-dien-3,17-dione (7b)

Following the same procedure as the above, 3.98g (11.8mmol) of 4b gave colourless crystalline solid 6b (2.14g, 58% total yield of two steps). m.p. 179.5~180^{0}C. UV: λ_{max}=293nm. ^{1}H NMR (90MHz): 8.01 (s, 1H, 11β-OOH), 5.81(s, 1H, Δ^4-H), 5.25(d, 1H, J=4.0Hz, 11α-H), 0.88(t, 3H, J=7.9Hz, 18-CH_3).

1.45g (4.59mmol) of the peroxide 6b gave colourless crystalline solid 7b (1.10g, 80% yield) m.p. (acetone) 209~211°C. ^{1}H NMR (90MHz): δ5.81(s, 1H, Δ^4-H), 5.05(d, 1H, J=4.0Hz, 11α-H), 4.68(s, 1H, 11β-OH), 0.92(t, 3H, J=7.9Hz, 18-CH_3).

D-11β,17β-dihydroxy-13β-ethyl-3-gon-4-en-3-one (8a)

To the suspension solution of 5% Pd/$SrCO_3$ catalyst (3.0g) and 600mg (1.99mmol) of 7a in pyridine (40ml) was bubbled a stream of hydrogen with stirring at room temperature for 2h until TLC indicated the disappearance of starting material 7a. The mixture was filtered, and concentrated under vacuum. The residue was poured into 5% HCl solution (20ml), and the precipitate was filtered and washed with cold water until PH=6. The raw product collected was separated by column chromatography to give colourless needles 8a (490mg, 81%). m.p. (petroleum ether/EtOAc) 199~201°C. [lit.[20] 197.5~198.5°C]. $[\alpha]_D^{20}$ +34° (c. 0.22, $CHCl_3$). UV: λ_{max}=242nm. ^{1}H NMR (300MHz): 5.85(s, 1H, Δ^4-H), 4.17(q, 1H, J=2.6Hz, 11α-H), 3.73(t, 1H, J=7.5Hz, 17α-H), 1.15(t, 3H, J=7.5Hz, 18-CH_3), 0.91(td, 1H, J=11.0, 3.2Hz, 9α-H). ^{13}C NMR (300MHz): 199.8(CO, 3), 154.5(C, 5), 124.7(CH, 4), 84.5(CH, 17), 66.6(CH, 11), 54.0(CH, 9), 51.9(CH, 14), 43.7(C, 13), 39.5(CH_2), 37.6(CH, 10), 36.5((CH_2), 35.2(CH_2), 34.5(CH, 8), 30.9(CH_2), 30.6(CH_2), 26.1(CH_2), 22.5(CH_2), 20.3(CH_2), 11.4(CH_3, 18-CH_3).

DL-13β--ethyl-11β-hydroxy-gon-4-en-3,17-dione (8b)

Following the same procedure as the above, 1.0g (3.33mmol) of 7b gave colorless needles 8b (445mg, 45% yield). m.p. (petroleum ether/EtOAc) 202~203°C. UV: λ_{max}=241nm. ^{1}H NMR (300MHz): 5.88(s, 1H, Δ^4-H), 4.26(d, 1H, $W_{1/2}$=8.0Hz, 11α-H), 2.64(td, 1H, J=5.8, 2.3Hz, 10β-H), 0.99(td, 1H, J=11.1, 3.2Hz, 9α-H), 0.88(t, 3H, J=7.5Hz, 18-CH_3). ^{13}C NMR (300MHz): 218(CO, 17),

199.7(CO, 3), 167.2(C, 5), 124.7(CH, 4), 66.3(CH, 11), 53.9(CH, 9), 51.7(CH, 14), 50.3(C, 13), 37.5(CH, 10), 36.5 (CH_2), 35.4(CH_2), 35.0(CH_2), 34.3(CH, 8), 34.0(CH_2), 30.1(CH_2), 26.0(CH_2), 20.9(CH_2), 19.5(CH_2), 8.3(CH_3, 18-CH_3).

D-13β--ethyl-gon-4-ene-3,11,17-trione (9a)

To the solution of 8a (320mg, 1.05mmol) in acetone (18ml) was added dropwise Jones' reagent 1.1ml (equivalent 3.02mmol CrO_3) at -12°C. After addition (5 min.), the mixture was stirred at -10°C for 30min. until TLC showed no starting material 8a to be present.. The solution was diluted with cold methanol (2ml) and neutralised with $NaHCO_3$ (sat.). After addition of 100ml saturated NaCl solution, the mixture was extracted with diethyl ether. The dry solution (anhydrous Na_2SO_4) was concentrated and filtered to give colourless rods 9a (300mg, 95% yield). m.p. (cyclohexane/EtOAc) 185~187°C. $[\alpha]_D^{20}$ +28° (c. 0.46, $CHCl_3$). UV: λ_{max}=238nm. It was found to be identical (m.p. and IR spectra) with an authentic sample.

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16. MS (EI) m/z (M^+) were as follows: 2a: 288 ($C_{19}H_{28}O_2$, 288.4); 2b: 286 ($C_{19}H_{26}O_2$, 286.4); 3b: 284 ($C_{19}H_{24}O_2$, 284.4); 4a: 339 ($C_{23}H_{33}NO$, 339.5); 4b: 337 ($C_{23}H_{31}NO$, 337.5); 6a: 318 ($C_{19}H_{26}O_4$, 318.4); 6b: 316 ($C_{19}H_{24}O_4$, 316.4); 7a: 302 ($C_{19}H_{26}O_3$, 302.4); 7b: 300 ($C_{19}H_{24}O_3$, 300.4); 8a: 286(M^+-H_2O) ($C_{19}H_{28}O_3$, 304.4).

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