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Regio and Stereo Selective Hydrogenation of 17-Substituted 13β-ethyl-11β-hydroxy-gona-4,9-dien-3-ones and NMR study

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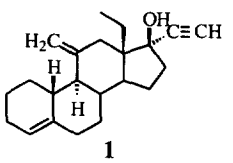
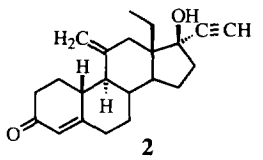
Abstract: Selective hydrogenation of 17-Substituted 13β-ethyl-11β-hydroxy-gona-4,9-dien-3-ones (**3a,b**) in Pd(0)/$SrCO_3$–pyridine media gives the corresponding 11β-hydroxy-gon-4-en-3-ones (**4a,b**). The complete assignments of ^1H and ^{13}C NMR spectra of the main products (**4a,b**) are made by one and two dimensional NMR techniques, such as J-MOD or ATP, ^1H-^1H COSY, HETCOR and COLOC, with the aid of the templates for recognition of proton signals suggested by Kirk and co-workers. The substituent effects of 10-CH_3, 11β-OH and 18-CH_3 in 4-en-3-one steroids are summarised from model compounds and the good correlation is found between experimental and calculated carbon-13 chemical shifts of **4a,b** and **15**. The high stereo selectivity is due to steric hindrance of substituents at β-side. The solvent effects are also discussed

The introduction of oxo functional group at the appropriate position of steroids is always an active area because it provides the activated site for the further elaboration of steroid rings. Our interest in the synthesis of desogestrel (**1**, Org2969), a powerful progestogen widely used in oral contraceptives,[1] and its active metabolite – 3-keto-desogestrel (**2**),[2] leads us to develop a new approach towards 11-oxo 4-en-3-one 19-nor steroids. The previous methods to introduce the 11-oxo functional group involve either the microbial oxidation of the corresponding 4-en-3-one compounds[3,4] or hydroboration–alkaline hydrogen peroxide oxidation of 9(11) double bond of 1,3,5(10),9(11)-tetraene steroids.[5] The 11α-hydroxy group resulting in both cases is oxidised to keto followed by olefination to construct 11-methylene substituent. We reported here an alternative method to the preparation of 11β-hydroxy-4-en-3-ones **4**, a new intermediate in the synthesis of desogestrel and its analogues, *via* Pd/$SrCO_3$ catalytic hydrogenation of 11β-hydroxy-4,9-dien-3-ones **3**, whose 11-oxo functional group was readily introduced by base catalysed molecular oxygen peroxidation of the corresponding 5(10),9(11)-dien-3-ones at 11β position.[6]



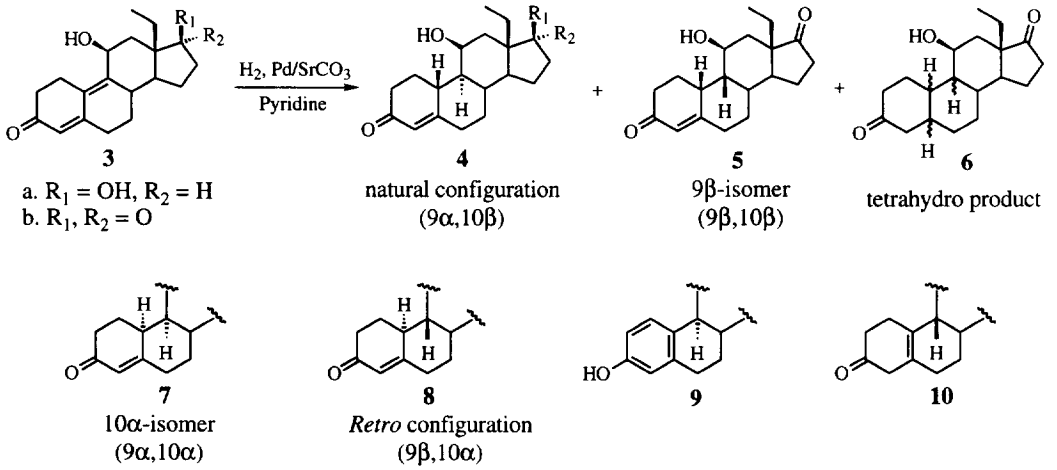
1
desogestrel
or Org2969



2
3-keto-desogestrel

RESULTS AND DISCUSSION

Selective hydrogenation of 4,9-dien-3-one steroids was sensitive to both catalyst and reaction media.[7] Except for the two 9,10-*cis* dihydro products, i.e., 10α-4-en-3-one (**7**) and 9β-4-en-3-one (**5**), the over-hydrogenated tetrahydro (**6**) or A-ring aromatised (**9**) products could be formed. Of the two dihydro products, only the 10α-isomer (**7**) could be transferred to natural configuration (9α,10β) (**4**) under mild acidic or basic conditions.[7a] However the 9β-isomer (**5**) was converted to *retro* configuration (9β, 10α) (**8**) or the nonconjugated 9β-5(10)-en-3-one (**10**) under more violent conditions.[7b] Therefore in order to generate the desired dihydro product (**4**) with the required natural configuration, it is important to improve the selectivity of hydrogenation to increase the 10α-isomer (**7**) and avoid 9β-isomer (**5**), and also to avoid side reactions. The palladium (0) on strontium carbonate catalyst in pyridine was found to be a useful system for the above purpose. The elucidation of the structure of the major products (**4a,b**) was achieved by NMR study which will be discussed later. Further evidence was from the possible chemical transformation. The major products (**4a, b**) did not change after refluxing in concentrated hydrochloric acid–acetone for 9h or 17h, which indicated the products already had the stable configuration (9α,10β) as opposed to (9α,10α). (**Scheme 1**)



3
a. R_1 = OH, R_2 = H
b. R_1, R_2 = O

4
natural configuration
(9α,10β)

5
9β-isomer
(9β,10β)

6
tetrahydro product

7
10α-isomer
(9α,10α)

8
Retro configuration
(9β,10α)

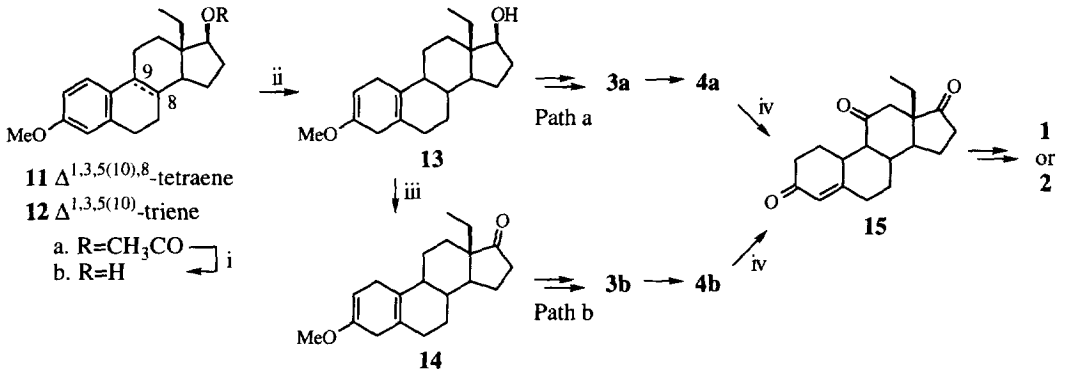
9

10

Scheme 1

The successful conversion of **3** to **4** established a new strategy to the synthesis of **1** and **2** *via* the most popular intermediate 4-en-3,11,17-trione **15** [4,8] from **11** or **12**, which were readily available by total synthesis [9] and also the common starting materials for 13-ethyl steroid drugs in the pharmaceutical industry. (**Scheme 2**)

Substituent effects. The steric hindrance of the 17 substituent directed the hydrogen to approach the reactant from the opposite side of the substituent.[7] The 17β substituent gave mainly 10α-isomer.[7a] With the increase of the size of 17α substituent, the ratio of 9β isomer increased.[7b] The selectivity of $Pd/SrCO_3$ catalytic hydrogenation of 11β-hydroxy-gona-4,9-dien-3-ones (**3**) was highly dependent on the 17 substituent. The 17β-hydroxy reactant **3a** gave only the (9α, 10β) dihydroproduct **4a** with a yield of 81%. However, 17-keto **3b** yielded two dihydro products, **4b** (9α, 10β) and **5** (9β, 10β), with the yield of 45% and 4%, respectively, as well as a small amount of tetrahydro product **6** (4%). From the *cis* reaction mechanism of heterogenous catalytic hydrogenation, the natural configuration (**4**) was formed from the initial hydrogenation product **7**



i. KOH, MeOH; ii. Li, NH_3, *iso*-PrOH, THF; iii. $[(CH_3)_3CO]_3Al$, acetone; iv. Jones' reagent, acetone
Path a. yield from **13** to **15** (8 steps), 44%.
Path b. yield from **14** to **15** (8 steps), 9.3%.

Scheme 2[8]

(9α, 10α) in pyridine basic condition. Generally, the allyl hydroxy group oriented the hydrogen to approach the reactant from the same side of the hydroxy group in the catalytic hydrogenation reaction.[10] However in our case, the steric hindrance played a more important effect on the stereoselectivity. 11β-hydroxy and 13β-ethyl groups blocked the β-side, therefore hydrogenation preferred the 10α-isomer. Furthermore, the existence of 17β-hydroxy increased the steric hindrance of the β-side and led to only 10α-isomer compared with 17-keto reactant. The high yield conversion to **4a** from **3a** provided a better approach (path a) to the corresponding 4-en-3,11,17-trione **15** than the route from 17-keto **3b** to **4b** (path b). (**Scheme 2**)

Solvent effect. In the previous study[7] of the conversion of 4,9-dien-3-one steroids without 11-functional groups to the corresponding 4-en-3-ones, it was found that the (9α,10α) dihydro product was formed mainly only in benzene[7a] and the better yield of (9β,10β) isomer was achieved in ethanol.[7b] This led us to develop a suitable media system to improve the stereoselectivity as well as regioselectivity. In order to avoid the aromatisation of the starting 11β-hydroxy-4,9-dien-3-ones, which was catalysed in the presence of palladium (II) ion, the $Pd/SrCO_3$ catalyst, prepared from palladium (II) chloride and strontium carbonate, must be pre-hydrogenated to zero valence completely and at the same time, the whole system including the solvent was degassed and saturated by hydrogen before the addition of the reactant. At the pre-hydrogenation step, hydrogen chloride was released. If the solvent could not absorb hydrogen chloride effectively, the catalyst agglomerated and formed uneven particles. This happened in the case of benzene and resulted in the complex mixture of hydrogenation products. In methanol the catalyst particles were very fine and reactive, the stoichiometric amount of hydrogen was difficult to control and yielded tetrahydro products (UV no absorption). In order to increase the active surface of the catalyst and at the same time decrease the activity of every catalytic site to improve selectivity, the amine such as pyridine was used.[10] Pyridine not only absorbed hydrogen chloride effectively but also deactivated the catalyst to some extent like Lindlar catalyst, and therefore improved the selectivity. In addition, pyridine provided basic media for the conversion of the initial 10α-isomer to the 10β-isomer, which made the hydrogenation and transformation happen in one pot and simplified the reaction procedure. Other media for hydrogenation, but all with pyridine as pre-hydrogenation

solvent, were also examined. Benzene, benzene-methylene chloride (v/v 2:1) or methylene chloride with trace acetic acid system[11,13] gave a mixture with over- hydrogenated isomers as major products as indicated by TLC(ethyl acetate).[14] Only in pyridine, pyridine-methylene chloride, or pyridine-benzene media, was the selectivity improved with the required dihydro product as only (**4a**) or major (**4b**) product.

NMR study. The ^{1}H NMR spectra (see **Table 1**) of the dihydroproducts (**4**), while quite complex due to the overlapping of many methylene groups in the steroid ring (generally called *methylene envelope*[15]), showed several characteristic features that facilitated the structure elucidation. In 4-en-3-one steroids, 4-olefin proton was deshielded to 5.7~6.0 ppm[16] because of the anisotropic effect of the double bond (H4: δ5.85, 5.88ppm in **4a** and **4b** respectively). The hydroxy substituent at 11-position induced the 11-proton downfield shift to 3.5–5.5 ppm.[4] Generally 11-protons in 11β-OH isomer appeared at the higher field compared with 11α-OH isomer. The stereochemistry of 11-hydroxy could be distinguished from the splitting pattern or coupling constant of H11. In 11β-OH isomer, H11α occupied an equatorial bond and therefore showed a smaller coupling constant with vicinal H10 and H12 (Jae=2~6Hz, Jee=1~5Hz, or $W_{1/2}$<12Hz). But in 11α-OH isomer, H11β was at axial

Table 1. ^{1}H NMR data of 4-en-3-one products and reference compounds

position	4a	27*	4b	28a*	5
1α	1.54 (m)	1.86	1.60 (m)	1.86	
1β	2.28 (dm)	2.20	2.31 (m)	2.22	
2α	2.36 (m)	2.36	2.01 (m)	2.37	
2β	2.36 (m)	2.47	2.45 (m)	2.49	
4	5.85 (s)	5.68	5.88 (s)	5.71	5.89 (s)
6α	2.45 (dt)	2.24	2.40 (m)	2.30	
6β	2.23 (m)	2.47	2.40 (m)	2.48	
7α	1.02 (m)	1.03	1.15 (ddd)	1.14	>1.60#
7β	1.88 (m)	2.00	2.04 (m)	2.12	>1.60#
8	1.68 (m)	2.00	1.97 (m)	2.20	
9	0.91 (td)	0.98	0.99 (td)	1.01	1.67 (m)
10	2.56 (m)	–	2.64 (td)	–	
11	4.17 (q)	4.40	4.26 (d)	4.47	4.30 (br s)
12α	1.06 (m)	1.38	1.27 (dt)	1.50	
12β	2.56 (dd)	1.98	2.32 (dd)	1.97	
14	1.00 (m)	0.95	1.39 (m)	1.25	
15α	1.53 (m)	1.66	1.95 (m)	2.00	
15β	1.39 (m)	1.38	1.76 (m)	1.67	
16α	2.09 (m)	2.09	2.41 (m)	2.08	
16β	1.52 (m)	1.48	2.41 (m)	2.52	
17	3.73 (t)	3.62	–	–	
18	1.57 (m)	1.05	2.14 (m)	1.17	2.22 (m)
			1.39 (m)		1.34 (m)
18-CH_3	1.15 (t)		0.88 (t)		0.87 (t)

*Reference compounds[16]. #The exact chemical shifts could not be unambiguously assigned.
[1]Chemical shifts in ppm, $CDCl_3$, TMS. [2]Assignment based on ^{1}H-^{1}H COSY, HETCOR and COLOC.

Table 2. ^{13}C NMR data of 4-en-3-one products and reference compounds

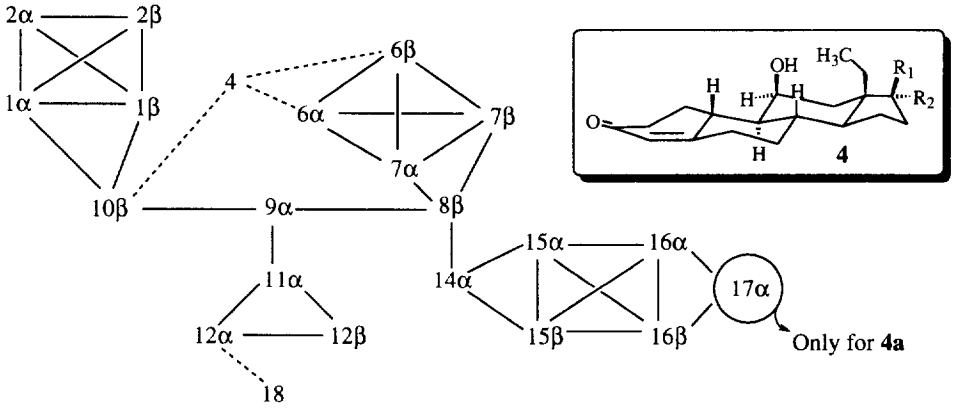
position	4a		16a*	4b		17a*	5#	15¶		28b*
	obs.	calc.		obs.	calc.			obs.	calc.	
1	26.1 (t)	26.0	27.0	26.0 (t)	26.1	27.1		27.7 (t)	26.1	34.8
2	35.2 (t)	36.7	36.6	35.4 (t)	36.8	36.7		35.4 (t)	36.5	33.7
3	199.8 (s)	198.4	198.6	199.7 (s)	197.8	198.0	199.5 (s)	198.7 (s)	198.9	198.8
4	124.7 (d)	123.3	124.8	124.7 (d)	123.5	125.0	125.5 (d)	125.7 (d)	125.3	124.6
5	154.5 (s)	167.4	166.2	167.2 (s)	166.6	165.4	166.0 (s)	163.6 (s)	162.9	167.5
6	36.5 (t)	36.3	35.6	36.5 (t)	36.3	35.6		34.0 (t)	35.5	32.0
7	30.9 (t)	30.4	31.3	30.1 (t)	31.1	32.0		29.2 (t)	30.3	31.0
8	34.5 (d)	37.1	41.0	34.3 (d)	36.4	40.3		35.4 (d)	40.6	36.4
9	54.0 (d)	51.7	49.2	53.9 (d)	52.6	50.1		59.4 (d)	58.7	63.3
10	37.6 (d)	43.6	42.9	37.5 (d)	43.4	42.7		39.6 (d)	42.4	38.3
11	66.6 (d)	73.1	27.1	66.3 (d)	72.1	26.1	68.8 (d)	208.1 (s)	212.6	207.1
12	39.5 (t)	43.7	37.1	34.0 (t)	37.1	30.5		45.1 (t)	48.2	50.4
13	43.7 (s)	44.7	43.5	50.3 (s)	48.9	47.7		54.3 (s)	51.8	49.8
14	51.9 (d)	50.4	47.1	51.7 (d)	53.8	50.5		49.9 (d)	50.7	49.6
15	22.5 (t)	22.5	22.9	20.9 (t)	21.5	21.9		20.1 (t)	20.9	21.6
16	30.6 (t)	30.9	30.6	35.0 (t)	35.7	35.4		36.4 (t)	36.7	36.0
17	84.5 (d)	83.6	81.3	218.1 (s)	220.9	218.6	218.1 (s)	214.5 (s)	218.3	216.2
18	20.3 (t)		11.3	19.5 (t)		13.8	18.9 (t)	18.9 (t)		14.7
18-CH_3	11.4 (q)			8.3 (q)			8.1 (q)	7.0 (q)		

*Reference compounds[18a]. #Only typical signals given. ¶Oxidative product from **4a**.[8]
[1]Chemical shifts in ppm, $CDCl_3$, TMS. [2]Multiplicities determined by J-MOD (**4a, 5, 15**) or ATP (**4b**) experiments. [3]Assignment based on HETCOR and COLOC experiments. [4]Calculated values based on the reference compounds and addictivity of substituent effects as shown in **Table 3**.

bond and a larger coupling constant was observed (Jaa=8~13Hz, or $W_{1/2}$>15Hz).[16,17] Our products all showed the typical splitting of H11α in 11β-OH isomers (H11: δ4.17ppm, d, J=3.2Hz, in **4a**; δ4.26ppm, q, J=3.0Hz, in **4b**). The other characteristic signals in 4-en-3-one steroids with natural configuration, such as the multiplets of 9α-H (td, J=11.0, 3.2Hz in **4a,b**) and 7α-H (ddd, J=13.9, 4.1, 1.4Hz in **4b**) at high field and 1β-H (dm) normally at ca. δ2.3ppm, were easily distinguished from other signals.[16] Recently Kirk and co-workers[16] established the templates for recognition of the characteristic splitting of proton signals in high field NMR (400 or 500MHz), which provided a fast technique to assign both proton position (δ) and orientation (α or β). The reliability and accuracy by using these templates for the structure elucidation was as good as infra-red spectra. The ^{13}C NMR spectra of the 4-en-3-one products obtained in our study also showed some characteristic signals.[18] (see **Table 2**) The typical carbonyl groups appeared at the region δ170~221ppm with the conjugated below δ200ppm and nonconjugated above δ200ppm (C3: δ199.8, 199.7, 199.5, 198.7ppm in **4a**, **4b**, **5**, and **15**, resp.; C11: δ208.1ppm in **15**; C17: δ218.1, 218.1, 214.5ppm in **4b**, **5**, **15**, resp.). The signals at δ124ppm and δ170ppm were the typical olefin carbon, and with the increase of the number of the substituents, the chemical shift shifted to the lower field. Therefore in the 4-en-3-one structure, $\delta_{C5} > \delta_{C4}$ (C5/C4: δ154.5/124.7, 167.2/124.7, 166.0/125.5, 163.6/125.7ppm in **4a**, **4b**, **5**, and **15**, resp.). The signals in the 60~80ppm region

were typical hydroxy or carboxyl substituted carbons (C11: δ66.6, 66.3, 68.8ppm in **4a**, **4b**, and **5**, resp.; C17: δ84.5ppm in **4a**). But care should be paid as the chlorine substituted carbon also appeared at this region. The multiplicity of the saturated carbons at 13~60ppm were easily established by J-MOD or APT spectroscopy. The complete assignments of ^1H and ^{13}C NMR spectra of the main products (**4**) were made by a variety of one or two dimensional NMR techniques, such as, ^1H-^1H COSY, HETCOR and COLOC. (see **Table 1** and **2**). The ^1H NMR spectrum of the 9β-isomer **5** showed a completely different splitting pattern compared with the natural configuration. Only the typical signals of **5** were assigned for comparison.

The ^1H-^1H COSY spectra gave the detailed information about the connectivity of the protons as illustrated in **Scheme 3**. The interesting long-range coupling between H10 and H4 (ω coupling), H4 and H6, and H12α and H18 were observed in the major dihydroproducts **4a**, **b**.



Scheme 3. Coupling network for the protons in 4a and 4b
(300MHz ^1H-^1H COSY, long-range couplings are indicated by dashed lines)

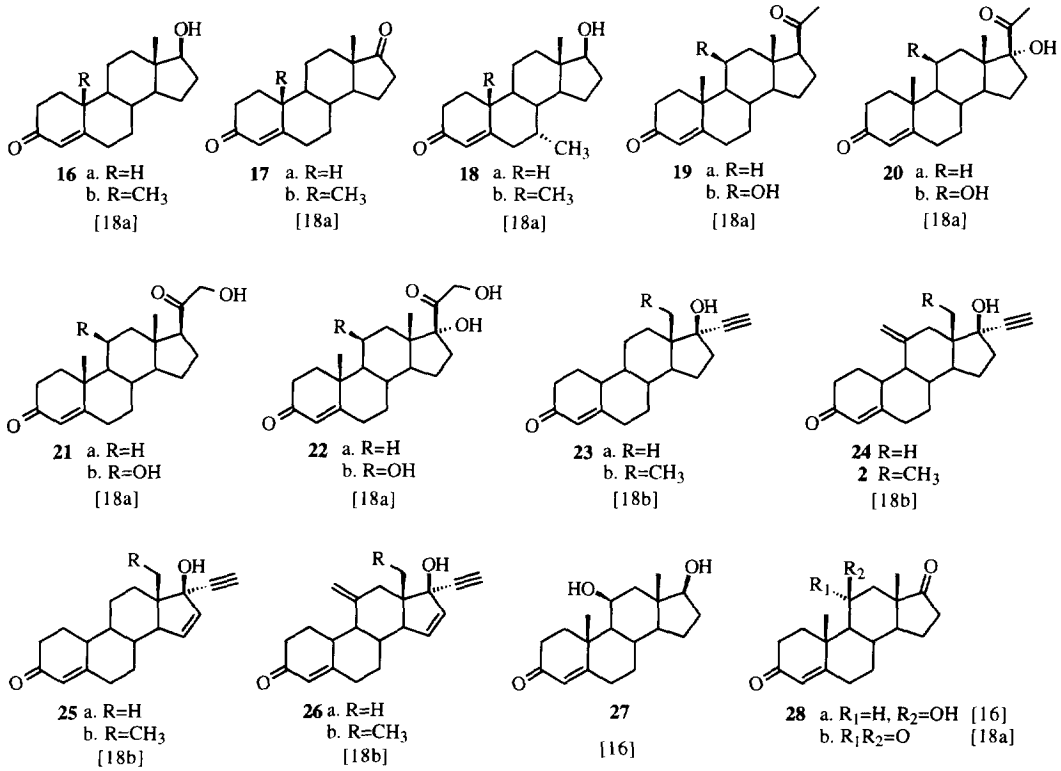
From analysis of the dihedral angles with the vicinal protons, the coupling patterns of the typical protons H9 and H10 in the four (9,10) diastereoisomers were compared, i.e., natural configuration (H9α, td/H10β, td), *retro* isomer (H9β, dt/H10α, td), 9β isomer (H9β, dt/H10β, dt) and 10α isomer (H9α, dt/H10α, dt). It was obvious that only in the (9α, 10β) isomer the proton at 9-position could be a triple doublet, which has also been found experimentally to be the characteristic splitting pattern for the steroids with natural configuration.[16] As there were no data reported about the substituent effects of 10-CH_3 ,11β-OH and 18-CH_3 in 4-en-3-one steroids, we collected the related model compounds[18a,b] (see **Scheme 4**) for comparison and the results are summarised in **Table 3**. Both the experimental and calculated ^{13}C chemical shifts of the hydrogenation products (**4a**,**b**), based on the reference compounds and substituent effects, are illustrated in **Table 2**. The good correlation between them supported the (9α,10β) configuration, as the calculated values were derived from the compounds with natural configuration. Both ^1H and ^{13}C NMR data showed good correlation with their similar compounds. Further application of the substiutent parameters to support the total assignment of ^{13}C NMR spectra of 4-en-3,11,17-trione **15** [8] was also successful. As 10-CH_3, 18-CH_3 and 11β-OH were the three major structure differences between the functional steroids, the substituent parameters obtained in our study could be used to predict chemical shifts of the new compounds based on their known analogues.

From the molecular model, only in (9β,10β) configuration of the four diastereoisomers, H11α bent towards underneath the 4-en-3-one deshielding area. Therefore H11α and C11 in the 9β-isomer (**5**) appeared at

Table 3. Substituent effects (^{13}C NMR) of 4-en-3-one steroids [Δδ, ppm] *

position	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
10-CH_3	8.8	-2.7	-0.4	-0.6	4.4	-3.5	0.2	-4.2	4.6	-4.1	-5.5	0	-0.2	0.6	0.2	0	0
11β-OH	-1.1	0	0.1	-1.6	1.4	0.7	-0.4	-3.9	2.5	0.7	46.0	9.0	-0.6	1.6	0.1	-0.4	0.2
18-CH_3	0.1	0.1	-0.3	0.1	-0.2	0	-0.5	0	0	0	0	-2.4	1.8	1.7	-0.5	0.7	2.1

*Data collected by comparison of the known compounds[18a,b] as illustrated in **Scheme 4**.



Scheme 4. Model compounds for calculation of additive substituent parameters [ref]

lower field compared with others (H11/C11: δ4.30/68.8, 4.17/66.6, 4.26/66.3ppm in **5**, **4a**, **4b**, resp.). When the ring skeleton was changed from (9α,10β) to (9β,10β), H7α was shifted from the shielding to deshielding zone of 4-en-3-one group, and H9 moved far away from the shielding zone of this group. Therefore H9 and H7α in 9β isomer appeared at a lower field than those in (9α,10β) isomer (H9/H7α: δ1.67/>1.60, 0.91/1.02, 0.99/1.15ppm in **5**, **4a**, **4b** resp.). Therefore the stereochemistry of the minor dihydroproduct **5** was determined as (9β,10β) configuration.

EXPERIMENTAL

NMR spectra, ^1H, ^{13}C, J-MOD (spin-echo J-Modulation), APT (Attached Proton Test), ^1H-^1H COSY (^1H-^1H Homonuclear Correlation Spectroscopy), HETCOR (^{13}C-^1H Heteronuclear Correlation Spectroscopy)

and COLOC (^{13}C-^{1}H Heteronuclear Correlation Spectroscopy *via* Long-Range Coupling) were recorded on JEOL FX-90Q (1D) or VXR-300 (1D and 2D) Spectrometer by using standard pulse program.

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. Optical rotations were measured with a polartronic-D-automatic Polarimeter. Column chromatography was performed on aluminium oxide (200~300 mesh, Shanghai Wushi Chemical Co.) with petroleum ether (60~90 ^{0}C)–ethyl acetate as eluent. 5% and 2% Pd/$SrCO_3$ catalyst[19] were prepared by following the reported procedure for 10% catalyst.[20]

Hydrogenation of d-11β,17β-dihydroxy-13β-ethyl-gona-4,9-dien-3-one (3a)

Method A. To the suspension solution of 3.0g of pre-hydrogenated 5% Pd(0)/$SrCO_3$ catalyst[21] and 600mg (1.99mmol) of **3a** in pyridine (40ml) was bubbled a stream of hydrogen with stirring at room temperature for 2h. The reaction was monitored by TLC (EtOAc) [14] and UV spectra, with the decrease of the absorption at 298nm (typical for 11-hydroxy-$\Delta^{4,9}$-3-one chromophore), the absorption at 240nm (typical Δ^4-3-one chromophore) became dominant. The catalyst was filtered (which could be recycled) and washed with 10ml of pyridine. The filtrate was concentrated under vacuum and poured into 5% HCl solution (20ml). The white precipitate was filtered and washed with cold water until PH=6. The raw product collected was subject to column chromatography to give colourless needles, d-11β,17β-dihydroxy-13β-ethyl-3-gon-4-en-3-one **4a** (490mg, 81%). m.p. 199~201 ^{0}C. [lit.[22] 197.5~198.5 ^{0}C]. $[\alpha]_D^{20}$ +34 ^{0} (c. 0.22, $CHCl_3$). UV: λ_{max}=242nm. IR: 1655, 1608 (s, $\nu_{C=O}$ and $\nu_{C=C}$, Δ^4-3-one), 1052, 1029 (m, ν_{C-O}, 11β and 17β-OH) cm^{-1}. ^{1}H, ^{13}C NMR data see **Table 1** and **2**.

Using pyridine-methylene chloride (2:1) as solvent gave similar result.

Method B. To the suspension solution of pre-hydrogenated 2% Pd(0)/$SrCO_3$ catalyst and 100mg (1.99mmol) of **3a** in pyridine–benzene (4ml/10ml) was bubbled hydrogen for 1h. Work-up as method A yielded **4a,** 60mg, 60%.

Hydrogenation of dl-13β-ethyl-11β-hydroxy-gona-4,9-dien-3,17-dione (3b)

Method A. 1.00g (3.33mmol) of **3b** gave three products after column chromatography. Fraction 1: colourless crystals, dl-(9β)-13β-ethyl-11β-hydroxy-gon-4-en-3,17-dione **5**, 40mg, 4%, m.p. 217~219 ^{0}C. UV: λ_{max}=241nm. Typical ^{1}H, ^{13}C NMR data see **Table 1** and **2**. Fraction 2: colourless needles, dl-13β-ethyl-11β-hydroxy-gon-4-en-3,17-dione **4b**, 445mg, 45%, m.p. 202~203 ^{0}C. UV: λ_{max}=241nm. ^{1}H, ^{13}C NMR data see **Table 1** and **2**. Fraction 3: colourless crystals, dl-13β-ethyl-11β-hydroxy-gona-3,17-dione **6**, 40mg, 4%, m.p. 216~218 ^{0}C. UV no absorption.

Treatment of 4a,b and 5 with strong acid

200mg of **4a** was dissolved in 30ml of acetone and 0.5ml of concentrated hydrochloric acid (32%) was added. The mixture was heated to reflux for 9h and then condensed under vacuum, diluted with 50ml of saturated sodium bicarbonate, and extracted with ethyl acetate (3x30ml). The combined ethyl acetate was washed with saturated brine (20ml) and then dried with anhydrous sodium sulphate. Filtration, condensation and column chromatography recovered **4a**, 190mg. (mixed m.p. no depression, and identical ^{13}C NMR with

the reactant **4a**).

Similarly both **4b** and **5** did not change after refluxing in conc. HCl–acetone for 17h.

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8. Conversion of **13/14** to **15** was reported previously by our group: Liu, L.-G.; Su, X.-D.; Li, Z.-S. *Syn. Commun.* **1995**, *25*, 3113. Conversion of **11** or **12** to **13**, and **13** to **14** was the typical procedure used in pharmaceutical industry for 13-ethyl steroid drugs. Conversion of **15** to **1** or **2** could be furnished *via* selective protection of 3,17-diketone [4] to introduce 11-methylene group followed by elaboration of 3,17-function groups. [3]
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19. Preparation of 5% and 2% $Pd/SrCO_3$ catalyst[20]: 1g of palladium (II) chloride powder was dissolved in 2ml of hot concentrated hydrochloric acid, and then diluted with 200ml of freshly distilled water, cooled to room temperature. Strontium carbonate powder was added in small portion to the above solution with stirring till no bubble evolved. Another portion of 12g of strontium carbonate was added and the mixture was stirred at r.t. overnight. The brown solid was filtered on suction and washed with distilled water to PH=7 followed by methanol and ether, respectively, and then dried at 50 °C for 5h. The brown powder 5% $Pd(II)/SrCO_3$ catalyst was ready for prehydrogenation. Similarly 2% $Pd(II)/SrCO_3$ catalyst was prepared by adding 30g of strontium carbonate instead of 12g.
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