Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# An Improved Synthesis of 13β-Ethyl-11-methylenegon-4-en-3,17-dione

Hongwu Gao [a] , Xiangdong Su [b] , Lei Huang [b] & Zhensu Li [b]
[a] Department of Chemistry , University of Missouri-Kansas City , Kansas City, MO, 64110-2499
[b] School of Pharmaceutical Sciences , Beijing Medical University , Beijing, 100083, People's Republic of China
Published online: 22 Aug 2006.

To cite this article: Hongwu Gao , Xiangdong Su , Lei Huang & Zhensu Li (1997) An Improved Synthesis of 13β-Ethyl-11-methylenegon-4-en-3,17-dione, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:11, 1981-1987, DOI: 10.1080/00397919708006801

To link to this article: http://dx.doi.org/10.1080/00397919708006801

SYNTHETIC COMMUNICATIONS, 27(11), 1981-1987 (1997)

# AN IMPROVED SYNTHESIS OF 13β-ETHYL-11-METHYLENEGON-4-EN-3,17-DIONE

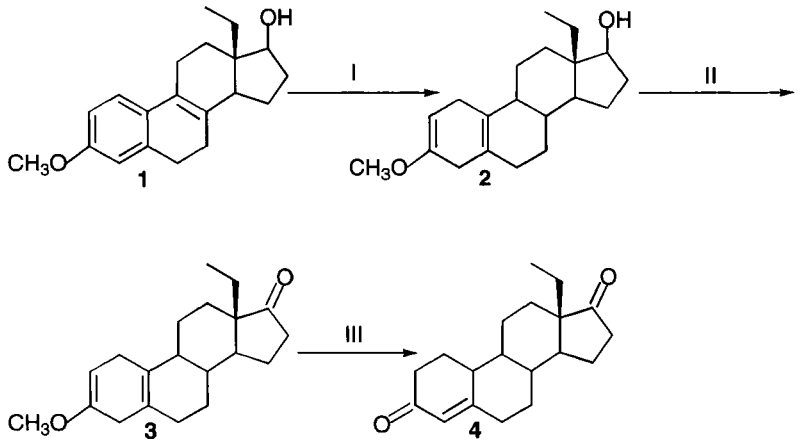
Hongwu Gao*
Department of Chemistry, University of Missouri-Kansas City
Kansas City, MO 64110-2499
and
Xiangdong Su, Lei Huang and Zhensu Li
School of Pharmaceutical Sciences, Beijing Medical University,
Beijing, 100083, People's Republic of China



**Abstract:** An improved synthesis of 13β-ethyl-11-methylenegon-4-en-3,17-dione with the total yield of 57% starting from 13β-ethyl-11α-hydroxy-gon-4-ene-3,17-dione is 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[1] and its active metabolite-3-keto-desogestrel.[2] The previous methods involved: 1). homologation of the 18-methyl group of on estrane derivative by intramolecular hypoiodite reaction;[3] 2). hydroboration-alkaline hydrogen peroxide oxidation of 9(11) double of 1,3,5(10),9(11)-tetraene;[4] 3). oxygen peroxidation of 5(10),9(11)-dien-3-ones at 11β position.[5] We have reported the microbial oxidation of 13β-ethyl-gon-4-ene-3,17-dione (**4**, Scheme 1[6]) to give 13β-ethyl-11α-hydroxy-gon-4-ene-3,17-dione (**5**).[7] Starting from **5**, we now report an improved syntheses of 13β-ethyl-5-ene-3,11,17-trione-3,17-diethylene ketal (**8b**) and 13β-ethyl-11-methylenegon-4-en-3,17-dione (**10**).

Compound **5** can be converted to **8b** by two pathways (Scheme 2). In the previously reported pathway (**5-6-8b**), the column separation in step VI gave the trouble in micro scale



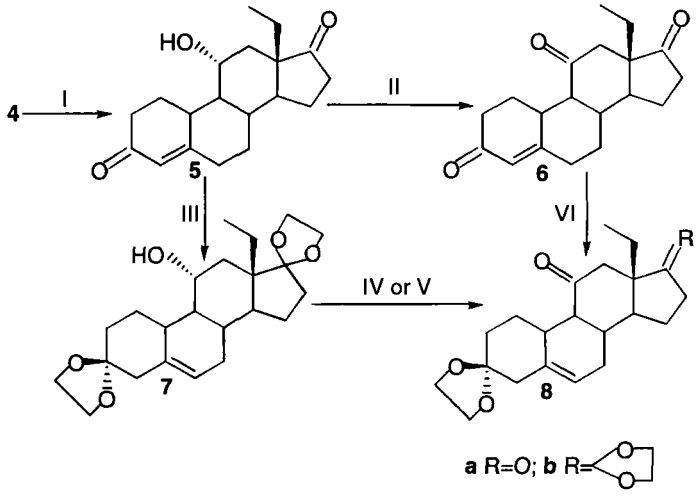

(I) Li, liq. $NH_3$, ethanol, THF, 63.2% (II) $(i\text{-}PrO)_3Al$, toluene, 85%

(III) HCl (conc.), acetone, 70%

**Scheme 1**

synthesis. With a prolonged reaction time, the 11-ketal can be formed.[8] In an alternative route, ketalization followed by oxidation was applied on 11β-OH derivatives.[3,9] We used this idea to design the second pathway (**5-7-8b**) which gave more satisfactory results. After reaction, compound 7 can be crystallized without column chromatography. In the oxidation of **7**, pyridinium chlorochromate (PCC) gave the by-product **8a** and **8b** with low yield (21%). Even with neutralization of sodium acetate, PCC can still hydrolyze 3,17-ketals. Pyridinium dichromate (PDC),[10] a neutral oxidant, finally gave the satisfactory results (87%).

The introduction of 11-methylene can be concluded in two pathways (Scheme 3). The first pathway (**8b-9-11**) included two steps: 1). Treatment of 11-ketone **8b** with methyllithium in diethyl ether and benzene, as described by *van den Broek* et al., produced the 11α-methyl-11β-hydroxy derivative **9**; 2). The subsequent formation of the 11-methylene and the removal of the



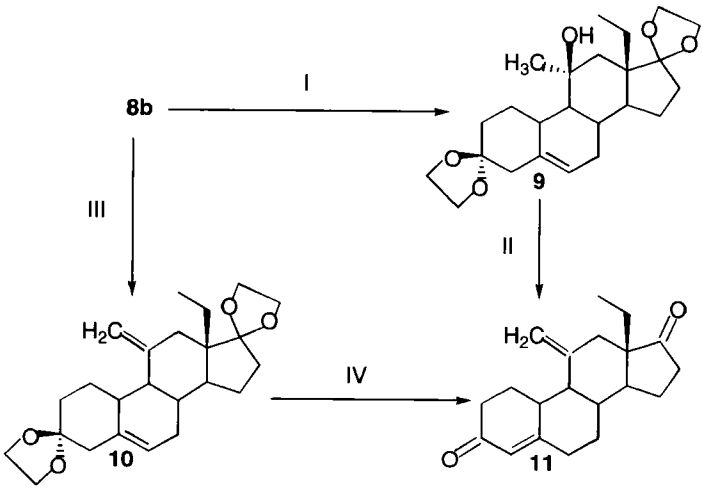

(I) Aspergillus ochraceus, 41% (II) Jones' reagent, 94%
(III) $HC(OEt)_3$, $(CH_2OH)_2$, PTS, 86% (IV) PCC, $CH_2Cl_2$, **8a**: 21%; **8b**: 21%
(V) PDC, $CH_2Cl_2$, **8b**:87% (VI) $HC(OEt)_3$, $(CH_2OH)_2$, PTS, 79%

**Scheme 2**

protecting acetal groups were accomplished together by heating in formic acid with PTS as the catalyst.[7] Instead of Grignard reaction, the second pathway (**8b-10-11**) applied Wittig reaction to introduced 11-methylene directly.[3,9] We successfully repeated this procedure to get our final product **11**.

## EXPERIMENTAL

$^1H$ 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 m.p. apparatus and are uncorrected. Infrared spectra were obtained on a




(I) $CH_3Li$, $Et_2O$, $C_6H_6$, 88% (II) PTS, HCOOH, 74%

(III) $Ph_3P{=}CH_2$, NaH, DMSO, 89% (IV) HCl, acetone, 86%

**Scheme 3**

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°C. 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-11α-hydroxygon-5-ene-3,17-dione-3,17-diethylene ketal (7).** To a solution of **5** (5g, 16.6 mmol) in benzene (90 mL) was added ethylene glycol (40 mL, 717 mmol), triethyl orthoformate (20 mL, 120 mmol) and *p*-toluenesulfonic acid hydrate (0.7g, 3.7 mmol). The

mixture was refluxed for 6 h under a nitrogen blanket and washed with satd. aqueous $NaHCO_3$ solution (50 mL). The organic layer was worked up to yield **7** (5.56g, 86%). An analytical sample was obtained by chromatography (acetone/cyclohexane, 1:20), mp. 161-162°C, $[\alpha]_D$ +63°. IR ($cm^{-1}$): 3507 (s, OH), 1268. $^1H$ NMR ($CDCl_3$): 0.78 (3H, t, 18-$CH_3$), 3.70 (1H, s, 11α-OH), 3.82 (4H, s, 17-ethylene ketal), 3.90 (4H, s, 3-ethylene ketal), 5.40 (1H, broad, H-6). MS (m/z): 390 $[M]^+$. Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.98; H, 9.09.

**D-13β-ethyl-5-ene-3,11,17-trione-3,17-diethylene ketal (8b)-PCC method.** To a stirred solution of PCC (1.5g, 7.2 mmol) and anhydrous sodium acetate (1g, 12.2 mmol) in methylene chloride (9 mL) was added the solution of **7** (0.5g, 1.3 mmol) in methylene chloride (8 mL) dropwise. After 9 h of stirring at rt., this solution was diluted with methylene chloride (60 mL); the decanted solution was filtered through a short pad of silica gel which was washed with ether. Combined eluates were evaporated to give a residue from which **8a** (0.06g, 13.6%) and **8b** (0.105g, 21%) were obtained by chromatography (ether/petroleum ether, 1:20). **8a**: mp. 227-229°C, $[\alpha]_D$+42.5° [ref.[11] mp. 227-229°C]. IR ($cm^{-1}$): 1724 (s, $C_{17}$=O), 1698 (s, $C_{11}$=O). $^1H$ NMR ($CDCl_3$): 0.80 (3H, t, 18-$CH_3$), 3.87 (4H, s, 3-ethylene ketal), 5.44 (1H, broad, H-6). MS (m/z): 344 $[M]^+$. Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 72.99; H, 8.50. **8b**: mp. 171-173°C, $[\alpha]_D$ +65° [ref.[3] mp. 175-177°C, $[\alpha]_D$ +69°]. IR ($cm^{-1}$): 1698 (s, $C_{11}$=O), 1257. $^1H$ NMR ($CDCl_3$): 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-5-ene-3,11,17-trione-3,17-diethylene ketal (8b)-PDC method.** To a stirred solution of **7** (14g, 35.9 mmol) in methylene chloride (350 mL) was added PDC (6.7g, mmol). After 8 h of stirring at rt., this solution was diluted with methylene chloride (500 mL); the decanted solution was filtered through a short pad of silica gel and activated carbon which was washed with ether. Combined eluates were evaporated to leave a residue which was triturated in

methanol to give **8b** (12.12g, 87%) as colorless crystals: mp. 173-175°C, $[\alpha]_D$ +67° [ref.[3] mp. 175-177°C, $[\alpha]_D$ +69°].

**D-13β-ethyl-11-methylenegon-5-en-3,17-dione-3,17-diethylene ketal (10).** To a stirred solution of methyltriphenylphosphosphonium bromide (5g, 13.8 mmol) in dry DMSO (25 mL) was added sodium hydride (0.4g, 80% oil dispersion, 13.3 mmol) under a nitrogen blanket. The reaction mixture was heated to 70°C and sitrred at this temperature for 1.5 h. After cooling to 60°C, **8b** (0.65g, 1.7 mmol) was added. The reaction mixture was stirred at 60°C for 5h and cooled to rt., quenched with water and extracted with ether. The combined organic phase were evaporated to give a residue from which **10** (0.58g, 89%) were obtained by chromatography (ether/petroleum ether, 1:20). mp. 190-191°C, $[\alpha]_D$ +37° [ref.[9] mp. 183-186°C, $[\alpha]_D$ +36°]. IR ($cm^{-1}$): 903 (m, $=CH_2$). $^1H$ NMR ($CDCl_3$): 0.80 (3H, t, 18-$CH_3$), 3.86 (4H, s, 17-ethylene ketal), 3.92 (4H, s, 3-ethylene ketal), 4.81 (1H, s, $=CH_2$), 4.97 (1H, s, $=CH_2$), 5.40 (1H, broad, H-6). MS (m/z): 386 $[M]^+$. Calcd for $C_{24}H_{34}O_4$: C, 74.61; H, 8.81. Found: C, 74.80; H, 8.64.

**D-13β-ethyl-11-methylenegon-4-en-3,17-dione (11).** To a stirred suspension of **10** (5g, 12.9 mmol) in acetone (100 mL) was conc. added hydrochloric acid (0.5 mL). Stirring was continued for 5 h at rt. The solution was then neutralized with saturated aqueous sodium hydrogen carbonate solution, concentrated *in vacuo*, and diluted with water to give crystals of **11** which were collected, washed with water and dried. Yield: g, 86%. Recrystallization from ether gave a pure sample: mp. 153-155°C, $[\alpha]_D$ +223° [ref.[9] mp. 153-154°C, $[\alpha]_D$ +223°]. $^1H$-NMR ($CDCl_3$): 0.80 (3H, t, 18-$CH_3$), 4.82 (1H, s, $=CH_2$), 4.96 (1H, s, $=CH_2$), 5.84 (1H, broad, 4-H). MS (m/z): 298 $[M]^+$. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.17; H, 9.00.

**ACKNOWLEDGEMENT**.- We thank Mr. J. Pang for recording MS spectra. ZSL thanks National Natural Science Foundation of PRC for partial financial support of the work.

## REFERENCES


1. (a) Hopkins, S. J. *Drugs Today* **1982**, 18, 361. (b) Corson, S. L. *Am. J. Obstet. Gynecol.* **1993,** 168, 1017. (c) Phillips, A.; Hahn, D. W.; Klimek, S.; McGuire, J. L. *Contraception* **1987,** 36, 181. (d) Bergink, E. W.; Hanburger, A. D.; De Jager, E.; Van der Vies, J. *J. Steroid Biochem.* **1981,** 14, 175. (e) Van Soest, T. C.; Van Dijck, L. A.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1980,** 99, 323.
2. (a) Back, D. J.; Grimmer, S. F. M.; Shenoy, N.; Orme, M. L. E. *Contraception* **1987**, 35, 619. (b) Hasenack, H. G.; Bosch, A. M. G.; Kaar, K. *Contraception* **1986**, 33, 591.
3. Van den Heuvel, M. J.; Van Bokhoven, C. W.; De Jong, H. P.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1988,** 107, 331.
4. (a) Schwarz, S.; Ring, S.; weber, G.; Teichmueller, G.; Palme, H.-J.; Pfeiffer, C.; Undetusch, B.; Erhart, B.; Grawe, D. *Tetrahedron* **1994,** 50, 10709. (b) Gao, H. W.; Su, X. D.; Li, Z. S. *Steroids* accepted.
5. (a) Liu, L. G.; Zhang, T.; Li, Z. S. *Tetrahedron* **1996,** 52, 4495. (b) Liu, L. G.; Su, X. D.; Li, Z. S. *Synth. Commun.* **1995,** 25, 3113.
6. Smith, H; Hughes, G. A.; Douglas, G. H.; Wendt, G. R.; Buzby jun., G. C.; Edgren, R. A.; Fisher, J.; Foell, T.; Gadsby, B.; Hartley, D.; Herbst, D.; Jansen, A. B. A.; Ledig, K.; McLoughlin, B. J.; McMenamin, J.; Pattison, T. W.; Phillips, P. C.; Rees, R.; Siddall, J.; Siuda, J.; Smith, L. L.; Tokolics, J.; Watson, D. H. P. *J. Chem. Soc.* **1964**, 4473.
7. Gao, H. W.; Su, X. D.; Zhou, L. M.; Li, Z. S. *Org. Prep. Proc. Int.* accepted.
8. Magerlein, B. J.; Levin, R. H. *J. Am. Chem. Soc.* **1955**, 77, 1904.
9. Van den Heuvel, M. J.; Van Bokhoven, C. W.; De Jong, H. P.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1975,** 94, 35.
10. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
11. Su, X. D.; Gao, H. W.; Huang, L.; Li, Z. S. *Synth. Commun.* **1995,** 25, 2807.


(Received in the USA 12 December 1996)