Marine Organic Chemistry. II. Synthesis of 3β,6α-Dihydroxy-5α-pregn-9(11)-en-20-one, the major Sapogenin of the Starfish *Asterias forbesi*

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A seven-step synthesis of 3β,6α-dihydroxy-5α-pregn-9(11)-en-20-one (**7**), starting from 11-oxoprogesterone, is presented.

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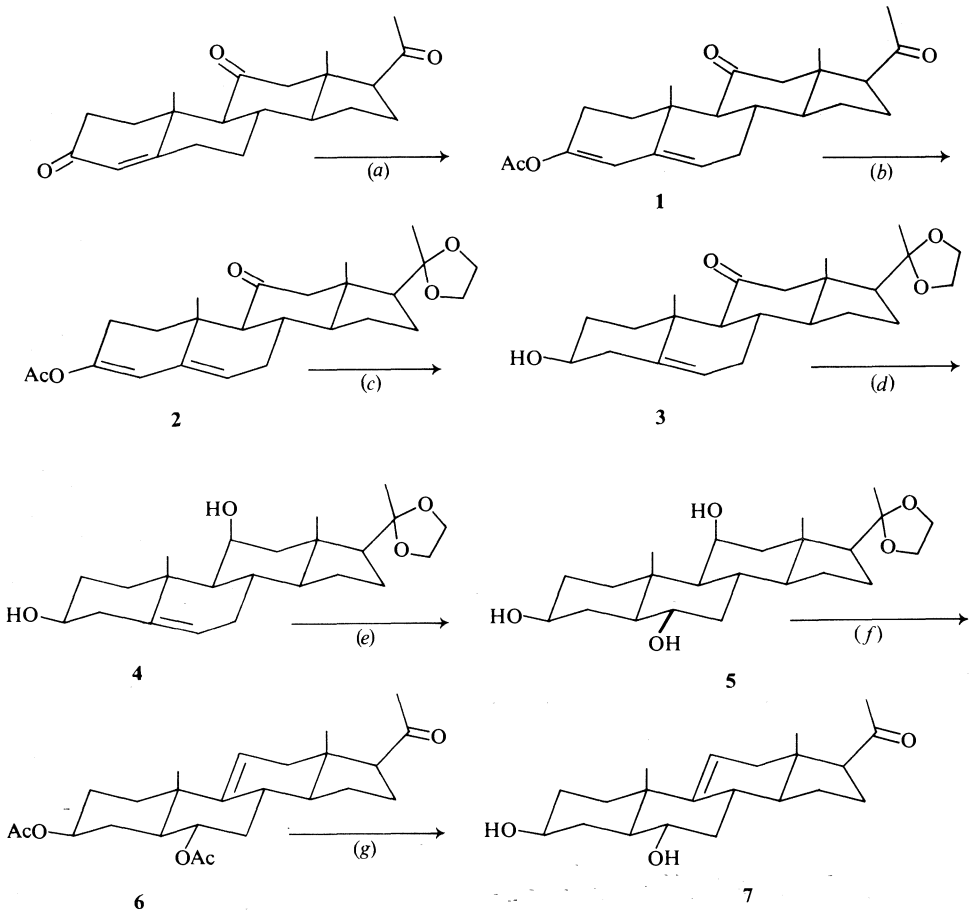
On présente la synthèse en sept étapes de la dihydroxy-3β,6α preg-5α ène-9 (11) one-20 (**7**), à partir de la oxo-11 progestérone. [Traduit par le journal]

Asterone, 3β,6α-dihydroxy-5α-pregn-9(11)-en-20-one (**7**), the major sapogenin isolated from the glycosides found in several starfish (1), can be considered as a potential source of corticosteroids. In order to study the conversion of asterone (**7**) to these steroids, a synthetic sequence, summarized in Scheme 1, was developed to obtain compound **7** in reasonable amounts. This route is described in this article. The 3β,6α-dihydroxy system found in asterone (**7**) can be derived from a steroidal 3-keto-4-ene by a deconjugation–reduction process, affording a 3β-hydroxy-5-ene system which in turn, after "hydroboration-oxidation," could provide the two equatorial hydroxyl groups characteristic of compound **7**. Ketalization of a 3-keto-4-ene steroid can provide the deconjugated, 5-unsaturated-ethylene ketal (2). However, the α-branch of the ketal blocks the α-side of the molecule (3) leading to hydroboration from the β-face, so that after oxidation of the organoborane, a 6β-hydroxy-5β-*H* derivative would result. Hence, we decided to proceed via a 3-acetoxy-3,5-diene, since sodium borohydride reduction of this system is known to give a 3β-hydroxy-5-ene species (4), and hydroboration–oxidation of this system is known to give a 5α-*H*,6α-hydroxy species (5). The 9(11)-double bond can be introduced by dehydration of an 11-axial hydroxyl group, which in turn can be obtained by metal hydride reduction of an 11-keto derivative (6). The preferential dehydration of the 11-axial hydroxyl group of triol **5** constitutes the major advantage of our approach over that recently reported by Turner and Smith (7). Starting from 11α-hydroxyprogesterone, they obtained a 3β,6α,11α-trihydroxypregnane derivative via an analogous series of reactions but were forced to protect two of the equatorial hydroxyl groups before being able to eliminate the third equatorial 11-hydroxyl group as the tosylate. Djerassi and co-workers (8) synthesized asterone (**7**) via a different sequence of reactions, from 3β,6α-diacetoxy-20-ethylenedioxy-5α-pregnane by reaction with iodobenzene dichloride, followed by hydroxylis in less than 11% yield.

Following the above strategy, we were able to obtain asterone (**7**) in 18% overall yield in a seven-step synthesis from 11-oxoprogesterone. Thus, treatment of 11-oxoprogesterone with acetic anhydride and perchloric acid in ethyl acetate at room temperature (9) gave the enol acetate **1** in 84% yield which was ketalized to yield the ketal **2** in 82% yield. Longer reaction times were observed to cause deacetylation, followed by ketalization resulting in formation of increasing amounts of 3,20-diketal. Cleavage and reduction of the dienol acetate **2** with sodium borohydride in ethanol afforded the 3β-hydroxy-5-ene compound **3**, which without purification was reduced with lithium aluminum hydride in diethyl ether to give the enediol **4** in 58% yield. Comparison of calculated (10) chemical shift values for the angular methyl groups with those observed, confirmed the structures assigned to compounds **4** and **5**. (See Table 1.) Hydroboration of compound **4** provided the desired triol **5** in 57% yield which on treatment with glacial acetic acid – perchloric acid at 100° underwent acetylation of the equatorial 3β- and 6α-hydroxyl groups, deblocking of the 20-keto function and dehydration of the axial 11β-hydroxyl group to



a EtOAc, Ac_2O, $HClO_4$
b Benzene, $HOCH_2CH_2OH$, TsOH, reflux
c $NaBH_4$, EtOH
d LAH, ether
e (*1*) B_2H_6, THF
(*2*) H_2O_2, NaOH
f AcOH, $HClO_4$, Δ
g MeOH, KOH, reflux

SCHEME 1

yield the crude diacetate **6** which was hydrolyzed with methanolic potassium hydroxide to afford asterone (**7**) (79% yield from compound **5**).

Experimental

Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. The n.m.r. spectra were obtained on a Varian T-60 or Varian XL-100 spectrometer with tetramethylsilane as internal standard and deuterio-chloroform as solvent. Chemical shifts are expressed in the δ scale and the following abbreviations apply: s, singlet; d, doublet; t, triplet; m, multiplet. Infrared spectra were determined on a Perkin–Elmer 257 i.r. spectrophotometer and run in methylene chloride unless stated otherwise. Ultraviolet spectra were obtained on a Perkin–Elmer 202 u.v.–visible spectrophotometer and were run in 95% ethanol.

11-Oxoprogesterone

Material obtained from Upjohn Co. was recrystallized from methanol, m.p. 178–179 °C; u.v.: λ_{max} 238 (14 900) n.m.; i.r.: $\bar{\nu}$ 1701 (CO), 1667 (α,β-unsaturated CO) cm^{-1}; n.m.r. 0.65 (s, 3, CH_3-18H), 1.42 (s, 3, CH_3-19H), 2.12 (s, 3, CH_3CO), 5.72 (s, 1, vinyl H).

*3-Acetoxypregna-3,5-diene-11,20-dione (**1**)*

To a solution of 11-oxoprogesterone (10.0 g, 30.5 mmol), dissolved in ethyl acetate (200 ml) was added a mixture of acetic anhydride (39 ml) and ethyl acetate (120 ml), followed by a solution of perchloric acid (0.04 ml) in ethyl acetate (40 ml). The resulting yellow solution was stirred for 15 min at room temperature. The reaction was stopped by addition of saturated sodium bicarbonate solution (100 ml). The mixture was added to a slurry of sodium bicarbonate (100 g) in water (200 ml) and was stirred till carbon dioxide evolution had

TABLE 1. Observed and calculated (10) chemical shifts of the 18- and 19-methyl group protons in the proton n.m.r. spectra of selected steroids

	Found		Calculated	
	19-H	18-H	19-H	18-H
11-Oxoprogesterone	1.42	0.65	1.418	0.651
dienol acetate **1**	1.20	0.64	1.251	0.642
dienol acetate ketal **2**	1.21	0.78	1.251	0.775
hydroxyenone **3**	1.21	0.75	1.242	0.751
enediol **4** (11β-OH compound)	1.28	1.00	1.283	1.026
(11α-OH compound)			1.142	0.809
triol **5** (6α-OH, 5α-H)	1.06	1.00	1.067	1.000
(6β-OH, 5β-H)			1.400	1.034
Asterone diacetate (**6**)	1.02	0.57	1.018	0.588
Asterone (**7**)	0.95	0.55	0.951	0.588

ceased. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate solution and with water till neutral and were dried (Na_2SO_4). The solvent was removed *in vacuo* and 11.3 g of a white solid was obtained. Recrystallization from methanol containing some pyridine afforded 9.5 g of white crystalline product, m.p. 145–147° (lit. (11) m.p. 143–145°), *i.e.* *84%* yield; u.v.: λ_{max} 233 (19 100) nm; i.r.: $\bar{\nu}$ 1751 (acetate CO), 1708 and 1701 (CO) cm^{-1}; n.m.r.: 0.64 (s, 3, CH_3-18H), 1.20 (s, 3, CH_3-19H), 2.12 (s, 3, CH_3CO), 2.14 (s, 3, CH_3COO), 5.35 (b, 1, vinyl H-6), 5.67 (s, 1, vinyl H-4).

3-Acetoxy-20-ethylenedioxypregna-3,5-dien-11-one (2)

A mixture of enolacetate **1** (10.0 g, 27.0 mmol) dissolved in benzene (500 ml), ethylene glycol (50 ml), and *p*-toluenesulfonic acid (0.5 g) was stirred at reflux temperature for 3 h. During this time water was removed using a Dean-Stark apparatus. To the cooled solution were added 200 ml of saturated sodium bicarbonate solution. The benzene layer was separated and the aqueous layer was extracted with benzene. The combined organic layers were washed with water till neutral and were dried (Na_2SO_4). The solvent was removed *in vacuo* and the resulting solid residue was recrystallized from methanol containing some pyridine to afford 9.2 g of white crystalline product, m.p. 116–118° (82% yield). Repeated recrystallization from methanol (pyridine) gave an analytical sample, m.p. 117–119°; u.v.: λ_{max} 232 (18 300) nm; i.r.: $\bar{\nu}$ 3033 (ketal C—H stretch), 1751 (acetate CO), 1701 (CO) cm^{-1}; n.m.r.: 0.78 (s, 3, CH_3-18H), 1.21 (s, 3, CH_3-19H), 1.28 (s, 3, CH_3-21H), 2.14 (s, 3, CH_3COO), 3.94 (m, 4, OCH_2CH_2O), 5.35 (b, 1, vinyl H-6), 5.66 (s, 1, vinyl H-4).

Anal. Calcd. for $C_{25}H_{34}O_5$: 72.43; 8.27 H. Found: 72.40 C; 8.18 H.

3β-Hydroxy-20-ethylenedioxypregn-5-en-11-one (3)

To a solution of enol acetate ketal **2** (5.5 g, 13.3 mmol), dissolved in 95% ethanol (550 ml), was added sodium borohydride (1.1 g). The colorless solution was stirred at room temperature for 23 h. After addition of 100 ml of water, the reaction mixture was stirred for 1 h more. The solvent was removed *in vacuo* and the residue was treated with a mixture of water and ether. The ether layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated sodium chloride solution and were dried (Na_2SO_4). Evaporation *in vacuo* of the solvent afforded 5.0 g of white solid (100% yield), which was used without purification in the next step; i.r.: $\bar{\nu}$ 3590 (OH), 1700 (CO) cm^{-1}; n.m.r.: 0.75 (s, 3, CH_3-18H), 1.21 (s, 3, CH_3-19H), 1.28 (s, 3, CH_3-21H), 3.94 (m, 4, OCH_2CH_2O), 3.6 (m, 1, *H*COH), 5.35 (b, 1, vinyl H).

20-Ethylenedioxypregn-5-ene-3β,11β-diol (4)

To a solution of 3β-hydroxy-20-ethylenedioxypregn-5-en-11-one (**3**) (5.0 g, 13.3 mmol) dissolved in anhydrous ether (500 ml) 2.5 g of lithium aluminum hydride was added. The reaction mixture was stirred at room temperature for 23 h, was then cooled to 0°, and was treated with 250 ml of saturated potassium sodium tartrate solution. The ether layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated sodium chloride solution, were dried (Na_2SO_4) and concentrated *in vacuo*. The white solid residue (5.0 g) was recrystallized from acetone to give 2.7 g (7.2 mmol) of crystalline product, m.p. 208–212° (lit. (12) m.p. 210–215.5°).

From the mother liquor an additional 0.2 g of product was obtained, m.p. 207–210°. Total yield amounted to *58%*; i.r.: $\bar{\nu}$ 3590 (OH) cm^{-1}, no absorption in CO region; n.m.r.: 1.00 (s, 3, CH_3-18H), 1.28 (s, 3, CH_3-19H), 1.28 (s, 3, CH_3-21H), 3.94 (m, 4, OCH_2CH_2O), 3.6 (m, 1, HCOH-3), 4.3 (b, 1, *H*COH-11), 5.23 (b, 1, vinyl H).

20-Ethylenedioxy-5α-pregnane-3β,6α,11β-triol (5)

To a solution of enediol **4** (3.0 g, 8.0 mmol) dissolved in 100 ml of dry tetrahydrofurane at 0 °C was added dropwise a solution of 0.1 *M* diborane in tetrahydrofurane (75 ml). The reaction was allowed to proceed for 2 h at 0 °C. A 3 *N* aqueous sodium hydroxide solution (75 ml) was added dropwise to the reaction mixture, followed by 40% aqueous hydrogen peroxide solution (75 ml). The reaction mixture was stirred for 1 h at room temperature. The tetrahydrofurane layer was separated and washed several times with saturated sodium chloride solution, was dried (Na_2SO_4) and was concentrated *in vacuo* to give 2.9 g (7.4 mmol, *92%* yield) of a white solid. Recrystallization from acetone afforded 1.8 g (4.6 mmol, *57%* yield) of crystalline product, m.p. 235–237°. Repeated recrystallization from acetone gave an analytical sample, m.p. 238–241°; i.r. (nujol): $\bar{\nu}$ 3530, 3478, 3406 (OH) cm^{-1}; n.m.r. (dilute solution of crude material for solubility reasons): δ 1.00 (s, 3, CH_3-18H), 1.06 (s, 3, CH_3-19H), 1.31 (s, 3, CH_3-21H), 3.93 (m, 4, OCH_2-CH_2O), 3.6 (m, 2, *H*COH), 4.3 (b, 1, *H*COH-3).

Anal. Calcd. for $C_{23}H_{38}O_5$: 70.01 C; 9.71 H. Found: 70.13 C; 9.80 H.

3β,6α-Diacetoxy-5α-pregn-9(11)-en-20-one (6)

A solution of triol **5** (0.90 g, 2.3 mmol) dissolved in 45 ml of glacial acetic acid, containing 0.45 ml of perchloric acid, was heated on a steam bath for 1 h. The reaction mixture was poured into 450 ml of water. The product was extracted into ether. The organic extracts

were washed with saturated sodium bicarbonate solution and with saturated sodium chloride solution till neutral. The dried solution (Na_2SO_4) was concentrated *in vacuo* and afforded 1.0 g (100%) of light brown resin; i.r.: $\bar{\nu}$ 3018 (=C—H), 1730 (acetate CO), 1700 (CO) cm^{-1}; n.m.r. 0.57 (s, 3, CH_3-18H), 1.02 (s, 3, CH_3-19H), 2.13 (s, 3, CH_3CO), 2.03 (s, 6, CH_3COO), 4.8 (m, 2, HCOAc), 5.40 (b, 1, vinyl H).

3β,6α-Dihydroxy-5α-pregn-9(11)-en-20-one (7)

To a solution of diacetate **6** (1.0 g, 2.3 mmol) in 33 ml of methanol was added a solution of 1.7 g of potassium hydroxide in 5 ml of water and 12 ml of methanol. The resulting solution was refluxed for 2 h. The solvent was removed *in vacuo* and the residue was taken up in methylene chloride and water. The organic layer was washed with water, was dried (Na_2SO_4), and concentrated *in vacuo* to give 0.7 g (92%) of a yellow solid. Recrystallization from benzene afforded 0.60 g (79%) of white crystalline product, m.p. 166–168°; recrystallization from acetone afforded a sample with m.p. 196–198° (lit. (1*c*) m.p. 193–196°; i.r.: $\bar{\nu}$ 3590, 3380 (OH), 3015 (=C—H), 1697 (CO) cm^{-1}; n.m.r.: 0.55 (s, 3, CH_3-18H), 0.95 (s, 3, CH_3-19H), 2.13 (s, 3, CH_3CO), 3.56 (m, 2, *H*COH), 5.35 (b, 1, vinyl H), 2.5–3.5 (s, 2, OH, concentration dependent).

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