Synthesis of 10β,17α-Dimethyl-17β-(1,2-dioxopropyl)estra-5,9-diene-3-ketal

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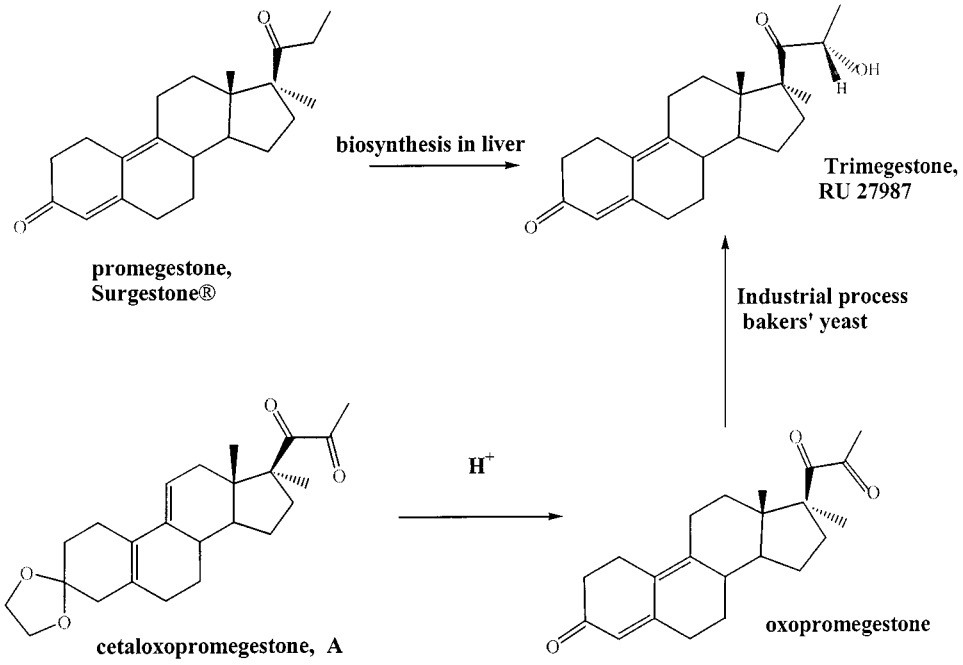
The synthesis of a new progestomimetic steroid, analogous to the cetaloxopromegestone precursor of Trimegestone has been carried out in eight steps from 9α-hydroxyandrost-4-ene-3,17-dione. This latter compound can be obtained from the fermentation of γ-sitosterol, a sterol extracted from soya bean oil.

Introduction

Trimegestone {17α-methyl-17β-[2(*S*)-hydroxy-1-oxopropyl]-estra-4,9-dien-3-one}, the active metabolite of the promegestone (Surgestone®) formed in the liver, is a new progestomimetic molecule developed for the treatment of postmenopausal diseases. Currently, trimegestone is prepared by an industrial bioreduction process developed by Hoechst–Marion–Roussel (HMR) with around 100% chemio-, regio- and diastereoselectivity from the oxopromegestone [17α-methyl-17β-(1,2-dioxopropyl)-estra-4,9-dien-3-one].[1] This latter compound is formed by acidic treatment of the cetaloxopromegestone **A**, Scheme 1.

The synthetic steroid, a mimetic of progesterone, was found from a search for molecules more active than natural hormones. Most of these compounds are 19-norsteroids. However, their synthesis, as for oxopromegestone [17α-methyl-17β-(1,2-dioxopropryl)-estra-4,9-dien-3-one], needs several steps from an already synthetic "methyl deltenone" 19-nor-17-ketosteroid.[1]

In this paper we report the synthesis of an analogue of the cetaloxopromegestone **A**, substituted at the C_{10} position by a methyl group **(A–Me)** from the cyanohydrin **1**.



Scheme 1. Synthetic route in 19-nor steroid series

Compound **1** was synthesised in three steps from a natural steroid, 9α-hydroxyandrost-4-ene-3,17-dione,[2] obtained by fermentation of γ-sitosterol, extracted from soya bean oil.[3] Since the discovery of BSE (Bovin Somatropine Encephalyphorm), the sitostereols {β (cotton seed) and γ

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(soya), the most abundant biosynthesised sterols (≈ 80%)}, are preferentially chosen as the starting material in the hemisynthesis of steroidal hormones.[3]

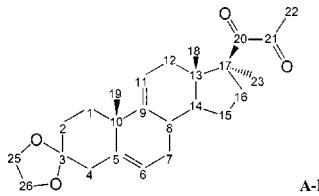
Results

The synthetic route used to obtain the α-diketone **A–Me** from the cyanohydrin **1**, which identical to that of cetaloxopromegestone,[1,2] is depicted in Scheme 2.

The Grignard reaction at the nitrile group cannot be performed directly on the cyanohydrin **1**, so the hydroxyl group in position 17α was first protected as a trimethylsilyl ether. Silylation of **1** was performed under neutral conditions with chlorotrimethylsilane in pyridine at 25 °C, giving **2** in 98% yield. No further purification of **2** was carried out, but it was characterised by ^{1}H and ^{13}C NMR spectroscopy (Table 1).

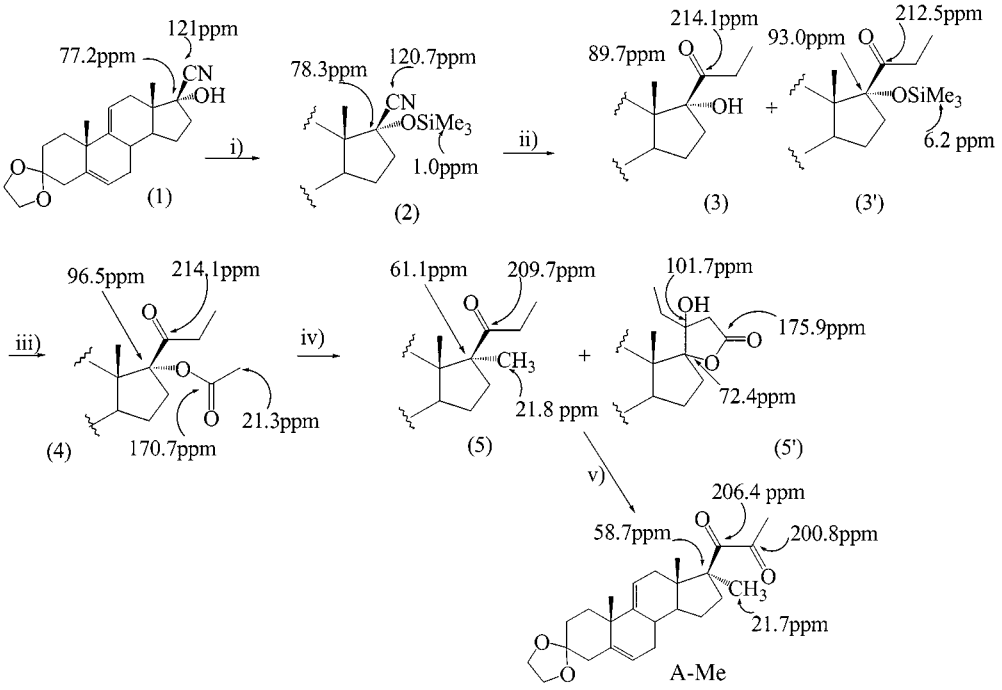
Nitriles (RCN) that do not contain an α-hydrogen normally react readily with Grignard reagents to afford, after hydrolysis, the ketone R′COR. However, the alkylation of **2** with the Grignard reagent required rather severe conditions. Compound **2** in solution in THF was added under argon to ethyl magnesium bromide in ether solution and, after distillation of the ether, the reaction medium was kept stirring at 65 °C for 16 hours. After cooling to 10 °C, aqueous ammonium chloride and then acetic acid (30%) were slowly added in order to hydrolyse the unreacted Grignard reagent. Under these conditions, the hydrolysis of the intermediate imine affords the ketol **3**, although TLC monitoring after hydrolysis showed a mixture of two or three products. However, compound **3** was the major product and was isolated in 63% yield after chromatography; it was fully characterised, in particular, by ^{13}C NMR spectroscopy. The chemical shift of C_{20} was shifted from 120.7 ppm (*C*N)to 214.1 ppm (*C*O), which supports the conversion of the ni-

Table 1. Characteristic ^{13}C NMR spectroscopic data of compounds **1** to **A–Me**



A-Me

Carbon	Compound					
	1	2	3	4	5	A-Me
3	109.4	109.1	109.4	109.2	109.4	109.2
5	145.1	144.9	145.1	145.2	145.4	145.4
6	121.5	121.2	121.6	121.4	121.6	121.6
8	34.8	34.8	34.6	34.4	35.0	34.9
9	138.0	138.6	138.5	138.5	138.6	138.6
10	38.3	38.4	38.5	38.5	38.5	38.5
11	116.0	116.7	116.8	116.5	117.0	117.0
13	48.1	49.1	47.1	45.9	43.8	43.8
14	46.0	46.1	48.3	49.1	48.8	48.8
17	77.2	78.3	89.7	96.5	61.1	58.7
18	15.7	15.5	15.0	14.2	15.6	16.0
19	27.1	27.2	27.2	27.2	27.1	27.2
20	121.0	120.7	214.1	207.0	209.7	206.4
21	/	/	41.7	41.7	41.8	200.8
22	/	/	7.8	7.8	8.3	26.2
23	/	1.0	/	170.7	21.8	21.7
24	/	/	/	21.3	/	/
25	64.2	64.2	64.3	64.3	64.4	64.4
26	64.2	64.2	64.3	64.3	64.4	64.4



Scheme 2. Synthetic route for **6** or **A–Me**; reaction conditions: i) Me_3SiCl, pyridine, 25 °C; ii) EtMgBr, THF, 65 °C; iii) Ac_2O, DMAP, toluene, 110 °C; iv) 1. Li, NH_3,THF, –78 °C, 2. CH_3I; v) *t*BuOK, O_2, DMF, –25 °C

trile function into ketone function. The C_{17} resonance shifted from 78.3 to 89.7 ppm and, in the ^1H NMR spectrum, a new triplet at 1 ppm due to the resonance of the methyl group 22 was observed (Table 1).

The two other products have been identified by spectral data as **4**, which is not always formed, (vide infra) and the derivative **3′** with a structure very close to that of **3**. The most significant difference was the presence in the ^{13}C NMR spectra of **3′** of a resonance at 0.6 ppm supporting the fact that the $-SiMe_3$ group was still present. This particular difficulty of regenerating the alcohol group at the C_{17} position, even with other reagents such as nBu$_4$NF[4]could be explained by a possible extra coordination of the silicon atom by the ketone in C_{20}, Scheme 2.[1]

Due to the presence of several functional groups in **3**, there are very few possibilities[5] for the transformation of the 17α-OH group into the 17α-CH_3 group with retention of configuration. One important method is the alkylation reaction with alkali metals in liquid ammonia as described for the synthesis of 17α-alkylpregn-20-one.[6,7] This approach requires that the 17α-OH group is protected with a good leaving group such as OAc.

Because of steric hindrance around C_{17}, the acetylation of **3** by acetic anhydride in the presence of a catalytic amount of 2,4-dimethylaminopyridine (DMAP) was complete only after 18 h at 110 °C. Acetate **4** was isolated in 63% yield after recrystallisation from methanol/pyridine (20:1), Scheme 2.

The alkylation of **4** at the position 17α was obtained by addition of methyl iodide at –78 °C to the 17,20-enolate generated by the reaction of lithium in a liquid ammonia/THF mixture at –78 °C. After slow evaporation of NH_3 and THF, the oily residue was extracted with ethyl acetate and then purified by column chromatography (eluent: cyclohexane/ethyl acetate, 80:20). The structure of **5** was supported by^{13}C NMR spectroscopic data (Scheme 2) and the infrared spectrum showed a single band ν(CO) at 1694 cm^{-1} instead of two bands at 1710 and 1729 cm^{-1} for **4**.

The addition of methyl iodide was essentially stereospecific as supported by the absence of an NOE between the methyl groups in the C_{17} and C_{13} positions. The fact that the alkylation occurred only on the α face is probably due to steric hindrance of the methyl group in the C_{18} position, as proposed in the mechanism of this alkylation step.[1,8]

In all attempts, the reaction of Li/NH_3 with **4** afforded a main by-product which was characterised as the lactone **5′**. This lactone results from the attack of lithium amide on the ester **4**. The lithium amide could result from the irreversible decomposition reaction of the solvated electron in ammonia. Its formation could be catalysed by any traces of organometallic derivatives, temperature or photochemistry.[9] Thus, even under strictly anhydrous conditions and careful control of the temperature, at –78 °C the formation of **5′** was always observed. Its quantity could be reduced by using lithium containing 0.5% sodium.

In the starting material **5**, the methyl groups α to the carbonyl can be oxidised with selenium dioxide,[10] with DMSO via an α-bromoketone,[11] or with molecular oxygen.[12–14] The possible industrial application of the final molecule led us to choose molecular oxygen as the oxidant. The autoxidation of the $-CH_2$ group α to a carbonyl group is extremely rapid in the presence of *tert*-butoxide ion. This synthetic route is often used in steroid chemistry.[13,15]

The autoxidation reaction occurred when the potassium enolate of **5** was oxidised by dry oxygen. The formation of the ketone at the C_{21} position probably results from the addition of O_2 to the anion R^-.[16] The new steroid **A–Me**, isolated in 70% yield as a yellow powder (m.p. 140–141 °C) was fully characterised. The formation of the α-diketone group was supported by the presence in the infrared spectra of two bands at 1701 and 1715 cm^{-1} for ν(CO) and in the ^{13}C NMR spectra of two resonances at 200.8 and 206.5 ppm in the carbonyl region (Scheme 2 and Table 1).

Discussion and Conclusion

Following a similar synthetic route as for **A**, we have synthesised an original steroid, **A–Me** in eight steps from 9α-

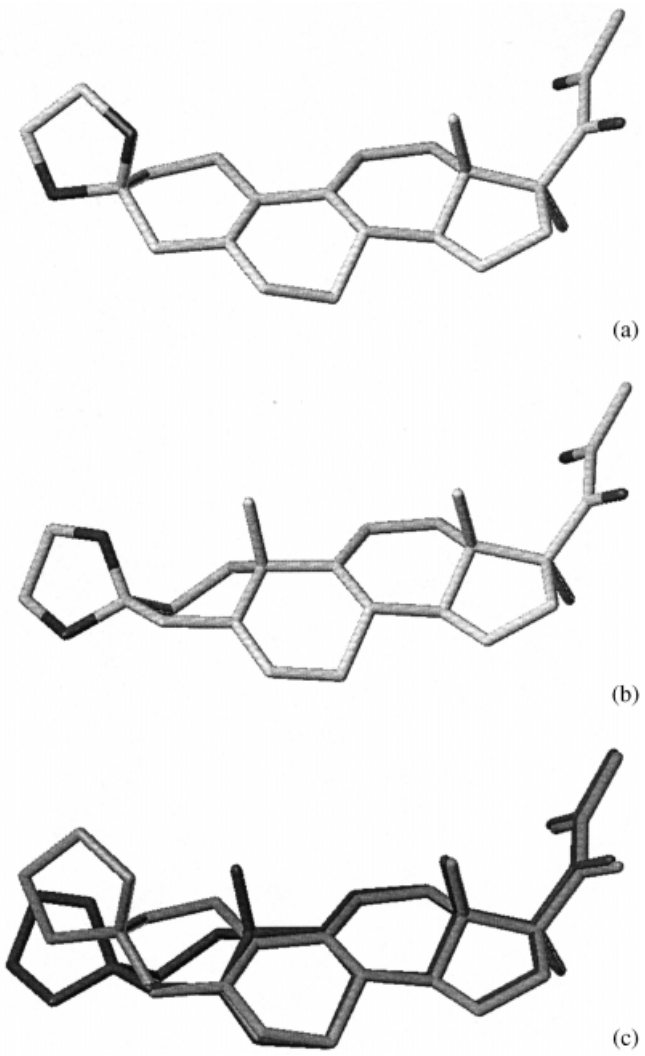


Figure 1. Comparison (c) of the lowest energy conformation of **A** (a) and of **A–Me** (b) determined by molecular modeling[17]

hydroxyandrost-4-ene-3,17-dione, a compound derived from the γ-sitostereol extracted from soy bean oil. However, the reactivity of each of the steroidal intermediates **1** → **5** containing a methyl group at the C_{10} position was lower than the 19-norsteroid analogue, and therefore more severe conditions were required which induced poorer yields and lower purity in some steps.

Molecular modelling was used to establish a possible correlation between the structure of **A–Me** and **A** and their difference in reactivity. The more stable conformations of **A–Me** and of **A** were determined using the molecular mechanics Tripos force field and the conformational analysis tools included in the software Sybyl (GRID).[17] In these low-energy conformations, it appears that the presence of a methyl group at the C_{10} position changes mainly the structure of the A and B rings, but not that of the C and D rings. These C and D rings of **A–Me** and **A** can be superimposed, as is clearly shown in Figure 1. This structural similarity between **A–Me** and **A** allowed us to synthesise the original steroid **A–Me** following a similar synthetic route as for **A**. However, as in many rigid systems, the presence of a functional group (in this case the Me group at C_{10}) strongly affects the rate of most of the reactions taking place on the chain at C_{17} by altering the conformation of the whole skeleton. This conformational transmission is a well-known effect in steroid chemistry.[18]

Experimental Section

General: All operations were carried out under anhydrous conditions and in an inert atmosphere. Anhydrous solvents were prepared according to standard procedures. – IR: Nicolet 205-FT-IR. – NMR: Bruker 300 MHz. For ^1H and ^{13}C NMR, $CDCl_3$ was used as solvent. Thin layer chromatograms were developed with a methanol/sulfuric acid mixture (95:5).

2: To a solution of **1** (5 g, 14×10^{-3} mol) in 15 mL of pyridine was slowly added 5 mL of Me_3SiCl. The mixture was stirred at room temperature. Residual gases were removed by passing through a solution of NaOH and then a solution of bleach. At the end of the reaction (TLC; eluent: cyclohexane/ethyl acetate 70:30), 10 mL of THF and 50 mL of a saturated solution of $NaHCO_3$ were added. The product was filtered, washed with a saturated solution of $NaHCO_3$ and dried under vacuum. Compound **2** (5.8 g, 96%) was obtained as yellow crystals, m.p. 177–178 °C. – IR (CH_2Cl_2): $\tilde{\nu}$ = 2242 cm^{-1} (C≡N), 2900 (CH). – ^1H NMR ($CDCl_3$): δ = 5.5 (d, J = 6.2 Hz 1 H,), 5.4 (d, J = 5.1 Hz, 1 H), 3.9 (m, 4 H), 1.3–2.6 (m, 16 H), 1.2 (s, 3 H), 0.8 (s, 3 H), 0.2 (s, 9 H).

3: To a solution of **2** (1 g, 2.3×10^{-3} mol) in THF (10 mL) 5.5 mL was slowly added a solution of $(C_2H_5)MgBr$ (3 M) in diethyl ether. The diethyl ether was then removed by distillation and the mixture stirred at 65 °C for 16 h. At 15–20 °C, 10 mL of a saturated solution of ammonium chloride was added very slowly. N.B. During the addition the temperature must be carefully controlled. Then a solution of acetic acid (10%, 20 mL) was added at 0 °C and the mixture stirred for 1 h. Extraction with dichloromethane and chromatographic purification (eluent: toluene/ethyl acetate 90:10) gave **3** (0.57 g, 63%) as colourless crystals, m.p. 179–180 °C. – IR (CH_2Cl_2): $\tilde{\nu}$ = 3508 cm^{-1} (OH), 1701 (C=O). – ^1H NMR ($CDCl_3$): δ = 5.5 (d, J = 6.2 Hz, 1 H), 5.4 (d, J = 5.1 Hz, 1 H), 3.9 (m, 4 H), 3.6 (s, 1 H), 1.3–2.8 (m, 18 H), 1.2 (s, 3 H), 1.0 (t, J = 7.1 Hz, 3 H), 0.6 (s, 3 H).

4: Compound **3** (3 g, 7.8×10^{-3} mol) and 2,4-dimethylaminopyridine (0.5 g, 4.1×10^{-3} mol) were dissolved in 40 mL of toluene. Acetic anhydride (1.5 mL, 15.9×10^{-3} mol) was then added slowly. The solution was stirred at reflux temperature for 18 h. At 0 °C, 20 mL of ethyl acetate then 60 mL of a saturated solution of ammonium chloride were added. The mixture was stirred for 1 h. Extraction by ethyl acetate gave a product that was crystallised from a solution of 15 mL of methanol and 0.5 mL of pyridine. Compound **4** (2.1 g, 63%) was obtained as white crystals, m.p. 188–189 °C. – IR (CH_2Cl_2): $\tilde{\nu}$ = 1710 and 1729 cm^{-1} (C=O), 1260 (C–O). – ^1H NMR ($CDCl_3$): δ = 5.5 (d, J = 6.2 Hz, 1 H), 5.4 (d, J = 5.1 Hz, 1 H), 3.9 (m, 4 H), 2.1–3.0 (m, 6 H), 2.0 (s, 3 H), 1.2–1.9 (m, 12 H), 1.2 (s, 3 H), 1.0 (t, J = 7.1 Hz, 3 H), 0.6 (s, 3 H).

5: At –70 °C, lithium powder (33 mg) was added to 8 mL of liquid ammonia. The solution became dark blue and was stirred for 15 min. Anhydrous THF (10 mL) was then added. This mixture was stirred at –75 °C for 30 min and then compound **4** (0.5 g, 1.2 × 10^{-3} mol) was added. After stirring for 1 h iodomethane (0.375 mL, 4×10^{-3} mol) was added. The solution was stirred for 1.5 h. At 0–5 °C, 25 mL of water was added. Extraction by ethyl acetate and chromatographic separation (eluent: cyclohexane/ethyl acetate 82:12) gave **5** (0.2 g, 51%) as light yellow crystals, m.p. 133–134 °C. – IR (CH_2Cl_2): $\tilde{\nu}$ = 1694 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ = 5.5 (d, J = 6.2 Hz, 1 H), 5.4 (d, J = 5.1 Hz, 1 H), 3.9 (m, 4 H), 1.2–2.8 (m, 18 H), 1.2 (s, 3 H), 1.1 (s, 3 H), 1.0 (t, J = 7.1 Hz, 3 H), 0.6 (s, 3 H).

A–Me: Compound **5** (1.5 g, 3.8×10^{-3} mol) was dissolved in 15 mL of *N*,*N*-dimethylformamide. The mixture was stirred for 10 min. Potassium *tert*-butoxide (1 g, 8.9 × 10–3 mol) was then added at 0–5 °C. The solution was stirred for 5 min and cooled to –25 °C. Then dry oxygen (flow rate: 0.5 cm^3 s^{-1})was bubbled through the solution for 1 h. Stirring was maintained at –25 °C for 1.5 h. After warming to room temperature a solution of $NaHPO_4$ (30 mL) was added. Extraction with ethyl acetate gave 1.3 g of light yellow crystals (70%), m.p. 140–141 °C. – IR (CH_2Cl_2): $\tilde{\nu}$ = 1701 and 1715 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ = 5.5 (d, J = 6.2 Hz, 1 H), 5.4 (d, J = 5.1 Hz, 1 H), 3.9 (m, 4 H), 1.2–2.8 (m, 16 H), 2.3 (s, 3 H), 1.2 (s, 3 H), 1.1 (s, 3 H), 0.6 (s, 3 H).

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