The chemistry of thujone. XIII.[1] Synthetic studies in the digitoxigenin series

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The thujone-derived chiral synthon **1** is converted, via selenium chmistry, to the important cross-conjugated dienone **2** and the latter is then convertible to the unsaturated cardenolide analogue **3**, which through known methodology (**3** → **26** → **27** → **4**), completes a formal synthesis of digitoxigenin (**4**). Extensive studies to afford **2** from androstenedione (**5**) are also described and a new approach to elaborate the essential butenolide ring system, characteristic of the cardiac active steroids, is developed.

Key words: thujone, steroid synthesis, digitoxigenin.

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En utilisant la chimie du sélénium, on a transformé le synthon chiral **1**, obtenu à partir de la thujone, en la diénone importante **2** à conjugaison croisée que l'on peut convertir en analogue cardénolide insaturé **3**; ce composé, par le biais d'une méthodologie connue (**3** → **26** → **27** → **4**), donne lieu à une synthèse formelle de la digitoxigénine (**4**). On décrit aussi les études poussées qui ont été effectuées pour obtenir le composé **2** à partir de l'androstènedione (**5**) et on a développé une nouvelle approche au système cyclique buténolide essentiel, caractéristique des stéroïdes actifs au niveau cardiaque.

Mots clés : thujone, synthèse des stéroïdes, digitoxigénine.

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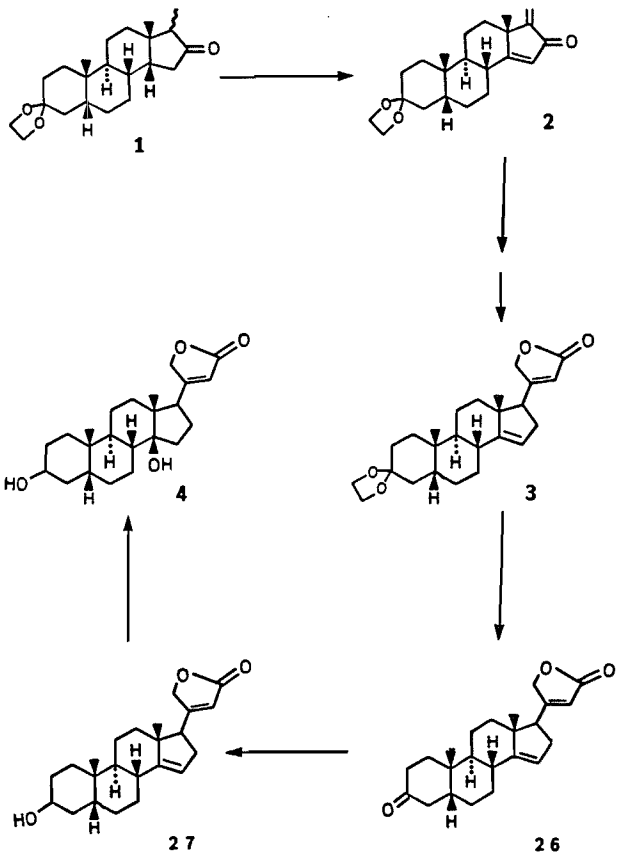
The cardiac active steroids are a well-known group of naturally occurring steroidal lactones of importance in the treatment of heart disease. One of the most commonly used cardiac active glycosides in medicine is digitoxin, isolated from *Digitalis purpurea* (Purple Foxglove) and the main constituent of the well-established heart drug, digitalis. This drug is responsible for one of the highest rates of drug-induced hospital admissions (2) since, to achieve the desired therapeutic effects, 60% of the lethal dose of the drug must be administered and, depending on the physical condition of the patient, the toxic dose can be much lower than anticipated (3). This latter effect is especially pronounced in the treatment of infants where the lethal dose can be much lower than the physician would estimate (4). As a result, there has been considerable incentive for medicinal chemists to synthesize analogues of the digitoxin system in the hope that an improved therapeutic index can be achieved.

Previous synthetic studies in various laboratories (5–17) have afforded synthetic routes to this series of compounds. In these studies, steroidal starting materials were employed and different routes to the butenolide ring system, characteristic of this family of natural products, were developed. We wish to present our studies involving thujone-derived chiral substrates as starting materials for the syntheses of compounds within this family.

Earlier studies in our laboratory (18, 19) revealed efficient routes to the chiral synthon **1** from thujone and we present herein the most recent results, in which **1** is converted into the appropriate building units for the digitoxigenin (**4**) series. The overall strategy of the synthetic program is summarized in Scheme 1.

It is well established that one of the important synthetic requirements in deriving the cardiac active steroid system involves the introduction of the C14-α hydroxyl group. With the exception of one study (11) involving remote functionalization, the utilization of conventional steroid substrates, normally lacking this functionality, requires a number of synthetic steps



SCHEME 1

to introduce this functional group. The majority of the studies reported thus far depend on C14—C15 unsaturated steroids, derived from C17 functionalized steroids, which, in turn, via established chemistry, allow introduction of the C14 hydroxyl group. We felt that our thujone-derived steroid analogues, obtained earlier (18, 19), may be advantageous in affording a more direct route to such unsaturated steroid systems. For

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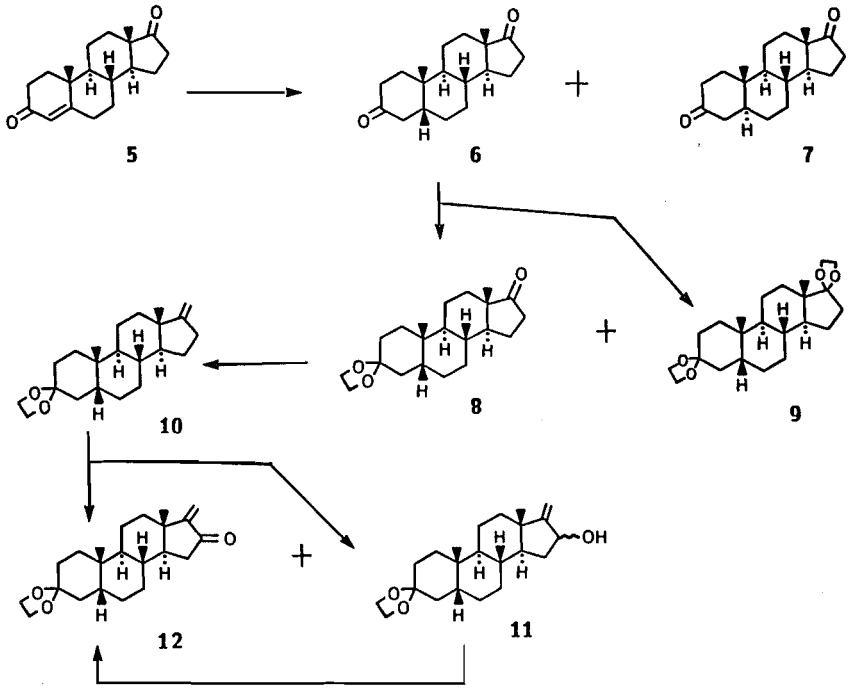


SCHEME 2

example, the thujone-derived intermediates possessing a cyclopropyl ring attached to ring D of the steroid system would, after cyclopropyl ring opening and oxidative cleavage of the resulting unsaturated side chain (18), allow facile entry into 16-keto-17-methyl steroids as exemplified by **1** (Scheme 1). The carbonyl group allows efficient introduction of the required C14—C15 double bond while the C17 methyl group provides for subsequent attachment of the butenolide ring. With **1** on hand, the conversion **1** → **2** (Scheme 1) was considered in our initial phases of this program.

Selenium chemistry, as developed by Barton *et al.* (20), appeared well suited for the above conversion although private discussions with Barton revealed that five-membered ring carbonyl systems were not generally susceptible to dehydrogenation with benzeneseleninic anhydride. Neverthless, after considerable study with various reaction conditions, it was found that the desired dehydrogenation could be accomplished when a weak base (sodium bicarbonate) was employed. The dienone **2**, obtained in 42% overall yield, revealed the expected spectral characteristics (λ_{max} 249 nm; δ 5.23 (1H, s) and 5.97 (2H, s) for the olefinic protons).

It is noteworthy that the stereochemistry at C14 reflects the time and (or) yield in the above dehydrogenation reaction. The thujone-derived intermediate with the 14-β stereochemistry undergoes this reaction under milder conditions (42%, 20 h) while the corresponding 14-α isomer (**12**) (see later) converts to **2** only after 72 h (38%).

As the above thujone related chemistry was under study, a complementary route to **2** from the readily available steroid, androstenedione (**5**), was being developed. The latter study would allow comparisons of compounds prepared from these routes and thereby establish with certainty the total structure and absolute stereochemistry of **2**, as shown in Scheme 1. The overall sequence from **5** to **2** is summarized in Scheme 2.

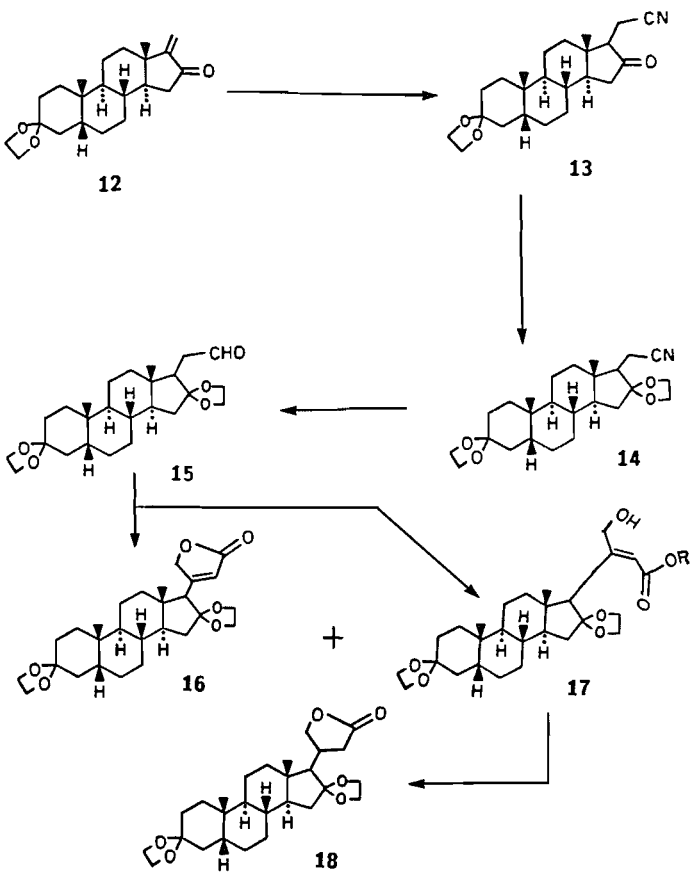
Catalytic hydrogenation ($Pd/CaCO_3$) of **5** afforded a mixture of C5β (**6**) and C5α (**7**) isomers in an approximate ratio of 2:1 respectively and in excellent overall yield (95%). These isomers are conveniently separated by preparative hplc.

The desired A/B *cis* isomer (**6**) was treated with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid to provide the required C3 monoketal **8** as a major product (76%), and the latter, upon reaction under conventional Wittig olefination conditions, yielded the exocyclic olefin **10** (91%).

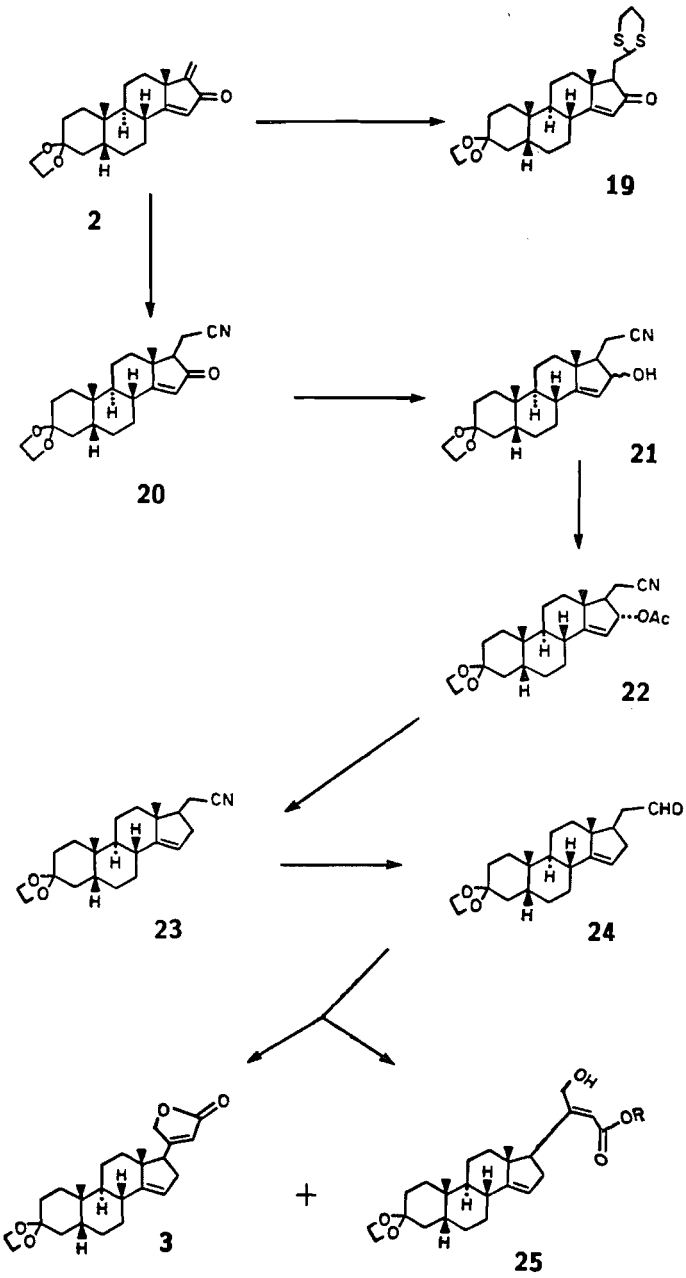
Allylic oxidation of **10** to a mixture of **11** and **12** followed essentially the procedure developed by Schmuff and Trost (21). The allylic alcohol **11** was the major product (75%) and facile separation from the ketone **12** could be achieved. However, for preparative purposes, the resulting mixture of **11** and **12** was subjected to treatment with oxalyl chloride and dimethyl sulfoxide to provide **12** in an overall yield of 82% from **10**. Dehydrogenation with benzeneseleninic anhydride afforded **2** (38%), identical in every respect with the product obtained earlier in the thujone sequence. As noted earlier, the conversion of **12** to **2** requires more drastic conditions (72 h vs. 20 h) than in the case of the corresponding C14-β isomer **1**. As we found later, an attractive alternative to the dehydrogenation reaction proved to be a method employed in the synthesis of the tricyclopentanoid (±)-coriolin (22). Thus, the enolate of the α,β-unsaturated ketone **12**, generated by treatment with lithium hexamethyldisilylamide in tetrahydrofuran at −40°C, was quenched with trimethylsilyl chloride to give the corresponding silyl-enol ether. Oxidation of this enol ether with 2,3-dichloro-5,6-dicyanoquinone resulted in the desired cross-conjugated dienone **2** in 84% yield.

The next phase of our synthetic program involved the development of appropriate chemistry for the elaboration of the required butenolide attached to ring D of the steroid skeleton. For this purpose, the conjugated ketone **12** was selected as starting material and the overall sequence is presented in Scheme 3.

Conjugate addition of cyanide proceeds smoothly to yield the cyano ketone **13** in 91% yield and the latter compound is



SCHEME 3



SCHEME 4

converted to the ketal **14** by conventional means. The proton and ^{13}C nmr spectra show that both compounds **13** and **14** are single isomers, rather than a mixture of C17 isomers as may be expected. To determine the configuration at C17, the nuclear Overhauser effect (nOe) was employed. Therefore, the nOe-difference experiment was performed for **13** and **14**. In the case of the cyano ketone **13**, irradiation at 0.75 ppm (C18 methyl group) resulted in the enhancement of a quartet at 2.17 ppm (assigned as one of the C20 proton signals). Similarly, in the case of the ketal derivative **14**, irradiation at 0.75 ppm (C18 methyl group) resulted in the enhancement of two quartets at 2.25 and 2.35 ppm (C20 hydrogens) but showed no effect on the C17 proton resonance. These results are consistent with the nitriles **13** and **14** having the desired C17-β configuration. DIBAL reduction of **14** afforded the important intermediate aldehyde **15** (79%). According to literature precedent, the conversion of the aldehyde function to the required butenolide ring system should be achieved. For example, Pettit *et al.*, in their extensive and elegant studies on syntheses of bufadienolides (23), established that steroidal ketones upon reaction with glyoxylic acid or its derivatives provide intermediates convertible to the desired lactones. Similarly Kreiser and Nazir (24) established that steroidal aldehydes undergo reaction with glyoxylic acid under acidic conditions (HCl or CH_3COOH, CH_3COONa) to afford the appropriate butenolide systems. Unfortunately, utilization of the latter conditions in the conversion **15** → **16** did not provide encouraging results and we turned our attention to the possibility of employing the stable methyl ester (25) in the condensation reaction with aldehyde **15**. Indeed reaction of **15** with potassium hydride and anhydrous menthyl glyoxylate, followed by borohydride reduction, afforded a mixture of the desired butenolide **16** (17%) and the unsaturated hydroxyester **17** (24%, R = *l*-menthyl). The latter compound, on catalytic reduction to the saturated ester followed by alkaline hydrolysis and cyclization, affords the saturated lactone **18**, thereby potentially providing an additional source of the butenolide **16** via a dehydrogenation process.

Having established the above synthetic procedures with the more readily available ketone **12**, we turned our attention to studies with the cross-conjugated ketone **2**. Unfortunately the introduction of cyanide via conjugate addition employing the above-noted procedure afforded a complex mixture of products resulting from cyanide attack at both of the olefinic sites. However the Nagata procedure (26), in which diethylaluminum cyanide is involved, provided the desired cyano derivative **20** as a mixture of C17 isomers. This mixture was very difficult to separate, but after extensive chromatographic separations, it

was possible to obtain a pure sample of the major C17-β isomer (ratio of C17-β to C17-α is 2:1) for detailed nmr studies. The nOe difference experiments established the stereochemistry of the major product. Thus irradiation at 1.24 ppm (C18 methyl) resulted in enhancement (8%) of a quartet at 2.26 ppm, which is assigned to one of the C20 protons. The corresponding enhancement of the C17 proton signals (doublet of doublets) was only 4%, thereby suggesting a *trans* relationship between the C17 proton and the C18 methyl group.

Since the chromatographic purification of the major isomer **20** was very inefficient, we decided to perform the next two reactions employing the mixture of isomers. Thus, the cyano ketones were reduced with sodium borohydride, in the presence of cesium chloride (27), to a mixture of allylic alcohols (**21**). This mixture was again difficult to separate so it was treated directly with acetic anhydride, in the presence of dimethylaminopyridine (DMAP) in CH_2Cl_2, to produce a mixture of four acetates. The major acetate produced from cyanoketone **20** in 68% yield was separated from the mixture by column chromatography on TLC grade silica gel. The results of the nOe experiment suggested that the structure of the major acetate **22** was as shown in Scheme 4, since irradiation at 1.06 ppm (C18 protons) resulted in enhancement of a quartet at 2.47 ppm, assigned to one of the C20 protons, and enhancement of a broad doublet corresponding to the proton at C16. However, to establish definitely the structure of **22**, the compound was submitted for X-ray crystallography. The details of the X-ray studies are provided as an appendix.

In accord with our synthetic strategy, the next consideration was removal of the C16 substituent in **22**. This was achieved via nucleophilic displacement of the acetate group with hydride anion and involving palladium intermediates (28). For this purpose, the palladium complex of the acetate **22** was initially formed in a reaction with tetrakis(triphenyl phosphine) palladium(0) followed by addition of sodium borohydride to yield the desired derivative **23** in 79% yield.

Utilizing methodology employed for the conversion **15** → **16** + **17** (Scheme 3), the cyano derivative **23** was reduced with DIBAL and the resultant aldehyde **24** (81% yield) was reacted with potassium hydride followed by menthyl glyoxylate and sodium borohydride to produce a mixture of butenolide **3** and unsaturated *trans* ester **25** in 24 and 20% yield respectively.

The butenolide system **3** produced in the course of our synthesis can be easily transformed into digitoxigenin with the employment of well-known methods previously established in the chemistry of cardenolides (29). Thus, after deketalization to the known ketone **26**, reduction (**26** → **27**, Scheme 1) with iridium reagents (30), and subsequent hydroxylation of the C14—C15 double bond (30, 31), the final product digitoxigenin (**4**) is obtained.

It should be noted that another approach for elaboration of the butenolide ring system was considered, and employed the thioketal derivative **19**. For this purpose, **2** was reacted with the anion of 1,3-dithiane in the presence of HMPA (32) to afford a mixture (86% yield) of the C17 isomers (ratio 2:1, as established by nmr). Unfortunately the separation of these isomers proved extremely difficult and subsequent studies to remove the sulfur protecting group led to extensive decomposition. This approach was therefore abandoned.

Finally, it should be indicated that the above studies allow a rather versatile synthetic entry into cardenolide analogues with functionality in ring D. The latter series is not presently available from natural sources or alternative synthetic routes. For example, intermediates **16**, **18**, and **22** afford convenient routes into such analogues. We believe that the latter compounds will afford the opportunity for further structure–activity studies in the hope that lower toxicity within this family of compounds can be obtained. Such studies are being presently considered.

Experimental

Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Ultraviolet spectra were recorded on a Cary 15 spectrometer in methanol solution. Infrared spectra were measured on Perkin Elmer 710 and 1710 (Fourier transform) spectrometers using chloroform as a solvent. The ^{1}Hmr spectra were recorded on Bruker WH-400 or Nicolet–Oxford H-270 instruments and the chemical shifts are in δ values. Deuteriochloroform was used as the solvent with TMS as internal standard. Low resolution mass spectra were determined on an AEI-MS-902 spectrometer. High resolution mass measurements were made on an AEI-MS-50. Optical rotations were measured on a Perkin Elmer 141 automatic polarimeter. Circular dichroism curves were recorded on a Jasco J-20 spectropolarimeter. Microanalyses were carried out by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia. Column chromatography utilized Merck silica gel 60 G. Petroleum ether refers to the fraction with boiling range 30–60°C. The hplc chromatography was performed on a Waters LC-500 instrument.

17-Methylene-5β-androst-14-en-3,16-dione-3,3-ethylene ketal (2)

From 1[3]

A mixture of ketone **1** (80 mg, 0.23 mmol), sodium bicarbonate (50 mg), and benzeneselenic anhydride (208 mg, 0.58 mmol) in chlorobenzene (2 mL) was heated at 70°C with stirring for 20 h. The mixture was then evaporated and the oily residue dissolved in ethyl ether and filtered. Evaporation of the solvent and purification by preparative layer chromotography with ether – petroleum ether (1:1, v/v) yielded 34 mg (42.5%) of pure **2**; mp 146°C (hexane); $[\alpha]_D$ +221 ± 6° (*c* 0.2320, CH_2Cl_2); uv λ_{max} (EtOH): 249 nm (*c* = 2.32 × 10); ir ν_{max} (KBr): 1695 cm^{-1}; ^{1}Hmr δ: 1.07 (3H, s), 1.27 (3H, s), 1.3–2.05 (16H, m), 2.47 (1H, dt, *J* = 4, 10 Hz), 3.93 (4H, 2), 5.23 (1H, s), 5.97 (2H, s); ms *m/z*: 342 (M^+), 327, 125, 99. High resolution molecular weight determination calcd. for $C_{22}H_{30}O_3$: 342.2197; found: 342.2199. *Anal.* calcd. for $C_{22}H_{30}O_3$: C 77.21, H 8.83; found: C 77.16, H 8.59.

From 12, Method A

A mixture of enone **12** (344 mg, 1 mmol), sodium bicarbonate (250 mg), and benzeneselenic anhydride (360 mg, 1 mmol) in chlorobenzene (9 mL) was heated at 60°C with stirring for 72 h. The reaction mixture worked up and purified as above gave 131 mg (38%) of dienone **2**.

From 12, Method B

A solution of lithium hexamethyldisilylamide was prepared by adding 5.67 mL (9.07 mmol) of a solution of *n*-butyllithium (1.6 M, hexanes) to a solution of hexamethyldisilazane (3.34 mL, 15.1 mmol) in dry THF (15 mL) at −40°C (CH_3CN/CO_2 bath), and added to a solution of the α,β-unsaturated ketone **1** (2.60 g, 7.56 mmol) in dry THF (15 mL) under Ar atmosphere. After 15 min at −40°C, the reaction was quenched with an excess of TMSCl (4.8 mL, 38 mmol) and allowed to warm up to room temperature. The above solution was then added to a solution of 2,3-dicyano-4,5-dichlorobenzoquinone (2.06 g, 9.07 mmol) in CH_3CN (150 mL) at room temperature. After stirring for 1 h, the resulting black mixture was evaporated to dryness, redissolved in 200 mL ethyl acetate, and washed with NaOH (3×, 100 mL, 10% aqueous) and brine (2×, 100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a brown foam. This crude product was then purified on a short silica gel column using ethyl acetate – toluene (5:95, v/v) to yield 2.19 g (84%) of the cross-conjugate diene **2**.

5β-Androstane-3,17-dione (6)

A solution of androstenedione (**5**) (5.72 g, 20 mmol) in 2-propanol (500 mL) containing 10% $Pd/CaCO_3$ (500 mg) was stirred under H_2 for 5 h. The catalyst was removed by filtration through Celite and washed with hot 2-propanol (2 × 50 mL). The combined filtrate and washings were evaporated to leave a colourless oil. The reaction yielded a mixture of 5α and 5β isomers of androstanedione. The mixture was separated by hplc chromatography with ethyl acetate – petroleum ether (2:3, v/v) to yield 3.84 g (67%) of pure **6** and 1.60 g (28%) of pure **7**.

The physical properties of **6** are as follows: mp 131.0–132.5°C (ligroin); $[\alpha]_D$ 106.2 ± 2° (*c* 1.0165, $CHCl_3$); cd (MeCN, $c = 6.58 \times 10^{-3}$): 280 (+2.92); ir ν_{max}: 1725, 1705 cm^{-1}; ^{1}Hmr δ: 0.9 (3H, s), 1.06 (3H, s), 1.15–2.23 (16H, m), 2.32 (2H, dt, *J* = 6, 16 Hz), 2.47 (1H, dd, *J* = 8, 20 Hz), 2.68 (2H, t, *J* = 16 Hz); ms *m/z*: 288 (M^+), 273, 255. High resolution molecular weight determination calcd. for $C_{19}H_{28}O_2$: 288.2089; found: 288.2086. *Anal.* calcd. for $C_{19}H_{28}O_2$: C 79.12, H 9.79; found: C 78.86, H 9.80.

And for **7**: mp 133.5–134.0°C (ether/pentane); $[\alpha]_D$ 116 ± 2.5° (*c* 1.0266, $CHCl_3$); cd (MeCN, $c = 7.229 \times 10^{-3}$): 286 (+5.15); ir ν_{max} (KBr): 1725, 1705 cm^{-1}; ^{1}Hmr δ: 0.89 (3H, s), 1.05 (3H, s), 1.23–2.48 (22H, m); ms *m/z*: 288 (M^+), 270, 255. High resolution molecular weight determination calcd. for $C_{19}H_{28}O_2$: 288.2089; found: 288.2093. *Anal.* calcd. for $C_{19}H_{28}O_2$: C 79.12, H 9.79; found: C 78.96, H 9.69.

5β-Androstane-3,17-dione-3,3-ethylene ketal (8)

To a solution of **6** (4.3 g, 14.9 mmol) in benzene (200 mL) was added *p*-toluenesulfonic acid (50 mg) and ethylene glycol (0.923 g, 14.9 mmol). The mixture was heated under reflux with azeotropic removal of H_2O for 3 h. The mixture was cooled, diluted with petroleum ether, washed with $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silical gel with ether – petroleum ether (2:3, v/v) to give the desired product (**8**) (3.77 g, 76%) and diketal (**9**) (0.58 g, 10.3%) in addition to some unreacted starting diketone **6** (0.22 g, 5%).

The physical properties of **8** are as follows: mp 130.5–131.0°C; $[\alpha]_D$ +96 ± 4° (*c* 0.2035, EtOH); ir ν_{max}: 1725 cm^{-1}; ^{1}Hmr δ: 0.87 (3H, s), 0.99 (3H, s), 1.09–2.07 (20H, m), 2.1 (1H, t, *J* = 8 Hz), 2.45 (1H, dd, *J* = 8, 20 Hz), 3.94 (4H, s); ms *m/z*: 332 (M^+), 317, 276, 125, 99. High resolution molecular weight determination calcd. for $C_{21}H_{32}O_3$: 332.2350; found: 332.2350. *Anal.* calcd. for $C_{21}H_{32}O_3$: C 75.92, H 9.71; found: C 76.00, H 9.76.

The physical properties of **9** are as follows: mp 58.0–59.0°C (methanol); $[\alpha]_D$ −6.19 ± 0.7° (*c* 1.115, CH_2Cl_2); ^{1}Hmr δ: 0.85 (3H, s), 0.96 (3H, s), 1.00–2.10 (22H, m), 3.80–4.00 (8H, m); ms *m/z*: 376 (M^+), 125, 99. High resolution mass measurement calcd. for $C_{23}H_{36}O_3$: 376.2614; found: 376.2614. *Anal.* calcd. for $C_{23}H_{36}O_3$: C 73.47, H 9.65; found: C 73.75, H 9.16.

17-Methylene-5β-androstan-3-one-3,3-ethylene ketal (10)

To a bright yellow mixture of methyltriphenylphosphonium bromide (5.86 g, 16.4 mmol) and potassium *tert*-butoxide (1.76 g, 15.6 mmol) in THF (20 mL) was added ketone **8** (3.69 g, 11.1 mmol) in THF (100 mL). After refluxing for 5 h, the mixture was portioned between hexane (220 mL) and water (180 mL). The organic layer was washed with 50% MeOH (200 mL) and brine (200 mL), dried ($MgSO_4$), and evaporated *in vacuo*. Column chromatography of the crude product with 5% of ethyl ether in petroleum ether (v/v) yielded **10** (3.34 g, 91%) as a colorless oil; $[\alpha]_D$ +38.2° (*c* 0.2120, EtOH); ir ν_{max}: 1655 cm^{-1}; ^{1}Hmr δ: 0.77 (3H, s), 0.98 (3H, s), 1.0–2.53 (22H, m), 3.95 (4H, s), 4.61 (1H, br s), 4.63 (1H, br s); ms *m/z*: 330 (M^+), 315, 268, 125, 99. High resolution molecular weight determination calcd. for $C_{22}H_{34}O_2$: 330.2559; found: 330.259. *Anal.* calcd. for $C_{22}H_{32}O_2$: C 80.01, H 10.38; found: C 80.20, H 10.50.

16-Hydroxy-17-methylene-5β-androstane-3-one-3,3-ethylene acetal (11) and 17-methylene-5β-androstane-3,16-dione-3,3-ethylene ketal (12)

From 10

To a suspension of selenium dioxide (558 mg, 5 mmol) in methylene dichloride (25 mL) at room temperature was added a 70% solution of *tert*-butyl hyperoxide (1.93 mL, 1.82 g, 20 mmol). The mixture was stirred at room temperature for 1 h. The steroidal olefin **10** (3.30 g, 10 mmol) in methylene dichloride (55 mL) was then added and stirring was continued for 5 h. The reaction mixture was diluted with ethyl ether (500 mL) and washed with 10% sodium hydroxide (2 × 250 mL) and water, separated, dried ($MgSO_4$), and evaporated. Chromatographic separation of the reaction mixture with ether – petroleum ether (3.7 v/v) gave allylic alcohol **11** (2.59 g, 75%) and unsaturated ketone **12** (0.61 g, 18%).

The physical properties of **11** are as follows: mp 167–168°C (EtOH); $[\alpha]_D$ 2.4 ± 0.3° (*c* 2.852, CH_2Cl_2); ir ν_{max}: 3580 cm^{-1}; ^{1}Hmr δ: 0.77 (3H, s), 0.97 (3H, s), 1.06–1.91 (20H, m), 1.98 (1H, t, *J* = 12 Hz), 3.92 (4H, s), 4.63 (1H, br s), 4.83 (1H, d, *J* = 2 Hz), 5.03 (1H, d, *J* = 2 Hz); ms *m/z*: 346 (M^+), 328, 313, 125, 99. High resolution molecular weight determination calcd. for $C_{22}H_{34}O_3$: 346.2499; found: 346.2503. *Anal.* calcd. for $C_{22}H_{34}O_3$: C 76.37, H 9.91; found: C 76.31, H 9.88.

17-Methylene-5β-androstan-3,16-dione-3,3-ethylene ketal (12)

From 11

To a solution of oxalyl chloride (670 μL, 975 mg, 7.68 mmol) in methylene dichloride (15 mL) at −78°C was added a solution of dimethyl sulfoxide (1.7 mL, 1.2 g, 15.36 mmol) in methylene dichloride (5 mL) and the mixture stirred at −78°C for 5 min. A solution of allylic alcohol (**11**) (2.39 g, 6.9 mmol) in methylene chloride was then added to this mixture at −78°C. After stirring for 15 min, neat triethylamine (2.85 mL, 2.07 mmol) was added. The solution was allowed to warm to −20°C and held at this temperature for 3 h. The reaction mixture was diluted with chloroform (75 mL), washed with 10% hydrochloric acid, water, sodium bicarbonate, and again with water. After drying ($MgSO_4$), and removal of the solvent the product was purified by column chromatography to give pure **12** (2.04 g, 86%); mp 99.5–100°C (isopropanol); $[\alpha]_D$ −119 ± 0.3° (*c* 0.2771, EtOH); uv λ_{max}: 227 (3.66); ir ν_{max}: 1722 cm^{-1}; ^{1}Hmr δ: 0.95 (3H, s), 1.01 (3H, s), 1.09–2.07 (19H, m), 2.24 (1H, dd, *J* = 18, 8 Hz), 3.94 (4H, s), 5.0 (1H, d, *J* = 1 Hz), 5.79 (1H, d, *J* = 1 Hz); ms *m/z*: 344 (M^+), 329, 287, 195, 125, 99. High resolution molecular weight determination calcd. for $C_{22}H_{32}O_3$: 344.2351; found: 344.2351. *Anal.* calcd. for $C_{22}H_{32}O_3$: C 76.71, H 9.36; found: C 76.49, H 9.35.

17-Cyanomethyl-5β-androstan-3,16-dione-3,3-ethylene ketal (13)

A mixture of enone **12** (1.85 g, 5.4 mmol), dimethylformamide (85 mL), potassium cyanide (0.84 g, 12.5 mmol in 5.6 mL H_2O), and ammonium chloride (0.5 g, 9.4 mmol in 5.6 mL H_2O) was refluxed for 3 h, cooled, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and evaporated. The crude product was purified on a short chromatography column with ether – petroleum ether (1:1, v/v), yielding pure cyano derivative **13** (1.82 g, 91.2%); mp 162–162.5°C (EtOH); $[\alpha]_D$ −126 ± 0.1° (*c* 1.3796, EtOH); ir ν_{max}: 2310, 1730 cm^{-1}, ^{1}Hmr δ: 0.77 (3H, s), 0.99 (3H, s), 1.12–1.95 (17H, m), 2.01 (1H, t, *J* = 12 Hz), 2.12–2.35 (4H, m), 2.72 (1H, dd, *J* = 18, 4 Hz), 3.94 (4H, s); ^{13}Cmr (75 MHz, $CDCl_3$) δ: 12.113 (C11), 13.158 (C18), 20.217 (C12), 22.879 (C19), 26.242 (C6), 29.886 (C1), 32.493 (C8), 33.678 (C2), 34.550 (C10), 35.477 (C4), 37.147 (C7), 37.404 (C20), 39.723 (C9), 40.4222 (C5), 41.776 (C13), 50.066 (C14), 58.773 (C17), 63.826 (C15), 63.885 and 64.016 (C3 ethyleneketal), 109.380 (C3), 118.434 (C21), 214.071 (C16); ms *m/z*: 371 (M^+), 356, 314, 125, 99. High resolution molecular weight determination calcd. for $C_{23}H_{33}O_3N$: 371.2460; found: 371.2460. *Anal.* calcd. for $C_{23}H_{33}O_3N$: C 74.36, H 8.95, N 3.77; found: C 74.24, H 9.02, N 3.99.

17-Cyanomethyl-5β-androstane-3,16-dione-3,3,16,16-diethylene diacetal (14)

To a solution of **13** (1.67 g, 4.5 mmol) in a mixture of toluene (100 mL) and benzene (100 mL) was added ethylene glycol (3.1 g, 50 mmol) and *p*-toluenesulfonic acid (50 mg). The mixture was refluxed with azeotropic removal of water for 48 h, then cooled, diluted with petroleum ether, washed with 10% sodium bicarbonate and water, dried ($MgSO_4$), and evaporated to dryness. The crude product was purified on a short column with ether – petroleum ether (1:1, v/v) to afford pure **14** (1.77 g, 94.5%); mp 149.0–149.5°C; $[\alpha]_{365}$ 21.4 ± 0.8°

(*c* 2.9192, CH_2Cl_2); ir ν_{max}: 2250 cm^{-1}, ^{1}Hmr δ: 0.77 (3H, s), 0.95 (3H, s), 1.00–2.20 (2H, m), 2.20–2.40 (2H, m), 3.75 (1H, q, J = 8 Hz), 3.94 (4H, s), 3.88–3.97 (2H, m), 4.0–4.06 (1H, m); ^{13}Cmr (75 MHz, $CDCl_3$) δ: 11.804 (C1), 12.753 (C18), 20.376 (C12), 23.062 (C19), 26.187 (C6), 26.518 (C7), 30.029 (C1), 33.991 (C2), 34.675 (C10), 34.798 (C8), 35.628 (C4), 37.775 (C15), 39.385 (C20), 39.893 (C9), 40.4729 (C5), 41.984 (C13), 51.953 (C14), 55.422 (C17), 63.456 (C16 ethyleneketal), 64.028 and 64.156 (C3 ethyleneketal), 65.266 (C16 ethyleneketal), 115.543 (C16), 109.716 (C3), 119.635 (C21); ms *m/z*: 415 (M^+), 375, 125, 99. High resolution molecular weight determination calcd. for $C_{25}H_{37}O_4N$: 415.2722; found: 415.2726. *Anal.* calcd. for $C_{25}H_{37}O_4N$: C 72.26, H 8.97, N 3.37; found: C 72.36, H 9.10, N 3.40.

20-Oxo-5β-pregnane-3,16-dione-3,3,16,16-diethylene ketal (15)

A solution of nitrile **14** (1.56 g, 3.5 mmol) in benzene (40 mL) was treated with a 1 M solution of diisobutylaluminum hydride in hexane solution (7.2 mL, 7.2 mmol) at room temperature. The mixture was stirred for 0.5 h, then quenched with saturated ammonium chloride solution and diluted with petroleum ether. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The product was purified on a chromatography column with ether – petroleum ether (2.3 /v) yielding pure **15** (1.25 g, 79.6%); mp 143–144°C; $[\alpha]_D$ −10.7° (*c* 0.01366,CCl_2H_2); ir ν_{max}: 1695 cm^{-1}; ^{1}Hmr δ: 0.74 (3H, s), 0.96 (3H, s), 1.03–1.92 (9H, m), 2.0 (1H, t, J = 12 Hz), 2.28 (1H, m), 2.45–2.53 (1H, m), 3.67–3.913 (4H, m), 3.93 (4H, s), 9.71 (1H, m); ms *m/z*: 418 (M^+), 403, 390, 128, 99. High resolution molecular weight determination calcd. for $C_{25}H_{38}O_5$: 418.2719; found: 418.2713. *Anal.* calcd. for $C_{25}H_{38}O_5$: C 71.74, H 9.15; found: C 71.92, H 9.27.

5β-Card-20(22)-enolide-3,16-dione-3,3,16,16-diethylene ketal (16) and R(−)-menthyl-21-hydroxy-3,3,16,16-diethylene-dioxy-24-nor-chol-20(22)-en-23-ate (17)

From ***15***

To a suspension of potassium hydride (244 mg of 22%, 122 mmol) in THF (6 mL) was added over 5 min at room temperature a solution of aldehyde **15** (418 mg, 1 mmol) in THF (6 mL). After hydrogen evolution had ceased, the turbid yellowish solution was stirred for another 15 min. Then freshly distilled anhydrous (*R*)-menthyl glyoxylate (318 mg, 1.5 mmol) in THF (2 mL) was added and the mixture was stirred for 1 h at room temperature. The reaction was quenched with H_2O (0.5 mL), diluted with 5 mL of MeOH, sodium borohydride (190 mg, 5 mmol) was added, and the mixture was stirred for 30 min. Excess of borohydride was decomposed with acetone. Then the reaction mixture was evaporated and partitioned between ethyl acetate (200 mL) and 1 M hydrochloric acid (200 mL). The organic layer was washed with water and sodium bicarbonate, dried ($MgSO_4$), and evaporated to give 970 mg of crude reaction product. Subsequent, careful separation on a chromatography column with ether – petroleum ether (2:3, v/v) yielded butenolide **16** (78 mg, 17.0%) and unsaturated hydroxyester **17** (147 mg, 24.0%).

The physical properties of **17** are as follows: mp 197–198°C (heptane); $[\alpha]_D$ 11.3 ± 0.7° (*c* 2.2629, CH_2Cl_2); ir ν_{max}: 3612, 1704 cm^{-1}; ^{1}Hmr δ: 0.75 (3H, d, J = 8 Hz), 0.85–0.98 (12H, m), 1.03–2.07 (30H, m), 2.28 (1H, t, J = 6 Hz), 3.72–3.95 (8H, m), 4.21 (1H, dd, J = 14, 8 Hz), 4.48 (1H, dd, J = 14, 8 Hz), 4.74 (1H, dt, J = 10, 2 Hz), 6.19 (1H, s); ms *m/z*: 614 (M^+), 552, 476, 125, 99. High resolution molecular weight determination calcd. for $C_{37}H_{58}O_7$: 614.4196; found: 614.4189. *Anal.* calcd. for $C_{37}H_{58}O_7$: C 72.32, H 9.15; found: C 72.12, H 9.38.

And for **16**: mp 94–95°C (EtOH); $[\alpha]_{365}$ (*c* 1.2505, EtOH); ir ν_{max}: 1782, 1747 cm^{-1}; ^{1}Hmr δ: 0.77 (3H, s), 0.98 (3H, s), 1.05–2.03 (20H, m), 3.64 (1H, s), 3.72–3.95 (4H, m), 3.93 (4H, s), 4.77 (2H, d, J = 2 Hz), 6.04 (1H, s); ms *m/z*: 458 (M^+), 414, 305, 125, 99. High resolution molecular weight determination calcd. for $C_{27}H_{38}O_6$: 458.2970; found: 458.2969. *Anal.* calcd. for $C_{27}H_{38}O_6$: C 70.74, H 8.30; found: C 70.98, H 8.49.

5β-Cardanolide-3,3,16,16-diethylene ketal (18)

A solution of **17** (100 mg, 0.16 mmol) in 2-propanol (20 mL) containing 10% Pd/$CaCO_3$ (30 mg) was stirred under H_2 for 2 h. The catalyst was removed by filtration and washed with hot propanol (10 mL). The combined filtrate and washings were evaporated. The crude reduction product was hydrolyzed in a mixture of 10% NaOH (50 mL) and ethanol (50 mL) for 10 min at reflux. Then the solution was diluted with water (50 mL) and, after evaporation of ethanol, neutralized (10% HCl) and extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate, dried ($MgSO_4$), and evaporated *in vacuo*. The column chromatography with ether – petroleum ether (1:1, v/v) yielded pure **18** (47 mg, 62.5%); ir ν_{max}: 1772 cm^{-1}; ^{1}Hmr δ: 0.84 (3H, s), 0.95 (3H, s), 1.04–1.92 (2H, m), 1.98 (1H, t, J = 12 Hz), 2.35–2.55 (2H, m), 2.78–2.89 (1H, m), 3.75–3.95 (9H, m), 4.45 (1H, t, J = 6 Hz); ms *m/z*: 460 (M^+), 375, 305, 125, 99. High resolution molecular weight determination calcd. for $C_{27}H_{40}O_6$: 460.2829; found: 460.2827. *Anal.* calcd. for $C_{27}H_{40}O_6$: C 70.43, H 8.69; found: C 70.40, H 8.59.

20,20-(1′, 3′-Propylene)-dithio-5β-pregn-14-ene-3-one-3, 3-ethylene ketal (19)

To a solution of 1,3-dithiane (77 mg, 0.64 mmol) and HMPA (222 μL, 1.28 mmol) in THF (6 mL), *n*-BuLi in hexane (1.6 M, 0.42 mL, 0.67 mmol) was added and the mixture was stirred at −25°C for 2 h to form anion. Then cross-conjugated ketone **2** (219 mg, 0.64 mmol) in THF (7 mL) was added and the mixture was allowed to warm up slowly to room temperature and stirred for another hour. Quenching with aqueous ammonium chloride followed by extraction (methylene dichloride), evaporation, and chromatographic separation yielded pure dithio derivative **18** (159 mg, 86.1%) as a mixture of two 17-isomers (2:1 ratio). The separation of the isomers proved to be very difficult and only a small sample of the pure major isomer was isolated for the purpose of characterization; mp 186°C; ir ν_{max} ($CHCl_3$): 1700 cm^{-1}; uv λ_{max} (EtOH): 232 nm; ^{1}Hmr δ: 1.04 (3H, s), 1.09 (3H, s), 1.26–2.27 (10H, m), 2.43–2.51 (2H, m), 2.87 (4H, m), 3.94 (4H, s), 3.8 (1H, dd), 5.75 (1H, s); ms *m/z*: 462 (M^+), 343, 330, 216, 133, 125, 99. *Anal.* calcd. for $C_{26}H_{38}O_3S_2$: C 67.53, H 8.23; found: C 67.52, H 8.36.

17-Cyanomethyl-5-β-androstene-3,16-dione-3,3-ethylene ketal (20)

A solution of the diene **2** (443 mg, 130 mmol) in dry benzene (12 mL) was prepared at room temperature and to this was quickly added 1.30 mL (1.30 mmol) of a solution of diethylaluminum cyanide (1 M, toluene). Upon addition of the diethylaluminum cyanide the solution turned deep orange and quickly faded (in about 30 s) to a light orange color. After stirring for 30 min at room temperature, the reaction was quenched with NaOH (2 mL, 10% aqueous), which caused the orange color to disappear. This mixture was then diluted with ethyl acetate (100 mL) and washed with NaOH (2 × 50 mL, 10% aqueous), brine (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a white foam. This crude product was purified on a short silica gel column using ethyl acetate – hexanes (1:4, v/v) to yield 360 mg (75%) of the unsaturated nitrile **20** as a mixture of C17 epimers. Gas–liquid chromatographic analysis of this mixture showed that the ratio of isomers was about 2:1. Repeated attempts to separate these isomers by column chromatography (hplc) was only partially successful. It was possible to enrich the mixture in the major isomer enough that the minor isomer could not be detected by ^{1}Hmr (but could be detected by capillary gas chromatography). The data given here are for this mixture.

The physical properties of the nitrile **20** are as follows: mp 54.0–55.0°C (hexanes); ir ν_{max}: (KBr): 2342, 1703, 1605 cm^{-1}; uv λ_{max}: 233 nm (9.64 × 10^3, ethanol); ^{1}Hmr δ: 1.05 (3H, s), 1.24 (3H, s), 0.83–2.35 (17H, m), 2.26 (1H, q, J = 18, 16 Hz, C20-H), 2.45 (1H, dd, J = 16.4 Hz, C17-H), 2.49 (1H, m, C8-H), 2.92 (1H, dd, J = 18.4 Hz, C20-H′), 3.93 (4H, s, C3 ketal), 5.80 (1H, s, C15-H); ms *m/z*: 369 (M^+), 125 ($C_7H_9O_2$), 99 ($C_5H_7O_2$). High resolution mass measurement for $C_{23}H_{31}O_3N$: 369.2292; found: 369.2298. *Anal.* calcd. for $C_{23}H_{31}O_3N$: C 74.79, H 8.40, N 3.79; found: C 74.40, H 8.86, N 3.58.

16-Hydroxy-17-cyanomethyl-5β-androstene-3-one-3,3-ethylene ketal (21)

The unsaturated cyanoketone **20** (mixture of C17 epimer, 1 g, 2.71 mmol) was dissolved in a 0.4 M solution (36 mL) of cerium

chloride hydrate in methanol. Then sodium borohydride (266 mg, 7 mmol) was added and the reaction was stirred at room temperature for 30 min. After evaporation of the solvent the residue was redissolved in ethyl acetate, washed with water, dried over $MgSO_4$, and evaporated again. Crude product (1.05 g) consisting of four isomeric allylic alkaloids was used in the next transformation without further purification.

A small sample of the major alcohol **21** was obtained after hplc separation; ir (neat) ν: 3600 (br), 2290; ^{1}Hmr δ: 0.98 (3H, s), 1.00 (3H, s), 1.24–2.11 (19H, m), 2.44 (1H, dd), 2.65 (1H, dd), 3.92 (4H, s), 4.46 (1H, m), 5.20 (1H, s); ms *m/z*: 371 (M^+), 353, 125, 99. *Anal.* calcd. for $C_{23}H_{33}NO_3$. C 74.36, H 8.95, N 3.77; found: C 74.10, H 8.87, N 3.90.

16-Acetoxy-17β-cyanomethyl-5β-androstene-3-one-3,3-ethylene ketal (22)

The crude mixture of the allylic alkaloids (**21** and isomers, 440 mg, 1.19 mol) was dissolved in methylene chloride (20 mL) and treated with acetic anhydride (380 μl, 1 mmol) in the presence of dimethylaminopyridine (146 mg, 1.2 mmol) at room temperature for 15 min. The reaction mixture was subsequently washed with 10% hydrochloric acid, water, and sodium bicarbonae, dried ($MgSO_4$), and evaporated to dryness. The column chromatography with ether – petroleum ether (3:7, v/v) of the crude product consisting of four isomeric allylic acetates yielded a pure major isomer **22** (255 mg, 68.1% from **17** cyanoketone; 54.2% from the mixture of **17**α and **17**β isomers); mp 158°C; ir ν_{max}: 2252, 1730 cm^{-1}; ^{1}Hmr δ: 0.98 (3H, s, C19), 1.06 (3H, s, C18), 1.26–2.14 (17H, m), 2.10 (3H, s, acetate), 2.2 (1H, m, C17), 2.47 (1H, dd, C20), 2.61 (1H, dd, C20), 3.92 (4H, s, ketal), 5.2 (1H, s, C15), 5.46 (1H, bd, C16); ms *m/z*: 413 (M^+), 370, 353, 338, 125, 99. *Anal.* calcd. for $C_{25}H_{35}NO_3$: C 72.64, H 8.47, 3.39; found: C 72.60, H 8.40, N 3.19.

17β-Cyanomethyl-4β-androstene-3-one-3,3-ethylene ketal (23)

A yellow solution of the acetate **22** (100 mg, 0.240 mmol) and tetrakis(triphenylphosphine) palladium (0) (9275 mg, 0.240 mmol) in 4 mL of THF was stirred at room temperature under an argon atmosphere. After 10–15 min, the mixture turned black, sodium borohydride (100 mg, 2.63 mmol) was added, and the stirring was continued until the starting material disappeared (tlc, 1–2 h). After the excess of sodium borohydride was decomposed with acetone, the reaction mixture was evaporated to dryness and purified on a short silica gel column with ether – petroleum ether (1:4, v/v) to yield 68 mg (79.1%) of cyano derivative **23**.

The physical properties of **23** are as follows: ir ν_{max}: 2248 cm^{-1}; ^{1}Hmr δ: 0.90 (3H, s, C18), 0.98 (3H, s, C19), 1.20–2.05 (18H, m), 2.165 (1H, m), 2.395 (2H, dd), 2.5 (1H, m), 3.94 (4H, s), 5.14 (1H, s); ms *m/z*: 355 (M^+), 340, 315, 298, 125, 99. High resolution mass measurement calcd. for $C_{23}H_{33}NO_2$: 355.2511; found: 355.2520.

20-Oxo-5β-pregn-14-ene-3-one-3,3-ethylene ketal (24)

A solution of nitrile **23** (355 mg, 1 mmol) in benzene (10 mL) was treated with a 1 M solution of diisobutylaluminum hydride in hexane solution (1.2 mL, 1.2 mmol) at room temperature. The mixture was stirred for 30 min, then quenched with saturated ammonium chloride solution and diluted with petroleum ether. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The chromatographic separation with ether – petroleum ether (3:7, v/v) yielded pure aldehyde **24** (290 mg, 81.0%); ir ν_{max}: 1719 cm^{-1}; ^{1}Hmr δ: 0.82 (3H, s, C18), 0.98 (3H, s, C19), 1.17–2.11 (1H, m), 2.27 (1H, m), 2.45 (2H, m), 2.56 (1H, m), 3.94 (4H, s), 5.18 (1H, s, C15), 9.8 (1H, 5); ms *m/z*: 358 (M^+), 330, 314, 125, 99. High resolution mass measurement calcd. for $C_{23}H_{34}O_3$: 358.2508; found: 358.2516.

5β-Card-14,20(22)-dienolide-3-one-3,3-ethylene ketal (23) and R *(−)-methyl-21-hydroxy-3,3-ethylenedioxy-24-nor-chol-14,20(22)-dien-23-153 (25)*

To a suspension of potassium hydride (50 mg of 30%, 0.36 mmol) in THF (2 mL), at room temperature, was slowly added a solution of aldehyde **24** (107 mg, 0.3 mmol) in THF (2 mL). After hydrogen evolution had ceased, the turbid yellow suspension was stirred for 20 min and the solution of freshly distilled anhydrous (*R*)-methylglyoxylate (95.4 mg, 0.45 mmol) in THF (2 mL) was added. The reaction was stirred for another hour at room temperature, then quenched with water (0.15 mL), diluted with methanol (1.5 ml), and treated with sodium borohydride (60 mg, 1.58 mmol). After 30 min of stirring the excess of sodium borohydride was decomposed with acetone. Then the reaction mixture was evaporated and partitioned between ethyl acetate (60 mL) and 10% hydrochloric acid (60 mL). The organic layer was washed with water and sodium bicarbonate, dried ($MgSO_4$), and evaporated to dryness. Separation of the crude product on a chromatography column with ether – petroleum ether (2:3, v/v) yielded butenolide **3** (29 mg, 24.4%) and hydroxyester **26** (33 mg, 19.9%).

The physical properties of **3** are as follows: ir ν_{max}: 1782, 1747, 1632 cm^{-1}; ^{1}Hmr δ: 0.81 (3H, s, C18), 0.97 (3H, s, C19), 1.23–2.11 (17H, m), 2.47 (2H, m, C16), 2.8 (1H, t, C17), 3.94 (4H, s, ketal), 4.77 (2H, dd, C2), 5.25 (1H, s, C15), 5.90 (1H, s, C22); ms *m/z*: 398 (M^+), 354, 125, 99. High resolution mass measurement calcd. for $C_{25}H_{34}O_4$: C 75.38, H 8.54; found: C 75.91, H 8.54.

And for the ester **25**: ir ν_{max}: 1690 cm^{-1}; ^{1}Hmr δ: 0.73–0.99 (15H, m), 1.23–2.22 (27H, m), 2.33 (2H, m, C16), 3.94 (4H, s, ketal), 4.25 (2H, t, C21), 4.29 (1H, s, OH), 4.71 (1H, dt), 5.17 (1H, s, C15), 6.17 (1H, s, C22); ms *m/z*: 554 (M^+), 536, 416, 398, 380, 354, 284, 125, 99. High resolution mass measurement calcd. for $C_{35}H_{54}O_5$: 554.3971; found: 554.3977. *Anal.* calcd. for $C_{35}H_{54}O_5$: C 75.77, H 9.81; found: C 75.70, H 9.62.

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Appendix

X-ray crystallographic analysis of the compound structure 22

A crystal bounded by the six faces (followed by the distances in mm between parallel faces): (0 0 1), 0.020, ±(0 1 −1), 0.30, (1 0 −1), 0.53 was mounted in a general orientation. Unit-cell parameters were refined by least squares on 2 sin θ/λ values for 25 reflections (2θ = 20–33°) measured on a diffractometer with Mo-$K\alpha$ radiation ($\lambda(K\alpha_1)$ = 0.70930, $\lambda(K\alpha_2)$ = 0.71359 Å). Crystal data at 22°C are as follows:

$C_{25}H_{35}NO_4$ f.w. = 413.56

Monoclinic, a = 6.526(1), b = 10.728(2), c = 17.011(2) Å, β = 94.867(8)°, V = 1137.5(3) Å^3, Z = 2, ρ_c = 1.207 Mg m^{-3}, $F(000)$ = 448, μ(Mo-$K\alpha$) = 0.75 cm^{-1}. Absent reflections: $0k0$, k odd, space group $P2_1$.

Intensities were measured with graphite-monochromated Mo-$K\alpha$ radiation on an Enraf–Nonius CAD4-F diffractometer. An ω–2θ scan at 1.3–10.0° min^{-1} over a range of (0.85 + 0.35 tan θ) degrees in ω (extended by 25% on both sides for background measurement) was employed. Data were measured to 2θ = 55°. The intensities of 3 check reflections, measured every 3600 s throughout the data collection, showed only small (<4%) random variations. Of the 2351 independent reflections measured and processed,[3] 1033(43.9%) had intensities greater than or equal to 2σ(I) above background where σ^2(I) = S + 2B + (0.04(S–B))^2 with S = scan count and B = normalized background count.

Since the molecule is chiral the space group was assumed to be $P2_1$. The structure was solved by direct methods, all non-hydrogen atoms being positioned from an E-map. In the

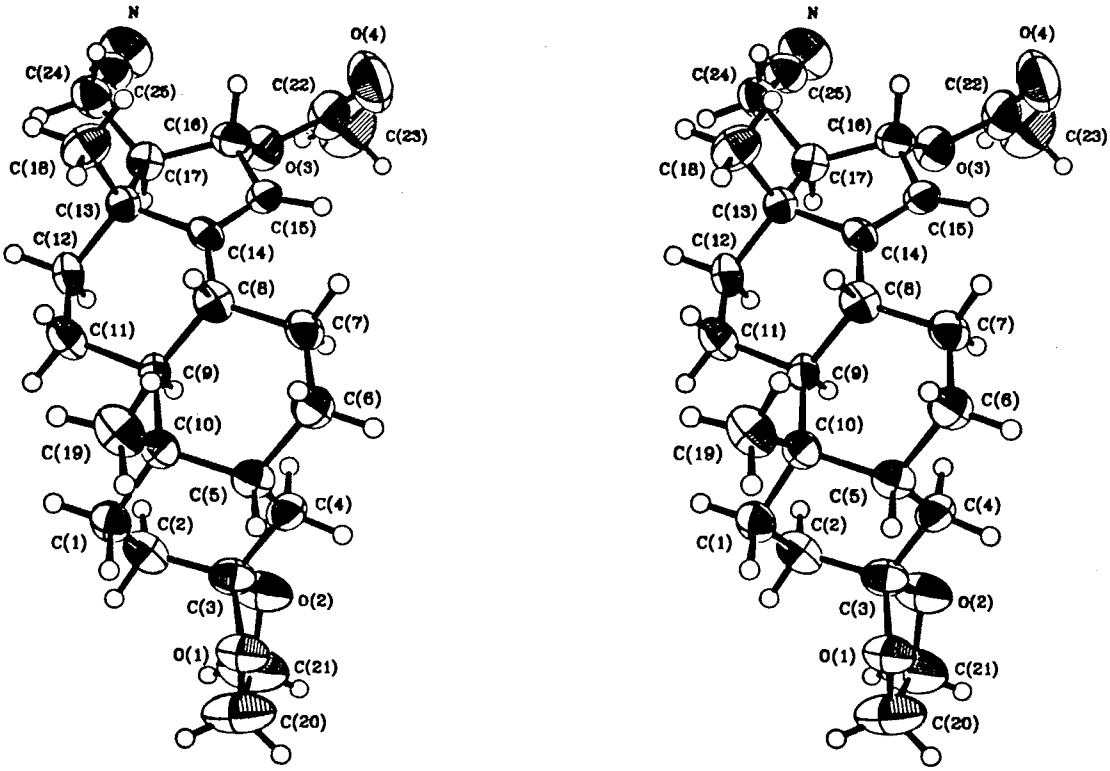
[3]The computer programs used include locally written programs for data processing and locally modified versions of the following: ORFLS, full-matrix least squares, and ORFFE, function and errors, by W. R. Busing, K. O. Martin and H. A. Levy; FORDAP, Patterson and Fourier syntheses, by A. Zalkin; ORTEP II, illustrations, by C. K. Johnson.

TABLE 1. Final positional (fractional × 10^4) and isotropic thermal parameters (U × 10^3 Å^2) with estimated standard deviations in parentheses

Atom	x	y	z	U_{eq}
O(1)	7687(7)	7306	10745(3)	57
O(2)	4912(8)	5964(6)	10541(3)	67
O(3)	3110(7)	2317(6)	6508(3)	56
O(4)	5397(12)	733(7)	6357(4)	103
N	−628(11)	2940(8)	4955(4)	84
C(1)	6843(10)	8182(8)	9053(4)	44
C(2)	5308(11)	7555(8)	9576(4)	49
C(3)	6417(11)	6668(8)	10136(4)	47
C(4)	7836(10)	5759(8)	9729(4)	45
C(5)	9324(9)	6407(8)	9196(3)	39
C(6)	10620(10)	5417(8)	8790(4)	47
C(7)	9261(9)	4669(8)	8174(4)	44
C(8)	8015(9)	5501(8)	7578(4)	39
C(9)	6749(9)	6539(7)	7967(3)	33
C(10)	8177(9)	7288(8)	8590(3)	38
C(11)	5529(10)	7335(8)	7329(4)	48
C(12)	3958(10)	6548(8)	6797(4)	45
C(13)	5041(10)	5474(8)	6395(4)	38
C(14)	6527(10)	4783(8)	6999(4)	33
C(15)	6334(10)	3560(7)	6922(4)	41
C(16)	4671(11)	3219(8)	6275(4)	44
C(17)	3443(10)	4434(8)	6110(4)	42
C(18)	6325(11)	5966(8)	5732(4)	59
C(19)	9798(10)	8093(8)	8192(4)	52
C(20)	6387(15)	7491(10)	11377(4)	95
C(21)	4574(15)	6586(10)	11230(5)	96
C(22)	3689(18)	1124(9)	6495(5)	70
C(23)	1830(17)	305(9)	6706(6)	114
C(24)	2380(11)	4580(8)	5278(4)	55
C(25)	674(13)	3658(9)	5094(5)	58

TABLE 2. Bond lengths (Å) with estimated standard deviations in parentheses

Bond	Length (Å)	Bond	Length (Å)
O(1)—C(3)	1.425(7)	C(8)—C(9)	1.548(8)
O(1)—C(20)	1.416(8)	C(8)—C(14)	1.507(8)
O(2)—C(3)	1.429(8)	C(9)—C(10)	1.551(8)
O(2)—C(21)	1.381(8)	C(9)—C(11)	1.532(8)
O(3)—C(16)	1.454(7)	C(10)—C(19)	1.532(8)
O(3)—C(22)	1.331(9)	C(11)—C(12)	1.533(8)
O(4)—C(22)	1.190(10)	C(12)—C(13)	1.527(8)
N—C(25)	1.131(8)	C(13)—C(14)	1.519(8)
C(1)—C(2)	1.520(9)	C(13)—C(17)	1.549(8)
C(1)—C(10)	1.533(8)	C(13)—C(18)	1.532(8)
C(2)—C(3)	1.478(9)	C(14)—C(15)	1.324(8)
C(3)—C(4)	1.524(9)	C(15)—C(16)	1.494(8)
C(4)—C(5)	1.522(8)	C(16)—C(17)	1.527(9)
C(5)—C(6)	1.535(8)	C(17)—C(24)	1.519(9)
C(5)—C(10)	1.532(8)	C(20)—C(21)	1.498(10)
C(6)—C(7)	1.522(8)	C(22)—C(23)	1.525(11)
C(7)—C(8)	1.516(8)	C(24)—C(25)	1.470(11)



Structure 22

TABLE 3. Bond angles (deg) with estimated standard deviations in parentheses

Bonds	Length (deg)	Bonds	Length (deg)
C(3)—O(1)—C(20)	107.4(6)	C(5)—C(10)—C(19)	110.8(5)
C(3)—O(2)—C(21)	108.0(5)	C(9)—C(10)—C(19)	110.8(5)
C(16)—O(3)—C(22)	116.5(6)	C(9)—C(11)—C(12)	111.6(5)
C(2)—C(1)—C(10)	115.0(5)	C(11)—C(12)—C(13)	113.2(5)
C(1)—C(2)—C(3)	112.2(6)	C(12)—C(13)—C(14)	109.5(5)
O(1)—C(3)—O(2)	104.7(5)	C(12)—C(13)—C(17)	112.6(5)
O(1)—C(3)—C(2)	111.2(6)	C(12)—C(13)—C(18)	110.5(6)
O(1)—C(3)—C(4)	109.1(6)	C(14)—C(13)—C(17)	101.7(5)
O(2)—C(3)—C(2)	111.0(6)	C(14)—C(13)—C(18)	109.7(5)
O(2)—C(3)—C(4)	108.3(6)	C(17)—C(13)—C(18)	112.5(5)
C(2)—C(3)—C(4)	112.3(6)	C(8)—C(14)—C(13)	120.1(5)
C(3)—C(4)—C(5)	112.8(6)	C(8)—C(14)—C(15)	128.1(6)
C(4)—C(5)—C(6)	109.0(6)	C(13)—C(14)—C(15)	111.8(6)
C(4)—C(5)—C(10)	114.1(5)	C(14)—C(15)—C(16)	111.6(6)
C(6)—C(5)—C(10)	111.1(5)	O(3)—C(16)—C(15)	113.8(5)
C(5)—C(6)—C(7)	112.9(5)	O(3)—C(16)—C(17)	106.2(5)
C(6)—C(7)—C(8)	112.1(5)	C(15)—C(16)—C(17)	103.6(5)
C(7)—C(8)—C(9)	113.0(5)	C(13)—C(17)—C(16)	104.8(5)
C(7)—C(8)—C(14)	112.9(5)	C(13)—C(17)—C(24)	116.0(5)
C(9)—C(8)—C(14)	109.7(5)	C(16)—C(17)—C(24)	115.7(5)
C(8)—C(9)—C(10)	112.3(5)	O(1)—C(20)—C(21)	104.9(6)
C(8)—C(9)—C(11)	109.9(5)	O(2)—C(21)—C(20)	106.7(6)
C(10)—C(9)—C(11)	114.7(5)	O(3)—C(22)—O(4)	126.3(9)
C(1)—C(10)—C(5)	106.6(5)	O(3)—C(22)—C(23)	109.6(9)
C(1)—C(10)—C(9)	111.6(5)	O(4)—C(22)—C(23)	124.0(8)
C(1)—C(10)—C(19)	106.5(5)	C(17)—C(24)—C(25)	112.4(6)
C(5)—C(10)—C(9)	110.5(5)	N—C(25)—C(24)	179.4(8)

TABLE 4. Intra-annular torsion angles (deg) with standard deviations in parentheses

Atoms	Angle (deg)
C(20)—O(1)—C(3)—O(2)	−28.5(8)
C(21)—O(2)—C(3)—O(1)	28.3(8)
C(3)—O(2)—C(21)—C(20)	−17.1(9)
O(1)—C(20)—C(21)—O(2)	−0.6(9)
C(3)—O(1)—C(20)—C(21)	18.1(9)
C(17)—C(13)—C(14)—C(15)	16.6(8)
C(13)—C(14)—C(15)—C(16)	−1.4(9)
C(14)—C(15)—C(16)—C(17)	−14.7(8)
C(15)—C(16)—C(17)—C(13)	24.1(6)
C(14)—C(13)—C(17)—C(16)	−24.4(6)
C(10)—C(1)—C(2)—C(3)	55.4(7)
C(1)—C(2)—C(3)—C(4)	−50.4(7)
C(2)—C(3)—C(4)—C(5)	50.0(8)
C(3)—C(4)—C(5)—C(10)	−53.1(7)
C(4)—C(5)—C(10)—C(1)	53.2(7)
C(2)—C(1)—C(10)—C(5)	−54.5(7)
C(10)—C(5)—C(6)—C(7)	−56.0(7)
C(5)—C(6)—C(7)—C(8)	53.0(7)
C(6)—C(7)—C(8)—C(9)	−50.3(7)
C(7)—C(8)—C(9)—C(10)	51.2(7)
C(8)—C(9)—C(10)—C(5)	−53.4(7)
C(6)—C(5)—C(10)—C(9)	55.5(7)
C(14)—C(8)—C(9)—C(11)	−52.8(7)
C(8)—C(9)—C(11)—C(12)	59.1(7)
C(9)—C(11)—C(12)—C(13)	−57.3(7)
C(11)—C(12)—C(13)—C(14)	47.3(7)
C(12)—C(13)—C(14)—C(8)	−45.5(8)
C(9)—C(8)—C(14)—C(13)	48.8(8)

final stages of refinement the non-hydrogen atoms were refined with anisotropic thermal parameters, and hydrogen atoms were fixed in idealized positions (methyl orientations based on observed positions, C(sp^2)–H = 0.97, C(cp^3)–H = 0.98 Å, $U_H \propto U_{\text{bonded atom}}$). The absolute configuration was based on the known configurations at atoms C(5), C(8), C(9), C(10), and C(13). Scattering factors for all atoms were taken from ref. 33. The weighting scheme $w = 1/\sigma^2(F)$, where $\sigma^2(F)$ is derived from the previously defined $\sigma^2(I)$, gave uniform average values of $w(|F_o| - |F_c|)^2$ over ranges of both $|F_o|$ and $\sin\theta/\lambda$ and was employed in the final stages of full-matrix refinement of 270 variables. Reflections with $I < 2\sigma(I)$ were not included in the refinement. Convergence was reached at $R = 0.047$ and $Rw = 0.041$ for 1033 reflections with $Ia \geqslant a2\theta(I)$. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$, $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $Rw = (\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2)^{1/2}$.

On the final cycle of refinement the mean and maximum parameter shifts corresponded to 0.01 and 0.21σ respectively. The mean error in an observation of unit weight was 1.406. A final difference map showed maximum fluctuations of −0.16 to +0.18 e Å^{-3}. The final position parameters for the non-hydrogen atoms appear in Table 1. Bond lengths, bond angles, and intra-annular torsion angles are given in Tables 2–4, respectively. Hydrogen atom parameters, anisotropic thermal parameters, torsion angles, and measured and calculated structure factors have been placed in the Depository of Unpublished Data.[4]

[4]Supplementary material mentioned in the text may be purchased from the Depository of Unpublished Data, CISTI, National Research Council of Canada, Ottawa, Ont., Canada K1A 0S2.