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SYNTHESIS OF A CARDENOLIDE, 3-O-METHYL UZARIGENIN, WITH 14β-HYDROXYANDROST-16-ENE AS THE KEY INTERMEDIATE

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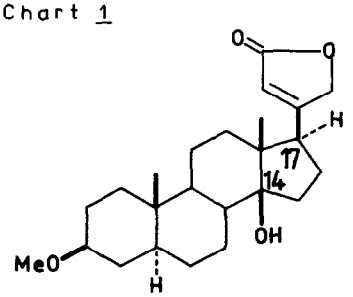
Abstract: A representative cardenolide 1 was synthesized starting from 17-oxo-14α-H androstane derivative 2, with the introduction of the hydroxy group into the position 14 prior to construction of the butenolide ring. Key steps of the synthesis involve: (1) hydroxylation of 15-ene-17-one 4 in the 14β-position with SeO_2, (2) oxidative, intramolecular cyclopropane ring formation in malonate 7, (3) regio- and stereoselective opening of the cyclopropane ring in 8 with thiophenolate anion, and (4) acid- catalyzed transformation of acetal 13 into hydroxy aldehyde 14.

The use of easily available androstane derivatives as starting materials for the cardenolide synthesis requires the development of two distinct sequences of transformations: (1) attachment of the butenolide ring in the 17β-position at the expense of the oxo-group, and (2) introduction of the hydroxy group into the 14β-position (cf. Chart 1, 2 → 1) The crux of the problem consists in combining

Chart 1



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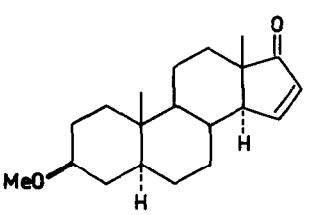


2

the operations at C-14 and C-17 in a most economical and convenient way. In the described syntheses[1], the construction of the butenolide substituent at C-17 precedes hydroxylation and inversion of the configuration at C-14. Such an order of steps allows for stereoselective formation of the chiral centre in the position 17 by hydrogenation of the C16-C17 double bond in an appropriate intermediate

with a trans junction of the C/D rings (hydrogen addition from the α-side).The reverse order of the major transformations seems, however, to also have some advantages. The most important one is that the 14β hydroxy group may be utilized for control of the stereochemistry of the C-C bond formation at C17 in the β orientation. Furthermore, in structure-activity studies of cardiotonic glycosides we have required a variety of 14β-hydroxyandrostane derivatives which, in our opinion,could be prepared along with the major synthetic intermediates in such an approach[2]. These considerations prompted us to investigate the methods for introduction of the hydroxy group into position 14β of 17-oxoandrostane, and subsequently to study synthetic routes from 14β-hydroxyandrostanes to cardenolides. In this paper we report the results on the synthesis of a representative cardenolide, 3-O-methyl uzarigenin 1, from 3β-methoxy-5α-androst-15-ene-17-one (2)(Chart 1), applying this new strategy and using cyclopropane derivative 8 and unsaturated aldehyde 14 as key intermediates[3].

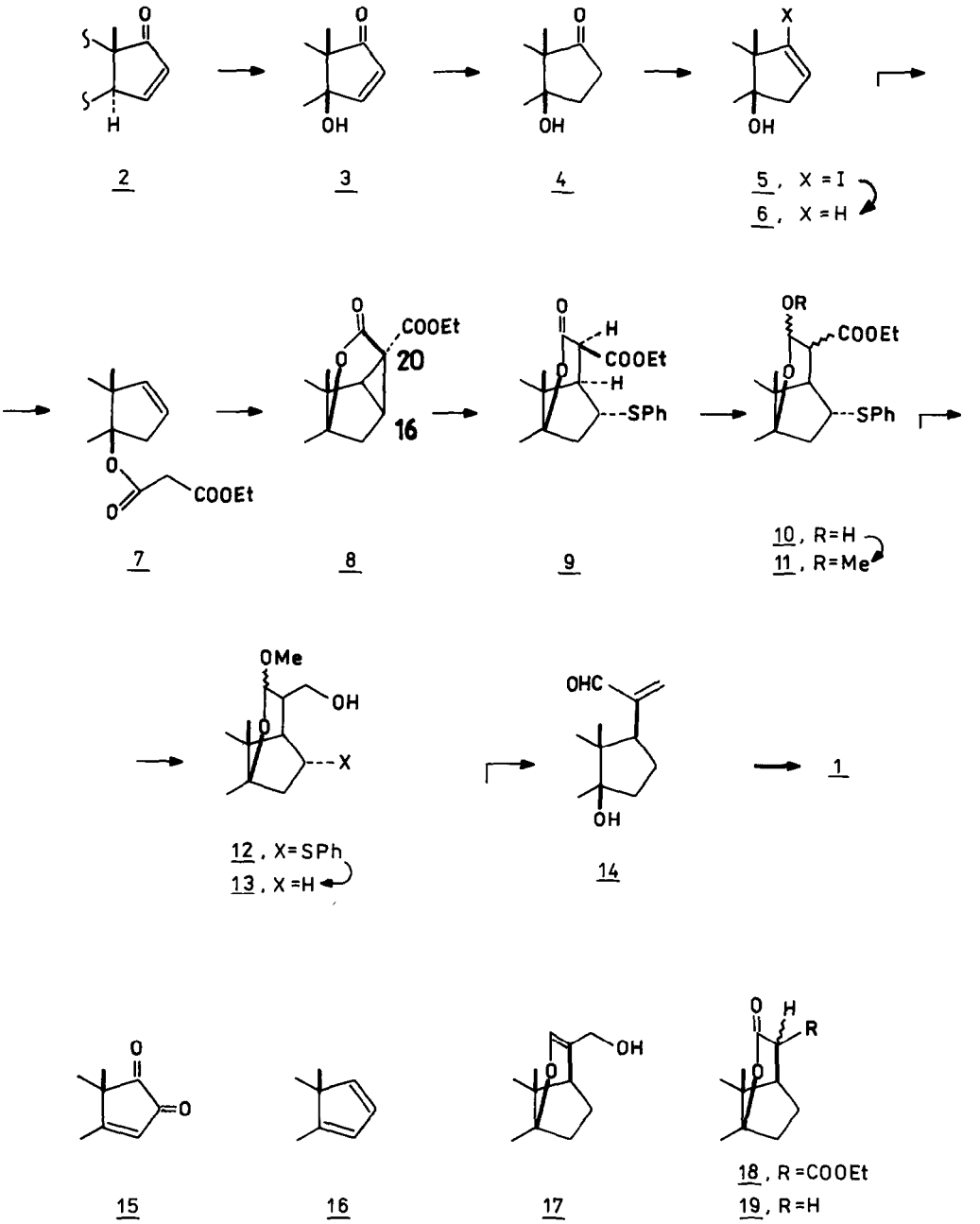
Synthesis of the cyclopropane derivative 8.

α,β-Unsaturated ketone 2 (Scheme 1) prepared from commercial 3β-hydroxy-androst-5-ene-17-one acetate by the known procedure[4] was treated with selenium dioxide in boiling dioxane[5] to give γ-hydroxy-α,β-unsaturated ketone 3 in a 60% yield. A minor by-product of this reaction was isolated and identified as diketone 15. Unsaturated hydroxy ketone 3 was hydrogenated over palladium-on-carbon to give the derivative 4 which was transformed into vinylic iodide by the Barton method.[6] In compound 5, the iodine atom was removed by reduction with sodium in ethanol to give homoallylic alcohol 6 in a 70% yield from 4.

Alcohol 6 was esterified with carboethoxyacetyl chloride in ether in the presence of N,N-diethylaniline. The progress of the reaction was monitored by TLC and the ester 7 contaminated with diene 16 was isolated in the crude form; it was found, however, that upon longer contact with silica gel (column), dissolution in inert solvents or storage, the required product (7) was relatively fast decomposed, this resulting in an increased proportion of diene 16.

Initially, it was intended to treat malonate 7 with tosylazide to form the corresponding diazoester which would then be submitted to carbene-mediated cyclopropanation, in accord with many reports on similar transformations[7]. The lability of the intermediate 7 urged us to search for a different methodological approach to this stage of the synthesis. One-step cyclopropanation described by Julia and coworkers[8] appeared to present a plausible alternative to the conventional method. These authors have observed that treatment of a mixture of alkene and diethylmalonate with cupric and lithium salts in dimethylformamide (DMF) at 100°C gave the corresponding derivative of 1,1-dicarboethoxycyclopro-

Scheme 1



All partial structures refer to 3β-methoxy-5α-androstane skeleton

pane in a 20-40% yield, together with some open-chain products.

We found that the Julia method applied with minor modifications to crude malonate 7 affords the cyclopropane derivative 8 in a 45% yield calculated against alcohol 6. Diene 16 was isolated as the only by-product. It should be noted that the above-given yield of cyclopropanation is comparable to those attainable for malonates of less hindered allylic or homoallylic alcohols by the method involving diazomalonates as intermediates.

Synthesis of α,β-unsaturated aldehyde 14

The molecular model of compound 8 shows a sterically congested structure in the area of the ring D. As concerns the positions 16 and 17, one can see that the latter is evidently more shielded, owing to the presence of a quaternary carbon atom in α-position. It was expected that this difference would allow for selective hydrogenolysis of the excessive C16-C20 bond by means of Michael-type addition of the thiophenolate anion to the dicarboalkoxycyclopropane unit, followed by hydrogenolysis of the C16-S bond at a further stage. The reaction of compound 8 with potassium thiophenolate in ethanolic solution[9] proceeded sluggishly. However, when 8 was treated with a mixture of diisobutylaluminium hydride (DIBAH) and an excess of thiophenol a clean reaction occurred affording sulphide 9 in a 77% yield[10]. The structure of compound 9 was confirmed by ^{1}H and ^{13}C NMR measurements, including extensive NOE experiment[11]. There was no trace of the product which would result from addition of thiophenolate in the 17 position of the cyclopropane derivative 8.

An attempt to reduce compound 9 with lithiumaluminium hydride to the respective triol failed, as instead a complex mixture of products was formed. Treatment of 9 with DIBAH in toluene resulted in virtually selective reduction of the lactone carbonyl to the lactol (10). The lactol function in 10 was protected with the methyl group (methanol-cat. $BF_3 \cdot Et_2O$), and the derivative 11 was further reduced with lithiumaluminium hydride in THF. Compound 12 was obtained in a 48% yield from lactone 9.

In order to remove the thiophenyl substituent, sulphide 12 was treated with tributyltin hydride in benzene in the presence of azobis(isobutyronitrile)(AIBN). Desulphurized product 13 was obtained in almost quantitative yield.

In compound 13, the oxidation level of the structural unit derived from the malonate moiety allowed for hydrolytic formation of α,β-unsaturated aldehyde 14. When attempting acid hydrolysis of acetal 13, we were aware that (1) the tertiary hydroxy group at C14 is exceptionally prone to elimination even under mild conditions, and that (2) a number of products may be formed as a result of the intramolecular reaction of the hydroxy group with the α,β-unsaturated aldehyde

and of parallel reactions with an external nucleophile (water or alcohol). We were pleased to find that compound 13 in a acetonitrile solution containing a trace of aqueous hydrochloric acid[12] gave hydroxy aldehyde 14 in a 72% yield and vinylic ether 17 (18% yield). The latter precipitated from the solution and could be easily removed. Furthermore, treatment of compound 17 with p-toluenesulphonic acid (pTSA) in acetone gave the required product 14.

Synthesis of cardenolide 1

It was planned to transform hydroxy aldehyde 14 into cardenolide by the one-pot procedure developed by Welzel et al.[13] for the respective 14α-H aldehyde. The procedure involves: (1) Wittig reaction of the aldehyde with the ylide prepared from (methoxymethyl)triphenylphosphonium bromide, (2) photochemical oxidation of the resulting methoxydiene with gaseous oxygen, and (3) rearrangement of the methoxy peroxide to a hydroxy ester with concomitant butenolide ring closure. An attempt to apply this method to compound 14 failed, supposedly because no condensation occured in the first step. The target cardenolide 1 could, however, be obtained upon replacement of the Wittig reagent by (methoxymethyl)-diphenylphosphine oxide[14] in the first step, the following steps being consistent with the original procedure. Compound 1 purified by chromatography showed expected analytical and spectroscopic properties.

Reduction of sulphide malonate 9; some comments on the mechanism of Julia cyclopropanation

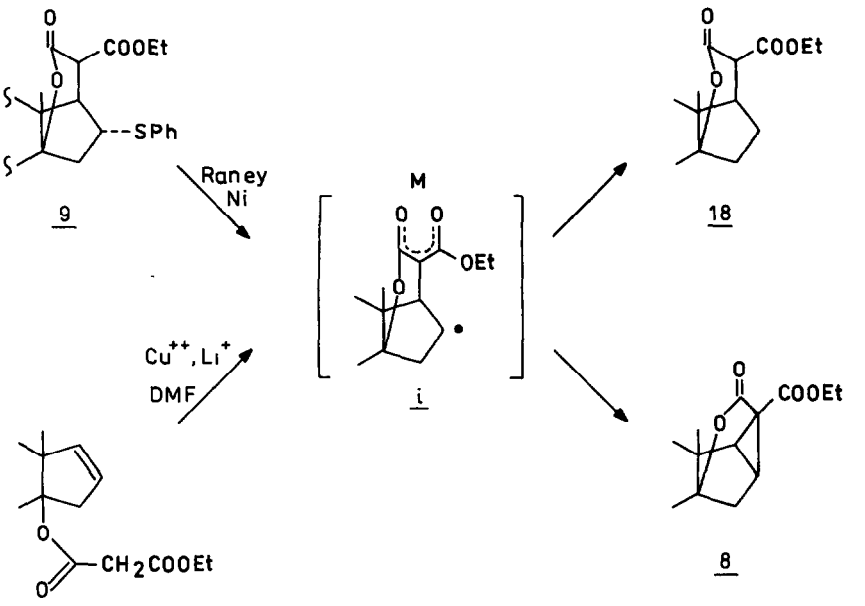
Our experiments with the reduction of sulphide having the malonate structural unit 9 are noteworthy, although they did not lead to selective transformations which could be included in the synthetic sequence. Treatment of compound 9 with tributyltin hydride in benzene in the presence of AIBN yielded two products which were identified as the required lactone ester 18(44% yield) and the product devoid of the carboethoxy group 19 (19% yield). Two mechanisms are feasible for formation of compound 19: (1) hydrostannolysis of the $O\text{-}CH_2CH_3$ bond (as observed for some alkyl benzoates[15]), followed by decarboxylation and replacement of the tin substituent by hydrogen, and (2) nucleophilic substitution of the ethoxy group by the thiophenyl group, followed by the reduction of the thiophenyl ester[16]. Decarboalkoxylation of dialkylmalonates by tributyltin hydride has not to our knowledge been recorded in the literature[17].

Treatment of compound 9 with Raney nickel (W 4) in ethanol afforded two products, the expected desulphuration product 18 and the cyclopropane derivative 8 in 36 and 40% yield, respectively. It may be envisioned that the radical i

(Scheme 2) generated by cleavage of the C-S bond in 9 combined with a hydrogen atom to give 18 or added intramolecularly to malonate enol co-ordinated by metal to give cyclopropane 8.

Formation of compound 8 under reductive conditions provided a clew for elucidation of the mechanism of Julia cyclopropanation. Originally, it has been postulated[8] that a free radical generated from malonate by the Cu^{++}/Li^{+}/DMF system adds to the ethylenic bond to form an adduct-radical (e.g. i). The

Scheme 2



destiny of this species was obscure, one of the possibilities involving its oxidation to carbocation and subsequent ionic cyclization. According to the present results, formation of the second C-C bond during cyclopropanation is likely to also be of a free-radical nature.

In conclusion, the synthesis of representative cardenolide 1 by a route involving 14β-hydroxyandrostane derivatives as intermediates was achieved. Some of the transformations developed appear to have a general application and are worthy of special mention. In particular, (1) intramolecular oxida-

tive cyclopropanation (7 → 8) based upon the methodology devised by Julia and coworkers some time ago but since then, to our knowledge, not used in the synthesis, (2) opening of the cyclopropane ring in a derivative of 1,1-dicarboalkoxycyclopropane 8 with a new two-component reagent, presumably consisting of diisobutyl(thiophenyl)aluminium in thiophenol. The course of reduction of the intermediate 9, having the malonate moiety and the thiophenyl group, with tributyltin hydride and with Raney nickel is of general interest in a view of free-radical transformations.

EXPERIMENTAL

M. ps were determined on a Kofler hot-stage apparatus. The spectra were recorded using the following instruments: IR, Beckmann 4240 or Unicam SP 200 spectrophotometers (unless otherwise stated, $CHCl_3$ solutions); ^1H NMR Varian EM 360 (60 MHz), Jeol JNM-4H-100 (100 MHz) and Bruker AM 400 (400 MHz)(in $CDCl_3$ solutions); mass - LKB 2091 spectrometer and high-resolution mass - Varian 731 spectrometer. Chemical shifts are reported in δ units,ppm, downfield from Me_4Si. Column chromatography was performed on silica gel, Merck, and TLC - on silica gel G, Merck. Organic solutions were dried over anhydrous Na_2SO_4 and solvents were removed under reduced pressure using a rotary evaporator. Microanalyses were performed at our analytical laboratory.

14-Hydroxy-3β-methoxy-5α,14β-androst-5-ene 3 and 3β-methoxy-5α-androst-14-ene-16,17-dione 15

A mixture of unsaturated ketone 2 (45.4 g, 0.15 mol), dioxane (800 mL) water (200 mL) and selenium dioxide (19 g, 0.17 mol) was heated under reflux for 6 h in an argon atmosphere whereupon it was cooled and filtered through celite (1-cm layer). The filtrate was concentrated under reduced pressure to ca. 250 mL and was extracted with chloroform (3x300 mL). The combined extracts were washed with brine and evaporated to dryness. The residue (82 g, red oil) was dissolved in acetone and was boiled for 1 h with norit. Filtration and removal of solvent gave the crude product which was chromatographed on a silica gel column (500 g, hexane-AcOEt, 9:1) to give alcohol 3 (28.7 g, 60% yield) as a pale yellow crystalline mass. An analytical sample was recrystallized twice from hexane - AcOEt, m.p. 154-155°C; ν_{max} 3600 (OH) 1710 (C=O) cm^{-1}; δ (100 MHz) 0.76 and 1.06 (2s, 6H, angular $C\underline{H}_3$), 3.10 (m, 1H, C_3-$\underline{H}$), 3.32 (s, 3H, $OC\underline{H}_3$), 6.18 (d, 1H, J=6 Hz, C_{16}-$\underline{H}$), 7.58 (d, 1H, J=6 Hz, C_{15}-$\underline{H}$)

(Found: C, 75.49; H, 9.81. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50%).

In an analogous experiment, the product obtained after evaporation of chloroform was examined by TLC and the less polar minor component of the mixture was isolated by preparative TLC to give diketone 15 (ca. 5% yield). A sample was recrystallized from acetone-hexane to give orange crystals, m.p. 171-174°C, ν_{max} 1770 (C=O), 1720 (C=O), 1590 (C=C) cm^{-1}; δ (400 MHz) 0.94(s, 3H, C_{19}-H), 1.30(s, C_{18}-H), 3.15 (m, 1H, C_3-H), 3.40(s, 3H, -OCH$_3$), 6.54 (d, 1H, J=1.5 Hz, C_{15}-H); (Found: C, 75.98; H, 8.99. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92%)

14-Hydroxy-3β-methoxy-5α,14β-androst-15-en -17-one 4

A mixture of compound 3 (14 g), 5% palladium-on-carbon (1.5 g) and THF (400 mL) was stirred under hydrogen until gas absorption ceased. The catalyst was filtered off, the solvent was evaporated and the remaining solid was crystallized from acetone-hexane. The product 4 was obtained (13 g, 92% yield); m.p. 172.5-174°C; ν_{max} 3600 (OH), 1735 (C=O) cm^{-1}; δ (100 MHz) 0.82 and 1.07 (2s, 6H, angular CH$_3$), 3.10(m, 1H, C_3-H), 3.40(s, 3H, OCH$_3$); (Found: C, 74.91; H, 10.17. Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06%).

17-Iodo-3β-methoxy-5α,14β-androst-16-en -14-ol 5

A mixture of ketone 4 (7.0 g), triethylamine (15 mL), hydrazine hydrate (80%, 12 mL) and ethanol (65 mL) was heated under reflux for 1.5 h whereupon it was diluted with water and left for crystallization. The precipitate was collected, washed with water and dried to give crude hydrazone.

The latter product was dissolved in THF (70 mL) containing triethylamine (10 mL) and was treated with iodine (ca. 10 g, in several portions) until persistence of brown colour. The mixture was concentrated to ca. 30 mL, diluted with chloroform (100 mL) and washed successively with water, aqueous sodium thiosulphate and water. The solvent was evaporated and the residue was crystallized from acetone to give iodide 5 (8.4 g, 84% yield); m.p. 140°C (decomposition); ν_{max} 3600 (OH) cm^{-1}; δ (100 MHz) 0.82 and 1.05 (2s, 6H, angular CH$_3$), 3.16(m, 1H, C_3-H), 3.40(s, 3H, OCH$_3$), 6.20(br s, 1H, C_{16}-H); (Found: C, 55.93; H, 7.42. Calcd. for $C_{20}H_{31}O_2I$: C, 55.81; H, 7.25%).

3β-Methoxy-5α,14β-androst-16-en -14-ol 6

To a vigorously stirred solution of iodide 5 (10.5 g) in absolute ethanol (300 mL), sodium (35 g) was added in portions at a rate allowing to maintain the mixture at boiling temperature whereupon water (500 mL) was cautiously added and the product was isolated with toluene. The crude product (10 g, oil) was purified by chromatography on silica gel (100 g, hexane-

acetone, 98:2) and by crystallization (hexane-acetone) to give compound 6 (6.7 g, 90% yield); m.p. 104-105°c; ν_{max} 3600 (OH) and 1610 (C=C) cm^{-1}; δ (60 MHz) 0.82 and 1.1(2s, 6H, angular CH_3), 3.2(m, 1H, C_3-H), 3.4 (s, 3H, $-OCH_3$), 5.73(br s, 2H, C_{16}- and C_{17}-H)(Found: C, 79.06; H, 10.76. Calcd. for $C_{22}H_{32}O_2$: C, 78.89; H, 10.59%).

20(S)-20-Carboethoxy-3β-methoxy-16β,20-cyclo-5α-pregnane-21,14β-lactone 8 and 3β-methoxy-5α-androsta-14,16-diene 16

To a stirred mixture of alcohol 6(1.84 g, 6.05 mmol), N,N-dimethylaniline (5.8 mL, 45.8 mmol) and anhydrous ether (50 mL), carboethoxyacetyl chloride (1.4 mL, 6.1 mmol) was added dropwise during 15 min. The mixture was diluted with toluene (100 mL), washed successively with 5% aqueous HCl, saturated aq. $NaHCO_3$ and water whereupon the solvent was evaporated. The residue (dark oil) was dried in high vacuum for 2 h.

So prepared the crude ester 7 was dissolved under argon in DMF (50 mL), cupric chloride dihydrate (2.11 g, 12.2 mmol) and lithium chloride (0.5 g, 11.9 mmol) were added. The mixture was heated at 100°C for 3 h, cooled, diluted with toluene (120 mL) and washed successively with 20% ammonium hydroxide and water. The solvent was removed and the residue (2.5 g) was chromatographed on a silica gel column (75 g) using for elution hexane-AcOEt, 95:5, to give:

1. diene 16 (0.175 g, 11%), colourless oil; λ_{max}(EtOH) 254 nm (ε=4370); ν_{max} 1605 cm^{-1}; δ (60 MHz, CCl_4) 0.9 and 1.0(2s, 6H, angular CH_3), 3.28(s, 3H, OCH_3), 5.80(br s, 1H, C_{15}-H), 6.28(br s,2H, C_{16}- and C_{17}-H); high resolution MS M^+, $C_{20}H_{30}O$ requires 286.2297; found 286.2297.

2.the cyclopropane derivative 8 (1.12 g, 45%); m.p. 185-186°C (acetone-hexane): δ (100 MHz) 0.82 and 1.05(2s, 6H, angular CH_3), 1.32(t, 3H, J=7 Hz, OCH_2-CH_3), 2.47(m, 2H, C_{16}- and C_{17}-H), 3.2(m, 1H, C_3-H), 3.38(s, 3H, OCH_3), 4.32 (q, 2H, J=7 Hz. OCH_2CH_3); ν_{max} 1760(C=O, lactone), 1735(C=O), 1070 (C-O-C)cm^{-1} (Found: C, 72.33; H, 8.68. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71%).

20(R)-20-Carboethoxy-3β-methoxy-16α-thiophenyl -5α-pregnane-21,14β-lactone 9

Thiophenol (1 mL) was treated under argon with DIBAH (0.8 M in toluene, 1.0 mL. 0.8 mmol) and the resulting clear solution was added by means of a syringe to a suspention of cyclopropane 8 (0.3 g, 0.72 mmol) in thiophenol (0.6 mL), stirred under argon. Stirring was continued for 15 min whereupon toluene (5 mL) and methanol (1 mL) were added. After 20 min, the mixture was diluted with toluene (50 mL), washed successively with 0.5% aqueous HCl, water and brine and the solvent was evaporated to dryness. The residue (0.5 g) was filtered through silica gel (10 g, hexane-acetone, 92:8) to give thio-

phenol and then compound 9 (0.292 g, 77%); m.p. 149.5-152.5°C (acetone-hexane); δ (400 MHz) 0.80(s, 3H, C_{19}-H), 1.08(s, 3H, C_{18}-H), 1.09 (t, 3H, $J_{24,23}$=7.3 Hz, C_{24}-H), 2.31(dd, 1H, $J_{15\alpha,15\beta}$=15.5 Hz, $J_{15\alpha,16\beta}$= 5.8 Hz, $C_{15\alpha}$-H, 2.44(d, 1H, $J_{17,20}$=4.4 Hz, C_{17}-H), 2.70(dd, 1H, $J_{15\beta,15\alpha}$=15.5 $J_{15\beta,16\beta}$=9.7 Hz, $C_{15\beta}$-H), 3.10(m, 1H, C_3-H), 3.32 (s, 3H, OCH_3), 3.75 (dq, 1 H, $J_{23a,23b}$=10.7 Hz, $J_{23,24}$=7.3 Hz, C_{23}-H), 3.79(d, 1H, $J_{20,17}$=4.4 Hz, C_{20}-H) 3.93(dd, 1H, $J_{16\beta,15\alpha}$=5.8 Hz, $J_{16\beta,15\beta}$=9.7 Hz, $C_{16\beta}$-H), 4.01 (dq, 1H, $J_{23a,23b}$ =10.7 Hz, $J_{23,24}$=7.3 Hz, C_{23}-H), 7.23-7.48 (m, 5H, aromat. H); ν_{max} 1755 (C=O, lactone), 1720(C=O), 1585 (phenyl), 1095 (C-O-C) cm^{-1} (Found: C, 70.36; H, 8.18; S, 6.11. Calcd. for $C_{31}H_{42}O_5S$: C, 70.69; H, 8.04; S, 6.08%).

14β,21-Epoxy-20ξ-carboethoxy-3β-methoxy-16α-thiophenyl-5α-pregnan-21ξ-ol 10

To a solution of lactone 9 (0.345 g, 0.65 mmol) in toluene (5 mL), stirred under argon at -78°C, DIBAH (1.2 M in toluene, 0.6 mL, 7.2 mmol) was added with a syringe. After 10 min the reaction was quenched with methanol (1 mL), the mixture was allowed to attain room temperature and was diluted with methanol (5 mL). After 2 h the mixture was filtered through celite and the filtrate was evaporated. The residue was chromatographed on a silica gel column (4 g, hexane-acetone) to give lactol 10 (0.27 g, 78%); δ (60 MHz) 0.80 and 1.10(2s, 6H, angular CH_3), 1.15(t,3H, J=7 Hz, OCH_2CH_3), 3.25(m, 1H, C_3-H) 3.40(s, 3H, OCH_3), 3.80(q, 2H, J=7 Hz, OCH_2CH_3), 5.35(br s, 0.5H, C_{21}-H), 5.50(br s, 0.5H, C_{21}-H), 7.4-7.5 (br s, 5H, aromat. H), ν_{max} 3600 (OH), 1725 (C=O) cm^{-1}; high resolution MS M^+, $C_{31}H_{44}O_5S$ requires 528.2909; found 528.2909.

3β,21ξ-Dimethoxy-14β,21-epoxy-20ξ-carboethoxy-16α-thiophenyl-5α-pregnane 11

To a solution of lactol 10 (0.265 g, 0.51 mmol) in methanol (5 mL), $BF_3 \cdot Et_2O$ (50 μL) was added and the mixture was set aside at room temperature for 12 h. Workup with toluene gave the crude product (0.300 g) which was chromatographed on a silica gel column (7 g, hexane-acetone, 99:1) to give:
1. acetal 11 (0.170 g, 63% yield); δ (60 MHz) 0.80 and 1.10(2s, 6H, angular CH_3), 1.15(t, 3H, J=7 Hz, OCH_2CH_3), 3.25(m, 1H, C_3-H), 3.40(s,3H,C_3-OCH_3) overlaping 3.53(s, 3H, C_{21}-CH_3), 4.85 and 5.00(2 br s, 1H, C_{21}-H), 7.40-7.60 (br s, 5H, aromatic H); ν_{max} 1725 and 1585 cm^{-1}; high resolution MS M^+ $C_{32}H_{46}O_5S$ requires 542.3066; found: 542.3066
2. side product (0.045 g) which was not investigated.

3β,21ξ-Dimethoxy-20ξ-(hydroxymethyl)-14β,21-epoxy-16α-thiophenyl-5α-pregnane 12

A mixture of ester 11 (0.143 g), lithiumaluminium hydride (0.200 g) and

THF (4 mL) was stirred at room temperature for 4 h. Workup with saturated aqueous Na_2SO_4 gave alcohol 12 (0.130 g, 98% yield); δ (60 MHz) 0.80 and 1.10 (2s, 6H, angular $C\underline{H}_3$), 3.20(m, 1H, C_3-$\underline{H}$), 3.40 and 3.55(2s, 6H, $OC\underline{H}_3$), 3.30-3.80(br m, 2H, C_{22}-$\underline{H}$), 4.30(d, 0.5H, J=7 Hz, C_{21}-$\underline{H}$), 4.80(d, 0.5H, J=6 Hz, C_{21}-$\underline{H}$), 7.40-7.70(br s, 5H, aromat. $\underline{H}$); ν_{max} 3620 ()H) cm^{-1}; high resolution MS, M^+ $C_{30}H_{44}O_4S$ requires 500.2960; found: 500.2958.

3β,21ξ-Dimethoxy-14β,21-epoxy-20ξ-(hydroxymethyl)-5α-pregnane 13

To a solution of sulphide 12 (0.141 g, 0.28 mmol) in benzene (2 mL), heated under reflux under argon, a mixture of tributyltin hydride (400μL, 1.44 mmol), AIBN (0.005 g, 0.03 mmol) and benzene (1 mL) was added in portions during 3.5 h. Heating was continued for further 5 h whereupon the reaction mixture was cooled and the solvent was removed under vacuum. The residue (0.6 g) was filtered through silica gel (5 g, hexane-acetone, 99:1) to give compound 13 (0.110 g, 98% yield); δ (60 MHz) 0.86 and 1.12(2s, 6H, angular $C\underline{H}_3$) 3.2(m, 1H, C_3-$\underline{H}$), 3.40 and 3.55(2s, 6H, C_3 and C_{21} $OC\underline{H}_3$), 3.30-3.80(m, 2H, C_{22}-$\underline{H}$), 4.30(d, 0.5H, J=7 Hz, C_{21}-$\underline{H}$), 4.80(d, 0.5H, J=6 Hz, C_{21}-$\underline{H}$); ν_{max} 3620 (OH) cm^{-1}; high resolution MS M^+ $C_{24}H_{40}O_4$ requires 392.2925; found: 392.2888.

Hydrolysis of acetal 13

To a solution of acetal 13 (0.090 g) in acetonitrile (25 mL), a mixture of acetonitrile (1 mL) and 0.3 N hydrochloric acid (100 μL) was added in an amount of 100μL. The solution was set aside for 24 h and a new portion of freshly prepared acidified acetonitrile (100 μL) was added. Addition of acidified acetonitrile was repeated two more times at 24-h intervals. The precipitate was collected, washed with a small amount of acetonitrile and dried. To the filtrate solid $NaHCO_3$ was added, the mixture was stirred for 1 h, the inorganic solid was removed, the solvent was evaporated and the oily residue was dried under high vacuum.

The products were identified as:

1. the precipitate, 14β,21-epoxy-20-hydroxymethyl-3β-methoxy-5α-pregn-20-ene 17, (0.015 g, 18% yield); δ (400 MHz) 0.81 and 0.85(2s, 6H, angular $C\underline{H}_3$), 3.10 (m, 1H, C_3-$\underline{H}$), 3.34(s, 3H, $OC\underline{H}_3$), 4.79(d, 2H, $J_{22,21}$=1.5 Hz, C_{22}-$\underline{H}$), 5.47 (br s, 1H, C_{21}-H); ν_{max} 3610 cm^{-1}; high resolution MS M^+-OH $C_{23}H_{35}O_2$ requires 343.2636; found 343.2629

2. 14β-hydroxy-3β-methoxy-20-methylidenepregnan -21-one 14 (0.060 g, 72% yield); δ (400 MHz) 0.72(s, 3H, C_{19}-$\underline{H}$), 0.77(s, 3H, C_{18}-$\underline{H}$), 3.14(m, 1H, C_3 -$\underline{H}$) 3.34(s, 3H, $OC\underline{H}_3$), 6.13(s, 1H, C_{22}-$\underline{H}$), 6.51(s, 1H, C_{22}-$\underline{H}$), 9.50(s, 1H, -$C\underline{H}$O); ν_{max} 3620(OH), 2850 and 1690(CHO), 1620(C=C) cm^{-1}; this compound decomposes on storage.

Hydrolysis of vinyl ether 17

A solution of compound 17 (15 mg) in acetone (10 mL) containing p-toluenesulphonic acid (0.5 mg) was stirred at room temperature for 5 h; saturated aqueous $NaHCO_3$ was added and the product was isolated with chloroform. Aldehyde 14 (12 mg) was obtained.

O-Methyl-3β,14β-dihydroxy-5α-card-20(22)-enolide (O-methyl uzarigenin) 1

To a mixture of diisopropylamine (200 μL) and THF (0.5 mL), stirred under argon at -5°C, BuLi (1.6 M in hexane, 880 μL) was added, whereupon after 10 min a solution of (methoxymethyl)diphenylphosphine oxide (0.190 g, 0.77 mmol) in THF (2 mL) was added. The resulting deep-red solution was allowed to attain 0°C and was treated with aldehyde 14 (0.045 g, 0.125 mmol) in THF (0.5 mL). The mixture was warmed to room temperature within 1.5 h, diluted with toluene (30 mL) and washed with 20% aqueous ammonium chloride. The solvent was evaporated and the residue (light-brown oil) was diluted with THF (6 mL) and treated with NaH (50% in mineral oil, in total 0.4 g, 8.3mmol) in 4 portions during 12 h. The mixture was diluted with toluene (40 mL), washed successively with 20% ammonium chloride and water and the solvent was evaporated. The residue was dissolved in a mixture of methylene chloride (2.5 mL) and methanol (0.5 mL), containing Bengal rose B (0.5 mg). Through this solution, during 15 min oxygen was passed, with concomitant irradiation using a 400 W mercury lamp, whereupon triethylamine was added (1 mL). After 15 min the solvent was evaporated and the residue (0.2 g, red oil) was chromatographed on a silica gel column (3.5 g, hexane-acetone, 92:8) and crystallized from acetone-hexane to give butenolide 1 (6.5 mg), m.p. 229-230°C; δ (400 MHz) 0.80 (s, 3H, C_{19}-H), 0.89(s, 3H, C_{18}-H), 2.78(m, 1H, C_{17}-H), 3.14 (m,1H, C_3-H), 3.34(s, 3H, OCH_3), 4.80(dd, 1H, $J_{21a,21b}$=17.5 Hz, $J_{21a,22}$=1.8 Hz,C_{21a}-H), 4.88(dd, 1H, $J_{21b,21a}$=17.5 Hz, $J_{21b,22}$=1 Hz, C_{21b}-H), 5.87(br s, W/2=4.4 Hz, C_{22}-H); ν_{max} 3600(OH), 1790, 1750 and 1630(butenolide) cm^{-1}; high resolution MS M^+ $C_{24}H_{36}O_4$ requires 388.2613; found: 388.2614.

Reduction of compound 9 with Raney nickel

A mixture of sulphide 9(0.2 g, 0.38 mmol), absolute ethanol (80 mL) and Raney nickel W-4 (0.8 g) was stirred under argon for 24 h, a new portion of nickel (0.4 g) was added and stirring was continued for 2 days. The solid was removed by filtration, the filtrate was evaporated and the residue was chromatographed on a silica gel column (16 g, benzene-acetone, 97:3) to give: 1. (20ξ)-20-Carboethoxy-3β-methoxy-5α-pregnane-21,14β-lactone 18, (0.075 g, 36% yield), m.p. 111-113°C (acetone-hexane); δ(60 MHz) 0.80 and 1.03(2s, 6H, angular CH_3), 1.25(t, 3H, J=7 Hz, OCH_2CH_3), 3.14(m, 1H, C_3-H), 3.34(s, 3H,

$OC\underline{H}_3$), 3.85(d, 1H, C_{20}-$\underline{H}$), 4.29(q, 2H, J=7Hz, $OC\underline{H}_2CH_3$); ν_{max} 1745 (C=O, lactone), 1720 (C=O, ester) cm^{-1}; high resolution MS M^+ $C_{25}H_{38}O_5$ requires 418.2720; found: 418.2719.

2. cyclopropane derivative 8 (0.09 g, 40% yield)

Reduction of compound 9 with tributyltin hydride

A mixture of compound 9(0.052 g, 0.1 mmol), benzene (1 mL), Bu_3SnH (600 µL, 2.16 mmol) and AIBN(82 mg) was heated under reflux under argon for 5 h. Bu_3SnH (100 µL) and AIBN (one crystal) were added and heating was continued for 4 h. The mixture was filtered through silica gel (4 g, benzene-acetone, 98:2) and the product was rechromatographed on silica gel (2.5 g, hexane-acetone, 96:4) to give:

1. 3β-methoxy-5α-pregnane-21,14β-lactone 19 (7.2 mg, 19% yield), an oil; δ (60 MHz) 0.80 and 1.00(2s, 6H, angular $C\underline{H}_3$), 3.14(m, 1H, C_3-$\underline{H}$), 3.35(s, 3H, $OC\underline{H}_3$); ν_{max} 1745(C+O) cm^{-1}; high resolution MS M^+ $C_{22}H_{34}O_3$ requires 346.2508; found: 346.2508
2. compound 18 (18.3 mg, 44% yield)

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