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SYNTHESIS OF (-) 4,8β-DIMETHYL TESTOLACTONE FROM (+) O-15-METHYL ISOAGATHATE

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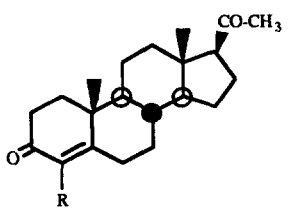
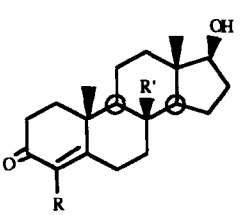
Abstract - The stereoselective synthesis of (-) 4,8β-dimethyl testolactone **18** from (+) O-15-methyl isoagathate **7** is described The construction of ring D by stereoselective electrophilic cyclization and the appropriate funcionalization of the A-ring were carried out in a nine-step process with a good overall yield

The methylation of steroids in many instances has been shown to enhance or prolong their biological activity, and in some cases to diminish undesirable side effects[1] 4-Methyl progesterone **2**[2] or 4-methyl testosterone **4**[3], which are more active than progesterone **1** and testosterone **3**, respectively, and the useful anabolic 8β-methyl testosterone **5**[4], are examples of evident interest.

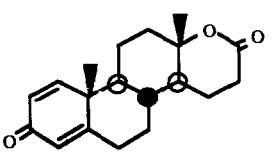
Whilst 4-methyl steroids are easily available by direct alkylation, 8β-methyl steroids are a relatively unknown type of compound[5], probably due to the difficulties encountered in the alkylation at the C-8 position of the steroid nucleus Proof of this fact is the lack of reports about general methods of their synthesis[6]



1 R = H
2 R = CH_3



3 R = H, R' = H
4 R = CH_3 R' = H
5 R = H R' = CH_3

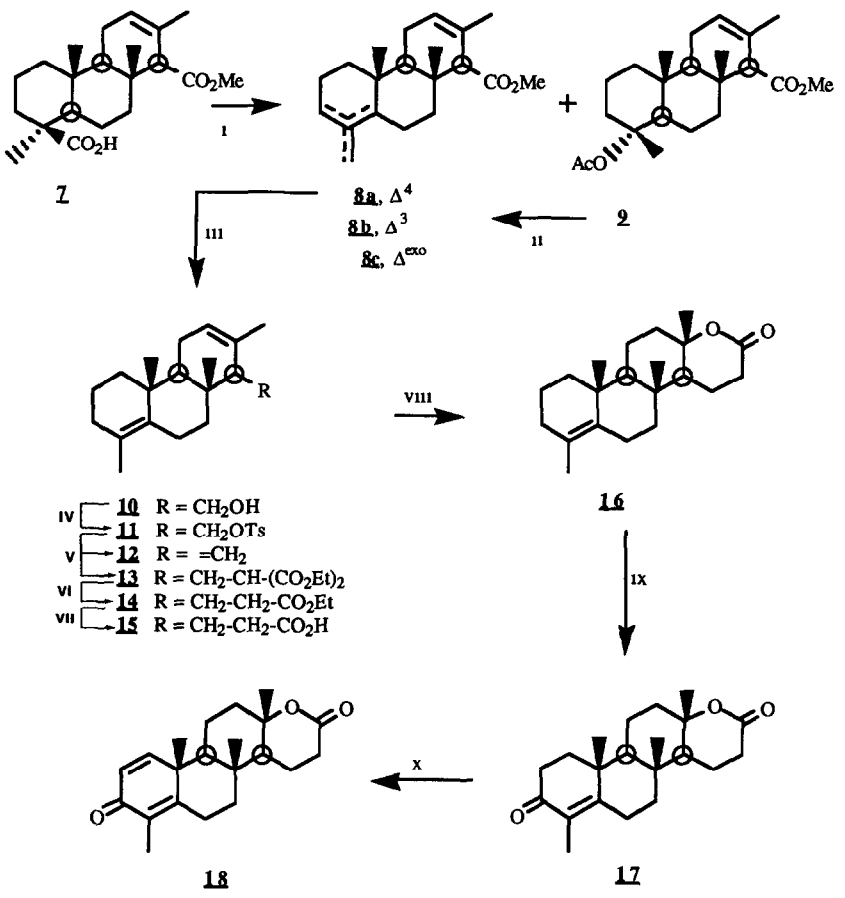


6

Prompted by this situation and by an early report of Baran[7] to the effect that testolactone **6** exhibits anabolic properties and objective regression in the breast cancer of some patients, we embarked on a

programme of the synthesis of methyl testolactones

Our specific target was 4,8β-methyl testolactone **18**. As the starting material we selected O-15-methyl isoagathate **7**, an inexpensive and readily available starting material The structure and situation of the functional groups makes compound **7** an ideal substrate for its conversion into 4,8β-methyl testolactone To accomplish this transformation, the following operations are required (1) Elimination of the carboxylic group at C-4, (2) elongation of the side chain, (3) construction of ring D, and (4) funcionalization of ring A



i, LTA, benzene-pyr , ii, 220 °C, iii, $LiAlH_4$, Et_2O, iv, p-TCl, pyr , v, diethyl malonate, Na, toluene, vi, NaCl, aq DMSO, vii, KOH aq , EtOH, viii, BF_3 Et_2O, benzene, ix, Na_2CrO_4, AcOH-Ac_2O, x, SeO_2, AcOH-t-BuOH

The first step was done by oxidative decarboxylation of acid **7** with lead tetra-acetate (LTA) in benzene-pyridine at reflux for 4 h which gave a 35:25 40 mixture of the unsaturated esters **8a-c** (50 %) and the diester **9** (25 %) Pyrolysis of **9** afforded a 1 2:3 mixture of the unsaturated esters **8a-c** in quantitative yield

Treatment of the whole mixture of **8a-c** with iodine in benzene at reflux for 3 h gave only the unsaturated ester **8a** Isomerization of the Δ^3 and Δ^{exo}-double bonds induced by iodine[8] occurs with remarkable chemoselectivity as observed in the experimental result, the Δ^{13}-double bond remain unaffected

Elongation and selective funcionalization of the side chain of **8a** was done by the following chemical transformations Reduction of **8a** with $LiAlH_4$ in diethyl ether gave the alcohol **10**, which by tosylation followed by condensation of the tosylester **11** with sodium diethyl malonate in refluxing toluene afforded a mixture of the diester **13** and the triene **12** Deethoxycarbonylation of diester **13** was carried out with a mixture of sodium chloride, dimethyl sulfoxide and water at 180 °C Hydrolysis of the ester **14** carried out with potassium hydroxide in ethanol-water followed by addition of hydrochloric acid gave the unsaturated acid **15** in 62 % overall yield from ester **8a**

Construction of ring D was achieved by electrophilic cyclization induced by Lewis acid[9] Thus, the reaction of **15** with boron trifluoride diethyl ether in benzene at room temperature afforded stereospecifically the δ-lactone **16** in 90 % yield

The axial position of the methyl group bonded to the newly created chiral centre at C-13 and also the trans ring C/D fusion was demostrated by the signal at δ_C 22 87 ppm This displacement value rules out the C-13 epimer in which the attached methyl group in a equatorial position will appear at a lower field[5].

The two last steps in our synthesis concerned the appropriate modification of the A-ring Allylic oxidation around the Δ^4-double bond of compound **16** was smooth and selectively carried out with anhydrous sodium chromate[10] at 50 °C for 18 h, in 71 % yield, to afford **17** The existence of the enone system was shown by an i r absortion at 1680 cm^{-1}, together with the presence of three signal at 186 89, 129 04 and 162 17 ppm in the ^{13}C nmr spectrum assigned to C-3, C-4 and C-5 respectively, and a singlet signal at δ 1 43 ppm in the ^1H n m r of the methyl group bonded to C-4 Dehydrogenation of **17** was selectively performed by treatment with selenium dioxide[11] in acetic acid/t-butanol at reflux for 20 h, to give the target dienone **18** in 45 % yield The position of the newly created double bond has been based on the spectral ^{13}C n m r data The signal at δ_C 184 84 ppm assigned to C=O (C-3) rules out the isomer Δ^6 for which it would appear at a lower field[12]

EXPERIMENTAL

General - Mps were determined on a Kofler hot-stage apparatus and are uncorrected I r spectra were recorded on a Beckman 33-IR spectrophotometer, film ^1H n m r (200 MHz) and ^{13}C n.m r (50 MHz) spectra were recorded on a Bruker WP-200-SY spectrometer Spectra were measured in deuteriochloroform Chemical shifts are given in ppm downfield from Tetramethylsilane Chemical shifts and coupling constants

were obtained from a first-order analysis of the spectra Optical rotations were measured on a digital Perkin Elmer 241 polarimeter in a 1-dm cell Mass spectra were measured on a V G TS-250 apparatus Microanalyses were performed using a Carlo Erba 1106 elemental analyser

Solvents were distilled before use and were dried, as necessary, by literature procedures Work-up of solutions involved evaporation under reduced pressure at below 40 °C Reactions were carried out under nitrogen Silicagel for column chromatography refers to Merck Kieselgel 60

Oxidative decarboxylation of methyl 15-isoagathate 7 - A mixture of the ester acid **7** (12g, 34 5 mmol), dry benzene (1100 ml), pyridine (25 ml) and freshly crystallized lead tetra acetate (22 g, 50 mmol) was stirred at reflux for 4 h The cooled mixture was filtered and the filtrate was washed consecutively with 2N hydrochloric acid, aqueous sodium hydrogen carbonate and brine, dried (Na_2SO_4) and concentrated to yield a yellow oil which was cromatographed (10 % light petroleum-ether) to give a fraction of olefinic esters **8a-c** (5 2 g, 50 %), whose ^1H n m r spectrum indicated the presence of 35% of **8a**, 25% of **8b** and 40% of **8c**

Further elution (20 % light petroleum-ether) gave methyl ent-4-acetoxy-19-norisocopal-12-en-15-oate **9** (3 1 g, 25 %) as a colourless oil, i r ν_{max} (film) 1730, 1450, 1250 cm^{-1}, n m r δ_H 0 98 (s, 6H), 1 42 (s, 3H), 1 60 (s, 3H), 1 90 (s, 3H), 2 85 (br s, 1H), 3 60 (s, 3H), 5 42 (br s, 1H) Anal Calcd for $C_{22}H_{34}O_4$, C 72 92, H 9 39 Found, C 72 94, H 9 41

Pyrolysis of methyl ent-4-acetoxy-19-norisocopal-12-en-15-oate 9 - The acetate ester **9** (3 1g, 8 5 mmol) was heated at 220 °C under reduce pressure for 25 min The residue was cooled and extracted with ether The organic layer was washed with aqueous 5 % $NaHCO_3$ and with water, dried (Na_2SO_4) and evaporated Chromatography of the residue gave the olefinic ester mixture **8a-c** (2 5 g, 98 %)

Methyl ent-19-norisocopal-4,12-dien-15-oate 8a -A solution of the olefinic esters mixture **8a-c** (6 5 g, 21 5 mmol) in dry benzene (650 ml) was heated under reflux with iodine (245 mg, 1 mmol) for 3 h, and the isomerization was quenched by cooling and washing with sodium thiosulphate solution and saturated sodium chloride solution, dried (Na_2SO_4) and evaporated Chromatography of the residue (10 % light petroleum-ether) gave the unsaturated ester **8a** (6 3 g, 97 %) as a yellow oil, $[\alpha]_D^{20}$ +18 7 (c 0 72, $CHCl_3$), i r ν_{max} (film) 1760, 1465, 1260, 840 cm^{-1}, n m r δ_H 0 96 (s, 3H), 1 00 (s, 3H), 1 53 (s, 3H), 1 55 (s, 3H), 3 60 (s, 3H), 5 47 (br s, 1H) Anal Calcd for $C_{20}H_{30}O_2$, C 79 47, H 9 93 Found, C· 79 51, H 9 81

Ent 19-norisocopal-4,12-dien-15-ol 10 - A solution of **8a** (5 5 g, 18 mmol) in anhydrous ether (80 ml) was gradually added to a stirred mixture of lithium aluminium hydride (1 4 g, 35 5 mmol) in anhydrous ether (20 ml) at room temperature After 5 1/2 h of stirring, the reaction mixture was carefully quenched with water and the solution was acidified with 2N H_2SO_4 The mixture was extracted with ether and the extract was washed with brine, dried (Na_2SO_4) and evaporated to give the crystalline compound **9** (4 8 g, 91 %), mp 117 °C, $[\alpha]_D^{20}$ +78 2 (c 1 52, $CHCl_3$), i r ν_{max} (film) 3386, 2940, 2860, 1050, 850 cm^{-1}, n m r δ_H 0 96 (s,

3H), 1 01 (s, 3H), 1 61 (s, 3H), 1 76 (s, 3H), 3 72 (dd, 1H, J 11 Hz and J 5 Hz), 3 85 (dd, 1H, J 11 Hz and J 3 5 Hz), 5.51 (br s, 1H). Anal Calcd for $C_{19}H_{30}O$, C 83 21, H: 10 95 Found, C. 83 33, H 10 83

Tosylate of ent 19-norisocopal-4,12-dien-15-ol 10 - P-toluenesulfonyl chloride (4 0 g, 20 mmol) was added to a solution of **10** (4 5 g, 16 4 mmol) in pyridine (95 5 ml) and the mixture was stirred until all the p-toluenesulfonyl chloride had dissolved. The reaction mixture was allowed to stand at 0 °C for four days Ice-water (250 ml) was added to afford a solution which was extracted with ether The organic layer was washed with 2N HCl, and brine, dried (Na_2SO_4) and evaporated to give the corresponding tosylate **11** (6 9 g, 98 %), ir ν_{max} (film) 1610, 1500, 1450 cm^{-1}

Preparation of ent 15-(ethoxycarbonyl-methyl)-19-norisocopal-4,12-diene 14 -

a) Condensation of the tosylate **11** with diethyl sodiomalonate - A solution of **11** (6 4 g, 14 9 mmol) in toluene (50 ml) was added to a solution of the diethyl sodiomalonate, prepared by refluxing toluene (62 ml), sodium (1 4 g, 62 mmol) and diethyl malonate (10 5 g, 66 5 mmol) Refluxing was continued for 23 h, the solution was cooled and the precipitated sodium toluene-p-sulfphonate was filtered off, washed with toluene, and the combined toluene extracts were evaporated The oil obtained was dissolved in ether and washed with water, and the solution was dried (Na_2SO_4) and evaporated to afford 12 1 g of crude product

b) Decthoxycarbonylation of the malonate ester - The crude product obtained in the preceding reaction (12 1 g), sodium chloride (6 5 g, 113 mmol) and water (2g, 113 mmol) in DMSO (60 ml) were heated at 180 °C for 20 h The reaction mixture was cooled and diluted with ethyl acetate (800 ml), this solution was washed with brine, dried (Na_2SO_4), filtered and evaporated The residue was chromatographed (light petroleum) to give ent 19-norisocopal-4,12,14-triene **12** (0 72 g, 19 %), as a crystalline solid, mp 95 °C, $[\alpha]_D^{20}$ +72 87 (c 1 88, $CHCl_3$), ir ν_{max} (film) 1610, 1450, 1230, 890 cm^{-1}, n.m r δ_H 1 07 (s, 3H), 1 09 (s, 3H), 1 64 (s, 3H), 1 79 (s, 3H), 4 79 (s, 1H), 4 80 (s, 1H), 5 66 (br s, 1H)

Further elution (5 % light petroleum-ether) gave the unsaturated ester **14** (3 8 g, 75 %) as a yellow oil, $[\alpha]_D^{20}$ +47 92 (c 1 64, $CHCl_3$), ir ν_{max} (film) 1760, 1480, 1280, 1050 cm^{-1}, n m r δ_H 0 87 (s, 3H), 0 99 (s, 3H), 1 24 (t, 3H, J 7 Hz), 1 60 (s, 3H), 1 67 (s, 3H), 4 11 (c, 2H, J 7 Hz), 5 58 (br s, 1H) Anal Calcd for $C_{23}H_{36}O_2$, C 80 23, H 10 46 Found, C 80 31, H 10 53

Ent 15-(carboxy-methyl)-19-norisocopal-4,12-diene 15 - The unsaturated ester **14** (1g, 2 9 mmol) was refluxed for 23 h in ethanol (25 mll) and water (2 ml) containing potassium hydroxide (0 4 g, 7 5 mmol) After cooling and removing the solvent, the residual solid was dissolved in water and the solution was extracted with ether The extract was washed with brine, dried (Na_2SO_4) and evaporated to afford the title compound **15** (0 85 g, 93 %) as a colourless oil, $[\alpha]_D^{20}$ +45 04 (c 1 13, $CHCl_3$), ir ν_{max} 3400-2900, 1720, 1470, 1290 cm^{-1}, n m r δ_H 0 86 (s, 3H), 0 99 (s, 3H), 1 60 (s, 3H), 1 66 (s, 3H), 5 40 (br s, 1H) Anal Calcd for $C_{21}H_{32}O_2$, C 79 75, H 10 12 Found, C 79 79, H 10 13

D-homo-17a-oxa-4,8β-dimethyl-androst-4-en-17-one 16 - Boron trifluoride etherate (0 5 ml) was gradually added to a solution of **15** (0 5 g, 1 5 mmol) in dry benzene (75 ml) and the reaction mixture was stirred at room temperature for 5 h Water (200 ml) was added and the water layer was extracted with ether The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to give the title compound **16** (0 45 g, 90 %) as a crystalline solid,mp 148 °C, $[\alpha]_D^{20}$ +27 6 (c 0 77, $CHCl_3$), ir ν_{max} (film) 1740 cm^{-1}, nmr δ_H 0 94 (s, 3H), 0 96 (s, 3H), 1 40 (s, 3H), 1 62 (s, 3H) Anal Calcd for $C_{21}H_{32}O_2$, C 79 75, H 10 12 Found, C 79 81, H 10 11

D-homo-17a-oxa-4,8β-dimethyl-androst-4-ene-3,17-dione 17 - Unsaturated lactone **16** (213 mg, 0 67 mmol) in benzene (1 1 ml), acetic acid (1 ml) and acetic anhydride (1 ml) was warmed to 40 °C and anhydrous sodium chromate (184 mg) was added The mixture was stirred for 18 h at 50 °C after which ice-water (10 ml) was added The solution was extracted with ether and the organic layer was washed with 10 % aqueous sodium carbonate and saturated sodium chloride solution, dried (Na_2SO_4) and evaporated The residue was chromatographed (80 % light petroleum-ether) to afford compound **16** (157 mg, 71 %) as a crystalline solid, m p 193 °C, $[\alpha]_D^{20}$ +24 2 (c 1 35, $CHCl_3$), ir ν_{max} (film) 1740, 1670, 1620, 980 cm^{-1}, nmr δ_H 1 04 (s, 3H), 1 12 (s, 3H), 1 43 (s, 3H), 1 79 (s, 3H) Anal Calcd for $C_{21}H_{30}O_3$, C 76 36, H 9 09 Found, C 76 41, H 9 09

D-homo-17a oxa-4,8β-dimethyl-androstan-1,4-diene-3,17-dione 18 - A mixture of **17** (120 mg, 0 36 mmol), selenium dioxide (192 mg), acetic acid (0 08 ml), and t-butyl alcohol (8 5 ml), was refluxed for 20 h The resultant mixture was concentrated to half the volumen, diluted with water and extracted with ether The combined extracts were washed with 5 % bicarbonate solution and brine, dried (Na_2SO_4), and evaporated Chromatography of the residue (10 % light petroleum-ether) gave the title compound **17** (55 mg, 45 %) as a crystalline solid, mp 182 °C, $[\alpha]_D^{20}$ -48 7 (c 0 77, $CHCl_3$), ir ν_{max} (film) 1740, 1680, 1640, 1620, 990 cm^{-1}, nmr δ_H 1 10 (s, 3H), 1 17 (s, 3H), 1 42 (s, 3H), 1 92 (s, 3H), 6 20 (d, 1H, J 10 Hz), 7 03 (d, 1H, J 10 Hz) Anal Calcd for $C_{21}H_{28}O_3$, C 76 83, H 8 53 Found, C 76 89, H 8 63

Table I

^{13}C Chemical Shifts

	(8a)	(9)	(14)	(15)	(16)	(17)	(18)
C-1	39 17	39 28	39 24	39 2	39 87	36 34	154 42
C-2	21 73	21 83	21 88	21 91	21 37	33 25	128 98
C-3	32.53	32 58	32 61	32 64	32 79	186 89	184 84
C-4	123 95	123 43	123 24	123 40	124 68	129 04	125 91
C-5	136 02	136 43	136 66	136 61	135 55	162 17	160 77
C-6	18 67	18 72	18 82	18 84	18 69	23 96	23 85
C-7	40 79	40 43	39 88	39 86	39 10	38 85	40 70
C-8	36 28	36 10	36 92	36 95	37 32	37 11	40 64
C-9	53 14	53 71	53 90	53 88	53 72	53 63	53 17
C-10	37 50	37 54	37 59	37 61	37 83	39 27	43 25
C-11	23 52	23 45	23 68	23 71	15 84	16 03	15 99
C-12	123 95	123 78	123 00	123 15	41 33	41 18	40 78
C-13	129 04	132 79	134 22	134 02	83 48	83 12	82 60
C-14	61 98	57 29	54 24	54 22	59 16	58 49	55 18
C-15	172 86	60 70	22 25	22 07	19 50	19 16	20 36
C-16			36 15	35 99	29 00	29 03	28 54
C-17			173 40	180 06	171 35	171 18	170 64
C-18	20 99	21 63	21 88	21 91	22 87	23 01	22 83
C-19	20 75	20 91	20 81	20 83	19 60	18 16	20 47
CH_3(C-4)	19 26	19 27	19 27	19 36	20 55	11 22	10 43
CH_3(C-8)	14 74	14 79	14 17	13 62	15 13	15 06	15 42
CH_3O-	50 66						
CH_2O-			60 01				
CH_3-(CH_2O)-			13 58				

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