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# TOTAL SYNTHESIS OF RING-C AROMATIC 18-NOR STEROID†

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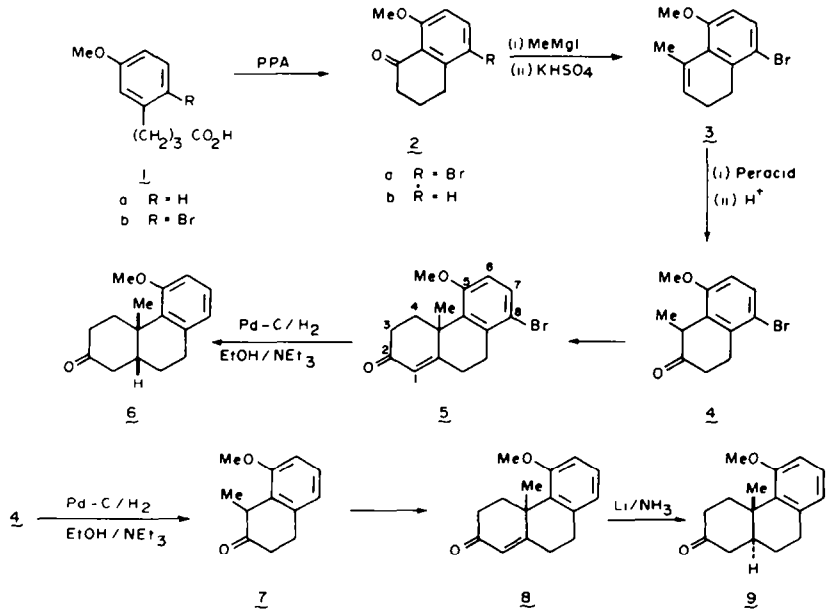
**Abstract**—The total synthesis of (±)-11-methoxy-18-nor-5α and 5β-androsta-8(9),11,13(14)-triene-3,17-dione is reported.

Partial synthesis of ring-C aromatic compounds through aromatisation of ring-C of suitably substituted steroids with concomitant migration of 13-Me group to C-12 or C-17 have been described by Stevenson *et al.*[1] and other workers.[2] The main interest for ring-C aromatic steroids was to evaluate the biological activities of this class of compounds. The transformation of C-aromatic diterpene to C-ring aromatic steroid has also been reported.[3] The impetus for such work comes from the isolation of viridin[4], the first naturally occurring C-ring aromatic steroid with remarkably high fungistatic activity.

Synthesis of ring-C aromatic bisnorsteroids have been reported by Birch *et al.*[5] and Windholz *et al.*[6] We first reported in a preliminary communication[7] the total synthesis of a ring-C aromatic compound with C-10 Me group, and steroidal oxygenation pattern at C-3, C-11 and C-17. A similar synthesis of a ring-C aromatic steroid was also achieved[8] by one of us in a different laboratory. We now wish to report here the experimental details, and also our initial attempts in this endeavour.

We initially planned to devise a method for an efficient synthesis of the phenanthrene derivative **5** substituted at C-8 by a Br atom. This substitution at C-8 was thought to serve as a handle for introducing the propionic acid chain necessary for building up the 5-membered ring to complete the synthesis of the title compound. The synthesis of the desired tricyclic compound **5** has been achieved, and this is shown in Scheme 1. γ-(*m*-Methoxyphenyl)butyric acid[9] **1a** was brominated to give the bromo-acid[10] **1b** in respectable yield. Alkaline permanganate oxidation of this acid **1b** provided the known 2-bromo-5-methoxybenzoic acid[11] thus establishing the position of bromine in the aromatic ring. Polyphosphoric acid (PPA) cyclisation of the acid **1b** afforded the α-tetralone derivative **2a** in high yield. Grignard reaction of **2a** with MeMgI and subsequent dehydration furnished the dihydronaphthalene derivative **3** in high overall yield. Peracid oxidation of this styrene **3** gave a product which on acid treatment afforded in good yield the β-tetralone derivative **4** for ring annelation reaction. Incidentally the α- and β-tetralone derivatives **2a** and **4** were




Scheme 1

† Abstracted in part from the Ph.D. thesis (1970) of B. G. H. A part of this work appeared in a preliminary communication (see [7]).

converted respectively to the debrominated products **2b** and **7**[12] through catalytic hydrogenolysis in presence of triethylamine.

The above β-tetralone **4** on reaction with the methiodide, prepared from 1-diethylamino-3-butanone, in presence of base provided the crystalline phenantrhene derivative **5** in moderate yield. The UV absorption maximum of this compound **5** at 230 nm (ε27,540) is anomalous in that maximum absorption at 240 nm is predicted from Woodward's rule.[13] Similar shifts have, however, been noted in the case of related phenanthrene derivatives studied by Robinson[14] and Turner.[15] Catalytic reduction of this unsaturated ketone **5** in presence of triethylamine removed the bromine and saturated the double bond. The crystalline product, m.p. 62–63°, isolated in 79% yield, has been assigned as the *cis*-isomer **6** from analogy.[16] This assignment is also supported from the fact that the known[12] tricyclic compound **8**, prepared from the 2-tetralone derivative **7**, on metal–ammonia reduction furnished in excellent yield an isomeric ketone, m.p. 71–72°. The *trans*-stereochemistry **9** for this ketone follows from the well-known stereochemical course of Birch reduction of a related system.[16,17] After the completion of our work, the synthesis of these isomeric compounds **6** and **9** was reported[18] by Stork *et al.*† through a novel stereospecific cyclisation of some cyclopropyl ketones, and also by the procedures reported above.

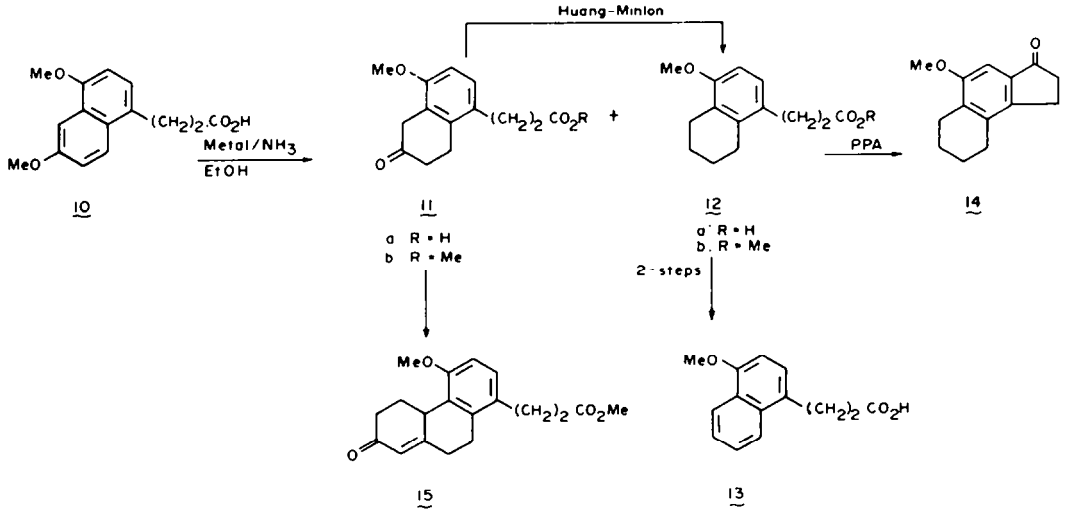
Due to paucity of the tricyclic ketone **5**, its potentialities as intermediate for the title compound could not be investigated further.

When the above work was in progress, we also considered the feasibility of another direct approach shown in Schemes 2 and 4 for our objective.

Two efficient routes to β-(4,6-dimethoxynaphthyl)-propionic acid **10**, the potential intermediate for the total synthesis, have been reported[19] from commercially available 1,7-dihydroxynaphthalene. Reduction of this acid **10** with lithium metal in liquid ammonia was carried out under different conditions, but always afforded a mixture of two crystalline compounds easily separable through careful chromatography over silica gel. Use of excess lithium favoured the formation of one of the compounds as the major product in about 66% yield, and the other in about 16% yield. The minor component **11a**, m.p. 126–127° formed a crystalline semicarbazone, and on Huang-Minlon reduction furnished the major product **12a**, m.p. 173° mentioned above. The 2-keto structure **11a** for the minor product is supported from the characteristic two proton singlet at τ6.44 in $^1$H NMR spectrum. With a view to improving the yield of the desired compound **11a**, reduction of the acid **10** with sodium metal in liquid ammonia was investigated. Under controlled conditions (Experimental), this reduction provided the desired 2-tetralone derivative **11a**, and the undesired demethoxylated product **12a** in 64 and 13% yields respectively. In this connection a similar reduction of γ-(4,6-dimethoxynaphthyl)butyric acid, the higher homologue of **10**, was reported[20] to be unsuccessful. In our hands this reduction afforded[21] the expected β-tetralone derivative in 63% yield.

Polyphosphoric acid cyclisation of the above tetralin derivative **12a** afforded a crystalline ketone in excellent yield. The structure **14** for this indanone derivative is supported by its spectral characteristics and elemental analysis. The acid **12a** was further converted to methyl ester **12b** which on careful dehydrogenation and subsequent alkaline hydrolysis furnished the known β-(4-methoxy-1-naphthyl)propionic acid[19b] **13**. Hydrogenolysis of OMe group during metal–ammonia reduction of naphthalene derivatives are well documented,[22] and the reductive removal of the OMe group in the present case may be rationalised by the pathways shown in Scheme 3.

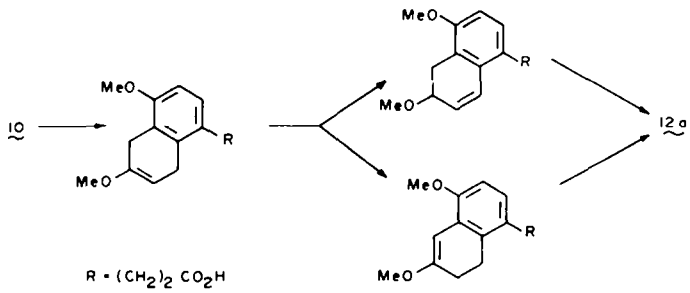
The β-tetralone acid **11a** was next esterified with diazomethane to give the crystalline methyl ester **11b** in excellent yield. Condensation of this ester with the methiodide, prepared from 1-diethylamino-3-butanone, afforded a crude product which was purified by evaporative distillation, and chromatography. The product thus obtained as a glass was characterised as **15**† from its spectral properties.




Scheme 2.

† Unfortunately the authors did not report the m.ps of **6** and **9**.

† This compound may serve as an intermediate for 18,19-bisnor ring-C aromatic steroid.



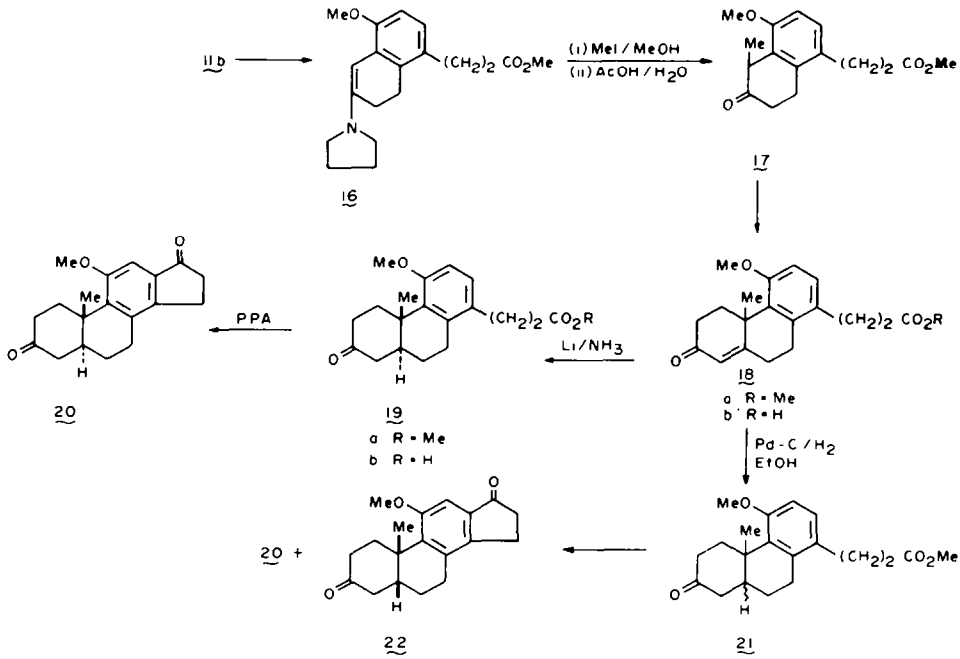

Scheme 3

and crystalline 2,4-dinitrophenylhydrazone derivative. The UV absorption maxima of this tricyclic ketone **15** at 227 and 265 nm, and the behaviour of the DNP derivative during crystallisation indicated that it is most probably contaminated with minor amount of its $\beta,\gamma$-isomer.

The enamine alkylation procedure has been found[23] to be advantageous especially for the monomethylation of $\beta$-tetralone derivatives in high yield. The keto-ester **11b** on reaction with pyrrolidine afforded the crystalline enamine **16** which on alkylation with methyl iodide followed by hydrolysis provided in high yield a product characterised as **17** from elemental and spectral analysis. This keto ester **17** on Mannich-Robinson reaction furnished a high boiling viscous oil in 62% yield. This material was found to be homogeneous (tlc), and its spectral characteristics are in agreement with the structure **18a** assigned to it. The special feature of its $^1$H NMR spectrum is the olefinic proton singlet at $\tau$4.32. Alkaline hydrolysis of this ester **18a** produced a non-crystalline acid characterised as **18b** through its crystalline semicarbazone derivative. Lithium-liquid ammonia reduction of this acid **18b** followed by esterification with diazomethane furnished in moderate yield the crystalline ester **19a**. The *trans*-stereochemistry for this ester was assigned for the reasons already mentioned above. Saponification of **19a** provided the crystalline keto-acid **19b** in excellent yield. PPA cyclisation of this acid **19b** finally afforded the desired C-ring aromatic compound **20** with steroidal oxygenation pattern at C-3, C-11 and C-17.

For the synthesis of C-ring aromatic steroid with *cis*-A/B junction, the tricyclic unsaturated ester **18a** was catalytically reduced under neutral conditions. The non-crystalline saturated ester, obtained as a mixture of stereoisomers **21**, provided expected elemental analysis and spectral properties. Alkaline hydrolysis of this mixture gave an acidic product which on cyclisation as before afforded a neutral product as a mixture. Fractional crystallisations of this mixture furnished the desired *cis*-compound **22**, m.p. 138–139°, and the *trans*-isomer **20** mentioned earlier as the major and minor component in the mixture.

Catalytic hydrogenation of $\Delta^4$-3-keto steroid generally affords[24] a mixture of 3-ketones with *cis*- and *trans*-A/B junctions. It has been recently reported[2b] that ring-C aromatic $\Delta^4$-3-keto steroid is hydrogenated stereospecifically from the $\beta$-face in neutral medium. The reasons for this stereospecificity have been discussed[2b] in terms of a delicate balance between the relative stability of catalyst-steroid complexes. In this context the formation of the *trans*-compound **20**.




Scheme 4

though in minor amount, from catalytic reduction of the tricyclic compound **18a** followed by hydrolysis and cyclisation is informative.

It may be mentioned that our tricyclic keto ester **18a**, prepared by our procedure† with slight modification, has been utilised[25] for the preparation of ring-C aromatic analogue of testosterone for biological testing.

## EXPERIMENTAL

All compounds described are racemic. The same experimental procedures and instruments were used as described[19b] previously.

*γ-(2-Bromo-5-methoxyphenyl)butyric acid* **1b**. To a cold (2–5°) and stirred soln of **1a**[9] (1 g) in $CHCl_3$ (20 ml) was added dropwise during 15 min a soln of $Br_2$ (0.45 g) in $CHCl_3$ (3.3 ml). After complete addition, the mixture was stirred for ½ hr at 5°. The resulting brown mixture was dissolved in a large volume of ether, and the solvent was washed repeatedly with cold water, dried and evaporated. The crude bromo-compound thus obtained on recrystallisation afforded pure **1b** (0.85 g, 61%), m.p. 97° reported,[10] m.p. 94–95° ($Et_2O$–benzene). (Found: C, 48.27; H, 4.75. Calc. for $C_{11}H_{13}O_3Br$: C, 48.35; H, 4.76%.)

Oxidation of this acid **1b** with alkaline permanganate provided the known *2-bromo-5-methoxybenzoic acid*, m.p. 160° ($Et_2O$–light petroleum) (reported[11] m.p. 162°. (Found: C, 41.80; H, 3.30. Calc. for $C_8H_7O_3Br$: C, 41.55; H, 3.03%.)

*5-Bromo-8-methoxy-1-tetralone* **2a**. The above **1b** (8 g) was added to polyphosphoric acid, prepared from $H_3PO_4$ (89%, 32 ml) and $P_2O_5$ (64 g). The resulting mixture was heated on a steam bath for 1 hr with occasional stirring. The mixture was then decomposed with water, and the product was extracted with ether (3 × 75 ml). The extract was successively washed with water, dil KOH aq and finally with water. Evaporation of the dry solvent furnished the desired **2a** (7 g, 94%), b.p. 148–150°/0.4 mm Hg. (Reported[10] b.p. 128–131°/0.09 mm Hg), $\lambda_{max}$ 226 (ε25,120), 256 (ε6310) and 327 nm (ε4169); $\nu_{max}$ (film) 1685 $cm^{-1}$. Tlc showed a bright single spot using benzene–MeOH (9:10) as eluting solvent and iodine vapour as a developing agent. (Found: C, 51.71; H, 4.59. Calc. for $C_{11}H_{11}O_2Br$: C, 51.77; H, 4.31%.) *2,4-Dinitrophenylhydrazone* (96%) separated from MeOH and had m.p. 258–260° (d) ($CHCl_3$-benzene). (Found: C, 46.74; H, 3.25; N, 12.77. Calc. for $C_{17}H_{15}O_5N_4Br$: C, 46.89; H, 3.45; N, 12.87%.) Semicarbazone derivative (87%) separated from MeOH and had m.p. 194–195°. (Found: C, 46.38; H, 4.44; N, 13.74. Calc. for $C_{12}H_{14}O_2N_3Br$: C, 46.15; H, 4.49; N, 13.46%.)

Regeneration of the ketone **2a** from its semicarbazone derivative also provided the ketone as a liquid material (91%), b.p. 130°/0.2 mm Hg.

*5-Bromo-8-methoxy-1-methyl-3,4-dihydronaphthalene* **3**. A soln of **2a** (3 g) in dry ether (40 ml) was added dropwise during 15 min to an ice-cold and stirred soln of the Grignard reagent prepared from Mg metal (0.56 g) and MeI (3.35 g) in dry ether (60 ml). The resulting mixture was stirred for 1 hr in the ice-cold, and then refluxed for 5 hr. After 14 hr. at r.t., the mixture was decomposed by careful addition of cold ammonium chloride soln (100 ml, 30%). The organic layer was separated, and the aqueous phase was extracted with ether (3 × 50 ml). The combined solvent was washed with water, dried and evaporated. The resulting heavy oil (3 g) was dehydrated by heating at 160–165° for 30 min with freshly fused $KHSO_4$ (5 g). The residue was distilled to give **3** as colourless oil (2.66 g, 90%), b.p. 120° (bath)/0.4 mm Hg. (Found: C, 57.12; H, 5.02. Calc. for $C_{12}H_{13}OBr$: C, 56.93; H, 5.14%.)

† During the progress of this work, one of us (B. G. H.) was a postdoctoral fellow (1974–75) in Sheehan Institute of Research, Cambridge, Mass., U.S.A. The publication[25] was available to us only in October 1979.

*5-Bromo-8-methoxy-1-methyl-2-tetralone* **4**. To an ice-cold soln of **3** (11.05 g) in anhyd ether (20 ml) was added a cold soln of monoperphthalic acid (9.76 g) in ether (150 ml). After stirring for 1 hr, the mixture was allowed to stand in the refrigerator for 64 hr for complete oxidation. The precipitated phthalic acid was filtered off and washed with ether. The combined solvent was successively washed with water, $NaHCO_3$ aq and finally with water. The crude semi-solid material, obtained after removal of the dry solvent, was heated under reflux for 3 hr with a mixture of EtOH (40 ml), water (32 ml) and conc $H_2SO_4$ (6.5 ml). The mixture was then cooled, diluted with water, and the product was extracted with ether (3 × 100 ml). Usual processing of the solvent afforded **4** as a colourless oil (7.78 g, 66%); $\nu_{max}$ (film) 1710 $cm^{-1}$. 2,4-Dinitrophenylhydrazone (80%) separated from MeOH and had m.p. 191–192° ($CHCl_3$–MeOH). (Found: C, 47.90; H, 3.87; N, 12.64. Calc. for $C_{18}H_{17}O_5N_4Br$: C, 48.11; H, 3.78; N, 12.47%.) The semicarbazone derivative (83%) had m.p. 195–196° (d). (Found: C, 47.86; H, 4.69. Calc. for $C_{13}H_{16}N_3O_2Br$: C, 47.85; H, 4.90%.)

The above semicarbazone derivative (1 g) was refluxed for 3 hr with an aqueous soln of oxalic acid (48 ml, 20%). Usual work up provided **4** as a colourless oil (0.82 g, 99%); $\nu_{max}$ 1710 $cm^{-1}$. Tlc indicated that the product is homogeneous.

*8-Methoxy-1-methyl-2-tetralone* **7**. A soln of **4** (3.13 g) in 95% EtOH (15 ml) was hydrogenated over Pd-C (0.3 g, 10%) in presence of triethylamine (1.70 ml). The theoretical amount of $H_2$ was absorbed within 45 min. The catalyst was then filtered off, washed with ether, and the combined filtrate was evaporated. The residue was diluted with water, and the product was extracted with ether (3 × 50 ml). The extract was successively washed with water, dil HCl (5%) and finally with water. Evaporation of the dry solvent afforded **7** as a colourless oil (2.1 g, 95%), b.p. 115°/0.3 mm Hg (reported[12] b.p. 142°/0.1 mm Hg); $\lambda_{max}$ 270 nm (ε 4892); $\nu_{max}$ (film) 1711 $cm^{-1}$. (Found: C, 75.40; H, 7.40. Calc. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%.) The semicarbazone derivative (87%) was prepared as needles, m.p. 206–207°. (Found: C, 63.21; H, 6.90; N, 17.01. Calc. for $C_{13}H_{17}O_2N_3$: C, 63.14; H, 6.93; N, 16.99%).

*8-Methoxy-1-tetralone* **2b**. Catalytic reduction of **2a** (8.69 g) in presence of triethylamine furnished **2b** (3.7 g, 65%) as colourless oil, b.p. 115–118°/0.4 mm Hg), $\lambda_{max}$ 255 (ε9772) and 315 nm (ε3890); $\nu_{max}$ (film) 1683 $cm^{-1}$. Tlc showed the product to be homogeneous. (Found: C, 75.29; H, 6.72. Calc. for $C_{11}H_{12}O_2$: C, 75.01; H, 6.81%.) Deep red 2,4-dinitrophenylhydrazone derivative (85%) had m.p. 239–240° (d) (MeOH–$CHCl_3$). (Found: C, 57.54; H, 4.67; N, 15.39. Calc. for $C_{17}H_{16}O_5N_4$: C, 57.30; H, 4.53; N, 15.72%.) The semicarbazone derivative (84%) separated as needles, m.p. 180–181° (dil MeOH). (Found: C, 62.00; H, 6.35; N, 18.28. Calc. for $C_{12}H_{15}O_2N_3$: C, 61.80; H, 6.44; N, 18.02%.)

*8-Bromo-5-methoxy-12-methyl-2-oxo-2,3,4,9,10,12-hexahydrophenanthrene* **5**. To the crystalline methoiodide, prepared from 1-diethylamino-3-butanone (0.6 ml) and MeI (0.2 ml) was added a soln of **4** (0.82 g) in dry thiophene free benzene (6 ml). This mixture was cooled in ice and a soln of Na metal (0.11 g) in dry MeOH (4 ml) was added during 10 min with stirring under $N_2$. Stirring was continued in the cold for 3 hr, and then the mixture was heated under reflux for 30 min. The resulting red mixture was cooled, acidified with dil $H_2SO_4$ (5%, 10 ml), and the product was extracted with ether (3 × 50 ml). The extract was washed with water, dried and evaporated. Trituration of the resulting crude brown material with ether provided a light yellow solid, m.p. 115–124°. Recrystallisation of this product afforded **5** (510 mg, 53%), m.p. 128° (ether–light petroleum); $\lambda_{max}$ 230 (ε25,540) and 280 nm (ε2884); $\nu_{max}$ 1665 $cm^{-1}$. (Found: C, 59.69; H, 5.34. Calc. for $C_{16}H_{17}O_2Br$: C, 59.81; H, 5.30%.) The red 2,4-dinitrophenylhydrazone derivative (96%) had m.p. 237–238° ($CHCl_3$–MeOH). (Found: C, 52.84; H, 4.39; N, 11.10. Calc for $C_{22}H_{21}O_5N_4Br$: C, 52.70; H, 4.19; N, 11.18%.)

*cis-5-Methoxy-12-methyl-2-oxo-1,2,3,4,9,10,11,12-octahydrophenanthrene* **6**. A soln of **5** (0.3 g) in EtOH (15 ml, 95%) was hydrogenated over Pd-C (0.1 g, 10%) in presence of triethylamine (0.15 ml). The required quantity of $H_2$ was

absorbed within 10 min. Work-up of the mixture furnished an oil which on trituration with light petroleum (40–60°) furnished a solid (0.23 g), m.p. 58–62°. Recrystallisation afforded pure **6** (0.18 g, 79%), m.p. 62–63° (light petroleum, 40–60°); $\lambda_{max}$ 271 (ε1445) and 279 nm (ε1549); $\nu_{max}$ 1706 $cm^{-1}$. (Found: C, 78.67; H, 8.42. Calc. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25%.) Semicarbazone derivative (88%) had m.p. 169–170° (dil MeOH).

trans-5-*Methoxy*-12-*methyl*-2-*oxo*-1,2,3,4,9,10,11,12-*octahydrophenanthrene* **9**. Compound **7** (1.62 g) on condensation with the methoiodide prepared from 1-diethylamino-3-butanone (1.6 ml) afforded **8** (1.12 g, 50%) m.p. 100° (reported [12] m.p. 100°) ($Et_2O$–light petroleum); $\lambda_{max}$ 228 (ε19.950) and 272 nm (ε2692); $\nu_{max}$ 1664 $cm^{-1}$. (Found: C, 79.45; H, 7.39. Calc. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49%.) The 2,4-dinitrophenylhdrazone (80%) separated as red needles, m.p. 217–218°. (Found: C, 62.63; H, 5.26. Calc. for $C_{22}H_{22}N_4O_5$: C, 62.55; H, 5.25%.)

To stirred liquid ammonia (150 ml, directly from the tank) was added Li-metal (0.07 g) in small pieces. To the resulting blue soln was added in a slow stream a soln of **8** (0.3 g) in dry ether (20 ml) during 3 min. The mixture was stirred for 10 min and ammonium chloride (1.5 g) was then added to discharge the blue colour. Ammonia was then evaporated, and the residue was diluted with water, and the product was extracted with ether (3 × 50 ml). Usual processing of the solvent gave an oil (0.3 g), and this was oxidised with Jones reagent to afford a solid material (0.3 g), m.p. 64–68°. Chromatography of this product on alumina (12 g), and elution of the chromatogram with benzene–light petroleum (30:70) afforded the pure *trans*-**9** (0.21 g, 70%), m.p. 71–72°; $\lambda_{max}$ 271 (ε1380) and 279 nm (ε1445); $\nu_{max}$ 1710 $cm^{-1}$ (Found: C, 78.53; H, 8.19. Calc. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25%.) The semicarbazone derivative (91%) was obtained as colourless needles, m.p. 211–212° (dil MeOH). (Found: C, 67.72; H, 7.42; N, 14.11. Calc. for $C_{17}H_{23}O_2N_3$: C, 67.75; H, 7.69; N, 13.94%.)

*Sodium–liquid ammonia reduction of β-(4,6-dimethoxy-1-naphthyl)-propionic acid* **10**; *formation of β-(8-methoxy-2-oxo-1,2,3,4-tetrahydro-5-naphthyl)propionic acid* **11a**, *and β-(8-methoxy-1,2,3,4-tetrahydro-5-naphthyl)propionic acid* **12a**. To a stirred liquid ammonia (175 ml, directly from the tank), taken in a 3-necked flask, was added a small piece of Na-metal ($\frac{1}{3}$ of total used). To the resulting blue soln was added in a slow stream during 1 min a soln of **10**[19] (0.5 g) in dry THF (35 ml). The rest of the Na-metal (0.35 g, total used) was added in small pieces during 1 min. After complete addition, the blue colour of the soln was discharged by dropwise addition of EtOH (3.5 ml) during 1 min. After complete evaporation of ammonia at r.t., the residue was diluted with water (50 ml), and the resulting clear soln was acidified with cold dil HCl (10 ml, 3N). To this mixture, a further quantity of dil HCl (10 ml, 3N) and EtOH (5 ml) was added, and the resulting mixture was heated under reflux for 10 min. Most of THF was removed under reduced pressure, the residue was diluted with water (300 ml), and the product was extracted with ether (3 × 50 ml). The extract was washed with water, dried and evaporated to furnish a solid product (0.5 g), m.p. 108–122°. This product was chromatographed over silica gel (20 g). Elution of the chromatogram with ether–light petroleum (20:80) afforded **12a** (0.06 g, 13%) as white plates, m.p. 173° ($Et_2O$–light petroleum), $\lambda_{max}$ 274 nm (ε1694); $\nu_{max}$ 1711 $cm^{-1}$. (Found: C, 71.56; H, 7.81; N.E. 235.1. Calc. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%, N.E. 234.3.) Elution of the chromatogram with ether–light petroleum (1:1) afforded **11a** (0.305 g, 64%) as short needles, m.p. 126–127° ($Et_2O$–light petroleum); $\lambda_{max}$ 275 (ε1995) and 283 nm (ε1963); $\nu_{max}$ 1712 $cm^{-1}$, $CHCl_3$ soln containing a drop of triethylamine showed bands at 1711, 1623 and 1381 $cm^{-1}$; τ6.77–7.57 (8H, m); 6.45 (2H, s), 6.22 (3H, s), 3.12 (2H, q, J8 Hz). (Found: C, 67.39; H, 6.81. Calc. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%.) The semicarbazone derivative (97%) had m.p. 213–214° (d). (Found: C, 58.92; H, 6.31; N, 13.83. Calc. for $C_{15}H_{19}O_4N_3$: C, 59.01; H, 6.27; N, 13.76%.)

The reduction of **10** with Li metal (15 g atoms per mole of the acid) afforded **12a** as the major product (66%), and the desired **11a** as the minor product (16%).

Using 6 g atom of Li-metal per mole of the acid **10** provided the demethoxylated acid **12a**, and the β-tetralone acid **11a** in 42 and 33% yields respectively.

*Huang Minlon reduction of β-8-methoxy-2-oxo-1,2,3,4-tetrahydro-5-naphthyl)propionic acid* **11a**. A mixture of **11a** (0.1 g), diethylene glycol (8 ml), KOH (2 g) and hydrazine hydrate (0.8 ml, 99%) was refluxed under $N_2$ for 1 hr. The water formed was then distilled out until the temp of the mixture reached 180°. Refluxing was continued for a further period of 4 hr at 180–185°. Acidification of the cooled mixture with dil HCl afforded some solid material. The product was then extracted with ether (3 × 50 ml). Usual processing of the solvent provided **12a** (0.07 g, 74%) m.p. 172–173° (ether–light petroleum), m.m.p. with the acid **12a** reported before was undepressed.

6-*Methoxy*-4,5-(1′,2′,3′,4′-*tetrahydrobenz*)*indan*-1-*one* **14**. Compound **12a** (0.15 g) was added to polyphosphoric acid, prepared from a mixture of $H_3PO_4$ (1.5 ml, 89%) and $P_2O_5$ (25 g). The mixture was heated in a direct flame for complete soln of the acid. The reaction was then completed by heating on a steam bath for 30 min. Usual work-up of this mixture provided **14** as white needles (0.13 g, 93%), m.p. 148–149° ($Et_2O$–light petroleum), $\lambda_{max}$ 263 (ε14.320) and 316 nm (ε6622); $\nu_{max}$ 1694 $cm^{-1}$; τ8.09–8.32 (4H, m), 7.23–7.48 (8H, m), 6.17 (3H, s); 3.02 (1H, s). (Found: C, 77.53; H, 7.54. Calc. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46%.) The deep red 2,4-dinitrophenylhydrazone (87%) had m.p. 283°. (Found: C, 60.48; H, 5.32; N, 14.26. Calc. for $C_{20}H_{20}N_4O_5$: C, 60.60; H, 5.09; N, 14.13%.)

*Methyl β-(8-methoxy-1,2,3,4-tetrahydro-5-naphthyl)-propionate* **12b**. The acid **12a** (0.7 g) was esterified with an ethereal soln of $CH_2N_2$ prepared from nitrosomethyl urea (1 g). Usual work-up afforded **12b** as an oil (0.6 g), b.p. 120–125° (bath)/0.3 mm Hg, $\nu_{max}$ 1733 $cm^{-1}$. (Found: C, 71.95; H, 7.96. Calc. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.)

*β-(4-Methoxy-1-naphthyl)propionic acid* **13**. The ester **12b** (0.25 g) was dehydrogenated with sulphur (0.097 g) by heating at 240–250° for 6 hr. The product was then extracted with ether (3 × 75 ml), and the extract was washed successively with water, saturated brine solution and finally with water. Evaporation of the dry solvent afforded a product as an oil (0.25 g). This product (0.25 g) was hydrolysed by refluxing for 3 hr with a soln of KOH (0.15 g) in MeOH (4 ml) and water (0.5 ml). Usual processing of the mixture furnished an acid as light brown solid (0.15 g, 64%). Purification of this solid by sublimation and crystallisation afforded **13** as white needles, m.p. and m.m.p. with an authentic sample[19b] was 170° (benzene).

*Methyl β-(8-methoxy-2-oxo-1,2,3,4-tetrahydro-5-naphthyl)-propionate* **11b**. The crystalline **11a** (1 g) was esterified with an ethereal soln of $CH_2N_2$ prepared from nitrosomethyl urea (1.21 g). Usual processing of the mixture afforded **11b** as needles (1 g, 91%), m.p. 84°, $\lambda_{max}$ 275 (ε1905) and 283 nm (ε1928); $\nu_{max}$ 1720 $cm^{-1}$; τ6.81–7.57 (8H, m), 6.46 (2H, s), 6.32 (3H, s), 6.20 (3H, s), 3.17 (2H, q, J8.6 Hz). (Found: C, 68.53; H, 6.90. Calc. for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92%.) The semicarbazone derivative (90%), obtained as needles, had m.p. 174–175° (MeOH). (Found: N, 12.88. Calc. for $C_{16}H_{21}N_3O_4$: N, 13.16%.)

*Methyl β-(5-methoxy-2-oxo-2,3,4,9,10,12-hexa-hydro-8-phenanthryl)-propionate* **15**. The reaction of methoiodide, prepared from 1-diethylamino-3-butanone (0.42 g) and MeI (0.474 g), with **11b** (0.7 g) in presence of base was performed as described. The crude product (0.8 g) was distilled to give a light yellow viscous material (0.39 g, 46%); b.p. 200° (bath)/0.1 mm Hg; $\lambda_{max}$ 227 (ε15,850) and 265 nm (ε4169); $\nu_{max}$ 1662 and 1720 $cm^{-1}$. This product (0.39 g) was further purified through chromatography over silica gel (16 g). Elution of the chromatogram with benzene–ether (75:25) afforded **15** as a glassy material (0.28 g), $\nu_{max}$ 1662(s) and 1720 $cm^{-1}$(s). The crude 2,4-dinitrophenylhydrazone derivative had m.p. 165–175°. This product on repeated recrystallisations

furnished an analytical sample as red crystals, m.p. 211 212° ($CHCl_3$–MeOH), $\lambda_{max}^{CHCl_3}$ 392 nm (ε32,630). (Found: C, 60.59; H, 5.46. Calc. for $C_{25}H_{26}N_4O_7$: C, 60.72; H, 5.30%.)

Alkaline hydrolysis of **15** (0.22 g) provided an acidic material as viscous liquid (0.18 g). This failed to give any crystalline product even after chromatography.

*Pyrrolidine enamine of methyl β-(8-methoxy-2-oxo-*1,2,3,4-*tetrahydro-5-naphthyl)propionate* **16.** A mixture of **11b** (1.05 g), dry thiophene free benzene (40 ml), pyrrolidine (1.14 g) and a catalytic amount of *p*-toluenesulfonic acid was heated under reflux under $N_2$ in a Dean and Stark water separator for 3 hr. The solvent and the excess pyrrolidine were then removed under reduced pressure to furnish a crystalline enamine derivative (1.25 g); m.p. 94–98°. A portion was recrystallised to furnish an analytical sample of **16** as silky needles, m.p. 98° (d) (light petroleum 40–60°), $\nu_{max}$ 1728, 1611 and 1568 $cm^{-1}$. (Found: C, 72.81; H, 7.93. Calc. for $C_{19}H_{25}O_3N$: C, 72.35; H, 7.99%.)

*Methyl β-(8-methoxy-1-methyl-2-oxo-*1,2,3,4-*tetrahydro-5-naphthyl)propionate* **17.** A soln of **16** (1.25 g) in abs MeOH (20 ml) was treated with MeI (10 ml), and the mixture was refluxed under $N_2$ for 4 hr. Excess MeI was removed, and the residue was heated under reflux for 2 hr under $N_2$ with glacial AcOH (1 ml), $CH_3COONa$ (1 g) and water (10 ml). Excess MeOH was then removed, and the residue was treated with cold dil HCl. The product was then extracted with ether (3 × 50 ml) and the extract was washed with cold water, $NaHCO_3$ aq and finally with water. Evaporation of the dry solvent afforded a colourless oil (0.95 g, 86%), b.p. 150° (bath)/0.1 mm Hg. This material was chromatographed over silica gel (30 g). Elution of the chromatogram with ether–light petroleum (20:80) afforded **17** again as a colourless oil (0.9 g), b.p. 150° (bath)/0.1 mm Hg; $\lambda_{max}$ 276 (ε1905) and 283 nm (ε1950); $\nu_{max}$ (film) 1733 and 1711 $cm^{-1}$; τ($CCl_4$) 8.74 (3H, d, J7.5 Hz), 7–7.8 (9H, m), 8.41 (3H, s), 6.23 (3H, s), 3.25 (2H, q, J7.2 Hz). (Found: C, 69.52; H, 7.22. Calc. for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30%.) Tlc showed a bright single spot using two solvent system: MeOH–benzene (15:85), and EtOAc–light petroleum (40:60). The semicarbazone derivative (91%) of the above keto-ester had m.p. 204°. (Found: C, 61.09; H, 7.04. Calc. for $C_{17}H_{23}O_4N_3$: C, 61.25; H, 6.95%.)

*Methyl-β-(5-methoxy-12-methyl-2-oxo-*2,3,4,9,10,12-*hexahydro-8-phenanthryl)propionate* **18a.** The reaction of **17** (1.5 g) with the crystalline methiodide, prepared from 1-diethylamino-3-butanone (0.55 g) and MeI (0.85 g), in presence of base provided a neutral material (1.2 g) and an acidic material (0.8 g). This acid was esterified with $CH_2N_2$ and the combined neutral product was distilled to give **18a** as light yellow viscous oil, (1.1 g), b.p. 200° (bath)/0.1 mm Hg; $\lambda_{max}$ 229 (ε22,280), 277 nm (ε3090) and 284 nm (ε3020); $\nu_{max}$ 1660 and 1715 $cm^{-1}$; τ($CCl_4$) 8.32 (3H, s), 6.95–8.22 (12H, m), 6.37 (3H, s), 6.18 (3H, s), 4.32 (1H, s), 3.20 (2H, q, J8.4 Hz). (Found: C, 73.07; H, 7.83. Calc. for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37%.) The deep red 2,4-dinitrophenylhydrazone (64%) had m.p. 182–183° ($CHCl_3$–MeOH). (Found: C, 61.13; H, 5.51; N, 10.92. Calc. for $C_{26}H_{28}O_7N_4$: C, 61.41; H, 5.55; N, 11.02%.) The semicarbazone derivative had m.p. 239–240° (d) (MeOH). (Found: N, 10.64. Calc. for $C_{21}H_{27}O_4N_3$: N, 10.90%.)

*β-(5-Methoxy-12-methyl-2-oxo-*2,3,4,9,10,12-*hexahydro-8-phenanthryl)propionic acid* **18b.** Compound **18a** (0.1 g) was hydrolysed by refluxing for 2 hr under $N_2$ with a soln of KOH (0.05 g) in MeOH (2 ml) and water (0.5 ml). The crude acidic material was purified by dissolving in $NaHCO_3$ aq which afforded a gummy acid (0.09 g, 92%). This acid was chromatographed over silica gel (6 g). Elution with $Et_2O$–light petroleum provided **18b** as viscous oil (0.07 g, 74%), $\lambda_{max}$ 230 nm (ε19,110); $\nu_{max}$ 1660 and 1711 $cm^{-1}$. The semicarbazone derivative (70%) had m.p. 244°. (Found: C, 64.35; H, 6.90; N, 10.74. Calc. for $C_{20}H_{25}O_4N_3$: C, 64.67; H, 6.78; N, 11.31%.)

trans-*methyl β-(5-methoxy-12-methyl-2-oxo-*1,2,3,4,9,10,-11,12-*octahydro-8-phenanthryl) propionate* **19a.** Li metal (0.15 g) in small pieces was added to liquid ammonia (200 ml, directly from the tank), and the mixture was stirred for 5 min. To the resulting blue soln was added rapidly with stirring a soln of **18b** (0.7 g) in dry ether (50 ml), and the mixture was stirred for 4 min. Ammonium chloride (1.5 g) was then added in small portions when the blue colour of the soln completely disappeared. Ammonia was evaporated and the residue was diluted with water and acidified with dil HCl. The product was then extracted with ether (3 × 50 ml) and afforded a gummy product which was oxidised with Jones reagent (0.2 ml) in acetone solution. Usual processing of the mixture provided an acidic material as an oil (0.7 g) which was directly esterified with $CH_2N_2$ (from 0.8 g of nitrosomethyl urea) to furnish an ester (0.5 g), b.p. 180° (bath)/0.1 mm Hg. After standing for a few days this ester partly solidified. Trituration with ether–light petroleum provided crystalline solid (0.28 g) m.p. 80–84°. The oily material (0.22 g) which failed to solidify was chromatographed over silica gel (12 g). Elution of the chromatogram with ether–light petroleum afforded an additional amount of the ester (0.09 g), the total yield of **19a** was (0.37 g, 51%). Recrystallisation of this material gave an analytical sample of **19a** as short needles, m.p. 89°, $\lambda_{max}$ 275 (ε1938) and 282 nm (ε1945); $\nu_{max}$ 1705 and 1723 $cm^{-1}$. (Found: C, 72.59; H, 7.84. Calc. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93%.)

trans-*β-(5-methoxy-*12-*oxo-*1,2,3,4,9,10,11,12-*octahydro-8-phenanthryl)propionic acid* **19b.** The ester **19a** (0.18 g) was hydrolysed by refluxing for 1 hr under $N_2$ with a soln of KOH (0.07 g) in MeOH (3 ml) and water (0.5 ml). Usual work up provided the acid initially as an oil (0.16 g). Chromatography of this material over silica gel (8 g), and elution with $Et_2O$–light petroleum (1:1) afforded **19b** (0.12 g) as crystalline needles, m.p. 140°, $\lambda_{max}$ 276 (ε1823) and 283 nm (ε1833); $\nu_{max}$ 1705 (broad). (Found: C, 72.00; H, 7.63. Calc. for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65%.)

(±)-11-*Methoxy-*18-*nor-*5α-*androsta-*8(9), 11,13(14)-triene-3,17-*dione* **20.** Acid **19b** (0.12 g) was added to PPA, prepared fro $H_3PO_4$ (25 ml), 89%) and $P_2O_5$ (4 g). The mixture was then heated on a free flame for 30 sec only to get the acid in soln. The mixture was further heated on the steam bath for 40 min. Usual work-up of the deep red mixture gave the crude **20** as a coloured solid (0.1 g), m.p. 156–163°. Chromatography over silica gel (6 g), and elution with light petroleum–benzene (1:1) afforded the pure *trans*-**20** (0.07 g, 62%), m.p. 172° (ether–light petroleum), $\lambda_{max}$ 264 (ε15,490) and 319 nm (ε6542); $\nu_{max}$ 1704 $cm^{-1}$ (broad); *m/e* 298 ($M^+$), 283 ($M^+$–Me), 241 (283–$CH_2CO$). (Found: C, 76.33; H, 7.38. Calc. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43%.)

cis-*Methyl-β-(5-methoxy-*12-*methyl-2-oxo-*1,2,3,4,9,10,11,12-*octahydro-8-phenanthryl)propionate, and the corresponding* trans *isomer* **21.** A soln of **18a** (0.75 g) in EtOH (95%, 20 ml) was hydrogenated over Pd–C (0.15 g, 10%). $H_2$ (56 ml) was absorbed within 30 min. The catalyst was filtered off and washed with ether. The combined filtrate was evaporated and the residue on distillation afforded **21** (0.55 g), b.p. 180° (bath)/0.1 mm Hg; $\lambda_{max}$ 277 (ε2141) and 283 nm (ε2157); $\nu_{max}$ 1720 $cm^{-1}$ (broad). (Found: C, 72.80; H, 7.83. Calc. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93%.)

(±)-11-*Methoxy-*18-*nor-*5 *β-androsta-*8(9),11,13(14)-*triene-*3,17-*dione* **22,** *and the corresponding* trans-*isomer* **20.** The above **21** (0.5 g) (from catalytic hydrogenation) on alkaline hydrolysis as before furnished a crude gummy acid (0.42 g) and this was purified through chromatography over silica gel (18 g). Elution with ether–light petroleum (40:60) furnished an acidic material (0.35 g) as viscous oil.

PPA cyclisation of the above oily acid (0.35 g) (as in the case of **19b**) provided a neutral material as glass (0.28 g), b.p. 180–190° (bath)/0.1 mm Hg. This material on keeping gave some solid product (0.12 g), m.p. 120–135°. Recrystallisation of this solid afforded the less soluble *trans*-**20** (0.01 g), m.p. 170–172° (ether–light petroleum) reported before. The mother liquors from these crystallisations on concentration afforded some solid which on repeated recrystallisation from the above solvent mixture furnished an analytical sample of the *cis*-**22** as silky needles (0.1 g), m.p. 138–139°); $\lambda_{max}$ 259 (ε14,290) and 317 nm (ε5715); $\nu_{max}$ 1702 $cm^{-1}$ (broad). (Found: C, 76.49; H, 7.35. Calc. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43%.)

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