A Novel Construction of the C Ring of an Aromatic Steroid: New Syntheses of Equilenin and Isoequilenin

Nurani S. Narasimhan and Chintamani P. Bapat
Department of Chemistry, University of Poona, Pune 411 007, India

A new approach for the construction of the C ring of an aromatic steroid, utilising the Diels–Alder reaction, is described. It has been used to synthesise equilenin and isoequilenin.

Several methods using the Diels–Alder reaction are known for the synthesis of estrone, the A ring aromatic steroid. One of the earliest used the diene (**1**), which led to the construction of the C ring,[1] while another, using the diene precursor (**2**), led to the construction of the B ring[2] (and also the C ring). A third method used compound (**4**) which, on condensation with (**3**), leads to simultaneous formation of the A and B rings (and also the C ring).[3]

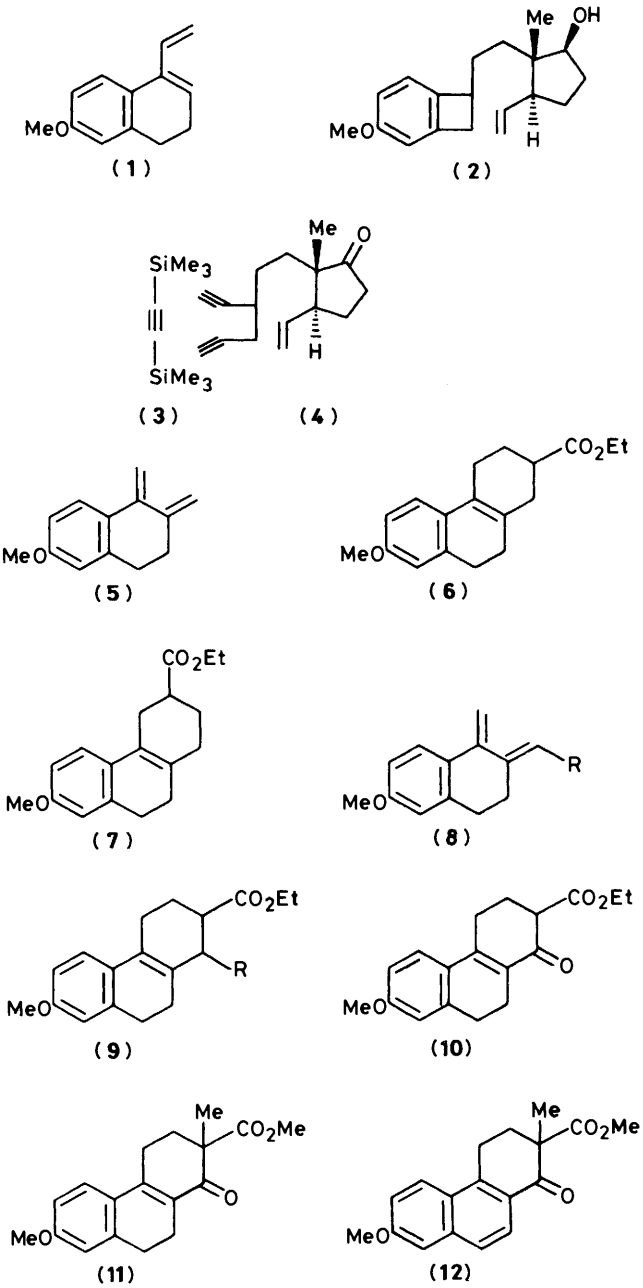
In this paper we report a new approach for the construction of the C ring of an A ring or AB ring aromatic steroid using dienes of type (**5**); such a disconnection has not been reported previously for the synthesis of steroidal molecules. The diene (**5**) on cycloaddition with ethyl acrylate, would give the two regiomers (**6**) and (**7**). It was, however, expected that the presence of a substituent R in the diene, as in (**8**), would lead to the preferential formation of the cycloadduct (**9**) according to the principle of *ortho* cycloadduct formation. If R were an oxygen function and further if the dienophile were methyl methacrylate, the adduct would be (**11**) which, on dehydrogenation, would give the ketone (**12**), an intermediate in the synthesis of equilenin.[4]

Our objective, in the first instance, was to synthesise the adducts (**10**) and (**11**), using ethyl acrylate and methyl methacrylate and then attempt to find another dienophile which would incorporate in the cycloaddition product the carbon atoms necessary for the construction of the D ring.

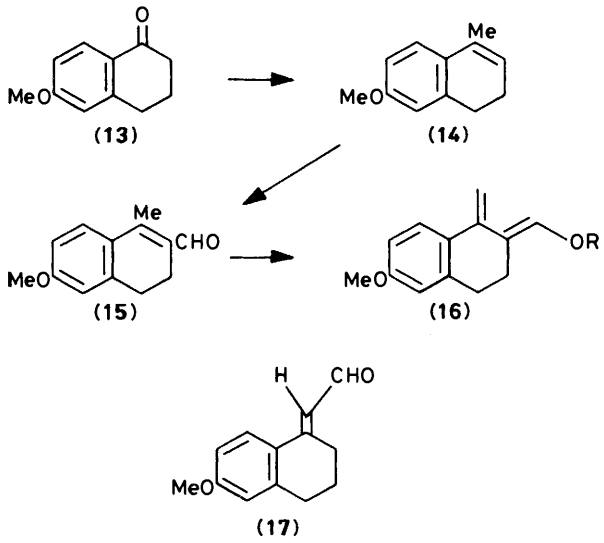
The diene (**16**) was synthesised as shown in Scheme 1. The tetrahydronaphthalenone (**13**) was treated with methylmagnesium iodide to furnish the dihydronaphthalene (**14**).[5] The latter, on reaction with dimethylformamide (DMF–$POCl_3$ Vilsmeier–Haack reaction) gave the aldehyde (**15**) in 57% yield; the aldehyde (**17**) was also formed, in 2.4% yield. Attempts to obtain the diene (**5**) as the enol acetate (**16**; R = COMe) of the α,β-unsaturated aldehyde (**15**), using acid catalysts and isopropenyl acetate, failed. However, the enol silyl ether (**16**; R = $SiMe_3$) was obtained readily using triethylamine and chlorotrimethylsilane. The enol silyl ether (**16**; R = $SiMe_3$) was then condensed with the dienophile, ethyl acrylate or methyl methacrylate. In the actual cycloaddition experiments the enol silyl ether was not isolated, but was generated *in situ* and treated with the dienophile. Reaction of the enol silyl ether with ethyl acrylate furnished compound (**18**), as a viscous oil in 74.9% yield. The compound was characterised by the spectral data and by further chemical transformation (*vide supra*). The use of methyl methacrylate in the Diels–Alder reaction furnished compound (**19**) in 78% yield.

The next objective was to hydrolyse the silyl ether moiety in the two compounds to give the alcohols (**20**) and (**21**), and to oxidise these to the ketones (**22**) and (**23**). The oxoester (**23**) is known in the literature.[6]

The hydrolysis of compounds (**18**) and (**19**) using tetrahydrofuran–acetic acid–water proceeded smoothly to give the products (**20**) and (**21**) in 88.6 and 89.6% yield, respectively. Surprisingly, however, oxidation of the allylic alcohols (**20**) and



(**21**) presented difficulties. The oxidation of (**21**) with active manganese dioxide[7] gave the tetrahydrophenanthrenone (**23**), but in poor yield (29.1%). Oxidation with γ-manganese dioxide,[8] on the other hand, gave the AB-ring aromatised phenanthrenone (**12**), also in poor yield (33.3%). Oxidation of (**21**) with

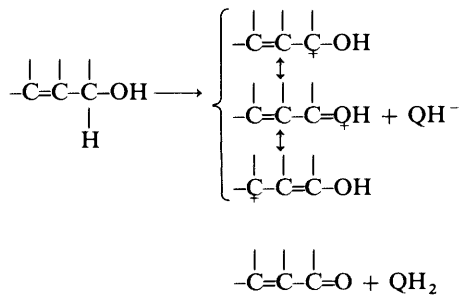


Scheme 1.

pyridinium chlorochromate (PCC)[9] either in the absence or presence of an acid buffer such as sodium acetate gave (**23**), but again in low yield (12.8 and 15.1% respectively).

Non-metallic oxidising agents were then tried. The oxidation of (**21**) with dimethyl sulphoxide–Ac_2O[10] surprisingly gave the oxoester (**12**), but in poor yield. However, oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) gave (**23**) in high yield (79.5%). Similarly, oxidation of compound (**20**) gave the ethyl ester (**22**) in 75.1% yield. The structure of compound (**22**) was confirmed by transforming it into a known ketone (**24**)[11] by hydrolysis and decarboxylation.

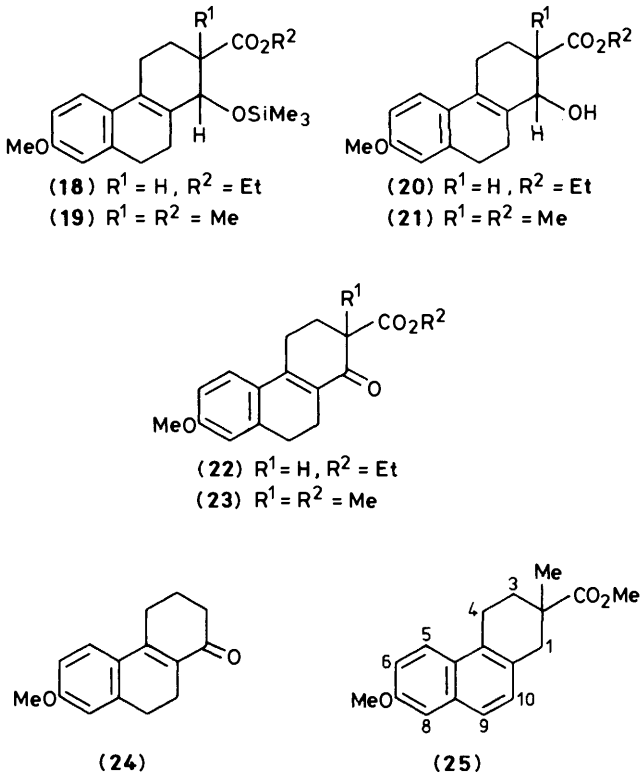
Next, the direct oxidation of the silyl ether (**19**) with DDQ was attempted. This oxidation takes place *via* abstraction of an activated hydrogen atom as a hydride ion, followed by proton elimination. The mechanism of the oxidation of allylic alcohols by quinones has been studied in detail by Braude *et al.*[12] They postulated that the reaction followed the course shown in Scheme 2.



Scheme 2.

On oxidation of the allyl alcohol (**21**), the hydrogen atom, abstracted as a hydride ion, is sufficiently activated for this mechanism to occur, as the resulting carbonium ion is stabilised by resonance. This also applies if the silyl ether (**19**) is used in place of the alcohol (**21**); once the carbonium ion is generated, oxidation to the ketone would be completed by cleavage of the O–Si bond.

The direct oxidation of (**19**) to (**23**) was achieved, but a prolonged contact time was required and because of this the reaction product was contaminated with the ring B dehydrogenated oxoester (**12**). The DDQ (1 equiv.) oxidation of the silyl ether (**19**) was also carried out in the presence of acetic acid; in this case the oxidation occurred more quickly and the product (**23**) was obtained, uncontaminated with (**12**), in high yield. (It is possible that in this reaction the silyl ether is first hydrolysed to the alcohol which is then oxidised by DDQ.)



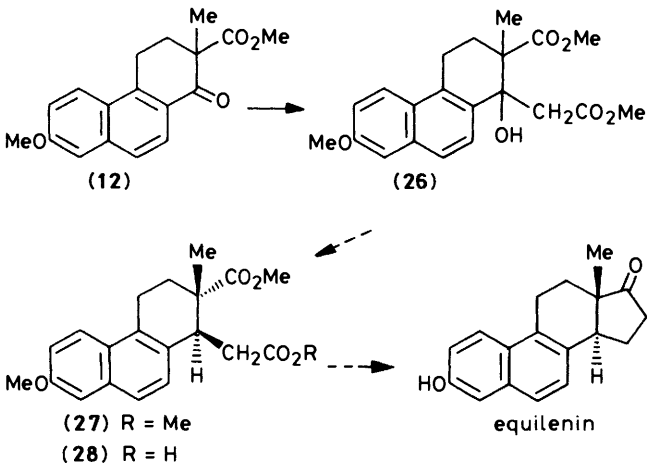
The oxoester (**23**) could be dehydrogenated to give compound (**12**) using 5% Pd–C in 73% yield. A minor product was the phenanthrene (**25**) in which the carbonyl group at C-1* had been hydrogenolysed.

The oxoester (**12**) without any admixture with (**25**) was, however, obtained in high yield either by the oxidation of (**23**) with DDQ or of the silyl ether (**19**) with DDQ (2 equiv.) in the presence of acetic acid (yields 82.8 and 78.7% respectively). Compound (**12**) was converted into equilenin by the sequence[4] shown in Scheme 3.

The Reformatsky product was deoxygenated by dehydration followed by reduction. A mixture of the stereoisomers of structure (**27**) was obtained in the first instance, from which (**27**) was separated. In a modification of the above route, the direct deoxygenation of compound (**26**) to give (**27**) was attempted by the recently reported method for the reduction of alcohols using triethylsilane–trifluoroacetic acid.[13]

Compound (**26**) was prepared by the Reformatsky reaction of the oxoester (**12**).[4] On reduction with triethylsilane–trifluoroacetic acid, it gave a product with m.p. 96—98 °C. Elemental analysis indicated it to have a gross structure corresponding to (**27**). However, it did not conform to either of the two diastereoisomeric forms reported in literature. One possible explanation for this was that the product was a mixture of the *cis*- and *trans*-isomers; it was therefore purified according to Bachmann's procedure, *via* hydrolysis with dilute sodium hydroxide in methanol to give an acid, m.p. 210—211 °C, followed by esterification with diazomethane to give the diester, m.p.

* The phenanthrene numbering is used throughout, as shown in structure (**25**).



Scheme 3.

111—112 °C, in 46% yield [from (**26**)], which was identified by its m.p. and spectral data as (**27**). The obtention of (**27**) constituted a formal synthesis of equilenin.

Compound (**26**) was reduced with chlorotrimethylsilane–sodium iodide–zinc–acetic acid, according to Morita's procedure.[14] This reduction provided a compound with m.p. 123—124 °C (methanol) in 68% yield. On admixture with (**27**), the m.p. was depressed; the m.p. and spectral data indicated that it was a stereoisomer of (**27**), having structure (**29**), which has been converted into isoequilenin.[4]

Experimental

All m.p.s and b.p.s are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 337 spectrophotometer, and ^{1}H n.m.r. spectra on a Perkin-Elmer R32 (90 MHz) spectrometer using Me_4Si as internal standard. Ether refers to diethyl ether.

3,4-*Dihydro*-6-*methoxy*-1-*methylnaphthalene* (**14**).—This compound was prepared by a Grignard reaction (MeMgI) of 3,4-dihydro-6-methoxynaphthalen-1(2*H*)-one (**13**).[5]

3,4-*Dihydro*-6-*methoxy*-1-*methyl*-2-*naphthalenecarbaldehyde* (**15**).—A Vilsmeier–Haack complex was prepared by mixing DMF (7.4 ml) and $POCl_3$ (9.2 ml), and compound (**14**) (13.8 g) dissolved in dichloromethane (70—75 ml) was then added slowly during 15 min with cooling and stirring. After the addition was complete, the reaction mixture, protected from moisture, was left at room temperature for 18 h. It was then poured over crushed ice with efficient stirring, the dichloromethane layer was separated, and the aqueous layer was extracted with ether (5 × 30 ml). The combined organic phases were washed with water, aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4). Removal of the solvent gave the aldehyde (**15**) as a solid, which was immediately crystallised from hexane (7.55 g). The aqueous phase was left overnight, resulting in the precipitation of a further crop of the aldehyde (**15**), which was filtered off, passed through a short column of silica gel, and crystallised from hexane (1.58 g). The total yield of the *aldehyde* (**15**) was thus 57%, m.p. 72 °C (Found: C, 76.9; H, 7.0. $C_{13}H_{14}O_2$ requires C, 77.20; H, 6.98%); $\nu_{max.}$(Nujol) 1 700 cm^{-1}; δ(CCl_4) 2.47 [3 H, s, ArC(CH_3)=C], 2.40—2.85 (4 H, m, ArCH_2CH_2), 3.80 (3 H, s, OCH_3), 6.63—6.80 (2 H, m, 5-H and 7-H), 7.37 (1 H, d, *J* 9 Hz, 8-H), and 10.22 (1 H, s, CHO).

The aqueous layer was then treated with sodium acetate and the solution heated on a water-bath for 2 h. Extraction with ether provided a sticky solid, from which 1,2,3,4-tetrahydro-6-methoxy-1-naphthylideneacetaldehyde (**17**) was obtained by chromatography over silica gel using benzene as eluant (0.38 g, 2.4%), m.p. 94 °C (benzene) (lit.,[15] m.p. 94—95 °C) (Found: C, 77.2; H, 7.0. Calc for $C_{13}H_{14}O_2$: C, 77.20% H, 6.98%); $\nu_{max.}$(Nujol) 1 645 cm^{-1}; δ($CDCl_3$) 1.92 (2 H, tt, *J* 6, 6 Hz, Ar$CH_2CH_2CH_2$), 2.85 (2 H, t, *J* 6 Hz, ArCH_2), 3.08 (2 H, br t, *J* 6 Hz, CH_2C=CHCHO), 3.80 (3 H, s, OCH_3), 6.42 (1 H, br d, *J* 8 Hz, C=C*H*CHO), 6.52—6.88 (2 H, m, 5-H and 7-H), 7.64 (1 H, d, *J* 8 Hz, 8-H), and 10.14 (1 H, d, *J* 8 Hz, CHO).

Methyl 1,2,3,4,9,10-*Hexahydro*-7-*methoxy*-2-*methyl*-1-*trimethylsilyloxyphenanthrene*-2-*carboxylate* (**19**).—A mixture of the aldehyde (**15**) (1.76 g), triethylamine (4 ml), methyl methacrylate (3.5 ml), and chlorotrimethylsilane (3 ml) in dry benzene (40 ml) was refluxed for a total of 30 h during 3 days. During this period the reaction mixture was stirred magnetically to avoid excessive bumping. The volatile matter was then removed under reduced pressure at *ca.* 45 °C. The residue was loaded on a short column of silica gel (30 g) as a suspension in 1% ethyl acetate in hexane. Elution with the same solvent mixture provided, in the first few fractions, *compound* (**19**) as an oil (2.55 g, 78%) (Found: C, 67.1; H, 8.1. $C_{21}H_{30}O_4Si$ requires C, 67.38%; H, 8.02%); $\nu_{max.}$(liquid film) 1 725 cm^{-1}.

Further elution (with 5% ethyl acetate in hexane) gave the unchanged starting aldehyde (**15**) (0.1 g, 5.7%).

Ethyl 1,2,3,4,9,10-*Hexahydro*-7-*methoxy*-1-*trimethylsilyloxyphenanthrene*-2-*carboxylate* (**18**).—The reaction was performed using the aldehyde (**15**) (1.8 g), triethylamine (4.0 ml), ethyl acrylate (3.5 ml), and chlorotrimethylsilane (3.0 ml) as in the cycloaddition using methyl methacrylate. Chromatography over silica gel with 1% ethyl acetate in hexane as eluant provided compound (**18**) as an oil (2.5 g, 74.9%) (Found: C, 67.0; H, 8.0. $C_{21}H_{30}O_4Si$ requires C, 67.38; H, 8.02%); $\nu_{max.}$(liquid film) 1 740 cm^{-1}.

Further elution with 5% ethyl acetate in hexane gave unchanged starting aldehyde (**15**) (0.1 g, 5.6%).

Methyl 1,2,3,4,9,10-*Hexahydro*-1-*hydroxy*-7-*methoxyphenanthrene*-2-*carboxylate* (**21**).—To a solution of the silyl ether (**19**) (2.5 g) in tetrahydrofuran (THF) (5 ml), acetic acid (2 ml) and water (2 ml) were added and the mixture stirred magnetically for 3 h. It was then diluted with ether, washed successively with 5% sodium chloride solution and aqueous sodium hydrogen carbonate, and dried (Na_2SO_4) and the solvent removed under reduced pressure to give *compound* (**21**) as an oil (1.89 g, 89.6%) (Found: C, 71.2; H, 7.1. $C_{18}H_{22}O_4$ requires C, 71.52; H, 7.28%); $\nu_{max.}$(liquid film) 3 450 (br) and 1 730 cm^{-1}.

Ethyl 1,2,3,4,9,10-*Hexahydro*-1-*hydroxy*-7-*methoxyphenanthrene*-2-*carboxylate* (**20**).—Hydrolysis of the silyl ether (**18**) (2.5 g), under the same reaction conditions as that of the silyl ether (**19**), provided compound (**20**) as an oil (1.78 g, 88.6%) (Found: C, 71.2; H, 7.0. $C_{18}H_{22}O_4$ requires C, 71.52; H, 7.28%); $\nu_{max.}$(liquid film) 3 450 (br) and 1 725 cm^{-1} (br).

Methyl 1,2,3,4,9,10-*Hexahydro*-7-*methoxy*-2-*methyl*-1-*oxophenanthrene*-2-*carboxylate* (**23**).—*Oxidation of compound* (**21**) *with active manganese dioxide.* A solution of compound (**21**)

(1.8 g) in carbon tetrachloride (60 ml) was oxidised with active manganese dioxide (prepared by Attenburrow's method; [7] 15 g) at room temperature for 14 h. The usual work-up gave an oil which was purified by chromatography over silica gel. Elution with 1—3% ethyl acetate in hexane provided the ketone (**23**) (0.52 g, 29.1%), m.p. 97—98 °C (methanol) (lit.,[6] m.p. 98—100 °C) (Found: C, 71.8; H, 6.8. Calc. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71%); $\nu_{max.}$(Nujol) 1 740, 1 685 cm^{-1}; $\delta(CCl_4)$ 1.36 (3 H, s, 2-CH_3), 1.70—2.90 (8 H, m, 3-H, 4-H, 9-H, 10-H), 3.65 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 6.50—6.68 (2 H, m, 6-H, 8-H), and 7.25 (1 H, d, *J* 9 Hz, 5-H).

Oxidation of compound (**21**) *with PCC.* To a well stirred, cooled (ice-bath) suspension of PCC (1.3 g) in dichloromethane (20 ml), a solution of compound (**21**) (1.55 g) in dichloromethane (5 ml) was added in one portion. The reaction mixture was stirred for 2 h, then diluted with ether and filtered through a short pad of alumina. The residue was washed well with ether and the combined filtrate washed with water, dilute hydrochloric acid, water, and brine, and dried (Na_2SO_4). Removal of the solvent gave an oil which was loaded, as a suspension in benzene, on a column of silica gel. Elution with hexane–benzene (2:1) gave compound (**23**) (0.19 g, 12.8%).

Oxidation of compound (**21**) *with PCC–sodium acetate.* To a well stirred suspension of PCC (1.6 g) and sodium acetate (0.8 g) in dichloromethane (20 ml), a solution of compound (**21**) (2.0 g) in dichloromethane (10 ml) was added in one portion. The reaction mixture was stirred for 3 h and worked up as usual to give an oil. Chromatography over silica gel then provided compound (**23**) (0.3 g, 15.1%).

Oxidation of compound (**21**) *with DDQ.* A solution of compound (**21**) (1.6 g) in dry ether (30—35 ml) was cooled thoroughly in an ice-bath and stirred. To this, DDQ (1.35 g) was added, in small portions, during 40—45 min. Stirring was continued for a further 1 h with cooling and then for 3 h at room temperature. The precipitate formed was allowed to settle and the ethereal solution decanted. The residue was washed with ether and the combined organic phases were washed with water, aqueous sodium hydrogen carbonate (until washings were pale yellow), and water, and dried (Na_2SO_4). Removal of the solvent gave a semisolid which was crystallised from methanol to give compound (**23**) (1.11 g). Additional product (0.16 g) was obtained by chromatography of the mother-liquor (total yield 79.9%).

Oxidation of compound (**19**) *with DDQ.* A solution of compound (**19**) (3.6 g) in dry ether was oxidised with DDQ (2.2 g), as above, to give the product (**23**) (1.85 g, 64.1%).

Oxidation of compound (**19**) *with DDQ in the presence of acetic acid.* A solution of compound (**19**) (2.5 g) in dry ether (40 ml) was oxidised with DDQ (1.6 g), as above. Before the addition of DDQ, acetic acid (1 ml) was added to the solution. The usual work-up furnished an oil which was crystallised from methanol to give the product (**23**) (1.3 g). Additional product (0.21 g) was obtained by chromatography of the mother-liquor (total yield 75.5%).

Ethyl 1,2,3,4,9,10-*Hexahydro*-7-*methoxy*-1-*oxophenanthrene*-2-*carboxylate* (**22**).—A solution of compound (**20**) (1.78 g) in dry ether (30 ml) was oxidised as above with DDQ (1.4 g) to provide the *oxoester* (**22**) as a pale yellow oil (1.33 g, 75.1%), m.p. 64—65 °C (methanol) (Found: C, 72.0; H, 6.9. $C_{18}H_{20}O_4$ requires C, 71.98; H, 6.71; $\nu_{max.}$(Nujol) 1 740 and 1 650 cm^{-1}; $\delta(CCl_4)$ 1.26 (3 H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.10—2.90 (8 H, m,3-H, 4-H, 9-H, 10-H), 3.32 (1 H, dd, *J* 8, 6 Hz, 2-H), 3.80 (3 H, s, OCH_3), 4.18 (2 H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 6.60—6.80 (2 H, m, 6-H and 8-H), and 7.28 (1 H, d, *J* 9 Hz, 5-H).

3,4,9,10-*Tetrahydro*-7-*methoxyphenanthren*-1(2H)-*one* (**24**).—To a solution of the oxoester (**22**) (200 mg) in acetic acid (1 ml), concentrated hydrochloric acid (0.3 ml) and water (0.3 ml) were added. The reaction mixture was heated on a water-bath for 5 h, then diluted with water and extracted with ether. The ethereal layer was washed with water, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and the solvent removed to give the ketone (**24**) as an orange-yellow oil (100 mg, 65.8%); $\nu_{max.}(CHCl_3)$ 1 650 cm^{-1}; $\delta(CCl_4)$ 1.96—2.26 (2 H, m, 3-H), 2.28—2.85 (8 H, m, 2-H, 4-H, 9-H, 10-H), 3.76 (3 H, s, OCH_3), 6.60—6.78 (2 H, m, 6-H and 8-H), and 7.23 (1 H, d, *J* 9 Hz, 5-H); 2,4-DNP, m.p. 248—249 °C (toluene) (lit.,[11] m.p. 250—252 °C) (Found: C, 62.0; H, 4.94. Calc. for $C_{21}H_{20}N_4O_5$: C, 61.76; H, 4.94%).

Methyl 1,2,3,4-*Tetrahydro*-7-*methoxy*-2-*methyl*-1-*oxophenanthrene*-2-*carboxylate* (**12**).—*Oxidation of compound* (**21**) *with* γ-*manganese dioxide.* A solution of (**21**) (0.85 g) in carbon tetrachloride (30—35 ml) was oxidised with γ-manganese dioxide (8 g) at room temperature for 4 h. Usual work-up gave an oil which was chromatographed over silica gel using hexane–benzene (1:1) as eluant to give an oil. The oil, from its saturated solution in methanol, slowly deposited the oxoester (**12**) (0.28 g, 33.3%), m.p. 83—84 °C (lit.,[4] m.p. 84.5—85 °C) (Found: C, 72.6; H, 6.0. Calc. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08%); $\nu_{max.}$(Nujol) 1 730, 1 690 cm^{-1}; $\delta(CDCl_3)$ 1.53 (3 H, s, 2-CH_3), 1.96—3.46 (4 H, m, 3-H, 4-H), 3.64 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 7.10—7.30 (2 H, m, 6-H, 8-H), 7.61 (1 H, d, *J* 9 Hz, 9-H), 7.95 (1 H, d, *J* 9 Hz, 5-H or 10-H), and 8.03 (1 H, d, *J* 9 Hz, ArH and 10-H or 5-H).

Dehydrogenation of compound (**23**) *with* Pd–C.—A solution of the oxoester (**23**) (200 mg) in dry toluene (4 ml) was dehydrogenated with 5% Pd–C (20 mg) at reflux temperature for 2 h to give a product which was placed, as a carbon tetrachloride solution, on a column of silica gel. Elution with 2% ethyl acetate in hexane gave, in the first few fractions, methyl 1,2,3,4-tetrahydro-7-methoxy-2-methylphenanthrene-2-carboxylate (**25**) as a colourless solid (22 mg, 11.6%), m.p. 110 °C (light petroleum, b.p. 40—60 °C) (lit.,[16] m.p. 107 °C) (Found: C, 75.9; H, 7.1. Calc. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09%); $\nu_{max.}$(Nujol) 1 725 cm^{-1}; $\delta(CDCl_3)$ 1.28 (3 H, s, 2-CH_3), 1.70—3.50 (6 H, m, 1-H, 3-H, 4-H), 3.61 (3 H, s, CO_2CH_3), 3.86 (3 H, s, OCH_3), 7.05—7.28 (3 H, m, 6-H, 8-H, 10-H), 7.51 (1 H, d, *J* 8 Hz, 9-H), and 7.83 (1 H, d, *J* 9 Hz, 5-H).

Further elution with 2—4% ethyl acetate in hexane provided the naphthalenic oxoester (**12**) as a colourless solid (145 mg, 73%).

Dehydrogenation of compound (**23**) *with DDQ.* A solution of the oxoester (**23**) (1.0 g) in dry benzene (15 ml) was refluxed with DDQ (0.8 g) for 4 h. Work-up as in the oxidation of (**21**) gave a semisolid which slowly crystallised from methanol to provide the oxoester (**12**) (0.82 g, 82.8%).

Oxidation of the silyl ether (**19**) *directly to the oxoester* (**12**). A solution of compound (19) (380 mg) in dry benzene (5 ml) containing acetic acid (0.2 ml) was oxidised with DDQ (500 mg) at reflux temperature as described earlier to give the product (**12**) (236 mg, 78.7%), m.p. 83—84 °C, identical in all respects with the product (**12**) obtained in earlier experiments.

Methyl 1,2,3,4-*Tetrahydro*-1-*hydroxy*-7-*methoxy*-1-*methoxycarbonylmethyl*-2-*methylphenanthrene*-2-*carboxylate* (**26**).—This compound was prepared by the Reformatsky reaction (Zn–$BrCH_2CO_2Me$) of (**12**).[4]

Methyl 1,2,3,4-*Tetrahydro*-7-*methoxy*-1β-*methoxycarbonylmethyl*-2β-*methylphenanthrene*-2α-*carboxylate* (**27**).—In a 10-ml two-necked flask, fitted with a calcium chloride guard tube and a rubber septum, was placed a solution of compound (**26**) (200 mg) and triethylsilane (0.2 ml) in dichloromethane (3 ml).

The solution was cooled in an ice–salt bath and trifluoroacetic acid (0.5 ml) was introduced dropwise by syringe. Stirring was continued for a further 15 min with cooling and for 30 min at room temperature. Volatile materials were removed under reduced pressure and the residue was placed, as a solution in carbon tetrachloride, on a column of neutral alumina. Elution with 1% ethyl acetate in hexane gave a colourless oil which crystallised slowly from methanol, m.p. 96—98 °C. This oil was subjected to partial hydrolysis with 1M-sodium hydroxide, as follows: to the solution of the oil in methanol (3 ml), 1M-sodium hydroxide solution (0.4 ml) was added, and the mixture left overnight at room temperature. Most of the methanol was then removed under reduced pressure and the residue diluted with water. The aqueous layer was extracted with ether (2 × 5 ml) and then acidified with dilute hydrochloric acid in the presence of ethyl acetate (0.2 ml). The precipitated acid was filtered off at the pump, washed with methanol, dried under reduced pressure, and crystallised to give 1,2,3,4-tetrahydro-7-methoxy-2α-methoxycarbonyl-2β-methylphenanthren-1β-ylacetic acid (**28**) (95 mg), m.p. 210—211 °C (lit.,[4] m.p. 211—212 °C) (Found: C, 69.85; H, 6.5. Calc. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48%), $\nu_{max.}$(Nujol) 1 740 and 1 710 cm^{-1}; δ[$CDCl_3$–$(CD_3)_2SO$] 1.30 (3 H, s, 2-CH_3), 1.65—3.30 (6 H, m, CH_2CO_2H and 3-H, 4-H), 3.52 (3 H, s, CO_2CH_3), 3.90 (3 H, s, OCH_3), 3.99 (1 H, br t, right wing hidden under OCH_3 signal, *J* 6 Hz, 1-H), 5.50—7.00 (1 H, br hump, CO_2H, exchanges with D_2O), 7.06—7.35 (3 H, m, 6-H, 8-H, 10-H), 7.51 (1 H, d, *J* 8 Hz, 9-H), and 7.81 (1 H, d, *J* 10 Hz, 5-H).

The above acid ester was dissolved in dry ethyl acetate and re-esterified with diazomethane to give the diester (**27**) (88 mg, 46%), m.p. 111—112 °C (methanol) (lit.,[4] m.p. 114—115.5 °C) (Found: C, 70.8; H, 6.7. Calc. for $C_{21}H_{24}O_5$: C, 70.76; H, 6.79%); $\nu_{max.}$(Nujol) 1 740 cm^{-1}; δ($CDCl_3$) 1.28 (3 H, s, 2-CH_3), 1.60—3.38 (6 H, m, $CH_2CO_2CH_3$ and 3-H, 4-H), 3.52 (3 H, s, CO_2CH_3), 3.68 (3 H, s, CO_2CH_3), 3.90 (3 H, s, OCH_3), 4.02 (1 H, br t, *J* 8 Hz, 1-H), 7.06—7.30 (3 H, m, 6-H, 8-H, 10-H), 7.40 (1 H, d, *J* 9 Hz, 9-H), and 7.85 (1 H, d, *J* 9 Hz, 5-H).

Methyl 1,2,3,4-*Tetrahydro*-7-*methoxy*-1α-*methoxycarbonylmethyl*-2β-*methylphenanthrene*-2α-*carboxylate* (**29**).—In a two-necked flask, equipped with a reflux condenser carrying a calcium chloride guard tube and a rubber septum, was placed powdered compound (**26**) (0.5 g). Acetonitrile was added to effect a clear solution followed by sodium iodide (1 g). Trimethylchlorosilane (1.0 ml) was then added dropwise by syringe and a dark brown suspension resulted. Stirring was continued for a further 3 h and then glacial acetic acid was introduced. The rubber septum was replaced by a ground glass stopper and powdered zinc (0.4 g) was added in small lots. On the addition of zinc the reaction mixture became hot, the colour of the suspension was slowly discharged, and a milky white suspension finally resulted. Stirring was continued for a further 2 h and the reaction mixture was then filtered and the precipitate washed with acetonitrile. Removal of the solvent under reduced pressure gave an oily residue which was partitioned between ether and water. The combined ether extracts were washed with water, aqueous sodium hydrogen carbonate, aqueous sodium bisulphite, and water, and dried (Na_2SO_4). Removal of the solvent provided an oil which was passed through a short column of silica gel, with 3% ethyl acetate in hexane as eluant, to give a colourless oil which was homogeneous on t.l.c. The oil was triturated with methanol and compound (**29**) (0.33 g, 68%) crystallised out on standing, m.p. 123—124 °C (methanol) (lit.,[4] m.p. 126—126.5 °C). A depression in the m.p. was observed when (**29**) was mixed with compound (**27**) (Found: C, 71.0; H, 6.8. Calc. for $C_{21}H_{24}O_5$: C, 70.76; H, 6.79%); $\nu_{max.}$(Nujol) 1 740 cm^{-1}; δ($CDCl_3$) 1.21 (3 H, s, 2-CH_3), 1.90—3.40 (7 H, m, $CH_2CO_2CH_3$, 3-H, 4-H, 1-H), 3.64 (3 H, s, OCH_3), 3.72 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 7.05—7.34 (3 H, m, 6-H, 8-H, 10-H), 7.55 (1 H, d, *J* 9 Hz, 9-H), and 7.85 (1 H, d, *J* 9 Hz, 5-H).

References

1 (*a*) J. E. Cole, W. S. Johnson, P. A. Robins, and J. Walker, *Proc. Chem. Soc.*, 1958, 144; (*b*) *J. Chem. Soc.*, 1962, 244; (*c*) R. A. Dickinson, R. Kubela, G. A. MacAlpine, Z. Stojanac, and Z. Valenta, *Can. J. Chem.*, 1972, **50**, 2377; (*d*) J. Das, R. Kubela, G. A. MacAlpine, Z. Stojanac, and Z. Valenta, *Can. J. Chem.*, 1979, **57**, 3308.

2 P. A. Grieco, T. Takigawa, and W. J. Schillinger, *J. Org. Chem.*, 1980, **45**, 2247.

3 R. L. Funk and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 1980, **102**, 5253.

4 W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, 1940, **62**, 824.

5 G. Stork, A. Meisels, and J. E. Davies, *J. Am. Chem. Soc.*, 1963, **85**, 3419.

6 W. E. Bachmann, S. Kushner, and A. C. Stevenson, *J. Am. Chem. Soc.*, 1942, **64**, 974.

7 J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1952, 1094.

8 A. Fatiadi, *Synthesis*, 1976, 65.

9 E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, **17**, 2647.

10 J. D. Albright, *J. Am. Chem. Soc.*, 1965, **87**, 4214.

11 G. Stork, *J. Am. Chem. Soc.*, 1947, **69**, 2936.

12 E. A. Braude, R. P. Linstead, and K. P. H. Wooldridge, *J. Chem. Soc.*, 1956, 3070.

13 D. N. Kursanov, Z. N. Parnes, and N. M. Loim, *Synthesis*, 1974, 633.

14 T. Morita, Y. Okamoto, and H. Sakurai, *Synthesis*, 1981, 32.

15 M. H. Tankard and J. S. Whitehurst, *J. Chem. Soc., Perkin Trans. 1*, 1973, 615.

16 J. Heer and K. Miescher, *Helv. Chim. Acta*, 1945, **28**, 1506.

Received 24*th October* 1983; *Paper* 3/1875