Synthetic Studies towards Complex Diterpenoids. Part 11.† Stereochemically Defined Synthesis of the Racemates of 1,2,3,4,4a,9a-Hexahydro-7-methoxy-1-methylfluorene-1-carboxylic Acid

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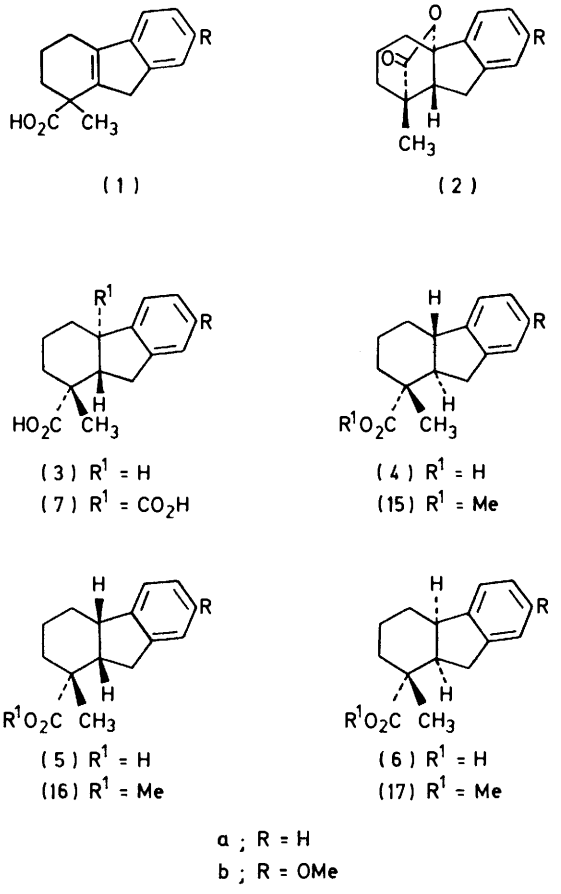
Two simple synthetic routes to 1,2,3,4-tetrahydro-7-methoxy-1-methylfluorene-1-carboxylic acid (1b), a potential intermediate towards gibberellins, and its stereochemically defined transformations to three racemates of 1,2,3,4,4a,-9a-hexahydro-7-methoxy-1-methylfluorene-1-carboxylic acid (4b)—(6b) are described. Catalytic hydrogenation of (1b) yields a mixture of (5b) and (6b) in a ratio of *ca.* 95 : 5, whereas, lithium–liquid ammonia reduction of (1b) gives (4b) and (6b) in a ratio of *ca.* 23 : 77. A mechanism is proposed to explain the stereochemical results in the lithium–ammonia reduction of (1b) and related systems.

THE successful development of stereocontrolled syntheses [1] of model hydrofluorene derivatives (1a)—(6a), featuring the ring A functionality of C_{19} gibberellins, prompted us to consider the extension of these methods to the preparation of the corresponding 7-methoxy analogues for elaboration [2] of ring D of gibberellins. Also, we have recently transformed the tetrahydrofluorene acids (1a and b) to the dicarboxylic acids (7a and b) by a novel route,[3] leading to important synthons towards C_{20} gibberellins. We had expected that the synthetic methods utilised for (1a)—(6a) would also be applicable to the preparation of the corresponding 7-methoxy analogues. These expectations, however, were only partially realised. We now describe in detail the results of these studies leading to the synthesis of the key intermediate (1b) and its transformations to the racemates (4b)—(6b).

For preparation of (1b) (Scheme 1) we utilised the methods used for the demethoxy analogue.[1] The unsaturated keto-ester (9b),[4] prepared in good yield from Hagemann's ester (8), on alkaline hydrolytic decarboxylation with boiling aqueous–ethanolic potassium hydroxide, gave the unsaturated ketone (10b) in 68% yield. Conjugate addition [5] of HCN to (10b) with boiling aqueous–ethanolic potassium cyanide followed by *in situ* hydrolysis with aqueous–ethanolic potassium hydroxide led to the keto-acid (11b) in 83% yield. This on treatment with ethereal diazomethane produced the methyl ester (12b). Unlike the corresponding demethoxy analogue,[1] attempted cyclodehydration of (12b) with sulphuric acid in benzene or chloroform resulted only in polymeric products. Polyphosphoric acid-catalysed cyclisation of (12b) produced a mixture of the cyclised ester (13b) along with unchanged material and decarboxylated products. The keto-ester, however, underwent smooth cyclodehydration with toluene-*p*-sulphonic acid in boiling benzene [4] affording the unsaturated ester (13b) in 85% yield. Saponification of (13b) gave the acid (1b) in 92% yield. Finally, this acid was also obtained in excellent yield by sulphuric acid-catalysed cyclisation of the keto-acid (11b). Interestingly, attempted cyclisation of the demethoxy analogue (11a) under similar conditions produced mainly the known diketone (14) [1] (68%) along with only a minor amount of the unsaturated acid (1a) (12%). The increased nucleophilicity of the methoxy-substituted aromatic-ring in (11b) is possibly responsible for its ready cyclodehydration to (1b).



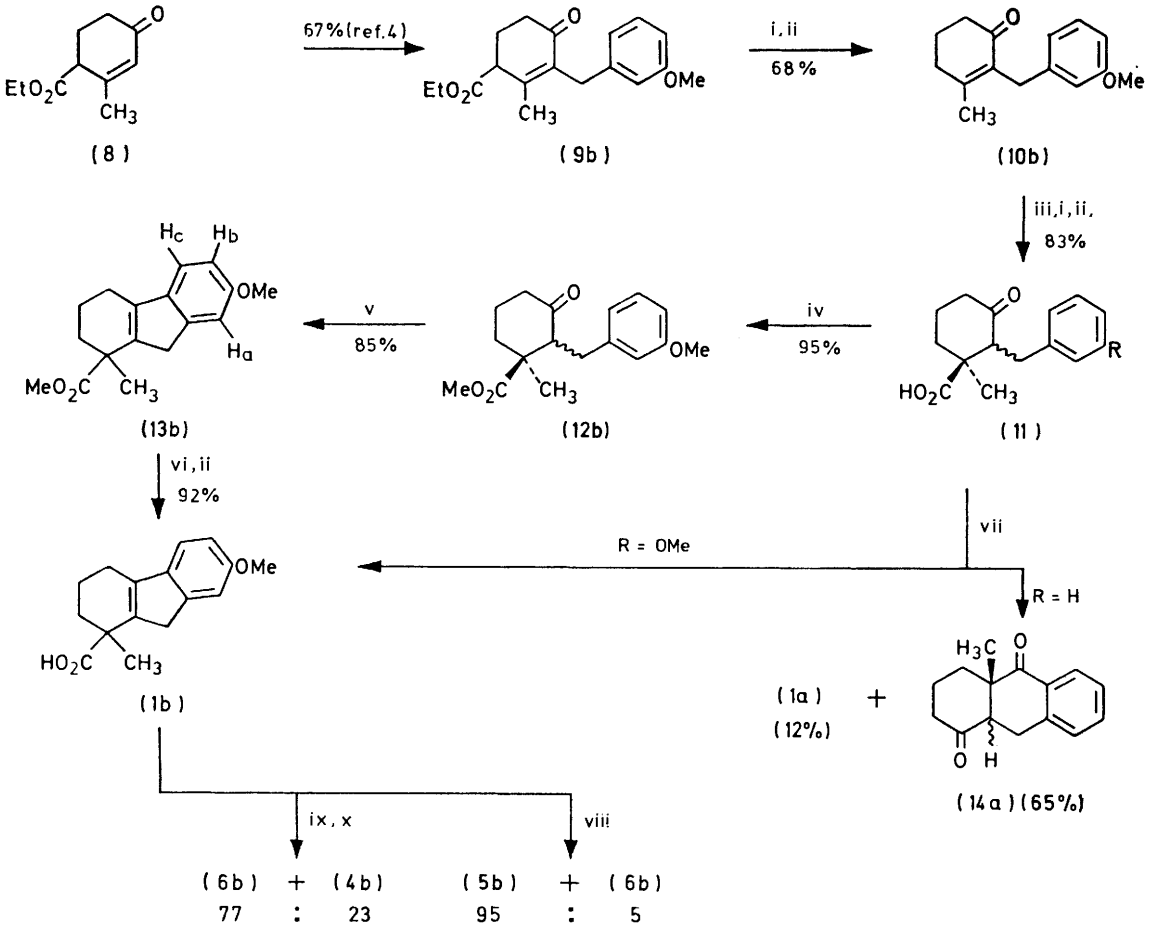
Catalytic hydrogenation of the unsaturated acid (1b) in ethanol over palladium–charcoal afforded a mixture of the epimeric *cis*-acids (5b) and (6b) in a ratio of 95 : 5, from which the major isomer could be isolated in *ca.* 90% yield. The high degree of stereoselectivity in the catalytic hydrogenation of a styrene bond containing a neighbouring carboxy group leading to the absorption of

† Part 10, U. R. Ghatak, Sh. K. Alam, and J. K. Ray, *J. Org. Chem.*, 1978, **43**, 4598.

hydrogen from the side opposite to that of the carboxy (or ester) function is now well established.[1,6-8]

Lithium–liquid ammonia reduction of the unsaturated acid (1b) afforded a mixture of (6b) and (4b) in a ratio of *ca.* 77 : 23, from which the *trans*-acid (4b) and the *cis*-benzylic monoanion (V) which gives good ring overlap leads to *cis*-acid (6b) and the less favoured anion (IV) generates the *trans*-acid (4b).

To complete the synthesis of the remaining *trans*-acid (3b), it was necessary to prepare the lactone (2b). How-



SCHEME 1 Reagents: i, KOH–H_2O–EtOH; ii, 6N-HCl; iii, KCN–H_2O–EtOH; iv, CH_2N_2–Et_2O; v, *p*-TsOH–benzene; vi, KOH–H_2O–$(CH_2OH)_2$; vii, H_2SO_4 (99%) (−12 to −10 °C); viii, H_2–Pd–C (10%)–EtOH; ix, Li–NH_3 (l); x, NH_4Cl

acid (6b) were isolated in 7 and 50% yields, respectively. This result is similar to that observed in the reduction of the demethoxy acid (1a). In earlier reports [1,6] we explained these stereochemical results by considering the initial stages of two isomeric dianions (Scheme 2) arising from the addition of two electrons to the styrene bond in (1a). The dianion (I) was considered energetically unfavourable compared with (II) owing to electrostatic repulsion of the axial C-1 carboxylate anion and benzylic anionic centre (at C-4a). However, on the basis of some recent findings [9,10] we feel that these stereochemical results can be rationally explained by considering the carboxy-assisted protonation of the highly basic neighbouring homobenzylic anion (at C-9a) in the radical anion (III) and/or in the dianion (II) stage [11] resulting in the *syn*-stereochemistry of the adjacent carboxy and the hydrogen (at C-9a) in these and the related systems. Finally, protonation of the conformationally favoured

ever, all the attempted lactonisation reactions of the acid (1b), following the procedures successfully utilised [1] for the preparation of the demethoxy lactone (2a), failed. Several other methods including bromolactonisation of

^{1}H N.m.r. spectral data for the methyl esters (15a and b), (16a and b), and (17a and b)

Compound	Chemical shift (δ) in $CDCl_3$	
	1-Me	1-CO_2Me
(15a)	1.28	3.66
(15b)	1.28	3.68
(16a)	1.36	3.68
(16b)	1.36	3.70
(17a)	1.22	3.68
(17b)	1.21	3.66

(1b) were also unsuccessful. The unusual passivity of the methoxy acid (1b) towards lactonisation may be attributed to the stabilisation of the C-4a cation due to the participation of the *p*-methoxy group.

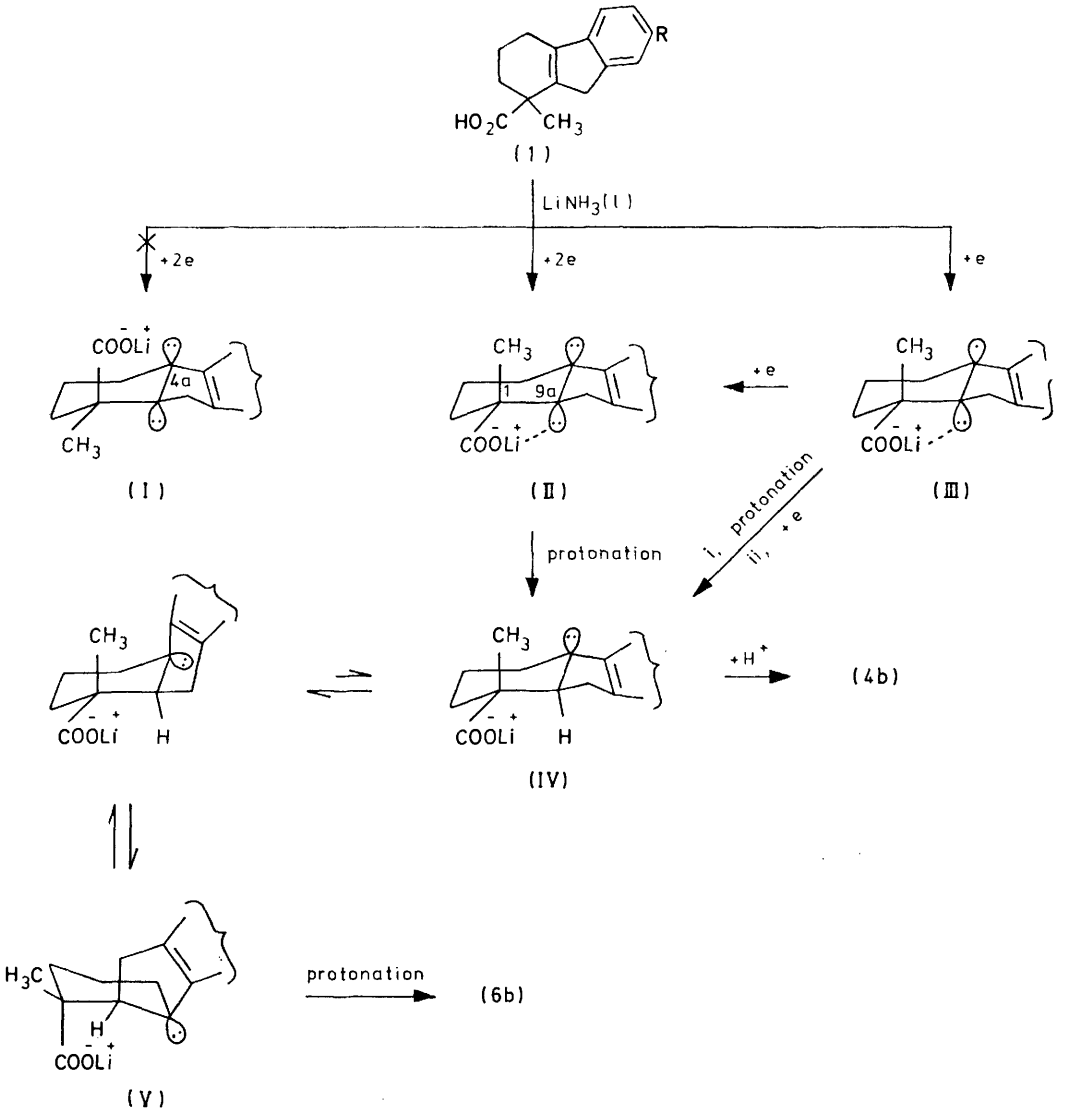
The stereochemical assignments of the three isomeric acids (4b)—(6b) are based upon the same argument and by analogy to the demethoxy analogues. Comparison of the chemical shifts of the 1-methyl group in the methyl esters (15b)—(17b) of the acids (4b)—(6b) with the methyl esters of the corresponding demethoxy acids (Table) also supports the assigned stereochemistry.

EXPERIMENTAL

The compounds described are all racemates. M.p.s and b.p.s are uncorrected. U.v. spectra were determined in 95% ethanolic solution on a Beckmann DU instrument, i.r. in $CHCl_3$ solution on a PE-21 machine, and unless otherwise mentioned, n.m.r. in CCl_4 with Me_4Si as internal standard on a Varian T-60A instrument. G.l.c. analyses were carried out on a Hewlett–Packard model 5730A apparatus using nitrogen as carrier gas. Microanalyses were performed by Mrs. C. Dutta of this laboratory. Petroleum refers to fraction of light petroleum, b.p. 60—80°. In a typical work-up, reaction mixtures were diluted with water and extracted with an organic solvent. The resulting organic phase was washed with water and brine, and then dried (Na_2SO_4). The solvent was removed under reduced pressure.

2-(m-*Methoxybenzyl*)-3-*methylcyclohex*-2-*enone* (10b).—A solution of the keto-ester (9b) [4] (112 g, 0.33 mol) in 95% ethanol (800 ml) was heated under reflux with aqueous KOH (112 g, 2 mol) in H_2O (112 ml) for 12 h under nitrogen. On cooling, the mixture was acidified with ice-cold 6N-HCl. The precipitated salt was filtered off and most of the ethanol was removed under reduced pressure. Work-up with benzene afforded a dark brown thick liquid which on distillation afforded (10b) as a *liquid* (58 g, 68%), b.p. 150—155° at 0.4 mmHg; $\lambda_{max.}$ 225 nm (log ε 4.14); δ 1.88 (3 H, s, CH_3), 2.23 (6 H, m, methylene), 3.53 (2 H, s, benzylic), 3.66 (3 H, s, OCH_3), and 6.36—7.15 (4 H, m, ArH) (Found: C, 78.4; H, 7.65. $C_{15}H_{18}O_2$ requires C, 78.25; H, 7.9%); deep red 2,4-*dinitrophenylhydrazone*, m.p. 132° (benzene–petroleum) (Found: C, 61.35; H, 5.25; N, 13.85. $C_{21}H_{22}N_4O_5$ requires C, 61.45; H, 5.4; N, 13.65%).

2-(m-*Methoxybenzyl*)-3-*methyl*-1-*oxocyclohexane*-3-*carb*-



SCHEME 2

oxylic Acid (11b).—A solution of unsaturated ketone (10b) (57 g, 0.24 mol) in 95% ethanol (535 ml) was heated under reflux with a solution of KCN (57 g, 0.87 mol) in H_2O (342 ml) for 14 h when the colour turned to brown. The cyano derivative without isolation was hydrolysed by refluxing with KOH (80 g) in H_2O (900 ml) for 96 h. Most of the alcohol was then removed. The organic phase after work-up of the acidified (6N-HCl) reaction mixture was repeatedly washed with aqueous Na_2CO_3 (5%) until alkaline. The basic washings after acidification (6N-HCl) were worked up with ethyl acetate to afford a solid (57 g, 83%), m.p. 130—140°. Recrystallisation from ether–petroleum afforded *rosettes* of (11b), m.p. 147°; $\lambda_{max.}$ 273 and 280 nm (log ε 3.3 and 3.28) (Found: C, 69.35; H, 7.3. $C_{16}H_{20}O_4$ requires C, 69.55; H, 7.3%).

The methyl ester (12b) was prepared in 95% yield by treatment of (11b) with ethereal diazomethane, b.p. 175—180° at 0.4 mmHg; $\lambda_{max.}$ 269 nm (log ε 4.01); $\nu_{max.}$ 1 730, 1 720, and 1 615 cm^{-1}; δ 1.38 (3 H, s, CH_3), 1.86 (4 H, m, methylene), 2.06—2.46 (4 H, m, methylene), 3.26 (1 H, dd, *J* 8 Hz, methine), 3.61 (3 H, s, CO_2CH_3), 3.71 (3 H, s, OCH_3), and 6.4—7.1 (4 H, m, ArH).

1,2,3,4-*Tetrahydro*-7-*methoxy*-1-*methylfluorene*-1-*carboxylic Acid* (1b).—*Method A*. A solution of the keto-ester (12b) (5.7 g, 20.05 mmol) in dry benzene (250 ml) was heated under reflux with toluene-*p*-sulphonic acid (800 mg, 4.6 mmol) for 10 h under nitrogen with azeotropic removal of water. The dark brown solution after washing successively with aqueous Na_2CO_3 (5%) and brine followed by removal of benzene, was distilled to afford a liquid (13b) (4.5 g, 85%), b.p. 170—175° at 0.4 mmHg; $\lambda_{max.}$ 269 nm (log ε 4.2); $\nu_{max.}$ 1 725 cm^{-1}; δ 1.41 (3 H, s, CH_3), 1.63—2.01 (4 H, m, methylenes), 2.1—2.76 (2 H, m, allylic), 3.3 (2 H, m, benzylic), 3.63 (3 H, s, CO_2CH_3), 3.76 (3 H, s, OCH_3), 6.58 (H_b, q, J_{bc} 8, J_{ab} 2 Hz), 6.88 (H_a, d, J_{ab} 2 Hz), and 7.0 (H_c, d, J_{bc} 8 Hz).

This ester (4.5 g, 17.3 mmol) was hydrolysed by heating under gentle reflux with a solution of KOH (4.5 g, 80.3 mmol) in H_2O (4.5 ml) and diethylene glycol (40 ml) for 2 h under nitrogen. The usual work-up of the acidified reaction mixture with ethyl acetate afforded (1b) as a brown solid (3.9 g, 92%), m.p. 148—152°. Recrystallisation from ethyl acetate–petroleum afforded the pure acid, m.p. 156—157°; $\lambda_{max.}$ 266 nm (log ε 4.3); $\nu_{max.}$ 1 710 cm^{-1} (Found: C, 74.4; H, 6.95. $C_{16}H_{18}O_3$ requires C, 74.4; H, 7.0%).

Method B. To cooled (−12 to −10°) and stirred H_2SO_4 (99%; 75 ml) was added in portions the powdered acid (11b) (5 g) for 5 min. The mixture immediately turned orange-red and was stirred for an additional 2 h when all solid went into solution. The solution was poured into crushed ice with vigorous stirring when the red colour disappeared and solid crystallised out. The solid was filtered off, washed with cold water, and dried. The filtrate, on usual work-up with ethyl acetate, afforded a little more of the acid, making a total of (1b) (4.3 g, 93%), m.p. 148—152°. A portion of it was recrystallised from ethyl acetate, m.p. and mixed m.p. 156—157°.

Cyclisation of (11a) *with Sulphuric Acid:* 10-*Methyl*-1,2,3,4,5,6,9,10-*octahydroanthracene*-4,9-*dione* (14a) *and the Unsaturated Acid* (1a).—To well stirred and cooled (−10 to −12°) H_2SO_4 (99%; 70 ml) was added powdered acid (11a) [1] (4.8 g) for 5—10 min. The mixture was stirred at −10 to −12° for a further 2 h and poured onto crushed ice with vigorous stirring. The organic material was extracted with ethyl acetate. The extract was washed with a 5% Na_2CO_3 solution and water and dried. Removal of solvent afforded (14a) (3.2 g, 65%) as a light brown thick liquid which solidified on scratching, m.p. 120—125°; $\nu_{max.}$ 1 700 and 1 670 cm^{-1}. Crystallisation from ether afforded a pure sample, m.p. and mixed m.p. 130°.[1] The basic aqueous part on acidification and usual work-up with ethyl acetate afforded the unsaturated acid (1a) (0.6 g, 12%), m.p. and mixed m.p. 146—147°.[1]

Catalytic Hydrogenation of the Unsaturated Acid (1b). (±)-1,2,3,4,4aβ,9aβ-*Hexahydro*-7-*methoxy*-1β-*methylfluorene*-1α-*carboxylic Acid* (5b).—The unsaturated acid (1b) (1.5 g) was hydrogenated in ethanol (50 ml) over 10% Pd–C (200 mg) for 30 min to afford a mixture, m.p. 142—147°, of (5b) and (6b) in 95 : 5 (g.l.c.* and n.m.r. of the crude methyl ester mixture by CH_2N_2 esterification). Repeated crystallisation from ether–petroleum afforded pure (5b) (1.35 g, 90%), m.p. 153°; $\lambda_{max.}$ 255, 260, and 280 nm (log ε 2.7, 2.8, and 3.4) (Found: C, 74.0; H, 7.9. $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.75%). The acid (5b) (100 mg) was esterified with an excess of ethereal diazomethane. The methyl ester (16b) thus obtained was purified by filtration through a short column of neutral alumina followed by crystallisation from light petroleum (b.p. 40—60°) to afford a solid, m.p. 66°; δ($CDCl_3$) 1.36 (3 H, s, CH_3), 1.51—1.76 (5 H, m), 2.43—3.08 (5 H, m), 3.70 (3 H, s, CO_2CH_3), 3.75 (3 H, s, OCH_3), and 6.55—7.1 (3 H, m, ArH); R_t (column A) 6.8 min.

Reduction of the Unsaturated Acid (1b) *with* Li–NH_3. (±)-1,2,3,4,4aα,9aα-*Hexahydro*-7-*methoxy*-1β-*methylfluorene*-1α-*carboxylic Acid* (6b) *and* (±)-1,2,3,4,4aβ,9aα-*Hexahydro*-7-*methoxy*-1β-*methylfluorene*-1α-*carboxylic Acid* (4b).—To a well stirred solution of the unsaturated acid (1b) (950 mg, 3.4 mmol) in dry tetrahydrofuran (7 ml) and anhydrous liquid ammonia (250 ml) distilled directly from the cylinder, was added freshly scraped lithium wire (500 mg, 0.07 mol) in small portions over 2 min. The mixture was decomposed by addition of powdered NH_4Cl. Evaporation of ammonia followed by the usual work-up with ether afforded a solid (800 mg), m.p. 172—175°, found to be a mixture of (4b) and (6b) in a ratio of 23 : 77 by g.l.c. and n.m.r. (of methyl esters). Fractional crystallisation from petroleum afforded first pure (4b) (70 mg, 7%), m.p. 148°; $\lambda_{max.}$ 280 nm (log ε 3.4) (Found: C, 73.55; H, 7.8. $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.75%).

The acid (4b) (50 mg) was esterified with an excess of ethereal diazomethane. The methyl ester (15b) was purified by filtration through a short column of neutral alumina to afford a liquid; δ($CDCl_3$) 1.28 (3 H, s, CH_3), 1.6—1.76 (5 H, m), 2.03—2.70 (5 H, m), 3.68 (3 H, s, CO_2CH_3), 3.75 (3 H, s, OCH_3), and 6.58—7.08 (3 H, m, ArH); R_t (column B) 10.7 min.

The mother-liquor on repeated crystallisation from ethyl acetate–petroleum afforded the *acid* (6b) (500 mg, 50%), m.p. 188° (Found: C, 73.75; H, 7.85. $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.75%). The acid (6b) (100 mg) was esterified with an excess of ethereal diazomethane. The methyl ester (17b) thus obtained was purified by filtration through a short column of neutral alumina to afford a liquid, δ($CDCl_3$) 1.21 (3 H, s, CH_3), 1.41—2.0 (5 H, m), 2.56—2.93 (5 H, m), 3.66 (3 H, s, CO_2CH_3), 3.73 (3 H, s, OCH_3), and

* G.l.c. was carried out using two different columns: SE–52 (6 ft × ⅛ in.) at 230°; column B, 10% UCW–982 (2.5 ft. × ⅛ in.) at 180°. R_t denotes retention time.

6.5—7.06 (3 H, m, ArH); R_t (columns A and B) 6 and 9.1 min, respectively.

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