Synthetic Studies in the Eremophilane Sesquiterpene Group. Synthesis of Flourensic Acid

Joe N. Herron and A. Reginald Pinder *
Department of Chemistry, Clemson University, Clemson, S. Carolina 29631, U.S.A.

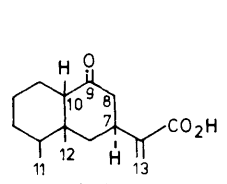
Experiments directed towards the synthesis of (±)-flourensic acid are described, starting with readily available bicyclic structures. Eremophilone was ultimately converted into the (+)-acid in eight steps, providing corroboration of the proposed structure and configuration.

Flourensic acid, a sesquiterpene of the non-isoprenoid eremophilane family, occurs in the flowers of the native Mexican shrub *Flourensia cernua* DC (Compositae). It was isolated therefrom by Kingston and collaborators,[1,2] who on the basis of chemical transformations and spectroscopic studies proposed structure and stereochemistry (1) for the acid. We describe here investigations which have culminated in its synthesis and which provide corroboration of the proposed structure and configuration.

Two aspects of structure (1) were borne in mind at the outset of a synthetic approach: the rings are *cis*-fused, and from stereochemical correlations [1,2] and because of the 7β and equatorial disposition of the side chain at C-7, the fusion must be steroidal in nature. Structure and conformation (2) represents a more detailed picture of the molecule.

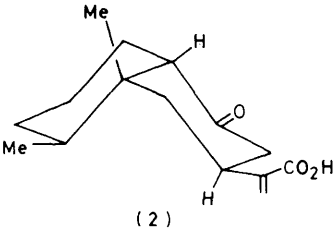
We began with the octalone (3) [3] and converted it into the acid (4),[4] both compounds being of established stereochemistry. Catalytic hydrogenation of the latter furnished a mixture of acids (5) and (6) in ratio about 3 : 2,[4] separation being tedious and wasteful. Efforts to increase the proportion of (5), convertible into flourensic acid by side-chain modification and keto-group transposition, working with both (4) and its ethyl ester, were unsuccessful. Similar experiments with the glyoxylate ester (7), obtainable from (3) by reaction with diethyl oxalate, were also unrewarding, a complex mixture of products resulting. An attempted selective dithioacetalisation of (7) to (8) failed, despite literature precedents [5] for preferred attack on conjugated enones. Desulphurisation of (8) would have led to (9), and thence to the target acid *via* several simple steps.

The octalone (10) was next explored as a synthon. It was prepared from (3) by epoxidation to (11), which with methanolic base gave the methoxy-enone (12).[6] This when subjected to a Bamford-Stevens reaction yielded the methoxydiene (13), acid hydrolysis of which afforded the desired enone (10) in good yield. The *trans* ring junction was established by comparison with (10) reached by a different pathway,[7] and by comparison of its dihydro-derivative with (14), also arrived at by a different route.[8] Seeking to improve the preparation of (10) we treated the *cis*-lactone (15) [3] with methylthiomethyl-lithium [9] (Belleau reaction) to obtain the dione (16), cyclised by base to (17). A similar Bamford-Stevens reaction then gave (18), hydrolysable to (10) in comparable overall yield. Usually organocuprates add to cyclic, conjugated ketones by approaching the β-carbon orthogonally to the enone plane,[10] leading to an axial adduct. It was hoped that with (10) such an addition would be accompanied by inversion at C-8a to yield a steroidal *cis* ring junction, so that the original 6β (axial) product (19) would become 6β-equatorial as in (20).[11] A non-steroidal union in (20) was not anticipated since in it both β-substituents at C-4 and C-6 would be axial. Attempts were therefore made to add to (10) the lithium organocuprates (21) and (22) [12] but, unfortunately, no addition occurred, even under forcing conditions. Slightly better results (19% yield) were realised with the Grieco reagents [13] (23) or (24), leading after hydrolysis to (25). The *trans* ring fusion in (25) was settled by n.m.r. spectral comparison with steroidal examples, using Zürcher's tables.[14] The product appeared stable to base and we therefore concluded that the 6-substituent was equatorial and α, in part confirmed by oxidation of (25) to the corresponding acid which proved not to be identical [mass spec., n.m.r., and i.r. (solution) spectral comparison] with natural flourensic acid (1). Evidently there is severe steric hindrance by the angular methyl group in (10) to conjugate addition.

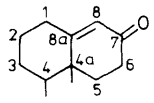


(1)

(Flourensic acid numbering)

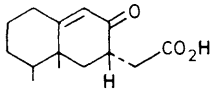


(2)

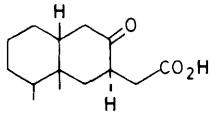


(3)

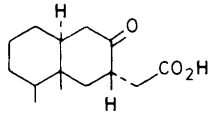
(Naphthalene numbering)



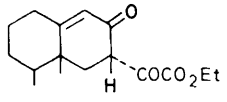
(4)



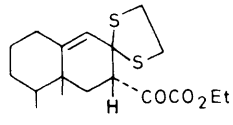
(5)



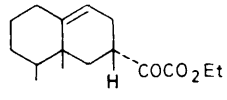
(6)



(7)

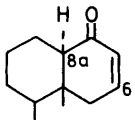


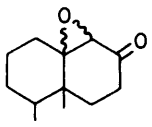
(8)

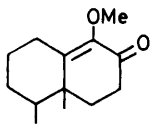


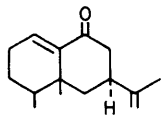
(9)

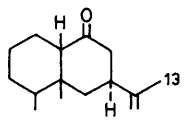
Attention was next turned to (−)-eremophilone (26) as starting point. It was converted into *cis*-1,10-dihydroeremophilone (27),[15] of proven stereochemistry corresponding to

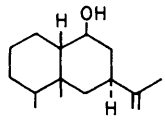

(10)

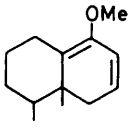

(11)

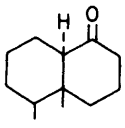

(12)

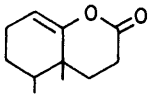

(26)

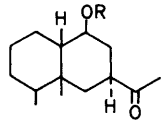

(27)

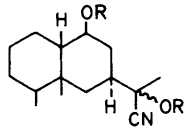

(28)

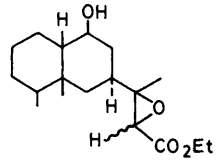

(13)

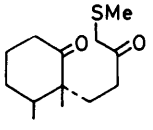

(14)

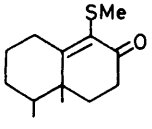

(15)

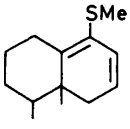

(29) R = H
(35) R = $SiMe_3$

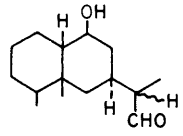

(30) R = $SiMe_3$
(31) R = H

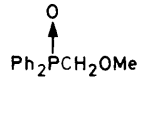

(32)

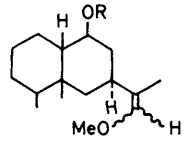

(16)

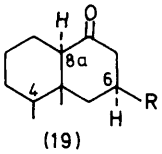

(17)

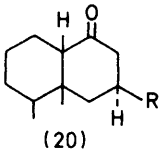

(18)

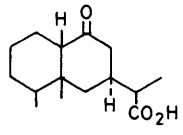

(33)

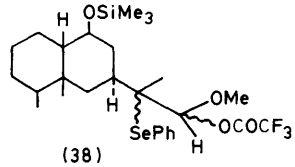

(34)

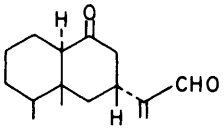

(36) R = $SiMe_3$
(36a) R = H

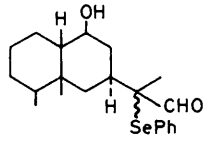

(19)

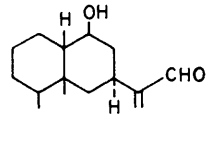

(20)

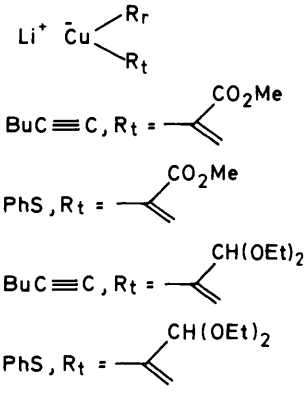

(37)


(38)


(25)


(39)


(40)


(21) R_r = BuC≡C, R_t =
(22) R_r = PhS, R_t =
(23) R_r = BuC≡C, R_t =
(24) R_r = PhS, R_t =

that of flourensic acid (1). Attempted selective 13-bromination of (27) failed, as did attempted selective oxidation at the same position with selenium dioxide or chromium trioxide–3,5-dimethylpyrazole complex;[16] in both cases mixtures of products resulted. It was hoped to modify the reactivity of the substrate by working with its 8-ethylene acetal, but we succeeded in effecting only a partial formation of this compound, presumably owing to steric hindrance of the keto-group in (27).

Ozonolysis of *cis*-dihydroeremophilol (28)[15] afforded the methyl ketone (29), which with trimethylsilyl cyanide (2 mol equiv.)[17] yielded the bistrimethylsilyl ether (30), hydrolysed by dilute acid to the diol (31). However the latter compound suffered a ready elimination of HCN, reverting to (29), when efforts were made to transform the side chain into an acrylic acid residue. A Darzens glycidic ester condensation between (29) and ethyl chloroacetate furnished the ester (32) as a pair of diastereoisomers. Hydrolysis gave the diastereoisomeric carboxylic acids, but attempts to decarboxylate these to the aldehydes (33) failed. A satisfactory route to (33) was treatment of the methyl ketone (35) in a Wittig-Horner reaction with the anion of diphenyl(methoxymethyl)phosphine oxide (34).[18] The product (78% yield) was the enol ether (36), which was smoothly hydrolysed to the hydroxy-aldehyde (33). Oxidation of the latter with Jones reagent afforded keto-acid (37), which proved to be identical (i.r., n.m.r., and mass spec. comparison) with dihydroflourensic acid.[2]

Treatment of the enol ether (36) with phenylseleninyl trifluoroacetate[19] gave the adduct (38), acid hydrolysis of which generated the aldehyde (39). Hydrogen peroxide then effected elimination *via* the selenoxide to the hydroxy-aldehyde (40); as anticipated, from an examination of molecular models (Newman projections) none of the isomeric product with an exocyclic double bond was encountered. Jones oxidation of (40) afforded a crystalline keto-acid which proved to be identical in all respects with an authentic sample of natural (+)-flourensic acid (1) (mixed m.p. and spectral comparisons).

Since (±)-, but not (−)-eremophilone, has been totally synthesised[20] this work constitutes a partial synthesis of (+)-flourensic acid, and corroborates the proposed structure and configuration.

Experimental

M.p.s are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 137 instrument. N.m.r. spectra were measured on a JEOL FX-90Q spectrometer, with $SiMe_4$ as internal standard. Mass spectra were obtained on a Hewlett-Packard

5895 GC/MS System. Gas chromatography was performed on an F. and M. Model 810 Research Chromatograph. Petroleum refers to light petroleum b.p. 30—60 °C. Silica gel refers to Fisher S-622, 60—200 mesh.

Ethyl 4β,4aβ-*Dimethyl*-8-*oxo*-1,2,3,4,5,6,7,8-*octahydronaphthalene*-6-*glyoxylate* (7).—Sodium metal (0.26 g, 11.2 mg-atom) was dissolved in dry ethanol (25 ml) and the solvent removed under reduced pressure. The cake of sodium ethoxide was broken up under dry benzene (20 ml) in helium and stirred magnetically during addition of the octalone (3) (0.92 g, 5.2 mmol) in a little dry benzene. After a few minutes' stirring diethyl oxalate (1.64 g, 11.2 mmol) in a little dry benzene was added during a few min, and the mixture stirred for 24 h at room temperature. Ice–water was added, and the layers were separated. The organic layer was washed once with cold, dilute alkali and the aqueous layers were combined, cooled in ice, and acidified. The liberated *keto-ester* was taken up in ether and the extract washed with water, dried, and concentrated. It distilled at 155—160 °C (bath) (0.05 mmHg) (1.11 g, 77%) as a yellow oil which gave an intense purple colour with ferric chloride; $\nu_{max.}$ (film) 3 300, 1 776, 1 742, 1 672, and 1 618 cm^{-1}; δ($CDCl_3$) 5.87 (1 H, s, vinyl H), 4.33 (2 H, q, *J* 6.6 Hz, OCH_2CH_3), 2.29 (2 H, m, $CH_2CHCOCO_2Et$), 1.38 (3 H, t, *J* 6.6 Hz, OCH_2Me), 0.99 (3 H, s, 4a-Me), and 0.97 (3 H, unresolved d, 4-Me); *m*/*z* 278 (M^+) (Found: C, 69.3; H, 7.85. $C_{16}H_{22}O_4$ requires C, 69.0; H, 8.0%).

4β,4aβ-*Dimethyl*-8-*methoxy*-1,2,3,4,5,6-*hexahydronaphthalen*-7(6H)-*one* (12).—A solution of the octalone (3) (3.93 g, 22.1 mmol) in methanol (25 ml) was treated with 30% (w/w) hydrogen peroxide [6] (6.5 ml, 67.8 mmol) and stirred at 15 °C during addition of 6M-aqueous sodium hydroxide (1.9 ml, 11 mmol) during 1 h. After a further 3 h at room temperature the whole was poured into ice–water and extracted with ether. The dried extract was concentrated, leaving the *epoxide* (11) (3.48 g, 81%), which appeared to be a single compound on g.l.c.; $\nu_{max.}$ (film) 1 709 cm^{-1}; *m*/*z* 194 (M^+). This epoxy-ketone (1.0 g, 5.2 mmol) in methanol (100 ml) was refluxed for 24 h with a solution of potassium hydroxide (2.3 g) in methanol (175 ml). The solvent was removed under reduced pressure, ice–water was added, and the product isolated with methylene chloride. Evaporation of the dried extract gave the *methoxy-enone* (12) (0.77 g, 71%), b.p. 100—110 °C (bath) (0.07 mmHg); $\nu_{max.}$ (film) 1 667 and 1 602 cm^{-1}; δ($CDCl_3$) 3.52 (3 H, s, OMe), 1.11 (3 H, s, 4a-Me), and 0.91 (3 H, unresolved d, 4-Me); $\lambda_{max.}$ (EtOH) 254 nm (ε 9 700); *m*/*z* 208 (M^+) (Found: C, 75.0; H, 9.55. $C_{13}H_{20}O_2$ requires C, 75.0; H, 9.7%).

4β,4aβ-*Dimethyl*-1,2,3,4,4a,5-*hexahydro*-8aα-*naphthalen*-8(8aH)-*one* (10).—The preceding methoxy-ketone (12) (0.87 g, 4.2 mmol) was refluxed in dry ethanol (5 ml) with toluene-*p*-sulphonylhydrazine (0.90 g, 4.8 mmol) for 1.5 h. The resulting hydrazone was taken up in dry ether (85 ml) and to the solution was added all at once methyl-lithium (10.0 ml of a 1.33M solution in ether, 13.3 mmol). The mixture was refluxed for 1.5 h under helium. Decomposition with ice–water and extraction with methylene chloride furnished, after evaporation, a reddish oil which was mixed with 5% HCl (30 ml) and kept at ambient temperature for 20 min. Ice–water was added and the product isolated with ether. Concentration yielded the *enone* (10), which distilled at 73—80 °C (bath) (0.025 mmHg) (0.43 g, 58%) as a pale yellow liquid; $\nu_{max.}$ (film) 1 684 and 1 615 cm^{-1}; δ($CDCl_3$) 6.70 (1 H, ddd, *J* 10.1, 5.6, 2.8 Hz, 6-H), 5.87 (1 H, ddd, *J* 10.1, 2.8, 1.2 Hz, 7-H), 0.80 (3 H, d, *J* 5.4 Hz, 4-Me), and 0.73 (3 H, s, 4a-Me); $\lambda_{max.}$ (EtOH) 231 nm (ε 5 800); *m*/*z* 178 (M^+). The 2,4-*dinitrophenylhydrazone* separated from ethanol in feathery, red needles, m.p. 158.5—160.5 °C (Found: C, 60.4; H, 6.2; N, 17.6. $C_{18}H_{22}N_4O_4$ requires C, 60.3; H, 6.2; N, 17.9%).

4β,4aβ-*Dimethyl*-8-*methylthio*-1,2,3,4,4a,5-*hexahydronaphthalen*-7(6H)-*one* (17).—Methylthiomethyl-lithium was prepared [9] by addition of dimethyl sulphide (6.42 ml, 87.4 mmol) to the complex formed by dropwise addition of tetramethylethylenediamine (13.2 ml, 87.5 mmol) to a cooled, stirred solution of n-butyl-lithium in hexane (46 ml of 1.9M; 87.4 mmol). The mixture was stirred at room temperature for 6 h; it was then added during 10 min to a stirred solution of the *cis*-enol lactone (15) [3] (15.3 g, 85.0 mmol) in dry ether (100 ml) at −40 °C, under helium. The mixture was stirred at −25 °C for 2 h, then allowed to reach ambient temperature and poured into ice-cold dilute HCl. The product, the *diketone* (16), isolated with ether, was mixed with water (105 ml), methanol (850 ml), and KOH (13.95 g) and refluxed for 1 h under nitrogen. The solvent was removed under reduced pressure and the residue diluted with brine and extracted with methylene chloride. Concentration of the dried extract gave a reddish oil (17.5 g) which was chromatographed on silica gel (350 g), with light petroleum–diethyl ether (3 : 1) elution. The oily *ketone* (17) distilled at 125—130 °C (bath) (0.15 mmHg) (11.5 g, 61%); $\nu_{max.}$ (film) 1 681 cm^{-1}; δ($CDCl_3$) 2.18 (3 H, s, SMe), 1.14 (3 H, s, 4a-Me), and 0.92 (3 H, d, *J* 5.7 Hz, 4-Me); $\lambda_{max.}$ (EtOH) 245 nm (ε 9 300); *m*/*z* 224 (M^+) (Found: C, 69.4; H, 9.0; S, 14.2. $C_{13}H_{20}OS$ requires C, 69.6; H, 9.0; S, 14.3%).

4β,4aβ-*Dimethyl*-1,2,3,4,4a,5-*hexahydro*-8aα-*naphthalen*-8(8aH)-*one* (10).—The foregoing enone (6.16 g, 27.5 mmol) in THF (60 ml) was treated with toluene-*p*-sulphonylhydrazine (5.67 g, 30.4 mmol) and a few crystals of toluene-*p*-sulphonic acid, and the whole refluxed for 4 h. The solvent was removed and the residue dissolved in dry ether (30 ml) and stirred during the addition of methyl-lithium (70 ml of 1.25M in ether, 87.5 mmol) during 20 min. The mixture was stirred a further 3½ h, then quenched with methanol, poured into ice-water, and extracted with light petroleum. The dried extract was concentrated and the residual oily diene (18) was purified by filtration of a petroleum solution through a plug of alumina. Concentration afforded a pale yellow oil (4.31 g, 75%), *m*/*z* 208 (M^+).

This product, acetonitrile (45 ml), water (15 ml), and mercuric chloride (10.6 g, 39.0 mmol) were refluxed for 2 h. The mixture was diluted with ice–water and extracted with light petroleum. The extract was dried, the solvent removed, and the residue (3.88 g) chromatographed on silica gel (100 g), with elution with 15% (v/v) diethyl ether in light petroleum. Evaporation afforded the enone (10) (1.76 g, 48%), identical with the product described above. Comparison of spectral data of both products with those reported by Hagiwara *et al.*[7] for ketone (10) indicated they were identical.

1,2,3,4,4a,5,6,7,8,8a-*Decahydro*-4β,4aβ-*dimethyl*-8-*oxo*-8aα-6-*naphthylacraldehyde* (25).—α-Bromoacrylaldehyde diethyl acetal [21] (3.76 g, 18.0 mmol) in dry ether (11 ml) at −78 °C was treated gradually with n-butyl-lithium (12.8 ml of 1.4M in hexane, 18.0 mmol) and stirred at this temperature for 2 h under helium. Sodium thiophenoxide was prepared by dropwise addition of n-butyl-lithium (quantity as above) at below 0 °C to a swirled ethereal solution of thiophenol (1.98 g, 18.0 mmol) in dry ether (11 ml), all under helium. This solution was kept for a few minutes, then added dropwise to a suspension of cuprous iodide (3.42 g, 18.0 mmol) in dry ether (11 ml) under helium. The yellow suspension was stirred at room temperature for a few minutes then cooled to −78 °C. To it was added during a few minutes the above α-lithio-

acrylaldehyde, and the mixture was then stirred for 1 h at −78 °C. The octalone (10) (429 mg, 2.41 mmol) in ether (11 ml) was then added during a few minutes at −78 °C. The mixture was stirred at −78 °C for 1 h and then allowed to warm to −40 °C; it was stirred at that temperature for 4 h. 10% Aqueous ammonium chloride was added at −40 °C, and the temperature allowed to reach ambient. Solid material was removed by filtration and the product isolated with ether. The extract was washed with dilute alkali and brine, dried, and concentrated. The residue (1.33 g) in ether (15 ml) was stirred with 10% HCl (40 ml) for 3½ h, the product being isolated with ether and chromatographed on silica gel (40 g). Elution with 40—50% diethyl ether in light petroleum afforded the *aldehyde* (25) (106 mg, 19%); $\nu_{max.}$ 2 717, 1 709, 1 618, and 856 cm^{-1}; δ($CDCl_3$) 9.54 (1 H, s, CHO), 6.30 (1 H, s, methylene H *cis* to CHO), 6.06 (1 H, s, methylene H *trans* to CHO), 0.81 (3 H, d, *J* 5.9 Hz, 4-Me_3), and 0.75 (3 H, s, 4a-Me); $\lambda_{max.}$ (EtOH) 220 nm (ε 6 100); *m/z* 234.1614 (M^+): ($C_{15}H_{22}O_2$ requires M^+, 234.1619). To this aldehyde (100 mg) in permanganate-stable acetone (10 ml) was added 8N-Jones reagent gradually, with stirring, until the orange colour persisted. Ice–water was added and the acid product extracted with chloroform. Concentration of the dried extract gave a gum which was chromatographed on silica gel with 5% methanol–chloroform elution. Evaporation afforded the acid product as a colourless gum which proved to be different from flourensic acid (1) by spectral comparison; $\nu_{max.}$ (film) 3 660—2 500, 1 709, 1 704, and 1 623 cm^{-1}; δ($CDCl_3$) 6.37 (1 H, s, methylene H *cis* to CO_2H), 5.68 (1 H, s, methylene H *trans* to CO_2H), 0.83 (3 H, d, *J* 5.7 Hz, 4-Me_3), 0.73 (3 H, s, 4a-Me); *m/z* 250 (M^+).

6β-*Acetyl*-1,2,3,4,4a,5,6,7,8,8a-*decahydro*-4β,4aβ-*dimethyl*-8aβ-*naphthalen*-8-*ol* (29).—Ozone was bubbled through a solution of dihydroeremophilol (28) [15] (2.20 g, 9.88 mmol) in glacial acetic acid (50 ml) for 5.5 h at room temperature. Zinc dust was added and the mixture kept for 2.5 h. The filtered solution was diluted with ice–water and the product secured by ether extraction. The extracts were washed with hydrogen carbonate until neutral, dried, and concentrated. The residual *ketone* distilled at 120—123 °C (bath) (0.05 mmHg) (1.55 g, 70%), single peak on g.l.c.; $\nu_{max.}$ (film) 3 251 and 1 709; δ($CDCl_3$) 3.98 (1 H, ddd, *J* 10.8, 10.8, 4.6 Hz, C*H*OH), 3.94br (1 H, CHO*H*), 2.58 (1 H, tt, *J* 12.7, 3.1 Hz, C*H*COMe), 2.13 (3 H, s, CoMe), 0.92 (3 H, s, 4a-Me), and 0.75 (3 H, d, *J* 6.4 Hz, 4-Me_3); *m/z* 224 (M^+) (Found: C, 74.8; H, 10.7. $C_{14}H_{24}O_2$ requires C, 74.95; H, 10.8%).

6β-(1-*Cyano*-1-*trimethylsilyloxyethyl*)-1,2,3,4,4a,5,6,7,8,8a-*decahydro*-4β,4aβ-*dimethyl*-8β-*trimethylsilyloxy*-8aβ-*naphthalene* (30).—The foregoing ketol (1.41 g, 6.3 mmol) in dry methylene chloride (10 ml) containing a trace of zinc iodide was treated dropwise with a 4.0M-solution of trimethylsilyl cyanide in methylene chloride (3.5 ml, 14 mmol), during 5 min.[17] After being stirred at 0 °C for 1 h and at room temperature for 12 h, the solution was concentrated under reduced pressure to give the *nitrile* (30), b.p. 124—130 °C (bath) (0.15 mmHg) (1.84 g, 74%) as a mixture of diastereoisomers; $\nu_{max.}$ (film) 1 247, 840, 753 (all SiMe), 1 035 (SiO), no noticeable CN band; [22] δ($CDCl_3$) 3.94 (1 H, ddd, *J* 10.3, 10.3, 4.4 Hz, C*H*OTMS), 1.50, 1.51 (3 H, two s, MeCCN), 0.91 (3 H, s, 4a-Me), 0.72 (3 H, d, *J* 6.2 Hz, 4-Me), 0.22 (9 H, s, Me_3SiOCCN), and 0.10 (9 H, s, Me_3SiOCH) (Found: C, 63.5; H, 10.4. $C_{21}H_{40}NO_2Si_2$ requires C, 63.9; H, 10.15%).

6β-(1-*Cyano*-1-*trimethylsilyloxyethyl*)-1,2,3,4,4a,5,6,7,8,8a-*decahydro*-4β,4aβ-*dimethyl*-8aβ-*naphthalen*-8β-*ol* (31).—The preceding disilyl ether (0.42 g, 1.1 mmol) was stirred with 10% HCl at room temperature for 3 h. The mixture was diluted with water and the product isolated with ether in the usual way. Concentration gave a semisolid mass (0.27 g) of the desired *diol* (31), which crystallised from chloroform–hexane as prisms, m.p. 186—189 °C (decomp.); $\nu_{max.}$ ($CHCl_3$) 3 533 cm^{-1}, no CN band; * δ[$(CD_3)_2SO$] 6.30br (1 H, HO–CCN), 4.46, 4.39br (1 H, 8-OH), 3.76br (1 H, C*H*OH), 1.43br (3 H, *Me*CCN) 0.88br (3 H, 4a-Me), 0.72, 0.70 (3 H, 2 d, *J* 6.4, 6.4 Hz) (Found: C, 71.5; H, 10.1. $C_{15}H_{25}NO_2$ requires C, 71.7; H, 10.0%). This cyanohydrin was found to be very labile, losing HCN readily to revert to the ketone (29).

6β-*Acetyl*-1,2,3,4,4a,5,6,7,8,8a-*decahydro*-4β,4aβ-*dimethyl*-8β-*trimethylsilyloxy*-8aβ-*naphthalene* (35).—Trimethylsilylacetamide (1.30 g, 9.9 mmol) [23] and the ketol (29) (1.42 g, 6.3 mmol) were heated together at 150 °C under He for 1.5 h. The *product* distilled at 110—113 °C (bath) (0.03 mmHg) (1.35 g, 72%); $\nu_{max.}$ (film) 1 733 (C=O), 1 253, 842, 752 (all $SiMe_3$)], and 1 083 cm^{-1} (SiO); δ($CDCl_3$) 3.97 (1 H, ddd, *J* 10.6, 10.6, 4.5 Hz, C*H*OTMS), 2.56 (1 H, tt, *J* 12.7, 3.1 Hz, CHCO), 2.13 (3 H, s, CO*Me*), 0.92 (3 H, s, 4a-Me), 0.76 (3 H, d, *J* 6.2 Hz, 4-Me), and 0.12 (9 H, s, $SiMe_3$) (Found: C, 68.8; H, 11.0. $C_{17}H_{32}O_2Si$ requires C, 68.9; H, 10.8%).

1,2,3,4,4a,5,6,7,8,8a-*Decahydro*-8β-*hydroxy*-4β,4aβ-*dimethyl*-8aβ-*naphthalen*-6-*ylpropanal* (33).—Lithium di-isopropylamide was prepared by mixing n-butyl lithium (4.3 ml of 1.16M in hexane, 5.0 mmol) and di-isopropylamine (0.53 g, 5.2 mmol) in THF (5 ml) at 0 °C under He. The mixture was stirred at 0 °C for 15 min. A solution of diphenyl(methoxymethyl)phosphine oxide [18] (1.25 g, 5.1 mmol) in THF (5 ml) was added during 5 min. The orange solution was stirred for 10 min at 0 °C and then the ketone (35) (0.3 g, 1.0 mmol) in THF (6 ml) was added during 20 min. The resulting solution was allowed to reach room temperature and then stirred for 65 h. It was then diluted with ice–water and extracted several times with diethyl ether. Evaporation of the dried extracts yielded a syrup which was dissolved in dry THF (50 ml) and stirred with sodium hydride (from 0.37 g 50% oil dispersion washed several times with light petroleum) for 24 h under helium. Ice–water was added cautiously and the product isolated with ether. The residue after evaporation was taken up in THF (30 ml), treated with 5% aqueous HCl (25 ml), and kept at room temperature 40 min. Ice–water was again added and the desired aldehyde (33) isolated with diethyl ether. It was chromatographed on silica gel (26 g) with elution with diethyl ether–petroleum (1 : 1). The product distilled at 120—125 °C (bath) (0.1 mmHg) (93 mg, 39%); $\nu_{max.}$ 3 496, 2 755, and 1 727 cm^{-1}; δ($CDCl_3$) 9.63 (1 H, s, CHO), 4.00 (1 H, ddd, *J* 10.8, 10.8, 4.4 Hz, C*H*OH), 1.05 (3 H, d, *J* 6.6 Hz, *Me*CHCHO), 0.88 (3 H, s, 4a-Me), and 0.72 (3 H, d, *J* 6.2 Hz, 4-Me); *m/z* 238 (M^+), 237.

Dihydroflourensic Acid (37).—The preceding aldol (33) (54 mg, 0.23 mmol) in permanganate-stable acetone (5 ml) was shaken during the gradual addition of 8N-Jones reagent (1.2 ml, 9.6 mequiv.) at room temperature. Next day the mixture was diluted with ice–water and extracted thoroughly with diethyl ether. Evaporation yielded a gum which was shaken with aqueous NaOH (1M; 25 ml), insoluble matter being removed with diethyl ether. The aqueous phase was acidified and extracted with diethyl ether. Concentration of the dried extracts yielded an acidic gum (45 mg) the spectral properties of which were identical with those of dihydroflourensic acid: [2] $\nu_{max.}$ (film) 3 700, 1 739, 1 701, 1 430, 1 381, 1 080, 960, 910 cm^{-1}; δ($CDCl_3$) 10.11 (1 H, s, CO_2H), 1.16 (3 H, d, *J*, 6.8 Hz, *Me*CHCO$_2$H), 1.04 (3 H, s, 5-Me),

* This spectral behaviour is common with cyanohydrins.[22]

0.77 (3 H, d, *J* 5.5 Hz, 4-Me); *m/z* 252 (M^+), 237, 234, 183, 179, 165, 161, 137, 119, 117.

1,2,3,4,4a,5,6,7,8,8a-*Decahydro*-6β-(2-*methoxy*-1-*methylvinyl*)-4β,4aβ-*dimethyl*-8aβ-*naphthalen*-8β-*ol* (36a).—A solution of diphenylmethoxymethylphosphine oxide [18] (3.43 g, 13.9 mmol) in dry THF (25 ml) was cooled to −78 °C and stirred during addition of s-butyl-lithium (10.9 ml of 1.16M in cyclohexane, 12.6 mmol) over 30 min. After being further stirred for 10 min at this temperature the mixture was allowed to reach room temperature (30 min). A solution of trimethylsilyloxyketone (35) (0.75 g, 2.53 mmol) in dry THF (10 ml) was added during 5 min, and the mixture was stirred for 21 h. Methanol (6 ml) was added, followed by ice–water, and the mixture was extracted thoroughly with diethyl ether. Evaporation of the dried extracts afforded a brown syrup (3.2 g) which was taken up in dry THF (125 ml) and stirred with sodium hydride (1.12 g of a 50% oil dispersion, washed by decantation with light petroleum, 23.3 mmol) for 42 h at room temperature under helium. Methanol (10 ml) was added cautiously, followed by ice–water, and the product isolated by diethyl ether extraction. Concentration yielded a reddish syrup which was chromatographed on silica gel (60 g), with elutions with diethyl ether–light petroleum. 10% Diethyl ether afforded, after evaporation, the *trimethylsilyl ethers* (36) (*Z*- and *E*-isomers) (93.4 mg, 11%) (*m/z* 324, M^+). Elution with 50% diethyl ether gave the alcohol (36a) (427 mg, 67%) (*Z*- and *E*-isomers), $\nu_{max.}$ (film) 3 533 and 1 664 (C=C); δ($CDCl_3$) 5.67br and 5.79br (1 H, vinyl H), 4.01 (1 H, m, C*H*OH), 3.54 and 3.49 (3 H, s, OMe), 1.56 and 1.45 (3 H, both d, *J* 1.3 Hz, C=CMe), 0.88 (3 H, s, 4a-Me), 0.74 and 0.72 (3 H, both d, *J* 6.4 Hz, 4-Me) (Found: C, 76.1; H, 11.2. $C_{16}H_{28}O_2$ requires C, 76.1; H, 11.2%).

1,2,3,4,4a,5,6,7,8,8a-*Decahydro*-8β-*hydroxy*-4β,4aβ-*dimethyl*-8aβ-*naphthalen*-6β-*ylpropenal* (40).—The preceding hydroxyenol ether (36a) (mixture of *Z*- and *E*-isomers, 0.41 g, 1.6 mmol) in dry ether (5 ml) was stirred at 0 °C whilst a solution of silver trifluoroacetate (0.44 g, 2.0 mmol) [24] in dry ether (5 ml) was added during a few minutes. After the mixture had been stirred for a further 10 min at 0 °C a solution of phenylseleninyl chloride (0.38 g, 2.0 mmol) [19] in dry ether (5 ml) was added during a few minutes. The mixture was stirred for 20 min at 0 °C and then at room temperature for 1 h. THF (50 ml) was added, followed by 5% HCl, and the mixture was stirred vigorously overnight. Ice–water was added and the product isolated with diethyl ether. It was taken up in THF (10 ml) and stirred at 0 °C during the dropwise addition of 30% hydrogen peroxide [25] (0.6 ml, 6.6 mmol) (5 min), then stirred at 0 °C for 20 min, and finally at room temperature for 2 h. Dilution with water and ether extraction afforded, after evaporation, a yellow syrup (0.50 g) which was dissolved in light petroleum, chromatographed on silica gel (12.5 g), and eluted with diethyl ether–light petroleum (1 : 1). The *aldehyde* (40) distilled at 95—100 °C (bath) (0.05 mmHg) (190 mg, 50%); $\nu_{max.}$ 3 484, 2 732, 1 686, 1 623, and 894 cm^{-1}; δ($CDCl_3$) 9.48 (1 H, s, CHO), 6.21 (1 H, d, *J* 1.1 Hz, vinyl H *cis* to CHO), 5.95 (1 H, d, *J* 1.1 Hz, vinyl H *trans* to CHO), 4.95 (1 H, ddd, *J* 10.8, 10.8, 4.4 Hz, C*H*OH), 2.74 (1 H, tm, *J* 12.4 Hz, allylic H), 0.87 (3 H, s, 4a-Me), and 0.76 (3 H, d, *J* 6.4 Hz, 4-Me); *m/z* 236 (M^+) (Found: C, 76.1; H, 10.0. $C_{15}H_{24}O_2$ requires C, 76.2; H, 10.2%).

(+)-*Flourensic Acid* (1).—The preceding aldehyde (190 mg, 0.80 mmol) in permanganate-stable acetone (15 ml) was stirred and cooled to 0 °C. Jones reagent (0.5 ml of 8 N) was added gradually from a burette during a few minutes. The mixture was stirred for 6 h at room temperature, then treated with M-NaOH (50 ml) and washed once with ether. The aqueous layer was acidified and thoroughly extracted with ether. The combined extracts were washed with ice-water, dried, and concentrated, to yield a glass (156 mg, 78%), which crystallized from hexane–acetone (4 : 1) as prisms, m.p. 158—159 °C. It was further purified by vacuum sublimation at 100 °C (bath) (0.05 mmHg), m.p. 159—160 °C, alone or admixed with an authentic sample of (+)-flourensic acid (1), m.p. 158—160 °C; [1,2] δ($CDCl_3$) 6.39 (1 H, s, vinyl H *cis* to CO_2H), 5.66 (1 H, s, vinyl H *trans* to CO_2H), 1.05 (3 H, s, 5-Me), 0.83 (3 H, d, *J* 5.0 Hz, 4-Me); *m/z* 250 (M^+); $[\alpha]_D^{24}$ +59.6° (MeOH, *c* 1.05); $\lambda_{max.}$ (EtOH) 203 nm (ε 9 000).

Acknowledgements

We thank Dr. D. G. I. Kingston (Virginia Polytechnic Institute and State University) for authentic samples of (+)-flourensic acid, Dr. R. A. Massy-Westropp (University of Adelaide) for generous gifts of natural eremophilone, Dr. E. Piers (University of British Columbia) for a sample of the keto-acid (5), and Dr. G. Rücker (Pharmazeutisches Institut der Universität Bonn) for mass spectra of *cis*- and *trans*-1,2,3,4,4a,5,6,7-octahydro-4β,4aβ-dimethylnaphthalen-8(8a*H*)-ones. Some of the preliminary experiments on the synthesis of the ketone (10) and on the selective bromination and oxidation of (27) were carried out by Dr. W. D. Saunders, formerly of this Department.[26] The JEOL FX-90Q n.m.r. spectrometer was purchased with funds provided by the National Science Foundation.

References

1 D. G. I. Kingston, M. M. Rao, and T. D. Spittler, *Tetrahedron Lett.*, 1971, 1613.
2 D. G. I. Kingston, M. M. Rao, T. D. Spittler, R. C. Pettersen, and D. L. Cullen, *Phytochemistry*, 1975, **14**, 2033.
3 E. Piers, R. W. Britton, and W. de Waal, *Can. J. Chem.*, 1969, **47**, 4307; A. R. Pinder and A. K. Torrence, *J. Chem. Soc. C*, 1971, 3410.
4 E. Piers and M. B. Geraghty, *Can. J. Chem.*, 1973, **51**, 2166.
5 J. W. Ralls and B. Riegel, *J. Am. Chem. Soc.*, 1954, **76**, 4479; J. R. Williams and G. M. Sarkisian, *Synthesis*, 1974, 32.
6 *Cf.* K. M. Patel and W. Reusch, *Synth. Commun.*, 1975, **5**, 27; R. W. Mouk, K. M. Patel, and W. Reusch, *Tetrahedron*, 1975, **31** 13.
7 H. Hagiwara, H. Uda, and T. Kodama, *J. Chem. Soc., Perkin Trans. 1*, 1980, 963.
8 G. Rücker, *Chem. Ber.*, 1969, **102**, 2697.
9 D. J. Peterson, *J. Org. Chem.*, 1967, **32**, 1717.
10 W. Carruthers, ' Some Modern Methods of Organic Synthesis,' 2nd edn., Cambridge University Press, Cambridge, 1978, pp. 69, 70. See also R. K. Boeckman, jun., *J. Am. Chem. Soc.*, 1973, **95**, 6867.
11 C. Djerassi, R. Mauli, and L. H. Zalkow, *J. Am. Chem. Soc.*, 1959, **81**, 3424.
12 J. P. Marino and D. M. Floyd, *J. Am. Chem. Soc.*, 1974, **96**, 7138; *Tetrahedron Lett.*, 1975, 3897.
13 P. A. Grieco, C. L. J. Wang, and G. Majetich, *J. Org. Chem.*, 1976, **41**, 726.
14 R. F. Zürcher, *Helv. Chim. Acta*, 1961, **44**, 1380; 1963, **46**, 2054.
15 A. E. Bradfield, A. R. Penfold, and J. L. Simonsen, *J. Chem. Soc.*, 1932, 2744.
16 W. G. Salmond, M. A. Barta, and J. L. Havens, *J. Org. Chem.*, 1978, **43**, 2057.
17 D. A. Evans and L. K. Truesdale, *Tetrahedron Lett.*, 1973, 4929; D. A. Evans, G. L. Carroll, and L. K. Truesdale, *J. Chem. Soc., Chem. Commun.*, 1973, 55; *J. Org. Chem.*, 1974, **39**, 914; P. G. Gassman and J. J. Talley, *Tetrahedron Lett.*, 1978, 3773.
18 S. Warren, C. Earnshaw, and C. J. Wallis, *J. Chem. Soc., Perkin Trans. 1*, 1979, 3099.
19 D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 1973, 695; H. J. Reich, *J. Org. Chem.*, 1974, **39**, 428.

20 F. E. Ziegler and P. A. Wender, *Tetrahedron Lett.*, 1974, 449; J. E. McMurry, J. H. Musser, M. S. Ahmad, and L. C. Blaszczak, *J. Org. Chem.*, 1975, **40**, 1829; F. E. Ziegler, G. R. Reid, W. L. Studt, and P. A. Wender, *J. Org. Chem.*, 1977, **42**, 1991.
21 M. Grard, *Ann. Chim.*, 1930, [10], **13**, 336.
22 See L. J. Bellamy, ' The Infrared Spectra of Complex Molecules,' 3rd edn., Chapman and Hall, London, 1975, p. 297.
23 L. Birkofer, A. Ritter, and H. Dickopp, *Chem. Ber.*, 1963, **96**, 1473; L. Birkofer, A. Ritter, and F. Bentz, *ibid.*, 1964, **97**, 2196.
24 D. E. Janssen and C. V. Wilson, *Org. Synth.* Coll. Vol. IV, 1963, p. 547.
25 K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, 1973, **95**, 2697.
26 W. D. Saunders, Ph.D. Thesis, Clemson University, 1977.

Received 8*th June* 1982; *Paper* 2/963