Synthetic Studies on Terpene Compounds. Part 13.[1] Total Synthesis of Fraxinellone [2]

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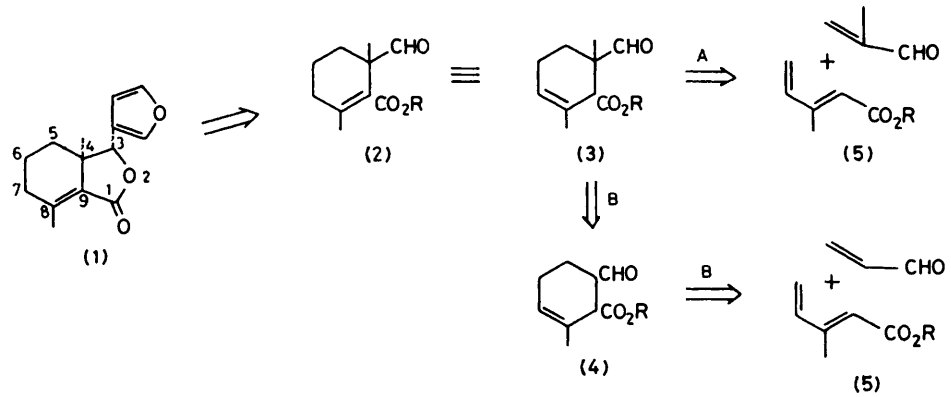
The total synthesis of fraxinellone (1), the simplest example of a degraded limonoid, *via* the 6-formyl-2,6-dimethylcyclohex-2-enecarboxylates (2) is described. In the initial approach the C-6 methylation of ethyl 6-formyl-2-methylcyclohex-2-enecarboxylate (7) was carried out by cyclopropanation and ring cleavage which unexpectedly gave the bicyclo[2.2.1]heptene compound (20), with a poor yield of the desired product. Subsequently, the key intermediate (2) was synthesized effectively by the Diels–Alder reaction between ethyl 3-methylpenta-2,4-dienoate and methacrolein. The reaction of the aldehyde ester (2) with furyl-lithium followed by double-bond isomerization with base afforded (±)-fraxinellone, together with the corresponding diastereoisomer.

FRAXINELLONE is a natural product of unique structure (1) with a β-substituted furan ring and occurs in the trees of both Rutaceae (*Dictamnus albus*,[3] *D. dasycarpus* [4]) and Meliaceae (*Melia azedarach* [5]) which are known as rich sources of limonoids.[6,7] The gross structure was determined in 1965 [8] and the absolute configuration was assigned on the basis of an *X*-ray analysis [9] and an o.r.d study.[4] The latter result underlines the biogenetic relationship between fraxinellone (1) and the limonoids. Thus fraxinellone (1) belongs to a rare group of natural products, the degraded limonoids,[10] and has the simplest structure among them. As an entry to the synthetic studies of limonoids,[11] the degraded limonoids are compounds of obvious interest. We report here the total synthesis of fraxinellone (1).

The antithetic analysis (Scheme 1) indicates that, when the aldehyde ester (2) is the key intermediate, this goal would be easily constructed by a Diels–Alder reaction † and a subsequent double-bond migration. The reaction of compound (2) with 3-furyl lithium would afford fraxinellone (1) and its diastereoisomer. The synthesis of the sub-goal (3) may be achieved by two pathways, A and B. We investigated path B first, but later found the more convergent path A to be superior.

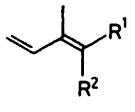


SCHEME 1

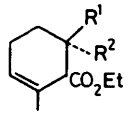
Our synthesis started from the preparation of the diene compound (5). The reaction of ethoxyethynylmagnesium bromide with methyl vinyl ketone and the subsequent acid treatment furnished ethyl 3-methylpent-2,4-dienoate as a mixture of the isomers [(6a) : (6b) 2 : 1 ~ 3 : 1]. The assignment of configuration for the isomers was possible on the basis of chemical-shift data [13] in the n.m.r. spectrum. The minor and major dienes exhibited quartets due to C-4 vinyl protons at δ 6.30 (*J* 11, 17 Hz) and 7.79 (*J* 12, 18 Hz), and singlets due to vinylmethyl protons at δ 1.96 and 2.22, respectively. Thus the minor diene has the *Z*-structure (6a) and the major diene is the *E*-isomer (6b). The Diels–Alder reaction of the diene mixture (6) with acrolein at 90—95 °C afforded an adduct (7a) and small amounts of the adducts (7b) and (8), the *Z*-diene (6a) being recovered unchanged. The preferred reactivity of the *E*-isomer (6b) is expected from steric considerations of the transition state.[14] The recovered *Z*-diene (6a) could be used for the reaction after irradiation in the presence of iodine which gave an equilibrium mixture with an *E* : *Z* ratio of 4 : 1. When the mixture of the adducts in benzene solution was treated with basic alumina, the ratio of the adducts (7a) and (7b) reversed, as revealed by g.l.c. analysis. Therefore (7a) must be the thermodynamically less stable *cis*-compound and (7b) is the *trans*-isomer. The remaining adduct may possibly be a regioisomer (8).

† For the preparation of this type of compound by the Claisen rearrangement, see ref. 12.

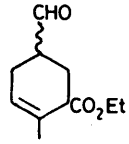
The introduction of a methyl group at the C-6 position of the aldehyde ester (7) was more difficult than expected. After the failure of preliminary experiments with enol alkylation, the problem was investigated by using the more easily accessible model compound (9).[15] Success was achieved by cyclopropanation and ring cleavage [16,*] of the corresponding enol ether (10). Treatment of the aldehyde ester (7) with triethyl orthoformate and toluene-*p*-sulphonic acid followed by distillation gave, quantitatively, the enol ether (10). The Simmons–Smith reaction [18] of (10) occurred regioselectively at the



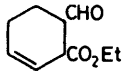
(6a) $R^1 = CO_2Et, R^2 = H$
(6b) $R^1 = H, R^2 = CO_2Et$



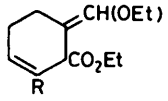
(7a) $R^1 = CHO, R^2 = H$
(7b) $R^1 = H, R^2 = CHO$



(8)



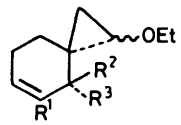
(9)



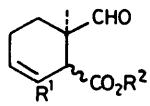
(10) R = H
(11) R = Me

enol ether double bond, giving the cyclopropanated product (12) as a mixture of stereoisomers (*cf.* Experimental section) in 88% yield, which was refluxed with a mixture of concentrated hydrochloric acid and ethanol (4 : 5). G.l.c. analysis of the crude product, obtained quantitatively, indicated the formation of two compounds in a ratio of 2 : 1, which were separated preparatively. The major product was the methylated aldehyde ester (15) (i.r., 2 680, 1 736, 1 723, and 1 660 cm^{-1}; n.m.r., 3 H singlet at δ 1.00). The pseudo-ester structure (18) was assigned to the minor product on the basis of spectroscopic data (i.r., 1 775 cm^{-1}; n.m.r., 3 H singlet at δ 1.08, as a mixture of the epimers, *cf.* Experimental section). Refluxing of the crude product with 2M hydrochloric acid and subsequent treatment of the acid obtained with diazomethane yielded solely the methyl ester (14). Alternatively, when the crude product was refluxed with 10% potassium hydroxide solution, the conjugated ester (22) was obtained after the methylation with diazomethane.

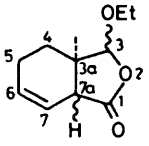
Having demonstrated the feasibility of the cyclopropanation–ring-cleavage method with a model compound, the C-6 methylation of the aldehyde ester (7) by this procedure was attempted. The ester (7) was converted firstly into the enol ethyl ether (11) in 81% yield, which was heated with a methylene iodide–zinc–copper couple complex in ether to afford the cyclopropanated product (13) quantitatively. Treatment of (13) with a mixture of concentrated hydrochloric acid and ethanol (3 : 4) under reflux gave a complex mixture of products. The acidic products were analysed, after methylation with diazomethane, by g.l.c. and spectroscopy and found to be composed mainly of the desired products (16) and (23) in a ratio of 7 : 2. The neutral and volatile fraction was treated with 20% aqueous potassium hydroxide and then methylated in order to convert any pseudo-ester present into the normal ester. G.l.c. of the products showed the presence of a peak with a retention time shorter than that of (16), the ratio of both peaks being approximately 2 : 1.† The major peak was easily separated by preparative g.l.c. to give the methyl ester (19). The corresponding ethyl ester (20) was obtained when the neutral fraction above was separated by g.l.c. without further treatment. Compound (20) gave a molecular peak with *m/e* 238 ($C_{14}H_{22}O_3$). The i.r. spectrum indicated the presence of a conjugated ester group (ν 1 715 and 1 620 cm^{-1}), which was substantiated by the



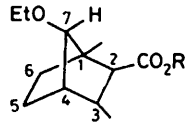
(12) $R^1 = H; R^2, R^3 = H, CO_2Et$
(13a) $R^1 = Me, R^2 = H, R^3 = CO_2Et$
(13b) $R^1 = Me, R^2 = CO_2Et, P^3 = H$



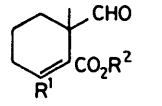
(14) $R^1 = H, R^2 = Me$
(15) $R^1 = H\ R^2 = Et$
(16) $R^1 = R^2 = Me$
(17) $R^1 = Me, R^2 = Et$



(18)



(19) R = Me, $\Delta^{2,3}$
(20) R = Et, $\Delta^{2,3}$
(21) R = Et



(22) $R^1 = H, R^2 = Me$
(23) $R^1 = R^2 = Me$

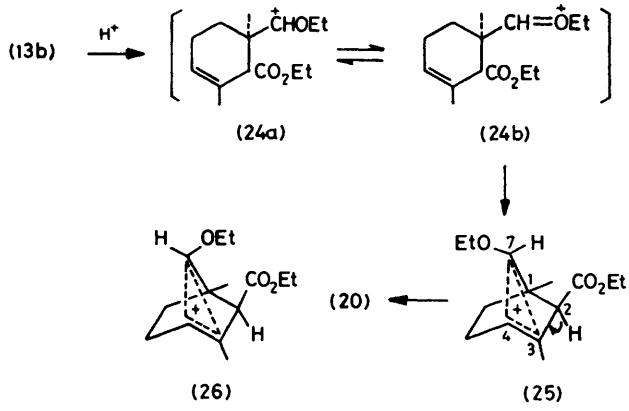
presence of u.v. maxima at λ 232 nm (ε 7 200).[19] N.m.r. analysis revealed the absence of the aldehyde group and showed resonances due to two ethoxy-groups (pairs of triplets and multiplets at δ 1.12, 4.16 and 1.23, 3.36), a tertiary methyl (δ 1.22), a vinyl methyl (δ 1.98), and two methine groups (double doublets at δ 2.48 with *J* 2, 4 Hz and a singlet at δ 2.76). These spectra indicated a bicyclo[2.2.1]heptane structure (20) for the by-product. The appearance of a shielded C-7 proton signal (δ 2.76) as a singlet was explained by assuming the *syn*-configuration, since in this position the C-7 proton is within the shielding cone of the olefinic bond and the dihedral angle between C-7 and C-4 protons is *ca.* 90°. In agreement with this assumption, the dihydro-compound (21), obtained by catalytic hydrogenation of (20), exhibited the n.m.r. signal due to the C-7 proton at δ 3.12. Notably, in the n.m.r. spectrum of (20) the methylene proton

* For examples of the application of this procedure to the introduction of angular substituents in natural product syntheses, see ref. 17.

† The larger amount of the methyl ester (19) in this fraction may indicate that the ester group in (20) is more sterically crowded and hence less liable to hydrolyse than that of (16).

signals of both the ethoxy-groups showed complex splittings of the ABX_3 system instead of quartets.[20,21] In the case of (21), only the methylene proton signal of the ether group appeared as a multiplet. The ethoxycarbonyl group in (20) occurs in approximately the same plane as the methyl groups at C-1 and C-3 and this would impose a severe restriction on the rotation of the ethoxy-group. In contrast, this restriction would be relaxed to some degree in the saturated compound (21).

The mechanism for the formation of the bicyclic compound (20) from (13) may be interpreted on the basis of the interaction of the olefinic π-orbital with the orbital of the intermediate carbonium ion (24) to form the non-classical carbonium ion (25) (Scheme 2). The

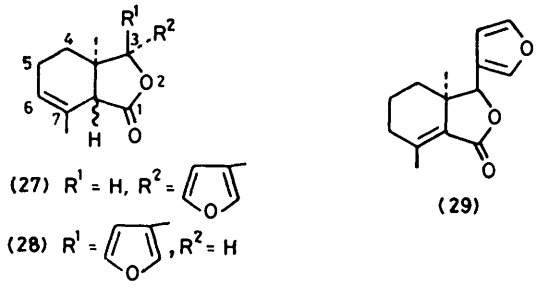


SCHEME 2

ion (25) will collapse by deprotonation at the carbon atom bearing the ethoxycarbonyl group to afford the final product (20). Two points must be explained. Firstly, the *anti*-product (20) forms stereospecifically. Secondly, in the case of the 6-de-methyl analogue, (12), of (13) the formation of the corresponding bicyclic product was not observed. To rationalize the exclusive formation of the *anti*-product (20), we assume the preferential reaction of the *cis*-compound (13b) with respect to the *trans*-counterpart (13a) because of the stereoelectronically favoured orientation of the C-2–H bond with respect to the partial bond between C-3 and C-7 in the intermediate cation (25). Then the intermediate (26) leading to the *syn*-product would be destabilized by the severe non-bonding interaction between the ethoxy and the ethoxycarbonyl groups. The preferential production of the bicyclic compound when (13) and not (12) is used is hard to understand. The presence of the additional methyl group would certainly contribute to the stabilization of the intermediate carbonium ion [akin to (25)], but further studies are necessary to determine whether this explanation is sufficient.

Although we synthesized the key intermediate (2) by way of path B envisaged at the outset, the low yield and the need of laborious separation led us to seek a more efficient method and path A was examined as an alternative. The Diels–Alder reaction of ethyl 3-methylpenta-2,4-dienoate (6) with methacrolein at 110—120 °C for 20 h afforded (17) directly in 77.8% yield [based on the *trans*-diene (6a)]. It exhibited i.r. peaks at ν 2 710, 1 732, and 1 725 cm^{-1}, and its n.m.r. spectrum was consistent with structure (17). The presence of the stereoisomer (*ca.* 15%) was indicated by the appearance of additional signals at δ 3.10 and 9.23, which corresponded to those due to the methine proton at δ 2.80 and the aldehyde proton at δ 9.21 in (17). The isomer ratio did not change substantially when the reaction was conducted in the presence of potassium carbonate. Although consideration of Alder's rule indicates the *cis*-configuration (17; β-CO_2Et) for the major product,[22] the assignment is not conclusive.[23]

Having synthesized compound (3) we proceeded to the final stage of the synthesis, attaching the β-furan ring before inducing the double-bond migration. The reaction of the aldehyde ester (17) with β-furyl-lithium [24] afforded a mixture of the diastereoisomeric furyl lactones (27) and (28) in a ratio of 2 : 1, which were easily separable by chromatography over alumina. In the n.m.r. spectra the signals due to the C-1 methyl protons appeared at δ 0.84 in the major product and at δ 1.08 in the minor one. Accordingly, the desired *cis*-structure (27) was assigned to the former and the *trans*-structure (28) to the latter, since in the *cis*-structure (27) paramagnetic shielding of the C-1 methyl protons by the furan



ring is expected. Treatment of the *cis*-compound (27) with 5% methanolic potassium hydroxide solution under refluxing yielded (±)-fraxinellone (1), m.p. 84—86 °C, which was identified by the comparison of the i.r. and n.m.r. spectra with those of natural fraxinellone.[4] The isomerization of the *trans*-compound (28) in the same way as above furnished *epi*-fraxinellone (29). Thus the first synthesis of a degraded limonoid has been accomplished.

EXPERIMENTAL

M.p.s and b.p.s were uncorrected. I.r. spectra were determined with a JASCO IRA-1 instrument and refer to liquid films, unless otherwise specified, and u.v. spectra were recorded for ethanolic solutions with a Hitachi EPS-2 spectrophotometer. ^1H N.m.r. spectra were taken on JEOL PS-100 or HL-60 spectrometers for solutions in CCl_4 (unless stated otherwise) with Me_4Si as the internal standard (in giving the n.m.r. data, the use of *cis* and *trans* is understood to mean the proton which is *cis* or *trans* to the radical). Alumina used for column chromatography was of activity grade I (Woelm, neutral) and was made up to the

desired activity grade by the addition of water prior to use. Silica gel columns used Merck Kieselgel (70—230 mesh). Usual work-up means the washing of extracts with water and then brine, drying (Na_2SO_4), filtration, and evaporation under reduced pressure.

Ethyl 3-*Methylpenta*-2,4-*dienoates* (6a) *and* (6b).—To a solution of ethylmagnesium bromide in ether [prepared from ethyl bromide (12.5 g), magnesium (2.7 g), and absolute ether (10 ml)] was added in drops a solution of ethoxyacetylene (8.4 g) in absolute ether (50 ml) during 40 min. After being refluxed for 30 min. the mixture was cooled to 0 °C, and a solution of methyl vinyl ketone (7.9 g) in ether (50 ml) was added in drops during 30 min. The mixture was then refluxed for a further 30 min, after which it was cooled to 0 °C, and a solution of ammonium chloride (20 g) in water (100 ml) was added. The product was extracted with ether (× 3) and the ether layer (400 ml) was shaken cautiously (exothermic) with 10% aqueous sulphuric acid (190 ml) for 10 min. The organic layer was washed successively with sodium hydrogencarbonate solution and brine, and then dried. The residue left after the evaporation of the solvent was distilled under reduced pressure to give the *ester* (6) (12.039 g, 65% yield) as a mixture of the *E*- (6a) and *Z*- (6b) isomers, b.p. 72—73 °C/13 mmHg, $\nu_{max.}$ 1 720, 1 710, 1 628, 1 610, 1 598, 1 252, 1 240, 1 160, 1 072, 1 037, 1 004, 989, 925, 872, and 860 cm^{-1}. After the Diels–Alder reaction of this mixture with acrolein or methacrolein, the almost pure *Z-isomer* (6b) was recovered; $\nu_{max.}$ 3 100, 1 720, 1 710, 1 628, 1 598, 1 250, 1 160, 1 072, 1 037, 1 004, 925, and 860 cm^{-1}, δ 1.26 (3 H, t, *J* 8 Hz, CH_2Me), 1.97, (3 H, s, CH=C*Me*), 4.07 (2 H, q, *J* 8 Hz, CH_2Me), 5.29 (1 H, dd, *J* 3,12 Hz, *trans*-HC=CH*H*), 5.44 (1 H, dd, *J* 3, 18 Hz, *cis*-HC=C*H*H), 5.57 (1 H, br s, C*H*=CMe), and 7.76 (1 H, dd, *J* 12,18 Hz, *H*C=CH_2). With reference to this data, the signals assigned for the *E*-isomer (6a) in the n.m.r. spectrum of the olefin mixture were δ 1.26 (3 H, t, *J* 8 Hz, CH_2Me), 2.23 (3 H, s, CH=C*Me*), 4.06 (2 H, q, *J* 8 Hz, CH_2Me), 5.24 (1 H, br d, *J* 11 Hz, *trans*-HC=CH*H*), 5.49 (1 H, br d, *J* 17 Hz, *cis*-HC=C*H*H), 5.63 (1 H, br. s, C*H*=CMe), and 6.30 (1 H, dd, *J* 11,17 Hz, *H*C=CH_2). The isomer ratios in the olefin mixture estimated from the integral were (6a) : (6b) 2—3 : 1. When a solution of the *Z*-isomer (6b) (11.6 g) in benzene (20 ml) with a small amount of iodine was refluxed under irradiation (tungsten lamp, 500 W) for 13.5 h, an equilibrium mixture of the *Z*- and *E*-compounds (1 : 4) was obtained.

Ethyl 6-*Formyl*-2-*methylcyclohex*-2-*enecarboxylates* (7a) *and* (7b).—A mixture of the ethyl 3-methylpenta-2,4-dienoates (6a) and (6b) (22 g) and acrolein (14.7 g) with a small amount of hydroquinone was heated at 90—95 °C for 12 h under a nitrogen atmosphere. The reaction mixture was distilled at 10 mmHg to (6b), b.p. 61.5—64 °C (10.47 g) and then at 0.2 mmHg to afford the *adduct* (7a), b.p. 80—85 °C; $\nu_{max.}$ 2 720, 1 730, and 1 710 cm^{-1}; δ 1.25 (3 H, t, *J* 8 Hz, CH_2Me), 1.72 (3 H, br s, CH=C*Me*), 4.10 (2 H, q, *J* 8 Hz, CH_2Me), 5.50 (1 H, m, C*H*=CMe), and 9.35 (1 H, s, CHO). G.l.c. analysis indicated contamination by small amounts of two other products with shorter and longer retention times, respectively. When a solution of the initial adduct (7a) in benzene was shaken with basic alumina, an equilibrium mixture was obtained after 12 h. G.l.c. analysis showed the predominance of the isomer with the shortest retention time, which is the thermodynamically more stable (7b); $\nu_{max.}$ 2 720, 1 740, 1 725, 1 190, and 1 160 cm^{-1}.

Ethyl Penta-2,4-*dienoate*.—This compound was prepared by the reported procedure,[15] b.p. 59—60 °C/18 mmHg; $\nu_{max.}$ 1 713, 1 640, 1 600, 1 200, 1 150, 925, and 870 cm^{-1}. ^1H N.m.r. analysis indicated that the product was the pure *trans*-isomer; δ 1.29 (3 H, t, *J* 8 Hz, CH_2Me), 4.20 (2 H, q, *J* 8 Hz, CH_2Me), 5.49 (1 H, dd, *J* 2,10 Hz, *trans*-HC=CH*H*), 5.59 (1 H, dd, *J* 2,16 Hz, *cis*-HC=C*H*H), 5.89 (1 H, d, *J* 16 Hz HC=C*H*CO_2Et), 6.45 (1 H, dt, *J* 16,10 Hz, *H*C=CH_2), and 7.28 (1 H, dd, *J* 11,16 Hz, *H*C=CHCO_2Et).

Ethyl 6-*Formylcyclohex*-2-*enecarboxylate* (9).[15]—A mixture of ethyl penta-2,4-dienoate (31 g) and acrolein (16 g) was heated at 90—95 °C for 12 h and the product was distilled to give the *adduct* (9) (33.4 g, 76% yield), b.p. 91—105 °C/1 mmHg; $\nu_{max.}$ 2 700, 1 738, 1 723, and 1 670 cm^{-1}; δ 1.25 (3 H, t, *J* 7 Hz, CH_2Me), 3.37 (1 H, dd, *J* 2.5 Hz, =CHC*H*CO_2Et), 4.08 (2 H, q, *J* 7 Hz, OCH_2Me), 5.77 (2 H, m, C*H*=C*H*), and 9.53 (1 H, s, CHO).

Ethyl 6-*Ethoxymethylenecyclohex*-2-*enecarboxylate* (10).—A mixture of the aldehyde ester (7a) (5 g, 28 mmol), triethyl orthoformate (3.61 g, 76 mmol), and anhydrous toluene-*p*-sulphonic acid (50 mg) was stirred, at first under ice-cooling, and then at room temperature for 24 h. Excess of the reagent and the generated ethyl formate was removed by distillation at reduced pressure (100 mmHg) and the bath temperature was raised to 150—160 °C as a vigorous reaction occurred. The mixture was held at this temperature under reduced pressure for 2 h to completely remove ethanol. Distillation gave the *enol ether* (10) as a colourless oil, b.p. 80—82 °C/0.3 mmHg (6.12 g, 100%); $\nu_{max.}$ 1 728, 1 680, and 1 650 cm^{-1}.

1-*Ethoxy*-4-*ethoxycarbonylspiro*[2.5]*oct*-5-*ene* (12).—A freshly prepared zinc–copper couple [25] (8.6 g, 0.13 mol) was mixed with a solution of methylene iodide (21.5 g, 0.08 mol) in absolute ether (50 ml) and, after addition of iodine (50 mg), the mixture was gently refluxed for 1.5 h. A solution of the enol ether (10) (11.8 g, 56 mmol) in ether (20 ml) was added in drops to the refluxing carbenoid mixture during 30 min. The refluxing was continued for another 30 min. Saturated ammonium chloride solution was added to the cooled reaction mixture and excess of the metal was filtered off. The ether layer was separated and the aqueous layer was extracted several times with ether. The combined organic layer was washed successively with saturated brine, sodium hydrogencarbonate solution, and water, and then dried ($MgSO_4$). The product was distilled to give the *cyclopropane compound* (12) as a colourless oil, b.p. 69—80 °C/0.2 mmHg [11.645 g (88%)]; ν_{max} 1 722 and 1 645 cm^{-1}. The n.m.r. spectrum indicated that the product was a mixture of, at least, four stereoisomers; δ 0.20 ~ 0.80 (2 H in total, $\overline{CC}H_2$CHOEt).

Methyl 6-*Formyl*-6-*methylcyclohex*-2-*enecarboxylate* (14).—A solution of the cyclopropane product (12) (11.1 g) in ethanol (50 ml) was refluxed with concentrated hydrochloric acid (40 ml) for 2.5 h. The reaction mixture was diluted with water and concentrated under reduced pressure. It was extracted several times with ether and the ether layer was washed with saturated sodium hydrogencarbonate solution and water, and then dried ($MgSO_4$). The residue, after evaporation of the solvent, afforded a distillate, b.p. 72.5—90 °C/0.2 mmHg (8.0 g). G.l.c. gave two major peaks (2 : 1 ratio) which were separately collected. The larger peak with shorter retention time was found to be *ethyl* 6-*formyl*-6-*methylcyclohex*-2-*enecarboxylate* (15); $\nu_{max.}$ 2 680, 1 736, 1 723, and 1 660 cm^{-1}; δ 1.01 (3 H, s, Me), 1.23 (3 H,

t, *J* 7 Hz, CH_2Me), 3.35 (1 H, s, =CHC*H*CO_2Et), 4.05 (2 H, q, C*H*$_2$Me), 5.75 (2 H, br s, CH=CH), and 9.40 (1 H, s, CHO). The other peak was 3-*ethoxy*-3a-*methyl*-3a,4,5,7a-*tetrahydrophthalide* (18); $\nu_{max.}$ 1 770, 1 640, 1 117, and 928 cm^{-1}; δ 1.08 (3 H, s, Me), 1.22 (3 H, t, *J* 7 Hz, CH_2Me), 3.2 ~ 4.1 (2 H in total, m, C*H*$_2$Me), 4.74 [1 H, s, C*H*(OEt)O], and 5.74 (2 H, m, CH=CH). For the conversion of the pseudo-ester (18) to the normal ester (15), the distillate above, *viz.* the 2 : 1 mixture of (15) and (18) (188 mg) was heated with 2M hydrochloric acid (10 ml) under reflux for 2 h. The product obtained from the usual work-up was treated with ethereal diazomethane and the *aldehyde methyl ester* (14) was obtained as an oil; $\nu_{max.}$ 2 680, 1 738, 1 726, and 1 660 cm^{-1}; δ 1.04 (3 H, s, Me), 3.00 (1 H, m, =CHC*H*CO_2), 3.42 (3 H, s, CO_2Me), 5.71 (2 H, m, CH=CH), and 9.48 (1 H, s, CHO). When the mixture of (15) and (18) above was refluxed with aqueous potassium hydroxide (10%) for 4 h and the product was treated with diazomethane, *methyl* 6-*formyl*-6 *methylcyclohex*-1-*enecarboxylate* (22) was obtained as an oil, b.p. 85—90 °C/0.4 mmHg (1.5 g); $\lambda_{max.}$ 213 nm (ε, 7 100); $\nu_{max.}$ 2 660, 1 705, 1 730, and 1 640 cm^{-1}; δ 1.26 (3 H, s, Me), 3.66 (3 H, s, CO_2Me), 7.08 (1 H, t, *J* 4 Hz, =C*H*CH_2), and 9.30 (1 H, s, CHO).

Ethyl 6-*Ethoxymethylene*-2-*methylcyclohex*-2-*enecarboxylate* (11).—The aldehyde ester (7a) (7.678 g) was stirred with triethyl orthoformate (11.4 g) and anhydrous toluene-*p*-sulphonic acid (40 mg) at room temperature for 4 d. After excess of the orthoformate and the ethyl formate formed was removed by distillation (bath temperature, 50—120 °C/80 mmHg), the elimination of ethanol was effected at 150—160 °C/80 mmHg. It took 4 h for completion, whereupon distillation of the product afforded the *enol ether* (11) as a mixture of the *E*- and *Z*-isomers (approximately 1 : 1 ratio) b.p. 79—80 °C/0.3 mmHg (7.524 g, 81% yield); $\nu_{max.}$ 1 730, 1 690, and 1 675 cm^{-1}; δ 1.24 (6 H, t, *J* 7 Hz, Me), 1.67 (3 H, br s, CH=CMe), 3.70 (3 H, t, *J* 7 Hz, C=C*H*OEt), 4.04 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 5.50 (1 H, m, C*H*=CMe), and 5.80 and 5.97 (1 H in total, each br s, C=CHOEt).

1-*Ethoxy*-4-*ethoxycarbonyl*-5-*methylspiro*[2.5]*oct*-5-*ene* (13).—To a refluxing zinc–carbenoid mixture, prepared from a zinc–copper couple (4 g), iodine (25 mg), methylene iodide (8 g, 0.03 mol), and absolute ether (40 ml) in the same way as before, was added in drops a solution of the enol ether (11) (6.4 g, 29 mmol) during 30 min and the refluxing was continued for a further 24 h. The usual work-up gave the crude *adduct* (13) (6.8 g, 100% yield); $\nu_{max.}$ 1 730 cm^{-1}; δ 0.2 ~ 0.7 (2 H, m, CCH_2CHOEt) and 5.50 (1 H, m, C=C*H*).

Acid Treatment of the Cyclopropane Compound (13).—The product (13) above (6.8 g) was heated with concentrated hydrochloric acid (25 ml) and ethanol (32 ml) under refluxing for 35 h. After dilution with water, most of the ethanol was evaporated under reduced pressure and the product was extracted with ether. The ether layers were washed thoroughly with water and then dried ($MgSO_4$). Evaporation of the solvent left the crude product as an oil (6 g). Distillation afforded a distillate, b.p. 90—105 °C/0.3 mmHg (3.6 g) and the residue (1.0 g). The distillate (410 mg) was hydrolysed by refluxing with 20% aqueous potassium hydroxide (10 ml) for 5 h. After dilution with water and washing with ether, the reaction mixture was acidified with 2M hydrochloric acid and then extracted with ether. The washed and dried (Mg_4SO) ether solution was treated with an excess of ethereal diazomethane for 10 min. Evaporation of the solvent gave an oily mixture (Fraction A). G.l.c. collection (polyethyleneglycol–succinate column, 200 °C) afforded *methyl* 6-*formyl*-2,6-*dimethylcyclohex*-2-*enecarboxylate* (16); $\nu_{max.}$ 2 720, 1 732, 1 722, and 1 115 cm^{-1}; δ 1.00 (3 H, s, Me), 1.74 (3 H, br s, CH=C*Me*), 2.80 (1 H, s, =CC*H*CO_2Me), 3.61 (3 H, s, CO_2Me), 5.51 (1 H, m, CH_2CH=C), and 9.49 (1 H, s, CHO) and 7-*ethoxy*-2-*methoxycarbonyl*-1,3-*dimethylbicyclo*[2.2.1]*hept*-2-*ene* (19); $\nu_{max.}$ 1 710 and 1 620 cm^{-1}; δ 1.14 (3 H, t, *J* 7 Hz, CH_2Me), 1.24 (3 H, s, Me). 2.00 (3 H, s, C=CMe), 2.52 (1 H, dd, *J* 2,4 Hz, CH_2-C*H*CHOEt), 2.76 (1 H, br s, CHC*H*OEt), 3.40 (2 H, m, OC*H*$_2$Me), and 3.64 (3 H, s, CO_2Me). Direct g.l.c. collection of the distillate above yielded 7-*ethoxy*-2-*ethoxycarbonyl*-1,3-*dimethylbicyclo*[2.2.1]*hept*-2-*ene* (20); *m/e* 238 (M^+); $\lambda_{max.}$ 232 nm (ε, 7 200); $\nu_{max.}$ (CCl_4) 1 710 and 1 620 cm^{-1}; δ 1.12 (3 H, t, *J* 7 Hz, OCH_2Me), 1.22 (3 H, s, Me), 1.23 (3 H, t, *J* 7 Hz, CO_2CH_2Me). 1.98 (3 H, s, CH=C*Me*), 2.48 (1 H, dd, *J* 2,4 Hz, CH_2CHOEt), 2.76 (1 H, br s, =CC*H*CO_2Me), 3.36 (2 H, m, OC*H*$_2$Me), and 4.16 (2 H, m, CO_2CH_2Me). The distillation residue from above was methylated with ethereal diazomethane and then distilled. G.l.c. of the distillate (Fraction B, 200 mg) showed a major peak accompanied by a smaller peak with a longer retention time. The major peak was identified as the methylated aldehyde ester (16). Treatment of this material with sodium methoxide (160 mg) in methanol (15 ml) under reflux gave, after re-methylation with diazomethane, an oil from which the peak with the longer retention time was intensified. The collection of this peak furnished *methyl* 6-*formyl*-2,6-*dimethylcyclohex*-1-*enecarboxylate* (23); $\nu_{max.}$ 2 700, 1 730, 1 720, and 1 640 cm^{-1}; δ 1.14 (3 H, s, Me), 1.96 (3 H, s, C=CMe), 3.64 (3 H, s, CO_2Me), and 9.07 (1 H, s, CHO).

Hydrogenation of 8-*Ethoxy*-2-*ethoxycarbonyl*-1,3-*dimethylbicyclo*[2.2.1]*hept*-2-*ene* (20).—A solution of the bicyclic compound (20) (100 mg) in ethanol (5 ml) was shaken under hydrogen with 10% palladium–charcoal (50 mg) for 21 h. Removal of the catalyst by filtration and evaporation of the solvent afforded 7-*ethoxy*-2-*ethoxycarbonyl*-1,3-*dimethylbicyclo*[2.2.1]*heptane* (21), $\nu_{max.}$ (CCl_4) 1 730 cm^{-1}; δ 0.98 (3 H, d, *J* 6.5 Hz, CH*Me*), 1.00 (3 H, s, Me), 1.16 (3 H, t, *J* 7 Hz, CH_2Me), 1.22 (3 H, t, *J* 7 Hz, CH_2Me), 2.44 (1 H, dd, *J* 2,12 Hz, CHC*H*CO_2Et), 3.12 (1 H, s, CHC*H*OEt), 3.44 (2 H, m, OCH_2Me), and 4.02 (2 H, q, *J* 7 Hz, CO_2CH_2Me).

Ethyl 6-*Formyl*-2,6-*dimethylcyclohex*-2-*enecarboxylate* (17).—A mixture of ethyl 3-methylpenta-2,4-dienoate (62% *E*-isomer) (21.0 g), methacrolein (12.1 g), hydroquinone (0.6 g), and potassium carbonate (80 mg) was heated at 110—120 °C under nitrogen atmosphere for 20 h. The product was distilled under reduced pressure to afford the *adduct* (17), b.p. 74—84 °C/0.2 mmHg (11.9 g, 55.3% based on the *E*-diene); $\nu_{max.}$ 2 710, 1 732, and 1 725 cm^{-1}; 0.96 (3 H, s, Me), 1.28 (3 H, t, *J* 7 Hz, C*H*Me), 1.72 (3 H, br s, CH=C*Me*), 2.80 (1 H, s, =CCHCO_2Et), 4.04 (2 H, q, *J* 7 Hz, C*H*$_2$Me), 5.48 (1 H, m, CH_2CH=C), and 9.48 (1 H, s, CHO).

Reaction of the Aldehyde Ester (17) *with* β-*Furyl-lithium.*—A solution of the aldehyde ester (17) (903 mg, 4.3 mmol) in absolute ether (8 ml) was added in drops during 15 min to a solution of β-furyl-lithium, prepared [24] from a solution of 3-bromofuran (632 mg, 4.3 mmol) in ether (10 ml), and n-butyl-lithium solution (1.2M in ether, 3.6 ml, 4.3 mmol) at −70 °C. The cooling bath (solid CO_2–acetone) was removed and the mixture was stirred at ambient temperature for 1.5 h. It was washed with 2M hydrochloric acid and brine, and then dried. Evaporation of the solvent left an oily product (1.08 g) which was chromatographed on a column

of neutral alumina (activity II, 30 g). Elution with benzene gave the 3α-*furyl*-3aα,7-*dimethyl*-3a,4,5,7a-*tetrahydrophthalide* (27) (250 mg); $\nu_{max.}$ 3 040, 1 780, 1 600, 1 500, and 875 cm^{-1}; δ 0.84 (3 H, s, Me), 1.84 (3 H, br s, CH=C*Me*), 2.56 (1 H, br s, =CCHCO$_2$), 5.00 [1 H, s, CO$_2$CH(OC$_4$H$_3$)], 5.52 (1 H, m, CH$_2$C*H*=C), 6.24 (1 H, m, OC$_4$H$_3$), and 7.32 (2 H, m, OC$_4$H$_3$). Elution with a mixture of benzene and ether (9 : 1) afforded the diastereoisomeric *furyl lactone* (28) as crystals (100 mg, m.p. 96—97 °C (from a mixture of light petroleum–ether) (Found: C, 72.2; H, 7.0%; $C_{14}H_{16}O_3$ requires C, 72.39; H, 6.94%); $\nu_{max.}$ 3 040, 1 770, 1 500, and 875 cm^{-1}; δ 1.16 (3 H, s, Me), 1.98 (3 H, br s, CH=C*Me*), 2.67 (1 H, br s, =CC*H*CO$_2$), 5.09 [1 H, s, CO$_2$CH(OC$_4$H$_3$)], 5.56 (1 H, m, CH$_2$C*H*=C), 6.36 (1 H, m, OC$_4$H$_3$), and 7.47 (2 H, m, OC$_4$H$_3$).

(±)-*Fraxinellone* (1).—The crude diastereoisomeric mixture of the furyl lactones obtained as above (2.0 g) was dissolved in 5% methanolic potassium hydroxide (25 ml) and the solution was refluxed for 18 h. After addition of water and washing with ether, it was acidified with 2M hydrochloric acid and the product was extracted with ether. The ether layer was washed with brine and dried. The oily material (1.546 g) obtained after evaporation of the solvent was chromatographed on a column of alumina (neutral, activity II, 70 g). Elution with benzene afforded (±)-*fraxinellone* (1), (478 mg), m.p. 84—86 °C [from ether, (−)-fraxinellone,[4] m.p. 116 °C] (Found: C, 72.1; H, 6.9%. Calc. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94%); *m/e* 232 (M^+), $\nu_{max.}$ ($CHCl_3$) 3 020, 1 750, 1 680, 1 600, 1 500, and 878 cm^{-1}; δ 0.84 (3 H, s, Me), 2.10 (3 H, br s, CH=C*Me*), 4.84 [1 H, s, CO$_2$CHOC$_4$H$_3$)], 6.28 (1 H, m, OC$_4$H$_3$), 7.38 (2 H, m, OC$_4$H$_3$). Similar treatment of the pure furyl lactone (27) also afforded (±)-fraxinellone.

(±)-epi-*Fraxinellone* (29).—The furyl lactone (28) (22 mg) was treated with 5% methanolic potassium hydroxide (1 ml) under refluxing for 18 h. The reaction mixture was diluted with water and extracted with ether. The aqueous layer was acidified by 2M hydrochloric acid and the crude product (20 mg) obtained by ether extraction was chromatographed (silica gel) to give (±)-epi-*fraxinellone* (29) as an oil (7 mg); $\nu_{max.}$ ($CHCl_3$) 3 000, 1 748, 1 678, 1 598, 1 500, and 878 cm^{-1}; δ 1.35 (3 H, s, Me), 2.16 (3 H, br s, CH=C*Me*), 5.15 [1 H, s, CO$_2$CH(OC$_4$H$_3$)], 6.12 (1 H, m, OC$_4$H$_3$), 7.30 (1 H, m, OC$_4$H$_3$), and 7.38 (1 H, m, OC$_4$H$_3$).

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