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CHEMISTRY OF *AYURVEDIC* CRUDE DRUGS—II*†

GUGGULU (RESIN FROM *COMMIPHORA MUKUL*)—2: DITERPENOID CONSTITUENTS

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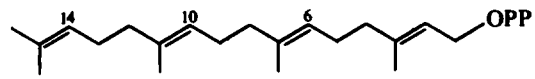
Abstract—Structures of two new diterpenoids, cembrene-A and mukulol are reported. Cembrene-A is one of the two most elementary tetraenes derivable from geranyl-geranyl pyrophosphate by $C_1 \rightarrow C_{14}$ cyclization. Mukulol is also a cembrane derivative and is biogenetically closely related to cembrene-A.

We have already described[1] the isolation of a new diterpene hydrocarbon and a new diterpene alcohol from the gum-resin of *Commiphora mukul* (Hook, ex Stocks) Engl. (Syn. *Balsamodendron mukul* Hook, ex Stocks), a crude *ayurvedic* drug. We now report on the structure elucidation of these two diterpenoids, which we have named cembrene-A and mukulol.

Cembrene-A

The compound analyses for $C_{20}H_{32}$ (M^+, *m/e* 272) and shows the following structural features: no Me on sp^3 C (PMR), four vinylic Me's (PMR: 9H, s, 1·57—1·58 ppm; 3H, d, 1·64 ppm, $J \sim 0{\cdot}5$ Hz), —C(=)=CH_2 (IR: 895, 1648, 3050 cm^{-1}. PMR: 2H, broad s, 4·63 ppm) and, three —C(=)=CH— (PMR: 3H, essentially superimposed triplets, 5·03 ppm, $W_H = 16$ Hz). In the UV, the compound shows no maximum above 210 nm. On catalytic hydrogenation (PtO_2), the olefin took up four mole equivalents of H_2 to give an octahydro-derivative, $C_{20}H_{40}$ (M^+, *m/e* 280) containing no olefinic bonds (TNM test, -ve; PMR). Thus, the new hydrocarbon has a total of four olefinic linkages and being $C_{20}H_{32}$, must be monocyclic and, from its structural features, is clearly a diterpene.

Making the reasonable assumption that the hydrocarbon arises in Nature, from geranyl-geranyl pyrophosphate (1), the normal diterpenoid precursor,[2] by a single cyclization, then three



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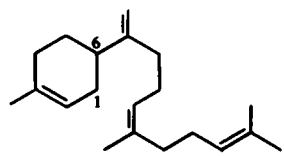

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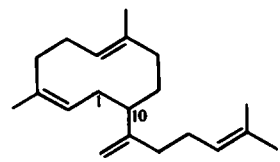

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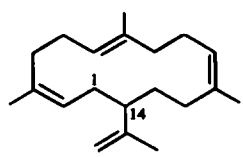

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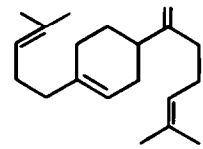

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structures (2, 3, 4) emerge for consideration, depending on whether a $1 \rightarrow 6$, or $1 \rightarrow 10$ or $1 \rightarrow 14$ cyclization (followed by deprotonation) is envisaged. All these structures‡ meet the structural requirements of the new diterpene. In addition the possibility that the compound may be α-camphorene (5) must also be considered, as it has been reported[3] earlier that the essential oil from *Commiphora mukul* gum-resin contains both myrcene and its dimer camphorene, though optical activity of our compound would argue against such a possibility (as α-camphorene is considered to be an artefact, derived by dimerization of myrcene[4]). A

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‡These structures represent three different cyclization modes. Other structures in types represented by 2 and 3 are possible (by olefinic bond isomerizations) which will still answer the structural requirements, but these need not be considered for the present purpose. No stereochemical significance is implied in the geometry of the olefinic bonds shown in structures 2–4.

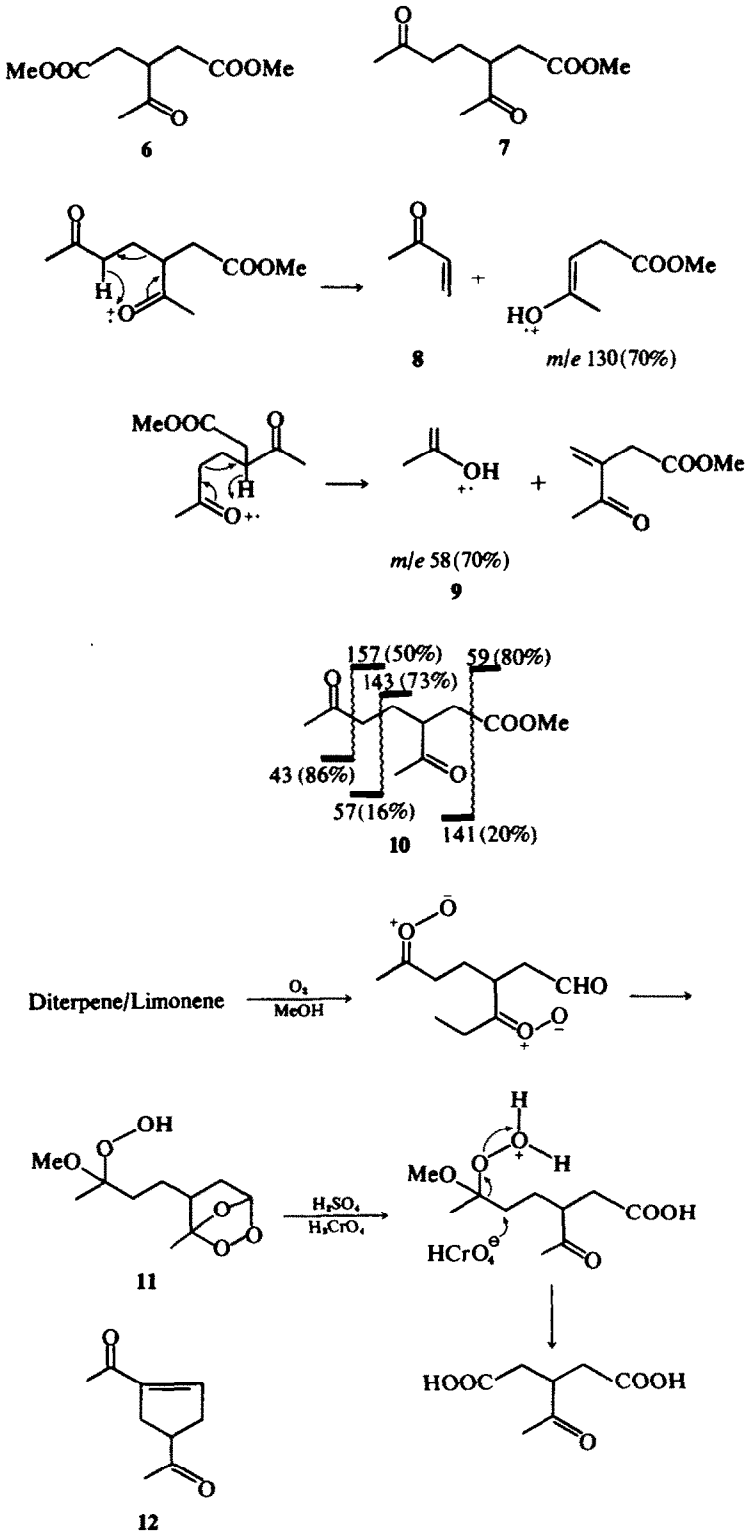
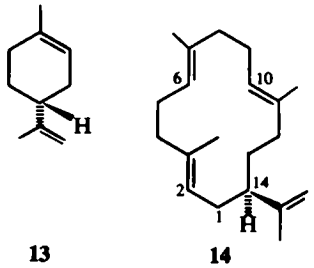


Fig 1. Possible pathway to the formation of β-acetyl-glutaric acid during ozonolysis (CrO_3 work-up) of limonene.

comparison of the PMR spectrum of the new diterpene with those recently reported[40] for α-camphor enes (*meta* and *para* isomers) clearly shows that the diterpene from *Commiphora mukul* is quite distinct from α-camphorene.

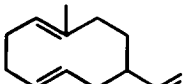
By double irradiation it was shown that in the PMR spectrum of the diterpene, the —C(=CH_2)— signal (4·63 ppm) and the vinylic Me signal at 1·64 ppm are mutually coupled ($J \sim 0{\cdot}5$ Hz), thus the grouping Me—C(=CH_2)— must be present. This favours structure **4** for the new diterpene.

Clear-cut chemical evidence in favour of structure **4**, was obtained as follows. Ozonolysis, followed by CrO_3 oxidation[5] of the crude 'ozonide' converted this hydrocarbon into a mixture of acids, which were esterified (CH_2N_2). GLC of the resulting Me esters showed the presence of three major components, which were separated by fractional distillation, followed by inverted-dry-column-chromatography (IDCC).[6] Of these, the compound with the lowest retention time (RRT = 1) was identified (GLC, IR, PMR, 2,4-dinitrophenylhydrazone) as methyl laevulinate. The second component (RRT = 6·6; M^+, *m/e* 202; IR in CCl_4: C=O 1725, 1740 cm^{-1}) shows in its PMR spectrum signals for COMe (3H, s, 2·21 ppm) two COOMe (6H, s, 3·64 ppm) and is optically inactive; it is thus, formulated as dimethyl β-acetyl-glutarate (**6**).[7] The third component (RRT = 11·3) analyses for $C_{10}H_{16}O_4$ (M^+, *m/e* 200) and from its spectral characteristics (IR: C=O 1716, 1740 cm^{-1}. PMR: two COMe, two 3H singlets at 2·07 and 2·16 ppm; COOMe, 3H, s, 3·61 ppm) is clearly methyl 3-acetyl-6-oxo-heptanoate (**7**); electron-impact-induced fragmentation supports this structure (cf. **8**, **9**, **10**). An authentic sample[8] of this compound (**7**) was prepared by ozonolysis (followed by CrO_3 oxidative workup) of (+)-limonene (**13**), and was found to be completely identical (GLC, IR, PMR, Mass) with the product from the diterpene. Compound **7** can be obtained only from structure **4** which must, then represent the new diterpene.* Since the diketo ester (**7**) obtained from diterpene has $[\alpha]^{CHCl_3}$ + 8·8°, which is same in sign and similar in magnitude to the $[\alpha]_D^{CHCl_3}$ (+ 6·4°) observed for the sample of **7**, prepared from (+)-limonene, of known[11] absolute stereochemistry **13**, the new diterpene must have the C_{14} absolute stereochemistry as depicted in **14**. The geometry of the ring-olefinic bonds, as shown in **14**, is not implied and still remains to be clarified.†‡



13 **14**

The new diterpene is, thus, one of the two most elementary tetraenes possible from geranyl-geranyl pyrophosphate by C_1–C_{14} cyclization (followed by deprotonation) and, in analogy with a suggestion[15] on the nomenclature of germacrenes (e.g. **15–17**), the corresponding biogenetically



Germacrene-A
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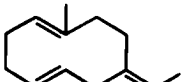

Germacrene-B
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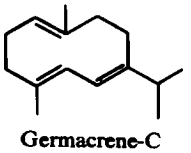

Germacrene-C
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*The formation of dimethyl β-acetyl-glutarate (**6**) from the diterpene during its ozonolysis (oxidative work-up, followed by esterification) requires a brief comment. In the first instance it should be mentioned that the same product (**6**), in essentially similar yield (relative to the normal product **8**), was also obtained by ozonolysis (same experimental conditions) of limonene.

Since, the ozonolysis was carried out in MeOH (+ CH_2Cl_2), it is reasonable to assume, in view of the generally accepted mechanistic ideas on ozonolysis,[9] the formation, to some extent, of the ozonide hydroperoxide **11** (Fig. 1). This, during oxidative work-up with Jones reagent, can conceivably lead to β-acetyl-glutaric acid (Fig. 1). In this connection, attention may be drawn to the recently described[10] facile fragmentations of tertiary allylhydroperoxides in acidic media. The alternative route, implicating the unsaturated diketone **12**, would appear less attractive.

†From molecular models it is clear that there are no geometric constraints on having one, two or all the three ring-ethylenic linkages either Z- or E-configurated. However, in view of the known[12] all-*trans* geometry of the naturally occurring geranyl–geraniol, it is considered most likely that in **14**, Δ^6, Δ^{10} are E-configurated; the configuration at Δ^2 could be E or Z as isomerization of this linkage in geranyl–geranyl pyrophosphate is possible through its allylic isomer geranyl–linalyl pyrophosphate.

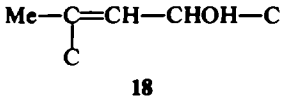
‡After completion of our work, isolation of the same diterpene from *Pinus koraensis* has been reported;[13] their method of structure elucidation is distinct from ours. Also, the trail substance from certain species of Australian termites (chiefly *Nasutitermes oxitiosus* Hill) has recently been assigned[14] the gross structure **4**. A specimen of our diterpene hydrocarbon was found by Prof. A. J. Birch[14] to be fully identical (including the biological activity) with their material.

equivalent sesquiterpene hydrocarbons, is named cembrene-A; the term cembrene is adopted from the name of the first diterpene of this class.[16]

Mukulol

The alcohol (IR: OH 3350, 1020 cm^{-1}), m.p. 37–38°, $[\alpha]_D$ +53°, analyses for $C_{20}H_{34}O$ (M^+, *m/e* 290; M^+-H_2O, *m/e* 272) and displays in its PMR spectrum the following structural features: Me_2CH (6H, pair of doublets centred at 0·93 and 0·97 ppm, *J* 7 Hz), three vinylic Me's (9H, essentially a broad singlet, 1·6 ppm), CHOH (1H, d, 4·46 ppm, *J* 9 Hz), two —C=CH—CH_2— (2H, broad unresolved multiplet centred at 5·0 ppm) and —C=CH— CH— (1H, broad doublet, 5·3 ppm, *J* 9 Hz). By decoupling experiments it was established that CHOH signal and the olefinic signal at 5·3 ppm are mutually coupled, the latter being also coupled with a vinylic Me; thus, grouping **18** must be present. Further, since the CHOH proton is coupled essentially only with the vinylic H, it must be flanked on the other side by, at best, a methine group; hence, **18** can be extended to **19**. The alcohol can be readily acetylated (Ac_2O, pyridine, 25°) to give a liquid acetate (IR: 1740, 1240 cm^{-1}), the PMR spectrum of which, besides displaying the expected shift for the CHOAc signal (d, 5·12 ppm, *J* 9 Hz), also shows a downfield shift for the coupled olefinic proton (d, 5·63 ppm, *J* 9 Hz) as might be expected,[17] for the part structure **18**. Mukulol shows no absorption maximum above 210 nm, hence the olefinic bonds may not be conjugated. However, in conformity with the part structure **18**, mukulol on oxidation with pyridine-CrO_3 complex gave the corresponding $\alpha\beta$-unsaturated ketone: M^+, *m/e* 288; λ_{max} 237 nm (ϵ, 13640); IR, C=O 1680 cm^{-1}, C=C 1615 cm^{-1}; PMR, —C=CH. CO—C (1H, s, 5·78 ppm), —C=CH.CH_2— (2H, broad unresolved multiplet centred at 4·83 ppm).

On quantitative catalytic hydrogenation (PtO_2 catalyst, 10% AcOH in EtOAc as solvent, ~ 25°, atmospheric pressure), mukulol consumed ~ 3·5 mole equiv. of H_2 to furnish a saturated hydrocarbon (hydrogenolysis product, $C_{20}H_{40}$, M^+ *m/e* 280, tetranitromethane test -ve) and a saturated alcohol (major, $C_{20}H_{40}O$, M^+ *m/e* 296). When hydrogenation was carried out in AcOH as the only solvent, the hydrogenolysis product predominated. The hydrogenolysis product was found to be identical (GLC, IR, PMR, Mass) with octahydrocembrene-A, described in the earlier section. Thus, mukulol must have the cembrane skeleton **20**. In view of the structural features described earlier, structure **21** emerges as the most likely formulation for mukulol. This structure appears all the more attractive on biogenetic considerations. The cation **22**, resulting from $C_1 \rightarrow C_{14}$ cyclization of geranyl-geranyl pyrophosphate and, which is also the immediate



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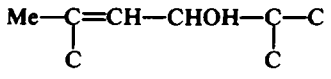

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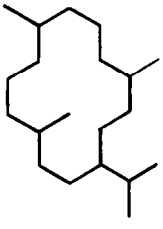

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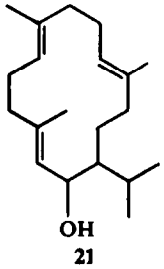

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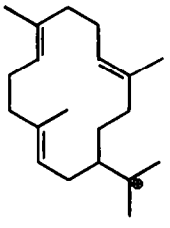

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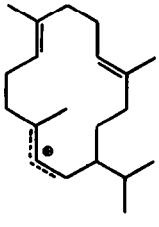

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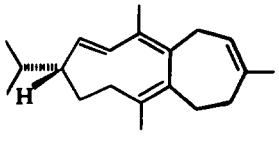

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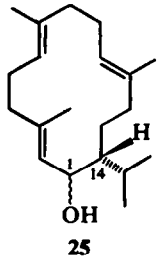

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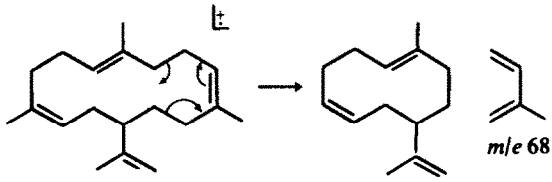
precursor of cembrene-A (14), the co-occurring diterpene hydrocarbon, can conceivably give, by a 1,3-hydride shift, the cation 13 which can generate mukulol by OH^- take-up. 1,3-Hydride shifts have often been postulated[18] in terpene biogenesis and have received support in recent years from biosynthetic experiments.[18b] Confirmation of structure 21 was forthcoming, when mukulol on being heated (~ 160°) in DMSO,[19] smoothly furnished the known[18] (+)-cembrene (24), which was identified in the usual manner (m.p., $[\alpha]_D$, UV, IR, PMR). This correlation also establishes R-chirality for C_{14} in mukulol (25); the configuration at C_1 as well as the geometry of the ethylenic linkages remains to be elucidated.*

Mukulol is quite labile and slowly deteriorates even at 0°. Its dehydration to cembrene (24) appears to be quite facile, as in two isolation experiments small amounts of cembrene were detected and this appeared to have been formed at the expense of mukulol.

Mass spectra of cembrene-A, mukulol and their derivatives

During the course of present investigations, the mass spectra of cembrene-A, mukulol and some of their derivatives were examined. It will be appropriate now to spotlight some observed fragmentations and rationalise these in terms of structures now elucidated.

*The geometry of the three trisubstituted ethylenic linkages in cembrene has not been clarified so far; the disubstituted olefinic linkage is *trans*-configurated (IR).[16a] The stereochemistry of double bonds shown in 21–23, 25 is not implied.



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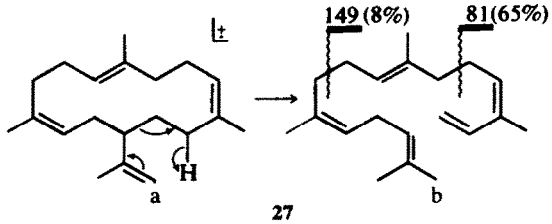

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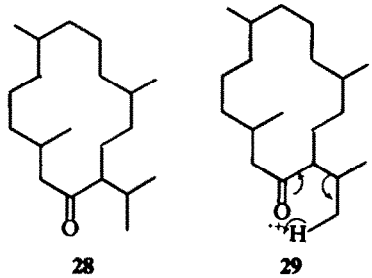
Cembrene-A gives a base peak at *m/e* 68. There are several possible modes for its formation, one involving a retro-Diels-Alder reaction[20] is shown in 26, the corresponding *m/e* 204 ion (5%) is also observed. The next less abundant ions are *m/e* 81 (65%) and *m/e* 93 (65%); rationalization of *m/e* 81, involving first a McLafferty rearrangement, is depicted in 27. Double-bond isomerization in 27b, followed by allylic cleavage can account for the ion *m/e* 93; double bond isomerizations during electron-impact-induced fragmentations are now well-recognized.[20] The mass spectrum is remarkably similar to that of cembrene (24).

Mukulol shows a strong M^+ ion (96%), $M^+ - H_2O$ (*m/e* 272) being the base peak. There does not appear to be any characteristic fragmentation except that the ions *m/e* 247 ($M^+ - C_3H_7$, 33%),



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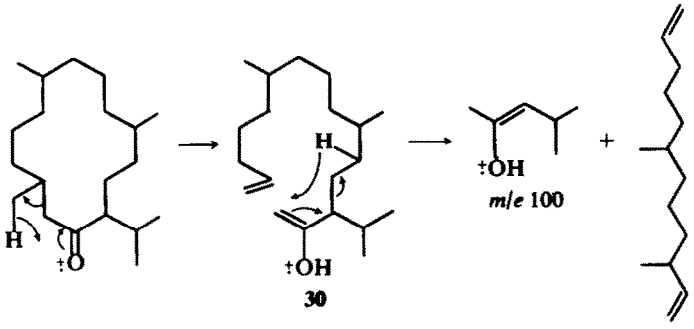

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257 (M^+—H_2O—CH_3, 23%) and 229 (M^+—H_2O—C_3H_7, 77%) are outstanding in the higher mass region of the spectrum. The mass spectrum of the corresponding unsaturated ketone is also very complex with essentially no prominent fragments; the molecular ion is the base peak.

The mass spectrum of the hexahydroketone (**28**; M^+ is the base peak) is clearly in accord with the relative positions of the carbonyl and the isopropyl groups as it shows ions at *m/e* 251 (M^+—C_3H_7, 6%; β-cleavage), 252 (M^+—C_3H_6, 8%; McLafferty rearrangement, **29**) and 100 (31%; double McLafferty rearrangement[21], **30**).

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Light petroleum refers to the fraction b.p. 40–60°. Optical rotations were measured in $CHCl_3$ at room temp. (22–30°).

SiO_2-gel for column chromatography was −100/+200 mesh, and was washed with hot distilled H_2O till sulphate-free, dried, activated at 125–130° (6–8 hr) and standardised.[22] $AgNO_3$-SiO_2-gel was made according to Gupta and Dev[23] and activated at 100–110° (4 hr). TLC was carried out on SiO_2-gel or 15% $AgNO_3$-SiO_2-gel layers (0·3 mm) containing 15% gypsum.

The following instruments were used for spectral/analytical data: Perkin-Elmer spectrophotometer, 350 (UV); Perkin-Elmer Infracord, 137E (IR); Varian Associates A-60 spectrometer (PMR; TMS as internal standard); CEC mass spectrometer, 21-110B (Mass; 70 eV, direct inlet system); 'Aerograph' model A-350-B (GLC; 300 cm × 0·5 cm Al columns packed with 20% diethylene glycol succinate on Chromosorb W of 60–80 mesh, H_2 carrier gas). Besides the molecular ion, ten most abundant ions in the mass spectrum (above *m/e* 50) are given with their relative intensities.

Cembrene-A (**4**). Isolation of this diterpene hydrocarbon (cembrene-A) has been described earlier:[1] b.p. 150–152°/0·8 mm; n_D^{30} 1·5102; $[\alpha]_D$ −19·7° (*c* 0·35%). *m/e* 272 (M^+, 21%), 68 (100%), 93 (63%), 81 (58%), 67 (57%), 53 (49%), 107 (42%), 79 (34%), 55 (34%), 121 (33%), 91 (30%). (Found: C, 88·21; H, 12·11. $C_{20}H_{32}$ requires: C, 88·16; H, 11·84%).

Hydrogenation of cembrene-A (**4**). Cembrene-A (0·505 g) in EtOAc (20 ml) consumed 200 ml of H_2 at 28°/715 mm (~ 4 mole equiv.) over prereduced Adam's PtO_2 catalyst (55 mg) during 4 hr when further H_2 up-take ceased. On usual work-up the octahydroderivative was obtained as an oil b.p. 140–145°(bath)/1·0 mm, n_D^{30} 1·4730, $[\alpha]_D$ +2·5° (*c*, 0·52%). PMR (CCl_4): $\underline{Me}_2CH$ (6H, d, 0·88 ppm, *J* 6 Hz). $\underline{Me}CH$ (9H, d, 0·88 ppm, *J* 6 Hz). *m/e* 280 (M^+, 21%), 236 (100%), 237 (84%), 83 (44%), 97 (43%), 111 (42%), 71 (42%), 57 (40%), 69 (39%), 55 (38%) and 125 (34%). (Found: C, 85·55; H, 14·22. $C_{20}H_{40}$ requires: C, 85·63; H, 14·37%).

Ozonolysis of cembrene-A (**4**): *isolation of methyl levulinate, dimethyl β-acetyl-glutarate* (**6**) *and methyl 3-acetyl-6-oxoheptanoate* (**7**). A stream of ozonized oxygen (O_3 conc. 0·7637 g/hr) was passed through a soln of **4** (1·2 g) in CH_2Cl_2-MeOH (1 : 1, 250 ml) at −80° till the soln turned faint blue (1·5 hr). After solvent removal at ~ 40°/50 mm, the resulting 'ozonide' was taken up in Me_2CO (25 ml), cooled to 0° and treated with Jones reagent[24] [8 ml; stock soln: CrO_3 (133 g), conc. H_2SO_4 (115 ml), H_2O (385 ml)] till the colour changed from deep blue to a faint brown and left overnight at 28°. The resulting product was separated into acidic (1·34 g) and neutral (0·37 g) fractions by aq. Na_2CO_3 (10%, 30 ml × 3). The former was esterified with CH_2N_2 and the resulting methyl ester (1·61 g, from two expts.) [GLC (200°, flow rate 90 ml/min): mixture of 3 major compounds with RRT 1, 6·6 and 11·3 respectively] was fractionally distilled to get two cuts: frac. 1, b.p. 130–135° (bath)/50 mm (0·65 g); frac. 2, b.p. 145–150° (bath)/3 mm (0·30 g).

Fraction 1 (0·650 g) was further purified by IDCC[6] (SiO_2-gel; 250 g, 25 cm × 4·7 cm; solvent: 50% EtOAc in light petroleum) to furnish pure methyl levulinate (0·236 g). IR (smear): C=O 1720, 1740 cm^{-1}. PMR (CCl_4): $\underline{Me}CO$ (3H, s, 2·15 ppm), —CO.$C\underline{H}_2$.$C\underline{H}_2$.COOMe (4H, 8-line A_2B_2, 2·56 ppm), COO$\underline{Me}$ (3H, s, 3·64 ppm). *m/e* 130 (M^+ 50%), 99 (100%), 115 (84%), 59 (74%), 55 (70%), 101 (57%), 71 (51%), 57 (51%), 88 (43%), 56 (37%) and 74 (36%). 2:4-*Dinitrophenylhydrazone* (H_2SO_4-method) m.p. 142–143°, m.m.p. with an uthentic sample (m.p. 142°) was undepressed.

Fraction 2 (0·30 g) [GLC (200°, flow rate 90 ml/min): major in 2 compds. with RRT 6·6 and 11·3 respectively] was resolved by IDCC[6] (SiO_2-gel; 250 g, 25 cm × 4·7 cm; solvent: 90% Et_2O in light petroleum) into 2 pure (TLC, GLC) fractions. The faster-moving *dimethyl β-acetyl-glutarate* (**6**) (67 mg) had b.p. 135–140° (bath)/2 mm, n_D^{30} 1·4480, $[\alpha]$ ±0°. *m/e* 202 (M^+, 17%), 160 (100%), 139 (83%), 171 (81%), 128 (81%), 100 (76%), 97 (72%), 127 (70%), 111 (70%), 59 (70%) and 82 (56%). The slower-moving *methyl 3-acetyl-6-oxo-heptanoate* (**7**) had b.p. 140–145° (bath)/2 mm, n_D^{30} 1·4473, $[\alpha]_D$ +8·8° (*c* 0·5%). *m/e* 200 (M^+, 15%), 182 (100%), 111 (97%), 98 (97%), 125 (91%), 168 (88%), 100 (87%), 55 (82%), 59 (81%), 169 (80%) and 151 (78%).

Ozonolysis of (+)-limonene: preparation of authentic methyl 3-acetyl-6-oxo-heptanoate. (+)-Limonene (α_D +134°, 1·19 g) was subjected to ozonolysis under the conditions described above. The acidic fraction (0·82 g) thus obtained was esterified (CH_2N_2) and the methyl ester fractionally distilled: frac. 1 b.p. 140–150° (bath)/50 mm (0·10 g; rejected) and frac. 2, b.p. 150–160° (bath)/4 mm (0·90 g). Frac. 2 [GLC (200°, flow rate 90 ml/min): major in 2 compds. with RRT 6·6 and 11·3] was separated by IDCC as before: the higher R_f compd. (86 mg) had b.p. 135–140° (bath)/2 mm, $[\alpha]_D$ ±0° (*c* 0·25%) and was identical with dimethyl β-acetyl-glutarate described earlier; the lower R_f compd. (125 mg) b.p. 140–145° (bath)/2 mm, $[\alpha]_D$ +6·4° (*c* 0·52%) was the required methyl 3-acetyl-6-oxo-heptanoate.

Mukulol (**21**). Isolation of this diterpene alcohol (mukulol) has been described before: m.p. 37–38°, $[\alpha]_D$ +53° (*c* 0·47%). *m/e* 290 (M^+ 94%), 272 (100%), 123 (92%), 83 (90%), 149 (83%), 136 (83%), 137 (82%), 135 (79%), 95 (78%), 121 (76%) and 229 (75%). (Found: C, 82·88; H, 11·81. $C_{20}H_{34}O$ requires: C, 82·69; H, 11·80%).

Acetylation of mukulol (Ac_2O-pyridine, 25°/12 hr) gave an *acetate*: colorless liquid, b.p. 160°–165° (bath)0·1 mm. PMR (CCl_4): $\underline{Me}_2CH$ (6H, pair of doublets, centred at 0·78 and 0·95 ppm, *J* 7 Hz), three $\underline{Me}$.C=C (6H, essentially a broad s, 1·56 ppm; 3H, essentially a broad s, 1·68 ppm), OCO$\underline{Me}$ (3H, s, 1·89 ppm), C$\underline{H}$OAc (1H, d, 5·12 ppm, *J* 9 Hz), —C=C$\underline{H}$—CHOAc (1H, d, 5·63 ppm, *J* 9 Hz), two —C=C$\underline{H}$.CH_2 (2H, ill-defined m, 4·7–5·1 ppm). *m/e* 332 (M^+ 100%), 272 (89%), 123 (86%), 149

(76%), 229 (75%), 189 (73%), 136 (72%), 135 (71%), 161 (69%), 81 (68%) and 107 (65%). (Found: C, 78·94; H, 10·93. $C_{20}H_{36}O_2$ requires: C, 79·46; H, 10·92%).

Sarett oxidation of mukulol (**21**). Mukulol (0·40 g) in dry pyridine (2·5 ml) was treated with Sarett reagent[25] (from 0·42 g of CrO_3 and 4 ml of pyridine) at 28°. After 6 hr the product was worked up as usual and the $\alpha\beta$-unsaturated ketone (0·41 g) purified by IDCC (SiO_2-gel, 125 g, 25 cm × 3·3 cm; solvent: 20% Et_2O in light petroleum) to furnish the pure compd. b.p. 155–158° (bath)/0·07 mm, $[\alpha]_D$ + 114·8° (*c* 0·495%), n_D^{30} 1·5115. PMR (CCl_4): $\underline{Me}_2CH$ (6H, d, 0·83 ppm, *J* 6 Hz), three $\underline{Me}C{=}C$ (3H singlets at 1·47, 1·55 and 2·05 ppm), —C=C$\underline{H}$—CO (1H, s, 5·78 ppm), two —C=C$\underline{H}$.CH_2 (2H, broad m, 4·83 ppm). *m/e* 288 (M^+ 100%), 82 (69%), 93 (67%), 109 (62%), 79 (59%), 148 (56%), 55 (56%), 149 (55%), 81 (55%), 53 (55%) and 107 (54%). (Found: C, 83·99; H, 11·21. $C_{20}H_{32}O$ requires: C, 83·27; H, 11·18%).

Hydrogenation of mukulol (**21**). (i) *In EtOAc-AcOH.* Mukulol (0·525 g) in EtOAc containing 10% AcOH (20 ml) consumed 160 ml (~ 3·5 mole equiv.) of H_2 at 25°/715 mm over prereduced Adams' PtO_2 catalyst (52 mg) during 5 hr when further H_2 up-take ceased. The product after usual work-up was found to be a mixture of at least 3 compds (TLC; solvent: C_6H_6). The product (1·5 g) from three such expts. was resolved by IDCC (SiO_2 gel 500 g, 25 cm × 6·6 mm; solvent: C_6H_6). Of the two pure compds. isolated, the fast-moving liquid (130 mg, purified further by $AgNO_3$-SiO_2 gel chromatography) had b.p. 140–145° (bath)/1 mm, TNM test: -ve, $[\alpha]_D$ + 2·4° (*c*, 0·5%) and was identified as *octahydrocembrene-A* (see above). The slower-moving saturated alcohol (0·63 g) had b.p. 125–130° (bath)/0·04 mm, $[\alpha]_D$ −28·3° (*c*, 0·47%), n_D^{30} 1·4822. IR (nujol): OH 3500, 1040 cm^{-1}. PMR (CCl_4): $\underline{Me}_2CH$ and $\underline{Me}CH$ (15H, overlapping signals centred at 0·93 ppm, *J* 6 Hz), C$\underline{H}$OH (1H, broad m, 3·97 ppm). *m/e* 296 (M^+ 48%), 123 (100%), 278 (98%), 109 (81%), 111 (79%), 71 (69%), 257 (68%), 126 (68%), 69 (66%), 97 (61%) and 56 (61%). (Found: C, 81·28; H, 13·29. $C_{20}H_{40}O$ requires: C, 81·00; H, 13·60%). (ii) *In AcOH:* Mukulol (2·2 g) in AcOH (25 ml) consumed 730 ml (3·6 mole equiv.) of H_2 at 28°/715 mm over prereduced PtO_2 catalyst (67 mg) during 16 hr when further H_2 up-take ceased. Usual work up gave a mixture (2·17 g) of 2 compds which was separated by IDCC (SiO_2 gel 500 g, 25 cm × 6·6 cm solvent: C_6H_6) to furnish octahydrocembrene-A (1·79 g, 81%) and the saturated alcohol (0·23 g, 11%) described under (i) above.

Hexahydroketone (**28**). Hexahydromukulol (0·116 g) in ether (20 ml) was stirred and treated with Brown's reagent[24] (0·3 ml; from 1 g $Na_2Cr_2O_7{:}2H_2O$, 0·75 ml conc. H_2SO_4, diluted to 5 ml with water) in portions, at 25–30°. After 3 hr the faint orange soln was treated with a few drops of MeOH to destroy excess reagent, diluted with water and the product isolated in the usual fashion. The resulting solid (0·12 g) was essentially pure (TLC; solvent; 70% C_6H_6 in light petroleum) and after recrystallisation from Me_2CO the pure hexahydroketone (**28**) was obtained as snow-white silky needles (51 mg), m.p. 96–97·5°, $[\alpha]_D$ + 35·5° (*c* 0·20%). IR (nujol): C=O 1700 cm^{-1}. *m/e* 294 (M^+ 100%), 69 (59%), 55 (55%), 57 (49%), 70 (47%), 56 (41%), 71 (40%), 83 (34%), 127 (31%), 100 (31%) and 111 (25%). (Found: C, 82·10; H, 13·00. $C_{20}H_{38}O$ requires: C, 81·56; H, 13·01%).

Dehydration of mukulol (**21**) *to cembrene* (**24**). Mukulol (0·742 g) in dry DMSO (2·5 ml, freshly distilled over CaH_2) was heated in an oil bath at 160° for 0·5 hr (N_2). Dilution with water and extraction with light petroleum gave a gummy material (0·65 g) which was chromatographed on $AgNO_3$-SiO_2 gel (60 g, 84 cm × 1·6 cm) and eluted with increasing amounts of EtOAc in light petroleum. A fraction (0·37 g) eluted with 2% EtOAc-light petroleum solidified (m.p. 55–58°) and was recrystallised from EtOH to snow-white needles (0·264 g) m.p. 58–59·5°, $[\alpha]_D$ + 233·7° (*c* 0·27%), λ_{max}^{EtOH} 244 nm (ε 13950). PMR (CCl_4): $\underline{Me}_2CH$ (6H, pair of doublets, centred at 0·80 and 0·85 ppm, *J* 6 Hz), three $\underline{Me}C{=}C$ (9H, broad 3H singlets at 1·49, 1·55 and 1·73 ppm), —CH=C(—CH=)—C$\underline{H}$ (1H, d, 6·03 ppm, *J* 15 Hz), vinylic H (4H, multiplet between 4·66–5·66 ppm). *m/e* 272 (M^+ 78%), 93 (100%), 81 (91%), 91 (89%), 55 (81%), 105 (80%), 107 (72%), 119 (61%), 79 (61%), 77 (52%) and 121 (48%) (lit.[16a]: m.p. 59–60°, $[\alpha]_D^{CHCl_3}$ + 238°; λ_{max}^{EtOH} 245 nm, ε 17,000).

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