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CHEMISTRY OF AYURVEDIC CRUDE DRUGS—IV[a]

GUGGULU (RESIN FROM *COMMIPHORA MUKUL*)—4 ABSOLUTE STEREOCHEMISTRY OF MUKULOL[b]

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Abstract—Absolute stereochemistry of mukulol, a diterpene alcohol, is established by chemical correlation with cembrene-A and (+)-*cis*-piperitol. Synthesis of (+)-*cis*-piperitol and (−)-*trans*-piperitol from (+)-Δ^2-carene is described. Δ^2-Carene oxide on exposure to silica gel passes into *cis* Δ^2-p-menthen-1,8-diol.

We have already described[1] the isolation and gross structure determination of mukulol (**1**), a diterpenoid from gum-resin of *Commiphora mukul*. We now present evidence for the geometry of the double bonds and the absolute stereochemistry as depicted in **2**.

In our earlier publication on Cembrene-A (**6**), we gave evidence for the absolute configuration at C_{14}, but the geometry of the three endocyclic olefinic linkages remained to be clearly defined. Since then, both nOe studies[2] and a total synthesis[3] have firmly established that these ethylenic linkages are *trans*-configurated. Since cembrene-A and mukulol co-occur in *Commiphora mukul*, the Absolute Stereochemistry Biogenetic Rule[4] suggests that mukulol should also have the same geometry of the double bonds and the same absolute configuration at C_{14}. This is now confirmed by a direct chemical correlation of mukulol and cembrane-A.

Cembrene-A was selectively hydrogenated (PtO_2) to its dihydroderivative (**7**), which was also obtained by reductive cleavage of mukulol acetate (**3**; with Li, liq. NH_3) or the corresponding tosylate (**4**; with LAH). Either of the two cleavage methods gave the hydrocarbon product in only fair yield (~30%) and this consisted of the desired **7** (~60%) and the anticipated[5] allylic rearrangement product, the epimeric pair **8**. Separation of these hydrocarbons was readily achieved by silver ion-silica gel chromatography. All three preparations of dihydrocembrene-A (**7**) were completely identical (IR, PMR, Mass, $[\alpha]_D$), thus securing the geometry of the ethylenic linkages and the absolute configuration† at C_{14} of mukulol as shown in **2**. Structure **8** for the two allylically rearranged hydrocarbons is obvious from their spectral data (Experimental). Both these hydrocarbons

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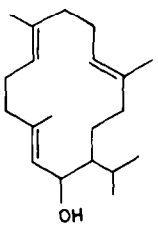
[b]MRC Communication No. 3.
†In our earlier publication,[1] configuration at C_{14} has been drawn as opposite to that shown in **2**. The earlier C_{14}-configuration assignment is based on the conversion of mukulol to (+)-cembrene (**9**), which is known[6] to have S-chirality at C_{14}, and this is consistent with **2**. The formula shown in our earlier publication has been incorrectly drawn as a consequence of wrong interpretation of sequence rule.[7]



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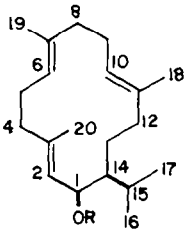

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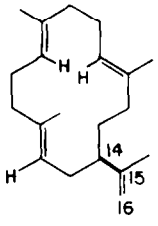

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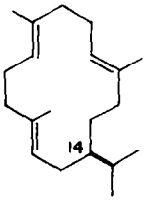

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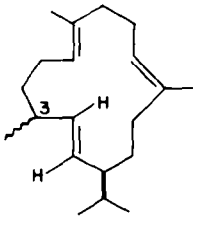

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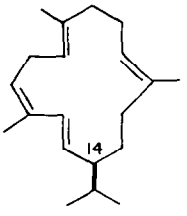

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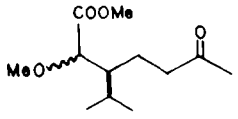

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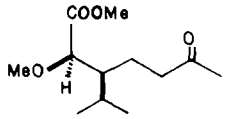

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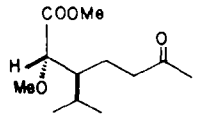

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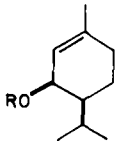

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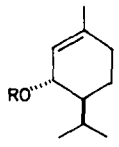

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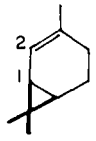

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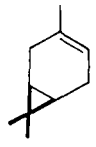


18

show a strong band at 975 cm^{-1} in their IR spectra, clearly indicating that the new disubstituted ethylenic linkage is *trans*-configurated. The mass spectra of the two compounds are virtually identical, while their PMR spectra differ somewhat only in the olefinic proton region.

Configuration at C_1. In order to establish the configuration of the OH function in mukulol, its methyl ether was degraded (O_3; CrO_3)[8] to **10**; this reaction was carried out on the methyl ether rather than on the alcohol, as ozonolysis of allylic alcohols is known[9] to lead, sometimes, to "abnormal" products. This product was to be compared with an authentic sample. Since, *a priori*, it is not possible to assess how much the two epimers **11**, **12** will differ in their spectral characteristics and other physical properties, it was decided to prepare authentic samples of both of these compounds. (+)-*cis*-piperitol (**13**) and (−)-*trans*-piperitol (**14**) needed for this purpose were prepared from (+)-Δ^2-carene (**17**) by a route, which is briefly discussed later. Each of these compounds was converted to its methyl ether, which was degraded in exactly the same manner as mukulol methyl ether. The IR, PMR spectra† and specific rotation of the final product (**11**), derived from (+)-*cis*-piperitol (**13**) were completely identical with the product from mukulol, thus fixing the hydroxyl configuration in mukulol, as shown in **2**.

Synthesis of piperitols (**13**, **14**) *from* Δ^2-*carene*

(+)-*cis*-Piperitol (**13**) and (−)-*trans*-piperitol (**14**), which were required for the above correlation, do not appear to have been described earlier.[10] We now report their preparation from (+)-Δ^2-carene (**17**). Epoxidation of Δ^2-carene[11] with peracetic acid (in presence of NaOAc and CH_2Cl_2) has been reported[12] to furnish **20** (rather than the epoxide **19**), which, conceivably, can be converted into piperitols. However, in our hands, epoxidation of Δ^2-carene with peracetic acid (aq.) or perbenzoic acid (C_6H_6) gave only **19**, which, of course, could be rearranged in a subsequent step of exposure to *m*-titanic acid,[13] to the required **20**. For preparing **20** in quantity, it proved expeditious to epoxidise the equilibrium mixture of Δ^2- and Δ^3-carene, obtainable from base-catalyzed isomerisation[11] of Δ^3-carene (**18**), and treat the product with *m*-titanic acid, when only the Δ^2-carene oxide (**19**) rearranges to **20**, which can be readily separated by fractional distillation. During these investigations, it was found that Δ^2-carene oxide on exposure to silica gel (chromatography conditions) rearranges[14] to *cis*-Δ^2-*p*-menthen-1,8-diol (**21**).[12a]

(+)-*cis*-$\Delta^{2,8}$-*p*-Menthadien-1-ol (**20**) on treatment with NaOAc and AcOH yielded a mixture of piperitenyl acetates (**22**; 40%).[15] This mixture was selectively hydrogenated over tris (triphenylphosphine) chlororhodium[16] to furnish piperityl acetates. The product was converted to the parent alcohol mixture by LAH and then separated by fractional distillation[17] into pure **13** and **14**. These compounds displayed $[\alpha]_D$ of the same order of magnitude (but of opposite sign) as have been recorded for the corresponding antipodes.[18]

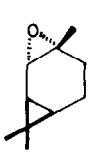
†The IR and PMR spectra of **11** and **12** are distinctly different.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Light petroleum refers to the fraction, b.p. 60–80°. Optical rotations were measured in $CHCl_3$, on a Schmidt + Haensch electronic polarimeter model Polatronic 1.

TLC was carried out on SiO_2-gel layers (0.25 mm) containing 15% gypsum and activated at 110–115° (2 hr). $AgNO_3$(15%)-SiO_2-gel layers without binder were employed.[19]

The following instruments were used for spectral/analytical data: Perkin–Elmer Infrared Spectrophotometer, model 267; Perkin–Elmer model R32 (90 MHz) NMR Spectrometer; Varian Mat CH7 Mass Spectrometer (70 eV, direct inlet system); Hewlett-Packard 5700A gas chromatograph (Column: 360 cm × 5 mm; 10% Carbowax 20M on Chromosorb W, 60–80; H_2, as



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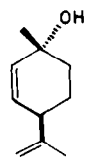

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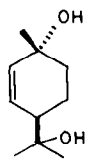

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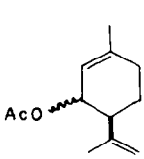

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carrier gas). All PMR spectra were taken in 15–20% soln in CCl_4 with TMS as internal standard; signals are reported in ppm (δ). While citing PMR data the following abbreviations have been used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and b (broad). While summarising mass spectral data, besides the molecular ion, ten most abundant ions (about *m/e*) are reported with their relative intensities.

Purity of all new compounds was ascertained by GLC and/or TLC.

2E,6E,10E-*Cembratriene* (7)

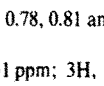
(i) *From cembrene-A.* Cembrene-A (600 mg) in EtOAc (5 ml) was hydrogenated over prereduced Adams PtO_2 catalyst (100 mg, 15 ml EtOAc) at 25° and atmospheric pressure, till one mole equiv of H_2 had been absorbed (3 hr). Usual work-up gave a product (550 mg), which was chromatographed over SiO_2–$AgNO_3$ (15% $AgNO_3$, 20 × 1.5 cm) with TLC monitoring over SiO_2–$AgNO_3$ (solvent: 20% ether in light petroleum): Frac. 1; light petroleum, 40 ml × 2, 30 mg. Frac. 2; 50% C_6H_6 in light petroleum, 30 ml × 2, 110 mg, TLC pure; M⁺, *m/e* 276, tetrahydroderivative. Frac. 3; C_6H_6, 40 ml × 3, 309 mg, TLC pure; M⁺, *m/e* 274, dihydroderivative.

Frac. 3 was distilled to give **7** (296 mg): b.p. 135–145° (bath)/0.2 mm, n_D^{25} 1.5019, $[\alpha]_D^{25}$ −21.53° (*c* 3.07%). IR (liq.): no significant band 890 cm^{-1}. PMR: Me_2CH (two 3H doublets at 0.82 and 0.92 ppm, J = 6 Hz), three Me–C(=)C (9H, bs, 1.56 ppm), three –C(=)CH–CH_2 (3H, m, 4.96 ppm). Mass: *m/e* 274 (M⁺, 36%), 123 (65%), 108 (50%), 107 (48%), 95 (68%), 81 (100%), 69 (100%), 68 (92%), 67 (86%), 55 (100%), 53 (59%). (Found: C, 87.7; H, 12.5. $C_{20}H_{34}$ requires: C, 87.6; H, 12.4%).

(ii) *From mukulyl acetate* (3). A soln of mukulyl acetate[1] (1.0 g) in dry ether (6 ml) was rapidly added with stirring to a soln of Li (1.0 g) in liquid ammonia (125 ml). After stirring for additional 20 min, the reaction was quenched by adding MeOH (10 ml) and worked up in the usual manner (extraction with ether) to give a product (1.0 g) which was chromatographed over SiO_2-gel (IIA, 20 × 1.5 cm): light petroleum (50 ml × 3) eluted a hydrocarbon mixture (365 mg), while 10% ether in light petroleum (50 ml × 2 gave unchanged acetate (68 mg) and, C_6H_6 (50 ml × 4) yielded mukulol (499 mg).

The hydrocarbon mixture (360 mg) was separated on a column of SiO_2-gel–15% $AgNO_3$ (20 × 1.5 cm) with TLC monitoring (SiO_2–gel–$AgNO_3$, 20% ether in light petroleum): Frac. 1; light petroleum, 50 ml × 2, rejected. Frac. 2; 5% ether in light petroleum, 50 ml × 3, 208 mg, single spot, R_f 0.55. Frac. 3; 10% ether in light petroleum, 25 ml × 5, 107 mg, single spot, R_f 0.25. Frac. 4; 20% ether in light petroleum, 50 ml × 3, 26 mg, single spot, R_f 0.20.

Frac. 2 was distilled: 170 mg, oil, n_D^{25} 1.5016, $[\alpha]_D^{25}$ −17.77; identified as 2E,6E,10E-cembratriene (7) by IR, PMR and mass spectra.

Frac. 3 was distilled to give an oil (98 mg), b.p. 150–160° (bath)/0.6 mm, n_D^{27} 1.4973, $[\alpha]_D^{27}$ +155 (*c* 0.99%). This hydrocarbon was recognised as 1E,6E,10E-cembratriene (**8**, epimer A). IR (liq.):  977 cm^{-1}. PMR: Me₂CH, MeCH (three 3H doublets at 0.78, 0.81 and 1.01 ppm, each J = 6 Hz), two Me–C(=)C (3H, s, 1.51 ppm; 3H, s, 1.58 ppm), two –C(=)CH–CH_2 (2H, m, 4.96 ppm), –C(–)–CH=CH–C(–)– (2H; proton A, bd, 4.95 ppm, J_{AB} 15 Hz; proton B, q, 5.62 ppm, J_{AB} 15 Hz, J_{BX} 4 Hz). Mass: *m/e* 274 (M⁺, 35%), 232 (42%), 121 (40%), 109 (59%), 107 (44%), 95 (59%), 93 (44%), 81 (100%), 69 (48%), 67 (40%), 55 (60%).

Frac. 4 was distilled: 21 mg, b.p. 140–155° (bath)/0.5 mm, n_D^{24} 1.4975, $[\alpha]_D^{24}$ −82.79 (*c* 0.53%). This compound is identified as 1E, 6E, 10E-*cembratriene* (**8**, epimer B). IR (liq.):  975 cm^{-1}. PMR: Me_2CH, MeCH (three 3H doublets at 0.78, 0.83 and 0.98 ppm), two Me–C(=)C (3H, s, 1.55 ppm; 3H, s, 1.58 ppm), 4 olefinic protons (overlapping signals located between 4.7–5.4 ppm). Mass: *m/e* 274 (M⁺, 11%), 232 (22%), 121 (32%), 109 (50%), 107 (45%), 95 (56%), 93 (41%), 81 (100%), 69 (50%), 67 (42%), 55 (55%).

(iii) *From mukulyl tosylate* (**4**). Since **4** could not be isolated, it was subjected to LAH cleavage without isolation.[20] Mukulol (580 mg, 2 mmole) in dry ether (20 ml) was added, dropwise, with stirring to a suspension of NaH (96 mg, 4 mmole) in dry ether (40 ml) at 25° (N_2). After stirring for 1 hr, *p*-toluenesulphonyl chloride (763 mg, 4 mmole) in ether (10 ml) was added and the mixture stirred for 12 hr. LAH (1.0 g, large excess) was added in small portions with stirring and after additional stirring for 6 hr at 25°, the mixture was worked up (by addition of 1 ml cold water, followed by 3 ml 15% NaOH aq and, 3 ml water) in the usual manner. The product (540 mg) was separated, as described under (ii) above, into a hydrocarbon portion (150 mg) and mukulol (350 mg). The hydrocarbon was resolved as before into **7** (45 mg and **8** (mixture of epimers, 30 mg).

Mukulol methyl ether (**5**)

Mukulol (2.32 g, 8 mmole) in THF (20 ml) was added to a suspension of NaH (600 mg, 25 mmole) in THF (15 ml) and stirred at room temp. (30–35°) for 6 hr. This was cooled (5°), MeI (4.32 g, 30 mmole) in THF (15 ml) introduced (5 min) and the reaction mixture stirred at room temp for 5 hr. Usual work-up gave a product (2.4 g) which was chromatographed over SiO_2-gel (IIA, 50 cm × 1.5 cm): after light petroleum (50 ml × 4), 50% C_6H_6 in light petroleum (100 ml × 3) eluted the required ether (**5**, 2.2 g): b.p. 140–160° (bath)/1 mm, $[\alpha]_D^{16}$ +65.58 (*c* 9.92%). IR (liq.): C=C 1667 cm^{-1}; C–OMe 1100 cm^{-1}. PMR: Me_2CH (two 3H doublets at 0.87 and 0.95 ppm, J = 7 Hz), three Me·C(=)C (3H singlets at 1.58, 1.59 and 1.60 ppm), OMe (3H, s, 3.11 ppm), C=CH–CH(–)OMe (1H, d, 3.92 ppm, J = 9 Hz), two –C(=)CH–CH_2 (2H, bm, 5.0 ppm), –C(=)CH–CH(–)OMe (1H, d, 5.23 ppm, J = 9 Hz). Mass: *m/e* 304 (M⁺, 9%), 272 (23%), 123 (40%), 98 (100%), 85 (26%), 83 (33%), 81 (41%), 69 (24%), 68 (37%), 67 (26%), 55 (41%).

Methyl (2R)-2-*methoxy*-(3S)-3-*isopropyl*-6-*oxo*-*heptanoate* (**11**)

(i) *From mukulol methyl ether.* Mukulol methyl ether (1.0 g) in MeOH (60 ml) was ozonised at −10° with ozonised O_2 (delivering 0.68 g O_3/hr) till further absorption ceased (KI–AcOH test). Solvent was removed under reduced pressure at 20°, the residue taken up in acetone (6 ml) and treated[8] with Jones reagent[21] at 0° till a brown colour persisted (10 ml). After overnight (12 hr) at 20°, the mixture was worked up in the usual manner to get total acid mixture, which was esterified (CH_2N_2) to give crude methyl ester mixture (679 mg). This was fractionated to remove a lower boiling fraction (b.p. 130–150°/50 mm, 250 mg, essentially methyl levulinate) and, the higher boiling fraction (b.p. 130–150°, bath/4 mm, 362 mg) purified by inverse-dry-column-chromatography[22] (IDCC, SiO_2-gel, 20% diisopropyl ether in C_6H_6 as solvent: n_D^{24} 1.4423, $[\alpha]_D^{24}$ +28.54 (*c* 4.6%). IR (liquid): C=O 1715, 1750 cm^{-1}. PMR: Me_2CH (6H, d, 0.93 ppm, J = 7 Hz), MeCO (3H, s, 2.03 ppm), C–OMe (3H, s, 3.31 ppm), COOMe (3H, s, 3.72 ppm). Mass: *m/e* 230 M⁺, 1%), 173 (85%), 171 (45%), 139 (59%), 113 (100%), 85 (63%), 81 (53%), 71 (94%), 69 (86%), 59 (53%), 55 (88%). (Found: C, 61.65; H, 9.26. $C_{12}H_{22}O_4$ requires: C, 62.58; H, 9.63%).

(ii) *From* (+)-cis-*piperityl methyl ether* (**15**). Methyl ether **15** (168 mg) in MeOH (30 ml) was degraded exactly as described under (i) above to furnish **11** (45 mg), $[\alpha]_D^{24}$ +28.2 (*c* 2.0%).

Methyl (2S)-2-*methoxy*-(3S)-3-*isopropyl*-6-*oxo*-*heptanoate* (**12**)

(−)-*trans* **16** (100 mg) was degraded exactly as above to furnish **12**: b.p. 100–120° (bath)/2 mm, $[\alpha]_D^{27}$ −31.43 (*c* 2.4%). RRT with respect to **11**, 1.05 (temp 190°). IR (liquid): C=O 1715, 1740 cm^{-1}. PMR: Me_2CH (3H, d, 0.89 ppm, J = 7 Hz; 3H, d, 0.92 ppm,

J = 7 Hz), MeCO (3H, s, 2.07 ppm), C–OMe (3H, s, 3.31 ppm), COOMe (3H, s, 3.72 ppm). Mass: *m/e* 230 (M^+).

(+)-2α,3α,*Epoxycarane* (**19**)

(+)-Δ^2-Carene[11] (1.5 g) in C_6H_6 (5 ml) was added to a soln of perbenzoic acid in benzene (60 ml, 0.24 molar) at 10°. After another 3 hr at the same temp, the mixture was worked up to furnish a product (1.5 g), b.p. 60–75° (bath)/2 mm, which by GLC was essentially pure: RRT with respect to 3α,4α-epoxycarane 0.95 (temp 150°); n_D^{20} 1.4702, $[\alpha]_D^{29}$ +67.67 (*c* 4.5%). IR (liquid): 1300, 1250, 1227, 1190, 1160, 1140, 1115, 1065, 1020, 965, 945, 880, 866, 850, 790, 770, 706 cm^{-1}. PMR: Me_2C– (6H, s, 1.07 ppm), Me–C–O (3H, s, 1.19 ppm), –C–CH– (1H, bs, 2.79 ppm).

In the above preparation, 35% aq. peracetic acid (prepared by the azeotropic distillation method)[23] can be substituted for perbenzoic acid with similar results.

cis-Δ^2-p-*Menthene*-1,8-*diol* (**21**)

The above carene oxide (300 mg) in light petroleum (2 ml) was charged in a dry column of SiO_2-gel (TLC grade, IIA, 6 g). After 5 hr, the product was eluted with C_6H_6 and C_6H_6 containing increasing quantities of EtOAc, when 60% EtOAc in C_6H_6 eluted a solid (190 mg), which was crystallised from acetone, white needles (125 mg), m.p. 113–114°, $[\alpha]_D^{26}$ +44.65 (*c* 1.0%). Lit.,[12b] m.p. 114.5°. Spectral (IR, PMR, mass) characteristics as reported in Lit.[12b]

(+)-cis-$\Delta^{2,8}$-p-Menthadien-1-ol (**20**)

The equilibrium mixture[11] of Δ^2- and Δ^3-carene (56 g; Δ^2-carene content ~40%) in toluene (100 ml) was introduced dropwise with stirring to a mixture of 35% peracetic acid aq[23] (150 ml), toluene (200 ml) and powdered K_2CO_3 (100 g), while maintaining the temp at 0 to −5°. After 3 hr at this temp, the toluene layer was separated, washed with 10% NaOH aq (60 ml × 3), water and brine and dried (Na_2SO_4). Solvent removal gave a product (58 g), shown by GLC (150°) to contain 82% oxide mixture consisting of 37% **19** and 63% Δ^3-carene oxide.

If in the above preparation lesser amounts (50–75 ml) of peracetic acid were used, the product was richer in **19**, as Δ^2-carene reacted preferentially. Thus, an epoxidation mixture (200 g) containing Δ^2-carene oxide (25%), Δ^3-carene oxide (23%) and unchanged hydrocarbons (52%), obtained this way, was slowly introduced, with stirring, to a suspension of *meta*-titanic acid (10 g) in light petroleum (200 ml), at a rate that the temperature was not allowed to exceed 35°. After stirring for another 3 hr at room temp (~30°), GLC (150°) indicated complete isomerisation of **19**, while Δ^3-carene oxide remained unchanged. The catalyst was removed by filtration, the product freed of solvent and carefully fractionated at 8 mm, when a pure fraction (40 g) of (+)-*cis* **20** was obtained: b.p. 100–105°/8 mm, n_D^{20} 1.4922, $[\alpha]_D^{30}$ +151.2° (*c* 4.2%). (cf. Lit.;[12b] spectral characteristics—IR, PMR, mass—as reported in Lit.).

Piperitenyl acetates (**22**)[24]

To a mixture of NaOAc (20 g) and AcOH (150 ml), the above alcohol (25 g) was added (10 min) and the mixture stirred and heated at 40–45° for 12 hr, and then worked up in the usual manner. The product consisted (GLC, 150°) of unreacted **20** (43%), **22** (42%) and hydrocarbons (15%). The product (44 g) was chromatographed over SiO_2-gel (IIA, 100 × 3.5 cm). Light petroleum (300 ml × 4) eluted hydrocarbons, while 50% benzene in light petroleum, (300 ml × 5), next eluted **22** (17 g): b.p. 60°/1 mm, n_D^{20} 1.4776, $[\alpha]_D^{30}$ −3.04 (*c* 12%). This product is a mixture of epimers (**22**), but showed a single peak in GLC (150°). The product (IR: OAc 1736, 1240 cm^{-1}; $C{=}CH_2$ 890, 910 cm^{-1}. PMR: –C=CH–CH–, a bd and a bs in the ratio 1:2, centered respectively at 5.6 and 5.33 ppm; –C=CH–CH–CH, illresolved broad signal centred at 5.30 ppm; –C=CH_2, bs, 4.75 ppm), without further separation was used in the next step.

Piperitols (**13**, **14**)[10]

The above piperitenyl acetates mixture (16 g) in thiophenefree benzene (30 ml) was introduced into prereduced Wilkinson catalyst[16] (800 mg) in benzene (30 ml) and hydrogenated at 25° and 760 mm till further absorption of H_2 became very sluggish (3 hr; H_2 absorption—1 mole equiv). Usual work-up gave a product (15 g, mixture of piperityl acetates) which was taken up in dry ether (100 ml) and reduced with LAH (excess, 2.0 g) in the usual manner (3 hr, 25°). Work-up with water and NaOH aq gave a product (13.5 g) containing chiefly **13**, **14** in the ratio 1:2 (GLC, 150°. RRT: **13**, 1; **14**, 1.17). This product (11 g) was fractionated at 15 mm, using a high efficiency column:[25]

(+)-cis-*Piperitol* (**13**). B.P. 96°/15 mm, m.p. 11°, $[\alpha]_D^{35}$ +218.3° (C_6H_6, *c* 2.1%). Lit.[18] $[\alpha]_D$ for the (−)-antipode, −246° (C_6H_6). PMR: Me_2CH (3H, d, 0.93 ppm, J = 6.5 Hz; 3H, d, 0.97 ppm, J = 6.5 Hz), Me–C=C (3H, s, 1.67 ppm), –CHOH (1H, unresolved m, 4.03 ppm, W_H = 6 Hz), –C=CH·CHOH (1H, bd, 5.60 ppm, J = 5 Hz). *Methyl ether* (**15**), prepared exactly as described above for **5**. $[\alpha]_D^{26}$ +316.8° (*c* 2.5%). IR (liq.): OMe 1088, 1098 cm^{-1}. PMR: Me_2CH (6H, d, 0.80 ppm, J = 7 Hz), Me–C=C (3H, s, 1.69 ppm), OMe (3H, s, 3.17 ppm), –CHOMe (1H, t, 3.44 ppm, J = 4.5 Hz), –C=CH·CHOMe (1H, bd, 5.60 ppm, J = 4.5 Hz).

(−)-trans-*Piperitol* (**14**). B.p. 98°/15 mm, $[\alpha]_D^{35}$ −25° (C_6H_6, *c* 2.1%). Lit.[18] $[\alpha]_D$ for the (+)-antipode, +28° (C_6H_6). PMR: Me_2CH (3H, d, 0.84 ppm, J = 7 Hz; 3H, d, 0.96 ppm, J = 7 Hz), Me–C=C (3H, s, 1.67 ppm), –CHOH (1H, unresolved m, 3.91 ppm, W_H = 7 Hz), –C=CH·CHOH (1H, bs, 5.34 ppm, W_H = 3.5 Hz). *Methyl ether* (**16**), $[\alpha]_D$ −77.43° (*c* 3.1%). PMR: Me_2CH (3H, s, 0.82 ppm, J = 7 Hz; 3H, s, 0.93 ppm, J = 7 Hz), Me–C=C (3H, s, 1.67 ppm), OMe (3H, S, 3.23 ppm), –CHOMe (1H, unresolved m, 3.55 ppm, W_H = 7 Hz), –C=CH·CHOMe (1H, bs, 5.44 ppm, W_H = 3.5 Hz).

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