Synthetic Studies towards Complex Diterpenoids. Part 18.[1] Total Synthesis of (±)-Isopisiferin and the Related Compounds

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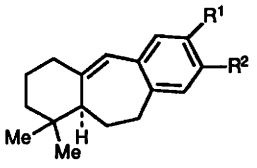
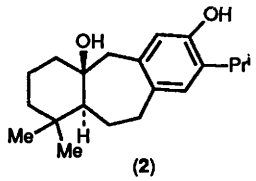
A simple convergent and general method has been developed for the synthesis of (±)-isopisiferin (**1c**), a rearranged abietane diterpene, having a hexahydrodibenzo[*a,d*]cycloheptene ring system, and the related model systems (**1a**) and (**1b**), through the respective enolisable tricyclic ketone mixtures (**12c**) and (**13c**), (**12a**) and (**13a**), and (**12b**) and (**13b**), obtained from the corresponding easily accessible 2-arylethyl-3,3-dimethylcyclohexanones (**7c**), (**7a**), and (**7b**). Demethylation of the styrenoid ethers (**15b**) and (**15c**) under acid conditions gave the tetracyclic dienones (**17b**) and (**17c**) through Ar_1-5 cyclisation.

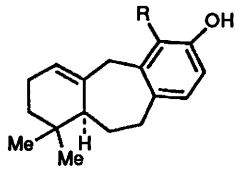
The recent structural elucidation[2,3] of isopisiferin (**1c**), pisiferanol (**2**), and a number of related compounds, isolated from the seeds of *Chamaecyparis pisifera* (Cupressaceae), along with the earlier reported phenols, pisiferin (**3a**)[4] and barbatusol (**3b**),[5] represent an interesting group of rearranged 9(10→20)-*abeo*-abieta-8,11,13-triene diterpenoids. Recently, the total syntheses of (±)-pisiferin (**3a**)[6] and (±)-barbatusol (**3b**)[7] have been reported. We present here the first total synthesis of (±)-isopisiferin (**1c**) and the related model compounds (**1a**) and (**1b**) by a simple and general convergent route.



(1) **a**; $R^1 = R^2 = H$
b; $R^1 = OH$, $R^2 = H$
c; $R^1 = OH$, $R^2 = Pr^i$



(2)



(3) **a**; R = H
b; R = OH

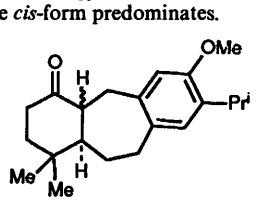
Results and Discussion

The *gem*-dimethylcyclohexanones (**7a**),[8] (**7b**),[8] and (**7c**), the key intermediates, were obtained in excellent yields by our recently developed procedure[8] of conjugate addition of a methyl group to the respective cyclohexenones (**6a**), (**6b**), and (**6c**) (Scheme 1). The previously unknown cyclohexenone (**6c**) was prepared by alkylation[9] of Hagemann's ester (**4**) with the bromide (**5**),[10] followed by alkaline hydrolytic decarboxylation. The ketones (**7a**), (**7b**), and (**7c**) were smoothly transformed to the respective alkenes (**8a**), (**8b**), and (**8c**) by Wittig reaction under forcing conditions.[11] Hydroboration of each of the alkenes (**8a**), (**8b**), and (**8c**), followed by oxidation[12] with alkaline hydrogen peroxide gave inseparable stereoisomeric mixtures of the corresponding alcohols (**9a**), (**9b**), and (**9c**). Each of these mixtures on further oxidation with Jones reagent[13] gave epimeric mixtures of the respective acids (**10a**), (**10b**), and (**10c**) in moderate to good yields, which were characterised as their respective methyl esters (**11a**), (**11b**), and (**11c**).

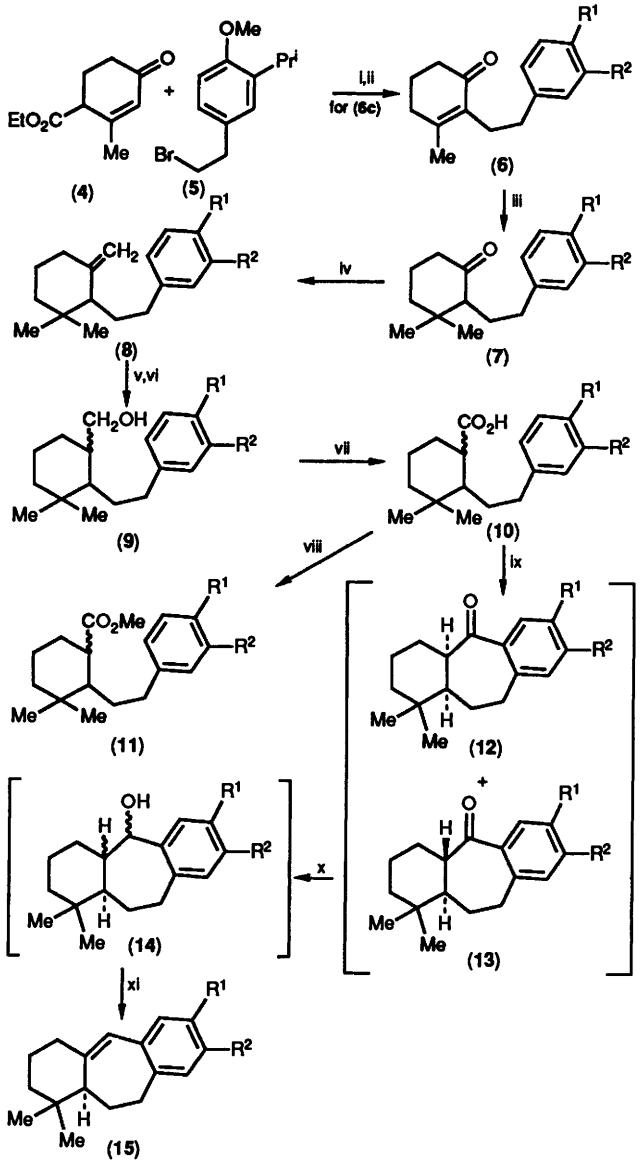
The cyclisation of the epimeric mixture of the acid (**10a**) with polyphosphoric acid (PPA) at 80–85 °C gave a solid stereoisomeric mixture of the *cis*- and *trans*-ketones (**12a**) and (**13a**) in a ratio of *ca.* 82:16 (GLC) in 95% yield. On recrystallisation the mixture readily afforded the major epimer (**12a**). Equilibration of the above mixture or the pure *cis*-ketone (**12a**) with methanolic sodium methoxide led to a *ca.* 5:1 mixture of (**12a**) and (**13a**). On repeating the cyclisation under identical conditions with PPA each of the epimeric mixture of the acids (**10b**) and (**10c**) led to the respective *cis*- and *trans*-ketones (**12b**) and (**13b**), and (**12c**) and (**13c**) in 75 and 69% yields respectively in *ca.* 5:1 and *ca.* 4:1 (^{1}H NMR) ratios. While the major epimer (**12b**)† from the aforementioned mixture could be separated by chromatography, (**12c**) could not be obtained in pure form. Reduction of the epimeric ketone mixtures (**12a–c**) and (**13a–c**) with sodium borohydride and dehydration of the crude alcohols (**14a–c**) with potassium hydrogen sulphate[14] gave the respective styrenes (**15a–c**) in excellent yield.

Not surprisingly,[5,6] our initial investigations of the demethylation of the model styrenoid ether (**15b**) with the acidic reagents Me_3SiCl–NaI in acetonitrile[15] or BBr_3–CH_2Cl_2[9] under various conditions led to many uncharacterisable mixtures of products. When (**15b**) was subjected to demethylation with $AlCl_3$–EtSH[16] at room temperature the dienone (**17b**) was isolated in 75% yield. The same product was also formed in an excellent yield by direct treatment of the epimeric alcohols (**14b**) under similar conditions. The structure of the dienone (**17b**) was assigned from its elemental analysis and spectral data (see Experimental section). As expected, exposure

† The stereochemistry depicted in the major and the minor epimers (**12**) and (**13**) is based on analogy with the isomeric enolisable tricyclic ketone (i),[6] where the *cis*-form predominates.



(i)

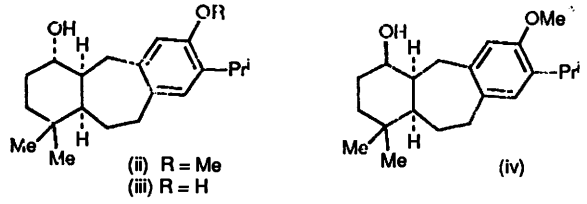


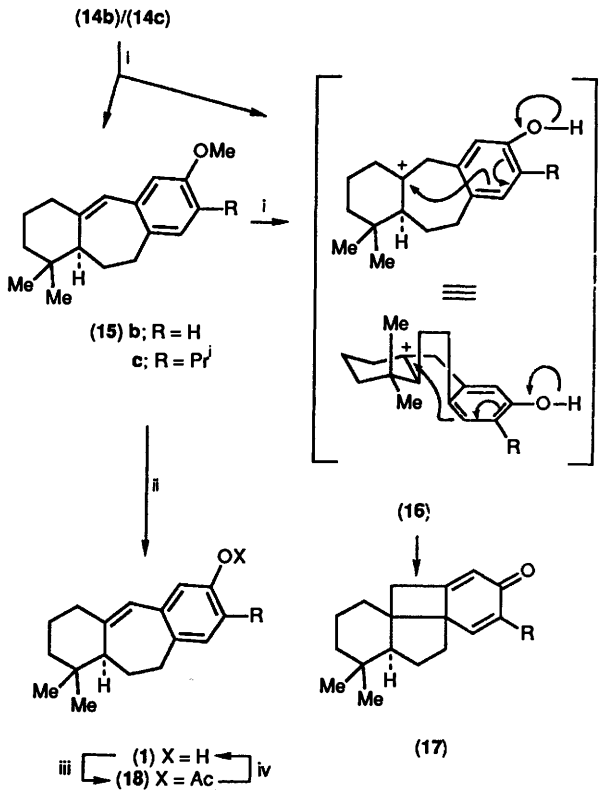
(6)–(15) **a**; $R^1 = R^2 = H$
b; R^1 = OMe, $R^2 = H$
c; R^1 = OMe, $R^2 = Pr^i$

Scheme 1. *Reagents:* i, Bu^tOK–Bu^tOH, H^+; ii, KOH–EtOH–H_2O, H^+; iii, $LiMe_2Cu$–BF_3·Et_2O–Et_2O; iv, sodium t-pentoxide–$Ph_3P^+MeI^-$–toluene; v, B_2H_6–tetrahydrofuran; vi, NaOH–H_2O_2; vii, Jones reagent; viii, CH_2N_2–Et_2O; ix, PPA; x, $NaBH_4$–EtOH; xi, $KHSO_4$ (heat).

Ratio of (**12**) to (**13**); **a**; *ca.* 5:1; **b**, *ca.* 5:1; **c**, *ca.* 4:1.

* It was reported[6] that the alcohol (ii) possessing an equatorial hydroxy group was normally demethylated with $AlCl_3$–EtSH to give the diol (iii), while under the same conditions, the epimer (iv) possessing an axial hydroxy group was easily dehydrated by antiperiplanar elimination to give pisiferin methyl ether which on demethylation and subsequent Ar_1-5 cyclisation of the resulting pisiferin (**3a**) gave the dienone (**17c**) *via* the carbocation (**16c**) (Scheme 2).





Scheme 2. *Reagents:* i, EtSH–$AlCl_3$–CH_2Cl_2; ii, NaSEt–DMF (heat); iii, Ac_2O–pyridine; iv, $LiAlH_4$–Et_2O.

of the epimeric alcohols (**14c**) or the styrenoid ether (**15c**) to $AlCl_3$–EtSH gave the known[6] tetracyclic dienone (**17c**) in excellent yield, as reported in the attempted demethylation of (±)-pisiferin methyl ether under similar conditions.

The facile formation of the tetracyclic dienones (**17b**) and (**17c**) in the acid-catalysed deprotection of the respective *O*-methyl ethers of the benzyl alcohols (**14b**) and (**14c**)* *via* the alkenes (**15b**) and (**15c**) (or the hydride transfer of the resulting benzylic cations arising from E_1-elimination) possibly proceeds through the respective phenols *via* the carbocations (**16b**) and (**16c**) through an Ar_1-5 cyclisation[17] (Scheme 2).

Deprotection of the *O*-methyl ether (**15b**), however, proceeded smoothly with NaSEt in boiling dimethylformamide (DMF)[18] to give the crude phenol (**1b**) which was characterised *via* the corresponding acetate (**18b**). Under identical conditions, (**15c**) gave the crude phenol (**1c**) in 95% yield which was directly converted to the acetate (**18c**), with IR and ^1H NMR spectra identical with those of natural isopisiferin acetate.[2] Finally, deacetylation of the acetate (**18c**) with $LiAlH_4$ regenerated (±)-isopisiferin (**1c**), the UV, IR, and ^1H NMR data of which are consonant with the reported[2] values (see Experimental section). Since natural isopisiferin has already been converted[3] to pisiferanol (**2**), the present work also represents a formal total synthesis of this diterpene.

In conclusion, in the present work a simple convergent and general synthetic route has been developed for the key tricyclic systems incorporating the skeletal structure of the newly discovered 9(10→20)-*abeo*-abieta-8,11,13-triene diterpenoids.

Experimental

The compounds described are all racemates. M.p.s and b.p.s are not corrected. UV spectra were recorded on a Beckman DU spectrophotometer for solutions in 95% ethanol. IR spectra of

solids (KBr) and liquids (film) were recorded on a Perkin-Elmer model PE 298 instrument. ^{1}H NMR spectra were recorded at 100 MHz (if specified) on a Jeol FX-100 spectrometer or at 200 MHz on an XL-200 spectrometer for solutions in $CDCl_3$ with $SiMe_4$ as internal standard. Analytical GLC was performed on a Shimadzu GC-9A model with a flame-ionisation detector employing a 1.5% OV-17 (6.5 ft × 0.25 in) column with N_2 as the carrier gas. Column chromatography was performed on neutral alumina (Brockmann Grade 1, of BDH, India) or silica gel [Glaxo Laboratories (India) Ltd.]. Petroleum and light petroleum refer to fractions of b.p. 60–80 and 40–60 °C, respectively. Ether refers to diethyl ether. Elemental analyses were performed by Mr. P. P. Bhattacharya of this laboratory.

2-(3-*Isopropyl*-4-*methoxyphenethyl*)-3-*methylcyclohex*-2-*enone* (**6c**).—This compound was prepared by adopting a general method[9] developed in this laboratory. Hagemann's ester (**4**) (7.8 g, 0.043 mol) was alkylated with the bromide (**5**)[10] (9.9 g, 0.039 mol) in the presence of Bu^{t}OK [prepared from potassium metal (1.68 g, 0.043 mol)] in Bu^{t}OH to afford the alkylation product, *ethyl* 3-(3-*isopropyl*-4-*methoxyphenethyl*)-2-*methyl*-4-*oxocyclohex*-2-*enecarboxylate* (11.38 g, 83%), as an oil, b.p. 200–210 °C (0.08 mmHg) (Found: C, 73.6; H, 8.7. $C_{22}H_{30}O_4$ requires C, 73.7; H, 8.4%); ν_{max} 1 735 (ester) and 1 670 cm^{-1} (α,β-unsaturated ketone); λ_{max} 228.8 nm (log ε 4.29); δ 1.20 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 1.28 (3 H, t, *J* 8 Hz, CO_2CH_2*Me*), 1.45–2.40 (7 H, m), 1.82 (3 H, s, vinyl Me), 2.50–2.70 (2 H, m, $ArCH_2$), 3.29 (1 H, m, C*H*Me$_2$), 3.80 (3 H, s, ArOMe), 4.22 (2 H, q, *J* 8 Hz, CO_2CH_2Me), 6.78 (1 H, d, *J* 8 Hz, 5-ArH), and 6.92–7.06 (2 H, m, 2- and 6-ArH).

The foregoing keto ester (10.58 g, 0.029 mol) was refluxed with a solution of KOH (10.34 g, 0.18 mol) in water (10 ml) and EtOH (90 ml) under N_2 for 14 h. The cooled reaction mixture was acidified with 6M-HCl. The usual work-up followed by distillation afforded the *enone* (**6c**) (5.48 g, 65%), b.p. 172 °C (0.2 mmHg) (Found: C, 79.8; H, 9.3. $C_{19}H_{26}O_2$ requires C, 79.7; H, 9.15%); ν_{max} 1 670 cm^{-1} (α,β-unsaturated ketone); λ_{max} 229.6 nm (log ε 4.24); δ 1.18 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 1.68 (3 H, s, vinyl Me), 1.84–2.04 (2 H, m), 2.19 (2 H, t, *J* 6 Hz, allylic CH_2), 2.42 (2 H, t, *J* 6 Hz, $COCH_2$), 2.55 (4 H, br s), 3.32 (1 H, m, C*H*Me$_2$), 3.79 (3 H, s, ArOMe), 6.78 (1 H, d, *J* 8 Hz, 5-ArH), and 6.96–7.24 (2 H, m, 2- and 6-ArH).

2-(3-*Isopropyl*-4-*methoxyphenethyl*)-3,3-*dimethylcyclohexanone* (**7c**).—This compound was prepared adopting a general procedure.[8] To a stirred suspension of CuI (5 g, 26.21 mmol) in dry ether (25 ml) under N_2 at −25 °C was added MeLi in ether (37 ml, 1.4M; 52.4 mmol). The resulting yellow suspension was cooled to −50 °C and BF_3·Et_2O (3.2 ml, 26.2 mmol) was added. After 5 min the cyclohexenone (**6c**) (2.5 g, 8.74 mmol) in ether (15 ml) was added dropwise and the mixture stirred at −30 °C for 15 min. Additional BF_3·Et_2O (3.2 ml, 26.2 mmol) was added and stirring continued at −30 °C for 1 h. The mixture was allowed to warm to 0 °C and then quenched with aqueous NH_4Cl. Work-up, followed by chromatography (neutral alumina) afforded the *cyclohexanone* (**7c**) (2.0 g, 77%) as an oil, b.p. 150 °C (0.05 mmHg) (Found: C, 79.6; H, 10.2. $C_{20}H_{30}O_2$ requires C, 79.4; H, 10.0%); ν_{max} 1 710 cm^{-1} (CO); δ 0.76 (3 H, s, Me), 1.00 (3 H, s, Me), 1.20 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 1.48–2.74 (11 H, m), 3.32 (1 H, m, C*H*Me$_2$), 3.80 (3 H, s, ArOMe), 6.79 (1 H, d, *J* 8 Hz, 5-ArH), and 6.94–7.06 (2 H, m, 2- and 6-ArH).

3,3-*Dimethyl*-1-*methylene*-2-*phenethylcyclohexane* (**8a**).—A suspension of methyl(triphenyl)phosphonium iodide (18.4 g, 45.63 mmol) in toluene (2 ml) and a toluene solution of freshly prepared sodium t-pentoxide (45.63 ml of 1M solution) was stirred at room temperature (~25 °C) for 20 min. The ketone (**7a**) (3.5 g, 15.21 mmol) in toluene (5 ml) was added dropwise, the mixture refluxed for 2 h, the reaction quenched with saturated aqueous NH_4Cl, and the mixture extracted with ether. The extract was washed with aqueous NH_4Cl and water and dried (Na_2SO_4). Evaporation yielded an oil which was immediately filtered through silica gel with ether–petroleum (1:19). The eluant was evaporated to give an oil (3.20 g) which was dissolved in petroleum (10 ml). Methyl iodide (3 ml) was added and the mixture set aside at room temperature for 1 h. The precipitated methyl(triphenyl)phosphonium iodide was filtered off and the filtrate concentrated *in vacuo* to give the pure *alkene* (**8a**) (3.15 g, 91%), b.p. 130 °C (0.1 mmHg) (Found: C, 89.1; H, 10.7. $C_{17}H_{24}$ requires C, 89.4; H, 10.6%); ν_{max} 1 640 cm^{-1} (C=C); δ 0.82 (3 H, s, Me), 0.90 (3 H, s, Me), 1.07–2.8 (11 H, m), 4.66 (1 H, m) and 4.86 (1 H, m) (C=CH_2), and 7.12–7.36 (5 H, m, ArH).

2-(4-*Methoxyphenethyl*)-3,3-*dimethyl*-1-*methylenecyclohexane* (**8b**).—The ketone (**7b**) (2.55 g, 9.78 mmol) was converted, in the same way as just described, into the *alkene* (**8b**) which was obtained as an oil (2.23 g, 88%), b.p. 130–135 °C (0.1 mmHg) (Found: C, 83.9; H, 9.8. $C_{18}H_{26}O$ requires C, 83.7; H, 10.1%); ν_{max} 1 645 cm^{-1} (C=C); δ(100 MHz) 0.80 (3 H, s, Me), 0.88 (3 H, s, Me), 1.12–2.76 (11 H, m), 3.76 (3 H, s, ArOMe), 4.62 (1 H, m), and 4.82 (1 H, m) (C=CH_2), 6.80 (2 H, d, *J* 8 Hz, 3- and 5-ArH), and 7.08 (2 H, d, *J* 8 Hz, 2- and 6-ArH).

2-(3-*Isopropyl*-4-*methoxyphenethyl*)-3,3-*dimethyl*-1-*methylenecyclohexane* (**8c**).—*Compound* (**8c**) was obtained in 91% yield from the ketone (**7c**), as an oil, b.p. 150 °C (0.02 mmHg) (Found: C, 83.95; H, 11.0. $C_{21}H_{32}O$ requires C, 83.9; H, 10.7%); ν_{max} 1 645 cm^{-1} (C=C); δ 0.83 (3 H, s, Me), 0.91 (3 H, s, Me), 1.20 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 1.40–2.68 (11 H, m), 3.32 (1 H, m, C*H*Me$_2$), 3.80 (3 H, s, ArOMe), 4.66 (1 H, m) and 4.87 (1 H, m) (C=CH_2), 6.80 (1 H, d, *J* 8 Hz, 5-ArH), and 6.94–7.10 (2 H, m, 2- and 6-ArH).

trans- *and* cis-(3,3-*Dimethyl*-2-*phenethylcyclohexyl*)*methanol* (**9a**).—Diborane gas [prepared from $NaBH_4$ (4.07 g, 106 mmol) and BF_3·Et_2O (16.3 ml, 130 mmol) in diglyme (15 ml)] was passed through a cold (0 °C) solution of the alkene (**8a**) (3.0 g, 13.1 mmol) in dry tetrahydrofuran (THF) (15 ml) for 2 h under a continuous stream of N_2. The cooled mixture was then carefully decomposed with water (10–15 °C) and added to 3M aqueous NaOH (45 ml). To the well-stirred cooled (10–15 °C) mixture, H_2O_2 (26 ml; 30% v/v) was added dropwise. Stirring was continued for an additional 30 min, further H_2O_2 (13 ml) was added, and the mixture set aside overnight. The mixture was then extracted with ether and the extract washed with water and dried (Na_2SO_4). Evaporation afforded the alcohol (**9a**) (3.17 g, 98%) as an oil, as a *ca.* 1:2 epimeric mixture (^{1}H NMR), b.p. 180 °C (0.1 mmHg) (Found: C, 82.55; H, 10 9. Calc. for $C_{17}H_{26}O$: C, 82.9; H, 10.6%); ν_{max} 3 340br cm^{-1} (OH); δ 0.78 and 0.88 (each s, CMe_2, minor epimer), 0.92 and 0.96 (each s, CMe_2, major), 1.06–2.20 (10 H, m), 2.40–2.88 (2 H, m), 3.40 and 3.46 (each s, OCH_2, minor and major, respectively), and 7.08–7.76 (5 H, m, ArH).

trans- *and* cis-[2-(4-*Methoxyphenethyl*)-3,3-*dimethylcyclohexyl*]*methanol* (**9b**).—As in the foregoing experiment, the alkene (**8b**) gave the alcohol (**9b**) (94%) as an oil, as a *ca.* 1:2 epimeric mixture (^{1}H NMR), b.p. 210 °C (0.06 mmHg) (Found: C, 78.6; H, 9.8. Calc. for $C_{18}H_{28}O_2$: C, 78.2; H, 10.2%); ν_{max} 3 400br cm^{-1} (OH); δ(100 MHz), 0.78 and 0.86 (each s, CMe_2, minor epimer), 0.90 and 0.98 (each s, CMe_2, major), 1.08–2.12 (10 H, m), 2.40–2.82 (2 H, m), 3.42 and 3.46 (each s, OCH_2, minor and major, respectively), 3.84 (3 H, s, ArOMe), 6.84 (2 H, d, *J* 8 Hz, 3- and 5-ArH), and 7.10 (2 H, d, *J* 8 Hz, 2- and 6-ArH).

trans- *and* cis-[2-(3-*Isopropyl*-4-*methoxyphenethyl*)-3,3-*dimethylcyclohexyl*]*methanol* (**9c**).—The alcohol (**9c**) was obtained, as in the foregoing experiment, from the alkene (**9b**) in 96% yield, as an oil, as a *ca.* 1:3 epimeric mixture (^{1}H NMR), b.p. 170 °C (0.02 mmHg) (Found: C, 79.4; H, 10.9. Calc. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8%); ν_{max} 3 360br, cm^{-1} (OH); δ 0.79 and 0.89 (each s, CMe_2, minor epimer), 0.95 and 0.99 (each s, CMe_2, major), 1.20 (6 H, d, *J* 7 Hz, $CHMe_2$), 1.26–2.04 (10 H, m), 2.40–2.80 (2 H, m), 3.32 (1 H, m, $CHMe_2$), 3.42 and 3.45 (each s, OCH_2, minor and major, respectively), 3.80 (3 H, s, ArOMe), 6.81 (1 H, d, *J* 8 Hz, 5-ArH), and 6.98–7.14 (2 H, m, 2- and 6-ArH).

trans- *and* cis-*Methyl* 3,3-*Dimethyl*-2-*phenethylcyclohexanecarboxylate* (**11a**).—The cooled alcohol (**9a**) (3 g, 12.2 mmol) in acetone (50 ml) was stirred with an excess of Jones reagent (4.68 ml, 12.5 mmol) for 45 min. After dilution with water, the mixture was extracted with ether. The ethereal extract was washed with 2% aqueous NaOH and then with water. The aqueous portion was acidified with 6M HCl and usual work-up afforded the acid (**10a**) (1.87 g, 59%) as a thick glass, ν_{max} 1 700 cm^{-1} (CO_2H). The acid (**10a**) was used directly in the next step.

The acid (**10a**) was esterified (CH_2N_2 in ether) to afford (**11a**) as a *ca.* 1:3 epimeric mixture (^{1}H NMR and GLC), b.p. 140 °C (0.05 mmHg) (Found: C, 78.75; H, 9.5. Calc. for $C_{18}H_{26}O_2$: C, 78.8; H, 9.55%); $\nu_{max.}$ 1 735 cm^{-1} (ester); δ 0.78 and 0.89 (each s, CMe_2, minor epimer), 0.95 and 1.00 (each s, CMe_2, major), 1.08–2.00 (9 H, m), 2.20–2.90 (3 H, m), 3.62 and 3.70 (each s, CO_2Me, major and minor, respectively), and 7.04–7.60 (5 H, m, ArH).

trans- *and* cis-2-(4-*Methoxyphenethyl*)-3,3-*dimethylcyclohexanecarboxylic Acid* (**10b**).—The acid (**10b**) was obtained from the alcohol (**9b**) on oxidation with Jones reagent, as in the foregoing experiment, in 71% yield as a crystalline solid, m.p. 126–128 °C (from Et_2O–light petroleum) (Found: C, 74.15; H, 9.1. Calc. for $C_{18}H_{26}O_3$: C, 74.4; H, 9.0%); ν_{max} 1 700 cm^{-1} (CO_2H).

The methyl ester (**11b**) obtained (ethereal CH_2N_2) from (**10b**) was found to be a *ca.* 1:3 epimeric mixture (^{1}H NMR), b.p. 140 °C (0.1 mmHg) (Found: C, 74.6; H, 9.5. Calc. for $C_{19}H_{28}O_3$: C, 75.0; H, 9.3%); ν_{max} 1 735 cm^{-1} (ester); δ(100 MHz) 0.78 and 0.86 (each s, CMe_2, minor epimer), 0.94 and 1.00 (each s, CMe_2, major), 1.08–1.86 (9 H, m), 2.52 (2 H, t, *J* 8 Hz, $ArCH_2$), 2.74 (1 H, m, $CHCO_2Me$), 3.62 and 3.70 (each s, CO_2Me, major and minor, respectively), 3.74 (3 H, s, ArOMe), 6.80 (2 H, d, *J* 8 Hz, 3- and 5-ArH), and 7.04 (2 H, d, *J* 8 Hz, 2- and 6-ArH).

trans- *and* cis-*Methyl*-2-(3-*Isopropyl*-4-*methoxyphenethyl*)-3,3-*dimethylcyclohexanecarboxylate* (**11c**).—The acid (**10c**) was obtained from the alcohol (**9c**), by oxidation with Jones reagent for 1.5 h, in 50% yield, as a viscous liquid, ν_{max} 1 705 cm^{-1} (CO_2H), and was used directly, in the next step.

The methyl ester (**11c**) obtained (ethereal CH_2N_2) from (**10c**) was a *ca.* 1:3 epimeric mixture (^{1}H NMR), b.p. 158–160 °C (0.02 mmHg) (Found: C, 76.45; H, 10.2. Calc. for $C_{22}H_{34}O_3$: C, 76.3; H, 9.9%); ν_{max} 1 735 cm^{-1} (ester); δ 0.79 and 0.91 (each s, CMe_2, minor epimer), 0.97 and 1.03 (each s, CMe_2, major), 1.21 (6 H, d, *J* 7 Hz, $CHMe_2$), 1.10–1.78 (9 H, m), 2.51 (2 H, t, *J* 8 Hz, $ArCH_2$), 2.68–2.88 (1 H, m, $CHCO_2Me$), 3.34 (1 H, m, $CHMe_2$), 3.65 and 3.75 (each s, CO_2Me, major and minor, respectively), 3.79 (3 H, s, ArOMe), 6.78 (1 H, d, *J* 8 Hz, 5-ArH), and 6.93–7.11 (2 H, m, 2-and 6-ArH).

cis-1,1-*Dimethyl*-1,2,3,4,4a,10,11,11a-*octahydrodibenzo*[a,d]-*cyclohepten*-5-*one* (**12a**) *and its* C-4a *Epimer* (**13a**).—To a well stirred homogeneous solution of PPA [prepared from P_2O_5 (21 g) and H_3PO_4 (10.5 ml)] was added the acid (**10a**) (1.75 g, 6.7 mmol) and the mixture was heated at 80–85 °C for 2 h. The red mixture was cooled, decomposed with crushed ice, and extracted with ether. The ether extract was washed successively with water, 2% aqueous NaOH, and water, and dried (Na_2SO_4). Removal of the solvent afforded a solid stereoisomeric mixture of the ketones (**12a**) and (**13a**) in a ratio of *ca.* 82:16 (t_R 4.15 and 3.2 min, respectively, at 220 °C) in 95% yield. Recrystallisaton afforded the pure major *isomer* (**12a**) (1.3 g, 80%), m.p. 98 °C (from Et_2O–petroleum) (Found: C, 84.2; H, 9.4. $C_{17}H_{22}O$ requires C, 84.25; H, 9.15%); ν_{max} 1 675 cm^{-1} (benzylic CO); λ_{max} 247 (log ε 3.91) and 2.85 nm (3.18); δ 0.94 (6 H, br s, CMe_2), 1.08–2.30 (9 H, m), 2.60–3.40 (3 H, m, $ArCH_2$ and COCH), 7.12–7.56 (3 H, m, ArH), and 7.66 (1 H, m, 6-ArH).

cis-7-*Methoxy*-1,1-*dimethyl*-1,2,3,4,4a,10,11,11a-*octahydrodibenzo*[a,d]*cyclohepten*-5-*one* (**12b**) *and its* C-4a-*Epimer* (**13b**).—The acid (**10b**) was cyclised as just described to afford a mixture of the ketones (**12b**) and (**13b**) in a ratio of *ca.* 5:1 (^{1}H NMR) in 75% yield. Chromatography on neutral alumina (5–10% Et_2O–petroleum) afforded the major *isomer* (**12b**) [55% based on (**10b**)] as a crystalline solid, m.p. 70 °C (from Et_2O–light petroleum) (Found: C, 79.6; H, 9.0. $C_{18}H_{24}O_2$ requires C, 79.4; H, 8.9%); ν_{max} 1 670 cm^{-1} (benzylic CO); λ_{max} 311 (log ε 3.44), 2.52 (3.82), and 222 nm (4.33); δ 0.97 (3 H, s, Me), 0.98 (3 H, s, Me), 1.28–1.88 (8 H, m), 2.17 (1 H, m), 2.76–3.22 (3 H, m, $ArCH_2$ and COCH), 3.82 (3 H, s, ArOMe), 6.92 (1 H, dd, *J* 8.3 and 2.85 Hz, 8-ArH), 7.14 (1 H, d, *J* 8.3 Hz, 9-ArH), and 7.24 (1 H, d, *J* 2.85 Hz, 6-ArH).

(±)-12-*Methoxy*-9(10→20)-abeo-*abieta*-8,11,13-*trien*-20-*one* (**13c**) *and its* C-10-*Epimer* (**12c**).—The acid (**10c**) was cyclised as just described to afford, as a thick glass, in 69% yield, the ketones (**12c**) and (**13c**) as a *ca.* 4:1 stereoisomeric mixture (^{1}H NMR), b.p. 160 °C (0.02 mmHg) (Found: C, 80.5; H, 10.0. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6%); ν_{max} 1 675 cm^{-1} (benzylic CO); λ_{max} 312 (log ε 3.57), 263 (3.92), and 227 nm (4.21); δ 0.98 and 0.99 (each s, for CMe_2, both isomers), 1.19 (3 H, d, *J* 7 Hz) and 1.21 (3 H, d, *J* 7 Hz) ($CHMe_2$), 1.35–2.28 (8 H, m), 2.65–3.36 (3 H, m, $ArCH_2$ and COCH), 3.49 (1 H, m, $CHMe_2$), 3.84 and 3.85 (each s, ArOMe, major and minor, respectively), 7.01 (1 H, s, 9-ArH), and 7.21 (1 H, s, 6-ArH) [proton numbering as for (**12**/**13a** and **b**)].

1,1-*Dimethyl*-1,3,4,10,11,11a-*hexahydro*-2H-*dibenzo*[a,d]-*cycloheptene* (**15a**).—$NaBH_4$ (1.32 g, 0.036 mol) was added portionwise to a stirred solution of the ketone mixture (**12a**) and (**13a**) (*ca.* 5:1) (1.40 g, 6 mmol) in 95% EtOH (50 ml). The mixture was left overnight and the excess of $NaBH_4$ was decomposed with water. Work-up afforded the alcohol (**14a**) (1.3 g, 92%) as a solid, as an epimeric mixture (35:65; GLC and ^{1}H NMR); ν_{max} 3 340br cm^{-1} (OH); δ 0.70 and 0.73 (each s, CMe_2, major isomer), 0.93 and 0.97 (each s, CMe_2, minor), 0.86–1.90 (8 H, m), 2.02–2.28 (2 H, m), 2.66–2.90 (2 H, m, $ArCH_2$), 4.66 (1 H, d, *J* 8 Hz, CHOH), 7.08–7.40 (3 H, m, ArH), and 7.54 (1 H, br d, *J* 8 Hz, 6-ArH).

The alcohol (**14a**) (1 g, 4.0 mmol) was fused with $KHSO_4$ (1.1 g, 8.0 mmol) at 140 °C for 40 min and the resulting mixture distilled to give the *styrenoid compound* (**15a**) (840 mg, 90%) as a low-melting solid, m.p. 44 °C (from light petroleum) (Found: C, 90.0; H, 10.0. $C_{17}H_{22}$ requires C, 90.2; H, 9.8%); ν_{max} 1 635 cm^{-1} (C=C); λ_{max} 262 (log ε 4.27) and 211 nm (4.35); δ 0.70 (3 H, s, Me), 0.96 (3 H, s, Me), 1.20–1.72 (6 H, m), 2.10–2.20 (3 H, m), 2.64–2.84 (2 H, m, $ArCH_2$), 6.40 (1 H, br s, C=CH), and 7.10–7.20 (4 H, m, ArH).

7-*Methoxy*-1,1-*dimethyl*-1,3,4,10,11,11a-*hexahydro*-2H-*dibenzo*[a,d]*cycloheptene* [(±)-*Deisopropyl*-O-*methylisopisiferin*] (**15b**).—The ketone mixture (**12b**) and (**13b**) (*ca.* 5:1) was reduced, as above, with $NaBH_4$ to give the alcohol

(**14b**), in 66% yield, as a *ca.* 1:1 diastereoisomeric mixture (GLC and ^{1}H NMR); ν_{max} 3 400br cm^{-1} (OH). The alcohol (**14b**) so obtained was dehydrated, as in the case of (**14a**), to give the *alkene* (**15b**) in 89% yield as a liquid, b.p. 160 °C (0.04 mmHg) (Found: C, 84.3; H, 9.8. $C_{18}H_{24}O$ requires C, 84.3; H, 9.4%); ν_{max} 1 640 cm^{-1} (C=C); λ_{max} 298 (log ε 3.46) and 261 nm (4.13); δ 0.70 (3 H, s, Me), 0.98 (3 H, s, Me), 1.24–1.80 (6 H, m), 2.08–2.50 (3 H, m), 2.52–2.74 (2 H, m, $ArCH_2$), 3.76 (3 H, s, ArOMe), 6.34 (1 H, s, C=CH), 6.54–6.76 (2 H, m, 6- and 8-ArH), and 6.94 (1 H, br d, *J* 8 Hz, 9-ArH).

(±)-12-*Methoxy*-9(10→20)-abeo-*abieta*-10(20),8,11,13-*tetraene* [(±)-O-*Methylisopisiferin*] (**15c**).—The ketone mixture (**12c**) and (**13c**) (*ca.* 4:1) was reduced with $NaBH_4$ to the diastereoisomeric alcohol mixture (**14c**) in 63% yield which, in turn, was dehydrated with $KHSO_4$ to give the *alkene* (**15c**) in 93% yield, as a liquid, b.p. 150 °C (0.05 mmHg) (Found: C, 84.3; H, 10.45. $C_{21}H_{30}O$ requires C, 84.5; H, 10.1%); ν_{max} 1 640 cm^{-1} (C=C); λ_{max} 290 (log ε 3.69), 265 (4.15), and 220 nm (4.31); δ 0.71 (3 H, s) and 1.20 (3 H, s), (CMe_2), 1.17 (3 H, d, *J* 7 Hz) and 1.20 (3 H, d, *J* 7 Hz) ($CHMe_2$), 1.34–1.74 (6 H, m), 2.08–2.48 (3 H, m), 2.60–2.74 (2 H, m, $ArCH_2$), 3.30 (1 H, m, $CHMe_2$), 3.79 (3 H, s, ArOMe), 6.31 (1 H, br s, C=CH), 6.61 (1 H, s, 6-ArH), and 6.83 (1 H, s, 9-ArH) [proton numbering as for (**15a**) and (**15b**)].

The Tetracyclic Dienone (**17b**).—(*a*) *Demethylation of the styrenoid O-methyl ether* (**15b**) *with aluminium chloride–ethanethiol.* Anhydrous $AlCl_3$ (30 mg, 0.22 mmol) was added to a stirred solution of (**15b**) (50 mg, 0.2 mmol) and EtSH (0.2 ml) in CH_2Cl_2 (3 ml) with cooling in an ice bath. The mixture was stirred at 0 °C for an additional 4 h and left overnight. It was then poured into 6M HCl and extracted with ether to afford the crude dienone (**17b**). This was chromatographed on silica gel using ether–petroleum (1:5 to 1:4) as eluant, to give the *dienone* (**17b**) (35 mg, 75%) as a thick liquid (Found: C, 84.5; H, 9.35. $C_{17}H_{22}O$ requires C, 84.25; H, 9.15%); ν_{max} 1 655 (dienone) and 1 620 cm^{-1} (C=C); λ_{max} 259 nm (log ε 4.02); δ 0.97 (3 H, s, Me), 1.05 (3 H, s, Me), 1.08–2.12 (13 H, m), 6.22 (1 H, dd, *J* 9 and 1 Hz, 13-H), 6.25 (1 H, d, *J* 1 Hz, 11-H), and 6.74 (1 H, d, *J* 9 Hz, 14-H).

(*b*) *Demethylation of the alcohol* (**14b**). The alcohol (**14b**) on similar treatment as above gave the dienone (**17b**) in 88% yield, identical (GLC, IR, ^{1}H NMR) with the sample obtained above.

The Tetracyclic Dienone (**17c**).—(*a*) *Demethylation of* (±)-*isopisiferin methyl ether* (**15c**) *with aluminium chloride–ethanethiol.* The dienone (**17c**) was obtained as described for (**17b**) in 74% yield from the alkene (**15c**), as a solid, m.p. 107 °C (from light petroleum) (lit.,[6] m.p. 107–109 °C); ν_{max} 1 655 (dienone) 1 620 cm^{-1} (C=C) (lit.,[6] ν_{max} 1 655 cm^{-1}); λ_{max} 255 nm (log ε 5.10) [lit.,[6] λ_{max}(EtOH) 255 nm (ε 15 300)]; δ 0.96 (3 H, s, Me), 1.04 (3 H, s, Me), 1.05 (3 H, d, *J* 7 Hz), and 1.07 (3 H, d, *J* 7 Hz) ($CHMe_2$), 1.18–1.50 (5 H, m), 1.58–1.90 (7 H, m), 2.01 (1 H, t, *J* 9 Hz, methine), 2.99 (1 H, m, $CHMe_2$), 6.23 (1 H, s, 11-H), and 6.40 (1 H, s, 14-H) [lit.,[6] (90 MHz) δ($CDCl_3$) 0.95 (3 H, s) and 1.03 (3 H, s) (CMe_2), 1.06 (6 H, d, *J* 7 Hz, $CHMe_2$), 2.98 (1 H, m, $CHMe_2$), 6.20 (1 H, s, 11-H), and 6.38 (1 H, br s, 14-H)].

(*b*) *Demethylation of the alcohol* (**14c**). The alcohol (**14c**) was similarly converted to the dienone (**17c**) in 83% yield, m.p. and mixed m.p. with the sample just described 107 °C.

(±)-*Deisopropylisopisiferin* (**1b**).—EtSH (0.17 ml, 2.0 mmol) was added dropwise to a stirred suspension of NaH (100 mg of 40% dispersion in oil, 1.56 mmol) in dry DMF (2 ml) under N_2. The ether (**15b**) (50 mg, 0.20 mmol) was added and the mixture was held at reflux for 4 h. Dilution with H_2O, acidification (2M HCl), and extraction with ether gave (±)-deisopropylisopisiferin (**1b**) (30 mg, 68%) as a liquid, ν_{max} 3 400br (phenolic OH) and 1 650 cm^{-1} (C=C); δ 0.69 (3 H, s, Me), 0.98 (3 H, s, Me), 1.12–1.80 (6 H, m), 2.14–2.76 (5 H, m), 6.26 (1 H, s, C=C*H*), 6.52 (1 H, dd, *J* 2.5 and 8 Hz, 8-ArH), 6.61 (1 H, d, *J* 2.5 Hz, 6-ArH), and 6.86 (1 H, d, *J* 8 Hz, 9-ArH).

Acetate of (±)-*Deisopropylisopisiferin* (**18b**).—The phenol (**1b**) obtained in the foregoing experiment (30 mg, 0.12 mmol) was treated with pyridine (2 ml) and Ac_2O (1 ml) and the mixture stirred overnight. Dilution with water and extraction with ether gave the *acetate* (**18b**) (20 mg, 57%), as a crystalline solid, m.p. 102 °C (from petroleum) (Found: C, 80.6; H, 8.2. $C_{19}H_{24}O_2$ requires C, 80.2; H, 8.5%); ν_{max} 1 755 (phenolic ester) and 1 210 cm^{-1} (acetate); λ_{max} 262 nm (log ε 4.26); δ 0.69 (3 H, s, Me), 0.98 (3 H, s, Me), 1.20–1.72 (6 H, m), 2.08–2.48 (3 H, m), 2.28 (2 H, s, OCOMe), 2.72 (2 H, m, $ArCH_2$), 6.29 (1 H, s, C=CH), 6.74 (1 H, dd, *J* 2.25 and 8.0 Hz, 8-ArH), 6.83 (1 H, d, *J* 2.25 Hz, 6-ArH), and 7.0 (1 H, d, *J* 8 Hz, 9-ArH).

(±)-*Isopisiferin Acetate* (**18c**).—The methyl ether (**15c**) (60 mg, 0.20 mmol) was treated with EtSH (0.18 ml, 2.04 mmol) and NaH (100 mg of 40% dispersion in oil, 1.7 mmol) in dry DMF (3 ml), as described in the preparation of (**1b**), to give the crude phenol (**1c**) (55 mg, 95%); ν_{max} 3 380br (phenolic OH) and 1 650 cm^{-1} (C=C).

The phenol (**1c**) so obtained was acetylated directly to afford the acetate (**18c**) as a white solid (60 mg, 95%), m.p. 128 °C (from petroleum), identical (IR and ^{1}H NMR) with natural isopisiferin acetate, m.p. 145–146 °C* (Found: C, 80.8; H, 9.4. Calc. for $C_{22}H_{33}O_2$: C, 80.9; H, 9.3%); ν_{max} 1 755 (phenolic ester) and 1 210 cm^{-1} (acetate); λ_{max} 266 nm (log ε 4.30); δ 0.70 (3 H, s, Me), 0.98 (3 H, s, Me), 1.17 (3 H, d, *J* 7 Hz) and 1.20 (3 H, d, *J* 7 Hz) ($CHMe_2$), 1.16–1.74 (4 H, m), 2.14–2.42 (4 H, m), 2.29 (3 H, s, OCOMe), 2.54–2.72 (3 H, m), 3.00 (1 H, m, $CHMe_2$), 6.26 (1 H, br s, C=CH), 6.73 (1 H, s, 6-ArH), and 6.92 (1 H, s, 9-ArH) [proton numbering as for (**15**)].

(±)-*Isopisiferin* (**1c**).—The acetate (**18c**) (40 mg, 0.12 mmol) in Et_2O (20 ml) was stirred at room temperature with $LiAlH_4$ (20 mg) for 30 min; decomposition with cold saturated aqueous Na_2SO_4 and extraction with Et_2O gave (±)-isopisiferin (**1c**) (20 mg, 57%), m.p. 116–118 °C (lit.,[2] m.p. 87–90 °C for naturally occurring optically active isopisiferin*); ν_{max} 3 520 (phenolic OH), 1 640 (weak) (C=C), and 1 610 cm^{-1} (aromatic) [lit.,[2] ν_{max}(KBr) 3 350 and 1 610 cm^{-1}]; λ_{max} 222 (ε 19 500), 264 (12 590), 301 (3 981), and 312 nm (shoulder) [lit.,[2] λ_{max}(EtOH) 262 (ε 11 083), 299 (3 307), and 310 nm (shoulder)]; δ 0.70 (3 H, s, Me), 0.98 (3 H, s, Me), 1.22 (3 H, d, *J* 7 Hz) and 1.25 (3 H, d, *J* 7 Hz), ($CHMe_2$), 1.34–1.70 (4 H, m), 2.14–2.40 (4 H, m), 2.56–2.72 (3 H, m), 3.16 (1 H, m, $CHMe_2$), 6.22 (1 H, br s, C=CH), 6.51 (1 H, s, 11-ArH), and 6.82 (1 H, s, 14-ArH) [lit.,[2] ^{1}H NMR (100 MHz) δ($CDCl_3$) 0.68 (3 H, s, Me), 0.93 (3 H, s, Me), 1.20 and 1.23 (each d, *J* 7 Hz, $CHMe_2$), 2.20 (2 H, m, 1-H), 2.62 (2 H, m, 7-H), 3.13 (1 H, sept, *J* 7 Hz, $CHMe_2$), 6.17 (1 H, br s, C=CH), 6.43 (1 H, s, 11-ArH), and 6.77 (1 H, s, 14-ArH)]. The discrepancies between our data and those reported[2] could arise from impurities, or could be instrumental artefacts.

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