# Synthesis of (±)-Pisiferin, (±)-Pisiferol, and Related Compounds by Intramolecular [4 + 2]Cycloaddition

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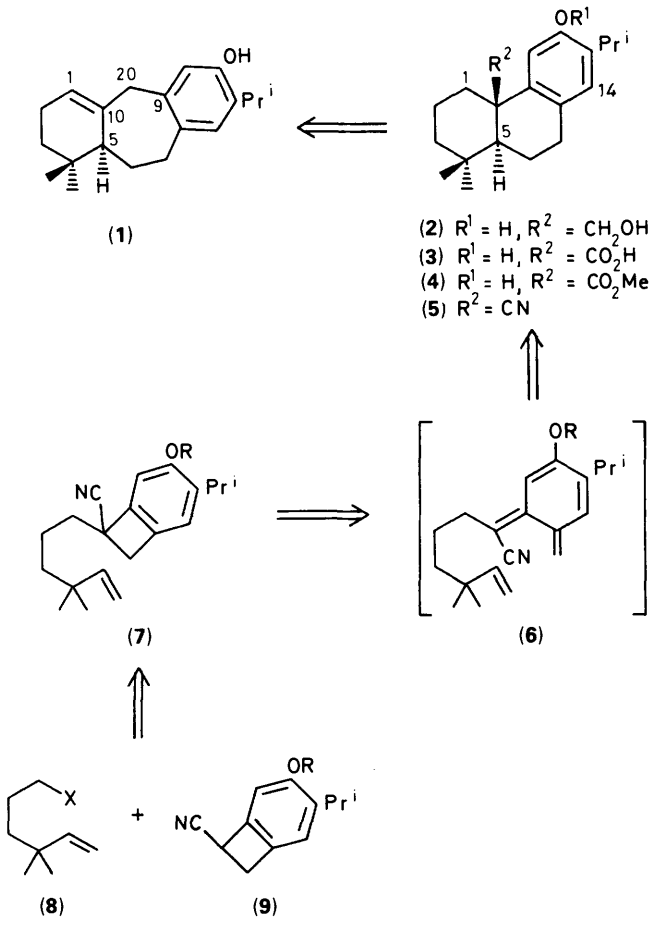
Thermolysis of the olefinic benzocyclobutene (**17**) afforded the tricyclic compounds (**18a**) and (**18b**), whose sequential reduction, *via* the aldehyde (**19**), gave rise to the pisiferol derivatives (**20a**) and (**20b**). Since (**20a**) was transformed into pisiferol (**2**), pisiferic acid (**3**), and methyl pisiferate (**4**), this synthesis constitutes their formal synthesis. Wolff–Kishner reduction of the hydrazone of (**19b**) yielded the known tricyclic compound (**21**), which has previously been transformed into xanthoperyl methyl ether (**22**). Furthermore, the predominantly *cis*-fused mixture of compound (**18**) (**a**/**b** = 1:4) was converted into the predominantly *trans*-fused mixture (**a**/**b** = 3:1) using catalytic hydrogenation of the enone (**24**) as a key reaction. Finally, a skeletal rearrangement of an abietane-type into a 9(10→20)*abeo*-abietane-type compound was demonstrated. Dehydration of the alcohol (**20a**) afforded the methyl ether (**26**) and its isomer (**27**) in the ratio of 3:1 as an inseparable mixture. Demethylation of the mixture (**26**) and (**27**) provided pisiferin (**1**) and compound (**28**). Interestingly, rearrangement of the *cis*-fused compound (**20b**) formed the methyl ether (**27**) as a sole product, which was converted into isopisiferin (**29**).

Pisiferin (**1**), pisiferol (**2**), pisiferic acid (**3**), and methyl pisiferate (**4**) have been isolated from the leaves of *Chamaecyparis pisifera* (Cupressaceae) by Yatagai *et al.*[1] Although pisiferin and pisiferol are closely related compounds, syntheses of these compounds have been accomplished by different routes[2] because a skeletal rearrangement of an abietane-type pisiferol into a 9(10→20)*abeo*-abietane-type pisiferin might be accompanied by the migration of double bonds.[1d,3] Since we have successfully applied this type of rearrangement to the synthesis of a A-homograyanotoxane-type skeleton,[4] we devised an alternative synthesis of (±)-pisiferin, (±)-pisiferol, and related compounds utilising benzocyclobutene chemistry.[5]

Our synthetic strategy is based on an intramolecular [4 + 2] cycloaddition of the *o*-quinodimethane (**6**), generated *in situ* by thermolysis of the olefinic benzocyclobutene (**7**) [prepared from (**8**) and (**9**)], to provide the tricyclic compound (**5**). The nitrile (**5**) could be transformed into pisiferol (**2**), whose further rearrangement might yield pisiferin (**1**) (Scheme 1).

As outlined in Scheme 2, the benzocyclobutene (**15**) was prepared by a known method.[6] Knoevenagel reaction of the aldehyde (**10**)[7] with cyanoacetic acid in benzene gave the adduct (**11**) (79%), which on reduction with sodium borohydride in methanol followed by decarboxylation of the acid (**12**) yielded the nitrile (**13**) [76% from (**11**)]. Bromination of (**13**) afforded the bromide (**14**) (99%), which gave the desired compound (**15**) (68%) *via* generation of a benzyne intermediate.

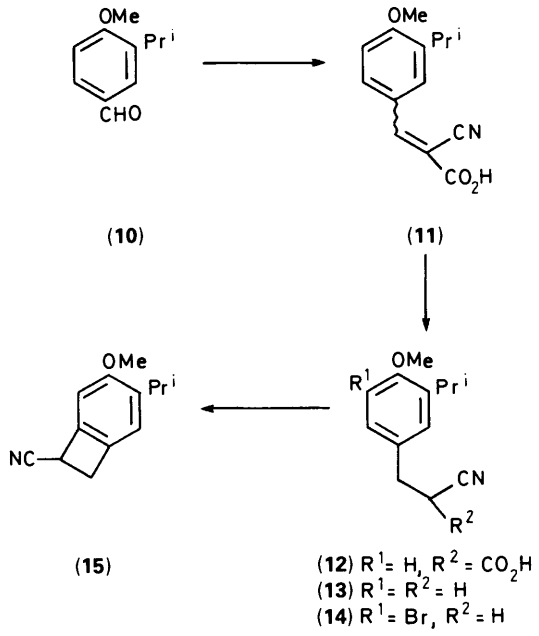
The requisite olefinic benzocyclobutene (**17**) was prepared by alkylation of (**15**) with the iodide (**16**)‡ in quantitative yield (Scheme 3). Thermolysis of (**17**) in *o*-dichlorobenzene at 180 °C for 3 h afforded the tricyclic compounds (**18a**, **b**) in 80% yield as an inseparable 1:4 mixture of diastereoisomers. The structures of (**18a**) and (**18b**) were deduced from the spectroscopic data and previous results[5a,b] and were confirmed together with the stereochemistry by conversion into the known compounds (**20a**) and (**21**). Reduction of the nitriles (**18a**, **b**) with di-



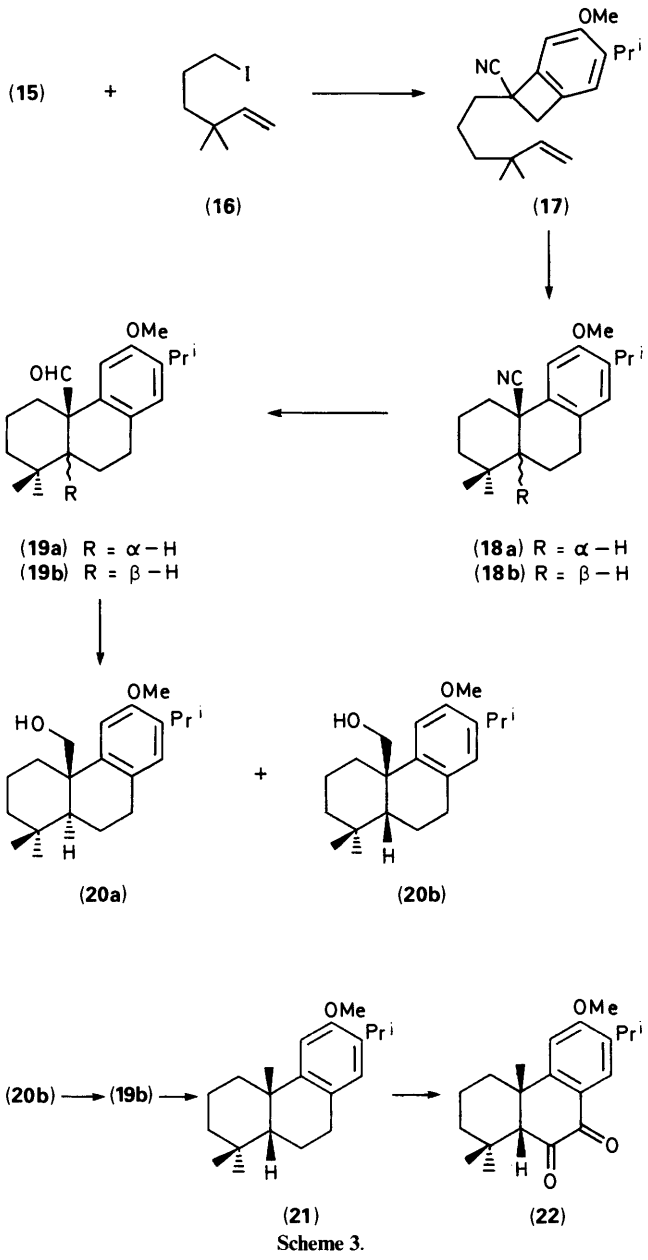

Scheme 1.

isobutylaluminium hydride afforded the aldehydes (**19a**, **b**), which on reduction with sodium borohydride gave the separable alcohols (**20a**) and (**20b**) in 14% and 62% yields from the

† Deceased October 11, 1988.
‡ The iodide (**16**) was prepared from 3,3-dimethylpent-4-enal[8] by standard procedures.




Scheme 2.



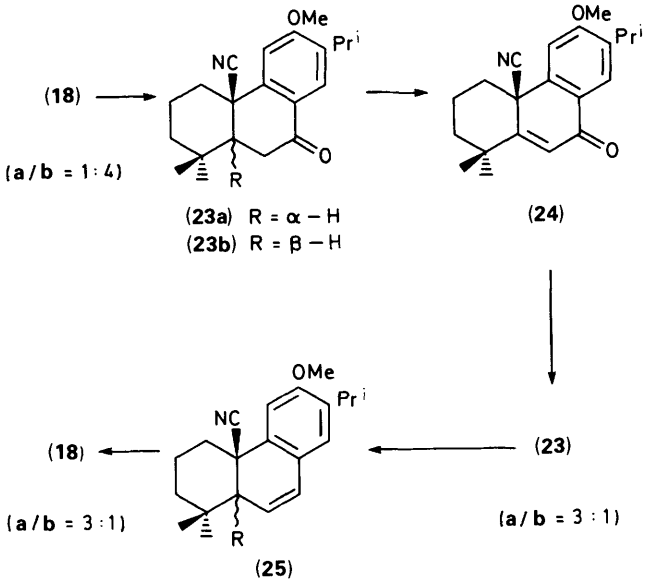

Scheme 3.

mixture (**18a, b**), respectively. Spectral data for compound (**20a**) thus obtained were identical with those of an authentic sample,[2a] which had previously been transformed into pisiferol (**2**), pisiferic acid (**3**), and methyl pisiferate (**4**). Swern oxidation[9] of the pure alcohol (**20b**) gave the aldehyde (**19b**), whose hydrazone was subjected to Wolff–Kishner reduction[10] to provide compound (**21**). The spectral data of (**21**) were identical with those reported.[11] Recently, (**21**) was oxidised with sodium dichromate to afford xanthoperyl methyl ether (**22**).[12]

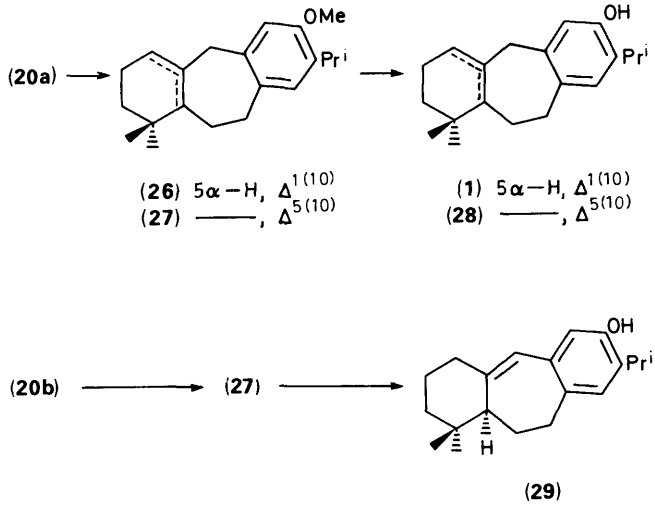
Conversion of (**18b**) into (**18a**) was investigated as follows (Scheme 4). Oxidation of the inseparable diastereoisomers (**18a, b**), in a ratio of 1:4 as described before, with pyridinium dichromate and t-butyl hydroperoxide[13] afforded the ketones (**23a, b**) in 66% yield as an inseparable mixture. Reaction of (**23a, b**) with bromine in acetic acid containing hydrogen bromide followed by treatment of the α-bromo ketone with DBU in *o*-xylene led to formation of the enone (**24**) [89% from (**23a, b**)]. Reduction of (**24**) with sodium cyanoborohydride[14] in methanol at pH 3—4 directly afforded the saturated compounds (**18a, b**) as a 1:1 mixture. However, hydrogenation[15] of (**24**) over 10% palladium on carbon in ethanol gave the ketones (**23a, b**) in a ratio of 3:1 as an inseparable mixture. Although the influence of catalyst and solvent polarity in the hydrogenation was investigated, no improvement was achieved. Compounds (**23a, b**) were then converted into (**18a, b**) (3:1) in 61% overall yield by three steps involving reduction with sodium borohydride, dehydration of the resulting alcohol with toluene-*p*-sulphonic acid in acetone to give the olefin (**25**), and hydrogenation of (**25**) over 10% palladium on carbon in ethyl acetate.

As described above, the mixture of nitriles (**18a, b**) was separated by conversion into the primary alcohols (**20a, b**) and column chromatography on silica gel.

Using the pure alcohols (**20a, b**) prepared above, we finally attempted a skeletal rearrangement of an abietane-type pisiferol to a 9(10→20)*abeo*-abietane-type pisiferin (Scheme 5). Reaction of (**20a**) with toluene-*p*-sulphonyl chloride[4] in pyridine at 70 °C furnished the rearrangement products (**26**) and (**27**) (83%) as a 3:1 mixture of inseparable double bond regioisomers. The major compound was deduced to be (**26**) on the basis of its n.m.r. spectrum which showed an olefinic proton signal at 5.44 p.p.m. as a triplet with a coupling constant of *J* 3.8 Hz. This result is very similar to those of previous work[3] except in the ratio of the products. On the other hand, under the same conditions (**20b**) gave (**27**) (90%) as the sole product. Although the reason for the formation of double bond regioisomers in this rearrangement is not clear, these results presumably concern the biosynthesis of pisiferin. In order to accomplish the synthesis of pisiferin and isopisiferin, deprotection of the methyl ethers was examined. Since previous work by Matsumoto[2d] has suggested that acidic demethylation would be unsatisfactory, we applied Koft's procedure[16] to the ethers (**26**) and (**27**). Treatment of the mixture (**26**) and (**27**), obtained from (**20a**), with sodium ethanethiolate in dimethylformamide afforded pisiferin (**1**) and (**28**) in 84% yield as a 3:1 inseparable mixture. Since the spectral data of the major compound (**1**) and its isomer (**28**) were identical with those reported,[1d] and the separation of this mixture was also achieved,[1d] our route constitutes a total synthesis of pisiferin, although difficulties were encountered in our attempted separation. On the other hand, when compound (**27**), obtained from (**20b**), was heated in the presence of pyridine




Scheme 4.




Scheme 5.

hydrochloride[17] double bond migration afforded isopisiferin (**29**) in 54% yield. Spectral data of (**29**) was also identical with those of an authentic sample.[1d]

Thus, we have described an alternative synthesis of (±)-pisiferin, (±)-pisiferol, and related compounds utilising an intramolecular [4 + 2] cycloaddition of an *o*-quinodimethane generated from a benzocyclobutene.

## Experimental

*General Methods.*—I.r. spectra were measured on a Hitachi 260-10 spectrophotometer. $^1$H n.m.r. spectra were recorded with JEOL PMX-60, JEOL JNM FX-100, JEOL JNM GX-270, or JEOL JNM GX-400 spectrometers with tetramethylsilane as internal standard. Mass spectra were obtained with JEOL JMS D-300 spectrometers. M.p.s are uncorrected.

2-*Cyano*-3-(3-*isopropyl*-4-*methoxyphenyl*)*propenoic Acid* (**11**).—A mixture of the aldehyde (**10**)[7] (3.75 g, 0.021 mol), cyanoacetic acid (2.31 g, 0.027 mol), pyridine (5 ml, 0.062 mol), and ammonium acetate (0.32 g, 4.6 mmol) in benzene (100 ml) was refluxed for 6 h using a Dean–Stark apparatus. The solvent was evaporated and the residue was diluted with water and extracted with ether. The aqueous layer was acidified with 10% HCl and extracted with ether, and the extract was washed with brine, dried, and evaporated to give the crude product. This was recrystallised from hexane–ethyl acetate (9:1) to yield (**11**) (4.1 g, 79%), m.p. 145—146 °C; $\nu_{max.}$(CHCl$_3$) 3 300 (OH), 2 240 (C≡N), and 1 700 cm$^{-1}$ (C=O); $\delta_H${60 MHz; [(CD$_3$)$_2$SO]} 1.19 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 3.17 (1 H, sept, *J* 7 Hz, C*H*Me$_2$), 3.85 (3 H, s, OMe), 6.90—7.87 (3 H, m, ArH), and 8.06 (1 H, s, ArC*H*=C); *m/z* 245 (*M*$^+$) (Found: C, 68.5; H, 6.1; N, 5.7. C$_{14}$H$_{15}$NO$_3$ requires C, 68.55; H, 6.15; N, 5.7%).

2-*Cyano*-3-(3-*isopropyl*-4-*methoxyphenyl*)*propionic Acid* (**12**).—To a stirred solution of (**11**) (50.10 g, 0.204 mol) in methanol (500 ml) and aqueous sodium hydrogen carbonate (150 ml) was added sodium borohydride (19.2 g, 0.505 mol) in small portions over 1 h at 0 °C, and the mixture was stirred for a further 2 h at 0 °C. The solvent was evaporated and the residue was diluted with water and extracted with ether. The aqueous layer was acidified with 10% HCl and extracted with ether. The extract was washed with brine, dried, and evaporated to yield a residue, which was recrystallised from hexane–ethyl acetate to give (**12**) (40.2 g, 80%), m.p. 87—88 °C; $\nu_{max.}$(CHCl$_3$) 3 300 (OH), 2 250 (C≡N), and 1 740 cm$^{-1}$ (C=O); $\delta_H${60 MHz; [(CD$_3$)$_2$SO]} 1.14 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 3.01—3.72 (4 H, m, C*H*Me$_2$ and ArCH$_2$CH), 3.72 (3 H, s, OMe), 6.55—7.04 (3 H, m, ArH); *m/z* 247 (*M*$^+$) (Found: *M*$^+$, 247.1208. C$_{14}$H$_{17}$NO$_3$ requires *M*, 247.1208) (Found: C, 67.05; H, 7.0; N, 5.65. C$_{14}$H$_{17}$NO$_3$·0.1H$_2$O requires C, 67.5; H, 6.95; N, 5.6%).

3-(3-*Isopropyl*-4-*methoxyphenyl*)*propionitrile* (**13**).—A solution of (**12**) (63.2 g, 0.256 mol) in *N*,*N*-dimethylacetamide (100 ml) was heated at 150 °C for 4 h. After cooling, the solvent was evaporated to give the oil, which was distilled under reduced pressure to afford the nitrile (**13**) (49.4 g, 95%), b.p. 165 °C at 2 mmHg; $\nu_{max.}$(CHCl$_3$) 2 270 cm$^{-1}$ (C≡N); $\delta_H$(60 MHz; CCl$_4$) 1.19 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 2.25—2.90 (4 H, m, ArCH$_2$CH$_2$), 3.72 (3 H, s, OMe), and 6.60—7.03 (3 H, m, ArH); *m/z* 203 (*M*$^+$) (Found: *M*$^+$, 203.1309. C$_{12}$H$_{17}$NO requires *M*, 203.1307).

3-(3-*Bromo*-5-*isopropyl*-4-*methoxyphenyl*)*propiononitrile* (**14**).—To a stirred mixture of (**13**) (50.03 g, 0.246 mol) and sodium acetate (34.29 g, 0.418 mol) in chloroform (700 ml) was added dropwise bromine (16.5 ml, 0.32 mol) at room temperature, and the mixture was stirred for 8 h at the same temperature. After dilution with water, the organic layer was washed with brine, aqueous sodium thiosulphate, and brine, dried (Na$_2$SO$_4$), and evaporated to give the oil. Distillation of the crude product under reduced pressure afforded (**14**) (69 g, 99%), b.p. 172 °C at 2 mmHg; $\nu_{max.}$(CHCl$_3$) 2 250 cm$^{-1}$ (C≡N); $\delta_H$(60 MHz; CCl$_4$) 1.20 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 2.33—2.97 (4 H, m, ArCH$_2$CH$_2$), 3.79 (3 H, s, OMe), 6.96 (1 H, d, *J* 2 Hz, ArH), and 7.15 (1 H, d, *J* 2 Hz, ArH); *m/z* 283 (*M*$^+$) (Found: *M*$^+$, 283.0396. C$_{13}$H$_{16}$NOBr requires *M*, 283.0409).

4-*Isopropyl*-5-*methoxy*-1,2-*dihydrobenzocyclobutene*-1-*carbonitrile* (**15**).—To a stirred solution of sodium amide [prepared from sodium (5.5 g, 0.24 mol) and liq. ammonia (2 l)] in liq. ammonia was added slowly a solution of (**14**) (15 g, 0.053 mol) in dry tetrahydrofuran (20 ml) and the resulting mixture was stirred for 4 h. After addition of crystalline ammonium chloride (40 g), the solvent was evaporated. The residue was taken up with ethyl acetate and washed with water, dried, and evaporated. The residue was purified by column chromatography on silica gel using benzene as eluant to afford (**15**) (7.2 g, 68%). An analytical sample was purified by recrystallisation from hexane, m.p. 47—48 °C; $\nu_{max.}$(CHCl$_3$) 2 240 cm$^{-1}$ (C≡N); $\delta_H$(60 MHz; CCl$_4$) 1.20 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 3.83 (3 H, s, OMe), 4.10 (1 H, t, *J* 4 Hz, 1-H), 6.77 (1 H, s, 3-H), and 7.98 (1 H, s, 6-H); *m/z*

201 ($M^+$) (Found: C, 77.6; H, 7.65; N, 6.85. $C_{13}H_{15}NO$ requires C, 77.6; H, 7.5; N, 6.95%).

1-(4,4-*Dimethylhex*-5-*enyl*)-4-*isopropyl*-5-*methoxy*-1,2-*dihydrobenzocyclobutene*-1-*carbonitrile* (**17**).—A solution of (**15**) (2.60 g, 12.9 mmol) and sodium hydride (60% dispersion in mineral oil; 0.78 g, 0.013 mol) in dry dimethylformamide (200 ml) was heated at 60 °C for 30 min after which a solution of 3,3-dimethyl-6-iodohexene (**16**)[8] (3.00 g, 0.013 mol) in dry dimethylformamide (30 ml) was added. The reaction mixture was stirred for a further 1 h at the same temperature and then cooled, diluted with water, and extracted with benzene. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel with benzene as eluant to yield (**17**) (4.04 g, 100%). An analytical sample was purified by recrystallisation from methanol, m.p. 74—75 °C; $\nu_{max.}(CHCl_3)$ 2 250 $cm^{-1}$ (C≡N); $\delta_H$(60 MHz; $CCl_4$) 1.03 (6 H, s, $CMe_2$), 1.16 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 3.06 and 3.58 (each 1 H, each d, *J* 14 Hz, ArC*H*$_2$), 3.80 (3 H, s, OMe), 4.87 (1 H, dd, *J* 2, 16 Hz, H*H*C=CH), 4.90 (1 H, dd, *J* 2, 10 Hz, *H*HC=CH), 5.75 (1 H, dd, *J* 10, 16 Hz, $CH_2$=C*H*), 6.62 (1 H, s, 6-H), and 6.90 (1 H, s, 3-H) (Found: C, 80.9; H, 9.7; N, 4.35. $C_{21}H_{29}NO$ requires C, 81.0; H, 9.4; N, 4.5%).

12-*Methoxy*-5β*H*-*abieta*-8,11,13-*triene*-20-*nitrile* (**18b**) *and Its* (5α*H*)-*Isomer* (**18a**).—A solution of benzocyclobutene (**17**) (574 mg, 1.8 mmol) in *o*-dichlorobenzene (200 ml) was refluxed for 3 h. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane–benzene (7:3) as eluant to afford an inseparable mixture (**18**) (**a**/**b** = 1:4) (462 mg, 80%). An analytical sample was purified by recrystallisation from methanol, m.p. 97—98 °C; $\nu_{max.}(CHCl_3)$ 2 230 $cm^{-1}$ (C≡N); *m*/*z* 311 ($M^+$) (Found: C, 81.0; H, 9.5; N, 4.5. $C_{21}H_{29}NO$ requires C, 81.0; H, 9.4; N, 4.5%). For (**18a**): $\delta_H$(270 MHz; $CDCl_3$) 1.00 and 1.15 (each 3 H, each s, $CMe_2$), 1.18 and 1.19 (each 3 H, each d, *J* 7.3 Hz, CH*Me*$_2$), 3.24 (1 H, sept, *J* 6.7 Hz, C*H*Me$_2$), 3.81 (3 H, s, OMe), 6.82 (1 H, s, 11-H), and 6.91 (1 H, s, 14-H). For (**18b**): $\delta_H$(270 MHz; $CDCl_3$) 1.02 and 1.45 (each s, each 3 H, $CMe_2$), 1.18 and 1.19 (each 3 H, each d, *J* 7.3 Hz, CH*Me*$_2$), 3.24 (1 H, sept, *J* 6.7 Hz, C*H*Me$_2$), 3.83 (3 H, s, OMe), 6.85 (1 H, s, 11-H), and 6.93 (1 H, s, 14-H).

12-*Methoxy*-5β*H*-*abieta*-8,11,13-*trien*-20-*al* (**19b**) *and Its* 5α*H*-*Isomer* (**19a**).—A solution of di-isobutylaluminium hydride in toluene (1M; 1.3 ml, 1.3 mmol) was added dropwise to a stirred solution of (**18**) (**a**/**b** = 1:4) (0.24 g, 0.77 mmol) in dry toluene (30 ml) at −78 °C, and the resulting mixture was stirred for 1 h at −78 °C. The reaction was quenched by addition of aqueous ammonium chloride after which the mixture was filtered through a Celite pad and the filtrate was extracted with ethyl acetate. The extract was washed with brine, dried, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane–ethyl acetate (7:3) as eluant to give an inseparable mixture (**19**) (**a**/**b** = 1:4) (0.22 g, 91%); $\nu_{max.}(CHCl_3)$ 1 690 $cm^{-1}$ (CHO); *m*/*z* 314 ($M^+$) (Found: $M^+$, 314.2244. $C_{21}H_{30}O_2$ requires *M*, 314.2243). For (**19a**): $\delta_H$(60 MHz; $CCl_4$) 0.83 and 0.98 (each 3 H, each s, $CMe_2$), 1.15 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 3.16 (1 H, m, C*H*Me$_2$), 3.70 (3 H, s, OMe), 6.44 (1 H, s, 11-H), 6.77 (1 H, s, 14-H), and 9.75 (1 H, s, CHO). For (**19b**): $\delta_H$(60 MHz; $CCl_4$) 0.96 and 1.02 (each 3 H, each s, $CMe_2$), 1.15 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 3.16 (1 H, m, C*H*Me$_2$), 3.69 (3 H, s, OMe), 6.20 (1 H, s, 11-H), 6.72 (1 H, s, 14-H), and 9.12 (1 H, s, CHO).

$NaBH_4$ *Reduction of* (**19**).—Sodium borohydride (860 mg, 22.63 mmol) was added to a stirred solution of (**19**) (**a**/**b** = 1:4) (204 mg, 0.646 mmol) in methanol (5 ml) and dichloromethane (5 ml) at 0 °C and the mixture was stirred for a further 1 h at 0 °C. After evaporation of the solvent, the residue was treated with water and extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated under reduced pressure, and the residue was then purified by column chromatography on silica gel using hexane–benzene (7:3) as eluant to yield (**20a**) (29.4 mg, 14%); $\nu_{max.}(CHCl_3)$ 3 400 $cm^{-1}$ (OH); $\delta_H$(60 MHz; $CCl_4$) 0.97 (6 H, s, $CMe_2$), 1.17 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 3.50 and 3.77 (each 1 H, each d, *J* 11 Hz, C*H*$_2$OH), 3.76 (3 H, s, OMe), 6.61 (1 H, s, 11-H), and 6.77 (1 H, s, 14-H); *m*/*z* 316 ($M^+$) (Found: $M^+$, 316.2422. $C_{21}H_{32}O_2$ requires *M*, 316.2412). The spectral data were identical with those reported.[2a]

Further elution afforded (**20b**) (128.1 mg, 62%); $\nu_{max.}(CHCl_3)$ 3 400 $cm^{-1}$ (OH); $\delta_H$(60 MHz; $CCl_4$) 0.46 and 0.97 (each 3 H, each s, $CMe_2$), 1.17 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 3.30 (2 H, s, C*H*$_2$OH), 3.77 (3 H, s, OMe), 6.60 (1 H, s, 11-H), and 6.71 (1 H, s, 14-H); *m*/*z* 316 ($M^+$) (Found: $M^+$, 316.2422. $C_{21}H_{32}O_2$ requires *M*, 316.2412).

12-*Methoxy*-5β*H*-*abieta*-8,11,13-*trien*-20-*al* (**19b**).—To a stirred solution of dry $CH_2Cl_2$ (5 ml) and oxalyl chloride (0.04 ml, 0.42 mmol) was added dry DMSO (0.05 ml, 0.71 mmol) in dry $CH_2Cl_2$ (2 ml) at −50 °C for 2 min. A solution of (**20b**) (102 mg, 0.32 mmol) in $CH_2Cl_2$ (1 ml) was then added to this solution at −78 °C within 5 min. The mixture was stirred for a further 15 min after which triethylamine (0.22 ml, 1.61 mmol) was added, the mixture was then further stirred for 5 min at the same temperature before being allowed to warm to room temperature. The mixture was diluted with water and extracted with benzene. Evaporation of the extract gave a residue, which was subjected to column chromatography on silica gel with hexane–ethyl acetate (9:1) as eluant to give the aldehyde (**19b**) (62.6 mg, 62%); spectral data were identical with those described above.

12-*Methoxy*-5β*H*-*abieta*-8,11,13-*triene* (**21**).—A mixture of (**19b**) (110 mg, 0.35 mmol), anhydrous $NH_2NH_2$ (5.2 ml, 0.16 mol), $NH_2NH_2$·2 HCl (1.08 g, 10.27 mmol), and ethylene glycol (10.8 ml) was heated at 140 °C for 14 h. After addition of pellets of potassium hydroxide (5.6 g), the mixture was heated at 150 °C for a further 2 h and then the temperature was slowly raised to 200 °C over 2 h. After being heated at 200—220 °C for an additional 3 h, the reaction mixture was poured into water and extracted with benzene. The extract was washed with brine, dried and evaporated to give a residue, which was purified by column chromatography on silica gel using hexane–benzene (9:1) as eluant to afford (**21**) (24 mg, 23%); $\delta_H$(60 MHz; $CCl_4$) 0.39 and 0.91 (each 3 H, each s, $CMe_2$), 1.13 (3 H, s, 10-Me), 3.17 (1 H, sept, C*H*Me$_2$), 3.82 (3 H, s, OMe), 6.59 (1 H, s, 11-H), and 6.64 (1 H, s, 14-H); *m*/*z* 300 ($M^+$).

12-*Methoxy*-7-*oxo*-5β*H*-*abieta*-8,11,13-*triene*-20-*nitrile* (**23b**) *and Its* 5α*H*-*Isomer* (**23a**).—To a stirred solution of (**18**) (**a**/**b** = 1:4) (98 mg, 0.315 mmol) in dry benzene (4 ml) and Celite (0.4 g) was added pyridinium dichromate (0.45 g, 1.26 mmol) and 70% t-butyl hydroperoxide (0.11 g, 1.26 mmol) at 10 °C. After being stirred for 30 min at 10 °C, the reaction mixture was stirred for a further 4 h at room temperature. Ether was added, and the reaction mixture was filtered through a Celite pad and washed twice with ether. The combined filtrates were evaporated, and the residue was purified by column chromatography on silica gel using hexane–ethyl acetate (9:1) as eluant to afford an inseparable mixture (**23**) (**a**/**b** = 1:4) (67.4 mg, 66%). An analytical sample was purified by recrystallisation from hexane, m.p. 166—168 °C; $\nu_{max.}(CHCl_3)$ 2 230 (C≡N) and 1 650 $cm^{-1}$ (C=O); *m*/*z* 325 ($M^+$) (Found: C, 77.5; H, 8.55; N, 4.25. $C_{21}H_{27}NO$ requires C, 77.5; H, 8.35; N, 4.3%). For (**23a**): $\delta_H$(60 MHz; $CDCl_3$) 0.98 and 1.21 (each 3 H, each s, $CMe_2$), 1.23 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 3.14 (1 H, m, C*H*Me$_2$), 3.90 (3 H, s, OMe),

6.85 (3 H, s, 11-H), and 7.96 (1 H, s, 14-H). For (**23b**): $\delta_H$(60 MHz; $CDCl_3$) 0.80 and 1.33 (each 3 H, each s, $CMe_2$), 1.22 (6 H, d, *J* 7 Hz, $CHMe_2$), 3.12 (1 H, m, $CHMe_2$), 3.94 (3 H, s, OMe), 7.02 (1 H, s, 11-H), and 7.88 (1 H, s, 14-H).

12-*Methoxy*-7-*oxoabieta*-5,8,11,13-*tetraene*-20-*nitrile* (**24**).—To a stirred solution of (**23**) (**a**/**b** = 1:4) (420 mg, 1.29 mmol) in acetic acid (10 ml), containing two drops of acetic acid saturated with hydrogen bromide gas, was added dropwise a solution of bromine (860 mg, 1.68 mmol) in acetic acid (5 ml) at room temperature and the reaction mixture was stirred for 1 h. After dilution with water, the product was extracted with ethyl acetate and the organic layer was washed with saturated aqueous sodium hydrogen carbonate, aqueous sodium thiosulphate, and brine, and dried ($Na_2SO_4$). The solvent was evaporated to give the α-bromo ketone (530 mg), which was used in the following reaction without further purification.

A solution of the above product (530 mg, 1.31 mmol) and DBU (0.39 ml, 2.62 mmol) in *o*-xylene (40 ml) was heated at 165 °C for 2 h. Removal of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane–benzene (9:1) as eluant to yield (**24**) (375 mg, 89%), m.p. 153—155 °C (hexane); $\nu_{max.}$($CHCl_3$) 2 240 (C≡N) and 1 660 $cm^{-1}$ (C=O); $\delta_H$(60 MHz; $CDCl_3$) 1.25 (6 H, d, *J* 7 Hz, $CHMe_2$), 1.31 and 1.57 (each 3 H, each s, $CMe_2$), 3.12 (1 H, m, $CHMe_2$), 3.93 (3 H, s, OMe), 6.46 (1 H, s, 6-H), 7.03 (1 H, s, 11-H), and 7.96 (1 H, s, 14-H); *m*/*z* 323 ($M^+$) (Found: C, 77.9; H, 7.8; N, 4.35. $C_{21}H_{25}NO_2$ requires C, 78.0; H, 7.8; N, 4.35%).

*Hydrogenation of Compound* (**24**).—A solution of (**24**) (215 mg, 0.665 mmol) and 10% palladium–carbon (220 mg) in ethanol (40 ml) was stirred under an atmosphere of hydrogen at ambient temperature for 2 h. The mixture was filtered to remove insoluble material and the solvent was evaporated. Purification of the residue by column chromatography on silica gel, with hexane–ethyl acetate (19:1) as eluant, afforded a colourless solid, which was recrystallised from hexane to give an inseparable mixture (**23**) (**a**/**b** = 3:1) (185 mg, 86%). Spectral data were identical with those of (**23**) (**a**/**b** = 1:4) obtained above except for the ratio of the products.

12-*Methoxy*-5αH-*abieta*-6,8,11,13-*tetraene*-20-*nitrile* (**25**).—To a stirred solution of the above compound (**23**) (**a**/**b** = 3:1) (185 mg, 0.569 mmol) in methanol (20 ml) and dichloromethane (20 ml) was added sodium borohydride (320 mg, 8.42 mmol) at 0 °C and the mixture was stirred for a further 1 h at the same temperature. After evaporation of the solvent, the residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried ($Na_2SO_4$) and evaporated to give the alcohol which was used without further purification. A solution of the alcohol in acetone (60 ml) containing a catalytic amount of toluene-*p*-sulphonic acid was refluxed for 2 h. Evaporation of the solvent gave a residue, which was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated to give a residue which was purified by column chromatography on silica gel, using hexane–ethyl acetate (19:1) as eluant, to afford an inseparable mixture of (**25**) (**a**/**b** = 3:1) (135 mg, 77%). An analytical sample was purified by recrystallisation from hexane, m.p. 152—154 °C; $\nu_{max.}$($CHCl_3$) 2 240 (C≡N) and 1 610 $cm^{-1}$ (C=C); $\delta_H$(60 MHz; $CDCl_3$) 0.52 (0.75 H, s, C*Me* Me), 1.01 (2.25 H, s, C*Me*Me), 1.21 (6 H, d, *J* 7 Hz, $CHMe_2$), 1.27 (3 H, s, CMe*Me*), 3.81 (3 H, s, OMe), 5.97 (1 H, distorted dd, *J* 2 and 10 Hz, 6-H), 6.51—7.95 (1 H, m, 7-H), 6.75 (1 H, s, 11-H), and 7.95 (1 H, s, 14-H); *m*/*z* 309 ($M^+$) (Found: C, 81.6; H, 8.9; N, 4.45. $C_{21}H_{27}NO$ requires C, 81.5; H, 8.8; N, 4.55%).

*Hydrogenation of* (**25**).—A solution of (**25**) (**a**/**b** = 3:1) (135 mg, 0.437 mmol) in dry ethyl acetate (10 ml) was hydrogenated in the presence of 10% palladium-on-carbon (22 mg) for 8 h. The mixture was filtered to remove insoluble material, and the filtrate was concentrated to give a residue, which was purified by column chromatography on silica gel, using hexane–ethyl acetate (7:3) as eluant, to yield an inseparable mixture (**18**) (107 mg, 79%) (**a**/**b** = 3:1). Spectral data were identical with those of the nitrile (**18**) (**a**/**b** = 1:4) obtained by the thermolysis of (**17**) except for the ratio of the products.

*Conversion of Compound* (**18**) (**a**/**b** = 3:1) *into* (**19**) (**a**/**b** = 3:1).—Compound (**18**) (**a**/**b** = 3:1) (106 mg, 0.341 mmol) was converted into an inseparable mixture of (**19**) (**a**/**b** = 3:1) (80 mg, 75%) by the same procedure described for the preparation of (**19**) (**a**/**b** = 1:4).

*Conversion of Compound* (**19**) (**a**/**b** = 3:1) *into* (**20a**) *and* (**20b**).—Compound (**19**) (**a**/**b** = 3:1) (260 mg, 0.83 mmol), under the same condition as described above, gave (**20a**) (160.5 mg, 61%) and (**20b**) (52.8 mg, 20%).

12-*Methoxy*-9(10→20)abeo-*abieta*-5(10),8,11,13-*tetraene* (**27**).—To a solution of (**20b**) (85 mg, 0.269 mmol) in pyridine (10 ml) at 70 °C was added toluene-*p*-sulphonyl chloride (0.1 g, 0.524 mmol) and the mixture was stirred for 8 h at the same temperature. After dilution of the mixture with water, the product was extracted with ethyl acetate and the organic layer was washed with brine, aqueous sodium hydrogen carbonate, aqueous potassium bisulphate, and brine and dried ($Na_2SO_4$). Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane–benzene (19:1) as eluant to give (**27**) (72 mg, 90%); $\nu_{max.}$($CHCl_3$) 1 600 $cm^{-1}$ (C=C); $\delta_H$(60 MHz; $CCl_4$) 1.00 (6 H, s, $CMe_2$), 1.15 (6 H, d, *J* 7 Hz, $CHMe_2$), 3.18 (2 H, br s, $CH_2Ar$), 3.73 (3 H, s, OMe), 6.30 (1 H, s, 11-H), and 6.65 (1 H, s, 14-H); *m*/*z* 298 ($M^+$) (Found: $M^+$, 298.2294. $C_{21}H_{30}O$ requires *M*, 298.2292).

*Rearrangement of Compound* (**20a**).—Compound (**20a**) (92.3 mg, 0.292 mmol) was subjected to the conditions described above for the preparation of (**27**) to afford an inseparable 3:1 mixture of 12-*methoxy*-9(10→20)abeo-*abieta*-1(10),8,11,13-*tetraene* (**26**) and (**27**) (72.3 mg, 83%); $\nu_{max.}$($CHCl_3$) 1 605 $cm^{-1}$ (C=C) (Found: $M^+$, 298.2296. $C_{21}H_{30}O$ requires *M*, 298.2296). For (**26**): $\delta_H$(270 MHz; $CDCl_3$) 0.88 and 0.92 (each 3 H, each s, $CMe_2$), 1.17 and 1.18 (each 3 H, each d, *J* 6.7 Hz, $CHMe_2$), 3.31 (2 H, br s, 20-H), 3.81 (3 H, s, OMe), 5.44 (1 H, t, *J* 3.8 Hz, 1-H), 6.61 (1 H, s, 11-H), and 6.89 (1 H, s, 14-H). For (**27**): $\delta_H$(270 MHz; $CDCl_3$) 1.00 (6 H, s, $CMe_2$), 1.19 and 1.20 (each 3 H, each d, *J* 6.7 Hz, $CHMe_2$), 3.31 (2 H, br s, 20-H), 3.80 (3 H, s, OMe), 6.52 (1 H, s, 11-H), and 6.86 (1 H, s, 14-H).

*Demethylation of Compounds* (**26**) *and* (**27**).—A mixture of compounds (**26**) and (**27**) (67.8 mg, 0.228 mmol), ethanethiol (0.22 ml, 2.97 mmol), and sodium hydride (60% dispersion in oil; 75.8 mg, 1.90 mmol) in dimethylformamide (2 ml) was heated at reflux under $N_2$ for 4 h. Dilution with water, acidification (2M HCl), and extraction with ether gave the crude product which was purified by column chromatography using hexane–ethyl acetate (11:1) as eluant to afford an inseparable mixture of pisiferin (**1**) and 9(10→20)*abeo*-abieta-5(10),8,11,13-tetraen-12-ol (**28**) (54.4 mg, 84%) in a ratio of (3:1); $\nu_{max.}$($CHCl_3$) 3 300 (OH) and 1 600 (C=C) $cm^{-1}$ (Found: $M^+$, 284.2138. $C_{20}H_{28}O$ requires *M*, 284.2137). For (**28**): $\delta_H$(270 MHz; $CDCl_3$) 0.99 (6 H, s, $CMe_2$), 1.24 and 1.25 (each 3 H, each d, *J* 6.7 Hz, $CHMe_2$), 3.13 (1 H, sept, *J* 6.9 Hz, $CHMe_2$), 3.24 (2 H, br s, 20-H), 6.44 (1 H, s, 11-H), and 6.85 (1 H, s, 14-H). For (**1**): $\delta_H$(270 MHz; $CDCl_3$) 0.88 and 0.91 (each 3 H, each s, $CMe_2$), 1.22 and 1.23

(each 3 H, each d, $J$ 6.7 Hz, CH$Me_2$), 3.12 (1 H, sept, $J$ 6.9 Hz, C$H$Me$_2$), 3.24 (2 H, br s, 20-H), 5.41 (1 H, t, $J$ 3.8 Hz, 1-H), 6.52 (1 H, s, 11-H), and 6.88 (1 H, s, 14-H). The $^1$H n.m.r. spectral data of (**1**) and (**28**) were identical with those of natural pisiferin and (**28**).[1d]

*Isopisiferin* (**29**).—A mixture of (**27**) (240 mg, 0.805 mmol) and pyridine hydrochloride (560 mg, 4.8 mmol) was heated at 200—220 °C for 5 h. The reaction mixture was poured into water, the aqueous layer was extracted with ethyl acetate, and the extract was washed with brine, dried, and evaporated. Purification of the residue over silica gel using hexane–ethyl acetate (7:3) as eluant yielded isopisiferin (**29**) (130 mg, 54%); $\nu_{max.}$($CHCl_3$) 3 350 (OH) and 1 600 (C=C) cm$^{-1}$; $\delta_H$(100 MHz; $CDCl_3$) 0.70 and 0.98 (each 3 H, each s, C$Me_2$), 1.22 and 1.24 (each 3 H, each d, $J$ 6.84 Hz, CH$Me_2$), 3.13 (1 H, m, C$H$Me$_2$), 4.51 (1 H, br s, OH), 6.22 (1 H, s, 20-H), 6.49 (1 H, s, 11-H), and 6.80 (1 H, s, 14-H) (Found: $M^+$, 284.2138, $C_{21}H_{32}O_2$ requires $M$, 284.2136).

## Acknowledgements

We thank T. Ogata, M. Yuyama, Y. Takahashi, H. Kasai, and M. Yamazaki of Hoshi University for spectral measurements, microanalyses, and manuscript preparation.

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*Received* 17*th November* 1988; *Paper* 8/04588G