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Total Synthesis of (±)-Pisiferic Acid, Methyl (±)-Pisiferate, and (±)-Pisiferol

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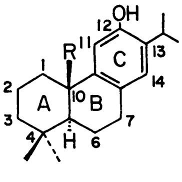
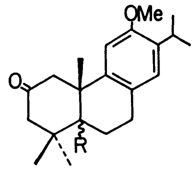
Acid catalyzed cyclization of 4-(3-isopropyl-4-methoxyphenethyl)-3,5,5-trimethyl-2-cyclohexen-1-one afforded 12-methoxyabieta-8,11,13-trien-2-one and its *cis*-isomer. Both compounds were further converted into 12-methoxyabieta-8,11,13-trien-2β-ol, which was treated with lead tetraacetate in the presence of iodine to yield 2β,20-epoxy-12-methoxyabieta-8,11,13-triene. Ether cleavage of the 2β,20-epoxy compound with acetyl *p*-toluenesulfonate, followed by catalytic hydrogenation, afforded 20-acetoxy-12-methoxyabieta-8,11,13-triene (**23**). This was then converted into methyl 12-methoxyabieta-8,11,13-trien-20-oate (**27**) *via* methyl 12-methoxy-7-oxo-abieta-8,11,13-trien-20-oate. Demethylation of **27** with $AlBr_3$–EtSH gave pisiferic acid, but with $AlCl_3$–EtSH **27** was partially demethylated to give methyl pisiferate. The acetate **23** was also converted into pisiferol by demethylation and reduction.

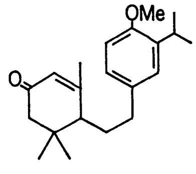
Recently three new ferruginol type diterpenes, pisiferic acid (**1**), methyl pisiferate (**2**), and pisiferol (**3**), have been isolated from the leaves of *Chamaecyparis pisifera* by Yatagai *et al.*[1] All these compounds are are tricyclic diterpenes possessing an oxidized angular methyl group. As an extension of our previous studies[2,3] of the syntheses of natural tricyclic diterpenes possessing an oxygen function in the ring A, we have attempted the syntheses of these rare natural compounds. This paper[4] describes the total syntheses of (±)-pisiferic acid (**1**), methyl (±)-pisiferate (**2**), and (±)-pisiferol (**3**), starting from (±)-12-methoxyabieta-8,11,13-trien-2-one (**4**),[3] which was prepared from (±)-4-(3-isopropyl-4-methoxyphenethyl)-3,5,5-trimethyl-2-cyclohexen-1-one (**5**).



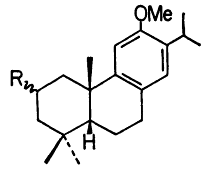
1 R = CO_2H
2 R = CO_2Me
3 R = CH_2OH



4 R = α-H
6 R = β-H

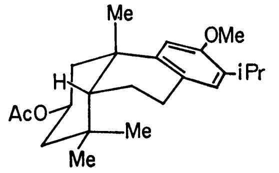


5

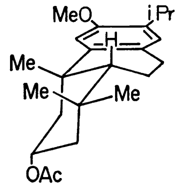


7 R = β-OAc
8 R = α-OAc

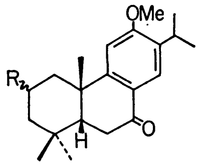
Cyclization of **5** in hexane with boron trifluoride etherate in the presence of 1,2-ethanedithiol, followed by hydrolysis with mercury (II) chloride in aqueous acetonitrile, gave **4** (28%) and its *cis*-isomer (**6**: 16%).[3] Since all natural compounds (**1**, **2**, and **3**) possess a trans A/B ring junction, conversion of the *cis*-isomer **6** into the trans compounds was carried out as follows. Reduction of **6** with lithium aluminium hydride in THF, followed by acetylation, gave two epimeric acetates, **7** (32%) and **8** (52%). The ^1H NMR spectrum of **7** showed signals at δ 0.35, 0.98, and 1.18 due to the C-4 dimethyl and C-10 methyl groups. The steroidal conformation (**7a**) of **7** was suggested by the appearance of the signal due to one of two C-4 methyl groups in very high field (δ 0.35), owing to the shielding effect of the aromatic C-ring. The ^1H NMR spectrum of **8** showed the corresponding signals at δ 1.02, 1.26, and 1.49. The appearance of these three tertiary methyl signals in a lower field than those in **7** suggested that **8** exists in a nonsteroidal conformation (**8a**).[5] The stereochemistry of the acetoxyl group at C-2 in **7** and **8** was assigned respectively to be β- and α-configuration by their ^1H NMR spectra, each of which showed a broad signal due to the C-2 proton at δ 4.4—5.1 in **7** and at δ 4.6—5.4 in **8**, suggesting the presence of an axial hydrogen. The acetate **7** in acetone was oxidized with Jones reagent to give the corresponding 7-oxo compound (**9**: 60%) along with the 6,7-dioxo compound (**10**: 13%). Bromination of **9** with pyridinium tribromide in dichloromethane afforded the 6β-bromo derivative (**11**: 91%), which was converted into 2β-acetoxy-12-methoxyabieta-5,8,11,13-tetraen-7-one (**12**: 86%) by treatment with lithium carbonate and lithium bromide in *N*,*N*-dimethylformamide at 110—130 °C. The tetraene **12** in ethyl acetate was catalytically hydrogenated with Pd–C in the presence of perchloric acid to yield 2β-acetoxy-12-methoxyabieta-8,11,13-triene (**13**: 72%) and **9** (17%). Treatment of **13** in THF with lithium aluminium hydride gave 12-methoxyabieta-8,11,13-trien-2β-ol (**14**). Similarly, the acetate **8** was also oxidized with Jones reagent to give the corresponding 7-oxo (**15**: 53%) and 6,7-dioxo (**16**: 16%) compounds. The 7-oxo compound **15** was further converted into 2α-acetoxy-12-methoxyabieta-5,8,11,13-tetraen-7-one (**18**) *via* the corresponding 6β-bromo derivative (**17**). The β-configuration of the bromine atom in **11** and **17** was supported by their ^1H NMR spectra, which showed signals due to the C-10 methyl group in low field (δ 1.57 in **11** and δ 1.68 in **17**), owing to the 1,3-diaxial interaction between the bromine atom and the C-10 methyl group. Catalytic hydrogenation of **18** in ethyl acetate over Pd–C afforded 2α-acetoxy-12-methoxyabieta-8,11,13-triene (**19**: 70%) and **8** (25%). The acetate **19** in THF was reduced with lithium aluminium hydride and the resulting alcohol was immediately oxidized with pyridinium chlorochromate in dichloromethane to afford **4** (88%), which was then converted into **14**[3] by reduction with lithium aluminium hydride in THF.



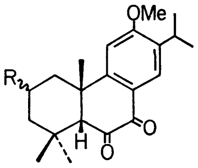
7a



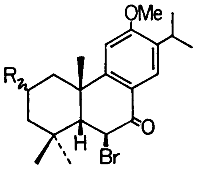
8a



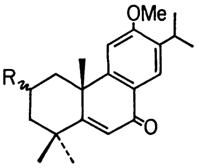
9 R=β-OAc
15 R=α-OAc



10 R=β-OAc
16 R=α-OAc

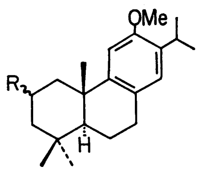


11 R=β-OAc
17 R=α-OAc

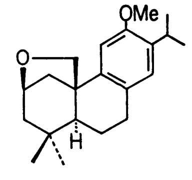


12 R=β-OAc
18 R=α-OAc

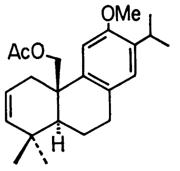
In order to oxidize the angular methyl group by transannular oxidation, the alcohol **14** in hexane was treated with lead tetraacetate in the presence of iodine at room temperature. Purification of the crude product by column chromatography on silica gel afforded 2β,20-epoxy-12-methoxyabieta-8,11,13-triene (**20**: 51 %). The structure of **20** was supported by the appearance of signals in its ^{1}H NMR spectrum due to methylene protons (ABq at δ 3.78) and by the disappearance of the signal due to angular methyl group. Treatment of **20** with acetyl *p*-toluenesulfonate[6] in dichloromethane gave an olefinic acetate (**21**: 83%) and a tosyloxy acetate (**22**: 11%). The ^{1}H NMR spectrum of **21** showed signals due to two vinylic protons at δ 5.55 (2H, m), methylene protons at δ 4.27 (2H, bs), an acetoxyl group at δ 1.90 (3H, s), and two tertiary methyl groups at δ 1.03 and 1.08 (each 3H and s). From these spectral data, the structure of **21** was assigned to be 20-acetoxy-12-methoxyabieta-2,8,11,13-tetraene. The spectrum of **22** showed the presence of a tosyloxyl group [δ 2.48 (3H, s), 7.34 and 7.83 (each 2H, d, and J=8 Hz)] and no vinylic proton. The α-configuration of the tosyloxyl group was supported by the broad signal at δ 4.2—4.9 (1H, m) due to the C-2 proton, suggesting the presence of an axial β hydrogen. Treatment of **22** with potassium carbonate in refluxing aqueous methanol yielded **20**. The olefinic acetate **21** in ethanol was submitted to catalytic hydrogenation over PtO_2 to afford 20-acetoxy-12-methoxyabieta-8,11,13-triene (**23**: 93%)



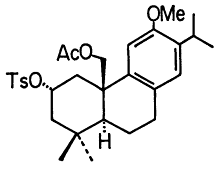
13 R=β-OAc
14 R=β-OH
19 R=α-OAc



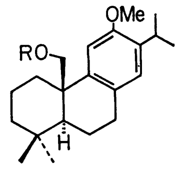
20



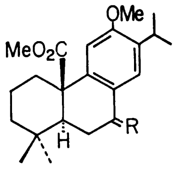
21



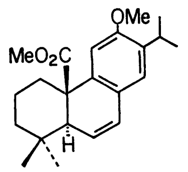
22



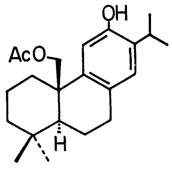
23 R=Ac
24 R=H



25 R=O
27 R=H2



26



28

which, on reduction with lithium aluminium hydride in THF, gave the corresponding alcohol (**24**: 95%). Oxidation of **24** in acetone with Jones reagent, followed by methylation with diazomethane, afforded methyl 12-methoxy-7-oxoabieta-8,11,13-trien-20-oate (**25**: 40%). The structure of **25** was supported by its IR (1720 and 1660 cm^{-1}) and ^{1}H NMR [δ 3.57 (CO_2CH_3), 6.70 (C_{11}-H), and 7.79 (C_{14}-H)] spectra. The 7-oxo compound **25** was then reduced with sodium borohydride in ethanol and the resulting mixture of epimeric alcohols was immediately dehydrated[7] with acetyl *p*-toluenesulfonate in dichloromethane to give methyl 12-methoxyabieta-6,8,11,13-tetraen-20-oate (**26**: 71%). Catalytic hydrogenation of **26** in ethanol over PtO_2 afforded methyl 12-methoxyabieta-8,11,13-trien-20-oate (**27**: 99%). Demethylation of **27** with anhydrous aluminium bromide and ethanethiol[8] at room temperature for 13 h gave pisiferic acid (12 hydroxyabieta-8,11,13-trien-20-oic acid) (**1**: 93%). Similar treatment of **27** with anhydrous aluminium chloride and ethanethiol[9] in dichloromethane at 0—5 °C for 4 h yielded methyl pisiferate (methyl 12-hydroxyabieta-8,11,13-trien-20-oate (**2**: 97%). Subsequently, the acetate **23** was demethylated with anhydrous aluminium chloride and ethanethiol in dichloromethane to give 20-acetoxyabieta-8,11,13-trien-12-ol

(**28**: 74%) which, on reduction with lithium aluminium hydride in THF, afforded pisiferol (abieta-8,11,13-triene-12,20-diol) (**3**: 88%). The IR and ^{1}H NMR spectra of the synthetic **1**, **2**, and **3** were identical with those of natural products.

Experimental

All melting points are uncorrected. The IR spectra were measured in chloroform, and the ^{1}H NMR spectra in carbon tetrachloride at 60 MHz, with tetramethylsilane as an internal standard, unless otherwise stated. The chemical shifts are presented in terms of δ values; s: singlet, bs: broad singlet, d: doublet, bd: broad doublet, dd: double doublet, t: triplet, bt: broad triplet, m: multiplet. Column chromatography was performed using Merck silica gel (0.063 mm).

Cyclization of 4-(3-Isopropyl-4-methoxyphenethyl)-3,5,5-trimethyl-2-cyclohexen-1-one (5). A stirred mixture of **5**[3] (5.03 g), 1,2-ethanedithiol (1.4 ml), boron trifluoride etherate (6.1 ml), and dry hexane (50 ml) was refluxed for 6 h. The mixture was cooled, poured into aqueous sodium hydroxide, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was refluxed for 3 h with mercury(II) chloride (13 g) in a mixture of acetonitrile (50 ml) and water (5.0 ml), filtered, and the filtrate was concentrated *in vacuo*. The residue was extracted with ether and the ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude products were purified by column chromatography on silica gel (Merck, 0.063—0.200 mm, 400 g), using ether–hexane (7:93 and then 1:9) as the eluent, to give 12-methoxyabieta-8,11,13-trien-2-one (**4**) (1.40 g: 28 %). Subsequent elution gave 12-methoxy-5β*H*-abieta-8,11,13-trien-2-one (**6**) (0.78 g: 16%). Further elution with ether–hexane (3:7) gave 12-methoxy-5β-methyl-18-norabieta-8,11,13-trien-2-one (1.02 g: 20%). The IR and ^{1}H NMR spectra of these products were identical with those of the authentic samples.[3]

Reduction and Acetylation of 6. A mixture of **6** (2.051 g) and lithium aluminium hydride (200 mg) in dry tetrahydrofuran (30 ml) was stirred at room temperature for 3 h. To the mixture was added successively water (0.20 ml), 10% aqueous sodium hydroxide (0.20 ml), and water (0.60 ml). The precipitate was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was acetylated with acetic anhydride (0.70 ml) and pyridine (2.0 ml) at room temperature for 13 h. After the usual work-up, the crude products were purified by column chromatography on silica gel (200 g), using ether–benzene (1:99) as the eluent, to give 2β-acetoxy-12-methoxy-5β*H*-abieta-8,11,13-triene (**7**) (749 mg: 32%). IR: 1718 cm^{-1}; ^{1}H NMR: 0.35 (3H, s, $C_{4\alpha}$–CH_3), 0.98 (3H, s, $C_{4\beta}$–CH_3), 1.18 (3H, s, C_{10}–CH_3), 1.18 (6H, d, *J*=7 Hz, –$CH(C\underline{H}_3)_2$), 2.00 (3H, s, –$OCOCH_3$), 3.92 (3H, s, –OCH_3), 4.4—5.1 (1H, m, C_2–H), 6.68 and 7.04 (each 1H and s, C_{11}–H and C_{14}–H). Found: C, 76.83; H, 9.66%. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56%.

Further elution gave 2α-acetoxy-12-methoxy-5β*H*-abieta-8,11,13-triene (**8**) (1.225 g: 52%). IR: 1720 cm^{-1}; ^{1}H NMR: 1.02 and 1.26 (each 3H and s, –$\overset{|}{C}(CH_3)_2$), 1.16 (6H, d, *J*=7 Hz, –$CH(C\underline{H}_3)_2$), 1.49 (3H, s, C_{10}–CH_3), 1.85 (3H, s, –$OCOCH_3$), 3.77 (3H, s, –OCH_3), 4.6—5.4 (1H, m, C_2–H), 6.63 (2H, bs, C_{11}–H and C_{14}–H). Found: C, 77.34; H, 9.76%. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56%.

Oxidation of 7. Jones reagent (2.5 M: 0.72 ml) was added dropwise at 0—5 °C to a stirred solution of **7** (427 mg) in acetone (8.0 ml). The mixture was further stirred at room temperature for 2 h, diluted with water, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (40 g), using ether–benzene (3:97) as the eluent, to give the starting **7** (63 mg: 15%) and 2β-acetoxy-12-methoxy-5β*H*-abieta-8,11,13-trien-7-one (**9**) (264 mg: 60%), which was recrystallized from methanol. Mp 163—164 °C; IR: 1720, 1655 cm^{-1}; ^{1}H NMR: 0.36 (3H, s, $C_{4\alpha}$–CH_3), 1.04 (3H, s, $C_{4\beta}$–CH_3), 1.25 (6H, bd, *J*=7 Hz, –$CH(C\underline{H}_3)_2$), 1.34 (3H, s, C_{10}–CH_3), 2.03 (3H, s, –$OCOCH_3$), 4.03 (3H, s, –OCH_3), 4.4—5.1 (1H, m, C_2–H), 7.09 (1H, s, C_{11}–H), 7.75 (1H, s, C_{14}–H). Found: C, 74.42; H, 8.87%. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66%.

Further elution gave 2β-acetoxy-12-methoxy-5βH-abieta-8,11,13-triene-6,7-dione (**10**) (60 mg: 13%), which was recrystallized from methanol. Mp 180—182 °C; IR: 1720, 1667 cm^{-1}; ^{1}H NMR: 0.48 (3H, s, $C_{4\alpha}$–CH_3), 1.06 (3H, s, $C_{4\beta}$–CH_3), 1.27 (6H, d, *J*=7 Hz, –$CH(C\underline{H}_3)_2$), 1.31 (3H, s, C_{10}–CH_3), 2.08 (3H, s, –$OCOCH_3$), 2.57 (1H, s, C_5–H), 4.11 (3H, s, –OCH_3), 4.5—5.3 (1H, m, C_2–H), 7.25 (1H, s, C_{11}–H), 7.86 (1H, s, C_{14}–H). Found: C, 71.50; H, 7.83%. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82%.

*2β-Acetoxy-6β-bromo-12-methoxy-5β*H*-abieta-8,11,13-trien-7-one (11).* A mixture of **9** (420 mg) and 80% pyridinium tribromide (450 mg) in dichloromethane (8.0 ml) was stirred at room temperature for 1 h. The mixture was diluted with water and extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (50 g), using ether–benzene (3:97) as the eluent, to give **11** (463 mg: 91%), which was recrystallized from benzene. Mp 212—213 °C; IR: 1720, 1663 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.31 (3H, s, $C_{4\alpha}$–CH_3), 1.18 (3H, s, $C_{4\beta}$–CH_3), 1.24 (6H, d, *J*=7 Hz, –$CH(C\underline{H}_3)_2$), 1.57 (3H, s, C_{10}–CH_3), 2.10 (3H, s, –$OCOCH_3$), 2.47 (1H, s, C_5–H), 4.07 (3H, s, –OCH_3), 4.5—5.2 (1H, m, C_2–H), 4.84 (1H, s, C_6–H), 7.18 (1H, s, C_{11}–H), 7.86 (1H, s, C_{14}–H). Found: C, 61.43; H, 7.00%. Calcd for $C_{23}H_{31}O_4Br$: C, 61.20; H, 6.92%.

2β-Acetoxy-12-methoxyabieta-5,8,11,13-tetraen-7-one (12). A mixture of **11** (210 mg), lithium carbonate (103 mg), and lithium bromide (81 mg) in *N*,*N*-dimethylformamide (3.0 ml) was stirred at 110—130 °C for 4 h in a stream of nitrogen. The mixture was cooled, poured into ice-dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (20 g), using ether–benzene (3:97) as the eluent, to give **12** (149 mg: 86%), which was recrystallized from ethanol. Mp 134—135 °C; IR: 1725, 1645 cm^{-1}; ^{1}H NMR: 1.23 and 1.26 (each 3H, d, and *J*=7 Hz, –$CH(C\underline{H}_3)_2$), 1.33, 1.46, and 1.66 (each 3H and s, –$\overset{|}{C}(CH_3)_2$ and C_{10}–CH_3), 2.07 (3H, s, –$OCOCH_3$), 3.92 (3H, s, –OCH_3), 5.10 (1H, m, $W_{1/2}$=17 Hz, C_2–H), 6.32 (1H, s, C_6–H), 6.77 (1H, s, C_{11}–H), 7.83 (1H, s, C_{14}–H). Found: C, 74.50; H, 8.14%. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16%.

Catalytic Hydrogenation of 12. A mixture of **12** (120 mg), 10% Pd-C (100 mg), and 70% perchloric acid (4 drops) in ethyl acetate (6.0 ml) was stirred at room temperature for 9 h in an atmosphere of hydrogen. After the usual work-up, the crude products were purified by column chromatography on silica gel (15 g), using ether–benzene (1:99) as the eluent, to give 2β-acetoxy-12-methoxyabieta-8,11,13-triene (**13**) (83 mg: 72%), whose IR and ^{1}H NMR spectra were identical with those of the authentic sample.[3]

Further elution with ether–benzene (5:95) gave **9** (21 mg: 17%).

*12-Methoxyabieta-8,11,13-trien-2β-ol (**14**).* A mixture of **13** (83 mg) and lithium aluminium hydride (10 mg) in dry tetrahydrofuran (2.0 ml) was stirred at room temperature for 1.5 h. The mixture was poured into dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (10 g), using ether–benzene (5:95) as the eluent, to give **14** (70 mg: 95%), whose IR and ^{1}H NMR spectra were identical with those of the authentic sample.[3]

*Oxidation of **8**.* A solution of **8** (978 mg) in acetone (20 ml) was oxidized with Jones reagent (2.5 M: 2.20 ml) at *ca.* 10 °C for 30 min and then at room temperature for 2 h. The mixture was diluted with water and extracted with ethyl acetate. The organic solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (100 g), using ether–benzene (3:97) as the eluent, to give the starting **8** (141 mg: 14%) and 2α-acetoxy-12-methoxy-5β*H*-abieta-8,11,13-trien-7-one (**15**) (541 mg: 53%), which was recrystallized from methanol. Mp 162.5—163 °C; IR: 1720, 1660 cm^{-1}; ^{1}H NMR: 0.68 (3H, s, $C_{4\alpha}-CH_3$), 1.03 (3H, s, $C_{4\beta}-CH_3$), 1.19 and 1.23 (each 3H, d, and J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.37 (3H, s, $C_{10}-CH_3$), 1.53 (3H, s, $-OCOCH_3$), 3.88 (3H, s, $-OCH_3$), 4.88 (1H, m, $W_{1/2}$=9 Hz, C_2–H), 6.65 (1H, s, C_{11}–H), 7.75 (1H, s, C_{14}–H). Found: C, 74.04; H, 8.73%. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66%.

Further elution with ether–benzene (5:95) gave 2α-acetoxy-12-methoxy-5β*H*-abieta-8,11,13-triene-6,7-dione (**16**), which was recrystallized from methanol. Mp 193—196 °C (changed the crystalline form at 140—145 °C); IR: 1725, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.79 (3H, s, $C_{4\alpha}-CH_3$), 1.02 (3H, s, $C_{4\beta}-CH_3$), 1.23 and 1.26 (each 3H, d, and J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.32 (3H, s, $C_{10}-CH_3$), 1.69 (3H, s, $-OCOCH_3$), 2.72 (1H, s, C_5–H), 3.96 (3H, s, $-OCH_3$), 5.10 (1H, m, $W_{1/2}$=8 Hz, C_2–H), 6.82 (1H, s, C_{11}–H), 7.99 (1H, s, C_{14}–H). Found: C, 71.51; H, 7.92%. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82%.

*2α-Acetoxy-6β-bromo-12-methoxy-5β*H*-abieta-8,11,13-trien-7-one (**17**).* A mixture of **15** (541 mg) and 80% pyridinium tribromide (610 mg) in dichloromethane (5.0 ml) was treated as described for the preparation of **11**. The crude product was purified by column chromatography on silica gel (70 g), using ether–benzene (3:97) as the eluent, to give **17** (639 mg: 93%), which was recrystallized from benzene. Mp 201—202 °C; IR: 1725, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.63 (3H, s, $C_{4\alpha}-CH_3$), 1.15 (3H, s, $C_{4\beta}-CH_3$), 1.19 and 1.24 (each 3H, d, and J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.68 (6H, s, $C_{10}-CH_3$ and $-OCOCH_3$), 2.47 (1H, s, C_5–H), 3.91 (3H, s, $-OCH_3$), 5.00 (1H, s, C_6–H), 5.03 (1H, m, $W_{1/2}$=7 Hz, C_2–H), 6.75 (1H, s, C_{11}–H), 7.92 (1H, s, C_{14}–H). Found: C, 61.26; H, 7.02%. Calcd for $C_{23}H_{31}O_4Br$: C, 61.20; H, 6.92%.

*2α-Acetoxy-12-methoxyabieta-5,8,11,13-tetraen-7-one (**18**).* A mixture of **17** (226 mg), lithium carbonate (111 mg), and lithium bromide (87 mg) in *N,N*-dimethylformamide (3.0 ml) was stirred at 120—130 °C for 1.5 h in a stream of nitrogen. After the same work-up as described for the preparation of **12**, the crude product was purified by column chromatography on silica gel (20 g), using ether–benzene (5:95) as the eluent, to give **18** (178 mg: 96%), which was recrystallized from ethanol. Mp 134—135 °C; IR: 1725, 1645 cm^{-1}; ^{1}H NMR: 1.22 and 1.26 (each 3H, d, and J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.32, 1.48, and 1.62 (each 3H and s, $-\overset{|}{C}(CH_3)_2$ and $C_{10}-CH_3$), 2.03 (3H, s, $-OCOCH_3$), 3.92 (3H, s, $-OCH_3$), 4.9—5.7 (1H, m, C_2–H), 6.29 (1H, s, C_6–H), 6.77 (1H, s, C_{11}–H), 7.84 (1H, s, C_{14}–H). Found: C, 74.52; H, 8.24%. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16%.

*Catalytic Hydrogenation of **18**.* A mixture of **18** (178 mg), 10% Pd–C (150 mg), and 70% perchloric acid (4 drops) in ethyl acetate (7.0 ml) was treated as described in the hydrogenation of **12**. The crude products were purified by column chromatography on silica gel (20 g), using benzene as the eluent, to give 2α-acetoxy-12-methoxyabieta-8,11,13-triene (**19**) (97 mg: 56%). IR: 1720 cm^{-1}; ^{1}H NMR: 1.06 (6H, s, $-\overset{|}{C}(CH_3)_2$), 1.17 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.29 (3H, s, $C_{10}-CH_3$), 2.03 (3H, s, $-OCOCH_3$), 3.79 (3H, s, $-OCH_3$), 4.8—5.4 (1H, m, C_2–H), 6.57 and 6.71 (each 1H and s, C_{11}–H and C_{14}–H). Further elution gave a mixture (*ca.* 1:1) of acetates (**19** and **8**) (48 mg: 28%) and pure **8** (18 mg: 11%).

*12-Methoxyabieta-8,11,13-trien-2-one (**4**).* A mixture of **19** (97 mg) and lithium aluminium hydride (10 mg) in dry tetrahydrofuran (2.0 ml) was stirred at room temperature for 1 h. After the same work-up as described for the preparation of **14**, the crude product was immediately oxidized with pyridinium chlorochromate (90 mg) in dichloromethane (2.0 ml) at room temperature for 1.5 h. The mixture was poured into aqueous sodium carbonate and extracted with ether. The ether extract was washed successively with brine, dilute hydrochloric acid, and brine. The dried extract was evaporated *in vacuo* to give a crude product, which was purified by column chromatography on silica gel (10 g), using ether–benzene (1:99) as the eluent, to give **4** (75 mg: 88%). The IR and ^{1}H NMR spectra of **4** were identical with those of the authentic sample.[3] Reduction[3] of **4** with lithium aluminium hydride in dry tetrahydrofuran gave **14**.

*2β,20-Epoxy-12-methoxyabieta-8,11,13-triene (**20**).* A mixture of **14** (250 mg), lead tetraacetate (90%: 390 mg), iodine (200 mg), and dry hexane (10 ml) was stirred at room temperature for 2 h and more lead tetraacetate (390 mg) was added. The mixture was stirred for an additional 4 h and diluted with ether. The organic solution was separated and washed successively with aqueous sodium hydrogencarbonate, aqueous sodium thiosulfate, and brine. The dried solution was evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (30 g), using ether–benzene (1:99) as the eluent, to afford **20** (126 mg: 51%), which was recrystallized from hexane. Mp 159—160 °C; ^{1}H NMR: 1.00 and 1.10 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.16 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.17 (1H, m, $-C\underline{H}(CH_3)_2$), 3.47 and 4.06 (each 1H, d, and J=9 Hz, $-OCH_2-$), 3.75 (3H, s, $-OCH_3$), 4.42 (1H, bt, J=5 Hz, C_2–H), 6.65 and 6.72 (each 1H and s, C_{11}–H and C_{14}–H). Found: C, 80.27; H, 9.72%. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62%.

*Ether Cleavage of **20**.* A mixture of **20** (145 mg) and acetyl *p*-toluenesulfonate (290 mg) in dichloromethane (2.0 ml) was stirred at room temperature for 2 h and then diluted with ether. The ether solution was washed successively with aqueous sodium carbonate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (15 g), using ether–benzene (1:99 and then 5:95) as the eluent, to give 20-acetoxy-12-methoxyabieta-2,8,11,13-tetraene (**21**) (137 mg: 83 %), which was recrystallized from methanol. Mp 116—117 °C; IR: 1727 cm^{-1}; ^{1}H NMR: 1.03 and 1.08 (each

3H and s, $-\overset{|}{C}(CH_3)_2$), 1.16 and 1.19 (each 3H, d, and $J=7$ Hz, $-CH(C\underline{H}_3)_2$), 1.90 (3H, s, $-OCOCH_3$), 3.79 (3H, s, $-OCH_3$), 4.27 (2H, bs, $-CH_2O-$), 5.55 (2H, m, C_2–H and C_3–H), 6.68 and 6.77 (each 1H and s, C_{11}–H and C_{14}–H). Found: C, 77.22; H, 9.10%. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05%.

Further elution gave 20-acetoxy-12-methoxy-2α-tosyloxyabieta-8,11,13-triene (**22**) (28 mg: 11%). IR: 1733 cm^{-1}; ^{1}H NMR: 0.96 and 0.99 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.16 (6H, bd, $-CH(C\underline{H}_3)_2$), 2.00 (3H, s, $-OCOCH_3$), 2.48 (3H, s, $-C_6H_4C\underline{H}_3$), 3.75 and 4.62 (each 1H, d, and $J=11$ Hz, $-CH_2O-$), 3.78 (3H, s, $-OCH_3$), 4.2—4.9 (1H, m, C_2–H), 6.55 and 6.75 (each 1H and s, C_{11}–H and C_{14}–H), 7.34 and 7.83 (each 2H, d, and $J=8$ Hz, $-C_6\underline{H}_4CH_3$).

*Conversion of **22** into **20**.* A mixture of **22** (59 mg), potassium carbonate (10 mg), methanol (3.0 ml), and water (2 drops) was refluxed for 2.5 h. The mixture was cooled, diluted with water, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was chromatographed on silica gel (5.0 g), using ether–benzene (1:99) as the eluent, to give **20** (24 mg: 69%).

*20-Acetoxy-12-methoxyabieta-8,11,13-triene (**23**).* A mixture of **21** (191 mg) and PtO_2 (20 mg) in ethanol (6.0 ml) was subjected to catalytic hydrogenation at room temperature for 70 min. After the usual work-up, the crude product was purified by column chromatography on silica gel (20 g), using ether–benzene (1:99) as the eluent, to give **23** (178 mg: 93%). IR: 1725 cm^{-1}; ^{1}H NMR: 1.00 (6H, s, $-\overset{|}{C}(CH_3)_2$), 1.14 and 1.17 (each 3H, d, and $J=7$ Hz, $-CH(C\underline{H}_3)_2$), 1.85 (3H, s, $-OCOCH_3$), 3.76 (3H, s, $-OCH_3$), 4.01 and 4.51 (each 1H, d, and $J=10$ Hz, $-CH_2O-$), 6.60 and 6.72 (each 1H and s, C_{11}–H and C_{14}–H). Found: C, 77.19; H, 9.58%. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56%.

*12-Methoxyabieta-8,11,13-trien-20-ol (**24**).* A mixture of **23** (178 mg) and lithium aluminium hydride (20 mg) in dry tetrahydrofuran (4.0 ml) was stirred at room temperature for 2.5 h. The mixture was poured into ice-dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (20 g), using ether–benzene (3:97) as the eluent, to give **24** (149 mg: 95%). IR: 3585 cm^{-1}; ^{1}H NMR: 0.98 (6H, s, $-\overset{|}{C}(CH_3)_2$), 1.18 (6H, d, $J=7$ Hz, $-CH(C\underline{H}_3)_2$), 3.53 and 3.80 (each 1H, d, and $J=11$ Hz, $-C\underline{H}_2OH$), 3.79 (3H, s, $-OCH_3$), 6.63 and 6.79 (each 1H and s, C_{11}–H and C_{14}–H).

*Methyl 12-Methoxy-7-oxoabieta-8,11,13-trien-20-oate (**25**).* Jones reagent (2.5 M: 1.1 ml) was added to a stirred solution of **24** (176 mg) in acetone (3.5 ml) at 5 °C. The mixture was stirred at this temperature for 30 min and then at room temperature for 1.5 h, diluted with water, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was methylated with diazomethane at room temperature. The crude product was purified by column chromatography on silica gel (20 g), using ether–benzene (1:99) as the eluent, to give **25** (80 mg: 40%), which was recrystallized from methanol. Mp 168.5—169 °C; IR: 1720, 1660 cm^{-1}; ^{1}H NMR: 0.83 and 0.98 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.20 and 1.25 (each 3H, d, and $J=7$ Hz, $-CH(C\underline{H}_3)_2$), 3.57 (3H, s, $-CO_2CH_3$), 3.89 (3H, s, $-OCH_3$), 6.70 (1H, s, C_{11}–H), 7.79 (1H, s, C_{14}–H). Found: C, 73.85; H, 8.72%. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44%.

*Methyl 12-Methoxyabieta-6,8,11,13-tetraen-20-oate (**26**).* A mixture of **25** (80 mg) and sodium borohydride (20 mg) in ethanol (2.0 ml) was stirred at room temperature for 4 h. The mixture was diluted with aqueous ammonium chloride and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was dissolved in dichloromethane (1.0 ml) and acetyl *p*-toluenesulfonate (140 mg) was added. The reaction mixture was stirred at room temperature for 30 min, diluted with aqueous sodium hydrogencarbonate, and extracted with ether. The ether extract was washed successively with aqueous sodium hydrogencarbonate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (10 g), using benzene as the eluent, to give **26** (55 mg: 71%), which was recrystallized from methanol. Mp 135—136 °C, IR: 1705 cm^{-1}; ^{1}H NMR: 0.85 and 1.03 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.16 and 1.19 (each 3H, d, and $J=7$ Hz, $-CH(C\underline{H}_3)_2$), 2.42 (1H, t, $J=3$ Hz, C_5–H), 3.43 (3H, s, $-CO_2CH_3$), 3.82 (3H, s, $-OCH_3$), 5.87 and 6.28 (each 1H, dd, and $J=3$, 9 Hz, C_6–H and C_7–H), 6.69 and 6.77 (each 1H and s, C_{11}–H and C_{14}–H). Found: C, 76.99; H, 9.06%. Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83%.

*Methyl 12-Methoxyabieta-8,11,13-trien-20-oate (**27**).* A mixture of **26** (23 mg) and PtO_2 (5.0 mg) in ethanol (6.0 ml) was subjected to catalytic hydrogenation at room temperature for 1.5 h. After the usual work-up, the crude product was purified by column chromatography on silica gel (Merck, 0.063—0.200 mm, 5.0 g), using benzene as the eluent, to give **27** (23 mg: 99%), which was recrystallized from methanol. Mp 111—112 °C, IR: 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.79 and 0.98 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.19 (6H, d, $J=7$ Hz, $-CH(C\underline{H}_3)_2$), 3.57 (3H, s, $-CO_2CH_3$), 3.76 (3H, s, $-OCH_3$), 6.74 and 6.88 (each 1H and s, C_{11}–H and C_{14}–H). Found: C, 76.43; H, 9.35%. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36%. The ^{1}H NMR spectrum of **27** was identical with that[1] of methyl pisiferate methyl ether.

*Pisiferic Acid (12-Hydroxyabieta-8,11,13-trien-20-oic Acid) (**1**).* A mixture of **27** (33 mg) and anhydrous aluminium bromide (250 mg) in ethanethiol (1.0 ml) was stirred at room temperature for 13 h. The mixture was poured into dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (Mallinckrodt, Silic AR CC-4, 5.0 g), using ether–benzene (1:9) as the eluent, to give **1** (28 mg: 93%), which was recrystallized from ether–hexane. Mp 226—227 °C (sublimed); IR: 3600, 3500—2400, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$: 90 MHz): 0.84 and 0.97 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.21 (6H, d, $J=7$ Hz, $-CH(C\underline{H}_3)_2$), 6.68 and 6.89 (each 1H and s, C_{11}–H and C_{14}–H). Found: C, 76.19; H, 9.19%. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92%. The IR and ^{1}H NMR spectra of the synthetic **1** were identical with those of natural pisiferic acid.

*Methyl Pisiferate (Methyl 12-Hydroxyabieta-8,11,13-trien-20-oate) (**2**).* A mixture of **27** (20 mg), anhydrous aluminium chloride (54 mg), ethanethiol (0.2 ml), and dichloromethane (1.0 ml) was stirred at 0—5 °C for 4 h. After the same work-up as described for the preparation of **1**, the crude product was chromatographed on silica gel (Merck, 0.063—0.200 mm, 5.0 g), using ether–benzene (5:95) as the eluent, to give **2** (19 mg: 97%), which was recrystallized from ether–hexane. Mp 170—171.5 °C; IR: 3610, 3350br, 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$: 90 MHz): 0.74 and 0.93 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.18 (6H, d, $J=7$ Hz, -CH-

$(C\underline{H}_3)_2)$, 3.12 (1H, m, $-C\underline{H}(CH_3)_2$), 3.53 (3H, s, $-CO_2CH_3$), 5.39 (1H, bs, –OH), 6.71 and 6.88 (each 1H and s, C_{11}–H and C_{14}–H). Found: C, 76.32; H, 9.36%. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15%. The IR and ^{1}H NMR spectra of the synthetic **2** were identical with those of natural methyl pisiferate.

20-Acetoxyabieta-8,11,13-trien-12-ol (28). A mixture of **23** (121 mg), anhydrous aluminium chloride (270 mg), ethanethiol (0.2 ml), and dichloromethane (2.0 ml) was stirred at 0—5 °C for 6.5 h. After the same work-up as described for the preparation of **1**, the crude product was purified by column chromatography on silica gel (15 g), using ether–benzene (5:95) as the eluent, to give **28** (87 mg: 74%); IR: 3610, 3375br, 1726 cm^{-1}; ^{1}H NMR: 0.99 (6H, s, $-\overset{|}{C}(CH_3)_2$), 1.21 (6H, d, $J=7$ Hz, $-CH(C\underline{H}_3)_2$), 1.85 (3H, s, $-OCOCH_3$), 4.10 and 4.50 (each 1H, d, and $J=11$ Hz, $-CH_2O-$), 5.85 (1H, s, –OH), 6.53 and 6.73 (each 1H and s, C_{11}–H and C_{14}–H).

Pisiferol (Abieta-8,11,13-triene-12,20-diol) (3). A mixture of **28** (87 mg) and lithium aluminium hydride (20 mg) in dry tetrahydrofuran (1.0 ml) was stirred at room temperature for 1 h. The mixture was poured into dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (10 g), using ether–benzene (1:9) as the eluent, to give **3** (67 mg: 88%), which was recrystallized from benzene. Mp 185—188 °C (softened at *ca.* 82 °C); IR: 3590, 3325br cm^{-1}; ^{1}H NMR ($CDCl_3$: 90 MHz): 0.91 and 0.93 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.22 (6H, d, $J=7$ Hz, $-CH(C\underline{H}_3)_2$), 3.17 (1H, m, $-C\underline{H}(CH_3)_2$), 3.61 and 3.97 (each 1H, d, and $J=11$ Hz, $-C\underline{H}_2OH$), 6.10 (1H, bs, –OH), 6.63 and 6.89 (each 1H and s, C_{11}–H and C_{14}–H). Found: C, 79.62; H, 10.23%. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00%. The IR and ^{1}H NMR spectra of the synthetic **3** were identical with those of natural pisiferol.

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