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The Total Synthesis of (±)-Pisiferin

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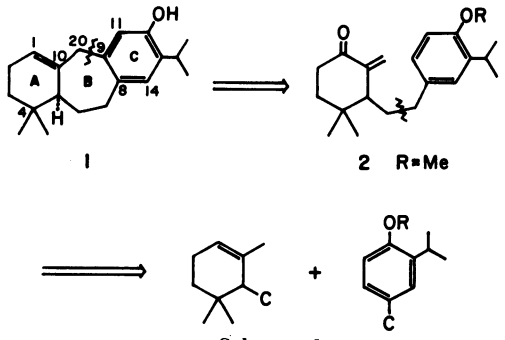
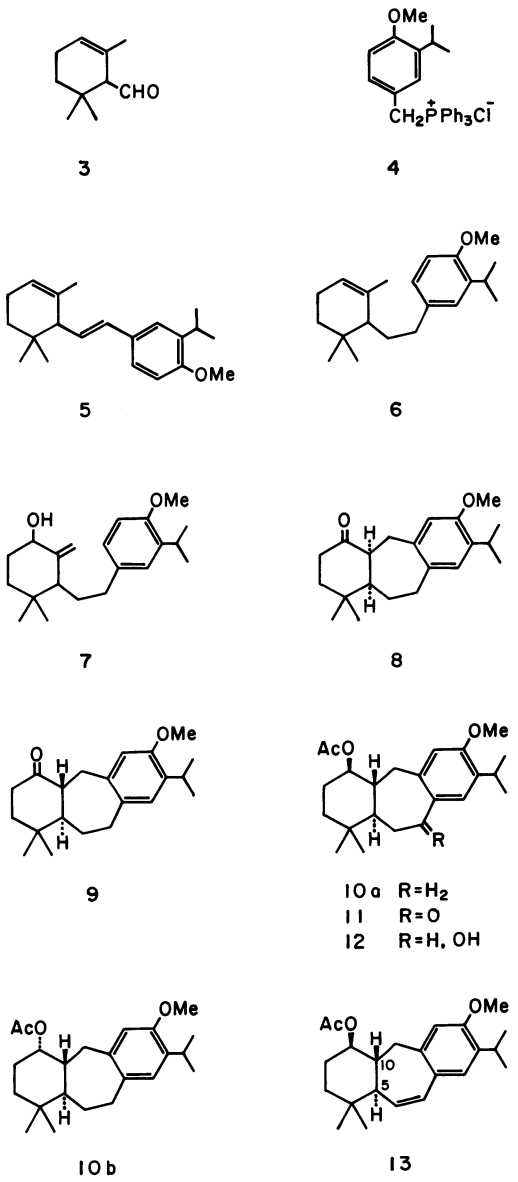
The conversion of racemic α-cyclocitral into 3-(3-isopropyl-4-methoxyphenethyl)-4,4-dimethyl-2-methylenecyclohexanone (**2**) was carried out in five steps via 3-(3-isopropyl-4-methoxyphenethyl)-2,4,4-trimethyl-1-cyclohexene. An intramolecular cyclization of **2** with polyphosphoric acid produced the corresponding two tricyclic ketones possessing *cis*- and *trans*-A/B ring junctions. Each of these ketones was further converted into 12-mesyloxy-9(10→20)-*abeo*-abieta-1(10),8,11,13-tetraene in four steps. The mesylate was reduced with lithium aluminium hydride to give (±)-pisiferin.

Pisiferin (**1**), a rare tricyclic diterpene phenol possessing a rearranged abietane skeleton, has been isolated from the leaves[1] and seeds[2] of *Chamaecyparis pisifera* (Cupressaceae). As a part of our synthetic studies in the naturally-occurring diterpenes, we have attempted a synthesis of pisiferin.[3] The synthetic strategy was developed from a retrosynthetic analysis of the natural product **1**, which involved the disconnection illustrated in Scheme 1. That is, two C_{10} units, including A and C rings of the natural compound, were first condensed to give a C_{20} unit which was converted into an α,β-unsaturated ketone (**2**). An intramolecular cyclization of **2** with acid led to the corresponding tricyclic ketone; this was then transformed into the natural compound.



Scheme 1.

The Wittig reaction[4] of racemic α-cyclocitral (**3**) with (3-isopropyl-4-methoxybenzyl)triphenylphosphonium chloride (**4**) in benzene in the presence of butyllithium gave 3-(3-isopropyl-4-methoxystyryl)-2,4,4-trimethyl-1-cyclohexene (**5**) in 75.3% yield. This was submitted to a partial catalytic hydrogenation to give the corresponding phenethyl derivative (**6**) in 86.3% yield. The oxidation of **6** with *m*-chloroperbenzoic acid in dichloromethane at room temperature afforded an epoxide which, without purification, was treated with lithium diethylamide[5,6] in refluxing hexane to give an alcohol (**7**) in 60.5% yield from **6**. The oxidation of **7** with pyridinium chlorochromate in dichloromethane at room temperature afforded the corresponding α,β-unsaturated ketone (**2**) in 89.1% yield. The IR spectrum of **2** showed a conjugated carbonyl band at 1693 cm^{-1} and its ^1H NMR spectrum showed two doublet signals at δ 4.91 (1H, J=2.5 Hz) and 5.69 (1H, J=2.5 Hz) due to an *exo*-methylene group. Intramolecular cyclization of **2** with polyphosphoric acid at 80—85 °C afforded two stereoisomers, **8** and **9**, in 73.2 and 17.4% yields, respectively. In order to determine the stereochemistry of the A/B ring junction in these tricyclic ketones, the following conversion was carried out. A reduction of the minor ketone **9** in ether with lithium aluminium hydride, followed by acetylation with acetic anhydride in pyridine, yielded a mixture of the C-1 epimeric acetates (**10a** and **10b**) in a ratio of ca. 7 : 3. The ^1H NMR spectrum of the mixture showed broad signals due to C-1 protons at δ 4.2—4.75 ($W_{1/2}$=19 Hz) for **10a** and at δ 5.10 ($W_{1/2}$=9 Hz) for **10b**, suggesting the presence of axial and equatorial C-1 protons, respectively. The crude mixture (**10a** and **10b**) in acetic acid was oxidized with chromium trioxide at room temperature to give a ketone (**11**) in 22.9% yield from **9**. The ^1H NMR spectrum of **11** showed a singlet signal due to a C-1 acetoxyl group at δ 2.18, a multiplet due to a C-1 proton at δ 4.35—4.75, and two singlets due to C-11 and C-14 aromatic protons at δ 6.46 and 7.60. The appearance of the C-14 proton signal in very low field (δ 7.60) suggested the presence of a carbonyl group at the C-7 position. The 7-oxo compound **11** was reduced with sodium borohydride in methanol to give a mixture of the C-7 epimeric alcohols (**12**), which was immediately dehydrated by refluxing with *p*-toluenesulfonic acid in benzene to give a tetraene derivative (**13**) in 97.8% yield from **11**. The ^1H NMR spectrum of **13** showed two double doublet signals due to the C-6 and C-7 olefinic protons at δ 5.78 (J=4 and 13 Hz) and 6.47 (J=2 and 13 Hz). When both olefinic proton signals at δ 5.78 and 6.47 were irradiated, the C-5 proton appeared at δ 1.88 as a doublet with a coupling constant of 12 Hz. The large coupling constant ($J_{5,10}$=12 Hz) indicated an axial-axial coupling and suggested that the relative configuration of the C-5 and C-10 protons in **13** is trans. Thus, the stereochemistries of the A/B ring junction in **8** and **9** were assigned to be cis and trans, respectively. A reduction of the major ketone **8** with lithium aluminium hydride afforded the C-1 epimeric alcohols, **14a** (82.2%) and **14b** (17.0%), which were converted into the corresponding acetates, **15a** and **15b**.

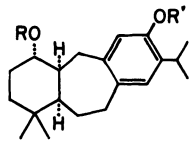


3 4 5 6 7 8 9 10a R=H2 11 R=O 12 R=H, OH 10b 13

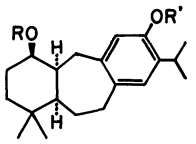
The stereochemistries of the acetoxyl groups in **15a** and **15b** were assigned, respectively, to be equatorial and axial conformations from their ^{1}H NMR spectra which showed signals due to the C-1 protons at δ 4.1—4.7 ($W_{1/2}$=19 Hz) and 5.09 ($W_{1/2}$=6 Hz). Thus, the conformations of the hydroxyl groups in **14a** and **14b** were also determined to be equatorial and axial, respectively. The *cis*-A/B-ring compound can exist in two A-ring chair conformations as shown in I and II. Of these two conformers, I is more stable than II because a 1,3-diaxial strain between the C-1 substituent (R=H, R'=OH or OAc) and the C-6 methylene group in I is fairly smaller than that between the C-4 methyl and the C-20 methylene groups in II. The other strains in the A-ring of both conformers are expected to be nearly equal. Thus, the *cis*-A/B-ring compound must exist in a preferred conformation I. From these considerations, the configurations of the hydroxyl groups in the C-1 epimeric alcohols were assigned to be an α disposition for **14a** and β for **14b**.

Mesylation of a mixture of **14a** and **14b** with mesyl chloride in pyridine at room temperature, followed by refluxing of the resulting mesylates (**16**) with 2,4-lutidine under a stream of nitrogen, produced a separable mixture of the disubstituted (**17**) and trisubstituted (**18**) olefins in 68.7% yield (ca. 2:9 ratio). A mixture of **17** and **18** was also obtained from a mixture of **14a** and **14b** by heating with hexamethylphosphoric triamide at 195—205 °C under a stream of nitrogen in 80.2% yield (ca. 5:8 ratio). Demethylation of **18** with anhydrous aluminium chloride and ethanethiol[7] in dichloromethane at room temperature provided only a dienone compound in 68.4% yield, but the desired pisiferin (**1**) could not be isolated. The dienone had the molecular formula $C_{20}H_{28}O$ based on the mass spectrum (M^+, m/z 284) and an elementary analysis. The IR spectrum indicated a conjugated carbonyl band at 1655 cm^{-1} but no hydroxyl band. The ^{1}H NMR spectrum showed signals at δ 0.95 (3H, singlet) and 1.03 (3H, singlet) due to a *gem*-dimethyl, at δ 1.06 (6H, doublet) and 2.98 (1H, multiplet) due to an isopropyl, and at δ 6.20 (1H, singlet) and 6.38 (1H, singlet) due to two olefinic protons. The ^{13}C NMR spectrum showed three singlet signals at δ 186.7, 176.1, 143.5, and two doublet signals at δ 147.2, 122.8 in the sp^2 carbon region, indicating the presence of a dienone moiety. The remaining fifteen carbons appeared in a δ 17—41 region as three singlets, two doublets, six triplets, and four quartets. From these spectral data the structure **19** was tentatively assigned to the dienone. Since the conversion of **18** into pisiferin (**1**) was unsuccessful, another synthetic route was examined. The alcohol **14a** was demethylated with anhydrous aluminium chloride and ethanethiol in dichloromethane to give a diol (**20a**) in 94.6% yield. On the other hand, a similar demethylation of **14b** gave only the dienone **19** in 90.3% yield. The expected diol **20b** corresponding to **20a** could not be isolated. These different results from demethylations of **14a** and **14b** can be explained as follows. The alcohol **14a** possessing an equatorial hydroxyl group was normally demethylated to give the expected diol **20a**, while under the same reaction conditions the epimer **14b** possessing an axial hydroxyl group was easily dehydrated by antiperiplanar elimination to give the trisubstituted olefin **18**. This was then demethylated and the resulting pisiferin (**1**) was further isomerized to the dienone **19**. Isomerization of **1** into **19** is described later. The diol **20a** was mesylated and the resulting dimesylate (**21**) was refluxed with 2,4-lutidine to give a mixture of the corresponding disubstituted (**22**) and trisubstituted (**23**) olefins in 87.1% yield (ca. 2:9 ratio), from which pure crystalline **23** was obtained by repeated column chromatography on silica gel and recrystallization. Treatment of **23** with lithium aluminium hydride in refluxing tetrahydrofuran afforded a phenolic compound (**1**) (98.4% yield) which gave an acetate (**24**). The ^{1}H NMR spectrum of the synthetic **1** was identical with that of natu-

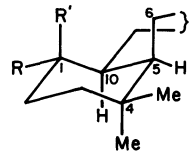
ral pisiferin. The synthetic **1** was further isomerized to the dienone **19** by a treatment with anhydrous aluminium chloride and ethanethiol at room temperature in 93.0% yield. Similarly, the *trans*-ketone **9** was also converted into a mixture of the corresponding mesylates, **25** and **23** in 40.7% yield (ca. 1 : 4 ratio) from **9**.



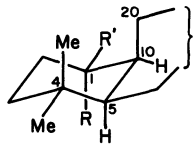
14a R=H, R'=Me
15a R=Ac, R'=Me
20a R=R'=H
21 R=R'=Ms



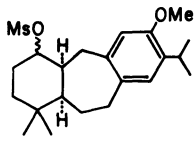
14b R=H, R'=Me
15b R=Ac, R'=Me
20b R=R'=H



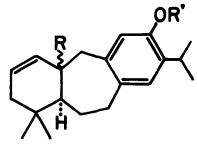
I



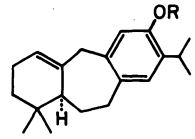
II



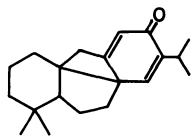
16



17 R=αH, R'=Me
22 R=αH, R'=Ms
25 R=βH, R'=Ms



18 R=Me
23 R=Ms
24 R=Ac



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Experimental

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

3-(3-Isopropyl-4-methoxyphenethyl)-2,4,4-trimethyl-1-cyclohexene (6). A solution of butyllithium in hexane (15%: 7.9 ml) was added at 7—9 °C to a suspension of (3-isopropyl-4-methoxybenzyl)triphenylphosphonium chloride (**4**) (5.816 g) in dry benzene (60 ml) under a stream of nitrogen. The mixture was stirred at 7—9 °C for 30 min and a solution of racemic α-cyclocitral[8] (**3**) (1.200 g) in dry benzene (2.0 ml) was added at 7—9 °C. After stirring at this temperature for 1 h and then at room temperature for 3 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 triturated with hexane (100 ml) and the precipitated triphenylphosphine oxide was removed by filtration. The filtrate was evaporated and the residue was chromatographed on silica gel (40 g), using hexane as the eluent, to give 3-(3-isopropyl-4-methoxystyryl)-2,4,4-trimethyl-1-cyclohexene (**5**) as an oil (1.772 g: 75.3%).

A suspension of **5** (5.124 g) and 10% Pd-C (1.30 g) in ethanol (55 ml) was stirred at room temperature in an atmosphere of hydrogen. After one equivalent of hydrogen had been absorbed, the mixture was filtered. The filtrate was evaporated and the residue was purified by column chromatography on silica gel (70 g), using hexane as the eluent, to give **6** as an oil (4.450 g: 86.3%). The IR and ^{1}H NMR spectra of **6** were identical with those of an authentic optically-active sample.[3]

3-(3-Isopropyl-4-methoxyphenethyl)-4,4-dimethyl-2-methylenecyclohexanol (7). A solution of **6** (4.111 g) and 80% *m*-chloroperbenzoic acid (2.951 g) in dichloromethane (105 ml) was stirred at room temperature for 1.5 h and then diluted with ether. The solution was washed successively with 10% aqueous potassium iodide, aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and brine. The dried solution was evaporated in vacuo to give a crude epoxide as an oil (4.530 g). ^{1}H NMR (CCl_4) δ=0.83 (3H, s) and 0.88 (3H, s) (-C(CH$_3$)$_2$), 1.21 (6H, d, J=7 Hz, -CH(CH$_3$)$_2$), 1.29 (3H, s, -O-CCH$_3$), 3.23 (1H, m, -CH(CH$_3$)$_2$), 3.78 (3H, s, -OCH$_3$).

A solution of the crude epoxide (4.530 g) in dry hexane (38 ml) was added at −50—−60 °C for 15 min to a stirred solution of lithium diethylamide which was prepared from butyllithium in hexane (15%: 42.8 ml) and diethylamine (7.1 ml) in dry hexane (40 ml) at −45—−60 °C for 30 min under a stream of nitrogen. The mixture was stirred at room temperature for 30 min, refluxed for 5 h, cooled, and then poured into aqueous ammonium chloride. The mixture was 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 (220 g), using ether-benzene (1 : 99) as the eluent, to give **7** as an oil (2.621 g: 60.5%); IR 3600, 3435, 1645 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.71 (3H, s) and 0.90 (3H, s) -C(CH$_3$)$_2$), 1.18 (6H, d, J= 7 Hz, -CH(CH$_3$)$_2$), 3.21 (1H, m, -CH(CH$_3$)$_2$), ca. 3.65—4.1 (1H, m, overlap, -CH(OH)-), 3.77 (3H, s, -OCH$_3$), 4.74 (1H, bs) and 5.17 (1H, bs) (-C=CH$_2$), 6.46—6.9 (3H, m, aromatic protons). Found: C, 79.98; H, 10.39%. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19%.

3-(3-Isopropyl-4-methoxyphenethyl)-4,4-dimethyl-2-methylenecyclohexanone (2). A solution of **7** (1.736 g) in dichloromethane (9.5 ml) was added to a stirred suspension of pyridinium chlorochromate (2.010 g) in dichloromethane (19.0 ml) at room temperature for 15 min. After stirring for 3 h, the mixture was poured into aqueous sodium carbonate (10%: 30 ml) 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 (60 g), using ether-benzene (1 : 99) as the eluent, to give **2** as an oil (1.537 g: 89.1%); IR 1693 cm^{-1}, ^{1}H NMR (CCl_4) δ=0.99 (3H, s) and 1.05 (3H, s) (-C(CH$_3$)$_2$), 1.18 (6H, d, J= 7 Hz, -CH(CH$_3$)$_2$), 3.22 (1H, m, -CH(CH$_3$)$_2$), 3.77 (3H, s,

$-OCH_3$), 4.91 (1H, d, J=2.5 Hz) and 5.69 (1H, d, J=2.5 Hz) ($-\underset{|}{C}=CH_2$), 6.48—6.9 (3H, m, aromatic protons). Found: C, 80.28; H, 9.86%. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62%.

Intramolecular Cyclization of 2. Polyphosphoric acid was prepared from 85% phosphoric acid (25 ml) and phosphorus pentaoxide (25 g) by heating at 100 °C for 2 h.

A stirred mixture of **2** (2.172 g) and polyphosphoric acid (32.6 ml) was heated at 80—85 °C for 1 h. After cooling, the mixture was 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 recrystallized from hexane to give 12-methoxy-9(10→20)-10α*H*-*abeo*-abieta-8,11,13-trien-1-one (**8**) (1.280 g: 58.9%), mp 155—156 °C; IR 1703 cm^{-1}, ^1H NMR (90 MHz, CCl_4) δ=0.98 (3H, s) and 1.01 (3H, s) ($-\underset{|}{C}(CH_3)_2$), 1.15 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.19 (1H, m, $-C\underline{H}(CH_3)_2$), 3.75 (3H, s, $-OCH_3$), 6.43 (1H, s, C_{11}-H), 6.84 (1H, s, C_{14}-H). Found: C, 80.41; H, 9.64%. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62%.

The mother liquor of recrystallization was evaporated in vacuo and the residue was chromatographed on silica gel (40 g), using benzene as the eluent, to give an additional **8** (0.310 g: 14.3%) and 12-methoxy-9(10→20)-*abeo*-abieta-8,11,13-trien-1-one (**9**) as an oil (0.378 g: 17.4%); IR 1702 cm^{-1}, ^1H NMR (CCl_4) δ=1.00 (3H, s) and 1.02 (3H, s) ($-\underset{|}{C}(CH_3)_2$), 1.14 (d, J=7 Hz) and 1.16 (d, J=7 Hz) (6H, $-CH(C\underline{H}_3)_2$), 3.75 (3H, s, $-OCH_3$), 6.54 (1H, s, C_{11}-H), 6.75 (1H, s, C_{14}-H).

1β-Acetoxy-12-methoxy-9(10→20)-*abeo*-abieta-8,11,13-trien-7-one (11). Lithium aluminium hydride (13 mg) was added to a stirred solution of **9** (70 mg) in dry ether (2.0 ml) with cooling in an ice-water bath. The mixture was stirred at room temperature for 1 h, 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 acetylated with acetic anhydride (0.5 ml) in pyridine (0.5 ml) at 75—80 °C for 2 h to give an oily mixture of the C-1 epimeric acetates (**10a** and **10b**) in a ratio of ca. 7:3. ^1H NMR of **10a** δ=0.76 (3H, s) and 0.94 (3H, s) ($-\underset{|}{C}(CH_3)_2$), 1.18 (d, J=7 Hz) and 1.20 (d, J=7 Hz) (6H, $-CH(C\underline{H}_3)_2$), 2.15 (3H, s, $-OCOCH_3$), 3.79 (3H, s, $-OCH_3$), 4.2—4.75 (1H, m, $W_{1/2}$=19 Hz, C_1-H), 6.52 (1H, s, C_{11}-H), 6.86 (1H, s, C_{14}-H). ^1H NMR of **10b** δ=0.76 (3H, s) and 0.98 (3H, s) ($-\underset{|}{C}(CH_3)_2$), 1.18 (d, J=7 Hz) and 1.20 (d, J=7 Hz), (6H, $-CH(C\underline{H}_3)_2$), 2.10 (3H, s, $-OCOCH_3$), 3.75 (3H, s, $-OCH_3$), 5.10 (1H, bs, $W_{1/2}$=9 Hz, C_1-H), 6.57 (1H, s, C_{11}-H), 6.86 (1H, s, C_{14}-H).

A stirred mixture of the C-1 epimeric acetates (**10a** and **10b**) was oxidized with chromium trioxide (43 mg) in acetic acid (2.0 ml) at room temperature for 5 h. The mixture was diluted with water and extracted with ether. The ether extract was washed successively with water, aqueous sodium hydrogencarbonate, and water. The dried solution was evaporated in vacuo. The residue was chromatographed on silica gel (10 g), using ether-benzene (2:98) as the eluent, to give **11** as an oil (19 mg: 22.9% from **9**); IR 1720, 1655 cm^{-1}; ^1H NMR, δ=0.92 (6H, s, $-\underset{|}{C}(CH_3)_2$), 1.21 (6H, bd, J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.18 (3H, s, $-OCOCH_3$), 3.86 (3H, s, $-OCH_3$), 4.35—4.75 (1H, m, C_1-H), 6.46 (1H, s, C_{11}-H), 7.60 (1H, s, C_{14}-H).

1β-Acetoxy-12-methoxy-9(10→20)-*abeo*-abieta-6,8,11,13-tetraene (13). Sodium borohydride (10 mg) was added to a stirred solution of **11** (19.0 mg) in methanol (2.0 ml) with cooling in a water bath. The solution was stirred at room temperature for 1 h, diluted with ether, poured into dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated in vacuo to give an oily mixture of the C-7 epimeric alcohols (**12**); IR 3600, 3410, 1720 cm^{-1}.

A mixture of the above crude **12** and *p*-toluenesulfonic acid (10 mg) in dry benzene (2.0 ml) was refluxed for 1 h. After cooling, the mixture was diluted with ether and the solution was washed with brine. The dried solution was evaporated in vacuo and the residue was chromatographed on silica gel (5.0 g), using benzene as the eluent, to give **13** as an oil (17.8 mg: 97.8% from **11**); IR 1720 cm^{-1}, ^1H NMR (90 MHz) δ=0.88 (3H, s) and 0.96 (3H, s) ($-\underset{|}{C}(CH_3)_2$), 1.18 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.10 (3H, s, $-OCOCH_3$), 3.25 (1H, m, $-C\underline{H}(CH_3)_2$), 3.80 (3H, s, $-OCH_3$), 4.45—4.8 (1H, m, C_1-H), 5.78 (1H, dd, J=13 and 4 Hz, C_6-H), 6.47 (1H, dd, J=13 and 2 Hz, C_7-H), 6.52 (1H, s, C_{11}-H), 6.92 (1H, s, C_{14}-H).

12-Methoxy-9(10→20)-10α*H*-*abeo*-abieta-8,11,13-trien-1α-ol (14a) and Its C-1 Epimer (14b). Lithium aluminium hydride (69.4 mg) was added to a stirred solution of **8** (1.150 g) in dry ether (50 ml) with cooling in an ice-water bath. The mixture was stirred at room temperature for 1 h, poured into ice-dilute hydrochloric acid, and extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated in vacuo. The residue was recrystallized from acetone-hexane to give **14a** (813 mg: 70.3%), mp 151—151.5 °C; IR 3600, 3430 cm^{-1}; ^1H NMR δ=0.75 (3H, s) and 0.94 (3H, s) ($-\underset{|}{C}(CH_3)_2$), 1.18 (d, J=7 Hz) and 1.20 (d, J=7 Hz) (6H, $-CH(C\underline{H}_3)_2$), 3.78 (3H, s, $-OCH_3$), 6.58 (1H, s, C_{11}-H), 6.99 (1H, s, C_{14}-H). Found: C, 79.59; H, 10.41%. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19%.

The mother liquor of recrystallization was evaporated in vacuo and the residue was repeatedly chromatographed on silica gel, using benzene as the eluent, to give an additional **14a** (138 mg: 11.9%) and **14b** as an oil (196 mg: 17.0%); IR 3620, 3440 cm^{-1}; ^1H NMR δ=0.72 (3H, s) and 0.98 (3H, s) ($-\underset{|}{C}(CH_3)_2$), 1.17 (d, J=7 Hz) and 1.20 (d, J=7 Hz) (6H, $-CH(C\underline{H}_3)_2$), 3.78 (3H, s, $-OCH_3$), 3.91 (1H, br, $W_{1/2}$=9 Hz, C_1-H), 6.54 (1H, s, C_{11}-H), 6.89 (1H, s, C_{14}-H).

Acetylation of 14a and 14b. a): The alcohol **14a** (100 mg) was acetylated with acetic anhydride (1.0 ml) in pyridine (1.0 ml) at 75—80 °C for 2 h to give a crude acetate (**15a**); IR 1718 cm^{-1}, ^1H NMR δ=0.77 (3H, s) and 0.96 (3H, s) ($-\underset{|}{C}(CH_3)_2$), 1.19 (d, J=7 Hz) and 1.21 (d, J=7 Hz) (6H, $-CH(C\underline{H}_3)_2$), 2.18 (3H, s, $-OCOCH_3$), 3.23 (1H, m, $-C\underline{H}(CH_3)_2$), 3.80 (3H, s, $-OCH_3$), 4.1—4.7 (1H, m, $W_{1/2}$=19 Hz, C_1-H), 6.58 (1H, s, C_{11}-H), 6.84 (1H, s, C_{14}-H).

b): The alcohol **14b** was acetylated with acetic anhydride in pyridine to give a crude acetate (**15b**); IR 1718 cm^{-1}, ^1H NMR δ=0.73 (3H, s) and 1.00 (3H, s) ($-\underset{|}{C}(CH_3)_2$), 1.15 (d, J=7 Hz) and 1.18 (d, J=7 Hz) (6H, $-CH(C\underline{H}_3)_2$), 2.11 (3H, s, $-OCOCH_3$), 3.78 (3H, s, $-OCH_3$), 5.09 (1H, bs, $W_{1/2}$=6 Hz, C_1-H), 6.52 (1H, s, C_{11}-H), 6.85 (1H, s, C_{14}-H).

12-Methoxy-9(10→20)-10α*H*-*abeo*-abieta-1,8,11,13-tetraene (17) and 12-Methoxy-9(10→20)-*abeo*-abieta-1(10),8,11,13-tetraene (Pisiferin Methyl Ether) (18). a): A mixture of **14a** and **14b** (100.7 mg) was mesylated with mesyl chloride (0.10 ml) in pyridine (0.7 ml) at room temperature for 3.5 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 to give a crude mesylate (**16**) (129 mg).

The crude **16** (129 mg) in 2,4-lutidine (0.7 ml) was refluxed for 2.5 h under a stream of nitrogen. The mixture was cooled, poured into dilute hydrochloric acid, and extracted with ether. The ether extract was washed successively with dilute hydrochloric acid, aqueous sodium hydrogencarbonate, and brine. The dried solution was evaporated in vacuo and the residue was repeatedly chromatographed on silica gel, using hexane as the eluent, to give two oily products, **17** (12.0 mg: 12.6%) and **18** (53.2 mg: 56.1%). ^{1}H NMR (90 MHz) of **17** δ=0.73 (3H, s) and 0.94 (3H, s) (-C(CH$_3$)$_2$), 1.18 (d, J=7 Hz) and 1.20 (d, J=7 Hz) (6H, -CH(CH$_3$)$_2$), 3.28 (1H, m, -CH(CH$_3$)$_2$), 3.79 (3H, s, -OCH$_3$), 5.4—5.7 (2H, m, C$_1$-H and C$_2$-H), 6.61 (1H, s, C$_{11}$-H), 6.96 (1H, s, C$_{14}$-H). ^{1}H NMR (90 MHz) of **18** δ=0.88 (3H, s) and 0.92 (3H, s) (-C(CH$_3$)$_2$), 1.18 (d, J=7 Hz) and 1.20 (d, J=7 Hz)(6H, -CH(CH$_3$)$_2$), 3.23 (1H, m, -CH(CH$_3$)$_2$), 3.30 (2H, s, C$_{20}$-H$_2$), 5.43 (1H, t, J=4 Hz, C$_1$-H), 6.60 (1H, s, C$_{11}$-H), 6.90 (1H, s, C$_{14}$-H).

b): A mixture of **14a** and **14b** (400 mg) was heated with hexamethylphosphoric triamide (4.0 ml) at 195—205 °C for 1 h under a stream of nitrogen. The solution was cooled, 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 (100 g), using hexane as the eluent, to give an oily mixture of **17** and **18** (302 mg: 80.2%) in a ratio of ca. 5 : 8.

Demethylation of 18. Anhydrous aluminium chloride (13.3 mg) was added to a stirred solution of **18** (10.0 mg) and ethanethiol (0.015 ml) in dichloromethane (0.5 ml) with cooling in an ice-water bath. The mixture was stirred at room temperature for 4 h, 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 chromatographed on silica gel (10 g), using ether-benzene (1 : 99) as the eluent, to give a dienone (**19**) (6.5 mg: 68.4%) as a solid, whose IR and ^{1}H NMR spectra were identical with those of the authentic sample (vide infra).

Demethylation of 14a and 14b. a): A solution of **14a** (597.0 mg) in dichloromethane (8.0 ml) was demethylated with anhydrous aluminium chloride (754.6 mg) and ethanethiol (0.85 ml) at room temperature for 4 h. After the work-up as described above, the crude product was recrystallized from acetone-hexane to give a diol (**20a**) (510.0 mg: 89.4%), mp 183.5—184.5 °C; IR 3600, 3360 cm^{-1}; ^{1}H NMR δ=0.75 3H, s) and 0.93 (3H, s) (-C(CH$_3$)$_2$), 1.24 (6H, d, J=7 Hz, -CH(CH$_3$)$_2$), 4.89 (1H, bs, -OH), 6.50 (1H, s, C$_{11}$-H), 7.00 (1H, s, C$_{14}$-H). Found: C, 79.48; H, 10.30%. Calcd for C$_{20}$H$_{30}$O$_2$: C, 79.42; H, 10.00%. The mother liquor of recrystallization was evaporated in vacuo and the residue was chromatographed on silica gel (20 g), using ether-benzene (5 : 95) as the eluent, to give an additional **20a** (27.9 mg: 5.2%).

b): A solution of **14b** (111.0 mg) in dichloromethane (2.1 ml) was demethylated with anhydrous aluminium chloride (139.8 mg) and ethanethiol (0.15 ml) at room temperature for 4 h. After the work-up as described above, the crude product was chromatographed on silica gel (10 g), using ether-benzene (5 : 95) as the eluent, to give a dienone (**19**) (90.1 mg: 90.3%), which was recrystallized from hexane, mp 107—109 °C; IR 1655 cm^{-1}, UV λ_{max}^{EtOH}: 255 nm (ε 15300). ^{1}H NMR (90 MHz) δ=0.95 (3H, s) and 1.03 (3H, s) (-C(CH$_3$)$_2$), 1.06 (6H, d, J=7 Hz, -CH(CH$_3$)$_2$), 2.98 (1H, m, -CH(CH$_3$)$_2$), 6.20 (1H, s, C$_{11}$-H), 6.38 (1H, bs, C$_{14}$-H). ^{13}C NMR ($CDCl_3$) δ=17.6 (t), 20.0 (q), 21.9 (q), 21.9 (q), 24.1 (q), 25.9 (d), 27.7 (t), 30.5 (t), 31.0 (t), 34.7 (s), 35.8 (t), 35.8 (t), 37.2 (d), 39.7 (s), 40.4 (s), 122.8 (d), 143.5 (s), 147.2 (d), 176.1 (s), 186.7 (s); MS m/z 284 (M$^+$). Found: C, 84.39; H, 10.04%. Calcd for C$_{20}$H$_{28}$O: C, 84.45; H, 9.92%.

12-Mesyloxy-9(10→20)-10α*H*-*abeo*-abieta-1,8,11,13-tetraene (22) and 12-Mesyloxy-9(10→20)-*abeo*-abieta-1(10),8,11,13-tetraene (23). a): A mixture of **20a** (102.0 mg) and mesyl chloride (0.08 ml) in pyridine (1.0 ml) was allowed to stand at room temperature for 16.5 h and then diluted with ether. The ether solution was washed successively with dilute hydrochloric acid and brine. The dried solution was evaporated in vacuo to give a crude dimesylate (**21**) (130 mg) which was used, without purification, in the next reaction. ^{1}H NMR δ=0.79 (3H, s) and 0.96 (3H, s) (-C(CH$_3$)$_2$), 1.23 (d, J=7 Hz) and 1.25 (d, J=7 Hz) (6H, -CH(CH$_3$)$_2$), 3.12 (3H, s) and 3.19 (3H, s) (2-OSO$_2$CH$_3$), 4.1—4.6 (1H, m, C$_1$-H), 7.03 (1H, s) and 7.10 (1H, s) (C$_{11}$-H and C$_{14}$-H).

b): A solution of the crude **21** (130 mg) in 2,4-lutidine (1.5 ml) was refluxed for 2.5 h under a stream of nitrogen. The solution was cooled, diluted with ether, and washed successively with dilute hydrochloric acid and brine. The dried solution was evaporated in vacuo and the residue was purified by repeated column chromatography on silica gel and recrystallization from methanol to give **22** (18.6 mg: 15.2%) as an oil and **23** (87.9 mg: 71.9%) as a crystalline, mp 138—140 °C. ^{1}H NMR (90 MHz) of **22** δ=0.73 (3H, s) and 0.95 (3H, s) (-C(CH$_3$)$_2$), 1.21 (d, J=7 Hz) and 1.23 (d, J=7 Hz) (6H, -CH(CH$_3$)$_2$), 3.16 (3H, s, -OSO$_2$CH$_3$), 5.5—5.7 (2H, m, C$_1$-H and C$_2$-H), 7.02 (1H, s) and 7.08 (1H, s) (C$_{11}$-H and C$_{14}$-H). ^{1}H NMR (90 MHz) of **23** δ=0.88 (3H, s) and 0.92 (3H, s) (-C(CH$_3$)$_2$), 1.21 (d, J=7 Hz) and 1.23 (d, J=7 Hz) (6H, -CH(CH$_3$)$_2$), 2.7—2.9 (2H, m, C$_7$-H$_2$), 3.16 (3H, s, -OSO$_2$CH$_3$), 3.25 (1H, m, -CH(CH$_3$)$_2$), 3.31 (2H, s, C$_{20}$-H$_2$), 5.43 (1H, t, J=4 Hz, C$_1$-H), 7.00 (1H, s) and 7.02 (1H, s) (C$_{11}$-H and C$_{14}$-H). Found: C, 69.61; H, 8.21%. Calcd for C$_{21}$H$_{30}$O$_3$S: C, 69.57; H, 8.34%.

(±)-Pisiferin (1). A solution of **23** (23.4 mg) in dry tetrahydrofuran (2.0 ml) was reduced with lithium aluminium hydride (9.8 mg) by refluxing 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 chromatographed on silica gel (5.0 g), using benzene as the eluent, to give **1** as an oil (18.1 mg: 98.4%); IR 3600, 3350 cm^{-1}; ^{1}H NMR (90 MHz) δ=0.88 (3H, s) and 0.91 (3H, s) (-C(CH$_3$)$_2$), 1.22 (d, J=7 Hz) and 1.24 (d, J=7 Hz) (6H, -CH(CH$_3$)$_2$), 2.74 (2H, m, C$_7$-H$_2$), 3.12 (1H, m, -CH(CH$_3$)$_2$), 3.27 (2H, s, C$_{20}$-H$_2$), 4.46 (1H, s, -OH), 5.41 (1H, t, J=4 Hz, C$_1$-H), 6.48 (1H, s, C$_{11}$-H), 6.88 (1H, s, C$_{14}$-H). The ^{1}H NMR spectrum of **1** was identical with that of natural pisiferin. MS m/z 284 (M$^+$).

Acetylation of 1. A solution of **1** (11.8 mg) and acetic anhydride (0.5 ml) in pyridine (0.5 ml) was heated at 75—80 °C for 2 h. After the usual work-up, the crude product was chromatographed on silica gel (5.0 g), using benzene as the eluent, to give an acetate (**24**) as an oil (12.2 mg: 90.4%), IR 1753 cm^{-1}, MS m/z 326 (M$^+$), ^{1}H NMR (90 MHz) δ=0.87 (3H, s) and 0.91 (3H, s) (-C(CH$_3$)$_2$), 1.18 (d, J=7 Hz) and 1.20 (d, J=7 Hz) (6H, -CH(CH$_3$)$_2$), 2.27 (3H, s, -OCOCH$_3$), 3.30 (2H, s, C$_{20}$-H$_2$), 5.42 (1H, t, J=4 Hz, C$_1$-H), 6.70 (1H, s, C$_{11}$-H), 6.98 (1H, s, C$_{14}$-H).

Conversion of 1 into 19. A solution of **1** (43.0 mg) and ethanethiol (0.07 ml) in dichloromethane (2.8 ml) was treated with anhydrous aluminium chloride (60.4 mg) at room temperature for 4 h. After the work-up as described above, the crude product was chromatographed on silica gel (10 g), using ether-benzene (5 : 95) as the eluent, to give **19** (40.0 mg: 93.0%), whose IR and ^{1}H NMR spectra were identical with those of the authentic sample.

Conversion of 9 into 23 and 12-Mesyloxy-9(10→20)-*abeo*-abieta-1,8,11,13-tetraene (25). The ketone **9** (261.1 mg) in dry ether (5.0 ml) was reduced with lithium aluminium hydride (15.8 mg) at room temperature for 1 h to give a mixture of the C-1 epimeric alcohols (240 mg).

A solution of the above crude alcohols (240 mg) and ethanethiol (0.37 ml) in dichloromethane (4.0 ml) was treated with anhydrous aluminium chloride (332.1 mg) at room temperature for 4 h. The crude product (235 mg) was immediately mesylated with mesyl chloride (0.2 ml) in pyridine (1.0 ml) at room temperature for 16 h and the resulting crude mesylate was refluxed with 2,4-lutidine (2.0 ml) for 2.5 h under a stream of nitrogen. After the work-up as described above, the crude product was chromatographed on silica gel (20 g), using hexane-benzene (1 : 1) as the eluent, to give a mixture of **23** and **25** (122.4 mg: 40.7% from **9**) in a ratio of ca. 4 : 1.

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