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The Total Synthesis of (15*R*)- and (15*S*)-16-Hydroxyferruginol

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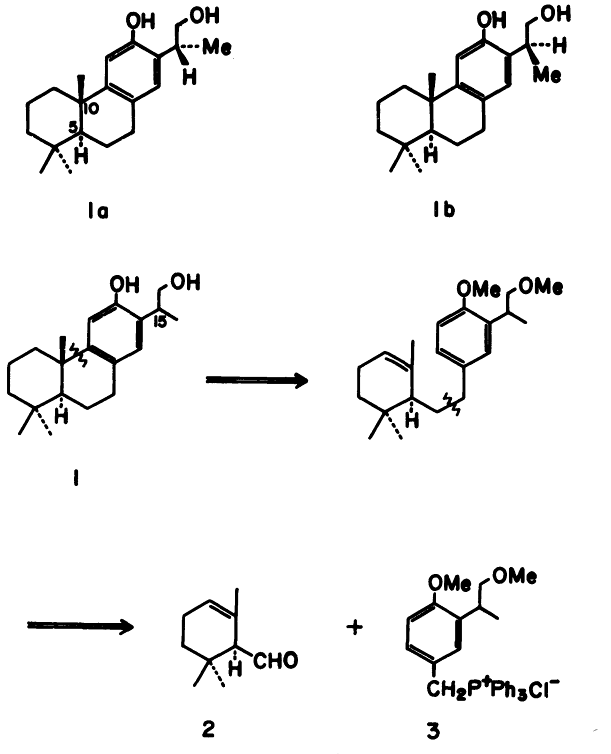
In order to assign the absolute configuration of C-15 in natural 16-hydroxyferruginol, (5*S*,10*S*,15*R*)- (**1a**) and (5*S*,10*S*,15*S*)-8,11,13-abietatriene-12,16-diol (**1b**) have been synthesized. Optical resolution of 2-(2-methoxyphenyl)propanoic acid, prepared from methyl (2-methoxyphenyl)acetate, with cinchonidine afforded (*R*)- and (*S*)-enantiomers, which were converted into [(*R*)-4-methoxy-3-(2-methoxy-1-methylethyl)benzyl]triphenylphosphonium chloride (**3a**) and its (*S*)-isomer (**3b**) respectively. The Wittig reaction of (*R*)-(−)-α-cyclocitral with **3a**, followed by partial catalytic hydrogenation and intramolecular cyclization gave (5*S*,10*S*,15*R*)-12,16-dimethoxy-8,11,13-abietatriene (**16a**) together with its (5*S*,10*R*,15*R*)-isomer. Similarly, **3b** was also converted into (5*S*,10*S*,15*S*)-12,16-dimethoxy-8,11,13-abietatriene (**16b**) and its (5*S*,10*R*,15*S*)-isomer. Demethylation of **16a** gave **1a** which was identical with natural 16-hydroxyferruginol. The dimethoxy compound **16b** was also demethylated to give **1b**.

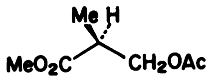
16-Hydroxyferruginol (**1**), a new tricyclic diterpene phenol possessing an abietane skeleton, has recently been isolated from the seed of *Thujopsis dolabrata* Sieb. et Zucc. var. *dolabrata* by Hasegawa and Hirose.[1] The structure **1** was elucidated by spectroscopic studies and by chemical transformation to the known (+)-ferruginol methyl ether. However, the absolute configuration at C-15 remained unsettled. In order to elucidate the unknown stereochemistry at C-15, we have attempted the total syntheses of (15*R*)-(**1a**) and (15*S*)-16-hydroxyferruginol (**1b**). The synthetic strategy was developed from the retrosynthetic analysis of the natural product (**1**), which involved the disconnection illustrated in Scheme 1.



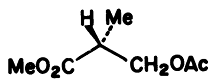
Scheme 1.

First, the optically active [4-methoxy-3-(2-methoxy-1-methylethyl)benzyl]triphenylphosphonium chloride (**3**) was prepared starting from methyl (2-methoxyphenyl)acetate (**4**) in the following manner. Methylation of **4** with methyl iodide in hexamethylphosphoric triamide and tetrahydrofuran in the presence of potassium *t*-butoxide afforded methyl 2-(2-methoxyphenyl)propanoate (**5**) which was hydrolyzed with aqueous sodium hydroxide in refluxing methanol to give the corresponding racemic acid (**6**). The racemic acid **6** was then resolved by means of cinchonidine to give (−)-acid (**6a**) and (+)-acid (**6b**), which were methylated with diazomethane to give the methyl esters, **5a** and **5b** respectively. Reduction of **5a** and **5b** with lithium aluminium hydride gave the corresponding alcohols, **7a** and **7b**. The absolute configurations of **7a** and **7b** were determined by the following correlation. Acetylation of **7a** with acetic anhydride in pyridine, followed by demethylation of the resulting acetate (**8a**) with anhydrous aluminium chloride and ethanethiol[2] in dichloromethane, afforded the phenolic compound (**9a**). This was then submitted to ozonization and the resulting acid was methylated with diazomethane to give the known methyl (*S*)-(+)-3-acetoxy-2-methylpropanoate[3] (**10a**). Similarly, the alcohol **7b** was correlated to methyl (*R*)-(−)-3-acetoxy-2-methylpropanoate (**10b**) *via* the corresponding acetate (**8b**) and phenol (**9b**). Thus, the absolute configurations of **7a** and **7b** were assigned to *R* and *S* respectively. The alcohols, **7a** and **7b**, were methylated respectively with methyl iodide and sodium hydride in 1,2-dimethoxyethane to give the dimethoxy compounds, **11a** and **11b**. Chloromethylation of **11a** with chloromethyl methyl ether in acetic acid, followed by treatment of the resulting benzyl chloride derivative (**12a**) with triphenylphosphine in refluxing benzene produced the desired [(*R*)-4-methoxy-3-(2-methoxy-1-methylethyl)benzyl]triphenylphosphonium chloride (**3a**). The dimethoxy compound **11b** was also converted into the corresponding (*S*)-isomer (**3b**) *via* the benzyl chloride derivative (**12b**).

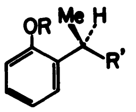
4 R=H, R'=Me
5 R=R'=Me
6 R=Me, R'=H

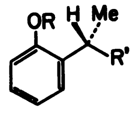


10a

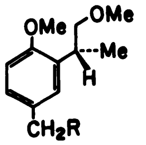


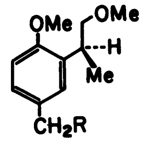
10b





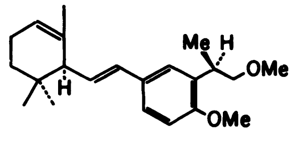
5a	R=Me, R'=CO_2Me	5b
6a	R=Me, R'=CO_2H	6b
7a	R=Me, R'=CH_2OH	7b
8a	R=Me, R'=CH_2OAc	8b
9a	R=H, R'=CH_2OAc	9b
11a	R=Me, R'=CH_2OMe	11b



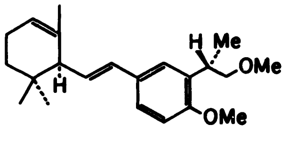


3a	R=$P^+Ph_3Cl^-$	3b
12a	R=Cl	12b

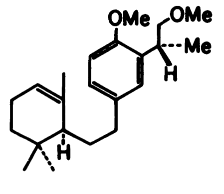
The Wittig reaction of (*R*)-(−)-α-cyclocitral (**2**)[4,5] with **3a** in benzene in the presence of butyllithium gave 6-[4-methoxy-3-(2-methoxy-1-methylethyl)styryl]-1,5,5-trimethylcyclohexene (**13a**) in 56.1% yield. The ^1H NMR spectrum of **13a** showed signals at δ 5.76 (double doublet, *J*=8.5 and 15 Hz) and 6.25 (doublet, *J*=15 Hz) due to the newly formed olefinic protons. These vicinal coupling constants (*J*=15 Hz) suggested the presence of a *trans*-disubstituted double bond in **13a**. The compound **13a** in ethanol was submitted to partial catalytic hydrogenation over Pd–C to afford the corresponding phenethyl derivative (**14a**: 94.1%). The intramolecular cyclization of **14a** with anhydrous aluminium chloride in benzene afforded (5*S*, 10*S*, 15*R*)-12,16-dimethoxy-8,11,13-abietatriene (**16a**: 49.0%) $[\alpha]_D$ +35.0° ($CHCl_3$) and its (5*S*,10*R*,15*R*)-isomer (**15a**: 35.3%). The *cis*-configuration of the A/B ring junction in **15a** was supported by its ^1H NMR spectrum which showed a signal due to the $C_{4\beta}$-methyl group at high field (δ 0.48) owing to the shielding effect of the aromatic C-ring. The Wittig reaction of **2** with **3b**, followed by partial catalytic hydrogenation of the resulting styryl derivative (**13b**: 54.9%) afforded the phenethyl derivative (**14b**: 89.4%). The intramolecular



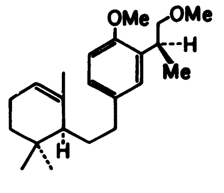
13a



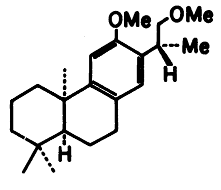
13b



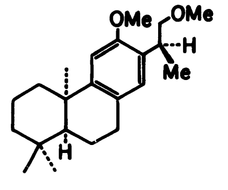
14a



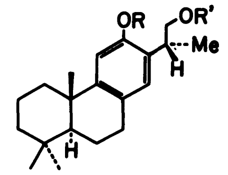
14b

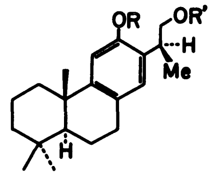


15a

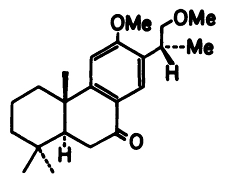


15b

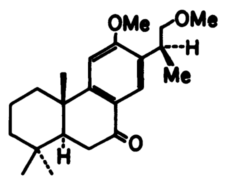




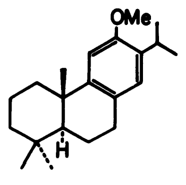
16a	R=R'=Me	16b
18a	R=R'=Ac	18b
19a	R=Me, R'=H	19b
20a	R=Me, R'=Ts	20b



17a



17b



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cyclization of **14b** with anhydrous aluminium chloride produced (5*S*,10*S*,15*S*)-12,16-dimethoxy-8,11,13-abietatriene (**16b**: 50.8%) $[\alpha]_D$ +60.4° ($CHCl_3$) together with its (5*S*,10*R*,15*S*)-isomer (**15b**: 40.5%). In order to increase the optical purity, the cyclization products (**16a** and **16b**) were oxidized with Jones reagent to give the crystalline 7-oxo derivatives, **17a** and **17b**. After recrystallization, **17a** and **17b** were converted into **16a** $[\alpha]_D$ +46.7° ($CHCl_3$) and **16b** $[\alpha]_D$ +68.7° ($CHCl_3$) by catalytic hydrogenation over Pd–C in the presence of perchloric acid. Demethylation of **16a** in dichloromethane with anhydrous aluminium chloride and sodium iodide in acetonitrile[6] at 35—40 °C under a stream of nitrogen afforded (5*S*,10*S*,15*R*)-8,11,13-abietatriene-12,16-diol (**1a**: 95.7%), mp 141—142.5 °C, $[\alpha]_D$ +65.7° ($CHCl_3$), which was identical with natural 16-hydroxyferruginol (lit,[1] mp 141—142 °C, $[\alpha]_D$ +36.6° ($CHCl_3$)). Similarly, the dimethoxy compound **16b** was also demethylated to give (5*S*,10*S*,15*S*)-8,11,13-abietatriene-12,16-diol (**1b**: 95.5%), mp 178—179 °C, $[\alpha]_D$ +44.6° ($CHCl_3$). Acetylation of **1a** and **1b** with acetic anhydride in pyridine gave the corresponding diacetates, **18a** and **18b**. Since the optical rotation value of the synthetic **1a** was somewhat larger than that reported for the natural product, the absolute configurations at C-5 and C-10 in **1a** and **1b** were subsequently confirmed by the following conversion. Methylation of **1a** with methyl iodide and anhydrous potassium carbonate in refluxing ethyl methyl ketone yielded 12-methoxy-8,11,13-abietatrien-16-ol (**19a**), which was converted into a tosylate[1] (**20a**). Reduction of **20a** with lithium aluminium hydride in ether afforded (+)-ferruginol methyl ether (**21**) $[\alpha]_D$ +63.3° ($CHCl_3$) (lit,[7] $[\alpha]_D$ +63.1° ($CHCl_3$)). The diol **1b** was also converted into **21** *via* the corresponding methyl ether (**19b**) and tosylate (**20b**).

From the above synthesis the absolute configuration of natural 16-hydroxyferruginol was conclusively assigned as 5*S*, 10*S*, 15*R*.

Experimental

All melting points are uncorrected. The IR spectra and optical rotations 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; s: singlet, bs: broad singlet, d: doublet, dd: double doublet, m: multiplet. The column chromatography was performed using Merck silica gel (0.063 mm).

Methyl (±)-2-(2-Methoxyphenyl)propanoate (5). (2-Methoxyphenyl)acetic acid in ether was methylated with diazomethane to give a methyl ester (**4**).

To a solution of **4** (25.00 g) and hexamethylphosphoric triamide (25.0 ml) in dry tetrahydrofuran (300 ml) under a stream of nitrogen at −40—−30 °C was added potassium *t*-butoxide (15.57 g) over a 5 min period and then methyl iodide (8.70 ml) over a 20 min period. The mixture was stirred at −40—−30 °C for 30 min, poured into dilute hydrochloric acid, and extracted with ether. The ether extract was washed successively with aqueous sodium thiosulfate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (300 g), using benzene as eluent, to give **5** (24.31 g: 93.7%). Found: C, 67.73; H, 7.36%. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27%.

(±)-2-(2-Methoxyphenyl)propanoic Acid (6). A mixture of **5** (2.58 g) and aqueous sodium hydroxide (20%: 4.8 ml) in methanol (20 ml) was refluxed for 1.5 h. After the methanol had been evaporated *in vacuo*, the residue was diluted with water, and then washed with ether. The alkaline solution was acidified with dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give **6** (2.23 g: 93.1%) as a solid. This was recrystallized from acetone-petroleum benzine, mp 101—102 °C. Found: C, 66.39; H, 6.65%. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71%.

Resolution of (±)-6. A mixture of (±)-**6** (34.69 g) and cinchonidine (56.68 g) in ethyl acetate (1000 ml) was refluxed for 20 h. The solution was concentrated, allowed to stand at room temperature, and then filtered to give colorless crystals. This was recrystallized from ethyl acetate to give a cinchonidine salt (35.72 g), mp 106—111 °C, $[\alpha]_D$ −46.1°.

The above cinchonidine salt was suspended in dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and then evaporated to dryness. The residue was recrystallized from acetone-petroleum benzine to give (*S*)-(+)-2-(2-methoxyphenyl)propanoic acid (**6b**) (9.87 g), mp 94—96 °C, $[\alpha]_D$ +62.7° (*c* 2.32). Found: C, 66.65; H, 6.81%. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71%.

The mother liquor from the above recrystallization of the cinchonidine salt was evaporated *in vacuo*. The residue was suspended in 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 recrystallized from acetone-petroleum benzine to give (*R*)-(−)-2-(2-methoxyphenyl)propanoic acid (**6a**) (8.91 g), mp 94—96°C, $[\alpha]_D$ −67.8° (*c* 2.62). Found: C, 66.63; H, 6.84%. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71%.

*(*R*)-(−)-2-(2-Methoxyphenyl)-1-propanol (7a) and Its (*S*)-(+)-Isomer (7b).* *a)*: **6a** (8.914 g) was methylated with a solution of diazomethane in ether. After the usual work-up, the crude product was chromatographed on silica gel (200 g), using benzene as eluent, to give (*R*)-(−)-ester (**5a**) (8.791 g: 91.6%), $[\alpha]_D$ −69.4° (*c* 3.35).

A solution of **5a** (7.959 g) in dry ether (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.436 g) in dry ether (80 ml) with cooling in an ice-water bath over a 15 min period. The mixture was stirred at room temperature for 1.5 h, poured into a mixture of ice and 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 (50 g), using ether-benzene (1:9) as eluent, to give **7a** (6.530 g: 95.7%), $[\alpha]_D$ −6.1° (*c* 17.9).

b): **6b** (9.870 g) was methylated with diazomethane in ether to give (*S*)-(+)-ester (**5b**) (10.594 g: 99.6%), $[\alpha]_D$ +65.2° (*c* 4.68).

A solution of **5b** (11.915 g) in dry ether (50 ml) was reduced with lithium aluminium hydride (2.333 g) in dry ether (150 ml) to give **7b** (9.939 g: 97.5%), $[\alpha]_D$ +6.5° (*c* 18.8).

*(*R*)-(−)-1-Acetoxy-2-(2-hydroxyphenyl)propane (9a) and Its*

(S)-(+)-Isomer (9b). *a)*: A mixture of **7a** (659 mg) and acetic anhydride (2.0 ml) in pyridine (3.0 ml) was heated at 80—85 °C for 1.5 h. After the usual work-up, the crude product was chromatographed on silica gel (15 g), using benzene as eluent, to give (*R*)-(−)-acetate (**8a**) (695 mg: 84.2%), [α]D −20.2° (*c* 3.92). Found: C, 69.01; H, 7.69%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%.

Anhydrous aluminium chloride (2.40 g) was added to a stirred solution of **8a** (620 mg) and ethanethiol (1.5 ml) in dichloromethane (7.0 ml) at 5—10 °C. The mixture was stirred at room temperature for 1 h, poured into a mixture of ice and 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 (15 g), using ether–benzene (2:98) as eluent, to give **9a** (566 mg: 97.9%), [α]D −11.6° (*c* 5.08).

b): **7b** (612 mg) was acetylated with acetic anhydride (1.5 ml) in pyridine (3.0 ml) to give (*S*)-(+)-acetate (**8b**) (652 mg: 85.0%), [α]D +21.0° (*c* 9.72). Found: C, 68.91; H, 7.58%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%.

8b (647 mg) was demethylated with anhydrous aluminium chloride (2.481 g) and ethanethiol (2.3 ml) in dichloromethane (7.0 ml) to give **9b** (523 mg: 86.6%), [α]D +12.4° (*c* 3.96).

Ozonization of 9a and 9b. *a)*: A solution of **9a** (523 mg) in methanol (20 ml) was ozonized at −20—−10 °C for 4 h. The solution was evaporated *in vacuo* and the residue was methylated with diazomethane in ether. The ether solution was washed successively with dilute hydrochloric acid and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel (15 g), using hexane–chloroform (3:7) as eluent, to give an ester (**10a**) (155 mg: 36.5%), [α]D +14.9° (*c* 4.16), whose IR and ¹H NMR spectra were identical with those of methyl (*S*)-(+)-3-acetoxy-2-methylpropanoate.[3]

b): Ozonization of **9b** (523 mg) in methanol (20 ml), followed by esterification with diazomethane yielded methyl (*R*)-(−)-3-acetoxy-2-methylpropanoate (**10b**) (244 mg: 56.6%), [α]D −15.2° (*c* 4.54).

(R)-(−)-1-Methoxy-2-(2-methoxyphenyl)propane (11a) and Its (S)-(+)-Isomer (11b). *a)*: A mixture of **7a** (6.530 g) and methyl iodide (3.3 ml) in 1,2-dimethoxyethane (20 ml) was added to a stirred suspension of sodium hydride (55%: 1.900 g) in 1,2-dimethoxyethane (20 ml) with cooling in an ice-water bath over a 35 min period. The mixture was stirred at room temperature for 2 h. After the addition of methanol, the mixture was poured into ice-dilute hydrochloric acid, and extracted with ether. The ether extract was washed successively with aqueous sodium thiosulfate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (50 g: Merck 0.063—0.200 mm), using benzene as eluent, to give **11a** (6.726 g: 95.0%), [α]D −29.8° (*c* 12.5).

b): The alcohol **7b** (9.939 g) was similarly methylated with methyl iodide (4.9 ml) and sodium hydride (55%: 2.890 g) in 1,2-dimethoxyethane (55 ml) to give **11b** (10.287 g: 95.5%), [α]D +27.6° (*c* 10.6).

(R)-4-Methoxy-3-(2-methoxy-1-methylethyl)benzyl Chloride (12a) and Its (S)-Isomer (12b). *a)*: A round-bottomed flask containing a solution of **11a** (4.00 g) and chloromethyl methyl ether (2.8 ml) in acetic acid (4.0 ml) was fitted with a rubber stopper and then heated at 35—40 °C for 6 h. The mixture was cooled, poured into ice–aqueous sodium hydrogencarbonate, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give the crude **12a** (5.00 g). This was used without purification in the next reaction. ¹H NMR: δ=1.21 (3H, d, *J*=7 Hz, $-\overset{|}{C}HC\underline{H}_3$), 3.25 (3H, s, $-OCH_3$), 3.73 (3H, s, $-OCH_3$), 4.42 (2H, s, $-CH_2Cl$).

b): A solution of **11b** (5.00 g) and chloromethyl methyl ether (3.5 ml) in acetic acid (5.0 ml) was treated as described in *a)* to give the crude **12b** (5.90 g). This was used without purification in the next reaction.

[(R)-4-Methoxy-3-(2-methoxy-1-methylethyl)benzyl]triphenylphosphonium Chloride (3a) and Its (S)-Isomer (3b). *a)*: A mixture of **12a** (5.00 g) and triphenylphosphine (5.73 g) in dry benzene (5.0 ml) was refluxed for 1 h and then cooled. The precipitates were collected by filtration and washed with dry benzene to give the crude **3a** (10.29 g), mp 175—185 °C. This was used without purification in the next reaction.

b): A mixture of **12b** (5.90 g) and triphenylphosphine (6.77 g) in dry benzene (6.0 ml) was refluxed for 1.5 h and then treated as described in *a)* to give the crude **3b** (11.92 g), mp 176—186 °C. This was used without purification in the next reaction.

The Wittig Reaction of (R)-(−)-α-Cyclocitral with 3a and 3b. *a)*: A solution of butyllithium in hexane (15%: 4.0 ml) was added at 10—20 °C to a stirred suspension of **3a** (2.500 g) in dry benzene (15 ml) under a stream of nitrogen. The mixture was stirred at room temperature for 15 min and a solution of (*R*)-(−)-α-cyclocitral (**2**) (0.485 g) in dry benzene (2.5 ml) was added at 10—20 °C. After stirring at room temperature for 1.5 h, the reaction 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 triturated with hexane and the precipitated triphenylphosphine oxide was removed by filtration. The filtrate was evaporated and the residue was chromatographed on silica gel (30 g), using ether–hexane (2:98) as eluent, to give 6-[4-methoxy-3-(2-methoxy-1-methylethyl)styryl]-1,5,5-trimethylcyclohexene (**13a**) (0.583 g: 56.1%), [α]D −316° (*c* 0.31); ¹H NMR: δ=0.89 (3H, s) and 0.95 (3H, s) ($-\overset{|}{C}(CH_3)_2$), 1.23 (3H, d, *J*=7 Hz, $-\overset{|}{C}HC\underline{H}_3$), 1.63 (3H, bs, $=\overset{|}{C}CH_3$), 3.28 (3H, s) and 3.79 (3H, s) (2-OCH_3), 5.40 (1H, br, $-CH=\overset{|}{C}-$), 5.76 (1H, dd, *J*=8.5 and 15 Hz, $-\overset{|}{C}HC\underline{H}=CH-$), 6.25 (1H, d, *J*=15 Hz, $-\overset{|}{C}HCH=C\underline{H}-$).

b): A solution of butyllithium in hexane (15%: 88.0 ml) was added at 10—20 °C to a stirred suspension of **3b** (48.0 g) in dry benzene (250 ml) under a stream of nitrogen. The mixture was stirred for 5 min and a solution of **2** (9.31 g) in dry benzene (50 ml) was added at 10—20 °C. After stirring at room temperature for 1.5 h, the mixture was treated as described in *a)* to give the styryl derivative (**13b**) (11.0 g: 54.9%), [α]D −287° (*c* 0.53). ¹H NMR: δ=0.89 (3H, s) and 0.95 (3H, s) ($-\overset{|}{C}(CH_3)_2$), 1.25 (3H, d, *J*=7 Hz, $-\overset{|}{C}HC\underline{H}_3$), 1.64 (3H, bs, $=\overset{|}{C}CH_3$), 3.28 (3H, s) and 3.76 (3H, s) (2-OCH_3), 5.40 (1H, br, $-CH=\overset{|}{C}-$), 5.77 (1H, dd, *J*=8.5 and 15 Hz, $-\overset{|}{C}HC\underline{H}=CH-$), 6.26 (1H, d, *J*=15 Hz, $-\overset{|}{C}HCH=C\underline{H}-$).

Partial Catalytic Hydrogenation of 13a and 13b. *a)*: A suspension of **13a** (438 mg) and 5% Pd–C (253 mg) in ethanol (10 ml) was stirred at room temperature in an atmosphere of hydrogen. After one mol equivalent of hydrogen had been absorbed, the mixture was filtered. The filtrate was evaporated *in vacuo* and the residue was chromatographed on silica gel (20 g), using ether-benzene (3:97) as eluent, to give the phenethyl derivative (**14a**) (414 mg: 94.1%), $[\alpha]_D$ −107° (*c* 5.22). Found: C, 79.65; H, 10.55%. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37%.

b): A suspension of **13b** (6.486 g) and 10% Pd-C (3.00 g) in methanol (50 ml) was stirred at room temperature in an atmosphere of hydrogen. After one mol equivalent of hydrogen had been absorbed, the mixture was treated as described in *a)* to give the phenethyl derivative (**14b**) (5.836 g: 89.4%), $[\alpha]_D$ −85.5° (*c* 6.12). Found: C, 79.85; H, 10.59%. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37%.

Intramolecular Cyclization of 14a and 14b. *a)*: Anhydrous aluminium chloride (2.246 g) was added at 5—15 °C to a solution of **14a** (5.565 g) in dry benzene (60 ml). The mixture was stirred at room temperature for 50 min, 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 (300 g), using ether-hexane (2:98) as eluent, to give (5*S*,10*R*,15*R*)-12,16-dimethoxy-8,11,13-abietatriene (**15a**) (1.963 g: 35.3%). This was recrystallized from methanol: mp 79—80 °C, $[\alpha]_D$ −48.4° (*c* 2.03); ^{1}H NMR (C_6D_6): δ=0.48 (3H, s) and 0.93 (3H, s) ($-\overset{|}{C}(CH_3)_2$), 1.17 (3H, s, C_{10}–CH_3), 1.40 (3H, d, *J*=7 Hz, C_{15}–CH_3), 3.18 (3H, s, C_{16}–OCH_3), 3.50 (3H, s, C_{12}–OCH_3), 6.76 (1H, s) and 6.93 (1H, s) (C_{11}–H and C_{14}–H). Found: C, 79.83; H, 10.53%. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37%.

Further elution gave (5*S*,10*S*,15*R*)-12,16-dimethoxy-8,11,13-abietatriene (**16a**) (2.727 g: 49.0%) as an oil, $[\alpha]_D$ +35.0° (*c* 4.28); ^{1}H NMR (C_6D_6): δ=0.92 (6H, s, $-\overset{|}{C}(CH_3)_2$), 1.20 (3H, s, C_{10}–CH_3), 1.42 (3H, d, *J*=7 Hz, C_{15}–CH_3), 3.19 (3H, s, C_{16}–OCH_3), 3.53 (3H, s, C_{12}–OCH_3), 6.70 (1H, s) and 6.95 (1H, s) (C_{11}–H and C_{14}–H). Found: C, 79.77; H, 10.67%. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37%.

b): A solution of **14b** (5.836 g) in dry benzene (60 ml) was treated with anhydrous aluminium chloride (2.355 g) as described in *a)*. The crude product was chromatographed on silica gel (300 g), using ether-hexane (2:98) as eluent, to give (5*S*,10*R*,15*S*)-12,16-dimethoxy-8,11,13-abietatriene (**15b**) (2.166 g: 40.5%). This was recrystallized from methanol: mp 81—82 °C, $[\alpha]_D$ −16.9° (*c* 3.56); ^{1}H NMR (C_6D_6): δ=0.51 (3H, s) and 0.95 (3H, s) ($-\overset{|}{C}(CH_3)_2$), 1.20 (3H, s, C_{10}–CH_3), 1.44 (3H, d, *J*=7 Hz, C_{15}–CH_3), 3.18 (3H, s, C_{16}–OCH_3), 3.50 (3H, s, C_{12}–OCH_3), 6.80 (1H, s) and 6.96 (1H, s) (C_{11}–H and C_{14}–H). Found: C, 79.87; H, 10.59%. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37%.

Further elution gave (5*S*,10*S*,15*S*)-12,16-dimethoxy-8,11,13-abietatriene (**16b**) (2.769 g: 50.8%) as an oil, $[\alpha]_D$ +60.4° (*c* 4.56); ^{1}H NMR (C_6D_6): δ=0.92 (6H, s, $-\overset{|}{C}(CH_3)_2$), 1.19 (3H, s, C_{10}–CH_3), 1.45 (3H, d, *J*=7 Hz, C_{15}–CH_3), 3.21 (3H, s, C_{16}–OCH_3), 3.53 (3H, s, C_{12}–OCH_3), 6.65 (1H, s) and 6.90 (1H, s) (C_{11}–H and C_{14}–H). Found: C, 79.68; H, 10.63%. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37%.

(5S,10S,15R)-12,16-Dimethoxy-8,11,13-abietatrien-7-one (17a) and Its (5S,10S,15S)-Isomer (17b). *a)*: Jones reagent (2.5 mol dm^{-3}: 4.25 ml) was added to a stirred solution of **16a** (2.465 g) in acetone (35 ml) with cooling in an ice-water bath over a 5 min period. The mixture was stirred at this temperature for 10 min and then 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 chromatographed on silica gel (150 g), using ether-benzene (2:98) as eluent, to give the recovered **16a** (0.236 g: 9.6%). Further elution with ether-benzene (2:98 and then 5:95) gave **17a** (1.968 g: 76.6%). This was recrystallized from ethanol: mp 128—134 °C, $[\alpha]_D$ +27.8° (*c* 2.10); IR: 1664, 1601 cm^{-1}; ^{1}H NMR (C_6D_6): δ=0.74 (3H, s) and 0.80 (3H, s) ($-\overset{|}{C}(CH_3)_2$), 1.04 (3H, s, C_{10}–CH_3), 1.32 (3H, d, *J*=6 Hz, C_{15}–CH_3), 3.11 (3H, s, C_{16}–OCH_3), 3.42 (3H, s, C_{12}–OCH_3), 6.56 (1H, s, C_{11}–H), 8.33 (1H, s, C_{14}–H). Found: C, 76.78; H, 9.57%. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36%.

b): A solution of **16b** (2.610 g) in acetone (40 ml) was oxidized with Jones reagent (2.5 mol dm^{-3}: 4.50 ml) as described in *a)* to give the recovered **16b** (0.227 g: 8.7%) and (5*S*,10*S*,15*S*)-12,16-dimethoxy-8,11,13-abietatrien-7-one (**17b**) 2.405 g: 88.2%). This was recrystallized from ethanol: mp 140—141.5 °C, $[\alpha]_D$ +30.7° (*c* 4.53); IR: 1662, 1600 cm^{-1}; ^{1}H NMR (C_6D_6): δ=0.75 (3H, s) and 0.80 (3H, s) ($-\overset{|}{C}(CH_3)_2$), 1.05 (3H, s, C_{10}–CH_3), 1.33 (3H, d, *J*=6 Hz, C_{15}–CH_3), 3.13 (3H, s, C_{16}–OCH_3), 3.46 (3H, s, C_{12}–OCH_3), 6.58 (1H, s, C_{11}–H), 8.28 (1H, s, C_{14}–H). Found: C, 76.74; H, 9.46%. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36%.

Catalytic Hydrogenolysis of 17a and 17b. *a)*: A suspension of **17a** (254 mg), 10% Pd-C (125 mg), and 60% perchloric acid (0.15 ml) in ethyl acetate (5.0 ml) was stirred at room temperature in an atmosphere of hydrogen. After the hydrogen had been absorbed, the mixture was filtered. The filtrate was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was chromatographed on silica gel (15 g), using ether-benzene (2:98) as eluent, to give **16a** (233 mg: 95.5%), $[\alpha]_D$ +46.7° (*c* 1.65). Found: C, 79.78; H, 10.53%. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37%.

b): A suspension of **17b** (500 mg), 10% Pd-C (250 mg), and 60% perchloric acid (0.30 ml) in ethyl acetate (10 ml) was hydrogenated to give **16b** (466 mg: 97.2%), $[\alpha]_D$ +68.7° (*c* 3.70). Found: C, 79.93; H, 10.55%. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37%.

(5S,10S,15R)-8,11,13-Abietatriene-12,16-diol (16-Hydroxyferruginol) (1a) and Its (5S,10S,15S)-Isomer (1b).

a): Anhydrous aluminium chloride (714 mg), sodium iodide (803 mg), and a solution of **16a** (177 mg) in dichloromethane (5.0 ml) were added in this order to acetonitrile (10.0 ml) with stirring at 0—5 °C under a stream of nitrogen over a 15 min period. The mixture was stirred at this temperature for 15 min and then at 35—40 °C for 5 h, poured into water, and extracted with ether. The ether extract was washed successively with aqueous sodium thiosulfate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (20 g), using ether-hexane (1:1) as eluent, to give **1a** (155 mg: 95.7%). This was recrystallized from ether-hexane: mp 141—142.5 °C, $[\alpha]_D$ +65.7° (*c* 1.85) (lit,[1] mp 141—142 °C, $[\alpha]_D^{29}$ +36.6°); IR (KBr): 3505, 3275 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ=0.94 (3H, s) and 0.96 (3H, s) ($-\overset{|}{C}(CH_3)_2$), 1.16 (3H, s, C_{10}–CH_3), 1.27 (3H, d, *J*=7 Hz, C_{15}–CH_3), 3.15 (1H, m, C_{15}–H), 3.64 (1H, dd, *J*=9 and 7 Hz) and 3.87 (1H, dd, *J*=9 and 4 Hz) ($-C\underline{H}_2OH$), 6.76 (2H, s, C_{11}–H and C_{14}–H). Found: C, 79.51; H, 10.18%. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00%.

A mixture of **1a** (31.4 mg) and acetic anhydride (0.5 ml) in pyridine (0.5 ml) was heated at 75—80 °C for 1 h. After the usual work-up, the crude product was chromatographed on silica gel (5.0 g), using ether-hexane (15:85) as eluent, to give a diacetate (**18a**) (35.0 mg: 87.3%), $[\alpha]_D$ +59.4° (*c* 1.75);

^{1}H NMR ($CDCl_3$): δ=0.95 (6H, s, $-\overset{|}{C}(CH_3)_2$), 1.19 (3H, s, C_{10}–CH_3), 1.24 (3H, d, J=6 Hz, C_{15}–CH_3), 2.04 (3H, s, C_{16}–$OCOCH_3$), 2.31 (3H, s, C_{12}–$OCOCH_3$), 4.06 (2H, d, J=7 Hz, $-C\underline{H}_2OAc$), 6.87 (1H, s) and 6.91 (1H, s) (C_{11}–H and C_{14}–H). Found: C, 74.92; H, 9.05%. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87%.

b): Anhydrous aluminium chloride (706 mg), sodium iodide (794 mg), and a solution of **16b** (175 mg) in dichloromethane (5.0 ml) were added in this order to acetonitrile (10.0 ml) with stirring at 0—5 °C under a stream of nitrogen over a 15 min period. The mixture was stirred at this temperature for 15 min and then at 35—40 °C for 5 h. After the work-up as described in *a)*, the crude product was recrystallized from acetone-hexane to give a diol (**1b**) (153 mg: 95.5%): mp 178—179 °C, $[\alpha]_D$ +44.6° (*c* 1.12); IR (KBr): 3545, 3260 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ=0.92 (6H, s $-\overset{|}{C}(CH_3)_2$), 1.15 (3H, s, C_{10}–CH_3), 1.28 (3H, d, J=7 Hz, C_{15}–CH_3), 3.16 (1H, m, C_{15}–H), 3.68 (1H, dd, J=9 and 7 Hz) and 3.91 (1H, dd, J=9 and 4 Hz) ($-C\underline{H}_2OH$), 6.77 (2H, s, C_{11}–H and C_{14}–H). Found: C, 79.28; H, 10.24%. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00%.

A mixture of **1b** (82.9 mg) and acetic anhydride (0.5 ml) in pyridine (0.5 ml) was heated at 75—80 °C for 1 h. After the usual work-up, the crude product was chromatographed on silica gel (10 g), using ether–hexane (7.5:92.5) as eluent, to give a diacetate (**18b**) (93.9 mg: 88.7%), $[\alpha]_D$ +37.1° (*c* 4.60), ^{1}H NMR ($CDCl_3$): δ=0.93 (6H, s, $-\overset{|}{C}(CH_3)_2$), 1.18 (3H, s, C_{10}–CH_3), 1.20 (3H, d, J=7 Hz, C_{15}–CH_3), 2.02 (3H, s, C_{16}–$OCOCH_3$), 2.31 (3H, s, C_{12}–$OCOCH_3$), 4.08 (2H, d, J=7 Hz, $-C\underline{H}_2OAc$), 6.86 (1H, s) and 6.91 (1H, s) (C_{11}–H and C_{14}–H). Found: C, 74.52; H, 9.16%. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87%.

(5S,10S,15R)-12-Methoxy-8,11,13-abietatrien-16-ol (19a) and Its (5S,10S,15S)-Isomer (19b). *a)*: A mixture of **1a** (80.0 mg), methyl iodide (0.24 ml), and anhydrous potassium carbonate (320 mg) in ethyl methyl ketone (3.2 ml) was refluxed for 5 h. The mixture was cooled, diluted with water, and extracted with ether. The ether extract was washed successively with aqueous sodium thiosulfate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (10 g), using ether–benzene (5:95) as eluent, to give **19a** (80.0 mg: 95.6%), $[\alpha]_D$ +62.3° (*c* 4.00); ^{1}H NMR: δ=0.95 (6H, s, $-\overset{|}{C}(CH_3)_2$), 1.17 (3H, d, J=6.5 Hz, C_{15}–CH_3), 1.18 (3H, s, C_{10}–CH_3), 3.74 (3H, s, C_{12}–OCH_3), 6.59 (1H, s) and 6.68 (1H, s) (C_{11}–H and C_{14}–H). Found: C, 79.72; H, 10.48%. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19%.

b): A mixture of **1b** (100 mg), methyl iodide (0.30 ml), and anhydrous potassium carbonate (400 mg) in ethyl methyl ketone (4.0 ml) was refluxed for 5 h. After the work-up as described in *a)*, the crude product was chromatographed on silica gel (10 g), using ether–hexane (5:95) as eluent, to give **19b** (96.5 mg: 92.3%), $[\alpha]_D$ +45.4° (*c* 4.83); ^{1}H NMR: δ=0.94 (6H, s, $-\overset{|}{C}(CH_3)_2$), 1.16 (3H, d, J=6.5 Hz, C_{15}–CH_3), 1.18 (3H, s, C_{10}–CH_3), 3.74 (3H, s, C_{12}–OCH_3), 6.60 (1H, s) and 6.68 (1H, s) (C_{11}–H and C_{14}–H). Found: C, 79.56; H, 10.46%. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19%.

(+)-Ferruginol Methyl Ether (21). *a)*: A mixture of **19a** (80.0 mg) and *p*-toluenesulfonyl chloride (80.0 mg) in pyridine (1.5 ml) was heated at 70—75 °C for 3.5 h. The mixture was cooled and diluted with ether. The ether solution was washed successively with dilute hydrochloric acid and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (10 g), using ether–benzene (3:97) as eluent, to give a tosylate (**20a**) (50.0 mg) and recovered **19a** (16.0 mg).

A mixture of **20a** (50.0 mg) and lithium aluminium hydride (45.0 mg) in dry ether (3.5 ml) was stirred at room temperature for 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 crude product was chromatographed on silica gel (8.0 g), using hexane–benzene (9:1) as eluent, to give **21** (7.0 mg), $[\alpha]_D$ +63.3° (*c* 0.30) (lit,⁷⁾ $[\alpha]_D$ +63.1°). Further elution with ether-benzene (5:95) gave the alcohol **19a** (20.2 mg).

b): A mixture of **19b** (86.0 mg) and *p*-toluenesulfonyl chloride (78.0 mg) in pyridine (1.5 ml) was heated at 70—75 °C for 3.5 h. The mixture was treated as described in *a)* to give a tosylate (**20b**) (73.0 mg).

A mixture of **20b** (73.0 mg) and lithium aluminium hydride (65.0 mg) in dry ether (4.0 ml) was stirred at room temperature for 5 h. The mixture was treated as described in *a)* to give **21** (15.3 mg), $[\alpha]_D$ +61.4° (*c* 0.70) and **19b** (36.5 mg).

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