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Stereocontrolled total syntheses of (±)-pisiferic acid and (±)-*O*-methylpisiferic acid

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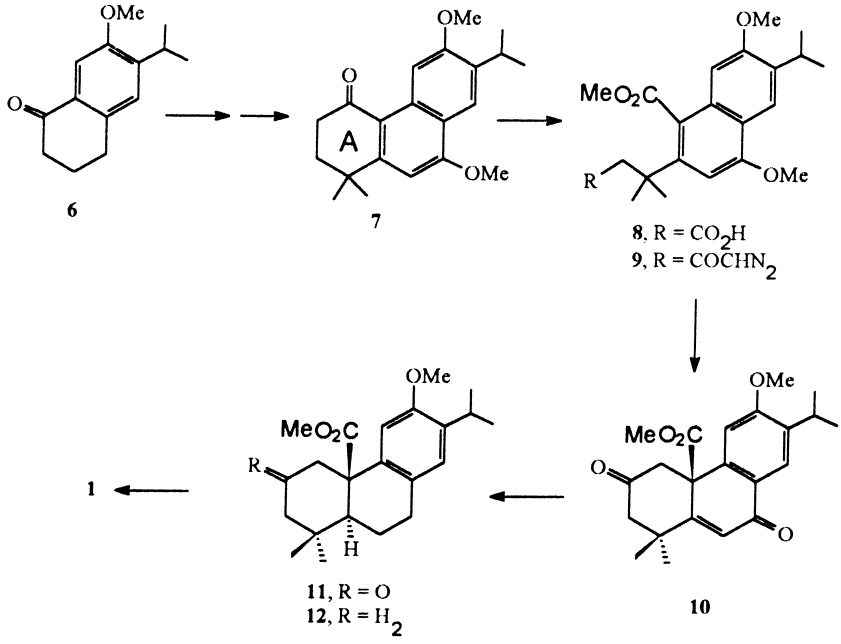
Abstract—A stereocontrolled approach to the construction of the angularly ester substituted *trans*-octahydrophenanthrene ring system related to diterpenes involving an aryl participated diazoketone cyclisation strategy is delineated. The tetrahydrophenanthrenone **7** was prepared from the tetralone **6** through the intermediates **13**, **14**, **16** and **17**. The formyl derivative of **7** was treated with alkaline H_2O_2 to give the diacid **18** which was converted into the diazomethyl ketone **9**. Aryl participated cyclisation of **9** afforded the enedione **10** which was stereoselectively converted into the keto-ester **11**. The transformation of **11** into the diterpenes **1** and **4** has been efficiently accomplished.

(+)-Pisiferic acid (**1**) and a few closely related tricyclic diterpenes, e.g. methyl (+)-pisiferate (**2**), (+)-pisiferol (**3**), (+)-*O*-methylpisiferic acid (**4**), and (+)-pisiferal (**5**) were isolated from the leaves of *Chamaecyparis pisifera* by Yatagai and co-workers.[1,2] The diterpenes **1**–**5** incorporate *trans*-fused octahydrophenanthrene ring system as the basic carbocyclic framework and possess oxygenated methyl groups as angular substituents. The abietane-type diterpene **1** bearing an angular carboxyl group has attracted attention as a synthetic target because of its antimicrobial activity[3] against all gram positive bacteria tested. Earlier methodologies for the synthesis of (±)-pisiferic acid (**1**)



Scheme 1.

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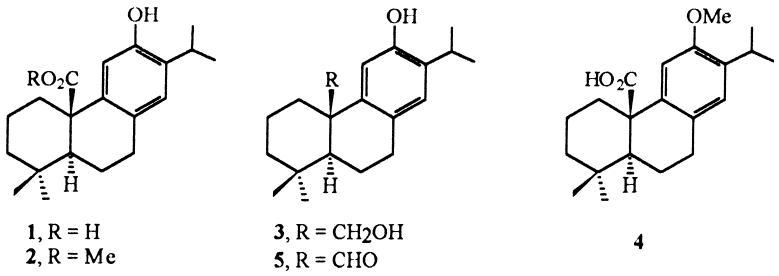
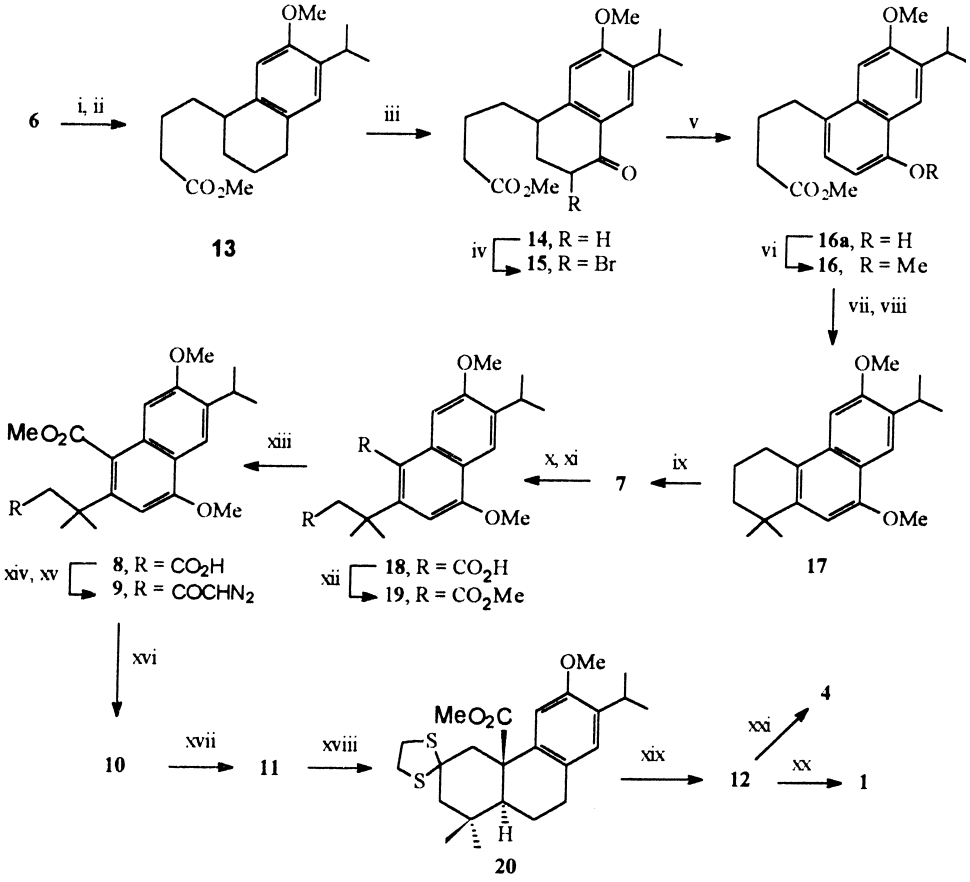


Figure 1.

most commonly employed[4,5] transannular oxidation of the angular methyl group as a key reaction. We describe herein a stereocontrolled total synthesis of (±)-pisiferic acid (**1**) using a conceptually different approach. Our basic strategy for the construction of an angularly ester substitued *trans*-octahydrophenanthrene ring system related to the diterpene **1** is shown in Scheme 1 and Fig. 1. The tetrahydrophenanthrenone **7**, easily prepared from 6-isopropyl-7-methoxy-1-tetralone (**6**), was smoothly converted into the half acid-ester **8** involving an oxidative cleavage of ring A. Aryl participated intramolecular cyclisation of the corresponding diazomethyl ketone **9** in the presence of acid afforded the tricyclic enedione **10** in good yield and this was stereoselectively converted into (±)-pisiferic acid (**1**) through the intermediates **11** and **12**. Aryl participated cyclisation of diazocarbonyl compounds to generate specifically functionalised hydrophenanthrene ring system related to naturally occurring ring C-aromatic tricyclic diterpenes has been relatively unexplored.

The bioactivity of *O*-methylpisiferic acid (**4**) as a mite growth regulator was reported by Ahn et al.[6] The diterpene **4** inhibits both the hatching and the feeding of the two-spotted spider mite, *Tetranychus urticae* Koch, which is a serious pest to many crops. During the present studies, the transformation of the ester **12** into (±)-*O*-methylpisiferic



Scheme 2. *Reagents and conditions*: (i) $BrCH_2CH{=}CHCO_2Me$, Zn, Et_2O, C_6H_6, reflux, 4.5 h; (ii) H_2, 10% Pd–C, AcOH, 71%; (iii) CrO_3, AcOH, H_2O, 0°C to rt, 4 h, 75%; (iv) Br_2, Et_2O, 10°C to rt, 16 h, 95%; (v) LiBr, Li_2CO_3, DMF, 120–125°C, 4 h; (vi) MeI, K_2CO_3, $(CH_3)_2CO$, reflux, 12 h, 78%; (vii) MeMgI, Et_2O, reflux, 4 h; (viii) P_2O_5, H_3PO_4, 90–95°C, 45 min, 82%; (ix) PCC, CH_2Cl_2, rt, 24 h, 87%; (x) NaH, HCO_2Et, C_6H_6, 0°C to rt, 20 h; (xi) aq. NaOH, H_2O_2, 0°C to rt, 18 h, H_3O^+, 87%; (xii) CH_2N_2, Et_2O, 0°C, 97%; (xiii) KOH, H_2O, THF, rt 24 h, 60°C 1 h, H_3O^+, 90%; (xiv) $ClCO_2Et$, Et_3N, Et_2O, THF, −10°C, 1 h; (xv) CH_2N_2, Et_2O, 0°C to rt, 14 h, 92%; (xvi) TFA, CH_2Cl_2, −20°C, 3 min, 62%; (xvii) H_2, 10% Pd–C, EtOAc, 94%; (xviii) $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, MeOH, rt, 20 h, 91%; (xix) Raney nickel, EtOH, reflux, 4 h, 88%; (xx) $AlBr_3$, EtSH, rt, 15 h, 92%; (xxi) *t*-BuOK, DMSO, 95°C, 70 min, 72%.

acid (**4**) has also been achieved. Both the enantiomers of the diterpene **4** were synthesised by Mori et al.[7] from (*S*)-3-hydroxy-2,2-dimethylcyclohexanone.

1. Results and discussion

Our synthesis of the diterpene acids **1** and **4** from the tetralone **6** is outlined in Scheme 2. Reformatsky reaction of the tetralone **6**[8] with methyl 4-bromocrotonate was carried out following essentially a procedure reported by Stork.[9] Catalytic hydrogenation of the crude product in acetic acid containing a few drops of perchloric acid provided the ester **13** in 71% overall yield. The spectral characteristics of **13** as revealed through its ^{1}H and ^{13}C NMR spectra were fully in accord with its structure. Oxidation of **13** with chromic acid in acetic acid gave the keto-ester **14** in high yield. Bromination of **14** in ether, according to a procedure reported by Johnson and co-workers,[10] furnished the bromoketone **15** in near quantitative yield. Dehydrobromination of **15** with LiBr and Li_2CO_3 in DMF followed by methylation of the crude product **16a** with MeI in acetone in the presence of K_2CO_3 afforded the ester **16** as a crystalline compound in high overall yield. The spectral and analytical data of the ester **16** were fully in agreement with the assigned structure. Undoubtedly, dehydrobromination of the bromoketone **15** proceeded with concomitant aromatisation yielding the phenol **16a** which underwent methylation to provide the ether **16**. A similar conversion of 6-methoxy-1-tetralone into 1-hydroxy-6-methoxynaphthalene through bromination and subsequent dehydrobromination was reported earlier by Kasturi et al.[11] The methyl ester **16** was treated with an excess of MeMgI in refluxing ether and the resulting crude carbinol was cyclised with polyphosphoric acid to give the tetrahydrophenanthrene derivative **17** as a crystalline compound in high yield. Oxidation of **17** with pyridinium chlorochromate in dichloromethane at room temperature yielded the tricyclic ketone **7** in excellent yield. Oxidation at the benzylic position was facilitated due to the presence of the *p*-methoxy group and the ^{1}H and ^{13}C NMR spectra of the ketone were in full accord with structure **7**. Due to deshielding effect of the carbonyl group, the aromatic proton at C-5 appeared in the ^{1}H NMR spectrum of **7** at a very low field (δ 9.01 ppm).

Having an efficient route to **7**, we turned our attention to convert **7** into the half acid-ester **8**. The ketone **7** was condensed with ethyl formate in the presence of NaH and the resulting crude hydroxymethelene derivative was treated with alkaline H_2O_2 to give the diacid **18** which on treatment with an excess of ethereal CH_2N_2 furnished the dimethyl ester **19** in high overall yield. Similar oxidative cleavage of the hydroxymethelene derivative of an octahydrophenanthrenone to give a *seco* diacid was reported by Arapakos et al.[12] Partial hydrolysis of the diester **19** under controlled conditions furnished the crystalline half acid-ester **8** in 90% yield. The spectral and analytical data of the compounds **18**, **19**, and **8** agree with the assigned structures. The conversion of **8** into the corresponding diazomethyl ketone **9** was successfully accomplished following a procedure reported by Tarbell and Price.[13] Reaction of **8** with ethyl chloroformate at -10°C in the presence of Et_3N followed by treatment of the resulting mixed anhydride with ethereal CH_2N_2 afforded the diazoketone **9** in excellent yield. For synthetic entry into the tricyclic ring system of methyl *O*-methylpisiferate (**12**), aryl participated cyclisation[14] of the diazoketone **9** was investigated. A brief treatment of **9** with trifluoroacetic acid in CH_2Cl_2 at -20°C furnished the crystalline enedione **10** in 62% yield. The IR, ^{1}H- and ^{13}C NMR spectra of this compound were in full accord with structure **10**. Catalytic hydrogenation of the enedione **10** proceeded stereoselectively with uptake of three moles of hydrogen to provide the *trans*-fused keto-ester **11** as the sole product. The construction of the basic tricarbocyclic framework of methyl *O*-methylpisiferate (**12**) was thus accomplished in a stereocontrolled manner. The stereostructure of the keto-ester **11** was conclusively established by single crystal X-ray crystallography.[15] The keto-ester **11** was subsequently transformed into several known compounds possessing *trans*-stereochemistry at the A/B ring juncture. It may be mentioned in this connection that catalytic hydrogenation by Matsumoto and co-workers[16,17] of closely related enones had generated exclusively *trans*-stereochemistry at A/B ring junctures.

In order to complete the synthesis of the diterpene acids **1** and **4**, the compound **11** was converted into the corresponding thioacetal **20** in 91% yield. Desulfurisation of **20** with Raney nickel furnished the ester **12**[18] in high yield. Demethylation of **12** with anhydrous $AlBr_3$ and EtSH[19] at room temperature afforded (±)-pisiferic acid (**1**) in excellent yield. Treatment of **12** with *t*-BuOK in DMSO[20] at room temperature furnished (±)-*O*-methylpisiferic acid (**4**) in high yield. The spectral data of the present compounds **12**, **1** and **4** agreed very well with those reported in the literature.

In conclusion, in the present work a stereocontrolled route has been developed for the synthesis of (±)-pisiferic acid and (±)-*O*-methylpisiferic acid involving aryl participated intramolecular cyclisation of an appropriately substitued diazometyl ketone as the key step.

2. Experimental

2.1. General

The compounds described and having asymmetric centres are all racemates. Melting points and boiling points are uncorrected. IR spectra were recorded on Perkin–Elmer model PE 298 and Shimadzu FTIR-8300 spectrophotometers. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ on a Bruker DPX-300 spectrometer with $SiMe_4$ as internal standard. The chemical shifts (δ ppm) are reported relative to $SiMe_4$ (δ_H 0.00) for ^{1}H and the central line of residual $CHCl_3$ (δ_C 77.0) for ^{13}C. Moisture sensitive reactions were carried out using standard syringe–septum technique. Anhydrous solvents were obtained by standard procedures. All solvent extracts were dried over anhydrous Na_2SO_4. Product purities were routinely checked by TLC. Ether refers to diethyl ether and light petroleum refers to the fraction of petroleum ether in the boiling point range 40–60°C.

2.1.1. Methyl 4-(1,2,3,4-tetrahydro-6-isopropyl-7-methoxy-1-naphthyl) butanoate (13). To a solution of methyl

4-bromocrotonate (7.6 g, 0.042 mol) and 6-isopropyl-7-methoxy-1-tetralone (**6**) (9.2 g, 0.042 mol) in a mixture of dry ether (50 mL) and dry benzene (15 mL) were added zinc wool[9] (5.5 g, 0.084 g-at.) and a crystal of iodine, and the mixture was refluxed with occasional shaking. Two additional lots of zinc wool (2×2.8 g) and methyl 4-bromocrotonate (2×3.8 g) were introduced at 45 min intervals and refluxing was continued for 3 h after the last addition. The reaction mixture was cooled, poured into crushed ice, acidified with glacial AcOH, and allowed to stand at room temperature for 16 h. The product was extracted repeatedly with ether. The combined ether extracts were washed with aqueous ammonia and water, dried and concentrated. Evaporative distillation of the residue at 175–178°C (bath temperature)/0.1 mmHg afforded a viscous oily product (10.3 g). This was dissolved in AcOH (40 mL) and hydrogenated over Pd–C (10%, 1.5 g) at room temperature and atmospheric pressure in the presence of a few drops of perchloric acid. Uptake of hydrogen ceased after 4 h. The mixture was filtered. The filtrate was diluted with water (50 mL) and extracted with $CHCl_3$ (3×70 mL). The organic extract was washed with aqueous $NaHCO_3$ and water, dried, and evaporated. The residue was evaporatively distilled to afford the methyl ester **13** (9.24 g, 72%) as a colourless oil, bp 164–166°C (bath temperature)/0.1 mmHg; (Found: C, 74.79; H, 9.16. $C_{19}H_{28}O_3$ requires C, 74.96; H, 9.27%); ν_{max} (film) 1735, 1600 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.87 (1H, s, Ar*H*), 6.62 (1H, s, Ar*H*), 3.80 (3H, s, ArO*Me*), 3.67 (3H, s, CO_2*Me*), 3.23 (1H, sept, *J*=6.9 Hz, C*H*Me$_2$), 2.74–2.63 (3H, m), 2.38–2.32 (2H, m), 1.85–1.57 (8H, m), 1.18 (6H, d, *J*=6.9 Hz, CH*Me*$_2$); δ_C (75 MHz, $CDCl_3$) 174.1, 154.8, 138.7, 134.5, 128.6, 126.5, 110.3, 55.5, 51.5, 37.4, 36.3, 34.2, 29.0, 27.3, 26.4, 22.9, 22.6, 20.0.

2.1.2. 4-(3-Methoxycarbonylpropyl)-6-methoxy-7-isopropyl-1-tetralone (14). A solution of CrO_3 (7.2 g, 0.072 mol) in 80% aqueous AcOH (35 mL) was added slowly to a stirred solution of the ester **13** (9 g, 0.03 mol) in glacial AcOH (70 mL) at 0°C. After the addition, the mixture was stirred at room temperature for 4 h and then diluted with water (100 mL). Solid Na_2CO_3 was added in portions to neutralise most of the acetic acid and the product was extracted with ether (3×100 mL). The combined ether extract was washed with aqueous $NaHCO_3$ and water, dried and evaporated. The residue was evaporatively distilled to furnish the tetralone **14** (7 g, 75%) as a colourless oil, bp 178–180°C/0.1 mmHg; (Found: C, 71.60; H, 8.47. $C_{19}H_{26}O_4$ requires C, 71.67; H, 8.23%); ν_{max} (film) 1737, 1672, 1599 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.90 (1H, s, 8-Ar*H*), 6.65 (1H, s, 5-Ar*H*), 3.90 (3H, s, ArO*Me*), 3.68 (3H, s, CO_2*Me*), 3.25 (1H, sept, *J*=6.9 Hz, C*H*Me$_2$), 2.92–2.50 (3H, m), 2.42–2.03 (4H, m), 1.90–1.71 (4H, m), 1.20 (6H, d, *J*=6.9 Hz, CH*Me*$_2$); δ_C (75 MHz, $CDCl_3$) 197.3, 173.8, 161.1, 148.0, 136.0, 125.6, 125.0, 108.7, 55.5, 51.6, 38.1, 34.5, 33.9, 26.7, 26.5, 23.0, 22.5, 22.4.

2.1.3. 2-Bromo-4-(3-methoxycarbonylpropyl)-6-methoxy-7-isopropyl-1-tetralone (15). A solution of bromine (1.7 g, 10.6 mmol) in AcOH (3 mL) was added dropwise during 15 min to a stirred solution of the tetralone **14** (3.2 g, 10 mmol) in anhydrous ether (280 mL) at 10°C, allowing each drop of bromine to decolourise before more was added. After the addition, the mixture was stirred at 10°C for 2 h and left at room temperature for 14 h. It was then washed successively with water (2×70 mL), saturated aqueous $NaHCO_3$ (40 mL) and water (2×50 mL), and dried. Evaporation of the solvent and purification of the product on a silica gel column using ether–light petroleum (1:19) as eluent furnished the bromotetralone **15** (3.8 g, 95%) as a viscous oil; (Found: C, 57.18; H, 6.51. $C_{19}H_{25}BrO_4$ requires C, 57.44; H, 6.34%); ν_{max} (film) 1738, 1675, 1603 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.97 (1H, s, 8-Ar*H*), 6.76 (1H, s, 5-Ar*H*), 4.81 (1H, t, *J*=4.0 Hz, COC*H*Br), 3.94 (3H, s, ArO*Me*), 3.69 (3H, s, CO_2*Me*), 3.50–3.00 (2H, m), 2.67–2.33 (4H, m), 2.03–1.67 (4H, m), 1.21 (6H, d, *J*=6.9 Hz, CH*Me*$_2$).

2.1.4. Methyl 4-(6-isopropyl-4,7-dimethoxy-1-naphthyl) butanoate (16). A mixture of **15** (3.7 g, 9.31 mmol), LiBr (2 g, 23 mmol), and Li_2CO_3 (1.6 g, 21.6 mmol) in dry DMF (30 mL) was stirred at 120–125°C for 4 h under nitrogen. The reaction mixture was cooled, poured into dilute HCl (3N, 30 mL) and extracted with ether (3×50 mL). The ether extract was washed with water (2×30 mL) and dried. Evaporation of the solvent furnished the crude phenol **16a** as a gummy material (2.8 g) which was dissolved in acetone (25 mL). Anhydrous K_2CO_3 (1.5 g, 10.8 mmol) and MeI (3 mL, 48 mmol) were added and the mixture was refluxed with stirring under nitrogen for 12 h. It was then cooled, diluted with water (30 mL) and extracted with ether (3×50 mL). The ether extract was washed with water (2×30 mL), dried, and concentrated. Evaporative distillation of the crude product followed by crystallisation from MeOH furnished the ester **16** (2.4 g, 78%) as colourless plates, mp 66–67°C; (Found: C, 72.83; H, 8.11. $C_{20}H_{26}O_4$ requires C, 72.70; H, 7.93%); ν_{max} (KBr) 1731, 1625, 1590 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.09 (1H, s, 5-Ar*H*), 7.24 (1H, s, 8-Ar*H*), 7.10 (1H, d, *J*=9.0 Hz, 2-Ar*H*), 6.58 (1H, d, *J*=9.0 Hz, 3-Ar*H*), 3.98 (3H, s, ArO*Me*), 3.94 (3H, s, ArO*Me*), 3.67 (3H, s, CO_2*Me*), 3.43 (1H, sept, *J*=7.0 Hz, C*H*Me$_2$), 2.96 (2H, t, *J*=7.0 Hz, ArC*H*$_2$), 2.42–2.00 (4H, m), 1.32 (6H, d, *J*=7.0 Hz, CH*Me*$_2$); δ_C (75 MHz, $CDCl_3$) 174.1, 156.5, 154.1, 137.3, 132.3, 127.8, 125.6, 120.7, 119.3, 101.4, 101.3, 55.3, 55.2, 51.4, 33.5, 32.1, 27.3, 25.4, 22.8.

2.1.5. 1,2,3,4-Tetrahydro-1,1-dimethyl-6,9-dimethoxy-7-isopropylphenanthrene (17). To a stirred solution of MeMgI (prepared from magnesium turnings (1.7 g, 0.07 g-at.) and MeI (9 g, 0.063 mol)) in anhydrous ether (40 mL) was added slowly under nitrogen a solution of the ester **16** (4.6 g, 0.014 mol) in ether (15 mL). The mixture was stirred at room temperature for 30 min and then refluxed for 4 h. It was then cooled in an ice-bath and decomposed carefully with saturated aqueous NH_4Cl (25 mL). The product was extracted with ether (3×30 mL). The ether extract was washed with water (2×25 mL) and dried. Evaporation of the solvent furnished the crude tertiary alcohol as an oil (4.6 g) (^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.09 (1H, s, 5-Ar*H*), 7.16 (1H, s, 8-Ar*H*), 7.12 (1H, d, *J*=7.8 Hz, 2-Ar*H*), 6.58 (1H, d, *J*=7.8 Hz, 3-Ar*H*), 3.96 (3H, s, ArO*Me*), 3.94 (3H, s, ArO*Me*), 3.43 (1H, sept, *J*=6.9 Hz, C*H*Me$_2$), 2.93 (2H, t, *J*=7.2 Hz, ArC*H*$_2$), 1.83–1.55 (5H, m), 1.32 (6H, d, *J*=6.9 Hz, CH*Me*$_2$), 1.19 (6H, s, C*Me*$_2$)) which was cyclised by heating with polyphosphoric acid (prepared by heating at 95–100°C for 2 h a mixture of P_2O_5 (40 g) and H_3PO_4 (85%,

20 mL)) at 90–95°C for 45 min. The reaction mixture was cooled, decomposed with crushed ice, and extracted with ether (3×50 mL). The ether extract was washed with saturated aqueous $NaHCO_3$ (30 mL) and water (2×30 mL), and dried. Evaporation of the solvent followed by purification of the residue on a silica gel column using ethyl acetate–light petroleum (1:49) as eluent furnished a crystalline compound which was recrystallised from MeOH to give colourless plates of **17** (3.57 g, 82%), mp 153–154°C; (Found: C, 80.55; H, 9.14. $C_{21}H_{28}O_2$ requires C, 80.73; H, 9.03%); ν_{max} (KBr) 1628, 1599, 1458, 1236, 1042 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.02 (1H, s, 8-Ar*H*), 7.13 (1H, s, 5-Ar*H*), 6.67 (1H, s, 10-Ar*H*), 3.97 (3H, s, ArO*Me*), 3.93 (3H, s, ArO*Me*), 3.41 (1H, sept, *J*=6.9 Hz, C*H*Me_2), 2.95 (2H, t, *J*=6.3 Hz, ArCH_2), 1.95–1.86 (2H, m), 1.74–1.70 (2H, m), 1.39 (6H, s, CMe_2), 1.30 (6H, d, *J*=6.9 Hz, CHMe_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 156.5, 153.4, 142.4, 136.5, 132.8, 121.5, 118.9, 118.9, 101.2, 100.9, 55.3, 55.1, 39.1, 34.5, 31.4, 27.2, 26.5, 22.8, 19.6.

2.1.6. 1,2,3,4-Tetrahydro-1,1-dimethyl-6,9-dimethoxy-7-isopropylphenanthren-4-one (7). To a solution of the compound **17** (2.5 g, 8 mmol) in dry CH_2Cl_2 (60 mL) was added a finely powdered and homogenised mixture of pyridinium chlorochromate (8.6 g, 40 mmol) and celite (6 g). The reaction mixture was stirred at room temperature for 24 h, diluted with ether (60 mL) and filtered through a column of silica gel (60 g). The column was washed with two 50 mL portions of ether and the combined filtrate was evaporated under reduced pressure. The solid residue was crystallised from methanol to afford the ketone **7** (2.27 g, 87%) as white needles, mp 163–164°C; (Found: C, 77.38; H, 8.24. $C_{21}H_{26}O_3$ requires C, 77.27; H, 8.03%); ν_{max} (KBr) 1660, 1627, 1588 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.01 (1H, s, 5-Ar*H*), 8.03 (1H, s, 8-Ar*H*), 6.70 (1H, s, 10-Ar*H*), 4.06 (3H, s, ArO*Me*), 3.99 (3H, s, ArO*Me*), 3.41 (1H, sept, *J*=6.9 Hz, C*H*Me_2), 2.79 (2H, t, *J*=7.2 Hz, COCH_2CH_2), 2.04 (2H, t, *J*=7.2 Hz, COCH_2CH_2), 1.44 (6H, s, CMe_2), 1.29 (6H, d, *J*=6.9 Hz, CHMe_2); δ_C (75 MHz, $CDCl_3$) 199.4, 159.7, 159.0, 156.4, 137.5, 133.0, 119.3, 118.6, 118.3, 105.1, 99.6, 55.5, 55.3, 37.0, 36.8, 35.5, 30.0, 27.2, 22.6.

2.1.7. 3-Methyl-3-(1-carboxy-6-isopropyl-4,7-dimethoxy-2-naphthyl) butanoic acid (18). Ethyl formate (2.22 g, 30 mmol) was added dropwise under nitrogen to a stirred suspension of NaH (0.55 g, 23 mmol) in benzene (16 mL). A solution of the ketone **7** (1.5 g, 4.6 mmol) in benzene (5 mL) containing MeOH (2 drops) was then added at 0°C during 25 min. After stirring at 0°C for 2 h and at room temperature for 18 h, cold water (30 mL) was added with stirring and the aqueous layer was separated. The benzene layer was extracted with cold 5% aqueous NaOH (2×15 mL). The combined aqueous extract containing the hydroxymethelene derivative of the ketone **7** was cooled to 0°C and H_2O_2 (30%, 20 mL) was added dropwise with stirring. After stirring at 0°C for 6 h, and at room temperature for 12 h, the reaction mixture was acidified with cold dilute HCl and extracted with ethyl acetate (3×70 mL). The organic extract was washed with water (2×40 mL), dried, and concentrated. The solid residue was crystallised from a mixture of ethyl acetate and light petroleum to furnish the diacid **18** (1.5 g, 87.5%) as white needles, mp 160–161°C; (Found: C, 67.21; H, 7.20. $C_{21}H_{26}O_6$ requires C, 67.36; H, 7.00%); δ_H (300 MHz, $CDCl_3$) 7.98 (1H, s, Ar*H*), 7.04 (1H, s, Ar*H*), 6.71 (1H, s, Ar*H*), 3.98 (3H, s, ArO*Me*), 3.87 (3H, s, ArO*Me*), 3.40 (1H, sept, *J*=7.0 Hz, C*H*Me_2), 2.89 (2H, s, CH_2), 1.63 (6H, s, CMe_2), 1.28 (6H, d, *J*=7.0 Hz, CHMe_2).

2.1.8. Preparation of the diester 19. A solution of the diacid **18** (1.4 g, 3.74 mmol) in ether (30 mL) was esterified with an ice-cold ethereal solution of diazomethane (excess). Usual work-up furnished a crystalline material which was recrystallised from light petroleum to afford the diester **19** (1.46 g, 97%) as colourless plates, mp 85–86°C; (Found: C, 68.78; H, 7.70. $C_{23}H_{30}O_6$ requires C, 68.64; H, 7.51%); ν_{max} (KBr) 1732, 1720, 1628, 1600 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.98 (1H, s, Ar*H*), 6.77 (2H, s, Ar*H*), 4.00 and 3.98 (3H×2, s×2, ArO*Me* and $ArCO_2Me$), 3.88 (3H, s, ArO*Me*), 3.55 (3H, s, CO_2Me), 3.38 (1H, sept, *J*=6.9 Hz, C*H*Me_2), 2.82 (2H, s, CH_2), 1.58 (6H, s, CMe_2), 1.28 (6H, d, *J*=6.9 Hz, CHMe_2); δ_C (75 MHz, $CDCl_3$) 172.7, 171.9, 157.2, 155.4, 142.3, 138.1, 131.3, 120.9, 118.8, 118.5, 101.8, 101.2, 55.3, 55.0, 52.0, 51.2, 47.8, 38.7, 29.2, 27.2, 22.7.

2.1.9. Preparation of the half acid-ester 8. A solution of KOH (0.4 g) in water (2 mL) was added under nitrogen to a solution of the diester **19** (1.4 g, 3.48 mmol) in THF (3 mL). The reaction mixture was stirred at room temperature for 24 h and at 60°C for 1 h. It was then cooled, diluted with water (20 mL) and extracted with ether (15 mL) to remove any unhydrolysed diester. The aqueous alkaline layer was acidified with cold dilute HCl and extracted with ether (3×30 mL). The ether extract was washed with water (20 mL), dried, and evaporated. The solid residue was crystallised from a mixture of benzene and light petroleum to afford the half acid-ester **8** (1.22 g, 90%) as white plates, mp 158–159°C; (Found: C, 67.91; H, 7.21. $C_{22}H_{28}O_6$ requires C, 68.02; H, 7.27%); ν_{max} (KBr) 1720, 1709, 1628, 1595 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.99 (1H, s, Ar*H*), 6.77 (1H, s, Ar*H*), 6.75 (1H, s, Ar*H*), 3.96 (6H, s, ArO*Me* and $ArCO_2Me$), 3.88 (3H, s, ArO*Me*), 3.38 (1H, sept, *J*=6.9 Hz, C*H*Me_2), 2.82 (2H, s, CH_2), 1.57 (6H, s, CMe_2), 1.28 (6H, d, *J*=6.9 Hz, CHMe_2); δ_C (75 MHz, $CDCl_3$) 176.9, 172.9, 157.2, 155.5, 142.0, 138.2, 131.3, 120.8, 118.8, 118.5, 101.8, 101.2, 55.3, 55.0, 52.1, 47.7, 38.5, 29.3, 27.2, 22.7.

2.1.10. Preparation of the diazoketone 9. The diazoketone **9** was prepared from the half acid-ester **8** following the method of Tarbell and Price.[13] A solution of freshly distilled ethyl chloroformate (330 mg, 3.04 mmol) in anhydrous ether (4 mL) was added dropwise under nitrogen to a stirred solution of **8** (1.17 g, 3 mmol) and Et_3N (0.31 g, 3.07 mmol) in dry THF (4 mL) at −10°C. After the addition, the reaction mixture was stirred at −10°C for 1 h. The precipitated Et_3N. HCl was filtered off and washed with two 3 mL portions of dry ether without exposure to moisture. The filtrate containing the mixed anhydride was added to an ice-cold ethereal solution of diazomethane (prepared from 3 g of nitrosomethyl urea). After standing at 0°C for 1 h, the mixture was allowed to reach room temperature overnight. Evaporation of the solvent under reduced pressure afforded the diazoketone **9** as a pale yellow viscous liquid (1.14 g, 92%) (ν_{max} (film) 2105, 1723, 1628, 1595 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.90 (1H, s, Ar*H*), 6.69 (2H, s, Ar*H*), 4.82 (1H, s, COC*H*N_2), 4.00, 3.96 and 3.93 (3H×3, s×3,

ArO*Me*×2 and ArCO$_2$*Me*), 3.50 (1H, sept, *J*=7.0 Hz, C*H*Me$_2$), 2.66 (2H, s, C*H*$_2$), 1.53 (6H, s, C*Me*$_2$), 1.30 (6H, d, *J*=7.0 Hz, CH*Me*$_2$)) which was used for the subsequent intramolecular cyclisation without further purification.

2.1.11. Methyl 12-methoxy-2,7-dioxoabieta-5,8,11,13-tetraen-20-oate (10). A solution of the diazoketone **9** (1.1 g, 2.67 mmol) in dry CH_2Cl_2 (15 mL) was added during 2 min under nitrogen to a stirred solution of trifluoroacetic acid (20 mL) in CH_2Cl_2 (25 mL) at −20°C. The mixture was stirred at −20°C for another 3 min and then diluted with CH_2Cl_2 (40 mL). The dichloromethane solution was washed with water (3×20 mL), dried and concentrated. The crude product was chromatographed on silica gel (30 g). Elution of the column with ether–light petroleum (1:3) furnished the crystalline enedione **10** which was recrystallised from light petroleum to afford colourless plates (0.61 g, 62%), mp 208–209°C; (Found: C, 71.25; H, 7.26. $C_{22}H_{26}O_5$ requires C, 71.33; H, 7.07%); ν_{max} (KBr) 1728, 1715, 1656, 1598 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.05 (1H, s, 14-Ar*H*), 6.83 (1H, s, 11-Ar*H*), 6.71 (1H, s, C*H*═C), 3.89 (3H, s, ArO*Me*), 3.64 (3H, s, CO$_2$*Me*), 3.30 (1H, sept, *J*=6.9 Hz, C*H*Me$_2$), 3.82, 2.39 (2H, AB$_q$, *J*=18.0 Hz, C*H*$_2$COCH$_2$CMe$_2$), 2.53, 2.34 (2H, AB$_q$, *J*=16.0 Hz, CH$_2$COC*H*$_2$CMe$_2$), 1.37 (3H, s, *Me*), 1.28 (3H, s, *Me*), 1.26 and 1.23 (3H×2, d×2, *J*=6.9 Hz each, CH*Me*$_2$); δ_C (75 MHz, $CDCl_3$) 206.5, 183.8, 172.1, 162.1, 160.9, 140.5, 138.4, 127.7, 124.8, 123.4, 106.1, 55.7, 53.5, 51.8, 51.5, 46.6, 38.0, 32.2, 30.5, 26.7, 22.4, 22.1.

2.1.12. Methyl 12-methoxy-2-oxoabieta-8,11,13-trien-20-oate (11). A solution of the enedione **10** (0.57 g, 1.54 mmol) in ethyl acetate (15 mL) was hydrogenated over Pd–C (10%, 0.3 g) at room temperature and atmospheric pressure. Uptake of hydrogen (125 mL) ceased after 2 h. The mixture was filtered from the catalyst. Evaporation of the solvent followed by crystallisation of the solid residue from light petroleum furnished the keto-ester **11** (0.52 g, 94%) as colourless plates, mp 150–151°C; (Found: C, 73.79; H, 8.61. $C_{22}H_{30}O_4$ requires C, 73.71; H, 8.44%); ν_{max} (KBr) 1724, 1710, 1600 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.96 (1H, s, Ar*H*), 6.52 (1H, s, Ar*H*), 3.73 (3H, s, ArO*Me*), 3.61 (3H, s, CO$_2$*Me*), 3.66–2.81 (4H, m), 2.46–2.23 (4H, m), 2.01–1.94 (2H, m), 1.19 and 1.17 (3H×2, d×2, *J*=6.9 Hz each, CH*Me*$_2$), 1.12 (3H, s, *Me*), 0.85 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 209.1, 175.2, 155.2, 136.3, 136.2, 128.0, 127.2, 106.8, 55.4, 55.4, 52.3, 51.4, 51.2, 50.5, 36.2, 32.2, 29.4, 26.5, 22.7, 22.4, 22.0, 19.1.

2.1.13. Methyl 2,2-ethylenedithio-12-methoxyabieta-8,11,13-trien-20-oate (20). Ethanedithiol (0.6 g) and $BF_3{\cdot}Et_2O$ (0.5 mL) were added to a solution of the keto-ester **11** (470 mg, 1.3 mmol) in MeOH (3 mL) and the mixture was stirred at room temperature for 20 h. The reaction mixture was then diluted with ice-cold aqueous NaOH (5%, 15 mL) and the product was extracted with ether (3×25 mL). The ether extract was washed with water (2×20 mL), dried and evaporated. The solid residue was crystallised from a mixture of ether and light petroleum to afford the thioacetal **20** (0.52 g, 91%) as white needles, mp 161–162°C; (Found: C, 66.08; H, 8.02. $C_{24}H_{34}O_3S_2$ requires C, 66.32; H, 7.88%); δ_H (300 MHz, $CDCl_3$) 6.87 (1H, s, Ar*H*), 6.84 (1H, s, Ar*H*), 3.80 (3H, s, ArO*Me*), 3.73–3.17 (6H, m), 3.58 (3H, s, CO$_2$*Me*), 2.92–2.52 (3H, m), 2.24–1.51 (5H, m), 1.17 (6H, d, *J*=7.0 Hz, CH*Me*$_2$), 1.10 (3H, s, *Me*), 1.06 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 174.2, 154.8, 137.9, 136.0, 128.9, 126.7, 108.5, 65.9, 55.8, 54.2, 51.3, 51.3, 50.1, 49.1, 39.1, 37.6, 35.5, 33.0, 29.0, 26.4, 22.8, 22.8, 22.5, 18.7.

2.1.14. Methyl 12-methoxyabieta-8,11,13-trien-20-oate (12). The thioacetal **20** (0.48 g, 1.1 mmol) was refluxed with freshly prepared Raney nickel (ca. 3 g) in EtOH (10 mL) for 4 h. The reaction mixture was filtered and the filtrate was diluted with water (20 mL). Extraction of the product with ether (3×25 mL) furnished the ester **12** as a crystalline compound which was recrystallised from methanol to afford **12** (335 mg, 88%) as colourless plates, mp 111–112°C; (Found: C, 76.59; H, 9.43. $C_{22}H_{32}O_3$ requires C, 76.70; H, 9.36%); ν_{max} (KBr) 1720, 1610 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.89 (1H, s, Ar*H*), 6.74 (1H, s, Ar*H*), 3.76 (3H, s, ArO*Me*), 3.56 (3H, s, CO$_2$*Me*), 3.21 (1H, sept, *J*=6.9 Hz, C*H*Me$_2$), 2.97–2.37 (4H, m), 2.01–1.85 (2H, m), 1.65–1.22 (5H, m), 1.18 and 1.17 (3H×2, d×2, *J*=6.9 Hz each, CH*Me*$_2$), 0.97 (3H, s, *Me*), 0.77 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 176.2, 154.8, 138.2, 135.5, 128.7, 127.0, 107.5, 55.5, 52.3, 51.5, 47.9, 41.8, 37.1, 33.9, 32.1, 29.4, 26.5, 22.8, 22.5, 20.4, 20.1, 18.7.

2.1.15. 12-Hydroxyabieta-8,11,13-trien-20-oic acid [(±)-pisiferic acid] (1). A mixture of the ester **12** (120 mg, 0.348 mmol) and anhydrous $AlBr_3$ (0.8 g) in ethanethiol (3.8 mL) was stirred at room temperature for 15 h. The mixture was poured into cold dilute HCl and extracted with ether (3×20 mL). The ether extract was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (4 g). The solid fractions eluted with ether–light petroleum (1:3) were crystallised from a mixture of ether and light petroleum to give pisiferic acid (**1**) (102 mg, 92%) as colourless crystals, mp 226–227°C (sublimed) (lit.,[4] mp 226–227°C (sublimed)); (Found: C, 76.01; H, 9.14. $C_{20}H_{28}O_3$ requires C, 75.91; H, 8.92%); ν_{max} (KBr) 3490, 3400, 3370, 2961, 2900, 1694, 1615, 1593 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.89 (1H, s, 14-Ar*H*), 6.69 (1H, s, 11-Ar*H*), 3.12 (1H, sept, *J*=6.9 Hz, C*H*Me$_2$), 2.93–2.74 (3H, m), 2.53–1.84 (3H, m), 1.66–1.56 (1H,m), 1.50 (1H, dd, *J*=12.9, 2.6 Hz, C*H*CH$_2$), 1.45–1.22 (3H, m), 1.21 (6H, d, *J*=6.9 Hz, CH*Me*$_2$), 0.96 (3H, s, *Me*), 0.84 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 180.2, 150.7, 138.2, 133.5, 129.1, 127.4, 112.3, 52.2, 47.5, 41.8, 36.7, 34.1, 32.1, 29.3, 26.9, 22.6, 22.4, 20.3, 20.2, 18.6. (Lit.,[4] IR ($CHCl_3$): 3600, 3500–2400, 1690 cm^{-1}; lit.,[4] ^{1}H NMR ($CDCl_3$, 90 MHz): 0.84 and 0.97 (each 3H and s, C*Me*$_2$), 1.21 (6H, d, *J*=7 Hz, CH*Me*$_2$), 6.68 and 6.89 (each 1H and s, C-11 H and C-14 H); lit.,[21] ^{13}C NMR ($CDCl_3$, 22.5 MHz): 18.6 (t, 2), 20.1 (q, 19), 20.4 (t, 6), 22.4 (q, 16 or 17), 22.6 (q, 16 or 17), 26.9 (d, 15), 29.3 (t, 7), 32.4 (q, 18), 34.1 (s, 4), 36.7 (t, 1), 41.8 (t, 3), 47.5 (s, 10), 52.3 (d, 5), 112.3 (d, 11), 127.3 (d, 14), 129.2 (s, 8), 133.6 (s, 13), 138.2 (s, 9), 150.6 (s, 12), 181.1 (s, 20).

2.1.16. 12-Methoxyabieta-8,11,13-trien-20-oic acid [(±)-*O*-methylpisiferic acid] (4). To a solution of the ester **12** (120 mg, 0.348 mmol) in dry DMSO (6 mL) was added *t*-BuOK (630 mg, 5.62 mmol) and the mixture was stirred at 95°C for 70 min. It was then cooled, diluted with water

(15 mL), acidified with HCl, and extracted with ether (3×25 mL). The ether extract was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (4 g). The solid fractions eluted with ether–light petroleum (1:4) were crystallised from light petroleum to afford *O*-methylpisiferic acid (**4**) (82 mg, 72%) as white needles, mp 124–125°C; (Found: C, 76.16; H, 9.19. $C_{21}H_{30}O_3$ requires C, 76.33; H, 9.15%); IR data in chloroform (ν_{max} ($CHCl_3$) 2968, 2940, 1690, 1614, 1460 cm^{-1}) are consistent with the literature values;[7] δ_H (300 MHz, $CDCl_3$) 6.90 (1H, s, 14-Ar*H*), 6.76 (1H, s, 11-Ar*H*), 3.74 (3H, s, ArO*Me*), 3.20 (1H, sept, *J*=6.9 Hz, C*H*Me_2), 2.93–2.74 (3H, m), 2.55–1.85 (3H, m), 1.66–1.57 (1H, m), 1.52 (1H, dd, *J*=13.0, 2.7 Hz, C*H*CH_2), 1.46–1.22 (3H, m), 1.17 (6H, d, *J*=6.9 Hz, CH*Me*$_2$), 0.96 (3H, s, *Me*), 0.84 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 180.6, 154.9, 137.8, 135.9, 128.8, 127.1, 107.6, 55.5, 52.3, 47.7, 41.8, 36.7, 34.1, 32.1, 29.3, 26.5, 22.8, 22.5, 20.4, 20.1, 18.6. (Lit.,[7] ^{1}H NMR δ (100 MHz, $CDCl_3$) 0.83 (3H, s), 0.97 (3H, s), 1.17 (6H, d, *J*=7 Hz), 1.31–2.68 (9H, m), 2.68–3.03 (2H, m), 3.21 (1H, sep, *J*=7 Hz), 3.73 (3H, s), 6.75 (1H, s), 6.90 (1H, s), 11.10 (1H, br.s); lit.,[7] ^{13}C NMR δ (25 MHz, $CDCl_3$) 18.54, 20.08, 20.37, 22.49, 22.78, 26.54, 29.32, 32.09, 34.07, 36.67, 41.82, 47.49, 52.37, 55.41, 107.51, 127.08, 128.81, 135.90, 137.88, 154.88, 182.10; lit.[7] ν_{max} ($CHCl_3$) 3650–3100 (br.m), 3040 (w.sh), 2970 (s), 2940 (s), 2920 (s), 2880 (s), 2700–2300 (br.m), 1690 (s), 1615 (m), 1575 (w), 1505 (s), 1460 (s), 1450 (m), 1405 (m), 1390 (m), 1370 (m), 1325 (m), 1315 (w), 1295 (w), 1275 (m), 1250 (s), 1230 (m), 1215 (m), 1200 (w), 1180 (w), 1160 (m), 1140 (w), 1120 (w), 1105 (w), 1085 (w), 1080 (w), 1060 (m), 1030 (w), 1000 (w), 990 (w), 980 (w), 955 (w), 940 (w), 920 (w), 900 (w), 890 (w), 850 (w) cm^{-1}).

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