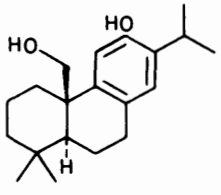
A Total Synthesis of (+)-Pisiferol

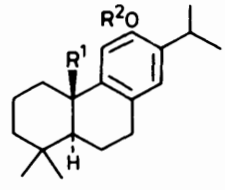
Yasufumi Tamai, Hisahiro Hagiwara, and Hisashi Uda *
Chemical Research Institute of Non-aqueous Solutions, Tohoku University, Katahira, Sendai 980, Japan

A total synthesis of (+)-pisiferol (**1**) has been accomplished by utilising an optically active Wieland–Miescher ketone analogue (*S*)-(+)-(**6**) bearing an angular protected hydroxymethyl group, as the key intermediate. Reductive methylation of the monoacetal (**7**) of compound (**6**), followed by Huang–Minlon reduction, gives the *trans*-decalone acetal (**9**). Construction of the remaining carbocycle leading to the dodecahydrophenanthrenone (**14**) is achieved through five sequential reactions (deprotection, methoxycarbonylation, Michael addition with methyl vinyl ketone, demethoxycarbonylation, and intramolecular aldol cyclisation). After introduction of the 2-hydroxypropan-2-yl side-chain, dehydration followed by base-catalysed aromatisation affords pisiferol methoxymethyl ether (**18**). Finally, hydrolysis furnishes (+)-pisiferol (**1**).

(+)-Pisiferol (**1**) is an abietane-type diterpene alcohol isolated from the leaves of *Chamaecyparis pisifera* (S. et Z.) Endl. (*Cupressaceae*),[1] together with the related diterpenoids bearing an angular oxygenated methyl group, (+)-pisiferic acid (**2**),[2] methyl (+)-pisiferate (**3**),[1] (+)-*O*-methylpisiferic acid (**4**),[3] and (+)-pisiferal (**5**).[3] Recently, Matsumoto and co-workers have



(**1**)



(**2**) $R^1 = CO_2H$, $R^2 = H$
(**3**) $R^1 = CO_2Me$, $R^2 = H$
(**4**) $R^1 = CO_2H$, $R^2 = Me$
(**5**) $R^1 = CHO$, $R^2 = H$

reported the synthesis of racemic pisiferol (**1**) through acid-catalysed cyclisation of a 4-(*p*-methoxyphenethyl)cyclohex-2-en-1-one derivative,[4] and of optically active (+)-(**1**) from (+)-abieta-8,11,13-trien-6-one,[5] in which introduction of the oxygen functionality to the angular methyl group has been attained by applying the remote oxidation procedure with lead tetra-acetate–iodine to the appropriate 2-[4] or 6-hydroxy[5] intermediate, respectively. Since we had successfully developed a preparative method for optically active Wieland–Miescher ketone analogues bearing an angular protected hydroxymethyl group, such as compound (**6**),[6] we have utilised an appropriate analogue for the synthesis of several diterpenes in optically active form. In this paper, we report the results of this investigation, which has resulted in a total synthesis of (+)-pisiferol (**1**) (Scheme).

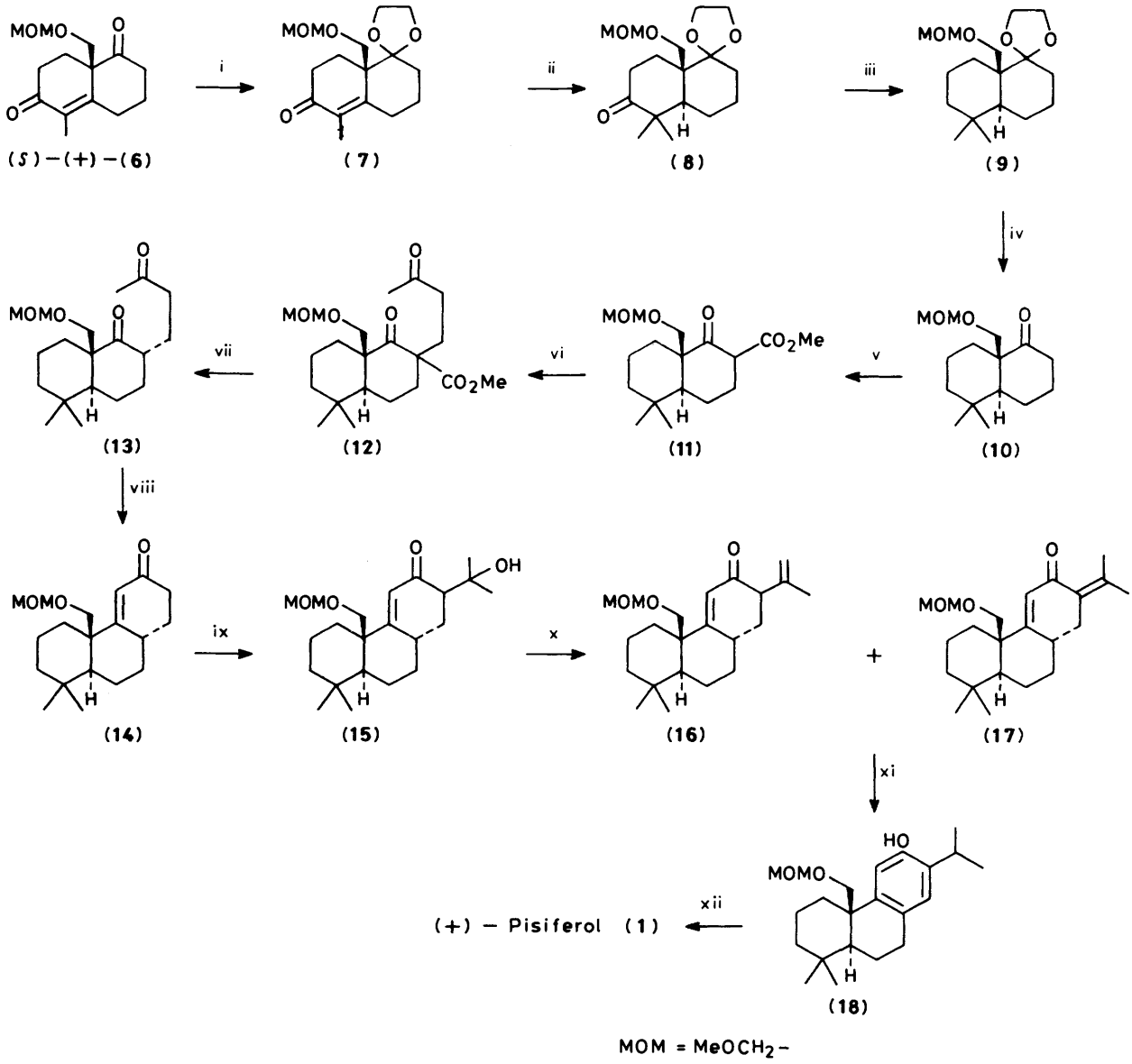
The methoxymethyl (MOM)-protected Wieland–Miescher ketone analogue (*S*)-(+)-(**6**) (93% e.e.)[6]† was chosen as the most suitable starting material. The saturated ketone function was selectively protected by D-camphor-10-sulphonic acid(CSA)-catalysed acetalisation with 2-methyl-2-ethyl-1,3-dioxolane to give the monoacetal (**7**) in 70% yield. Reductive methylation of compound (**7**) with lithium in liquid ammonia followed by methyl iodide afforded the *trans*-decalone (**8**) in 94% yield as a single product. Assignment of the *trans* stereochemistry at the ring junction in compound (**8**) followed from the fact that reductive alkylation of the analogous octalone derivatives was known to produce only *trans*-fused decalones,[7] and by conversion of (**8**) into the natural product (**1**). The Huang–Minlon reduction of compound (**8**) followed by selective hydrolysis of the ketone acetal function of the product (**9**) with pyridinium toluene-*p*-sulphonate (PPTS) in acetone, provided the desired decalone (**10**) in 87% overall yield.

In order to construct the remaining aromatic carbocycle, compound (**10**) was transformed quantitatively into the β-keto ester (**11**) by reaction of the enolate of compound (**10**) with dimethyl carbonate. The β-keto ester (**11**) reacted smoothly with methyl vinyl ketone (MVK) to produce the oily and crystalline diastereoisomeric oxobutyl-β-keto esters (**12**) (1.1:1) in 94% yield. However, the stereochemistry of each isomer could not be determined. Treatment of each diastereoisomer with lithium chloride in hexamethylphosphoric triamide (HMPA) gave the same diketone (**13**) in good yield. The diketone (**13**) thus obtained was stable to heat and base, indicating an equatorial (*S*) configuration of the oxobutyl side-chain. Base-catalysed internal aldol cyclisation of compound (**13**) was attempted under a variety of conditions, among which the most effective and reproducible was the use of sodium hydride in dimethoxyethane (DME) at 70—90 °C, affording the desired tricyclic enone (**14**) in 73% yield. With pyrrolidine–benzoic acid in benzene the enone (**14**) was formed in only 13% yield, and with sodium methoxide in methanol the starting diketone remained unchanged.

With the tricyclic nucleus of pisiferol successfully constructed, we next attempted introduction of the α′-isopropyl functionality. Thus, zinc chloride-assisted aldol reaction of the kinetic enolate of compound (**14**) with acetone produced the crystalline and oily diastereoisomeric aldol adducts (**15**) (2.8:1) in 60% combined yield. Dehydration of the major crystalline diastereoisomer (**15**) with thionyl chloride–HMPA led to the isopropenyl- (**16**) and isopropylidene-enone (**17**) (1:1) in 84.2% total yield.

With compounds (**16**) and (**17**) in hand, aromatisation of the newly constructed ring, followed by acetal hydrolysis, would complete the synthesis of (+)-pisiferol (**1**). Thus, double-bond isomerisation and aromatisation were achieved by treatment of either the isopropenyl- (**16**) or the isopropylidene-enone (**17**) with potassium t-butoxide in refluxing DME to give the pisiferol MOM ether (**18**) in 64% yield. Finally, acid-catalysed

† e.e. = enantiomeric excess.



Scheme. *Reagents and conditions:* i, D-camphor-10-sulphonic acid–ethylene glycol–2-methyl-2-ethyl-1,3-dioxolane, 35 °C; ii, Li–liq.NH_3–THF, then MeI, reflux; iii, NH_2NH_2·H_2O–KOH–water–EtOH–diethylene glycol, reflux—200 °C; iv, PPTS–acetone, reflux; v, NaH–KH–$(MeO)_2CO$–THF, reflux; vi, NaOMe–MeOH–methyl vinyl ketone, 0 °C–room temp.; vii, LiCl–HMPA, 120—140 °C; viii, NaH–DME, 70—90 °C; ix, LDA–ether–hexane–$ZnCl_2$, then acetone, 0 °C; x, $SOCl_2$–HMPA–CH_2Cl_2, room temp.; xi, $KOBu^t$–DME, reflux; xii, HCl–MeOH, 70 °C

hydrolysis of compound (**18**) furnished (+)-pisiferol (**1**) (94% e.e.) in 61% yield, identical with an authentic sample of natural pisiferol (i.r., n.m.r., mass, high-pressure liquid chromatography, mixed m.p., specific rotation).

In view of the prior conversion of pisiferol into pisiferic acid (**2**),[8] methyl pisiferate (**3**),[8] and pisiferal (**5**),[5] the work described herein constitutes a new total synthesis of these diterpenes in natural enantiomeric form.

Experimental

All m.p.s were determined with a Mitamura Rilsen hot-stage apparatus and are uncorrected. I.r. spectra were recorded on a Jasco A-3 spectrophotometer. ^1H N.m.r. spectra were obtained for solutions in deuteriochloroform with a Jeol PS-100 (100 MHz) instrument with tetramethylsilane as internal standard. Mass spectra were run on a Jeol JMS-DX300 spectrometer. Optical rotations $[\alpha]_D$ were determined for solutions in chloroform, except in the case of (+)-pisiferol, on a Jasco DIP-4S polarimeter at 20 °C. Medium-pressure liquid chromatography (m.p.l.c.) and high-pressure liquid chromatography (h.p.l.c.) were carried out on a Kusano CIG-Column System and a Jasco PRC-50 instrument with a silica gel packed column, respectively. Merck 60 GF-254 silica gel was used for preparative t.l.c. (p.l.c.). Anhydrous sodium sulphate was used for drying organic extracts. Microanalyses were carried out in the microanalytical laboratory of this Institute. Ether refers to diethyl ether, and light petroleum refers to the fraction boiling in the range 35—50 °C.

(8aS)-(+)-3,4,8,8a-*Tetrahydro*-8a-*methoxymethoxymethyl*-5-*methylnaphthalene*-1,6(2H,7H)-*dione* 1-*Ethylene Acetal* (**7**).—A solution of the (*S*)-(+)-MOMoxymethylenedione (**6**)[6] (1.2 g, 4.76 mmol), CSA (213 mg, 0.92 mmol), and ethylene glycol (1.8

ml) in 2-methyl-2-ethyl-1,3-dioxolane (90 ml) was stirred at 40 °C for 6 days under argon. The cooled reaction mixture was poured into a mixture of ether and aqueous sodium hydrogen carbonate in a separatory funnel. The organic layer was washed with brine and dried. Evaporation of the solvent, followed by column chromatography of the residue on silica gel, gave the monoacetal (**7**) [990 mg, 83% based on the consumed (**6**)] identical with the sample derived from the (*S*)-(+)-acetoxy analogue.[6]

(4aS,8aS)-(+)3,4,4a,7,8,8a-*Hexahydro*-8a-*methoxymethoxymethyl*-5,5-*dimethylnaphthalene*-1,6(2H,5H)-*dione* 1-*Ethylene Acetal* (**8**).—To a solution of lithium (99 mg, 14.3 mmol) in refluxing liquid ammonia (60 ml) was added dropwise a solution of the monoacetal (**7**) {$[\alpha]_D$ +88.3° (*c* 0.5), 93% e.e.} (1.4 g, 4.72 mmol) in anhydrous tetrahydrofuran (THF) (22 ml) during 15 min under nitrogen. After 15 min, methyl iodide (1.5 ml, 23.6 mmol) was added in one portion, and the reaction mixture was gently refluxed for 15 min. Ammonium chloride (2.4 g) was added and the mixture was kept at room temperature until almost all of the ammonia had evaporated. The residue was poured into water, and the product was extracted three times with methylene dichloride. The combined extracts were washed with brine, dried, and freed from the solvent. Column chromatography of the residue on silica gel [eluant hexane–ethyl acetate (2:1)] gave the *ethylenedioxydecalone* (**8**) (1.4 g, 94.4%), $[\alpha]_D$ + 5.0° (*c* 0.2); $\nu_{max.}$(neat) 2 973, 1 705, 1 460, 1 110, and 1 040 cm^{-1}; δ 1.07 (6 H, s, 5-Me_2), 1.40—2.60 (11 H, m, 5 × ring CH_2 and 4a-H), 3.32 (3 H, s, OMe), 3.71 and 3.86 (each 1 H, AB-type q, *J* 10 Hz, 8a-CH_2O), 3.92 (4 H, s, OCH_2CH_2O), and 4.55 (2 H, s, OCH_2O) (Found: C, 65.0; H, 9.4. $C_{17}H_{28}O_5$ requires C, 65.4; H, 9.0%).

(4aS,8aS)-(−)-3,4,4a,5,6,7,8,8a-*Octahydro*-8a-*methoxymethoxymethoxymethyl*-5,5-*dimethylnaphthalen*-1(2H)-*one* (**10**).—The ethylenedioxydecalone (**8**) (1.29 g, 4.13 mmol), hydrazine hydrate (27 ml), and potassium hydroxide (25.9 g) were dissolved in a mixture of water (25 ml), ethanol (95 ml), and diethylene glycol (152 ml), and the resulting solution was stirred and heated under reflux for 2 h. Then, the bath temperature was gradually raised to 200 °C to distil off the low boiling material, and was then maintained at this temperature for 2.5 h. After the mixture had cooled to room temperature, it was poured into water and extracted three times with methylene dichloride. The combined extracts were washed successively with water and brine, and dried. After removal of the solvent under reduced pressure, column chromatography of the residue on silica gel [eluant hexane–ethyl acetate (4:1)] gave the *ethylene acetal* (**9**) (1.07 g, 87%), $[\alpha]_D$ − 57.0° (*c* 0.2); $\nu_{max.}$(neat) 2 930, 1 455, 1 120, 1 105, and 1 045 cm^{-1}; δ 0.88 and 0.91 (each 3 H, s, 5-Me_2), 1.00—2.10 (13 H, m, 6 × ring CH_2 and 4a-H), 3.35 (3 H, s, OMe), 3.80—4.00 (6 H, d-like m, 8a-CH_2O and OCH_2CH_2O), and 4.61 (2 H, s, OCH_2O) (Found: C, 68.1; H, 9.8. $C_{17}H_{30}O_4$ requires C, 68.4; H, 10.1%).

A solution of the acetal (**9**) (1.013 g, 3.4 mmol) and PPTS (305 mg, 1.7 mmol) in acetone (155 ml) was heated under reflux for 6 h and the solvent was evaporated under reduced pressure. Water was added to the residue, and the product was extracted with ethyl acetate twice. The combined extracts were washed with brine, dried, and evaporated to dryness. Column chromatography of the residue on silica gel [eluant hexane–ethyl acetate (4:1)] gave the *decalone* (**10**) [838 mg, 99% based on consumed starting material (**9**)], $[\alpha]_D$ −38.9° (*c* 0.2); $\nu_{max.}$(neat) 1 715, 1 220, 1 150, 1 115, 1 105, 1 060, and 1 040 cm^{-1}; δ 0.84 and 0.89 (each 3 H, s, 5-Me_2), 1.00—2.82 (13 H, m, 6 × ring CH_2 and 4a-H), 3.29 (3 H, s, OMe), 3.86 and 4.04 (each 1 H, AB-type q, *J* 9 Hz, 8a-CH_2O), and 4.55 (2 H, s, OCH_2O) (Found: C, 70.6; H, 10.0. $C_{15}H_{26}O_3$ requires C, 70.8; H, 10.3%).

Methyl (4aS,8aS)-(−)-*Decahydro*-8a-*methoxymethoxymethyl*-5,5-*dimethyl*-1-*oxonaphthalene*-2-*carboxylate* (**11**).—To a refluxing slurry of sodium hydride (79 mg, 3.3 mmol) and a catalytic amount of potassium hydride in anhydrous THF (4 ml) and freshly distilled dimethyl carbonate (327 μl, 3.83 mmol) was added dropwise, during 15 min, a solution of the decalone (**10**) (329 mg, 1.3 mmol) in THF (4 ml), under nitrogen, and the mixture was refluxed for 14 h. After having cooled to room temperature, the mixture was poured into dil. (1M) hydrochloric acid–ice, and the product was extracted twice with ether. The combined extracts were washed thoroughly with water and then with brine, and dried. Evaporation of the extract, followed by p.l.c. of the residue [developer hexane–ethyl acetate (4:1)], gave the β-*keto ester* (**11**) (398 mg, 98.5%), which crystallised on evacuation. An analytical sample was purified by recrystallisation from ether–hexane and had m.p. 92—93 °C. Compound (**11**) had $[\alpha]_D$ −39.9° (*c* 0.2); $\nu_{max.}$(CCl_4) 1 750, 1 725, 1 655, 1 610, 1 440, 1 370, 1 180, 1 155, 1 150, and 1 050 cm^{-1}; δ 0.85 and 0.92 (each 3 H, s, 5-Me_2), 1.04—2.44 (12 H, m, 5 × ring CH_2 and 2- and 4a-H), 3.40 (3 H, s, CH_2-O*Me*), 3.76 (3 H, s, CO_2Me), 3.90 and 4.08 (each 1 H, AB-type q, *J* 10 Hz, 8a-CH_2O), and 4.65 (2 H, s, OCH_2O) (Found: M^+, 312.195 54; C, 65.1; H, 8.7. $C_{17}H_{28}O_5$ requires *M*, 312.193 74; C, 65.4; H, 9.0%).

Methyl (2ξ,4aS,8aS)-*Decahydro*-8a-*methoxymethoxymethyl*-5,5-*dimethyl*-1-*oxo*-2-(3-*oxobutyl*)*naphthalene*-2-*carboxylate* (**12**).—To a stirred solution of sodium methoxide in methanol, prepared from sodium (20 mg, 0.83 mg-atom) and anhydrous methanol (1.1 ml), at 0 °C was added a solution of the β-keto ester (**11**) (196 mg, 0.63 mmol) in methanol (5.5 ml), under nitrogen. Then, MVK (220 μl, 2.2 mmol) was added to the above solution in one portion, and the reaction mixture was stirred at room temperature for 20 h. The mixture was poured into aqueous ammonium chloride, and the products were extracted twice with ether. The combined extracts were washed with brine and dried. After removal of the solvent under reduced pressure, p.l.c. [developer hexane–ethyl acetate (2:1)] and then m.p.l.c. [eluant hexane–ethyl acetate (3:1)] of the residue gave the oily (120 mg) and crystalline (106 mg) diastereoisomers (at C-2) of the *oxobutyl*-β-*keto ester* (**12**) (total 94%). The oily diastereoisomer had $[\alpha]_D$ +23.0° (*c* 0.2); $\nu_{max.}$(neat) 1 740, 1 710, 1 460, 1 440, 1 370, 1 155, 1 110, and 1 050 cm^{-1}; δ 0.92 (6 H, br s, 5-Me_2), 1.00—2.70 (15 H, m, 7 × ring and side-chain CH_2 and 4a-H), 2.13 (3 H, s, COMe), 3.34 (3 H, s, CH_2O*Me*), 3.76 (3 H, s, CO_2Me), 3.78 and 3.94 (each 1 H, AB-type q, *J* 10 Hz, 8a-CH_2O), and 4.56 (2 H, s, OCH_2O) (Found: M^+, 382.235 16. $C_{21}H_{34}O_6$ requires *M*, 382.235 46). The crystalline diastereoisomer [analytical sample, m.p. 101 °C (from light petroleum)] had $[\alpha]_D$ +38.1° (*c* 0.202); $\nu_{max.}$(KBr) 1 720sh, 1 710, 1 370, 1 260, 1 210, 1 180, 1 150, 1 115, and 1 045 cm^{-1}; δ 0.88 and 0.92 (each 3 H, s, 5-Me_2), 1.00—2.80 (15 H, m, 7 × ring and side-chain CH_2 and 4a-H), 2.14 (3 H, s, COMe), 3.32 (3 H, s, CH_2O*Me*), 3.65 (3 H, s, CO_2Me), 3.62 and 4.00 (each 1 H, AB-type q, *J* 10 Hz, 8a-CH_2O), and 4.48 (2 H, s, OCH_2O) (Found: C, 66.3; H, 9.1. $C_{21}H_{34}O_6$ requires C, 65.9; H, 9.0%).

(2S,4aS,8aS)-(−)-3,4,4a,5,6,7,8,8a-*Octahydro*-8a-*methoxymethoxymethyl*-5,5-*dimethyl*-2-(3-*oxobutyl*)*naphthalen*-1(2H)-*one* (**13**).—A solution of the crystalline oxobutyl-β-keto ester (**12**) (168 mg, 0.45 mmol) and anhydrous lithium chloride (110 mg, 2.59 mmol) in anhydrous HMPA (2 ml) was heated at 120—140 °C for 8 h under argon. After having cooled to room temperature, the mixture was diluted with water, and the product was extracted twice with ether. The combined extracts were washed with brine and dried. Evaporation of the ether followed by p.l.c. and m.p.l.c. [developer and eluant hexane–

ethyl acetate (2:1)] of the residue afforded the *diketone* (**13**) (119 mg, 84%) as a single product.

In a similar manner, reaction of the oily isomer (**12**) (204 mg, 0.53 mmol) with lithium chloride (140 mg, 3.3 mmol) in HMPA (2 ml) gave the same *diketone* (**13**) (141 mg, 82%) [analytical sample, m.p. 78.5—79.5 °C (from hexane)], $[\alpha]_D$ −39.87° (*c* 0.2); $\nu_{max.}$(KBr) 1 710, 1 440, 1 365, 1 260, 1 165, 1 100, and 1 035 cm^{-1}; δ 0.84 and 0.88 (each 3 H, s, 5-Me_2), 1.00—2.90 (16 H, m, 7 × ring and side-chain CH_2 and 2- and 4a-H), 2.09 (3 H, s, COMe), 3.29 (3 H, s, OMe), 3.85 and 3.98 (each 1 H, AB-type q, *J* 10 Hz, 8a-CH_2O), and 4.52 (2 H, narrow AB-type q, *J* 8 Hz, OCH_2O) (Found: C, 70.5; H, 9.9. $C_{19}H_{32}O_4$ requires C, 70.3; H, 10.0%).

(4bR,8aS,10aS)-(−)-1,4b,5,6,7,8,8a,9,10,10a-*Decahydro*-4b-*methoxymethoxymethyl*-8,8-*dimethylphenanthren*-3(2H)-*one* (**14**).—A stirred suspension of the diketone (**13**) (151 mg, 0.47 mmol) and sodium hydride (54 mg, 2.25 mmol) in anhydrous DME (20 ml) was heated at 70—90 °C for 2.5 h under argon. After the mixture had cooled to room temperature, several pieces of chopped ice were added, and the resulting mixture was passed through a short column of silica gel with the aid of ethyl acetate. After removal of the solvent under reduced pressure, p.l.c. [developer hexane–ethyl acetate (2:1)] and then m.p.l.c. [eluant hexane–ethyl acetate (3:1)] of the residue gave the *tricyclic enone* (**14**) [101 mg, 73% based on recovered diketone (**13**) (5.5 mg, 3.6%)] [analytical sample, m.p. 152—153 °C (from ether–light petroleum)], $[\alpha]_D$ −123.1° (*c* 0.204); $\nu_{max.}$(CCl_4) 1 680, 1 615, 1 155, 1 110, 1 050, and 915 cm^{-1}; δ 0.86 and 0.88 (each 3 H, s, 8-Me_2), 1.00—2.80 (16 H, m, 7 × ring CH_2 and 8a- and 10a-H), 3.26 (3 H, s, OMe), 3.81 (2 H, s, 4b-CH_2O), 4.50 (2 H, s, OCH_2O), and 5.83 (1 H, s, 4-H) (Found: C, 74.8; H, 10.0. $C_{19}H_{30}O_3$ requires C, 74.5; H, 9.9%).

(2ξ,4bR,8aS,10aS)-1,4b,5,6,7,8,8a,9,10,10a-*Decahydro*-2-(1-*hydroxy*-1-*methylethyl*)-4b-*methoxymethoxymethyl*-8,8-*dimethylphenanthren*-3(2H)-*one* (**15**).—To a solution of lithium di-isopropylamide (0.56 mmol) in anhydrous ether (0.4 ml)–hexane (0.37 ml) at 0 °C under argon was added dropwise a solution of the tricyclic enone (**14**) (80 mg, 0.26 mmol) in ether (1.4 ml), and the mixture was stirred at 0 °C for 30 min. A chilled solution of zinc chloride (42 mg, 0.32 mmol) in ether (4 ml) was added in one portion, and then, after the mixture had been stirred for 5 min, a solution of anhydrous acetone (39 μl, 0.53 mmol) in ether (0.6 ml) was added in one portion. The resulting mixture was stirred at 0 °C for 20 min and the reaction was quenched by the addition of aqueous ammonium chloride. The products were extracted twice with ether. The combined extracts were washed with brine, dried, and evaporated to dryness. The residue was purified by p.l.c. and m.p.l.c. [developer and eluant hexane–ethyl acetate (2:1)] to give the crystalline (42 mg) and oily (15 mg) diastereoisomers of the *aldol adduct* (**15**) [total 60% based on the recovered enone (**14**) (4 mg)]. The crystalline diastereoisomer [analytical sample, m.p. 154—155 °C (from ethyl acetate)] had $[\alpha]_D$ −268.3° (*c* 0.17); $\nu_{max.}$($CHCl_3$) 3 450, 1 640, and 1 045 cm^{-1}; δ 0.86 and 0.89 (each 3 H, s, 8-Me_2), 1.22 [6 H, s, C(OH)Me_2], 1.00—2.20 (15 H, m, 6 × ring CH_2 and 2-, 8a-, and 10a-H), 2.70 (1 H, br, OH), 3.30 (3 H, s, OMe), 3.87 (2 H, s, 4b-CH_2O), 4.53 (2 H, s, OCH_2O), and 5.80 (1 H, s, 4-H) (Found: C, 72.7; H, 10.4. $C_{22}H_{36}O_4$ requires C, 72.5; H, 10.0%). The oily diastereoisomer had $[\alpha]_D$ +47.6° (*c* 0.202); $\nu_{max.}$($CHCl_3$) 3 450, 1 650, 1 380, 1 160, 1 055, and 1 045 cm^{-1}; δ 0.90 and 0.92 (each 3 H, s, 8-Me_2), 1.22 [6 H, s, C(OH)Me_2], 1.00—2.50 (15 H, m, 6 × ring CH_2 and 2-, 8a-, and 10a-H), 2.60 (1 H, br, OH), 3.28 (3 H, s, OMe), 3.73 and 3.83 (each 1 H, AB-type q, *J* 10 Hz, 4b-CH_2O), 4.50 (2 H, s, OCH_2O), and 5.88 (1 H, s, 4-H) (Found: M^+, 364. $C_{22}H_{36}O_4$ requires *M*, 364).

(2ξ,4bR,8aS,10aS)-(−)-1,4b,5,6,7,8,8a,9,10,10a-*Decahydro*-2-*isopropenyl*- *and* (4bR,8aS,10aS)-(−)-1,4b,5,6,7,8,8a,9,10,10a-*Decahydro*-2-*isopropylidene*-4b-*methoxymethoxymethyl*-8,8-*dimethylphenanthren*-3(2H)-*one* (**16**) *and* (**17**).—To a solution of the crystalline aldol adduct (**15**) (75 mg, 0.21 mmol) and HMPA (0.6 ml) in methylene dichloride (2 ml) at 0 °C under nitrogen was added thionyl chloride (75 μl, 1.03 mmol), and the reaction mixture was stirred at 0 °C for 20 min. The reaction was quenched by addition of ice, and the products were extracted twice with ether. The combined extracts were thoroughly washed with water and then with brine, and dried. After removal of the solvent, h.p.l.c. of the residue [eluant hexane–ethyl acetate (3:1)] gave the *isopropenyl enone* (**16**) (30 mg) and the *isopropylidene enone* (**17**) (30 mg) (total 84.2%). These compounds crystallised in a freezer. The isopropenyl enone (**16**) had m.p. 74—76 °C; $[\alpha]_D$ −163.8° (*c* 0.202); $\nu_{max.}$(CCl_4) 1 675, 1 610, 1 450, 1 150, 1 050, and 910 cm^{-1}; δ 0.86 and 0.89 (each 3 H, s, 8-Me_2), 1.00—2.40 (13 H, m, 6 × ring CH_2 and 8a-H), 1.75 (3 H, s, =CMe), 2.47—2.87 (1 H, m, 10a-H), 3.05 (1 H, q, *J* 5 Hz, 2-H), 3.29 (3 H, s, OMe), 3.83 (2 H, narrow AB-type q, *J* 11 Hz, 4b-CH_2O), 4.51 (2 H, s, OCH_2O), 4.77 and 4.93 (each 1 H, br s, =CH_2), and 5.89 (1 H, s, 4-H) (Found: C, 76.4; H, 10.1; M^+, 346. $C_{22}H_{34}O_3$ requires C, 76.3; H, 9.9%; *M*, 346). The isopropylidene enone (**17**) had m.p. 80—82 °C; $[\alpha]_D$ −174.4° (*c* 0.201); $\nu_{max.}$(CCl_4) 1 665, 1 630, 1 310, 1 150, 1 110, 1 045, and 910 cm^{-1}; δ 0.87 and 0.89 (each 3 H, s, 8-Me_2), 1.00—1.90 (13 H, m, 6 × ring CH_2 and 8a-H), 1.85 and 2.07 (each 3 H, s, =CMe_2), 2.40—2.90 (1 H, m, 10a-H), 3.26 (3 H, s, OMe), 3.83 (2 H, s, 4b-CH_2O), 4.52 (2 H, s, OCH_2O), and 5.87 (1 H, s, 4-H) (Found: C, 76.0; H, 10.2%; M^+, 346).

(4bR,8aS)-(+)-4b,5,6,7,8,8a,9,10-*Octahydro*-2-*isopropyl*-4b-*methoxymethoxymethyl*-8,8-*dimethylphenanthren*-3-*ol* = (+)-*Pisiferol MOM Ether* (**18**).—A slurry of the isopropenyl enone (**16**) (15 mg, 0.04 mmol) and potassium t-butoxide (21 mg, 0.19 mmol) in anhydrous DME (4 ml) was heated under reflux for 1 h under nitrogen. After having cooled to room temperature, the mixture was passed through a short column of silica gel with the aid of ether. Evaporation of the solvent followed by h.p.l.c. of the residue [eluant hexane–ethyl acetate (3:1)] afforded (+)-*pisiferol MOM ether* (**18**) (9.6 mg, 64%).

In similar fashion, reaction of the isopropylidene enone (**17**) (54 mg, 0.15 mmol) with potassium t-butoxide (61 mg, 0.54 mmol) in DME (6 ml) and work-up in the same manner gave the *MOM ether* (**18**) (31.3 mg, 58%), $[\alpha]_D$ +37.0° (*c* 0.154); $\nu_{max.}$(CCl_4) 3 600, 3 350, 1 160, 1 130, 1 055, 920, 730, and 660 cm^{-1}; δ 0.93 (6 H, s, 8-Me_2), 1.29 (6 H, d, *J* 7 Hz, CHMe_2), 1.00—2.86 (12 H, m, 5 × CH_2, 8a-H, and C*H*Me_2), 3.08 (3 H, s, OMe), 3.54 and 3.96 (each 1 H, AB-type q, *J* 10 Hz, 4b-CH_2O), 4.32 and 4.44 (each 1 H, AB-type q, *J* 7 Hz, OCH_2O), 5.06 (1 H, s, OH), 6.71 (1 H, s, ArH), and 6.85 (1 H, s, ArH) (Found: C, 76.1; H, 10.3; M^+, *m/z* 346.251 71. $C_{22}H_{34}O_3$ requires C, 76.3; H, 9.9%; *M*, 346.250 81).

(+)-*Pisiferol* = (4bR,8aS)-(+)-4b,5,6,7,8,8a,9,10-*Octahydro*-4b-*hydroxymethyl*-2-*isopropyl*-8,8-*dimethylphenanthren*-3-*ol* (**1**).—A solution of the MOM ether (**18**) (28.7 mg) in methanol (2 ml) containing conc. hydrochloric acid (1 drop) was heated at 70 °C for 7 h. Carbon tetrachloride (10 ml) was added, and the resulting solution was evaporated to dryness under reduced pressure. H.p.l.c. of the residue [eluant hexane–ethyl acetate (3:1)] gave (+)-pisiferol (**1**) (15.2 mg, 61%), $[\alpha]_D$ +83.7° (*c* 0.092 methanol, 94% e.e. based on the value determined by Dr. Yatagai: $[\alpha]_D$ +88.8°); m.p. 101—102 °C (thrice from hexane) (the freshly isolated natural specimen had m.p. 102—104 °C; mixed m.p. 101—102 °C); $\nu_{max.}$($CHCl_3$) 3 590, 3 460, 3 350, 1 620, 1 500, 1 420, 1 365, 1 200, 1 160, and 1 030 cm^{-1}; δ 0.89 and 0.93 (each 3 H, s, 8-Me_2), 1.21 (6 H, d, *J* 8 Hz, CHMe_2),

0.90—2.86 (11 H, m, 5 × ring CH_2 and 8a-H), 3.18 (1 H, septet, *J* 7 Hz, C*H*Me_2), 3.52 and 3.96 (each 1 H, AB-type q, *J* 11 Hz, 4b-CH_2O), 6.50 (2 H, br, 2 × OH), 6.68 (1 H, s, ArH), and 6.87 (1 H, s, ArH); *m/z* 302 (M^+, 17%), 271 (100), 229 (13), 215 (10), 201 (26), 189 (46), 175 (45), and 69 (55); these data were identical with those of natural pisiferol (Found: M^+, 302.223 98. Calc. for $C_{20}H_{30}O_2$: *M*, 302.224 48).

It has been reported[5] that the m.p. of (+)-pisiferol rises to a range of 146.6—148.5 °C by repeated recrystallisation from hexane. However, we did not attempt further purification, because of the very limited amounts of both synthetic and natural samples available, and so we could not confirm this observation.

Acknowledgements

We thank Dr. M. Yatagai, Forestry and Forest Products Research Institute, for providing the spectra (i.r., n.m.r., mass) and the specific rotation value of natural pisiferol. This work was supported by a Grant-in-Aid for Scientific Research (No. 58470023) from the Ministry of Education, Science, and Culture of Japan.

References

1 M. Yatagai and T. Takahashi, *Phytochemistry*, 1979, **18**, 176.
2 M. Yatagai, T. Shirato, Y. Hayashi, N. Fukuhara, and T. Takahashi, *Mokuzai Gakkaishi*, 1978, **24**, 267; H. Fukui, K. Koshimizu, and H. Egawa, *Agric. Biol. Chem.*, 1978, **42**, 1419.
3 M. Yatagai and T. Takahashi, *Phytochemistry*, 1980, **19**, 1149.
4 T. Matsumoto and S. Usui, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 1599.
5 T. Matsumoto, Y. Endo, and M. Okimoto, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 2018.
6 Y. Tamai, Y. Mizutani, H. Hagiwara, H. Uda, and N. Harada, *J. Chem. Res.*, 1985, (*S*) 148; (*M*) 1746.
7 G. Stork, S. Uyeo, T. Wakamatsu, P. Grieco, and J. Labovitz, *J. Am. Chem. Soc.*, 1971, **93**, 4945; M. E. Jung, *Tetrahedron*, 1976, **32**, 3; J. S. Dutcher, J. G. Macmillan, and C. H. Heathcock, *J. Org. Chem.*, 1976, **41**, 2663.
8 T. Matsumoto and S. Usui, Abstracts of Papers of the 25th Symposium on Aromatics, Terpenes, and Essential Oils in Japan, Yamaguchi, October 1981, p. 291.

Received 4*th November* 1985; *Paper* 5/1925