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SYNTHESIS OF BOTH THE ENANTIOMERS OF O-METHYL PISIFERIC ACID, A MITE GROWTH REGULATOR ISOLATED FROM CHAMAECYPARIS PISIFERA ENDL†

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Abstract -- Both the enantiomers of O-methyl pisiferic acid (12-methoxyabieta-8,11,13-trien-20-oic acid) were synthesized from (S)-3-hydroxy-2,2-dimethylcyclohexanone.

(+)-O-Methyl pisiferic acid **1a** was first isolated in 1980 by Yatagai and Takahashi from the leaves of Chamaecyparis pisifera Endl. (Japanese name: sawara).[1] Discovery of its bioactivity as a mite growth regulator by Ahn et al.[2] prompted us to synthesize it. The abietane-type diterpene **1a** inhibits both the hatching and the feeding of the two-spotted spider mite, Tetranychus urticae Koch, which is a serious pest to many crops. Herein we report a synthesis of both the enantiomers of O-methyl pisiferic acid (**1a** and **1a'**).

Synthesis of cyclic diterpenes has been actively pursued for almost half a century resulting in the preparation of many racemic diterpenes.[3] Synthesis of optically active diterpenes, however, was not so easy and achieved mostly either by optical resolution or by derivation from other abundant diterpenes such as resin acids. For example, the first synthesis of the natural enantiomer of podocarpic acid was achieved by resolution of an intermediate.[4] Commercially available natural podocarpic acid was subsequently converted into the natural enantiomer of taxodione, an anti-tumor diterpene.[5] Although an asymmetric synthesis of podocarpic acid was later reported by Yamada and co-workers, the optical yield in the key-step was only 42 %.[6]

Our strategy in the present work was to construct the abietane skeleton of **1a** starting from a simple chiral compound of high optical purity. The synthetic plan for **1a** is shown in Fig.1. (S)-3-Hydroxy-2,2-dimethylcyclohexanone **A** is employed as our starting material. This ketol **A** is readily available in high optical purity and has been utilized extensively by us in synthesizing various terpenes.[7~12] For the construction of ring C, we adopt the method developed by Meyer et al.[13] The ketol **A** is to be converted to the key-intermediate **C** via **B**. The bicyclic intermediate **C**, when coupled with **D**, affords **E** after aromatization. Further functional group transformations of **E** yields (+)-O-methyl pisiferic acid **1a**. In the course of the annulation step to give **B**, a stereoisomer **F** is also generated, which leads to (-)-O-methyl pisiferic acid **1a'**.

†Diterpenoid Total Synthesis -- 24. Part 23, K. Mori and M. Waku, Tetrahedron **41**, 5653 (1985). The experimental part of this work was taken from the forthcoming doctoral dissertation of H. M.

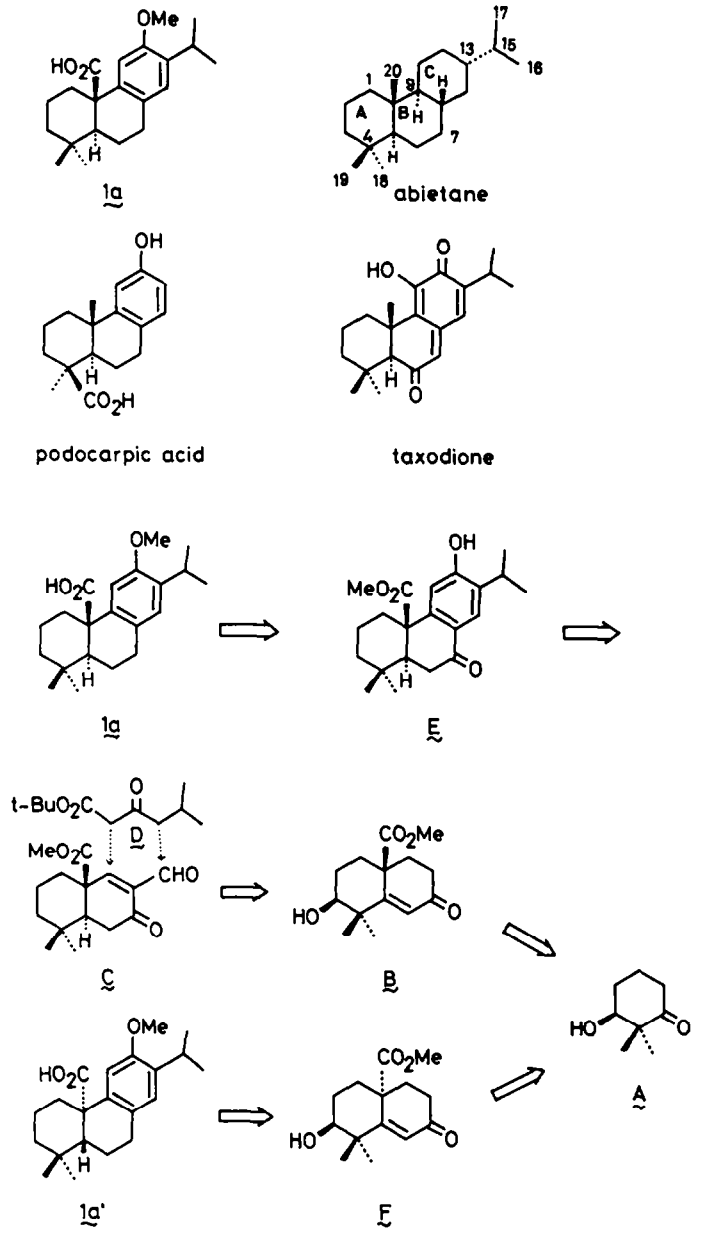

Fig.1. Structures of diterpenes and the synthetic plan for 1a and 1a'.

In Fig.2 is shown the actual synthetic route. Reduction of 2,2-dimethylcyclohexane-1,3-dione with baker's yeast gave **2a**, which was estimated to be of 98.3 % e.e. by the HPLC analysis of the corresponding (R)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester) **2c**.[7,8] After protecting the OH group of **2a** as a THP ether, the resulting **2b** was methoxycarbonylated with $CO(OMe)_2$ and NaH-KH[14] to give **3** quantitatively. Michael addition of **3** to methyl vinyl ketone was effected with a small amount of NaOMe in MeOH-C_6H_6 to give **4** in 93 % yield as a stereoisomeric mixture. To complete the annulation process, **4** was heated under reflux with pyrrolidine in C_6H_6 to give **5** in 85 % yield as a stereoisomeric mixture. Separation of the mixture was the next problem. To remove the complexity due to a chiral center in the THP protective group, deprotection of **5** was executed by treatment with p-TsOH in MeOH. Unexpectedly, the product was a mixture of a lactone **6** and a hydroxy ester

7a. Apparently, the stereoisomer of **5** with a β-oriented CO_2Me group was cleanly transformed into the lactone **6** by an intramolecular acid-catalyzed transesterification reaction with the β-OH group regenerated by deprotection of **5**. Chromatographic separation of the mixture yielded the less polar **6** (51.4 %) and the more polar **7a** (14.0 %), both as crystals. The stereochemistries of **6** and **7a** as depicted were self-evident from the S-absolute configuration of the OH group of **2a**. The lactone **6** was therefore regarded as an appropriate intermediate leading to the natural ditepene (+)-**1a**, while **7a** would yield (-)-**1a'**. The optical purity of **7a** was proved to be ~100 % by the HPLC analysis of its (R)- and (S)-MTPA esters **7b** and **7c**.

The next task was the conversion of the lactone **6** to a decalone derivative **10**, whose racemate (as Et ester) had previously been prepared by Meyer and Levinson.[15] We first tried to cleave the lactone ring of **6** by transesterificaion with NaOMe in MeOH, but the lactone **6** was recovered unchanged. Treatment of **6** with Me_3SiCl-NaI was also attempted in vain. The successful procedure for the conversion of **6** to **8a** was alkaline hydrolysis (KOH-MeOH) of **6** followed by acidification (AcOH), isolation of the hydroxy acid (**8a**, CO_2H instead of CO_2Me), and its esterificaion (CH_2N_2). A crystalline hydroxy ester **8a** was obtained in 70 % yield from **6**. The optical purity of **8a** was estimated to be ~100 % by the HPLC analysis of the corresponding MTPA esters **8b** and **8c**. Treatment of **8a** with 2.5 eq of TfCl and 5 eq of 4-N,N-dimethylaminopyridine (DMAP) in CH_2Cl_2[9] yielded **9** in 89 % yield. It should be noted that even with an eq OH group of **8a**, the elimination reaction proceeded smoothly to give **9**. When the hydrogenaion of **9** was carried out with Pd-C, the major product was not the expected **10** but a hydrogenolysis product without a ketone CO group. The hydrogenation was therefore executed with PtO_2. In this case, both the olefinic double bonds and the CO group were reduced to give a saturated hydroxy ester, which was oxidized with Jones CrO_3 to give **10**, $[\alpha]_D^{22}$ -7.21° ($CHCl_3$), in 80 % overall yield from **9**. Similarly, **7a** gave **9'** in 75.1 % yield, and **9'** was converted to **10'**, $[\alpha]_D^{23}$ +7.33° ($CHCl_3$), in 89 % yield. The IR, ^1H NMR and mass spectra of **10** and those of **10'** were of course identical.

The third phase of the synthesis is the construction of ring C. Conversion of the decalone derivative **10** to the key Michael acceptor **12** was executed as reported by Meyer et al.[13] Formylation of **10** with HCO_2Me and NaH in C_6H_6 furnished **11**, which was dehydrogenated with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) to give the desired unsaturated keto aldehyde **12**. The Michael donor for the construction of ring C was t-butyl isovalerylacetate **13**. This had previously been obtained by acylation of t-butyl acetoacetate with isovaleryl chloride followed by the removal of the Ac group.[16] We prepared **13** by alkylating a dianion derived from t-butyl acetoacetate.[17] Thus treatment of t-butyl acetoacetate with NaH and n-BuLi was followed by the addition of i-PrI to give **13** in 75 % yield. Addition of the Na-enolate of **13** to **12** was achieved in quantitative yield giving **14**. Treatment of **14** with p-TsOH in refluxing AcOH brought about the removal of t-BuO_2C group and an intramolecular aldol condensation to give crystalline **15** in 84 % yield. The trans-syn-cis stereochemistry of **15** as depicted was assigned on the basis of Meyer's work on analogous tricyclic compounds.[18] Aromatization of the C-ring of **15** was effected with $C_5H_5NHBr_3$ in AcOH to give **16** in quantitative yield. The C-8 CO group of **16** was then removed by hydrogenolysis (H_2/Pd-C/EtOAc-H_2SO_4) to give **17** in 89 % yield. Conventional methylation of **17** with Me_2SO_4 and K_2CO_3 furnished **1b** in 82 % yield. Finally **1b** was treated with t-BuOK in DMSO[19] to give (+)-O-methyl pisiferic acid **1a**, m.p. 128~129.5°, $[\alpha]_D^{16}$ +202° (MeOH). Its IR and ^1H NMR spectra were identical to the authentic spectra kindly sent to us by Prof. K. Wada and Dr. M. Yatagai. The mixture m.p. determination with an authentic sample (m.p. 123~125°) showed no m.p. depression (m.m.p. 123.6~126.8°). The overall yield of **1a** from **2a** was 6.6 % in 18 steps. The synthesis of (-)-**1a'** was also achieved in the same manner as above starting from **10'**. The overall yield of **1a'** from **2a**

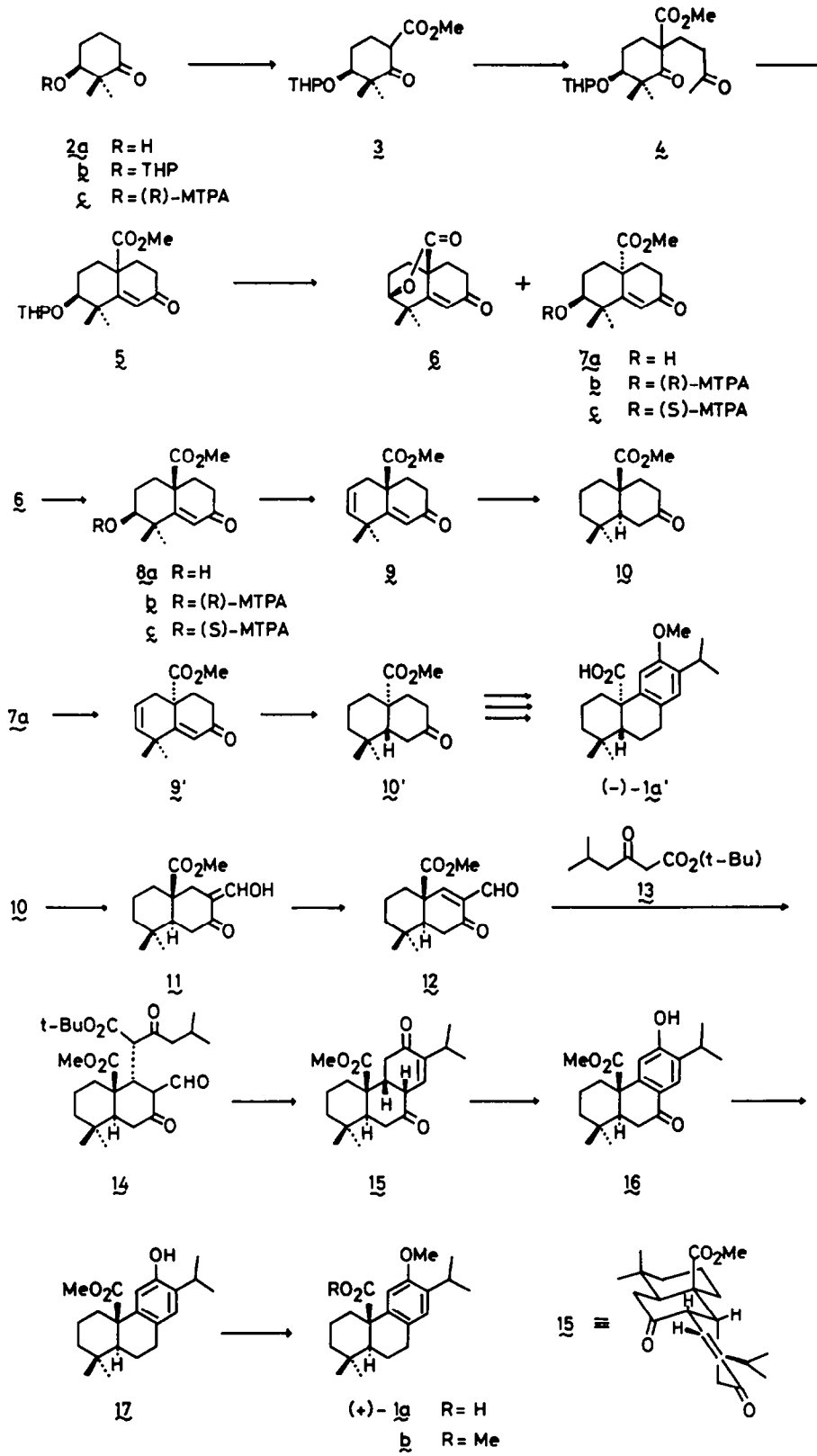

Fig. 2. Synthesis of O-methyl pisiferic acid.

was 1.8 % in 16 steps.

In summary we completed a chiral synthesis of O-methyl pisiferic acid starting from ketol **2a** of microbial origin. The present work proved the utility of ketol **2a** in chiral syntheses of diterpenes. The bioactivity of **1a** and **1a'** is now under investigation by Prof. K. Wada of Nagoya University.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils or as nujol mulls for solids on a Jasco IRA-102 spectrometer. NMR spectra were recorded with TMS as an internal standard at 60 MHz on a Hitachi R-24A spectrometer or at 100 MHz on a JEOL JMN FX-100 spectrometer or at 400 MHz on a JEOL JMN FX-400 spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. Mass spectra were recorded on a JEOL DX-303 spectrometer at 70 eV. Fuji Davison BW-820 MH was used for SiO_2 column chromatography.

(S)-(+)-2-Methoxycarbonyl-6,6-dimethyl-5-tetrahydropyranyloxycyclohexanone **3**. A mixture of NaH (10.9 g, 60 % dispersion in mineral oil, 272.5 mmol) and dimethyl carbonate (210 ml) in dry dioxane (90 ml) was stirred and heated under reflux under Ar. To this suspension was added dropwise a soln of **2b** [30.9 g, 136.5 mmol, 98.3 % e.e. (determined by the HPLC analysis of the corresponding (R)-MTPA ester **2c**)] in dry dioxane (90 ml). After a addition of a 10 ml portion of the soln of **2b**, KH (30 % dispersion in mineral oil, 1 ml) was added via a syringe to initiate the reaction. The addition of **2b** was continued over 65 min. After the complete addition, the mixture was stirred and heated under reflux for 70 min. It was then cooled in an ice-bath, and AcOH (8.22 g) was added slowly to quench the reaction. The mixture was acidified with AcOH to pH 6, diluted with brine (400 ml) and extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (47.5 g) was chromatographed over SiO_2 (300 g) to give 38.9 g (quantitative) of **3** as an oil, n_D^{24} 1.4874; $[\alpha]_D^{24}$ +0.75° (c=0.935, $CHCl_3$); νmax 3470~3100 (br.m), 1750 (m), 1715 (m), 1660 (s), 1615 (s), 1260 (s), 1205 (s), 1190 (s), 1135 (s), 1080 (s), 1060 (s), 1030 (s), 995 (s) cm^{-1}; δ (CCl_4) 1.13, 1.17, 1.23 (total 6H, each s), 1.36~2.05 (8H, m), 2.05~2.36 (2H, m), 3.21~4.10 (3H, m), 3.70 (3H, s), 4.51~4.85 (1H, m), 12.80 and 13.00 (total 1H, each s). (Found: C, 63.59; H, 8.50. Calc for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51 %).

(2RS,5S)-(+)-2-Methoxycarbonyl-6,6-dimethyl-2-(3'-oxobutyl)-5-tetrahydropyranyloxycyclohexanone **4**. A soln of **3** (38.9 g, 136.8 mmol) in dry C_6H_6 (200 ml) was added dropwise to a stirred soln of NaOMe (350 mg, 4.68 mmol) in dry MeOH (120 ml) at room temp under Ar. The mixture was stirred at room temp for 7 min and a soln of methyl vinyl ketone (21 ml, 18.2 g, 259.4 mmol) in dry MeOH (30 ml) and dry C_6H_6 (90 ml) was added dropwise over 65 min. The mixture was stirred at room temp for 2 h and treated with brine (100 ml) and water (200 ml). The organic layer was separated and the aq layer was extracted with ether. The combined extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (63 g) was chromatographed over SiO_2 (350 g) to give 45.1 g (93.2 %) of **4** as a viscous oil, n_D^{23} 1.4792; $[\alpha]_D^{23}$ +45.4° (c=0.863, $CHCl_3$); νmax 1740 (s), 1720 (s), 1715 (s), 1255 (m), 1205 (s), 1170 (s), 1130 (s), 1120 (s), 1080 (s), 1030 (s), 1005 (s) cm^{-1}; δ (CCl_4) 0.91, 0.93, 0.98, 1.00, 1.03, 1.10 (total 6H, each s), 1.24~1.75 (8H, m), 1.75~2.60 (6H, m), 2.05 (3H, s), 3.05~4.05 (3H, m), 3.60 (3H, s), 4.40~4.76 (1H, m). (Found: C, 64.21; H, 8.52. Calc for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53 %).

(3S,10RS)-(-)-Methoxycarbonyl-4,4-dimethyl-3-tetrahydropyranyloxy-Δ^5-7-octalone **5**. A soln of **4** (40.2 g, 113.4 mmol) and freshly distilled pyrrolidine (9.32 g, 136.6 mmol) in dry C_6H_6 (350 ml) was stirred and heated under reflux for 22 h with azeotropic removal of water. The mixture was cooled to room temp and concentrated in vacuo. The residue (55 g) was chromatographed over SiO_2 (270 g) to give 32.4 g (84.8 %) of **5** as a viscous oil, n_D^{21} 1.4965; $[\alpha]_D^{21}$ -6.00° (c=0.79, $CHCl_3$); νmax 3070 (w), 1735 (s), 1680 (s), 1615 (m), 1265 (m), 1205 (s), 1175 (s), 1120 (s), 1080 (s), 1035 (s), 1000 (s) cm^{-1}; δ ($CDCl_3$) 0.96, 1.19, 1.30 (total 6H, each s), 1.39~1.77 (8H, m), 1.80~2.30 (4H, m), 2.40~2.77 (2H, m), 3.10~4.15 (3H, m), 3.68 and 3.71 (total 3H, each s), 4.40~4.86 (1H, m), 6.14, 6.19, 6.21, 6.25 (total 1H, each s). (Found: C, 67.44; H, 8.53. Calc for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39 %).

(1S,8S)-(-)-7,7-Dimethyl-9-oxatricyclo[6,2,2,$0^{1,6}$]dodec-5-ene-4,10-dione **6** and (3S,10R)-(+)-3-hydroxy-10-methoxycarbonyl-4,4-dimethyl-Δ^5-7-octalone **7a**. p-TsOH was added to a stirred soln of **5** (26.7 g, 79.4 mmol) in MeOH (300 ml). The mixture was stirred for 2 h at room temp. $NaHCO_3$ (700 mg) was added to neutralize p-TsOH and the reaction mixture was concentrated in vacuo, diluted with brine (350 ml) and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in C_6H_6 (300 ml) and p-TsOH (300 mg) was added. The mixture was stirred for 2 h at room temp and treated with sat $NaHCO_3$ soln (300 ml). The organic layer was separated and the aq layer was extracted with EtOAc. The combined extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (350 g). Elution with C_6H_6-ether (20:1~6:1) gave 8.99 g (51.4 %) of **6** as crystals. This was recrystallized from n-haxane-EtOAc (5:1) to give colorless needles, m.p. 175~176°; $[\alpha]_D^{21}$ -29.6° (c=0.72, $CHCl_3$); νmax 3040 (w), 1755 (s), 1670 (s), 1625 (m), 1265 (m), 1255 (m), 1200 (s), 1140 (s), 1080 (s), 1005 (s), 980 (m), 945 (m), 930 (m) cm^{-1}; δ ($CDCl_3$) 1.26 (6H, s), 1.60~2.19 (6H, m), 2.20~2.56 (2H, m), 4.23~4.45 (1H, m), 5.97 (1H, s). (Found: C, 70.89; H, 7.30. Calc for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32 %). Further elution with C_6H_6-ether (5:1~1:2) gave 2.8 g (14.0%) of **7a** as crystals. This was recrystallized from n-hexane-EtOAc (5:1) to give colorless rods, m.p. 128~129°; $[\alpha]_D^{22}$ +277° (c=0.69, $CHCl_3$); νmax 3380 (s), 1720 (s), 1650 (s), 1605 (m), 1280 (m), 1265 (m), 1220 (s), 1195 (s), 1170 (s), 1100 (s), 1065 (m), 1030 (m), 980 (m) cm^{-1}; δ ($CDCl_3$) 0.98 (3H, s), 1.23 (3H, s), 1.40~2.70 (8H, m), 3.30 (1H, s, OH), 3.50~3.85 (1H, m), 3.70 (3H, s), 6.17 (1H, s). (Found: C, 66.49; H, 7.90. Calc for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99 %).

(3S,10S)-(-)-3-Hydroxy-10-methoxycarbonyl-4,4-dimethyl-Δ^5-7-octalone **8a**. A soln of KOH (2.50 g, 44.6 mmol) in water (30 ml) was added to a stirred soln of **6** (6.19 g, 28.1 mmol) in MeOH (120 ml). The mixture was stirred for 5 h at room temp and concentrated in vacuo to remove about 70 ml of MeOH. The reaction mixrture was cooled in an ice bath and acidified with AcOH to pH 5 and extracted with EtOAc. The extract was concentrated in vacuo to give ~100 ml of a soln of a hydroxy acid. This was used for the next step immediately. The above soln was cooled in an ice bath and treated with CH_2N_2 soln

in ether [prepared from 6 g (58.3 mmol) of N-nitroso-N-methylurea in the usual manner]. The mixture was stirred for 2 min at 0° and excess CH_2N_2 was destroyed by the dropwise addition of AcOH. The mixture was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 4.98 g (70.2 %) of **8a** as crystals. This was recrystallized from n-hexane-EtOAc (4:1) to give pale yellow needles, m.p. 120~121°; $[\alpha]_D^{19}$ -226° (c=0.945, $CHCl_3$); νmax 3520 (s), 1745 (s), 1675 (s), 1610 (m), 1275 (m), 1245 (m), 1225 (m), 1200 (m), 1175 (m), 1060 (s), 990 (m) cm^{-1}; δ ($CDCl_3$) 0.92 (3H, s), 1.25 (3H, s), 1.50~2.21 (6H, m), 2.25~2.80 (3H, m), 3.21~3.65 (1H, m), 3.71 (3H, s), 6.26 (1H, s). (Found: C, 66.57; H, 7.98. Calc for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99 %).

Determination of the optical purity of **7a**. According to the reported procedure,[20] (R)- and (S)-MTPA esters **7b** and **7c** were prepared from **7a**. HPLC [column, Nucleosil® 50-5, 25 cm x 4.6 mm; Solvent, n-hexane-THF (8:1), 1.0 ml/min; Detected at 254 nm] co-injection of (R)- and (S)-MTPA ester **7b** and **7c**: Rt 35.73 min and 40.15 min; (R)-MTPA ester **7b**: Rt 39.17 min (single peak). Therefore the optical purity of **7a** was determined to be ~100 % e.e.

Determination of the optical purity of **8a**. In the same manner as described for the preparation of **7b** and **7c**, **8b** and **8c** were prepared from **8a**. HPLC [column, Nucleosil® 50-5, 25 cm x 4.6 mm; Solvent, n-hexane-THF (60:1), 1.1 ml/min; Detected at 254 nm] co-injection of (R)- and (S)-MTPA ester **8b** and **8c**: Rt 12.44 min and 14.0 min; (R)-MTPA ester **8b**: Rt 12.14 min (single peak). Therefore the optical purity of **8a** was determined to be ~100 % e.e.

(R)-4a-Methoxycarbonyl-8,8-dimethyl-2,3,4,4a,5,8-hexahydronaphthalen-2-one **9**. To a stirred and ice-cooled soln of **8a** (2.33 g, 9.235 mmol) and DMAP (5.64 g, 46.16 mmol) in dry CH_2Cl_2 (100 ml) was added TfCl (8.39 g, 23.08 mmol) slowly under Ar. The mixture was stirred for 15 min at 0° and for 1 h at room temp. Water (50 ml) was added to the mixture and the stirring was continued for 15 min. The organic layer was separated and the aq layer was extracted with ether. The combined extract was washed with dil HCl, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (3 g) was chromatographed over SiO_2 (24 g) to give 1.92 g (88.7 %) of **9** as an oil, νmax 3050 (w), 1730 (s), 1675 (s), 1610 (m), 1260 (m), 1220 (s), 1205 (s) cm^{-1}; δ (CCl_4) 1.22 (3H, s), 1.27 (3H, s), 1.53~1.93 (2H, m), 1.95~2.50 (4H, m), 3.64 (3H, s), 5.43~5.73 (2H, m), 6.08 (1H, s); MS m/z 234 (M^+, 35 %), 219 (M^+-15, 7 %), 175 (100 %), 119 (59 %). This was used for the next step without further purification.

(5S,10S)-(-)-10-Methoxycarbonyl-4,4-dimethyl-7-decalone **10**. A suspension of PtO_2 (15 mg) in a soln of **9** (1.92 g, 8.20 mmol) in EtOAc (30 ml) was vigorously stirred for 36 h under H_2 at room temp. The mixture was filtered through Celite and the filter-cake was washed with EtOAc. The combined filtrate and washings were concentrated in vacuo to give crude alcohol as an oil, νmax 3440 (m), 1720 (s), 1390 (w), 1370 (m), 1210 (s), 1195 (s), 1140 (s), 1065 (m), 1035 (m) cm^{-1}; The above alcohol was dissolved in acetone (30 ml) and the mixture was cooled in an ice-bath. 8 N Jones reagent was added dropwise with stirring until the characteristic orange color of the reagent persisted. The mixture was stirred for 10 min at room temp and MeOH was added to destroy the excess Jones reagent. 10 % NaCl soln was added to dissolve the green salt and the mixture was extracted with ether. The extract was washed with water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (40 g) to give 1.56 g (80 %) of **10** as an oil. An analytical sample was obtained by distillation, b.p. 110~110.5°/0.2 Torr; n_D^{22} 1.4910; $[\alpha]_D^{22}$ -7.21° (c=1.165, $CHCl_3$); νmax 1725 (s), 1715 (s), 1390 (m), 1370 (m), 1295 (m), 1245 (s), 1235 (s), 1210 (s), 1200 (s), 1145 (s), 1100 (m), 985 (m) cm^{-1}; δ (CCl_4) 0.71 (3H, s), 0.86 (3H, s), 1.00~1.97 (9H, m), 2.00~2.56 (4H, m), 3.65 (3H, s); MS m/z 238 (M^+, 77 %), 223 (13.8 %), 206 (100 %), 178 (87.8 %), 156 (43.9 %), 124 (49.8 %), 109 (57.6 %) (Found: C, 70.27; H, 9.11. Calc for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31 %).

(5S,10R)-8-Formyl-10-methoxycarbonyl-4,4-dimethyl-Δ^8-7-octalone **12**. To a stirred and ice-cooled suspension of NaH (117.3 mg, 2.93 mmol, 60 % dispersion in mineral oil) in dry C_6H_6 (3 ml) was added dropwise a soln of **10** (351.2 mg, 1.47 mmol) in dry C_6H_6 (6 ml). HCO_2Me (244 mg, 4.05 mmol) was added and the mixture was stirred for 1 h at 5° and for 20 h at room temp. Water (10 ml) was added slowly to the mixture and the aq layer was separated. The organic layer was extracted with 1.5 % NaOH soln. The combined aq soln was acidified with conc HCl to pH 2 at 5° and extracted with EtOAc. The extract was dried (Na_2SO_4) and concentrated in vacuo to give 395 mg (quantitative) of the hydroxymethylene derivative **11**, νmax 3600~3300 (br. m), 1730 (s), 1640 (s), 1590 (s), 1210 (s) cm^{-1}; This was used for the next step without purification. To a stirred soln of the above **11** and 4 drops of AcOH in dry dioxane (4 ml) was added DDQ (336 mg, 1.48 mmol). The mixture was stirred for 15 min at room temp, diluted with $CHCl_3$ and filtered through Celite. The filter-cake was washed with $CHCl_3$. The combined filtrate and washings were washed several times with sat $NaHCO_3$ soln until the washings became colorless. The organic soln was dried (Na_2SO_4) and concentrated in vacuo to give 367.1 mg (93.7 % from **10**) of **12** as an oil, νmax 1720 (s), 1700 (s), 1680 (s), 1615 (m), 1395 (m), 1370 (m), 1340 (m), 1255 (s), 1220 (s), 1205 (s), 1125 (s), 880 (s) cm^{-1}; δ (CCl_4) 0.77 (3H, s), 0.92 (3H, s), 1.07~2.18 (7H, m), 2.18~2.88 (2H, m), 3.67 (3H, s), 7.12 (1H, s), 9.93 (1H, s); MS m/z 264 (M^+, 31 %), 249 (1.3 %), 236 (48 %), 205 (28 %), 169 (100 %), 135 (20 %), 109 (17 %). This was used for the next step without purification.

t-Butyl isovalerylacetate **13**. To a stirred and cooled suspension of NaH (760 mg, 19 mmol, 60 % dispersion in mineral oil) in dry THF (40 ml) was added dropwise a soln of t-butyl acetoacetate (3 g, 18.96 mmol) in dry THF (5 ml) at -5° under Ar. The mixture was stirred for 15 min at -5° and n-BuLi in n-hexane (1.65 N, 11.5 ml) was added dropwise below 0°. The mixture was stirred for 15 min at -5° and a soln of i-PrI (3.87 g, 22.8 mmol) in dry THF (5 ml) was added. The mixture was stirred for 3 h at -5~0° and for 1.5 h at room temp, poured into ice-3 N HCl and extracted with ether. The extract was washed with 5 % $Na_2S_2O_3$ soln, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled to give 2.86 g (75.3 %) of **13**, b.p. 54~57°/3 Torr. Its IR and NMR were identical with those reported previously.[16]

(5S,8RS,9S,10R,1'RS)-9-(1'-t-Butoxycarbonyl-2'-oxo-4'-methylpentyl)-8-formyl-10-methoxycarbonyl-4,4-dimethyl-7-decalone **14**. To a suspension of NaH (70.2 mg, 1.76 mmol, 60 % dispersion in mineral oil) in dry C_6H_6 (5 ml) was added dropwise a soln of **13** (312 mg, 1.56 mmol) in dry C_6H_6 (5 ml) at 0° under Ar. The mixture was stirred for 15 min at room temp and a soln of **12** (343.9 mg, 1.30 mmol) in dry C_6H_6 (10 ml) was added dropwise over 10 min. The mixture was stirred for 30 min at room temp. AcOH was added to quench the reaction and the mixture was poured into ice-water. The organic layer was separated and the aq layer was extracted with $CHCl_3$. The combined extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give 684.2 mg (quantitative) of **14** as an oil, νmax 1730 (s), 1640 (s), 1595 (s), 1395 (s), 1370 (s), 1255 (s), 1220 (s), 1150 (s) cm^{-1}; This was used for the next step immediately without purification.

(+)-Methyl (5S,8R,9R,10R)-7,12-dioxoabiet-13-en-20-oate **15**. A soln of **14** (661.8 mg, 1.43 mmol) and p-TsOH (20 mg) in AcOH (16 ml) was stirred and heated under reflux for 3.5 h under Ar. The mixture was cooled to room temp, treated with NaOAc (50 mg) and concentrated in vacuo. The residue was diluted with water and extracted with $CHCl_3$. The extract was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 379.5 mg (84.2 %) of **15** as crystals. This was recrystallized from n-hexane-EtOAc (5:1) to give colorless needles, m.p. 201~202°; $[\alpha]_D^{17}$ +52.0° (c=0.49, $CHCl_3$); νmax 1715 (s), 1705 (s), 1660 (s), 1220 (s), 1185 (m), 1155 (m), 1135 (m), 1075 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 0.82 (3H, s), 0.92 (3H, s), 1.02 (3H, d, J=7 Hz), 1.08 (3H, d, J=7 Hz), 1.12~1.80 (8H, m), 2.00~2.76 (4H, m), 2.88 (1H, sep, J=7 Hz), 3.72 (1H, t, J=5 Hz), 3.78 (3H, s), 6.73 (1H, dd, J=1 and 6 Hz). (Found: C, 73.16; H, 8.82. Calc for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73 %).

Methyl (5S,10R)-12-hydroxy-7-oxoabieta-8,11,13-trien-20-oate **16**. $C_5H_5NHBr_3$ (326.5 mg, 1.02 mmol) was added to a stirred soln of **15** (336.6 mg, 0.972 mmol) in AcOH (17 ml). The mixture was stirred for 1 h at room temp, treated with water (2 ml) and concentrated in vacuo. The residue was extracted with $CHCl_3$. The extract was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 333 mg (quantitative) of **16** as an amorphous solid. νmax ($CHCl_3$ soln) 3300 (br. m), 3040 (w), 1725 (s), 1660 (s), 1600 (s), 1505 (w), 1390 (w), 1370 (w), 1300 (s), 1270 (s), 1220 (s) cm^{-1}; This was used for the next step without purification.

Methyl (5S,10R)-12-hydroxyabieta-8,11,13-trien-20-oate **17**. 10 % Pd-C (150 mg) was added to a soln of **16** (280 mg, 0.813 mmol) and conc H_2SO_4 (3 drops) in EtOAc (20 ml) and the mixture was stirred vigorously for 13 h under H_2 at 35°. The mixture was filtered through Celite and the filtrate was washed with water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 239.8 mg (89.3 %) of **17** as a gum. νmax ($CHCl_3$ soln) 3450 (br.m), 3040 (w), 1720 (s), 1615 (w), 1510 (m), 1390 (m), 1370 (m), 1325 (m), 1220 (s) cm^{-1}; δ ($CDCl_3$) 0.77 (3H, s), 0.97 (3H, s), 1.21 (6H, d, J=7 Hz), 1.34~2.63 (9H, m), 2.63~3.21 (3H, m), 3.58 (3H, s), 6.82 (1H, s), 6.96 (1H, s); MS m/z 330 (M^+, 42 %), 271 (100 %), 255 (4 %), 229 (9 %), 215 (7 %), 201 (22 %), 189 (34 %), 175 (33 %). This was used for the next step without purification.

(+)-Methyl (5S,10R)-12-methoxyabieta-8,11,13-trien-20-oate **1b**. Anhydrous K_2CO_3 (8.7 g) was added to a soln of **17** (214 mg, 0.65 mmol) and Me_2SO_4 (0.55 ml) in dry acetone (35 ml). The mixture was stirred and heated under reflux for 17 h, cooled to room temp and filtered through Celite. The filter-cake was washed with ether. The combined filtrate and washings were concentrated in vacuo. The residue was treated with water (20 ml) and extracted with ether. The extract was washed with dil NH_3 aq, water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (230 mg) was chromatographed over SiO_2 (2 g) to give 182.8 mg (81.9 %) of **1b** as a viscous oil, n_D^{20} 1.5235; $[\alpha]_D^{19}$ +116° (c=0.44, MeOH); νmax 1720 (s), 1615 (m), 1505 (s), 1250 (s), 1220 (s), 1160 (s), 1135 (s), 1060 (s), 990 (m) cm^{-1}; δ ($CDCl_3$) 0.76 (3H, s), 0.95 (3H, s), 1.16 (6H, d, J=7 Hz), 1.32~2.60 (9H, m), 2.69~2.92 (2H, m), 2.95 (1H, sep, J=7 Hz), 3.53 (3H, s), 3.73 (3H, s), 6.75 (1H, s), 6.90 (1H, s); MS m/z 344 (M^+, 59 %), 329 (2 %), 285 (100 %), 269 (3 %), 243 (11.5 %), 229 (7 %), 215 (18.5 %), 203 (20.6 %), 189 (28.7 %).

(5S,10R)-(+)-12-Methoxyabieta-8,11,13-trien-20-oic acid [(5S,10R)-(+)-O-Methyl pisiferic acid] **1a**. A soln of **1b** (162 mg, 0.47 mmol) and t-BuOK (840 mg, 7.49 mmol) in dry DMSO (8.5 ml) was stirred and heated for 70 min at 95°. The mixture was cooled to room temp, poured into ice-water, acidified with conc HCl to pH 2 and extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (2 g) to give 110 mg of **1a** as crystals. This was recrystallized from n-hexane to give colorless needles, m.p. 128~129.5°, m.m.p. 123.6~126.8° (authentic sample: m.p. 123~125°); $[\alpha]_D^{16}$ +202° (c=0.16, MeOH) [lit.[2] $[\alpha]_D^{31}$ +214° (c=0.13, MeOH)]; CD (c=0.100 g/l, MeOH) $[\theta]_{239}^{24}$ +89000, $[\theta]_{219}^{24}$ -29000; νmax ($CHCl_3$ soln) 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), 950 (w) cm^{-1}; ^{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); ^{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; The IR and ^{1}H-NMR spectra were identical with the authentic spectra kindly sent to us by Prof. K. Wada and Dr. M. Yatagai. (Found: C, 76.48; H, 9.32. Calc for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15 %).

(S)-4a-Methoxycarbonyl-8,8-dimethyl-2,3,4,4a,5,8-hexahydronaphthalen-2-one **9'**. To a stirred and ice-cooled soln of **7a** (2 g, 7.93 mmol) and DMAP (4.84 g, 39.6 mmol) in dry CH_2Cl_2 (85 ml) was added TfCl (3.34 g, 19.8 mmol) dropwise under Ar. The mixture was stirred for 30 min at 0° and overnight at room temp. Water (50 ml) was added to the mixture and the stirring was continued for 30 min. The organic layer was separated and the aq layer was extracted with ether. The combined extract was washed with dil HCl, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (2.8 g) was chromatographed over SiO_2 (30 g). Elution with n-hexane-EtOAc (15:1) gave 830 mg (75.1 %, based on the consumed **7a**) of **9'**. Further elution with n-hexane-EtOAc (3:1) gave unchanged **7a** (810 mg). The IR, NMR and mass spectra of **9'** were identical with those of **9**. This was used for the next step without further purification.

(5R,10R)-(+)-10-Methoxycarbonyl-4,4-dimethyl-7-decalone **10'**. In the same manner as described for the preparation of **10**, 810 mg (3.46 mmol) of **9'** yielded 735 mg (89.2 %) of **10'**, b.p. 100~105°/0.1 Torr; n_D^{23} 1.4900; $[\alpha]_D^{23}$ +7.33° (c=1.03, $CHCl_3$); The IR, NMR and mass spectra were identical with those of **10**. (Found: C, 70.13; H, 9.43. Calc for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31 %).

(5R,10S)-8-Formyl-10-methoxycarbonyl-4,4-dimethyl-Δ^8-7-octalone **12'**. In the same manner as described for the preparation of **12**, 520 mg (2.18 mmol) of **10'** yielded 429.9 mg (74.5 %) of **12'**. The IR, NMR and mass spectra were identical with those of **12**. This was used for the next step without purification.

(5R,8RS,9R,10S,1'RS)-9-(1'-t-Butoxycarbonyl-2'-oxo-4'-methylpentyl)-8-formyl-10-methoxycarbonyl-4,4-dimethyl-7-decalone **14'**. In the same manner as described for the preparation of **14**, 429.9 mg (1.63 mmol) of **12'** yielded 780 mg (quantitative) of **14'**. The IR spectrum was identical with that of **14**. This was used for the next step without purification.

(-)-Methyl (5R,8S,9S,10S)-7,12-dioxoabiet-13-en-20-oate **15'**. In the same manner as described for the preparation of **15**,

780 mg (1.67 mmol) of **14'** yielded 450.0 mg (79.9 % from **12'**) of **15'** as crystals. This was recrystallized from n-hexane-EtOAc (5:1) to give colorless needles, m.p. 200-201°; $[\alpha]_D^{23}$ -50.8° (c=0.48, $CHCl_3$); The IR and NMR spectra were identical with those of **15**. (Found: C, 72.99; H, 8.60. Calc for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73 %).

Methyl (5R,10S)-12-hydroxy-7-oxoabieta-8,11,13-trien-20-oate **16'**. In the same manner as described for the preparation of **16**, 407.4 mg (1.18 mmol) of **15'** yielded 420 mg (quantitative) of **16'**. The IR spectrum was identical with that of **16**. This was used for the next step without purification.

Methyl (5R,10S)-12-hydroxyabieta-8,11,13-trien-20-oate **17'**. In the same manner as described for the preparation of **17**, 420 mg (1.22 mmol) of **16'** yielded 353.9 mg (91.1 % from **15'**) of **17'**. The IR, NMR and mass spectra were identical with those of **17**. This was used for the next step without purification.

(-)-Methyl (5R,10S)-12-methoxyabieta-8,11,13-trien-20-oate **1b'**. In the same manner as described for the preparation of **1b**, 340 mg (1.03 mmol) of **17'** yielded 251 mg (70.8 %) of **1b'**, n_D^{23} 1.5246; $[\alpha]_D^{23}$ -122° (c=0.75, MeOH); The IR, NMR and mass spectra were identical with those of **1b**.

(5R,10S)-(-)-12-Methoxyabieta-8,11,13-trien-20-oic acid [(5R,10S)-(-)-O-methyl pisiferic acid] **1a'**. In the same manner as described for the preparation of **1a**, 212.3 mg (0.62 mmol) of **1b'** yielded 131 mg (64.3 %) of **1a'** as crystals. This was recrystallized from n-hexane to give colorless needles, m.p. 125-126°; $[\alpha]_D^{23}$ -203° (c=0.15, MeOH); CD (c=0.120 g/l, MeOH) $[\theta]_{239}^{24}$ -110000, $[\theta]_{219}^{24}$ +26000; The IR and NMR spectra were identical with those of **1a**. (Found: C, 76.43; H, 9.21. Calc for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15 %).

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