BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 44, 2766—2770 (1971)

The Total Synthesis of (±)-Taxodione, A Tumor Inhibitor[1]

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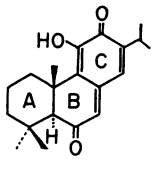
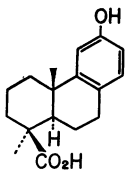
(Received March 19, 1971)

A total synthesis of (±)-taxodione (I) has been achieved. The Friedel and Crafts reaction of 1,2-dimethoxy-3-isopropylbenzene (IV) with succinic anhydride gave β-(4-hydroxy-3-isopropyl-5-methoxybenzoyl)propionic acid (V), which was then converted to γ-(4,5-dimethoxy-3-isopropylphenyl)butyric acid (IX). Since the cyclization of IX gave 6,7-dimethoxy-8-isopropyl-1-tetralone (X), the acid (IX) was subjected to bromination, cyclization, and then debromination. Subsequently, 7,8-dimethoxy-6-isopropyl-1-tetralone (XIII) was converted to (±)-7,8-dimethoxy-6-isopropyl-1-methyl-2-tetralone (XV). The condensation of (±)-XV with the methyl vinyl ketone gave a (±)-hexahydro-2-oxo-phenanthrene derivative (XVI), which was then further converted to (±)-11,12-dimethoxyabieta-5,8,11,13-tetraene (XIX). The introduction of a carbonyl group at the 6 position was achieved by the hydroboration of (±)-XIX, followed by the oxidation of the resulting 6-hydroxyl derivative. Finally, (±)-11,12-dimethoxyabieta-8,11,13-trien-6-one (XXI) was converted to (±)-I, whose IR, UV, and NMR spectra were identical in every respect with those of natural taxodione.

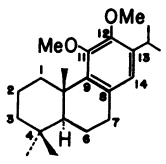
Taxodione, a tumor-inhibitory diterpenoid quinone methide, was recently isolated from *Taxodium distichum* Rich (Taxodiaceae) by Kupchan *et al.*[2,3] On the basis of spectral and chemical studies, they deduced the structure of taxodione to be I. Because of its unique structure and, especially, its significant tumor-inhibitory activity against the Walker carcinosarcoma 256 in rats, we planned the total synthesis of I by the route of C→B→A ring construction. During the course of the present work, Mori and Matsui[4] reported on the synthesis of I starting from podocarpic acid (II) *via* 11,12-dimethoxyabieta-8,11,13-triene (III). The appearance of their publication prompts us to report our own results. The present paper will describe the total synthesis of (±)-taxodione.



I



II



III

1,2-Dimethoxy-3-isopropylbenzene (IV),[5] which corresponds to the C ring in I, was chosen as our starting material. The Friedel and Crafts reaction of IV with succinic anhydride in dichloromethane gave a keto-acid (V), which was then methylated with diazomethane to a methyl ester (VI). The V acid gave a positive ferric chloride reaction in ethanol and showed bands at 1703 (CO_2H) and 1659 cm^{-1} (C=O) in its IR spectrum. The NMR spectrum of V in $CDCl_3$ showed signals at δ 7.41 ppm and δ 7.54 ppm (each 1H doublet and J=2 Hz) due to aromatic protons, thus suggesting the presence of two meta-coupling protons. Further, the signal due to the methine proton of the isopropyl group appeared at δ *ca.* 3.3 ppm in $CDCl_3$ and at δ *ca.* 3.7 ppm in pyridine-d_5. This pyridine-induced solvent shift[6] suggested the presence

1) Although the formulas depicted represent only one enantiomer, they are taken to indicate a racemate.

2) S. M. Kupchan, A. Karim, and C. Marcks, *J. Amer. Chem. Soc.*, **90**, 5923 (1968).

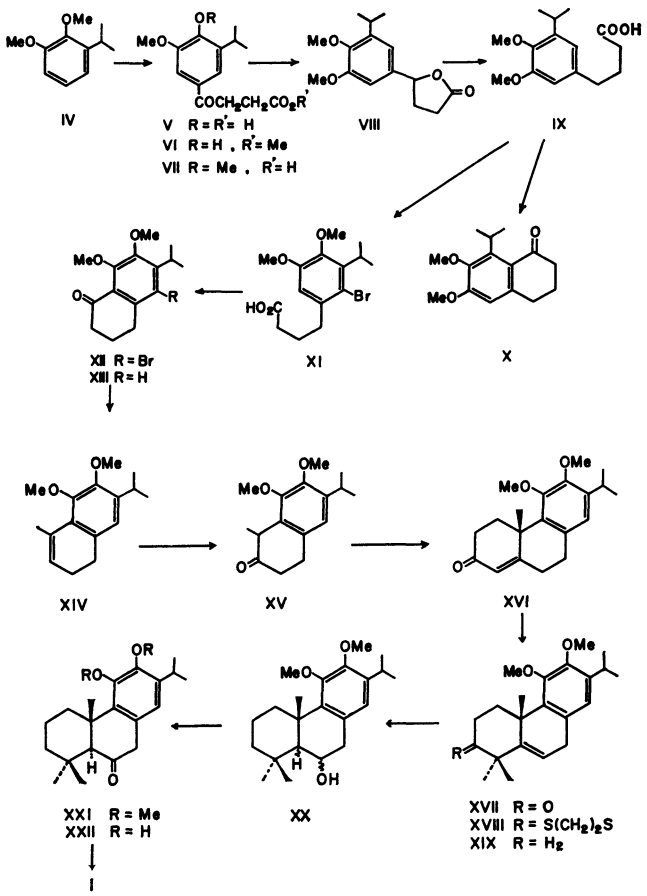
3) S. M. Kupchan, A. Karim, and C. Marcks, *J. Org. Chem.*, **34**, 3912 (1969).

4) K. Mori and M. Matsui, *Tetrahedron*, **26**, 3467 (1970).

5) J. D. Edwards, Jr., and J. L. Cashaw, *J. Org. Chem.*, **20**, 847 (1955).

6) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968).

of a hydroxyl group at the position ortho to the isopropyl group. From the above results, the structure of V was identified as β-(4-hydroxy-3-isopropyl-5-methoxy benzoyl)propionic acid. The methylation of V with dimethyl sulfate in an alkaline solution, followed by alkaline hydrolysis, afforded the corresponding methyl ether (VII), which gave a negative ferric chloride reaction. The reduction of the carbonyl group in VII to the corresponding methylene group in an almost quantitative yield was carried out in the following manner. That is, the ketone (VII) in aqueous sodium hydroxide was treated with sodium borohydride at room temperature; the resulting crude product was then heated on a steam bath to give a γ-lactone (VIII). The hydrogenolysis of VIII in methanol in the presence of Pd-C gave γ-(4,5-dimethoxy-3-isopropylphenyl) butyric acid (IX). Subsequently, the treatment of IX in benzene with phosphorous pentachloride, followed by the intramolecular cyclization of the resulting acid chloride with anhydrous stannic chloride, gave a 1-tetralone derivative (X), the NMR spectrum of which showed a signal at δ 4.11 ppm due to the methine proton of the isopropyl group. This chemical-shift value indicates that the methine proton in X is deshielded by a newly-formed carbonyl group, because the spectrum of IX showed a signal at δ 3.36 ppm attributable to the methine proton of the isopropyl group. From this spectral evidence, the structure of X was identified as 6,7-dimethoxy-8-isopropyl-1-tetralone, as had been expected. Since this (X) was not a useful intermediate for the synthesis of (±)-I, the IX acid was subjected to bromination in carbon tetrachloride; γ-(2-bromo-4,5-dimethoxy-3-isopropylphenyl)butyric acid (XI) was thus obtained. The structure of XI was also assigned on the basis of its NMR spectrum, which showed signals, at δ 3.70 ppm and at δ 6.68 ppm, attributable to the methine proton of the isopropyl group and an aromatic proton respectively. The treatment of XI with phosphorous pentachloride and then with stannic chloride gave a 5-bromo-1-tetralone derivative (XII); this was hydrogenated at room temperature in methanolic potassium hydroxide in the presence of Pd-C to give 7,8-dimethoxy-6-isopropyl-1-tetralone (XIII). The Grignard reaction of XIII with methylmagnesium iodide afforded the corresponding alcohol, which was then dehydrated with dilute sulfuric acid to give 3,4-dihydro-7,8-dimethoxy-6-isopropyl-1-methylnaphthalene (XIV). Subsequently, the naphthalene derivative (XIV) was treated with lead tetraacetate in acetic acid; the resulting crude product was then refluxed with ethanol containing concentrated sulfuric acid to give (±)-7,8-dimethoxy-6-isopropyl-1-methyl-2-tetralone (XV). The construction of the A ring was achieved by the condensation of (±)-XV with methyl vinyl ketone in the presence of sodium ethoxide; after chromatographic purification, (±)-2,3,4,9,10,12-hexahydro-5,6-dimethoxy-7-isopropyl-12-methyl-2-oxophenanthrene (XVI) was thus obtained. The methylation of (±)-XVI with methyl iodide in *t*-butanol in the presence of potassium *t*-butoxide gave (±)-11,12-dimethoxyabieta-5,8,11,13-tetraen-3-one (XVII), which was then further converted to (±)-11,12-dimethoxyabieta-5,8,11,13-tetraene (XIX) *via* a thioketal derivative (XVIII). The IR and NMR spectra of (±)-XIX were in good agreement with those of an optically-active sample[3] derived from natural taxodione. The introduction of a carbonyl group at the 6 position was achieved by the hydroboration of (±)-XIX, followed by the oxidation of the resulting 6-hydroxyl derivative (XX) with the Jones reagent.[7] Thus, (±)-11,12-dimethoxyabieta-8,11,13-trien-6-one (XXI) was obtained. Its IR and NMR spectra were also identical with the data reported for an optically-active XXI.[3,4] Mori and Matsui[4] had reported that the demethylation of XXI[8] with boron tribromide in dichloromethane gave 11,12-dihydroxyabieta-8,11,13-trien-6-one (XXII), which was then further oxidized with silver oxide in chloroform to give taxodione (I). On the other hand, the conversion of XXII[8] to I by aerial oxidation on silica gel had also been reported by Kupchan *et al.*[3] Therefore, our final step in the total synthesis of (±)-I was carried out as follows. By the method of Mori and Matsui,[4] (±)-XXI was demethylated with boron tribromide to give (±)-XXII, which was then immediately chromatographed on silica gel according to the method of Kupchan *et al.*[3] to give (±)-I as a yellow oil. The IR, UV, NMR, and mass spectra of the synthetic (±)-I were identical in every respect with those of natural taxodione.[3]



7) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, **1953**, 2548.

8) Optically-active substance.

Experimental

All the melting and boiling points are uncorrected. The NMR spectra were taken on a Hitachi Model R-20 NMR spectrometer (60 MHz), using tetramethylsilane as the internal standard. Their chemical shifts are presented in terms of δ values; s: singlet; bs: broad singlet; d: doublet; t: triplet; q: quartet; m: multiplet. The column chromatography was performed on Merck silica gel (0.08 mm).

β-(4-Hydroxy-3-isopropyl-5-methoxybenzoyl)propionic Acid (V). Anhydrous aluminum chloride (6.66 g) was stirred, over a period of 15 min, into a mixture of IV (3.60 g), succinic anhydride (2.10 g), and dry dichloromethane (20 m*l*) with cooling at 5—8°C. After the addition was complete, the mixture was stirred at room temperature for 4 hr and was then gently refluxed for 10 min. The mixture was poured into a mixture of concentrated hydrochloric acid (15 m*l*) and ice (*ca.* 100 g) and extracted with ethyl acetate, after which the ethyl acetate solution was extracted with aqueous sodium hydroxide (5%). After the alkaline extract had been acidified with dilute sulfuric acid, the yellow precipitate was collected, washed with water, and then recrystallized from aqueous methanol to give colorless needles, mp 169—171°C, which gave a green ferric chloride reaction in ethanol; yield, 3.2 g (60%). NMR in $CDCl_3$: 1.26 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.80 (2H, t, J=6 Hz, $-C\underline{H}_2CO_2H$), 3.32 (2H, t, J=6 Hz, $-COC\underline{H}_2-$), *ca.* 3.3 (1H, m, overlap, $-C\underline{H}(CH_3)_2$), 3.93 (3H, s, $-OC\underline{H}_3$), 7.41 and 7.54 (each 1H d and J=2 Hz, aromatic protons) ppm. NMR in pyridine-d_5: 1.34 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.08 (2H, t, J=6 Hz, $-C\underline{H}_2CO_2H$), 3.56 (2H, t, J=6 Hz, $-COC\underline{H}_2-$), *ca.* 3.7 (1H, m, overlap, $-C\underline{H}(CH_3)_2$), 3.68 (3H, s, $-OC\underline{H}_3$), 7.71 and 7.91 (each 1H d and J=2 Hz, aromatic protons) ppm.

Found: C, 63.11; H, 6.58%. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81%.

The starting IV (1.2 g) was recovered from the ethyl acetate solution.

Methyl β-(4-Hydroxy-3-isopropyl-5-methoxybenzoyl)propionate (VI). A solution of V (500 mg) in acetone (40 m*l*) was methylated with an excess ethereal diazomethane solution at room temperature for 3 hr. After a usual work-up, the product was recrystallized from a mixture of ether and petroleum ether (cooled on dry ice) to give VI as colorless prisms, mp 80.5—81.5°C, which gave a blue ferric chloride reaction in ethanol; yield, 410 mg. NMR in $CDCl_3$: 1.25 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.74 (2H, t, J=6 Hz, $-C\underline{H}_2CO_2-$), 3.30 (2H, t, J=6 Hz, $-COC\underline{H}_2-$), *ca.* 3.3 (1H, m, overlap, $-C\underline{H}(CH_3)_2$), 3.69 (3H, s, $-CO_2C\underline{H}_3$), 3.92 (3H, s, $-OC\underline{H}_3$), 6.26 (1H, s, $-O\underline{H}$), 7.39 and 7.55 (each 1H d and J=2 Hz, aromatic protons) ppm. NMR in pyridine-d_5: 1.32 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.87 (2H, t, J=6 Hz, $-C\underline{H}_2CO_2-$), 3.46 (2H, t, J=6 Hz, $-COC\underline{H}_2-$), *ca.* 3.6 (1H, m, overlap, $-C\underline{H}(CH_3)_2$), 3.59 (3H, s, $-CO_2C\underline{H}_3$), 3.68 (3H, s, $-OC\underline{H}_3$), 7.64 and 7.85 (each 1H d and J=2 Hz, aromatic protons) ppm.

Found: C, 64.50; H, 7.33%. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19%.

β-(4,5-Dimethoxy-3-isopropylbenzoyl)propionic Acid (VII). Dimethyl sulfate (37.8 g) was stirred, drop by drop at 60—65°C over a period of 1 hr, into a solution of V (26.6 g) in aqueous sodium hydroxide (10%: 100 m*l*). After the stirring had been continued for an additional hour, the mixture was hydrolyzed with aqueous sodium hydroxide (10%: 50 m*l*) at this temperature for 1 hr. The cold solution was then acidified with dilute sulfuric acid, and the precipitate was collected, washed with water, and then recrystallized from aqueous methanol to give VII as colorless needles, mp 131—133°C, which gave a negative ferric chloride reaction in ethanol; yield, 25.0 g (89%). NMR in $CDCl_3$: 1.24 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.80 (2H, t, J=6 Hz, $-C\underline{H}_2CO_2H$), 3.30 (2H, t, J=6 Hz, $-COC\underline{H}_2-$), 3.37 (1H, m, J=7 Hz, $-C\underline{H}(CH_3)_2$), 3.88 and 3.90 (each 3H and s, 2-$OC\underline{H}_3$), 7.42 and 7.53 (each 1H d and J=2 Hz, aromatic protons), 9.15 (1H, bs, $-CO_2\underline{H}$) ppm.

Found: C, 64.00; H, 7.20%. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19%.

γ-Hydroxy-γ-(4,5-dimethoxy-3-isopropylphenyl)butyric Acid γ-Lactone (VIII). A mixture of sodium borohydride (380 mg) and VII (4.8 g) in aqueous sodium hydroxide (2%: 40 m*l*) was allowed to stand at room temperature for 24 hr, after which it was acidified with dilute sulfuric acid. The mixture was heated on a steam bath for 20 min and then cooled. The precipitate was collected, washed with water, and then recrystallized from aqueous methanol to give VIII as colorless needles, mp 128—129°C; yield, 4.2 g (93%). IR in nujol: 1765 cm^{-1} (γ-lactone). NMR in $CDCl_3$: 1.22 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.8—2.9 (4H, m, $-(C\underline{H}_2)_2-$), 3.38 (1H, m, J=7 Hz, $-C\underline{H}(CH_3)_2$), 3.82 and 3.87 (each 3H and s, 2-$OC\underline{H}_3$), 5.47 (1H, t, J=6 Hz, $-C\underline{H}-O-$), 6.77 (2H, s, aromatic protons) ppm.

Found: C, 68.16; H, 7.62%. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63%.

γ-(4,5-Dimethoxy-3-isopropylphenyl)butyric Acid (IX). A solution of VIII (4.2 g) in methanol (150 m*l*) was hydrogenated at room temperature in the presence of Pd-C (10%: 1.4 g). After the absorption of hydrogen had ceased (after *ca.* 40 min), the mixture was filtered and washed with hot methanol; the filtrate was then evaporated. The residue was recrystallized from aqueous methanol to give IX as colorless needles (mp 83.5—84.5°C); yield, 4.1 g (98%). NMR in $CDCl_3$: 1.22 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.8—2.8 (6H, m, $-(C\underline{H}_2)_3-$), 3.36 (1H, m, J=7 Hz, $-C\underline{H}(CH_3)_2$), 3.81 and 3.87 (each 3H and s, 2-$OC\underline{H}_3$), 6.62 and 6.68 (each 1H d and J=2 Hz, aromatic protons), 8.65 (1H, bs, $-CO_2\underline{H}$) ppm.

Found: C, 67.39; H, 8.37%. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%.

6,7-Dimethoxy-8-isopropyl-1-tetralone (X). A mixture of IX (1.33 g), phosphorous pentachloride (1.04 g), and dry benzene (20 m*l*) was stirred at room temperature for 30 min, and then heated at 50°C for 5 min. After the solution had been cooled, a solution of anhydrous stannic chloride (1.5 m*l*) in dry benzene (5.0 m*l*) was added, drop by drop at 5—10°C, over a period of 15 min. The mixture was then further stirred at room temperature for 75 min, heated at 45—50°C for 1 hr, and then poured into dilute hydrochloric acid (5%: 25 m*l*). The organic layer was separated, washed with aqueous sodium carbonate and water successively, and then dried over sodium sulfate. After the removal of the solvent, the residue was recrystallized from aqueous methanol to give X as colorless prisms, mp 87.5—88.5°C; yield, 1.10 g (89%). NMR in $CDCl_3$: 1.34 (6H, d, J=7.5 Hz, $-CH(C\underline{H}_3)_2$), 2.02 (2H, m, J=6 Hz, $-CH_2C\underline{H}_2CH_2-$), 2.63 and 2.88 (each 2H t and J=6 Hz, 2-$C\underline{H}_2-$), 3.84 and 3.91 (each 3H and s, 2-$OC\underline{H}_3$), 4.11 (1H, m, J=7.5 Hz, $-C\underline{H}(CH_3)_2$), 6.65 (1H, s, aromatic proton) ppm.

Found: C, 72.41; H, 8.41%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

γ-(2-Bromo-4,5-dimethoxy-3-isopropylphenyl)butyric Acid (XI). A solution of bromine (10.9 g) in carbon tetrachloride (30 m*l*) was stirred, drop by drop at 3—5°C over a period of 1.5 hr, into a solution of IX (18.0 g) in carbon tetrachloride (120 m*l*).

After the stirring had then been continued for an additional 1.5 hr, the reaction mixture was washed successively with water, aqueous sodium thiosulfate, and water. The subsequent removal of the dried solvent gave a solid which was recrystallized from cyclohexane to give colorless crystals, mp 77.5—78.5°C; yield, 22.5 g (96%). This gave a positive Beilstein halogen test. NMR in $CDCl_3$: 1.34 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.95—2.95 (6H, m, $-(C\underline{H}_2)_3-$), 3.70 (1H, m, J=7 Hz, $-C\underline{H}(CH_3)_2$), 3.83 (6H, s, $2\text{-}OC\underline{H}_3$), 6.68 (1H, s, aromatic proton) ppm.

Found: C, 52.32; H, 6.14%. Calcd for $C_{15}H_{21}O_4Br$: C, 52.17; H, 6.09%.

7,8-Dimethoxy-6-isopropyl-1-tetralone (XIII). A solution of XI (20.7 g) in dry benzene (100 m*l*) was treated with phosphorous pentachloride (12.5 g) and then with anhydrous stannic chloride (25 m*l*) by a method similar to that used for X. The crude product was distilled under a vacuum to give XII as an oil, bp 168—174°C/0.85 mmHg; yield, 17.0 g (87%). NMR in $CDCl_3$: 1.36 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.10 (2H, m, J=6 Hz, $-CH_2C\underline{H}_2CH_2-$), 2.64 and 3.03 (each 2H t and J=6 Hz, $2\text{-}C\underline{H}_2-$), *ca.* 3.8 (1H, m, overlap, J=7 Hz, $-C\underline{H}(CH_3)_2$), 3.87 and 3.93 (each 3H and s, $2\text{-}OC\underline{H}_3$) ppm.

To a solution of the above XII (15 g) in methanol (30 m*l*), methanolic potassium hydroxide (10%: 100 m*l*) and Pd - C (10%: 5.0 g) were added; the mixture was then subjected to hydrogenolysis at room temperature. After the absorption of hydrogen had ceased, the mixture was filtered and the filtrate was evaporated under a vacuum. The residue was extracted with ether, which had been washed with water and then dried over sodium sulfate. After the removal of the solvent, the crude product was distilled under a vacuum to give XIII as an oil, bp 138—143°C/0.8 mmHg, which gave a negative Beilstein halogen test; yield, 10.8 g (95%). NMR in $CDCl_3$: 1.23 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.05 (2H, m, J=6 Hz, $-CH_2C\underline{H}_2CH_2-$), 2.61 and 2.90 (each 2H t and J=6 Hz, $2\text{-}C\underline{H}_2-$), 3.33 (1H, m, J=7 Hz, $-C\underline{H}(CH_3)_2$), 3.88 (6H, s, $2\text{-}OC\underline{H}_3$), 6.87 (1H, s, aromatic proton) ppm.

Found: C, 72.72; H, 8.12%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

3,4-Dihydro-7,8-dimethoxy-6-isopropyl-1-methylnaphthalene (XIV). A solution of XIII (8.20 g) in dry benzene (50 m*l*) was stirred, drop by drop over a period of 30 min, to a Grignard reagent which had been prepared from magnesium (960 mg), methyl iodide (5.70 g), and dry ether (30 m*l*). The mixture was refluxed for 5 hr, cooled, decomposed with dilute hydrochloric acid (10%: 60 m*l*), and then extracted with ether. The extract was washed with water and dried over sodium sulfate. After the removal of the solvent, the residue was dissolved in dry toluene (60 m*l*) containing *p*-toluenesulfonic acid (0.5 g) and the solution was refluxed for 3 hr. Then, the solvent was slowly distilled off over a period of 3 hr and the residue was extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate and water successively, dried over sodium sulfate, and then evaporated. The product was distilled under a vacuum to give an oil (5.4 g), bp 114—136°C/0.9 mmHg (mainly 118—119°C/0.9 mmHg). This was purified by means of column chromatography on silica gel (220 g), using benzene containing 2% ether as the eluent, to give XIV as a colorless oil (4.49 g). NMR in $CDCl_3$: 1.23 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.24 (3H, s, $=\overset{|}{C}C\underline{H}_3$), 2.65 (4H, t, J=7 Hz, $-(C\underline{H}_2)_2-$), 3.23 (1H, m, J=7 Hz, $-C\underline{H}(CH_3)_2$), 3.81 and 3.87 (each 3H and s, $2\text{-}OC\underline{H}_3$), 5.90 (1H, bt, J=4 Hz, $=C\underline{H}-$), 6.86 (1H, s, aromatic proton) ppm.

In another experiment, the dehydration of the Grignard reaction product was also carried out by the refluxing of the crude alcohol with dilute sulfuric acid (20 %) for 5.5 hr, similar results were obtained.

Found: C, 78.21; H, 9.11%. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00%.

(±)-7,8-Dimethoxy-6-isopropyl-1-methyl-2-tetralone (XV). A solution of XIV (530 mg) in acetic acid (4.0 m*l*) was stirred into a lead tetraacetate solution which had been freshly prepared from red lead oxide (2.06 g) and acetic acid (5.0 m*l*) at 55—60°C. After the stirring had been continued at room temperature for 1.5 hr, a few drops of ethylene glycol were added. The mixture was further stirred for 20 min, diluted with water (40 m*l*), and then extracted with ether which had been washed successively with aqueous sodium hydrogen carbonate and a saturated sodium chloride solution. After the removal of the ether, the residue was refluxed for 3 hr with ethanol (5.0 m*l*) containing concentrated sulfuric acid (0.5 m*l*), diluted with water, and then extracted with ether. The extract was washed successively with aqueous sodium hydrogen carbonate and water, dried over sodium sulfate, and then evaporated. The residue was chromatographed on silica gel (20 g), using benzene containing 2% ether as the eluent, to give XV as an oil (412 mg). IR in $CHCl_3$; 1706 cm^{-1} (C=O). NMR in $CDCl_3$; 1.24 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$, 1.40 (3H, d, J=8 Hz, $-\overset{|}{C}HC\underline{H}_3$), 3.87 and 3.90 (each 3H and s, $2\text{-}OC\underline{H}_3$), 6.88 (1H, s, aromatic proton) ppm.

Found: C, 73.20; H, 8.28. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45%.

(±)-2,3,4,9,10,12-Hexahydro-5,6-dimethoxy-7-isopropyl-12-methyl-2-oxophenanthrene (XVI). A solution of XV (3.56 g) in dry ether (20 m*l*) was stirred, at −10°C under a stream of nitrogen, into a sodium ethoxide solution which had been prepared from sodium (400 mg) and absolute ethanol (13 m*l*). After the stirring had been continued at this temperature for 30 min, methyl vinyl keton (1.0 g) was added. The mixture was further stirred at −10°C for 5 hr, at room temperature for 30 min, and then refluxed for 30 min. After cooling, the mixture was poured into dilute hydrochloric acid (10%: 50 m*l*) and extracted with ether. The extract was washed successively with aqueous sodium hydrogen carbonate and water, and then dried over sodium sulfate. After the removal of the ether, the crude product was purified by column chromatography on silica gel (250 g), using benzene containing 5% ether as the eluent, to give XVI as an oil (2.64 g: 61%). IR in $CHCl_3$; 1660 cm^{-1} (C=O). NMR in CCl_4; 1.17 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.63 (3H, s, $-\overset{|}{C}C\underline{H}_3$), 3.69 and 3.82 (each 3H and s, $2\text{-}OC\underline{H}_3$), 5.64 (1H, s, $-COC\underline{H}=$), 6.56 (1H, s, aromatic proton) ppm.

Found: C, 76.70; H, 8.36%. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34%.

(±)-11,12-Dimethoxyabieta-5,8,11,13-tetraen-3-one (XVII). A solution of XVI (2.51 g) in absolute *t*-butanol (20 m*l*) was stirred, at room temperature over a period of 10 min under a stream of nitrogen, to a potassium *t*-butoxide solution which had been prepared from potassium (1.19 g) and absolute *t*-butanol (20 m*l*). The mixture was stirred for 30 min, and to this was added methyl iodide (4.30 g). Under a stream of nitrogen, the mixture was stirred for 2 hr, refluxed for 30 min, cooled, poured into dilute hydrochloric acid (5%: 50 m*l*), and then extracted with ether. The ether extract was washed successively with water, aqueous sodium thiosulfate, and water. The solvent, after drying over sodium sulfate, was evaporated; the residue was then recrystallized from methanol to give XVII as colorless crystals (1.75 g), mp 154—154.5°C. The mother liquor of crystallization was evaporated, and the residue was chromatographed on silica gel (80 g), using benzene containing 3% ether as the eluent to give an addition-

al XVII (0.67 g). IR in $CHCl_3$; 1700 cm^{-1} (C=O). NMR in $CDCl_3$; 1.21 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.31 (6H, s, 2-$\dot{C}C\underline{H}_3$), 1.37 (3H, s, $-\dot{C}C\underline{H}_3$), 3.43 (2H, d, J=4 Hz, $=CH-C\underline{H}_2-$), 3.77 and 3.88 (each 3H and s, 2-$OC\underline{H}_3$), 5.80 (1H, t, J=4 Hz, $=C\underline{H}CH_2-$), 6.74 (1H, s, aromatic proton) ppm.

Found: C, 77.28; H, 9.06%. Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83%.

(±)-11,12-Dimethoxyabieta-5,8,11,13-tetraene (XIX). A mixture of XVII (1.90 g), ethanedithiol (1.0 m*l*), and freshly-distilled boron trifluoride etherate (3.0 m*l*) was allowed to stand overnight at room temperature. After a usual work-up, the crude product was recrystallized from a mixture of ether and petroleum ether to give a thioketal (XVIII: 1.72 g), mp 156—157.5°C, which showed no carbonyl absorption band in its IR spectrum. NMR in $CDCl_3$; 1.18 and 1.21 (each 3H d and J=7 Hz, $-CH(C\underline{H}_3)_2$, 1.48 (3H, s, $-\dot{C}C\underline{H}_3$), 1.51 (6H, s, 2-$\dot{C}C\underline{H}_3$), 3.73 and 3.85 (each 3H and s, 2-$OC\underline{H}_3$), 5.94 (1H, t, J=4 Hz, $=C\underline{H}CH_2-$), 6.63 (1H, s, aromatic proton) ppm.

Found: C, 69.08; H, 8.27%. Calcd for $C_{24}H_{34}O_2S_2$: C, 68.87; H, 8.19%.

A solution of XVIII (2.15 g) in hot ethanol (200 m*l*) was refluxed for 3 hr with Raney nickel (W-7) prepared from Raney alloy (50 g), allowed to stand overnight at room temperature, and then filtered. The filtrate was evaporated, and, to the residue dilute hydrochloric acid (10%: 10 m*l*) was added. The mixture was extracted with ether. The extract was washed with water, dried over sodium sulfate, and then evaporated. The crude product was purified by column chromatography on silica gel (150 g), using hexane containing 30% benzene as the eluent, to give XIX as an oil (1.27 g), the IR and NMR spectra of which were identical with the data[3] reported for an optically-active sample. NMR in $CDCl_3$; 1.16 and 1.23 (each 3H and s, $-\dot{C}(C\underline{H}_3)_2$), 1.18 and 1.21 (each 3H d and J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.46 (3H, s, $-\dot{C}C\underline{H}_3$), 3.13 (1H, m, overlap), 3.32 (2H, d, J=4 Hz, $=CHC\underline{H}_2-$), 3.75 and 3.84 (each 3H and s, 2-$OC\underline{H}_3$), 5.84 (1H, t, J=4 Hz, $=C\underline{H}CH_2-$), 6.67 (1H, s, aromatic proton) ppm. Literature.[3,8] NMR in $CDCl_3$: 1.08 (3H), 1.18 (3H), 1.24 (6H), 1.47 (3H, s), 3.12 (1H, septet), 3.28 and 3.37 (2H), 3.78 (3H, s), 3.88 (3H, s), 5.87 (1H, t, J=4 Hz), 6.67 (1H, bs) ppm.

(±)-11,12-Dimethoxyabieta-8,11,13-trien-6-one (XXI). A solution of XIX (1.470 g) in dry tetrahydrofuran (10 m*l*) was added to a suspension of sodium borohydride (210 mg) in dry tetrahydrofuran (10 m*l*). To the stirred and cooled (0—5°C) suspension, a solution of freshly-distilled boron trifluoride etherate (1.1 m*l*) in dry tetrahydrofuran (3.0 m*l*) was added over a period of 5 min. After the stirring had been continued for 3 hr at 0—10°C, a few drops of water were added to decompose the excess diborane, and then aqueous sodium hydroxide (12%: 1.6 m*l*) and hydrogen peroxide (30%: 1.6 m*l*) were added to the stirred solution. The mixture was stirred for 30 min, poured into a saturated sodium chloride solution, and then extracted with ether. The extract was washed with a saturated sodium chloride solution, dried over sodium sulfate, and then evaporated. The residual oil was chromatographed on silica gel (150 g) to give the crude XX as an oil (590 mg), the IR spectrum of which showed a band at 3600 cm^{-1}(OH).

A solution of the above XX (550 mg) in acetone (10 m*l*) was oxidized with the Jones reagent[7] (2N: 1.3 m*l*) at room temperature for 5 min. The mixture was then poured into water, and extracted with ether, after which the extract was washed with aqueous sodium chloride and then dried over sodium sulfate. After the removal of the ether, the residue was chromatographed on silica gel (50 g), using benzene as the eluent, to give XXI as a solid (126 mg). This was recrystallized from ether containing petroleum ether to give colorless crystals, mp 102—103.5°C. The IR and NMR spectra of XXI were identical with the data reported for an optically-active sample. IR in $CHCl_3$; 1718, 1605, 1560, 1470, 1450, 1405, 1363, 1318, 1065, 1020 $cm.^{-1}$ NMR in $CDCl_3$; 1.02 and 1.27 (each 3H and s, $-\dot{C}(C\underline{H}_3)_2$), 1.18 and 1.21 (each 3H d and J=7 Hz, $-CH-(C\underline{H}_3)_2$), 1.36 (3H, s, $-\dot{C}C\underline{H}_3$), 2.60 (1H, s, $-\dot{C}\underline{H}CO-$), 3.16 (1H, m, $-C\underline{H}(CH_3)_2$), 3.55 (2H, q, $-COC\underline{H}_2-$), 3.77 and 3.84 (each 3H and s, 2-$OC\underline{H}_3$), 6.62 (1H, s, aromatic proton) ppm.

Found: C, 76.89; H, 9.25%. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36%.

Literature: IR in $CHCl_3$[3] 1724, 1605, 1565, 1471, 1449, 1406, 1362, 1316, 1068, 1025 cm^{-1}. NMR in $CDCl_3$[3] 1.01 (3H), 1.11 (3H), 1.28 (6H, s), 1.36 (3H, s), 2.59 (1H, s), 3.15 (1H, septet), 3.46 and 3.58 (2H), 3.79 (3H, s), 3.87 (3H, s), 6.62 (1H, s) ppm, and NMR in $CDCl_3$[4] 1.08 (3H, s), 1.23 (3H, d, J=7 Hz), 1.25 (3H, d, J=7 Hz), 1.30 (3H, s), 1.40 (3H, s), 2.61 (1H, s), 3.15 (1H, septet, J=7 Hz), 3.50 (2H, q), 3.76 (3H, s), 3.85 (3H, s), 6.56 (1H, s) ppm.

(±)-Taxodione (I). A solution of XXI (110 mg) in dichloromethane (1.5 m*l*) was treated with a solution of boron tribromide (0.6 m*l*) in dichloromethane (1.5 m*l*) by the method of Mori and Matsui[4] to give a crude product (XXII), which was then immediately chromatographed on silica gel (15 g).

According to the method of Kupchan *et al.*,[3] elution with benzene was carried out; (±)-taxodione (I) was thus obtained as a yellow oil (47 mg). The identity of I with natural taxodione was confirmed by a comparison of their spectra. UV; λ_{max}^{EtOH} nm (ε): 322 (21000), 334 (21800), 405 (2700). IR in CCl_4; 3333, 1676, 1644, 1628, 1618, 1425, 1357, 1249, 1145, 1055, 907 cm^{-1} NMR in benzene-d_6; 0.96 and 1.02 (each 3H d and J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.15 and 1.22 (each 3H and s, $-C(C\underline{H}_3)_2$), 1.34 (3H, s, $-\dot{C}C\underline{H}_3$), 2.29 (1H, s, $-\dot{C}\underline{H}CO-$), 2.98 (1H, m, $-C\underline{H}(CH_3)_2$), 5.81 and 6.37 (each 1H and s, $2=C\underline{H}-$), 7.65 (1H, s, $-O\underline{H}$) ppm. Mass; *m/e* 314 (M^+), 299, 287, 286, 272, 271, 245, 232, 231.

The following spectral data have been reported for natural taxodione: UV[3] λ_{max}^{MeOH} nm (ε): 320 (25000), 332 (26000), 400 (2000). IR in CCl_4[3] 3344, 1681, 1647, 1631, 1621, 1427, 1361, 1252, 1149, 1060, 910 cm^{-1}. NMR in benzene-d_6[3] 0.97 (3H, d, J=7 Hz), 1.04 (3H, d, J=7 Hz), 1.18, 1.25, and 1.38 (each 3H and s) 2.32 (1H, s), 2.95 (1H, septet), 5.87 and 6.42 (each 1H and s), 7.70 (1H, s) ppm. Mass[3] *m/e* 314 (M^+), 299, 286, 245, 232, 231. Mass[4] *m/e* 314 (M^+), 299, 287, 286, 272, 271, 245, 232, 231.

The authors are grateful to Professor S. Morris Kupchan, University of Virginia, for his gift of natural taxodione.