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# AN APPROACH TO TAXODIONE INVOLVING BIOMIMETIC POLYENE CYCLIZATION METHODOLOGY[1,2]†

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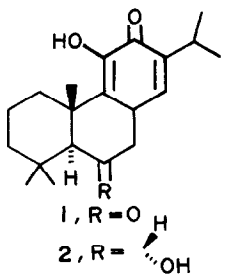
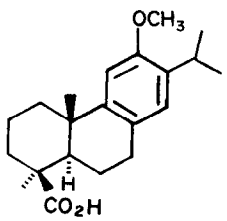
**Abstract**—A novel synthesis of 11,12-dimethoxyabieta-8,11,13-triene (**4**), involving the biomimetic cyclization of allylic alcohol **5** is described. This represents a formal total synthesis of taxodione (**1**), a tumor-inhibitory diterpenoid quinone methide. Treatment of the sodium salt of **18** with allyl bromide gave a 91% yield of allyl ether **19** which readily underwent a Claisen rearrangement to give (after methylation with dimethyl sulfate) the dimethoxy olefin **21** in 90% yield. Hydroboration with disiamylborane, followed by oxidative work-up gave alcohol **17** in 98% yield. Oxidation with Collins' reagent afforded **22** in 83% yield. which, upon treatment with isopropenylmagnesium bromide, gave allylic alcohol **23** in 91% yield. Conversion of **23** into chloro ketone **25** was readily effected in 80% yield *via* a chloro ketal Claisen rearrangement. This substance afforded epoxide **26** in 94% yield when treated with isopropenyllithium. Reduction of **26** with lithium in liquid ammonia gave the desired substrate **5** in 93% yield. When **5** was treated with trifluoroacetic acid in methylene chloride at *ca* −45° for 45 min, a 90% yield of the desired tricyclic material **6** was obtained. Conversion of **6** to *dl*-11,12-dimethoxy-abieta-8,11,13-triene (**4**) was effected in 59% yield by ruthenium tetroxide oxidation (to give **30**) followed by sodium cyanoborohydride reduction of the corresponding tosylhydrazone of **30**. Resolution of **30** involved the separation of the diastereomeric ketals **31**. Conversion of *d*-**30** into *d*-11,12-dimethoxyabieta-8,11,13-triene (**4**) was effected in the aforementioned manner used in the *dl*-series.

Several diterpenes were isolated and characterized in 1969 from the seed of *Taxodium distichum* Rich (Taxodiaceae).[3] Two of these substances, the quinone methides taxodione (**1**) and taxodone (**2**) showed significant activity *in vivo* against the Walker intramuscular carcinosarcoma 256 in rats and *in vitro* against cells derived from human carcinoma of the nasopharynx (KB).[3]




The novel structures of these substances in addition to their promising tumor-inhibitory properties, has stimulated many synthetic efforts.[4] In the first of these studies Mori and Matsui,[4a] completed a synthesis which was based on the conversion of podocarpic acid (**3**), into 11,12-dimethoxyabieta-8,11,13-triene (**4**). The latter substance was transformed, in 6 steps (commencing with lead tetraacetate-induced hydroxylation at C-7), into taxodione (**1**). We were intrigued with the possibility of using a biomimetic polyene cyclization[2,5] of a dienic alcohol such as **5**, to produce a tricyclic substance **6**, with the appropriate *trans* stereochemistry at the A/B ring juncture, which could then be readily converted to **4**.

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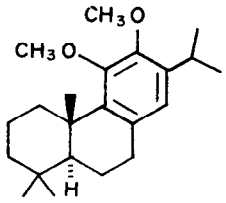


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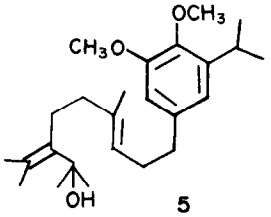
Such a synthesis would constitute a formal total synthesis of taxodione (**1**), which is the subject of the present paper.

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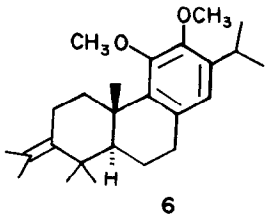


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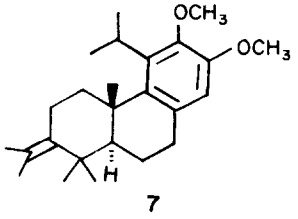


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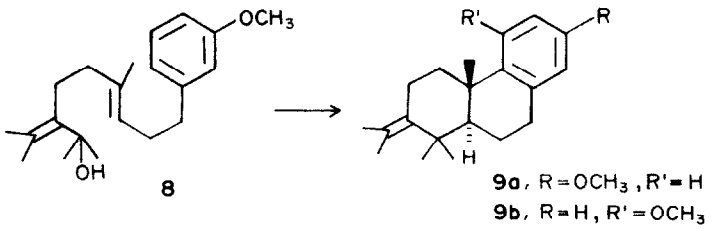
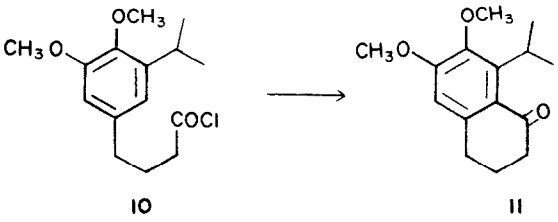
The cyclization of the substrate **5** (see below) was actually carried out prior to the study of the closely related cyclization **8**→**9a** that was employed in the reported total synthesis of the pentacyclic triterpenoid

†This publication is respectfully dedicated to the memory of Professor Frantisek Šorm.



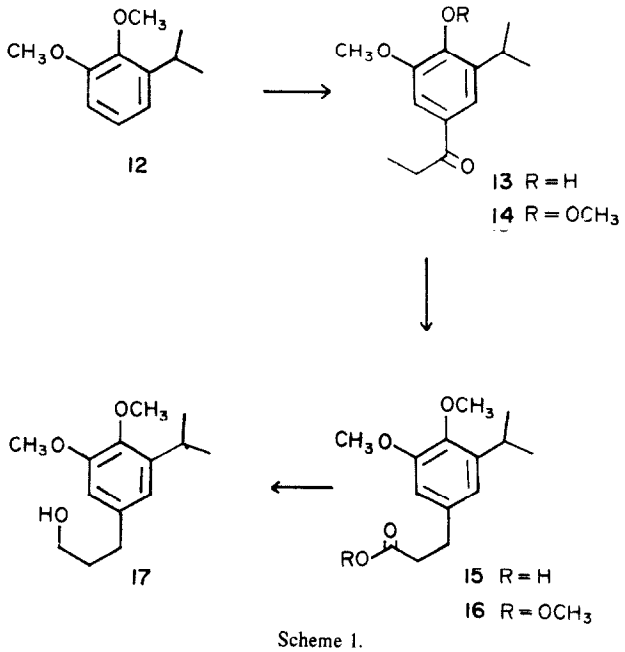

serratenediol.[6] There is always a problem of regioselectivity in such cyclizations; thus substrate **8** yields **9b** as well as **9a** in a ratio of 1:5.7. In the case of the cyclization of **5** it seemed reasonable to expect that ring closure would occur preferentially ortho to the methoxy group so as to minimize steric interaction with the more bulky isopropyl substituent and thusly afford predominantly the desired product **6**. On the other hand, Matsumoto[4b] observed that the intramolecular Friedel–Crafts acylation of **10** with Stannic chloride led to the unexpected ring closure ortho to the isopropyl group to give **11**. Therefore it was not obvious *a priori* whether the cyclization would proceed in the desired manner to give **6** or in the opposite sense to yield the undesired product. Fortunately the result was favorable as described below.



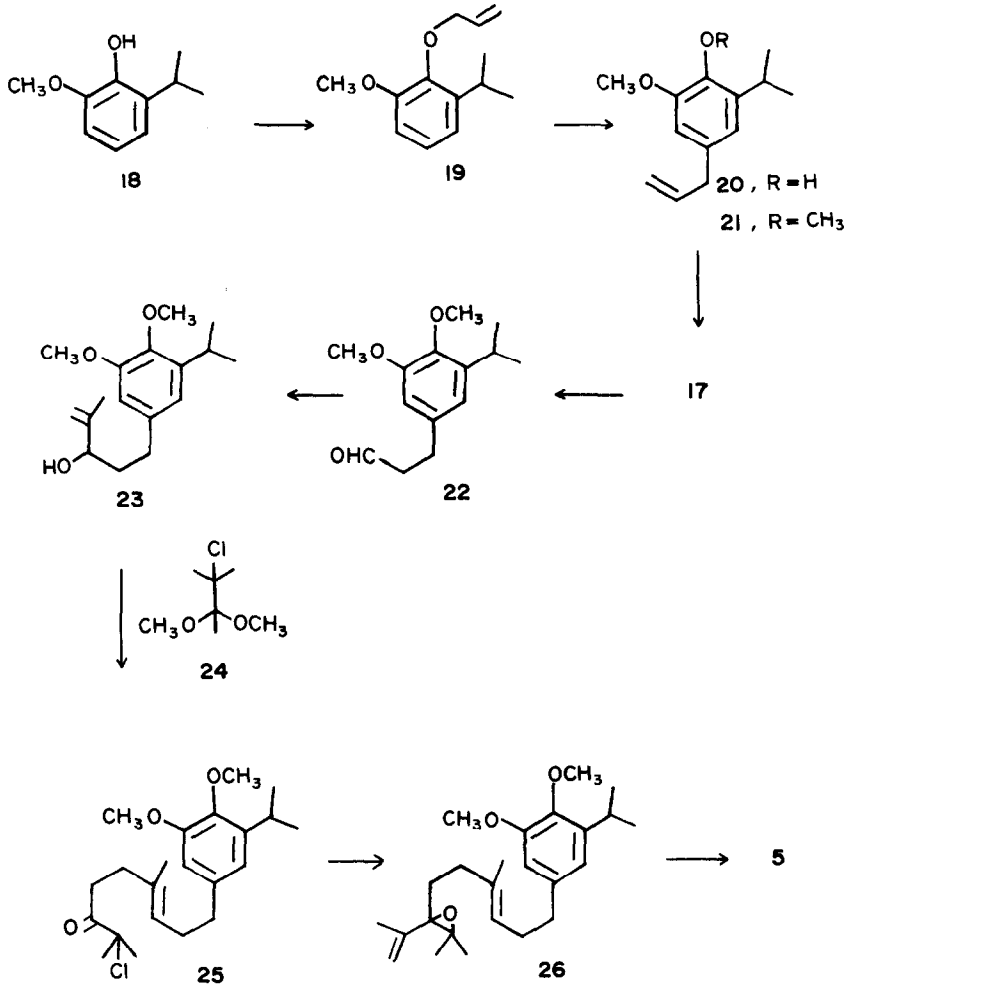

The general strategy for the synthesis of the cyclization substrate **5** is outlined in Scheme 2. The key intermediate, alcohol **17**, was prepared also by the route shown in Scheme 1. The alternative approach shown in Scheme 2, however, was preferred as it was more efficient and also avoided the Willgerodt reaction (**13**→**15**) which afforded intermediary products containing sulfur contaminants that were difficult to remove. The conversion of alcohol **17** into substrate **5** was effected by application of methodology (**23**→**25**→**26**→**5**) developed in our laboratories by Norman R. Hunter. The Hunter method has also been employed in the synthesis of serrantenediol.[6]

Attention is now turned to the individual steps of the synthesis. The first approach to alcohol **5** utilized the known[7] dimethoxybenzene **12** as the starting material. Treatment of **12** with propionic anhydride in methylene chloride in the presence of aluminum chloride, followed by methylation with dimethyl sulfate, gave ketone **14** in 66% yield. This material was subjected to the Willgerodt reaction[8] to give acid **15** which was not purified but was esterified directly with 2,2-dimethoxy-propane-hydrochloric acid[9] to give **16**. Reduction of **16** with ethereal lithium aluminum hydride gave the desired alcohol **17** in 24% yield from ketone **14**.

A more convenient synthesis involved the Claisen rearrangement of allyl ether **19**, prepared in 94% yield from the sodium salt of the known[10] phenol **18** and allyl bromide. When ether **19** was heated at reflux for 16 h in N,N-dimethylaniline, a 90% yield of the olefin **20** was isolated after distillation. Methylation with dimethyl sulfate gave the desired dimethoxy olefin **21** in quantitative yield which was then converted into alcohol **17** in 98% yield, by a hydroboration procedure[11] using disiamylborane.



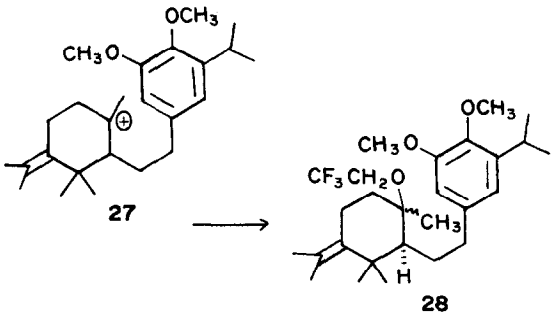

Scheme 1.



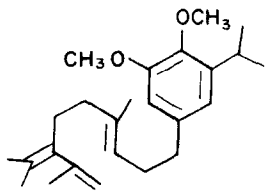

Scheme 2.

Oxidation of alcohol **17** with Collins reagent[12] afforded aldehyde **22** in 82% yield. Treatment of **22** with isopropenylmagnesium bromide gave allylic alcohol **23** in 89% yield which was converted to chloro ketone **25** via a chloro ketal Claisen rearrangement,[13] i.e. heating a solution of **23** in toluene with chloro ketal **24**[13] in the presence of 2,4-dinitrophenol at *ca* 105° for 36 h gave the desired chloro ketone **25** in 80% yield. Treatment of this material with ethereal isopropenyl-lithium at −78° led to epoxide **26** in 94% yield, which was then reduced with lithium in liquid ammonia to give the desired substrate **5** in 93% yield.

Initial efforts to cyclize **5** using stannic chloride in methylene chloride at −100°C for 3–12 h, the method of choice for cyclization of **8**,[6] led to only polymeric material. However, cyclization at −30°C with 1% trifluoroacetic acid in trifluoroethanol led to the formation of a mixture which showed three peaks on VPC in a ratio of 2:1:1. Chromatography on silica gel afforded a specimen of the major component which appeared to be tricyclic material as the $^1$H NMR spectra indicated the presence of only one aromatic proton. The other two components, separated on silver nitrate impregnated alumina, had $^1$H NMR spectra which were similar to starting allylic alcohol in the aromatic region; however, contained a multiplet of two protons at 3.6 ppm indicating the presence of a trifluoroethoxy residue. Trapping of a cationic species such as **27** could presumably lead to the formation of products like **28**. When the




trifluoroethanol was eliminated and the cyclization of allylic alcohol **5** was conducted in methylene chloride containing 0.5% trifluoroacetic acid at *ca* −45° for 45 min, a 90% yield of the desired product **6** was isolated. At lower temperatures (−78°) the substrate failed to cyclize and starting material was recovered, even with reaction times of up to 3 h. Higher temperatures (−20°) seemed to afford only the dehydrated uncyclized material **29** as evidenced by the $^1$H NMR spectra.



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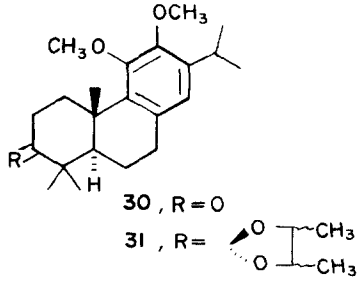
The constitution of substance **6** was established by a two-step conversion into the racemic form of 11,12-dimethoxyabieta-8,11,13-triene (**4**). Treatment of **6** with ruthenium tetroxide[14] in carbon tetrachloride afforded ketone **30** in 80% yield. This substance failed to provide



30, R = O

31, R = 

respectable yields of triene **4** when subjected to the Huang-Minlon modification[15] of the Wolff-Kishner reaction; however, using the method[16] involving the formation of the p-toluenesulfonylhydrazone and then reduction of this material with sodium cyanoborohydride afforded the desired triene **4** in 74% yield. The $^1$H NMR and IR spectra were identical with the corresponding spectra of authentic (naturally derived) 11,12-dimethoxyabieta-8,11,13-triene (**4**),[4a] and the two samples showed identical behavior in VPC coinjection experiments and on tlc. Since this material has been converted to taxodione,[4a] the present synthesis represents a route to racemic taxodione **1**. Moreover, in view of the successful resolution experiments described below a formal total synthesis has been completed.

Attempted resolution of **30** by crystallization of the diastereomeric hydrazone of (-)-menthyl N-aminocarbamate[17] gave crystalline material which appeared to equilibrate on standing in solution. This phenomenon, attributed to equilibration of the syn and anti isomers of the resulting hydrazones has been noted previously.[18] A more satisfactory method proved to be the separation of the diastereomeric ketals **31**, formed by treating *dl*-ketone **30** with (-)-2,3-butanediol[19] in benzene containing *p*-toluenesulfonic acid, by thick layer chromatography. Hydrolysis of the higher $R_f$ material gave a specimen of *d*-ketone **30**, m.p. 124–125°, $[\alpha]_D^{24}$ 147° (c = 0.62, $CHCl_3$). This material was shown to be identical with *dl*-ketone **30** by comparison of the $^1$H NMR spectra and VPC retention times. Reduction of this material as described above for the *dl*-ketone **30** afforded a specimen of optically active 11,12-dimethoxyabieta-8,11,13-triene (**4**), m.p. 90.0–90.5°C (reported[4a] m.p. 89.5–90.5°); $[\alpha]_D^{24}$ + 82.5° (c = 0.145, EtOH), [reported[4e] $[\alpha]_D$ + 92.0° (EtOH)]. An authentic specimen[4a] of *d*-**4** had the following properties as determined in our laboratory: m.p. 86–87°, $[\alpha]_D^{24}$ + 81.5° (c = 0.145, EtOH).

## EXPERIMENTAL

*General considerations.* The prefix *dl* has been omitted from the names of most of the racemic compounds described in this section. Microanalyses were performed by E. H. Meier and J. Consul, Department of Chemistry, Stanford University. Melting points were determined on a Kofler hot-stage microscope calibrated against totally immersed Anschutz thermometers. NMR spectra were recorded under the supervision of Dr L. J. Durham on Varian Associates T-60 and XL-100 spectrometers. Deuteriochloroform was used as the solvent and chemical shifts are reported as $\delta$ values in parts per million relative to tetramethylsilane equal to zero. Infrared (IR) spectra were recorded on Perkin-Elmer Models 137 and 421 spectrometers. Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter at the indicated temperature in the indicated solvent in a 1-dm tube. Vapor-phase chromatographic (VPC) analyses were performed on a Hewlett-Packard HP 402 chromatograph using the following 1/8 in glass columns: 6 ft 3% XE-60 on Gas-Chrom Q, 6 ft 3% OV-17 on Gas-Chrom Q, 9.5 ft 5.5% SE-30 on Chromsorb Q, 5 ft 20% SE-30 on Chromsorb W, 9.5 ft 3% OV-3 on Gas-Chrom Q, 6 ft 3% OV-1 on Gas-Chrom Q, 6 ft 3% OV-210 on Gas-Chrom Q. Helium was used as the carrier gas and disk-chart integrations are uncorrected for detector response. High-pressure liquid chromatography (lc) was performed on a Waters Model 8000 liquid chromatograph equipped with an ultraviolet absorbance detector. Refractive indices were determined on a Bausch and Lomb Refractometer. Analytical and preparative thin-layer chromatography (tlc) were performed using silica gel G or $GF_{254}$ (E. Merck AG) as the adsorbent at 0.25 mm and 1.0 mm thicknesses, respectively. Analytical plates were visualized by spraying with a solution of 10% phosphomolybdic acid in ethanol and then heating the plate at 180°C for 5 min. "Evaporative distillation" refers to bulb-to-bulb short-path distillation in which the bulb was heated in a hot-air oven (Büchi Kugelrohrofen). The cited temperatures for these distillations refer to the maximum temperature attained by the oven during the distillation and are thus not true boiling points.

1,2-*Dimethoxy*-3-*isopropylbenzene* (**12**). A suspension of 13.1 g (0.095 mol) of anhydrous potassium carbonate and 6.08 g (0.04 mol) of 1,2-dihydroxy-3-isopropylbenzene in 40 ml of dry acetone was stirred at room temperature under nitrogen while 7.5 ml (9.97 g, 0.079 mol) of dimethyl sulfate was added over a period of 30 min. The mixture was stirred at room temperature for 3 h; 20 ml of water was added, and then the solvent was removed under reduced pressure (water aspirator). Ether extraction using a base wash followed by an acid wash[20] gave a yellow oil which was purified by short-path distillation to give 6.5 g (90% yield) of ether **12** as a colorless liquid, bp 80–84°C (3 mm); $N_D^{20}$ 1.5072; [reported[7] b.p. 84° (3 mm); $N_D^{20}$ 1.5069]. This material was 98% one peak on VPC (3% XE-60, 100°): IR (film) 6.18 $\mu$ (aromatic C=C); $^1$H NMR 1.2 (d, $J$ = 7 Hz, 6, $CH(CH_3)_2$), 3.45 (sept., $J$ = 7 Hz, 1, $CH(CH_3)_2$), 3.80 and 3.83 (2 s, 6, $OCH_3$'s), 6.9 ppm (m, 3, ArH).

3-*Methoxy*-4-*hydroxy*-5-*isopropylpropiophenone* (**13**). A suspension of 3.69 g (0.02 mol) of the aforementioned 1,2-dimethoxy-3-isopropylbenzene (**12**), 6.68 g (0.05 mol) of anhydrous aluminum chloride and 20 ml of methylene chloride was stirred at 0° under nitrogen while 2.7 ml (2.73 g, 0.021 mol) of propionic anhydride was added over a period of 15 min. The mixture was stirred at room temperature for 4 h, and then treated at reflux for 15 min. The mixture was cooled to room temperature and then was poured onto *ca* 100 g of ice containing 15 ml of concentrated hydrochloric acid. Ether extraction[20] gave 4.45 g of a brown solid which was purified by chromatography on 200 g of silica gel (5:1 hexane–ether) to afford 3.02 g (83% based on recovery of 764 mg of starting material) of phenol **13** as a white solid, which was one peak on VPC (3% XE-60, 140°). Recrystallization from hexane afforded an analytical specimen of **13** as colorless prisms, m.p. 87.5–88.0°: IR (KBr) 3.0 (OH), 6.02 $\mu$ (C=O). $^1$H NMR 1.2 (m, 9, $CH(CH_3)_2$, $CH_3CH_2$), 2.93 (q, $J$ = 7 Hz, $CH_3CH_2$), 3.33 (septet, $J$ = 7 Hz, 1, $CH(CH_3)_2$), 3.90 (s, 3, $OCH_3$), 6.16 (s, 1, OH), 7.40 ppm (q, $J$ = 2 Hz, 2, ArH). Calc. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.29; H, 8.16%.

*3,4-Dimethoxy-5-isopropylpropiophenone* (**14**). A suspension of 1.73 g (0.0125 mol) of anhydrous potassium carbonate, 2.78 g (0.0125 mol) of the aforementioned phenol **13**, and 10 ml of dry acetone was stirred at room temperature under nitrogen while 1.17 ml (1.55 g, 0.0123 mol) of dimethyl sulfate was added. The mixture was stirred at room temperature for 1 h, and then an additional 790 mg (5.7 mmol) of anhydrous potassium carbonate and 0.58 ml (771 mg, 6.1 mmol) of dimethyl sulfate were added. The mixture was stirred at room temperature dimethyl sulfate were added. The mixture was stirred at room temperature an additional hour, and then 10 ml of water was added. The solvent was removed under reduced pressure (water aspirator) and the resulting residue was extracted with ether[20] to give a pale yellow oil which was purified by short-path distillation to give 2.81 g (95% yield) of ether **14** as a colorless liquid, b.p. 130–132° (0.5 mm) which was one peak on VPC (3% XE-60, 140°C), $n_D^{24}$ 1.5310.

An analytical specimen of **14** was prepared by an evaporative distillation at 135°C (0.5 mm). IR (film) 5.96 $\mu$ (C=O); $^1$H NMR 1.2 (m, 9, $CH(CH_3)_2$, $CH_2CH_3$), 3.0 (q, $J = 7$ Hz, 3, $CH_2CH_3$), 3.33 (septet, $J = 7$ Hz, 1, $CH(CH_3)_2$), 3.86 and 3.90 (2 s, 6, $OCH_3$'s), 7.4 ppm (q, $J = 2$ Hz, 2, ArH). Calc. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.92; H, 8.45.

*3-(3,4-Dimethoxy-5-isopropylphenyl)propanol* (**17**). *From dimethoxy ketone* **14**. A published procedure[8] was used. A suspension of 716 mg (23 mmol) of sulfur, 2.63 g (11.1 mmol) of the aforementioned ketone **14**, and 2 ml of morpholine was heated at reflux for 8 h. After this time, 15 ml of 10% alcoholic potassium hydroxide solution was added and the resulting mixture was heated at reflux for an additional 6 h. Water was added (5 ml) and the solvent was removed by distillation. The residue was poured into 10 ml of concentrated hydrochloric acid and extracted with ether. The organic phase was washed with saturated aqueous potassium carbonate and then the resulting basic aqueous extract was adjusted to pH 2 with 10% hydrochloric acid. Ether extraction[20] gave 1.34 g of acid **15** as a brown solid which was dissolved in 2 ml of methanol containing 2.1 g of 2,2-dimethoxypropane. One drop of concentrated hydrochloric acid was added and the mixture was stirred overnight at room temperature.[9] The solvent was removed at reduced pressure and the residue extracted with ether[20] to give 1.97 g of a brown liquid. This material was heated at reflux for 3 h with 150 mg of Raney nickel in 10 ml of methanol. The catalyst was removed by filtration and the solvent was removed at reduced pressure to give 1.9 g of ester **16** as a brown oil which was not characterized but was reduced directly to alcohol **17** as described below.

A suspension of 416 mg (11 mmol) of lithium aluminum hydride in 10 ml of dry ether was stirred at room temperature under nitrogen while a solution of the aforementioned brown oil (1.9 g) in 5 ml of dry ether was added slowly. The mixture was heated at reflux for 4 h, and then was quenched by the slow addition of ethyl acetate. The mixture was poured into 25 ml of 10% hydrochloric acid, and then was extracted with ether[20] to give a brown oil which was purified by filtration through silica gel (ethyl acetate) to give 656 mg (24% yield) of alcohol **17** as a colorless liquid which was one peak on VPC (3% XE-60, 150°), $n_D^{25}$ 1.5146. The IR and $^1$H NMR spectra were identical with the spectra of alcohol **17** obtained by the route described below.

*1-Methoxy-2-hydroxy-3-isopropylbenzene* (**18**). A suspension of 6.68 g (0.048 mol) of anhydrous potassium carbonate in 40 ml of dry acetone, containing 6.08 g (0.04 mol) of 1,2-dihydroxy-3-isopropylbenzene was stirred at room temperature under nitrogen while 3.8 ml (5.05 g, 0.04 mol) of dimethyl sulfate was added over a period of 15 min. The mixture was stirred at room temperature for 1.5 h, and then was diluted with 10 ml of water. The solvent was removed at reduced pressure (water aspirator) and then the residue was extracted with hexane using a base wash.[20] The basic extract was acidified to pH 2 with concentrated hydrochloric acid, and then was extracted with ether[20] to give a brown oil. Chromatography on 160 g of silica gel (33:1 hexane-ether) gave 4.65 g (70% yield) of methoxy benzene **18** as a pale yellow oil which was one peak on VPC (3% OV-17, 100°); $n_D^{24}$ 1.5201 (reported[10] $n_D^{20}$ 1.5203); IR (film) 2.87 $\mu$ (OH); $^1$H NMR 1.23 (d, $J = 7$ Hz, 6, $CH(CH_3)_2$), 3.33 (septet, $J = 7$ Hz, 1, $CH(CH_3)_2$), 3.86 (s, 3, $ArOCH_3$), 5.73 (s, 1, OH), 6.8 ppm (m, 3, ArH).

*1-Methoxy-2-allyloxy-3-isopropylbenzene* (**19**). A solution of 3.18 g (0.019 mol) of the aforementioned phenol **18** in 75 ml of dry benzene was stirred at room temperature under nitrogen while 1.1 g (*ca* 0.023 mol) of sodium hydride (50% oil dispersion) was added. The mixture was stirred at room temperature for 0.5 h, and then was heated at reflux for 2 h. After this time, 1 ml of water was added, and the solvent was removed by distillation to afford the sodium salt of **18** as a white solid. A mixture of this material, 55 ml of 3-pentanone and 2.3 ml (3.22 g, 0.027 mol) of allyl bromide was stirred at room temperature for 2 h, and then was heated at reflux for 12 h. The mixture was diluted with 20 ml of water, and then the solvent was removed under reduced pressure. Ether extraction[20] gave a pale yellow oil which was purified by short-path distillation to give 3.39 g (91% yield) of ether **19**, as a colorless liquid, b.p. 86–89° (0.4 mm) which was one peak on VPC (3% OV-17, 100°), $n_D^{24}$ 1.5072.

An analytical specimen of **19** as a colorless liquid was prepared by an evaporative distillation at 90° (0.4 mm): IR (film) 6.06 $\mu$ (C=$CH_2$); $^1$H NMR 1.2 (d, $J = 7$ Hz, 6, $CH(CH_3)_2$), 3.4 (septet, $J = 7$ Hz, $CH(CH_3)_2$), 3.76 (s, 3, $ArOCH_3$), 4.50 (m, 2, $OCH_2CH=CH_2$), 5.33 (m, 2, $-CH=CH_2$), 6.15 (m, 1, $-CH=CH_2$), 6.9 ppm (m, 3, ArH). Calc. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.81; H, 8.90%.

*1-Methoxy-2-hydroxy-3-isopropyl-5-allylbenzene* (**20**). A modification of a published procedure[21] was used. A solution of 3.55 g (0.017 mol) of the aforementioned allyl ether **19** in 85 ml of N,N-dimethylaniline was heated at reflux under nitrogen for 16 h. Most of the solvent was removed by distillation, and then the residue was poured into dilute hydrochloric acid. Ether extraction using an acid wash[20] gave a brown liquid which was purified by shortpath distillation to afford 3.24 g (91% yield) of phenol **20** as a pale yellow oil, b.p. 98–100° (0.3 mm) which was 98% one peak on VPC (3% OV-17, 120°C), $n_D^{24}$ 1.5228. An analytical specimen of **20**, as a colorless liquid, was prepared by chromatography on silica gel (33:1 hexane-ether) followed by an evaporative distillation at 100°C (0.3 mm): IR (film) 2.84 (OH), 6.0 $\mu$ (C=$CH_2$); $^1$H NMR 1.25 (d, $J = 7$ Hz, 6, $CH(CH_3)_2$), 3.27 (m, 3, $ArCH$, $ArCH_2$), 3.77 (s, 3, $ArOCH_3$), 5.0 (m, 2, $CH=CH_2$), 5.63 (s, 1, OH), 5.96 (m, 1, $CH=CH_2$), 6.5 ppm (q, $J = 2$ Hz, 2, ArH). Calc. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.70; H, 8.73%.

*1,2-Dimethoxy-3-isopropyl-5-allylbenzene* (**21**). A suspension of 1.63 g (0.012 mol) of anhydrous potassium carbonate in 10 ml of dry methanol containing 2.67 g (0.013 mol) of the aforementioned phenol **20** was stirred at room temperature under nitrogen while 1.21 ml (1.61 g, 0.013 mol) of dimethyl sulfate was added. The mixture was stirred at room temperature for 1 h, and then 0.6 ml (0.80 g, 6.3 mmol) of dimethylsulfate was added, and the stirring was continued for 2 h. Ether extraction using a base wash followed by an acid wash[20] gave a pale yellow oil which was purified by short-path distillation to afford 2.85 g (100% yield) of **21** as a colorless liquid, b.p. 96–97°C (0.3 mm) which was 98% one peak on VPC (3% XE-60, 100°), $n_D^{20}$ 1.5120. An analytical specimen was prepared by thick layer chromatography ($R_f$ 0.5, hexane) followed by an evaporative distillation at 100° (0.3 mm): IR (film) 5.93 $\mu$ (C=$CH_2$); $^1$H NMR 1.2 (d, $J = 7$ Hz, 6, $CH(CH_3)_2$), 3.33 (m, 3, $ArCH$, $ArCH_2$), 3.73 and 3.80 (2 s, 6, $OCH_3$'s), 5.1 (m, 2, $CH=CH_2$), 6.0 (m, 1, $CH=CH_2$), 6.66 ppm (q, $J = 2$ Hz, 2, ArH). Calc. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.48; H, 9.40%.

*3-(3,4-Dimethoxy-5-isopropylphenyl)propanol* (**17**). A published procedure[11] was modified. A cold (0°) solution of 10.6 ml (7.0 g, 0.1 mol) of 2-methyl-2-butene in 50 ml of THF was stirred under nitrogen while a cold (0°) solution of 75 ml (0.048 mol) of 0.65 M diborane in THF was added over a period of 15 min. The mixture was stirred at 0° for 45 min, and then 70 ml (ca. 25 mmol) of the resulting disiamylborane solution was added over a 15 min period at 0° to a solution of 4.0 g (18.2 mmol) of the aforementioned allyl benzene **21** in 20 ml of THF. The mixture was stirred at room temperature for an additional 5 h. Excess hydride was destroyed by the addition of *ca* 0.5 ml of water; the mixture was heated to 50°, and then 11.6 mmol of 3M aqueous potassium

hydroxide and 11.6 ml of 30% $H_2O_2$ were added while the heating was continued. The mixture was stirred at room temperature for an additional 2 h, and then was extracted with ether[20] to give a yellow oil which was purified by short-path distillation to give 4.24 g (98% yield) of alcohol **17** as a colorless viscous oil, b.p. 145–148°C (0.3 mm), which was one peak on VPC (3% XE-60, 150°C), $n_D^{24}$ 1.5160. An analytical specimen of **17** as a viscous colorless oil was obtained by an evaporative distillation at 150°C (0.3 mm): IR (film) 3.0 $\mu$ (OH); $^1$H NMR 1.13 (d, $J$ = 7 Hz, $CH(CH_3)_2$), 1.83 (m, 2, $CH_2$), 3.4 (m, 3, $ArCH$, $ArCH_2$) 3.76 and 3.80 (2 s, 6, $OCH_3$'s), 5.8 (m, 3, $CH_2OH$), 6.6 ppm (q, $J$ = 2 Hz, 2, ArH). Calc. for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.28; H, 9.07%

3-(3,4-*Dimethoxy*-5-*isopropylphenyl*)*propanal* (**22**). Collins reagent[12a] was prepared *in situ*[12b] by adding 19.7 g (0.2 mol) of chromium trioxide to a solution of 32 ml (31.4 g, 0.4 mol) of dry pyridine in 500 ml of dry methylene chloride. A solution of 5.86 g (0.024 mol) of the aforementioned alcohol **17** in 25 ml of dry methylene chloride was added in one portion to the solution of Collins reagent, and the resulting mixture was stored at room temperature under nitrogen for 30 min. The methylene chloride solution was decanted, and then the residue was rinsed with ether. The organic solutions were washed with base and then acid[20] to give a brown liquid. Short-path distillation gave 4.72 g (83% yield) of aldehyde **22** as a colorless oil, b.p. 122–125° (0.55 mm), which was one peak on VPC (3% XE-60, 150°C); $n_D^{22}$ 1.5155. An analytical specimen was obtained by chromatography on silica gel (1:1 hexane-ethyl acetate) followed by an evaporative distillation at 125° (0.5 mm): IR (film) 5.85 $\mu$ (C=O); $^1$H NMR 1.23 (d, $J$ = 7 Hz, 6, $CH(CH_3)_2$), 2.83 (m, 4, methylene envelope), 3.33 (septet, $J$ = 7 Hz, 1, $CH(CH_3)_2$), 3.76 and 3.80 (2 s, 6, $OCH_3$'s), 6.6 (q, $J$ = 2 Hz, 2, ArH), 9.73 ppm (t, $J$ = 1 Hz, 1, CHO). Calc. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.21; H, 8.63%.

2-*Methyl*-5-(3,4-*dimethoxy*-5-*isopropylphenyl*)-1-*penten*-3-*ol* (**23**). A solution of 3.63 g (0.015 mol) of the aforementioned aldehyde **22** in 5 ml of dry THF was added slowly over a period of 30 min to a cold (−78°) solution of isopropenylmagnesium bromide, prepared from 1.5 g (0.062 g-atom) of magnesium turnings and 2.74 ml (3.72 g, 0.031 mol) of 2-bromopropene in 50 ml of dry THF. The mixture was stirred at room temperature under nitrogen for 3 h, then cooled to 0°C and quenched by the addition of saturated aqueous ammonium chloride solution. The resulting slurry was filtered and then the filtrate was extracted with ether[20] to give a pale yellow oil, which was purified by short-path distillation to afford 3.82 g (91% yield) of alcohol **23** as a colorless oil, b.p. 164–165° (0.08 mm) which was one spot on tlc ($R_f$ 0.3, 5:1 hexane-ether), $n_D^{22}$ 1.5175. An analytical specimen of **23** was obtained by an evaporative distillation at 165°C (0.08 mm): IR (film) 3.0 $\mu$ (OH); $^1$H NMR 1.2 (d, $J$ = 7 Hz, 6, $CH(CH_3)_2$), 1.77 (m, 6, vinylic $CH_3$, OH, C-4 $CH_2$), 2.67 (t, $J$ = 6 Hz, 2, $ArCH_2$), 3.33 (septet, $J$ = 7 Hz, 1, $CH(CH_3)_2$), 3.8 and 3.85 (2 s, 6, $OCH_3$'s), 4.1 (t, $J$ = 6 Hz, 1, $CHOH$), 4.93 (m, 2, vinylic H), 6.6 ppm (q, $J$ = 2 Hz, 2, ArH). Calc. for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.14; H, 9.41%.

2-*Chloro*-2,6-*dimethyl*-9-(3,4-*dimethoxy*-5-*isopropylphenyl*)-*trans*-6-*nonen*-3-*one* (**25**). A mixture of 3.62 g (0.013 mol) of alcohol **23**, 6.9 g (0.042 mol) of the known[13] chloro ketal **24**, 60 ml of toluene and 288 mg (1.5 mmol) of 2,4-dinitrophenol was heated at 105–108° under nitrogen for 36 h in a flask equipped with a condenser and a Dean–Stark trap. The mixture was cooled to room temperature and then extracted with ether using a base wash[20] to give a pale yellow oil which was purified by chromatography on 200 g of silica gel (10:1 hexane-ether) to afford 3.98 g (80% yield) of chloro ketone **25** as a colorless oil which was one peak on VPC (3% XE-60, 200°C), $n_D^{20}$ 1.5135. An analytical specimen was prepared by an evaporative distillation at 170°C (0.006 mm): IR (film) 5.80 $\mu$ (C=O); $^1$H NMR 1.2 (d, $J$ = 7 Hz, 6, $CH(CH_3)_2$), 1.63 (3 s, 9, vinylic $CH_3$, $ClC(CH_3)_2$), 2.10–3.03 (m, 8, methylene envelope), 3.33 (septet, $J$ = 7 Hz, 1, $CH(CH_3)_2$), 3.76 and 3.83 (2 s, 6, $OCH_3$'s), 5.22 (t, $J$ = 1 Hz, C-7 H), 6.62 ppm (q, $J$ = 2 Hz, 2, ArH). Calc. for $C_{22}H_{33}O_3Cl$: C, 69.38; H, 8.73; Cl, 9.31. Found: C, 69.37; H, 8.80; Cl, 9.31%.

2,6-*Dimethyl*-2,3-*epoxy*-3-*isopropenyl*-9-(3,4-*dimethoxy*-5-*isopropylphenyl*)-*trans*-6-*nonene* (**26**). A suspension of 0.45 g (0.065 g.-atom) of lithium wire (1% sodium) in 20 ml of dry ether was stirred at 0° under nitrogen while 4.22 g (3.1 ml, 0.035 mol) of 2-bromopropene was added over a period of 15 min. The mixture was stirred at 0°C until the lithium had reacted (*ca* 1 h) and then 15 ml of ether was added. The resulting mixture was cooled to −78°C, and then a solution of 1.00 g (2.6 mmol) of the aforementioned chloro ketone **25** in 10 ml of dry ether was added over a period of 15 min. The mixture was stirred at −78°C for 30 min and then was quenched by the addition of 3 ml of ethanol, stirred at room temperature for 1 h, and then diluted with 5 ml of water. Ether extraction[20] gave a yellow oil which was chromatographed on 45 g of basic alumina (activity grade 2, Woelm; 20:1 hexane-ether) to afford 956 mg (94% yield) of epoxide **26** as a colorless oil which was one peak on VPC (3% OV-17, 190°C) $n_D^{21}$ 1.5088. An analytical sample was obtained by evaporative distillation at 180° (0.007 mm): IR (film) 6.33 $\mu$ (aromatic C=C); $^1$H NMR 1.20 (d, $J$ = 7 Hz, 6, $CH(CH_3)_2$), 1.16 and 1.33 (2 s, 6, $(CH_3)_2CO$), 1.53 (s, 3, vinylic $CH_3$), 1.73 (m, 3, isopropenyl $CH_3$), 1.9–2.8 (m, 8, methylene and methine H), 3.76 and 3.80 (2 s, 6, $OCH_3$'s), 4.8–5.4 (m, 3, vinylic H), 6.62 ppm (q, $J$ = 2 Hz, 2, ArH). Calc. for $C_{25}H_{38}O_3$: C, 77.68; H, 9.91. Found: C, 77.54; H, 9.91%.

2,6-*Dimethyl*-3-*isopropylidene*-9-(3,4-*dimethoxy*-5-*isopropylphenyl*)-*trans*-6-*nonen*-2-*ol* (5). A solution of 860 mg (2.2 mmol) of epoxide **26** in 10 ml of dry ether was added over a period of 15 min to a cold (−78°C), stirred mixture of 83 mg (0.012 g atom) of lithium were (1% sodium) in 30 ml of ammonia and 10 ml of dry ether. The mixture was stirred at reflux (−33°) for 45 min under nitrogen, was quenched by the addition of *ca* 1 ml of 1,2-dibromoethane, and then was allowed to warm to room temperature. Dilution with 3 ml of water followed by extraction with ether[20] gave a yellow oil which was purified by chromatography on 50 g of basic alumina (activity grade 4, Woelm; 10:1 hexane-ether) to afford 796 mg (93% yield) of alcohol **5** as a colorless oil which was one spot on tlc ($R_f$ 0.4, 1:1 hexane-ether). An analytical specimen was prepared by an evaporative distillation at 180°C (0.007 mm): IR (film) 2.86 $\mu$ (OH); $^1$H NMR 1.25 (d, $J$ = 7 Hz, 6, $CH(CH_3)_2$), 1.4 (s, 6, C-1 and C-2 $CH_3$'s), 1.6 (s, 3, C-6 vinylic $CH_3$), 1.7 and 1.9 (2 s, 6, isopropylidene $CH_3$'s), 2.1–2.8 (m, 9, OH, methylene envelope), 3.33 (septet, $J$ = 7 Hz, 1, $CH(CH_3)_2$), 3.76 and 3.80 (2 s, 6, $OCH_3$'s), 5.23 (t, $J$ = 6 Hz, 1, vinylic H), 6.66 ppm (q, $J$ = 2 Hz, 2, ArH. Calc. for $C_{25}H_{40}O_3$: C, 77.27; H, 10.38. Found: C, 77.32; H, 10.1%.

3-*Isopropylidene*-11,21-dimethoxyabieta-8,11,13-triene (6). A solution of 209 mg (0.54 mmol) of the aforementioned alcohol **5** in 70 ml of dry methylene chloride was stirred at −78° under nitrogen while 0.35 ml (58 mg, 4.54 mmol) of trifluoroacetic acid was added. The mixture was stirred at −45 to −50° for 45 min and then quenched by the addition of 5 ml of saturated aqueous sodium carbonate solution. Ether extraction[20] followed by chromatography on 10 g of silica gel (50:1 hexane-ether) gave 180 mg (90% yield) of **6** as a white solid. An analytical specimen of **6** as colorless prisms, was prepared by recrystallization from ethanol, m.p. 144.0–144.5°C: IR (KBr) 6.3$\mu$ (aromatic C=C); $^1$H NMR 1.17 (s, 3, angular $CH_3$), 1.27 (d, $J$ = 7 Hz, 6, $CH(CH_3)_2$), 1.38 and 1.50 (2 s, 6, $C(CH_3)_2$), 1.76 and 1.82 (2 s, 6, isopropylidene $CH_3$'s), 1.83–2.90 (m, 9, methylene and methine protons), 3.72 and 3.85 (2 s, 6, $OCH_3$'s), 6.6 ppm (s, 1, ArH). Calc. for $C_{25}H_{38}O_2$: C, 81.03; H, 10.34. Found: C, 81.10; H, 10.27%.

11,12-*Dimethoxyabieta*-8,11,13-*trien*-3-*one* (30). A solution of 353 mg (0.95 mmol) of chromatographed tricyclic product **6**, prepared as described directly above, in 19 ml of carbon tetrachloride was stirred at 0° while 24 ml (1.15 mmol) of a freshly prepared 0.048M solution of ruthenium tetroxide[14] in carbon tetrachloride was added over a period of 10 min. The mixture was stirred at room temperature under nitrogen for 10 min and then the excess ruthenium tetroxide was decomposeed by the addition of 1 ml of iso-propyl alcohol. The mixture was filtered through Celite, and then the solvent was removed from the filtrate to give 264 mg (80% yield) of ketone **30** as a white solid, which was one spot on tlc ($R_f$ 0.3, 10:1 hexane-ether) and one peak on VPC (3% OV-17, 200°C).

An analytical specimen of **30** as colorless prisms, m.p. 112–113°, was obtained by recrystallization from methanol: IR (KBr) 5.85 $\mu$ (C=O); $^1$H NMR 1.25 (d, $J$ = 7 Hz, 6, CH($CH_3$)$_2$), 1.2 (s, 9, $CH_3$'s), 1.5–3.10 (m, 9, methylene and methine H's), 3.33 (septet, $J$ = 7 Hz, 1, CH($CH_3$)$_2$), 3.76 and 3.86 (2 s, 6, $OCH_3$'s), 6.70 ppm (s, 1, ArH). Calc. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.73; H, 9.52%.

11,12-*Dimethoxyabieta*-8,11,13-*triene* (**4**). A published procedure[16] was used. A mixture of 24 mg (0.07 mmol) of the aforementioned crude ketone **30**, 30 mg (0.16 mmol) of p-toluenesulfonylhydrazine and 4 mg (0.02 mmol) of p-toluenesulfonic acid monohydrate in 2 ml of acetonitrile was heated at reflux for 4 h under nitrogen in a flask equipped with a condenser and a Dean–Stark trap. The solvent was removed under reduced pressure (water aspirator) and the resulting residue was heated at reflux for 6 h with 2 ml of 1:1 DMF-sulfolane, 2 ml of cyclohexane, 20.5 mg (0.33 mmol) of sodium cyanoborohydride and 4 mg (0.02 mmol) of p-toluenesulfonic acid monohydrate. Additional sodium cyanoborohydride (20.5 mg) and p-toluenesulfonic acid monohydrate (4 mg) were added and the heating was continued for 4 h. The same portions of hydride and acid were added one more time nd heating was continued for another 4 h. Ether extraction[20] gave a yellow oil which was purified by filtration through silica gel (ethyl acetate) to afford 17 mg (74% yield) of a solid. Recrystallization from methanol gave colorles prisms of *dl*-11,12-dimethoxyabieta-8,11,13-triene (**4**), m.p. 85–86°: IR (KBr) 6.25, 6.41, 7.14, 7.55, 7.69, 9.43, 9.8, 9.9 $\mu$; $^1$H NMR 0.90 and 0.92 (2 s, 6, C-18 and C-19 $CH_3$'s), 1.13 and 1.18 (2 d, $J$ = 7 Hz, 6, C-16 and C-17 $CH_3$'s), 1.26 (s, 3, C-20 $CH_3$), 2.75 (m, 2, C-7 H), 3.16 (sept., $J$ = 7 Hz, 1, C-15 H), 3.69 and 3.78 (2 s, 6, $OCH_3$'s), 6.54 ppm (s, 1, ArH). The IR (6.5–11 $\mu$ region) and $^1$H NMR spectra of **4** were identical with the corresponding spectra of naturally derived 11,12-dimethoxyabieta-8,11,13-triene (**4**).[4a] Also the VPC as well as TLC behavior (coinjection experiments, 3% OV-17, 170°C, 3% XE-60, 150°C; $R_f$ 0.4, 10:1 hexane-ether) for the two substances was identical.

*Resolution of* dl-11,12-*dimethoxyabieta*-8,11,13-*trien*-3-*one* (**30**). A published procedure[19] was used. A mixture of 145 mg (0.42 mmol) of the aforementioned crude *dl*-ketone **30**, 90 mg (1 mmol) of (-)-2,3-butanediol, $[\alpha]_D^{24}$ -12.8°, 10 mg (0.052 mmol) of *p*-toluenesulfonic acid monohydrate and 20 ml of benzene was heated at reflux for 14 h under nitrogen in a flask equipped with a condenser and a Dean–Stark trap. The mixture was cooled and then extracted with ether[20] to give a pale yellow oil which was purified by filtration through silica gel (ethyl acetate) to give 160 mg (91% yield) of a mixture of diasteriomeric ketals **31** which solidified on standing. This material showed one peak on VPC (6-ft columns as follows: 3% XE-60, 200°; 3% OV-17, 190°; 5.5% SE-30, 240°; 20% SE-30, 240°; 3% OV-3, 230°; 3% OV-1, 200°; 3% OV-210, 190°) and one peak on hplc (250 × 10 mm Corasil or Microporosil, 35–50 $\mu$, 3:1 heptane-ethyl acetate). $^1$H NMR 1.0 and 1.15 (2 d, $J$ = 6 Hz, 6, ketal $CH_3$'s), 1.1 and 1.2 (2 s, 6, C-4 $CH_3$'s), 1.18 (d, $J$ = 7 Hz, 6, CH($CH_3$)$_2$), 1.33 (s, 3, angular $CH_3$), 1.6–1.9 (m, 12, methylene and methine H's), 3.77 and 3.87 (2s, 6, $OCH_3$'s), 6.6 ppm (s, 1, ArH).

Preparative tlc (200:1 hexane-ethyl acetate, continuous elution for 12 h) gave two bands $R_f$ 0.9 and 0.8. The higher $R_f$ material ($R_f$ 0.9) gave 40 mg of a colorless oil which showed one spot on tlc (200:1 hexane-ethyl acetate, continuous elution for 12 h, $R_f$ 0.85), $[\alpha]_D^{24}$ + 42° (c = 3.5, $CHCl_3$). A solution of 35 mg (0.084 mmol) of the aforementioned ketal **31**, $[\alpha]_D^{24}$ + 42° (c = 3.5, $CHCl_3$) in 4 ml of ethanol containing 0.4 ml of 20% aqueous sulfuric acid was heated at 65° for 5 h under nitrogen. The mixture was poured into saturated aqueous sodium carbonate and then extracted with ether[20] to give a pale yellow solid. Filtration through silica gel (ethyl acetate) gave 29 mg (23% yield from *dl*-ketone **30**) of *d*-ketone **30**, m.p. 118–125°C, $[\alpha]_D^{24}$ + 147° (c = 0.62, $CHCl_3$) which was one spot on TLC (10:1 hexane, ether, $R_f$ 0.3). VPC coinjection experiments (3% OV-17) of this material and *dl*-ketone **30** showed one peak. The $^1$H NMR spectrum of the resolved material was also identical with the spectrum of the *dl*-ketone **30** described above. Recrystallization of a sample of *d*-ketone **30**, $[\alpha]_D^{24}$ + 147° (c = 0.62, $CHCl_3$), from methanol gave colorless prisms, m.p. 124–125°.

d-11,12-*Dimethoxyabieta*-8,11,13-*triene* (**4**). A 28-mg (0.0815 mmol) sample of the aforementioned *d*-ketone **30**, m.p. 118–125°, was reduced to *d*-triene **4** as described above for *dl*-ketone **30** to give 20 mg (75% yield) of solid material which was recrystallized three times from methanol to afford colorless prisms of *d*-11,12-dimethoxyabieta-8,11,13-triene (**4**), m.p. 90.0–90.5°C; $[\alpha]_D^{24}$ + 82.5° (c = 0.145, EtOH); [reported[4e] m.p. 89.5–90.5°; $[\alpha]_D$ + 92.0°C (EtOH)] on admixture with an authentic specimen of *d*-11,12-dimethoxyabieta-8,11,13-triene (**4**),[4a] m.p. 86–87°, $[\alpha]_D^{24}$ + 81.5° (c = 0.145, EtOH), the m.p. was undepressed. The IR and the $^1$H NMR spectra of the two samples were identical. Also VPC (coinjection experiments, 3% OV-17, 170°; 3% XE-60, 150°) as well as tlc behavior ($R_f$ 0.4, 10:1 hexane-ether) for the two substances was identical.

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[20]In cases where products were isolated by solvent extraction, the procedure generally followed was to extract the aqueous

layer with several portions of the indicated solvent, and then the organic layers were combined and washed with saturated aqueous sodium bicarbonate solution followed by saturated brine. The organic layer was dried over anhydrous magnesium sulfate or anhydrous potassium carbonate, and the solvent was evaporated under reduced pressure (water aspirator) by using a rotary evaporator. The remaining material was dried *in vacuo* at room temperature (0.1 mm) for *ca* 2 h. The use of the term "wash" indicates washing the combined organic layers with 10% aqueous sodium hydroxide solution ("base wash") or with 10% aqueous hydrochloric acid ("acid wash").

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