heating. The residue was diluted with 50 mL of 1:1 ethyl acetate/petroleum ether and this solution was washed with water (2 × 10 mL), dried, and concentrated. The resulting viscous material was purified by MPLC on silica gel (elution with 24% ethyl acetate in petroleum ether) to give 60.6 mg (70%) of **24** as colorless crystals, mp 86.5–87.5 °C (from petroleum ether): IR (CH_2Cl_2 8 Cm^{-1}) 2967, 2937, 2870, 1658, 1598, 1338; ^1H NMR (300 MHz, $CDCl_3$) δ 3.30 (heptet, J = 6.8 Hz, 1 H), 2.91 ($^1/_2$AB d, J = 14.6 Hz, 1 H), 2.81 ($^1/_2$AB d, J = 13.4 Hz, 1 H), 2.55 ($^1/_2$AB d, J = 13.4 Hz, 1 H), 2.51–2.43 (m, 4 H), 2.42 ($^1/_2$AB d, J = 14.6 Hz, 1 H), 1.85 (s, 3 H), 1.97–1.75 (m, 4 H), 1.18 (s, 3 H), 1.08 (s, 3 H), 1.02 (d, J = 6.8 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 200.67, 198.25, 162.44, 159.77, 141.97, 132.13, 54.92, 49.28, 41.76, 40.85, 38.60, 37.28, 33.83, 29.20, 28.02, 25.50, 23.53, 20.97, 20.68, 12.46; MS, m/z (M^+) calcd 300.2089, obsd 300.2071. Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.34; H, 9.34.

X-ray Crystal Structure Analysis of 16. Suitable crystals of **16** ($C_{20}H_{32}O_2$) for X-ray diffraction studies formed with space group symmetry of $P2_1/c$ and cell constants of a = 19.409 (5) Å, b = 7.627 (2) Å, c = 12.267 (1) Å, and β = 91.92 (1)° for Z = 4 and a calculated density of 1.114 g/cm^3. Of the 2443 reflections measured with an automatic four-circle diffractometer equipped with Cu radiation, 2047 were observed ($I > 3\sigma I$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined by using full-matrix least-squares techniques.[39] Hydrogen were assigned isotropic temperature factors corresponding to their attached atoms. The function $\sum w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.069. Tables I, II, and III containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Figure 3 is a computer-generated perspective drawing of **16** from the final X-ray coordinates showing the relative stereochemistry.

Acknowledgment. We thank the National Institutes of Health for their financial support of this work through Grant CA-12115.

Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for **16** (3 pages). Ordering information is given on any current masthead page.

(39) The following library of crystallographic programs was used: MULTAN 80, Main, P. et al., University of York, York, England (1980); ORTEP-II, Johnson, C. K., Oak Ridge National Laboratory, Oak Ridge, TN (1970); SDP PLUS V1.1, Okaya, Y. et al., Frenz, B. A. and associates, College Station Texas (1984).

Total Syntheses of Atrovenetin and Scleroderodione

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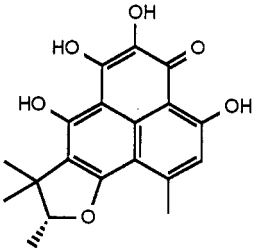
Received April 11, 1986

Total syntheses of (±)-atrovenetin (**1**) and (±)-scleroderodione (**26**) in 11 steps are described. The novel regioselective Claisen rearrangement–cyclization of the dianion **11** to the dihydrobenzofuran **7** and the regioselective, acid-catalyzed cyclization of **15** to the naphthalenes **16** and **17** constitute the critical phases of the syntheses.

Atrovenetin (**1**), a fungal metabolite of *Penicillium atrovenetum*,[1] belongs to the class of naturally occurring phenalenones. It is also produced by *Penicillium herquei*[2]



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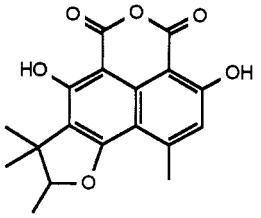


2

and was found to be responsible for the antibiotic activity displayed by extracts of this fungus.[3] The metabolite **1** and related phenalenones have been the subject of many chemical and biosynthetic studies.[1,4] An unambiguous structural assignment emerged from an X-ray analysis of atrovenetin trimethyl ether ferrichloride.[4b] By chemical correlation with (−)-(*S*)-ethyl lactate, **1** was shown to have the *R* configuration at its single chiral center.[4i] Atrovenetin has been synthesized.[5] A second, more efficient, synthesis that also allowed the preparation of its cometabolite **2**[6] is presented in this paper.

Alkylation of dimethyl 3,5-dihydroxyhomophthalate (**3**)[7]

(1) (a) Neill, K. G.; Raistrick, H. *Biochem. J.* **1957**, *65*, 166. (b) Barton, D. H. R.; deMayo, P.; Morrison, G. A.; Raistrick, H. *Tetrahedron* **1959**, *6*, 48.

(2) Narasimhachari, N.; Vining, L. C. *Can. J. Chem.* **1963**, *41*, 641.

(3) Narasimhachari, N.; Gopalkrishnan, K. S.; Haskins, R. H.; Vining, L. C. *Can. J. Microbiol.* **1963**, *9*, 134.

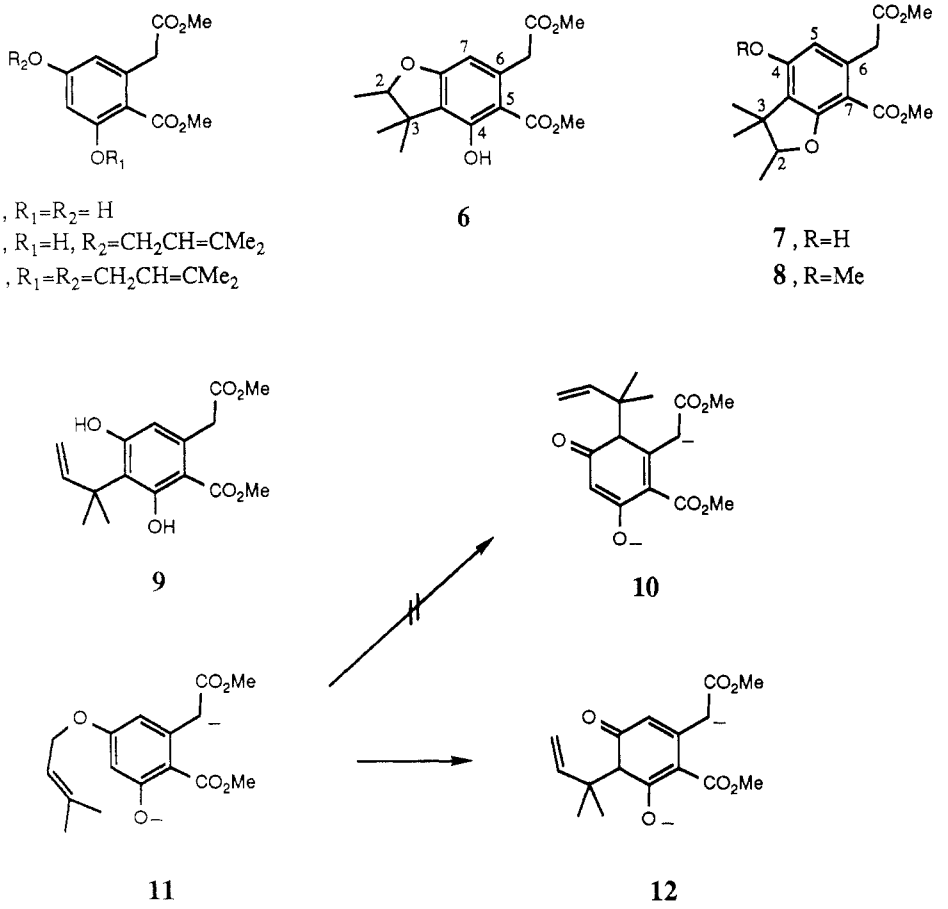
(4) (a) Thomas, R. *Biochem. J.* **1961**, *78*, 807. (b) Paul, I. C.; Sim, G. A. *J. Chem. Soc.* **1965**, 1097. (c) Cason, J.; Koch, C. W.; Correia, J. S. *J. Org. Chem.* **1970**, *35*, 179. (d) Kriegler, A. B.; Thomas, R. *J. Chem. Soc., Chem. Commun.* **1971**, 738. (e) Brooks, J. S.; Morrison, G. A. *J. Chem. Soc., Perkin Trans. 1* **1972**, 421. (f) Narasimhachari, N.; Vining, L. C. *J. Antibiot.* **1972**, *25*, 155. (g) Frost, D. A.; Morrison, G. A. *Tetrahedron Lett.* **1972**, *46*, 4729. (h) Thomas, R. *Pure Appl. Chem.* **1973**, *34*, 515. (i) Brooks, J. S.; Morrison, G. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2114. (j) Simpson, T. J. *Ibid.* **1979**, 1233. (k) Quick, A.; Thomas, R.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1051. (l) Yoshioka, T.; Hirata, T.; Aoki, T.; Suga, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3847. (m) Suga, T.; Yoshioka, T.; Hirata, T.; Aoki, T. *ibid.* **1983**, *56*, 3661.

(5) Frost, D. A.; Morrison, G. A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2388.

(6) A synthesis of the naphthalic anhydride **2** from lamellicolic anhydride was reported: McCorkindale, N. J.; Hutchinson, S. A.; McRitchie, A. C.; Sood, G. R. *Tetrahedron* **1983**, *39*, 2283.

0022-3263/86/1951-4813$01.50/0

Scheme I



with 1-chloro-3-methyl-2-butene afforded the allyl ether **4** (79%) accompanied by the diallyl ether **5** (7%). Heating **4** at various temperatures in different solvents caused slow and inefficient conversion to the dihydrobenzofuran **6**, by cyclization of the intermediate resorcylic ester **9**. The regiochemical outcome of this cyclization is probably dictated by the relative acidities of the two phenolic hydroxyl groups (methyl *p*-hydroxybenzoate, pK_a 9.58, is a stronger acid than methyl salicylate, pK_a 11.28[10]). Aliphatic Claisen rearrangements have been accelerated by placing a carbanionic center adjacent to the vinyl ether double bond,[8a,b] and similar observations were reported for the Carroll rearrangement.[8c] Furthermore, base-catalyzed rearrangements of catechol monoallyl ethers were found to be faster than those of the corresponding phenols,[9a] and analogous rate accelerations were noted with heterocyclic phenols.[9b] Treatment of **4** with 2 equiv of sodium hydride in refluxing *N*,*N*-dimethylformamide yielded the two isomeric dihydrobenzofurans **6** and **7** in 3% and 24% yields, respectively (5% and 35% based on unrecovered starting material). The proton NMR spectrum of **6** exhibited a signal at δ 11.60 due to a hydrogen-bonded hydroxyl group, and in an NOE experiment the intensity of the C-7 proton (δ 6.19) increased by 20% upon irradiation of the methylene proton signal (δ 3.80). In marked contrast, rearrangement within the dianion **11** leads mostly to the desired dihydrobenzofuran **7**, presumably via intermediate **12** (not **10**!) and the sodium diphenolate of **9**. Relevant to the cyclization is the work of Kirby[11] who described nucleophilic intramolecular additions of phenolates to identically substituted, unactivated double bonds. The striking change in the regiochemistry of the cyclization on going from a "thermal" to an anionic process is of considerable theoretical interest, but we are unable to propose a convincing mechanistic rationale (Scheme I).

Dihydrobenzofuran **7** was then methylated under phase-transfer conditions to give **8** which was saponified to the dicarboxylic acid and decarboxylated to **13** in hot aqueous sulfuric acid. Methyl ester **14** accessible by esterification of **13** was then deprotonated with lithium *N*-isopropylcyclohexylamide in THF at approximately −75 °C. The resulting lithium species was condensed with excess (*E*)-3-methoxy-2-butenoyl chloride to afford the anticipated β-keto ester **15**. Cyclization to a mixture of naphthalenes **16** (50% from **14**) and **17** (4% from **14**) was accomplished by heating **15** in methanolic sulfuric acid at 40 °C. The remarkable regioselectivity in this cyclization can be rationalized if it is assumed that the *gem*-dimethyl

(7) Hurd, R. N.; Shah, D. H. *J. Org. Chem.* **1973**, *38*, 610. Compound **3** was obtained by decarboxylation of dimethyl 4-carboxy-3,5-dihydroxyhomophthalate, which is a minor product resulting from self-condensation of dimethyl 1,3-acetonedicarboxylate with sodium: (a) Theilacker, W.; Schmid, W. *Justus Liebigs Ann. Chem.* **1950**, *570*, 15. (b) Hardegger, E.; Rieder, W.; Walser, A.; Kugler, F. *Helv. Chim. Acta* **1966**, *49*, 1283. We found that the major product, dimethyl 4-carbomethoxy-3,5-dihydroxyhomophthalate, could be converted to dimethyl 4-carboxy-3,5-dihydroxyhomophthalate in over 70% yield by heating with LiCl (2 equiv) and H_2O (1 equiv) in Me_2SO at 130 °C for 1.5 h. This constitutes an improved synthesis of **3**.

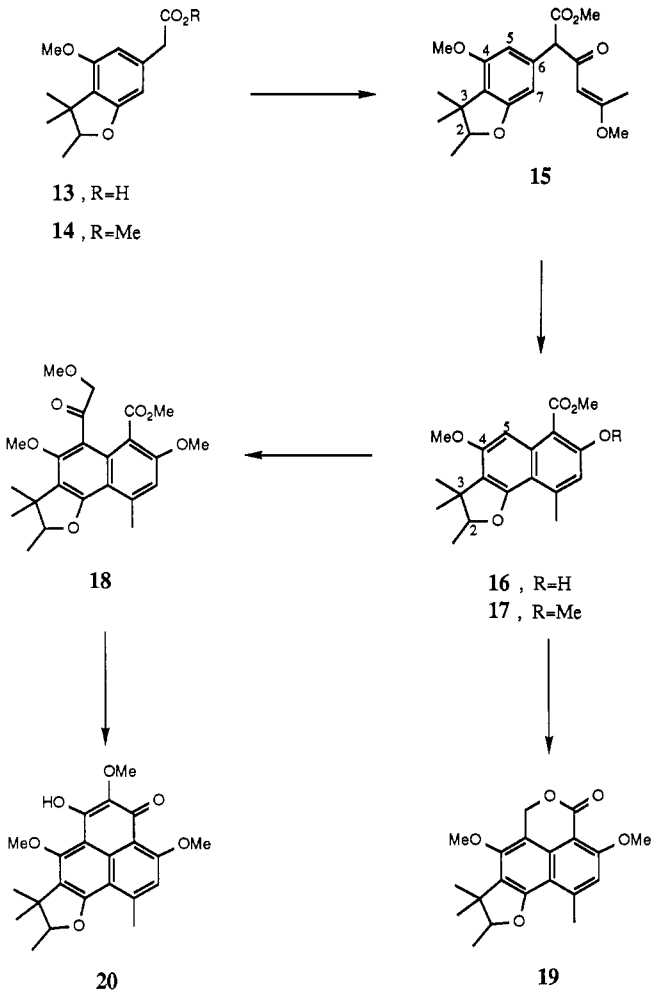
(8) (a) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972. (b) Büchi, G.; Vogel, D. E. *J. Org. Chem.* **1985**, *50*, 4664. (c) Wilson, S. R.; Price, M. F. *J. Org. Chem.* **1984**, *49*, 722.

(9) (a) Ollis, W. D.; Somanathan, R.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1974**, 494. (b) Frihard, C. R.; Leonard, N. J. *J. Am. Chem. Soc.* **1973**, *95*, 7174.

(10) Schwarzenbach, G.; Rudin, E. *Helv. Chim. Acta* **1939**, *22*, 360.

(11) Evans, C. M.; Kirby, A. J. *J. Am. Chem. Soc.* **1982**, *104*, 4705. Polycyclic hydroxy olefins have also been cyclized in basic media: (a) Grob, C. A.; Katayama, H. *Helv. Chim. Acta* **1977**, *60*, 1890. (b) Ramos Tombo, G. M.; Pfund, R. A.; Ganter, C. *Helv. Chim. Acta* **1981**, *64*, 813. (c) Ramos Tombo, G. M.; Ganter C. *Helv. Chim. Acta* **1985**, *68*, 2226.

Scheme II



group forces the methyl substituent of the methoxy group at C_4 into a conformation in which it destabilizes, by steric congestion, any tetrahedral intermediate resulting from substitution at C_5. The structure of **16** was determined in an NOE experiment in which irradiation of the C-4-methoxy signal (δ 3.92) caused a 22% intensity increase of the C-5 proton signal (δ 7.79). Methylation of **16** afforded **17**, thus clarifying the relationship between the two products formed in the acid-catalyzed cyclization (Scheme II).

The remaining two skeletal carbon atoms in atrovenetin (**1**) were introduced by condensation of **17** with excess methoxyacetyl chloride in methylene chloride containing 2 equiv of titanium(IV) chloride. The desired methoxymethyl ketone **18** was isolated in 37% yield (76% considering recovered starting material). Interestingly, lactone **19** was the major product when tin(IV) chloride was used. Methodology for the chloromethylation of aromatic compounds with methoxyacetyl chloride and aluminum chloride was developed by McKillop[12] who postulated the intermediacy of a methoxymethyl cation **21**. This same

$$MeOCH_2COCl + AlCl_3 \rightarrow \underset{\mathbf{21}}{MeO\overset{+}{C}H_2} + CO$$

mechanism can be invoked to rationalize the formation of lactone **19** resulting from Lewis-acid induced cyclization of the intermediate methoxymethyl derivative. The fourth ring in atrovenetin was closed by exposing keto ester **18** to potassium *tert*-butoxide in THF. Somewhat surprisingly, heating **20** with pyridine hydrochloride at 220 °C turned out to be the most efficient, yet ancient, procedure for cleaving the three methoxy groups in the trimethyl ether **20** (87% yield!). Racemic atrovenetin (**1**) exhibited spectroscopic properties identical with those of the optically active metabolite supplied by Professor Leo C. Vining.

For the synthesis of the cometabolite **2**, intermediate **17** was condensed with acetic anhydride and the resulting methyl ketone **22** cyclized with the aid of potassium *tert*-butoxide. Oxidation of the potassium enolate of the β-diketone **23** with molybdenum peroxide (MoO_5·py·HMPA)[13] gave, depending on the amount of oxidant used, either the yellow anhydride **24** or its precursor, the yellow-orange α-diketone **25**. Ether cleavage of the former afforded the racemic anhydride **2** whose ultraviolet, infrared, mass, and ^1H NMR spectra were identical with those reported by McCorkindale.[6] Racemic scleroderodione (**26**) was prepared by cleavage of the dimethyl ether **25** with pyridine hydrochloride. The spectral properties of both the dimethyl ether **25** and scleroderodione (**26**) itself were identical with those of materials prepared by a totally different synthesis.[14] Synthetic (±)-scleroderodione (**26**)[14] was previously identified with the authentic, natural metabolite produced by *Gremmeniella abietina*,[15] a virulent pathogenic ascomyces. A deep green cometabolite **28** is most probably identical with a pigment isolated[16] from the fungus *Roesleria hypogea*, which could be synthesized[15] from atrovenetinone **27** and ammonia as suggested by Vining[2] (Chart I).

Experimental Section

Melting points were determined on a Reichert hot-stage microscope or a Büchi SMP-20 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 397 spectrophotometer. Proton nuclear magnetic resonance (^1H NMR) spectra were measured on a Bruker 250-MHz FT spectrometer and are reported (δ) downfield from tetramethylsilane as an internal standard. Ultraviolet (UV) spectra were recorded on a Hitachi Perkin-Elmer 200 spectrophotometer. Mass spectra were obtained on a Finnigan MAT 8200 spectrometer. Elemental analyses were performed by Robertson Laboratory, Florham Park, NJ. Analytical thin-layer chromatography (TLC) was carried out on precoated silica gel 60 F-254 plates (Merck).

1-Chloro-3-methyl-2-butene was purchased from Wiley Organics. Methoxyacetyl chloride and pyridine hydrochloride were purchased from Aldrich Chemical Co. These reagents were used without further purification. *N*-Isopropylcyclohexylamine was distilled under reduced pressure and stored over 4-Å molecular sieves. Dichloromethane and *N*,*N*-dimethylformamide (DMF) were dried by prolonged storage over 4-Å molecular sieves; DMF was degassed shortly before use. THF was freshly distilled from sodium benzophenone ketyl before use. Acetic anhydride was distilled prior to use.

Dimethyl 3-Hydroxy-5-[(3,3-dimethylallyl)oxy]homophthalate (4). A mixture of dimethyl 3,5-dihydroxyhomophthalate (**3**; 10.8 g, 0.045 mol), 1-chloro-3-methyl-2-butene (8.0 g, 0.077 mol), and anhydrous potassium carbonate (12.6 g, 0.091 mol) was refluxed in 600 mL of acetone for 18 h. After removal of most of the acetone in vacuo, 500 mL of water was added, and the mixture was extracted with three 350-mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography of the

(12) McKillop, A.; Madjdabadi, F. A.; Long, D. A. *Tetrahedron Lett.* **1983**, *24*, 1933.

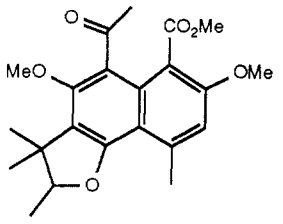
(13) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944.

(14) Steglich, W.; Jendrzejewski, S., unpublished. Jendrzejewski, S. Inaugural Dissertation, Rheinischen Friedrich-Wilhelms-Universität, Bonn, BRD, 1984.

(15) Ayer, W. A.; et al. *Metabolites of Plant Disease Causing Fungi, IX*; International Symposium on Natural Products Chemistry, Monterrey, Nuevo Leõn, Mexico, 1982.

(16) Bachmann, O.; Kemper, B.; Musso, H. *Liebigs, Ann. Chem.* **1986**, 305.

Chart I



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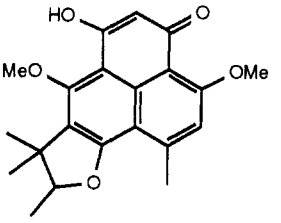

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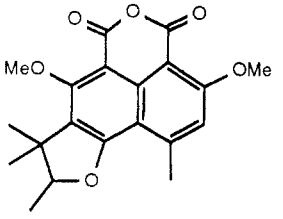

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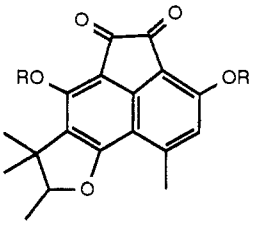
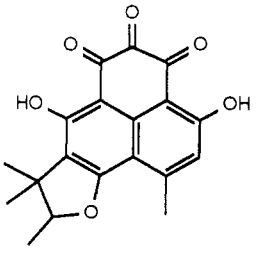


25, R=Me

26, R=H



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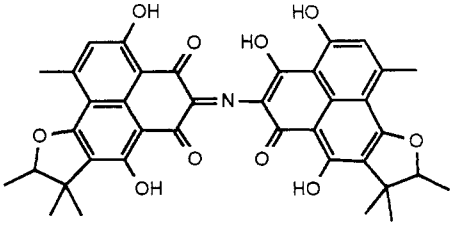

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residue on silica gel with 1:5 ether/petroleum ether afforded 10.4 g (75%, 79% based on starting material recovered, vide infra) of **4** as a white solid. Recrystallization from ether/pentane gave white needles: mp 64.5–66 °C; R_f 0.44 (1:2 ether/petroleum ether); IR ($CHCl_3$) 1734,1655, 1619, 1580, 1438, 1333, 1260, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 1.80 (2 s, 6), 3.69 (s, 3), 3.82 (s, 2), 3.85 (s, 3), 4.51 (d, 2, J = 6.8 Hz), 5.46 (m, 1), 6.30 (d, 1, J = 2.7 Hz), 6.43 (d, 1, J = 2.7 Hz), 11.66 (s, 1); mass spectrum, m/z (relative intensity) 308 (M^+, 17), 277 (8), 276 (9), 240 (59), 208 (100), 180 (81), 165 (19).

Further elution afforded 1.1 g (6.5%) of diallyl ether **5** as a yellow oil: R_f 0.34 (1:2 ether/petroleum ether); ^1H NMR ($CDCl_3$) δ 1.68, 1.73, 1.74, 1.78 (4 s, 12), 3.64 (s, 2), 3.66 (s, 3), 3.83 (s, 3), 4.49 (d, 4, J = 6.6 Hz), 5.42 (m, 2), 6.38 (d, 1, J = 2.2 Hz), 6.41 (d, 1, J = 2.2 Hz).

The water layer was acidified with dilute hydrochloric acid and extracted with ether. The combined ether extracts were dried and evaporated to give 0.5 g (4.6%) of starting material **3**.

Methyl 6-(7-Carbomethoxy-2,3-dihydro-4-hydroxy-2,3,3-trimethylbenzofuranyl)acetate (7) and Methyl 6-(5-Carbomethoxy-2,3-dihydro-4-hydroxy-2,3,3-trimethylbenzofuranyl)acetate (6). To a stirred solution of hexane-washed sodium hydride (0.85 g, 60%, 21.2 mmol) in 150 mL of dry DMF at −5 °C was added rapidly dropwise allyl ether **4** (3.27 g, 10.6 mmol) in 100 mL of dry DMF under argon. Stirring was continued for 1.25 h at room temperature, and the solution was then heated at reflux for 5 h. The cooled solution was quenched with cold water and acidified with dilute hydrochloric acid. After dilution to 1200 mL with more water, the solution was extracted with four 400-mL portions of ethyl acetate.

The above procedure was repeated five times. All ethyl acetate extracts were combined and dried ($MgSO_4$). Evaporation of the solvent in vacuo and flash chromatography of the residue on silica gel with 1:8 ether/petroleum ether afforded 0.65 g (3.3%, 4.9% based on starting material recovered, vide infra) of **6** as a pale yellow solid. Recrystallization from methanol gave white needles: mp 128–129 °C; R_f 0.45 (1:3 ether/petroleum ether); IR ($CHCl_3$) 3500–2600, 1732, 1655, 1627, 1591, 1440, 1330, 1290, 1245, 1168 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (s, 3), 1.36 (d, 3, J = 6.6 Hz), 1.45 (s, 3), 3.69 (s, 3), 3.76 (d, 1, J = 17 Hz), 3.84 (d, 1, J = 17 Hz), 3.84 (s, 3), 4.44 (q, 1, J = 6.6 Hz), 6.19 (s, 1), 11.60 (s, 1); mass spectrum, m/z (relative intensity) 308 (M^+, 37), 293 (29), 277 (14), 276 (31), 261 (100), 249 (10), 233 (58), 229 (14). Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.27; H, 6.61.

Further elution afforded 6.40 g (33%) of starting ether **4**.

Further elution with 1:1 ether/petroleum ether afforded 4.69 g (24%, 35% based on starting material recovered) of **7** as a pale yellow solid. Recrystallization from acetone/hexane gave white crystals: mp 151–152.5 °C; R_f 0.32 (3:2 ether/petroleum ether); IR ($CHCl_3$) 3570, 3360, 1732, 1718, 1700, 1605, 1420, 1280, 1190, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (s, 3), 1.37 (d, 3, J = 6.6 Hz), 1.39 (s, 3), 3.70 (s, 3), 3.73 (d, 1, J = 17 Hz), 3.80 (d, 1, J = 17 Hz), 3.83 (s, 3), 4.42 (q, 1, J = 6.6 Hz), 6.03 (br s, 1, D_2O exch), 6.13 (s, 1); mass spectrum, m/z (relative intensity) 308 (M^+, 44), 293 (25), 277 (43), 276 (100), 261 (98), 249 (30), 248 (43), 234 (20), 233 (91). Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.45; H, 6.63.

Methyl 6-(2,3-Dihydro-4-methoxy-2,3,3-trimethylbenzofuranyl)acetate (14). A mixture of the ester **7** (5.04 g, 16.4 mmol), benzyltributylammonium bromide (0.62 g, 1.7 mmol), dimethyl sulfate (4.0 mL, 42.0 mmol), 1 M aqueous NaOH (24.9 mL, 24.9 mmol), water (50 mL), and dichloromethane (75 mL) was stirred at room temperature for 3 h. The organic layer was then separated, and the aqueous layer was extracted twice with 50-mL portions of dichloromethane. After evaporation of the dichloromethane, water was added, and the mixture was extracted with ether. The ether extracts were washed twice with 2 M ammonia solution and saturated aqueous NaCl and dried. Removal of the solvent under pressure afforded **8** as a yellow oil: R_f 0.46 (1:2 ethyl acetate/hexane).

The product thus obtained was refluxed in 97 mL of 1 M aqueous NaOH and 35 mL of water for 24 h. After cooling, the solution was acidified with 100 mL of 10% aqueous H_2SO_4 (the first few milliliters with extreme caution). It was then heated at reflux for 4.5 h, cooled, and extracted with ether. The crude acid was further purified by reextraction with aqueous $NaHCO_3$, acidification of this aqueous $NaHCO_3$, and extraction with ether. The ether extracts were dried and evaporated to give the acid **13** as a yellow solid, which was mixed with anhydrous potassium carbonate (2.84 g, 20.5 mmol), dimethyl sulfate (1.4 mL, 14.7 mmol), and acetone (70 mL), and heated at 50 °C overnight. After the addition of 70 mL of water, the solution was stirred at room temperature for 1.5 h. Following evaporation of the acetone and extraction of the remaining solution with ether, the combined ether extracts were dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue on silica gel with 1:5 ether/petroleum ether afforded 2.19 g (51% from **7**) of **14** as a pale yellow oil: R_f 0.50 (1:3 ether/petroleum ether); IR (neat) 1735, 1614, 1597, 1426, 1300, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (s, 3), 1.34 (d, 3, J = 6.6 Hz), 1.38 (s, 3), 3.54 (s, 2), 3.69 (s, 3), 3.80 (s, 3), 4.33 (q, 1, J = 6.6 Hz), 6.32 (s, 1), 6.34 (s, 1); mass spectrum, m/z (relative intensity) 264 (M^+, 31), 249 (73), 205 (8), 189 (100), 175 (14); exact mass calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1362.

(*E*)-3-Methoxy-2-butenoyl Chloride. A mixture of methyl (*E*)-3-methoxy-2-butenoate[17] (77.1 g, 0.593 mol), sodium hydroxide pellets (23.7 g, 0.593 mol), water (320 mL), and methanol (350

(17) Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455.

mL) was refluxed overnight. The solvent was evaporated under reduced pressure, with the last traces of water being removed by azeotropic distillation with benzene (several times if necessary). The remaining white solid was dried thoroughly to give sodium (*E*)-3-methoxy-2-butenoate in quantitative yield, which was finely powdered for the next step.

To a stirred mixture of the sodium salt (25.0 g, 0.181 mol) thus obtained in 160 mL of anhydrous ether at −5 °C was added dropwise oxalyl chloride (39.5 mL, 0.453 mol) under argon. Stirring was continued for 2 h at room temperature, and excess oxalyl chloride and solvent were then distilled under atmospheric pressure. Vacuum distillation afforded 12.2 g (50%) of (*E*)-3-methoxy-2-butenoyl chloride as a pale yellow oil: bp 64 °C (4 mmHg); IR (neat) 1750, 1570, 1432, 1385, 1268, 1074, 1050 cm^{-1}. This acid chloride is unstable and was stored at −78 °C prior to use.

Methyl 2,3-Dihydro-7-hydroxy-4-methoxy-2,3,3,9-tetramethylnaphtho[1,2-*b*]furan-6-carboxylate (16) and Its Methyl Ether 17. To a stirred solution of 0.63 mL (3.83 mmol) of *N*-isopropylcyclohexylamine in 10 mL of THF at −5 °C was added dropwise 1.54 mL (3.83 mmol) of a 2.5 M solution of *n*-butyllithium in hexane. After the mixture was stirred for 0.5 h and cooled to −78 °C, a solution of 0.38 g (1.44 mmol) of the ester **14** in 5 mL of THF was added dropwise. Stirring was continued for 0.5 h at −78 °C, and then 1.50 g (11.2 mmol) of (*E*)-3-methoxy-2-butenoyl chloride was added dropwise. The mixture was quenched with cold water after 0.5 h, poured into aqueous NH_4Cl, and extracted with ethyl acetate. Following removal of the solvent in vacuo, the residue was dissolved in ether, washed with saturated aqueous $NaHCO_3$, and dried. Evaporation of the solvent under reduced pressure and flash chromatography of the residue on silica gel with 1:5 ether/petroleum ether afforded 0.47 g of **15** as a yellow oil: R_f 0.24 (1:3 ether/petroleum ether); IR (neat) 1740, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (s, 3), 1.33 (d, 3, J = 6.6 Hz), 1.38 (s, 3), 2.29 (s, 3), 3.58 (s, 3), 3.75 (s, 3), 3.80 (s, 3), 4.34 (q, 1, J = 6.6 Hz), 4.61 (s, 1), 5.45 (s, 1), 6.43 (m, 2); mass spectrum, m/z (relative intensity) 362 (M^+, 5.5), 331 (0.5), 315 (0.7), 290 (1.9), 275 (2.1), 263 (0.7), 232 (1.5), 219 (1.8), 217 (1.9), 205 (0.7), 189 (1.0), 175 (0.7), 149 (0.7), 99 (100).

The product thus obtained was mixed with methanol (40 mL), water (20 drops), and concentrated H_2SO_4 (15 drops), and heated at 45 °C overnight. Half of the methanol was then evaporated under reduced pressure, resulting in the precipitation of white crystals. These were filtered and washed with cold methanol to give 197 mg of **16**: mp 128–129 °C; R_f 0.60 (1:4 ether/petroleum ether); IR ($CHCl_3$) 3350, 1640, 1618, 1598, 1439, 1288, 1225, 1126, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (s, 3), 1.39 (d, 3, J = 6.5 Hz), 1.44 (s, 3), 2.76 (s, 3), 3.92 (s, 3), 4.06 (s, 3), 4.44 (q, 1, J = 6.5 Hz), 6.69 (s, 1), 7.79 (s, 1), 12.05 (s, 1); UV λ_{max} (MeOH) 221 nm (ϵ 44 200), 254 (21 600), 269 (20 700), 277 (23 000), 341 (6900), 361 (sh) (5600); mass spectrum, m/z (relative intensity) 330 (M^+, 61), 315 (41), 298 (8), 283 (100), 255 (10), 225 (4). Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.15; H, 6.53.

The methanol filtrate was worked up in the following manner: After removal of most of the methanol in vacuo, water was added, and the mixture was extracted witth dichloromethane. The combined organic extracts were dried over Na_2SO_4, evaporated, and separated by preparative TLC silica gel (eluted with 1:4 ether/petroleum ether) to give 40 mg of **16** (combined with 197 mg obtained above: 50% from **14**) and 19 mg (4% from **14**) of **17**, which afforded white needles: mp 128–129.5 °C (from MeOH); R_f 0.30 (1:4 ether/petroleum ether); IR ($CHCl_3$) 1718, 1622, 1590, 1460, 1350, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 3), 1.39 (d, 3, J = 6.5 Hz), 1.42 (s, 3), 2.82 (s, 3), 3.86 (s, 3), 3.90 (s, 3), 3.99 (s, 3), 4.44 (q, 1, J = 6.5 Hz), 6.51 (s, 1), 6.77 (s, 1); UV λ_{max} (MeOH) 222 nm (ϵ 33 200), 240 (sh) (30 300), 254 (56 200), 319 (4900), 337 (sh) (3800); mass spectrum, m/z (relative intensity) 344 (M^+, 91), 329 (100), 313 (16), 297 (51), 270 (10), 255 (4).

Naphthalene 17 from 16. A mixture of the ester **16** (1.11 g, 3.36 mmol), benzyltributylammonium bromide (0.20 g, 0.57 mmol), dimethyl sulfate (0.80 mL, 8.40 mmol), 1 M aqueous NaOH (5.0 mL, 5.0 mmol), water (30 mL), and dichloromethane (30 mL) was stirred at room temperature for 4 h. The organic layer was then separated, and the aqueous layer was extracted twice with 30-mL portions of dichloromethane. After evaporation of the dichloromethane, water was added, and the mixture was extracted with ether. The ether extracts were washed twice with 2 M ammonia solution, 5% aqueous NaOH, and saturated aqueous NaCl and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded 1.32 g of crude **17** as a pink solid, which was used directly in the next step.

Methyl 2,3-Dihydro-4,7-dimethoxy-5-(methoxyacetyl)-2,3,3,9-tetramethylnaphtho[1,2-*b*]furan-6-carboxylate (18). To a stirred solution of the crude ester **17** (402 mg, 1.02 mmol) and methoxyacetyl chloride (1.10 mL, 12.0 mmol) in 8 mL of dichloromethane at −5 °C was added dropwise titanium(IV) chloride (0.225 mL, 2.04 mmol) under argon. After 0.5 h, the solution was poured into a mixture of ice and 10% aqueous HCl and extracted with dichloromethane. The combined organic extracts were washed twice with saturated aqueous $NaHCO_3$ and dried. Evaporation of the solvent under reduced pressure and flash chromatography of the residue on silica gel with 1:4 ether/petroleum ether afforded 179 mg of pure starting ester **17**. Further elution with 1:1 ether/petroleum ether afforded 159 mg (37%, 76% based on starting material recovered) of **18** as a viscous yellow oil: R_f 0.40 (3:2 ether/petroleum ether); IR ($CHCl_3$) 1712, 1594, 1460, 1330, 1268 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (s, 3), 1.42 (d, 3, J = 6.5 Hz), 1.46 (s, 3), 2.84 (s, 3), 3.56 (s, 3), 3.78 (s, 3), 3.89 (s, 3), 3.90 (s, 3), 4.48 (q, 1, J = 6.5 Hz), 4.54 (s, 2), 6.90 (s, 1); UV λ_{max} (MeOH) 218 nm, 253, 311 (sh), 323, 346; mass spectrum, m/z (relative intensity) 416 (M^+, 3.3), 385 (1.8), 371 (100), 341 (5.0).

(±)-Atrovenetin Trimethyl Ether (20). To a stirred solution of potassium *tert*-butoxide (52 mg, 0.46 mmol) in 3 mL of THF at −5 °C was added dropwise a solution of the keto ester **18** (87 mg, 0.21 mmol) in 5 mL of THF under argon. After 10 min, the solution was poured into 100 mL of cold 5% aqueous HCl and extracted with five 40-mL portions of chloroform. The combined organic extracts were washed with two 100-mL portions of saturated aqueous NaCl, dried, and evaporated to give a yellow-orange solid. Recrystallization from dichloromethane/hexane afforded 64 mg (80%) of **20** as yellow-orange crystals: R_f 0.36 (1:9 methanol/chloroform); IR ($CHCl_3$) 3360, 1652, 1606, 1580, 1551, 1445, 1386, 1298, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3), 1.48 (d, 3, J = 6.6 Hz), 1.54 (s, 3), 2.91 (s, 3), 3.97 (s, 3), 4.08 (s, 3), 4.19 (s, 3), 4.61 (q, 1, J = 6.6 Hz), 7.00 (s, 1), 9.45 (br s, 1, D_2O exchange). One additional recrystallization from dichloromethane/hexane afforded an analytical sample: yellow crystals, mp 214–218 °C; UV λ_{max} (MeOH) 215 nm (ϵ 35 300), 274 (32 700), 365 (12 300), 416 (14 400); mass spectrum, m/z (relative intensity) 384 (M^+, 100), 369 (88), 367 (26), 355 (45), 353 (37), 351 (20), 341 (18), 339 (16), 337 (22), 314 (59), 311 (18). Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.47; H, 6.24.

(±)-Atrovenetin (1). A mixture of (±)-atrovenetin trimethyl ether (**20**; 58 mg, 0.15 mmol) and pyridine hydrochloride (1.40 g, 12.1 mmol) was heated at 220 °C under argon for 8 min after the solid mixture had melted. Dilute sulfuric acid was added, and the precipitated solid was filtered, washed with water, and dried to give (±)-atrovenetin [45 mg (87%)] as a yellow-brown powder: mp 285 °C dec with prior darkening from 255 °C (from acetone/water). The synthetic racemic material was identical with an authentic sample of natural (+)-atrovenetin by spectral comparison (IR, ^1H NMR, UV, mass).

Methyl 5-Acetyl-2,3-dihydro-4,7-dimethoxy-2,3,3,9-tetramethylnaphtho[1,2-*b*]furan-6-carboxylate (22). To a stirred solution of ester **17** (400 mg, 1.16 mmol) in 15 mL of acetic anhydride at −5 °C was added dropwise tin(IV) chloride (0.28 mL, 2.38 mmol) under argon. After 2 h, the solution was poured into a mixture of ice and 10% aqueous HCl and extracted with dichloromethane. The combined organic extracts were dried and evaporated under reduced pressure, with traces of $HOAc/Ac_2O$ being removed by azeotropic distillation with toluene (several times if necessary). The residue was separated by preparative TLC silica gel (eluted twice with 1:2 ether/petroleum ether) to give 79 mg of **17** and 306 mg (68%, 85% considering recovered starting material) of **22** as a pale yellow solid: mp 127–129 °C (from dichloromethane/hexane); R_f 0.26 (1:2 ether/petroleum ether); IR ($CHCl_3$) 1712, 1594, 1460, 1330, 1271 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (s, 3), 1.41 (d, 3, J = 6.6 Hz), 1.46 (s, 3), 2.64 (s, 3), 2.84 (d, 3, J = 0.7 Hz), 3.78 (s, 3), 3.87 (s, 3), 3.89 (s, 3), 4.47 (q, 1, J = 6.6 Hz), 6.89 (s, 1); UV λ_{max} (MeOH) 217 nm (ϵ 23 400), 253 (45 000), 312 (sh) (4800), 324 (5900), 347 (6500); mass spectrum,

m/z (relative intensity) 386 (M^+, 29), 371 (11), 355 (6), 343 (4), 327 (100), 297 (8). Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.18; H, 6.97.

8,9-Dihydro-3,7-dimethoxy-6-hydroxy-1,8,8,9-tetramethylphenaleno[1,2-*b*]furan-4-one (23). To a stirred solution of potassium *tert*-butoxide (6.4 mg, 0.057 mmol) in 1.5 mL of THF at 0 °C was added dropwise a solution of keto ester **22** (10 mg, 0.026 mmol) in 2 mL of THF under argon. After 10 min, the solution was poured into aqueous NH_4Cl and extracted with chloroform. The combined organic extracts were dried, evaporated, and separated by preparative TLC silica gel to give 7.5 mg of **23** as a yellow solid: R_f 0.37 (1:9 methanol/chloroform); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3), 1.48 (d, 3, J = 6.5 Hz), 1.54 (s, 3), 2.90 (s, 3), 4.06 (s, 3), 4.17 (s, 3), 4.61 (q, 1, J = 6.5 Hz), 6.20 (s, 1), 6.96 (s, 1), 9.84 (br, 1, D_2O exch); UV λ_{max} (MeOH) 214 nm, 269 (sh), 276, 362, 390, 411, 432; mass spectrum, m/z (relative intensity) 354 (M^+, 90), 339 (69), 325 (100), 309 (32), 297 (24), 284 (94).

2,3-Dihydro-4,7-dimethoxy-2,3,3,9-tetramethylnaphtho[1,2-*b*]furan-5,6-dicarboxylic Acid Anhydride (24) and (±)-Scleroderodione Dimethyl Ether (25). To a stirred solution of potassium *tert*-butoxide (79 mg, 0.70 mmol) in 4 mL of THF at 0 °C was added dropwise a solution of keto ester **22** (124 mg, 0.32 mmol) in 9 mL of THF under argon. After 15 min, MoOPH (680 mg, 1.57 mmol) was added in one portion, followed by 5 mL of THF, at 0 °C. Stirring was continued for 20–24 h at room temperature. The mixture was then cooled at 0 °C, quenched with aqueous NH_4Cl, and extracted with ether. The combined organic extracts were washed with 5% aqueous $NaHCO_3$, 5% aqueous HCl, saturated aqueous NaCl and dried. Evaporation of the solvent under reduced pressure and chromatography of the residue by preparative TLC silica gel (eluted three times with 2:3 ethyl acetate/hexane) gave 23 mg (21%) of **25**, which afforded fine yellow-orange needles: mp 152.5–154 °C (from acetone/hexane); R_f 0.40 (2:3 ethyl acetate/hexane); IR ($CHCl_3$) 1719, 1704, 1614, 1592, 1502, 1351, 1309 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 3), 1.47 (d, 3, J = 6.6 Hz), 1.47 (s, 3), 2.83 (d, 3, J = 0.9 Hz), 4.08 (s, 3), 4.37 (s, 3), 4.62 (q, 1, J = 6.6 Hz), 6.82 (s, 1); UV λ_{max} (MeOH) 221 nm (ϵ 30600), 260 (75400), 286 (13200), 333 (7200), 352 (7600), 370 (sh) (5600); mass spectrum, m/z (relative intensity) 340 (M^+, 42), 325 (39), 311 (28), 297 (25), 295 (22), 283 (18), 267 (14).

The bright blue fluorescent band afforded 53 mg (46%) of **24**, which crystallized from dichloromethane/hexane as fine yellow needles: mp 85–87 °C; R_f 0.21 (2:3 ethyl acetate/hexane); IR ($CHCl_3$) 1748, 1713, 1592, 1561, 1466, 1354, 1307, 1277, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3), 1.49 (d, 3, J = 6.6 Hz), 1.53 (s, 3), 2.91 (s, 3), 4.09 (s, 3), 4.13 (s, 3), 4.65 (q, 1, J = 6.6 Hz), 7.01 (s, 1); UV λ_{max} (MeOH) 263 nm (ϵ 33900), 344 (10700), 379 (11500), 393 (sh) (10100); mass spectrum, m/z (relative intensity) 356 (M^+, 42), 341 (100), 323 (8), 313 (7), 297 (23), 169 (18).

In the event that 2.5 equiv of MoOPH was used instead of 5 equiv the distribution ratio of products **25** to **24** became 6:1.

(±)-Scleroderodione (26). A mixture of (±)-scleroderodione dimethyl ether (**25**; 25 mg, 0.074 mmol) and pyridine hydrochloride (1.78 g, 15.4 mmol) was heated at 220 °C under argon for 8 min after the solid mixture had melted. Dilute hydrochloric acid was added and the mixture was extracted with chloroform. The combined organic extracts were washed with 5% aqueous HCl and saturated aqueous NaCl, dried, and evaporated to give 17 mg (74%) of (±)-scleroderodione as a reddish brown solid. Recrystallization from dichloromethane/hexane afforded reddish brown plates: mp 204–207 °C; R_f 0.23 (1:9 methanol/chloroform); IR ($CHCl_3$) 3485, 1713, 1688, 1628, 1430, 1371, 1302 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3), 1.47 (d, 3, J = 6.6 Hz), 1.51 (s, 3), 2.75 (s, 3), 4.67 (q, 1, J = 6.6 Hz), 6.67 (s, 1), 7.60 (br, 2, D_2O exch); UV λ_{max} (MeOH) 219 nm (ϵ 27200), 231 (sh) (23000), 255 (65500), 286 (13600), 333 (8100), 343 (7700), 360 (sh) (5500); mass spectrum, m/z (relative intensity) 312 (M^+, 61), 297 (100), 269 (82).

Naphthalic Anhydride 2. A mixture of dimethyl ether **24** (36 mg, 0.101 mmol) and pyridine hydrochloride (2.17 g, 18.8 mmol) was heated at 210 °C under argon for 8 min after the solid mixture had melted. Dilute hydrochloric acid was added, and the mixture was extracted with chloroform. The combined organic extracts were washed with 5% aqueous HCl and saturated aqueous NaCl and dried. Evaporation of the solvent and chromatography of the residue by preparative TLC silica gel (eluted with 1:49 methanol/chloroform) gave 28 mg (85%) of **2**, which afforded fine pale yellow needles: mp 252–253 °C (from dichloromethane/hexane); R_f 0.52 (1:49 methanol/chloroform); IR ($CHCl_3$) 3300–2850, 1705, 1665, 1625, 1613, 1461, 1308, 1047 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3), 1.49 (d, 3, J = 6.5 Hz), 1.54 (s, 3), 2.81 (s, 3), 4.71 (q, 1, J = 6.5 Hz), 6.83 (s, 1), 11.40, 11.61 (2 s, 2); UV λ_{max} (EtOH) 215 nm (ϵ 28500), 256 (32000), 297 (9300), 310 (8200), 347 (13500), 361 (13800), 378 (12300); UV λ_{max} (EtOH, NaOH) 234 nm (ϵ 37200), 253 (sh) (23900), 308 (18100), 320 (sh) (15400), 375 (sh) (14700), 390 (20600); mass spectrum, m/z (relative intensity) 328 (M^+, 59), 313 (100), 295 (22), 285 (29), 269 (29).

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Registry No. (±)-**1**, 105015-48-3; (±)-**2**, 104974-22-3; **3**, 6110-30-1; **4**, 104875-24-3; **5**, 104875-25-4; (±)-**6**, 104875-26-5; (±)-**7**, 104875-27-6; (±)-**8**, 104875-28-7; (±)-**13**, 104875-29-8; (±)-**14**, 104875-30-1; **15**, 104875-32-3; (±)-**16**, 104875-33-4; (±)-**17**, 104875-34-5; (±)-**18**, 104875-35-6; (±)-**20**, 104875-36-7; (±)-**22**, 104875-37-8; (±)-**23**, 104875-38-9; (±)-**24**, 104974-20-1; (±)-**25**, 104875-39-0; (±)-**26**, 104974-21-2; methyl (*E*)-3-methoxy-2-butenoate, 4525-28-4; sodium (*E*)-3-methoxy-2-butenoate, 104875-31-2; (*E*)-3-methoxy-2-butanoyl chloride, 95187-87-4; dimethyl 4-carbomethoxy-3,5-dihydroxyhomophthalate, 104875-40-3; dimethyl 4-carboxy-3,5-dihydroxyhomophthalate, 104875-41-4; 1-chloro-3-methyl-2-butene, 503-60-6; methoxyacetyl chloride, 38870-89-2; dimethyl 1,3-acetonedicarboxylate, 1830-54-2.