considerably lower than in the undeuterated material. The carbonyl band was unchanged (1710 $cm^{-1}$) while other significant bands fell at 1600, 1460, 1425, 1363, 1340, 1222, 1122, and 837 $cm^{-1}$. (See text for a discussion of the NMR spectrum.) The mass spectrum gave parent ion *m/e* 304 and indicated the absence of any oxidative product or material that was deuterated additionally.

Irradiation of **1c** under identical conditions in monodeuteriomethanol ($CH_3OD$) yielded **13c'** also.

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**Registry No.**—**1a**, 64490-61-5; **1b**, 64490-62-6; **1c**, 64490-63-7; **3a**, 64490-64-8; **3b**, 64490-65-9; **3c**, 64490-66-0; **4a**, 455-19-6; **4b**, 874-42-0; **4c**, 7311-34-4; **5**, 18294-87-6; **6a**, 64490-67-1; *E*-**6b**, 64490-68-2; *Z*-**6b**, 64490-69-3; **6c**, 64490-70-6; **7a**, 2062-26-2; **7b**, 1201-99-6; **8a**, 64490-71-7; **8b**, 64490-72-8; **9a**, 64490-73-9; **10b**, 64490-74-0; **13c**, 64490-75-1; **13c'**, 64490-76-2.

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# Synthetic Studies on Lignan Lactones: Aryl Dithiane Route to (±)-Podorhizol[1] and (±)-Isopodophyllotoxone and Approaches to the Stegane Skeleton

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The details of the conjugate addition of aryl dithiane anions to 2-butenolide are discussed. The results of the trapping of the resultant lactone enolates with an aryl halide and aryl aldehyde are detailed. The transformation of these intermediates into podorhizol (**4a**) and isopodophyllotoxone (**12a**) is also explored. The structures of products from attempted intramolecular Ullmann couplings in the stegnane series are established.

The antileukemic lignan lactones steganacin (**1a**) and steganangin (**1b**)[4] are but only two members of a growing class of naturally occurring bis(benzyl)[*a,c*]cyclooctadienes which include among their members schizandrin,[5] kadsurin, kadsuranin,[6] and gomisins A, B (**2a**), C (**2b**),[7] and D (**2c**).[8] The unusual ring system present in these substances and the close biogenetic relationship between the structures **1** and the antitumor lactone podophyllotoxin[9] **3** and its derivatives[10] have both initiated and renewed interest in the development of new methodology for the synthesis of these substances. To date the syntheses of steganacin,[11] steganone,[11,12] isostegane,[13] and deoxyschizandrin[14] have been realized.

Our concern in this area lay in the development of an efficient synthetic method which would be amenable to the construction of members of the stegane, podophyllane, and secopodophyllane (e.g., podorhizol (**4a**)) families. It appeared attractive to employ an acyl anion equivalent of piperonal which could undergo conjugate addition to 2-butenolide and whose resultant lactone anion could effect subsequent alkylation or aldol condensation with the appropriate benzylic halide or aromatic aldehyde (Scheme I).

Although the anions **5a–d** failed to give clean addition products, the thioethyl acetal anion provided the Michael adduct **7a** in 50% yield when exposed to 2-butenolide in THF at −78 °C[15] followed by low-temperature protonation. This yield was measurably improved (88%) by employing the dithiane **5f**, thereby providing the congener **7b**. Anion **5f** and the dithiane anion of benzaldehyde both added in a conjugate fashion to methyl cinnamate and methyl crotonate in 70–85% yield. The lactone enolate of **7b** could be generated successfully with lithium diisopropylamide (LDA) in THF at −78 °C followed by alkylation (−78 → 25 °C) with 3,4,5 trimethoxybenzyl chloride in the presence of 1 equiv of hexamethylphosphoramide (HMPA) in 56% yield. A more efficient route involved the direct alkylation[17] of the lactone enolate generated by Michael addition, thereby providing all of the required carbon atoms present in these lactones in a one-pot reaction. It was assumed at this point that the stereochemistry of **6a** was trans since it would be expected that alkylation would occur trans to the bulky aryl dithiane moiety. The assignment was confirmed when the dithiane was cleaved with HgO–$BF_3$ in aqueous THF to provide the ketone **6d**, prepared by Drake[18] some 20 years earlier. Moreover, the dithiane **6a** was transformed as described by Schlessinger[13] (Ni(R); $VOF_3$) to isostegane (**8**), whose unnatural biphenyl twist and trans-fused lactone have been defined by x-ray analysis. Any conversion of isostegane (**8**) to steganone (**1c**) would be dependent upon a selective benzylic oxidation to introduce oxygen and relieve the unnatural biphenyl twist.[19]

The intramolecular oxidative coupling of electron-rich aromatic rings appears to be unsuccessful only in instances where the benzylic position is capable of forming a cation, is deactivated (i.e., carbonyl), or is capable of oxidation.[11,13,20] Thus, oxidation of dithiane **6a** with either $VOF_3$ or $Mn(acac)_3$ or by anodic oxidation efficiently provided dihydronaphthalene **9**, without any indication of biaryl coupling. Although the biaryl couplings require a strong acid medium [e.g., trifluoroacetic acid (TFA)], the dithiane underwent cyclization even in the absence of TFA. Dihydronaphthalene **9** could be further oxidized to the naphthalene by either overexposure

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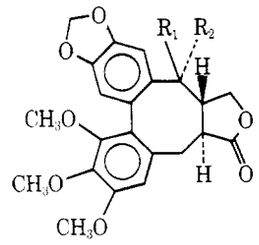
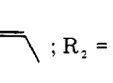
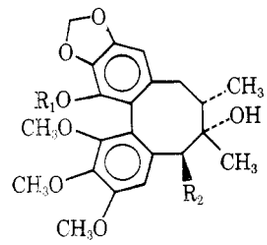
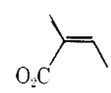


1a, $R_1$ = OAc; $R_2$ = H

b, $R_1$ =  ; $R_2$ = H

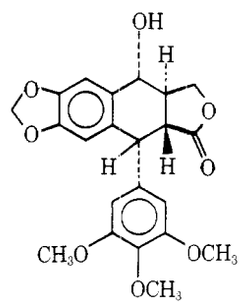
c, $R_1$, $R_2$ = O



2a, $R_1$ = $CH_3$; $R_2$ = 

b, $R_1$ = $CH_3$; $R_2$ = $CO_2C_6H_5$

c, $R_1 \rightarrow R_2$ = $CH_2CHCH_3CHCH_3(OH)CO_2$



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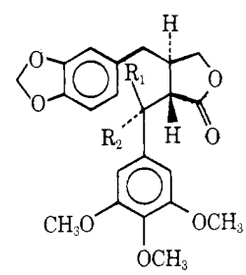


4a, $R_1$ = OH; $R_2$ = H

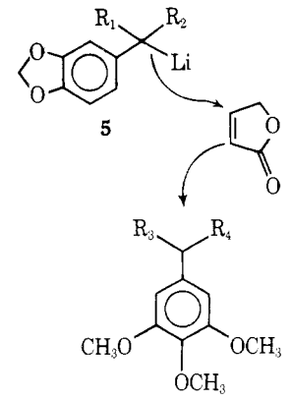
b, $R_1$ = H; $R_2$ = OH

to $Mn(acac)_3$ or treatment with manganese dioxide and was found to be identical with the naphthalene prepared by a different route.[21]

The keto lactone **6d** gave a complex mixture of products with $VOF_3$ and provided, upon oxidation with $Mn(acac)_3$, the cinnamate **10**, whose structure was assigned in part on the appearance of a vinylic one-proton doublet at $\delta$ 7.72 ($J$ = 2 Hz) in accord with established values.[22,24] Attempts to oxidatively cyclize the alcohols **6e** or their acetates **6f** led to the tetrahydronaphthalene **11**. The appearance of a one-proton C–H at $\delta$ 3.95 ($J$ = 15 Hz) served to establish the trans relationship between the protons at C-1 and C-2. This cyclization is not effected by the oxidants but rather by the solvent, trifluoroacetic acid.

The anion of lactone **7b** in THF at −78 °C was efficiently trapped with 3,4,5-trimethoxybenzaldehyde to provide the erythro and threo aldol products **6b** and **6c** in ratio of 52:48, respectively. House[23] has shown that the aldol condensation kinetically provides more of the threo isomer in solvents of low polarity. Accordingly, when the aldol condensation was conducted in 1:1 ether–1,2-dimethoxyethane, the isomer **6c** (threo) predominated over isomer **6b** (erythro) in a 3:1 ratio. Since it has been established[23] that $J_{threo}$ (6–9 Hz) > $J_{erythro}$ (2–4 Hz) due to hydrogen bonding in the aldol products, the stereochemical assignments could be readily made since isomer **6b** displayed a doublet ($R_4$ = H) at $\delta$ 5.16 ($J$ = 2.0 Hz) and

Scheme I



a, $R_1$ = $R_2$ = $CO_2CH_3$

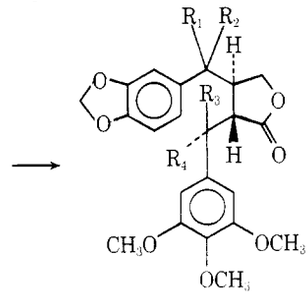
b, $R_1$ = CN; $R_2$ = $OCH(OC_2H_5)CH_3$

c, $R_1$ = CN; $R_2$ = $N(CH_2CH_2)_2$

d, $R_1$ = H; $R_2$ = $SOC_6H_5$

e, $R_1$ = $R_2$ = $SC_2H_5$

f, $R_1$, $R_2$ = $SCH_2CH_2CH_2S$



6a, $R_1$, $R_2$ = $SCH_2CH_2CH_2S$; $R_3$ = $R_4$ = H

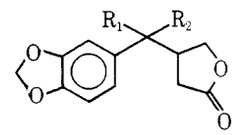
b, $R_1$, $R_2$ = $SCH_2CH_2CH_2S$; $R_3$ = OH; $R_4$ = H

c, $R_1$, $R_2$ = $SCH_2CH_2CH_2S$; $R_3$ = H; $R_4$ = OH

d, $R_1$, $R_2$ = O; $R_3$ = $R_4$ = H

e, $R_1$ = OH; $R_2$ = $R_3$ = $R_4$ = H

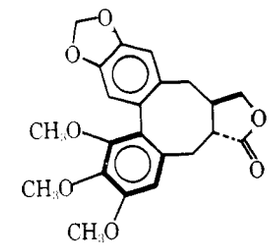
f, $R_1$ = OAc; $R_2$ = $R_3$ = $R_4$ = H



7a, $R_1$ = $R_2$ = $SC_2H_5$

b, $R_1$, $R_2$ = $SCH_2CH_2CH_2S$

c, $R_1$, $R_2$ = O



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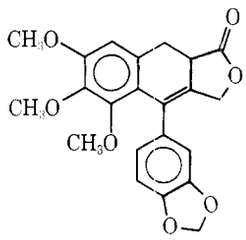
isomer **6c** revealed a doublet ($R_3$ = H) at $\delta$ 4.77 ($J$ = 6.8 Hz).

Desulfurization of erythro dithiane **6b** with Raney nickel W-2 in refluxing ethanol gave rise to (±)-podorhizol (**4a**), identical (solution IR, HPLC, TLC, 270-MHz NMR) with a sample of natural (−)-podorhizol.[24] In a similar manner, the threo isomer gave rise to (±)-epipodorhizol (**4b**), whose spectral properties were in accord with reported[24] values.

Acid hydrolysis of the naturally occurring glycoside of (−)-podorhizol effects cyclization to deoxyisopodophyllotoxin (**12a**) as the major component and deoxypodophyllotoxin (**12b**) as the minor product, without prior dehydration to the anhydro derivative prior to cyclization.[24] Treatment of erythro dithiane **6b** with stannic chloride in methylene chloride produced a homogeneous solution which cleanly afforded a single product of cyclization. The 270-MHz NMR spectrum clearly revealed this compound to be the dithiane of isopodophyllotoxone (**12c**) since the C-1 proton appeared as a doublet at $\delta$ 4.01 ($J_{1,2}$ = 11 Hz) and the C-2 proton appeared as a doublet of doublets at $\delta$ 3.42 ($J_{1,2}$ = 11, $J_{2,3}$ = 15 Hz). Under the mild cyclization conditions, only a single stereoisomer is produced



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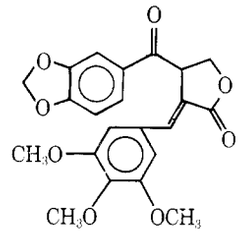

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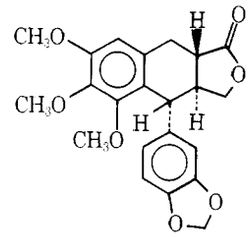

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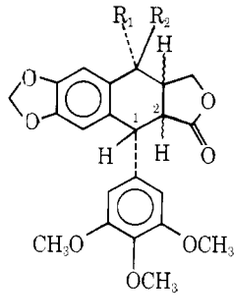


12a, 2αH; 3βH; $R_1 = R_2 = H$
b, 2βH; 3αH; $R_1 = R_2 = H$
c, 2αH; 3βH; $R_1 = R_2 = O$ (isopodo)
d, 2βH; 3αH; $R_1 = R_2 = O$ (podo)
e, 2αH; 3αH; $R_1 = R_2 = O$ (picro)
f, 2βH; 3βH; $R_1 = R_2 = O$ (isopicro)
g, 2αH; 3βH; $R_1 = H$; $R_2 = OH$
h, 2βH; 3αH; $R_1 = OH$; $R_2 = H$
i, 2αH; 3βH; $R_1$, $R_2 = SCH_2CH_2CH_2S$

with the trans-fused lactone remaining intact. On the other hand, the threo isomer **6c** formed an insoluble precipitate from which the starting material could be isolated. However, prolonged refluxing of the solution eventually effected cyclization to the same material. This discrepancy in solubility and reactivity can be considered due to the threo isomer being more prone to forming a stable cyclic tin salt, having the trimethoxybenzene ring equatorially oriented. The erythro isomer would have the same substituent in the less stable axial arrangement, thereby allowing more facile decomposition to the benzylic cation. This minor inconvenience was circumvented by accomplishing the ring closure with trifluoroacetic acid in methylene chloride. Moreover, podorhizol and epipodorhizol were readily cyclized under both of these sets of conditions to deoxyisopodophyllotoxin (**12a**).

Oxidative removal of the dithiane function in the cyclization product produced (±)-isopodophyllotoxone (**12c**), based upon the appearance of the C-1 proton at δ 4.28 ($J_{1,2}$ = 11 Hz) and the C-2 proton at δ 3.06 ($J_{1,2}$ = 11, $J_{2,3}$ = 15 Hz) in the 270-MHz NMR spectrum. The physical and spectral properties of our racemic **12c** were not in accord with those of the same material prepared by Gensler[25] by the oxidation of (±)-isopodophyllotoxin (**12g**) with $MnO_2$. The structure of (±)-**12g** was on firm ground since hydrogenolysis of its *O*-acetate provided the known (±)-deoxyisopodophyllotoxin (**12a**).

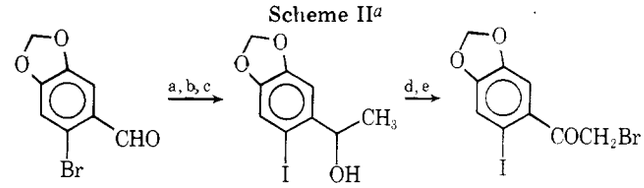
The 270-MHz NMR spectrum of Gensler's racemic ketone[26,27] was found to be identical with a sample of picropodophyllone[27] (**12e**) prepared from (−)-podophyllotoxin (**12h**) by C-2 epimerization[28] and room temperature $MnO_2$ oxidation.[29] This epimerization may have arisen in refluxing dioxane from traces of base present in the $MnO_2$. The 270-MHz NMR spectra of the remaining two ketones, podophyllotoxone (**12d**) (from (−)-**12h** by oxidation) and (−)-isopicropodophyllone (**12f**),[30] were recorded and found to be distinctly different from **12c** and **12d.** In particular, the trans-fused lactones podophyllotoxone (**12d**) and isopodophyllotoxone (**12c**) are highly resolved spectra relative to their cis counterparts.

The inability to form the dibenzocyclooctadiene skeleton by oxidative means prompted consideration of an intramolecular Ullmann coupling of the two aromatic rings. Although it was possible to achieve bromination of the trimethoxybenzene ring of **6d** under various conditions, it was not possible to brominate the 6 position of the deactivated methylenedioxybenzene ring. In fact, dibromination of the trimethoxybenzene ring occurred preferentially. An attempt to circumvent this difficulty by preparing the lithiodithiane of 6-bromopiperonal was unsuccessful since *n*-butyllithium effected metal–halogen exchange followed by proton exchange to give the lithiodithiane **5f.**

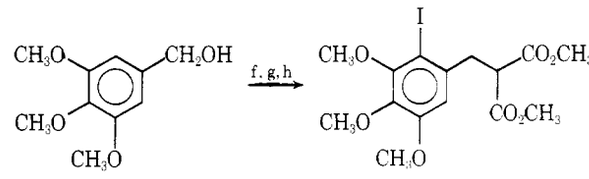
The requisite aryl halides **18a** and **18b** were synthesized by modification of Drake's method[18] (Scheme II). Attempted intramolecular coupling with copper bronze in refluxing DMF afforded as the major product the monodehalogenated iodide **18c,** in accord with the observations of Semmelhack[31] in a related system employing tetrakis(triphenylphosphine)-nickel(0) in DMF. On occasion a product of longer retention time (HPLC) could be detected, but never produced in sufficient quantity. Variations in reaction temperatures, concentration, sources of copper powder, or activation of the copper[32] powder gave approximately the same yield of the reduced iodide **18c.**

Cuprous triflate[33] in DMF at reflux (150–160 °C) also reduced the diiodide **18a** to the monoiodide **18c** along with

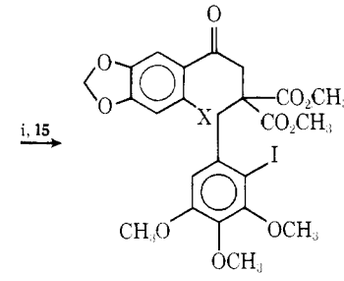
Scheme II[a]



13 14 15



16 17



18a, X = I
b, X = Br
c, X = H
d, X = symmetrical dimer
e, X = $PO(OC_2H_5)_2$

[a] a, $CH_3MgBr$; b, 2 equiv of *n*-BuLi; c, $I_2$; d, Jones reagent; e, $Br_2$/HBr; f, $Hg(OAc)_2/I_2$; g, $SOCl_2$; h, $NaCH(CO_2COCH_3)_2$/THF; i, NaH/THF

minor amounts of the longer retention-time material. When the reaction temperature was reduced to 100 °C, the starting material was completely consumed with reproducible formation of the longer retention-time product and the absence of the monoiodide **18c**. Lower temperatures resulted in the recovery of starting material. This new product was assigned the symmetrical dimeric structure **18d** on the basis of spectral data and combustion analysis. Since bromine exchnges slower than iodine in the Ullmann reaction,[34] it was considered that iodobromide **18b** at higher dilution would favor intramolecular over intermolecular coupling. This did not prove to be the case since dimer **18d** was obtained in approximately the same yield as was previously obtained. This indicates that the bromide with its ortho carbonyl is still a more reactive moiety than the doubly ortho-flanked iodide.

The halogen of the trimethoxybenzene ring, which is flanked by two ortho substitutents (methoxy and alkyl chain), is reduced in reactivity by not only steric factors, but probably electronic factors as well. The Ullmann cyclization of 2-iodo-3-ethylbenzoic anhydride (7-membered ring) has been realized in 90% yield by employing copper powder in refluxing DMF. Although the electron-withdrawing carbonyl group ortho to the halogen plays a role in activating the halogen, the ring size and intramolecular nature of the coupling play a significant role since methyl 2-iodo-3-ethylbenzoate coupled in only 41% yield.[35]

When the diiodide **18a** was heated in the presence of the copper(I) iodide–triethyl phosphite complex in DMF at 100 °C, a crystalline product was isolated in 89% yield. The elemental combustion analysis (C, H, I) was in accord with structure **18e**. The site of the phosphorus residue was revealed by the large coupling of the ortho ($J$ = 12 Hz) and meta ($J$ = 4 Hz) protons in the methylenedioxybenzene ring. This aromatic Michaelis–Arbuzov reaction has been observed by Tavs[36] when aromatic halides and triethyl phosphite are heated in the presence of copper powder, albeit in low yield.

It can be concluded from these results and efforts in this area on a related system[31] [**18b**, bis(decarbomethoxy)] that the enhanced reactivity of the halogen ortho to an electron-withdrawing group permits either reduction or intermolecular reactions faster than intramolecular coupling with doubly ortho-flanked aryl halides. When one of the two groups is electron withdrawing, intramolecular couplings may occur. This intramolecular reaction can be applied in systems where steric hindrance, halide activation, ring size, and reagents are optimized.[37]

## Experimental Section

Melting points were obtained on a Fisher-Johns apparatus and are corrected. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. Infrared spectra were determined on a Perkin-Elmer Model 700A or 421 spectrometer. Nuclear magnetic resonance spectra were obtained on either a Varian Model A-60A, JEOL minimar 100, Perkin-Elmer Model R-32, or Bruker HX-270. Chemical shifts are reported in $\delta$ units using tetramethylsilane as an internal reference.

Solvents are reagent grade and were used as received. Chloroform and methylene chloride, when used as reaction solvents, were distilled from phosphorus pentoxide under a nitrogen atmosphere. Tetrahydrofuran, ether, and glyme were distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Dimethylformamide (DMF) was distilled from calcium hydride at atmospheric pressure under a nitrogen atmosphere. Butyllithium was purchased from Alfa–Ventron and titrated according to the method of Gilman or Kofron.[38] Low temperatures were maintained with $CO_2$–acetone baths. In all workup procedures the drying process involved treatment with anhydrous magnesium sulfate and filtering in vacuo prior to concentration in vacuo.

In reactions requiring anhydrous conditions the apparatus and transfer equipment were dried at 100–110 °C for at least 2 h and cooled to 25 °C under a nitrogen atmosphere before use.

Analytical high-pressure chromatograms were obtained using a 50 × 2 mm Porasil T column eluted with 30% THF–hexane with a 0.5 mL/min flow rate in conjunction with an Isco UV-type 6 detector and electronic integrator system.

**3-(3′,4′-Methylenedioxybenzoyl)butyrolactone Dithiane (7b).** To a stirred solution of 1.20 g (5.0 mmol) of piperonal dithiane dissolved in 10 mL of dry THF maintained under a nitrogen atmosphere at −78 °C was added a solution of 2.18 mL (5.10 mmol, 2.34 M) of $n$-butyllithium in hexane.[39] The resultant orange solution was stirred for 0.5 h and then treated with a solution of 0.42 g (5.0 mmol) of 2-butenolide in 1 mL of THF. The reaction mixture was stirred for 0.5 h and then quenched with 10% aqueous acetic acid (5 mL) and allowed to warm to 25 °C. The solution was extracted thoroughly with ethyl acetate, and the extracts were combined, washed with water, and dried. Evaporation of the solvent afforded a yellow solid. Recrystallization from benzene–ether gave the lactone **7b** (88%) as fine white crystals: mp 154–155 °C; IR ($CHCl_3$) 2930, 1780, 1249 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.97 (2, H, m), 2.68 (6 H, m), 4.28 (2 H, m), 6.02 (2 H, s), 6.78 (1 H, d, $J$ = 10 Hz), 7.48 (3 H, m).

Anal. Calcd for $C_{15}H_{16}O_4S_2$: C, 55.53; H, 4.97; S, 19.76. Found: C, 55.50; H, 4.98; S, 19.76.

**3-(3′,4′-Methylenedioxybenzoyl)butyrolactone (7c).** To a stirred solution of 10 mL of 15% aqueous THF maintained under a nitrogen atmosphere was added 0.91 g (4.2 mmol) of red mercuric oxide and 0.52 mL (4.2 mmol) of freshly distilled boron trifluoride etherate.[40] A solution of 0.47 g (1.5 mmol) of butyrolactone dithiane **7b** dissolved in 10 mL of THF was added, and the reaction mixture was allowed to stir at 25 °C for 12 h. The reaction mixture was diluted with 20 mL of ether followed by filtration to remove the precipitated salts. The ether solution was successively washed to pH 10 with saturated sodium carbonate and to neutrality with saturated sodium chloride and dried. Removal of the solvent left a white powder. Crystallization from ether–pentane afforded the keto lactone **7c** (85%) as long white needles: mp 118–119 °C (lit.[16] 118–119 °C); IR ($CHCl_3$) 1780, 1675, 1250 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.88 (2 H, m), 4.45 (3 H, m), 6.10 (2 H, s), 6.94 (1 H, d, $J$ = 9 Hz), 7.45 (1 H, s), 7.55 (1 H, d, $J$ = 9 Hz).

Anal. Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.43; H, 4.31.

***trans*-2-(3″,4″,5″-Trimethoxybenzyl)-3-(3′,4′-methylenedioxybenzoyl)butyrolactone Dithiane (6a) (Michael-Alkylation Procedure).** To a stirred solution of 2.40 g (10.0 mmol) of piperonal dithiane in 20 mL of dry THF maintained under a nitrogen atmosphere at −78 °C was added a solution of 4.35 mL (10.0 mmol, 2.3 M) of $n$-butyllithium in hexane. The resulting orange solution was stirred for 0.5 h before addition of 0.84 g (10.0 mmol) of 2-butenolide dissolved in 2 mL of THF. The reaction mixture was stirred for 0.5 h and then treated dropwise with a solution of 2.61 g (10.0 mmol) of 3,4,5-trimethoxybenzyl bromide and 1.80 mL (10.0 mmol) of HMPA dissolved in 5 mL of THF. The reaction mixture was slowly warmed to room temperature overnight followed by the addition of water. The reaction mixture was thoroughly extracted with ethyl acetate, and the extracts were combined, washed with water, and dried. Evaporation of the solvent left an orange gum. Crystallization from benzene afforded the lactone dithiane **6a** (86%) as fine white crystals: mp 146–146.5 °C; IR ($CHCl_3$) 1765, 1595, 1500 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.84 (2 H, m), 2.76 (8 H, m), 3.83 (9 H, s), 4.03 (1 H, d, $J$ = 10 Hz), 4.64 (1 H, dd, $J$ = 6, 10 Hz), 6.03 (2, H, s), 6.25 (2 H, s), 6.78 (1 H, d, $J$ = 9 Hz), 7.35 (1 H, s), 7.46 (1 H, d, $J$ = 9 Hz).

Anal. Calcd for $C_{25}H_{28}O_7S_2$: C, 59.50; H, 5.59; S, 12.71. Found: C, 59.32; H, 5.63; S, 12.75.

**2-(3″,4″,5″-Trimethoxybenzyl)-3-(3′,4′-methylenedioxybenzoyl)butyrolactone (6d).** To a stirred solution of 2 mL of 15% aqueous THF maintained under a nitrogen atmosphere was added 87 mg (0.40 mmol) of red mercuric oxide and 56 mg (0.40 mmol) of freshly distilled boron trifluoride etherate. A solution of 100 mg (0.20 mmol) of butyrolactone dithiane **6a** dissolved in 10 mL of THF was added, and the reaction mixture was allowed to stir for 2 h at room temperature. Methylene chloride (20 mL) was added followed by filtration of the precipitated salts. The methylene chloride solution was successively washed to pH 10 with saturated sodium carbonate and to neutrality with saturated sodium chloride and dried. Evaporation of the solvent left a white solid. Recrystallization from methylene chloride–ether gave the keto lactone **6d** (95%) as flat white plates: mp 142–143.5 °C (lit.[18] 140–143 °C); IR ($CHCl_3$) 1785, 1680 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 3.07 (2 H, m), 3.56 (2 H, m), 3.73 (6 H, s), 3.78 (3 H, s), 4.31 (2 H, m), 6.05 (2 H, s), 6.32 (2 H, s), 6.83 (1 H, d, $J$ = 10 Hz), 7.31 (3 H, m).

**5-Oxopodorhizol Dithiane (6b) and 5-Oxoepipodorhizol Dithiane (6c).** To a stirred solution of 2.40 g (10.0 mmol) of piperonal

dithiane dissolved in 20 mL of dry THF maintained under a nitrogen atmosphere at −78 °C was added a solution of 4.6 mL (10.2 mmol, 2.1 M) of *n*-butyllithium in hexane. The resulting orange solution was stirred for 0.5 h followed by the addition of 0.84 g (10.0 mmol) of 2-butenolide in 2 mL of dry THF. The reaction mixture was stirred for 0.5 h and then treated with 1.96 g (10.0 mmol) of 3,4,5-trimethoxybenzaldehyde[41] in 5 mL of THF. After an additional 2 h the reaction mixture was quenched with 10% acetic acid and allowed to warm to ambient temperature. Ethyl acetate was added, and the resulting organic phase was washed with water and dried. The solution was concentrated on a steam bath and, upon cooling, crystallization occurred yielding fine white needles (93%) consisting of a 52:48 diastereomeric mixture of **6b** and **6c** as shown by analytical HPLC. Fractional crystallization from ethyl acetate gave 2.47 g (47%) of hydroxylactone **6b:** mp 205–206 °C; IR ($CHCl_3$) 1755, 1590, 1490 $cm^{-1}$; NMR ($CDCl_3$) δ 1.82 (2 H, m), 2.82 (6 H, m), 3.86 (9 H, s), 4.03 (1 H, m), 4.47 (1 H, m), 4.97 (1 H, d, $J$ = 9.2 Hz), 5.16 (1 H, d, $J$ = 2.0 Hz), 6.08 (2 H, d, $J$ = 3.6 Hz), 6.37 (2 H, s), 6.66 (1 H, d, $J$ = 9 Hz).

Anal. Calcd for $C_{25}H_{28}O_8S_2$: C, 57.67; H, 5.42; S, 12.32. Found: C, 57.61; H, 5.43; S, 12.26.

The mother liquors provided 1.85 g (36%) of the hydroxylactone **6c** (from ethyl acetate): mp 180–181 °C; IR ($CHCl_3$) 3500, 1760, 1590, 1480 $cm^{-1}$; NMR ($CDCl_3$) δ 1.85 (2 H, m), 2.91 (7 H, m), 3.88 (9 H, s), 4.05 (1 H, m), 4.69 (1 H, d, $J$ = 9.9 Hz), 4.77 (1 H, d, $J$ = 6.8 Hz), 6.09 (2 H, d, $J$ = 13.5 Hz), 6.52 (2 H, s), 6.84 (1 H, d, $J$ = 7.9 Hz), 7.35 (1 H, s), 7.48 (1 H, d, $J$ = 7.9 Hz).

Anal. Calcd for $C_{25}H_{28}O_8S_2$: C, 57.67; H, 5.42; S, 12.32. Found: C, 57.51; H, 5.44; S, 12.18.

**(±)-Podorhizol (4a).** A suspension of 8 mL of W-2 Raney nickel and 1.04 g (2.0 mmol) of 5-oxopodorhizol dithiane (**6b**) in 60 mL of absolute ethanol was refluxed for 2 h under a nitrogen atmosphere. The cooled reaction mixture was filtered through Celite and evaporated. The residue was passed through a short silica gel column employing ether as the eluent. Evaporation of the solvent and trituration of the residue from diisopropyl ether afforded an amorphous white solid. Recrystallization from ether provided lactone **4a** (72%) as fine white crystals, identical in all respects (IR, NMR, TLC, HPLC) with a natural sample of (−)-podorhizol:[42] mp 125–126 °C: IR ($CHCl_3$) 3500, 1760, 1595, 1490 $cm^{-1}$; NMR ($CDCl_3$) δ 2.25 (1 H, m), 2.48 (1 H, m), 2.61 (1 H, m), 2.81 (1 H, m), 3.83 (9 H, s), 3.97 (1 H, m), 4.39 (1 H, m), 5.27 (1 H, d, $J$ = 2.2 Hz), 5.92 (2 H, d, $J$ = 9.2 Hz), 6.23 (1 H, s), 6.31 (1 H, d, $J$ = 7.7 Hz), 6.47 (2 H, s), 6.59 (1 H, d, $J$ = 7.7 Hz).

Anal. Calcd for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found: C, 63.46; H, 5.81.

**(±)-Epipodorhizol (4b).** In the manner described (vide supra), 0.40 g (0.80 mmol) of dithiane **6c** gave, upon crystallization from ethanol, lactone **4b** (74%) as white plates: mp 133.5–134.5 °C; IR ($CHCl_3$) 3500, 1750, 1590. 1490 $cm^{-1}$; NMR ($CDCl_3$) δ 2.18 (3 H, m), 2.45 (1, H, m), 2.60 (1 H, m), 3.83 (3 H, s), 3.89 (6 H, s), 4.06 (2 H, m), 4.81 (1 H, d, $J$ = 6.6 Hz), 5.92 (2 H, s), 6.34 (2 H, m), 6.65 (3 H, m).

Anal. Calcd for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found: C, 63.48; H, 5.84.

**(±)-Isodeoxypodophyllotoxone (12a).** To a stirred solution of 42 mg (0.10 mmol) of (±)-podorhizol (**4a**) dissolved in 10 mL of methylene chloride maintained under a nitrogen atmosphere at 25 °C was added 0.12 mL (1.0 mmol) of stannic chloride. The clear solution was stirred for 1 h, poured into saturated sodium bicarbonate solution, and extracted with methylene chloride. The combined extracts were dried and evaporated, affording a white powder which was homogeneous by high-resolution NMR and HPLC. Crystallization from chloroform–ether provided the lactone **12a** (78%) as fine white crystals: mp 256.5–257 °C (lit.[25] 255–256 °C); IR ($CHCl_3$) 2925, 1785, 1485 $cm^{-1}$; NMR ($CDCl_3$) δ 2.55 (2 H, m), 2.94 (2 H, m), 3.82 (6 H, s), 3.85 (3 H, s), 4.01 (3 H, m), 4.52 (1 H, m), 5.89 (2 H, d, $J$ = 2.9 Hz), 6.35 (1 H, s), 6.41 (2 H, s), 6.60 (1 H, s).

Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.30; H, 5.59.

**(±)-Isopodophyllotoxone Dithiane (12i).** To a stirred solution of 0.52 g (1.0 mmol) of 5-oxopodorhizol dithiane (**6b**) dissolved in 25 mL of methylene chloride maintained under a nitrogen atmosphere at 25 °C was added 0.12 mL (1.0 mmol) of stannic chloride. The clear solution was stirred for 1 h, poured into saturated sodium bicarbonate solution, and extracted with methylene chloride. The combined extracts were dried and evaporated, providing a white solid which was diastereomerically pure as determined by high-resolution NMR and HPLC. Recrystallization from chloroform–ether afforded the dithiane **12i** (90%) as fine white crystals: mp 290–300 °C dec; IR ($CHCl_3$) 2930, 1785, 1505 $cm^{-1}$; NMR ($CDCl_3$) δ 2.12 (1 H, m), 2.24 (1 H, m), 2.87 (2 H, m), 3.01 (2 H, m), 3.23 (1 H, m), 3.42 (1 H, dd, $J$ = 11, 13.9 Hz), 3.82 (6 H, s), 3.84 (3 H, s), 4.01 (1 H, d, $J$ = 11 Hz), 4.54 (1 H, dd, $J$ = 8, 11 Hz), 4.72 (1 H, t), 5.93 (2 H, s), 6.27 (1 H, s), 6.43 (2 H, s).

Anal. Calcd for $C_{25}H_{26}O_7S_2$: C, 59.74; H, 5.21; S, 12.76. Found: C, 59.49; H, 5.31; S, 12.63.

**(±)-Isopodophyllotoxone (12c).** To a stirred solution of 1.14 g (5.0 mmol) of *N*-iodosuccinimide in 10 mL of 10% aqueous acetone cooled in an ice–water bath (0–5 °C) was added 602 mg (1.2 mmol) of isopodophyllotoxone dithiane **12i** dissolved in 50 mL of acetone. The deep red reaction mixture was slowly warmed to 25 °C over 2 h, followed by the addition of 10 mL of aqueous sodium sulfite solution. The acetone was evaporated in vacuo, and the aqueous residue was extracted with ethyl acetate. The combined extracts were washed with water and dried. Evaporation of the solvent and crystallization from chloroform–ether provided the keto lactone **12c** (68%) as fine white crystals: mp 223–225 °C; IR ($CHCl_3$) 2950, 1780, 1695, 1480 $cm^{-1}$; NMR ($CDCl_3$) δ 3.06 (1 H, dd, $J$ = 11, 15.3 Hz), 3.41 (1 H, m), 3.82 (6 H, s), 3.87 (3 H, s), 4.23 (1 H, d, $J$ = 11 Hz), 4.44 (1 H, t, $J$ = 9.9 Hz), 4.64 (1 H, dd, $J$ = 9.2, 9.9 Hz), 6.02 (2 H, s), 6.39 (3 H, brd s), 7.46 (1 H, s).

Anal. Calcd for $C_{22}H_{20}O_8$: C, 64.08; H, 4.89. Found: C, 63.87; H, 4.93.

**1,2-Dihydro-3-hydroxymethyl-4-(3′,4′-methylenedioxyphenyl)-5,6,7-trimethoxy-2-naphthoic Acid γ-Lactone (9).** A stirred solution of 504 mg (1.0 mmol) of lactone dithiane **6a** dissolved in 50 mL of 10% trifluoroacetic acid–methylene chloride maintained under a nitrogen atmosphere was cooled to −20 °C. The temperature was not allowed to drop below −25 °C as the trifluoroacetic acid froze and precipitated from solution. A solution of 1.05 g (3.0 mmol) of manganese(III) tris(acetylacetonate) (MTA[43]) dissolved in 15 mL of methylene chloride was added rapidly to the dithiane solution. Upon addition of the MTA the reaction mixture became a brilliant blue which slowly changed to dark green as excess MTA was added. The solution was stirred for 1 h, zinc dust was added, and the reaction mixture was warmed to room temperature. The solvent was removed under reduced pressure. The residue was triturated with methylene chloride and filtered. The filtrate was washed with saturated sodium bicarbonate solution and water, and dried. Evaporation of the solvent and acetylacetone left a white foam. Crystallization from ether–chloroform afforded the dihydronaphthalene lactone **9** (50%) as needles: mp 180–182 °C; IR ($CHCl_3$) 1770, 1220 $cm^{-1}$; NMR ($CDCl)_3$ δ 2.97 (2 H, m), 3.35 (3 H, s), 3.79 (3 H, s), 3.82 (3 H, s), 4.71 (1 H, dd, $J$ = 3.5, 16 Hz), 5.12 (1 H, dd, $J$ = 3.5, 16 Hz), 6.00 (2 H, s), 6.65 (3 H, m), 6.83 (1 H, d, $J$ = 9 Hz).

Anal. Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.62; H, 5.09.

**(*E*)-2-(3″,4″,5″-Trimethoxybenzylidene)-3-(3′-4′-methylenedioxybenzoyl)butyrolactone (10).** To a stirred solution of 352 mg (1.0 mmol) of manganese(III) tris(acetylacetonate) dissolved in 40 mL of 30% trifluoroacetic acid–methylene chloride was added dropwise a solution of 103 mg (0.25 mmol) of keto lactone **6d** dissolved in 1 mL of methylene chloride. The reaction mixture was stirred for 12 h, zinc dust was added, and the solvent was evaporated. The residue was dissolved in methylene chloride, filtered, washed with water, and dried. Evaporation of the solvent and acetylacetone left a dark brown foam which was preabsorbed on silica gel (1 g) and chromatographed. Elution with 1:1 ether–hexane gave a yellow powder. Crystallization from ethanol afforded 30% of the benzylidene lactone (**10**) as fine yellow crystals: mp 177–178 °C; IR ($CHCl_3$) 2960, 1750, 1675 $cm^{-1}$; NMR ($CDCl_3$) δ 3.59 (6 H, s), 3.82 (3 H, s), 4.39 (1 H, dd, $J$ = 3, 9 Hz), 4.73 (1 H, t, $J$ = 9.5 Hz), 5.13 (1 H, d, $J$ = 9.5 Hz), 6.10 (2 H, s), 6.51 (2 H, s), 6.91 (1 H, d, $J$ = 8 Hz) 7.42 (1 H, s), 7.54 (1 H, d, $J$ = 8 Hz), 7.72 (1 H, d, $J$ = 2.2 Hz).

Anal. Calcd for $C_{22}H_{20}O_8$: C, 64.08; H, 4.89. Found: C, 63.84; H, 4.86.

**1,2β,3α,4β-Tetrahydro-3-hydroxymethyl-4-(3′,4′-methylenedioxyphenyl)-5,6,7-trimethoxy-2-naphthoic Acid γ-Lactone (11).** To a stirred suspension of 828 mg (2.0 mmol) of keto lactone **6d** in 40 mL of absolute methanol cooled in an ice–water bath (0–5 °C) was added 150 mg (4.0 mmol) of sodium borohydride. The reaction mixture was stirred for 3 h, during which time the solution became homogeneous. Dilute hydrochloric acid (1%) was added until the reaction mixture was acidic, and the solvent was evaporated at room temperature. The aqueous solution was extracted with methylene chloride. The organic extracts were combined, washed with water, and dried. Removal of the solvent afforded lactone alcohol **6e** as a foam (99%). This product was used without further purification: IR ($CHCl_3$) 3500, 1770 $cm^{-1}$; NMR ($CDCl_3$) δ 2.69 (4 H, m), 3.82 (9 H, s), 3.93 (2 H, d, $J$ = 8 Hz), 4.61 (1 H, d, $J$ = 6 Hz), 6.00 (2 H, s), 6.43 (2 H, s), 6.80 (3 H, s).

A solution of 832 mg (2.0 mmol) of lactone alcohol **6e** dissolved in 5 mL of methylene chloride was added dropwise to 40 mL of 10%

trifluoroacetic acid–methylene chloride solution at 25 °C maintained under a nitrogen atmosphere. After stirring for 3 h the solvent was evaporated, and the residue was dissolved in chloroform and filtered, providing the tetrahydronaphthalene lactone (**11**, 90%) upon recrystallization from benzene–ether: mp 218.5–219.5 °C; IR ($CHCl_3$) 2960, 1780, 1495, 1125 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.41 (2 H, m), 3.07 (1 H, m), 3.20 (3 H, s), 3.74 (3 H, s), 3.87 (3 H, s), 3.95 (1 H, d, $J$ = 15.4 Hz), 4.07 (1 H, d, $J$ = 15.4 Hz), 4.19 (1 H, m), 5.93 (2 H, s), 6.58 (3 H, m), 6.73 (1 H, d, $J$ = 7.7 Hz).

Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.32; H, 5.60.

**α-Methyl-6-bromopiperonyl Alcohol.** Methylmagnesium bromide was prepared from 6.08 g (0.25 mol) of magnesium turnings and 28.50 g (17 mL, 0.30 mol) of methyl bromide in 200 mL of ether maintained under a nitrogen atmosphere. To this solution was added 45.80 g (0.20 mol) of 6-bromopiperonal (**13**) in small portions. After completion of the addition the reaction mixture was refluxed for 2 h, cooled, and then carefully poured into 75 mL of saturated ammonium chloride solution. The layers were separated, and the aqueous phase was extracted well with ether. The combined organic extracts were washed once with water, dried, and evaporated, affording a white solid. Crystallization from ether–hexane gave the alcohol as fluffy white crystals (93%): mp 53.5–54 °C; IR ($CHCl_3$) 3440, 3075, 2900, 1470, 1220, 1035 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.39 (3 H, d, $J$ = 6 Hz), 5.14 (1 H, q, $J$ = 6 Hz), 5.95 (2 H, s), 6.92 (1 H, s), 7.06 (1 H, s).

Anal. Calcd for $C_9H_9O_3Br$: C, 44.11; H, 3.70; Br, 32.60. Found: C, 44.05; H, 3.72; Br, 32.53.

**α-Methyl-6-iodopiperonyl Alcohol (14).** To a stirred solution of 2.45 g (10.0 mmol) of the above bromo alcohol in 50 mL of dry THF under a nitrogen atmosphere and cooled to −78 °C was added a solution of 9 mL (21.0 mmol, 2.34 M) of $n$-butyllithium in hexane. The faint yellow solution was stirred for 0.5 h and then treated dropwise with a solution of 5.59 g (22.0 mmol) of iodine dissolved in 15 mL of THF. The iodine color was discharged immediately upon contact with the solution. At no time during the reaction was the temperature allowed to rise above −65 °C. After the addition was completed the cooling bath was removed, and the reaction mixture was quenched at 0 °C by the addition of 20 mL of saturated aqueous sodium sulfite solution. Ether and water were then added, the layers were separated, and the aqueous phase was extracted well with ether. The combined extracts were washed once with water, dried, and evaporated. The residue was crystallized from ether–hexane affording alcohol **14** (71%) as white crystals: mp 72–73 °C; IR ($CHCl_3$) 3440, 3075, 2900, 1470, 1035 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.37 (3 H, d, $J$ = 6 Hz), 4.96 (1 H, q, $J$ = 6 Hz), 5.94 (2 H, s), 7.06 (1 H, s), 7.17 (1 H, s).

Anal. Calcd for $C_9H_9O_3I$: C, 37.01; H, 3.11; I, 43.45. Found: C, 36.89; H, 3.15; I, 43.50.

**3,4-Methylenedioxy-6-iodoacetophenone.** To a well-stirred solution of 6.28 g (21.5 mmol) of iodo alcohol **14** dissolved in 50 mL of reagent grade acetone and cooled in an ice–water bath to 5 °C was added 6 mL (48 mequiv) of 8 N Jones reagent. After stirring for 0.5 h 3 mL of isopropyl alcohol was added, and the dark solution was warmed to 25 °C. Water was added and the acetone was evaporated. The aqueous phase was then extracted well with ether. The combined organic extracts were washed once with water and once with saturated sodium bicarbonate solution and dried. Removal of the solvent gave a brown residue. Two crystallizations from ether–hexane afforded the acetophenone (72%) as white crystals: mp 84.5–85 °C; IR ($CHCl_3$) 3025, 2910, 1690, 1475, 1380 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.85 (3 H, s), 6.05 (2 H, s), 7.06 (1 H, s), 7.38 (1 H, s).

Anal. Calcd for $C_9H_7O_3I$: C, 37.27; H, 2.43; I, 43.75. Found: C, 37.23; H, 2.45; I, 43.72.

**α-Bromo-3,4-methylenedioxy-6-iodoacetophenone (15).** To a solution of 2.90 g (10.0 mmol) of 3,4-methylenedioxy-6-iodoacetophenone in 50 mL of chloroform was added 1.76 g (11.0 mmol) of bromine followed by 1 drop of 48% hydrobromic acid. After a short induction period a vigorous reaction ensued as hydrogen bromide was evolved. The reaction mixture was stirred for 12 h at 25 °C with protection from moisture. Saturated aqueous sodium sulfite solution (10 mL) was added, the layers were separated, and the aqueous phase was extracted thoroughly with chloroform. The extracts were combined, washed once with water, and dried. Evaporation of the solvent afforded a dark oil which slowly solidified. Recrystallization from ether–pentane afforded the phenacyl bromide **15** (71%) as sparkling yellow crystals: mp 74.5–75 °C; IR ($CHCl_3$) 2910, 1690, 1475, 1235 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 4.40 (2 H, s), 6.07 (2 H, s), 7.05 (1 H, s), 7.35 (1 H, s).

Anal. Calcd for $C_9H_6O_3BrI$: C, 29.30; H, 1.64; Br, 21.66; I, 34.40. Found: C, 29.31; H, 1.67; Br, 21.55; I, 34.26.

**2-Iodo-3,4,5-trimethoxybenzyl Alcohol.** To a stirred suspension of 14.34 g (45.0 mmol) of mercuric acetate and 8.92 g (45.0 mmol) of 3,4,5-trimethoxybenzyl alcohol (**16**) in 100 mL of methylene chloride was added dropwise 11.43 g (45.0 mmol) of iodine in 100 mL of the same solvent. The iodine color was discharged immediately upon contact with the solution. The reaction mixture was stirred for 3 h and filtered, and the precipitated salts were washed well with methylene chloride. The filtrate was washed with water and dried. Evaporation of the solvent left an oil contaminated with red mercuric iodide. The oil was taken up in boiling ether and filtered. Hexane was added to the filtrate, and the cloudy solution was allowed to cool slowly, affording the iodo alcohol as a white fluffy powder (76%). Recrystallization from hexane gave the iodo alcohol (70%) as long white crystals: mp 56.5–57.5 °C; IR ($CHCl_3$) 3450, 2950, 1105 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 3.88 (3 H, s), 3.90 (6 H, s), 4.66 (2 H, s), 6.97 (1 H, s).

Anal. Calcd for $C_{10}H_{13}O_4I$: C, 37.06; H, 4.04; I, 39.15. Found: C, 36.98; H, 4.02; I, 39.05.

**2-Iodo-3,4,5-trimethoxybenzyl Chloride.** To a mixture of 4.57 g (14.1 mmol) of 2-iodo-3,4,5-trimethoxybenzyl alcohol and 1.82 g (15.0 mmol) of *N,N*-dimethylaniline in 50 mL of dry benzene cooled in an ice-water bath to 5 °C was added dropwise 1.79 g (15.0 mmol) of thionyl chloride in 10 mL of benzene. The cooling bath was removed, and the dark solution was refluxed for 1 h. The reaction mixture was cooled, washed successively with water, 10% hydrochloric acid, saturated aqueous sodium bicarbonate, and water and dried. Evaporation of the solvent left an oil which solidified upon standing. Recrystallization from ether–hexane afforded the benzyl chloride (92%) as white prisms: mp 69–69.5 °C; IR ($CHCl_3$) 2950, 1330, 1105 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 3.92 (9 H, s), 4.74 (2 H, s), 6.96 (1 H, s).

Anal. Calcd for $C_{10}H_{12}O_3ClI$: C, 35.06; H, 3.53; Cl, 10.35; I, 37.05. Found: C, 35.15; H, 3.54; Cl, 10.29; I, 36.94.

**Dimethyl 2-Iodo-3,4,5-trimethoxybenzylmalonate (17).** To a suspension of 0.58 g (12.0 mmol) of sodium hydride (Alfa–Ventron, 50% dispersion in mineral oil) in 80 mL of THF under a nitrogen atmosphere was added 13.21 g (100 mmol) of distilled dimethyl malonate in 20 mL of THF. After the initial gas evolution had subsided the solution was refluxed for 0.5 h and then treated dropwise with a solution of 3.42 g (10 mmol) of 2-iodo-3,4,5-trimethoxybenzyl chloride in 20 mL of THF over a 2-h period. The reaction mixture was refluxed for 24 h and then cooled and acidified with 10% aqueous acetic acid. Ether and water were added, and the layers were separated. The organic phase was washed twice with water, once with brine, and dried. Evaporation of the solvent and excess dimethyl malonate (~5 mm with a heat gun) left a residual oil which solidified upon cooling. Recrystallization from ether–hexane afforded the benzyl malonate **17** (93%) as fine white needles: mp 49.5–51.5 °C; IR ($CHCl_3$) 2950, 1735, 1095 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 3.35 (2 H, d, $J$ = 4.5 Hz), 3.69 (6 H, s), 3.80 (3 H, s), 3.82 (3 H, s), 3.84 (3 H, s), 6.60 (1 H, s).

Anal. Calcd for $C_{15}H_{19}O_7I$: C, 41.11; H, 4.37; I, 28.96. Found: C, 41.08; H, 4.39; I, 28.87.

**Dimethyl 2-Iodo-3,4,5-trimethoxybenzyl-3′,4′-methylenedioxy-6′-iodophenacylmalonate (18a).** To a stirred solution of 3.16 g (7.2 mmol) of dimethyl 2-iodo-3,4,5-trimethoxybenzyl malonate (**17**) dissolved in 20 mL of dry THF under a nitrogen atmosphere was added 0.35 g (7.3 mmol) of sodium hydride (Alfa–Ventron, 50% dispersion in mineral oil). After the vigorous reaction had subsided the solution was refluxed for 0.5 h, cooled in an ice–water bath to 5 °C, and treated dropwise with a solution of 2.73 g (7.4 mmol) of α-bromo-3,4-methylenedioxy-6-iodoacetophenone (**15**) dissolved in 8 mL of THF. A white precipitate formed immediately upon addition of the phenacyl bromide. The reaction mixture was slowly warmed to 25 °C overnight. Water and ethyl acetate were added, and during extraction a heavy emulsion formed which was filtered through Celite. The organic phase was dried, and removal of the solvent left a yellow solid. Two recrystallizations from methylene chloride–ether gave the malonic ester **18a** (59%) as fine light yellow needles: mp 141–142 °C; IR ($CHCl_3$) 3020, 2960, 1735, 1695, 1220 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 3.56 (2 H, s), 3.62 (2 H, s), 3.78 (6 H, s), 3.83 (3 H, s), 3.85 (6 H, s), 6.02 (2 H, s), 6.57 (1 H, s), 7.03 (1 H, s), 7.35 (1 H, s).

Anal. Calcd for $C_{24}H_{24}O_{10}I_2$: C, 39.69; H, 3.33; I, 34.95. Found: C, 39.69; H, 3.35; I, 35.01.

**Dimer 18d.** A mixture of 0.20 g (0.28 mmol) of dimethyl 2-iodo-3,4,5-trimethoxybenzyl-3′,4′-methylenedioxy-6′-iodophenacylmalonate (**18a**) and 0.58 g (2.0 mmol) of cuprous(I) triflate[33] in 10 mL of dry DMF was stirred and heated at 100 °C under a nitrogen atmosphere for 16 h. The reaction mixture was then cooled, and the solvent was evaporated at 5 mm with the aid of a heat gun. The residue was preabsorbed on silica gel, and elution from a silica gel column (10/1) with ether afforded a solid (70 mg). The solid was further purified using (GLC (64 × 10 cm Merck 60H silica gel column eluted with 30% ethyl acetate–benzene, flow rate 1 mL/min). Crystallization of

the solid from ether–chloroform afforded dimer **18d** (48%) as white prisms: mp 179–180 °C; IR ($CHCl_3$) 2950, 1735, 1685, 1475 $cm^{-1}$; NMR ($CDCl_3$) δ 3.23 (4, h, s), 3.56 (4 H, s), 3.63 (12 H, s), 3.71 (6 H, s), 3.85 (12 H, s), 6.02 (4 H, s), 6.47 (2 H, s), 6.50 (2 H, s), 7.19 (2 H, s).

Anal. Calcd for $C_{48}H_{48}O_{20}I_2$: C, 48.06; H, 4.04. Found: C, 47.99; H, 4.19.

**Phosphonate 18e.** A mixture of 0.363 g (0.50 mmol) of dimethyl 2-iodo-3,4,5-trimethoxybenzyl-3′,4′-methylenedioxy-6′-iodophenacylmalonate (**18a**) and 0.893 g (2.50 mmol) of cuprous iodide–triethyl phosphite complex[44] in 15 mL of dry DMF was heated at 100 °C for 16 h with stirring under a nitrogen atmosphere. The reaction mixture was cooled, and the solvent was evaporated at 5 mm with the aid of a heat gun. The residue was chromatographed on silica gel (20/1), and elution with 30% ether–hexane gave the unreacted cuprous iodide–triethyl phosphite complex. Elution with ether afforded an oil which slowly crystallized. Recrystallization from ether afforded the analytically pure phosphonate **18e** (89%) as fine white needles: mp 128.5–129.5 °C; IR ($CHCl_3$) 2975, 1730, 1245, 1030 $cm^{-1}$; NMR ($CDCl_3$) δ 1.33 (6 H, t, $J$ = 7.5 Hz), 3.62 (2 H, s), 3.71 (2 H, s), 3.76 (9 H, s), 3.84 (6 H, s), 4.14 (4 H, qt, $J$ = 7.5 Hz), 6.07 (2 H, s), 6.77 (1 H, s), 6.95 (1 H, d, $J$ = 4.5 Hz), 7.37 (1 H, d, $J$ = 12 Hz).

Anal. Calcd for $C_{28}H_{34}IO_{13}P$: C, 45.66; H, 4.65; I, 17.23. Found: C, 45.69; H, 4.68; I, 17.20.

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