Synthesis and Modeling Studies with Monocyclic Analogues of Mycophenolic Acid

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Two stepwise procedures, developed for the introduction of the (*E*)-4-methyl-4-hexenoic acid side chain of mycophenolic acid, were used in the synthesis of monocyclic mycophenolic acid analogues **2a**−**i**. The derivatives with a methyl group or hydrogen at C-4 and lacking the lactone moiety were much less cytotoxic than mycophenolic acid. The monocyclic analogues with a C-4 chloro group did show some activity, albeit much less than mycophenolic acid. The observed differences in potency are rationalized by semiempirical calculations of intramolecular H-bonds.

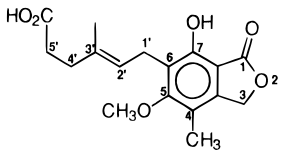
Introduction

Inosine monophosphate dehydrogenase (IMP:NAD^+ oxireductase, EC 1.1.1.205), the rate-limiting enzyme in *de novo* guanine nucleotide biosynthesis, catalyzes the conversion of inosine 5′-monophosphate (IMP) to xanthosine 5′-monophosphate (XMP), presumably through a tetrahedral[1,2] intermediate. Inhibition of this enzyme (IMPD) leads to elevated IMP levels which inhibit one of the principal salvage pathways through feedback regulation of hypoxanthine-guanine phosphoribosyl transferase (HGPRT). The biosynthesis of purine nucleosides is subject to complex control mechanisms, and the consequences of IMPD inhibition extend to the adenine nucleotide pool. For example, as IMPD inhibition reduces GTP levels, GTP feedback inhibition of AMP deaminase is reduced, and the extent of AMP deamination (to IMP) increases. The conversion of IMP to AMP via adenylosuccinic acid is also inhibited by reduced levels of the required cofactor, GTP. Thus, inhibitors of IMPD inhibit both the *de novo* and salvage pathways to GMP and have an indirect, down-regulatory effect on AMP.

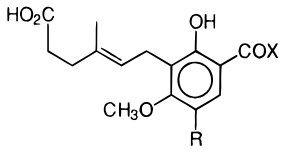
Inhibitors of IMPD reduce GTP and deoxyGTP pool levels and have been shown to possess antineoplastic, antiparasitic, antiviral[3] (including anti-HIV[4]), and immunosuppressive activity. Inhibitors of IMPD have also been shown to induce differentiation[5] in certain cell lines. The utility of the IMPD inhibitor tiazofurin in the treatment of human leukemia is a result of cytotoxicity and differentiation−induction (maturation−induction). IMPD inhibitors also act in synergy with antiviral nucleosides, including 2′,3′-dideoxy nucleosides active against HIV, by stimulating nucleoside phosphorylation.[6] For convenience, we have broadly classified the inhibitors into three groups based on the mode of enzyme binding:[7] (group I) IMP/XMP analogues, (group II) NAD^+/NADH analogues, and (group III) multisubstrate inhibitors.

Human IMPD exists as two tetrameric isoforms, types I and II, with 84% amino acid identity.[8] Both isoforms follow Ordered Bi-Bi kinetics and have similar k_{cat} values and comparable K_m values for IMP and NAD^+. Inhibitors of the two isoforms do, however, show different K_i values; for example, the K_i for mycophenolic acid is 4.8-fold lower for the type II isoform than for the type I isoform. The higher activity of mycophenolic acid against the type II isoform is significant because the type II isoform of IMPD has been shown to be selectively upregulated in human tumor cells.[9]

Mycophenolic acid (**1**, MPA) is a group II IMPD inhibitor that requires no metabolic activation (i.e., it is a "direct acting" inhibitor). It has been shown to possess significant antineoplastic,[10] antiparasitic,[11] antiviral,[12] and immunosuppressive[13] activity [the morpholinoethyl ester prodrug of MPA (mycophenolate mofetil, RS-61443) is undergoing extensive clinical studies for the prevention and reversal of tranplant rejection]. MPA is also very active against psoriasis.[14] Low toxicity and the fact that the toxic effects (GIT irritation caused by the glucuronide conjugate of MPA) are reversible upon withdrawal of the drug are attractive features. The major problem with MPA *as an antitumor drug in humans* is that rapid conjugation of the C-7 phenolic hydroxyl group with glucuronic acid[15] makes it very difficult to achieve the drug levels needed for antitumor activity.[16] The dilemma is that a free C-7 hydroxyl group is an absolute requirement for MPA activity.[17]



1 [mycophenolic acid ("MPA")]



2a-i

The MPA structure has been extensively modified, and except for derivatives that can be converted to MPA *in vivo*, all the reported analogues are either inactive or have markedly diminished activity. A summary of the major structure−activity relationships (activity against murine lymphosarcoma or suppression of mitosis in mouse fibroblasts) for MPA follows. In the side chain the terminal carboxylic acid is essential, 2′,3′-dihydroMPA is 15-fold less active than MPA, and analogues with shorter or longer side chains have poor to no activity. Replacement of the carboxylic acid with a 5-tetrazolyl moiety, a carboxamido group, or a nitrile function produced inactive compounds. Replacement of the C-5 methoxy with ethoxy, propoxy, and hydroxy gives analogues that are 4, 8, and 15 times less active

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than MPA, respectively. Methylation of the C-7 phenol eliminates activity; esters (prodrugs) are active only if the ester can be hydrolyzed *in vivo*. Replacement of the C-7 phenolic hydroxyl with a thiol produced an inactive compound. The lactone is also important: MPA analogues with a free C-7 carboxylic acid are inactive, and reduction of the carboxylic acid (in the ring-opened hydroxy acid form of MPA) to a methyl group completely abolishes activity. Removal of the C-4 methyl group results in a 30-fold decrease in activity [the C-4 methyl group destabilizes the ring-opened hydroxy acid form of the phthalide lactone[18] (a steric effect between C-3 and the methyl at C-4)]. The MPA side chain was incorporated into a small series of *N*-substituted pyridones and glutarimides, but none of the compounds possessed appropriate replacements for the substituted phthalide moiety in MPA and all were inactive.[19] Two new cytotoxic phenols related to MPA have recently been reported: the lactam, hericenone B, was 16-fold more cytotoxic to HeLa cells *in vitro* than the lactone, hericenone A, but no biochemical data (IMPD inhibition) were reported for either compound.[20] The IMPD inhibitory and immunosuppressive activities of a series of side chain modified MPA analogues has been reported.[21] The compounds were side chain analogues in which the (*E*)-alkene was replaced by other π-electron groups or mimics (a (*Z*)-alkene, an alkyne, an allene, a thioether, or cyclopropyl moieties), but the analogues were either inactive or showed markedly reduced activities.

The monocyclic analogues reported in the present study were *designed to retain the MPA carbonyl but replace the lactone with other uncharged carbonyl moieties* such as esters, carboxamides, or ketones. The important MPA hexenoic acid side chain was unmodified in this series. Furthermore, the MPA C-5 methoxy group was retained because of its potential influence on the conformation of the critical hexenoic acid side chain. The change from a bicyclic phthalide, in the MPA lactone, to a series of monocyclic compounds would be expected to influence intramolecular hydrogen bonding between the phenol and the carbonyl moiety which could interfere with *in vivo* conjugation of the phenol. The monocyclic analogues were also designed as part of our larger study to develop an IMPD inhibitor binding site model (to be published elsewhere); as such, these MPA analogues more closely mimicked the nicotinamide riboside segment of the NAD^+.

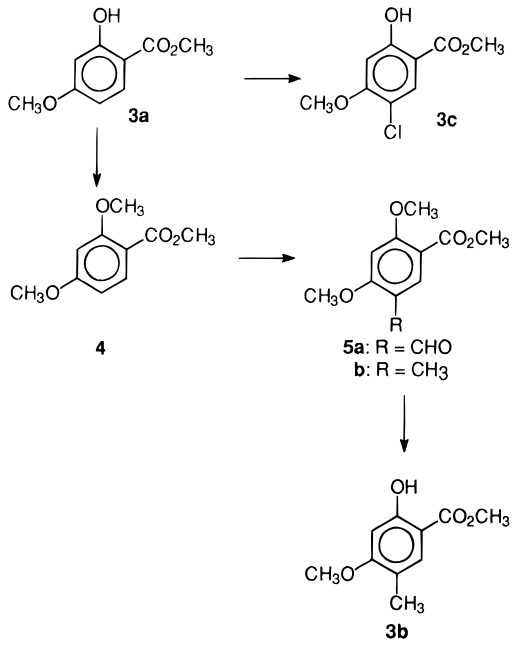
This report describes the synthesis of the monocyclic MPA analogues **2a**−**i** as part of an ongoing project in our laboratory on MPA structure−activity requirements and the study of inosine monophosphate dehydrogenase inhibitors.[22]

Chemistry

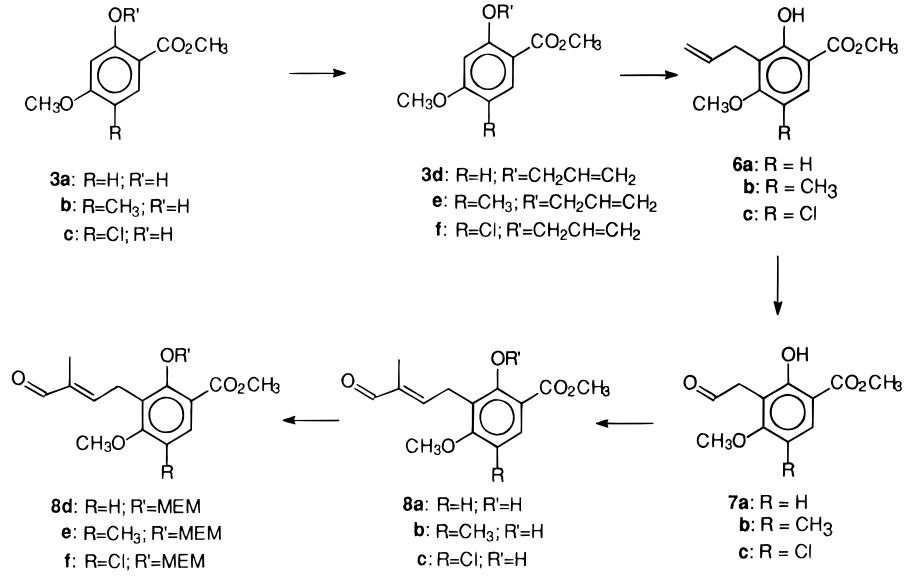
The monocyclic aromatic moieties were synthesized in the stepwise approach summarized in Scheme 1. The approach is a variant of that used in the original synthesis of MPA by Birch[23] (several other total[24] and formal[25] syntheses of MPA have also been published). The syntheses of the monocyclic MPA analogues **2a**−**i** are summarized in Schemes 1−4. The starting phenols were synthesized from the commercially available 2-hydroxy-4-methoxybenzoate **3a**. The chlorophenol **3c** was synthesized from **3a** in 93% using sulfuryl chloride. Methylation of **3a** afforded **4** which was formylated with α,α-dichloromethyl methyl ether and titanium tetrachloride to give **5a.** This aldehyde was reduced to **5b** in 62% yield. The *o*-methoxy group was selectively removed with boron trichloride to give the desired phenol **3b** (86%). The resulting phenols **3a**−**c** were converted to the *O*-allyl derivatives **3d**−**f**. The crude allyl phenyl ethers were then heated at 210 ± 5 °C for 3−4 h to give **6a** (99% for the two steps), **6b** (81% from **5a**), and **6c** (46% for the two steps; the rearrangement of **3f** was slow, presumably because of the electron-withdrawing property of the chloro group) (Scheme 2). Ozonolysis of **6a**−**c** in dichloromethane−methanol (3:1) allowed the initially formed ozonide to be converted to the more stable methyl hemiacetal hydroperoxide which, upon reduction with triphenylphosphine, gave the aldehydes **7a**, **7b**, and **7c** (85, 77 and 91%, respectively). Homologation of the aldehydes **7a**−**c** using the stabilized ylide (1-formylethylidene)triphenylphosphorane gave the *E*-alkenes **8a**−**c** (based on NOE studies) in average yields of 92%. Protection of the free phenols was accomplished using MEM chloride and a slight excess of sodium hydride. For **8a**, when large quantities of base was used, markedly lower yields resulted. The yields are 87, 77, and 92% for **8d**, **8e**, and **8f,** respectively (based on unrecovered starting material). The enals were then reduced, in good yields, to the enols **9a**−**c** with sodium borohydride (Scheme 3). The alcohols were then converted to the allylic bromides **10a**−**c** (85, 79, and 83% yield, respectively) with triphenylphosphine−tetrabromomethane in the presence of *N*,*N*-diisopropylethylamine (to prevent cleavage of the MEM protecting groups).

The displacement of the allylic bromide **10a** with anions such as those derived from *tert*-butyl acetate or acetic acid proved problematic; however, the reaction with the softer anion derived from methyl (phenylsulfonyl)acetate gave the sulfone **11a** (**11b** and **11c** were prepared similarly); reductive cleavage of the activating sulfonyl group in **11a**,**b** gave **12a**,**b** (81% from **10a** and 68% from **10b**). Reductive cleavage of **11c** resulted in concomitant reduction of the aromatic chloro group; therefore an alternate route was investigated. Selective base hydrolysis of the side chain ester of **12a** followed by TFA cleavage of the MEM ether gave **2a** (61%). The

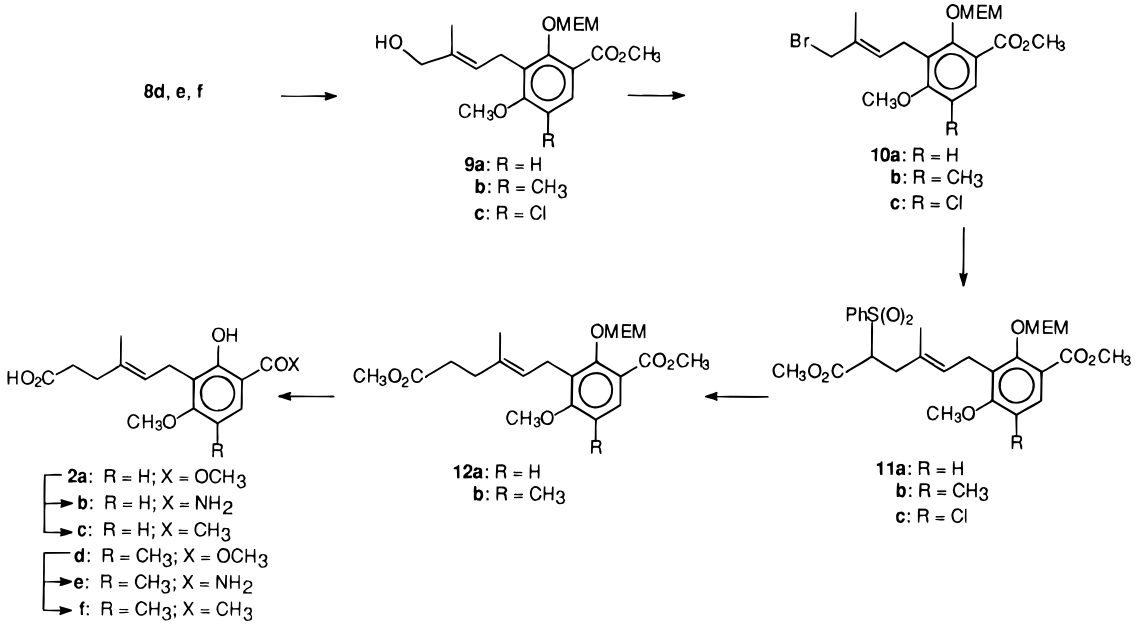
Scheme 1



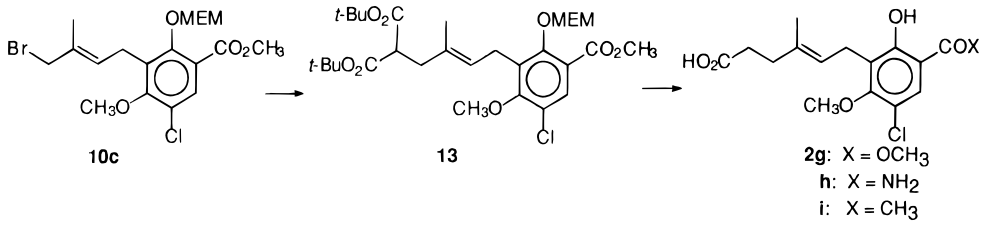
Scheme 2



Scheme 3



Scheme 4



MEM group of **12b** was removed by TFA followed by base hydrolysis of the ester to afford **2d** in 78% yield. The displacement of the allylic bromide **10c** was carried out using the anion derived from di-*tert*-butyl malonate to give the diester **13** (84%) (Scheme 4). Hydrolysis of the di-*tert*-butyl ester (by formic acid) occurred concomitantly with cleavage of the MEM group. The resulting crude diacid phenol was subjected to thermal decarboxylation to give **2g** in 60% yield. Aminolysis of **2a**, **2d**, and **2g** gave **2b**, **2e**, and **2h** (68, 63, and 98%, respectively). The esters **2a**, **2d**, and **2g** were converted to the corresponding β-keto sulfoxides using excess sodium hydride in DMSO. Subsequent reductive cleavage afforded the methyl ketones **2c**, **2f**, and **2i** (23, 64, and 61%, respectively, over the two steps).

Biological Evaluation

Two of the nine monocyclic MPA analogues showed activity against L1210 leukemia cells in tissue culture.[26] The chloro compounds **2g** and **2i** showed modest activity: the ester **2g** had an $IC_{50} = 61\ \mu M$ whereas the ketone exhibited 21% inhibition at 100 μM, the highest concentration tested ($IC_{50} > 100\ \mu M$ for **2a**–**f** and **2h**). Mycophenolic acid (**1**) had an $IC_{50} = <0.2\ \mu M$ in this

Table 1. Calculation of the Intramolecular H-Bonds and Rotational Barriers of Phenolic Hydroxy

compd	HO---O=C(1) distance (Å)	barrier around C(7)−OH bond (kcal/mol)
1	3.269	5.92
2a	2.649	10.00
2d	2.649	9.82
2e	2.640	11.32
2f	2.634	10.29
2g	2.648	10.12
2i	2.632	9.74

assay. Compounds **2a**, **2b**, and **2c** were also inactive against a HT-29 human colon adenocarcinoma cell line (MPA had an IC_{50} = 0.4 μM). The ketone **2c** was inactive (>32.5 μM) against human A121 ovarian, A549 lung carcinoma, and MCF7 breast adenocarcinoma cell lines (MPA had IC_{50} = 0.2−0.3 μM). The chloro compound is 2 orders of magnitude less active than MPA, but it is significant that the compound represents the first monocyclic MPA analogue with any antitumor activity.

Discussion

Superposition of the minimized conformations of **2a**−**i** on that of MPA (PM3, precise criteria) showed the expected fit in the alignment of the hexenoic acid side chains. Furthermore, the carbonyl groups (which replaced the MPA lactone in these monocyclic analogues) were projected along a similar vector in comparison with the MPA lactone. This was due to stabilization by intramolecular hydrogen bonding with the phenolic hydroxyls. Thus, compounds **2a**−**i** retained the hydrogen-bonding character of the MPA lactone oxygen. The absence of the C-3 methylene group in the monocyclic analogues is unlikely to result in major loss in binding energy.

The molecular electrostatic potential surfaces were calculated[27] (from Mulliken population derived from semiempirical PM3) and compared with MPA. Two significant differences between MPA and the monocyclic analogues were the electrostatic potential around the phenolic hydrogen and the intramolecular distance between the phenol and the *o*-carbonyl oxygen (HO---O=C). The appropriate angles and distances for intramolecular hydrogen bonding between the phenol and the adjacent carbonyl were found to be less favorable for MPA (**1**) compared to the monocyclic analogues. The (HO---O=C) distance in the X-ray structure of MPA (**1**) was 3.022 Å (ca. 0.2 Å shorter than the calculated value), but the trends in Table 1 are still significant. The conclusion that the monocyclic MPA analogues form stronger intramolecular H-bonds was confirmed in calculations of the rotational barrier around the C−OH bond. These data show the monocyclic analogues have a 4−5 kcal/mol higher barrier than MPA (**1**).

The low levels of antitumor activity exibited by the monocyclic analogues emphasize the importance of the bicyclic lactone in MPA. It is possible, considering the absolute requirement for the MPA phenol moiety, that the hydroxyl group serves as a H-bond donor, binding to a specific site on the enzyme IMPD. Thus, the strength of the intramolecular hydrogen bond in the unbound compounds may be an important factor. The intramolecular hydrogen bonds are significantly stronger in the monocyclic analogues compared to MPA (Table 1). The activity for the 5-chloro-substituted benzoate analogues **2g** and **2i** suggests a possible role for groups at that position in MPA which may enhance the acidity of the phenol.

Experimental Section

Melting points (uncorrected) were determined in an open capillary with a Thomas-Hoover Unimelt apparatus. IR spectra were determined with a Matteson FT-IR interferometer. ^{1}H NMR spectra were determined at 90 MHz with a Varian EM 390 or at 300 MHz with a Varian Gemini spectrometer in $CDCl_3$ solution (unless noted otherwise) with TMS as internal standard. Microanalyses were performed by Atlantic Microlab, Atlanta, GA. Silica gel for flash column chromatography (230−400 mesh ASTM) was obtained from EM Science. Organic solutions were dried with anhydrous sodium sulfate unless otherwise noted.

(*E*)-4-Methyl-6-[3-(2-hydroxy-1-(methoxycarbonyl)-4-methoxyphenyl)]-4-hexenoic Acid (2a). A solution of **12a** (2.53 g, 6.16 mmol) in methanol (65 mL) was treated with aqueous sodium hydroxide (0.98 M, 6.6 mL, 6.47 mmol) and stirred for 60 h at 43 °C (the disappearance of starting material was monitored by TLC, silica gel−ether). Water (150 mL) was added, and the mixture was extracted with ether (2 × 150 mL). The aqueous phase was acidified (3 M HCl, 2.4 mL) and then extracted with ethyl acetate (3 × 100 mL). The combined ethyl acetate extract was dried and concentrated to give the crude monoacid as a colorless oil. The crude acid was dissolved in dichloromethane (15 mL), and TFA (0.52 mL, 6.7 mmol) was added. Removal of the MEM group was monitored by TLC [silica gel, hexane−formic acid−ethyl acetate (70:1:29)]. The reaction was complete after 10 min. The solution was extracted with water (3 × 10 mL). The combined aqueous extract was washed with ethyl acetate (4 × 10 mL); addition of sodium chloride to the aqueous solution was necessary to break the emulsion which formed. The combined organic solution was dried and evaporated to afford a yellow oil. Flash column chromatography (silica gel, hexane−formic acid−ethyl acetate, 80:1:19) of the crude oil provided **2a** (1.16 g, 61% from **12a**) as a white solid. A sample was crystallized from ethyl acetate−hexane (1:6) to give fine white needles: mp 106.5−107.5 °C; ^{1}H NMR δ 1.79 (s, 3 H), 2.30 (m, 4 H), 3.33 (d, 2 H), 3.83 (s, 3 H), 3.87 (s, 3 H), 5.24 (t, 1 H), 6.42 (d, 1 H), 7.69 (d, 1 H), 10.0 (br s, 1 H), 11.03 (s, 1 H); IR (KBr) 3571−3352, 1718, 1670, 1618 cm^{-1}; UV (CH_3OH) 300 (4800), 264.5 (14 000) nm. Anal. ($C_{16}H_{20}O_6$) C, H.

(*E*)-4-Methyl-6-[3-(1-(aminocarbonyl)-2-hydroxy-4-methoxyphenyl)]-4-hexenoic Acid (2b). A solution of the ester **2a** (1.069 g, 34.7 mmol) in methanol (50 mL) in a 3 oz Fisher-Porter aerosol pressure vessel was cooled to 0 °C, and anhydrous ammonia was bubbled through the solution for 15 min. The vessel was closed and then heated at 55 °C with stirring for 45 h [TLC analysis (silica gel, hexane−formic acid−ethyl acetate, 70:1:29) showed only a trace of starting material]. The solution was concentrated to dryness, and the brown residue was purified by successive column chromatography (silica gel, column 1 eluant, ethyl acetate−hexane, 40:60; column 2 eluant, hexane−formic acid−ethyl acetate, 20:1:79; the sample was preadsorbed silica gel using methanol for the second column) to give **2b** (0.69 g, 68%) as an off-white solid: mp 193−195 °C; ^{1}H NMR (DMSO-d_6) δ 1.72 (s, 3 H), 2.20 (br s, 4 H), 3.22 (d, 2 H), 3.81 (s, 3 H), 5.16 (t, 1 H), 6.52 (d, 1 H), 7.71 (d, 1 H), 7.80 (obscured br s, 1 H), 8.11 (br s, 2 H), 12.00 (br s, 1 H); IR (KBr): 3569−3200, 1701, 1618 cm^{-1}. Anal. ($C_{15}H_{19}NO_5$) C, H, N.

(*E*)-4-Methyl-6-[3-(2-hydroxy-4-methoxy-1-acetylphenyl)]-4-hexenoic Acid (2c). Sodium hydride (60% dispersion in mineral oil, 0.40 g, 10.0 mmol) was washed with dry hexanes (2 mL). The flask was evacuated and purged several times with nitrogen, and while under a flow of nitrogen, DMSO (7 mL, distilled from calcium hydride) was added. The resulting gray solution was warmed to 75−80 °C. After the evolution of hydrogen had subsided, the flask was cooled to *ca*. 8 °C and a solution of **2a** (0.497 g, 1.62 mmol) in dry DMSO (4 mL) was added dropwise. The cooling bath was removed, and the resulting brown solution was allowed to warm to room temperature over 0.5 h. The reaction mixture

was then poured into 20 mL of water, and the yellow solution was acidified (pH 1−2, pH test paper) with concentrated HCl. The white cloudy solution was extracted with chloroform (4 × 50 mL). The combined organic layer was washed with water (50 mL) and brine (50 mL), then dried, filtered, and concentrated to give 0.61 g of a yellow-white solid. The product was crystallized from chloroform to give the β-keto sulfoxide as a white powdery solid (0.438 g, 74%): mp 122−124.5 °C dec; ^{1}H NMR ($CDCl_3$−DMSO-d_6) δ 1.76 (s, 3 H), 2.26 (m, 2 H), 2.75 (s, 3 H), 3.31 (m, 2 H), 3.91 (s, 3 H), 4.40 (s, 2 H), 5.19 (t, 1 H), 6.56 (d, 1 H), 7.76 (d, 1 H), 12.38 (s, 1 H); IR 3300−2500, 1733, 1629, 1283, 1117, 1083, 1067 cm^{-1}. Anal. ($C_{17}H_{22}O_6S$) C, H, S.

The β-keto sulfoxide (0.180 g, 0.51 mmol) was dissolved in 10% aqueous THF (11 mL), cooled to 0 °C, and treated with aluminum foil [(0.141 g, 5.10 mmol) in 1 cm squares, which had been immersed in a 2% aqueous solution of mercuric chloride for 15 s, and then rinsed in absolute methanol and anhydrous ether]. The resulting yellow-green solution was stirred at 0 °C for 50 min and then filtered through a pad of Celite. The solids were washed with THF (100 mL), and then most of the THF was evaporated. Ethyl acetate (30 mL) was added, and the mixture was washed several times with water (30 mL), dried, and concentrated to a yellow oily residue. The residue was subjected to flash chromatography (hexanes−ethyl acetate, 3:2, 10% formic acid) to give **2c** as an off-white solid (0.044 g, 31%): mp 120−121 °C dec; ^{1}H NMR δ 1.76 (s, 3 H), 2.33 (m, 4 H), 2.53 (s, 3 H), 3.34 (m, 2 H), 3.86 (s, 3 H), 5.26 (t, 1 H), 6.38 (d, 1 H), 7.58 (d, 1 H), 12.73 (s, 1 H); IR 3160, 3000−2500, 1719, 1629, 1275, 1096 cm^{-1}. Anal. ($C_{16}H_{20}O_5$) C, H.

(*E*)-4-Methyl-6-[3-(2-hydroxy-1-(methoxycarbonyl)-4-methoxy-5-methylphenyl)]-4-hexenoic Acid (2d). TFA (0.06 mL, 0.794 mmol) was added to a solution of **12b** (0.281 g, 0.662 mmol) in dichloromethane (2 mL) at 0 °C. The mixture was stirred at 0 °C for 20 min and then allowed to warm to room temperature over 45 min. The reaction was then partitioned between dichloromethane (5 mL) and water (5 mL). The aqueous layer was extracted with dichloromethane (3 × 5 mL), and the combined organic layer was dried, filtered, and concentrated *in vacuo*. The resulting oil was subjected to flash chromatography (hexanes−ether, 7:3) to give the phenol (0.199 g, 89%) as a cloudy oil: ^{1}H NMR δ 1.77 (s, 3 H), 2.19 (s, 3 H), 2.30 (m, 2 H), 2.38 (m, 2 H), 3.36 (d, 2 H), 3.58 (s, 3 H), 3.70 (s, 3 H), 3.89 (s, 3 H), 5.24 (t, 1 H), 7.52 (s, 1 H), 10.87 (s, 1 H); IR (neat) 908, 984, 1095, 1168, 1348, 1382, 1442, 1464, 1668, 1731 cm^{-1}. Anal. ($C_{18}H_{24}O_6$) C, H.

A solution of the phenol (0.666 g, 1.98 mmol) in THF (7 mL) was treated with 1 N LiOH (4.4 mL, 4.40 mmol) at 0 °C. The mixture was stirred at 0 °C for 7 h and then acidified (pH 2) with 1 N HCl. The THF was then removed *in vacuo*, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with brine (5 mL), dried, and concentrated *in vacuo*. The resulting oil was subjected to flash chromatography (ethyl acetate−hexanes, 3:7 with 1% formic acid) to give **2d** (0.564 g, 88%) as an off-white solid: mp 74−76 °C; ^{1}H NMR δ 1.81 (s, 3 H), 2.22 (s, 3 H), 2.28 (m, 2 H), 2.43 (m, 2 H), 3.39 (d, 2 H), 3.73 (s, 3 H), 3.92 (s, 3 H), 5.28 (t, 1 H), 7.54 (s, 1 H), 10.90 (s, 1 H); IR (neat) 1228, 1283, 1352, 1442, 1678, 1708, 2952, 3160 cm^{-1}. Anal. ($C_{17}H_{22}O_6$) C, H.

(*E*)-4-Methyl-6-[3-(1-(aminocarbonyl)-2-hydroxy-4-methoxy-5-methylphenyl)]-4-hexenoic Acid (2e). A solution of **2d** (1.07 g, 3.32 mmol) in methanol (35 mL) was saturated with ammonia and heated at 55 ± 5 °C for 133 h in a Fisher-Porter bottle. The resulting dark brown solution was filtered and concentrated *in vacuo*. The brown residue was dissolved in ethyl acetate, filtered through a pad of Celite, and concentrated *in vacuo*. The resulting brown solid was subjected to flash chromatography (ethyl acetate−hexanes, 1:1 with 1% formic acid) and then crystallized from ethyl acetate to give **2e** (0.642 g, 63%) as a gray crystalline solid: mp 185−188 °C; ^{1}H NMR (CD_3OD) δ 1.72 (s, 3 H), 2.12 (s, 3 H), 2.20 (t, 2 H), 2.28 (t, 2 H), 3.27 (d, 2 H), 3.63 (s, 3 H), 5.18 (t, 1 H), 7.35 (s, 1 H); IR (KBr) 1109, 1276, 1448, 1622, 1650, 1698, 3236, 3451 cm^{-1}. Anal. ($C_{16}H_{21}NO_5$) C, H, N.

(*E*)-4-Methyl-6-[3-(2-hydroxy-4-methoxy-5-methyl-1-acetylphenyl)]-4-hexenoic Acid (2f). Sodium hydride (60% dispersion in mineral oil, 0.385 g, 9.63 mmol) was washed with dry hexanes (2 × 2 mL). The flask was evacuated and purged several times, and while under a flow of nitrogen, DMSO (10 mL) was added. The resulting gray solution was warmed to 75−80 °C until the evolution of hydrogen had subsided. The flask was then cooled to 0 °C, and a solution of **2d** (0.500 g, 1.55 mmol) in DMSO (7 mL) was quickly added. The ice bath was removed immediately, and the reaction mixture was allowed to warm to room temperature over 0.5 h. The reaction mixture was then poured into chloroform (50 mL) and water (50 mL). The aqueous layer was acidified with concentrated HCl (pH 2) and then extracted with chloroform (2 × 25 mL). The combined organic layer was washed with water (25 mL) and brine (25 mL), dried, filtered, and concentrated *in vacuo*. The resulting oil was subjected to flash chromatography (ethyl acetate−hexanes, 8:2 with 1% formic acid) to give a yellow oily solid that was crystallized from dichloromethane and hexanes to give the β-keto sulfoxide (0.385 g, 67%) as a cream-colored solid: mp 120−122 °C dec; ^{1}H NMR δ 1.81 (s, 3 H), 2.25 (s, 3 H), 2.37 (m, 4 H), 2.79 (s, 3 H), 3.37 (d, 2 H), 3.76 (s, 3 H), 4.36 (dd, 2 H), 5.24 (t, 1 H), 7.43 (s, 1 H); IR ($CHCl_3$) 754, 1127, 1286, 1352, 1433, 1626, 1713, 2944 cm^{-1}. Anal. ($C_{18}H_{24}O_6S$) C, H, S.

A solution of the β-keto sulfoxide (0.200 g, 0.543 mmol) in acetic acid (6 mL) and ethanol (2 mL) was slowly treated with zinc dust (0.359 g, 5.49 mmol). The reaction mixture was sonicated at 28 ± 2 °C for 55 min and then vacuum filtered. The solid was washed with ethanol (10 mL) and ethyl acetate (25 mL). Ethyl acetate (30 mL) was added to the filtrate. The aqueous layer was removed, and the organic phase was washed with water (2 × 25 mL) and brine (25 mL), dried, filtered, and concentrated *in vacuo*. The resulting oily solid was subjected to flash chromatography (ethyl acetate−hexanes, 1:1 with 1% formic acid) to give **2f** (0.160 g, 96%) as a slightly yellow solid: mp 91−93.5 °C; ^{1}H NMR δ 1.81 (s, 3 H), 2.25 (s, 3 H), 2.30 (t, 2 H), 2.43 (t, 2 H), 2.58 (s, 3 H), 3.38 (d, 2 H), 3.74 (s, 3 H), 5.27 (t, 1 H), 7.43 (s, 1 H), 12.57 (s, 1 H); IR (KBr) 1096, 1206, 1289, 1372, 1435, 1636, 1719, 2925 cm^{-1}. Anal. ($C_{17}H_{22}O_5$) C, H.

(*E*)-4-Methyl-6-[3-(5-chloro-2-hydroxy-1-(methoxycarbonyl)-4-methoxyphenyl)]-4-hexenoic Acid (2g). Method A. A mixture of **13** (0.204 g, 0.347 mmol) and formic acid (2 mL) was stirred at room temperature for 4 h. The reaction mixture was partitioned between water (10 mL) and ethyl acetate (10 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried, filtered, and concentrated *in vacuo*. The resulting slightly pink oily solid was heated for 1 h at 160 ± 5 °C, while under a flow of argon. The resulting yellowish solid was subjected to column chromatography (hexanes−ethyl acetate, 7:3 with 1% formic acid) to give **2g** (0.071 g, 60%) as a white solid: mp 122−123.5 °C; ^{1}H NMR δ 1.81 (s, 3 H), 2.31 (t, 2 H), 2.44 (t, 2 H), 3.41 (d, 2 H), 3.86 (s, 3 H), 3.94 (s, 3 H), 5.25 (t, 1 H), 7.76 (s, 1 H), 11.01 (s, 1 H); IR (KBr) 1206, 1269, 1345, 1428, 1615, 1670, 1719, 2917, 3084 cm^{-1}. Anal. ($C_{16}H_{19}O_6Cl$) C, H, Cl.

Method B. TFA (0.09 mL, 1.11 mmol) was added to an ice-cold solution of **13** (0.200 g, 0.341 mmol) in dichloromethane (2 mL). The resulting mixture was stirred at 0 °C for 15 min and then allowed to warm to room temperature over a 1 h period. The solvent was concentrated *in vacuo*, and the resulting oil was dissolved in ethyl acetate (10 mL). The organic layer was washed with water (2 × 10 mL) and brine (10 mL), dried , filtered and concentrated *in vacuo*. The resulting oil was stirred with formic acid (1 mL), at room temperature, for 7 h. The white solid that formed was partitioned between water (10 mL) and ethyl acetate (10 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried, filtered, and concentrated *in vacuo*. The resulting white solid was heated to 150 ± 5 °C, while under a flow of argon, for 1 h. The resulting solid was subjected to flash chromatography (hexanes−ethyl acetate, 7:3 with 1% formic acid) to give **2g** (0.072 g, 63%) as a white solid, identical with the sample prepared by method A (TLC, NMR, melting point).

(*E*)-4-Methyl-6-[3-(1-(aminocarbonyl)-5-chloro-2-hydroxy-4-methoxyphenyl)]-4-hexenoic Acid (2h). A solution of **2g** (1.03 g, 3.01 mmol) in methanol (35 mL) was

saturated with ammonia and heated to 60 ± 5 °C for 4 days in a Fisher-Porter bottle. The resulting dark reaction mixture was filtered, preadsorbed onto silica gel (10 g), and subjected to flash chromatography (1% formic acid in ethyl acetate−hexanes, 3:7) to give **2h** (0.97 g, 98%) as a cream-colored solid: mp 172−175 °C dec; ^{1}H NMR (CD_3OD) δ 1.60 (s, 3 H), 2.12 (m, 4 H), 3.18 (d, 2 H), 3.62 (s, 3 H), 5.04 (t, 1 H), 7.52 (s, 1 H); IR (KBr) 1269, 1435, 1615, 1657, 1684, 2945, 3195, 3423 cm^{-1}. Anal. ($C_{15}H_{18}O_5ClN$) C, H, Cl, N.

(*E*)-4-Methyl-6-[3-(5-chloro-2-hydroxy-4-methoxy-1-acetylphenyl)]-4-hexenoic Acid (2i). Sodium hydride (60% dispersion in mineral oil, 0.90 g, 22.50 mmol) was washed with dry hexanes (2 × 4 mL). The flask was evacuated and purged several times, and while under a flow of nitrogen, DMSO (25 mL) was added. The resulting gray solution was warmed to 75−80 °C until the evolution of hydrogen had subsided. The flask was then cooled to 0 °C, and **2g** (1.25 g, 3.65 mmol) in DMSO (15 mL) was quickly added. The ice bath was removed immediately, and the reaction mixture was then allowed to warm to room temperature over a 0.5 h period. The green mixture was then poured into chloroform (150 mL) and water (150 mL). The yellow aqueous layer was acidified with concentrated HCl (pH 2) and extracted with chloroform (2 × 80 mL). The combined organic layer was washed with water (90 mL) and brine (90 mL), dried, filtered, and concentrated *in vacuo*. The resulting yellow solid was crystallized from chloroform and hexanes to give the β-keto sulfoxide as a yellow solid (1.06 g, 75%): mp 139−140 °C; ^{1}H NMR δ 1.80 (s, 3 H), 2.37 (m, 4 H), 2.80 (s, 3 H), 3.40 (d, 2 H), 3.89 (s, 3 H), 4.32 (s, 2 H), 5.22 (t, 1 H), 7.65 (s, 1 H), 12.17 (s, 1 H); IR ($CHCl_3$) 1036, 1111, 1273, 1342, 1423, 1630, 1711 cm^{-1}. Anal. ($C_{17}H_{21}O_6ClS$) C, H, Cl, S.

The β-keto sulfoxide (0.250 g, 0.643 mmol) was dissolved in acetic acid (5 mL) and ethanol (2 mL), and then zinc dust (0.420 g, 6.43 mmol) was slowly added. The reaction mixture was sonicated at 28 ± 5 °C for 1 h, and then the reaction mixture was vacuum filtered. The solids were washed with ethanol and ethyl acetate. The resulting filtrate was washed with water (1 × 20 mL, 3 × 10 mL) and brine (10 mL), dried, filtered, and concentrated *in vacuo*. The remaining acetic acid was removed by azeotrope with benzene. The resulting oily solid was subjected to flash chromatography (1% formic acid in hexanes−ethyl acetate, 7:3) to give **2i** (0.170 g, 81%) as a cream-colored solid: mp 102.5−105.5 °C; ^{1}H NMR δ 1.81 (s, 3 H), 2.37 (m, 2 H), 2.59 (s, 3 H), 3.41 (d, 2 H), 3.87 (s, 3 H), 5.24 (t, 1 H), 7.63 (s, 1 H), 12.63 (s, 1 H); IR ($CHCl_3$) 724, 1273, 1323, 1368, 1431, 1640, 1708, 2935 cm^{-1}. Anal. ($C_{16}H_{19}O_5Cl$) C, H, Cl.

Methyl 2-Hydroxy-4-methoxy-5-methylbenzoate (3b). A stirred solution of **5b** (4.11 g, 19.55 mmol) in dichloromethane (50 mL) was cooled in an ice−salt bath, and 1 M boron trichloride (80 mL) was slowly added. After the addition was completed, the ice−salt bath was removed and the resulting lime-colored solution was stirred at room temperature for 2 h. The solution was then cooled in an ice bath, and 10 mL of 3 N HCl was added. The ice bath was removed, and the solution was stirred at room temperature for 3 h. The dichloromethane was then removed *in vacuo*, and the resulting aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layer was concentrated, and the yellow solid residue was subjected to flash chromatography (chloroform) to give **3b** as an off-white crystalline solid (3.31 g, 86%), mp 93.5−95 °C (lit.[28] mp 95−96 °C).

Methyl 5-Chloro-2-hydroxy-4-methoxybenzoate (3c). A solution of **3a** (0.88 g, 4.83 mmol) in dichloromethane (10 mL) was treated with sulfuryl chloride (0.43 mL, 5.35 mmol), and the mixture was heated at reflux for 25 h. Then, additional sulfuryl chloride (0.200 mL, 2.49 mmol) was added, and the mixture was heated at reflux for another 15.5 h. The yellow solution was concentrated *in vacuo*, and the resulting white solid was subjected to flash chromatography (ethyl acetate−hexanes, 1:1) to give **3c** as a white solid (0.971 g, 93%): mp 127−129 °C; ^{1}H NMR δ 3.93 (s, 6 H), 6.50 (s, 1 H), 7.83 (s, 1 H), 10.93 (s, 1 H); IR ($CHCl_3$) 1671, 1443, 1348, 1250, 908 cm^{-1}. Anal. ($C_9H_9O_4Cl$) C, H, Cl.

Methyl 2-(Allyloxy)-4-methoxybenzoate (3d). A mixture of methyl 2-hydroxy-4-methoxybenzoate (**3a**, 3.20 g, 17.6 mmol), allyl bromide (5.30 g, 43.8 mmol), and anhydrous potassium carbonate (2.68 g, 19.4 mmol) was heated at reflux in dry acetone (25 mL) for 34 h under an atmosphere of argon. The mixture was filtered, and the filter cake was washed with ether. Evaporation of the filtrate gave **3d** as a pale yellow oil (3.9 g, 100%). This material was pure by ^{1}H NMR and TLC (silica gel, ether−petroleum ether, 2:8) and was used directly in the Claisen rearrangement. A sample, purified by TLC (silica gel, ether−petroleum ether, 2:8) had the following properties: ^{1}H NMR δ 3.81 (s, 3 H), 3.83 (s, 3 H), 4.62 (m, 2 H), 5.32 (m, 2 H), 6.09 (m, 2 H), 6.49 (t, 2 H), 7.87 (d, 1 H); IR (neat) 3011, 2949, 2905, 2837, 1718, 1693, 1608, 1575 cm^{-1}. Anal. ($C_{12}H_{14}O_4$) C, H.

Methyl 2-(Allyloxy)-4-methoxy-5-methylbenzoate (3e). A solution of **3b** (3.23 g, 16.46 mmol) in acetone (35 mL) was heated at reflux with potassium carbonate (3.41 g, 24.69 mmol) and allyl bromide (3.56 mL, 41.15 mmol) for 84 h. The reaction mixture was filtered and concentrated *in vacuo* to give **3e** (3.55 g, 92% crude yield) as an off-white crystalline solid. An analytical sample was obtained by crystallization from hexanes: mp 55.5−56.5 °C; ^{1}H NMR δ 2.15 (s, 3 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.64 (d, 2 H), 5.32 (d, 1 H), 5.57 (d, 1 H), 6.11 (m, 1 H), 6.45 (s, 1 H), 7.69 (s, 1 H); IR ($CHCl_3$) 908, 1155, 1258, 1614, 1709 cm^{-1}. Anal. ($C_{13}H_{16}O_4$) C, H.

Methyl 2-(Allyloxy)-5-chloro-4-methoxybenzoate (3f). A mixture of **3c** (7.50 g, 34.62 mmol), potassium carbonate (7.18 g, 51.93 mmol), and allyl bromide (7.5 mL, 86.55 mmol) in acetone (350 mL) was heated at reflux for 7.25 h. The reaction mixture was filtered and concentrated *in vacuo*, and the resulting white solid was subjected to flash chromatography (dichloromethane−hexanes, 4:1) to give **3f** (8.03 g, 90%) as a white solid: mp 68−70 °C; ^{1}H NMR δ 3.84 (s, 3 H), 3.90 (s, 3 H), 4.66 (d, 2 H), 5.26 (d, 1 H), 5.48 (d, 1 H), 6.00 (dt, 1 H), 6.44 (s, 1 H), 7.85 (s, 1 H); IR ($CHCl_3$) 907, 1105, 1443, 1603, 1718 cm^{-1}. Anal. ($C_{12}H_{13}O_4Cl$) C, H, Cl.

Methyl 3-Allyl-2-hydroxy-4-methoxybenzoate (6a). The crude allyl ether **3d** (85.6 mmol) was degassed at 10^{-1} Torr for 15 min. The material was then heated under an atmosphere of argon at 210 °C for 3 h and cooled to room temperature to give crude **6a** as yellow crystals (18.95 g, 99%). ^{1}H NMR and TLC analysis (silica gel, ether−petroleum ether, 2:8) showed the material to be pure so it was used directly in the ozonolysis step. A sample was chromatographed (TLC, silica gel, ether−petroleum ether, 2:8) for analysis: ^{1}H NMR δ 3.43 (dd, 2 H), 3.86 (s, 3 H), 3.90 (s, 3 H), 5.01 (m, 2 H), 5.98 (m, 1 H), 6.45 (s, 1 H), 7.72 (d, 1 H), 11.03 (s, 1 H); IR ($CHCl_3$) 3178, 1669, 1619 cm^{-1}. Anal. ($C_{12}H_{14}O_4$) C, H.

Methyl 3-Allyl-2-hydroxy-4-methoxy-5-methylbenzoate (6b). The crude allyl ether **3e** (34.85 g, 148.78 mmol) was heated to 210 ± 5 °C for 4 h while under nitrogen. The resulting light brown oil was subjected to flash chromatography (dichloromethane−hexanes, 1:1) to give **6b** (30.47 g) as a clear slightly yellow oil (81% from methyl 2,4-dimethoxy-5-methylbenzoate): ^{1}H NMR δ 2.24 (s, 3 H), 3.46 (d, 2 H), 3.78 (s, 3 H), 3.90 (s, 3 H), 4.95 (m, 2 H), 6.09 (m, 1 H), 7.65 (s, 1 H), 10.99 (s, 1 H); IR ($CHCl_3$) 908, 1359, 1442, 1670 cm^{-1}. Anal. ($C_{13}H_{16}O_4$) C, H.

Methyl 3-Allyl-5-chloro-2-hydroxy-4-methoxybenzoate (6c). Neat **3f** (0.70 g, 2.73 mmol) was heated to 210 ± 5 °C for 4 h while under a flow of nitrogen. The reaction mixture was allowed to cool to room temperature, and the resulting brown oil was subjected to flash chromatography (dichloromethane−hexanes, 1:1) to give **6c** (0.358 g, 51%) as a white oily solid: mp 38−39.5 °C; ^{1}H NMR δ 3.44 (d, 2 H), 3.84 (s, 3 H), 3.90 (s, 3 H), 5.00 (m, 2 H), 6.00 (m, 1 H), 7.78 (s, 1 H), 11.0 (s, 1 H); IR ($CHCl_3$) 908, 1213, 1269, 1338, 1476, 1670 cm^{-1}. Anal. ($C_{12}H_{13}O_4Cl$) C, H, Cl.

2-(2-Hydroxy-4-methoxy-1-(methoxycarbonyl)-3-phenyl)ethanal (7a). A solution of **6a** (5.046 g, 22.7 mmol) in dichloromethane−methanol (720 mL, 3:1) was cooled to −76 °C. A stream of ozone in oxygen was bubbled through the solution. When the colorless solution acquired a bluish tint, indicating the presence of excess ozone (*ca*. 30 min), nitrogen was bubbled through the solution. TLC analysis (silica gel, dichloromethane) showed complete reaction. Triphenylphosphine (7.761 g, 29.6 mmol) was added, and the solution was stirred for 30 min; aqueous sodium bicarbonate (5%, 100 mL)

was then added to the vigorously stirring solution, and the mixture was allowed to warm to room temperature. The aqueous phase was extracted with dichloromethane (2 × 100 mL). The combined organic solution was dried and concentrated. The crude yellow oil was purified by flash column chromatography (silica gel, ether−hexane, 4:6) to give **7a** as a white solid (4.33 g, 85%): mp 85−86.5 °C; ^{1}H NMR δ 3.71 (d, 2 H), 3.84 (s, 3 H), 3.91 (s, 3 H), 6.47 (d, 2 H), 7.78 (d, 1 H), 9.61 (t, 1 H), 11.18 (s, 1 H); IR ($CHCl_3$) 3148, 3028, 1724, 1668, 1619 cm^{-1}. Anal. ($C_{11}H_{12}O_5$) C, H.

2-(2-Hydroxy-4-methoxy-5-methyl-1-(methoxycarbonyl)-3-phenyl)ethanal (7b). A solution of **6b** (0.656 g, 2.80 mmol) in dichloromethane (9 mL) and methanol (3 mL) was cooled to −76 °C. Ozone (2 psi, 2.0 mL/min) was bubbled through the solution for 5 min, at which time a TLC of the reaction mixture showed no starting material. Nitrogen was then bubbled through the solution for 5 min, and then triphenylphosphine (0.881 g, 3.36) was added to the reaction mixture. The resulting solution was stirred for 15 min, then 5% sodium bicarbonate (10 mL) was added, and the mixture was allowed to warm to room temperature. The organic layer was separated from the aqueous layer, and the aqueous layer was extracted with dichloromethane (4 × 10 mL). The combined organic layer was dried, filtered, and concentrated *in vacuo* to yield 1.45 g of an orange oil. The oil was subjected to flash chromatography to give **7b** (0.516 g, 77%) as an off-white solid: mp 89.5−92.5 °C; ^{1}H NMR δ 2.24 (s, 3 H), 3.86 (s, 3 H), 3.88 (d, 1 H), 3.92 (s, 2 H), 7.67 (s, 1 H), 9.75 (s, 1 H), 10.99 (s, 1 H); IR ($CHCl_3$) 902, 1352, 1442, 1678, 1719 cm^{-1}. Anal. ($C_{12}H_{14}O_5$) C, H.

2-(5-Chloro-2-hydroxy-4-methoxy-1-(methoxycarbonyl)-3-phenyl)ethanal (7c). A solution of **6c** (11.19 g, 43.60 mmol) in dichloromethane (420 mL) and methanol (140 mL) was cooled to −76 °C, and ozone (2 in/min, and 2 psi) was bubbled through the solution for 50 min. When the solution turned blue, nitrogen was bubbled through for 15 min, triphenylphosphine (13.72 g, 52.31 mmol) was added, and the mixture was stirred for 20 min at −76 °C. A solution of 5% sodium bicarbonate (100 mL) was added to the solution, and the mixture was allowed to warm to room temperature. The resulting yellow organic layer was separated from the aqueous layer. The aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layer was dried, filtered, and concentrated *in vacuo* to yield 27.44 g of an orange oil that was subjected to flash chromatography to give **7c** (10.30 g, 91%) as a yellow solid: mp 114−115.5 °C; ^{1}H NMR δ 3.70 (d, 2 H), 3.79 (s, 3 H), 3.89 (s, 3 H), 7.79 (s, 1 H) 9.69 (t, 1 H), 11.01 (s, 1 H); IR ($CHCl_3$) 908, 1380, 1470, 1678, 1726 cm^{-1}. Anal. ($C_{11}H_{11}O_5Cl$) C, H, Cl.

(*E*)-2-Methyl-4-(2-hydroxy-1-(methoxycarbonyl)-4-methoxy-3-phenyl)-2-butenal (8a). A mixture of aldehyde **7a** (7.651 g, 34.12 mmol) and (1-formylethylidene)triphenylphosphorane (11.953 g, 37.55 mmol) in benzene (200 mL) was heated at reflux for 28.5 h. The solvent was evaporated, and the crude solid was purified by flash column chromatography (silica gel, ether−hexanes, 3:7) to afford **8a** as white crystals (8.05 g, 89%): mp 86.0−87.5 °C; ^{1}H NMR δ 1.91 (s, 3 H), 3.72 (d, 2 H), 3.89 (s, 3 H), 3.91 (s, 3 H), 6.49 (d, 1 H), 6.57 (t, 1 H), 7.79 (d, 1 H), 9.37 (s, 1 H), 11.17 (s, 1 H); IR ($CHCl_3$) 3025, 1675, 1620, 1501 cm^{-1}. Anal. ($C_{14}H_{16}O_5$) C, H.

(*E*)-2-Methyl-4-(2-hydroxy-1-(methoxycarbonyl)-4-methoxy-5-methyl-3-phenyl)-2-butenal (8b). A mixture of **7b** (1.50 g, 6.30 mmol) and (α-formylethylidene)triphenylphosphorane (2.20 g, 6.91 mmol) in benzene (70 mL) was heated at reflux for 28 h. The solvent was removed *in vacuo*, and the residue was subjected to flash chromatography (ether−hexanes, 3:7) to give **8b** (1.57 g, 90%) as a yellow oil: ^{1}H NMR δ 1.92 (s, 3 H), 2.25 (s, 3 H), 3.72 (d, 2 H), 3.73 (s, 3 H), 3.95 (s, 3 H), 6.57 (complex t, 1 H), 7.62 (s, 1 H), 9.39 (s, 1 H), 10.99 (s, 1 H); IR (neat) 1005, 1172, 1206, 1283, 1345, 1442, 1622, 1685 cm^{-1}. Anal. ($C_{15}H_{18}O_5$) C, H.

(*E*)-2-Methyl-4-(5-chloro-2-hydroxy-1-(methoxycarbonyl)-4-methoxy-3-phenyl)-2-butenal (8c). A mixture of **7c** (10.0 g, 38.66 mmol) and (α-formylethylidene)triphenylphosphorane (14.77 g, 46.39 mmol) in benzene (500 mL) was heated at reflux for 8 h. The solvent was removed *in vacuo*, and the resulting residue was subjected to flash chromatography (ether−hexanes, 3:7) to give **8c** (11.1 g, 96%) as a yellow oily solid: mp 49−53 °C; ^{1}H NMR δ 1.94 (s, 3 H), 3.80 (d, 2 H), 3.92 (s, 3 H), 3.97 (s, 3 H), 6.57 (tq, 1 H), 7.90 (s, 1 H), 9.48 (s, 1 H), 11.24 (s, 1 H); IR ($CHCl_3$) 1267, 1346, 1438, 1616, 1681 cm^{-1}. Anal. ($C_{14}H_{15}O_5Cl$) C, H, Cl.

(*E*)-2-Methyl-4-[2-((2-methoxyethoxy)methoxy)-1-(methoxycarbonyl)-4-methoxy-3-phenyl]-2-butenal (8d). A solution of the phenol **8a** (10.93 g, 41.4 mmol) in dry THF (200 mL) was cooled to 0 °C under an atmosphere of argon. Sodium hydride (1.91 g of a 60% dispersion, 47.6 mmol) was added, followed after 40 min by chloroethoxymethoxymethane (7.0 mL, 61.3 mmol). The mixture was stirred for an additional 15 min at 0 °C and then at 25 °C for 25 h. The mixture was concentrated to *ca*. 50 mL. The yellow residue was dissolved in ether−THF (500−600 mL), and the solution was extracted sequentially with water (3 × 200 mL) and saturated aqueous sodium chloride (100 mL). The organic phase was dried and concentrated *in vacuo* to give a yellow solid. Purification by flash column chromatography (silica gel, ether−hexane, 1:1) provided the starting phenol (1.32 g, 12%) and **8d** as a white solid (10.91 g, 87% based on unrecovered starting material): mp 83.5−84.5 °C; ^{1}H NMR δ 1.92 (s, 3 H), 3.36 (s, 3 H), 3.74 (m, 6 H), 3.87 (s, 6 H), 5.20 (s, 2 H), 6.57 (t, 1 H), 6.74 (d, 1 H), 7.89 (d, 1 H), 9.39 (s, 1 H); IR ($CHCl_3$) 3016, 1715, 1681, 1596 cm^{-1}. Anal. ($C_{18}H_{24}O_7$) C, H.

(*E*)-2-Methyl-4-[2-((2-methoxyethoxy)methoxy)-1-(methoxycarbonyl)-4-methoxy-5-methyl-3-phenyl]-2-butenal (8e). A stirred solution of **8b** (1.0 g, 3.59 mmol) in dry THF (20 mL) was maintained under a flow of nitrogen, treated with 60% sodium hydride (0.161 g, 4.03 mmol) at 0 °C for 20 min, and then chloroethoxymethoxymethane (0.45 mL, 3.95 mmol) was added. The resulting mixture, with a yellow solid precipitate, was allowed to warm to room temperature over a 1 h period. The mixture was then cooled to 0 °C, methanol (2 mL) was added, and the mixture was stirred at 0 °C for 15 min and then allowed to warm to room temperature over a 30 min period. The solvent was then removed *in vacuo*, and the oily residue was subjected to flash chromatography (ethyl acetate−hexane, 4:6) to give **8e** (0.761 g, 77% based on unrecovered **8b**) as a yellow oil: ^{1}H NMR δ 1.90 (s, 3 H), 2.28 (s, 3 H), 3.36 (s, 3 H), 3.54 (m, 2 H), 3.72 (s, 3 H), 3.84 (m, 4 H), 3.88 (s, 3 H), 5.16 (s, 2 H), 6.59 (t, 1 H), 7.66 (s, 1 H), 9.37 (s, 1 H); IR ($CHCl_3$) 908, 1345, 1448, 1615, 1678, 2932 cm^{-1}. Anal. ($C_{19}H_{26}O_7$) C, H.

(*E*)-2-Methyl-4-[5-chloro-2-((2-methoxyethoxy)methoxy)-1-(methoxycarbonyl)-4-methoxy-3-phenyl]-2-butenal (8f). A solution of **8c** (2.00 g, 6.70 mmol) in dichloromethane (30 mL) was treated with *N*,*N*-diisopropylethylamine (2.00 mL, 11.48 mmol) and methoxyethoxymethyl chloride (1.30 mL, 11.48 mmol), and the mixture was stirred at room temperature for 1 h. The solvent was then concentrated *in vacuo*, and the residue was subjected to flash chromatography (ethyl acetate−hexanes, 2:3) to give **8f** (2.26 g, 92% based on unrecovered **8c**) as a slightly yellow solid: mp 52−53.5 °C; ^{1}H NMR δ 1.91 (s, 3 H), 3.36 (s, 3 H), 3.54 (m, 2 H), 3.74 (m, 4 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 5.18 (s, 2 H), 6.55 (t, 1 H), 7.88 (s, 1 H), 9.38 (s, 1 H); IR ($CHCl_3$) 911, 1053, 1161, 1276, 1431, 1472, 1681, 1723, 2929, 3025 cm^{-1}. Anal. ($C_{18}H_{24}O_7Cl$) C, H, Cl.

(*E*)-Methyl 3-(3-Methyl-4-hydroxy-2-butenyl)-4-methoxy-2-((2-methoxyethoxy)methoxy)benzoate (9a). A cooled (ice bath) stirred suspension of the aldehyde **8d** (7.07 g, 20.1 mmol) in methanol (50 mL) at 0 °C was treated with sodium borohydride (0.84 g, 22.3 mmol). The ice bath was removed, and the mixture was stirred for 4.5 h. The resulting clear solution was evaporated, and the residue was dissolved in chloroform (40 mL) and extracted with 0.5 M HCl (40 mL). The aqueous phase was washed with chloroform (2 × 15 mL), and the combined chloroform solution was extracted with saturated sodium chloride (20 mL) and dried. The solution was concentrated *in vacuo*, and the yellow oily residue was purified by flash column chromatography (silica gel, ether−hexane, 8:2) to afford **9a** (6.44 g, 91%) as a colorless oil which slowly solidified: mp 44.5−46.0 °C; ^{1}H NMR δ 1.82 (s, 3 H), 2.13 (bs, 1 H), 3.36 (s, 3 H), 3.50 (m, 4 H), 3.83 (s, 6 H), 3.87 (m, 4 H), 5.13 (s, 2 H), 5.47 (bt, 1 H), 6.67 (d, 1 H), 7.78 (d, 1 H); IR ($CHCl_3$) 3012, 2941, 1714, 1595 cm^{-1}. Anal. ($C_{18}H_{26}O_7$) C, H.

(*E*)-Methyl 3-(3-Methyl-4-hydroxy-2-butenyl)-4-methoxy-((2-methoxyethoxy)methoxy)-5-methylbenzoate (9b). A solution of **8e** (1.82 g, 4.97 mmol) in methanol (20 mL) was stirred at 0 °C for 15 min with sodium borohydride (0.207 g, 5.46 mmol). The yellow reaction mixture was then allowed to warm to room temperature over 45 min. The solvent was then removed *in vacuo*, and the residue was partitioned between chloroform (10 mL) and 0.5 N HCl (10 mL). The aqueous layer was extracted with chloroform (3 × 10 mL). The combined chloroform layer was washed with saturated sodium bicarbonate (10 mL) and brine (10 mL), dried, filtered, and concentrated *in vacuo*. The resulting oil was subjected to flash chromatography (dichloromethane−ether, 1:1) to give **9b** (1.56 g, 85%) as a clear oil: ^{1}H NMR δ 1.82 (s, 3 H), 2.26 (s, 3 H), 3.37 (s, 3 H), 3.53 (m, 4 H), 3.72 (s, 3 H), 3.87 (s, 3 H), 3.88 (m, 2 H), 3.97 (s, 2 H), 5.11 (s, 2 H), 5.50 (t, 1 H), 7.57 (s, 1 H); IR (neat) 1087, 1256, 1287, 1420, 1571, 1577, 2881, 2405, 3422, 3432, 3455, 3462, 3471, 3481 cm^{-1}. Anal. ($C_{19}H_{28}O_7$) C, H.

(*E*)-Methyl 3-(3-Methyl-4-hydroxy-2-butenyl)-5-chloro-4-methoxy-2-((2-methoxyethoxy)methoxy)benzoate (9c). A suspension of **8f** (4.23 g, 10.94 mmol) in methanol (45 mL) was cooled to 0 °C and treated with sodium borohydride (0.455 g, 12.03 mmol). The resulting yellow mixture was stirred at 0 °C until the bubbling subsided. The ice bath was then removed, and the slightly yellow reaction mixture was allowed to warm to room temperature over a 1 h period. The solvent was then evaporated, and the oily residue was partitioned between 0.5 N HCl (22 mL) and chloroform (22 mL). The aqueous layer was extracted with chloroform (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried, filtered, and concentrated *in vacuo*. The resulting cloudy oil was purified by flash chromatography (dichloromethane−ether, 7:3) to give **9c** (4.11 g, 97%) as a clear oil: ^{1}H NMR δ 1.82 (s, 3 H), 3.37 (s, 3 H), 3.54 (m, 4 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 3.90 (m, 2 H), 3.98 (s, 2 H), 5.14 (s, 2 H), 5.48 (t, 1 H), 7.79 (s, 1 H); IR (neat) 1054, 1165, 1276, 1435, 1463, 1581, 1727, 2947, 3436 cm^{-1}. Anal. ($C_{18}H_{25}O_7Cl$) C, H, Cl.

(*E*)-Methyl 3-(4-Bromo-3-methyl-2-butenyl)-4-methoxy-2-((2-methoxyethoxy)methoxy)benzoate (10a). *N,N*-Diisopropylethylamine (0.81 mL, 4.7 mmol) was added to a mixture of **9a** (6.44 g, 18.2 mmol) and tetrabromomethane (7.31 g, 22.0 mmol) in dichloromethane (60 mL), under a nitrogen atmosphere. The solution was cooled to −78 °C, and a solution of triphenylphosphine (5.25 g, 20.0 mmol) in dichloromethane (20 mL) was introduced dropwise over a 30 min period. After 3 h, the cooling bath was removed and the white slurry was stirred for 16 h. The solvent was evaporated, and the resulting residue was purified by flash column chromatography (silica gel, ether−dichloromethane, 0.5:9.5) to provide **10a** (6.47 g, 85%) as a clear oil, which slowly crystallized to a white solid: mp 66−68 °C; ^{1}H NMR δ 1.92 (s, 3 H), 3.03 (s, 3 H), 3.55 (m, 6 H), 3.83 (s, 6 H), 3.93 (s, 2 H), 5.13 (s, 2 H), 5.67 (t, 1 H), 6.67 (d, 1 H), 7.79 (d, 1 H); IR ($CHCl_3$) 3010, 2952, 1714, 1668, 1595 cm^{-1}. Anal. ($C_{18}H_{25}O_6Br$) C, H, Br.

(*E*)-Methyl 3-(4-Bromo-3-methyl-2-butenyl)-4-methoxy-2-((2-methoxyethoxy)methoxy]-5-methylbenzoate (10b). A solution of **9b** (2.62 g, 7.11 mmol), tetrabromomethane (2.83 g, 8.53 mmol), and *N,N*-diisopropylethylamine (0.62 mL, 3.56 mmol) in dry dichloromethane (35 mL) was cooled to −76 °C in a dry ice−ethanol bath and maintained under a flow of nitrogen. A solution of triphenylphosphine (2.24 g, 8.53 mmol) in dry dichloromethane (15 mL) was added slowly dropwise. The resulting solution was stirred at −76 °C for 15 min and then allowed to warm to room temperature, with stirring, over a 10.5 h period. The resulting solution was concentrated *in vacuo*, and the green residue was subjected to flash chromatography (ethyl acetate−hexanes, 3:7) to give **10b** (2.41 g, 79%) as a clear oil: ^{1}H NMR δ 1.93 (s, 3 H), 2.27 (s, 3 H), 3.39 (s, 3 H), 3.50 (d, 2 H), 3.57 (t, 2 H), 3.73 (s, 3 H), 3.87 (s, 3 H), 3.89 (t, 2 H), 3.96 (s, 2 H), 5.13 (s, 2 H), 5.72 (t, 1 H), 7.60 (s, 1 H); IR (neat) 908, 1096, 1387, 1470, 1719 cm^{-1}. Anal. ($C_{19}H_{27}O_6Br$) C, H, Br.

(*E*)-Methyl 3-(4-Bromo-3-methyl-2-butenyl)-5-chloro-4-methoxy-2-((2-methoxyethoxy)methoxy)benzoate (10c). A solution of **9c** (7.42 g, 19.08 mmol), tetrabromomethane (7.59 g, 22.90 mmol), and *N,N*-diisopropylethylamine (1.0 mL, 5.74 mmol) in dichloromethane (110 mL) was cooled to −76 °C in a dry ice−ethanol bath and treated dropwise with a solution of triphenylphosphine (6.01 g, 22.90 mmol) in dichloromethane (40 mL). The yellow mixture was stirred at −76 °C for 20 min and then allowed to warm to room temperature over 12 h. The solvent was concentrated *in vacuo*, and the resulting residue was subjected to flash chromatography (ethyl acetate−hexanes, 3:7) to give **10c** (7.13 g, 83%) as a clear oil: ^{1}H NMR δ 1.93 (s, 3 H), 3.38 (s, 3 H), 3.55 (m, 4 H), 3.89 (s, 2 H), 3.95 (s, 2 H), 5.14 (s, 2 H), 5.68 (t, 1 H), 7.81 (s, 1 H); IR (neat) 910, 1052, 1161, 1197, 1257, 1274, 1433, 1728 cm^{-1}. Anal. ($C_{18}H_{24}O_6ClBr$) C, H, Cl, Br.

(*E*)-Methyl 2-(Phenylsulfonyl)-4-methyl-6-{3-[1-(methoxycarbonyl)-2-((2-methoxyethoxy)methoxy)-4-methoxyphenyl]}-4-hexenoate (11a). A stirred suspension of sodium hydride (0.079 g, 1.97 mmol) in dry DMF under an atmosphere of nitrogen was cooled to 0 °C and treated with methyl (phenylsulfonyl)acetate (0.33 mL, 1.97 mmol). After the evolution of hydrogen had subsided (5 min), the ice bath was removed and stirring was continued for 10 min. The bromide **10a** (0.615 g, 1.47 mmol, in 2 mL dry DMF) was then introduced, and the resulting yellow solution was stirred for 18 h. The DMF was distilled at *ca.* 10^{-1} Torr, and the remaining residue was partitioned between water and ether (30 mL of each). The organic phase was washed with water (25 mL) and saturated sodium chloride (25 mL), dried, and concentrated to dryness *in vacuo* to give a yellow oil which could be used directly in the desulfonylation step or further purified by flash column chromatography (silica gel, ether−hexane, 9:1) to give **11a** (0.652 g, 81%) as a colorless oil: ^{1}H NMR δ 1.74 (s, 3 H), 2.58 (m, 2 H), 3.37 (s, 3 H), 3.43 (m, 4 H), 3.46 (s, 3 H), 3.84 (br s, 8 H), 4.10 (m, 1 H), 5.10 (s, 2 H), 5.21 (t, 1 H), 6.67 (d, 1 H), 7.74 (m, 6 H); IR (neat) 2950, 1743, 1718, 1594 cm^{-1}. Anal. ($C_{27}H_{34}O_{10}S$) C, H, S.

(*E*)-Methyl 2-(Phenylsulfonyl)-4-methyl-6-{3-[1-(methoxycarbonyl)-2-(2-methoxyethoxymethoxy)-4-methoxy-5-methylphenyl]}-4-hexanoate (11b). Methyl (phenylsulfonyl)acetate (1.1 mL, 6.75 mmol) was added to an ice-cold suspension of 60% sodium hydride (0.27 g, 6.75 mmol) and DMF (10 mL). After the evolution of hydrogen subsided, the reaction mixture was stirred at room temperature for an additional 15 min, and then a solution of **10b** (2.24 g, 5.19 mmol) in DMF (15 mL) was added. The reaction mixture was stirred at room temperature for 12 h, at which time the mixture was partitioned between ether (75 mL) and water (75 mL). The aqueous layer was extracted with ether (2 × 75 mL). The combined ether layer was washed with water (75 mL) and brine (75 mL), then dried, filtered, and concentrated *in vacuo*. The resulting amber oil was subjected to flash chromatography (ether−hexanes, 4:1) to give **11b** (2.54 g, 87%) as a clear oil: ^{1}H NMR δ 1.75 (s, 3 H), 2.23 (s, 3 H), 2.60 (m, 2 H), 3.36 (s, 3 H), 3.38 (m, 2 H), 3.51 (s, 3 H), 3.53 (m, 2 H), 3.66 (s, 3 H), 3.83 (m, 2 H), 3.85 (s, 3 H), 4.11 (m, 1 H), 5.06 (s, 2 H), 5.24 (t, 1 H), 7.69 (m, 6 H); IR (neat) 943, 1003, 1257, 1474, 2934, 2950 cm^{-1}. Anal. ($C_{28}H_{30}O_{10}S$) C, H, S.

(*E*)-Methyl 2-(Phenylsulfonyl)-4-methyl-6-{3-[5-chloro-1-(methoxycarbonyl)-2-((2-methoxyethoxy)methoxy)-4-methoxyphenyl]}-4-hexenoate (11c). Sodium hydride, 60% (0.81 g, 20.18 mmol) was suspended in DMF (30 mL) and cooled to 0 °C in an ice bath. Methyl (phenylsulfonyl)acetate (3.4 mL, 20.18 mmol) was quickly added to the stirring ice-cold solution. After the evolution of hydrogen subsided, the ice bath was removed, the reaction mixture was stirred for an additional 15 min, and then a solution of **10c** (7.01 g, 15.52 mmol) in DMF (30 mL) was added in one portion. The reaction mixture was stirred at room temperature for 5 h, and then the DMF was removed by distillation. The resulting yellow residue was partitioned between ether (200 mL) and water (200 mL). The ether layer was washed with water (100 mL) and brine (100 mL), then dried, filtered, and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography (ether−hexanes, 4:1) to give **11c** (8.03 g, 88%) as a sticky oil: ^{1}H NMR δ 1.74 (s, 3 H), 2.60 (m, 2 H), 3.36 (s, 3 H), 3.41 (d, 2 H), 3.51 (s, 3 H), 3.53 (m, 2 H), 3.80 (s, 3 H), 3.83 (m, 2 H), 3.85 (s, 3 H), 4.10 (m, 1 H), 5.07 (s, 2 H), 5.25 (t, 1 H), 7.59 (m, 6 H); IR (neat) 1158, 1200, 1258, 1272, 1310, 1326, 1424, 1587, 1733 cm^{-1}. Anal. ($C_{27}H_{33}O_{10}SCl$) C, H, S, Cl.

(*E*)-Methyl 4-Methyl-6-{3-[1-(methoxycarbonyl)-2-((2-methoxyethoxy)methoxy)-4-methoxyphenyl]}-4-hexenoate (12a). Crude sulfone **11a** (from 23.6 mmol of bromide **10a**) was dissolved in methanol (120 mL). Anhydrous dibasic sodium phosphate (6.73 g, 47.4 mmol) was introduced, and the suspension was placed under a nitrogen atmosphere and cooled to 0 °C. Sodium amalgam (6%, 18.17 g, 47.4 mmol Na) was added, and the mixture was stirred vigorously for 3.25 h. A significant amount of starting sulfone was still present (TLC, silica gel, ether−hexane, 7:3), so additional aliquots of anhydrous dibasic sodium phosphate (1.69 g, 11.9 mmol) and sodium amalgam (4.59 g, 12.0 mmol Na) were added. The mixture was stirred for 75 min at 0 °C, whereupon more sodium phosphate and sodium amalgam (1.69 g, 11.9 mmol and 4.54 g, 11.8 mmol Na respectively) was introduced. The mixture was stirred for 45 min and filtered through Celite, and the filter cake was rinsed with ether (2 × 40 mL). Ether was added to the filtrate to bring the volume to *ca*. 300 mL after which the solution was extracted with water (300 mL). The aqueous layer was extracted with ether (4 × 100 mL). The combined organic solution was dried (over Na_2SO_4 and then $MgSO_4$) and evaporated to give a yellow oil which was further dried by azeotropic distillation (at *ca*. 20 Torr) with toluene. Purification of the residue by flash column chromatography (silica gel, ether−hexane, 7:3) afforded **12a** (7.80 g, 81% from **10a**) as a colorless oil: ^{1}H NMR δ 1.78 (s, 3 H), 2.33 (br s, 4 H), 3.38 (s, 3 H), 3.48 (m, 4 H), 3.60 (s, 3 H), 3.86 (s, 6 H), 3.88 (m, 2 H), 5.13 (s, 2 H), 5.22 (t, 1 H), 6.68 (d, 1 H), 7.79 (d, 1 H); IR (neat): 2949, 1717, 1594 cm^{-1}. Anal. ($C_{21}H_{30}O_8$) C, H.

(*E*)-Methyl 4-Methyl-6-{3-[1-(methoxycarbonyl)-2-((2-methoxyethoxy)methoxy)-4-methoxy-5-methylphenyl]}-4-hexenoate (12b). Sodium phosphate (0.378, 2.66 mmol) and 6% sodium amalgam (1.02 g, 2.66 mmol) was added to a solution of **11b** (0.500 g, 0.886 mmol) in anhydrous methanol (5 mL) at 0 °C, while under a flow of argon. The mixture was stirred at 0 °C for 4 h. The reaction mixture was then filtered and partitioned between ether (25 mL) and water (25 mL). The aqueous layer was extracted with ether (3 × 10 mL). The combined organic layer was dried, filtered, and concentrated *in vacuo*. The resulting clear oil was subjected to flash chromatography (ether-hexanes, 3:2) to give **12b** (0.293 g, 78%) as a clear oil: ^{1}H NMR δ 1.78 (s, 3 H), 2.27 (s, 3 H), 2.33 (m, 4 H), 3.39 (s, 3 H), 3.45 (d, 2 H), 3.57 (t, 2 H), 3.62 (s, 3 H), 3.72 (s, 3 H), 3.87 (s, 3 H), 3.89 (t, 3 H), 5.11 (s, 2 H), 5.26 (t, 1 H), 7.57 (s, 1 H); IR (neat) 943, 982, 1024, 1112, 1287, 1467, 1473, 1574, 1601, 1726, 2950 cm^{-1}. Anal. ($C_{22}H_{32}O_8$) C, H.

Di-*tert*-butyl {(*E*)-4-[5-Chloro-1-(methoxycarbonyl)-2-((2-methoxyethoxy)methoxy)-4-methoxyphenyl]-2-methyl-2-butenyl}malonate (13). Di-*tert*-butyl malonate (1.8 mL, 8.37 mmol) was added to a suspension of sodium hydride (60% in mineral oil, 0.33 g, 8.37 mmol) in DMF (30 mL). The mixture was stirred at room temperature for 20 min, and then a solution of **10c** (2.91 g, 6.44 mmol) in DMF (30 mL) was quickly added. The resulting mixture was stirred at room temperature for 14 h, and then the solvent was removed by distillation. The residue was then subjected to flash chromatography (ether−hexanes, 3:2) to give **13** (3.13 g, 84%) as a clear, sticky oil: ^{1}H NMR δ 1.38 (s, 18 H), 1.80 (s, 3 H), 2.47 (d, 2 H), 3.31 (t, 1 H), 3.38 (s, 3 H), 3.46 (d, 2 H), 3.56 (t, 2 H), 3.87 (m, 8 H), 5.11 (s, 2 H), 5.28 (t, 1 H), 7.76 (s, 1 H); IR (neat) 1151, 1276, 1372, 1470, 1581, 1733, 2932, 2980 cm^{-1}. Anal. ($C_{29}H_{43}O_{10}Cl$) C, H, Cl.

Methyl 2,4-Dimethoxybenzoate (4). A solution of **3a** (50.00 g, 0.274 mol) in acetone (1750 mL) was treated with dimethyl sulfate (100.00 g, 0.791 mol) and potassium carbonate (312.93 g, 2.264 mol), and then the heterogeneous mixture was heated at reflux, with stirring, for 24 h. The reaction mixture was then filtered through a pad of Celite and then concentrated to give an amber oil. Water (250 mL) was added to the oil, and the solution was stirred at room temperature for 0.5 h. The organic and aqueous layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 500 mL), dried, and concentrated *in vacuo* to yield (51.61 g, 96%) of **4** as an amber oil: ^{1}H NMR δ 3.81 (s, 6 H), 3.84 (s, 3 H), 6.48 (m, 2 H), 7.84 (d, 1 H); IR 1723, 1609, 1435, 1257 cm^{-1}.

Methyl 5-Formyl-2,4-dimethoxybenzoate (5a) was prepared by a previously reported procedure,[28] in 69% yield, except 3 molar equiv of α,α-dichloromethyl methyl ether was used and the reaction mixture was stirred at room temperature for 2 h. Also during the workup, the quenched reaction mixture was extracted with dichloromethane instead of ether.

Methyl 2,4-Dimethoxy-5-methylbenzoate (5b). A suspension of **5a** (5.37 g, 23.95 mmol) in ethyl acetate (200 mL) and glacial acetic acid (15 mL) containing 10% palladium on carbon (1.0 g) was stirred in an atmosphere of hydrogen for 48 h. The reaction mixture was filtered through a pad of Celite, and the solvent was then removed *in vacuo* to give **5b** (4.72 g, 94%) as a grayish crystalline solid: mp 90−91 °C; ^{1}H NMR δ 2.13 (s, 3 H), 3.80 (s, 3 H), 3.83 (s, 3 H), 3.86 (s, 3 H), 6.40 (s, 1 H), 7.63 (s, 1 H); IR 1709, 1260, 1152 cm^{-1}.

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