Design, Synthesis, Anti-HIV Activities, and Metabolic Stabilities of Alkenyldiarylmethane (ADAM) Non-nucleoside Reverse Transcriptase Inhibitors

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The alkenyldiarylmethane (ADAM) HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) are effective anti-HIV agents in cell culture. However, the potential clinical utility of the ADAMs is expected to be limited by the presence of methyl ester moieties that are likely to be metabolized by nonspecific esterases in blood plasma to biologically inactive carboxylic acid derivatives. The present investigation was therefore undertaken to investigate the anti-HIV activities of the ADAMs versus HIV-1_{IIIB} and HIV-2_{ROD} in MT-4 cells and the stabilities of the biologically active ADAMs in rat plasma. The ADAMs displayed a wide range of metabolic stabilities in rat plasma, with half-lives ranging from 0.9 to 76.6 min. A wide assortment of structural modifications was tolerated, with 18 of the 32 compounds tested displaying EC_{50} values between 0.3 and 3.7 μM versus HIV-1_{IIIB} in MT-4 cells, 3 compounds in the EC_{50} = 13.2−35.4 μM range, and the remaining compounds inactive. Consistent with the mechanism of action of the ADAMs as NNRTIs, they were inactive or displayed comparatively low activity versus HIV-2_{ROD}. The replacement of the two aromatic methyl ester substituents in one of the most active ADAMs (EC_{50} = 0.6 μM) with two methyl thioester groups resulted in an increase in plasma half-life from 5.8 to 55.3 min, while maintaining the antiviral potency at the EC_{50} = 1.8 μM level. At the same time, the bis(thioester) modification was less cytotoxic to uninfected MT-4 cells, with a CC_{50} of >224 μM versus 160 μM for the parent compound.

Introduction

Reverse transcriptase (RT) provides essential enzymatic activity for the human immunodeficiency virus, the active pathogen for acquired immunodeficiency syndrome (AIDS).[1] Thus, the enzyme has been identified to be a target for the therapeutic treatment of AIDS.[2−4] The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are a structurally diverse class of compounds that bind to RT and act as allosteric inhibitors.[5,6] The NNRTIs bind near the substrate binding site of RT and induce a conformational change that results in reduced enzymatic activity.[7] Three NNRTIs (nevirapine, delavirdine, and efavirenz) have been approved for the treatment of AIDS.[8−11] Although the therapeutic use of the NNRTIs is complicated by the rapid development of viral resistance and drug toxicity, they have nevertheless proven to be useful in combination therapy with nucleoside reverse transcriptase inhibitors and protease inhibitors.[12] Employment of NNRTIs with these agents has resulted in decreased HIV-1 RNA levels, delayed disease progression, and increased CD4 lymphocyte counts. However, adverse side effects, cross-resistance, and drug incompatibilities limit the use of NNRTIs for combination therapy.[13−17] Therefore, new NNRTIs are needed that do not suffer from these restrictions.

The alkenyldiarylmethanes (ADAMs) are a novel class of NNRTIs that was discovered a decade ago.[18−26] The interest in the ADAMs in general has resulted from their anti-HIV activities against AZT-resistant strains of HIV-1. In addition, certain ADAMs have displayed synergistic activity with AZT and have shown enhanced activity when tested against AZT-resistant strains of HIV-1.[19,20,22,23] Although the ADAMs are effective inhibitors of the cytopathic effect of HIV-1 in vitro, their potential therapeutic usefulness is likely to be compromised by their expected metabolic instability. More specifically, the ester moieties in the ADAM pharmacophore are likely to be hydrolyzed by nonspecific esterases present in human blood plasma. The present investigation was therefore undertaken to determine the metabolic stabilities of biologically active ADAMs in blood plasma, with the goal of finding ADAMs that retain antiviral activity and have enhanced metabolic stabilities. In this paper, we report the anti-HIV activities of some previously existing and newly synthesized ADAMs versus HIV-1_{IIIB} in MT-4 cells, as well as the stabilities of the biologically active compounds in rat blood plasma.

Chemistry

In general, the ADAMs having identically substituted aromatic rings have been synthesized by McMurry reactions of aldehydes or ketones with symmetrical benzophenones in the presence of low-valent titanium species.[22,23] Alternatively, in other cases, Wittig ap-

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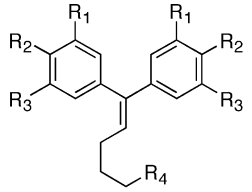
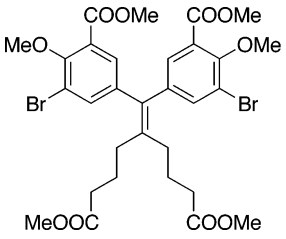
proaches have been used to generate the alkene moiety.[19,20] Alkenyldiarylmethanes **1**−**3**,[20,22,23] **5**−**19**,[23,26] and **30**[25] were synthesized as previously reported.



1 R_1= R_4 = COOMe; R_2 = OMe; R_3 = Br
2 R_1= R_4 = COOMe; R_2 = OMe; R_3 = Cl
3 R_1= R_4 = COOMe; R_2 = OMe; R_3 = Me
4 R_1= R_4 = COOMe; R_2 = OMe; R_3 = CN
5 R_1= COOMe; R_2 = OMe; R_3 = Br; R_4 = C≡C
6 R_1= COOMe; R_2 = OMe; R_3 = Cl; R_4 = C≡C
7 R_1= COOMe; R_2 = OMe; R_3 = Br; R_4 = C=C
8 R_1= COOMe; R_2 = OMe; R_3 = Cl; R_4 = C=C
9 R_1= COOMe; R_2 = OMe; R_3 = Br; R_4 = Ph
10 R_1= COOMe; R_2 = OMe; R_3 = Cl; R_4 = Ph
11 R_1= COOMe; R_2 = OMe; R_3 = Br; R_4 = COOPr
12 R_1= COOMe; R_2 = OMe; R_3 = Cl; R_4 = COOPr
13 R_1= COOMe; R_2 = OMe; R_3 = Me; R_4 = COOPr
14 R_1= COOMe; R_2 = OMe; R_3 = Br; R_4 = COOiPr
15 R_1= COOMe; R_2 = OMe; R_3 = Me; R_4 = COOiPr
16 R_1= R_4 = COOMe; R_2 = OEt; R_3 = Me
17 R_1= R_4 = COOMe; R_2 = OPr; R_3 = Me
18 R_1= COOEt; R_2 = OEt; R_3 = Me; R_4 = COOMe
19 R_1= COOPr; R_2 = OPr; R_3 = Me; R_4 = COOMe
20 R_1= COOMe; R_2 = OMe; R_3 = Br; R_4 = CH_2OMe
21 R_1= CSOMe; R_2 = OMe; R_3 = Cl; R_4 = Et
22 R_1= R_4 = CSOMe; R_2 = OMe; R_3 = Cl
23 R_1= COSMe; R_2 = OMe; R_3 = Cl; R_4 = COOMe
24 R_1= COMe; R_2 = OMe; R_3 = Cl; R_4 = Et
25 R_1= R_4 = CH_2OH; R_2 = OMe; R_3 = Cl
26 R_1= R_4 = CH_2OMe; R_2 = OMe; R_3 = Cl
27 R_1= CH_2OMe; R_2 = OMe; R_3 = Cl; R_4 = CH_2OH



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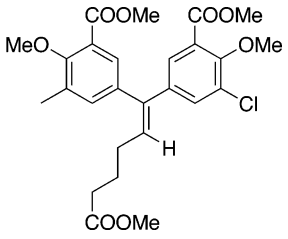

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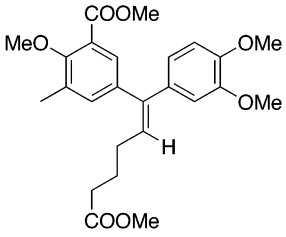

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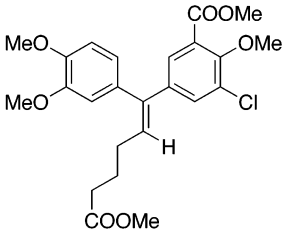

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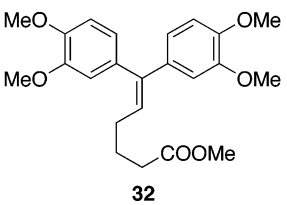

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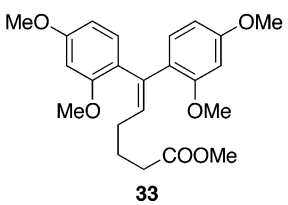

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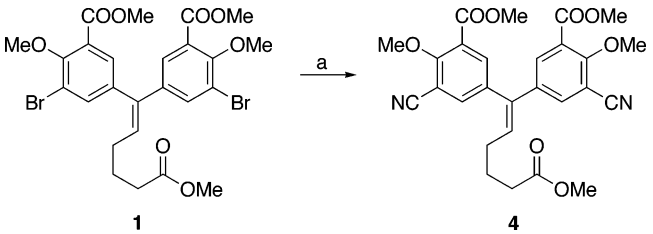
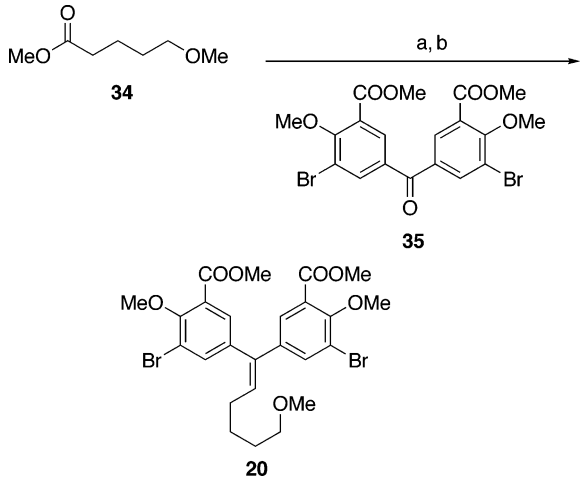
Scheme 1[a]



1 **4**

[a] Reagents and conditions: (a) CuCN, DMF, reflux 22 h.

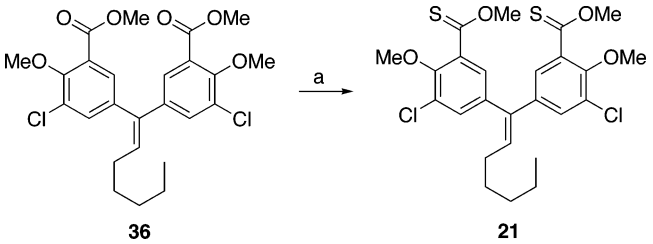
Scheme 2[a]



34 **35** **20**

[a] Reagents and conditions: (a) (1) DIBAL-H, CH_2Cl_2, −78 °C, 2 h; (b) (1) $TiCl_4$·2THF, Zn^0, THF, reflux 3 h, (2) **35**, THF, reflux 3.5 h.

Scheme 3[a]



36 **21**

[a] Reagents and conditions: (a) 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, toluene, reflux, 96 h.

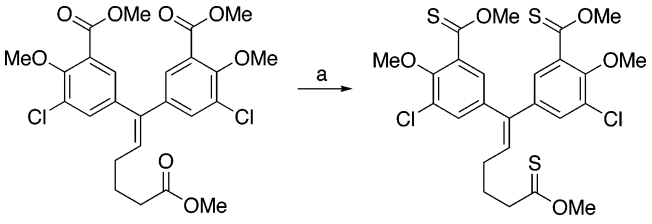
Alkenyldiarylmethane **4** was prepared from alkenyldiarylmethane **1** as outlined in Scheme 1. Treatment of ADAM **1**[22] with cuprous cyanide in *N*,*N*-dimethylformamide yielded ADAM **4**.

Reduction of methyl 5-methoxypentanoate (**34**) to the corresponding aldehyde (Scheme 2) with diisobutylaluminum hydride in dichloromethane and subsequent McMurry coupling with benzophenone **35** yielded alkenyldiarylmethane **20**. Methyl 5-methoxypentanoate (**34**)[27] and benzophenone **35**[19] were synthesized as previously described.

The reaction of alkenyldiarylmethanes **36** (Scheme 3) and **2** (Scheme 4) with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) in either refluxing toluene or xylenes afforded the corresponding thiono esters **21** and **22**.[28]

As shown in Scheme 5, hydrolysis of benzophenone **37** in methanol with potassium hydroxide as the base yielded 3,3′-dichloro-4,4′-dimethoxy-5,5′-dicarboxybenzophenone (**38**). Treatment of **38** with thionyl chloride

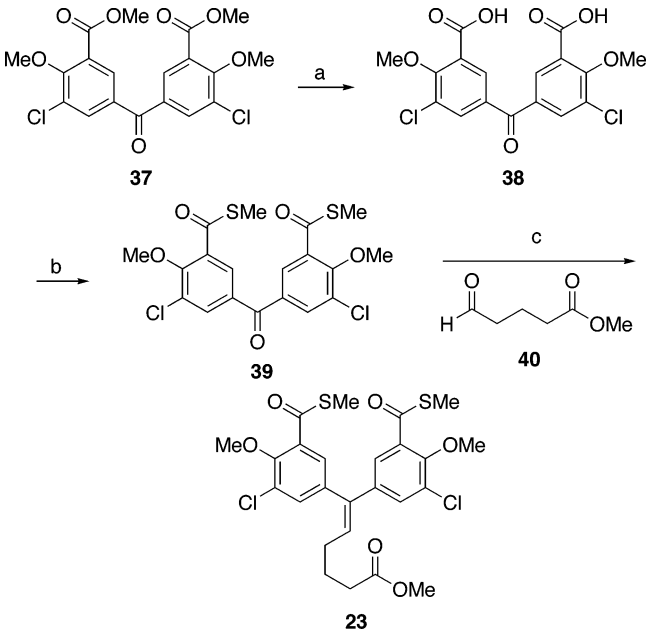
Scheme 4[a]



2 **22**

[a] Reagents and conditions: (a) 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, xylenes, reflux 48 h.

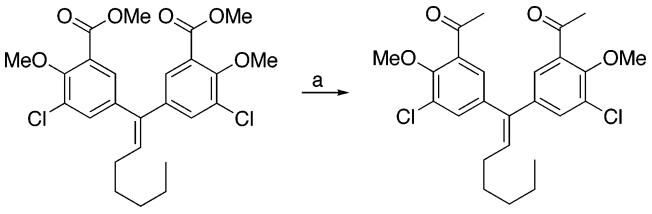
Scheme 5[a]



37 **38** **39** **40** **23**

[a] Reagents and conditions: (a) KOH, MeOH, reflux, 24 h; (b) (1) $SOCl_2$, reflux, 8 h; (2) NaSMe, benzene, ambient temperature, 5 h; (c) (1) $TiCl_4$·2THF, Zn^0, THF, reflux 2 h, (2) methyl 5-oxopentanoate (**40**) and **39**, THF, reflux 1.5 h.

Scheme 6[a]



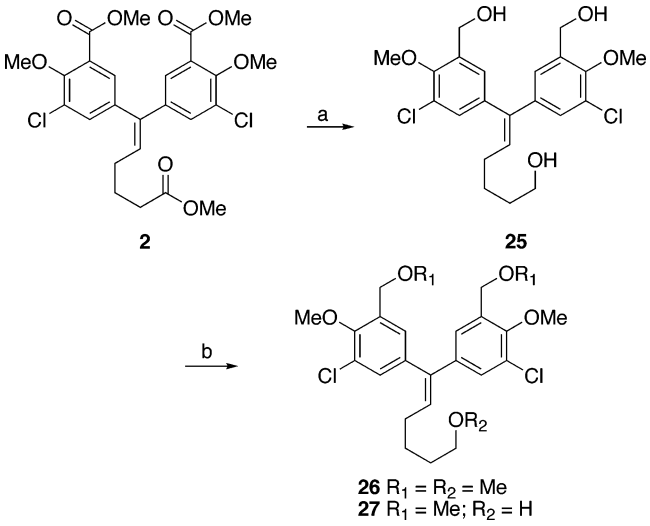
36 **24**

[a] Reagents and conditions: (a) [μ-chloro-μ-methylene[bis(cyclopentadienyl)titanium]dimethylaluminum], THF, 0 °C−ambient temperature, 24 h.

and subsequent reaction with sodium thiomethoxide yielded the thioester **39**. McMurry coupling of benzophenone **39** with methyl 5-oxopentanoate (**40**) afforded alkenyldiarylmethane **23**. Benzophenone **37**[29] and methyl 5-oxopentanoate (**40**)[30] were synthesized as previously reported.

Alkenyldiarylmethane **24** (Scheme 6) was synthesized by treating alkenyldiarylmethane **36**[19] with [μ-chloro-μ-methylene[bis(cyclopentadienyl)titanium]dimethylaluminum] (Tebbe reagent). The conversion of a lactone to a hydroxylated methyl ketone with Tebbe reagent has recently been reported.[31]

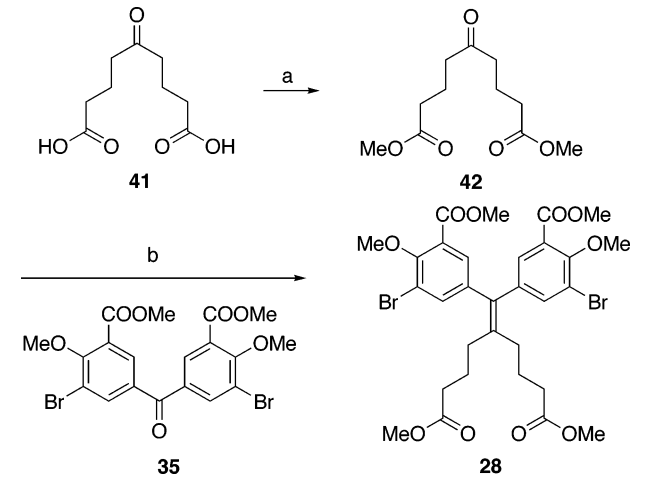
Scheme 7[a]



2 **25** **26** $R_1 = R_2 = Me$ **27** $R_1 = Me$; $R_2 = H$

[a] Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, −78 °C, 3 h; (b) CH_3I, NaH, THF, 0 °C−ambient temperature, 24 h.

Scheme 8[a]



41 **42** **35** **28**

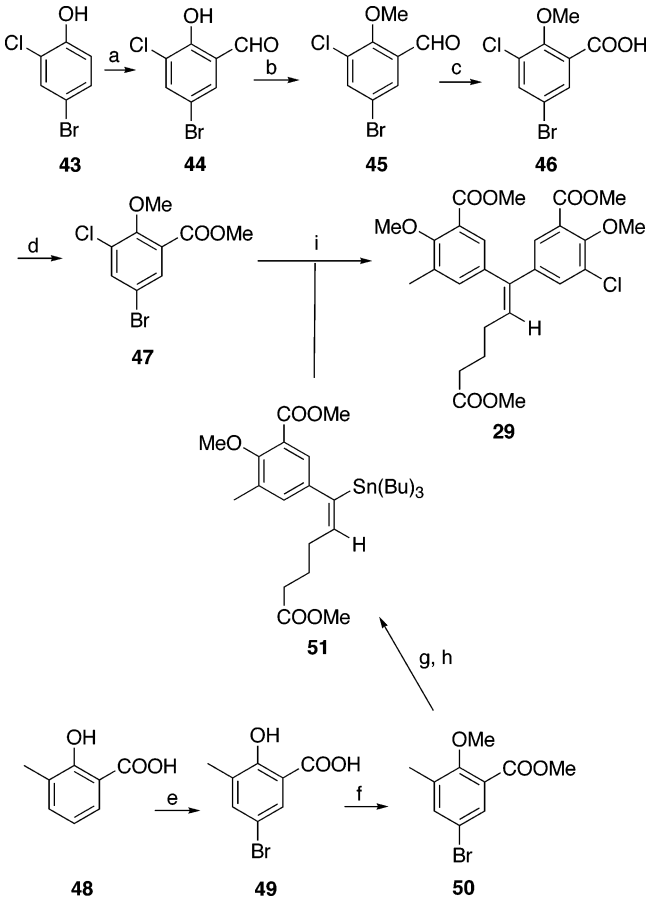
[a] Reagents and conditions: (a) CH_3I, DMF, K_2CO_3, ambient temperature, 24 h; (b) (1) $TiCl_4$·2THF, Zn^0, THF, reflux 2.5 h, (2) **35** and **42**, THF, reflux 1.5 h.

Reduction of ADAM analogue **2** using diisobutylaluminum hydride in dichloromethane yielded alkenyldiarylmethane **25** (Scheme 7). *O*-Alkylation of alkenyldiarylmethane **25** with iodomethane in tetrahydrofuran, using sodium hydride as a base, afforded ADAM analogues **26** and **27**, which were separated by column chromatography. ADAM **26** is an analogue of the active triester **2** in which the three ester carbonyls are replaced by methylene groups.

As shown in Scheme 8, dimethyl 5-oxononanedioate (**42**) was synthesized via *O*-alkylation of 5-oxoazelaic acid (**41**) with methyl iodide in *N*,*N*-dimethylformamide, using potassium carbonate as a base. McMurry coupling of benzophenone **35** with dimethyl 5-oxononanedioate (**42**)[19] afforded ADAM analogue **28**, having two ester side chains instead of the usual single side chain.

The stereoselective synthesis of ADAM **29**, having nonidentical aromatic substituents, is outlined in Scheme 9. The synthesis relies on the Stille reaction of the aromatic bromide **47** with the tributyltin derivative **51**.[24,25] Formylation of 4-bromo-2-chlorophenol (**43**) with hexamethylenetetramine (HMT) using conditions for the

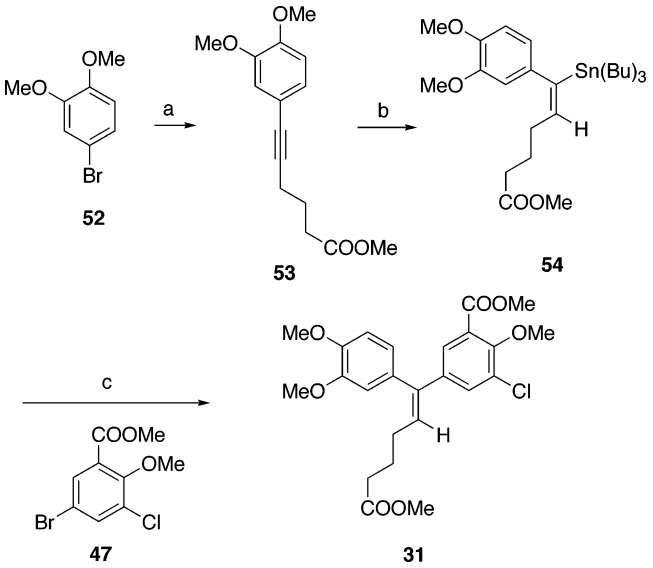
Scheme 9[a]



[a] Reagents and conditions: (a) HMT, TFA, 90 °C, 20 h; (b) CH_3I, DMF, K_2CO_3, ambient temperature, 22 h; (c) $KMnO_4$, acetone, water, 0 °C−ambient temperature, 24 h; (d) CH_3I, DMF, K_2CO_3, ambient temperature, 24 h; (e) bromine, acetic acid, ambient temperature, 24 h; (f) CH_3I, DMF, K_2CO_3, ambient temperature, 26 h; (g) methyl 5-hexynoate, CuI, TEA, $(PPh_3)_2PdCl_2$, reflux, 24 h; (h) Bu_3SnH, $(PPh_3)_4Pd$, THF, ambient temperature, 1.5 h; (i) **47**, $Pd_2(dba)_3$, $As(Ph)_3$, CsF, THF, reflux, 24 h.

Duff reaction yielded the expected aldehyde **44**. *O*-Alkylation of intermediate **44** with methyl iodide in *N*,*N*-dimethylformamide, utilizing potassium carbonate as the base, afforded 5-bromo-3-chloro-2-methoxybenzaldehyde (**45**). The corresponding acid **46** was synthesized by oxidation of **45** using potassium permanganate in acetone. *O*-Alkylation of the carboxylic acid **46** with methyl iodide in *N*,*N*-dimethylformamide, utilizing potassium carbonate as the base, provided methyl 5-bromo-3-chloro-2-methoxybenzoate (**47**). To make the organotin intermediate **51**, 3-methylsalicylic acid **(48)** was brominated to yield **49**. Methyl 5-bromo-2-methoxy-3-methylbenzoate (**50**) was synthesized by *O*-alkylation of intermediate **49** with methyl iodide in *N*,*N*-dimethylformamide, utilizing potassium carbonate as the base. Sonagashira coupling of methyl 5-hexynoate with methyl 5-bromo-2-methoxy-3-methylbenzoate (**50**), followed by hydrostannation with tributyltin hydride, yielded vinyl stannane **51**.[24,25] Stille coupling of methyl 5-bromo-3-chloro-2-methoxybenzoate (**47**) with vinyl stannane **51** afforded alkenyldiarylmethane **29**. The *E* stereochemistry of the alkene **29** results from the regiochemically defined cis addition to the alkyne intermediate during the hydrostannation reaction to afford **51** and the retention of the stereochemical integrity of the coupling partners during the Stille reaction.[24,25,32,33]

Scheme 10[a]



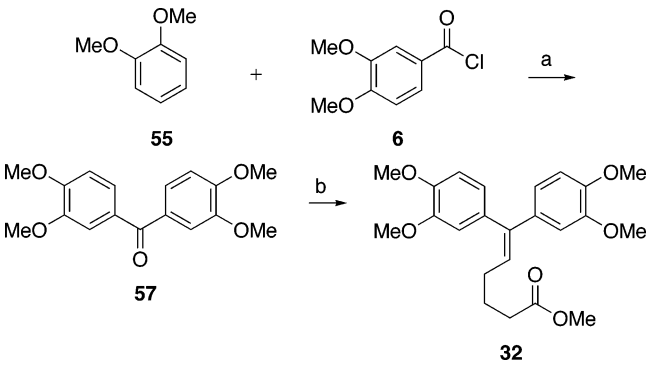
[a] Reagents and conditions: (a) methyl 5-hexynoate, CuI, TEA, $(PPh_3)_2PdCl_2$, reflux, 8 h; (b) Bu_3SnH, $(PPh_3)_4Pd$, THF, ambient temperature, 2 h; (c) **47**, $Pd_2(dba)_3$, $As(Ph)_3$, CsF, THF, reflux, 24 h.

The Stille approach was also employed for the synthesis of ADAM **31** having nonidentical aromatic rings (Scheme 10). Sonagashira coupling of methyl 5-hexynoate with 4-bromoveratrole (**52**) yielded intermediate **53**. Vinyl stannane **54** was synthesized by hydrostannation of intermediate **53** with tributyltin hydride in the presence of tetrakis(triphenylphosphine)palladium-(0). Stille coupling of methyl 5-bromo-3-chloro-2-methoxy-3-benzoate (**47**) with vinyl stannane **54** afforded alkenyldiarylmethane **31**.

As outlined in Scheme 11, Friedel−Crafts acylation of veratrole (**55**) with 3,4-dimethoxybenzoyl chloride (**57**), utilizing aluminum chloride in dichloromethane as a catalyst, yielded benzophenone **57**. McMurry coupling of benzophenone **57** with methyl 5-oxopentanoate (**40**) yielded alkenyldiarylmethane **32**.

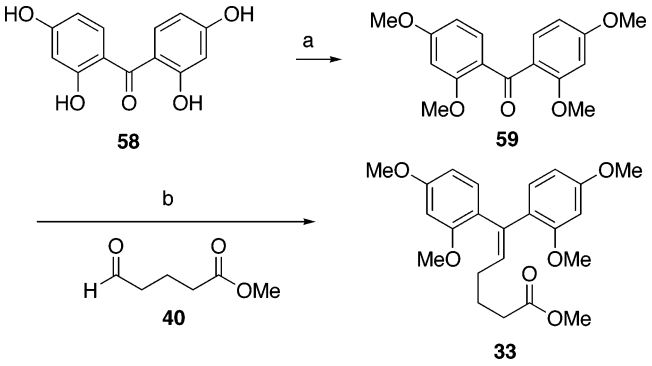
Benzophenone **59** was synthesized via *O*-alkylation of commercially available 2,2′,4,4′-tetrahydroxybenzophenone (**58**) with methyl iodide in *N*,*N*-dimethylformamide, using potassium carbonate as the base

Scheme 11[a]



[a] Reagents and conditions: (a) veratrole (**55**) and 2,4-dimethoxybenzoyl chloride (**56**), $AlCl_3$, CH_2Cl_2, reflux, 2 h; (b) (1) $TiCl_4$·2THF, Zn^0, THF, reflux 2.5 h, (2) methyl 5-oxopentanoate (**40**) and **57**, THF, reflux 2 h.

Scheme 12[a]



[a] Reagents and conditions: (a) CH_3I, DMF, K_2CO_3, ambient temperature, 24 h; (b) (1) $TiCl_4$·2THF, Zn^0, THF, reflux 2.5 h, (2) methyl 5-oxopentanoate (**40**) and **59**, THF, reflux 1 h.

(Scheme 12). McMurry coupling of benzophenone **59** with methyl 5-oxopentanoate (**40**) afforded alkenyldiarylmethane **33**.

Biological Results and Discussion

The goal of the present study was to investigate structural modifications that could reasonably be expected to enhance the metabolic stability of the ADAMs while maintaining their anti-HIV activity. Accordingly, the ADAMs of the present series were tested for inhibition of the cytopathic effects of both HIV-1_{IIIB} and HIV-2_{ROD} in MT-4 cells, and the resulting EC_{50} values are listed in Table 1, along with their cytotoxicities (CC_{50} values) in uninfected MT-4 cells. In addition, the metabolic stabilities of the biologically active ADAMs were investigated in rat plasma, and the resulting half-lives of the compounds are also listed in Table 1.

The data in the table indicate that, in general, a wide variety of structural modifications can be made without a large decrease in activity. Of the 32 compounds tested, 18 displayed EC_{50} values versus HIV-1_{IIIB} between 0.3 and 3.7 μM. Of the remaining compounds, three had intermediate EC_{50} values from 13.2 to 35.4 μM, and the rest were inactive. With the exception of the methyl thioester **23** (EC_{50} = 1.8 μM), all of the compounds in the more active range (0.3−3.7 μM) possess methyl ester substituents meta to the bridging carbon atom on each aromatic ring. Also, except for compound **16** (EC_{50} = 3.7 μM), which had ethyl ether substituents, all of the more active compounds had methyl ether substituents at the para position of each aromatic ring. Compound **18** (EC_{50} = 14.4 μM), having both ethyl ester and ethyl ether substituents, had intermediate activity, whereas compounds **17** and **19**, with propyl ether or both propyl ether and propyl ester substituents, were inactive, documenting an apparent steric limitation on biological activity. The inactive compound **26**, in which the three ester carbonyls of **2** were replaced by methylene groups, revealed a critical role played by the ester carbonyls on the antiviral activity of the ADAMs. Replacement of the three ester groups of **2** with thiono esters in **22** decreased the potency from an EC_{50} of 0.6 to 35.4 μM. On the other hand, the replacement of the two aromatic methyl ester groups of **2** with the methyl thioester groups of **23** only decreased the potency from an EC_{50} of 0.6 to 1.8 μM. Compound **24**, with two methyl ketones, was totally inactive, even though the corresponding compound with two methyl ester groups is active.[19] Other previously reported inactive replacements for the aromatic methyl esters of various compounds in the ADAM series include carboxylic acids,[20] primary, secondary, and tertiary amides,[19,20] alcohols,[22] and aldehydes.[22]

Table 1. Anti-HIV Activities, Cytotoxicities, and Metabolic Stabilities of ADAM Analogues

compd	HIV-1_{IIIB} EC_{50}[a] (μM ± SD)	HIV-2_{ROD} EC_{50}[a] (μM ± SD)	HIV-1_{IIIB} CC_{50}[b] (μM ± SD)	rat plasma $t_{1/2}$[c] (min ± SD)
1	0.3 ± 0.1	NA[d]	91 ± 31	6.2 ± 0.4
2	0.6 ± 0.1	25.0 ± 9.5	160 ± 25	5.8 ± 0.9
3	1.0 ± 0.2	NA[d]	6.1 ± 0.4	42.9 ± 4.0
4	0.8 ± 0.1	NA[d]	>247	12.4 ± 0.7
5	0.7 ± 0.2	NA[d]	57.8 ± 16.1	18.9 ± 1.6
6	1.1 ± 0.5	NA[d]	143 ± 32	20.6 ± 2.6
7	3.0 ± 0.1	NA[d]	62.3 ± 4.0	58.5 ± 4.9
8	3.7 ± 0.1	26.4 ± 14.0	>253	39.3 ± 0.7
9	2.6 ± 0.4	29.3 ± 10.5	>198	55.0 ± 5.6
10	13.2 ± 2.7	113 ± 121	>230	76.6 ± 3.8
11	2.2 ± 0.0	NA[d]	113.9 ± 11.2	3.4 ± 0.2
12	3.1 ± 0.4	NA[d]	159.2 ± 45.5	7.4 ± 1.0
13	3.5 ± 0.0	NA[d]	93.4 ± 36.8	5.2 ± 0.1
14	2.7 ± 0.1	NA[d]	35.3 ± 6.8	5.7 ± 0.3
15	3.5 ± 0.1	NA[e]	59.5 ± 25.5	1.7 ± 1.6
16	3.7 ± 1.4	NA[d]	73 ± 27	9.0 ± 0.4
17	NA[d]	NA[d]	>231	NT[e]
18	14.1 ± 5.5	NA[d]	>231	37.7 ± 3.7
19	NA[d]	NA[d]	>209	NT[e]
20	2.8 ± 0.3	NA[d]	28.6 ± 4.0	35.1
21	NA[d]	NA[d]	180.6 ± 47.5	NT[e]
22	35.4 ± 1.9	NA[d]	>218	NT[e]
23	1.8 ± 0.7	NA[d]	>224	55.3 ± 5.1
24	NA[d]	NA[d]	47.1 ± 6.4	NT[e]
25	NA[d]	NA[d]	30.7 ± 0.3	NT[e]
26	NA[d]	NA[d]	34.0 ± 2.6	NT[e]
28	NA[d]	NA[d]	78.1 ± 3.5	NT[e]
29	0.8 ± 0.5	NA[d]	19.1 ± 6.1	9.0 ± 0.7
30	NA[d]	NA[d]	0.25 ± 0.07	19.2 ± 1.6
31	NA[e]	NA[d]	8.7 ± 0.9	NT[e]
32	NA[d]	NA[d]	7.4 ± 0.9	0.9 ± 0.01
33	NA[d]	NA[d]	5.9 ± 0.2	2.6 ± 0.3

[a] EC_{50} is the 50% inhibitory concentration for inhibition of cytopathicity of HIV-1_{IIIB} or HIV-1_{ROD} in MT-4 cells. [b] CC_{50} is the 50% cytotoxic concentration in mock-infected MT-4 cells. [c] $t_{1/2}$ is the half-life in rat plasma. [d] Not active. [e] Not tested.

Although the new ADAMs in the present series of compounds were not tested for enzyme inhibitory activity versus isolated RT, one can assume on the basis of prior studies that the new compounds are probably acting as RT inhibitors. The prior evidence includes inhibition of isolated RT, the presence of resistance mutations located in RT, time of addition studies, and inactivity or low activity in a wide range of antiviral assays against targets representing other mechanisms of action.[19,20,22,23] In addition, as observed in the present study, the new ADAMs were much more potent versus HIV-1 than versus HIV-2, which is a hallmark of the NNRTIs.

The design of the potential NNRTIs described in this study was aided through molecular modeling of their complexes formed with HIV-1 RT. The hypothetical models were constructed using Sybyl (Tripos, Inc., version 6.9, 2002). The X-ray crystal structure of HIV-1 RT complexed with nevirapine (1VRT)[34] was utilized as a starting point. The structures of the potential NNRTIs were overlapped with the ligand, which was then deleted, and the energies of the new complexes minimized using the MMFF94s force field and MMFF94

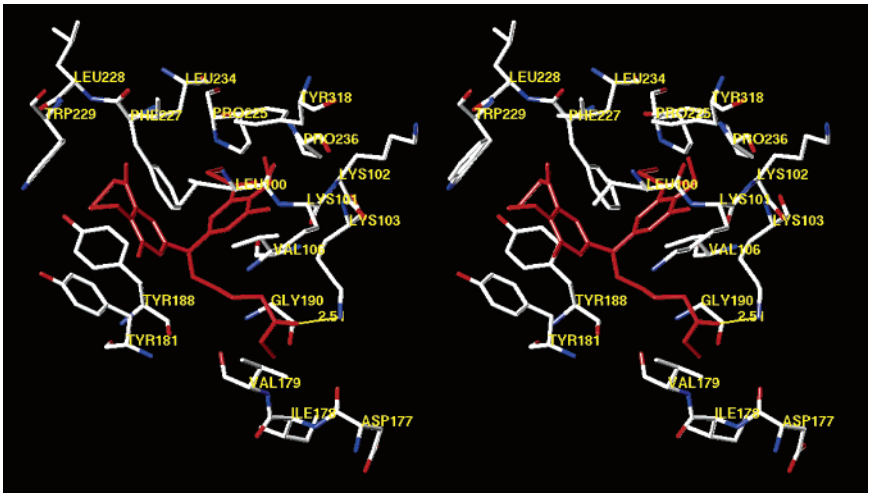


Figure 1. Hypothetical model of the ADAM **23** docket in the NNRTI binding site of HIV-1 reverse transcriptase. The ligand is displayed in red. The figure is programmed for walleyed viewing.

charges. During energy minimization, the structure of the ligand and a 6 Å sphere surrounding the ligand were allowed to move, whereas the protein was maintained either semirigid (12 Å sphere) or frozen. Figure 1 displays a model derived from ADAM **23**, which is very similar to the previously published molecular models derived from several of the other ADAMs.[20,22,23] In the present case, one can conclude that the NNRTI binding pocket can readily accommodate the increased size of the sulfurs in **23** relative to the corresponding ester oxygens of **1** or **2**.[20,22,23] Previous molecular modeling studies with ADAM **1** have indicated the possibility for either bifurcated hydrogen bonding between the side chain ester carbonyl of the ligand, the terminal amino group of Lys103, and the backbone amide N−H of Lys101[22] or hydrogen bonding to the backbone amide N−H of Lys101 only.[23] In the present case, the model displays a hydrogen bond from the side-chain ester carbonyl and Lys103 only, and this may result from displacement of the side chain more in the direction of Lys103 resulting from the larger steric bulk of a thioester group in **23** versus an ester group in **1**. However, the general features of the model derived from **23** are similar to those seen with **1**, and the two have the general "butterfly shape" seen in the X-ray crystal structures of nevirapine and a number of other NNRTIs.[35,36]

With regard to stability in blood plasma, the ester groups of the ADAMs are a potential source of instability. However, prior antiviral testing of ADAM **2** was performed in the presence of fetal calf serum (FCS), and various tests with the compound in different levels of FCS or time in FCS did not reveal any decrease in activity that would result from metabolism.[20] These results seemed to suggest that hydrolysis of **2** by nonspecific esterases present in FCS is unlikely under the assay conditions.[20] In contrast, the present investigation has revealed that there is a wide range of stabilities in rat plasma. First-order disappearance of the ADAMs was observed, with half-lives spanning from 0.9 min (compound **32**) to 76.6 min (compound **10**). The most stable of the more active compounds is the bis(thioester) **23**, which has an EC_{50} of 1.8 μM and a plasma half-life of 55.3 min. In addition, compound **3** (EC_{50} = 1.0 μM), having methyl substituents in the meta position of each aromatic ring, was considerably more stable metabolically (half-life = 42.9 min) than the corresponding dibromo compound **1** (half-life = 6.2 min), the dichloro compound **2** (half-life = 5.8 min), or the dicyano compound **4** (half-life = 12.4 min). However, the replacement of the two bromine atoms of **1** or the two chlorine atoms of **2** with the two methyl groups of **3** results in greater cytotoxicity in uninfected MT-4 cells (CC_{50} = 6.1 μM). This trend is also present in the methyl-chloro compound **29** (CC_{50} = 19.1 μM) versus the dichloro compound **2** (CC_{50} = 160 μM). The increased cytotoxicity of these methylated compounds does not seem to result from the methyl groups per se, because the effect was not seen in the **11**−**13** series or with **14** versus **15**.

The replacement of the terminal methyl ester of the side chain with the more hindered propyl esters in **11** and **12**, or with isopropyl esters in **13**−**15**, did not result in an increase in metabolic stability. On the other hand, replacement with the alkyne, alkene, and phenyl substituents in the **5**−**10** series did increase the half-life in rat blood plasma significantly (see Table 1). Furthermore, with the exception of compound **10**, these latter substitutions did not cause a large decrease in antiviral activity when tested versus HIV-1_{IIIB} in MT-4 cells.

Some of the results seemed counterintuitive from the purely chemical point of view. For example, on the basis of the number of metabolically unstable ester groups per molecule, one might have expected the triester **3** (half-life = 49.2 min) to be less stable than the corresponding monoester **32** (half-life = 0.9 min), but the observed order was the reverse of the expected order. Moreover, relatively small structural changes at the end of the alkenyl side chain were discovered to have a significant effect on stability. For example, the alkyne **5** had a half-life of 18.9 min, whereas the corresponding alkene **7** had a half-life of 58.8 min. A similar trend of lesser magnitude was observed with the corresponding chloro compounds, the alkyne **6** (half-life = 20.6 min) and the alkene **8** (half-life = 39.3 min). These results would be difficult to rationalize solely on the basis of the relative stabilities of the esters to simple chemical (nonenzymatic) hydrolysis, and they indicate that remote structural changes can affect the propensities of the esters to undergo enzymatic hydrolysis. Obviously,

although the esterases present in plasma are relatively nonspecific, the rates of ester hydrolysis depend largely on the overall structure of the substrate.

In summary, the structural modifications introduced in the present series of ADAMs result in some favorable properties, including a decrease in cytotoxicity and an increase in metabolic stability. In particular, the thioester **23** displays enhanced stability ($t_{1/2}$ = 55.3 min) and diminished cytotoxicity (CC_{50} > 224 μM) while maintaining reasonable potency (EC_{50} = 1.8 μM) relative to the corresponding dichloro ADAM **2**.

Experimental Section

^{1}H NMR spectra were recorded on an ARX300 300 MHz or a DRX500 500 MHz Bruker NMR spectrometer. IR spectra were obtained using a Perkin-Elmer 1600 series FTIR or a Perkin-Elmer Spectrum One spectrometer. IR spectra of neat solid compounds were obtained with a single reflection horizontal attenuated total reflectance (HATR) device (Pike Technologies, Inc., Madison, WI). Flash chromatography was performed with 230−400 mesh silica gel. Thin-layer chromatography was performed using Baker-flex silica gel IB2-F plates of a 2.5 mm thickness. Melting points were taken in capillary tubes on a Mel-Temp or Thomas-Hoover apparatus and are uncorrected. Unless otherwise stated, chemicals and solvents were of reagent grade and used as obtained from commercial sources without further purification. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone ketyl radical prior to use. Dichloromethane was freshly distilled from calcium hydride prior to use. Microanalyses were performed at the Purdue University Microanalysis Laboratory.

Methyl 3′,3″-Dicyano-4′,4″-dimethoxy-5′,5″-dimethoxycarbonyl-6,6-diphenyl-5-hexenoate (4). Methyl 3′,3″-dibromo-4′,4″-dimethoxy-5′,5″-dimethoxycarbonyl-6,6-diphenyl-5-hexenoate (**1**) (0.31 g, 0.50 mmol) was added to an oven-dried 10 mL round-bottom flask, under an argon atmosphere, equipped with a condenser and a magnetic stir bar. The solid was then dissolved in *N*,*N*-dimethylformamide (4 mL). Cuprous cyanide (0.24 g, 2.7 mmol) was added to the flask. The reaction mixture was heated at reflux for 22 h. The reaction solution was then cooled to ambient temperature, and both water (100 mL) and ethyl acetate (100 mL) were added. The solution was then filtered on a Büchner funnel, and the inorganic salts were washed with ethyl acetate. The filtrate was poured into a separatory funnel, and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were then washed with brine (2 × 100 mL) and dried over anhydrous magnesium sulfate. The organic extracts were filtered, and the solvent was removed in vacuo to yield a crude green oil. The crude oil was purified by flash column chromatography using silica gel (25 g, 2 × 18 cm) and eluted with a gradient eluant from 0 to 45% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a colorless oil (0.04 g, 19%): IR (film) 2952, 2232, 1733, 1479, 1436, 1258, 993 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 2.35 Hz, 1 H), 7.76 (d, J = 2.10 Hz, 1 H), 7.51 (d, J = 2.23 Hz, 1 H), 7.43 (d, J = 2.37 Hz, 1 H), 6.14 (t, J = 7.51 Hz, 1 H), 4.16 (s, 3 H), 4.09 (s, 3 H), 3.96 (s, 3 H), 3.95 (s, 3 H), 3.66 (s, 3 H), 2.33 (t, J = 7.23 Hz, 2 H), 2.15 (q, J = 7.41 Hz, 2 H), 1.81 (qn, J = 7.34 Hz, 2 H); CIMS, *m*/*z* (relative intensity) 507 (100, MH^+). Anal. ($C_{27}H_{26}N_2O_8$) C, H, N.

1,1-Bis[3-bromo-4-dimethoxy-5-dimethoxycarbonylphenyl]-6-methoxyhexene (20). Methyl 5-methoxypentanoate (**34**)[27] (1.86 g, 12.8 mmol) was added to a flame-dried 50 mL round-bottom flask equipped with a stirring bar and rubber septum. An inert argon atmosphere was introduced into the flask. Dry dichloromethane (25 mL) was then added to the flask via syringe. The flask was cooled to −78 °C in a dry ice acetone bath. A 1.0 M solution of diisobutylaluminum hydride (DIBAL-H) in dichloromethane (12.9 mL, 12.9 mmol) was added to the flask dropwise via syringe. The reaction solution was then stirred at −78 °C for an additional 2 h. The reaction solution was quenched with ice-cold 1 M HCl (50 mL). This solution was poured into a separatory funnel, and dichloromethane (100 mL) was added. The aqueous and organic layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The organic extracts were dried over anhydrous sodium sulfate. The combined organic layer was filtered and solvent removed in vacuo to yield a crude colorless oil. The crude oil was then dissolved in dry THF (20 mL) and added to a flame-dried 50 mL pear-shape flask. 3′,3″-Dibromo-4′,4″-dimethoxy-5′,5″-dimethoxycarbonylbenzophenone (**35**) (0.27 g, 0.5 mmol) was added to the flask under an argon atmosphere. Titanium tetrachloride bis(tetrahydrofuranate) (1.24 g, 3.7 mmol) was added to a flame-dried two-neck 100 mL flask, under an argon atmosphere, equipped with a condenser, magnetic stir bar, and a rubber septum. Zinc dust (0.45 g, 6.9 mmol) was then added to the flask. The solids were suspended in dry THF (20 mL). The suspension was heated at reflux for 3 h. The solution in the pear-shape flask was transferred via cannula under an argon atmosphere to the titanium suspension. The resulting suspension was heated at reflux for 3.5 h. The suspension was then cooled to ambient temperature, and 1 M HCl (50 mL) was added. The reaction mixture was stirred at ambient temperature for 15 min. The reaction mixture was then poured into a separatory funnel, and both water (100 mL) and ethyl acetate (100 mL) were added. The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (100 mL) and dried over anhydrous sodium sulfate. Solvents were removed in vacuo yielding a brown oil. The crude oil was separated by flash column chromatography using silica gel (50 g, 2 × 30 cm) and a gradient eluant from 0 to 20% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a crude red-brown oil. The crude oil was purified again using silica gel (12 g, 2 × 10 cm) and a gradient eluant of 0−10% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a crude red oil. This crude oil was further purified using silica gel (5 g, 1 × 12 cm) and a gradient eluant of 0−14% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a colorless oil (0.076 g, 24%): IR (film) 2933, 2858, 1732, 1473, 1434, 1281, 1260, 1206, 1088, 998, 729 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 2.28 Hz, 1 H), 7.52 (d, J = 1.6 Hz, 1 H), 7.49 (d, J = 2.18 Hz, 1 H), 7.47 (d, J = 2.35 Hz, 1 H), 6.05 (t, J = 7.47 Hz, 1 H), 3.99 (s, 3 H), 3.92 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.33 (t, J = 2.59 Hz, 2 H), 3.31 (s, 3 H), 2.12 (q, J = 7.35 Hz, 2 H), 1.63−1.41 (m, 4 H); CIMS, *m*/*z* (relative intensity) 599/601/603 (75/100/50, MH^+), 567/569/571 (46/74/34, MH^+ − MeOH). Anal. ($C_{25}H_{28}Br_2O_7$) C, H.

3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-dimethoxythiocarbonyl-1,1-diphenyl-1-heptene (21). 3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-dimethoxcarbonyl-1,1-diphenyl-1-heptene (**36**) (0.40 g, 0.8 mmol) was added to an oven-dried 10 mL round-bottom flask, under an argon atmosphere, equipped with a condenser and a magnetic stir bar. Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide; 2.63 g, 6.5 mmol] was then added to the flask. The solids were suspended in toluene (5 mL). The suspension was heated at reflux for 96 h. The suspension was then cooled to ambient temperature, and the contents of the round-bottom flask were filtered on a Büchner funnel. The filter cake was washed with hexane (100 mL) and benzene (100 mL). The filtrate was then collected, and solvent was removed in vacuo to yield a crude oil. The crude oil was purified by flash column chromatography using silica gel (25 g, 2 × 19 cm) and a gradient eluant from 0 to 9% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a yellow oil (0.040 g, 10%): IR (film) 2932, 2361, 2341, 1473, 1244, 998 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 2.11 Hz, 1 H), 7.39 (d, J = 1.85 Hz, 1 H), 7.24 (d, J = 1.88 Hz, 1 H), 7.20 (d, J = 2.05 Hz, 1 H), 6.06 (t, J = 7.53 Hz, 1 H), 4.31 (s, 3 H), 4.29 (s, 3 H), 3.95 (s, 3 H), 3.89 (s, 3 H), 2.11 (q, J = 7.44 Hz, 2 H), 1.46 (m,

2 H), 1.31−1.26 (m, 4 H), 0.89 (t, J = 6.69 Hz, 3 H); ESIMS, m/z (relative intensity) 527/529 (100/75, MH^+). Anal. ($C_{25}H_{28}Cl_2O_4S_2$) C, H, S.

Methyl 3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-dimethoxythiocarbonyl-6,6-diphenyl-5-hexene-1-methoxythione (22). Methyl 3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-dimethoxcarbonyl-6,6-diphenyl-5-hexenoate (**2**) (0.42 g, 0.8 mmol) was added to an oven-dried 25 mL round-bottom flask, under an argon atmosphere, equipped with a condenser and a magnetic stir bar. Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide; 2.10 g, 5.2 mmol] was then added to the flask. The solids were suspended in xylene (10 mL). The suspension was heated at reflux for 48 h. The suspension was then cooled to ambient temperature, and both hexanes (20 mL) and water (20 mL) were added. The contents of the round-bottom flask were added to a beaker. The round-bottom flask was rinsed with toluene (20 mL), and this was added to the beaker. The contents of the beaker were filtered on a Büchner funnel. The filter cake was washed with hexane (100 mL) and toluene (100 mL). The filtrate was collected and solvent removed in vacuo, yielding a crude oily solid. The crude solid was purified by flash column chromatography using silica gel (25 g, 2 × 24 cm) and eluted with a gradient eluant from 0 to 10% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a yellow oil (0.200 g, 43%): IR (film) 2939, 1592, 1550, 1474, 1439, 1244, 997, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 2.27 Hz, 1 H), 7.35 (d, J = 2.11 Hz, 1 H), 7.20 (d, J = 2.14 Hz, 1 H), 7.17 (d, J = 2.25 Hz, 1 H), 6.02 (t, J = 7.49 Hz, 1 H), 4.28 (s, 3 H), 4.26 (s, 3 H), 4.02 (s, 3 H), 3.92 (s, 3 H), 3.85 (s, 3 H), 2.73 (t, J = 7.42 Hz, 2 H), 2.15 (q, J = 7.31 Hz, 2 H), 1.89 (qn, J = 7.42 Hz, 2 H); CIMS, m/z (relative intensity) 573/575/577 (100/79/13, MH^+). Anal. ($C_{25}H_{26}Cl_2O_5S_3$) C, H.

Methyl 5′,5″-Dichloro-4′,4″-dimethoxy-3′,3″-di(methylthiocarbonyl)-6,6-diphenyl-5-hexenoate (23). Titanium tetrachloride bis(tetrahydrofuranate) (1.56 g, 4.7 mmol) was added to a dry 100 mL two-neck flask, under an argon atmosphere, equipped with a condenser, magnetic stir bar, and a rubber septum. Zinc dust (0.650 g, 10.0 mmol) was then added to the flask. The solids were suspended in dry THF (15 mL). The suspension was heated at reflux for 2 h. A solution of 3,3′-dichloro-4,4′-dimethoxy-5,5′-di(methylthiocarbonyl)benzophenone (**39**) (0.78 g, 1.6 mmol) and methyl 5-oxopentanoate (**40**) (0.436 g, 3.3 mmol) in dry THF (15 mL) was transferred via cannula under an argon atmosphere to the titanium suspension. The resulting suspension was heated at reflux for 1.5 h. The suspension was cooled to ambient temperature, and 1 M HCl (50 mL) was added. The reaction mixture was poured into a separatory funnel, and ethyl acetate (100 mL) and water (100 mL) were added. The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (100 mL) and dried over anhydrous sodium sulfate. Solvents were removed in vacuo, yielding a yellow oil. The crude oil was purified by flash column chromatography using silica gel (50 g, 2 × 34 cm) and eluted with a gradient eluant from 0 to 15% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a colorless oil (0.196 g, 21%): IR (film) 2929, 1736, 1674, 1643, 1473, 1423, 1248, 1136, 992, 882, 780, 747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 2.37 Hz, 1 H), 7.25 (d, J = 2.12 Hz, 1 H), 7.13 (d, J = 2.18 Hz, 1 H), 7.12 (d, J = 2.12 Hz, 1 H), 5.89 (t, J = 7.65 Hz, 1 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.48 (s, 3 H), 2.29 (s, 3 H), 2.28 (s, 3 H), 2.15 (t, J = 7.34 Hz, 2 H), 1.99 (q, J = 7.25 Hz, 2 H), 1.63 (qn, J = 7.37 Hz, 2 H); CIMS, m/z (relative intensity) 509/511/513 (100/75/9, MH^+ − SMe). Anal. ($C_{25}H_{26}Cl_2O_6S_2$) C, H, S.

3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-dimethylcarbonyl-1,1-diphenyl-1-heptene (24). 3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-dimethoxcarbonyl-1,1-diphenyl-1-heptene (**36**) (0.41 g, 0.8 mmol) was added to an oven-dried 50 mL round-bottom flask, under an argon atmosphere, equipped with a condenser and a magnetic stir bar. The solid was dissolved in dry THF (5 mL). The reaction mixture was then cooled to 0 °C using an ice bath, and [μ-chloro-μ-methylene[bis(cyclopentadienyl)-titanium]dimethylaluminum] (Tebbe reagent) (0.5 M) (3.3 mL, 1.7 mmol) was added to the flask dropwise via syringe. The reaction mixture was stirred and allowed to warm to ambient temperature for 24 h. The reaction mixture was then cooled to 0 °C using an ice bath, and ether (30 mL) was added to the round-bottom flask. Ten drops of NaOH (0.1 M) were slowly added over a 10 min period to quench the reaction. Anhydrous sodium sulfate was added, and the contents of the flask were stirred for an additional 10 min. The reaction mixture was then filtered over a pad of Celite on a Büchner funnel. The filter cake was washed with ether (100 mL). The filtrate was then added to a separatory funnel, and water (100 mL) was added. The aqueous layer was extracted with ether (3 × 100 mL). The combined extracts were then dried over anhydrous sodium sulfate. The organic extracts were then filtered, and solvent was removed in vacuo to yield a crude oil. The crude oil was purified by flash column chromatography using silica gel (25 g, 3 × 14 cm) and a gradient eluant from 0 to 14% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a colorless oil (0.169 g, 44%): IR (film) 2920, 2855, 1685, 1473, 1246, 996, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 2.26 Hz, 1 H), 7.33 (d, J = 1.97 Hz, 1 H), 7.31 (d, J = 2.06 Hz, 1 H), 7.29 (d, J = 2.28 Hz, 1 H), 6.08 (t, J = 7.52 Hz, 1 H), 3.98 (s, 3 H), 3.91 (s, 3 H), 2.67 (s, 3 H), 2.64 (s, 3 H), 2.08 (q, J = 7.42 Hz, 2 H), 1.45 (m, 2 H), 1.29−1.28 (m, 4 H), 0.89 (t, J = 6.58 Hz, 3 H); ESIMS, m/z (relative intensity) 463/465 (100/83, MH^+). Anal. ($C_{25}H_{28}Cl_2O_4$) C, H.

3′,3″-Dichloro-5′,5″-dihydroxymethyl-4′,4″-dimethoxy-1,1-diphenyl-1-hexen-6-ol (25). Methyl 3′,3″-dichloro-4′,4″-dimethoxy-5′,5″-dimethoxcarbonyl-6,6-diphenyl-5-hexenoate (**2**) (0.74 g, 1.4 mmol) was added to a flame-dried 50 mL round-bottom flask, equipped with a stir bar and a rubber septum. The contents of the flask were then placed under an argon atmosphere. Dry dichloromethane (25 mL) was added to the flask via syringe. The flask and its contents were cooled to −78 °C using a dry ice acetone bath. A 1.0 M DIBAL-H solution in dichloromethane (8.5 mL, 8.5 mmol) was added dropwise to the cooled flask via a syringe, while the bath temperature was maintained at −78 °C. The reaction solution was allowed to stir at −78 °C for an additional 3 h. The reaction solution was then poured over ice-cold 1 M HCl (25 mL). The quenched solution was placed into a separatory funnel, and both water (100 mL) and dichloromethane (100 mL) were added. The aqueous layer was extracted with dichloromethane (3 × 150 mL). The combined organic extracts were washed with brine (2 × 100 mL) and dried over anhydrous magnesium sulfate. The organic extracts were filtered, and solvent was removed in vacuo to yield a colorless oil (0.467 g, 74%): IR (film) 3343, 2935, 1476, 1430, 1405, 1230, 1002, 883 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (s, 1 H), 7.10 (s, 3 H), 6.03 (t, J = 7.54 Hz, 1 H), 4.75 (s, 2 H), 4.68 (d, J = 2.54 Hz, 2 H), 3.96 (s, 3 H), 3.91 (s, 3 H), 3.57 (t, J = 5.47 Hz, 2 H), 2.10 (q, J = 7.43 Hz, 2 H), 1.56 (qn, J = 5.73 Hz, 4 H); CIMS, m/z (relative intensity) 423/425/427 (100/62/11, $MH^+ - H_2O$). Anal. ($C_{22}H_{26}Cl_2O_5$) C, H.

3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-dimethoxymethyl-6-methoxy-1,1-diphenyl-1-hexene (26). 3′,3″-Dichloro-5′,5″-dihydroxymethyl-4′,4″-dimethoxy-1,1-diphenyl-1-hexen-6-ol (**25**) (0.16 g, 0.4 mmol) was added to a flame-dried 10 mL round-bottom flask equipped with a stir bar and a rubber septum. An inert argon atmosphere was introduced into the flask. Dry THF (5 mL) was then added to the flask via syringe. Sodium hydride (0.047 g, 2.0 mmol) was added to the flask. The flask was cooled to 0 °C in an ice bath. Iodomethane (0.070 mL, 1.1 mmol) was added to the reaction solution dropwise via syringe. The reaction solution was allowed to warm to ambient temperature for 24 h. The reaction solution was poured over ice (10 mL). Water (50 mL) was added, and the reaction solution was added to a separatory funnel, followed by the addition of ethyl acetate (50 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic extracts were dried over

anhydrous sodium sulfate. The organic layer was filtered, and solvent was removed in vacuo to yield a crude oil. The crude oil was purified by flash column chromatography using silica gel (25 g, 3 × 8 cm) and a gradient eluant from 0 to 30% ethyl acetate in hexanes. Like fractions were combined, and solvent removed in vacuo to yield a colorless oil (0.07 g, 41%): IR (film) 2933, 1478, 1376, 1232, 1119, 1100, 1001, 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 2.28 Hz, 1 H), 7.11 (d, J = 2.09 Hz, 1 H), 7.09 (d, J = 2.28 Hz, 1 H), 7.07 (d, J = 2.07 Hz, 1 H), 6.00 (t, J = 7.44 Hz, 1 H), 4.51 (s, 2 H), 4.46 (s, 2 H), 3.92 (s, 3 H), 3.86 (s, 3 H), 3.41 (s, 3 H), 3.40 (s, 3 H), 3.33 (t, J = 6.11 Hz, 2 H), 3.31 (s, 3 H), 2.11 (q, J = 7.38 Hz, 2 H), 1.62−1.44 (m, 4H); CIMS, m/z (relative intensity) 451/453 (100/80, MH^+ − MeOH). Anal. ($C_{25}H_{32}Cl_2O_5 \cdot 0.5H_2O$) C, H.

3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-dimethoxymethyl-1,1-diphenyl-1-hexen-6-ol (27). This compound (0.039 g, 22%) was obtained as a side product from the reaction to synthesize (**26**): IR (film) 3440, 2926, 1478, 1377, 1229, 1095, 1000, 875 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 2.25 Hz, 1 H), 7.11 (d, J = 2.15 Hz, 1 H), 7.10−7.09 (m, 2 H), 6.01 (t, J = 7.50 Hz, 1 H), 4.51 (s, 2 H), 4.45 (s, 2 H), 3.92 (s, 3 H), 3.86 (s, 3 H), 3.56 (t, J = 5.85 Hz, 2 H), 3.42 (s, 3 H), 3.41 (s, 3 H), 2.11 (q, J = 6.96 Hz, 2 H), 1.60−1.49 (m, 4H); CIMS, m/z (relative intensity) 437/439 (100/75, MH^+ − MeOH). Anal. ($C_{24}H_{30}Cl_2O_5$) C, H.

Dimethyl-5-[bis(3-bromo-4-methoxy-5-methoxycarbonylphenyl)methylene]nonane-1,9-dioate (28). Titanium tetrachloride bis(tetrahydrofuranate) (1.67 g, 5.00 mmol) was added to a dry 50 mL two-neck flask, under an argon atmosphere, equipped with a condenser, magnetic stir bar, and a rubber septum. Zinc dust (0.495 g, 7.57 mmol) was then added to the flask. The solids were suspended in dry THF (10 mL). The suspension was heated at reflux for 2.5 h. A solution of 5,5′-dibromo-4,4′-dimethoxy-3,3′-dimethoxycarbonylbenzophenone (**35**) (0.468 g, 0.91 mmol) and dimethyl 5-oxononanedioate (**42**) (0.217 g, 0.91 mmol) in dry THF (10 mL) was transferred via cannula under an argon atmosphere to the titanium suspension. The resulting suspension was heated at reflux for 1.5 h. The suspension was then cooled to ambient temperature, and 1 M HCl (20 mL) was added. The reaction solution was then poured into a separatory funnel, and ethyl acetate (100 mL) was added. The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (100 mL) and dried over anhydrous sodium sulfate. Solvents were removed in vacuo, yielding a yellow oil. The crude oil was purified by flash column chromatography using silica gel (40 g, 2 × 24 cm) and eluted with a gradient eluant from 0 to 30% ethyl acetate in hexanes. Like fractions were combined, and solvent removed in vacuo to yield a crude colorless oil. The crude oil was purified a second time using silica gel (50 g, 2 × 38 cm) and eluted with a gradient eluant from 0 to 25% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield another crude colorless oil. This crude oil was purified a third time using silica gel (25 g, 2 × 18 cm) and eluted with a gradient eluant from 0 to 10% acetone in dichloromethane. Like fractions were combined, and solvent was removed in vacuo to yield a crude colorless oil. The crude oil was purified one more time using silica gel (5 g, 1 × 14 cm) and eluted with a gradient eluant from 0 to 1% acetone in dichloromethane. Like fractions were combined, and solvent was removed in vacuo to yield a pure colorless oil (0.060 g, 9%): IR (film) 2951, 1732, 1471, 1435, 1259, 1202, 1089, 997 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 2.15 Hz, 2 H), 7.40 (d, J = 2.19 Hz, 2 H), 3.91 (s, 12 H), 3.60 (s, 6 H), 2.21 (t, J = 7.49 Hz, 4 H), 2.13 (t, J = 6.65 Hz, 4 H), 1.72 (qn, J = 7.65 Hz, 4 H); GC-MS, m/z (relative intensity) 712/714/716 (43/100/49, M^+). Anal. ($C_{30}H_{34}Br_2O_{10}$) C, H.

6-(3-Chloro-4-methoxy-5-methoxycarbonylphenyl)-6-(4-methoxy-5-methoxycarbonyl-3-methylphenyl)hex-5-enoate (29). Methyl 5-bromo-3-chloro-2-methoxybenzoate (**47**) (0.06 g, 0.2 mmol), triphenylarsine (0.02 g, 0.1 mmol), cesium fluoride (0.081 g, 0.5 mmol), and tris(dibenzylideneacetone)-dipalladium(0) (0.02 g, 0.02 mmol) were added to a flame-dried 50 mL two-neck flask equipped with a condenser, stirbar, and rubber septum under an argon atmosphere. Dry THF (10 mL) was added via syringe to the round-bottom flask. Methyl 6-(4-methoxy-5-methoxycarbonyl-3-methylphenyl)-6-(tributylstannyl)hex-5-enoate (**51**) (0.1 g, 0.2 mmol) was dissolved in dry THF (10 mL) and added to the round-bottom flask via syringe. The reaction mixture was heated at reflux for 24 h. Solvent was removed in vacuo to yield a crude oily solid. The crude oily solid was purified via flash column chromatography using silica gel (15 g, 2 × 10 cm) and a gradient eluant of 0−20% ethyl acetate in hexanes. Like fractions were combined, and solvents were removed in vacuo to yield a crude brown oil. The crude oil was purified again via flash column chromatography using silica gel (5 g, 1 × 10 cm) and a gradient eluant of 0−25% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a light brown oil (0.031 g, 28%): IR (film) 2951, 1737, 1514, 1475, 1255, 1027, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 2.34 Hz, 1 H), 7.38 (d, J = 2.19 Hz, 1 H), 7.27 (d, J = 2.35 Hz, 1 H), 7.07 (d, J = 2.22 Hz, 1 H), 5.98 (t, J = 7.43 Hz, 1 H), 3.90 (s, 3 H), 3.89 (s, 6 H), 3.86 (s, 3 H), 3.61 (s, 3 H), 2.30 (s, 3 H), 2.28 (t, J = 7.51 Hz, 2 H), 2.11 (q, J = 7.33 Hz, 2 H), 1.75 (qn, J = 7.25 Hz, 2 H); CIMS, m/z (relative intensity) 505/507 (83/33, MH^+), 473/475 (100/39, MH^+ − MeOH). Anal. ($C_{26}H_{29}ClO_8$) C, H.

6-(3,4-Dimethoxyphenyl)-6-(3-chloro-4-methoxy-5-methoxycarbonylphenyl)hex-5-enoate (31). Methyl 5-bromo-3-chloro-2-methoxybenzoate (**47**) (0.058 g, 0.2 mmol), triphenylarsine (0.03 g, 0.1 mmol), cesium fluoride (0.078 g, 0.5 mmol), and tris(dibenzylideneacetone)dipalladium(0) (0.02 g, 0.02 mmol) were added to a flame-dried 50 mL two-neck flask equipped with a condenser, stirbar, and rubber septum under an argon atmosphere. Dry THF (10 mL) was added via syringe to the round-bottom flask. Methyl 6-(3,4-dimethoxyphenyl)-7,7-dibutyl-7-stannaundec-5-enoate (**54**) (0.2 g, 0.2 mmol) was dissolved in dry THF (10 mL) and added to the round-bottom flask via syringe. The reaction mixture was heated at reflux for 24 h. Solvent was removed in vacuo to yield a crude oily solid. The crude oily solid was purified via flash column chromatography using silica gel (25 g, 2 × 20 cm) and a gradient eluant of 0−30% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a light brown oil (0.020 g, 21%): IR (film) 2951, 1733, 1477, 1436, 1258, 1003, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 2.30 Hz, 1 H), 7.30 (d, J = 2.32 Hz, 1 H), 6.86 (d, J = 8.17 Hz, 1 H), 6.66 (dd, J = 8.12, 1.73 Hz, 1 H), 6.57 (d, J = 1.82 Hz, 1 H), 5.97 (t, J = 7.50 Hz, 1 H), 3.89 (s, 6 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 3.60 (s, 3 H), 2.27 (t, J = 7.43 Hz, 2 H), 2.13 (q, J = 7.36 Hz, 2 H), 1.74 (qn, J = 7.46 Hz, 2 H); GC-MS m/z (relative intensity) 463/465 (100/35, MH^+). Anal. ($C_{24}H_{27}ClO_7$) C, H.

Methyl 3′,3″,4′,4″-Tetramethoxy-6,6-diphenyl-5-hexenoate (32). Titanium tetrachloride bis(tetrahydrofuranate) (3.33 g, 10.0 mmol) was added to a flame-dried two-neck 100 mL flask, under an argon atmosphere, equipped with a condenser, magnetic stir bar, and a rubber septum. Zinc dust (1.04 g, 15.9 mmol) was then added to the flask. The solids were suspended in dry THF (15 mL). The suspension was heated at reflux for 2.5 h. A solution of 3,3′,4,4′-tetramethoxybenzophenone (**57**) (0.41 g, 1.36 mmol) and methyl 5-oxopentanoate (**40**) (0.41 g, 3.10 mmol) in dry THF (10 mL) was transferred via cannula under an argon atmosphere to the titanium suspension. The resulting suspension was stirred at reflux for 2 h. The suspension was then cooled to ambient temperature, and 1 M HCl (50 mL) was added. The reaction solution was stirred at ambient temperature for 15 min. The reaction solution was then poured into a separatory funnel, and both water (100 mL) and ethyl acetate (100 mL) were added. The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (100 mL) and dried over anhydrous sodium sulfate. The organic extracts were filtered, and solvents were removed in

vacuo yielding a crude oil. The crude oil was purified by flash column chromatography using silica gel (25 g, 2 × 19 cm) and a gradient eluant from 0 to 25% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a colorless oil (0.383 g, 70%): IR (film) 2950, 1737, 1600, 1579, 1513, 1463, 1247, 1169, 1136, 1027, 810, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.94−6.71 (m, 6 H), 6.09 (t, J = 6.47 Hz, 1 H), 4.33 (s, 3 H), 4.29 (s, 3 H), 4.26 (s, 3 H), 4.25 (s, 3 H), 4.09 (s, 3 H), 2.94 (t, J = 6.47 Hz, 2 H), 2.81 (q, J = 6.46 Hz, 2 H), 2.49 (qn, J = 6.30 Hz, 2 H); CIMS, *m/z* (relative intensity) 401 (100, MH^+). Anal. ($C_{23}H_{28}O_6$) C, H.

2,2′,4,4′-Tetramethoxy-6,6-diphenyl-5-hexenoate (33). Titanium tetrachloride bis(tetrahydrofuranate) (3.2 g, 9.6 mmol) was added to a dry 100 mL two-neck flask, under an argon atmosphere, equipped with a condenser, magnetic stir bar, and a rubber septum. Zinc dust (0.91 g, 14.0 mmol) was then added to the flask. The solids were suspended in dry THF (20 mL). The suspension was heated at reflux for 2.5 h. A solution of 2,2′,4,4′-tetramethoxybenzophenone (**59**) (0.59 g, 1.94 mmol) and methyl 5-oxopentanoate (**40**) (0.53 g, 4.1 mmol) in dry THF (10 mL) was transferred via cannula under an argon atmosphere to the titanium suspension. The resulting suspension was heated at reflux for 1 h. The suspension was then cooled to ambient temperature, and 1 M HCl (30 mL) was added. The reaction mixture was then poured into a separatory funnel, and ethyl acetate (100 mL) was added. The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (100 mL) and dried over anhydrous sodium sulfate. Solvents were removed in vacuo, yielding a yellow oil. The crude oil was purified by flash column chromatography using silica gel (50 g, 2 × 38 cm) and eluted with a gradient eluant from 0 to 20% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a colorless oil (0.400 g, 52%): IR (film) 2949, 2835, 1734, 1605, 1576, 1503, 1454, 1437, 1414, 1362, 1301, 1259, 1207, 1158, 1127, 1034, 937, 831 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, J = 9.04 Hz, 1 H), 6.92 (d, J = 8.19 Hz, 1 H), 6.45 (d, J = 2.33 Hz, 1 H), 6.42 (d, J = 2.38 Hz, 1 H), 6.40−6.35 (m, 2 H), 5.90 (t, J = 7.29 Hz, 1 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.71 (s, 3 H), 3.62 (s, 3 H), 3.60 (s, 3 H), 2.27 (t, J = 7.49 Hz, 2 H), 2.01 (q, 7.27 Hz, 2 H), 1.71 (qn, J = 7.55 Hz, 2 H); ESIMS, *m/z* (relative intensity) 401 (100, MH^+). Anal. ($C_{23}H_{28}O_6$) C, H.

5,5′-Dicarboxy-3,3′-dichloro-4,4′-dimethoxybenzophenone (38). 3,3′-Dichloro-4,4′-dimethoxy-5,5′-dimethoxycarbonylbenzophenone **(37)** (0.58 g, 1.3 mmol) was added to a 250 mL round-bottom flask equipped with a condenser. The solid was dissolved in methanol (100 mL). Potassium hydroxide (0.75 g, 13.3 mmol) was added to the flask. The reaction mixture was heated at reflux for 24 h. The reaction mixture was added to a separatory funnel, and water (200 mL) and dichloromethane (200 mL) were added. The aqueous layer was separated and extracted with ethyl acetate (3 × 125 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. Solvents were removed in vacuo, yielding a white solid (0.363 g, 67%): mp 194−195 °C (lit.[37] mp 224−226 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 7.94 (d, J = 2.17, 2 H), δ 7.89 (d, J = 2.17 Hz, 2 H), δ 3.93 (s, 6 H).

3,3′-Dichloro-4,4′-dimethoxy-5,5′-di(methylthiocarbonyl)benzophenone (39). 5,5′-Dicarboxy-3,3′-dichloro-4,4′-dimethoxybenzophenone (**38**) (1.02 g, 2.5 mmol) was added to an oven-dried 10 mL round-bottom flask equipped with a stirbar and a rubber septum. An inert argon atmosphere was introduced into the flask. Thionyl chloride (10 mL) was then added to the flask via syringe. The reaction mixture was heated at reflux for 8 h. The reaction mixture was cooled to ambient temperature, and benzene (10 mL) was added. Solvent was removed in vacuo to yield a crude colorless oil. Additional benzene (4 × 25 mL) was added to the crude oil and evaporated to azeotrope any excess thionyl chloride. The crude oil was then dissolved in benzene (10 mL), and sodium thiomethoxide (0.41 g, 5.8 mmol) was added to the flask. The suspension was stirred at ambient temperature for 5 h. Water (10 mL) was added to the suspension, and this was poured into a separatory funnel. Ethyl acetate (50 mL) and water (50 mL) were added. The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (100 mL) and dried over anhydrous sodium sulfate. Solvents were removed in vacuo, yielding a pale brown glassy oil (0.914 g, 73% over two steps): IR (film) 2929, 1667, 1588, 1473, 1300, 1273, 1137, 990, 782 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 2.15 Hz, 2 H), 7.97 (d, J = 2.11 Hz, 2 H), 4.03 (s, 6 H), 2.47 (s, 6 H); GC-MS *m/z* (relative intensity) 459/461 (100/84, MH^+). Anal. ($C_{19}H_{16}Cl_2O_5S_2$) C, H, S.

Dimethyl 5-oxononanedioate (42). 5-Oxoazelaic acid (**41**) (0.51 g, 2.54 mmol) was added to an oven-dried 100 mL round-bottom flask equipped with a stir bar and a rubber septum. *N*,*N*-Dimethylformamide (25 mL) was added to the flask. An inert argon atmosphere was introduced in the reaction flask. Potassium carbonate (3.59 g, 26.0 mmol) was added to the flask. Iodomethane (0.45 mL, 7.2 mmol) was then added to the flask via syringe. The reaction solution was stirred at ambient temperature for 24 h. Water (75 mL) was added to the reaction flask. The reaction solution was added to a separatory funnel, and both water (100 mL) and ethyl acetate (100 mL) were added. The aqueous layer was separated and extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were washed with both water (3 × 200 mL) and brine (2 × 100 mL) and dried over anhydrous sodium sulfate. The organic extracts were filtered, and the solvent was removed in vacuo to yield a white solid (0.217 g, 37%): mp 33−34 °C (lit.[38] mp 29−30 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 3.64 (s, 6 H), 2.45 (t, J = 7.21 Hz, 4 H), 2.32 (t, J = 7.23 Hz, 4 H), 1.87 (qn, J = 7.18 Hz, 4 H).

5-Bromo-3-chlorosalicylaldehyde (44). 4-Bromo-2-chlorophenol (**43**) (5.40 g, 26.0 mmol) was added to a 100 mL Teflon-coated bomb apparatus. Trifluoroacetic acid (20 mL) was added to the reaction vessel. Hexamethylenetetramine (7.41 g, 52.9 mmol) was then added to the bomb apparatus. The bomb apparatus was placed in a preheated oven at 90 °C for 20 h. The reaction mixture was cooled to ambient temperature, and water (30 mL) was added. An aqueous 50% sulfuric acid solution (14 mL) was added, and the reaction solution was stirred for an additional 2 h at ambient temperature. Water (50 mL) was added, and yellow precipitate formed. The precipitate was collected by vacuum filtration on a Büchner funnel. The crude yellow solid was then recrystallized from a 20% aqueous ethanol solution to yield yellow crystals (2.22 g, 36%): mp 100−102 °C (lit.[39] mp 86 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 11.36 (s, 1 H), 9.83 (s, 1 H), 7.72 (d, J = 2.25 Hz, 1 H), 7.61 (d, J = 2.19 Hz, 1 H).

5-Bromo-3-chloro-2-methoxybenzaldehyde (45). 5-Bromo-3-chlorosalicylaldehyde (**44**) (2.28 g, 9.68 mmol) was added to a flame-dried 100 mL round-bottom flask equipped with a stir bar and a rubber septum. *N*,*N*-Dimethylformamide (50 mL) was added to the flask. An inert argon atmosphere was then introduced in the reaction flask. Potassium carbonate (14.5 g, 105 mmol) was added to the flask. Iodomethane (0.900 mL, 14.5 mmol) was then added to the flask via syringe. The reaction solution was stirred at ambient temperature for 22 h. Water (75 mL) was added to the reaction flask. A white precipitate formed and was collected by vacuum filtration on a Büchner funnel. The solid was washed with water (500 mL). The solid was then dissolved in dichloromethane (100 mL) and added to a separatory funnel. Water (100 mL) was added, and the aqueous and organic layers were separated. The organic layer was washed with brine (100 mL) and dried over anhydrous sodium sulfate. The organic extracts were then filtered, and solvent was removed in vacuo to yield a white solid (2.22 g, 92%): mp 96−98 °C; IR (film) 2881, 1690, 1466, 1421, 1216, 977, 872 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1 H), 7.87 (d, J = 2.35 Hz, 1 H), 7.78 (d, J = 2.36 Hz, 1 H), 4.01 (s, 3 H); ESIMS, *m/z* (relative intensity) 249/251/253 (85/100/20, MH^+). Anal. ($C_8H_6BrClO_2$) C, H, Br.

5-Bromo-3-chloro-2-methoxybenzoic Acid (46). 5-Bromo-3-chloro-2-methoxybenzaldehyde (**45**) (3.78 g, 15.2 mol) was

added to a 100 mL round-bottom flask. Acetone (50 mL) and water (10 mL) were added to the flask. The reaction mixture was cooled to 0 °C in an ice bath. Potassium permanganate (0.80 g, 17.0 mol) was then slowly added to the flask. The reaction mixture was allowed to warm to ambient temperature for 24 h. The inorganic salts were removed by filtration on a Büchner funnel and washed with acetone (400 mL). The filtrate was concentrated in vacuo to yield a white solid. The solid was dissolved in water (100 mL) and added to a separatory funnel. Ethyl acetate (100 mL) was added to the funnel. The aqueous layer was separated and acidified to pH 1.0 using concentrated hydrochloric acid. The white precipitate (0.924 g, 23%) that formed was collected by vacuum filtration using a Büchner funnel: mp 177−179 °C; IR (film) 3073, 2955, 2660, 1710, 1679, 1468, 1416, 1305, 1238, 988 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.87 (d, J = 2.50 Hz, 1 H), 7.85 (d, J = 2.50 Hz, 1 H), 3.92 (s, 3 H); ESIMS, m/z (relative intensity) 263/265/267 (65/100/20, M^-). Anal. ($C_8H_6BrClO_3$) C, H.

Methyl 5-Bromo-3-chloro-2-methoxybenzoate (47). 5-Bromo-3-chloro-2-methoxybenzoic acid (**46**) (1.75 g, 6.59 mmol) was added to an oven-dried 250 mL round-bottom flask equipped with a stirbar and rubber septum. *N*,*N*-Dimethylformamide (100 mL) was added to the flask. An inert argon atmosphere was introduced in the reaction flask. Potassium carbonate (9.62 g, 69.6 mmol) was added to the flask. Iodomethane (0.41 mL, 6.6 mmol) was then added to the flask via syringe. The reaction mixture was stirred at ambient temperature for 24 h. Water (200 mL) was added, and a white precipitate formed. The precipitate was collected by vacuum filtration on a Büchner funnel. The solid was washed with water (400 mL). The solid was dissolved in ethyl acetate (300 mL) and added to a separatory funnel. Water (200 mL) was added to the separatory funnel, and the aqueous layer was separated from the organic layer. The organic layer was washed with water (3 × 150 mL) and brine (2 × 100 mL) and dried over anhydrous sodium sulfate. The organic layer was filtered and solvent removed in vacuo to yield a white solid (0.910 g, 49%): mp 37−39 °C; IR (film) 2950, 1738, 1466, 1416, 1282, 1240, 997 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 2.49 Hz, 1 H), 7.66 (d, J = 2.48 Hz, 1 H), 3.91 (s, 3 H), 3.90 (s, 3 H); GC-MS, m/z (relative intensity) 279/281/283 (80/100/24, MH^+). Anal. ($C_9H_8BrClO_3$) C, H.

5-Bromo-3-methylsalicylic Acid (49). 3-Methylsalicylic acid (**48**) (2.06 g, 13.6 mmol) was added to an oven-dried 100 mL round-bottom flask equipped with a stir bar and rubber septum. Acetic acid (30 mL) was added to the flask. Bromine (0.700 mL, 13.7 mmol) was added to the flask via syringe. The contents of the flask were stirred at ambient temperature for 24 h. Water (30 mL) was added to the flask, and a white precipitate formed. The white precipitate was collected by vacuum filtration on a Büchner funnel (2.51 g, 80%): mp 236−237 °C (lit.[40] mp 231−232 °C); ^1H NMR (300 MHz, acetone-d_6) δ 7.84 (d, J = 2.55 Hz, 1 H), 7.55 (d, J = 2.45 Hz, 1 H), 2.22 (s, 3 H).

Methyl 5-Bromo-2-methoxy-3-methylbenzoate (50). 5-Bromo-3-methylsalicylic acid (**49**) (2.12 g, 9.19 mmol) was added to an oven-dried 100 mL round-bottom flask equipped with a stirbar and a rubber septum. *N*,*N*-Dimethylformamide (50 mL) was added to the flask. An inert argon atmosphere was then introduced in the reaction flask. Potassium carbonate (12.9 g, 93.4 mmol) was added to the flask. Iodomethane (1.5 mL, 24 mmol) was then added to the flask via syringe. The reaction solution was stirred at ambient temperature for 26 h. Water (50 mL) was added to the reaction flask. A white precipitate formed and was collected by vacuum filtration on a Büchner funnel. The solid was washed with water (400 mL). The solid was then dissolved in dichloromethane (200 mL) and added to a separatory funnel. Water (200 mL) was added to the separatory funnel, and the aqueous layer was separated from the organic layer. The organic layer was washed with brine (100 mL) and dried over anhydrous sodium sulfate. The organic layer was then filtered and solvent removed in vacuo to yield a white solid (2.06 g, 86%): mp 59−60 °C; IR (film) 2951, 1731, 1578, 1470, 1434, 1417, 1293, 1251, 1225, 1194, 1156, 1007, 875, 849, 795 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 2.58 Hz, 1 H), 7.47 (d, J = 2.58 Hz, 1 H), 3.91 (s, 3 H), 3.81 (s, 3 H), 2.30 (s, 3 H); CIMS, m/z (relative intensity) 259/261 (100/97, MH^+). Anal. ($C_{10}H_{11}BrO_3$) C, H.

Methyl 6-[4-Methoxy-5-methoxycarbonyl-3-methylphenyl]-6-(tributylstannyl)hex-5-enoate (51). Cuprous iodide (0.50 g, 2.6 mmol) and dichlorobis(triphenylphosphine)-palladium(II) (1.7 g, 2.4 mmol) were added to a flame-dried 100 mL round-bottom flask under an argon atmosphere. Triethylamine (75 mL) was added to the flask. Methyl 5-bromo-2-methoxy-3-methylbenzoate (**50**) (3.05 g, 11.8 mmol) and methyl 5-hexynoate (3.08 g, 24.4 mmol) were then added to the flask. The round-bottom flask was equipped with a condenser, and the reaction mixture was heated at reflux for 24 h. The reaction mixture was cooled, and solvent was removed in vacuo to yield a crude black oily solid. The crude solid was purified by flash column chromatography using silica gel (125 g, 5 × 15 cm) and a gradient eluant from 0 to 10% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a crude red oil. The crude oil was purified a second time using silica gel (125 g, 5 × 15 cm) and a gradient eluant from 0 to 8% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a crude yellow oil. The crude oil was dissolved in dry THF (200 mL) and added to a flame-dried 500 mL round-bottom flask under an argon atmosphere. Tetrakis-(triphenylphoshpine)palladium(0) (0.20 g, 0.17 mmol) was added to the flask. Tributyltin hydride (2.37 mL, 8.14 mmol) was added dropwise via syringe to the round-bottom flask over a 5 min period. The reaction solution was stirred at ambient temperature for 1.5 h. Solvent was removed in vacuo to yield a crude black oil. The oil was purified by flash column chromatography using silica gel (75 g, 3 × 38 cm) and a gradient eluant from 0 to 10% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield the product **51**[25] as a colorless oil (2.39 g, 49%, over two steps): ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 2.06 Hz, 1 H), 6.85 (d, J = 2.06 Hz, 1 H), 5.69 (t, J = 6.91 Hz, 1 H), 3.87 (s, 3 H), 3.79 (s, 3 H), 3.60 (s, 3 H), 2.26 (s, 3 H), 2.23 (t, J = 7.68 Hz, 2 H), 2.04 (q, J = 7.17 Hz, 2 H), 1.66 (qn, J = 7.46 Hz, 2 H), 1.45−1.20 (m, 11 H), 0.86−0.69 (m, 16 H).

Methyl 6-(3,4-Dimethoxyphenyl)hex-5-ynoate (53). Cuprous iodide (0.56 g, 3.0 mmol) and dichlorobis(triphenylphosphine)palladium(II) (1.0 g, 1.5 mmol) were added to a flame-dried 100 mL round-bottom flask under an argon atmosphere. Triethylamine (50 mL) was added to the flask. 4-Bromoveratrole (**52**) (1.2 mL, 8.3 mmol) and methyl 5-hexynoate (2.10 g, 16.6 mmol) were then added to the flask. The round-bottom flask was equipped with a condenser, and the reaction mixture was heated at reflux for 8 h. The reaction mixture was cooled and solvent was removed in vacuo to yield a crude black oily solid. The crude solid was purified by flash column chromatography using silica gel (125 g, 5 × 14 cm) and a gradient eluant from 0 to 20% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a brown oily solid. The solid was purified a second time using silica gel (50 g, 3 × 22 cm) and a gradient eluant from 0 to 10% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a brown solid (0.620 g, 28%): mp 53−55 °C; IR (film) 2952, 1736, 1513, 1440, 1208, 1169, 1025, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (dd, J = 1.75 and 8.25 Hz, 1 H), 6.88 (d, J = 1.68 Hz, 1 H), 6.75 (d, J = 8.28 Hz, 1 H), 3.85 (s, 6 H), 3.66 (s, 3 H), 2.49 (t, J = 7.40 Hz, 2 H), 2.45 (t, J = 6.90 Hz, 2 H), 1.91 (qn, J = 7.18 Hz, 2 H); GC-MS, m/z (relative intensity) 263 (100, MH^+). Anal. ($C_{15}H_{18}O_4$) C, H.

Methyl 6-(3,4-Dimethoxyphenyl)-7,7-dibutyl-7-stannaundec-5-enoate (54). Methyl 6-(3′,4′-dimethoxyphenyl)-hex-5-ynoate (**53**) (0.1 g, 0.4 mmol) was added to a flame-dried 100 mL round-bottom flask under an argon atmosphere. The solid was dissolved in dry THF (40 mL). Tetrakis(triphenylphoshpine)palladium(0) (0.02 g, 0.02 mmol) was added to the flask. Tributyltin hydride (0.17 mL, 0.63 mmol) was added dropwise via syringe to the round-bottom flask over a

5 min period. The reaction solution was stirred at ambient temperature for 2 h. Solvent was removed in vacuo to yield a crude black oil. The oil was purified by flash column chromatography using silica gel (10 g, 2 × 7 cm) and a gradient eluant from 0 to 10% ethyl acetate in hexanes. Like fractions were combined, and solvent was removed in vacuo to yield a colorless oil (0.101 g, 43%); IR (film) 2954, 2927, 1740, 1508, 1463, 1439, 1252, 1234, 1136, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (d, J = 8.63 Hz, 1 H), 6.44−6.41 (m, 2 H), 5.67 (t, J = 6.95 Hz, 1 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.60 (s, 3 H), 2.23 (t, J = 7.46 Hz, 2 H), 2.05 (q, J = 7.32 Hz, 2 H), 1.67 (qn, J = 7.39 Hz, 2 H), 1.47−1.19 (m, 11 H), 1.0−0.70 (m, 16 H); ESIMS, m/z (relative intensity) 551/553/555 (44/78/100, MH^+). Anal. ($C_{27}H_{46}O_4Sn$) C, H.

3,3′,4,4′-Tetramethoxybenzophenone (57). Veratrole (**55**) (0.64 mL, 5.0 mmol) and 3,4-dimethoxybenzoyl chloride (**56**) (1.0 g, 5.1 mmol) were added to a flame-dried two-neck 25 mL round-bottom flask equipped with a condenser, magnetic stir bar, and rubber septum. An argon atmosphere was introduced, and dry dichloromethane (10 mL) was added via syringe. Aluminum chloride (0.92 g, 6.87 mmol) was slowly added in three equal portions. The reaction solution was then heated at reflux in an oil bath for 2 h. The reaction solution was cooled to ambient temperature and poured over ice (5 mL) and 1 M HCl (5 mL). This solution was added to a separatory funnel, and water (100 mL) and dichloromethane (100 mL) were added. The aqueous layer was separated and extracted with dichloromethane (3 × 50 mL). The combined extracts were washed with brine (100 mL) and dried over anhydrous sodium sulfate. The extracts were then filtered, and solvent was removed in vacuo to yield a crude white solid. The oily solid was recrystallized from ethanol to yield a pure white solid (0.990 g, 65%): mp 143−144 °C (lit.[41] mp 142−144 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 1.69 Hz, 2 H), 7.34 (dd, J = 1.71, 7.19 Hz, 2 H), 6.92 (d, J = 7.23 Hz, 2 H), 4.37 (s, 6 H), 4.36 (s, 6 H).

2,2′,4,4′-Tetramethoxybenzophenone (59). 2,2′,4,4′-Tetrahydroxybenzophenone (**58**) (2.0 g, 8.1 mmol) was added to an oven-dried 250 mL round-bottom flask equipped with a stirbar and rubber septum. *N*,*N*-Dimethylformamide (100 mL) was added to the flask. An inert argon atmosphere was then introduced in the reaction flask. Potassium carbonate (11.7 g, 85.0 mmol) was added to the flask. Iodomethane (2.5 mL, 40 mmol) was then added to the flask via syringe. The reaction solution was stirred at ambient temperature for 24 h. Water (300 mL) was added to the reaction flask. A white precipitate formed and was collected by vacuum filtration on a Büchner funnel. The solid was washed with water (400 mL). The solid was then dissolved in ethyl acetate (200 mL) and added to a separatory funnel. Water (200 mL) was added to the separatory funnel, and the aqueous layer was separated from the organic layer. The organic layer was washed with brine (200 mL) and dried over anhydrous sodium sulfate. The organic layer was then filtered and solvent removed in vacuo to yield an orange-white solid (1.93 g, 79%): mp 135−139 °C (lit.[42] mp 135−136 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 7.39 Hz, 2 H), 6.58 (dd, J = 1.95, 7.40 Hz, 2 H), 6.51 (d, J = 1.91 Hz, 2 H), 4.29 (s, 6 H), 4.12 (s, 6 H).

In Vitro Antiviral Assays. Evaluation of the antiviral activity of the compounds against HIV-1 strain III_B and HIV-2 strain (ROD) in MT-4 cells was performed using the MTT assay as previously described.[43] Stock solutions (10 × final concentrations) of test compounds were added in 25 μL volumes to two series of triplicate wells so as to allow simultaneous evaluation of their effects on mock- and HIV-infected cells at the beginning of each experiment. Serial 5-fold dilutions of test compounds were made directly in flat-bottom 96-well microtiter trays using a Biomek 2000 robot (Beckman Instruments, Fullerton, CA). Untreated control HIV- and mock-infected cell samples were included for each sample.

HIV-1(III_B)[44] or HIV-2 (ROD)[45] stock (50 μL) at 100−300 $CCID_{50}$ (50% cell culture infectious dose) or culture medium was added to either the infected or mock-infected wells of the mictotiter tray. Mock-infected cells were used to evaluate the effect of test compound on uninfected cells in order to assess the cytotoxicity of the test compound. Exponentially growing MT-4 cells[46] were centrifuged for 5 min at 1000 rpm, and the supernatant was discarded. The MT-4 cells were resuspended at 6 × 10^5 cells/mL, and 50 μL volumes were transferred to the microtiter tray wells. Five days after infection, the viability of mock- and HIV-infected cells was examined spectrophotometrically in the MTT assay.

The MTT assay is based on the reduction of yellow 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Acros Organics, Geel, Belgium) by mitochondrial dehydrogenase of metabolically active cells to a blue-purple formazan that can be measured spectrophotometrically. The absorbances were read in an eight-channel computer-controlled photometer (Multiscan Ascent Reader, Labsystems, Helsinki, Finland), at two wavelengths (540 and 690 nm). All data were calculated using the median OD (optical density) value of three wells. The 50% cytotoxic concentration (CC_{50}) was defined as the concentration of the test compound that reduced the absorbance (OD540) of the mock-infected control sample by 50%. The concentration achieving 50% protection from the cytopathic effect of the virus in infected cells was defined as the 50% effective concentration (EC_{50}).

In Vitro Rat Plasma Stability Assay. The alkenyldiarylmethanes were tested for their hydrolytic stability, utilizing rat plasma in vitro using methods as previously described.[47−54] The alkenyldiarylmethanes (4.6−15.8 mg) and 1,1-diphenylethylene (1.6−4.3 μL), an internal standard, were dissolved in DMSO (1.0 mL). This solution was filtered through a 0.45 μM filter (Millex-HN). This solution became the "stock solution" of the alkenyldiarylmethane and 1,1-diphenylethylene. Lyophilized rat plasma (1.0 mL) (lot 119H7505, Sigma Chemical Co., St. Louis, MO) was reconstituted with Milli-Q water (1.0 mL). This plasma solution was incubated at 37 °C for 15 min. The plasma solution was diluted with 0.01 M phosphate-buffered saline (0.250 mL), pH 7.0, to afford an 80% plasma solution. The solution was incubated at 37 °C for an additional 5 min. An aliquot (100 μL) of the stock solution was added to the rat plasma (1.0 mL, 80% plasma). The final concentrations for the drug in the plasma solution ranged from 0.8 to 2.2 mM. Aliquots (10 μL) of this solution were then collected at various time intervals and diluted with acetonitrile (90 μL) to precipitate any protein. The aliquots were thoroughly mixed and then centrifuged at 10000 rpm for 5 min to pellet the precipitated protein. After centrifugation, the supernatant (20 μL) of these aliquots was analyzed via HPLC to determine the residual amount of alkenyldiarylmethane. The HPLC system consisted of a Rainin solvent delivery system (model HPXL), a Dynamax absorbance detector (model UV-1) set at a wavelength of 254 nM, and a Rheodyne injector (model 7125) with a 20 μL injection loop. Data were collected and processed using the Rainin Dynamax HPLC controller and data acquisition software (version 1.4) on an Apple Computer, Inc. 7600 Power Macintosh personal computer. The mobile phase consisted of either 75:25 (v/v %) acetonitrile/water or 80:20 (v/v %) acetonitrile/water. The mobile phase flow rate was 1.0 mL/min, and the HPLC column (150 mm × 4.6 mm) was packed with 5 μm Kromasil C_{18} from Phenomenex (Torrance, CA). A Security Guard C_{18} (ODS, octadecyl, 4 mm × 3 mm) column from Phenomenex preceded the analytical column. The column temperature was maintained at ambient temperature.

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Supporting Information Available: Elemental analyses of compounds **4**, **20**−**29**, **31**−**33**, **39**, **45**−**47**, **50**, **53**, and **54**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Katz, R. A.; Skalka, M. A. The Retroviral Enzymes. *Annu. Rev. Biochem.* **1994**, *63*, 133−173.

(2) De Clercq, E. Perspective Towards Improved Anti-HIV Chemotherapy: Therapeutic Strategies for Intervention with HIV Infections. *J. Med. Chem.* **1995**, *38*, 2491−2517.

(3) Mitsuya, H.; Yarchoan, R.; Broder, S. Molecular Targets for AIDS Therapy. *Science* **1990**, *249*, 1533−1543.

(4) De Clercq, E. New Perspectives for the Treatment of HIV Infections. *Collect. Czech. Chem. Commun.* **1998**, *63*, 449−479.

(5) Tantillo, C.; Ding, J.; Jacobo-Molina, A.; Nanni, R. G.; Boyer, P. L.; Hughes, S. H.; Pauwels, R.; Andries, K.; Janssen, P. A. J.; Arnold, E. Locations of Anti-AIDS Drug Binding Sites and Resistance Mutations in the Three-dimensional Structure of HIV-1 Reverse Transcriptase. *J. Mol. Biol.* **1994**, *242*, 369−387.

(6) De Clercq, E. The Role of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) in the Therapy of HIV-1 Infection. *Antiviral Res.* **1998**, *38*, 153−179.

(7) Spence, R. A.; Kati, W. M.; Anderson, K. S.; Johnson, K. A. Mechanism of Inhibition of HIV-1 Reverse Transcriptase by Nonnucleoside Inhibitors. *Science* **1995**, *267*, 988−993.

(8) Drake, S. M. NNRTIs—A New Class of Drugs for HIV. *J. Antimicrob. Chemother.* **2000**, *45*, 417−420.

(9) Pedersen, O. S.; Pedersen, E. B. Non-Nucleoside Reverse Transcriptase Inhibitors: the NNRTI Boom. *Antiviral Chem. Chemother.* **1999**, *10*, 285−314.

(10) De Clercq, E. Perspectives of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) in the Therapy of HIV-1 Infection. *Farmaco* **1999**, *54*, 26−45.

(11) Pedersen, O. S.; Pedersen, E. B. The Flourishing Syntheses of Non-Nucleoside Reverse Transcriptase Inhibitors. *Synthesis* **2000**, *4*, 479−495.

(12) Tavel, J. A.; Miller, K. D.; Masur, H. Guide to Major Clinical Trials of Antiretroviral Therapy in Human Immunodeficiency Virus-Infected Patients: Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, and Nucleoside Reverse Transcriptase Inhihitors. *Clin. Infect. Dis.* **1999**, *28*, 643−676.

(13) Carpenter, C. C. J.; Fischl, M. A.; Hammer, S. M.; Hirsch, M. S.; Jacobsen, D. M.; Katzenstein, D. A.; Montaner, J. S. G.; Richman, D. D.; Saag, M. S.; Schooley, R. T.; Thompson, M. A.; Vella, S.; Yeni, P. G.; Volberding, P. A. Antiretroviral Therapy for HIV Infections in 1998. *JAMA−J. Am. Med. Assoc.* **1998**, *280*, 78−86.

(14) Barry, M.; Mulcahy, F.; Back, D. J. Antiretroviral Therapy for Patients with HIV Disease. *Br. J. Clin. Pharmacol.* **1998**, *45*, 221−228.

(15) Beach, J. W. Chemotherapeutic Agents for Human Immunodeficiency Virus Infection: Mechanism of Action, Pharmacokinetics, Metabolism, and Adverse Reactions. *Clin. Ther.* **1998**, *20*, 2−25.

(16) Fischl, M. A. Antiretroviral Therapy in 1999 for Antiretroviral-Naive Individuals with HIV Infection. *AIDS* **1999**, *13* (Suppl. 1), S49−S59.

(17) Vajpayee, M.; Dar, L. Antiretroviral Drugs in HIV Infection. *Indian J. Pharmacol.* **1999**, *31*, 96−103.

(18) Cushman, M.; Golebiewski, M.; Buckheit, R. W., Jr.; Graham, L.; Rice, W. G. Synthesis and Biological Evaluation of an Alkenyldiarylmethane (ADAM) which Acts as a Novel Non-nucleoside HIV-1 Reverse Transcriptase Inhibitor. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2713−2716.

(19) Cushman, M.; Golebiewski, W. M.; Graham, L.; Turpin, J. A.; Rice, W. G.; Fliakas-Boltz, V.; Buckheit, R. W., Jr. Synthesis and Biological Evaluation of Certain Alkenyldiarylmethanes as Anti-HIV-1 Agents Which Act as Non-Nucleoside Reverse Transcriptase Inhibitors. *J. Med. Chem.* **1996**, *39*, 3217−3227.

(20) Cushman, M.; Casimiro-Garcia, A.; Hejchman, E.; Ruell, J. A.; Huang, M.; Schaeffer, C. A.; Williamson, K.; Rice, W. G.; Buckheit, R. W., Jr. New Alkenyldiarylmethanes with Enhanced Potencies as Anti-HIV Agents Which Act as Non-Nucleoside Reverse Transcriptase Inhibitors. *J. Med. Chem.* **1998**, *41*, 2076−2089.

(21) Cushman, M.; Casimiro-Garcia, A.; Williamson, K.; Rice, W. G. Synthesis of a Non-Nucleoside Reverse Transcriptase Inhibitor in the Alkenyldiarylmethane (ADAM) Series with Optimized Potency and Therapeutic Index. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 195−198.

(22) Casimiro-Garcia, A.; Micklatcher, M.; Turpin, J. A.; Stup, T. L.; Watson, K.; Buckheit, R. W.; Cushman, M. Novel Modifications in the Alkenyldiarylmethane (ADAM) Series of Non-Nucleoside Reverse Transcriptase Inhibitors. *J. Med. Chem.* **1999**, *42*, 4861−4874.

(23) Xu, G.; Micklatcher, M.; Silvestri, M.; Hartman, T. L.; Burrier, J.; Osterling, M. C.; Wargo, H.; Turpin, J. A.; Buckheit, R. W., Jr.; Cushman, M. The Biological Effects of Structural Variation at the Meta Position of the Aromatic Rings and at the End of the Alkenyl Chain in the Alkenyldiarylmethane Series of Non-Nucleoside Reverse Transcriptase Inhibitors. *J. Med. Chem.* **2001**, *44*, 4092−4113.

(24) Xu, G.; Loftus, T. L.; Wargo, H.; Turpin, J. A.; Buckheit, R. W.; Cushman, M. Solid-Phase Synthesis of the Alkenyldiarylmethane (ADAM) Series of Non-Nucleoside Reverse Transcriptase Inhibitors. *J. Org. Chem.* **2001**, *66*, 5958−5964.

(25) Xu, G.; Hartman, T. L.; Wargo, H.; Turpin, J. A.; Buckheit, R. W., Jr.; Cushman, M. Synthesis of Alkenyldiarylmethane (ADAM) Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors with Non-Identical Aromatic Rings. *Bioorg. Med. Chem.* **2002**, *10*, 283−290.

(26) Silvestri, M.; Miles, D.; Rothwell, A. P.; Wood, K. V.; Cushman, M. The "Apparent" Hydrolysis of Alkyl Esters During Electrospray Ionization. *Rapid Commun. Mass Spectrom.* **2003**, *17*, 1703−1708.

(27) King, S. A. Ortho ester-Dependent Alcoholysis of Lactones. Facile Preparation of 4-Alkoylbutanoates and 5-Alkoxypentanoates. *J. Org. Chem.* **1994**, *59*, 2253−2256.

(28) Jones, B. A.; Bradshaw, J. S. Synthesis and Reduction of Thiocarboxylic *O*-Esters. *Chem. Rev.* **1984**, *84*, 17−30.

(29) Cushman, M.; Golebiewski, W. M.; McMahon, J. B.; Buckheit, R. W., Jr.; Clanton, D. J.; Weislow, O.; Haugwitz, R. D.; Bader, J.; Graham, L.; Rice, W. G. Design, Synthesis, and Biological Evaluation of Cosalane, a Novel anti-HIV Agent which Inhibits Multiple Features of Virus Replication. *J. Med. Chem.* **1994**, *37*, 3040−3050.

(30) Huckstep, M.; Taylor, R. J. K.; Caton, M. P. L. A Convenient Method of Preparing the Leukotriene Precursor Methyl 5-Oxopentanoate. *Synthesis* **1982**, 881−882.

(31) Harmana, M.; Rashatasakhon, P. Observations on the Regioselectivity of some Baeyer−Villiger Reactions. *Tetrahedron Lett.* **2002**, *43*, 3641−3644.

(32) Zhang, H. X.; Guibé, F.; Balavoine, G. Palladium- and Molybdenum-Catalyzed Hydrostannation of Alkynes. A Novel Access to Regio- and Stereodefined Vinylstannanes. *J. Org. Chem.* **1990**, *55*, 1857−1867.

(33) Huang, X.; Zhong, P. A Facile Regio- and Stereocontrolled Synthesis of (*Z*)-1-En-3-yl-2-ylstannanes via Alkynyliodonium Tosylates Coupling with Stannyl Zirconocene Alkenes. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1543−1545.

(34) Moebius, U.; Clayton, L. K.; Abraham, S.; Harrison, S.; Reinhertz, E. L. The Human Immunodeficiency Virus gp120 Binding Site on CD4: Delineation by Quantitative Equilibrium and Kinetic Binding Studies of Mutants in Conjunction with a High-resolution CD4 Atomic Structure. *J. Exp. Med.* **1992**, *176*, 507−517.

(35) Ding, J.; Das, K.; Moereels, H.; Koymans, L.; Andries, K.; Janssen, P. A.; Hughes, S. H.; Arnold, E. Structure of HIV-1 RT/TIBO R 86183 Complex Reveals Similarity in the Binding of Diverse Nonnucleoside Inhibitors. *Nat. Struct. Biol.* **1995**, *2*, 407−415.

(36) Schäfer, W.; Friebe, W.-G.; Leinert, W.; Mertens, A.; Poll, T.; von der Saal, W.; Zilch, H.; Nuber, H.; Ziegler, M. L. Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase: Molecular Modeling and X-ray Structure Investigations. *J. Med. Chem.* **1993**, *36*, 726−732.

(37) Casimiro-Garcia, A. New Anti-HIV Agents. Part I. The Alkenyldiarylmethanes as Non-nucleoside Reverse Transcriptase Inhibitors. Part II. Design and Synthesis of Two Series of Cosalane Analogs. In *Department of Medicinal Chemistry and Molecular Pharmacology*; Purdue University: West Lafayette, IN, 1999; p 208.

(38) Smirnov, E. A.; Kirichenko, L. N. Structure and Color of Salicylideneaniline Derivatives Containing Additional Substituents in the Aldehyde Component. *Dokl. Chem.* **1968**, *179*, 240−243.

(39) Plooard, P. I.; Guillet, J. E. Photochemistry of Ketone Polymers. VI. Photolysis of Keto Diesters and Their Copolymers. *Macromolecules* **1972**, *5*, 405−410.

(40) Borsche, W.; Bolser, C. E. Regarding Several Oxyazoaldehydes. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2094−2104.

(41) Upton, M.; Jaeda, M. J.; Upton, C. Novel 5,8-Diazabenzo[*c*]-phenanthrenes: Synthesis and Mutagenicity. *J. Pharm. Pharmacol.* **1998**, *50*, 475−482.

(42) VanAllan, J. A. Derivatives of Benzoylresorcinol. *J. Org. Chem.* **1958**, *23*, 1679−1682.

(43) Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. Rapid and Automated Tetrazolium-based Colorimetric Assay for the Detection of anti-HIV Compounds. *J. Virol. Methods* **1988**, *20*, 309−321.

(44) Popovic, M.; Sarngadharan, M. G.; Read, E.; Gallo, R. C. Detection, Isolation and Continuous Production of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and pre-AIDS. *Science* **1984**, *224*, 497−500.

(45) Barré-Sinoussi, F.; Chermann, J. C.; Nugeyre, M. T.; Chamaret, S.; Gruest, J.; Dauguet, C.; Axler-Blin, C.; Vézinet-Brun, F.; Rouzioux, C.; Rozenbaum, W.; Montagnier, L. Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for AIDS. *Science* **1983**, *220*, 868−871.

(46) Miyoshi, I.; Taguchi, H.; Kobonishi, I.; Yoshimoto, S.; Ohtsuki, Y.; Shiraishi, Y.; Akagi, T. Type C Virus-producing Cell Lines Derived from Adult T Cell Leukemia. *Gann. Monogr.* **1982**, *28*, 219−228.
(47) Patel, J. U.; Prankerd, R. J.; Sloan, K. B. A Prodrug Aproach to Increasing the Oral Potency of a Phenolic Drug. 1. Synthesis, Characterization, and Stability of an *O*-(Imidomethyl) Derivative of 17β-Estradiol. *J. Pharm. Sci.* **1994**, *83*, 1477−1481.
(48) Goskonda, V. R.; Khan, M. A.; Bodor, N. S.; Reddy, I., K. Chemical Delivery Systems: Evaluation of Physicochemical Properties and Enzymatic Stability of Phenylephrone Derivatives. *Pharm. Dev. Technol.* **1999**, *4*, 189−198.
(49) Bonina, F.; Puglia, C.; Santagati, N. A.; Saija, A.; Tomaino, A.; Tita, B. Oligoethylene Ester Derivatives of Ketoprofen, Naproxen and Diclofenac as Oral Prodrugs: A Pharmacological Evaluation. *Pharmazie* **2002**, *57*, 552−555.
(50) Bodor, N.; Visor, G. Improved Delivery Through Biological Membranes. XVII. A Site-Specific Chemical Delivery System as a Short-Acting Mydriatic Agent. *Pharm. Res.* **1984**, *1*, 168−173.
(51) Aungst, B. J.; Blake, J. A.; Rogers, N. J.; Saitoh, H.; Hussain, M. A.; Ensinger, C. L.; Pruitt, J. R. Prodrugs to Improve the Oral Bioavailability of a Diacidic Nonpeptide Angiotensin II Antagonist. *Pharm. Res.* **1995**, *12*, 763−767.
(52) Bundgaard, H.; Buur, A.; Chang, S.; Lee, V. H. Timolol Prodrugs: Synthesis, Stability and Lipophilicity of Various Alkyl, Cycloalkyl and Aromatic Esters of Timolol. *Int. J. Pharm.* **1988**, *46*, 77−88.
(53) Bundgaard, H.; Rasmussen, G. J. Prodrugs of Peptides. 11. Chemical and Enzymatic Hydrolysis Kinetics of N-Acyloxymethyl Derivatives of a Peptide-like Bond. *Pharm. Res.* **1991**, *8*, 1238−1242.
(54) Anderson, B. D.; Galinsky, R. E.; Baker, D. C.; Chi, S.; Hoesterey, B. L.; Morgan, M. E.; Murakami, K.; Mitsuya, H. Approaches Toward the Opimization of CNS Uptake of Anti-AIDS Agents. *J. Controlled Release* **1991**, *19*, 219−230.

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