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Synthesis of Alkenyldiarylmethane (ADAM) Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors with Non-Identical Aromatic Rings

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Abstract—The existing methods for the synthesis of alkenyldiarylmethane (ADAM) non-nucleoside reverse transcriptase inhibitors proceed from symmetrical benzophenones and therefore result in products with identical aromatic rings. New methods have therefore been devised for the preparation of stereochemically defined ADAMs with non-identical aromatic rings. The new routes rely on palladium-catalyzed reactions, including Sonogashira, Suzuki, Stille, and hydroarylation methodology. Several of the new ADAMs inhibited the cytopathic effect of HIV-1 in cell culture and HIV-1 reverse transcriptase at submicromolar concentrations.

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are a structurally diverse set of compounds that act by an allosteric mechanism.[1] A number of NNRTIs, including nevirapine, delavirdine, and efavirenz, are used in combination chemotherapy for the treatment of AIDS.[2–4] However, drug incompatibilities, adverse effects, the emergence of resistant viral strains, and cross-resistance continue to limit the clinical usefulness of the NNRTIs.[5–9] Additional NNRTIs are therefore needed that might have improved pharmacokinetics, limited toxicities, and more favorable resistance mutation profiles. The alkenyldiarylmethanes (ADAMs) have recently been identified as a new class of NNRTIs.[10–13] Several of the ADAMs, including compounds **1**–**3**, are potent inhibitors of the cytopathic effect of HIV-1 in cell culture, with EC_{50} values in the low nanomolar range. A number of HIV-1 strains containing AZT resistance mutations have shown increased sensitivity to some of the ADAMs, indicating a possible therapeutic role for the ADAMs in combination with AZT.[12]

The existing ADAM syntheses include the attachment of the alkenyl chain to symmetrical benzophenone derivatives by Wittig,[10–12,14] McMurry,[13,15] or Horner–Emmons[12] reactions. These methods are not ideal for the synthesis of ADAMs having differently substituted aromatic rings because they would lead to mixtures of *cis* and *trans* isomers when employed with benzophenones having non-identical aromatic rings. In addition, benzophenones with different substituents on each aromatic ring are not as readily available as those with identical substituents. Since the two aromatic rings of the ADAMs are not in identical environments when bound in the NNRTI binding pocket of HIV-1 reverse transcriptase,[12,13] it is logical to conclude that ADAMs with identical aromatic substituents are not the ideal choice to 'fit' the binding site. Consequently, a need does exist for ADAMs with non-identical aromatic rings, and we have therefore recently investigated ADAM syntheses that do not proceed from benzophenones, including the use of palladium-catalyzed reactions in the solid phase synthesis of ADAMs **4** and **5**.[16]

The present communication details the use of the Sonogashira, Suzuki, Stille, and hydroarylation reactions in stereochemically defined, solution phase syntheses of new ADAMs **6**–**8** with differently substituted

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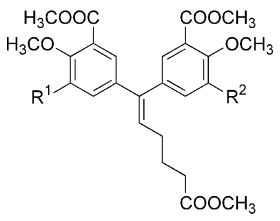

1, $R^1 = R^2 = Br$
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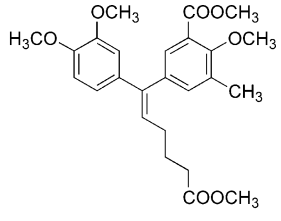
5, $R^1 = H$, $R^2 = Cl$
8, $R^1 = R^2 = H$



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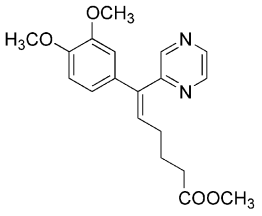

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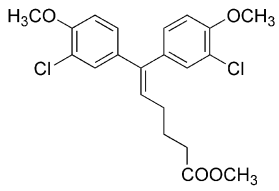

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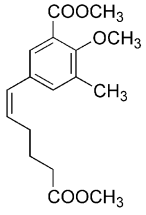

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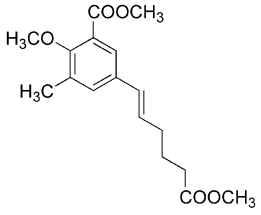

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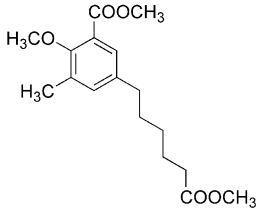

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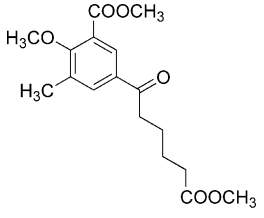
aromatic rings. These compounds were chosen to explore the importance of the aromatic methyl ester groups and halogen atoms for biological activity. In addition, the truncated compounds **10** and **11**, in which one of the aromatic rings of **3** has been eliminated, were prepared. The corresponding reduction product **12**, as well as the oxidized compound **13**, were also synthesized. The investigation of the biological activities of these compounds should be helpful in the identification of the ADAM 'pharmacophore'.



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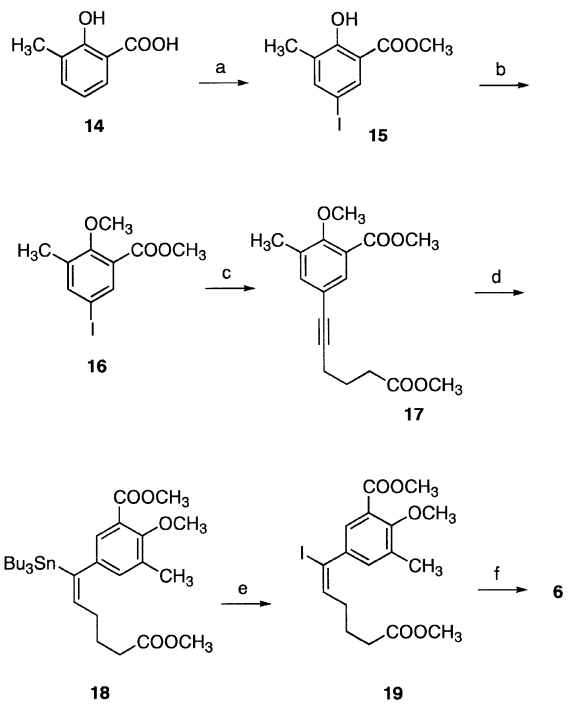
Results and Discussion

3-Methylsalicylic acid (**14**) was quantitatively converted into its methyl ester using $TMSCHN_2$ in a mixture of



Scheme 1. Reagents and conditions: (a) (i) $TMSCHN_2$, MeOH, benzene, 23 °C (2 h); (ii) NaI, NaOH, MeOH, then NaOCl (5.25%), 0–3 °C (3 h); (b) Me_2SO_4, K_2CO_3, acetone, reflux (24 h); (c) methyl 5-hexynoate, $Pd(OAc)_2$, PPh_3, CuI, triethylamine, EtOAc, 23 °C (12 h); (d) Bu_3SnH, $Pd(PPh_3)_4$, THF, 23 °C (1 h); (e) I_2, CH_2Cl_2, 23 °C (50 min); (f) 3,4-dimethoxyphenylboronic acid, Na_2CO_3, $Pd(PPh_3)_4$, CH_3CN/H_2O, 90 °C (19 h).

methanol and benzene.[17] The resulting methyl ester was iodinated using sodium iodide in the presence of sodium hypochlorite as an oxidant to afford intermediate **15** (Scheme 1).[18] Treatment of the iodinated ester **15** with dimethyl sulfate and K_2CO_3 produced methyl 5-iodo-3-methyl-2-methoxybenzoate **16** in 90% overall yield. Palladium-catalyzed Sonogashira coupling of methyl 5-hexynoate with iodinated ester **16** afforded the alkyne **17**,[19,20] which underwent hydrostannation in the presence of $Pd(PPh_3)_4$ to give the regiochemically and stereochemically defined vinylstannane **18** in 39% overall yield.[21] Subsequent treatment of **18** with I_2 in CH_2Cl_2 produced vinyl iodide **19**.[22] The Suzuki coupling of **19** with 3,4-dimethoxyphenylboronic acid in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 afforded the desired ADAM **6** in 53% yield.[23,24]

Palladium-catalyzed Sonogashira coupling of 2-iodopyrazine (**20**) with methyl 5-hexynoate afforded alkyne **21** in 81% yield (Scheme 2). Subsequent hydrostannation and I_2 displacement of the tributyltin group produced vinyl iodide **23** in 76% yield. Coupling of **23** with 3,4-dimethoxyphenylboronic acid under Suzuki conditions afforded ADAM **7** in 52% yield.

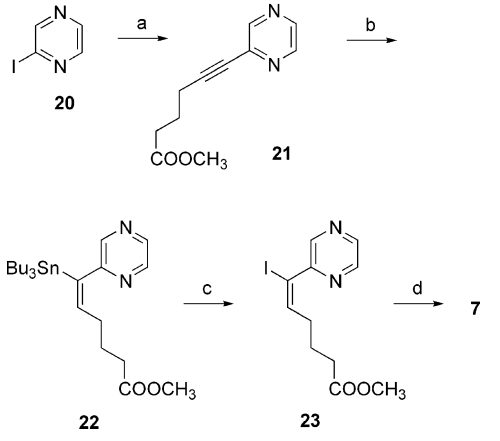
As shown in Scheme 3, treatment of 5-iodosalicylic acid **24** with dimethyl sulfate and K_2CO_3 produced **25**, which coupled with methyl 5-hexynoate under Sonogashira reaction conditions to afford alkyne **26**. Palladium-catalyzed hydroarylation of alkyne **26** served as a key step to construct the second aromatic ring in compound **8**.[25]

Since the addition can happen at both positions of the carbon–carbon triple bond, two structural isomers (**8** and **27**) are formed in almost equal yield. Careful preparative TLC isolation afforded pure ADAM **8** in 31% yield, and well as pure **27** in 30% yield.

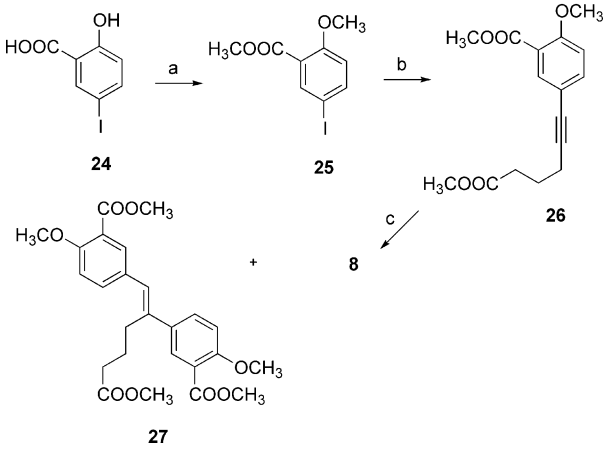
The same strategy was employed to construct ADAM **9** as outlined in Scheme 4. 2-Chlorophenol was iodinated using sodium iodide in the presence of sodium hypochlorite as an oxidant. Treatment of the iodinated phenol **29** with dimethyl sulfate and K_2CO_3 produced **30**. Sonogashira coupling of iodo compound **30** with methyl 5-hexynoate gave alkyne **31**. Palladium-catalyzed hydroarylation of alkyne **31** gave a mixture of compounds **9** and **32**. Purification of both **9** and **32** was achieved by preparative TLC.

The syntheses of compounds **10**–**13** are illustrated in Scheme 5. Hydrogenation of **17** using Lindlar's catalyst gave the *cis*-alkene **10**. Palladium-catalyzed Heck coupling of methyl 5-hexenoate with **16** produced the *trans*-alkene **11**. Additional analogues (**12**–**13**) were also made through complete hydrogenation of **17** or by heating **17** in refluxing formic acid.[26]

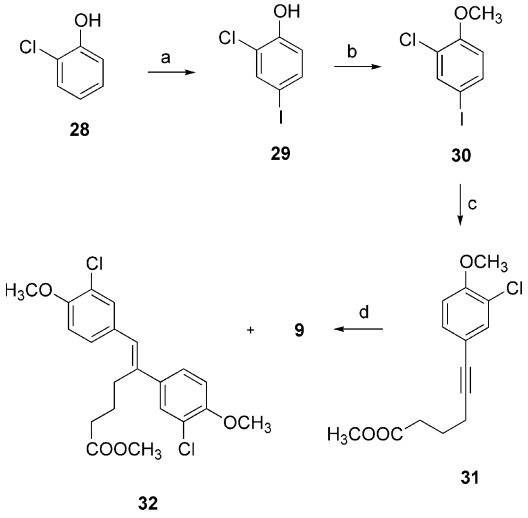
The new ADAMs synthesized in this study were evaluated for inhibition of the cytopathic effect of HIV-1_{RF} in CEM-SS cells, and the resulting EC_{50} values are listed in Table 1. The cytotoxic concentrations in uninfected CEM-SS cells (CC_{50} values) were determined as well. These compounds were also tested for inhibition of HIV-1 RT, and the resulting IC_{50} values are also included in Table 1. Two of the new ADAMs (**6** and **8**) inhibited the cytopathic effect of HIV-1_{RF} with EC_{50} values of 0.21 and 0.47 μM, respectively. These analogues were also found to inhibit HIV-1 RT with poly(rC)·oligo(dG) as the template primer with IC_{50} values of 0.074 and 0.504 μM. Compound **7**, with a heterocyclic ring, was inactive. The esters on the aromatic ring seem to be essential for the anti-HIV activity (ADAM **9** was inactive, vs ADAM **2** with EC_{50} of 13 nM). However, the halogen atoms on the aromatic ring



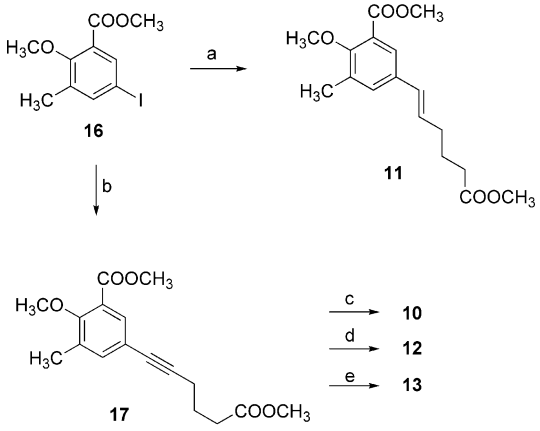
Scheme 2. Reagents and conditions: (a) methyl 5-hexynoate, $Pd(OAc)_2$, PPh_3, CuI, triethylamine/EtOAc, 23 °C (12 h); (b) Bu_3SnH, $Pd(PPh_3)_4$/THF, 23 °C (1 h); (c) I_2/CH_2Cl_2, 23 °C (30 min); (d) 3,4-dimethoxyphenylboronic acid, Na_2CO_3, $Pd(PPh_3)_4$, CH_3CN/H_2O, 90 °C (14 h).



Scheme 3. Reagents and conditions: (a) $(CH_3)_2SO_4$, K_2CO_3, acetone, reflux (14 h); (b) methyl 5-hexynoate, $Pd(OAc)_2$, PPh_3, CuI, TEA, EtOAc, 23 °C (12 h); (c) Compound **25**, $Pd_2(dba)_3$, Et_2NH, HCOOH, EtOAc, reflux (12 h).



Scheme 4. Reagents and conditions: (a) NaI, NaOH, NaOCl/MeOH, 23 °C (2 h); (b) $(CH_3)_2SO_4$, K_2CO_3, acetone, reflux (14 h); (c) methyl 5-hexynoate, $Pd(OAc)_2$, PPh_3, CuI, TEA, EtOAc, 23 °C (12 h); (d) Compound **30**, $Pd_2(dba)_3$, Et_2NH, HCOOH, EtOAc, reflux (12 h).



Scheme 5. Reagents and conditions: (a) Methyl 5-hexenoate, $Pd(OAc)_2$, TEA, EtOAc, 70 °C (18 h); (b) Methyl 5-hexynoate, $Pd(OAc)_2$, PPh_3, CuI, TEA, EtOAc, 23 °C (12 h); (c) H_2, Pd (5%) on $BaSO_4$, quinoline, 23 °C (18 h); (d) H_2, Pd (5%) on activated carbon (14 h); (e) HCOOH, reflux (2–4 h).

significantly increase the activity (ADAM **2**, $EC_{50}=13$ nM; ADAM **8**, $EC_{50}=470$ nM). The large difference in lipophilicity between ADAM **2** and ADAM **8** due to the incorporation of halogen atoms on the aromatic ring may account for the lower activity of ADAM **8**. Both *cis*- and *trans*-alkenes **10** and **11** were inactive against HIV-1 viruses and HIV-1 RT. This suggests that both aromatic rings are required for targeting the hydrophobic pocket of the RT enzyme, and is also consistent with the 'butterfly model' proposed for the binding of NNRTIs to HIV-1 RT.[10,12,13,27]

It is apparent from the data in Table 1 that there is not a perfect correlation between the anti-HIV-1 EC_{50} values and the reverse transcriptase IC_{50} values. For example, compound **6** is one of the most potent reverse transcriptase inhibitors ever synthesized in the ADAM series (IC_{50} 0.074 μM), but it is about three fold less potent as an inhibitor of the cytopathic effect of HIV-1 in cell culture (EC_{50} 0.21 μM). In contrast, ADAM **1** is less potent than **6** versus RT in the cell-free assay system (IC_{50} 0.3 μM), but it is considerably more potent as an antiviral agent (EC_{50} 0.0013 μM). However, this difference is not unusual for the non-nucleoside reverse transcriptase inhibitors.[28-31] The reverse transcriptase inhibition studies were performed in a cell-free system with a synthetic template/primer, poly(rC).oligo(dG). As discussed elsewhere, the discrepancy in EC_{50} values for inhibition of the cytopathic effect of the virus and the IC_{50} values for reverse transcriptase inhibition may simply reflect the differences between the in vitro assay, in which synthetic template/primer has been added, and the cellular system.[30] In spite of the lack of close correlation of reverse transcriptase inhibitory activity with antiviral activity in the ADAM series, prior work with ADAM-resistant HIV-1 strains having mutations in reverse transcriptase leaves little doubt that in general, the ADAMs are in fact acting as non-nucleoside reverse transcriptase inhibitors.[10,12,13]

Table 1. Anti-HIV activities of the ADAMs

Compd	RT (IC_{50}, μM)[a]	EC_{50} (μM)[b]	CC_{50} (μM)[c]	TI[d]
1[13]	0.3	0.0013	13	10,000
2[12]	0.3	0.013	31.6	2431
3[33]	1.0	0.25	6.0	24
4[16]	0.516	0.020	1.46	73
5[16]	0.587	0.080	2.17	27
6	0.074	0.21	1.14	5.48
7	100	NA[e]	19.40	
8	0.504	0.47	2.0	4.27
9	100	NA	≥6.25	
10	88.2	NA	157.0	
11	100	NA	1.70	
12	1.75	NA	108	
13	100	NA	200	
17	100	NA	62.50	
32	100	NA	≥6.25	

[a]Inhibitory activity versus HIV-1 reverse transcriptase with rCdG as the template primer.
[b]The EC_{50} is the 50% inhibitory concentration for cytopathicity of HIV-1_{RF} in CEM-SS cells.
[c]The CC_{50} is the 50% cytotoxic concentration for mock-infected CEM-SS cells.
[d]The TI is the therapeutical index, which is the CC_{50} divided by the EC_{50}.
[e]NA (not active): no observed inhibition of HIV-1 cytopathicity up to the cytotoxic concentration in uninfected cells.

The methyl ester groups present in the most potent ADAMs are likely to be substrates for a variety of esterases present in the body. Future work in the ADAM series should therefore focus on the exchange of these ester groups with metabolically stable replacements that will retain the anti-HIV activity.

Experimental

Melting points were obtained in capillary tubes and are uncorrected. ^{1}H NMR spectra were determined at 300 MHz. Chemical ionization mass spectra (CIMS) were run using isobutane as the reagent gas. Microanalyses were performed at the Purdue University Microanalysis Laboratory. Silica gel flash chromatography was accomplished using 230–400 mesh silica gel. Unless otherwise stated, chemicals and solvents were reagent grade and used as obtained from commercial sources without further purification. Compounds **15** and **16** were synthesized as described elsewhere.[16]

Methyl 6-[4-methoxy-5-(methoxycarbonyl)-3-methylphenyl]hex-5-ynoate (17). Methyl 5-hexynoate (0.593 g, 4.71 mmol), methyl 5-iodo-3-methyl-2-methoxybenzoate **16** (1.2 g, 3.92 mmol), $Pd(OAc)_2$ (62.4 mg, 0.278 mmol), Ph_3P (145.8 mg, 0.556 mmol), copper(I) iodide (0.15 g, 0.788 mmol), and triethylamine (1.14 g, 11.25 mmol) were stirred in ethyl acetate (30 mL) at room temperature overnight under argon. The mixture was diluted with water (15 mL), and the layers were separated. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated to give a black residue, which was purified by flash chromatography on silica gel (120 g, column: 5×30 cm, hexanes–EtOAc 3:1) to afford **17** as a brown liquid (488 mg, 41%): ^{1}H NMR ($CDCl_3$) δ 7.67 (d, $J=2.08$ Hz, 1H), 7.36 (d, $J=1.69$ Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.68 (s, 3H), 2.50 (t, $J=6.20$ Hz, 2H), 2.46 (t, $J=5.65$ Hz, 2H), 2.27 (s, 3H), 1.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.51, 166.11, 157.81, 137.71, 132.82, 132.26, 124.38, 118.98, 88.64, 80.07, 61.46, 52.12, 51.49, 32.74, 23.72, 18.68, 15.78; EIMS m/z 304 (M^+); HRMS calcd for $C_{17}H_{20}O_5$ 304.1311, found 304.1318. Anal. calcd for $C_{17}H_{20}O_5$: C, 67.07; H, 6.58. Found: C, 66.95; H, 6.47.

Methyl (5E)-6-[4-methoxy-5-(methoxycarbonyl)-3-methylphenyl]-6-(tributylstannyl)hex-5-enoate (18). To a stirred solution of alkyne **17** (67 mg, 0.22 mmol) in dry THF (20 mL) at room temperature was added $(Ph_3P)_4Pd$ (7.6 mg, 0.007 mmol) and, dropwise, Bu_3SnH (96.2 mg, 0.33 mmol). The reaction mixture was kept stirring for 1 h under argon. The solvent was evaporated and the brown residue was purified by flash chromatography on silica gel (30 g, hexanes–EtOAc 3:1, v/v) to afford a colorless oil (116 mg, 94%): ^{1}H NMR ($CDCl_3$) δ 7.16 (d, $J=2.25$ Hz, 1H), 6.86 (d, $J=2.15$ Hz, 1H), 5.70 (t, $J=6.92$ Hz, $J_{SnH}=31.24$ Hz, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.60 (s, 3H), 2.27 (s, 3H), 2.23 (t, $J=7.66$ Hz, 2H), 2.01 (dt, $J=7.31$ and 6.90 Hz, 2H), 1.65 (m,

2H), 1.18–1.44 (m, 18H), 0.83 (t, $J=7.25$ Hz, 9H); ESIMS m/z 595 (MH^+). Anal. calcd for $C_{29}H_{48}SnO_5$: C, 58.59; H, 8.08. Found: C, 58.47; H, 7.96.

Methyl (5E)-6-iodo-6-[4-methoxy-5-(methoxycarbonyl)-3-methylphenyl]hex-5-enoate (19). The vinyl tributylstannane **18** (80 mg, 0.13 mmol) was dissolved in dry CH_2Cl_2 (5 mL). Finely divided I_2 (49.3 mg, 0.19 mmol) was added and the mixture was stirred vigorously at room temperature for 50 min. Saturated aqueous $Na_2S_2O_3$ (5 mL) was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (30 g, hexanes–EtOAc 3:1, v/v) to afford a colorless oil (50.5 mg, 90%): ^{1}H NMR ($CDCl_3$) δ 7.51 (d, $J=2.01$ Hz, 1H), 7.24 (d, $J=2.0$ Hz, 1H), 6.44 (t, $J=7.41$ Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.62 (s, 3H), 2.30 (s, 3H), 2.26 (t, $J=7.43$ Hz, 2H), 2.01 (dt, $J=7.41$ and 7.52 Hz, 2H), 1.70 (m, 2H); CIMS m/z 433 (MH^+). Anal. calcd for $C_{17}H_{21}IO_5$: C, 47.22; H, 4.86. Found: C, 47.21; H, 4.70.

Methyl (5Z)-6-(3,4-dimethoxyphenyl)-6-[4-methoxy-3-(methoxycarbonyl)-5-methylphenyl]hex-5-enoate (6). The vinyl iodide **19** (44.7 mg, 0.103 mmol) and 3,4-dimethoxyphenylboronic acid (18.8 mg, 0.103 mmol) were added to a solution of sodium carbonate (21.8 mg, 0.21 mmol) in water (1 mL) and CH_3CN (2 mL). To the above degassed solution was added $Pd(PPh_3)_4$ (6.0 mg, 0.005 mmol). The resulting mixture was heated at 90 °C (oil bath) under argon for 14 h. The reaction mixture was concentrated and subjected to flash column chromatography on silica gel (30 g, hexanes–EtOAc 3:1, v/v) to afford a light yellow oil (24 mg, 52.7%): ^{1}H NMR ($CDCl_3$) δ 7.43 (d, $J=1.60$ Hz, 1H), 7.12 (d, $J=1.60$ Hz, 1H), 6.79 (d, $J=1.60$ Hz, 1H), 6.75 (d, $J=6.57$ Hz, 1H), 6.63 (dd, $J=6.57$ and 1.60 Hz, 1H), 5.94 (t, $J=7.46$ Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.63 (s, 3H), 2.31 (s, 3H), 2.30 (t, $J=7.30$ Hz, 2H), 2.10 (dt, $J=7.52$ and 7.34 Hz, 2H), 1.77 (m, 2H); EIMS m/z 442 (M^+). Anal. calcd for $C_{25}H_{30}O_7$: C, 67.87; H, 6.79. Found: C, 67.85; H, 6.70.

Methyl 6-pyrazin-2-ylhex-5-ynoate (21). Methyl 5-hexynoate (800 mg, 6.35 mmol), 2-iodopyrazine (872 mg, 4.23 mmol), $Pd(OAc)_2$ (76 mg, 0.34 mmol), PPh_3 (178 mg, 0.68 mmol), copper(I) iodide (161 mg, 0.85 mmol), and triethylamine (930 mg, 9.2 mmol) were added to ethyl acetate (40 mL). The reaction mixture was stirred at room temperature overnight under argon and then concentrated. The residue was purified by flash chromatography on silica gel (80 g, EtOAc–hexanes 2:3, v/v) to afford **21** as a brown liquid (700 mg, 81.1%): ^{1}H NMR ($CDCl_3$) δ 8.61 (br, 1H), 8.50 (d, $J=2.37$ Hz, 1H), 8.43 (d, $J=2.37$ Hz, 1H), 3.68 (s, 3H), 2.56 (t, $J=6.98$ Hz, 2H), 2.52 (t, $J=7.35$ Hz, 2H), 1.96 (m, 2H); CIMS m/z 204 (M^+). Anal. calcd for $C_{11}H_{12}N_2O_2$: C, 64.71; H, 5.88. Found: C, 64.64; H, 5.81.

Methyl (5E)-6-pyrazin-2-yl-6-(tributylstannyl)hex-5-enoate (22). To a stirred solution of alkyne **21** (350 mg, 1.72 mmol) in dry THF (20 mL) at room temperature was added $(Ph_3P)_4Pd$ (99 mg, 0.086 mmol) and, dropwise, Bu_3SnH (749 mg, 2.57 mmol). The reaction mixture was kept stirring for 1 h under argon. The solvent was evaporated and the brown residue was purified by flash chromatography on silica gel (30 g, hexanes–EtOAc 3:1, v/v) to afford a colorless oil (750 mg, 88.3%): ^{1}H NMR ($CDCl_3$) δ 8.48 (br, 1H), 8.34 (s, 1H), 8.28 (d, $J=1.90$ Hz, 1H), 5.93 (t, $J=7.10$ Hz, $J_{SnH}=31.56$ Hz, 1H), 3.63 (s, 3H), 2.36 (t, $J=7.47$ Hz, 2H), 2.28 (t, $J=7.34$ Hz, 2H), 1.77 (m, 2H), 1.23–1.47 (m, 12H), 0.90 (t, $J=7.48$ Hz, 6H), 0.84 (t, $J=7.27$ Hz, 9H); EIMS m/z 436/438 ($M^+ - C_4H_9$). Anal. calcd for $C_{23}H_{40}N_2SnO_2$: C, 55.87; H, 8.10; N, 5.67. Found: C, 55.87; H, 8.17; N, 5.62.

Methyl (5E)-6-iodo-6-pyrazin-2-ylhex-5-enoate (23). The vinyl tributylstannane **22** (600 mg, 1.21 mmol) was dissolved in dry CH_2Cl_2 (10 mL). Finely divided I_2 (463 mg, 1.82 mmol) was added and the mixture was stirred vigorously at room temperature for 30 min. Saturated aqueous $Na_2S_2O_3$ (10 mL) was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (35 g, hexanes–EtOAc 3:1, v/v) to afford a light yellow oil (347 mg, 86.4%): ^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1H), 8.58 (br, 1H), 8.44 (br, 1H), 6.76 (t, $J=7.82$ Hz, 1H), 3.63 (s, 3H), 2.29 (t, $J=7.30$ Hz, 2H), 2.18 (dt, $J=7.29$ and 7.60 Hz, 2H), 1.77 (m, 2H); EIMS m/z 332 (M^+). Anal. calcd for $C_{11}H_{13}N_2IO_2$: C, 39.76; H, 3.92; N, 8.43. Found: C, 39.79; H, 4.00; N, 8.24.

Methyl (5E)-6-(3,4-dimethoxyphenyl)-6-pyrazin-2-ylhex-5-enoate (7). The vinyl iodide **23** (214 mg, 0.64 mmol) and 3,4-dimethoxyphenylboronic acid (117 mg, 0.64 mmol) were added to sodium carbonate (150 mg, 1.42 mmol) in water (1 mL) and CH_3CN (2 mL). To the above degassed solution was added $Pd(PPh_3)_4$ (52.1 mg, 0.045 mmol). The resulting mixture was heated at 90 °C (oil bath) under argon for 14 h. The reaction mixture was concentrated and subjected to flash column chromatography on silica gel (80 g, hexanes–EtOAc 1:1, v/v) to afford **7** as a light yellow oil (114 mg, 51.8%): ^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1H), 8.49 (br, 2H), 6.78 (d, $J=8.28$ Hz, 1H), 6.77 (br, 1H), 6.65 (dd, $J=8.28$ and 1.86 Hz, 1H), 6.17 (t, $J=7.25$ Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.64 (s, 3H), 2.33 (t, $J=7.40$ Hz, 2H), 2.22 (dt, $J=7.46$ and 7.45 Hz, 2H), 1.83 (m, 2H); EIMS m/z 342 (M^+). Anal. calcd for $C_{19}H_{22}N_2O_4$: C, 66.67; H, 6.43. Found: C, 66.91; H, 6.68.

Methyl 5-iodo-2-methoxybenzoate (25). 5-Iodosalicylic acid (7.0 g, 26.5 mmol) was dissolved in acetone (40 mL). Anhydrous K_2CO_3 (5.5 g, 39.75 mmol) and dimethylsulfate (3.8 mL, 39.75 mmol) were added. The reaction mixture was heated at reflux for 14 h, and then the inorganic salts were filtered. The solvent was evaporated and the residue was washed with water (3×20 mL). The crude residue was crystallized from acetone to afford **25** as white solid (7.0 g, 90.4%): mp 47–48 °C; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, $J=2.15$ Hz, 1H), 7.70 (dd, $J=8.57$ and 2.30 Hz, 1H), 6.73 (d, $J=8.68$ Hz, 1H), 3.88 (s, 6H).

Methyl 6-[4-methoxy-5-methoxycarbonyl)phenyl]hex-5-ynoate (26). Methyl 5-hexynoate (441 mg, 3.5 mmol), iodide **25** (984 mg, 3.5 mmol), $Pd(OAc)_2$ (63 mg, 0.28 mmol), copper(I) iodide (133 mg, 0.70 mmol), and triethylamine (990 mg, 9.8 mmol) were mixed in ethyl acetate (40 mL) and the mixture was kept stirring at room temperature overnight under argon. Then the mixture was concentrated and the residue was purified by flash chromatography on silica gel (80 g, solvent: EtOAc–hexanes 1:2, v/v) to give **26** as a yellow oil (380 mg, 26%): ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J = 2.15 Hz, 1H), 7.45 (dd, J = 8.57 and 2.30 Hz, 1H), 6.87 (d, J = 8.68 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.66 (s, 3H), 2.48 (t, J = 7.40 Hz, 2H), 2.44 (t, J = 6.87 Hz, 2H), 1.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.47, 165.80, 158.37, 136.33, 134.83, 119.91, 115.63, 111.85, 88.00, 80.01, 55.96, 51.96, 51.46, 32.76, 23.75, 18.68; CIMS m/z 291 (MH^+).

Hydroarylation of compound 26 to afford 8 and 27. Compound **26** (374 mg, 1.29 mmol), aryl iodide **25** (414 mg, 1.42 mmol), and $Pd_2(dba)_3$ (83 mg, 0.09 mmol) were dissolved in ethyl acetate (40 mL). Diethylamine (310 mg, 4.26 mmol) was added, followed by formic acid (131 mg, 2.84 mmol), and the solution was heated to reflux overnight. The reaction mixture was then cooled to room temperature and washed with diluted HCl and brine. The organics were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The products **8** and **27** were isolated by flash chromatography (hexane/EtOAc 3:1, v/v; silica gel: 100 g) and preparative TLC (hexanes/EtOAc 5:1, v/v).

Methyl 6,6-bis[4-methoxy-3-(methoxycarbonyl)phenyl]-hex-5-enoate (8). Light yellow oil. Yield: 188 mg (32%). ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J = 2.39 Hz, 1H), 7.56 (d, J = 2.22 Hz, 1H), 7.23 (dd, J = 2.03 and 2.08 Hz, 1H), 7.18 (d, J = 2.49 Hz, 1H), 6.98 (d, J = 8.62 Hz, 1H), 6.85 (d, J = 8.76 Hz, 1H), 5.96 (t, J = 7.45 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.86 (s, 6H), 3.62 (s, 3H), 2.29 (t, J = 7.50 Hz, 2H), 2.14 (dt, J = 7.32 and 7.47 Hz, 2H), 1.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.83, 166.71, 166.52, 158.14, 139.77, 134.80, 134.71, 132.88, 132.25, 131.52, 129.98, 128.54, 119.85, 111.91, 111.70, 56.05, 52.02, 51.44, 33.48, 29.11, 25.03; CIMS m/z 457 (MH^+). Anal. calcd for $C_{25}H_{28}O_8$: C, 65.78; H, 6.14. Found: C, 65.13; H, 6.22.

Methyl 5,6-bis[4-methoxy-3-(methoxycarbonyl)phenyl]-hex-5-enoate (27). Light yellow oil. Yield: 176 mg (30%). ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 2.30 Hz, 1H), 7.74 (d, J = 2.22 Hz, 1H), 7.54 (dd, J = 2.30 and 2.22 Hz, 1H), 7.41 (dd, J = 2.30 and 2.22 Hz, 1H), 6.98 (s, 1H), 6.96 (s, 1H), 6.62 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.59 (s, 3H), 2.68 (t, J = 7.73 Hz, 2H), 2.28 (t, J = 7.32 Hz, 2H), 1.71 (m, 2H); CIMS m/z 457 (MH^+). Anal. calcd for $C_{25}H_{28}O_8$: C, 65.78; H, 6.14. Found: C, 65.47; H, 6.35.

2-Chloro-4-iodophenol (29). 2-Chlorophenol (10.0 g, 77.82 mmol) was dissolved in MeOH (200 mL). Sodium iodide (11.70 g, 77.82 mmol) and sodium hydroxide (3.12 g, 77.82 mmol) were added, and the mixture was cooled to 0 °C in an ice-water bath. Aqueous sodium hypochlorite (119.2 g of 5% solution) was added dropwise. The mixture was stirred at room temperature for 2 h and the excess hypochlorite was quenched with 10% aqueous sodium thiosulfate (30 mL). The mixture was adjusted to pH 4 using 1 N HCl. The mixture was extracted with ether (3×40 mL). The ether layers were combined and dried over Na_2SO_4. After the solvent was evaporated, the crude solid was crystallized from acetone–hexanes (1:1, v/v) to give 2-chloro-4-iodophenol as a light brown solid (19.35 g, 99%): mp 54.5–55.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 1.98 Hz, 1H), 7.45 (dd, J = 8.47 and 1.90 Hz, 1H), 6.78 (d, J = 8.65 Hz, 1H), 5.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 151.34, 137.29, 136.90, 121.08, 118.17, 81.54.

2-Chloro-4-iodoanisole (30). The above phenol **29** (8.0 g, 31.45 mmol) was dissolved in acetone (50 mL), followed by addition of anhydrous K_2CO_3 (6.52 g, 47.17 mmol) and dimethylsulfate (4.46 mL, 47.17 mmol). The reaction mixture was heated at reflux for 14 h, and then the inorganic salts were filtered. The solvent was evaporated and the residue was washed with water (3×20 mL). The crude residue was crystallized from acetone to afford **30** as light brown needles (8.0 g, 94%): mp 83–84 °C: ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J = 2.03 Hz, 1H), 7.49 (dd, J = 8.58 and 1.96 Hz, 1H), 6.69 (d, J = 8.63 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.05, 138.15, 136.51, 123.75, 113.89, 81.81, 56.13; EIMS m/z 269 (MH^+).

Methyl 6-(3-chloro-4-methoxyphenyl)hex-5-ynoate (31). Methyl 5-hexynoate (504 mg, 4.0 mmol), iodide compound **30** (1.07 g, 4.0 mmol), $Pd(OAc)_2$ (71.8 mg, 0.32 mmol), copper(I) iodide (152 mg, 0.80 mmol), and triethylamine (1.17 g, 11.56 mmol) were mixed in ethyl acetate (40 mL) and the mixture was kept stirring at room temperature overnight under argon atmosphere. The mixture was then concentrated and the residue was purified by flash chromatography on silica gel (80 g, eluent: EtOAc–hexanes 1:4, v/v) to give **31** as a brown oil (827 mg, 78%): ^{1}H NMR ($CDCl_3$) δ 7.41 (d, J = 1.95 Hz, 1H), 7.25 (dd, J = 8.57 and 2.0 Hz, 1H), 6.83 (d, J = 8.57 Hz, 1H), 3.89 (s, 3H), 3.68 (s, 3H), 2.50 (t, J = 7.42 Hz, 2H), 2.46 (t, J = 7.86 Hz, 2H), 1.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.51, 154.66, 133.15, 131.08, 122.12, 116.79, 111.63, 88.28, 79.89, 56.10, 51.55, 32.82, 23.80, 18.77; CIMS m/z 267 (MH^+).

Hydroarylation of compound 31 to afford 9 and 32. Compound **31** (508 mg, 1.90 mmol), aryl iodide **30** (563.6 mg, 2.1 mmol), and $Pd_2(dba)_3$ (122 mg, 0.133 mmol) were dissolved in ethyl acetate (45 mL). Diethylamine (458 mg, 6.27 mmol) was added, followed by formic acid (210 mg, 4.56 mmol), and the solution was heated to reflux under argon overnight. The reaction mixture was then cooled to room temperature and washed with diluted HCl and brine. The organics were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The products were isolated through flash chromatography (hexane–EtOAc 3:1, v/v; silica gel: 100 g) and preparative TLC (hexane–EtOAc 5:1, v/v).

Methyl 6,6-bis(3-chloro-4-methoxyphenyl)hex-5-enoate (9). Colorless oil. Yield: 295 mg (38%). ^{1}H NMR ($CDCl_3$) δ 7.22 (d, J = 2.26 Hz, 1H), 7.14 (d, J = 1.99 Hz, 1H), 7.02 (dd, J = 3.92 and 2.13 Hz, 1H), 6.98 (dd, J = 3.50 and 1.88 Hz, 1H), 6.93 (d, J = 8.38 Hz, 1H), 6.81 (d, J = 8.61 Hz, 1H), 5.92 (t, J = 7.44 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.63 (s, 3H), 2.29 (t, J = 7.44 Hz, 2H), 2.13 (dt, J = 7.33 and 7.37 Hz, 2H), 1.77 (m, 2H); CIMS m/z 409 (MH^+). Anal. calcd for $C_{21}H_{22}Cl_2O_4$: C, 61.62; H, 5.42; Cl, 17.32. Found C, 61.50; H, 5.46; Cl, 17.30.

Methyl 5,6-bis(3-chloro-4-methoxyphenyl)hex-5-enoate (32). Colorless oil. Yield: 287 mg (37%). ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 2.12 Hz, 1H), 7.30 (m, 2H), 7.16 (dd, J = 8.49 and 2.0 Hz, 1H), 6.93 (d, J = 8.57 Hz, 2H), 6.56 (s, 1H), 3.92 (s, 6H), 3.63 (s, 3H), 2.66 (dt, J = 7.11 and 2.41 Hz, 2H), 2.29 (t, J = 7.27 Hz, 2H), 1.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.52, 154.27, 153.65, 140.22, 135.61, 131.20, 130.43, 128.27, 128.03, 126.80, 125.69, 122.40, 122.16, 111.88, 111.79, 56.14, 51.49, 33.45, 29.14, 23.63; CIMS m/z 409 (MH^+). Anal. calcd for $C_{21}H_{22}Cl_2O_4$: C, 61.62; H, 5.42; Cl, 17.32. Found C, 61.65; H, 5.62; Cl, 17.32.

Methyl (5Z)-6-[4-methoxy-5-(methoxycarbonyl)-3-methylphenyl]hex-5-enoate (10). The alkyne **17** (112 mg, 0.37 mmol) was hydrogenated using 5% palladium on barium sulfate (20 mg) and pure quinoline (20 mg) in 10 mL of MeOH. After 18 h, the catalyst was removed by filtration and the solvent was evaporated. The resulting residue was purified by flash chromatography on silica gel (20 g, column: 1×30 cm), using hexanes–EtOAc (3:1 v/v) as eluent, to give a colorless oil (100 mg, 88.5%): ^{1}H NMR ($CDCl_3$) δ 7.51 (d, J = 2.03 Hz, 1H), 7.23 (d, J = 1.58 Hz, 1H), 6.36 (d, J = 11.63 Hz, 1H), 5.62 (dt, J = 11.60 and 5.84 Hz, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 3.64 (s, 3H), 2.34 (t, J = 5.67 Hz, 2H), 2.31 (s, 3H), 2.23 (dt, J = 7.2 and 5.9 Hz), 1.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.78, 166.77, 156.79, 135.16, 132.76, 132.31, 131.76, 129.18, 128.31, 124.08, 61.35, 52.03, 51.34, 33.28, 27.61, 24.84, 15.96; EIMS m/z 306 (M^+); HRMS calcd for $C_{17}H_{22}O_5$ 306.1467, found 306.1467. Anal. calcd for $C_{17}H_{22}O_5$: C, 66.66; H, 7.19. Found: C, 66.47; H, 7.28.

Methyl (5E)-6-[4-methoxy-5-(methoxycarbonyl)-3-methylphenyl]hex-5-enoate (11). A solution of methyl 5-iodo-3-methyl-2-methoxybenzoate **16** (673 mg, 2.2 mmol), methyl 5-hexenoate (256 mg, 2.0 mmol), palladium acetate (7 mg, 0.03 mmol), tri-*o*-tolyphosphine (37 mg, 0.12 mmol), triethylamine (7 mL), and acetonitrile (15 mL) was heated under argon at 70 °C for 18 h. The cooled reaction mixture was evaporated and diluted with water (8 mL) and methylene chloride (40 mL). The methylene chloride layer was separated, washed with water, and dried over anhydrous sodium sulfate. Evaporation of the solvent then gave a brown residue, which was further purified by flash chromatography on silica gel (80 g, hexanes/EtOAc 4:1, v/v) to afford a yellow oil (300 mg, 42.1%): ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 2.35 Hz, 1H), 7.32 (d, J = 2.06 Hz, 1H), 6.32 (d, J = 15.83 Hz, 1H), 6.12 (dt, J = 15.72 and 6.96 Hz, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H), 2.36 (t, J = 7.42 Hz, 2H), 2.29 (s, 3H), 2.24 (dt, J = 7.18 and 6.83 Hz, 2H), 1.80 (m, 2H); EIMS m/z 306 (M^+); HRMS calcd for $C_{17}H_{22}O_5$ 306.1467, found 306.1465. Anal. calcd for $C_{17}H_{22}O_5$: C, 66.66; H, 7.19. Found: C, 66.54; H, 7.30.

Methyl 6-[4-methoxy-5-(methoxycarbonyl)-3-methylphenyl]hexanoate (12). The alkyne **17** (231 mg, 0.76 mmol) was hydrogenated at atmospheric pressure over palladium (5%) on activated carbon (40 mg) in ethyl acetate (15 mL). After TLC (silica gel, hexanes–EtOAc 4:1, v/v) had shown that all the starting material was consumed (14 h), the catalyst was removed by filtration and the solvent was removed at reduced pressure to give a brown oil. This crude product was flash chromatographed on silica gel (10 g) using hexanes–EtOAc (4:1 v/v) as eluent. Evaporation of the solvent gave the product **12** (200 mg, 85.5%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.42 (d, J = 2.22 Hz, 1H), 7.14 (d, J = 2.11 Hz, 1H), 3.90 (s, 3H), 3.79 (s, 3H), 3.66 (s, 3H), 2.54 (t, J = 7.72 Hz, 2H), 2.30 (t, J = 7.0 Hz, 2H), 2.28 (s, 3H), 1.62 (m, 4H), 1.34 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.11, 166.98, 156.65, 137.56, 135.10, 132.32, 128.57, 124.43, 61.34, 52.00, 51.37, 34.72, 33.84, 30.88, 28.57, 24.62, 15.91; CIMS m/z 309 (MH^+); HRMS calcd for $C_{17}H_{25}O_5$ (MH^+) 309.1702, found 309.1689. Anal. calcd for $C_{17}H_{24}O_5$: C, 66.23; H, 7.79. Found: C, 66.20; H, 7.81.

Methyl 6-[4-methoxy-5-(methoxycarbonyl)-3-methylphenyl]-6-oxohexanoate (13). The alkyne **17** (124 mg, 0.41 mmol) and formic acid (10 mL) were placed in a 25 mL round-bottomed flask equipped with reflux condenser that was properly connected to a 100 mL graduate cylinder inverted in a breaker of water in order to monitor the evolution of carbon monoxide gas. The reaction flask was immersed in an oil bath at 100 °C. Gas evolution ceased after 1 h, and the system was left for 1 h to reach ambient temperature. The solvent was evaporated to give pure ketone **13** as a yellow oil (120 mg 90.9%): ^{1}H NMR ($CDCl_3$) δ 8.20 (d, J = 2.17 Hz, 1H), 7.94 (d, J = 1.47 Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.66 (s, 3H), 2.96 (t, J = 6.78 Hz, 2H), 2.36 (t, J = 7.09 Hz, 2H), 2.34 (s, 3H), 1.73 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 198.16, 173.77, 166.14, 162.12, 134.24, 133.22, 131.93, 129.50, 124.14, 61.51, 52.32, 51.44, 37.84, 33.75, 24.39, 23.45, 16.15; CIMS m/z 323 (MH^+); HRMS calcd for $C_{17}H_{23}O_6$ (MH^+) 323.1495, found 323.1489. Anal. calcd for $C_{17}H_{22}O_6$: C, 63.35; H, 6.83. Found: C, 63.20; H, 6.79.

In vitro anti-HIV assay. Anti-HIV screening of test compounds against various viral isolates and cell lines was performed as previously described.[32] This cell-based microtiter assay quantitates the drug-induced protection from the cytopathic effect of HIV-1. Data are presented as the percent control of MTS (CellTiter®, Promega, Madison, WI, USA) values for the uninfected, drug-free control. EC_{50} values reflect the drug concentration that provides 50% protection from the cytopathic effect of HIV-1 in infected cultures, while the CC_{50} reflects the concentration of drug that causes 50% cell death in the uninfected cultures. MTS-based results were confirmed

by measurement of cell-free supernatant RT and p24 levels. All MTS cytoprotection data were derived from triplicate tests on each plate with the EC_{50} value representing the average of the triplicates. The error of the triplicates was less than 10% for all determinations.

Assay for inhibition of HIV-1 RT. The effects of the compounds on the HIV-1 RT enzyme were performed using purified p66/51 RT (a kind gift of S. Hughes, ABL-Basic Research Program, NCI-FCRDC). Inhibition of reverse transcription was measured by the level of incorporation of [^{32}P]GTP into the poly(rC)-oligo(dG) (rCdG) homopolymer template primer system.[5]

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