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

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In an effort to elucidate a set of structure−activity relationships in the alkenyldiarylmethane (ADAM) series of non-nucleoside reverse transcriptase inhibitors, a number of modifications were made at two locations: (1) the meta positions of the two aromatic rings and (2) the end of the alkenyl chain. Forty-two new ADAMs were synthesized and evaluated for inhibition of the cytopathic effect of HIV-1_{RF} in CEM-SS cell culture and for inhibition of HIV-1 reverse transcriptase. The size of the aromatic substituents was found to affect anti-HIV activity, with optimal activity appearing with Cl, CH_3, and Br substituents and with diminished activity occurring with smaller (H and F) or larger (I and CF_3) substituents. The substituents at the end of the alkenyl chain were also found to influence the antiviral activity, with maximal activity associated with methyl or ethyl ester groups and with diminished activity resulting from substitution with higher esters, amides, sulfides, sulfoxides, sulfones, thioesters, acetals, ketones, carbamates, ureas, and thioureas. Twelve of the new ADAMs displayed submicromolar EC_{50} values for inhibition of the cytopathic effect of HIV-1_{RF} in CEM-SS cells. Selected ADAMs, **19** and **21**, were compared to previously published ADAMs **15** and **17** for antiviral efficacy and activity against the HIV-1 reverse transcriptase enzyme. All four ADAMs were found to inhibit HIV-1 reverse transcriptase enzyme activity, to inhibit the replication of a variety of HIV-1 clinical isolates representing syncytium-inducing, nonsyncytium-inducing, and subtype representative isolates, and to inhibit HIV-1 replication in monocytes. Subsequent assessment against a panel of site-directed reverse transcriptase mutants in NL4-3 demonstrated no effect of the K103N mutation on antiviral efficacy and a slight enhancement (6- to 11-fold) in sensitivity to AZT-resistant viruses. Additionally, ADAMs **19** (44-fold) and **21** (29-fold) were more effective against the A98G mutation (found in association with nevirapine resistance in vitro), and ADAM **21** was 5-fold and 2-fold more potent against the Y181C inactivation mutation than the previously reported ADAMs **15** and **17**, respectively. All four ADAMs were tested for efficacy against a multidrug-resistant virus derived from a highly experienced patient expressing resistance to the reverse transcriptase enzyme inhibitors AZT, ddI, 3TC, d4T, foscarnet, and nevirapine, as well as the protease inhibitors indinavir, saquinavir, and nelfinavir. ADAM **21** was 2-fold more potent than ADAM **15** and 6-fold more potent than ADAMs **17** and **19** at preventing virus replication. Thus, we have identified a novel series of reverse transcriptase inhibitors with a favorable profile of antiviral activity against the primary mutation involved in clinical failure of non-nucleoside reverse transcriptase inhibitors, K103N, and that retain activity against a multidrug-resistant virus.

Introduction

The three currently available non-nucleoside reverse transcriptase inhibitors (NNRTIs) for the treatment of AIDS are nevirapine, delavirdine, and efavirenz.[1−3] Although the therapeutic use of the NNRTIs is complicated by the rapid development of viral resistance and drug toxicity, they have proven to be useful in combination therapy with nucleoside reverse transcriptase inhibitors and protease inhibitors.[4] The employment of NNRTIs in combination with two additional anti-HIV agents has been reported to result in decreased HIV-1 RNA levels, increased CD4 lymphocyte counts, and delayed disease progression. However, drug incompatibilities, adverse effects, and cross-resistance continue to restrict the selection of anti-HIV agents for combination chemotherapy.[5−9] Therefore, the synthesis of additional NNRTIs, which might have novel resistance mutation profiles and pharmacokinetic properties, remains a worthwhile goal. The new compounds synthesized in the present investigation were evaluated as inhibitors of the HIV-1 reverse transcriptase and HIV-1 replication in vitro. The lead alkenyldiarylmethanes exhibited a broad range of antiviral activity against a variety of clinical isolates including subtype representa-

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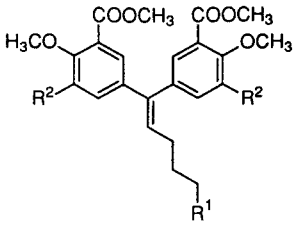


1 R^1 = Et; R^2 = H

2 R^1 = Et; R^2 = F

3 R^1 = Et; R^2 = Cl

4 R^1 = Et; R^2 = CH_3

5 R^1 = Et; R^2 = Br

6 R^1 = Et; R^2 = I

7 R^1 = Et; R^2 = CF_3

8 R^1 = C≡CH; R^2 = Cl

9 R^1 = C≡CH; R^2 = Br

10 R^1 = $CH{=}CH_2$; R_2 = Cl

11 R^1 = $CH{=}CH_2$; R_2 = Br

12 R^1 = Ph; R_2 = Cl

13 R^1 = Ph; R_2 = Br

14 R^1 = COOMe; R_2 = F

15 R^1 = COOMe; R_2 = Cl

16 R^1 = COOMe; R_2 = CH_3

17 R^1 = COOMe; R_2 = Br

18 R^1 = COOMe; R_2 = CF_3

19 R^1 = COOEt; R_2 = Cl

20 R^1 = COOEt; R_2 = CH_3

21 R^1 = COOEt; R_2 = Br

22 R^1 = COO*n*-Pr; R_2 = Cl

23 R^1 = COO*n*-Pr; R_2 = CH_3

24 R^1 = COO*n*-Pr; R_2 = Br

25 R^1 = COO*i*-Pr; R_2 = Cl

26 R^1 = COO*i*-Pr; R_2 = CH_3

27 R^1 = COO*i*-Pr; R_2 = Br

28 R^1 = $CONMe_2$; R_2 = Cl

29 R^1 = $CONMe_2$; R_2 = CH_3

30 R^1 = CO*N*-piperidyl; R_2 = Cl

31 R^1 = CO*N*-piperidyl; R_2 = CH_3

32 R^1 = $COOCH_2CH_2SiMe_3$; R_2 = CH_3

33 R^1 = SMe; R_2 = Cl

34 R^1 = SOMe; R_2 = Cl

35 R^1 = SO_2Me; R_2 = Cl

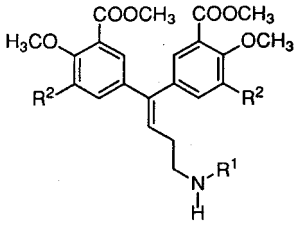
36 R^1 = COSMe; R_2 = Cl

37 R^1 = COSEt; R_2 = Cl

38 R^1 = $CH(OMe)_2$; R_2 = Cl

tive isolates, monocyte tropic isolates, and virus derived from a retroviral experienced patient with resistance to the RT inhibitors AZT, ddI, 3TC, d4T, foscarnet, and nevirapine, as well as the PR inhibitors indinavir, saquinavir, and nelfinavir.

Several recent publications from our laboratory have documented a new class of NNRTIs, the alkenyldiarylmethanes (ADAMs).[10−14] Interest in this class of NNRTIs has resulted from the extremely potent anti-HIV activities of several members of this series as inhibitors of the cytopathic effect of HIV-1_{RF} in CEM-SS lymphocytes, including ADAM **17** (EC_{50} = 1.3 nM). In addition, certain HIV-1 strains containing AZT-resistance mutations displayed increased sensitivity to ADAM **15**, indicating a possible therapeutic role for the ADAMs in combination with AZT.[13] In the present communication, we report the synthesis of an extensive set of ADAMs with structural alterations at the meta positions of the aromatic rings and at the terminus of the alkenyl chain, and we report a detailed analysis of the biological effects of these variations. The new



39 R^1 = $COCH_3$; R^2 = Cl

40 R^1 = COOMe; R^2 = Cl

41 R^1 = COOMe; R^2 = CH_3

42 R^1 = COOMe; R^2 = Br

43 R^1 = COOEt; R^2 = Cl

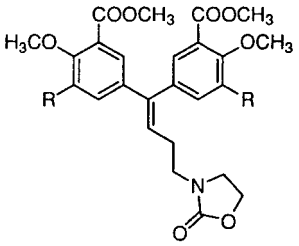
44 R^1 = COOEt; R^2 = CH_3

45 R^1 = CONHEt; R^2 = Cl

46 R^1 = $CO(=S)NHCH_3$; R^2 = Cl

47 R^1 = $COOCH_2CH(CH_3)_2$; R^2 = Cl

48 R^1 = $COOCH_2CH(CH_3)_2$; R^2 = CH_3



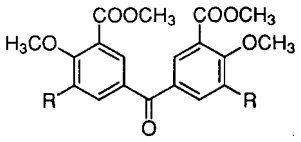
49 R = Cl

50 R = Br

compounds were evaluated as inhibitors of the cytopathic effect of HIV-1_{RF} in CEM-SS cell culture and as inhibitors of HIV-1 reverse transcriptase.

Chemistry

The alkenyldiarylmethanes **1**−**50** were synthesized either directly through McMurry reactions of the benzophenones **51**−**57** with the appropriate aldehydes or



51 R = H

52 R = F

53 R = Cl

54 R = CH_3

55 R = Br

56 R = I

57 R = CF_3

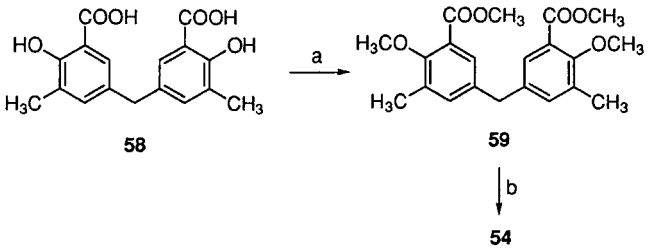
Table 1. Anti-HIV Activities of the ADAMs

compd	RT (IC_{50}, μM)[a]	EC_{50} (μM)[b]	CC_{50} (μM)[c]	TI[d]
1[e]	3.2	NA[f]	14.0	
2[g]	10	NA[f]	13.4	
3[h]	NT[i]	16	>29.1	>1.8
4	1.0	6.8	17.2	2.5
5[e]	0.38	9.2	138	15
6[e]	11	NA[f]	>316	
7	NT[i]	NA[f]	106	
8	NT[i]	1.3	42.7	33
9	6.0	4.7	>200	>43
10	258	13	>200	>15
11	99	8.2	>200	>24
12	>100	1.7	>200	>43
13	>100	13.1	>200	>15
14[g]	NT[i]	1.9	68.3	36
15[e]	0.3	0.013	31.6	2431
16	<1.0	0.25	6.0	24
17[g]	0.3	0.0013	13	10000
18	>200	14.3	17.2	1.2
19	0.233	0.01	16.0	1600
20	0.181	0.03	8.91	297
21	0.359	0.007	16.5	2357
22	8.3	1.29	13.9	10.8
23	29.7	1.29	5.40	4.20
24	9.15	1.14	>20	>17.5
25	>100	0.84	36.1	42.9
26	60.4	NA[f]	4.32	
27	70.8	4.33	16.4	3.79
28	0.687	0.38	2.65	6.94
29	5.65	1.51	7.40	4.91
30	>100	NA[f]	3.59	
31	7.12	5.37	14.7	2.74
32	>100	95.4	>200	>2.10
33	>100	5.31	>20	>3.77
34	NT[i]	11.7	36.9	3.15
35	NT[i]	NA[f]	14.9	
36	NT[i]	2.42	12.5	5.15
37	NT[i]	3.95	12.6	3.20
38	>100	NA[f]	18.1	
39	> 100	NA[f]	19.10	
40	4.43	1.22	12.40	10.19
41	4.93	0.21	12.40	59.05
42	2.39	0.20	8.10	40.5
43	1.93	0.71	12.20	17.17
44	0.016	0.67	3.59	5.34
45	>100	NA[f]	14.60	
46	>100	NA[f]	1.36	
47	65.4	NA	17.20	
48	2.95	0.76	5.13	6.73
49	9.47	2.15	13.00	6.02
50	0.499	0.02	1.95	104.5

[a] Inhibitory activity vs HIV-1 reverse transcriptase with rCdG as the template primer. [b] The EC_{50} is the 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 therapeutic index, which is the CC_{50} divided by the EC_{50}. [e] The synthesis and biological evaluation of this compound was reported previously: Cushman, M.; Casimiro-Garcia, A.; Hejchman, E.; Ruell, J. A.; Huang, M.; Schaeffer, C. A.; Williamson, K.; Rice, W. G.; Buckheit, R. W., Jr. *J. Med. Chem.* **1998**, *41*, 2076−2089. [f] NA (not active): no observed inhibition of HIV-1 cytopathicity up to the cytotoxic concentration in uninfected cells. [g] The synthesis and biological evaluation of this compound was reported previously: Casimiro-Garcia, A.; Micklatcher, M.; Turpin, J. A.; Stup, T. L.; Watson, K.; Buckheit, R. W., Jr.; Cushman, M. *J. Med. Chem.* **1999**, *42*, 4861−4874. [h] The synthesis and biological evaluation of this compound was reported previously: Cushman, M.; Golebiewski, W. M.; Graham, L.; Turpin, J. A.; Rice, W. G.; Filakas-Boltz, V.; Buckheit, R. W., Jr. *J. Med. Chem.* **1996**, *39*, 3217−3227. [i] NT: not tested. All data are derived from triplicate tests with the variation of the mean averaging 10%.

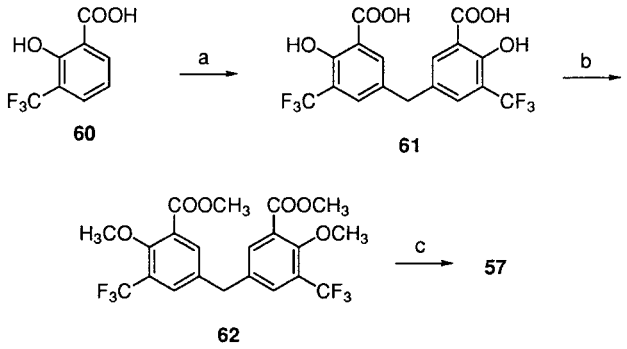
indirectly by McMurry reactions that afforded precursors to alkenyldiarylmethanes that were then converted into the desired products.[15−18] The syntheses of **1**,[13] **2**,[19] **3**,[11] **5**,[13] **6**,[13] **14**,[14] **15**,[13] and **17**[19] were carried out as

Scheme 1[a]



[a] Reagents and conditions: (a) K_2CO_3, Me_2SO_4, Me_2CO, reflux (20 h); (b) aqueous AcOH, CrO_3, 23 °C (18 h).

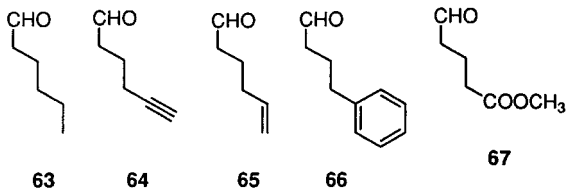
Scheme 2[a]



[a] Reagents and conditions: (a) H_2CO, MeOH, aqueous H_2SO_4, −78 to 23 °C (12 h); (b) Me_2SO_4, K_2CO_3, MeOH, reflux (12 h); (c) CrO_3, Ac_2O, 23 °C (12 h).

previously reported and are included in Table 1 for comparison purposes. The required benzophenones **51**,[13] **52**,[19] **53**,[21] **55**,[11] and **56**[13] were prepared as previously described, and the remaining two benzophenones **54** and **57** were synthesized as outlined in Schemes 1 and 2. Alkylation of both phenoxide anions and both carboxylates derived from the substituted diphenylmethane **58**[22] with dimethyl sulfate, using potassium carbonate in acetone as the base, afforded intermediate **59**, which was then oxidized to the desired benzophenone **54** with chromium trioxide in acetic acid (Scheme 1). As shown in Scheme 2, treatment of 3-(trifluoromethyl)salicylic acid (**60**)[23] with formaldehyde under acidic conditions afforded the diphenylmethane **61**, which was methylated and oxidized to yield the substituted benzophenone **57**.

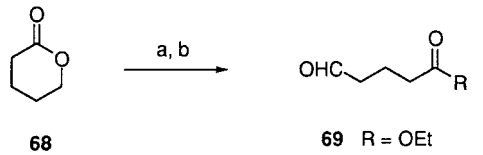
Aldehydes **64**,[24] **65**,[25] **66**,[26] and **67**[27] were synthesized by pyridinium chlorochromate (PCC) oxidation of the corresponding alcohols, while **63** was commercially available. Alcoholysis or aminolysis of δ-valerolactone



(**68**) afforded the corresponding primary alcohols, which were oxidized with PCC to yield the aldehydes **69**−**73** (Scheme 3).

The trimethylsilylated aldehyde **75** was prepared as outlined in Scheme 4. Protection of the aldehyde group of ethyl 5-oxopentanoate (**69**) was accomplished by converting it to the dimethylacetal **74** with methanol

Scheme 3[a]



68

69 R = OEt

70 R = O-*n*-Pr

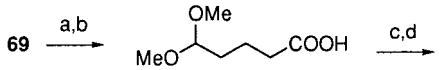
71 R = O-*i*-Pr

72 R = NMe_2

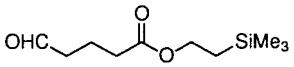
73 R = *N*-piperidyl

[a] Reagents and conditions: (a) ROH, H_2SO_4, reflux (3−5 h), or amines, THF, 23 °C (48−72 h); (b) PCC, CH_2Cl_2, 23 °C (1.5−4.0 h).

Scheme 4[a]



74

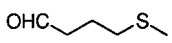


75

[a] Reagents and conditions: (a) 2,2-dimethoxypropane, HCl, $CHCl_3$, 23 °C (6 h); (b) NaOH, EtOH, 23 °C (12 h); (c) BOP-Cl, $Me_3SiCH_2CH_2OH$, Et_3N, CH_2Cl_2, 23 °C (2 h); (d) HCl, Me_2CO, 23 °C (2 h).

under acidic conditions. Esterification of the acid of **74** with 2-(trimethylsilyl)ethanol in the presence of BOP-Cl, followed by deprotection of the aldehyde in the presence of HCl in acetone, afforded **75**, which was used in the synthesis of ADAM **32**.

Commercially available 4-(methylthio)-1-butanol was oxidized to afford the aldehyde **76** using Dess−Martin



76

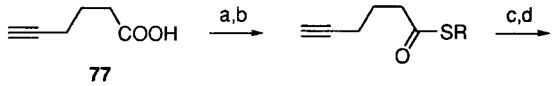
periodinane. McMurry coupling of **76** with the dichlorobenzophenone **53** afforded ADAM **33**, which was converted to the sulfoxide **34** with sodium periodate on acidic alumina in ethanol.[28] On the other hand, the sulfone **35** was obtained by oxidation of **33** with oxone (potassium peroxymonosulfate) in aqueous methanol.[29]

As shown in Scheme 5, 5-hexynoic acid (**77**) was converted to the corresponding acid chloride with oxalyl chloride, followed by reaction with methanethiolate or ethanethiol, to afford the thioesters **78** and **79**. The two alkynes **78** and **79** were converted to the alkenes by hydrogenation with Lindlar catalyst in the presence of quinoline in ethyl acetate, and the alkenes were transformed to the aldehydes **80** and **81** by ozonolysis.

The previously reported aldehyde **82**[19] was converted to its dimethylacetal derivative **38** with 2,2-dimethoxypropane in acetonitrile in the presence of a catalytic amount of HCl.

The aldehydes required for the synthesis of the ADAMs **40**−**44**, **47**, and **48** were prepared as shown in Scheme 6. Commercially available 3-amino-1-propanol was converted to the carbamates **84**, **85**, and **86** by reaction with the required alkyl chloroformates. Swern

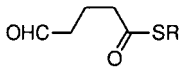
Scheme 5[a]



77

78 R = Me

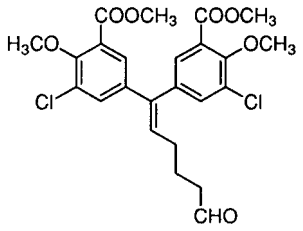
79 R = Et



80 R = Me

81 R = Et

[a] Reagents and condtitions: (a) $(COCl)_2$, DMF, THF, 23 °C; (b) RSNa, DMF, 0 °C (12 h) or RSH, Et_3N, DMF, 23 °C (12 h); (c) H_2, $Pd/BaSO_4$, quinoline, EtOAc, 23 °C; (d) O_3, 23 °C (40 min), then Me_2S, 23 °C (2 h).



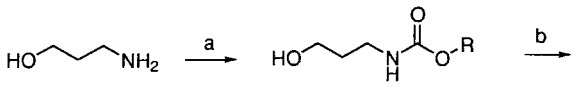
82

oxidation of these alcohols afforded the desired aldehydes **87**, **88**, and **89**.

The aldehyde **92** used in the synthesis of the oxazolidinone-containing ADAMs **49** and **50** were obtained as portrayed in Scheme 7. Reaction of 4-bromo-1-butene (**90**) with 2-oxazolidinone using cesium carbonate as the base gave the alkene **91**.[30] Oxidation of the double bond present in **91** with 4-methylmorpholine *N*-oxide and osmium tetroxide afforded the vicinal diol, which was cleaved with sodium periodate, yielding the aldehyde **92**.

The amide **39**, urea **45**, and thiourea **46** derivatives were synthesized from *N*-Fmoc-*β*-alanine (**93**) as shown in Scheme 8. The conversion of **93** to its acid chloride was accomplished with oxalyl chloride and a catalytic amount of DMF, followed by reduction with $(Ph_3P)_4Pd$ and tri-*n*-butyltin hydride in THF to afford the aldehyde

Scheme 6[a]

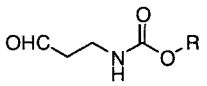


83

84 R = Me

85 R = Et

86 R = $CH_2CH(CH_3)_2$



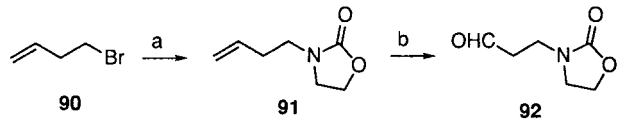
87 R = Me

88 R = Et

89 R = $CH_2CH(CH_3)_2$

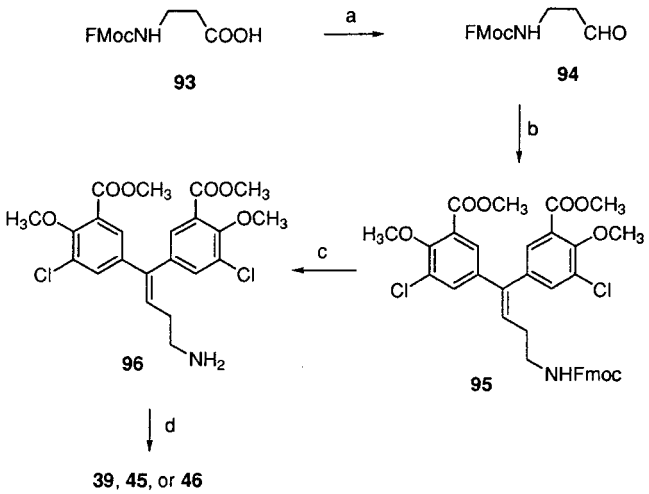
[a] Reagents and conditions: (a) ROCOCl, aqueous K_2CO_3, 0 °C (2 h); (b) $(COCl)_2$, DMSO, Et_3N, −78 °C (1 h).

Scheme 7[a]



[a] Reagents and conditions: (a) 2-oxazolidinone, Cs_2CO_3, Me_2CO, reflux (12 h); (b) 4-methylmorpholine *N*-oxide, OsO_4, aqueous MeOH, 23 °C (12 h), then $NaIO_4$, aqueous Me_2CO, 23 °C (4 h).

Scheme 8[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMF, THF, 23 °C (2 h), then $(Ph_3P)_4Pd$, Bu_3SnH, THF, 23 °C (1 h); (b) $TiCl_4$/THF (1:2), Zn, reflux (2 h), then **53** and **94**, reflux (6 h); (c) piperidine, THF, 23 °C (3 h); (d) MeCOCl, EtNCO, or SCNMe, Et_3N, THF.

94. McMurry coupling of the aldehyde **94** with the substituted dichlorobenzophenone **53** resulted in the formation of the Fmoc-protected ADAM **95**. The Fmoc protecting group was then removed from intermediate **95** in the presence of piperidine in THF to provide the amine **96**. Reaction of **96** with acetyl chloride, ethyl isocyanate, or methyl isothiocyanate afforded the amide **39**, urea **45**, and thiourea **46** derivatives, respectively.

Biological Results and Discussion

The 42 new ADAMs synthesized in this study were evaluated for inhibition of the cytopathic effect of HIV-1_{RF} in CEM-SS cells and for cytotoxicity in uninfected CEM-SS cells, and the results are listed in Table 1, along with the results from eight previously synthesized ADAMs that are included in the table for comparison purposes. These compounds were also tested for inhibition of HIV-1 reverse transcriptase, and the resulting IC_{50} values are also included in Table 1.

The present series of ADAMs was designed in order to more completely define the structure−activity relationships in two specific regions of the ADAM template. First, several new analogues incorporate a variety of functionalities at or near the terminus of the alkenyl side chain (see R_1 in structures **1**−**48**). Second, several new compounds incorporate modifications in the aromatic region in the position that is typically occupied by a halogen (R_2 in structures **1**−**48**). As seen from examination of the results listed in Table 1, structural variation at these two locations has resulted in a wide range of biological activity. In addition to the 12 compounds that were inactive as inhibitors of the cytopathic effect of HIV-1_{RF} in CEM cells, there were 38 ADAMs ranging in EC_{50} values from 95 to 0.0013 μM. Of the 42 compounds tested vs HIV-1 reverse transcriptase, 11 were found to be inactive and the remaining 31 compounds displayed IC_{50} values ranging from 258 to 0.181 μM.

Aromatic Substitutions. Considering first the effect of substituting different aromatic groups (R_2 in the structures displayed here), the two sets with the greatest structural variation are the alkenes **1**−**7** and the methyl esters **14**−**18**. The effective van der Waals radii of the groups involved, determined by rotational barriers, are 1.20 Å (H), 1.47 Å (F), 1.73 Å (Cl), 1.80 Å (CH_3), 1.86 Å (Br), 1.97 Å (I), and 2.2 Å (CF_3).[31] In the alkene **1**−**7** series, the ADAMs with the two smallest substituents (H and F) are inactive as inhibitors of the cytopathic effect of HIV-1, as are the two members of the series with the largest substituents (I and CF_3). Of the three remaining substituents, the CH_3 group conferred the greatest activity (EC_{50} = 6.8 μM), followed closely by Br (EC_{50} = 9.2 μM) and Cl (EC_{50} = 16 μM). Comparison of these values with those present in the substantially more active methyl ester series **14**−**18** reveals similar trends, although in this case all of the compounds were active. The most active compound proved to be the dibromo compound **17** (EC_{50} = 0.0013 μM), followed by the dichloro congener **15** (EC_{50} = 0.013 μM), the dimethyl analogue **16** (EC_{50} = 0.25 μM), the difluoro derivative **14** (EC_{50} = 1.9 μM), and the bis(trifluoromethyl) compound **18** (EC_{50} = 14.3 μM). The results in the two series **1**−**7** and **14**−**18** seem to indicate that as the effective van der Waals radii of the substituents increase from H or F to CH_3 or Br, there is an increase in activity. The activity peaks with CH_3 or Br and then decreases as the size of the substituents is increased farther. Accordingly, the aromatic substituents employed in the remaining series of compounds were restricted to Cl, CH_3, and Br.

In the remaining four series of compounds **19**−**21**, **22**−**24**, **25**−**27**, and **40**−**42** in which all three substituents were present (Cl, CH_3, and Br), the dibromo compound was the most active in inhibiting the cytopathic effect of the virus in three series while the dichloro compound was the most active in the remaining one (**25**−**27**). If one compares the relative activities of the four pairs of compounds in which only Cl and CH_3 are present (**28** and **29**, **30** and **31**, **43** and **44**, and **47** and **48**), the methyl groups confer greater activity in three of the cases, and chlorine confers greater activity in the remaining one (**28** vs **29**). There are also four pairs of compounds containing Br and Cl, namely, **8** and **9**, **10** and **11**, **12** and **13**, and **49** and **50**. In two of these four pairs, the Cl compound is more active than the Br compound, while in the remaining two pairs, the Br compound is more active. Overall, it seems clear that Br (radius 1.86 Å), CH_3 (radius 1.80 Å), and Cl (radius 1.73 Å) are more active than any of the other substituents tried, but there is no clear decision that can be made regarding which of the three would confer maximal activity in an unknown series. However, the three most active compounds in the whole series (**17**, **21**, and **50**) are all brominated.

Aliphatic Substitutions. Turning to the biological effects of changing the substituent at the end of the alkenyl chain, one would of course want to compare

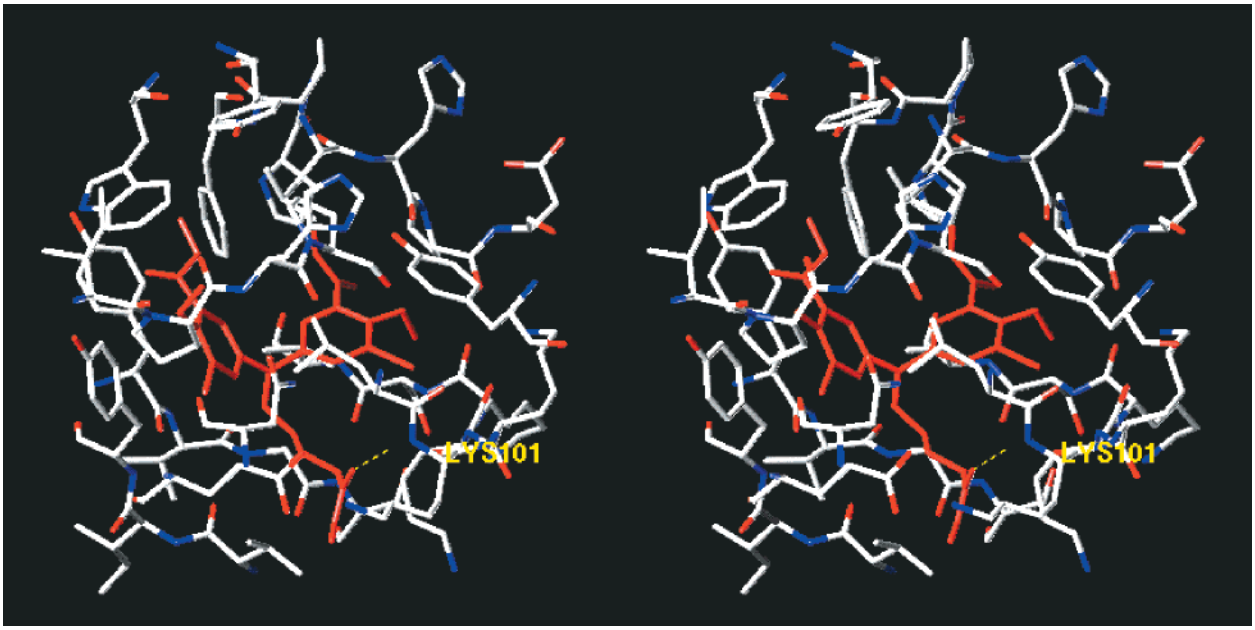


Figure 1. Hypothetical model of ADAM **17** docked in the NNRTI binding site of HIV-1 reverse transcriptase. The ligand is displayed in red. The figure is programmed for walleyed viewing.

compounds having identical aromatic substituents. The most extensive set of compounds differing at the end of the alkenyl chain, but having identical aromatic substituents, consists of the dichlorinated derivatives. This includes 20 compounds, with 15 active compounds and 5 inactive compounds. The active compounds range in anti-HIV potency from 0.01 to 16 μM and contain, in order of decreasing activity, the following end groups: CH_2COOMe (**15**, EC_{50} = 0.013 μM), CH_2COOEt (**19**, EC_{50} = 0.01 μM), CH_2CONMe_2 (**28**, EC_{50} = 0.38 μM), NHCOOEt (**43**, EC_{50} = 0.71 μM), CH_2COO*i*-Pr (**25**, EC_{50} = 0.84 μM), NHCOOMe (**40**, EC_{50} = 1.22 μM), CH_2COO*n*-Pr (**22**, EC_{50} = 1.29 μM), $CH_2C{\equiv}CH$ (**8**, EC_{50} = 1.3 μM), CH_2Ph (**12**, EC_{50} = 1.7 μM), CH_2COSMe (**36**, EC_{50} = 2.42 μM), CH_2COSEt (**37**, EC_{50} = 3.95 μM), CH_2SMe (**33**, EC_{50} = 5.31 μM), CH_2SOMe (**34**, EC_{50} = 11.7 μM), $CH_2CH{=}CH_2$ (**10**, EC_{50} = 13 μM), and CH_2Et (**3**, EC_{50} = 16 μM). The inactive compounds contained CH_2-piperidyl, $CH_2SO_2CH_3$, $CH_2CH(OCH_3)_2$, $NHCOCH_3$, and $CH_2COOCH_2CH(CH_3)_2$ end groups. From this list it is apparent that the most active compounds all have carbonyl groups in the same location. These carbonyl groups are present in ester, amide, or carbamate functional groups, and it is proposed that they might act as hydrogen bond acceptors from the backbone amide of Lys101 of reverse transcriptase (Figure 1).[13,19] In Figure 1, the originally proposed bifurcated hydrogen bond involving the side chain ester carbonyl of ADAM **17** with the terminal amino group of Lys103 and the backbone NH of Lys101 has been modified to include bonding between the backbone NH of Lys101 and the ester carbonyl only, which seems to be more consistent with the present observation of resilience of ADAMs **15**, **17**, **19**, and **21** to the K103E mutation (Table 3).[13,19] As judged from the activities displayed by **36** and **37**, the thioesters are not as active as the corresponding esters **15** and **19**, amide **28**, or carbamates **40** and **43**. Because sulfur is not a good electron donor toward the carbonyl group in a thioester,[32,33] the lower activity of the thioesters is consistent with prior work that demonstrated that electron donation toward the carbonyl group from an attached oxygen atom increased activity relative to the corresponding ketone (CH_2COOCH_3 vs $CH_2COCH_2CH_3$).[19] The carbonyl oxygens of thioesters more closely resemble ketone carbonyl oxygens than ester carbonyl oxygens and have been claimed to have about 40% less net negative charge than ester carbonyl oxygens.[33] In the present case, the activity observed for the thioester **36** (EC_{50} = 2.42 μM) is very close to that previously recorded for the corresponding ethyl ketone (EC_{50} = 2.8 μM), in which the sulfur of **36** is replaced by a methylene group.[19] Calculation of the Gasteiger–Hückel charges using the Sybyl program provided charges for the carboxyl oxygens of −0.537 esu for ester **17**, −0.392 esu for the corresponding ethyl ketone, and −0.379 esu for thioester **36**.

The phenyl analogues **12** and **13** were designed in order to take advantage of a potential cation π interaction between the protonated Lys103 side chain of the protein and the phenyl groups at the end of the alkenyl chain of the ligands (see Figure 1).[34] This strategy seems to have some merit when one compares the activity of the dichloro compound **12** (EC_{50} = 1.2 μM) vs the alkenyl compound **3** (EC_{50} = 16 μM). However, in the dibromo series **5** (EC_{50} = 9.2 μM) and **13** (EC_{50} = 13.1 μM), the phenyl group at the end of the chain had decreased activity. In any case, the activities of these phenyl analogues indicate a tolerance for steric bulk at the end of the alkenyl chain.

The sulfoxide **35** and sulfone **36** analogues were designed in order to place an electron-rich, negatively charged oxygen in the same location as the carbonyl oxygens of the highly active esters, amides, and carbamates in this series. However, as judged from their anti-HIV activities, the sulfoxide **35** (EC_{50} = 11.7 μM) and the sulfone **36** (not active) were not good mimics of the carbonyl groups. In fact, the corresponding sulfide **34** (EC_{50} = 5.31 μM) was more active than either compound. The greater activity of the sulfide **34** in comparison to the corresponding hydrocarbon **3** (EC_{50}

Table 2. Antiviral Range of Action

isolate	cell type	virus	ADAM IC_{50}[a] (μM) **15**	**17**	**19**	**21**	TC_{50} (μM)	IC_{50} AZT[a] (μM)
clinical isolates	PBLs[b]	ROJO (SI)[c]	0.75	0.54	0.39	0.2	>190	0.001
		WEJO (SI)	0.6	0.4	0.7	ND[d]	>190	0.001
		SLKA NSI)	1.3	1	0.9	1.1	>190	0.001
		TEKI (NSI)	0.8	0.9	1.0	1.0	>190	0.002
subtype isolates	PBLs	A	0.1	0.2	0.2	0.2	>180	0.001
		B	12.7	5.4	12.5	4.9	>200	0.009
		C	0.41	0.31	0.82	0.15	>200	0.004
		D	0.18	0.18	0.15	0.03	>200	0.007
		E	0.3	0.2	0.2	0.1	>170	0.002
		F	1.3	1.9	0.3	0.76	>200	0.002
		G	0.6	0.3	0.8	0.4	>170	0.002
		O	12	16	30	21	>170	0.001
monocyte tropic isolate	monocyte	Ba-L	5.4	3.6	8.9	4.4	>200	0.002
multidrug resistant	PBLs	MDR769[e]	16.9	48.8	45.2	6.3	>172	0.025

[a] Concentration required for 50% inhibition of viral replication as determined by measurement of supernatant RT activity in PBMCs or by ELISA for p24 antigen in monocyte macrophage cell cultures. All data are derived from triplicate tests with the variation of the mean averaging 10%. [b] Peripheral blood lymphocytes. [c] SI: syncytium-inducing. NSI: non-syncytium-inducing. [d] ND: not determined. [e] Multidrug-resistant HIV-1 isolate from a highly experienced patient. In vivo engendered resistance to AZT, ddI, 3TC, d4T, foscarnet, nevirapine, indinavir, saquinavir, and nelfinavir. Primary mutations in the reverse transcriptase gene: M41L, K65R, D67N, V75I, F116Y, Q151M, Y181I.

= 16 μM) agrees with the general observation that increasing electron density near the end of the chain increases activity. The same effect seems to be operating with the alkenes and alkynes **8**−**11**.

Effects on Reverse Transcription. With regard to the HIV-1 reverse transcriptase inhibitory activities reported in Table 1, it is obvious that there is not a perfect correlation between the anti-HIV-1 EC_{50} values and the reverse transcriptase IC_{50} values. For example, the IC_{50} values observed for the more potent anti-HIV-1 agents in the series, including **15**−**17** and **19**−**21**, are significantly higher than their EC_{50} values. However, this difference is not unusual for the non-nucleoside reverse transcriptase inhibitors.[35−38] The reverse transcriptase inhibition studies were performed in a cell-free system with recombinant purified enzyme and a synthetic homopolymeric 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.[37] Although, generally speaking, the compounds with submicromolar EC_{50} values also have submicromolar IC_{50} values, there are obvious exceptions provided by compounds **25**, **41**−**43**, and **48**. In the case of **25**, it is unlikely that inhibition of RT is responsible for the antiviral activity. However, the prior work with ADAM-resistant HIV-1 strains having mutations in reverse transcriptase has established that in general the ADAMs are in fact acting as non-nucleoside reverse transcriptase inhibitors.[11,13,14] Furthermore, a number of the ADAMs have displayed inactivity or very low activity when tested against a number of other potential antiviral targets, including HIV-1 integrase, protease, nucleocapsid p7 protein, virion attachment, and syncytia formation.[11,13]

Range of Antiviral Action. We selected ADAMs **15**, **17**, **19**, and **21** for further analysis because of their efficacy in the cytoprotection assay and against HIV RT. Anti-HIV-1 and reverse transcriptase activity has already been reported for ADAMs **15**[13] and **17**,[39] but they have not been assessed for activity in peripheral blood lymphocytes (PBLs) or monocyte/macrophages against clinical isolates of HIV-1. Therefore, ADAMs **15**, **17**, **19**, and **21** were evaluated as inhibitors of viral replication in PBLs and monocytes, as monitored by supernatant RT activity or p24 antigen, and the results are listed in Table 2. The ADAMs were significantly less cytotoxic (10- to 20-fold) to PBLs and primary monocyte/macrophages than CEM-SS cells (Table 2). The TC_{50} was greater than 170 μM for ADAMs **15**, **17**, **19**, and **21**, thus resulting in significantly better therapeutic indexes for all compounds. Additionally, the ADAMs were effective against all HIV-1 isolates tested. This includes low-passage pediatric clinical isolates with defined syncytium-inducing (SI) or nonsyncytium-inducing (NSI) phenotypes and HIV-1 subtype representative viruses. The ADAMs were least effective against subtype O viruses. The ADAMs also inhibited the replication of the monocyte tropic virus Ba-L in primary monocyte/macrophages. Thus, in contrast to efficacy determinations in CEM-SS cells, the ADAMs **15**, **17**, **19**, and **21** are less cytotoxic on primary lymphocytes and monocyte/macrophages and display antiviral activity against a wide range of clinically relevant virus isolates.

Activity of the ADAMs against Viruses Expressing HIV Resistance Mutations. The ADAMs **15**, **17**, **19**, and **21** were tested in CEM-SS cells using viruses with specific reverse transcriptase resistance mutations placed in the molecular clone NL4-3 by site mutagenesis. The anti-HIV-1 activities of the compounds were determined by monitoring inhibition of the cytopathic effect of the virus or p24 expression, depending on the replication competency of the virus. Antiviral effects of the ADAMs on the A98G, K103E, L74V, 4XAZT/L100I, and 4XAZT mutants were measured with p24 levels, while effects on the other mutants were determined by inhibition of the cytopathic effect. The 4XAZT virus contains the mutations D67N, K70R, T215Y, and K219Q. The NL4-3 replication was measured by both methods and gave IC_{50} values within 2-fold of each other. Thus, for NL4-3 sensitivity calculations, an average of the p24 and cytopathic effect IC_{50} values were used.

The IC_{50} values for the anti-HIV-1 effects of the compounds against the panel of mutant viruses are

Table 3. Antiviral Activity [IC_{50} (μM) (Fold Resistance vs Wild Type)] of ADAMs **15**, **17**, **19**, and **21** Against a Site-Directed Panel of Resistant Isolates in CEM Cells[a]

mutation	AZT	nevirapine	ADAM **15**	ADAM **17**	ADAM **19**	ADAM **21**
L74V	0.04	0.061	0.469	0.284	0.885	0.352
A98G	0.008	0.222 (7.6)	0.31	0.46	0.013 (−44.6)[b]	0.015 (−29)[b]
L100I	0.006 (−2.8)[b]	0.18 (6.2)	0.408	0.084 (−4.7)[b]	0.08 (−7.2)[b]	0.015 (−29)[b]
K101E	0.046 (2.7)[b]	0.005 (−5.8)[b]	0.366	0.594	0.164	0.957
K103N	0.007 (−2.4)[b]	1.44 (49.6)	0.6	0.35	0.27	0.46
V106A	0.014	1.88(65)	>20(>23)	9.84 (24)	10.3 (17.8)	7.02 (15.9)
V179D	0.02	0.07	1.3	1.3 (3.2)	2.3 (4)	2.5 (5.7)
Y181C	0.08 (4.7)	8.27 (285)	>20(>23)	8.3 (21)	19.1 (33)	4.4 (10)
Y188C	0.087 (5)	8.3 (286)	3.3 (3.9)	2 (5)	4.1 (7)	1.8 (4)
4X AZT +L100I[c]	0.87 (51)	0.207 (7.1)	0.49	0.32	0.37	0.37
4X AZT[c]	0.082 (4.8)	0.008 (−3.6)[b]	0.075 (−11)[b]	0.032 (−12.5)[b]	0.076 (−7.6)[b]	0.07 (−6.3)[b]
NL4−3 WT[d]	0.017	0.029	0.85	0.40	0.58	0.44

[a] Antiviral effects on the A98G, K103E, L74V, 4XAZT/L101I, and 4XAZT mutants were measured with p24 levels, while effects on the other mutants were determined by inhibition of the cytopathic effect. All data are derived from triplicate tests with the variation of the mean averaging 10%. [b] Enhanced sensitivity. [c] AZT-resistant. [d] Wild-type enzyme.

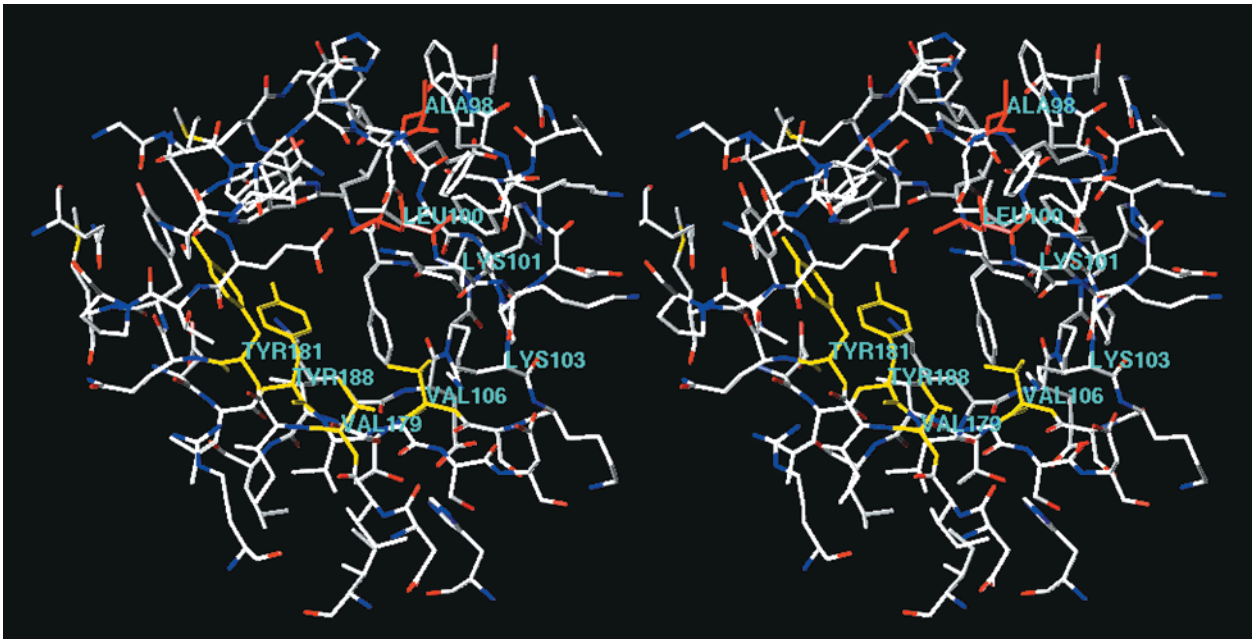


Figure 2. Non-nucleoside reverse transcriptase inhibitor (MMRTI) binding site. Mutation of the yellow residues results in resistance to three or more of the ADAMs **15**, **17**, **19**, and **21**, while mutation of the red residues results in increased sensitivity to two or more of the ADAMs **15**, **17**, **19**, and **21**. The figure is programmed for walleyed viewing.

listed in Table 3. The resistance mutations to all four of the ADAMs include V106A, Y181C, and Y188C. Although the Y181C mutation, a nevirapine, and NNRTI resistance mutation engendered a 10-fold resistance to ADAM **21**, this resistance was significantly less than that seen with ADAMs **15**, **17**, or **19**, and ADAM **21** was 28-fold less resistant than nevirapine in the presence of this mutation. The V179D mutation conferred slight resistance to ADAMs **17**, **19**, and **21** but not to ADAM **15**. On the other hand, increased sensitivity to the antiviral effects of ADAMs **19** and **21**, but not ADAMs **15** and **17**, was seen with the A98G mutation. Similarly, the L100I mutation conferred increased sensitivity to the antiviral effects of ADAMs **17**, **19**, and **21** but not ADAM **15**. In some cases, the increase in sensitivity seen with the A98G and L100I mutations was large. Examples are the 45-fold increase in sensitivity seen with ADAM **19** vs that of the A98G mutant, and the 29-fold increase in sensitivity seen with ADAM **21** vs that of the A98G mutant. The L100I mutation caused a 29-fold increase in sensitivity to ADAM **21**. Significantly, the AZT-resistant virus 4X AZT showed increased sensitivity to all four ADAMs, suggesting their possible use against AZT-resistant HIV-1 infections. The ADAMs retained activity against K101E.

Table 3 also lists the effects of the resistance mutations on the activity of nevirapine, a non-nucleoside reverse transcriptase inhibitor that is presently used in combination with other anti-HIV agents for the treatment of AIDS.[3,40] Several of the mutations conferring nevirapine resistance did not affect sensitivity to the ADAMs. Examples include the A98G mutation vs ADAM **17**, the K103N mutation vs all four ADAMs, and the L100I mutation vs ADAM **15**. The activity of the ADAMs vs the K103N mutant is noteworthy because K103N is the primary mutation found in vivo to be resistant to the NNRTIs, and it confers cross-resistance among nevirapine, delavirdine, and efaviranz.[41] In the case of the Y188C mutation, the degree of resistance vs the ADAMs was much less than that seen with nevirapine. A number of the nevirapine resistance mutations conferred increased sensitivity to the ADAMs. These included the A98G mutation vs ADAMs **19** and **21** and the L100I mutation vs ADAMs **17**, **19**, and **21**.

These effects are significant because one of the strategies for dealing with NNRTI resistance to a particular agent is to switch to another NNRTI that remains effective against the virus, or even has enhanced activity resulting from the mutation.[42,43] All four of the ADAMs, as well as nevirapine and AZT, also remained active in the presence of the L74V mutation, which confers resistance to ddI and abacavir.[44−48]

Figure 2, which was obtained by erasing nevirapine from the crystal structure of the nevirapine/RT complex, shows the amino acid residues in the p66 subunit surrounding the NNRTI binding pocket.[49] Mutation of the yellow residues results in resistance to three or more of the ADAMs **15**, **17**, **19**, or **21**, while mutation of the red residues results in increased sensitivity to two or more of the ADAMs **15**, **17**, **19**, or **21**. Taken together, the yellow and red residues shown in Figure 2 depict a constellation of amino acid residues that are likely to be involved in ADAM binding, and they surround a well-defined cavity that constitutes the ADAM binding site.

In vivo resistance to antiviral species is often engendered through a number of key mutations, along with secondary mutations that may or may not alter compound sensitivity. To verify that the ADAMs would be effective against nevirapine- and AZT-resistant viruses, we obtained a clinical isolate expressing resistance to nevirapine and AZT. This isolate is multidrug-resistant, expressing additional resistance to the reverse transcriptase enzyme inhibitors ddI, 3TC, d4T, and foscarnet, as well as the protease inhibitors indinavir, saquinavir, and nelfinavir. Table 2 shows that all four lead ADAMs were active against this multidrug-resistant virus in the presence of a 12-fold reduction in sensitivity to AZT and a >20-fold reduction in sensitivity to nevirapine (data not shown). Thus, the ADAMs represent a new class of NNRTIs with activity against viruses that arises from in vivo therapeutic failure.

Experimental Section

Melting points were determined in capillary tubes and are uncorrected. ^{1}H NMR spectra were determined at 200 or 300 MHz. ^{13}C NMR spectra were obtained at 75 MHz. ^{19}F NMR spectra were recorded at 282 MHz using trifluoroacetic acid in DMSO as the external standard. Chemical ionization mass spectra (CIMS) were determined using isobutane as the reagent gas. Microanalyses were performed at the Purdue University Microanalysis Laboratory. Silica gel flash chromatography was performed using 230−400 mesh silica gel. Unless otherwise stated, chemicals and solvents were reagent grade and were used as obtained from commercial sources without further purification. Tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl radical prior to use. Compounds **1**, **3**, **5**, **6**, **15**, and **17** were synthesized as previously described.[11,13,14]

3′,3″-Difluoro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-heptene (2). $TiCl_4$/THF 1:2 complex (2.05 g, 6.15 mmol) and zinc dust (0.804 g, 12.3 mmol) were heated at reflux in THF (20 mL) under an argon atmosphere for 1 h. Di[3-fluoro-4-methoxy-5-(methoxycarbonyl)phenyl] ketone (**52**, 0.486 g, 1.23 mmol) and hexanal (0.22 mL, 1.85 mmol) were taken up in THF (20 mL) and were added in one portion via cannula under argon pressure to the refluxing mixture. TLC (SiO_2, EtOAc/hexanes, 1:1) showed the reaction to be complete in 30 min. The reaction mixture was cooled to ambient temperature, and silica gel (10 g) was added to the reaction mixture. The slurry was transferred to a chromatography column containing silica gel (80 mL), and the inorganic salts were filtered off by elution of the product mixture with EtOAc. The eluent was removed in vacuo to give the crude product. Purification of the crude product by flash column chromatography on silica gel (20 mL), using a gradient of 0−4% EtOAc in hexanes as the eluent yielded pure **2** as a slightly yellow oil (0.373 g, 66%): IR (neat on NaCl) 2953, 2858, 1732, 1613, 1574, 1493, 1436, 1420, 1373, 1260, 1201, 1168, 1112, 1004, 884, 793, 774, 677, 650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 2 H), 7.02 (m, 2 H), 6.07 (t, J = 7.5 Hz, 1 H), 4.03 (s, 3 H), 3.96 (s, 3 H), 3.90 (s, 6 H), 2.08 (m, 2 H), 1.43 (m, 2 H), 1.26 (m, 4 H), 0.87 (t, J = 6.9 Hz, 3 H). Anal. ($C_{25}H_{28}F_2O_6$) C, H.

4′,4″-Dimethoxy-3′,3″-di(methoxycarbonyl)-5′,5″-dimethyl-1,1-diphenyl-1-heptene (4). $TiCl_4$/THF 1:2 complex (4.32 g, 12.9 mmol) and zinc dust (1.69 g, 25.9 mmol) were suspended in THF (43 mL) under an argon atmosphere, and the resulting mixture was heated under reflux for 1 h. Di(4-methoxy-3-methoxycarbonyl-5-methylphenyl) ketone (**54**, 1.00 g, 2.59 mmol) and hexanal (0.47 mL, 3.91 mmol) were taken up in THF (43 mL) and added in one portion via cannula under argon pressure to the refluxing mixture. TLC (SiO_2,EtOAc/hexanes, 1:1) showed the reaction to be complete in 30 min. The reaction mixture was cooled to ambient temperature, and silica gel (15 g) was added to the reaction mixture. The slurry was transferred to a chromatography column containing silica gel (25 g), and the inorganic salts were filtered off by elution of the product mixture with EtOAc. The eluent was removed to give the crude product. Purification of the crude product by flash column chromatography on silica gel (50 g), using a gradient of 0−7.5% EtOAc in hexanes as the eluent yielded pure **4** as a colorless oil (1.03 g, 87%): IR (neat on NaCl) 2953, 2930, 2857, 1731, 1600, 1577, 1481, 1437, 1379, 1365, 1298, 1259, 1227, 1195, 1173, 1143, 1122, 1040, 1011, 887, 800, 737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 2.0 Hz, 1 H), 7.42 (d, J = 1.9 Hz, 1 H), 7.10 (s, 2 H), 5.99 (t, J = 7.3 Hz, 1 H), 3.90 (s, 6 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 2.31 (s, 3 H), 2.25 (s, 3 H), 2.07 (q, J = 7.3 Hz, 2 H), 1.42 (m, 2 H), 1.27 (m, 4 H), 0.87 (t, J = 6.8 Hz, 3 H). Anal. ($C_{27}H_{34}O_6$) C, H.

3′,3″-Bis(methoxycarbonyl)-5′,5″-bis(trifluoromethyl)-4)′,4″-dimethoxy-1,1-diphenyl-1-heptene (7). $TiCl_4$/THF 1:2 complex (0.392 g, 1.17 mmol) and Zn dust (0.153 g, 2.34 mmol) were suspended with stirring in THF (5 mL). The mixture was heated under reflux in an oil bath for 1 h. Di[4-methoxy-3-methoxycarbonyl-5-(trifluoromethyl)phenyl] ketone (**57**, 0.116 g, 0.235 mmol) and hexanal (0.035 g, 0.35 mmol) were dissolved in THF (5 mL) and were added in one portion to the $TiCl_4$/Zn mixture. The reaction mixture was heated under reflux for 1 h, at which time TLC (SiO_2, EtOAc/hexanes, 1:1) verified that the reaction was complete. The reaction mixture was cooled to ambient temperature, and silica gel (2.5 g) was added to the stirring reaction mixture. The slurry was transferred to a chromatography column containing silica gel (10 g). The inorganic salts were filtered off by elution of the product with EtOAc. The eluent was removed on a rotary evaporator to give the crude product. Purification of the crude product by flash column chromatography on silica gel (10 g), using a gradient of 0−10% EtOAc in hexanes as the eluent afforded the pure product as a slightly yellow oil (0.069 g, 52%): IR (neat on NaCl) 3002, 2962, 2878, 1732, 1607, 1582, 1486, 1434, 1347, 1300, 1252, 1130, 1096, 999, 918, 858, 811, 768, 707, 677 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 7.94 (d, J = 2.1 Hz, 1 H), 7.91 (d, J = 2.5 Hz, 1 H), 7.70 (d, J = 2.4 Hz, 1 H), 7.67 (d, J = 1.5 Hz, 1 H), 5.83 (d, J = 7.6 Hz, 1 H), 3.64 (s, 3 H), 3.62 (s, 3 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 1.88, (dt, J = 7.3, 7.7 Hz, 2 H), 1.27 (m, 6 H), 0.83 (t, J = 6.9 Hz, 3 H); ^{19}F NMR (282 MHz, C_6D_6, rel to TFA external standard) δ 13.73 (s, 3 F), 13.67 (s, 3 F). Anal. ($C_{27}H_{28}F_6O_6$) C, H.

1,1-Bis[3-chloro-4-methoxy-5-(methoxycarbonyl)phenyl]hept-1-en-6-yne (8). $TiCl_4$/THF 1:2 complex (1.1282 g, 3.378 mmol) was added to a dry two-necked flask, under an argon atmosphere, equipped with a condensor, magnetic stir bar, and a rubber septum. Zinc dust (0.4130 g, 6.3179 mmol) was then added to the flask. The solids where suspended in dry THF (25 mL). The suspension was heated at reflux for 2 h. A solution of 3,3′-dichloro-4,4′-dimethoxy-5,5′-bis(methoxy-

carbonyl)benzophenone (**53**) (0.4438 g, 1.053 mmol) and 5-hexyn-1-al (**64**) (0.1967 g, 2.046 mmol) in dry THF (20 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 0.5 M HCl (50 mL) was added. The reaction solution was stirred at ambient temperature overnight. The reaction solution was then poured into a separatory funnel, and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous magnesium sulfate. Solvents were removed in vacuo, yielding a yellow oil. The crude oil was purified by flash chromatography using silica (75 g, 3 cm × 30 cm), with a gradient eluent from 10 to 12.5% ethyl acetate in hexanes. Like fractions were combined and solvent was removed in vacuo to yield **8** as an amorphous solid (0.130 g, 25.0%). 3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1,6-heptadiene (**10**) was also obtained after chromatography as a side product (0.010 g, 2%). ADAM **8**: IR (film) 3303.5, 2950.3, 1732.8, 1596.1, 1557.7, 1476.9, 1435.7, 1402.0, 1287.2, 1261.0, 1208.7, 998.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 2.38 Hz, 1 H), 7.45 (d, J = 2.19 Hz, 1 H), 7.32 (d, J = 2.18 Hz, 1 H), 7.28 (d, J = 2.38 Hz, 1 H), 6.04 (t, J = 7.54 Hz, 1 H), 3.97 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 2.23−2.15 (m, 4 H), 1.90 (t, J = 2.62 Hz, 1 H), 1.66 (dt, J = 7.05 Hz, J = 7.15 Hz, 2 H); CIMS m/z 490.92 (MH^+), 458.88 (MH^+ − MeOH). Anal. ($C_{25}H_{24}Cl_2O_6$) C, H.

1,1-Bis[3-bromo-4-methoxy-5-(methoxycarbonyl)phenyl]hept-1-en-6-yne (9). $TiCl_4$/THF 1:2 complex (0.9861 g, 2.953 mmol) was added to a dry two-necked flask, under an argon atmosphere, equipped with a condensor, magnetic stir bar, and a rubber septum. Zinc dust (0.4093 g, 6.2613 mmol) was then added to the flask. The solids where suspended in dry THF (20 mL). The suspension was heated at reflux for 3 h. A solution of 3,3′-dibromo-4,4′-dimethoxy-5,5′-bis(methoxycarbonyl)benzophenone (**55**) (0.2984 g, 0.5781 mmol) and 5-hexyn-1-al (**64**) (0.1747 g, 1.8172 mmol) in dry THF (20 mL) was transferred via cannula under an argon atmosphere to the titanium suspension. The resulting suspension was heated at reflux for 2 h. The suspension was cooled to ambient temperature, and 0.5 M HCl (50 mL) was added. The reaction solution was stirred at ambient temperature overnight. The reaction solution was then poured into a separatory funnel, and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous magnesium sulfate. Solvents were removed in vacuo, yielding a yellow oil. The crude oil was purified by flash chromatography using silica (50 g, 3 cm × 15 cm), with a gradient eluent from 0 to 12% ethyl acetate in hexanes. Like fractions were combined and solvent was removed in vacuo to yield **9** as an amorphous solid (0.0899 g, 27%). 3′,3″-Dibromo-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1,6-heptadiene (**11**) was also obtained after chromatography as a side product (0.0176 g, 5%). ADAM **9**: IR (film) 3299.7, 3000.0, 2949.6, 2865.1, 2117.4, 1731.7, 1714.7, 1594.2, 1548.1, 1471.6, 1434.7, 1260.5, 1208.8, 998.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52−7.45 (m, 4 H), 6.03 (t, J = 7.64 Hz, 1 H), 3.96 (s, 3 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 2.28−2.16 (m, 4 H), 1.92 (t, J = 2.28 Hz, 1 H), 1.70−1.61 (m, 2 H); ESIMS m/z 601 (MNa^+). Anal. ($C_{25}H_{24}Br_2O_6$) C, H.

3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1,6-heptadiene (10). $TiCl_4$/THF 1:2 complex (0.7034 g, 2.1066 mmol) was added to a dry two-necked flask, under an argon atmosphere, equipped with a condensor, magnetic stir bar, and a rubber septum. Zinc dust (0.2754 g, 4.2131 mmol) was then added to the flask. The solids were suspended in dry THF (20 mL). The suspension was heated at reflux for 2 h. A solution of 3,3′-dichloro-4,4′-dimethoxy-5,5′-bis(methoxycarbonyl)benzophenone (**53**) (0.300 g, 0.702 mmol) and 5-hexen-1-al (**65**) (0.1575 g, 1.6044 mmol) in dry THF (20 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 0.5 M HCl (20 mL) was added. The reaction solution was stirred at ambient temperature overnight. The reaction solution was then poured into a separatory funnel, and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous magnesium sulfate. Solvents were removed in vacuo, yielding a yellow oil. The crude oil was purified by flash chromatography using silica (40 g, 2 cm × 30 cm), with a 4:1 hexane/ethyl acetate eluent. Like fractions were combined and solvent was removed in vacuo to yield a colorless oil that crystallized upon standing to a white solid (0.1349 g, 33.16%): mp 89−90 °C; IR (film) 2934.6, 1735.8, 1476.8, 1436.1, 1261.1, 998.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 2.41 Hz, 1 H), 7.47 (d, J = 2.19 Hz, 1 H), 7.32 (d, J = 2.20 Hz, 1 H), 7.30 (d, J = 2.33 Hz, 1 H), 6.07 (t, J = 7.57 Hz, 1 H), 5.76 (ddt, J = 6.68 Hz, 10.22 Hz, 16.90 Hz, 1 H), 5.02−4.92 (m, 2 H), 3.99 (s, 3 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 2.15−2.02 (m, 3 H), 1.60−1.50 (m, 3 H); CIMS m/z 493 (MH^+), 461 (MH^+ − MeOH). Anal. ($C_{25}H_{26}Cl_2O_6$) C, H.

3′,3″-Dibromo-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1,6-heptadiene (11). $TiCl_4$/THF 1:2 complex (0.9953 g, 2.980 mmol) was added to a dry two-necked flask, under an argon atmosphere, equipped with a condensor, magnetic stir bar, and a rubber septum. Zinc dust (0.3871 g, 5.9216 mmol) was then added to the flask. The solids were suspended in dry THF (25 mL). The suspension was heated at reflux for 3 h. A solution of 3,3′-dibromo-4,4′-dimethoxy-5,5′-bis(methoxycarbonyl)benzophenone (**55**) (0.3153 g, 0.6108 mmol) and 5-hexen-1-al (**65**) (0.1337 g, 1.362 mmol) in dry THF (20 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 0.5 M HCl (50 mL) was added. The reaction solution was stirred at ambient temperature overnight. The reaction solution was then poured into a separatory funnel, and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous magnesium sulfate. Solvents were removed in vacuo, yielding a yellow oil. The crude oil was purified by flash chromatography using silica (40 g, 2 × 30 cm), with an 8:1 hexane/ethyl acetate eluent. Like fractions were combined and solvent was removed in vacuo to yield a colorless oil (0.1870 g, 52.5%) that crystallized upon standing to a white solid: mp 87−88 °C; IR (film) 2949.4, 1731.8, 1639.7, 1593.9, 1546.2, 1472.1, 1435.0, 1285.5, 1258.7, 1207.2, 998.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 2.40 Hz, 1 H), 7.50 (d, J = 3.05 Hz, 1 H), 7.47 (d, J = 2.20 Hz, 1 H), 7.46 (d, J = 2.40 Hz, 1 H), 6.04 (t, J = 7.53 Hz, 1 H), 5.74 (ddt, J = 6.73 Hz, 10.28 Hz, 16.83 Hz, 1 H), 4.99−4.91 (m, 2 H), 3.96 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 2.13−2.00 (m, 3 H), 1.57−1.48 (m, 3 H); CIMS m/z 580.78 (MH^+), 548.84 (MH^+ − MeOH). Anal. ($C_{25}H_{26}Br_2O_6$) C, H.

1,1-Bis[3-chloro-4-methoxy-5-(methoxycarbonyl)phenyl]-5-phenyl-1-pentene (12). $TiCl_4$/THF 1:2 complex (0.7064 g, 2.2771 mmol) was added to a dry two-necked flask, under an argon atmosphere, equipped with a condensor, magnetic stir bar, and a rubber septum. Zinc dust (0.3021 g, 4.6214 mmol) was then added to the flask. The solids where suspended in dry THF (20 mL). The suspension was heated at reflux for 2 h. A solution of 3,3′-dichloro-4,4′-dimethoxy-5,5′-bis(methoxycarbonyl)benzophenone (**53**) (0.3122 g, 0.7307 mmol) and 4-phenyl-1-butanal (**66**) (0.2323 g, 1.5674 mmol) in dry THF (20 mL) was transferred via cannula under an argon atmosphere to the titanium suspension. The resulting suspension was heated at reflux for 2 h. The suspension was then cooled to ambient temperature, and 0.5 M HCl (50 mL) was added. The reaction solution was stirred at ambient temperature overnight. The reaction solution was then poured into a separatory funnel, and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl

acetate (3 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous magnesium sulfate. Solvents were removed in vacuo, yielding a yellow oil. The crude oil was purified by flash chromatography using silica (50 g, 2 cm × 29 cm), with a gradient eluent from 0 to 16% ethyl acetate in hexanes. Like fractions were combined and solvent was removed in vacuo to yield an amorphous solid (0.2312 g, 58.22%): IR (film) 3060.9, 3026.9, 2949.5, 2856.5, 1732.1, 1596.2, 1557.4, 1477.2, 1454.0, 1435.7, 1287.5, 1260.0, 1207.9, 999.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46−7.44 (m, 2 H), 7.29−7.09 (m, 7 H), 6.05 (t, J = 7.51 Hz, 1 H), 3.97 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 2.59 (t, J = 7.43 Hz, 2 H), 2.15−2.08 (m, 2 H), 1.80−1.73 (m, 2 H); ESIMS m/z 565 (MNa^+). Anal. ($C_{29}H_{28}Cl_2O_6$) C, H.

1,1-Bis[3-bromo-4-methoxy-5-(methoxycarbonyl)phenyl]-5-phenyl-1-pentene (13). $TiCl_4$/THF 1:2 complex (0.9344 g, 2.7982 mmol) was added to a dry two-necked flask, under an argon atmosphere, equipped with a condensor, magnetic stir bar, and a rubber septum. Zinc dust (0.4040 g, 6.1802 mmol) was then added to the flask. The solids where suspended in dry THF (20 mL). The suspension was heated at reflux for 3 h. A solution of 3,3′-dibromo-4,4′-dimethoxy-5,5′-bis(methoxycarbonyl)benzophenone (**55**) (0.3157 g, 0.6116 mmol) and 4-phenyl-1-butanal (**66**) (0.1874 g, 1.2645 mmol) in dry THF (20 mL) was transferred via cannula under an argon atmosphere to the titanium suspension. The resulting suspension was heated at reflux for 2 h. The suspension was cooled to ambient temperature, and 0.5 M HCl (50 mL) was added. The reaction solution was stirred at ambient temperature overnight. The reaction solution was then poured into a separatory funnel, and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous magnesium sulfate. Solvents were removed in vacuo, yielding a yellow oil. The crude oil was purified by flash column chromatography using silica (50 g, 3 cm × 18 cm), with a gradient eluent from 0 to 10% ethyl acetate in hexanes. Like fractions were combined and solvent was removed in vacuo to yield an amorphous solid (0.2485 g, 64%): IR (film) 3001.9, 2947.7, 2860.3, 1733.3, 1594.6, 1542.3, 1473.6, 1435.5, 1285.4, 1258.4, 1206.1, 998.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.42 (m, 4 H), 7.26−7.09 (m, 5 H), 6.04 (t, J = 7.48 Hz, 1 H), 3.96 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 2.59 (t, J = 7.51 Hz, 2 H), 2.15−2.07 (m, 2 H), 1.81−1.73 (m, 2 H). ESIMS m/z 653 (MNa^+). Anal. ($C_{29}H_{28}Br_2O_6$) C, H, Br.

Methyl 3′,3″-Difluoro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-6,6-diphenyl-5-hexenoate (14). $TiCl_4$/THF 1:2 complex (1.64 g, 4.9 mmol) and zinc dust (0.641 g, 9.8 mmol) were heated under reflux in THF (16 mL) under an argon atmosphere for 1 h. Di[3-fluoro-4-methoxy-5-(methoxycarbonyl)phenyl] ketone (**52**, 0.387 g, 0.98 mmol) and methyl 5-oxopentanoate[27] (**67**, 0.255 g, 2.0 mmol) were taken up in THF (16 mL) and were added in one portion via cannula under argon pressure to the refluxing mixture. TLC (SiO_2, EtOAc/hexanes, 1:1) showed the reaction to be complete in 45 min. The reaction mixture was cooled to ambient temperature, and silica gel (10 g) was added to the reaction mixture. The slurry was transferred to a chromatography column containing silica gel (40 g), and the inorganic salts were filtered off by elution of the product mixture with EtOAc. The eluent was removed in vacuo to give the crude product. The crude product was purified by flash column chromatography on silica gel (10 g), using a gradient of 0−18% EtOAc in hexanes as the eluent. Evaporation of the eluent yielded the pure product as a slightly yellow oil that crystallized on cooling in a freezer (−10 °C) to give a slightly yellow solid (0.220 g, 46%): mp 54−56 °C; IR (KBr pellet) 2956, 1734, 1708, 1492, 1438, 1347, 1307, 1267, 1199, 993, 878, 788, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 2.3 Hz, 1 H), 7.31 (d, J = 2.1 Hz, 1 H), 7.03 (dd, J_{H-H} = 2.1 Hz, J_{H-F} = 9.7 Hz, 1 H), 6.99 (dd, J_{H-H} = 2.3 Hz, J_{H-F} = 11.2 Hz, 1 H), 6.04 (t, J = 7.4 Hz, 1 H), 4.15 (s, 3 H), 4.04 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.64 (s, 3 H), 2.31 (t, J = 7.4 Hz, 2 H), 2.14 (dt app q, J = 7.4 Hz, 2 H), 1.78 (m, J = 7.5 Hz, 2 H); ^{19}F NMR (282 MHz, $CDCl_3$, rel to TFA external standard) δ −13.5 (d, J = 11.3 Hz, 1 F), −13.9 (d, J = 12.2 Hz, 1 F). Anal. ($C_{25}H_{26}F_2O_8$) C, H.

Methyl 4′,4″-Dimethoxy-3′,3″-di(methoxycarbonyl)-5′,5″-dimethyl-6,6-diphenyl-5-hexenoate (16). $TiCl_4$/THF 1:2 complex (1.75 g, 5.25 mmol) and zinc dust (0.686 g, 10.5 mmol) were suspended in THF (17 mL) under an argon atmosphere, and the resulting mixture was heated under reflux for 1 h. Di(4-methoxy-3-methoxycarbonyl-5-methylphenyl) ketone (**54**, 0.404 g, 1.05 mmol) and methyl 5-oxopentanoate[27] (**67**, 0.204 g, 1.6 mmol) were taken up in THF (17 mL) and were added in one portion via cannula under argon pressure to the refluxing mixture. After 45 min, the reaction mixture was cooled to ambient temperature and silica gel (5 g) was added. The slurry was transferred to a chromatography column containing silica gel (25 g), and the inorganic salts were filtered off by elution of the product mixture with EtOAc. The eluent was removed in vacuo to give the crude product. Flash column chromatography on silica gel (25 g), using a gradient of 0−15% EtOAc in hexanes as the eluent afforded the pure product as a thick, slightly yellow oil (0.250 g, 49%): IR (neat on NaCl) 2951, 1732, 1601, 1481, 1436, 1367, 1299, 1257, 1228, 1197, 1173, 1135, 1009, 883, 802 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.46 (d, J = 2.5 Hz, 1 H), 7.41 (d, J = 2.3 Hz, 1 H), 7.09 (d, J = 2.3 Hz, 2 H), 5.96 (t, J = 7.4 Hz, 1 H), 3.90 (s, 6 H), 3.88 (s, 3 H) 3.81 (s, 3 H), 3.63 (s, 3 H), 2.36−2.30 (m, 2 H), 2.32 (s, 3 H), 2.25 (s, 3 H), 2.13 (m, 2 H), 1.77 (m, 2 H). Anal. ($C_{27}H_{32}O_8$) C, H.

Methyl 3′,3″-Di(methoxycarbonyl)-5′,5″-bis(trifluoromethyl)-4′,4″-dimethoxy-6,6-diphenyl-5-hexenoate (18). $TiCl_4$/THF 1:2 complex (2.09 g, 6.25 mmol) and zinc dust (0.817 g, 12.5 mmol) were suspended with stirring in THF (30 mL) under an atmosphere of argon. The resulting mixture was heated under reflux in an oil bath for 1.5 h. Di[4-methoxy-3-methoxycarbonyl-5-(trifluoromethyl)phenyl] ketone (**57**, 0.640 g, 1.25 mmol) and methyl 5-oxopentanoate[27] (**67**, 0.244 g, 1.88 mmol) were taken up in THF (30 mL), and the resulting mixture was added in one portion to the $TiCl_4$/Zn mixture. The reaction mixture was heated under reflux for 1 h, at which time TLC (SiO_2, EtOAc/hexanes, 1:1) verified that the reaction was complete. The reaction mixture was cooled to ambient temperature, and silica gel (7 g) was added to the stirring reaction mixture. The resulting slurry was transferred to a chromatography column containing silica gel (50 g). The inorganic salts were filtered off by elution of the product with EtOAc. The eluent was removed on a rotary evaporator to give the crude product. Purification of the crude product by flash column chromatography on silica gel (50 g), using a gradient of 0−16% EtOAc in hexanes as the eluent afforded the pure product as a colorless oil (0.356 g, 48%): IR (neat on NaCl) 2954, 2844, 1737, 1582, 1485, 1437, 1290, 1263, 1207, 1135, 999 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 2.3 Hz, 1 H), 7.72 (d, J = 2.3 Hz, 1 H), 7.51 (m, 2 H), 6.09 (t, J = 7.4 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 3.62 (s, 3 H), 2.31 (t, J = 7.4 Hz, 2 H), 2.13 (m, 2 H), 1.79 (m, 2 H); ^{19}F NMR (282 MHz, $CDCl_3$, rel to TFA external standard) δ 13.38 (s, 3 F), 13.32 (s, 3 F). Anal. ($C_{27}H_{26}F_6O_8$) C, H.

Ethyl 3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-6,6-diphenylhexenoate (19). A mixture of $TiCl_4$/THF 1:2 complex (1.0 g, 3.0 mmol) and Zn powder (0.39 g, 6.0 mmol) in dry THF (30 mL) was heated under reflux for 1.5 h under nitrogen. A solution of benzophenone **53** (0.43 g, 1.0 mmol) and aldehyde **69** (0.20 g, 1.5 mmol) in dry THF (15 mL) was added. The reaction mixture was stirred at room temperature for 1 h and then heated under reflux for 3 h. The mixture was allowed to cool, and 10% aqueous potassium carbonate (25 mL) was added. The resulting mixture was stirred at room temperature overnight, then filtered through a Celite pad, and washed with ethyl acetate (3 × 30 mL). The organic solvents were evaporated, and the crude residue was purified by silica gel flash chromatography (hexanes/EtOAc 3:1, v/v) to afford a colorless liquid (220 mg, 40.8%): ^1H NMR ($CDCl_3$) δ 7.46 (d, J = 2.31 Hz, 1 H), 7.43 (d, J = 2.16 Hz, 1 H), 7.28 (d, J = 2.23 Hz, 1 H), 7.26 (d, J = 2.28 Hz, 1 H), 6.01 (t, J = 7.46 Hz, 1 H),

4.05 (q, J = 7.16 Hz, 2 H), 3.95 (s, 3 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 2.29 (t, J = 7.26 Hz, 2 H), 2.09 (m, 2 H), 1.76 (m, 2 H), 1.18 (t, J = 7.13 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.07, 165.73, 165.43, 155.03, 154.73, 138.31, 137.87, 135.20, 134.93, 132.38, 132.03, 130.94, 129.72, 129.42, 128.02, 126.81, 126.63, 61.92, 60.26, 52.44, 33.58, 29.11, 24.69, 14.11; CIMS m/z (relative intensity) 540 (MH^+, 100), 508 ($M^+ - OCH_3$, 78). Anal. ($C_{26}H_{28}Cl_2O_8$) C, H.

Ethyl 3′,3″-Dimethyl-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-6,6-diphenylhexenoate (20). A mixture of $TiCl_4$/THF 1:2 complex (1.45 g, 4.35 mmol) and Zn dust (0.57 g, 8.7 mmol) was slurried in dry THF (15 mL) under argon. After 1.5 h of reflux, the black mixture was cooled and a solution of benzophenone **54** (0.56 g, 1.45 mmol) and aldehyde **69** (0.31 g, 2.18 mmol) in dry THF (10 mL) was added. The mixture was stirred for 1 h at room temperature and then heated at reflux for 14 h. After the mixture was cooled to room temperature, it was poured into 10% aqueous potassium carbonate (20 mL). It was then filtered through a pad of Celite. The filtrate was concentrated, dissolved in CH_2Cl_2 (1 mL), and subjected to flash chromatography (EtOAc/hexanes 1:2, v/v) to afford a light-yellow liquid (150 mg, 20.8%): ^{1}H NMR ($CDCl_3$) δ 7.43 (d, J = 1.93 Hz, 1 H), 7.39 (d, J = 1.93 Hz, 1 H), 7.07 (s, 2 H), 5.94 (t, J = 7.32 Hz, 1 H), 4.06 (q, J = 7.17 Hz, 2 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 2.29 (s, 3 H), 2.24 (t, J = 7.72 Hz, 2 H), 2.22 (s, 3 H), 2.11 (m, 2 H), 1.76 (m, 2 H), 1.18 (t, J = 7.18 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.36, 166.96, 166.72, 157.40, 157.31, 140.08, 137.81, 136.28, 134.74, 133.76, 132.71, 132.30, 130.26, 129.68, 127.47, 124.29, 61.44, 60.19, 52.12, 33.73, 29.09, 24.98, 16.08, 14.12; CIMS m/z 499 (MH^+); HRMS (CI) calcd for $C_{28}H_{34}O_8$ 499.2332, found 499.2316. Anal. ($C_{28}H_{34}O_8$) C, H.

Ethyl 3′,3″-Dibromo-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-6,6-diphenyl-5-hexenoate (21). A slurry of $TiCl_4$/THF 1:2 complex (0.95 g, 2.83 mmol) and Zn powder (0.37 g, 5.67 mmol) was heated under reflux for 1.5 h. The resulting dark suspension was cooled to room temperature, and a mixture of benzophenone **55** (0.45 g, 0.87 mmol) and aldehyde **69** (0.25 g, 1.74 mmol) in THF (15 mL) was added. The mixture was heated at reflux and stirred for 20 h, cooled, and poured into 10% aqueous potassium carbonate (20 mL). It was then filtered through a pad of Celite. The filtrate was evaporated, and the resulting crude residue was purified by flash chromatography (EtOAc/hexanes 1:3, v/v) to afford a colorless liquid (122 mg, 22.0%): ^{1}H NMR ($CDCl_3$) δ 7.51 (d, J = 2.71 Hz, 1 H), 7.50 (d, J = 2.71 Hz, 1 H), 7.46 (d, J = 2.37 Hz, 1 H), 7.45 (d, J = 2.42 Hz, 1 H), 6.01 (t, J = 7.48 Hz, 1 H), 4.07 (q, J = 7.12 Hz, 2 H), 3.96 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 2.27 (t, J = 7.41 Hz, 2 H), 2.12 (m, 2 H), 1.76 (m, 2 H), 1.19 (t, J = 7.20 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.13, 165.67, 165.39, 156.04, 155.76, 138.85, 137.98, 137.66, 135.69, 135.47, 132.21, 131.80, 128.97, 126.62, 126.47, 119.26, 119.04, 62.13, 60.32, 52.51, 33.63, 29.13, 24.73, 14.16; EIMS m/z 627 (M^+); HRMS (EI) calcd for $C_{26}H_{28}Br_2O_8$ 626.0151, found 626.0131. Anal. ($C_{26}H_{28}Br_2O_8$) C, H, Br.

Propyl 3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-6,6-diphenylhexenoate (22). A mixture of $TiCl_4$/THF 1:2 complex (1.0 g, 3.0 mmol) and Zn powder (0.39 g, 6.0 mmol) in dry THF (10 mL) was heated under reflux for 1.5 h under nitrogen. A solution of benzophenone **53** (400 mg, 0.939 mmol) and aldehyde **70** (252 mg, 1.6 mmol) in dry THF (10 mL) was added. The reaction mixture was stirred at room temperature for 1 h, then heated under reflux for 14 h. The mixture was allowed to cool, and 10% aqueous potassium carbonate (25 mL) was added. The resulting mixture was stirred at room temperature overnight, then filtered through a Celite pad, and washed with ethyl acetate (3 × 20 mL). The organic solvents were evaporated, and the crude residue was purified by silica gel flash chromatography (hexanes/EtOAc 7:2, v/v) to afford a colorless liquid (210 mg, 40.5%): ^{1}H NMR ($CDCl_3$) δ 7.49 (d, J = 2.49 Hz, 1 H), 7.46 (d, J = 2.10 Hz, 1 H), 7.31 (d, J = 2.21 Hz, 1 H), 7.29 (d, J = 2.19 Hz, 1 H), 6.04 (t, J = 7.44 Hz, 1 H), 4.00 (t, J = 6.85 Hz, 2 H), 3.99 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 2.30 (t, J = 7.42 Hz, 2 H), 2.14 (dt, J = 7.40 and 7.34 Hz, 2 H), 1.77 (m, 2 H), 1.60 (m, 2 H), 0.90 (t, J = 7.42 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.20, 165.72, 165.38, 154.99, 154.69, 138.27, 137.75, 135.15, 134.89, 132.37, 131.97, 130.88, 129.68, 129.38, 127.98, 126.73, 126.56, 65.92, 61.91, 52.42, 33.57, 29.09, 24.69, 21.82, 10.23; EIMS m/z 553 (M^+); HRMS calcd for $C_{27}H_{29}Cl_2O_8$ ($M - H$)$^+$ 552.1318, found 552.1306. Anal. ($C_{27}H_{30}Cl_2O_8$) C, H, Cl.

Propyl 3′,3″-Dimethyl-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-6,6-diphenyl-5-hexenoate (23). A mixture of $TiCl_4$/THF 1:2 complex (1.04 g, 3.1 mmol) and Zn dust (405 mg, 6.2 mmol) was slurried in dry THF (10 mL) under argon. After 1 h of reflux, the black mixture was cooled and a solution of benzophenone **54** (386 mg, 1.0 mmol) and aldehyde **70** (237 mg, 1.5 mmol) in dry THF (10 mL) was added. The mixture was stirred for 1 h at room temperature and then heated at reflux for 14 h. After the mixture was cooled to room temperature, it was poured into 10% aqueous potassium carbonate (20 mL). Then it was filtered through a pad of Celite. The filtrate was concentrated and subjected to flash chromatography on silica gel (45 g, EtOAc/hexanes 1:3, v/v) to afford a light-yellow liquid (250 mg, 48.8%): ^{1}H NMR ($CDCl_3$) δ 7.45 (d, J = 1.93 Hz, 1 H), 7.40 (d, J = 1.93 Hz, 1 H), 7.09 (s, 2 H), 5.96 (t, J = 7.41 Hz, 1 H), 3.98 (t, J = 6.71 Hz, 2 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 2.31 (s, 3 H), 2.27 (t, J = 7.38 Hz, 2 H), 2.24 (s, 3 H), 2.13 (dt, J = 7.38 and 7.23 Hz, 2 H), 1.78 (m, 2 H), 1.62 (m, 2 H), 0.90 (t, J = 7.44 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.42, 166.94, 166.67, 157.36, 157.24, 140.01, 137.77, 136.24, 134.68, 133.72, 132.65, 132.26, 130.22, 129.62, 127.43, 124.22, 65.81, 61.40, 52.09, 33.70, 29.06, 24.98, 21.83, 16.03, 10.24; CIMS m/z 513 (MH^+); HRMS calcd for $C_{29}H_{36}O_8$ 512.2410, found 512.2400. Anal. ($C_{29}H_{36}O_8$) C, H.

Propyl 3′,3″-Dibromo-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-6,6-diphenylhexenoate (24). A slurry of $TiCl_4$/THF 1:2 complex (932 mg, 2.79 mmol) and Zn powder (365 mg, 5.58 mmol) in dry THF (10 mL) was heated under reflux for 2 h. The resulting dark suspension was cooled to room temperature, and a mixture of benzophenone **55** (0.45 g, 0.87 mmol) and aldehyde **70** (234 mg, 1.48 mmol) in THF (10 mL) was added. The mixture was heated at reflux and stirred for 16 h, cooled, and poured into 10% aqueous potassium carbonate (20 mL). Then it was filtered through a pad of Celite. The filtrate was evaporated, and the resulting crude residue was purified by flash chromatography (EtOAc/hexanes 1:3, v/v) to afford a colorless liquid (114 mg, 20.4%): ^{1}H NMR ($CDCl_3$) δ 7.52 (d, J = 2.70 Hz, 1 H), 7.51 (d, J = 2.43 Hz, 1 H), 7.48 (d, J = 2.06 Hz, 1 H), 7.46 (d, J = 2.41 Hz, 1 H), 6.02 (t, J = 7.42 Hz, 1 H), 3.99 (t, J = 6.72 Hz, 2 H), 3.97 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 2.29 (t, J = 7.36 Hz, 2 H), 2.13 (dt, J = 7.37 and 7.40 Hz, 2 H), 1.76 (m, 2 H), 1.61 (m, 2 H), 0.90 (t, J = 7.38 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.14, 165.59, 165.32, 155.97, 155.71, 138.78, 137.91, 137.60, 135.61, 135.40, 132.13, 131.72, 128.90, 126.54, 126.40, 119.19, 118.98, 65.90, 62.04, 52.43, 33.56, 29.08, 24.69, 21.83, 10.23; HRMS calcd for $C_{27}H_{30}Br_2O_8$ 642.0464, found 642.0441. Anal. ($C_{27}H_{30}Br_2O_8 \cdot 0.3H_2O$) C, H, Br.

Isopropyl 3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-6,6-diphenyl-5-hexenoate (25). A mixture of $TiCl_4$/THF 1:2 complex (953 mg, 2.85 mmol) and Zn powder (373 mg, 5.71 mmol) in dry THF (10 mL) was heated under reflux for 1.5 h under nitrogen. A solution of benzophenone **53** (380 mg, 0.892 mmol) and aldehyde **71** (282 mg, 1.78 mmol) in dry THF (10 mL) was added. The reaction mixture was stirred at room temperature for 1 h and then heated under reflux for 14 h. The mixture was allowed to cool, and 10% aqueous potassium carbonate (25 mL) was added. The resulting mixture was stirred at room temperature overnight and then filtered through a Celite pad and washed with ethyl acetate (3 × 20 mL). The organic solvents were evaporated and the crude residue was purified by silica gel flash chromatography (silica gel, 50 g, hexanes/EtOAc 3:1, v/v) to afford a colorless liquid (190 mg, 38.5%): ^{1}H NMR ($CDCl_3$) δ 7.49 (d, J = 2.17 Hz, 1 H), 7.46 (d, J = 2.10 Hz, 1 H), 7.31 (d, J = 2.10 Hz, 1 H), 7.29 (d, J = 2.23 Hz, 1 H), 6.04 (t, J = 7.45 Hz, 1 H),

4.98 (m, 1 H), 3.99 (s, 3 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 2.26 (t, J = 7.43 Hz, 2 H), 2.14 (dt, J = 7.36 and 7.34 Hz, 2 H), 1.78 (m, 2 H), 1.19 (d, J = 6.23 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 172.58, 165.72, 165.42, 155.01, 154.71, 138.31, 137.79, 135.17, 134.89, 132.36, 132.02, 130.88, 129.67, 129.37, 127.97, 126.76, 126.61, 67.52, 61.91, 52.40, 33.96, 29.12, 24.77, 21.67; EIMS m/z 553 (M^+); HRMS calcd for $C_{27}H_{29}Cl_2O_8$ ($M - H)^+$ 552.1318, found 552.1309. Anal. ($C_{27}H_{30}Cl_2O_8$) C, H, Cl.

Isopropyl 3′,3″-Dimethyl-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-6,6-diphenylhexenoate (26). A mixture of $TiCl_4$/THF 1:2 complex (969 mg, 2.90 mmol) and Zn dust (379 mg, 5.80 mmol) was slurried in dry THF (8 mL) under argon. After 1 h of reflux, the black mixture was cooled and a solution of benzophenone **54** (350 mg, 0.907 mmol) and aldehyde **71** (265 mg, 1.54 mmol) in dry THF (10 mL) was added. The mixture was stirred for 1 h at room temperature and then heated at reflux for 14 h. After the mixture was cooled to room temperature, it was poured into 10% aqueous potassium carbonate (20 mL). It was then filtered through a pad of Celite. The filtrate was concentrated and subjected to flash chromatography on silica gel (60 g, EtOAc/hexanes 1:4, v/v) to afford a light-yellow liquid (125 mg, 26.9%): ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 2.37 Hz, 1 H), 7.41 (d, J = 2.02 Hz, 1 H), 7.09 (br, 2 H), 5.96 (t, J = 7.39 Hz, 1 H), 4.96 (m, 1 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 2.31 (s, 3 H), 2.27 (t, J = 7.38 Hz, 2 H), 2.24 (s, 3 H), 2.13 (dt, J = 7.38 and 7.23 Hz, 2 H), 1.75 (m, 2 H), 1.17 (d, J = 6.44 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 172.82, 166.92, 166.69, 157.37, 157.24, 139.95, 137.77, 136.21, 134.68, 133.69, 132.22, 130.20, 129.68, 127.40, 124.23, 67.37, 61.38, 52.04, 34.08, 29.05, 25.03, 21.66, 16.01; CIMS m/z 513 (MH^+); HRMS calcd for $C_{29}H_{36}O_8$ 512.2410, found 512.2400. Anal. ($C_{29}H_{36}O_8$) C, H.

Isopropyl 3′,3″-Dibromo-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-6,6-diphenyl-5-hexenoate (27). A slurry of $TiCl_4$/THF 1:2 complex (870 mg, 2.61 mmol) and Zn powder (341 mg, 5.21 mmol) in dry THF (8 mL) was heated under reflux for 1.5 h. The resulting dark suspension was cooled to room temperature, and a mixture of benzophenone **55** (420 mg, 0.81 mmol) and aldehyde **71** (218 mg, 1.38 mmol) in THF (10 mL) was added. The mixture was heated at reflux and stirred for 20 h, cooled, and poured into 10% aqueous potassium carbonate (20 mL). Then it was filtered through a pad of Celite. The filtrate was evaporated, and the resulting crude residue was purified by flash chromatography (EtOAc/hexanes 1:3, v/v) to afford a colorless liquid (175 mg, 33.6%): ^{1}H NMR ($CDCl_3$) δ 7.53 (d, J = 2.33 Hz, 1 H), 7.52 (d, J = 2.43 Hz, 1 H), 7.48 (d, J = 2.11 Hz, 1 H), 7.46 (d, J = 2.19 Hz, 1 H), 6.03 (t, J = 7.46 Hz, 1 H), 4.97 (m, 1 H), 3.98 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 2.26 (t, J = 7.44 Hz, 2 H), 2.13 (dt, J = 7.49 and 7.28 Hz, 2 H), 1.78 (m, 2 H), 1.19 (d, J = 6.23 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 172.63, 165.62, 165.33, 155.98, 155.75, 138.82, 137.93, 137.56, 135.64, 135.43, 132.20, 131.75, 128.92, 126.56, 126.41, 119.22, 119.01, 67.54, 62.06, 52.45, 33.96, 29.11, 24.77, 21.68; CIMS m/z 641.9 ($MH)^+$; HRMS calcd for $C_{27}H_{30}Br_2O_8$ 640.0307, found 640.0306. Anal. ($C_{27}H_{30}Br_2O_8$) C, H, Br.

***N,N*-Dimethyl-3′,3″-dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-6,6-diphenyl-5-hexenamide (28).** A mixture of $TiCl_4$/THF 1:2 complex (1.04 g, 3.10 mmol) and Zn dust (0.41, 6.20 mmol) was heated at reflux in dry THF (15 mL) under argon. After 1 h at reflux, the black mixture was cooled and a solution of benzophenone **53** (0.426 g, 1.0 mmol) and aldehyde **72** (172 mg, 1.2 mmol) in dry THF (15 mL) was added dropwise. The mixture was heated at reflux for 14 h and then cooled to room temperature, and 10% aqueous K_2CO_3 (15 mL) was added. The resulting mixture was stirred overnight, then filtered through a Celite pad, and washed with ethyl acetate (3 × 10 mL). The solvents were removed under reduced pressure, and the crude residue was purified by flash chromatography on silica gel (25 g, 2.5 cm × 31 cm), eluting with ethyl acetate, to afford a colorless oil (215 mg, 40%): ^{1}H NMR ($CDCl_3$) δ 7.50 (d, J = 2.45 Hz, 1 H), 7.45 (d, J = 2.11 Hz, 1 H), 7.31 (d, J = 2.11 Hz, 1 H), 7.28 (d, J = 2.40 Hz, 1 H), 6.08 (t, J = 7.49 Hz, 1 H), 3.98 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 2.95 (broad s, 6 H), 2.28 (t, J = 7.47 Hz, 2 H), 2.14 (dt, J = 7.61 and 7.37 Hz, 2 H), 1.80 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 172.39, 165.79, 165.55, 154.98, 154.73, 138.41, 137.56, 135.37, 135.02, 132.59, 132.45, 130.98, 129.69, 129.45, 128.07, 126.82, 126.63, 61.98, 52.48, 32.51, 29.44, 24.83; HRMS (EI) calcd for $C_{26}H_{29}NCl_2O_7$ 537.1321, found 537.1336. Anal. ($C_{26}H_{29}NCl_2O_7$) C, H, Cl.

***N,N*-Dimethyl-3′,3″-dimethyl-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-6,6-diphenylhexenamide (29).** A mixture of $TiCl_4$/THF 1:2 complex (1.24 g, 3.72 mmol) and Zn dust (0.49, 7.44 mmol) was heated at reflux in dry THF (15 mL) under argon. After 2 h of reflux, the black mixture was cooled and a solution of benzophenone **54** (0.463 g, 1.2 mmol) and aldehyde **72** (0.257 g, 1.8 mmol) in dry THF (10 mL) was added. The mixture was stirred for 40 min at room temperature and then heated at reflux for 5 h. The mixture was cooled to room temperature, and 10% aqueous K_2CO_3 (15 mL) was added. The resulting mixture was stirred overnight, then filtered through a Celite pad, and washed with ethyl acetate (3 × 10 mL). The solvents were removed under reduced pressure, and the crude residue was purified by silica gel (33 g) flash chromatography (column, 2.5 cm × 31 cm), eluting with ethyl acetate, to afford a colorless oil (104 mg, 17.4%): ^{1}H NMR ($CDCl_3$) δ 7.40 (d, J = 2.33 Hz, 1 H), 7.36 (d, J = 2.14 Hz, 1 H), 7.14 (d, J = 2.22 Hz, 1 H), 7.09 (d, J = 1.85 Hz, 1 H), 5.99 (t, J = 7.34 Hz, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.77 (s, 3 H), 3.01 (s, 3 H), 2.96 (s, 3 H), 2.46 (t, J = 7.89 Hz, 2 H), 2.28 (s, 3 H), 2.22 (s, 3 H), 2.14 (dt, J = 7.34 and 7.07 Hz, 2 H), 1.83 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 175.67, 166.98, 166.83, 157.37, 157.31, 140.09, 137.72, 136.40, 134.78, 133.85, 132.80, 132.38, 130.18, 129.60, 127.53, 124.26, 61.43, 52.15, 37.97, 36.32, 32.97, 29.35, 25.35, 16.12, 16.04; CIMS m/z 498 (MH^+); HRMS (CI) calcd for $C_{28}H_{36}NO_7$ (MH^+) 498.2492, found 498.2477. Anal. ($C_{28}H_{35}NO_7$) C, H, N.

6,6-Bis(3-chloro-4-methoxy-5-methoxycarbonylphenyl)-1-piperidylhex-5-en-1-one (30). A mixture of $TiCl_4$/THF 1:2 complex (1.04 g, 3.10 mmol) and Zn dust (0.41 g, 6.20 mmol) was heated at reflux in dry THF (10 mL) under argon. After 2 h at reflux, the black mixture was cooled and a solution of benzophenone **53** (0.426 g, 1.0 mmol) and aldehyde **73** (0.275 g, 1.5 mmol) in dry THF (15 mL) was added dropwise. The mixture was heated at reflux for 14 h and then cooled to room temperature, and 10% aqueous K_2CO_3 (15 mL) was added. The resulting mixture was stirred overnight, then filtered through a Celite pad, and washed with ethyl acetate (3 × 10 mL). The solvents were removed under reduced pressure, and the crude residue was purified by flash chromatography on silica gel (25 g, 2.5 cm × 31 cm), eluting with ethyl acetate, to afford a colorless oil (234 mg, 40.5%): ^{1}H NMR ($CDCl_3$) δ 7.45 (d, J = 2.21 Hz, 1 H), 7.42 (d, J = 2.15 Hz, 1 H), 7.27 (d, J = 2.11 Hz, 1 H), 7.24 (d, J = 2.45 Hz, 1 H), 6.03 (t, J = 7.46 Hz, 1 H), 3.93 (s, 3 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.46 (t, J = 5.40 Hz, 2 H), 3.30 (t, J = 5.27 Hz, 2 H), 2.23 (t, J = 7.51 Hz, 2 H), 2.10 (dt, J = 7.53 and 7.48 Hz, 2 H), 1.73 (m, 2 H), 1.42−1.59 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.44, 165.70, 165.46, 154.94, 154.67, 138.38, 137.47, 135.32, 134.96, 132.59, 132.39, 130.95, 129.64, 129.38, 128.04, 126.78, 126.60, 61.91, 60.25, 52.42, 46.47, 42.54, 32.55, 29.47, 26.43, 25.47, 25.08, 24.45, 20.91, 14.08; EIMS m/z 578 (M^+); HRMS (EI) calcd for $C_{29}H_{33}NCl_2O_7$ 578.1712, found 578.1697. Anal. ($C_{29}H_{33}NCl_2O_7$) C, H, N.

6,6-Bis(3-methyl-4-methoxy-5-methoxycarbonylphenyl)-1-piperidylhex-5-en-1-one (31). $TiCl_4$/THF 1:2 complex (1.35 g, 4.03 mmol) was added to a stirred suspension of zinc dust (0.53 g, 8.06 mmol) in dry THF (15 mL) under argon. The resulting dark mixture was heated under reflux for 2 h. The suspension was cooled to room temperature, and a solution of benzophenone **54** (501 mg, 1.3 mmol) and aldehyde **73** (357 mg, 1.95 mmol) in dry THF (15 mL) was added. The mixture was heated at reflux for 14 h and then cooled to room temperature. An aqueous 10% K_2CO_3 solution (20 mL) was added, and the mixture was stirred for 2 h, followed by filtration through a pad of Celite. The filtrate was evaporated, and the brown residue was purified by flash chromatography

on silica gel (32 g, 2.5 cm × 31 cm), eluting with ethyl acetate, to afford a pale-yellow oil (217 mg, 31%): ^{1}H NMR ($CDCl_3$) δ 7.43 (d, J = 2.23 Hz, 1 H), 7.38 (d, J = 1.94 Hz, 1 H), 7.07 (br s, 2 H), 5.97 (t, J = 7.42 Hz, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.49 (t, J = 5.46 Hz, 2 H), 3.32 (t, J = 5.26 Hz, 2 H), 2.28 (s, 3 H), 2.25 (t, J = 7.73 Hz, 2 H), 2.22 (s, 3 H), 2.13 (dt, J = 7.43 and 7.42 Hz, 2 H), 1.73 (m, 2 H), 1.43−1.63 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.85, 166.96, 166.76, 157.37, 157.28, 139.78, 137.87, 136.36, 134.86, 133.77, 132.68, 132.29, 130.26, 130.17, 127.48, 124.26, 61.44, 52.12, 46.53, 42.54, 32.76, 29.42, 26.45, 25.47, 25.41, 24.48, 16.07; CIMS m/z 538 (MH^+); HRMS (CI) calcd for $C_{31}H_{40}NO_7$ 538.2805, found 538.2828. Anal. ($C_{31}H_{39}NO_7$) C, H, N.

2-(Trimethylsilyl)ethyl 3′,3″-Dimethyl-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-6,6-diphenyl-5-hexenoate (32). A mixture of $TiCl_4$/THF 1:2 complex (0.53 g, 1.58 mmol) and Zn (0.21 g, 3.16 mmol) in dry THF (8 mL) was heated under reflux for 2 h under argon. A solution of benzophenone **54** (0.20 g, 0.51 mmol) and aldehyde **75** (0.11 g, 0.51 mmol) in dry THF (14 mL) was added. The mixture was stirred for 1 h at room temperature and then heated at reflux for 14 h. After the mixture was cooled to room temperature, it was poured into 10% aqueous potassium carbonate (5 mL). Then it was filtered through a pad of Celite. The filtrate was concentrated, dissolved in chloroform (1.5 mL), and subjected to flash chromatography (hexanes/EtOAc 3:1, v/v) to afford a light-yellow liquid (80 mg, 28%): ^{1}H NMR ($CDCl_3$) δ 7.45 (d, J = 2.39 Hz, 1 H), 7.40 (d, J = 2.20 Hz, 1 H), 7.09 (d, J = 1.92 Hz, 2 H), 5.95 (t, J = 7.42 Hz, 1 H), 4.13 (t, J = 8.08 Hz, 2 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 2.30 (s, 6 H), 2.24 (t, J = 7.70 Hz, 2 H), 2.10 (m, 2 H), 1.75 (m, 2 H), 0.94 (t, J = 8.08 Hz, 2 H), 0.02 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 173.51, 166.98, 166.74, 157.43, 157.31, 140.05, 137.84, 136.28, 134.75, 133.76, 132.68, 132.30, 130.26, 129.71, 127.50, 124.29, 62.43, 61.45, 52.13, 33.91, 29.15, 25.02, 17.23, 16.09, −1.58; CIMS m/z 571 (MH^+). Anal. ($C_{31}H_{42}SiO_8$) C, H.

3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-di(methoxycarbonyl)-1,1-diphenyl-5-(methylthio)-pent-1-ene (33). $TiCl_4$/THF 1:2 complex (2.92 g, 5.65 mmol) and zinc dust (0.739 g, 11.3 mmol) were suspended with stirring in THF (35 mL) under an atmosphere of argon. The resulting suspension was heated under reflux for 2 h. Di[3-chloro-4-methoxy-5-(methoxycarbonyl)phenyl] ketone (**53**, 0.482 g, 1.13 mmol) and 4-(methylthio)butanal (**76**, 0.200 g, 1.69 mmol) were taken up in THF (35 mL). The solution of ketone and aldehyde was tranferred to a suspension of low-valent titanium via cannula after the initial 2 h of heating. The resulting suspension was heated under reflux for 1.5 h. TLC (SiO_2, EtOAc/hexanes, 1:1) at this time showed the reaction to be complete. The entire reaction mixture was poured onto a column of silica gel (30 g), and the product was eluted from the column with ethyl acetate. The solvent was removed from this mixture with a rotary evaporator, yielding the crude product. The product was further purified by flash column chromatography on silica gel (50 g), using a gradient of 0−18% ethyl acetate in hexanes as the eluent. Fractions containing the product were evaporated, yielding the pure product as a slightly yellow solid (0.423 g, 73%): mp 90−93 °C; IR (KBr pellet) 2929, 2829, 1733, 1594, 1558, 1475, 1425, 1364, 1291, 1249, 1210, 1090, 995, 968, 919, 894, 833, 805, 744, 679, 619 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 2.1 Hz, 1 H), 7.46 (d, J = 2.2 Hz, 1 H), 7.31 (d, J = 2.2 Hz, 1 H), 7.27 (d, J = 2.2 Hz, 1 H), 6.05 (t, J = 7.2 Hz, 1 H), 3.99 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 2.47 (t, J = 7.3, 2 H), 2.19 (q, J = 7.6 Hz, 2 H), 2.07 (s, 3 H), 1.73 (dt, J = 7.2, 7.4 Hz, 2 H). Anal. ($C_{24}H_{26}Cl_2O_6S$) C, H, Cl.

3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-dimethoxycarbonyl-5,5-diphenyl-1-(methylsulfinyl)pent-4-ene (34). A slurry of $NaIO_4$ supported on acidic alumina[28] (0.200 g, 0.60 mmol) in ethanol (absolute, 3 mL) was stirred in a 10 mL round-bottomed flask. 3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-dimethoxycarbonyl-5,5-diphenyl-1-(methylthio)-pent-4-ene (**33**, 0.150 g, 0.292 mmol) was added to the slurry in one portion. The reaction mixture was placed under an argon atmosphere, and stirring was continued for 22 h. TLC analysis (SiO_2, EtOAc/hexanes, 1:1) at this time showed the reaction to be incomplete. However, the solution was filtered to remove the solids. The solids were washed with CH_2Cl_2 (10 mL). The solvent was removed on a rotary evaporator. The crude product was purified by column chromatography on silica gel (20 g), using a gradient of 0−15% ethyl acetate in hexanes to elute the starting material (0.041 g recovered) followed by a gradient of 0−20% acetone in CH_2Cl_2 to elute the product. The fractions containing the product were combined and condensed on a rotary evaporator to yield the pure product as a glassy solid (0.075 g, 48%): mp 120−122 °C; IR (thin film on NaCl) 2951, 1733, 1477, 1436, 1257, 1209, 1167, 1095, 1051, 998, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 2.3 Hz, 1 H), 7.45 (d, J = 2.2 Hz, 1 H), 7.30 (d, J = 2.2 Hz, 1 H), 7.27 (d, J = 2.3 Hz, 1 H), 6.04 (t, J = 7.4 Hz, 1 H), 3.99 (s, 3 H), 3.92 (s, 6 H), 3.91 (s, 3 H), 2.76−2.59 (m, 2 H), 2.57 (s, 3 H), 2.32−2.24 (m, 2 H), 1.99−1.88 (m, 2 H). Anal. ($C_{24}H_{26}Cl_2O_7S$) C, H, Cl.

3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-dimethoxycarbonyl-5,5-diphenyl-1-(methylsulfonyl)pent-4-ene (35). 3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-dimethoxycarbonyl-5,5-diphenyl-1-(methylthio)-pent-4-ene (**33**, 0.150 g, 0.292 mmol) was taken up with stirring in MeOH (8 mL). The resulting solution was cooled in an ice bath. A solution of oxone (0.270 g, 0.876 mmol $KHSO_5$) dissolved in water (4 mL) was added in one portion to the stirring mixture. Stirring was continued for 22 h at which time TLC analysis (SiO_2, acetone/CH_2Cl_2, 1:9) showed the reaction to be complete. The reaction mixture was poured into H_2O (50 mL) and extracted with $CHCl_3$ (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and condensed to yield the crude product. The crude product was purified by column chromatography on silica gel (30 g), using a gradient of 0−6% acetone in CH_2Cl_2 to elute the product. The fractions containing the product were combined and condensed on a rotary evaporator to yield the pure product as a slightly yellow oil (0.121 g, 76%): IR (thin film on NaCl) 3008, 2952, 1732, 1596, 1557, 1479, 1436, 1404, 1360, 1290, 1210, 1168, 1132, 1095, 998, 963, 885, 851, 804, 741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 2.6 Hz, 1 H), 7.46 (d, J = 2.2 Hz, 1 H), 7.30 (d, J = 2.2 Hz, 1 H), 7.28 (d, J = 2.6 Hz, 1 H), 6.03 (t, J = 7.4 Hz, 1 H), 4.00 (s, 3 H), 3.94 (s, 3 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.02−2.96 (m, 2 H), 2.90 (s, 3 H), 2.29 (dt, J = 7.4, 7.5 Hz, 2 H), 2.06−1.96 (m, 2 H). Anal. ($C_{24}H_{26}Cl_2O_8S$) C, H, Cl.

Methyl 5-{1-[3-Chloro-4-methoxy-5-(methoxycarbonyl)phenyl]-6-methylthio-6-oxohex-1-enyl}-3-chloro-2-methoxybenzoate (36). A mixture of $TiCl_4$/THF 1:2 complex (866 mg, 2.59 mmol) and Zn dust (339 mg, 5.18 mmol) was heated at reflux in dry THF (25 mL) under argon. After 1 h of reflux, a mixture of the substituted dichlorobenzophenone **53** (345 mg, 0.81 mmol) and aldehyde **80** (120 mg, 0.82 mmol) in dry THF (15 mL) was added dropwise. The resulting mixture was heated again at reflux for 14 h and then was cooled to room temperature and poured into a 10% K_2CO_3 solution (10 mL). The white precipitate was filtered off, and the filtrate was partitioned between ethyl acetate and water. The organic layers were combined and dried over Na_2SO_4 and then evaporated to give a light-yellow residue. The residue was purified by flash chromatography (silica gel 45 g, eluent hexanes/ethyl acetate 3:1, v/v) to afford a colorless oil (131 mg, 30%): ^{1}H NMR ($CDCl_3$) δ 7.48 (m, 1 H), 7.46 (d, J = 2.12 Hz, 1 H), 7.31 (m, 1 H), 7.28 (d, J = 2.32 Hz, 1 H), 6.02 (t, J = 7.47 Hz, 1 H), 3.99 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 2.55 (t, J = 7.31 Hz, 2 H), 2.27 (s, 3 H), 2.13 (dt, J = 7.30 and 7.41 Hz, 2 H), 1.82 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 194.61, 161.12, 160.85, 150.47, 149.76, 133.65, 133.44, 131.67, 130.51, 130.33, 129.54, 127.80, 127.12, 126.31, 125.26, 125.12, 124.84, 123.41, 122.18, 122.03, 57.33, 47.85, 38.42, 24.34, 20.65, 6.85; CIMS m/z 541 (MH^+), 509 (M − MeOH).

Methyl 5-{1-[3-Chloro-4-methoxy-5-(methoxycarbonyl)phenyl]-6-ethylthio-6-oxohex-1-enyl}-3-chloro-2-methoxybenzoate (37). A mixture of $TiCl_4$/THF 1:2 complex (0.73 g, 2.18 mmol) and Zn dust (286 mg, 4.37 mmol) was heated at reflux in dry THF (12 mL) under argon. After 1 h of reflux, a mixture of the substituted dichlorobenzophenone **53** (292 mg,

0.68 mmol) and aldehyde **81** (112 mg, 0.70 mmol) in dry THF (15 mL) was added dropwise. The resulting mixture was heated again at reflux for 14 h, then was cooled to room temperature and poured into a 10% K_2CO_3 solution (10 mL). The white precipitate was filtered off, and the filtrate was partioned between ethyl acetate and water. The organic layers were combined and dried over Na_2SO_4 and then evaporated to give a light-yellow residue. The residue was purified by flash chromatography (silica gel 50 g, solvent hexanes/ethyl acetate 2:1, v/v) to afford a colorless oil (75 mg, 20%): ^{1}H NMR ($CDCl_3$) δ 7.48 (d, J = 2.42 Hz, 1 H), 7.46 (d, J = 2.29 Hz, 1 H), 7.30 (d, J = 2.19 Hz, 1 H), 7.28 (d, J = 2.42 Hz, 1 H), 6.02 (t, J = 7.51 Hz, 1 H), 3.99 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 2.85 (q, J = 7.36 Hz, 2 H), 2.53 (t, J = 7.32 Hz, 2 H), 2.12 (dt, J = 7.51 and 7.30 Hz, 2 H), 1.81 (m, 2 H), 1.23 (t, J = 7.33 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 194.37, 161.15, 161.06, 160.85, 150.46, 149.77, 133.68, 133.41, 131.67, 130.50, 130.35, 129.55, 127.81, 127.18, 126.34, 125.28, 125.14, 124.84, 123.43, 122.19, 122.03, 57.30, 47.84, 38.61, 35.12, 24.34, 20.65, 18.58, 10.02; CIMS (MH^+) m/z 554. Anal. ($C_{26}H_{28}Cl_2SO_7$) C, H, S.

Methyl 5-{1-[3-Chloro-4-methoxy-5-(methoxycarbonyl)phenyl]-6,6-dimethoxyhex-1-enyl}-3-chloro-2-methoxybenzoate (38). Aldehyde **82**[19] (22 mg, 0.047 mmol) was dissolved in an acetonitrile solution (4 mL) containing 2,2-dimethoxypropane (1.5 mL). To this mixture was added one drop of concentrated HCl. The resulting solution was stirred for 4 h and then concentrated. The residue was subjected to flash chromatography on silica gel (15 g, hexanes/EtOAc 3:2 as eluent) to give the dimethyl acetal **38** as a colorless oil (20.9 mg, 82%): ^{1}H NMR ($CDCl_3$) δ 7.53 (d, J = 2.21 Hz, 1 H), 7.51 (d, J = 2.16 Hz, 1 H), 7.36 (d, J = 2.11 Hz, 1 H), 7.33 (d, J = 2.20 Hz, 1 H), 6.10 (t, J = 7.44 Hz, 1 H), 4.36 (t, J = 5.22 Hz, 1 H), 4.04 (s, 3 H), 3.97 (s, 3 H), 3.96 (s, 3 H), 3.95 (s, 3 H), 3.34 (s, 6 H), 2.16 (dt, J = 7.27 and 7.40 Hz, 2 H), 1.64 (m, 2 H), 1.54 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 171.21, 165.75, 165.45, 154.94, 154.64, 138.43, 137.35, 135.31, 134.95, 132.80, 132.38, 130.91, 129.62, 129.38, 127.99, 126.72, 126.57, 61.94, 52.64, 52.40, 31.92, 29.41, 24.50; ESI m/z 541 (MH^+). Anal. ($C_{26}H_{30}Cl_2O_8$) C, H, Cl.

Methyl 5-{4-(Acetylamino)-1-[3-chloro-4-methoxy-5-(methoxycarbonyl)phenyl]but-1-enyl}-3-chloro-2-methoxybenzoate (39). Amine **96** hydrochloride salt (42.0 mg, 0.083 mmol) was dissolved in dry THF (8 mL) containing triethylamine (31.5 mg, 0.31 mmol). Acetyl chloride (9.8 mg, 0.125 mmol) was added. The mixture was stirred for 2 h at 0 °C, and then the reaction was quenched with methanol (10 mL). The solvent was removed, and the residue was purified by flash chromatography on silica gel (silica gel 25 g, EtOAc as eluent) to afford a light-yellow solid (30 mg, 70.8%): ^{1}H NMR ($CDCl_3$) δ 7.50 (d, J = 2.27 Hz, 1 H), 7.46 (d, J = 2.18 Hz, 1 H), 7.31 (d, J = 2.13 Hz, 1 H), 7.28 (d, J = 2.35 Hz, 1 H), 6.05 (t, J = 7.73 Hz, 1 H), 3.99 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.75 (t, J = 7.51 Hz, 2 H), 2.35 (dt, J = 7.64 and 7.73 Hz, 2 H), 2.31 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.81, 165.60, 165.33, 155.26, 155.02, 139.71, 137.62, 134.67, 132.35, 130.63, 129.98, 129.56, 128.03, 127.64, 127.01, 126.65, 61.92, 52.48, 44.00, 29.47, 26.17; CIMS m/z 510 (MH^+). Anal. ($C_{24}H_{25}NCl_2O_7$) C, H, Cl.

4-(*N*-Methoxycarbonyl)amino-3′,3″-dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenylbutene (40). A mixture of $TiCl_4$/THF 1:2 complex (1.01 g, 3.02 mmol) and Zn dust (395 mg, 6.05 mmol) was heated at reflux in dry THF (8 mL) under argon. After 1 h of reflux, a mixture of benzophenone **53** (379 mg, 0.89 mmol) and aldehyde **87** (163 mg, 1.02 mmol) in dry THF (12 mL) was added dropwise. The mixture was heated again at reflux for 14 h, then concentrated. The resulting residue was filtered through a pad of Celite and washed with ethyl acetate (30 mL). The filtrate was evaporated, and the brown residue was further purified by flash chromatography on silica gel (35 g, 1.5 cm × 31 cm, eluent ethyl acetate/hexanes 3:2, v/v) to afford a colorless oil (150 mg, 32%): ^{1}H NMR ($CDCl_3$) δ 7.48 (d, J = 2.19 Hz, 1 H), 7.45 (d, J = 2.10 Hz, 1 H, 7.30 (d, J = 2.50 Hz, 1 H), 7.28 (d, J = 2.80 Hz, 1 H), 6.03 (t, J = 7.45 Hz, 1 H), 4.77 (br, 1 H), 3.98 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.64 (s, 3 H), 3.28 (dt, J = 6.35 and 6.31 Hz, 2 H), 2.30 (dt, J = 7.08 and 6.88 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 165.66, 165.39, 156.88, 155.08, 154.84, 139.32, 138.04, 134.92, 134.84, 132.43, 130.84, 129.77, 129.44, 129.08, 128.06, 126.80, 126.59, 61.89, 52.44, 52.03, 40.42, 30.59; ESI-MS m/z 526 (MH^+); HRMS calcd for $C_{24}H_{25}NCl_2O_8$ 525.0957, found 525.0934. Anal. ($C_{24}H_{25}NCl_2O_8$) C, H, N: C, 54.75; H, 4.75; N, 2.66; Cl, 13.50. Found: C, 55.02; H, 5.02; N, 2.51; Cl, 13.43.

4-(*N*-Methyloxycarbonyl)amino-3′,3″-dimethyl-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenylbutene (41). $TiCl_4$/THF 1:2 complex (965 mg, 2.89 mmol) was added to a stirred suspension of zinc dust (378 mg, 5.78 mmol) in dry THF (8 mL). The resulting black mixture was heated under reflux for 1 h under argon. The suspension was cooled to room temperature, and a solution of benzophenone **54** (328 mg, 0.85 mmol) and aldehyde **87** (167 mg, 1.27 mmol) in dry THF (15 mL) was added. The mixture was heated at reflux for 14 h and then concentrated. The concentrated residue was passed through a short column (silica gel 5 g, eluent ethyl acetate 30 mL) to removed the black solid. The combined fractions were evaporated, and the brown residue was purified by flash chromatography on silica gel (50 g, 1.5 cm × 31 cm), eluting with hexanes/ethyl acetate (2:1, v/v), to give a colorless oil (160 mg, 38.8%): ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 2.32 Hz, 1 H), 7.41 (d, J = 1.98 Hz, 1 H), 7.09 (m, 2 H), 5.95 (t, J = 7.39 Hz, 1 H), 4.67 (br, 1 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.81 (d, J = 7.67 Hz, 2 H), 3.80 (s, 3 H), 3.65 (s, 3 H), 3.28 (td, J = 6.12 and 6.27 Hz, 2 H), 2.31(s, 3 H), 2.29 (dt, J = 7.02 and 6.88 Hz, 2 H), 2.25 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.87, 166.65, 157.48, 157.42, 156.88, 141.70, 137.43, 136.12, 134.41, 133.72, 132.82, 132.34, 130.11, 127.46, 126.52, 124.29, 61.39, 52.09, 51.93, 40.70, 30.40, 16.00; ESI-MS m/z 486 (MH^+); HRMS calcd for $C_{26}H_{31}NO_8$ (M^+) 485.2050, found 485.2046. Anal. ($C_{26}H_{31}NO_8 \cdot H_2O$) C, H, N.

4-(*N*-Methoxycarbonyl)amino-3′,3″-dibromo-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenylbutene (42). A slurry of $TiCl_4$/THF 1:2 complex (968 mg, 2.90 mmol) and Zn dust (379 mg, 5.80 mmol) in THF (10 mL) was heated under reflux for 1 h. A mixture of benzophenone **55** (0.44 g, 0.85 mmol) and aldehyde **87** (201 mg, 1.54 mmol) in dry THF (15 mL) was added. The black mixture was stirred at room temperature for 30 min and then heated under reflux for 14 h. The solvent was evaporated, and the residue was filtered through a pad of Celite. The filtrate was concentrated and purified by flash chromatography on silica gel (40 g, 1.5 cm × 31 cm, eluent ethyl acetate/hexanes 1;2, v/v) to afford a colorless oil (200 mg, 38.1%): ^{1}H NMR ($CDCl_3$) δ 7.53 (d, J = 2.28 Hz, 1 H), 7.51 (d, J = 2.16 Hz, 1 H), 7.48 (d, J = 2.16 Hz, 2 H), 6.04 (t, J = 7.45 Hz, 1 H), 4.73 (br, 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 3.66 (s, 3 H), 3.28 (td, J = 6.34 and 6.32 Hz, 2 H), 2.31 (td, J = 7.07 and 6.92 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 165.60, 165.33, 156.88, 156.10, 155.86, 139.15, 138.54, 137.87, 135.49, 135.41, 131.69, 129.23, 128.99, 126.62, 126.44, 119.31, 119.05, 62.08, 52.48, 52.09, 40.38, 30.60. Anal. ($C_{24}H_{25}NBr_2O_8$) C, H, Br.

4-(*N*-Ethoxycarbonyl)amino-3′,3″-dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenylbutene (43). A mixture of $TiCl_4$/THF 1:2 complex (1.07 g, 3.2 mmol) and Zn dust (418 mg, 6.4 mmol) was heated at reflux in dry THF (8 mL) under argon. After 1 h of reflux, a mixture of benzophenone **53** (426 mg, 1.0 mmol) and aldehyde **88** (290 mg, 2.0 mmol) in dry THF (15 mL) was added dropwise. The mixture was heated again at reflux for 14 h and then concentrated. The resulting residue was filtered through a pad of Celite and washed with ethyl acetate (30 mL). The filtrate was evaporated, and the brown residue was further purified by flash chromatography on silica gel (60 g, 2.5 cm × 31 cm, eluent ethyl acetate/hexanes 3:2, v/v) to afford a colorless oil (180 mg, 33.3%): ^{1}H NMR ($CDCl_3$) δ 7.49 (d, J = 2.20 Hz, 1 H), 7.46 (d, J = 2.24 Hz, 1 H), 7.31 (d, J = 2.25 Hz, 1 H), 7.29 (d, J = 2.61 Hz, 1 H), 6.04 (t, J = 7.47 Hz, 1 H), 4.10 (q, J = 7.10 Hz, 2 H), 3.99 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.26 (dt, J = 6.26 and 6.10 Hz, 2 H), 2.31 (dt, J = 7.13

and 6.90 Hz, 2 H), 1.70 (br, 1 H), 1.22 (t, J = 7.17 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.68, 165.39, 156.47, 155.11, 154.89, 139.30, 138.88, 138.06, 134.95, 134.86, 132.44, 130.82, 129.80, 129.46, 129.11, 128.06, 126.83, 126.62, 61.94, 60.77, 52.43, 40.31, 30.66, 14.49; CIMS m/z 540 (MH^+); HRMS (CI) calcd for $C_{25}H_{27}Cl_2NO_8$ 540.1192, found 540.1180. Anal. ($C_{25}H_{27}Cl_2NO_8 \cdot 0.15H_2O$) C, H, N, Cl.

4-(*N*-Ethoxycarbonyl)amino-3′,3″-dimethyl-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenylbutene (44). A mixture of $TiCl_4$/THF 1:2 complex (1.45 g, 4.35 mmol) and Zn dust (0.57 g, 8.7 mmol) was heated at reflux in dry THF (15 mL) under argon. After 1 h of reflux, a mixture of benzophenone **54** (0.56 g, 1.45 mmol) and aldehyde **88** (0.32 g, 2.18 mmol) in dry THF (15 mL) was added dropwise. The mixture was heated again at reflux for 14 h and then concentrated. The resulting residue was filtered through a pad of Celite and washed with ethyl acetate (30 mL). The filtrate was evaporated, and the brown residue was further purified by flash chromatography on silica gel (75 g, 2.5 cm × 31 cm, eluent ethyl acetate/hexanes 3:2, v/v) to afford a colorless oil (300 mg, 41.5%): ^{1}H NMR ($CDCl_3$) δ 7.40 (d, J = 2.34 Hz, 1 H), 7.37 (d, J = 2.12 Hz, 1 H), 7.30 (d, J = 1.87 Hz, 1 H), 7.25 (d, J = 1.64 Hz, 1 H), 6.26 (br, 1 H), 6.10 (t, J = 7.42 Hz, 1 H), 4.04 (q, J = 7.10 Hz, 2 H), 3.85 (s, 6 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.25 (m, 2 H), 2.32 (s, 3 H), 2.30 (t, J = 6.87 Hz, 2 H), 2.25 (s, 3 H), 1.16 (t, J = 7.05 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.60, 171.25, 162.36, 162.26, 161.50, 145.95, 142.95, 141.09, 139.80, 138.37, 137.76, 137.32, 137.0, 134.86, 132.91, 132.26, 130.06, 65.88, 64.76, 56.50, 45.41, 35.79, 20.39, 19.25; EIMS m/z 499 (M^+); HRMS calcd for $C_{27}H_{33}NO_8$ 499.2206, found 499.2212. Anal. ($C_{27}H_{33}NO_8$) C, H, N.

Methyl 5-{1-[3-Chloro-4-methoxy-5-(methoxycarbonyl)phenyl]-4-[(ethylamino)carbonylamino]but-1-enyl}-3-chloro-2-methoxybenzoate (45). Amine **96** hydrochloride salt (21.0 mg, 0.0416 mmol) was dissolved in dry THF (5 mL) containing triethylamine (10.5 mg, 0.104 mmol). Ethyl isocyanate (8.9 mg, 0.125 mmol) was added. The mixture was stirred for 2 h and then quenched with methanol (10 mL). The solvent was removed under reduced pressure, and the residue was passed through a short column (silica gel 5 g, EtOAc as eluent) to afford the desired urea compound **45** as white needles in quantitative yield: mp 103−104 °C; ^{1}H NMR ($CDCl_3$) δ 7.49 (d, J = 2.20 Hz, 1 H), 7.46 (d, J = 2.24 Hz, 1 H), 7.31 (d, J = 2.25 Hz, 1 H), 7.29 (d, J = 2.61 Hz, 1 H), 6.04 (t, J = 7.45 Hz, 1 H), 4.67 (br, 1 H), 4.10 (q, J = 7.14 Hz, 2 H), 3.99 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.26 (m, 2 H), 2.31 (dt, J = 7.13 and 6.90 Hz, 2 H), 1.22 (t, J = 7.27 Hz, 3 H); HRMS calcd for $C_{25}H_{28}N_2Cl_2O_7$ 539.1352, found 539.1342. Anal. ($C_{25}H_{28}N_2Cl_2O_7$) C, H, Cl.

Methyl 5-(1-[3-Chloro-4-methoxy-5-(methoxycarbonyl)phenyl]-4-{[(methylamino)thioxomethyl]amino}but-1-enyl)-3-chloro-2-methoxybenzoate (46). Amine **96** hydrochloride salt (23.2 mg, 0.0046 mmol) was dissolved in dry THF (5 mL) containing triethylamine (11.6 mg, 0.115 mmol). Methyl isothiocyanate (10.1 mg, 0.138 mmol) was added. The mixture was stirred for 40 min and then concentrated and subjected to flash chromatography on silica gel (30 g, EtOAc as eluent) to give the thiourea **46** (17.9 mg, 71.9%) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 7.51 (d, J = 2.42 Hz, 1 H), 7.46 (d, J = 2.21 Hz, 1 H), 7.32 (d, J = 2.31 Hz, 1 H), 7.31 (d, J = 2.25 Hz, 1 H), 6.08 (t, J = 7.46 Hz, 1 H), 5.80 (br, 1 H), 3.98 (s, 3 H), 3.92 (s, 6 H), 3.90 (s, 3 H), 3.63 (m, 2 H), 2.95 (d, J = 4.60 Hz, 3 H), 2.41 (dt, J = 7.21 and 7.14 Hz, 2 H), 1.70 (br, 1 H); ^{13}C NMR ($CDCl_3$) δ 182.76, 165.69, 165.59, 155.13, 154.90, 139.45, 137.79, 134.86, 132.45, 130.79, 129.92, 129.50, 128.54, 128.06, 126.89, 126.57, 61.98, 61.91, 52.54, 52.46, 43.89, 29.84, 14.04; CIMS m/z 541 (MH^+); HRMS calcd for $C_{24}H_{26}N_2Cl_2SO_6$ 540.0889, found 540.0865. Anal. ($C_{24}H_{26}N_2Cl_2SO_6$) C, H, Cl.

4-(*N*-Isobutyloxycarbonyl)amino-3′,3″-dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenylbutene (47). A slurry of $TiCl_4$/THF 1:2 complex (1.09 g, 3.27 mmol) and Zn dust (428 mg, 6.55 mmol) in THF (10 mL) was heated under reflux for 1 h. A mixture of benzophenone **53** (0.45 g, 1.06 mmol) and aldehyde **89** (274 mg, 1.58 mmol) in dry THF (15 mL) was added. The black mixture was stirred at room temperature for 30 min and then heated under reflux for 14 h. The solvent was evaporated, and the residue was filtered through a pad of Celite. The filtrate was concentrated and purified by flash chromatography on silica gel (40 g, 1.5 cm × 31 cm, eluent ethyl acetate/hexanes 1;2, v/v) to afford a colorless oil (240 mg, 39.8%): ^{1}H NMR ($CDCl_3$) δ 7.48 (d, J = 2.30 Hz, 1 H), 7.45 (d, J = 2.14 Hz, 1 H), 7.30 (d, J = 2.06 Hz, 1 H), 7.29 (d, J = 2.01 Hz, 1 H), 6.04 (t, J = 7.41 Hz, 1 H), 4.74 (br, 1 H), 3.98 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.82 (d, J = 6.61 Hz, 2 H), 3.28 (td, J = 6.34 and 6.39 Hz, 2 H), 2.31 (td, J = 6.87 and 7.16 Hz, 2 H), 1.85 (m, 1 H), 0.88 (d, J = 6.72 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 165.66, 165.39, 156.65, 155.08, 154.84, 139.21, 138.07, 134.95, 134.85, 132.44, 130.82, 129.80, 129.44, 129.19, 128.09, 126.80, 126.59, 70.97, 61.92, 52.44, 40.32, 30.70, 27.85, 18.90; CIMS m/z 568 (MH^+); HRMS calcd for $C_{27}H_{32}Cl_2NO_8$ (MH^+) 568.1505, found 568.1487. Anal. ($C_{27}H_{31}Cl_2NO_8$) C, H, Cl.

4-(*N*-Isobutyloxycarbonyl)amino-3′,3″-dimethyl-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenylbutene (48). Titanium tetrachloride/THF 1:2 complex (1.35 g, 4.03 mmol) was added to a stirred suspension of zinc dust (0.53 g, 8.03 mmol) in dry THF (15 mL). The resulting black mixture was heated under reflux for 1 h under argon. The suspension was cooled to room temperature, and a solution of benzophenone **54** (0.50 g, 1.3 mmol) and aldehyde **89** (340 mg, 1.95 mmol) in dry THF (15 mL) was added. The mixture was heated at reflux for 14 h and then concentrated. The concentrated residue was passed through a short column (silica gel 5 g, eluent ethyl acetate 30 mL) to remove the black solid. The combined fractions were evaporated, and the brown residue was purified by flash chromatography on silica gel (35 g, 1.5 cm × 31 cm), eluting with hexanes/ethyl acetate (2:1, v/v), to give a colorless oil (219 mg, 32%): ^{1}H NMR ($CDCl_3$) δ 7.45 (d, J = 2.34 Hz, 1 H), 7.40 (d, J = 2.06 Hz, 1 H), 7.09 (m, 2 H), 5.95 (t, J = 7.41 Hz, 1 H), 4.68 (br, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.81 (d, J = 7.67 Hz, 2 H), 3.80 (s, 3 H), 3.27 (td, J = 6.12 and 6.27 Hz, 2 H), 2.31 (t, J = 7.02 Hz, 2 H), 2.30 (s, 3 H), 2.24 (s, 3 H), 1.89 (m, 1 H), 0.88 (d, J = 6.72 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 166.86, 166.62, 157.48, 157.42, 156.65, 141.60, 137.51, 136.14, 134.44, 133.72, 132.82, 132.31, 130.12, 127.48, 126.63, 124.29, 70.90, 61.40, 52.08, 40.64, 30.48, 27.86, 18.90, 16.04; CIMS m/z 527 (MH^+); HRMS calcd for $C_{29}H_{38}NO_8$ (MH^+) 528.2597, found 528.2588. Anal. ($C_{29}H_{38}NO_8$) C, H, N.

Methyl 5-{1-[3-Chloro-4-methoxy-5-(methoxycarbonyl)phenyl]-4-(2-oxo(1,3-oxazolidin-3-yl))but-1-enyl}-3-chloro-2-methoxybenzoate (49). A mixture of $TiCl_4$/THF 1:2 complex (1.46 g, 4.37 mmol) and Zn dust (571 mg, 8.74 mmol) was heated at reflux in dry THF (12 mL) under argon. After 1 h of reflux, a mixture of substituted benzophenone **53** (583 mg, 1.37 mmol) and aldehyde **92** (204 mg, 1.43 mmol) in dry THF (15 mL) was added dropwise. The resulting mixture was heated again at reflux for 14 h and then cooled to room temperature and poured into a 10% K_2CO_3 solution (15 mL). The white precipitate was filtered off, and the filtrate was partioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4 and then evaporated to give a light-yellow residue. The residue was purified by flash chromatography (silica gel 70 g, solvent hexanes/ethyl acetate 2:3, v/v) to afford a colorless oil (235 mg, 32%): ^{1}H NMR ($CDCl_3$) δ 7.47 (d, J = 2.13 Hz, 1 H), 7.46 (d, J = 1.96 Hz, 1 H), 7.32 (d, J = 2.04 Hz, 2 H), 6.03 (t, J = 7.49 Hz, 1 H), 4.28 (t, J = 7.76 Hz, 2 H), 3.98 (s, 3 H), 3.91 (s, 6 H), 3.89 (s, 3 H), 3.38 (t, J = 7.50 Hz, 2 H), 3.37 (t, J = 6.90 Hz, 2 H), 2.36 (dt, J = 7.19 and 6.88 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 165.63, 165.36, 158.41, 155.10, 154.91, 139.44, 137.82, 134.92, 134.74, 132.46, 130.65, 129.85, 129.47, 128.51, 128.16, 126.92, 126.63, 61.95, 61.86, 61.52, 52.47, 52.38, 44.40, 43.68, 27.93; CIMS m/z 538 $(MH)^+$; Anal. ($C_{25}H_{25}NCl_2O_8$) C, H, N.

Methyl 5-{1-[3-Bromo-4-methoxy-5-(methoxycarbonyl)phenyl]-4-(2-oxo(1,3-oxazolidin-3-yl))but-1-enyl}-3-bromo-2-methoxybenzoate (50). A mixture of $TiCl_4$/THF 1:2 complex (898 mg, 2.69 mmol) and Zn dust (351 mg, 5.38 mmol)

was heated at reflux in dry THF (12 mL) under argon. After 1 h of reflux, a mixture of substituted benzophenone **55** (433 mg, 0.84 mmol) and aldehyde **92** (156 mg, 1.09 mmol) in dry THF (15 mL) was added dropwise. The resulting mixture was heated again at reflux for 14 h, cooled to room temperature, and poured into a 10% K_2CO_3 solution (15 mL). The white precipitate was filtered off, and the filtrate was partioned between ethyl acetate and water. The organic layers were combined and dried over Na_2SO_4 and evaporated to give a light-yellow residue. The residue was purified by flash chromatography (silica gel 70 g, solvent hexanes/ethyl acetate 2:3, v/v) to afford a colorless oil (268 mg, 51%): ^{1}H NMR ($CDCl_3$) δ 7.46 (dd, J = 2.55 and 0.70 Hz, 2 H), 7.43 (dd, J = 2.75 and 0.77 Hz, 2 H), 5.97 (t, J = 7.55 Hz, 1 H), 4.23 (t, J = 7.72 Hz, 2 H), 3.92 (s, 3 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.34 (t, J = 6.91 Hz, 2 H), 3.31 (t, J = 6.82 Hz, 2 H), 2.32 (dt, J = 7.28 and 6.92 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 165.64, 165.36, 158.38, 156.19, 156.04, 139.35, 138.39, 137.83, 135.61, 135.44, 131.57, 129.16, 128.72, 126.83, 126.56, 119.45, 119.16, 62.23, 62.10, 61.54, 52.59, 52.54, 44.50, 43.80, 28.03; CIMS *m/z* 626 (MH^+), 594 (M − MeOH). Anal. ($C_{25}H_{25}NBr_2O_8$) C, H, N, Br.

Di(4-methoxy-3-methoxycarbonyl-5-methylphenyl) Ketone (54). Di(4-methoxy-3-methoxycarbonyl-5-methylphenyl)-methane (**59**, 4.23 g, 11.4 mmol) was taken up in glacial acetic acid (550 mL). A solution of chromic anhydride (3.19 g, 31.9 mmol) in glacial acetic acid (25 mL) and water (15 mL) was prepared and added dropwise to the stirring solution of the diaryl methane. The resulting solution was stirred for 18 h. The reaction mixture was diluted to 3 L with water, and the resulting solution was saturated with NaCl. Portions (500 mL) of the resulting solution were extracted twice with ethyl acetate (100 mL). The organic extracts were combined and dried over anhydrous $MgSO_4$. The solids were removed by filtration, and the solvent was removed on a rotary evaporator. The resulting crude yellow solid was purified by chromatography on silica gel (200 g), using a gradient elution of 10−15% ethyl acetate in hexane to elute the product. The eluent was removed on a rotary evaporator to give the product as a white solid (2.21 g, 50%). An analytical sample of the product was prepared by recrystallization from methylene chloride and hexane: mp 130−132 °C; IR (KBr pellet) 3000, 2959, 2856, 1731, 1664, 1597, 1577, 1474, 1429, 1413, 1382, 1336, 1290, 1254, 1218, 1172, 1136, 1120, 1013, 993, 926, 911, 880, 803, 762, 736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 2.0 Hz, 2 H), 7.80 (s, 2 H), 3.92 (s, 6 H), 3.92 (s, 6 H), 2.38 (s, 6 H). Anal. ($C_{21}H_{22}O_7$) C, H.

Di[4-methoxy-3-methoxycarbonyl-5-(trifluoromethyl)-phenyl] Ketone (57). Di[3-methoxycarbonyl-4-methoxy-5-(trifluoromethyl)phenyl]methane (**62**, 0.377 g, 0.785 mmol) was taken up in acetic anhydride (15 mL) with stirring. Chromic anhydride (0.330 g, 3.30 mmol) was added in one portion, and the reaction mixture was stirred overnight. The reaction mixture was filtered through a plug of Celite in a sintered glass funnel. The Celite plug was washed with ethyl acetate (50 mL). The solvents were removed on a rotary evaporator, giving the crude product as a dark-green paste. The product was purified by flash column chromatography on silica gel (30 g), using a gradient of 0−20% ethyl acetate in hexanes as the eluent. The fractions containing the product were evaporated to dryness, yielding the product as a colorless oil (0.349 g, 90%): IR (neat on NaCl) 3005, 2957, 1737, 1670, 1606, 1484, 1439, 1343, 1304, 1262, 1232, 1210, 1137, 1096, 993, 928, 767, 746, 689, 659 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 2.3 Hz, 2 H), 8.20 (d, J = 2.2 Hz, 2 H), 4.02 (s, 6 H), 3.97 (s, 6 H); ^{19}F NMR (282 MHz, $CDCl_3$, rel to TFA external standard) δ 12.80 (s, 6 F). Anal. ($C_{21}H_{16}F_6O_7$).

Di(4-methoxy-3-methoxycarbonyl-5-methylphenyl)-methane (59). Di(3-carboxy-4-hydroxy-5-methyl)methane (**58**,[22] 0.500 g, 1.58 mmol) and potassium carbonate (2.11 g) were suspended with stirring in acetone (10 mL). The solution was heated to reflux for 30 min. Dimethyl sulfate (1.65 mL, 17.4 mmol) was added via cannula under argon pressure. The solution was stirred under reflux for 20 h. The reaction mixture was then cooled to ambient temperature, filtered to remove the solids, and condensed on a rotary evaporator to yield the crude product as a white solid. The product was purified by flash column chromatography on silica gel (25 g), using a gradient of 10−20% ethyl acetate in hexanes as the eluent. The solvent was removed on a rotary evaporator to give the product as a white solid (0.430 g, 73%). An analytical sample was prepared by recrystallization from diethyl ether and hexane, giving clear colorless crystals: mp 74−77 °C; IR (KBr pellet) 3010, 2945, 2826, 1720, 1577, 1480, 1444, 1377, 1331, 1274, 1248, 1228, 1198, 1126, 1006, 867, 802 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 2.2 Hz, 2 H), 7.12 (d, J = 2.0 Hz, 2 H), 3.90 (s, 6 H), 3.84 (s, 2 H), 3.80 (s, 6 H), 2.27 (s, 6 H). Anal. ($C_{21}H_{24}O_6$) C, H.

Di[3-carboxy-4-hydroxy-5-(trifluoromethyl)phenyl]-methane (61). 3-(Trifluoromethyl)salicylic acid (**60**,[23] 0.254 g, 1.23 mmol) was taken up in methanol (0.90 mL) and water (0.16 mL) with stirring. The solution was cooled to −78 °C, and concentrated sulfuric acid (2.16 mL) was added dropwise via an addition funnel. The reaction mixture was warmed to 0 °C, stirred for 1 h, and recooled to −78 °C. Formaldehyde (0.52 mL, 19 mmol, 37% aqueous solution) was added dropwise through the addition funnel. The reaction mixture was allowed to slowly come to ambient temperature overnight. The reaction mixture was poured over ice (20 g). When all of the ice was melted, the precipitate was collected on a Büchner funnel. The solid was taken up in acetone, dried over $MgSO_4$, filtered, and condensed to afford the product as an off-white solid (0.198 g, 76%). An analytical sample was purified by column chromatography on silica gel (10 g) using AcOH/EtOH/$CHCl_3$ (1:5:94) as the eluent: mp 306−310 °C (dec); IR (KBr pellet) 3052, 2919, 2861, 1676, 1611, 1445, 1292, 1235, 1167, 1143, 1120, 1096, 946, 911, 802, 690 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.08 (d, J = 1.9 Hz, 2 H), 7.84 (d, J = 1.8 Hz, 2 H), 4.15 (s, 2 H), 3.08 (br. s, 4 H); ^{19}F NMR (282 MHz, acetone-d_6, rel to TFA external standard) δ 12.66 (s, 6 F). Anal. ($C_{17}H_{10}F_6O_6$).

Di[3-methoxycarbonyl-4-methoxy-5-(trifluoromethyl)-phenyl]methane (62). Di[3-carboxy-4-hydroxy-5-(trifluoromethyl)phenyl]methane (**61**, 0.950 g, 2.24 mmol) was taken up with stirring in acetone (27 mL). Potassium carbonate (2.48 g, 17.9 mmol) and dimethyl sulfate (0.66 mL, 7.0 mmol) were added, and the resulting mixture was heated to reflux in an oil bath. The reaction mixture was heated at reflux overnight and then cooled to ambient temperature. Water (25 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 25 mL). The organic extracts were combined and dried ($MgSO_4$). The solution was filtered to remove the solids and condensed on a rotary evaporator to yield the crude product. The product was purified by chromatography on silica gel (45 g), using a gradient of 0−15% EtOAc in hexanes as the eluent. Evaporation of the eluent yielded the pure product as a white solid (0.314 g, 29%). An analytical sample was prepared by recrystallization from diethyl ether and hexane: mp 96−98 °C; IR (KBr pellet) 3074, 3006, 2962, 2845, 1728, 1593, 1484, 1436, 1352, 1296, 1257, 1212, 1122, 989, 944, 890, 855, 808, 777, 760, 693, 668 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 7.64 (d, J = 2.1 Hz, 2 H), 7.31 (d, J = 2.1 Hz, 2 H), 3.60 (s, 6 H), 3.33 (s, 6 H), 3.19 (s, 2 H); ^{19}F NMR (282 MHz, C_6D_6, rel to TFA external standard) δ 13.8 (s, 6 F). Anal. ($C_{21}H_{18}F_6O_6$) C, H.

Ethyl 5-Oxopentanoate (69). A solution of δ-valerolactone (4.0 g, 40 mmol) and concentrated H_2SO_4 (4 drops) in dry ethanol (80 mL) was heated under reflux for 5 h. The mixture was cooled in an ice/salt bath, and $NaHCO_3$ (0.4 g) was added. Stirring was continued for 10 min, the solid was separated by filtration, and the solvent was removed at 25 °C. The light-tan residue was dissolved in dry CH_2Cl_2 (25 mL) and used for the next step. PCC (13.0 g, 60.3 mmol) was suspended in dry CH_2Cl_2 (50 mL). The CH_2Cl_2 solution of the alcohol was then added, and the mixture was stirred under nitrogen for 2 h. Dry ethyl ether (80 mL) was added, and the dark mixture was allowed to stand overnight. The solid was filtered off and washed with ethyl ether (2 × 25 mL). The combined solvents were removed, and the residue was purified by flash chromatography (hexanes/EtOAc 4:1, v/v) to afford aldehyde **69** as a colorless oil (3.0 g, 52.1%): ^{1}H NMR ($CDCl_3$) δ 9.76 (s, 1 H),

4.12 (q, $J = 7.09$ Hz, 2 H), 2.52 (t, $J = 7.24$ Hz, 2 H), 2.35 (t, $J = 7.26$ Hz, 2 H), 1.94 (m, 2 H), 1.24 (t, $J = 7.14$ Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 197.66, 172.86, 60.40, 42.87, 33.13, 17.28, 14.15; CIMS *m/z* 145 (MH^+).

Propyl 5-Oxopentanoate (70). A solution of δ-valerolactone (4.0 g, 40 mmol) and concentrated H_2SO_4 (6 drops) in dry propanol (80 mL) was heated under reflux for 3 h. The mixture was cooled in an ice/NaCl salt bath, and $NaHCO_3$ (0.8 g) was added. Stirring was continued for 10 min, the solid was separated by filtration, and the solvent was removed at 25 °C. The light-tan residue was used for the next step without further purification. PCC (13.2 g, 61.2 mmol) was suspended in dry CH_2Cl_2 (50 mL). The alcohol was then added, and the mixture was stirred under nitrogen for 2 h. Dry ethyl ether (100 mL) was added, and the dark mixture was allowed to stand overnight. The solid was filtered off and washed with ethyl ether (2 × 30 mL). The combined solvents were removed, and the residue was purified by flash chromatography (hexanes/EtOAc 4:1, v/v) on silica gel (120 g) to afford aldehyde **70** as a colorless oil (3.5 g, 55%): ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1 H), 4.03 (t, $J = 6.74$ Hz, 2 H), 2.53 (t, $J = 7.20$ Hz, 2 H), 2.37 (t, $J = 7.26$ Hz, 2 H), 1.95 (m, 2 H), 1.64 (m, 2 H), 0.93 (t, $J = 7.42$ Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 201.51, 172.90, 65.99, 42.83, 33.05, 21.83, 17.24, 10.24. EIMS *m/z* (relative intensity) 175 (74, hydrate form of aldehyde **2**), 157 (100).

Isopropyl 5-Oxopentanoate (71). A solution of δ-valerolactone (3.5 g, 35 mmol) and concentrated H_2SO_4 (8 drops) in dry 2-propanol (100 mL) was heated under reflux for 3 h. The mixture was cooled in an ice/NaCl salt bath, and $NaHCO_3$ (1.0 g) was added. Stirring was continued for 20 min. The solid was separated by filtration, and the solvent was removed at 25 °C. The light-tan liquid residue was used for the next step without further purification. PCC (11.3 g, 52.5 mmol) was suspended in dry CH_2Cl_2 (50 mL). The alcohol was then added, and the mixture was stirred under nitrogen for 1.5 h. Dry ethyl ether (100 mL) was added, and the dark mixture was allowed to stand overnight. The solid was filtered off and washed with ethyl ether (2 × 30 mL). The combined solvents were removed, and the residue was purified by flash chromatography (hexanes/EtOAc 4:1, v/v) on silica gel (110 g) to afford aldehyde **71** as a colorless oil (2.15 g, 38.9%): ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1 H), 5.00 (m, 1 H), 2.52 (t, $J = 7.22$ Hz, 2 H), 2.33 (t, $J = 7.26$ Hz, 2 H), 1.94 (m, 2 H), 1.23 (d, $J = 6.21$ Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 201.43, 172.28, 67.67, 42.82, 33.40, 21.69, 17.28; EIMS *m/z* (relative intensity) 175 (74, hydrate form of aldehyde **3**), 157 (100).

***N,N*-Dimethyl 5-Oxopentanamide (72).** *N,N*-Dimethylamine (15 mL of 2 M dimethylamine in THF) was added to a solution of δ-valerolactone (1.5 g, 15 mmol) in THF (10 mL). The mixture was stirred at room temperature for 72 h, and the solvent and excess dimethylamine were removed to give a brown liquid, which was used for the next step without further purification. PCC (4.3 g, 20 mmol) was suspended in dry CH_2Cl_2 (25 mL). The above alcohol was added, and the reaction mixture was stirred under nitrogen for 2 h. Dry ethyl ether (30 mL) was then added, and the dark mixture was filtered through a pad of Celite. The solvents were removed, and the residue was purified by flash chromatography on silica gel (45 g, 5 cm × 17.5 in.), eluting with EtOAc/MeOH (6:1, v/v), to afford aldehyde **72** as a colorless oil (0.76 g, 35%): ^{1}H NMR ($CDCl_3$) δ 9.73 (s, 1 H), 2.93 (s, 6 H), 2.52 (t, $J = 6.17$ Hz, 2 H), 2.33 (t, $J = 6.78$ Hz, 2 H), 1.92 (t, $J = 6.62$ Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 202.20, 172.17, 43.13, 33.22, 31.92, 17.41; CIMS *m/z* 144 (MH^+); HRMS (CI) calcd for $C_7H_{14}NO_2$ 144.1025, found 144.1018.

1-(5-Oxopentanoyl)piperidine (73). δ-Valerolactone (4 g, 40 mmol) was added to piperidine (10.2 g, 120 mmol). The reaction mixture was stirred for 48 h at room temperature, and then the excess amine was removed through rotary evaporation. The tan residue was dissolved in CH_2Cl_2 (10 mL) and used for the next step. PCC (12.93 g, 60 mmol) was suspended in dry CH_2Cl_2 (40 mL). The above alcohol was added, and the mixture was kept stirring for 4 h. Dry ethyl ether (100 mL) was added, and the resulting dark solid was filtered off. The filtrate was evaporated, and the crude residue was purified by flash chromatography on silica gel (120 g, 5 cm × 30 cm), eluting with EtOAc, to give pure aldehyde **73** as a light-yellow oil (2.1 g, 29%): ^{1}H NMR ($CDCl_3$) δ 9.78 (t, $J = 1.20$ Hz, 1 H), 3.53 (t, $J = 5.45$ Hz, 2 H), 3.38 (t, $J = 5.30$ Hz, 2 H), 2.56 (dt, $J = 6.87$ and 1.21 Hz, 2 H), 2.36 (t, $J = 7.23$ Hz, 2 H), 1.96 (m, 2 H), 1.48−1.66 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 202.19, 170.16, 46.45, 43.24, 42.57, 31.99, 26.42, 25.48, 24.45, 17.65. CIMS *m/z* 184 (MH^+); HRMS (CI) calcd for $C_{10}H_{18}NO_2$ 184.1338, found 184.1333 (MH^+).

5,5-Dimethoxypentanoic Acid (74). 2,2-Dimethoxypropane (5.9 g, 56.65 mmol) and a small amount of concentrated HCl (6 drops) were added to a chloroform solution (15 mL) containing ethyl 5-oxopentanoate (**69**) (1.25 g, 8.68 mmol). The reaction mixture was stirred at room temperature for 6 h and then evaporated in vacuo to afford almost pure acetal (1.56 g, 95%) that was used without further purification: ^{1}H NMR ($CDCl_3$) δ 4.36 (t, $J = 5.27$ Hz, 1 H), 4.11 (q, $J = 7.16$ Hz, 2 H), 3.30 (s, 6 H), 2.31 (t, $J = 6.92$ Hz, 2 H), 1.63 (m, 4 H), 1.23 (t, $J = 7.08$ Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.08, 104.92, 60.37, 52.63, 33.88, 31.75, 20.02, 14.17. The acetal compound (1.39 g, 7.34 mmol) was dissolved in a solution of 1 N NaOH (20 mL) and EtOH (10 mL). The mixture was stirred overnight and then neutralized to pH 5.5−6.0 by addition of 0.5 N HCl. The mixture was evaporated and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were evaporated to afford acid **74** as a viscous liquid (1.07 g, 90%): ^{1}H NMR ($CDCl_3$) δ 4.38 (t, $J = 5.04$ Hz, 1 H), 3.33 (s, 6 H), 2.39 (t, $J = 6.77$ Hz, 2 H), 1.68 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 179.17, 104.08, 52.63, 34.13, 31.70, 19.94.

2-(Trimethylsilyl)ethyl 5-Oxopentanoate (75). BOP-Cl (1.68 g, 6.60 mmol) was added to a solution of acid **74** (1.07 g, 6.60 mmol), 2-(trimethylsilyl)ethanol (0.86 g, 7.27 mmol), and triethylamine (1.33 g, 13.20 mmol) in dry CH_2Cl_2 (30 mL). The reaction mixture was stirred at room temperature under argon for 2 h. A 5% aqueous sodium carbonate solution (40 mL) was added, and the phases were separated. The organic phase was diluted with ethyl acetate (2 × 20 mL) and washed with water (30 mL). The organic solvents were evaporated, and the crude residue was immediately hydrolyzed in 0.5 N HCl/acetone (1:1, v/v, 40 mL) for 2 h. The solution was then concentrated, and the crude product was purified by flash chromatography on silica gel (100 g, 5 cm × 17.5 in.), eluting with hexanes/EtOAc (1:1, v/v) to afford aldehyde **75** as a colorless liquid (0.60 g, 42%): ^{1}H NMR ($CDCl_3$) δ 9.76 (s, 1 H), 4.15 (t, $J = 8.50$ Hz, 2 H), 2.51 (t, $J = 7.16$ Hz, 2 H), 2.33 (t, $J = 7.24$ Hz, 2 H), 1.93 (t, $J = 7.20$ Hz, 2 H), 0.96 (t, $J = 8.52$ Hz, 2 H), 0.02 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 201.47, 172.95, 62.61, 42.87, 33.23, 17.25, 1.59; CIMS *m/z* 217 (MH^+); HRMS calcd for $C_{10}H_{21}SiO_3$ (MH^+) 217.1260, found 217.1261.

4-(Methylthio)butanal (76). 4-(Methylthio)-1-butanol (3.09 g, 25.7 mmol) was taken up with stirring in dichloromethane (360 mL). Dess−Martin periodinane (10.91 g, 25.7 mmol) was added in one portion to the stirring reaction mixture. The reaction mixture was allowed to stir at ambient temperature for 3 h. The reaction mixture was washed with a saturated aqueous soluton of sodium bicarbonate (2 × 100 mL). The organic layer was separated and was washed with brine (2 × 100 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed on a rotary evaporator. The crude product was purified by distillation under reduced pressure (25 mmHg). The fraction that was distilled between 75 and 80 °C was collected (0.601 g, 20%): IR (neat on NaCl) 2917, 2834, 2724, 1723, 1428, 1127, 1062, 958 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 9.24 (s, 1 H), 2.05 (t, $J = 7.0$ Hz, 2 H), 1.83 (t, $J = 7.1$ Hz, 2 H), 1.67 (s, 3 H), 1.55−1.45 (m, 2 H). Anal. ($C_5H_{10}OS \cdot 0.15H_2O$) C, H.

1-(Methylthio)hex-5-yn-1-one (78). 5-Hexynoic acid (2.24 g, 20 mmol) was dissolved in dry THF (20 mL). Oxalyl chloride (2.10 mL, 24 mmol) was added, followed by a catalytic amount of DMF (2 drops). The mixture was stirred under nitrogen at room temperature for 2 h, and the solvents were removed. The crude acid chloride residue was dissolved in dry THF (40 mL). $NaSCH_3$ (2.1 g, 30 mmol) in 20 mL of DMF was added at 0

°C. The reaction mixture was stirred under nitrogen overnight. The mixture was diluted with water (20 mL), and the organic layer was separated. The water layer was further extracted with ethyl acetate (2 × 30 mL). The combined extracts were dried over Na_2SO_4 and then were evaporated. The crude residue was purified by flash chromatography on silica gel (70 g, eluent hexanes/EtOAc 5:1, v/v) to afford a light-yellow liquid (1.4 g, 50%): ^{1}H NMR ($CDCl_3$) δ 2.65 (t, J = 7.36 Hz, 2 H), 2.23 (s, 3 H), 2.20 (m, 2 H), 1.93 (t, J = 2.46 Hz, 1 H), 1.86 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 199.09, 82.92, 69.18, 42.24, 24.97, 17.61, 11.43; ESI m/z 142 (M^+).

1-(Ethylthio)hex-5-yn-1-one (79). 5-Hexynoic acid (1.68 g, 15 mmol) was dissolved in dry THF (20 mL). Oxalyl chloride (1.44 mL, 16.5 mmol) was added, followed by a catalytic amount of DMF (2 drops). The mixture was stirred under nitrogen at room temperature for 2 h, and the solvents were removed. The crude acid chloride residue was dissolved in dry THF (40 mL). Triethylamine (1.82 g, 18 mmol) was added, followed by ethanethiol (1.16 mL, 15.75 mmol). The reaction mixture was stirred under nitrogen overnight. The mixture was diluted with water (20 mL), and the organic layer was separated. The water layer was extracted with ethyl acetate (2 × 20 mL). The combined extracts were dried over Na_2SO_4 and then were evaporated. The crude residue was purified by flash chromatography on silica gel (50 g, eluent hexanes/EtOAc 5:1, v/v) to afford a light-yellow liquid (1.5 g, 64%): ^{1}H NMR ($CDCl_3$) δ 2.83 (q, J = 7.40 Hz, 2 H), 2.68 (t, J = 7.37 Hz, 2 H), 2.25 (td, J = 6.89 and 2.59 Hz, 2 H), 1.98 (t, J = 2.58 Hz, 1 H), 1.86 (m, 2 H), 1.25 (t, J = 7.49 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 198.81, 82.98, 69.14, 42.44, 24.05, 23.15, 17.62, 14.61; EIMS m/z 157 (MH^+); HRMS calcd for $C_8H_{13}OS$ (MH^+) 157.0687, found 157.0682.

5-(Methylthio)-5-oxopentanal (80). The alkyne **78** (1.4 g, 10 mmol) was hydrogenated using 5% palladium on barium sulfate (100 mg) and quinoline (115 mg) in ethyl acetate (30 mL) for 14 h. The catalyst was removed by filtration, and the solvent was evaporated. The residue was passed through a short column (silica gel 10 g, eluent hexanes/EtOAc 5:1, v/v) to remove quinoline and to afford an almost pure alkene intermediate: ^{1}H NMR ($CDCl_3$) δ 5.75 (m, 1 H), 4.97−5.05 (m, 2 H), 2.56 (t, J = 7.31 Hz, 2 H), 2.28 (s, 3 H), 2.09 (dt, J = 6.72 and 7.08 Hz, 2 H), 1.77 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 195.07, 132.79, 110.85, 38.42, 28.15, 20.04, 6.84. The alkene (1.0 g, 6.94 mmol) was dissolved in CH_2Cl_2 (40 mL) and then cooled to −78 °C. Ozonized oxygen was bubbled through this solution for 40 min. As the reaction progressed, the solution turned blue. Nitrogen was then passed through the reaction mixture until the blue color disappeared. Dimethyl sulfide (861 mg, 13.8 mmol) was added, and the reaction mixture was stirred for 2 h at room temperature. The mixture was washed with water (2 × 10 mL) and dried over Na_2SO_4. The solvent and excess dimethyl sulfide were evaporated in the hood, and the residue was purified by flash chromatography (silica gel 70 g, eluent EtOAc/hexanes 1:3, v/v) to afford aldehyde **80** as a yellow oil (240 mg, 24%): ^{1}H NMR ($CDCl_3$) δ 9.76 (d, J = 1.03 Hz, 1 H), 2.61 (t, J = 7.23 Hz, 2 H), 2.52 (dt, J = 7.01 and 1.03 Hz, 2 H), 2.29 (s, 3 H), 1.99 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 196.53, 37.96, 37.82, 13.25, 6.88; CIMS (MH^+) m/z 147.

5-(Ethylthio)-5-oxopentanal (81). The alkyne **79** (1.5 g, 10 mmol) was hydrogenated using 5% palladium on barium sulfate (100 mg) and pure quinoline (115 mg) in ethyl acetate (30 mL). After 14 h, the catalyst was removed by filtration and the solvent was evaporated. The residue was passed through a short column (silica gel 10 g, eluent hexanes/EtOAc 5:1, v/v) to remove quinoline. The combined fractions were evaporated, dissolved in CH_2Cl_2 (40 mL), and then cooled to −78 °C. Ozonized oxygen was bubbled through this solution for 40 min. As the reaction progressed, the solution turned blue. Nitrogen was then passed through the reaction mixture until the blue color disappeared. Dimethyl sulfide (1.24 g, 20 mmol) was added, and the reaction mixture was stirred for 2 h at room temperature. Then the mixture was washed with water (2 × 10 mL) and dried over Na_2SO_4. The solvent and excess dimethyl sulfide were evaporated, and the residue was purified by flash chromatography (silica gel 70 g, eluent EtOAc/hexanes 1:3, v/v) to afford aldehyde **81** as a yellow oil (0.7 g, 44%): ^{1}H NMR ($CDCl_3$) δ 9.76 (s, 1 H), 2.87 (q, J = 7.40 Hz, 2 H), 2.59 (t, J = 7.25 Hz, 2 H), 2.50 (t, J = 7.03 Hz, 2 H), 1.98 (m, 2 H), 1.24 (t, J = 7.39 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 201.21, 198.79, 42.55, 23.18, 20.24, 17.78, 14.58. Anal. ($C_7H_{12}SO_2$) C, H, S.

General Procedure for Preparation of 3-Hydroxypropylcarbamates. 3-Aminopropanol (3.0 g, 40 mmol) was dissolved in water (10 mL). A solution of potassium carbonate (8.85 g, 64 mmol) in water (10 mL) was added, followed by slow addition of alkyl chloroformate (60 mmol) at 0 °C. Stirring was continued at 0 °C for 2 h. Then the reaction mixture was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried (Na_2SO_4) and evaporated to give almost pure 3-hydroxypropylcarbamate, which was oxidized without further purification.

Methyl 3-Hydroxypropylcarbamate (84). Colorless liquid (4.7 g, 90%): ^{1}H NMR ($CDCl_3$) δ 3.66 (t, J = 5.70 Hz, 2 H), 3.54 (s, 3 H), 3.34 (t, J = 6.0 Hz, 2 H), 1.68 (m, 2 H).

Ethyl 3-Hydroxypropylcarbamate (85). Colorless liquid (5.4 g, 94%): ^{1}H NMR ($CDCl_3$) δ 4.10 (q, J = 7.14 Hz, 2 H), 3.66 (t, J = 5.75 Hz, 2 H), 3.31 (t, J = 6.26 Hz, 2 H), 1.68 (m, 2 H), 1.22 (t, J = 7.09 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 157.45, 60.93, 59.40, 37.46, 32.52, 14.46.

Isobutyl 3-Hydroxypropylcarbamate (86). Colorless liquid (6.37 g, 99%): ^{1}H NMR ($CDCl_3$) δ 3.85 (d, J = 5.51 Hz, 2 H), 3.68 (t, J = 5.60 Hz, 2 H), 3.34 (t, J = 6.0 Hz, 2 H), 1.88 (m, 1 H), 1.70 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 155.26, 71.14, 61.72, 59.29, 32.59, 27.88, 18.88.

Swern Oxidation of 3-Hydroxypropylcarbamates. Oxalyl chloride (3.31 g, 26.05 mmol) was dissolved in CH_2Cl_2 (20 mL) at −78 °C. Dimethyl sulfoxide (5.34 g, 56.84 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was kept stirring for 20 min, followed by addition of 3-hydroxypropylcarbamate (23.68 mmol) in CH_2Cl_2 (10 mL) and triethylamine (11.96 g, 118.4 mmol). The resulting mixture was stirred for another 1 h at room temperature and washed with water (2 × 20 mL). The CH_2Cl_2 extracts were dried (Na_2SO_4) and evaporated. The crude residue was purified by flash chromatography on silica gel (120 g, 5 cm × 31 cm, ethyl acetate/hexanes 1:1, v/v) to afford the corresponding aldehyde in more than 60% yield.

Methyl 3-Oxopropylcarbamate (87). Colorless liquid (2.01 g, 65%): ^{1}H NMR ($CDCl_3$) δ 9.70 (s, 1 H), 3.54 (s, 3 H), 3.36 (td, J = 6.04 and 5.93 Hz, 2 H), 2.64 (t, J = 5.67 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 201.37, 156.94, 51.97, 43.94, 34.32; CIMS m/z 132 (MH)$^+$; HRMS calcd for $C_5H_9NO_3$ 131.0582, found 131.0577.

Ethyl 3-Oxopropylcarbamate (88). Colorless liquid (2.47 g, 72%): ^{1}H NMR ($CDCl_3$) δ 9.80 (s, 1 H), 4.04 (q, J = 7.10 Hz, 2 H), 3.46 (td, J = 6.04 and 5.93 Hz, 2 H), 2.73 (t, J = 5.67 Hz, 2 H), 1.16 (t, J = 7.05 Hz, 3 H).

Isobutyl 3-Oxopropylcarbamate (89). Colorless liquid (3.2 g, 85%): ^{1}H NMR ($CDCl_3$) δ 9.80 (s, 1 H), 3.84 (d, J = 6.13 Hz, 2 H), 3.46 (td, J = 6.04 and 5.93 Hz, 2 H), 2.73 (t, J = 5.67 Hz, 2 H), 1.87 (m, 1 H), 0.90 (d, J = 6.53 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 201.22, 157.18, 71.02, 44.06, 34.24, 27.83, 18.89.

3-But-3-enyl-1,3-oxazolidin-2-one (91). 4-Bromo-1-butene (2.21 g, 16.4 mmol) was added to a mixture containing 2-oxazolidinone (1.10 g, 12.6 mmol) and cesium carbonate (12.3 g, 37.9 mmol) in acetone (45 mL). The mixture was heated at 60 °C for 48 h, cooled to room temperature, and filtered. The filtrate was evaporated, and the residue was purified by flash chromatography on silica gel (60 g), eluting with hexanes/ethyl acetate (1:1, v/v), to afford the desired product **91** (1.39 g, 78%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.80 (ddt, J = 17.07, 3.50 and 6.74 Hz, 1 H), 5.09−5.19 (m, 2 H), 4.34 (t, J = 7.83 Hz, 2 H), 3.60 (t, J = 6.66 Hz, 2 H), 3.38 (t, J = 7.12 Hz, 2 H), 2.36 (dt, J = 7.05 and 7.00 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 153.82, 129.97, 112.62, 56.99, 39.89, 38.75, 24.55.

3-(2-Oxo-1,3-oxazolidin-3-yl)propanal (92). 3-But-3-enyl-1,3-oxazolidin-2-one **91** (1.0 g, 7.09 mmol) and 4-methylmorpholine *N*-oxide (1.66 g, 14.18 mmol) were dissolved in an

aqueous MeOH solution (40 mL, MeOH/H_2O 3:1, v/v). Five drops of OsO_4 (1% solution in water) were added to the solution at 0 °C. After the reaction mixture was stirred at room temperature overnight, the TLC showed the complete disappearance of the starting material. The reaction mixture was then concentrated, and the diol compound was too hydrophilic to be extracted with CH_2Cl_2. Therefore, the crude diol was used for the next step without puification. Sodium periodate (3.03 g, 14.2 mmol) was added to the diol (redissolved in 20 mL of acetone/H_2O, 1:1) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. As the reaction progressed, a white precipitate was formed. The the reaction mixture was filtered, the residue was washed with acetone, and the combined filtrates were concentrated on a rotary evaporator. The residue was treated with water and extracted with $CHCl_3$ (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated on a rotary evaporator to furnish the product, which was further purified by passing through a short column on silica gel (60 g, EtOAc as eluent) to afford the desired compound as a colorless oil: yield 0.64 g (63%); ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 2.13 Hz, 1 H), 7.45 (d, J = 1.96 Hz, 1 H), 7.32 (d, J = 2.04 Hz, 2 H), 6.03 (t, J = 7.54 Hz, 1 H), 4.28 (t, J = 8.00 Hz, 2 H), 3.98 (s, 3 H), 3.91 (s, 6 H), 3.89 (s, 3 H), 3.38 (t, J = 7.50 Hz, 4 H), 2.36 (q, J = 7.01 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 165.63, 165.36, 158.41, 155.10, 154.91, 139.44, 137.82, 134.92, 134.74, 132.46, 130.65, 129.85, 129.47, 128.51, 128.16, 126.92, 126.63, 61.95, 61.86, 61.52, 52.47, 52.38, 44.40, 43.68, 27.93; CIMS m/z 144 $(MH)^+$.

***N*-Fluorenylmethoxycarbonyl-3-aminopropanal (94).** *N*-Fmoc-β-alanine (1.5 g, 4.82 mmol) was dissolved in dry THF (10 mL). Oxalyl chloride (0.60 mL, 6.8 mmol) was added, followed by a catalytic amount of DMF (2 drops). The mixture was stirred for 2 h at room temperature. Excess oxalyl chloride and THF were removed. The residue was dissolved in dry THF (10 mL), and $(Ph_3P)_4Pd$ (56 mg, 0.048 mmol) was added. Tributyltin hydride (1.55 mL, 5.78 mmol) was added dropwise. The mixture was stirred for another 1 h. The solvent was removed, and the residue was washed with hexanes. The solid was dissolved in a minimum amount of CH_2Cl_2 and applied to a silica gel (55 g) column. Elution with hexanes/EtOAc (1:2, v/v) afforded aldehyde **94** (1.1 g, 78%) as white needles: mp 109−110 °C; ^{1}H NMR ($CDCl_3$) δ 9.80 (s, 1 H), 7.76 (d, J = 7.30 Hz, 2 H), 7.57 (d, J = 7.30 Hz, 2 H), 7.38 (t, J = 7.30 Hz, 2 H), 7.30 (t, J = 7.30 Hz, 2 H), 5.15 (s, 1 H), 4.38 (d, J = 6.70 Hz, 2 H), 4.18 (t, J = 6.70 Hz, 1 H), 3.47 (dd, J = 11.10 and 5.40 Hz, 2 H), 2.73 (t, J = 5.40 Hz, 2 H); PDMS m/z 295 (MH^+). Anal. ($C_{18}H_{17}NO_3$) C, H, N.

4-(*N*-Fluorenylmethoxycarbonyl)amino-3′,3″-dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-butene (95). A slurry of $TiCl_4$/THF 1:2 complex (0.71 g, 2.2 mmol) and Zn dust (0.30 g, 4.3 mmol) in THF (25 mL) was heated under reflux for 2 h. A mixture of substituted benzophenone **53** (0.30 g, 0.70 mmol) and aldehyde **94** (0.31 g, 1.05 mmol) in dry THF (10 mL) was added. The dark mixture was heated under reflux for 6 h. It was then cooled to room temperature, and water (10 mL) was added. The mixture was stirred at room temperature for 2 h. The precipitate was filtered off and washed with EtOAc (3 × 15 mL). The filtrate was concentrated, and the residue was chromatographed on silica gel (45 g, 2.5 cm × 31 cm), eluting with EtOAc/hexanes (1:2.5, v/v) to provide **95** as a white foam (0.30 g, 62.1%): mp 71−73 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 7.50 Hz, 2 H), 7.58 (d, J = 7.50 Hz, 2 H), 7.49 (d, J = 1.90 Hz, 2 H), 7.46 (d, J = 2.0 Hz, 2 H), 7.37 (t, J = 7.40 Hz, 2 H), 7.27 (t, J = 7.40 Hz, 2 H), 6.04 (t, J = 7.20 Hz, 1 H), 4.78 (t, J = 7.40 Hz, 1 H), 4.41 (d, J = 7.0 Hz, 2 H), 4.20 (t, J = 7.0 Hz, 2 H), 3.96 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.84 (s, 3 H), 3.31 (q, J = 6.53 Hz, 2 H), 2.26 (q, J = 6.75 Hz, 2 H); PDMS m/z 691 (MH^+). Anal. ($C_{37}H_{33}Cl_2NO_8$) C, H, N.

4-Amino-3′,3″-dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-butene (96). Compound **95** (0.30 g, 0.435 mmol) was dissolved in dry THF (20 mL). Piperidine (5 mL) was added to the above solution, and the reaction mixture was stirred at room temperature for 3 h. The organic solvents were removed through rotatory evaporation, and the crude residue was purified by flash chromatography on silica gel (35 g, 2.5 cm × 31 cm), eluting with EtOAc/hexanes (1.5:1, v/v) to afford a light-yellow oil (201 mg, 99%): ^{1}H NMR ($CDCl_3$) δ 7.50 (d, J = 2.40 Hz, 1 H), 7.47 (d, J = 2.16 Hz, 1 H), 7.33 (d, J = 2.23 Hz, 1 H), 7.32 (d, J = 2.23 Hz, 1 H), 6.08 (t, J = 7.41 Hz, 1 H), 3.96 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.39 (br, 2 H), 2.87 (t, J = 6.70 Hz, 2 H), 2.38 (dt, J = 7.49 and 7.05 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 165.84, 165.61, 155.09, 154.85, 139.27, 138.11, 135.08, 134.99, 132.50, 130.95, 129.81, 129.48, 129.24, 128.13, 126.84, 126.63, 61.98, 52.52, 41.21, 32.31; FABMS m/z 468 (MH^+).

Antiviral Evaluations. Cells and Viruses. CEM-SS cells were obtained from the NIAID AIDS Research and Reference Reagent Program (Bethesda, MD). The CEM-SS cells were maintained in RPMI 1640 medium supplemented with 10% heat-inactivated fetal bovine serum, 2 mM glutamine, penicillin (100 U/mL), and streptomycin (100 μg/mL). Human immunodeficiency virus type 1 (HIV-1) strains subtype A (92/UG/037), subtype B (92/BR/014), subtype C (93/MW/959), subtype D (92/UG/001), subtype E (92/THA/037), subtype F (93/BR/020), subtype G (G3), and subtype O (BCOF-01) Ba-L and RF were obtained from the NIAID AIDS Research and Reference Reagent Program. The low-passage pediatric clinical isolates ROJO, WEJO, SLKA, and TEKI were derived as previously described.[50] The MDR769 virus was generously provided by the laboratory of T. C. Merigan (Stanford University).

HIV Cytoprotection Assay and Cross-Resistance Assays. The inhibitory activities of the compounds were evaluated as previously described with the cytopathic RF strain of HIV-1 and CEM-SS cells.[51] These are microtiter assays, which quantitate the ability of a compound to inhibit HIV-1 induced cell killing via syncytium formation. Cytoprotection and compound cytotoxicity are measured with the CellTiter 96 Reagent (Promega, Madison, WI) 6 days after infection. This reagent contains the tetrazolium compound [3-(4,5-dimethylthiazol-2-yl)-5-(carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium, inner salt (MTS), and the electron-coupling agent phenazine ethosulfate in a colorless stable solution, which upon reduction by viable cells forms a colored solution with absorbance at 490 nm. Antiviral and toxicity data are reported as the concentration of compound required to inhibit 50% virus-induced cell killing (50% effective concentration [EC_{50}]) and the concentration of compound required to reduce cell viability by 50% (cytotoxicity). All data are derived from triplicate tests with the variation of the mean averaging 10%. The efficacy of the ADAMs against the molecular cloned virus NL4-3 expressing specific reverse transcriptase resistant mutations by site mutagenesis in the RT gene was determined as described above in CEM-SS cells. However, for the A98G, K103E, L74V 4X AZT (D67N, K70R, T215Y, and K219Q), and 4X AZT/L100I, virus replication was assessed by p24 ELISA (Coulter Immunotech, Hialeah FL) rather than cytoprotection by CellTiter 96 reagent because of low cytopathogeneicity of the resistant virus. The effect of nevaripine and AZT on wild-type NL4-3 replication was determined by both methods, and the resulting IC_{50} values were within 2-fold of each other. Thus, for calculation of increased or decreased sensitivity to the ADAMs, a mean of the two IC_{50} values were used.

PBMC and Monocyte/Macrophage Antiviral Assays. Human peripheral blood mononuclear cells (PBMC) and monocytes were isolated from hepatitis and HIV sero-negative donors by ficoll hypaque gradient centrifugation as previously described.[52] Antiviral assays were accomplished with 3-day-old phytohemagglutinin/IL-2 stimulated PBMC or 6-day-cultured monocyte/macrophages. All antiviral evaluations were performed in triplicate in RPMI 1640 supplemented with 10% fetal bovine serum, L-glutamate (2 mM), penicillin (100 U/mL), and streptomycin (100 μg/mL). HIV replication in PBMC cultures was determined by measurement of supernatant reverse transcriptase activity[53] and in monocyte macrophage cultures by ELISA for p24 antigen expression 6 days post-infection. Cell viability by formazan dye reduction was deter-

mined using CellTiter 96 reagent (Promega, Madison, WI). Antiviral and toxicity data are reported as concentration of the drug required to inhibit 50% virus production (IC_{50}) and the concentration of drug required to reduce cell viability by 50% (TC_{50}). All determinations were performed in triplicate, and the standard deviation within triplicate was less than 10%. The HIV reverse transcriptase inhibitor 3′-azido-3′-deoxythymidine (AZT) was used as a positive control for all assays.

RT Inhibition Assay. Analysis of the effects of the compounds on recombinant HIV-1 RT enzyme (p66/51 dimer) was performed as previously described.[54] Briefly, inhibition of purified recombinant reverse transcriptase enzyme was measured by the incorporation of [^{32}P] GTP into poly(rC)/oligo(dG) (rCdG) homopolymer template primers.

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