Correlation of Anti-HIV Potency with Lipophilicity in a Series of Cosalane Analogs Having Normal Alkenyl and Phosphodiester Chains as Cholestane Replacements

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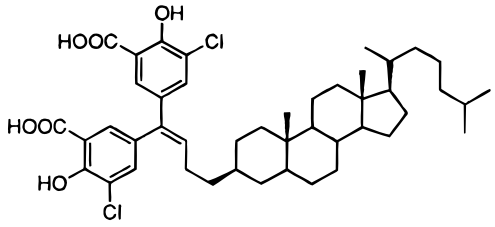
Received September 8, 1995[⊗]

In order to define the role of the cholestane moiety in the anti-HIV agent cosalane, a series of cosalane analogs was synthesized in which the cholestane ring system was replaced by normal alkenyl and phosphodiester substituents having varied chain lengths and lipophilicities. The compounds containing simple alkenyl substituents were found to be more potent as inhibitors of the cytopathic effect of HIV-1 in cell culture than the phosphodiesters. In addition, the potencies of the alkene congeners correlated positively with chain length and lipophilicity of the alkene. The results indicate that the cholestane moiety of cosalane functions as a lipophilic accessory appendage to escort the dichlorodisalicylmethane pharmacophore to a lipid environment.

Cosalane (**1**) is a recently reported anti-HIV agent displaying a wide range of activity against a variety of laboratory, drug-resistant, and clinical HIV-1 isolates, as well as HIV-2.[1,2] The mechanism of action of cosalane (**1**) involves inhibition of gp120−CD4 binding as well as inhibition of a postattachment event prior to reverse transcription.[2] Cosalane (**1**) was designed conceptually by taking a dichlorinated disalicylmethane fragment **2**[3] of the polymeric anti-HIV agent aurintricarboxylic acid (ATA, represented schematically as **3**)[4−8] and attaching a cholestane moiety to it through a three-carbon linker chain. During the cosalane (**1**) design process, it was reasoned that the dichlorodisalicylmethane would act as the "pharmacophore" and the cholestane fragment would serve as an accessory module to increase potency by directing the molecule to the lipid environment of the cell membrane and the viral envelope. Consistent with this idea, the dichlorinated disalicylmethane fragment **2**[3] does have some, albeit very low, anti-HIV activity (EC_{50} 329 μM against HIV-1 strain RF in CEM-SS cells) compared to that of cosalane (**1**) (EC_{50} 3.0 μM against HIV-1 strain RF in CEM-SS cells). In order to further test the validity of this design concept, a series of cosalane (**1**) analogs was prepared in which the lipophilicity of the accessory appendage attached to the proposed pharmacophore (**2**) was modulated in a systematic fashion. Several *n*-alkenyl- and phosphodiester-containing chains of varying lengths and lipophilicities were attached to the central carbon atom of the dichlorodisalicylmethane fragment **2**, and the potencies of the resulting compounds **9**−**12** (Scheme 1) and **25**−**29** (Scheme 2) as anti-HIV agents were determined in an assay which monitors inhibition of HIV-1_{RF} cytopathicity in CEM-SS.[9] If the design concept were valid, then the potencies of **9**−**12** and **25**−**29** might be expected to correlate in a positive fashion with the lipophilicities of the substituents attached to the dichlorodisalicylmethane unit.

It has been suggested that the steroid moiety of cosalane (**1**) may imbed perpendicularly in the lipid bilayer of the cell membrane and viral envelope, with the dichlorodisalicylmethane fragment pointing outward



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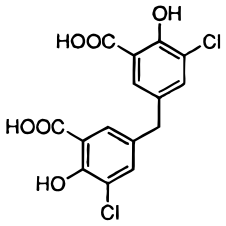

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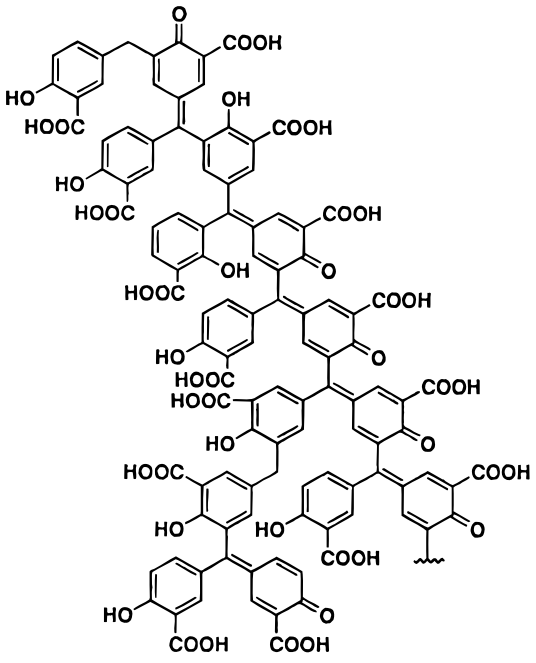

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[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1995.

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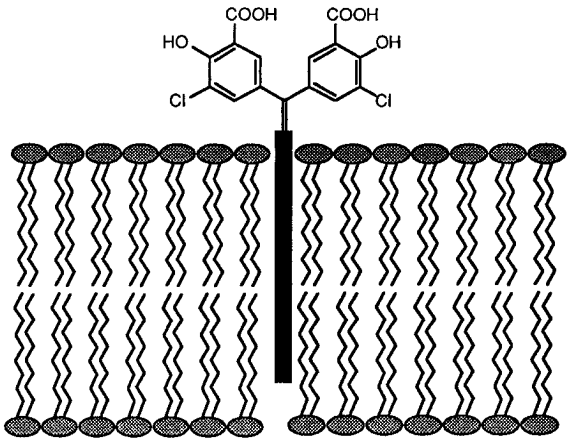
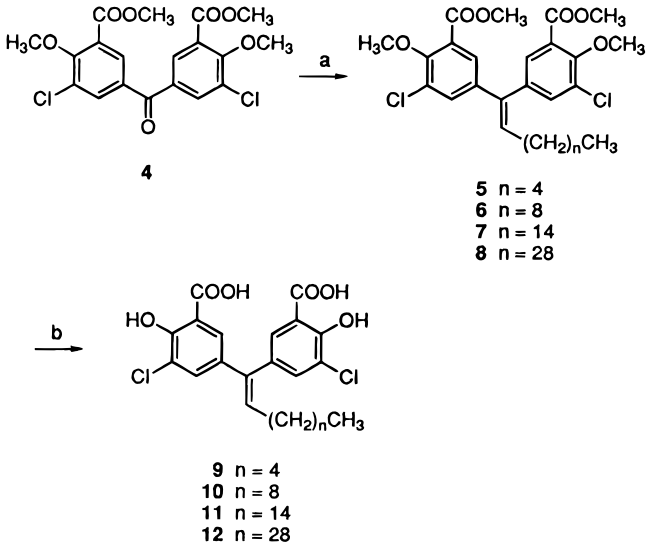


Figure 1. Schematic representation of the anchoring of the disalicylmethane moiety of cosalane and cosalane analogs to the cell membrane and viral envelope by the steroid nucleus of cosalane or the hydrocarbon moieties of the cosalane analogs.

Scheme 1[a]



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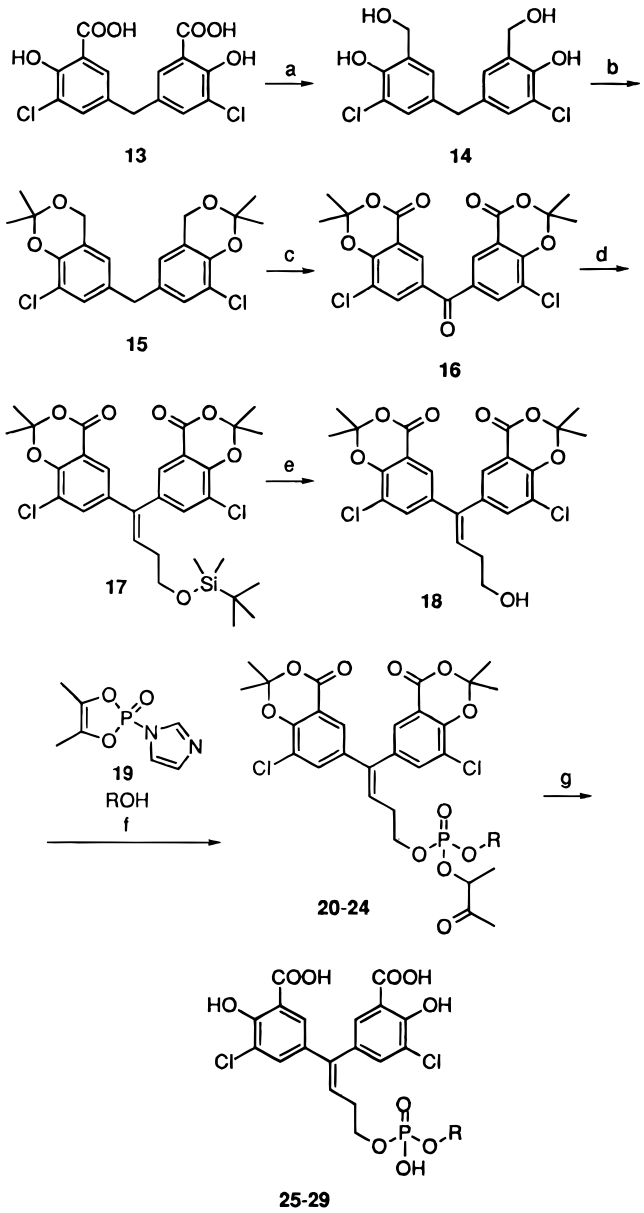
5 n = 4
6 n = 8
7 n = 14
8 n = 28

9 n = 4
10 n = 8
11 n = 14
12 n = 28

[a] Reagents: (a) $Ph_3P{=}CHR$; (b) BBr_3, CH_2Cl_2.

in an obstructive mode (Figure 1).[2] An interaction of cosalane (**1**) with the cell membrane and viral envelope lipid bilayers may be involved in the inhibition of the fusion of the viral envelope with the cell membrane. This hypothesis is consistent with the fact that cosalane inhibits the cytopathic effect of the Rauscher murine leukemia virus, which does not depend on gp120−CD4 binding.[2] In addition, cosalane (**1**) inhibits HIV-1 cytopathicity if added immediately after attachment of the virion to the cell membrane, and time of addition experiments have established that it acts prior to reverse transcription.[2] If viral and cellular membranes are in fact acting as a cosalane receptor, then biologically active analogs of cosalane might be obtained by replacement of the steroid unit with lipophilic alkenyl or phospholipid moieties that could also enter into phospholipid membrane bilayers. Various phospholipids have already demonstrated anti-HIV activity, and although the mechanism of antiviral action is not completely understood, it is thought that it involves insertion of the phospholipids into cellular and viral membranes.[10−14] Prior studies of anti-HIV phospholipids have correlated increased lipid chain length with

Scheme 2[a]



20, 25 R = $(CH_2)_{13}CH_3$
21, 26 R = $(CH_2)_{15}CH_3$
22, 27 R = $(CH_2)_{17}CH_3$
23, 28 R = *cis,cis*-$(CH_2)_8CH{=}CHCH_2CH{=}CH(CH_2)_4CH_3$
24, 29 R = *cis*-$(CH_2)_8CH{=}CH(CH_2)_7CH_3$

[a] Reagents and conditions: (a) B_2H_6, THF, reflux (3.5 h); (b) $CH_3C(OCH_3)_2CH_3$, *p*-TsOH, DMF, 75 °C (24 h); (c) CrO_3, Ac_2O, 0−23 °C (18 h); (d) (1) $Ph_3P^+(CH_2)_3OTBDMSBr^-$, $NaN[Si(CH_3)_3]_2$, THF, 0 °C (30 min); (2) compound **16**, THF, 23 °C (24 h); (e) *n*-Bu_4NF, THF, 0 °C (1 h); (f) (1) alcohol **18**, $CHCl_3$, −10 °C (15 min), 23 °C (2.5 h); (2) ROH, −10 to 23 °C (24 h); (g) (1) aqueous K_2CO_3, 1,4-dioxane, reflux (3 h); (2) 3 N HCl, 23 °C (1.5 h).

increased potency.[11,14] Recently, it has been reported that certain membrane-interactive phospholipids inhibit HIV-1-induced membrane fusion by an unidentified mechanism.[15]

Chemistry

The desired 1,1-diphenyl-1-alkenes **9**−**12** were synthesized from the known benzophenone **4**[2] in two steps as outlined in Scheme 1. Reaction of **4** with the appropriate Wittig reagents derived from *n*-alkyltri-

phenylphosphonium bromides of various chain lengths afforded the intermediates **5**−**8**. These compounds were demethylated with boron tribromide in methylene chloride to afford the cosalane analogs **9**−**12**.

The syntheses of the phospholipid cosalane analogs **25**−**29**, outlined in Scheme 2, was more problematic because of the instability of phosphodiesters to the demethylation conditions used in the conversion of **5**−**8** to **9**−**12**. Therefore, an alternative strategy for the protection and deprotection of the carboxylic acid and phenolic hydroxyl groups had to be devised. The protection of these four groups as two cyclic acetonides as in **16** seemed appealing, but all attempts to directly convert **13** to **16** proved fruitless. Accordingly, the two carboxylic acids present in **13**[2] were reduced to alcohols with diborane in refluxing THF, and the resulting product **14** was converted to the diacetonide **15** on heating with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in *N*,*N*-dimethylformamide. The three benzylic methylene groups present in **15** were then oxidized with chromium trioxide in acetic anhydride to give the desired benzophenone derivative **16**. Treatment of **16** with the Wittig reagent derived from deprotonation of triphenyl(3-((*tert*-butyldimethylsilyl)oxy)propyl)phosphonium bromide provided the alkene **17**. The *tert*-butyldimethylsilyl protecting group was removed from **17** using tetra-*n*-butylammonium fluoride in tetrahydrofuran to afford the primary alcohol **18**. The acetoin enediol cyclophosphoimidazole reagent (**19**) was chosen for the conversion of the primary alcohol **18** to the desired analogs **25**−**29** because it is particularly well suited for the synthesis of unsymmetrical phosphodiesters.[16] Sequential treatment of **19** with **18**, followed by various primary alcohols, provided intermediate phosphotriesters **20**−**24**. Both of the acetonide protecting groups as well as the 3-keto-2-butyl group were removed from the intermediates **20**−**24** by potassium carbonate in refluxing 1,4-dioxane to yield the final products **25**−**29**.

Biological Results and Discussion

The new cosalane analogs **9**−**12** and **25**−**29** were tested for inhibition of the cytopathic effect of HIV-1_{RF} in CEM-SS cell culture as well as for cytotoxicity in uninfected CEM-SS cells. The results are listed in Table 1. In comparing the EC_{50} values for prevention of HIV-1 cytopathicity for compounds **9** (not active), **10** (EC_{50} 43.2 μM), **11** (19.8 μM), and **12** (EC_{50} 13.1), it is apparent that greater potency correlates with longer chain length and increased lipophilicity. This indicates that the antiviral activity displayed by cosalane is not structurally specific with regard to the cholestane moiety, since activity remains after replacement of the steroid moiety with straight chain hydrocarbons, provided they are sufficiently long and lipophilic. These results are consistent with the idea that the role of the cholestane fragment of cosalane is to escort the dichlorodisilicylmethane pharmacophore to a lipid environment.

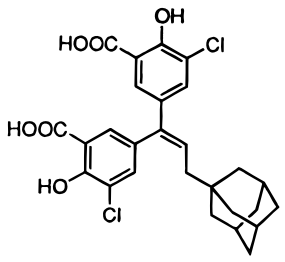
Unlike the active compounds **10**−**12** having normal alkenyl side chains, the phosphodiester cosalane analogs **25**−**27** were inactive as anti-HIV agents. None of these compounds prevented the cytopathic effect of HIV-1 in CEM cells at concentrations lower than the cytotoxic concentrations. However, the phosphodiesters **28** and **29**, containing linoleyl and oleyl substituents, respectively, did show anti-HIV activity. Compound **28** had an EC_{50} of 51.8 μM for prevention of the cytopathic effect of HIV-1 in cell culture, while the corresponding value of **29** was 49.0 μM. In contrast to cosalane (**1**) and the analogs **9**−**12**, the phosphodiesters proved to be more cytotoxic in uninfected CEM-SS cells, with the IC_{50} values for **28** and **29** being close to the EC_{50} values. This degree of cytotoxicity effectively eliminates these phosphodiesters as potential therapeutic agents for the treatment of AIDS, and it also does not bode well for the general idea of replacing the cholestane structural unit of cosalane with phospholipid fragments resembling membrane components.

Table 1. Anti-HIV Activities of Cosalane Analogs

compd	EC_{50}[a] (μM)	IC_{50}[b] (μM)
1	3.0	>300
2	329	>364
9	NA[c]	>95
10	43.2	>49
11	19.8	>35
12	13.1	>220
25	NA[d]	101
26	NA[d]	84
27	NA[d]	74
28	51.8	86
29	49.0	61.3
30	NA[d]	105

[a] The EC_{50} is the 50% inhibitory concentration for cytopathicity of HIV-1_{RF} in CEM-SS cells. The values are the averages of at least two determinations. All compounds were tested as their ammonium salts. [b] The IC_{50} is the 50% cytotoxic concentration for mock-infected CEM-SS cells. The values are the averages of at least two determinations. All compounds were tested as their ammonium salts. [c] No antiviral activity was observed at concentrations up to 95 μM. [d] No antiviral acticity was observed at the IC_{50} concentration.

The results seen with the phosphodiester analogs **25**−**29** is reminiscent of the anti-HIV activities reported for simple alkylphosphatidylethanolamines, which increased in potency in the order *n*-hexyl < *n*-dodecyl < *n*-octadecyl < oleyl.[11,14] As a group, the phosphodiester analogs **25**−**29** were less potent as anti-HIV agents than the simpler alkenes **9**−**12**. This difference in activity is rather intriguing and may reflect the reduced lipophilicity expected as a result of introducing a polar phosphate group into an otherwise very lipophilic side chain. Another possibility is that the phosphate moiety restrict the sliding motion of the side chain in the membrane (Figure 1), thus making it more difficult to achieve the optimal positioning of the compound in the membrane for biological activity. Additional phosphodiester analogs in which the location of the phosphate moiety in the side chain is varied might be useful in probing this question further. In connection with the discussion of the inactive analogs, it is interesting to note that the cosalane congener (**30**), having an adamantyl-containing side chain, is also inactive as an anti-



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HIV agent.[17] In this case, the bulky nature of the adamantyl substituent may prevent its packing efficiently between the alkyl chains in the membrane phospholipid bilayer.

In conclusion, the present studies have helped to define the cholestane moiety of cosalane (**1**) as a lipophilic accessory module involved in ushering the dichlorodisalicylmethane pharmacophore to a lipid environment. This concept may prove to be useful in the design of additional cosalane analogs of potential use in the treatment of AIDS.

Experimental Section

General. Melting points were determined in capillary tubes on a Mel-Temp apparatus and are uncorrected. Spectra were obtained as follows: CI mass spectra on a Finnegan 4000 spectrometer; FAB mass spectra and EI mass spectra on a Kratos MS50 spectrometer; ^{1}H NMR spectra on Varian VXR-500S, XL-200A, and Brüker ARX-300 spectrometers; IR spectra on a Beckman IR-33 spectrometer or on a Perkin-Elmer 1600 series FTIR. Microanalyses were performed at the Purdue Microanalysis Laboratory.

3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-heptene (5). Sodium hydride (54 mg, 1.35 mol, 60% dispersion in mineral oil) was washed with *n*-hexane (3 × 5 mL). Dimethyl sulfoxide (2 mL) was introduced *via* a syringe, and the mixture was heated at 75 °C until the evolution of hydrogen ceased. The clear solution was cooled in an ice−water bath, and a solution of the *n*-hexyltriphenylphosphonium bromide[18] (576 mg, 1.35 mmol) in DMSO (3 mL) was added dropwise. The resulting solution was stirred at room temperature for 15 min. A solution of the ketone **4**[2] (0.86 mmol, 369 mg) in warm DMSO (6 mL) was added dropwise and the reaction mixture heated at 55 °C for 27 h. It was then cooled in an ice bath. A solution of ammonium chloride (143 mg) in water (5 mL) was added, and the reaction mixture was extracted with ethyl ether (5 × 5 mL). The organic extracts were washed twice with brine, dried over sodium sulfate, and evaporated *in vacuo*. Flash chromatography on silica gel (230−400 mesh), eluting with *n*-hexane/ethyl acetate, 4:1, yielded starting ketone (39 mg) and heptene **8** (320 mg, 75%): mp 88 °C; IR (KBr) 3046, 1732, 1595, 1364, 1250, 1211 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49 (d, J = 2.4 Hz, 1 H), 7.48 (d, J = 2.2 Hz, 1 H), 7.32 (d, J = 2.2 Hz, 1 H), 7.30 (d, J = 2.4 Hz, 1 H), 6.07 (t, J = 7.6 Hz, 1 H), 4.00 (s, 3 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 2.08 (m, 2 H), 1.44 (m, 2 H), 1.27 (m, 4 H), 0.88 (t, J = 6.9 Hz, 3 H); CIMS *m/z* (relative intensity) 495 (MH^+, 100), 463 (12). Anal. ($C_{25}H_{28}Cl_2O_6$) C, H.

3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-undecene (6). Finely ground and freshly dried decyltriphenylphosphonium bromide[19] (1.14 g, 2.60 mmol) was placed in a dry 50 mL, two-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a reflux condenser connected to an argon flow line, and a rubber septum. The apparatus was flushed with argon, and the argon atmosphere was maintained throughout the reaction. THF (18 mL, freshly distilled from sodium benzophenone) was added via the septum, the suspension of the phosphonium salt was cooled in an ice bath, and a 1 M solution of sodium bis(trimethylsilyl)amide in THF (2.6 mL) was added dropwise. The ice bath was removed and the mixture stirred at room temperature until a homogeneous solution was obtained (15 min). The orange solution was cooled again in the ice bath, and a solution of the ketone **4** (1.00 g, 2.34 mmol) in THF (5 mL) was added dropwise through the septum via the syringe. The bath was removed, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with a solution of ammonium chloride (0.25 g) in water (10 mL). The organic layer was separated and the aqueous layer extracted with ether (1 × 5 mL). The combined organic extracts were dried (sodium sulfate), and the solvent was removed *in vacuo* to yield a crystallizing oil (2.05 g) which was flash chromatographed on silica gel (85 g). Elution with hexane−ethyl acetate mixture (6:1) afforded undecene **6** (1.07 g, 83%): mp 71 °C; IR (KBr) 2927, 2853, 1736, 1476, 1250, 1210, 1092, 1000, 843, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 2.4 Hz, 1 H), 7.46 (d, J = 2.2 Hz, 1 H), 7.31 (d, J = 2.2 Hz, 1 H), 7.28 (d, J = 2.4 Hz, 1 H), 6.05 (t, J = 7.5 Hz, 1 H, H-6), 3.98 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 2.06 (q, J = 7.4 Hz, 2 H, H-3), 1.42 (m, 2 H, H-4), 1.26 (m, 2 H, H-5), 1.23 (m, 10 H), 0.85 (t, J = 6.9 Hz, 3 H, H-11); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 165.81, 165.49, 154.88, 154.53, 138.67, 136.83, 135.51, 135.07, 133.66, 132.44, 131.03, 129.60, 129.36, 128.04, 126.64, 126.56, 62.05, 62.00, 52.55, 52.52, 31.90, 29.83, 29.66, 29.54, 29.46, 29.32, 29.27, 22.70, 14.15; CIMS *m/z* (relative intensity) 551 (MH^+, 100), 522 (10), 519 (15). Anal. ($C_{29}H_{36}Cl_2O_6$) C, H.

***n*-Hexadecyltriphenylphosphonium Bromide.** Triphenylphosphine (10.18 g, 38.81 mmol) was dissolved in hot acetonitrile (15 mL). *n*-Hexadecyl bromide (11.85 mL, 38.81 mmol), was added, and the solution was heated at reflux with stirring for 30 h. The solvent was removed *in vacuo*, and the resulting oil was triturated three times with *n*-hexane with decantation of the solvent each time until crystallization came to completion. The salt (18.31 g, 83%) was dried in the vacuum desiccator: mp 103 °C; ^{1}H NMR (CD_3OD, 200 MHz) δ 8.9−8.7 (m, 15 H), 1.6 (m, 4 H), 1.27 (bs, 26 H), 1.89 (t, J = 6.7 Hz, 3 H); FABMS *m/z* (relative intensity) 487 (100). Anal. ($C_{34}H_{48}$BrP) C, H.

3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-heptadecene (7). Compound **7** was prepared similarly to the alkene **5** from *n*-hexadecyltriphenylphosphonium bromide (1.065 g, 1.876 mmol) and benzophenone **4** (536 mg, 1.255 mmol) in DMSO. The flash chromatography yielded the starting material **4** (65 mg) and the heptadecene **7** (210 mg, 58%): mp 75 °C; IR (KBr) 2923, 2852, 1735, 1476, 1435, 1251, 1211, 1092, 1000, 841, 743 cm^{-1}; CIMS *m/z* (relative intensity) 635 (MH^+, 100), 603 (13); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (d, J = 2.4 Hz, 1 H), 7.46 (d, J = 2.2 Hz, 1 H), 7.31 (d, J = 2.2 Hz, 1 H), 7.28 (d, J = 2.4 Hz, 1 H), 6.05 (t, J = 7.5 Hz, 2 H), 3.98 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 2.06 (q, J = 6.8 Hz, 2 H), 1.26 (m, 2 H), 1.25 (m, 2 H), 1.23 (m, 22 H), 0.85 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 165.80, 165.47, 154.87, 154.52, 138.65, 136.82, 135.49, 135.06, 133.65, 132.40, 132.02, 129.59, 129.35, 128.03, 126.62, 126.55, 31.93, 29.83, 29.71, 29.70, 29.67, 29.59, 29.47, 29.38, 29.27, 22.71, 14.16. Anal. ($C_{35}H_{48}Cl_2O_6$) C, H.

Triacontanyl Bromide. A solution of triacontanol (946 mg, 2.156 mmol) and carbon tetrabromide (1.43 mg, 4.31 mmol) in dry acetonitrile (12 mL) was heated under reflux with stirring, and a solution of triphenylphosphine (1.696 mg, 6.466 mmol) was added dropwise over 2 min. The mixture was heated at reflux for 2 h and cooled, the solvent was removed *in vacuo*, and the residue was extracted with benzene (3 × 10 mL). The combined extracts were filtered, and the solvent was removed *in vacuo*. The residue was flash chromatographed on silica gel (85 g, hexane−ethyl acetate, 6:1) and the product (0.936 g, 85.5%) recrystallized from acetone: mp 67 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.41 (t, J = 6.9 Hz, 2 H), 1.85 (m, 54 H), 0.88 (t, J = 5.8 Hz, 3 H); CIMS *m/z* (relative intensity) 499 ($(M - H)^+$, 2), 421 ($MH^+ - HBr$, 31). Anal. ($C_{10}H_{61}Br$) C, H.

Triacontanyltriphenylphosphonium Bromide. Bromide **2** (737.3 mg, 1.47 mmol) and triphenylphosphine (385.5 mg, 1.47 mmol) were dissolved in chlorobenzene (5 mL), and the solution was heated at reflux for 4 days under argon with stirring. The solvent was removed *in vacuo*. The residue was triturated with hexane, filtered, and washed with hexane to afford a solid (1.049 g, 93.4%). The analytical sample was prepared by crystallization from acetone: mp 106−107 °C; ^{1}H NMR (CD_4OD, 200 MHz) δ 7.0−7.7 (m, 15 H), 3.38 (m, 2 H), 1.57 (m, 4 H), 1.27 (bs, 52 H), 0.89 (t, 3 H); FABMS *m/z* (relative intensity) 683 (M^+, 100). Anal. ($C_{48}H_{76}$BrP) C, H.

3′,3″-Dichloro-4′,4″-dimethoxy-5′,5″-bis(methoxycarbonyl)-1,1-diphenyl-1-untriacontene (8). Triacontanyltriphenylphosphonium bromide (857 g, 1.12 mmol) was suspended in dry THF (25 mL), the mixture was cooled in an ice bath, and sodium bis(trimethylsilyl)amide (1 M solution in THF, 1.12 mL) was added dropwise. The mixture was stirred

for 15 min, and a solution of ketone **4** (0.479 g, 1.12 mmol) in THF (7 mL) was added dropwise. The ice bath was removed, and the reaction mixture was stirred 9 h at 70 °C. The reaction was quenched with ammonium chloride solution, the THF phase was separated, and aqueous phase was extracted with ether. The combined organic extracts were dried (sodium sulfate) and evaporated to dryness, and the residue was subjected to flash chromatography on silica gel (hexane−ethyl acetate, 9:1) followed by recrystallization from ethanol to yield the product as a solid (0.73 g, 78%): mp 88 °C; IR (KBr) 2919, 2851, 1735, 1475, 1435, 1362, 1287, 1251, 1209, 797, 742, cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.49 (d, $J = 2.3$ Hz, 1 H), 7.48 (d, $J = 2.1$ Hz, 1 H), 7.32 (d, $J = 2.1$ Hz, 1 H), 7.30 (d, $J = 2.3$ Hz, 1 H), 6.07 (t, $J = 7.8$ Hz, 1 H), 4.00 (s, 3 H), 3.93 (s, 3 H), 3.92 (s, 6 H), 2.08 (m, 2 H), 1.42 (m, 2 H), 1.25 (m, 52 H), 0.88 (t, $J = 5.7$ Hz, 3 H); FABMS *m/z* relative intensity 831 (M^+, 9), 799 (M^+ − MeOH, 16). Anal. ($C_{49}H_{76}Cl_2O_6$) C, H.

3′,3″-Dichloro-5′,5″-dicarboxy-4′,4″-dihydroxy-1,1-diphenyl-1-heptene (9). A solution of methoxy ester **5** (148.6 mg, 0.3 mmol) in dry methylene chloride (2.5 mL) was added by syringe through a septum under an argon atmosphere to a stirred solution of boron tribromide (1 M) in methylene chloride (1.6 mL) cooled in a dry ice−acetone bath. The cooling bath was removed after 2 h and stirring continued at ambient temperature for 2 days. More BBr_3 (0.8 mL) was added on the second day. The reaction was quenched with water (2 mL), stirring was continued for 30 min, and the product was extracted with 20% aqueous KOH. The alkaline solution was acidified on cooling with concentrated hydrochloric acid and the product extracted with ethyl acetate. The organic extracts were washed with brine, dried (sodium sulfate), and concentrated *in vacuo*. The product was crystallized from methylene chloride: mp 234−236 °C; IR (KBr) 3500−2500, 2926, 2856, 1670, 1600, 1443, 1232, 1179, 901, 799, 715 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.68 (m, 2 H), 7.50 (d, $J = 1.6$ Hz, 1 H), 7.41 (d, $J = 1.6$ Hz, 1 H), 6.13 (t, $J = 7.2$ Hz, 1 H), 2.11 (m, 2 H), 1.48 (m, 2 H), 1.28 (m, 14 H), 0.85 (t, $J = 6.3$ Hz, 3 H); FABMS *m/e* (relative intensity) 438 (M^+, 2), 307 (10). Anal. ($C_{21}H_{20}Cl_2O_6 \cdot {}^1/_2H_2O$) C, H.

3′,3″-Dicarboxy-5′,5″-dichloro-4′,4″-dihydroxy-1,1-diphenyl-1-undecene (10). Boron tribromide (1 M solution in methylene chloride, 1.75 mL) was cooled in a dry ice−acetone bath, and a solution of compound **6** (181 mg, 0.328 mmol) in dry methylene chloride (3 mL) was added via septum in an argon atmosphere with magnetic stirring. The cooling bath was removed after 1 h and stirring continued in an ambient temperature for 16 h. The reaction was quenched with water (3 mL), stirring was continued for 30 min, and the product was extracted with 10% KOH (3 × 3 mL). The alkaline solution was washed with methylene chloride and acidified on cooling with concentrated HCl (1.2 mL), and the product was extracted with ethyl acetate (3 × 3 mL). The organic extracts were washed with brine, dried (sodium sulfate), and concentrated *in vacuo* to afford an oil (93 mg, 57%), which crystallized on trituration with methylene chloride: mp 207 °C; IR (KBr) 3500−2500, 2925, 2855, 1665, 1445, 1232, 1177, 899, 799, 719 cm^{-1}; FABMS *m/z* (relative intensity) 494 (M^+, 18), 477 ($MH^+ - H_2O$, 20); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.60 (bs, 2 H), 7.42 (bs, 1 H), 7.34 (bs, 1 H), 6.06 (t, 1 H), 2.08 (m, 2 H), 1.46 (m, 2 H), 1.25 (m, 12 H), 0.88 (t, 3 H). Anal. ($C_{25}H_{28}Cl_2O_6$) C, H.

3′,3″-Dicarboxy-5′,5″-dichloro-4′,4″-dihydroxy-1,1-diphenyl-1-untriacontene (11). A stirred solution of boron tribromide (1 M in methylene chloride, 3.47 mL) under argon was cooled in a dry ice−acetone bath, and a solution of compound **8** (247 mg, 0.296 mmol) in dry methylene chloride (6 mL) was added by syringe through a septum. The cooling bath was removed after 1 h and stirring continued at an ambient temperature for 2 days. The reaction was quenched with water (3 mL), stirring was continued for 30 min, and the product was extracted with 10% $NaHCO_3$ (3 × 3 mL). The alkaline solution was washed with methylene chloride and acidified on cooling with concentrated HCl, and the product was extracted with ethyl acetate (3 × 3 mL). The organic extracts were washed with brine, dried (sodium sulfate), concentrated *in vacuo*, and recrystallized from chloroform−acetone to afford a solid (150 mg, 65%): mp 173−174 °C; IR (KBr) 3500−2600, 2919, 2851, 1672, 1604, 1468, 1236, 1181, 900, 798, 720 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz) δ 7.70 (d, $J = 2$ Hz, 1 H), 7.67 (d, $J = 2.2$ Hz, 1 H), 7.56 (d, $J = 2.2$ Hz, 1 H), 7.48 (d, $J = 2$ Hz, 1 H), 6.18 (t, $J = 7.4$ Hz, 1 H), 2.13 (m, 2 H), 1.48 (m, 2 H), 1.27 (m, 54 H), 0.86 (t, $J = 6.4$ Hz, 3 H); FABMS *m/z* (relative intensity) 797 (MNa^+, 7), 774 (M^+, 11). Anal. ($C_{45}H_{68}Cl_2O_6 \cdot 2H_2O$) C, H.

3′,3″-Dichloro-4′,4″-dihydroxy-5′,5″-bis(hydroxymethyl)-1,1-diphenylmethane (14). Compound **13**[2] (0.807 g, 2.30 mmol) was dissolved in anhydrous THF (40 mL) and placed under an argon atmosphere. A 1 M solution of borane−tetrahydrofuran complex (9.1 mL, 9.10 mmol) was added dropwise. The reaction mixture was heated at reflux for 3.5 h and then allowed to cool. Brine (20 mL) was slowly added, and stirring was continued for 30 min. The layers were then separated, and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The extracts were combined and washed with saturated sodium bicarbonate (2 × 100 mL). The extracts were dried over sodium sulfate and filtered, and the solvent was removed *in vacuo*. The material was purified by flash chromatography (silica gel 230−400 mesh, ethyl acetate) to give **14** (0.555 g, 74%) as a white solid: mp 143−145 °C; ^1H NMR (acetone-d_6, 300 MHz) δ 7.10 (s, 2 H), 7.09 (s, 2 H), 4.75 (s, 4 H), 3.80 (s, 2 H); IR (KBr) 3286, 2927, 1581, 1481, 1311, 1250, 1184, 1115, 1008, 891, 789, 696, 634 cm^{-1}; EIMS *m/z* (relative intensity) 328 (M^+, 17), 310 (35), 292 (100), 257 (35), 229 (32), 194 (24), 165 (51). Anal. ($C_{15}H_{14}Cl_2O_4$) C, H.

8,8′-Dichloro-2,2,2′,2′-tetramethyl-4,4′-dioxo-6,6′-di(1,3-benzodioxyl)methane (15). Compound **14** (0.100 g, 0.305 mmol) was dissolved in anhydrous DMF (0.50 mL) and placed under an argon atmosphere. 2,2-Dimethoxypropane (0.15 mL, 1.23 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (0.0015 g, 0.0079 mmol) were added. The reaction mixture was then heated to 75 °C for 24 h. Distilled water (5 mL) was added, and the resulting solution was extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with distilled water (5 × 20 mL), followed by brine (20 mL). The extracts were dried over sodium sulfate and filtered, and the solvent was removed *in vacuo*. Purification by flash chromatography (silica gel 230−400 mesh, $CHCl_3$) gave **15** (0.110 g, 88%) as a white solid: mp 135−137 °C; ^1H NMR ($CHCl_3$, 300 MHz) δ 7.03 (s, 2 H), 6.63 (s, 2 H), 4.78 (s, 4 H), 3.72 (s, 2 H), 1.56 (s, 12 H); IR (KBr) 2999, 2944, 2873, 1480, 1385, 1353, 1309, 1278, 1206, 1122, 1059, 954, 878, 800, 724, 657, 604, 519 cm^{-1}; FABMS *m/z* (relative intensity) 409 (MH^+, 25), 350 (55), 292 (50).

8,8′-Dichloro-2,2,2′,2′-tetramethyl-4,4′-dioxo-6,6′-di(1,3-benzodioxyl) Ketone (16). Compound **15** (2.43 g, 6.00 mmol) was suspended in acetic anhydride (55 mL) and the mixture cooled to 0 °C (internal monitoring) in an ice bath. Chromium(VI) oxide (7.86 g, 78.6 mmol) was added in small portions. Once the addition was complete, the temperature was gradually allowed to rise to room temperature. *CAUTION*: in order to avoid a violent exothermic reaction, do not allow the temperature to exceed 35 °C. Stirring was continued at room temperature for 18 h. The acetic anhydride was removed *in vacuo*, and the residue was taken up in a mixture of ethyl acetate (200 mL) and distilled water (200 mL) and vacuum-filtered through a pad of Celite. The layers were separated, and the aqueous layer was washed with ethyl acetate (3 × 200 mL). The combined extracts were washed with distilled water (3 × 200 mL), followed by brine (200 mL). The extracts were dried (Na_2SO_4), and filtered, and the solvent was removed *in vacuo*. Purification by flash chromatography (ethyl acetate/hexanes, 50/50) gave pure **16** (1.51 g, 56%): mp 189−191 °C: ^1H NMR ($CDCl_3$, 300 MHz) δ 8.23 (d, $J = 2.1$ Hz, 2 H), 8.13 (d, $J = 2.1$ Hz, 2 H), 1.86 (s, 12 H); IR (KBr) 3080, 3006, 1749, 1655, 1603, 1482, 1388, 1285, 1236, 1196, 1062, 928, 873, 717 cm^{-1}.

1,1-Bis[8′,8″-dichloro-2′,2′,2″,2″-tetramethyl-4′,4″-dioxo-6′,6″-(1,3-benzodioxyl)]-4-((*tert*-butyldimethylsilyl)oxy)-1-butene (17). Triphenyl(3-((*tert*-butyldimethylsilyl)oxy)-propyl)phosphonium bromide[2] (1.73 g, 3.35 mmol) was suspended in anhydrous THF (55 mL) under argon. The suspension was cooled to 0 °C in an ice bath, and a 1 M solution of

sodium bis(trimethylsilyl)amide (3.66 mL, 3.66 mmol) was added dropwise. Stirring was continued at 0 °C for 30 min, and then a solution of benzophenone **16** dissolved in anhydrous THF (18 mL) was added slowly. The cooling bath was removed, and the reaction mixture was allowed to stir at room temperature for 24 h. Saturated NH_4Cl (50 mL) was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (75 mL), followed by brine (2 × 50 mL). The extracts were dried (Na_2SO_4) and filtered, and the solvent was removed *in vacuo*. Purification by flash chromatography (ethyl acetate/hexanes, 50/50) gave pure **17** (1.32 g, 98%): mp 56−59 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (d, J = 1.8 Hz, 2 H), 7.49 (d, J = 2.0 Hz, 1 H), 7.41 (d, J = 2.2 Hz, 1 H), 6.10 (t, J = 7.0 Hz, 1 H), 3.69 (t, J = 6.4 Hz, 2 H), 2.30 (q, J = 7.3 Hz, 2 H), 1.81 (s, 6 H), 1.77 (s, 6 H), 0.87 (s, 9 H), 0.03 (s, 6 H). Anal. ($C_{30}H_{36}Cl_2O_7Si$) C, H.

4,4-Bis[8′,8″-dichloro-2′,2′,2″,2″-tetramethyl-4′,4″-dioxo-6′,6″-(1,3-benzodioxyl)]-3-buten-1-ol (18). Silyl ether **17** (1.05 g, 1.70 mmol) was dissolved in anhydrous THF (20 mL) and placed under an argon atmosphere. The solution was cooled to 0 °C in an ice bath, and a 1 M solution of tetrabutylammonium fluoride (3.47 mL, 3.47 mmol) was added dropwise. Stirring was continued at 0 °C for 1 h, and then brine was added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The organic layers were combined and washed with distilled water (2 × 50 mL), followed by brine (50 mL). The extracts were dried (Na_2SO_4) and filtered, and the solvent was removed *in vacuo*. Purification by flash chromatography (silica gel, 230−400 mesh, ethyl acetate/hexanes, 50/50) gave pure **18** (0.524 g, 63%): mp 185−188 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (d, J = 2.0 Hz, 1 H), 7.70 (d, J = 2.2 Hz, 1 H), 7.47 (d, J = 2.0 Hz, 1 H), 7.45 (d, J = 2.2 Hz, 1 H), 6.17 (t, J = 7.5 Hz, 1 H), 3.77 (t, J = 6.4 Hz, 2 H), 2.40 (q, J = 6.4 Hz, 2 H), 1.84 (s, 6 H), 1.80 (s, 6 H).

General Procedure for the Synthesis of Phosphotriesters 20−24. Acetoin enediol cyclophosphoimidazole (**19**)[16] (0.146 g, 0.728 mmol) was dissolved in anhydrous $CHCl_3$ (1.2 mL) and placed under an argon atmosphere. The solution was cooled to −10 °C in an ice/salt bath, and a solution of alcohol **18** (0.275 g, 0.560 mmol) dissolved in anhydrous $CHCl_3$ (1 mL) was added dropwise over a 40−50 min period. Once the addition was complete, the reaction mixture was stirred at −10 °C for 15 min and at room temperature for 2.5 h. The reaction mixture was cooled back to −10 °C, and a solution of the second required primary alcohol (ROH, Scheme 2) (0.560 mmol) dissolved in anhydrous $CHCl_3$ (1.0 mL) was added slowly. The cooling bath was removed, and stirring was continued for 24 h. Saturated NH_4Cl (5 mL) was added. The solution was extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed with distilled water (50 mL), followed by brine (50 mL). The extracts were dried (Na_2SO_4) and filtered, and the solvent was removed *in vacuo*. Purification by flash chromatography (silica gel, 230−400 mesh, ethyl acetate/hexanes, 50/50) gave pure phosphodiesters **20−24**.

4,4-Bis[8′,8″-dichloro-2′,2′,2″,2″-tetramethyl-4′,4″-dioxo-6′,6″-(1,3-benzodioxyl)]-3-butenyl 2-Keto-1-methylpropyl Tetradecyl Phosphate (20). Compound **20** (272 mg, 60.8%) was obtained as an amorphous mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68 (d, J = 2.1 Hz, 1 H), 7.67 (d, J = 2.2 Hz, 1 H), 7.48 (d, J = 2.2 Hz, 0.5 H), 7.47 (d, J = 2.2 Hz, 0.5 H), 7.43 (t, J = 1.8 Hz, 1 H), 6.12 (m, 1 H), 4.77 (m, 1 H), 4.12 (m, 4 H), 2.52 (m, 2 H), 2.23 (d, J = 4.5 Hz, 3 H), 1.84 (s, 6 H), 1.80 (s, 6 H), 1.68 (m, 2 H), 1.47 (m, 3 H), 1.25 (s, 22 H), 0.88 (t, J = 6.3 Hz, 3 H); IR (neat) 2925, 2853, 1748, 1608, 1483, 1380, 1282, 1199, 1004, 876, 836, 777 cm^{-1}; FABMS m/z (relative intensity) 839 (MH^+, 40), 475 (45), 417 (98), 359 (100). Anal. ($C_{42}H_{57}Cl_2PO_{11}$) C, H.

4,4-Bis[8′,8″-dichloro-2′,2′,2″,2″-tetramethyl-4′,4″-dioxo-6′,6″-(1,3-benzodioxyl)]-3-butenyl Hexadecyl 2-Keto-1-methylpropyl Phosphate (21). Compound **21** was obtained as an amorphous mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, J = 2.1 Hz, 1 H), 7.65 (d, J = 2.2 Hz, 1 H), 7.46 (d, J = 2.2 Hz, 0.5 H), 7.45 (d, J = 2.2 Hz, 0.5 H), 7.41 (t, J = 1.8 Hz, 1 H), 6.10 (m, 1 H), 4.75 (q, J = 7.8 Hz, 1 H), 4.07 (m, 4 H), 2.50 (m, 2 H), 2.20 (d, J = 3.2 Hz, 3 H), 1.82 (s, 6 H), 1.77 (s, 6 H), 1.66 (m, 2 H), 1.45 (m, 3 H), 1.23 (s, 26 H), 0.86 (t, J = 6.4 Hz, 3 H); IR (neat) 2925, 2854, 1749, 1608, 1484, 1380, 1282, 1199, 1062, 1005, 876, 836, 777 cm^{-1}; FABMS m/z (relative intensity) 867 (MH^+, 10), 617 (35), 475 (20), 417 (95), 359 (100). Anal. ($C_{44}H_{61}Cl_2PO_{11}\cdot H_2O$) C, H.

4,4-Bis[8′,8″-dichloro-2′,2′,2″,2″-tetramethyl-4′,4″-dioxo-6′,6″-(1,3-benzodioxyl)]-3-butenyl 2-Keto-1-methylpropyl Octadecyl Phosphate (22). Compound **22** (169.2 mg, 31%) was obtained as an amorphous mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, J = 2.1 Hz, 1 H), 7.67 (d, J = 2.2 Hz, 1 H), 7.48 (d, J = 2.2 Hz, 0.5 H), 7.47 (d, J = 2.2 Hz, 0.5 H), 7.44 (t, J = 1.8 Hz, 1 H), 6.08 (m, 1 H), 4.81 (m, 1 H), 4.09 (m, 4 H), 2.52. (m, 2 H), 2.24 (d, J = 3.2 Hz, 3 H), 1.84 (s, 6 H), 1.80 (s, 6 H), 1.66 (m, 2 H), 1.48 (m, 3 H), 1.26 (s, 30 H), 0.88 (t, J = 6.4 Hz, 3 H); IR (neat) 2925, 2854, 1747, 1608, 1484, 1391, 1380, 1283, 1200, 1063, 1008, 912, 734 cm^{-1}; FABMS m/z (relative intensity) 895 (MH^+, 15), 475 (30), 416 (100), 359 (80). Anal. ($C_{46}H_{65}C_{12}PO_{11}$) C, H.

4,4-Bis[8′,8″-dichloro-2′,2′,2″,2″-tetramethyl-4′,4″-dioxo-6′,6″-(1,3-benzodioxyl)]-3-butenyl 2-Keto-1-methylpropyl Linoleyl Phosphate (23). Compound **23** (179.1 mg, 40%) was obtained as an amorphous mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68 (d, J = 1.7 Hz, 1 H), 7.67 (d, J = 2.0 Hz, 1 H), 7.48 (d, J = 2.0 Hz, 0.5 H), 7.47 (d, J = 2.5 Hz, 0.5 H), 7.43 (t, J = 1.6 Hz, 1 H), 6.15 (m, 1 H), 5.34 (m, 4 H), 4.79 (m, 1 H), 4.14 (m, 4 H), 2.77 (t, J = 5.8 Hz, 2 H), 2.52 (m, 2 H), 2.23 (d, J = 3.0 Hz, 3 H), 2.03 (m, 8 H), 1.84 (s, 6 H), 1.80 (s, 6 H), 1.68 (m, 2 H), 1.48 (m, 3 H), 1.26 (m, 12 H), 0.89 (t, J = 6.3 Hz, 3 H); IR (neat) 2927, 2855, 1748, 1608, 1484, 1380, 1282, 1199, 1062, 1005, 876 cm^{-1}; FABMS m/z (relative intensity) 913 (MNa^+, 45), 855 (10), 797 (5), 417 (50), 359 (100). Anal. Calcd for $C_{46}H_{61}Cl_2PO_{11}$: C, 61.95; H, 6.89. Found: C, 61.81; H, 6.93.

4,4-Bis[8′,8″-dichloro-2′,2′,2″,2″-tetramethyl-4′,4″-dioxo-6′,6″-(1,3-benzodioxyl)]-3-butenyl 2-Keto-1-methylpropyl Oleyl Phosphate (24). Compound **24** (272.0 mg, 61%) was obtained as an amorphous mixture of diastereomers. This mixture was used directly in the next step without being characterized.

General Procedure for the Synthesis of Phosphates 25−29. Phosphotriesters **20−24** (0.293 mmol) were dissolved in 1,4-dioxane (4 mL). A 0.74 M solution of aqueous K_2CO_3 (0.242 g, 1.75 mmol) was added. The yellow solution was heated at reflux for 3 h. Distilled water (10 mL) was added, and the solution was acidified with 3 N HCl. The solution was extracted with ethyl acetate (5 × 25 mL). The combined extracts were washed with brine (1 × 50 mL). The extracts were dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification by preparative TLC, eluting with *n*-BuOH, H_2O, and HOAc (4:1:1), gave a salt. Distilled water (10 mL) was added. The solution was acidified with 3 N HCl and stirred at room temperature for 1.5 h. The solution was extracted with EtOAc (5 × 25 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate gave the desired phosphodiesters **25−29**.

4,4-(3′,3″-Dicarboxy-5′,5″-dichloro-4′,4″-dihydroxydiphenyl)-3-buten-1-yl Tetradecyl Phosphate (25). Phosphate **25** was obtained as an amorphous solid in 33% yield: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.48 (d, J = 2.1 Hz, 2 H), 7.31 (d, J = 1.7 Hz, 1 H), 7.25 (d, J = 1.5 Hz, 1 H), 5.98 (t, J = 7.2 Hz, 1 H), 3.93 (q, J = 6.1 Hz, 2 H), 3.80 (q, J = 6.6 Hz, 2 H), 2.33 (q, J = 6.5 Hz, 2 H), 1.47 (m, 2 H), 1.06 (m, 22 H), 0.70 (t, J = 6.8 Hz, 3 H); IR (KBr) 2923, 2852, 1665, 1595, 1460, 1233, 1181, 1024, 800 cm^{-1}; FABMS m/z (relative intensity) 733 [($MNa_2 - H)^+$, 20], 711 (100), 395 (60), 333 (45), 217 (40), 149 (65). Anal. ($C_{32}H_{43}Cl_2PO_{10}$) C, H.

4,4-(3′,3″-Dicarboxy-5′,5″-dichloro-4′,4″-dihydroxydiphenyl)-3-buten-1-yl Hexadecyl Phosphate (26). Phosphate **21** was obtained as an amorphous solid in 62% yield: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.54 (t, J = 1.1 Hz, 2 H), 7.38 (d, J = 2.2 Hz, 1 H), 7.32 (d, J = 2.1 Hz, 1 H), 6.04 (t, J = 7.2 Hz, 1 H),

3.99 (q, J = 6.1 Hz, 2 H), 3.86 (q, J = 6.6 Hz, 2 H), 2.39 (q, J = 6.1 Hz, 2 H), 1.52 (m, 2 H), 1.13 (m, 26 H), 0.79 (t, J = 6.3 Hz, 3 H); IR (KBr) 2923, 2853, 1665, 1460, 1234, 1182, 1024, 799 cm^{-1}; FABMS m/z (relative intensity) 739 (MNa^+, 90), 533 (15), 415 (30), 395 (100) 359 (80). Anal. ($C_{34}H_{47}Cl_2PO_{10}$) C, H.

4,4-(3′,3″-Dicarboxy-5′,5″-dichloro-4′,4″-dihydroxydiphenyl)-3-buten-1-yl Octadecyl Phosphate (27). Phosphate **27** was obtained as an amorphous solid in 40% yield: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.63 (t, J = 1.9 Hz, 2 H), 7.47 (d, J = 2.2 Hz, 1 H), 7.41 (d, J = 2.1 Hz, 1 H), 6.13 (t, J = 7.3 Hz, 1 H), 4.08 (q, J = 6.2 Hz, 2 H), 3.95 (q, J = 6.5 Hz, 2 H), 2.48 (q, J = 6.4 Hz, 2 H), 1.62 (t, J = 6.9 Hz, 2 H), 1.23 (m, 30 H), 0.88 (t, J = 6.1 Hz, 3 H). FABMS m/z (relative intensity) 767 (MNa^+, 50), 395 (40), 205 (30), 149 (100). Anal. ($C_{36}H_{51}Cl_2PO_{10}$) C, H.

4,4-(3′,3″-Dicarboxy-5′,5″-dichloro-4′,4″-dihydroxydiphenyl)-3-buten-1-yl Linoleyl Phosphate (28). Phosphate **28** was obtained as an amorphous solid in 57% yield: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.53 (t, J = 1.8 Hz, 2 H), 7.38 (d, J = 2.4 Hz, 1 H), 7.32 (d, J = 1.7 Hz, 1 H), 6.03 (t, J = 7.2 Hz, 1 H), 5.20 (m, 4 H), 3.99 (q, J = 5.8 Hz, 2 H), 3.85 (q, J = 6.5 Hz, 2 H), 2.64 (t, J = 5.4 Hz, 2 H), 2.39 (q, J = 6.5 Hz, 2 H), 1.92 (m, 8 H), 1.52 (m, 2 H), 1.17 (m, 12 H), 0.78 (t, J = 6.7 Hz, 3 H); IR (KBr) 2924, 2854, 1667, 1600, 1454, 1233, 1181, 1023, 800 cm^{-1}; FABMS m/z (relative intensity) 763 (MNa^+, 18), 136 (100). Anal. ($C_{36}H_{47}Cl_2PO_{10}\cdot{}^1/_2H_2O$) C, H.

4,4-(3′,3″-Dicarboxy-5′,5″-dichloro-4′,4″-dihydroxydiphenyl)-3-buten-1-yl Oleyl Phosphate (29). Phosphate **29** was obtained as an amorphous solid in 65% yield: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.64 (t, J = 2.0 Hz, 2 H), 7.48 (d, J = 2.2 Hz, 1 H), 7.42 (d, J = 2.1 Hz, 1 H), 6.14 (t, J = 7.3 Hz, 1 H), 5.30 (t, J = 5.5 Hz, 2 H), 4.08 (q, J = 6.2 Hz, 2 H), 3.95 (q, J = 6.6 Hz, 2 H), 2.49 (q, J = 6.1 Hz, 2 H), 1.99 (m, 4 H), 1.62 (m, 2 H), 1.27 (m, 22 H), 0.88 (t, J = 7.0 Hz, 3 H); IR (KBr) 2925, 2854, 1667, 1603, 1455, 1232, 1182, 1025, 901, 800, 709 cm^{-1}; FABMS m/z (relative intensity) 764 (MNa^+, 80), 704 (20), 395 (100), 376 (70). Anal. ($C_{36}H_{49}Cl_2PO_{10}$) C, H.

Anti-HIV Screening. The anti-HIV screening was performed as previously described.[9] This microtiter assay quantitates drug-induced protection from the killing of CD4(+)-lymphoid cells by HIV-1_{RF}. Briefly, cosalane or 3′-azido-3′-deoxythymidine (AZT, NSC 602670, used as a reference compound) were serially diluted in complete medium and added to 96-well test plates. Exponentially growing target cells were pelleted, suspended in complete medium, and added at 5000 cells/well. Frozen virus stock solutions were thawed immediately before use, suspended in complete medium to yield the desired multiplicity of infection (MOI = 0.01), and added in the microtiter wells. Test plates were incubated at 37 °C in 5% CO_2 for 6 days. On day 6 aliquots of cell-free supernatant were removed from each well and analyzed for reverse transcriptase (RT) activity, p24 antigen, and/or infectious virions. Cellular growth or viability was estimated with the remaining contents of each well by the XTT assay.[20] Effective antiviral concentrations (EC_{50}) and cellular growth inhibitory concentrations (IC_{50}) were calculated.

Acknowledgment. This research was made possible by NIH Grant RO1-AI-36624 and Contract NO1-CM-17513.

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JM950666H