

Supplementary Information

A clue to unprecedented strategy to HIV eradication:

“Lock-in and apoptosis”

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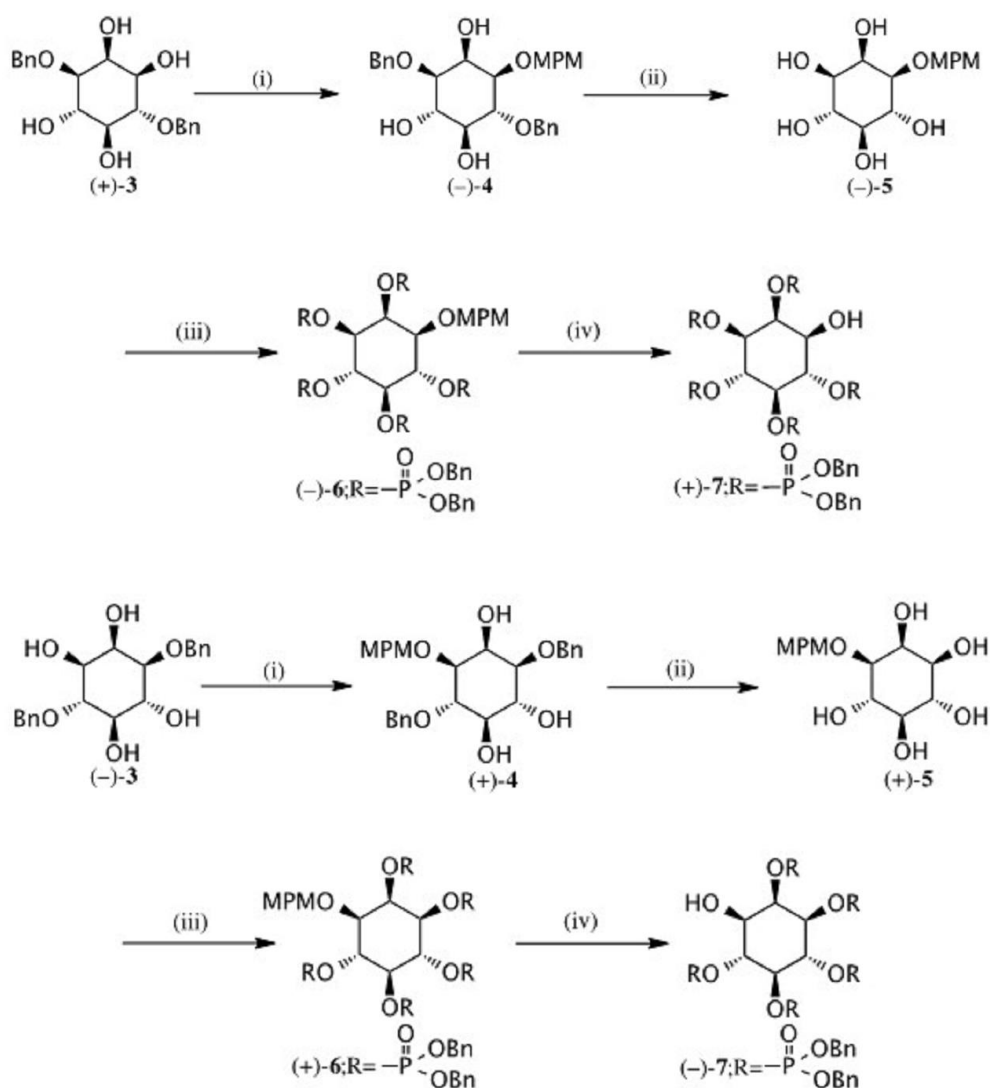
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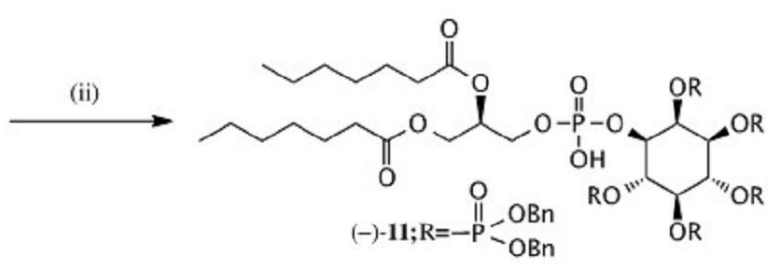
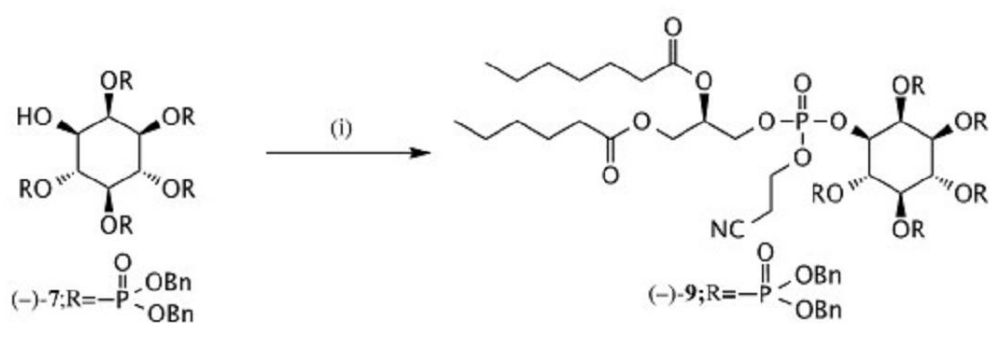
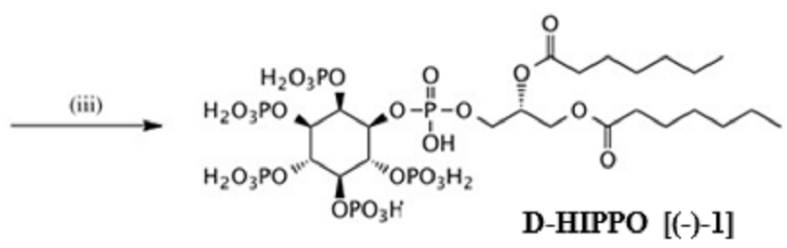
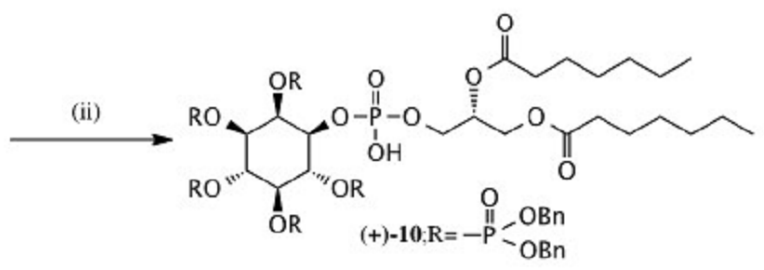
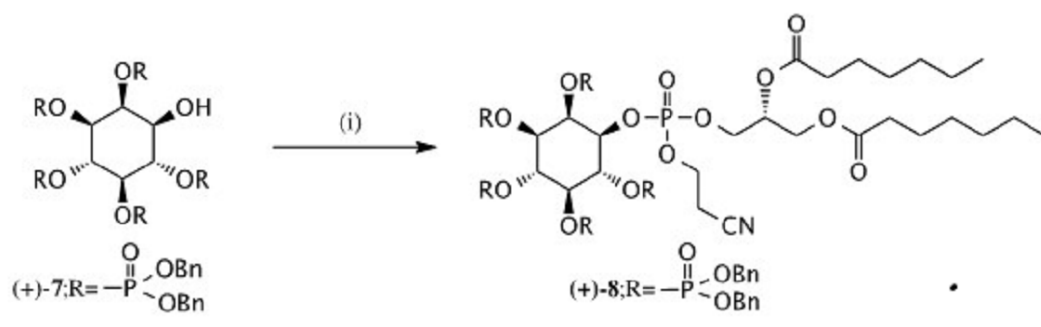
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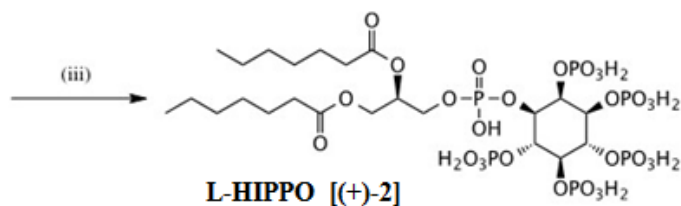
Supplementary Information A:

Preparation of D-HIPPO [(-)-1] and L-HIPPO [(+)-2]



Reagents and conditions: (i) (a) Bu_2SnO , toluene, reflux, 3 h; (b) CsF, MPN-Cl, FMD, -78°C then r.t., 48 h, (-)-4 (85%), (+)-4 (93%). (ii) $\text{H}_2/\text{W-2}$ Raney-Ni, MeOH, 50°C , 1 h, (-)-5 (75%), (+)-5 (65%). (iii) (a) dibenzyl *N,N*-diethyl phosphoramidite, 1*H*-tetrazole, CH_2Cl_2 , r.t., overnight; (b) *m*CPBA, CH_2Cl_2 , -78°C then r.t., 1 h, (-)-6 (80%), (+)-6 (80%). (iv) CAN, $\text{CH}_3\text{CN-H}_2\text{O}$, r.t., 1 h, (+)-7 (64%), (-)-7 (62%).





Reagents and conditions: (i) (a) 1,2-Di-*O*-heptanoyl-glycerol, (2-cyanoethyl)-*N, N, N', N'*-tetraisopropylphosphoramidite, 1*H*-tetrazole, CH₂Cl₂, r.t., 1 h; (b) (+)-**7** or (-)-**7**, 1*H*-tetrazole, CH₂Cl₂, r.t., overnight; (c) *tert*-BuOOH, CH₂Cl₂, r.t., 5 min, (+)-**8** (69%), (-)-**9** (62%). (ii) Et₃N, CH₂Cl₂, r.t., overnight, (+)-**10** (71%), (-)-**11** (88%). (iii) H₂/Pd-C, *t*-BuOH-H₂O, r.t., 24 h, D-HIPPO [(-)-**1**] (40%), L-HIPPO [(+)-**2**] (43%).

General methods

Chemicals were purchased from Aldrich, Fluka, Kanto Chemical, Nacalai tesque, and Wako. Thin layer chromatography (TLC) was performed on precoated plates (Merck TLC sheets silica 60 F₂₅₄): products were visualized by spraying phosphomolybdic acid in EtOH or basic potassium permanganate and heated at high temperature. Chromatography was carried out on Silica Gel 60 N (40–100 mesh). Reverse phase chromatography was performed using a C₁₈ column (Cole-Parmer, USA). Cation exchange chromatography was performed using Dowex 50WX8 (H⁺, 100-200 mesh). NMR spectra (JEOL JNM-AL300 or BRUKER AVANCE 600) were referenced to SiMe₄ or HDO. Infrared spectra were recorded on a JASCO FT/IR-410. The samples were prepared as KBr discs or thin films between sodium chloride discs. Micro-analysis was carried out using a Yanaco MT-3S. High resolution MS (HRMS) were recorded with a JEOL JMS-DX303HF by using positive and negative FAB with 3-nitrobenzyl alcohol (NBA) (containing HMPA or not) as the matrix. Optical rotation values were measured in a 5 cm cell with JASCO DIP-1000.

D-3,6-Di-*O*-benzyl-1-*O*-(*p*-methoxybenzyl)-*myo*-inositol (–)-**4**

A mixture of (+)-**3**¹ (0.88 g, 2.44 mmol) and dibutyltin oxide (0.79 g, 3.14 mmol) in toluene (30 ml) was refluxed for 3h in a Dean-Stark apparatus to remove water². The mixture was concentrated under reduced pressure. To the residue was added cesium fluoride (0.74 g, 4.88 mmol), and the mixture was suspended in heated DMF (30 ml) at 100 °C. To the resulting solution was added *p*-methoxybenzyl chloride (0.40 ml, 2.93 mmol) at –78 °C, and the mixture was stirred at room temperature under argon for 48 h³. After concentration of the reaction mixture under reduced pressure, the residue was purified

by silica gel column chromatography (CH₂Cl₂–MeOH=10:1) to afford (–)-**4** (1.00 g, 85%) as a white solid.

¹H NMR (CDCl₃) δ: 2.47 (1H, bs, OH), 2.62 (2H, bs, OH), 3.22 (1H, dd, *J* = 9.3, 2.7 Hz, CH), 3.37 (1H, dd, *J* = 9.3, 2.7 Hz, CH), 3.39 (1H, t, *J* = 9.3 Hz, CH), 3.78–3.82 (4H, m, OCH₃, CH), 3.96 (1H, t, *J* = 9.3 Hz, CH), 4.21 (1H, t, *J* = 2.7 Hz, CH), 4.61–4.97 (6H, m, CH₂ × 3), 6.86 (2H, d, *J* = 8.5 Hz, CH₃OC₆H₄(CH × 2)), 7.23–7.42 (12H, m, C₆H₅ × 2, CH₃OC₆H₄(CH × 2)).

¹³C NMR (CDCl₃) δ: 55.3, 66.9, 71.9, 72.1, 72.2, 74.1, 75.5, 79.0, 79.4, 80.4, 113.9, 127.8, 127.9, 128.0, 128.5, 128.6, 129.5, 129.8, 137.7, 138.7, 159.4, 164.3.

IR (KBr) 3600, 3100, 1610, 1520, 1450, 1050, 810, 750 cm⁻¹.

HRMS(FAB) *m/z* calcd for C₂₈H₃₂O₇Na (M+Na)⁺ 503.2046 Found:503.2078.

Anal. Calcd for C₂₈H₃₂O₇: C, 69.98; H, 6.71. Found: C, 69.86; H, 6.58.

TLC; R_f 0.50 (CH₂Cl₂–MeOH=10:1).

[α]_D²⁰ = –8.4 (c=1 in MeOH)

L-1,4-Di-*O*-benzyl-3-*O*-(*p*-methoxybenzyl)-*myo*-inositol (+)-**4**

(–)-**3**¹ (0.42 g, 1.18 mmol) was allowed to react, under the same conditions as described for the preparation of (–)-**4**, to give (+)-**4** (0.52 g, 93%) as a white solid.

¹H NMR (CDCl₃) δ: 2.78 (1H, bs, OH), 3.15 (1H, dd, *J* = 9.5, 2.6 Hz, CH), 3.27–3.42 (4H, m, CH × 2, OH × 2), 3.74–3.78 (4H, m, CH₃, CH), 3.93 (1H, t, *J* = 9.5 Hz, CH), 4.13 (1H, t, *J* = 2.4 Hz, CH), 4.56–4.90 (6H, m, CH₂ × 3), 6.82 (2H, d, *J* = 8.6 Hz, CH₃OC₆H₄(CH × 2)), 7.20–7.34 (12H, m, C₆H₅ × 2, CH₃OC₆H₄(CH × 2)).

¹³C NMR (CDCl₃) δ: 55.1, 66.9, 71.8, 71.9, 72.1, 74.2, 75.2, 78.8, 79.2, 80.4, 113.8, 127.4, 127.8, 128.2, 128.4, 129.4, 129.8, 137.7, 138.7, 159.2.

IR (KBr) 3600, 3100, 2870, 1610, 1520, 1450, 1050, 810, 750 cm⁻¹.

HRMS(FAB) *m/z* calcd for C₂₈H₃₂O₇Na (M+Na)⁺ 503.2046 Found:503.2097.

Anal. Calcd for C₂₈H₃₂O₇: C, 69.98; H, 6.71. Found: C, 69.74; H, 6.63.

TLC; R_f 0.50 (CH₂Cl₂–MeOH=10:1).

[α]_D²⁰ = 7.0 (c=1 in MeOH)

D-1-*O*-(*p*-Methoxybenzyl)-*myo*-inositol (–)-**5**

To a solution of (–)-**4** (0.97 g, 2.02 mmol) in MeOH (10 ml) was added W-2 RANEY[®] Nickel (0.20 g, 3.03 mmol), and the resulting mixture was stirred at 50 °C under hydrogen for 1 h⁴. The mixture was filtrated through pad of celite and concentrated under reduced pressure. The residue was washed

with heated AcOEt, and the resulting crystals were filtrated. Drying of the crystals under reduced pressure afforded (–)-**5** (0.46 g, 75%) as a white solid.

¹H NMR (DMSO) δ: 2.93 (1H, t, *J* = 9.2 Hz, CH), 3.06 (2H, dd x 2, *J* = 9.7, 2.3 Hz, CH x 2), 3.35 (1H, t, *J* = 9.3 Hz, CH), 3.45 (1H, t, *J* = 9.3 Hz, CH), 3.69 (3H, s, OCH₃), 3.83–3.85 (1H, m, CH), 4.40–4.53 (2H, m, CH₂), 6.84 (2H, d, *J* = 8.2 Hz, CH₃OC₆H₄(CH × 2)), 7.27 (2H, d, *J* = 8.2 Hz, CH₃OC₆H₄(CH × 2)).

¹³C NMR (DMSO) δ: 55.0, 69.3, 70.3, 71.8, 72.0, 72.5, 75.4, 79.6, 113.4, 129.1, 131.2, 158.5.

IR (KBr) 3390, 2910, 1610, 1590, 1510, 1250, 1120, 890, 820 cm⁻¹.

HRMS(FAB) *m/z* calcd for C₁₄H₂₀O₇Na (M+Na)⁺ 323.1107 Found:323.1109.

Anal. Calcd for C₁₄H₂₀O₇: C, 55.99; H, 6.71. Found: C, 56.03; H, 6.85.

TLC; R_f 0.39 (CH₂Cl₂–MeOH = 3 : 1).

[α]_D²⁰ = –11.7 (c=1 in DMSO)

L-3-O-(*p*-Methoxybenzyl)-*myo*-inositol (+)-5****

(+)-**4** (0.53 g, 1.09 mmol) was allowed to react, under the same conditions as described for the preparation of (–)-**5**, to give (+)-**5** (0.21 g, 65%) as a white solid.

¹H NMR (DMSO) δ: 2.94 (1H, t, *J* = 9.2 Hz, CH), 3.06 (2H, dd x 2, *J* = 9.0, 2.2 Hz, CH x 2), 3.35 (1H, t, *J* = 9.3 Hz, CH), 3.45 (1H, t, *J* = 9.3 Hz, CH), 3.68 (3H, s, OCH₃), 3.90–3.95 (1H, m, CH), 4.39–4.52 (7H, m, OH × 5, CH₂), 6.84 (2H, d, *J* = 8.4 Hz, CH₃OC₆H₄(CH × 2)), 7.27 (2H, d, *J* = 8.4 Hz, CH₃OC₆H₄(CH × 2)).

¹³C NMR (DMSO) δ: 55.0, 69.3, 70.3, 71.8, 71.9, 72.0, 72.5, 72.8, 75.4, 79.6, 113.4, 129.1, 131.2, 158.5.

IR (KBr) 3700, 2800, 1610, 1590, 1510, 1250, 1170, 890, 820 cm⁻¹.

HRMS(FAB) *m/z* calcd for C₁₄H₂₀O₇Na (M+Na)⁺ 323.1107 Found:323.1107.

TLC; R_f 0.39 (CH₂Cl₂–MeOH = 3 : 1).

[α]_D²⁰ = 11.4 (c=1 in DMSO)

D-1-O-(*p*-Methoxybenzyl)-2,3,4,5,6-penta-O-dibenzylphosphoryl-*myo*-inositol (–)-6****

To suspension of (–)-**5** (0.1 g, 0.33 mmol) in CH₂Cl₂ (10 ml) was added MS4A, and the resulting suspension was stirred at room temperature under argon for 15 min. To the mixture was added dibenzyl *N,N*-diethyl phosphoramidite (1g, 3.32 mmol) folowed by 1*H*-terazole (0.23 g, 3.32 mmol), the resulting mixture was stirred at room temperature under argon for overnight. To the mixture was added *m*-chloroperbenzoic acid (0.57 g, 3.30 mmol) in small portions, and the resulting mixture was stirred

-78 °C to room temperature for 1 h. The mixture was purified by silica gel column chromatography (Hexane-AcOEt=1:2) to afford (-)-**6** (0.43 g, 80%) as a colorless oil.

¹H NMR (CDCl₃) δ: 3.56 (1H, d, *J* = 9.9Hz, CH), 3.66 (3H, s, CH₃), 4.41 (1H, t, *J*=9.5, CH), 4.43 (1H, d, *J* = 10.3Hz, CH), 4.57 (1H, dd, *J* = 19.4, 9.5 Hz, CH), 4.66 (1H, d, *J* = 10.6Hz, CH), 4.74-5.24 (22H, m, CH₂C₆H₅ x 10, CH x 2), 5.54 (1H, d, *J* = 9.5Hz, CH), 6.68 (2H, d, *J* = 8.8, C₆H₄(CH x 2)), 7.06-7.35 (52H, m, C₆H₅ x 10, C₆H₄(CH x 2)).

¹³C NMR (CDCl₃) δ: 55.0, 69.1, 69.2, 69.4, 69.5, 69.6, 69.7, 69.8, 69.9, 71.7, 73.4, 73.8, 74.9, 76.3, 76.6, 113.5, 127.6, 127.7, 127.8, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 129.4, 129.8, 130.5, 132.5, 135.5, 135.6, 135.7, 135.8, 135.9, 136.0, 166.6.

IR (neat) 2970, 1710, 1610, 1515, 1500, 1280, 1215, 1014, 880, 740, 700 cm⁻¹.

HRMS(FAB) *m/z* calcd for C₈₄H₈₅O₂₂P₅Na (M+Na)⁺ 1623.4118 Found:1623.4196.

TLC; Rf 0.40 (Hexane-AcOEt=1:2).

[α]_D²⁰ = -0.8 (c=1 in CHCl₃)

L-3-*O*-(*p*-Methoxybenzyl)-1,2,4,5,6-penta-*O*-dibenzylphosphoryl-*myo*-inositol (+)-**6**

(+)-**5** (0.1 g, 0.33 mmol) was allowed to react, under the same conditions as described for the preparation of (-)-**6**, to give (+)-**6** (0.42 g, 80%) as a colorless oil.

¹H NMR (CDCl₃) δ: 3.55 (1H, d, *J* = 9.9 Hz, CH), 3.67 (3H, s, CH₃), 4.37 (1H, d, *J* = 9.7 Hz, CH), 4.42 (1H, *J* = 10.4 Hz, CH), 4.57 (1H, dd, *J* = 19.4, 9.7 Hz, CH), 4.65 (1H, d, *J* = 9.7 Hz, CH), 4.36-5.23 (20H, m, CH₂C₆H₅ x 10), 5.52 (1H, d, *J* = 9.3 Hz, CH), 6.67 (1H, d, *J* = 8.4, C₆H₄(CH x 2)), 7.07-7.35 (52H, m, C₆H₅ x 10, C₆H₄(CH x 2)).

¹³C NMR (CDCl₃) δ: 55.0, 69.1, 69.2, 69.4, 69.6, 69.7, 69.8, 69.9, 71.8, 73.5, 73.9, 75.0, 76.3, 76.5, 113.6, 127.6, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 129.4, 129.8, 130.5, 132.5, 135.5, 135.6, 135.7, 135.8, 135.9, 136.0, 159.3.

IR (neat) 3030, 2970, 2900, 2835, 1710, 1610, 1515, 1500, 1280, 1215, 1015, 880, 740, 700 cm⁻¹.

HRMS(FAB) *m/z* calcd for C₈₄H₈₅O₂₂P₅Na (M+Na)⁺ 1623.4118 Found:1623.4087.

Anal. Calcd for C₈₄H₈₅O₂₂P₅: C, 63.00; H, 5.35. Found: C, 63.12; H, 5.53.

TLC; Rf 0.40 (Hexane-AcOEt=1:2).

[α]_D²⁰ = 0.6 (c=1 in CHCl₃)

D-2,3,4,5,6-Penta-*O*-dibenzylphosphoryl-*myo*-inositol (+)-**7**

To a solution of (-)-**6** (0.16g, 0.10 mmol) in CH₃CN-H₂O (9:1, 5 ml) was added diammonium cerium(IV) nitrate (0.12 g, 0.21 mmol)⁵ and the resulting mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under reduced pressure, and the residue was purified by

silica gel column chromatography (CH₂Cl₂-AcOEt=1:5) to afford (+)-7 (0.10 g, 64%) as a colorless oil.

¹H NMR (CDCl₃) δ: 4.03 (1H, d, *J* = 8.4 Hz, CH), 4.57 (1H, t, *J* = 9.2 Hz, CH), 4.61-5.29 (23H, m, CH₂C₆H₅ x 10, CH x 3), 5.40 (1H, d, *J* = 8.8 Hz, CH), 5.65 (1H, bs, OH), 7.07-7.35 (50H, m, C₆H₅ x 10).

¹³C NMR (CDCl₃) δ: 69.0, 69.4, 69.5, 69.6, 69.7, 69.8, 70.0, 70.1, 73.6, 74.9, 76.5, 77.7, 78.9, 127.5, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 129.4, 129.9, 132.6, 134.2, 135.4, 135.6, 135.7, 135.8, 136.0, 167.0.

IR (neat) 3255, 3030, 2925, 1610, 1500, 1455, 1280, 1215, 1015, 880, 740, 700 cm⁻¹.

HRMS(FAB) *m/z* calcd for C₈₄H₈₅O₂₂P₅Na (M+Na)⁺ 1503.3543 Found:1503.3604.

TLC; R_f 0.31 (CH₂Cl₂-AcOEt=1:5).

[α]_D²⁰ = 14.5 (c=1 in CHCl₃)

L-1,2,4,5,6-Penta-*O*-dibenzylphosphoryl-*myo*-inositol (-)-7

(+)-6 (0.30 g, 0.19 mmol) was allowed to react, under the same conditions as described for the preparation of (+)-7, to give (-)-7 (0.17 g, 62%) as a colorless oil.

¹H NMR (CDCl₃) δ: 3.86 (1H, d, *J* = 8.1 Hz, CH), 4.39-4.68 (3H, m, CH x 3), 4.84-5.26 (21H, m, CH₂C₆H₅ x 10, CH), 5.34 (1H, d, *J* = 8.4 Hz, CH), 5.51 (1H, bs, OH), 7.10-7.34 (50H, m, C₆H₅ x 10).

¹³C NMR (CDCl₃) δ: 69.3, 69.4, 69.5, 69.6, 69.8, 69.9, 70.0, 70.1, 70.2, 73.7, 76.6, 77.4, 79.1, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 129.9, 135.5, 135.6, 135.8, 135.9, 136.9, 160.5.

IR (neat) 3320, 3065, 3035, 2960, 1720, 1500, 1455, 1280, 1215, 1015, 880, 740, 700 cm⁻¹.

HRMS(FAB) *m/z* calcd for C₈₄H₈₅O₂₂P₅Na (M+Na)⁺ 1503.3543 Found:1503.3535.

TLC; R_f 0.31 (CH₂Cl₂-AcOEt=1:5).

[α]_D²⁰ = -13.9 (c=1 in CHCl₃)

D-1-*O*-[(1',2'-Di-*O*-heptanoyl-*sn*-glycero)cianoethyl]phosphoryl-2,3,4,5,6-pentakis-*O*-dibenzylphosphoryl-*myo*-inositol (+)-8

The mixture of 1,2-Di-*O*-heptanoyl-*sn*-glycerol (0.051 g, 0.16 mmol) in CH₂Cl₂ (5 ml) was added (2-cyanoethyl)-*N,N,N',N'*-tetraisopropylphosphoramidite (0.051 ml, 0.16 mmol) followed by MS4A, and the resulting mixture was stirred at room temperature under argon for 15 min. To the mixture was added 1*H*-tetrazole (0.011 g, 0.16 mmol), and the resulting mixture was stirred at room temperature under argon for 10 min. To the mixture was added, completely dissolved compound (+)-7 (0.052 g, 0.032 mmol) in CH₂Cl₂ (5 ml) with MS4A, followed by adding 1*H*-tetrazole (0.011 g, 0.16 mmol), and the resulting mixture was stirred at room temperature for 24 h. To the mixture was added *tert*-

butylhydroperoxide (0.032 ml, 0.32 mmol), and stirred at room temperature for further 5 min. The mixture was purified by silica gel column chromatography (hexane-acetone=2:1) to afford (+)-**8** (0.042 g, 69%) as a yellow oil.

^1H NMR (CDCl_3) δ : 0.86 (6H, t, $J = 6.6$ Hz, $\text{CH}_3 \times 2$), 1.14-1.38 (12H, m, $\text{CH}_2 \times 6$), 1.55 (4H, quin, $J = 6.6$ Hz, $\text{CH}_2 \times 2$), 2.17-2.26 (4H, m, CH_2), 2.51 (2H, t, $J = 6.6$ Hz, CNCH_2), 4.13-4.54 (10H, m, CH_2CHCH_2 , $\text{CH} \times 4$, CNCH_2CH_2), 4.89-5.28 (22H, m, $\text{CH}_2\text{C}_6\text{H}_5 \times 10$, $\text{CH} \times 2$), 5.52-5.58 (1H, m, CH), 7.09-7.40 (50H, m, $\text{C}_6\text{H}_5 \times 10$).

^{13}C NMR (CDCl_3) δ : 13.9, 22.4, 24.6, 24.7, 28.7, 31.3, 33.8, 33.9, 34.0, 61.5, 69.3, 69.6, 69.7, 69.8, 69.9, 73.0, 73.7, 74.5, 75.1, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 135.6, 135.7, 135.8, 135.9, 172.9, 173.2.

IR (neat) 3035, 2960, 1740, 1455, 1380, 1280, 1020, 880, 740, 700 cm^{-1} .

HRMS(FAB) m/z calcd for $\text{C}_{96}\text{H}_{111}\text{O}_{28}\text{NP}_6\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 1934.5616 Found:1934.5614.

TLC; Rf 0.38 (hexane-acetone=2:1).

$[\alpha]_{\text{D}}^{20} = 3.2$ ($c=1$ in CHCl_3)

L-3-O-[(1',2'-Di-O-heptanoyl-*sn*-glycero)cianoethyl]phosphoryl-1,2,4,5,6-pentakis-O-dibenzylphosphoryl-*myo*-inositol (-)-9****

(-)-**7** (0.15 g, 0.099 mmol) was allowed to react, under the same conditions as described for the preparation of (+)-**8**, to give (-)-**9** (0.12 g, 62%) as a yellow oil.

^1H NMR (CDCl_3) δ : 0.86 (6H, t, $J = 6.8$ Hz, $\text{CH}_3 \times 2$), 1.19-1.29 (12H, m, $\text{CH}_2 \times 6$), 1.49-1.63 (4H, m, $\text{CH}_2 \times 2$), 2.15-2.37 (4H, m, CH_2), 2.45-2.57 (2H, m, CNCH_2), 4.00-4.36 (7H, m, CH_2CHCH_2 , $\text{CH} \times 3$, CNCH_2CH_2), 4.46-4.60 (3H, m, CH, CNCH_2CH_2), 4.89-5.29 (22H, m, $\text{CH}_2\text{C}_6\text{H}_5 \times 10$, $\text{CH} \times 2$), 5.53-5.55 (1H, m, CH), 7.10-7.39 (50H, m, $\text{C}_6\text{H}_5 \times 10$).

^{13}C NMR (CDCl_3) δ : 14.0, 22.4, 24.8, 28.7, 31.4, 33.9, 34.0, 34.2, 61.4, 61.5, 69.7, 69.8, 73.1, 73.7, 73.9, 74.5, 75.0, 75.3, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 135.6, 135.8, 135.9, 172.9, 173.2.

IR (neat) 2860, 1740, 1455, 1280, 1015, 880, 740, 700 cm^{-1} .

HRMS(FAB) m/z calcd for $\text{C}_{96}\text{H}_{111}\text{O}_{28}\text{NP}_6\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 1934.5616 Found:1934.5569.

TLC; Rf 0.38 (hexane-acetone=2:1).

$[\alpha]_{\text{D}}^{20} = -1.0$ ($c=1$ in CHCl_3)

D-1-O-(1',2'-Di-O-heptanoyl-*sn*-glycero)phosphatidyl-2,3,4,5,6-pentakis-O-dibenzylphosphoryl-*myo*-inositol (+)-10****

To the solution of (+)-**8** (0.042 g, 0.022 mmol) in CH_3CN (3 ml) was added Et_3N (1 ml) and stirred for overnight. After concentration of the reaction mixture under reduced pressure, the residue was

purified by silica gel column chromatography (CH₂Cl₂-MeOH=9:1) to afford (+)-**10** (0.029 g, 71%) as a colorless oil.

¹H NMR (CDCl₃) δ: 0.83 (6H, t, *J* = 6.6 Hz, CH₃ x 2), 1.20-1.26 (12H, m, CH₂ x 6), 1.47-1.51 (4H, m, CH₂ x 2), 2.16 (2H, t, *J* = 7.7 Hz, CH₂), 2.23 (2H, t, *J* = 7.7 Hz, CH₂), 4.10-4.49 (9H, m, CH₂, CH x 5), 4.54-5.30 (20H, m, CH₂C₆H₅ x 10, CH), 5.47-5.53 (1H, m, CH), 6.10 (1H, d, *J* = 9.2 Hz CH), 6.85-7.35 (50H, m, C₆H₅ x 10).

¹³C NMR (CDCl₃) δ: 14.0, 22.4, 24.7, 24.8, 28.7, 31.4, 34.0, 34.2, 62.6, 69.3, 70.0, 70.2, 70.3, 70.5, 70.6, 71.3, 73.4, 75.1, 75.3, 76.3, 127.2, 127.5, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.8, 135.0, 135.1, 135.9, 136.0, 136.1, 173.0, 173.2.

IR (neat) 3035, 2930, 1740, 1455, 1380, 1280, 1020, 880, 740, 690 cm⁻¹.

MS (FAB) *m/z* 1880.79 (M + Na)⁺.

TLC; R_f 0.36 (CH₂Cl₂-MeOH=9:1).

[α]_D²⁰ = 5.6 (c=1 in CHCl₃)

L-3-O-(1',2'-Di-O-heptanoyl-*sn*-glycero)phosphatidyl-1,2,4,5,6-pentakis-O-dibenzylphosphoryl-*myo*-inositol (-)-11

(-)-**9** (0.12 g, 1.04 mmol) was allowed to react, under the same conditions as described for the preparation of (+)-**10**, to give (-)-**11** (0.093 g, 88%) as a colorless oil.

¹H NMR (CDCl₃) δ: 0.86 (6H, t, *J* = 6.6 Hz, CH₃ x 2), 1.23-1.32 (12H, m, CH₂ x 6), 1.34-1.57 (4H, m, CH₂ x 2), 2.18 (2H, t, *J* = 7.7 Hz, CH₂), 2.26 (2H, t, *J* = 7.7 Hz, CH₂), 4.12-4.34 (4H, m, CH₂CHCH₂, CH x 2), 4.62-4.68 (1H, dd, *J* = 11.4, 7.7 Hz, CH), 4.77-5.55 (23H, m, CH₂C₆H₅ x 10, CH₂CHCH₂), 6.12 (1H, d, *J* = 9.2 Hz CH), 6.86-7.41 (50H, m, C₆H₅ x 10).

¹³C NMR (CDCl₃) δ: 14.0, 22.4, 24.7, 24.8, 28.7, 31.4, 33.9, 34.2, 62.5, 64.0, 69.2, 69.3, 69.5, 69.7, 70.0, 70.2, 70.3, 70.4, 70.5, 70.6, 71.0, 71.1, 73.4, 75.2, 76.3, 127.6, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 129.3, 135.0, 135.2, 135.4, 135.7, 135.8, 135.9, 136.0, 136.1, 136.3, 173.0, 173.2.

IR (neat) 3000, 2820, 1735, 1455, 1380, 1040, 740, 700 cm⁻¹.

MS (FAB) *m/z* 1857.1 (M + H)⁺.

TLC; R_f 0.36 (CH₂Cl₂-MeOH=9:1).

[α]_D²⁰ = -6.2 (c=1 in CHCl₃)

D-1-O-(1',2'-Di-O-heptanoyl-*sn*-glycero)phosphatidyl-*myo*-inositol-2,3,4,5,6-pentakisphosphate D-HIPPO [(-)-1]

To the solution of (+)-**10** (0.029 g, 0.016 mmol) in *t*-BuOH (8 ml) and H₂O, (1.5 ml) was added 10% Pd-C (0.032 g, 0.030 mmol), and the resulting mixture was stirred at room temperature under hydrogen for 24 h. The mixture was filtered through a pad of celite, and then celite pad was washed with H₂O. The resulting filtrate was lyophilized. The residue was dissolved in H₂O (2 ml), and filtered through cation-exchange resin. To the resulting filtrate was added triethylamine (0.020 ml), and concentrated under reduced pressure. The resulting residue was lyophilized to afford (-)-**1** (0.013 g, 40%) as a white solid.

¹H NMR (D₂O) δ: 0.87 (6H, bs, CH₃ x 2), 1.22-1.31 (11H, m, CH₂ x 6, NCH₂CH₃ x 33), 1.54-1.61 (4H, m, CH₂ x 2), 2.40 (2H, t, *J* = 7.1 Hz, CH₂), 2.42 (2H, t, *J* = 7.1 Hz, CH₂), 3.17-3.24 (66H, q, *J* = 7.1 Hz, NCH₂CH₃ x 33), 4.34-4.82 (10H, m, CH₂CHCH₂, CH x 6), 5.34 (1H, bs, CH).

¹³C NMR (D₂O + 1,4-dioxan) δ: 8.8, 13.9, 22.4, 24.9, 28.5, 31.3, 34.3, 34.4, 34.6, 39.3, 44.0, 47.3, 51.7, 63.6, 64.9, 65.8, 68.8, 71.6, 73.9, 76.0, 76.7, 78.0, 176.9, 177.2.

IR (KBr) 3020, 2830, 2700, 2640, 2495, 1735, 1465, 1065 cm⁻¹.

HRMS(FAB) *m/z* calcd for C₂₃H₄₇O₂₈P₆ (M - H)⁻ 957.0597 Found: 957.0782.

[α]_D²⁰ = -4.5 (c=0.5 in H₂O)

L-3-*O*-(1',2'-Di-*O*-heptanoyl-*sn*-glycero)phosphatidyl-*myo*-inositol-1,2,4,5,6- pentakisphosphate L-HIPPO [(+)-**2**]

(-)-**11** (0.93 g, 0.050 mmol) was allowed to react, under the same conditions as described for the preparation of (-)-**1**, to give (+)-**2** (0.044 g, 43%) as a colorless oil.

¹H NMR (D₂O) δ: 0.82-0.84 (6H, m, CH₃ x 2), 1.26 (75H, bs, CH₂ x 6, CH₃ x 21), 1.54-1.59 (4H, m, CH₂ x 2), 2.37 (2H, t, *J* = 7.3 Hz, CH₂), 2.41 (2H, t, *J* = 7.0 Hz, CH₂), 3.18 (42H, bs, CH₂ x 21), 4.10-4.58 (9H, m, CH₂CHCH₂, CH x 5), 4.92-4.95 (1H, m, CH), 5.30 (1H, bs, CH).

¹³C NMR (D₂O + 1,4-dioxan) δ: 8.9, 14.0, 22.5, 24.9, 28.5, 31.3, 31.4, 34.5, 34.6, 47.3, 63.5, 64.8, 71.5, 71.6, 73.8, 73.9, 76.0, 76.3, 76.8, 76.9, 78.0176.8, 177.2.

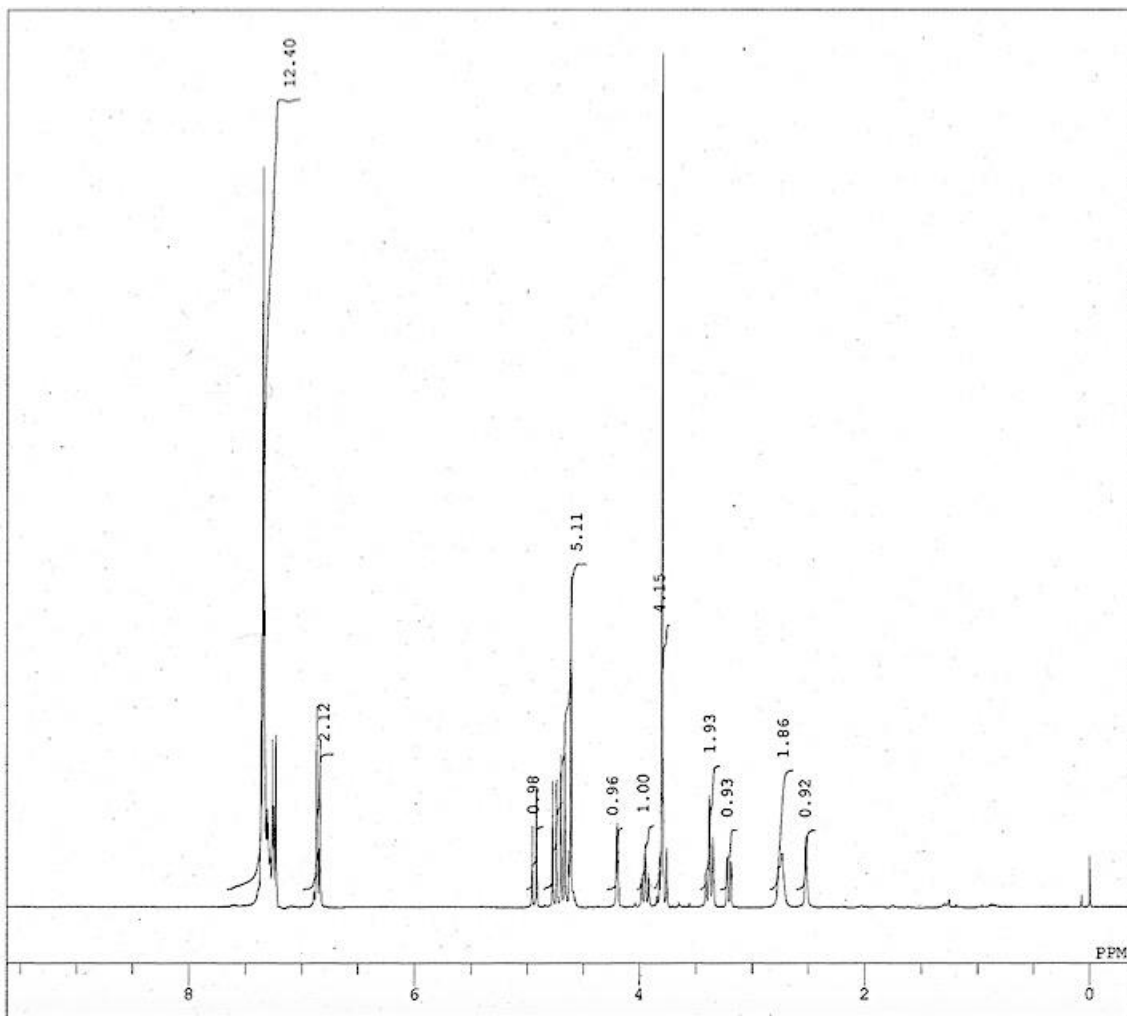
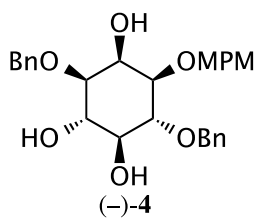
IR (KBr) 3440, 2940, 2730, 2670, 1735, 1465, 1065 cm⁻¹.

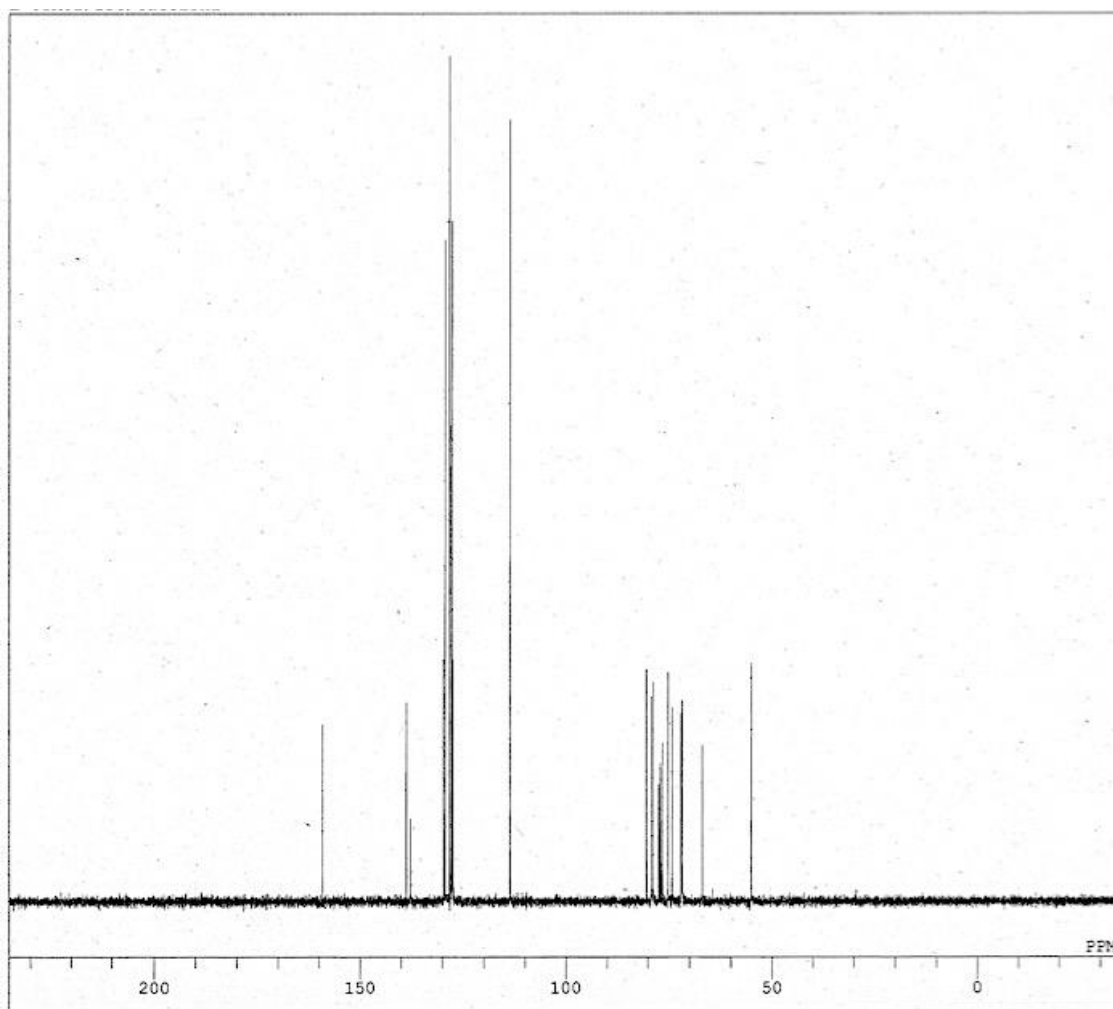
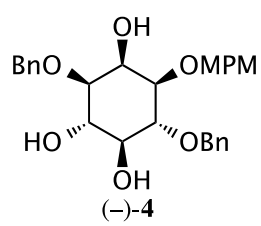
HRMS(FAB) *m/z* calcd for C₂₃H₄₇O₂₈P₆ (M - H)⁻ 957.0597 Found: 957.0638.

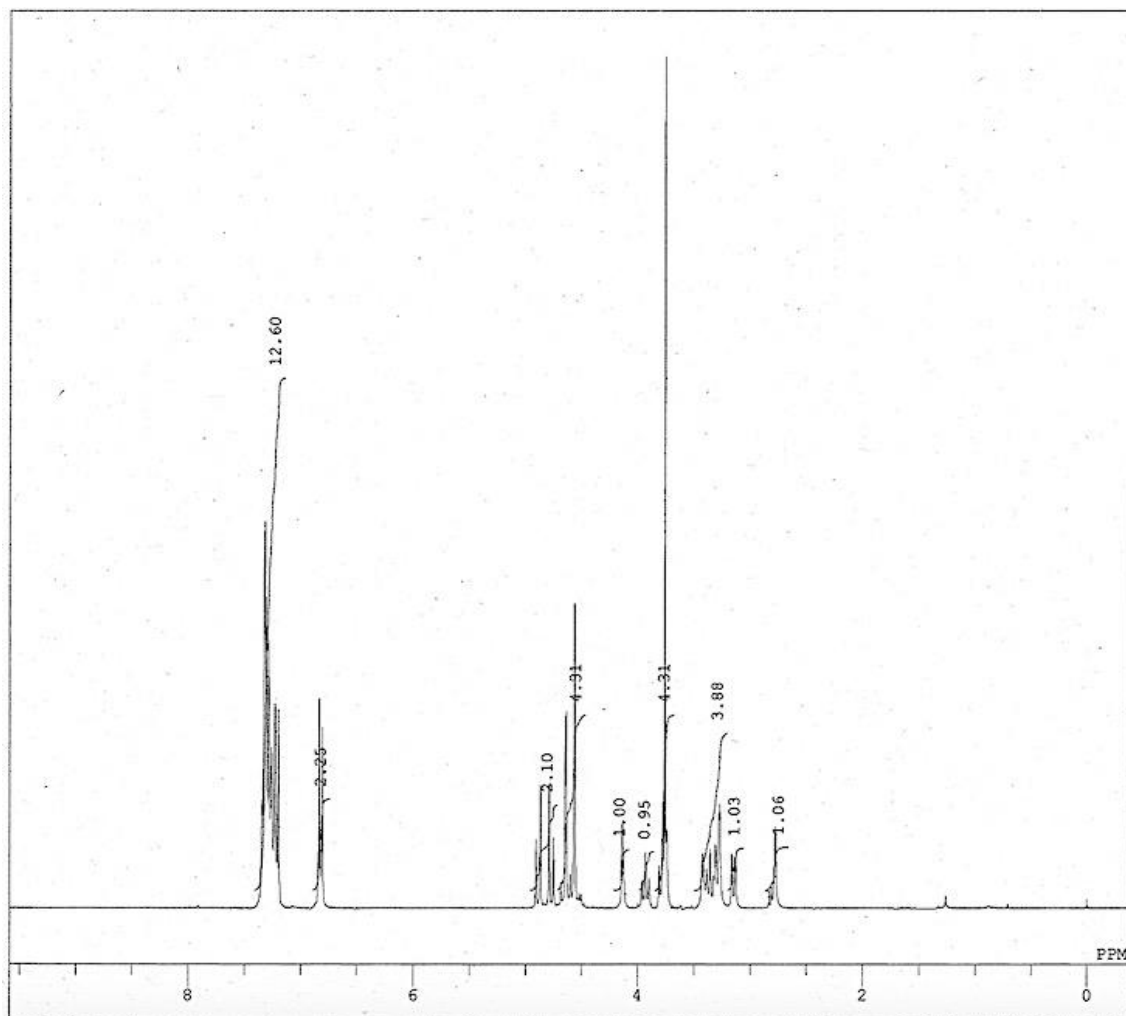
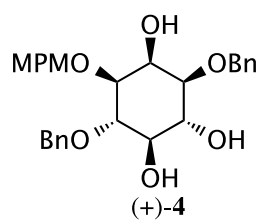
[α]_D²⁰ = 1.4 (c=0.5 in H₂O)

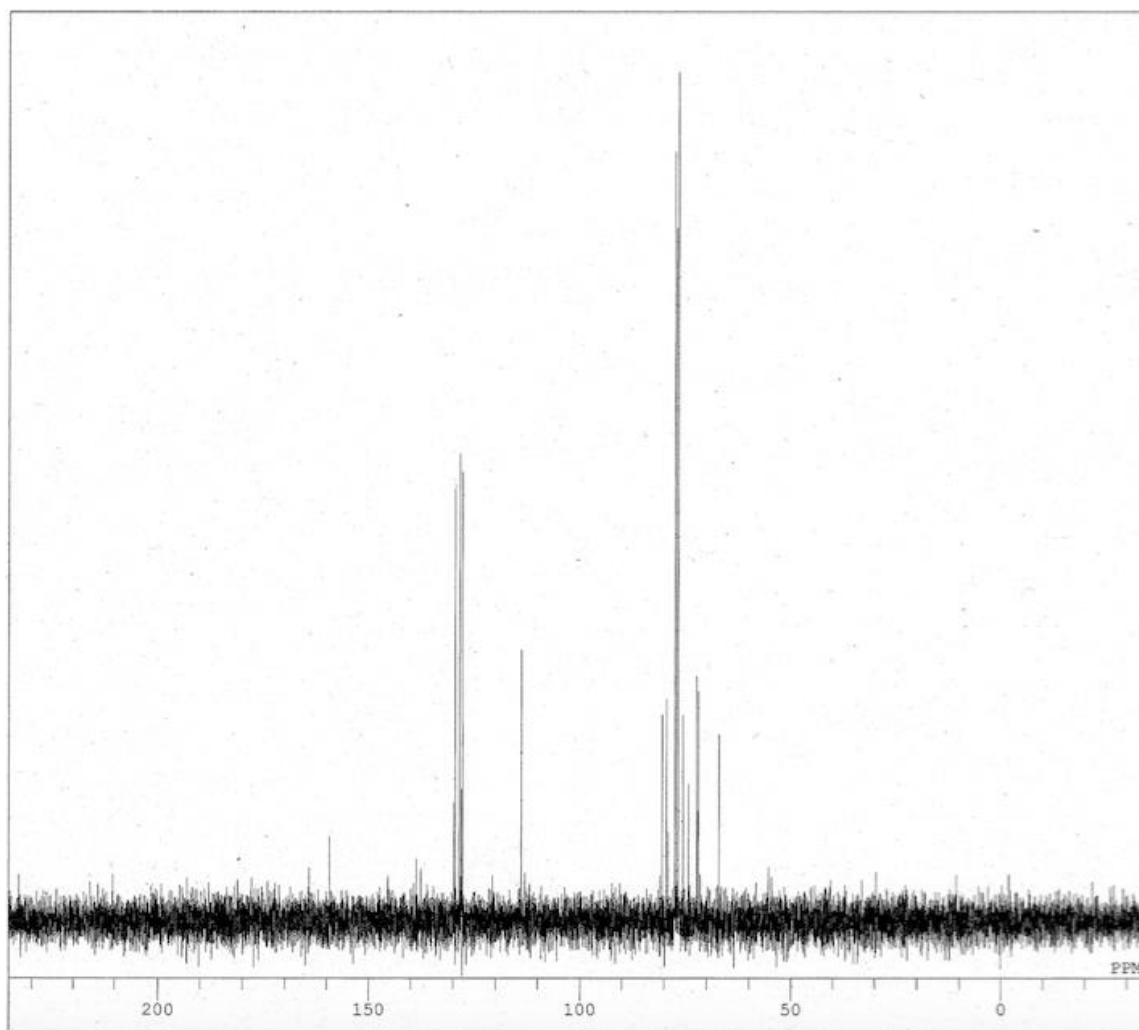
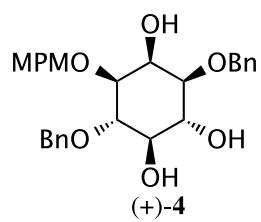
- 1 Mills, S. J. & Potter B. V. L. Synthesis of the enantiomers of *myo*-inositol 1,2,4,5-tetrakisphosphate, a regioisomer of *myo*-inositol 1,3,4,5-tetrakisphosphate. *Journal of the Chemical Society, Perkin Transactions 1*, 1279-1286 (1997).
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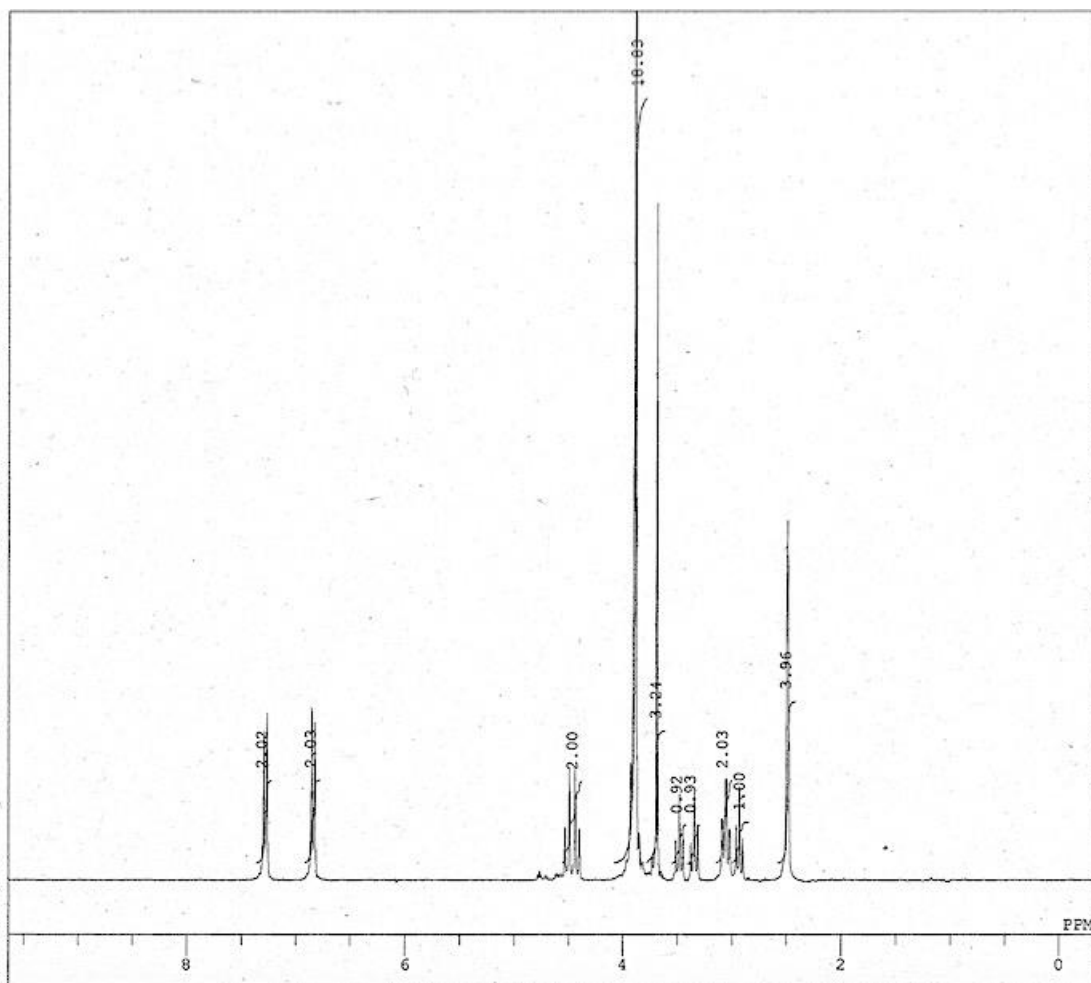
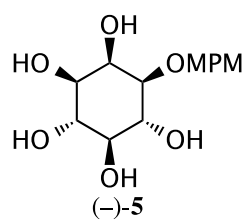
- 3 Liu, C. & Potter, B. L. Synthesis of 3-Position-Modified Analogues of *myo*-Inositol 1,4,5-Trisphosphate, Tools for Investigation of the Polyphosphoinositide Pathway of Cellular Signaling. *The Journal of Organic chemistry* **62**. 8835-8340 (1997).
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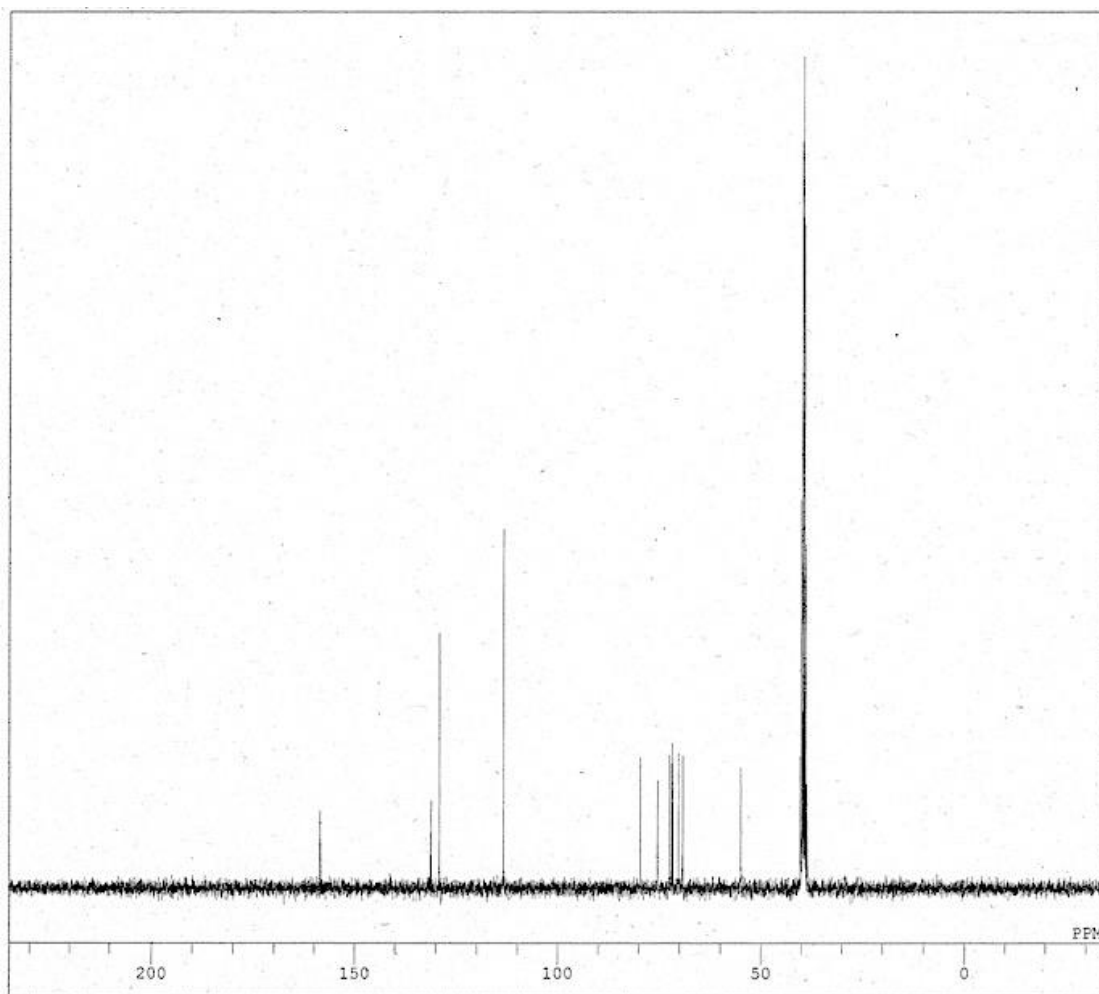
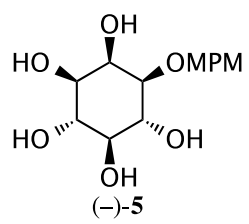


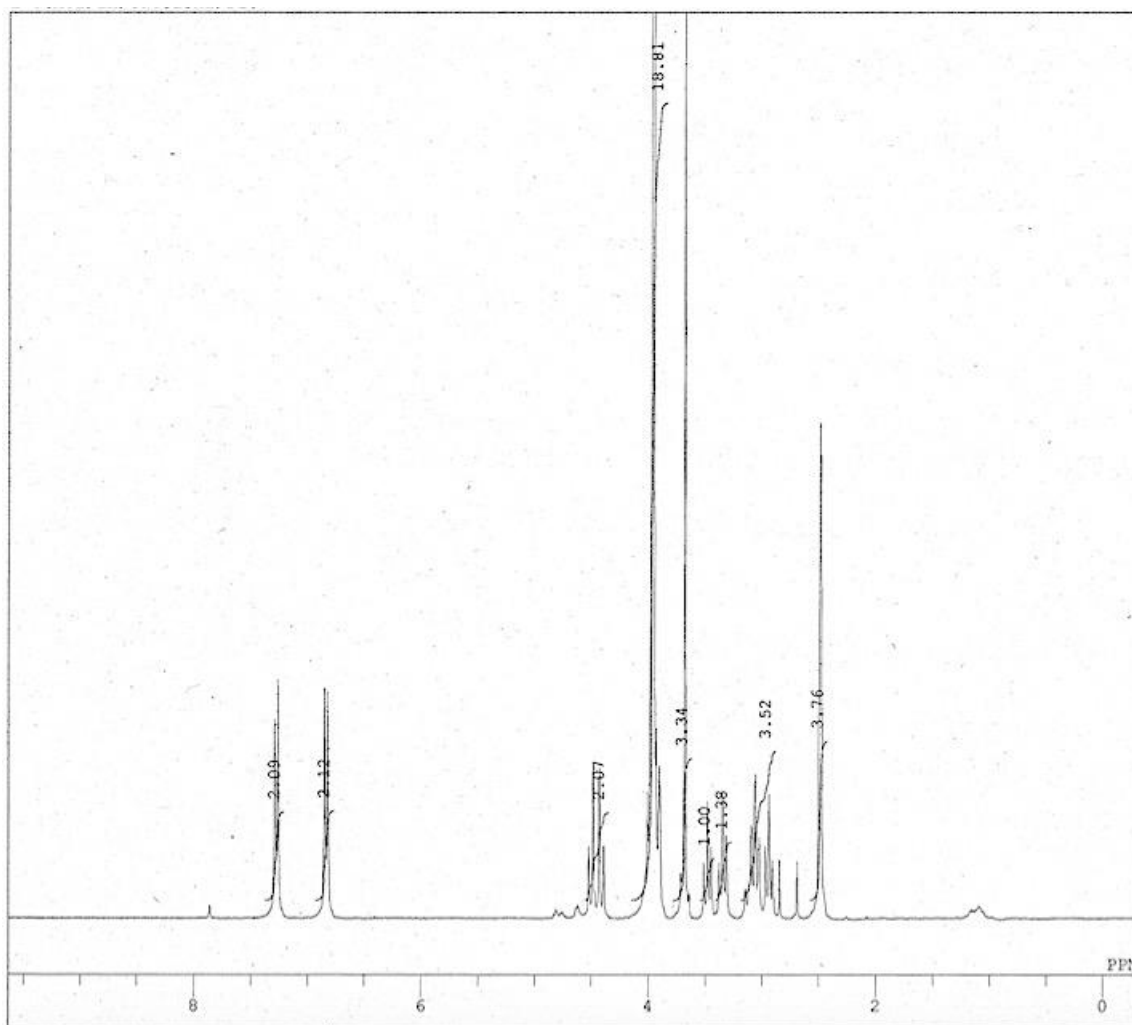
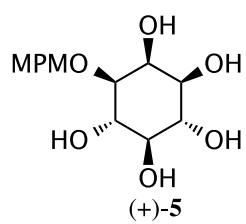


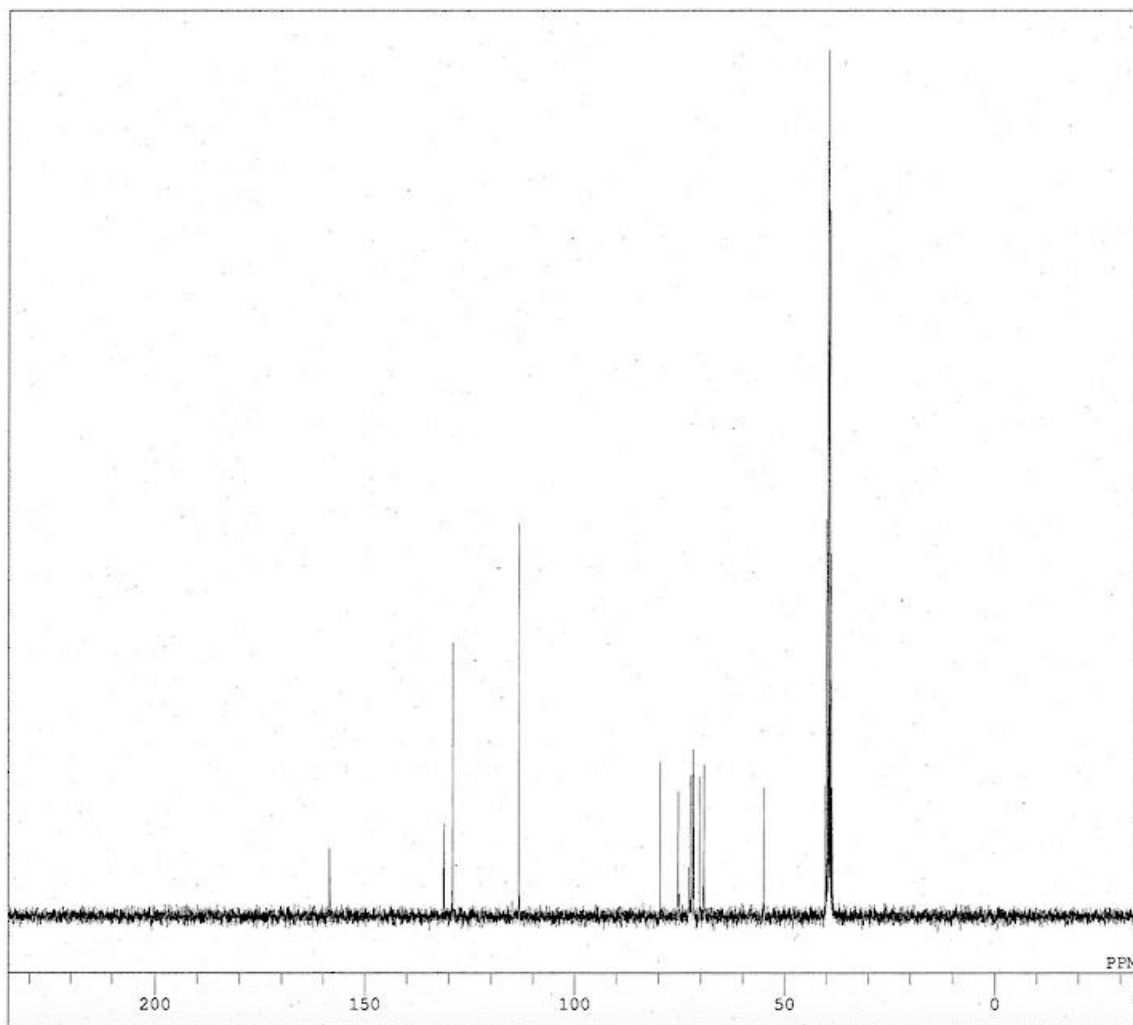
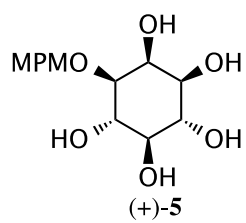


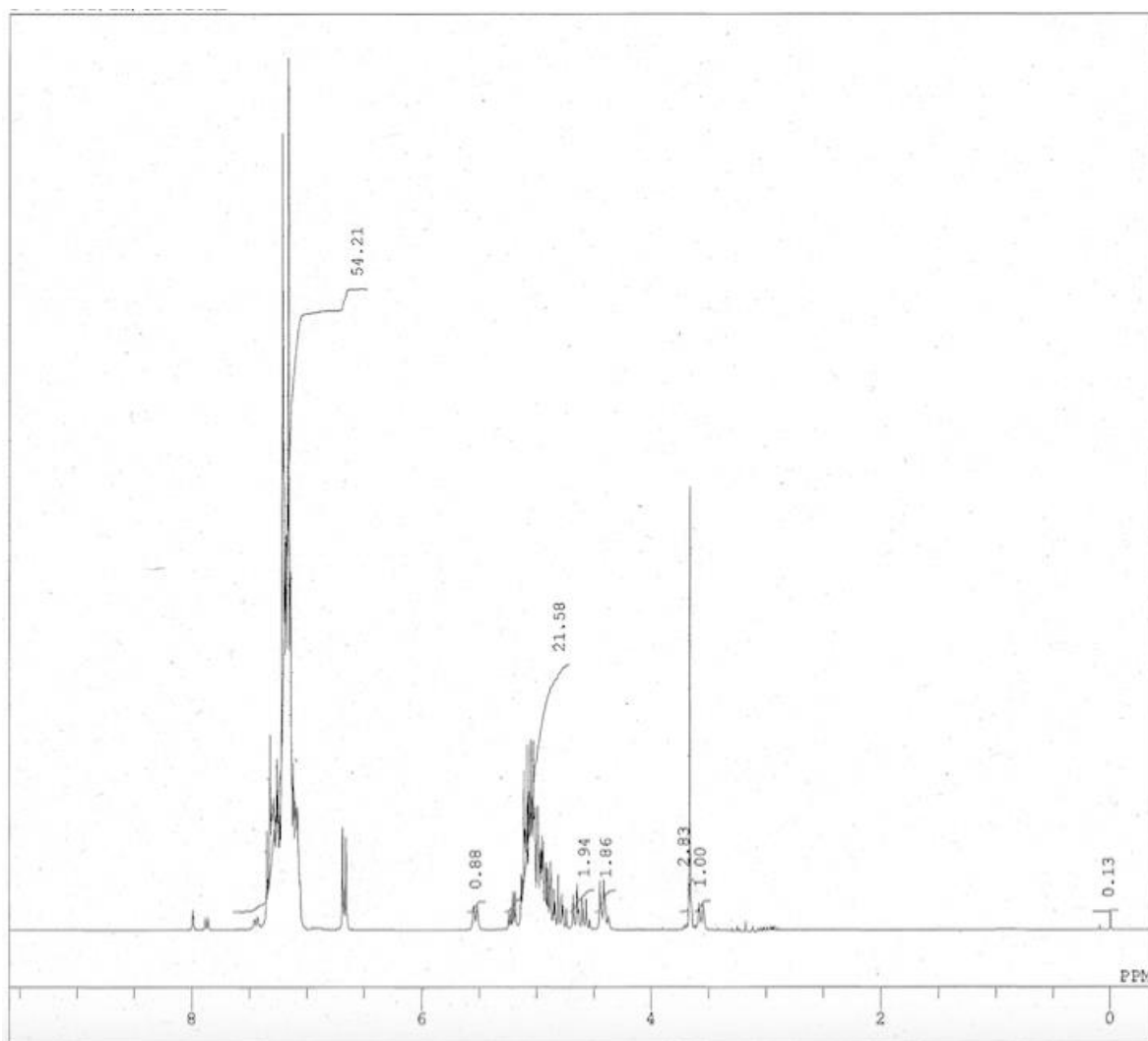
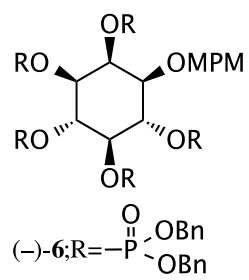


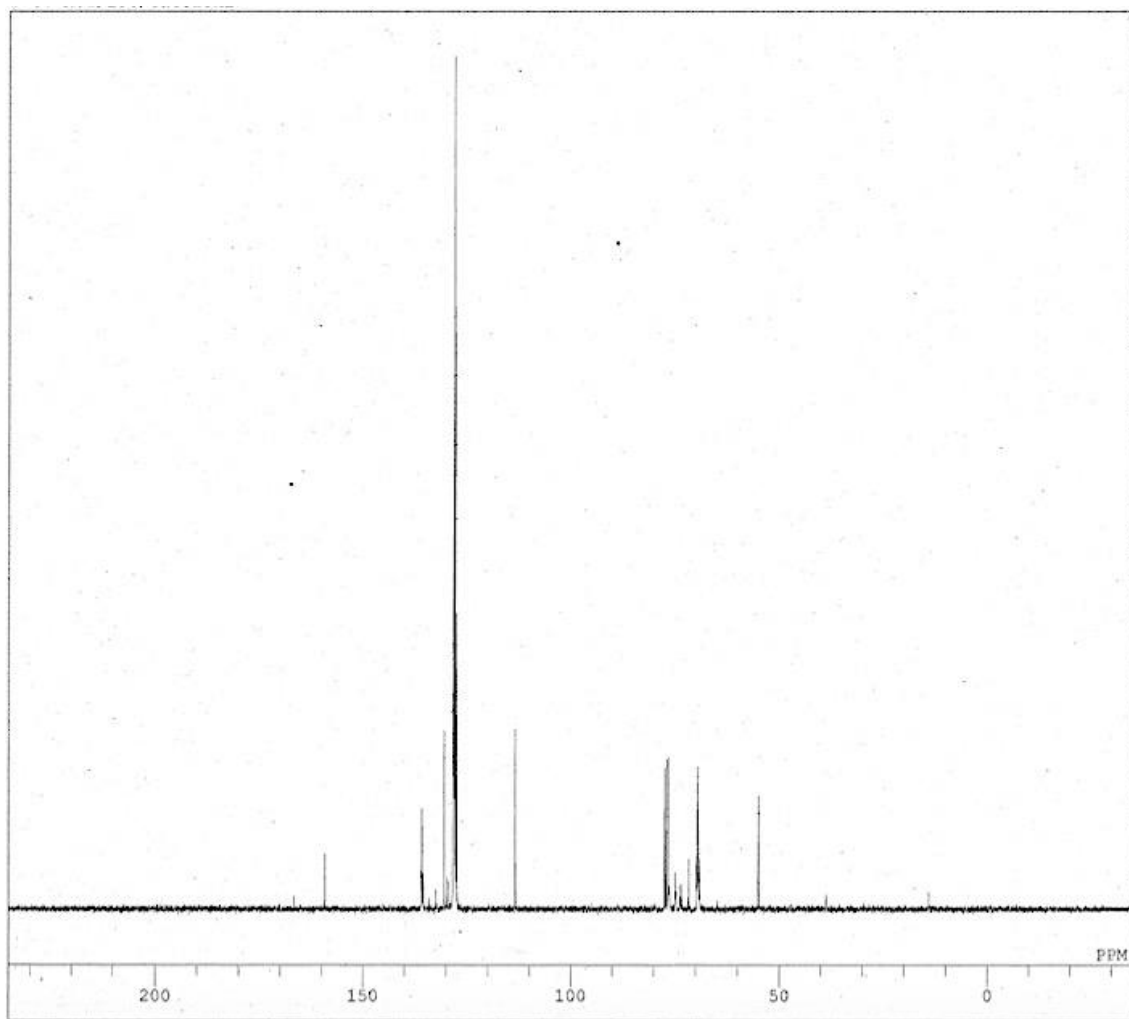
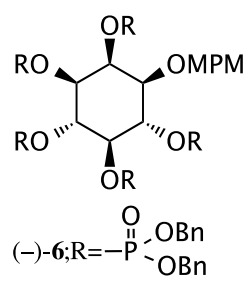


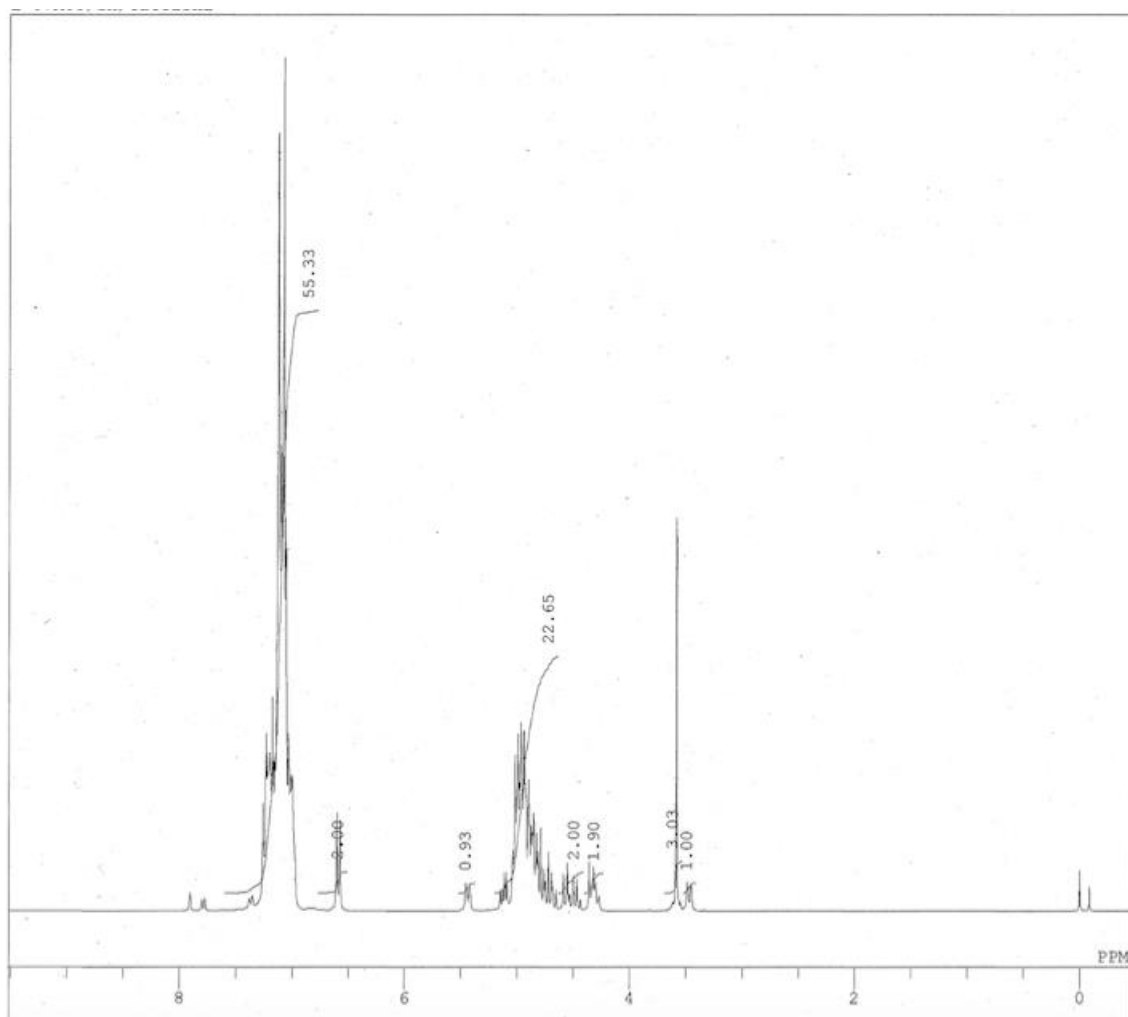
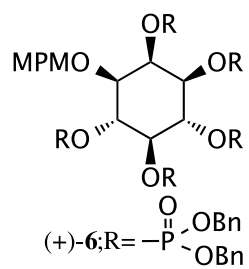


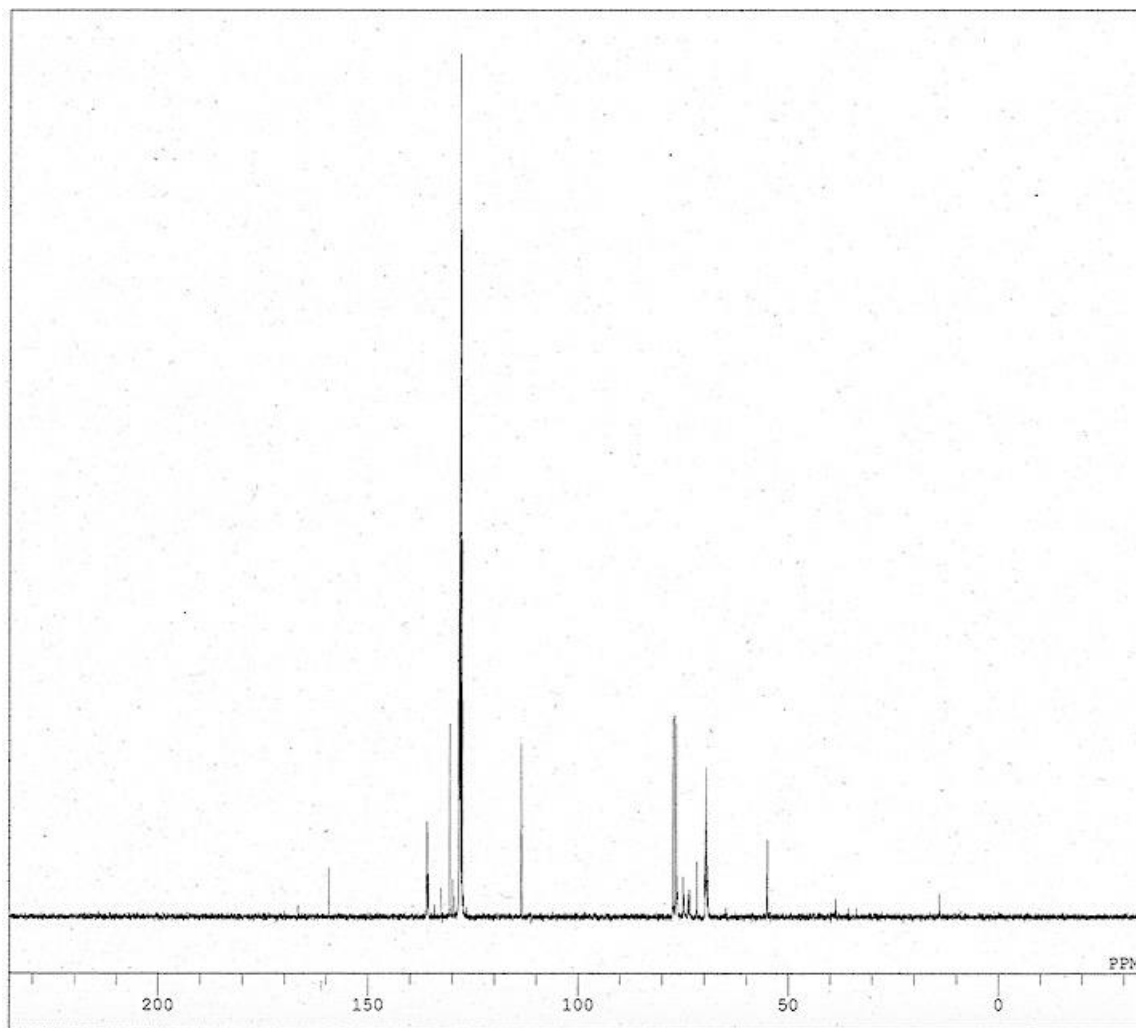
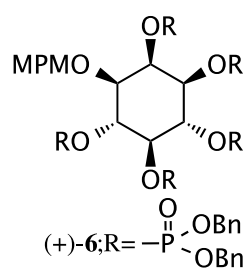


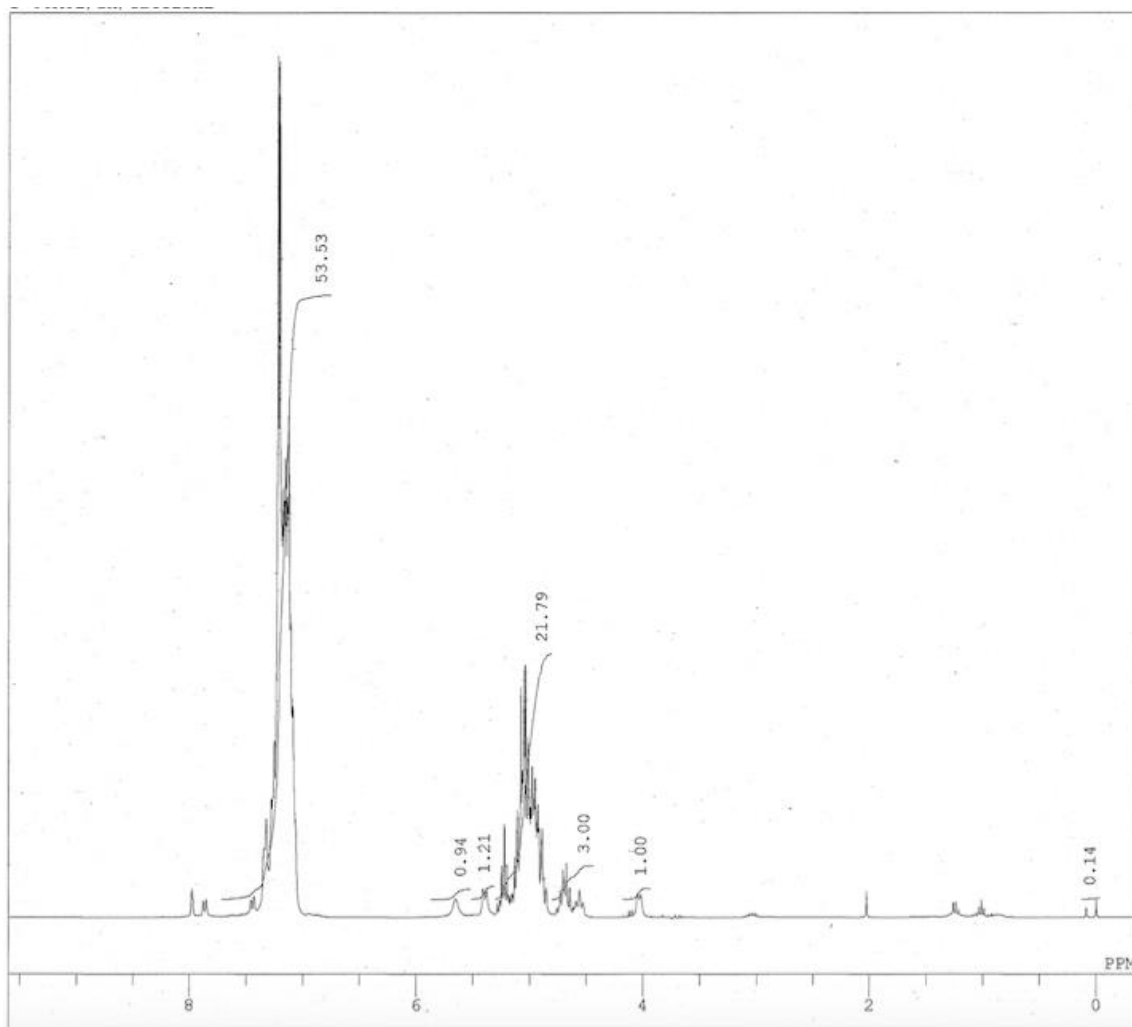
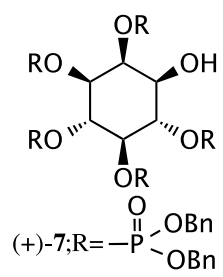


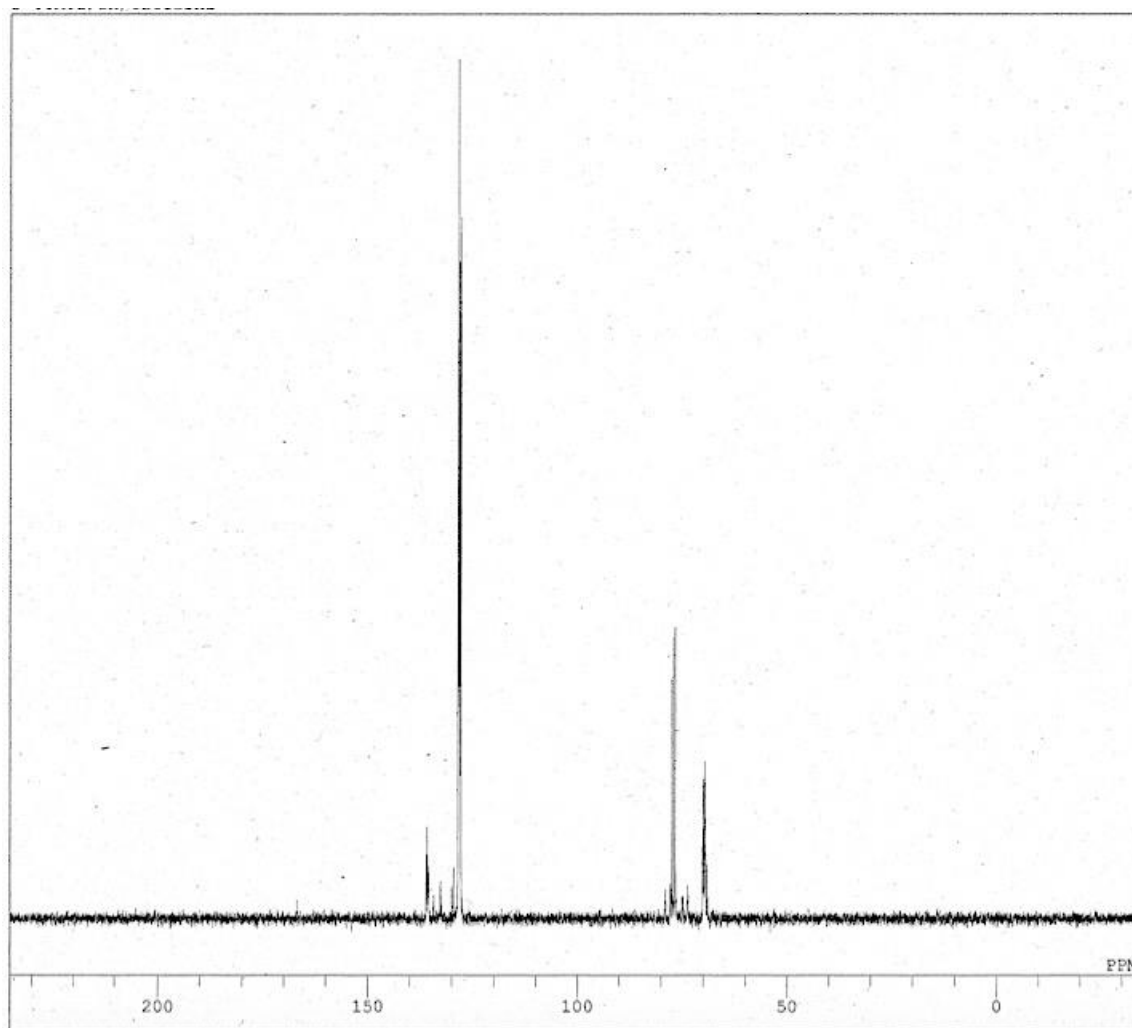
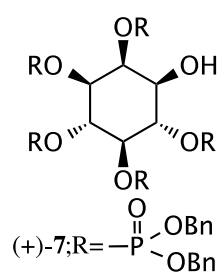


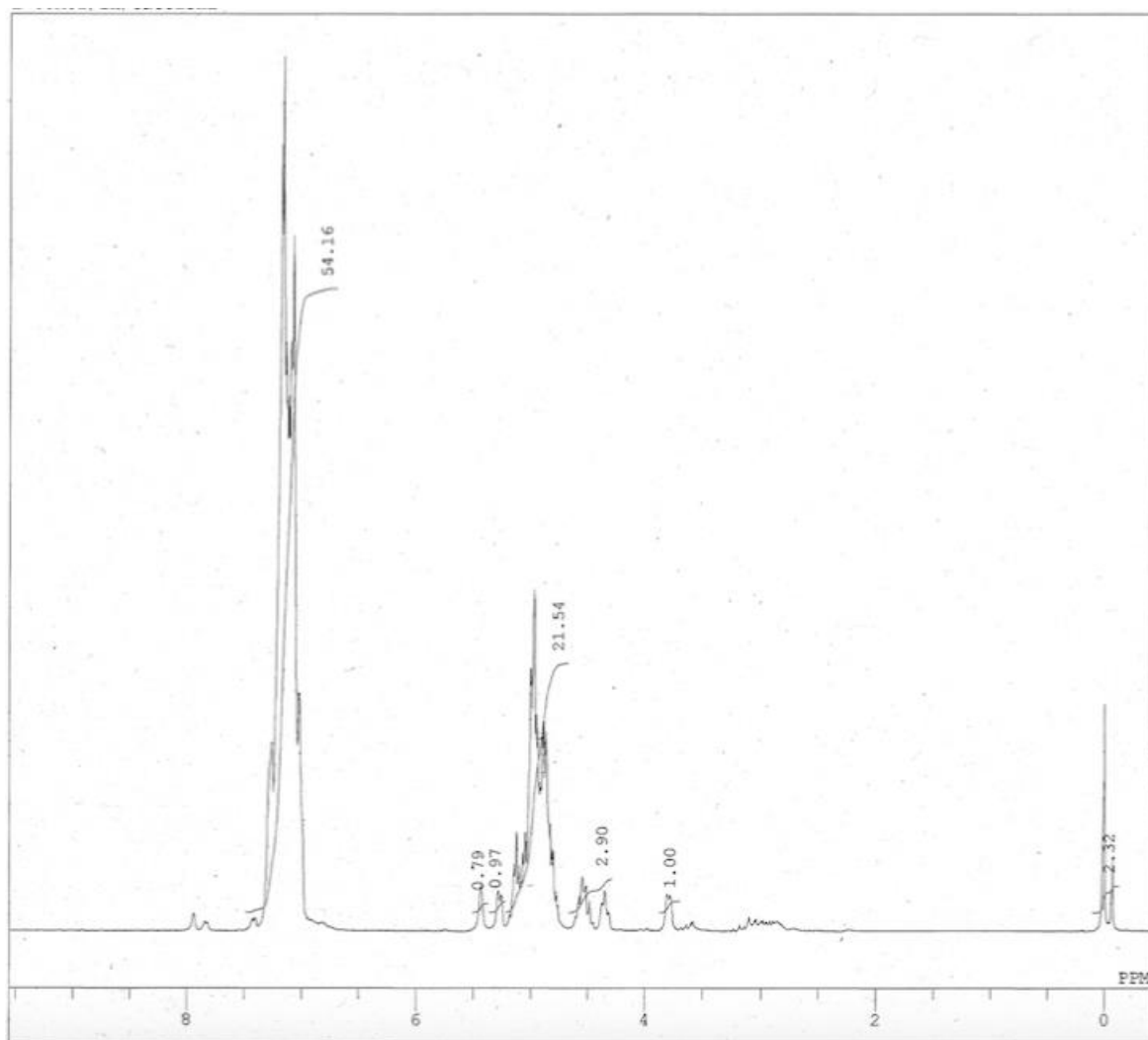
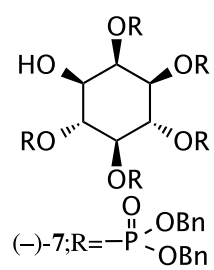


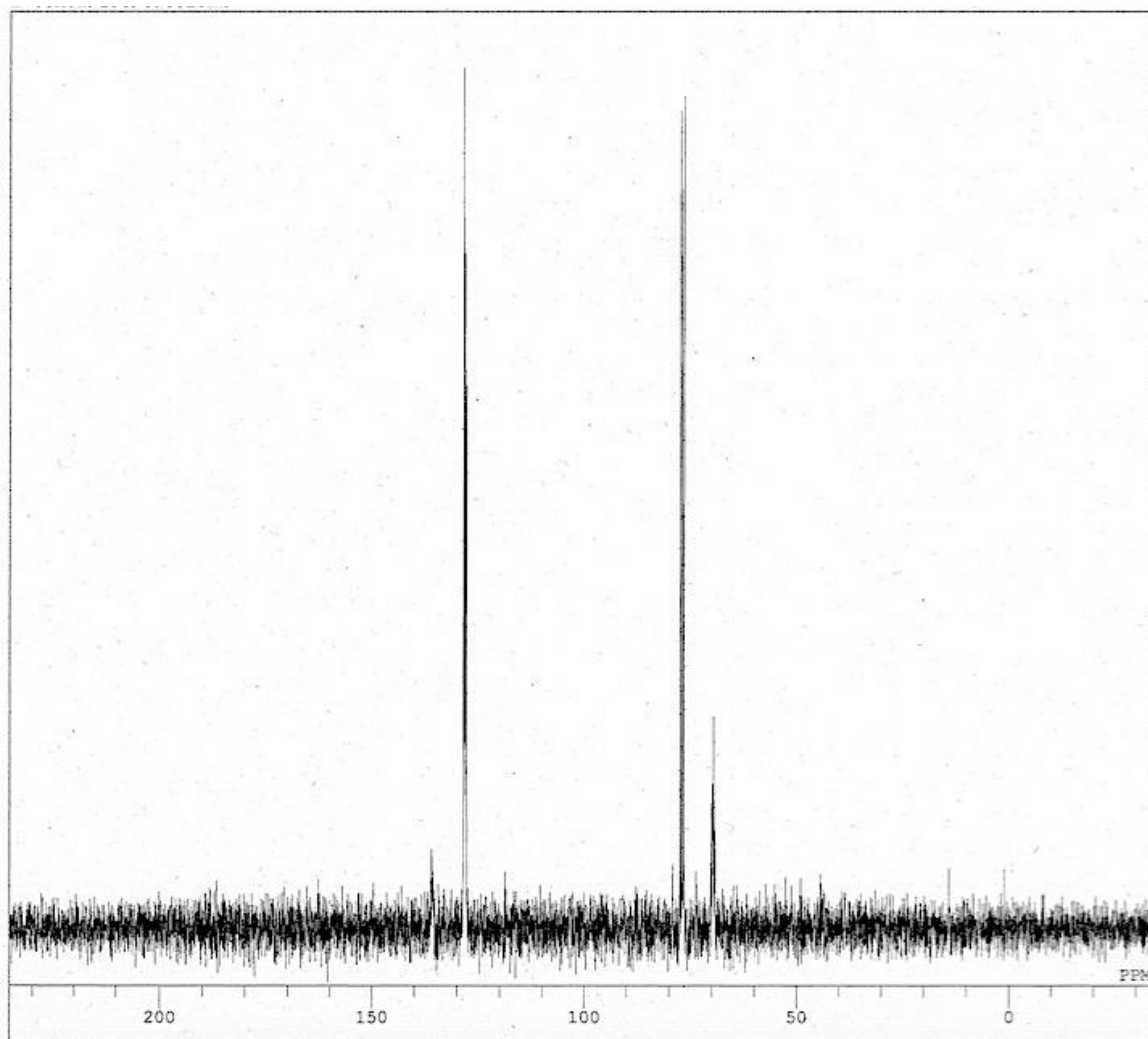
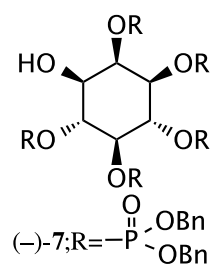


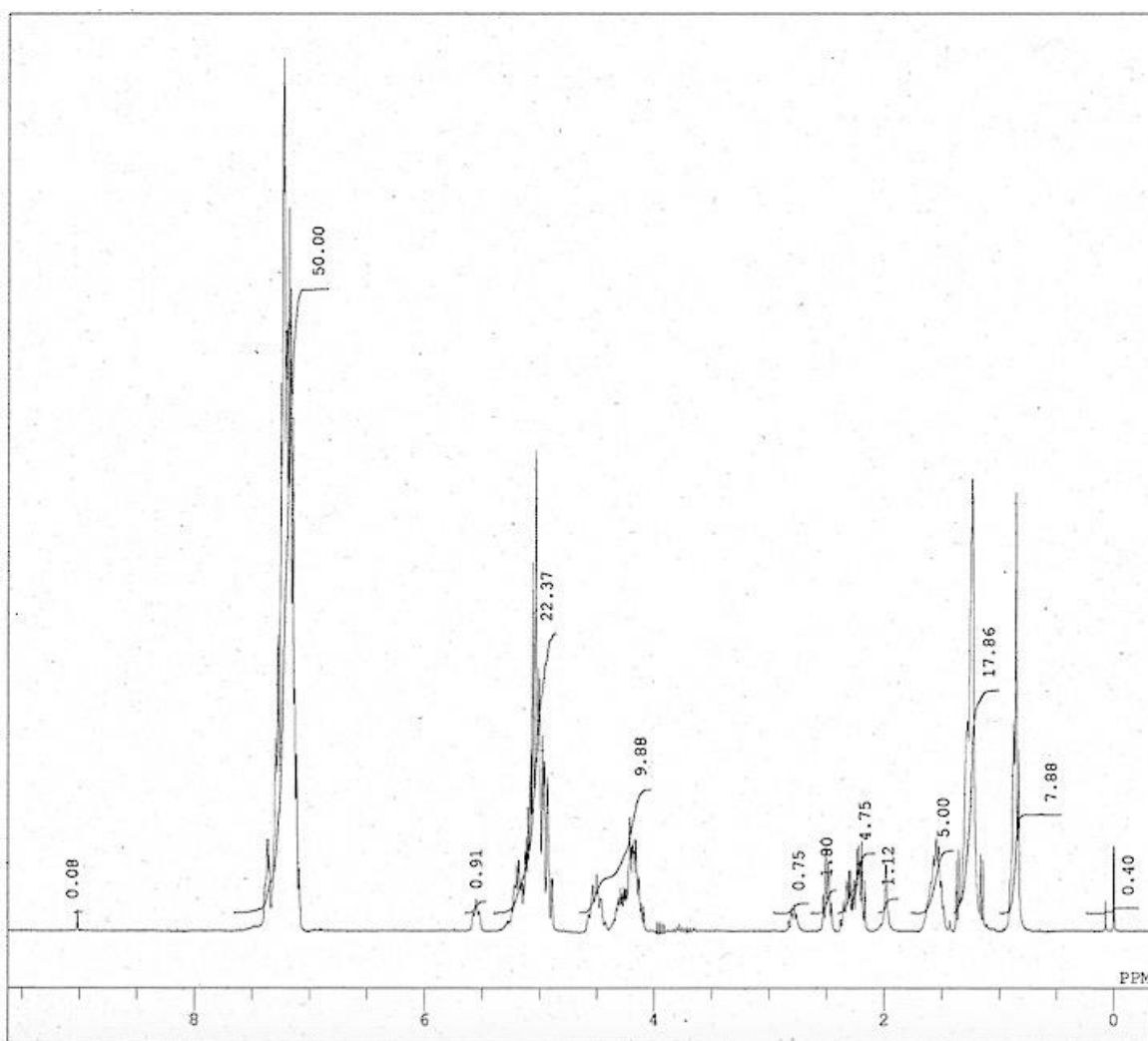
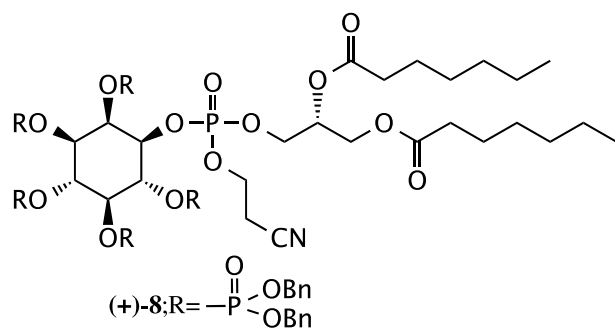


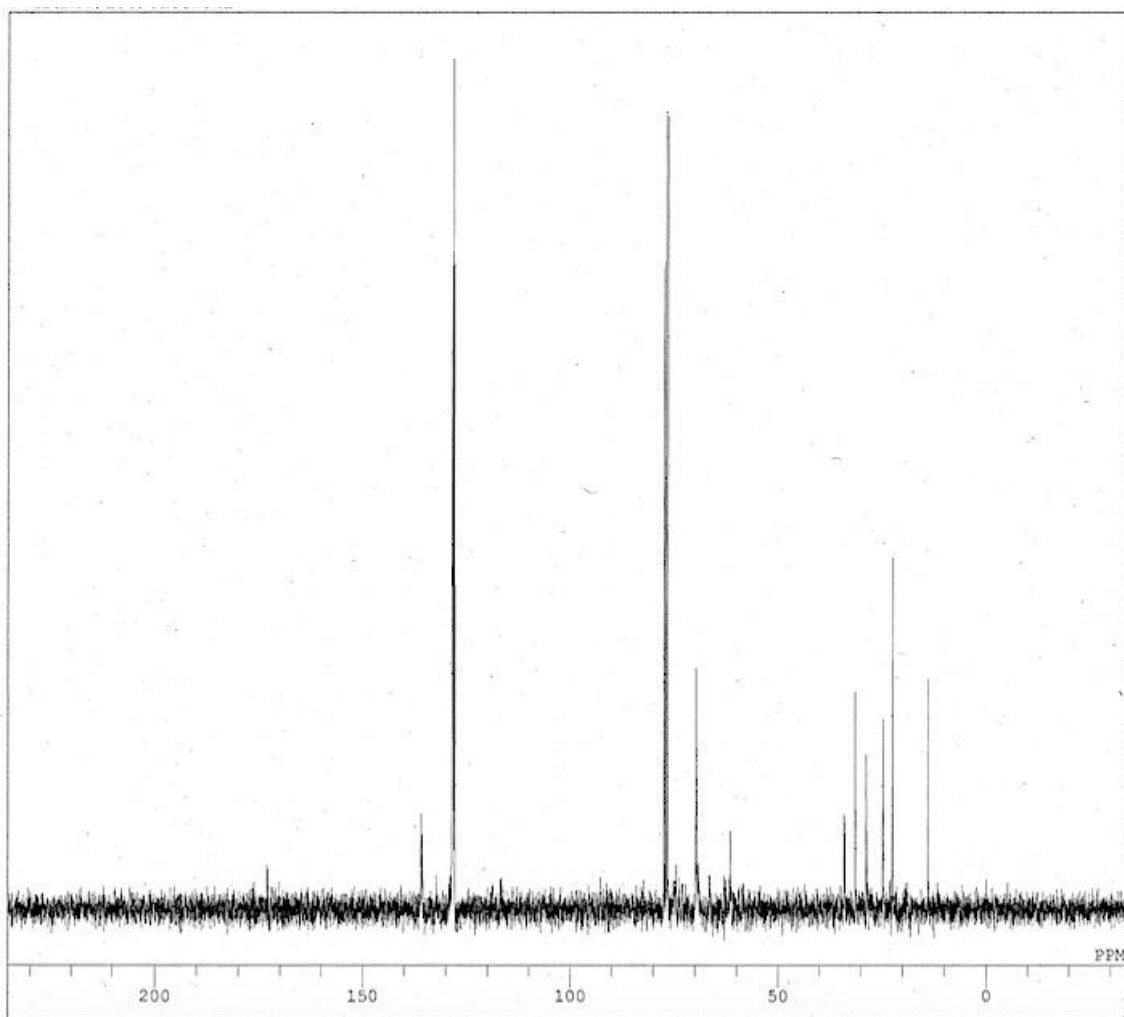
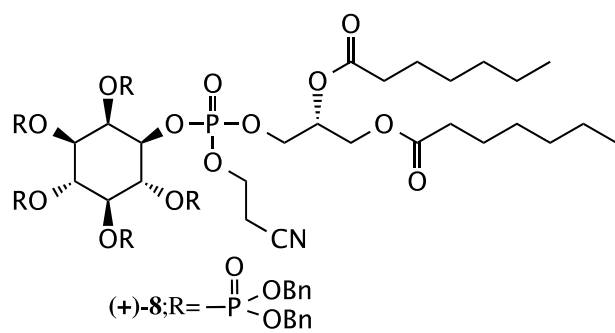


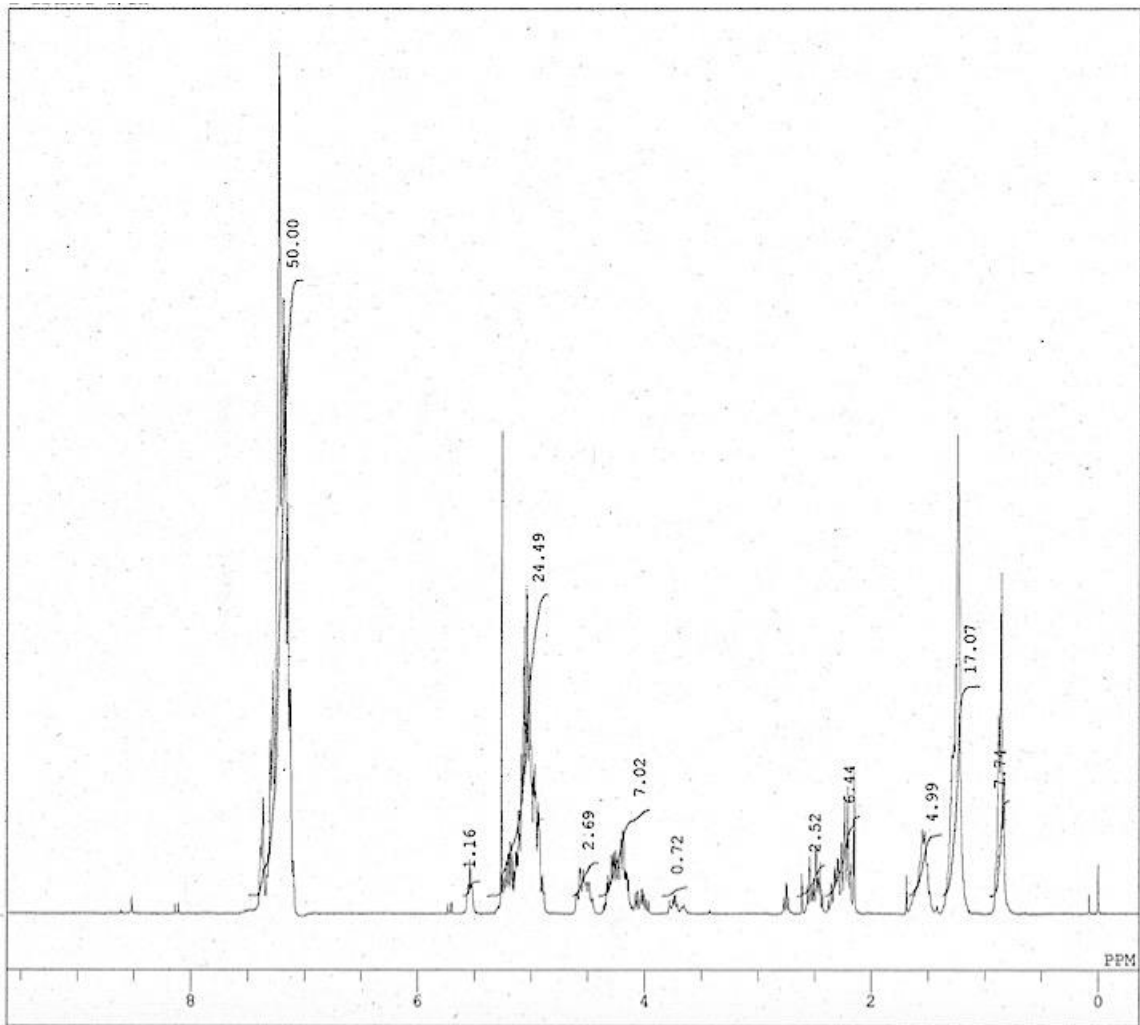
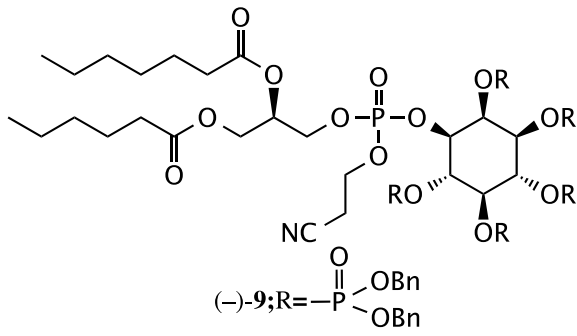


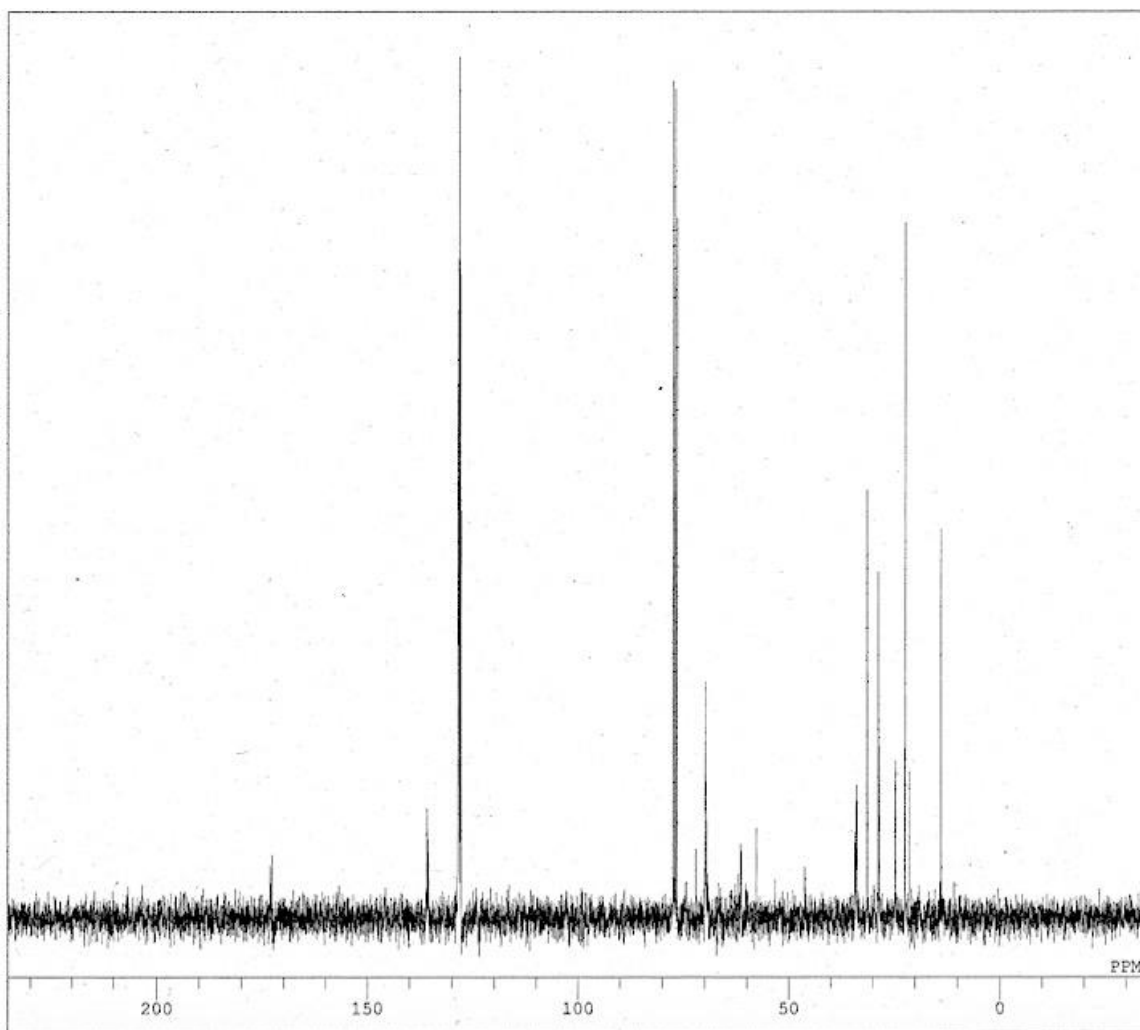
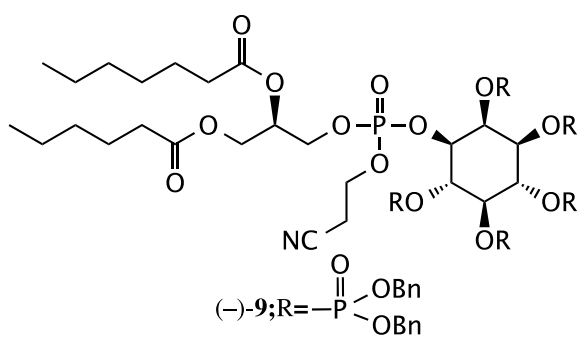


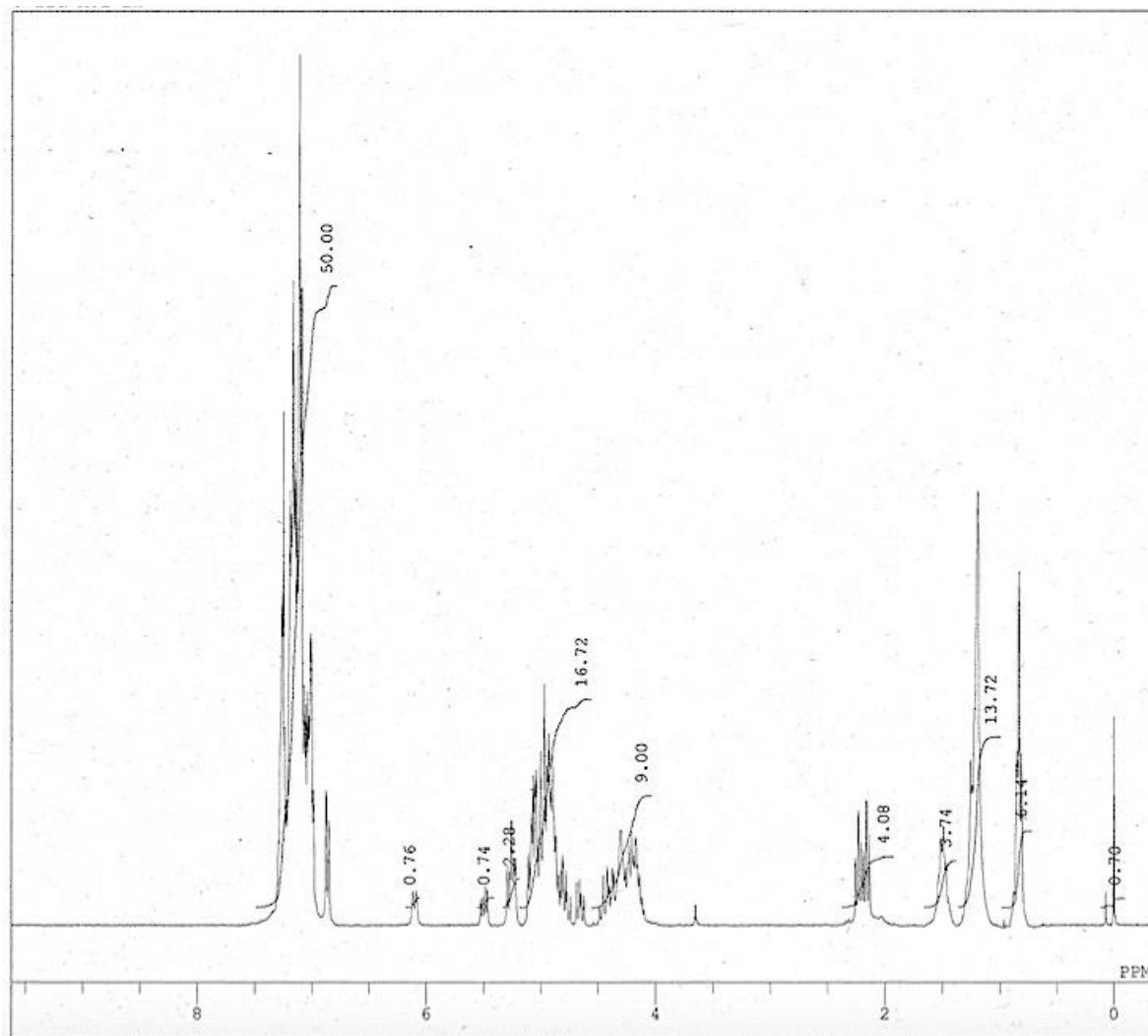
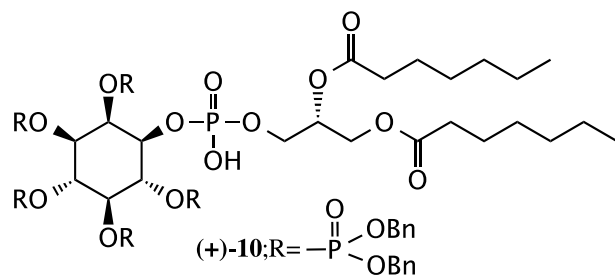


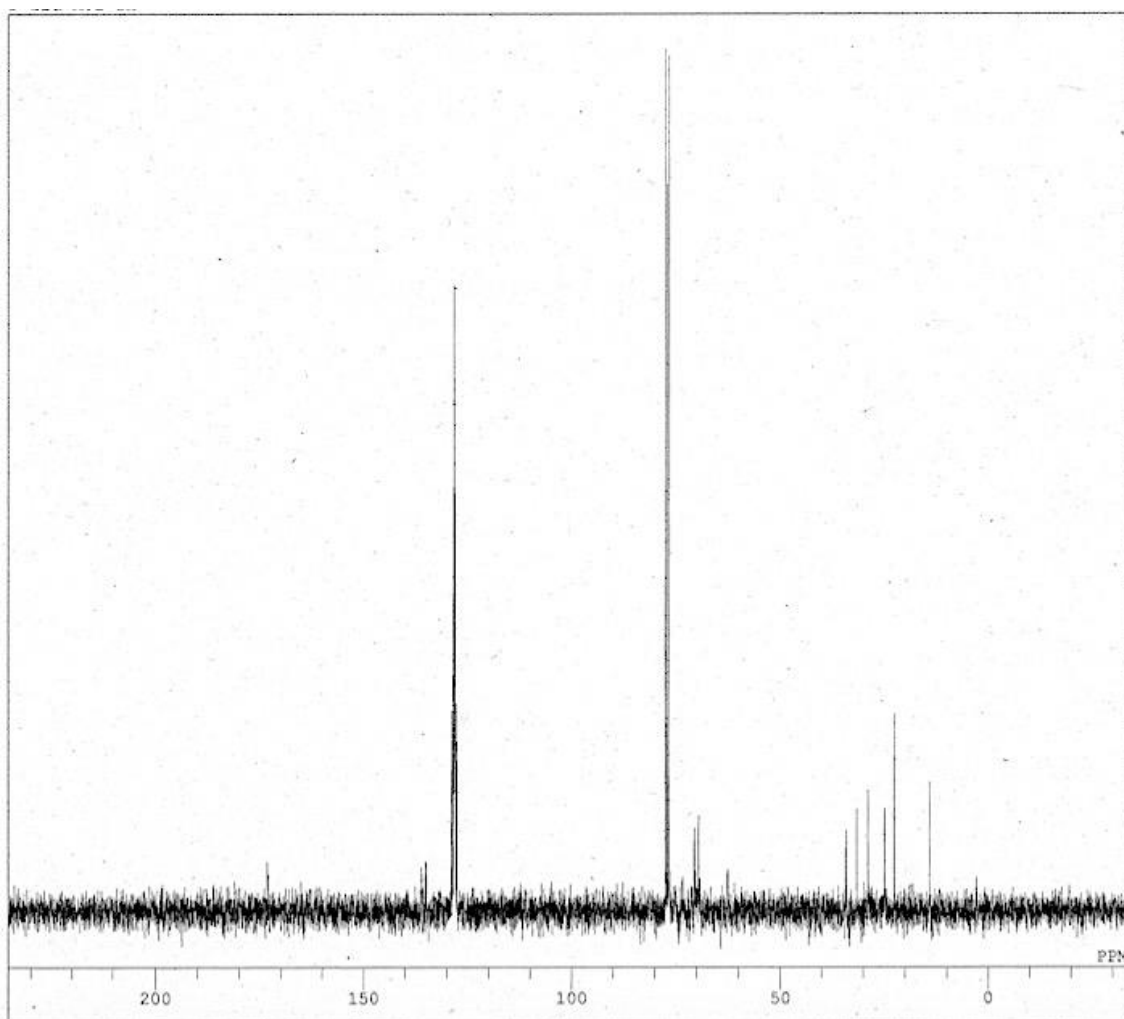
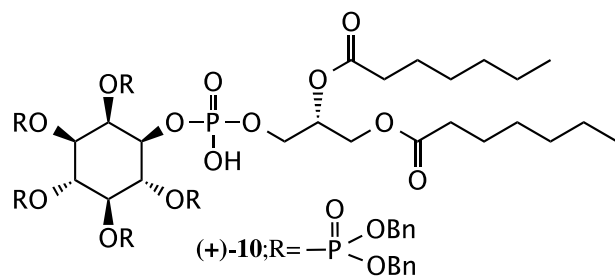


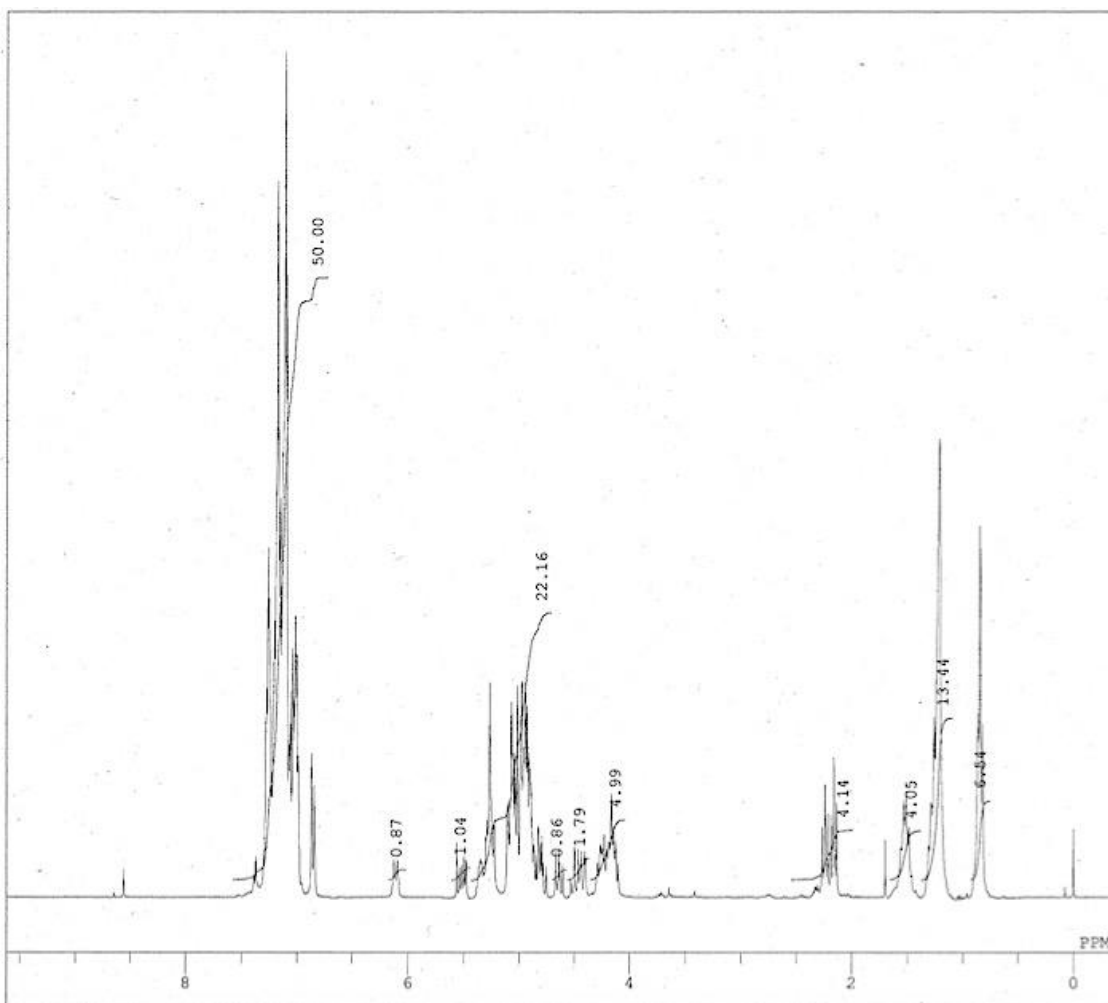
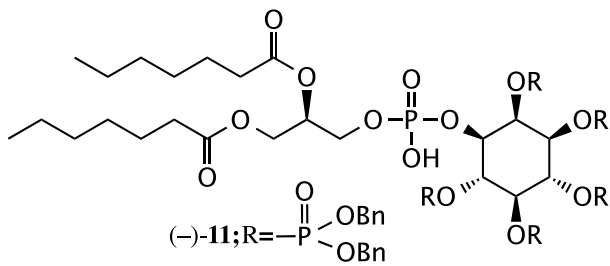


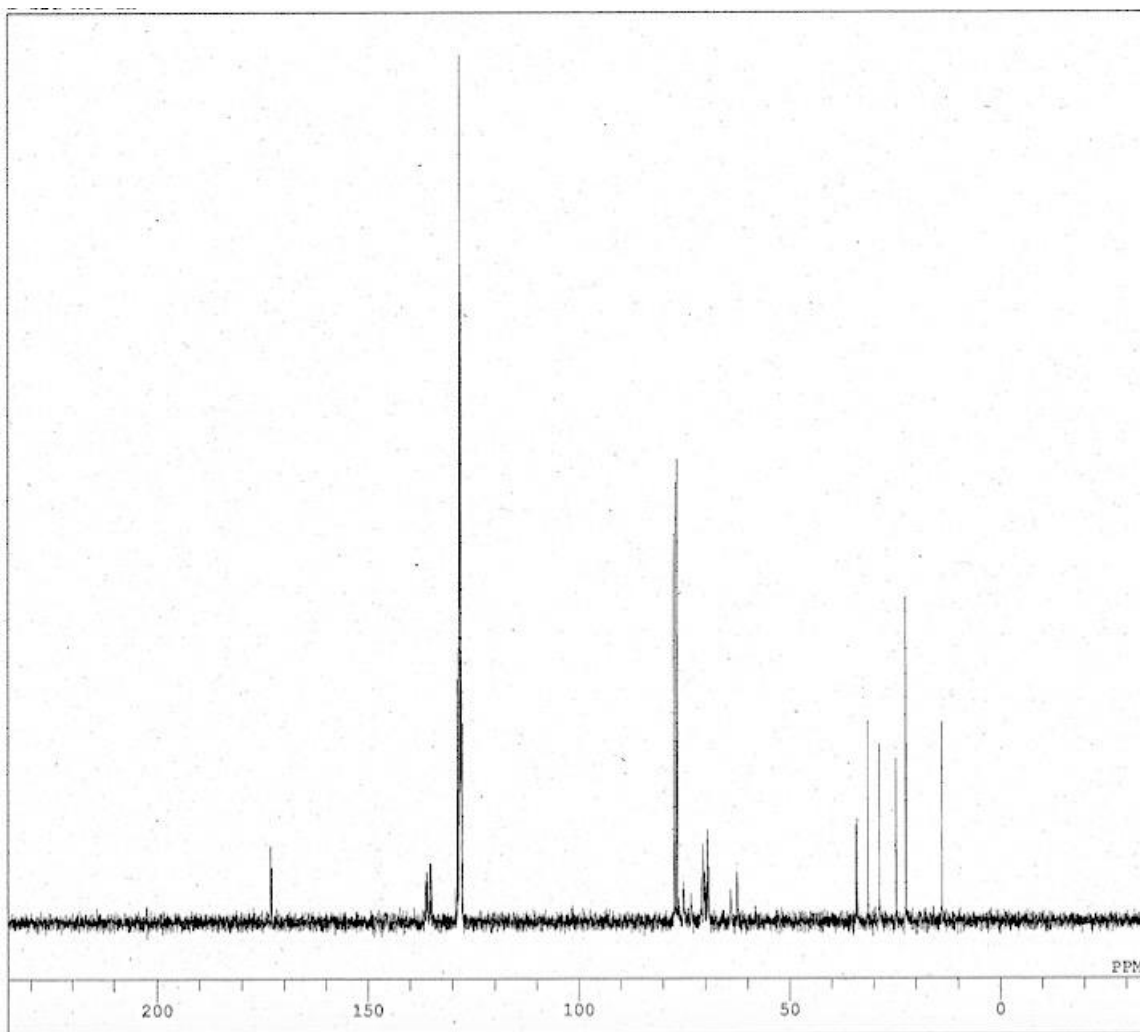
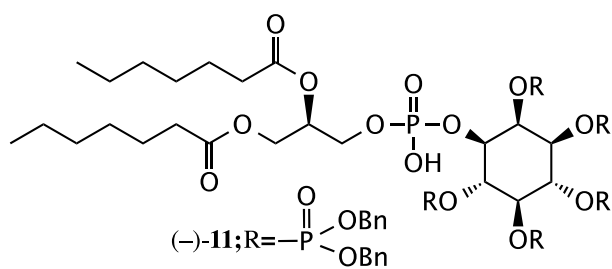


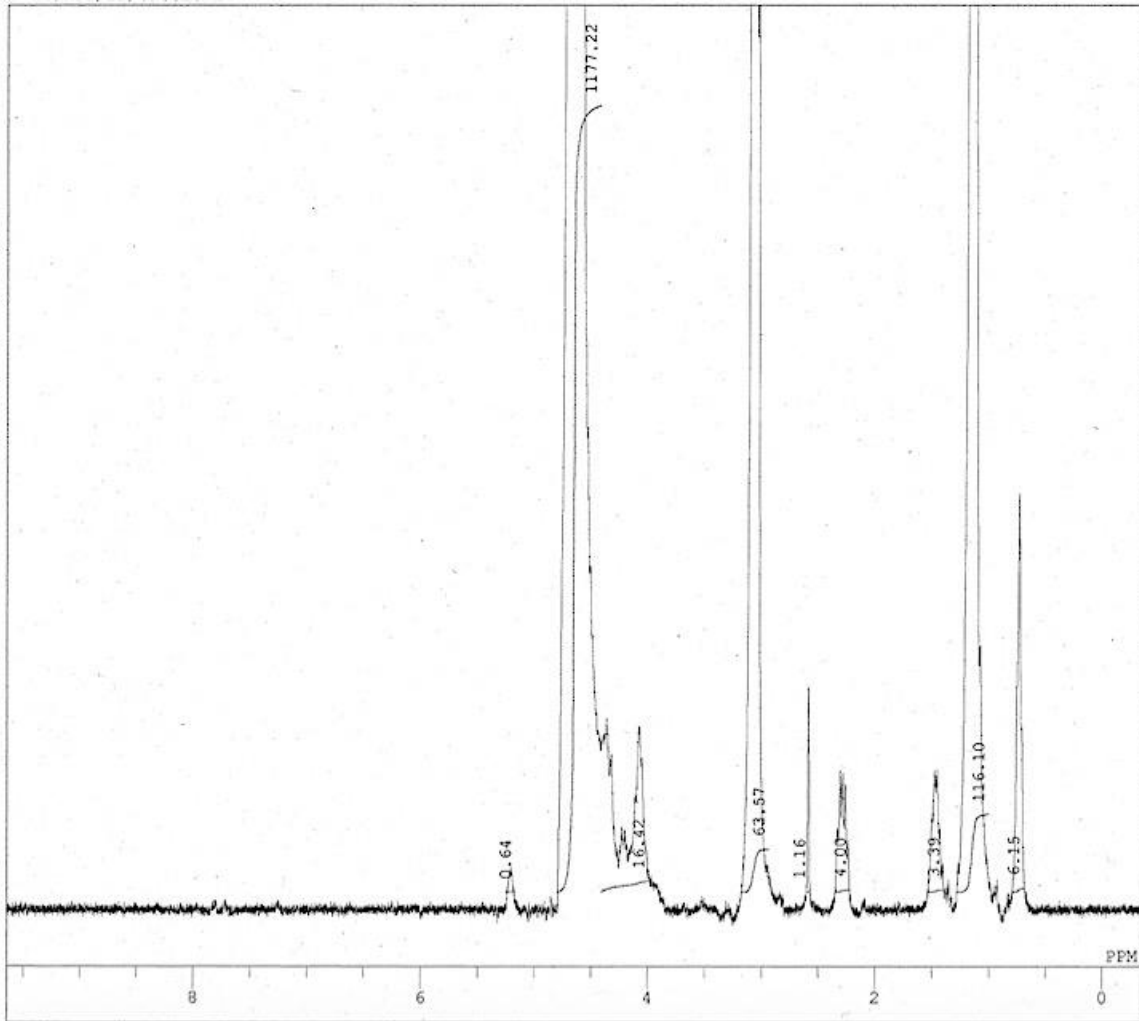
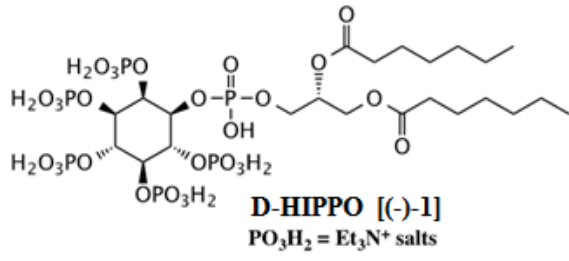


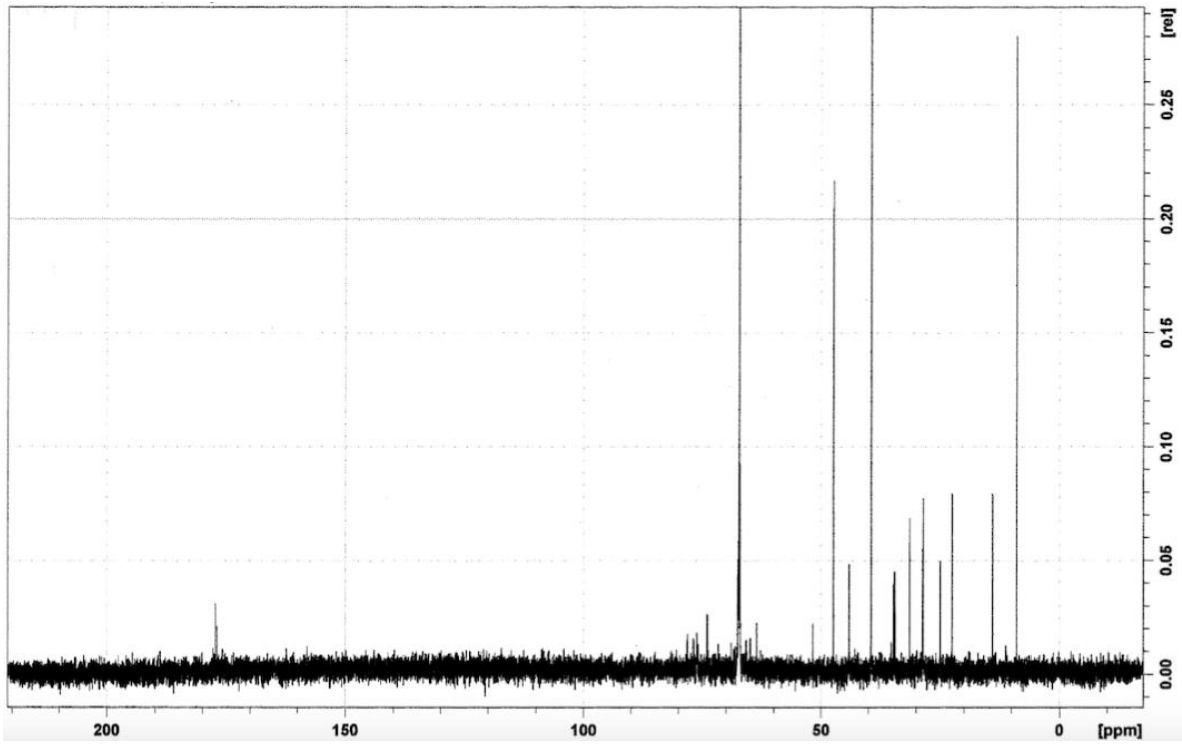
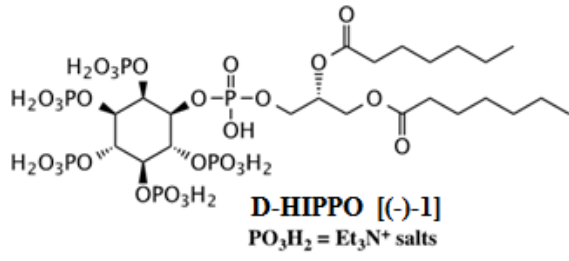


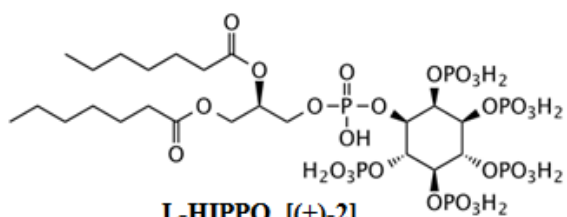




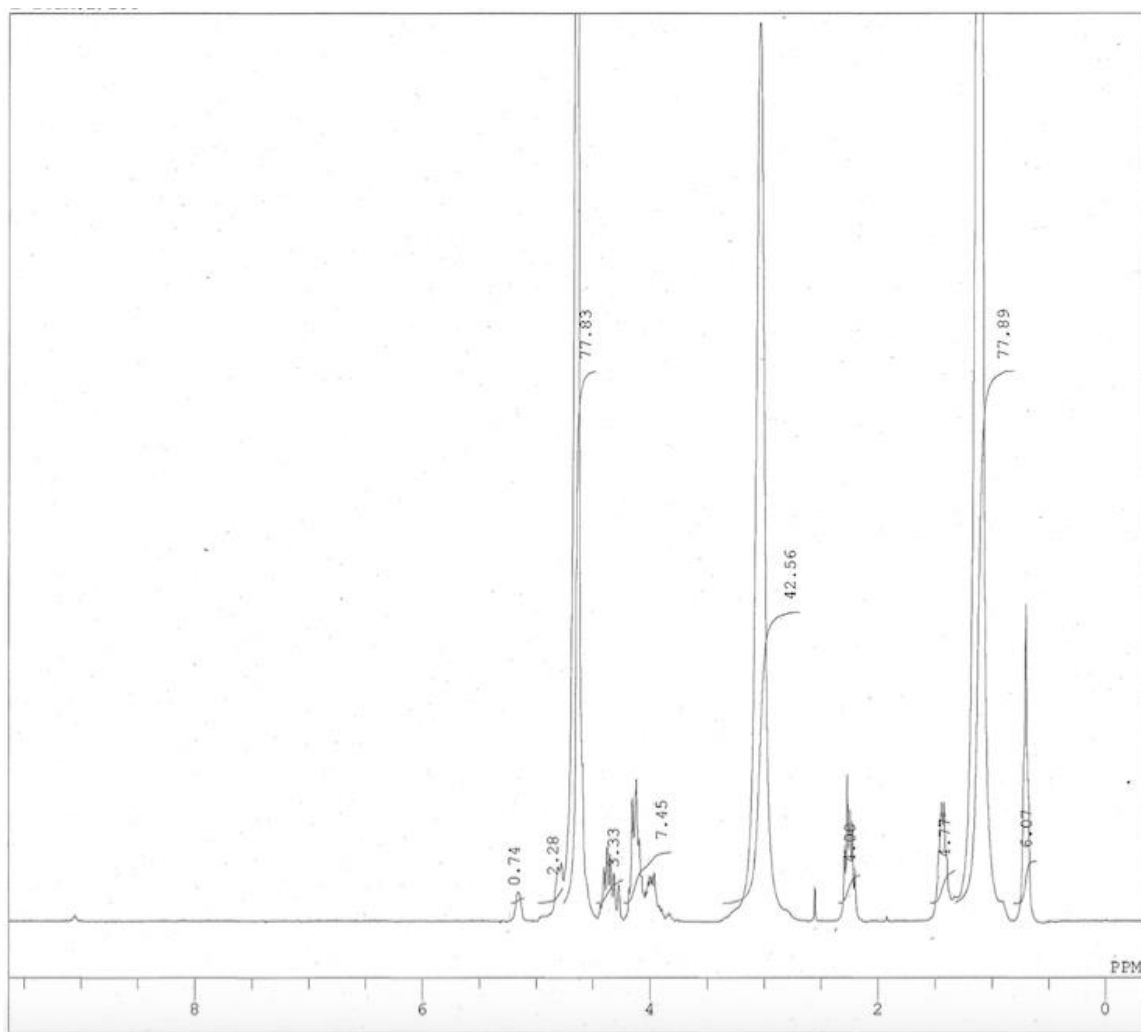


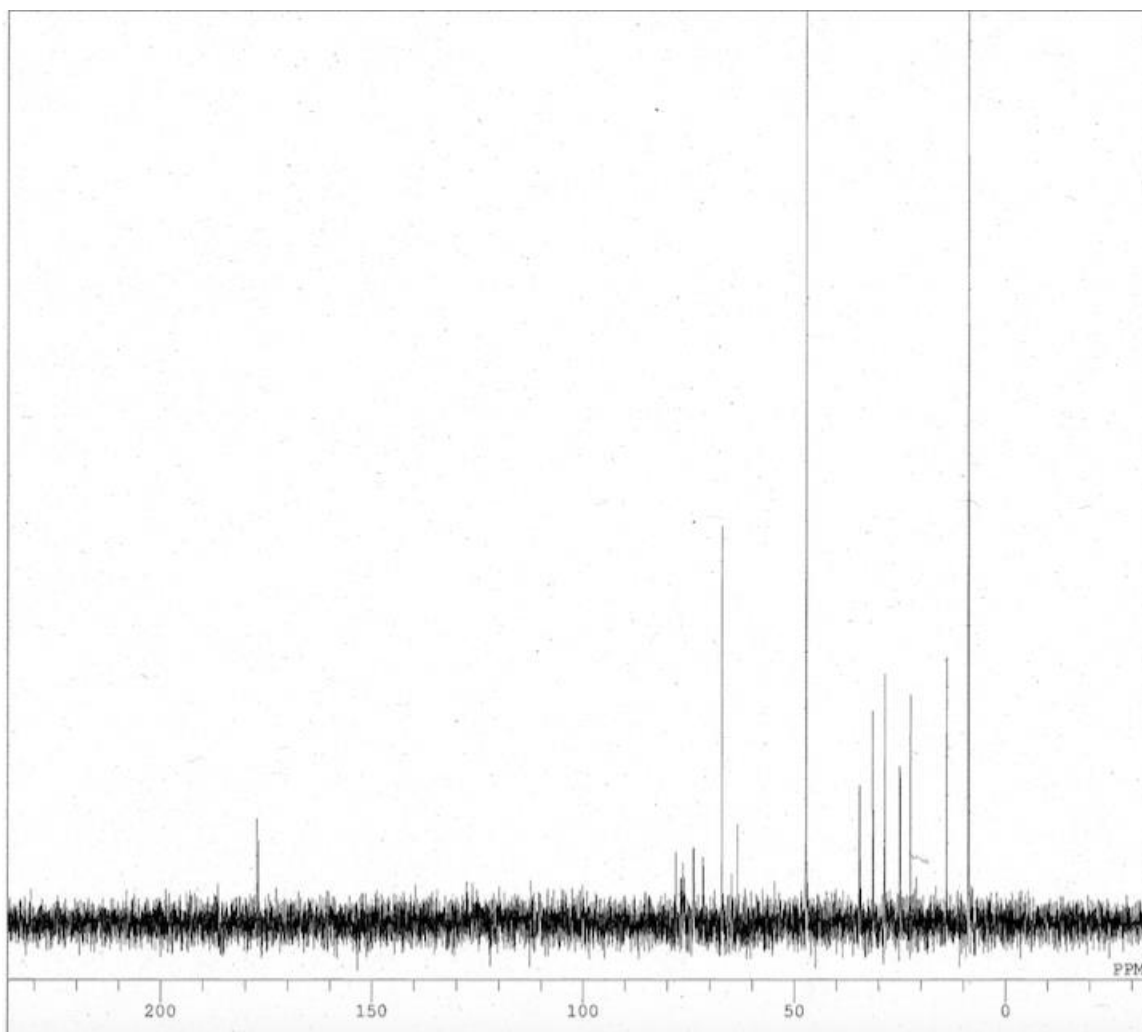
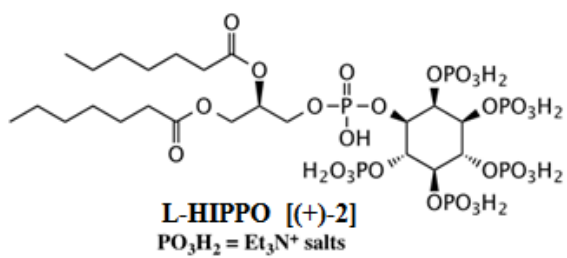






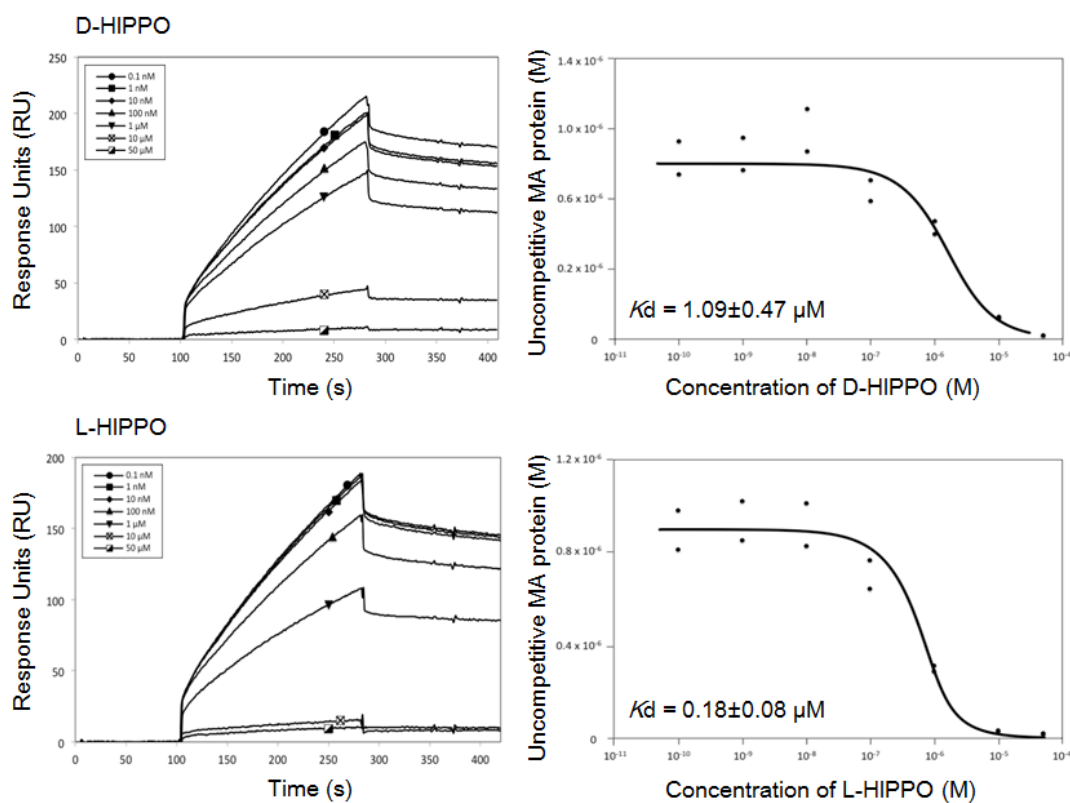
L-HIPPO [(+)-2]
 $\text{PO}_3\text{H}_2 = \text{Et}_3\text{N}^+$ salts





Supplementary Information B:
Binding affinity of D-HIPPO and L-HIPPO to HIV-1 MA domain

Competition assay using surface plasmon resonance (SPR) was performed and dissociation constants (K_d) for MA-binding of the compounds were calculated as previously described⁶.

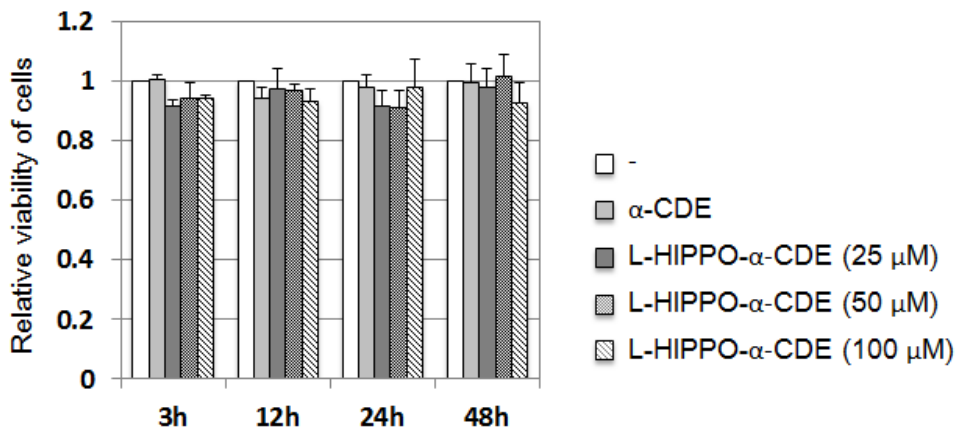


6. Tateishi, H. *et al.* Design and synthesis of lipid-coupled inositol 1,2,3,4,5,6-hexakisphosphate derivatives exhibiting high-affinity binding for the HIV-1 MA domain. *Organic & biomolecular chemistry* **12**, 5006-5022 (2014).

Supplementary Information C:
Death analysis of HeLa cells introduced with L-HIPPO- α -CDE

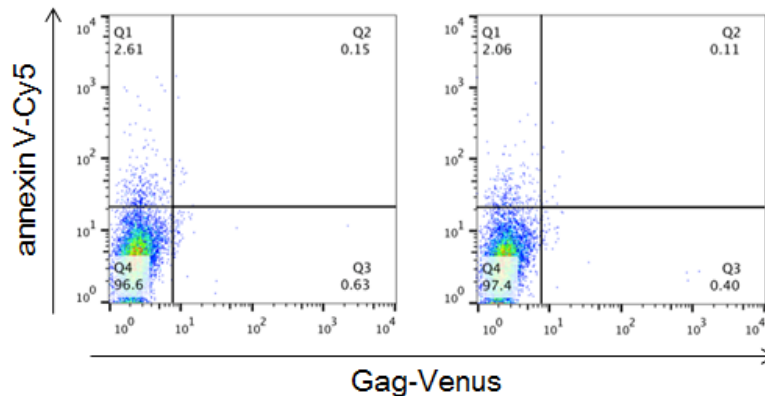
(a) Cytotoxicity of complex prepared from L-HIPPO (25, 50 or 100 μ M) and α -CDE (25 μ M) (L-HIPPO- α -CDE) without HIV-1 protein. HeLa cells were treated with the complex, MTT assay was performed at the indicated incubation time. Data from three different experiments are shown as means \pm standard deviations. P values were determined using Student's t test. (b) Apoptotic effect of L-HIPPO- α -CDE without HIV-1 protein. HeLa cells were transfected with pUC19, and after 10 h, L-HIPPO- α -CDE [prepared from L-HIPPO (25 or 50 μ M) and α -CDE (25 μ M)] was added. After a further 12 h incubation, FACS analysis using annexin V-Cy5 was performed.

(a)



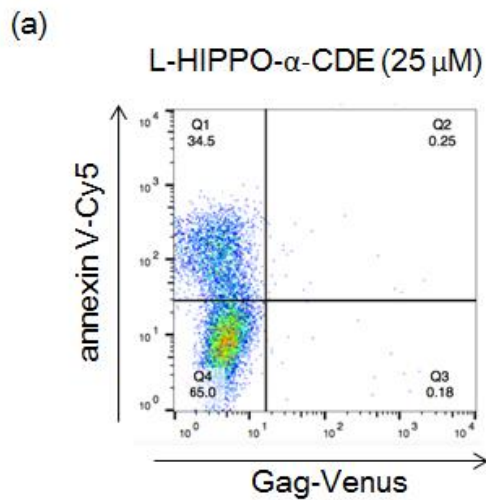
(b) 12h incubation

(1) L-HIPPO- α -CDE (25 μ M) (2) L-HIPPO- α -CDE (50 μ M)

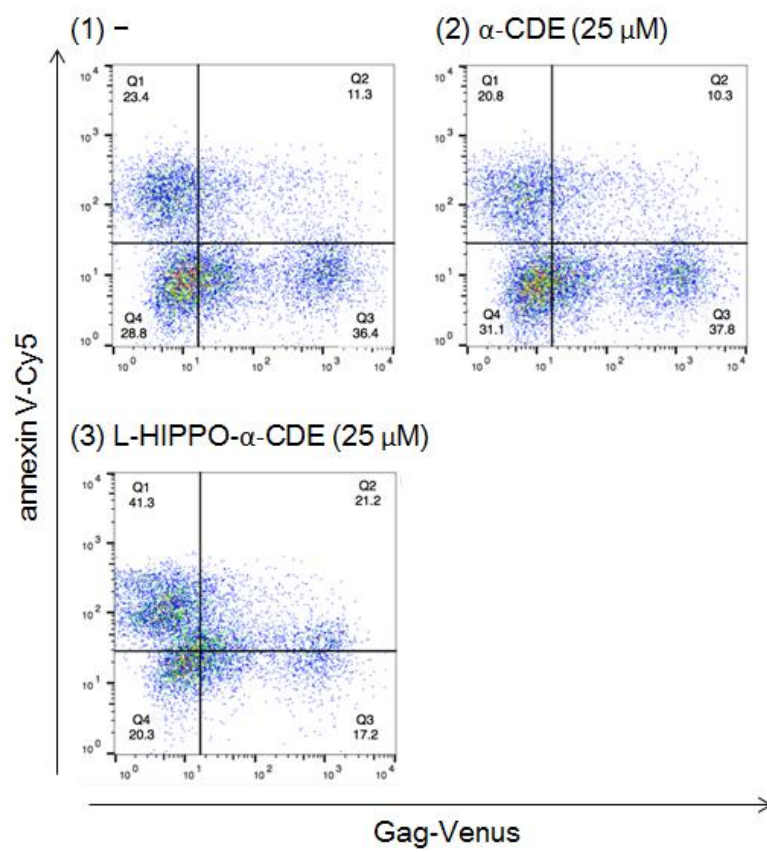


Supplementary Information D:
Bystander effect of cells introduced with L-HIPPO- α -CDE
in the presence of HIV-1 protein

(a) Apoptotic effect of L-HIPPO- α -CDE without HIV-1 protein. HeLa cells were transfected with pUC19 by Lipofectamine 2000 (Life Technologies), and after 10 h, a complex prepared from L-HIPPO (25 μ M) and α -CDE (25 μ M) (L-HIPPO- α -CDE) was added. After a further 12 h incubation, FACS analysis using annexin V-Cy5 was performed. (b) Apoptotic effect of L-HIPPO- α -CDE with HIV-1 protein. HeLa cells were transfected with pNL4-3/GagVenus by Lipofectamine 2000, and after 10 h, none, α -CDE or L-HIPPO- α -CDE was added. After a further 12 h incubation, FACS analysis using annexin V-Cy5 was performed.



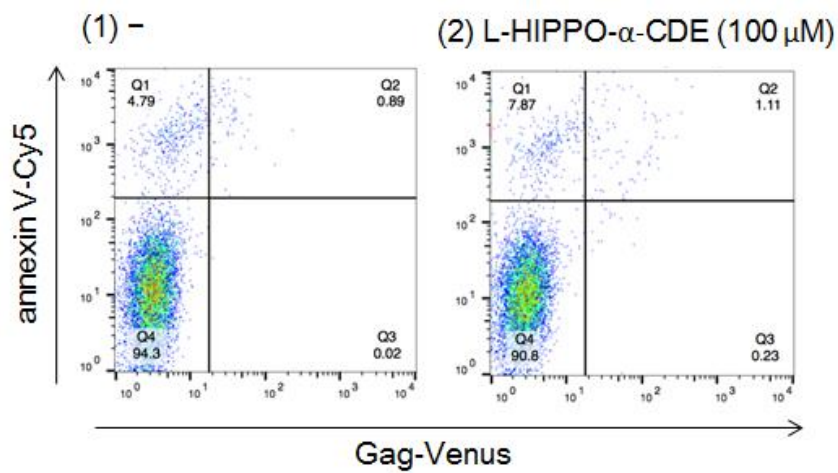
(b)



Supplementary Information E:

Death analysis of Jurkat cells introduced with L-HIPPO- α -CDE

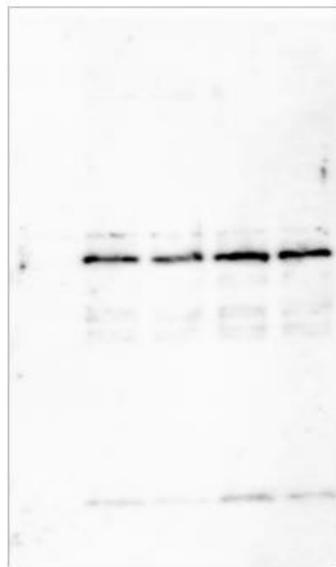
Apoptotic effect of a complex L-HIPPO- α -CDE without HIV-1 protein. To Jurkat cells, a complex prepared from L-HIPPO (100 μ M) and α -CDE (25 μ M) (L-HIPPO- α -CDE) was added. After a further 12 h incubation, FACS analysis using annexin V-Cy5 was performed.



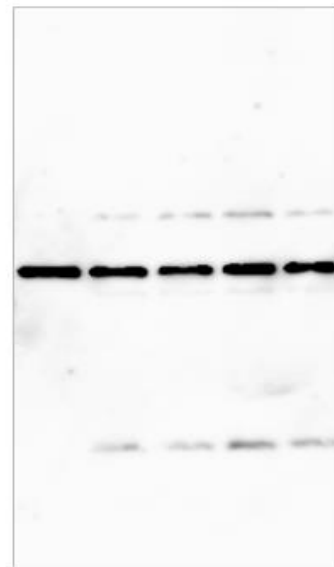
**Supplementary Information F:
Wider images of immunoblotting**

Full images of “cell” and wider image of “virion” in Figure 2c are shown. In blotting of virion samples, antibody strongly reacted with fetal bovin serum in medium in upper part. Thus only lower part is shown.

cell

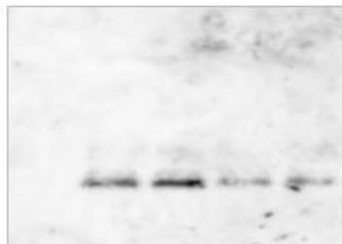


Pr55^{Gag} + p24



β-actin

virion



p24