

Supplementary Information

Synthetic channel that efficiently inserts into mammalian cell membranes and destroys cancer cells

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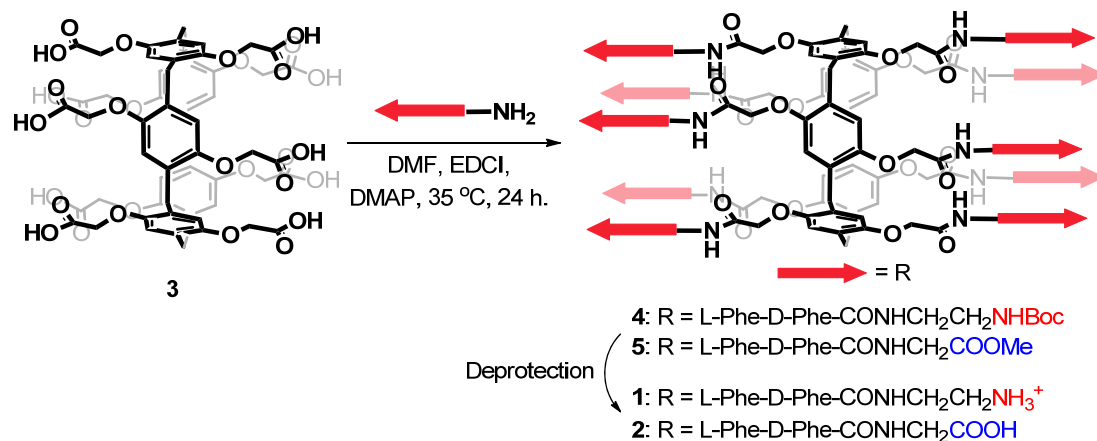
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1. General:

^1H and ^{13}C NMR spectra were recorded at 400 MHz with Mercury 400 at 298 K. Chemical shifts were referenced to solvent residue. Mass spectra were recorded with Bruker MicroTOF II spectrometer by using positive or negative mode. The peptides were synthesized according to the classical liquid phase synthesis method by employing EDCI as condensation reagent. diphytanoylphosphatidylcholine (diPhyPC), 1,2-dipalmitoyl-sn-glycero-sn-glycero-3-phosphatidyl-glycerol (DPPG), and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) were obtained from Avanti Polar Lipids. The conductance measurement on planar lipid bilayer was performed on Warner Planar Lipid Bilayer Workstation. The confocal laser scanning microscopy image was recorded on Leica TCS SP8 STED 3X instrument.

2. Synthetic procedures and characterization data:



Scheme S1. Synthetic protocols for **1** and **2**.

General procedures for compound **4** and **5**:

To a solution of **3**¹ (0.08 mmol) in anhydrous DMF (5 mL) was added amino terminated peptide (1.2 mmol), DMAP (3.2 mmol), and EDCI (2.0 mmol). The mixture was stirred at 35 °C for 24 h and then poured into aqueous HCl solution (2%, 100 mL). The formed precipitate was collected by filtration and washed with water to give the crude product. This residue was subject to purification by column chromatography (CH_2Cl_2 : MeOH = 10:1) to yield the required product as white solid.

Compound 4. Yield: 20%. ^1H NMR (DMSO- d_6) δ 8.62 (s, 10 H), 8.13 (s, 10 H), 7.56 (s, 10 H), 7.26 – 7.15 (m, 50 H), 6.93 (s, 30 H), 6.68 (s, 40 H), 4.69 (s, 10 H), 4.53 (s, 10 H), 4.29 (s, 10 H), 4.21 (s, 10 H), 3.46 (s, 10 H), 3.19 (s, 10 H), 3.02 - 2.94 (m, 40 H), 2.75 (s, 20 H), 2.58 (s, 10 H), 1.34 (s, 90 H). ^{13}C NMR (DMSO- d_6) δ 171.6, 170.7,

168.2, 156.0, 148.9, 138.2, 136.9, 129.7, 129.5, 128.5, 128.2, 127.9, 126.8, 126.6, 114.5, 78.1, 67.5, 54.7, 53.4, 38.5, 38.3, 31.4, 28.6. HRMS: $C_{305}H_{370}N_{40}O_{60}Na_2$ $[M+2Na]^{2+}$: 2800.8508, found 2800.8504.

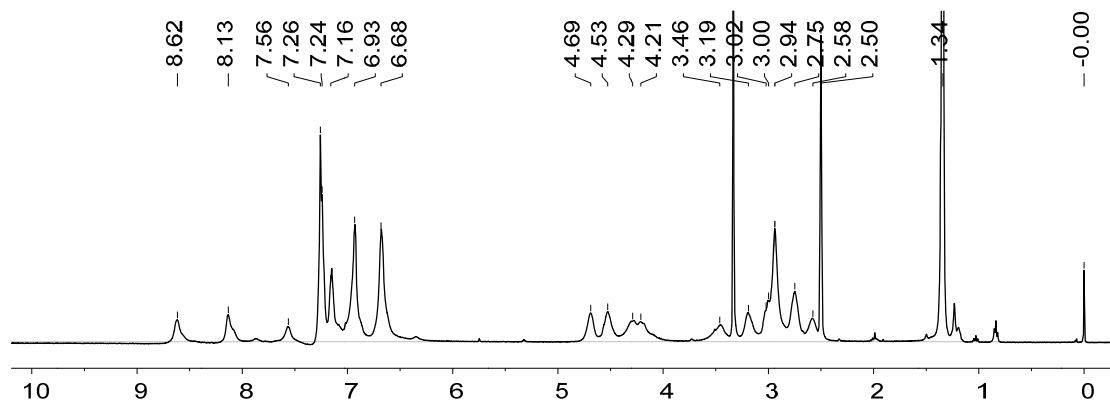


Figure S1. 1H NMR spectrum of **4** in $DMSO-d_6$.

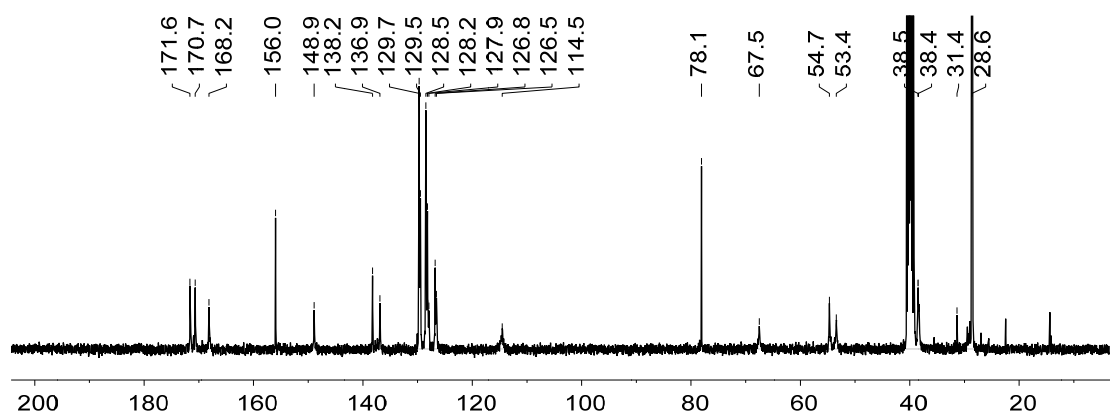


Figure S2. ^{13}C NMR spectrum of **4** in $DMSO-d_6$.

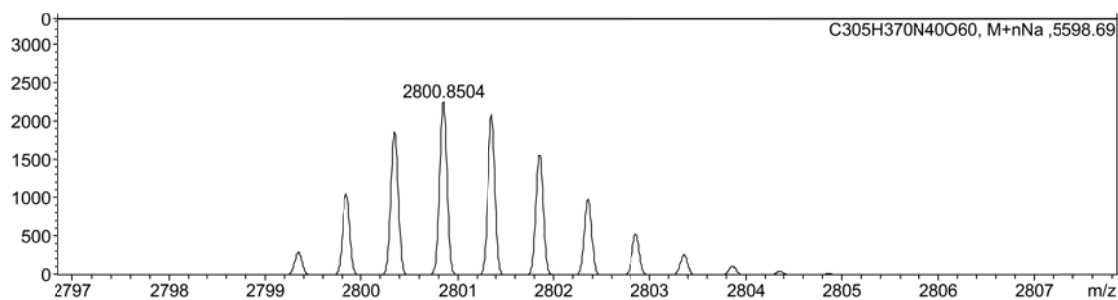


Figure S3. HR-MS of **4**.

Compound 5. Yield: 18%. 1H NMR ($DMSO-d_6$) δ 8.71 (s, 10 H), 8.57 (s, 10 H), 7.52 (s, 10 H), 7.31 – 6.90 (m, 80 H), 6.61 (s, 20 H), 4.64 (s, 20 H), 4.26 (s, 10 H), 4.18 (s, 10 H), 3.90 – 3.81 (m, 20 H), 3.55 (s, 30 H), 3.41 (s, 10 H), 3.06 (s, 10 H), 2.73 – 2.71 (m, 20 H). ^{13}C NMR ($DMSO-d_6$) δ 172.3, 170.8, 170.4, 168.3, 148.9, 138.3, 137.8,

136.8, 130.1, 129.7, 129.6, 129.4, 128.5, 128.2, 126.8, 126.6, 114.6, 67.6, 54.4, 53.4, 52.1, 41.0, 38.1, 29.0, 27.0. HRMS: $C_{265}H_{282}N_{30}O_{60}$ $[M+2H]^{2+}$: 2422.9997, found 2422.9996.

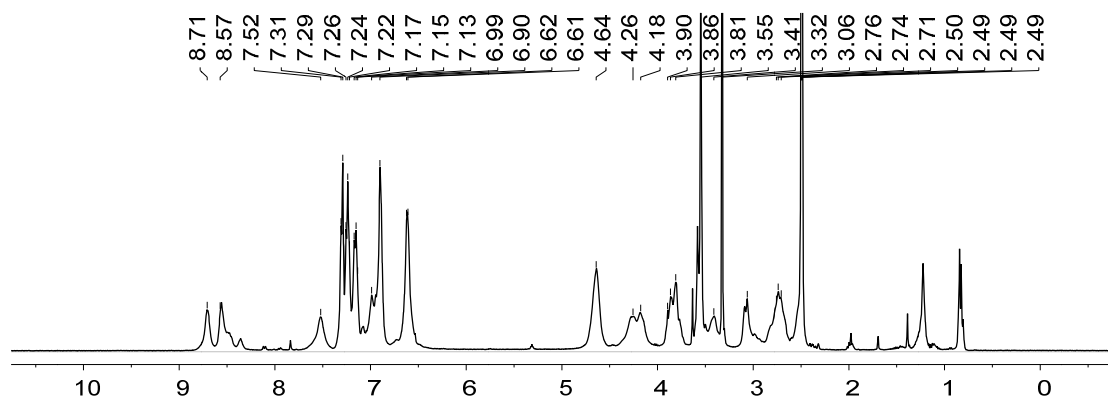


Figure S4. 1H NMR spectrum of **5** in $DMSO-d_6$.

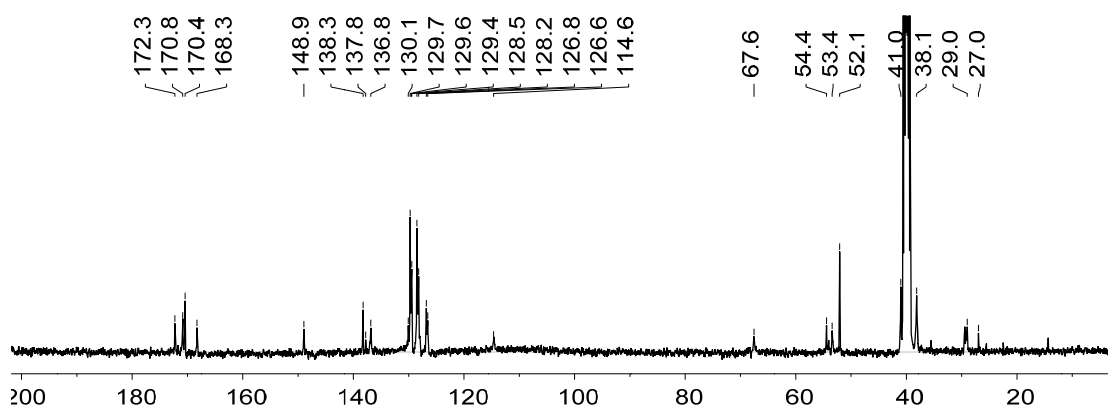


Figure S5. ^{13}C NMR spectrum of **5** in $DMSO-d_6$.

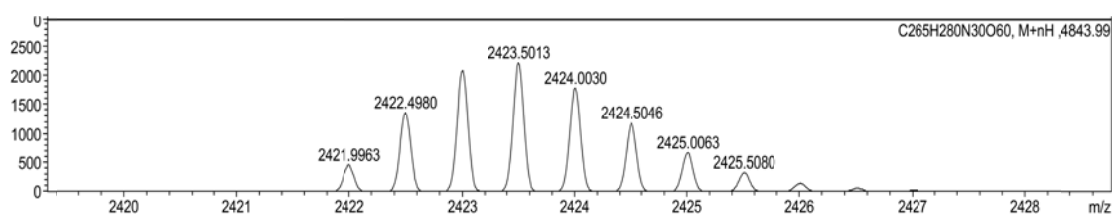


Figure S6. HR-MS of **5**.

Synthetic procedure for compound **1**:

To a solution of **4** (0.1 g, 0.016 mmol) in CH_2Cl_2 (8 mL) was added TFA (4 mL). The mixture was stirred at 25 °C for 5 h. After removing of the solvent, the crude product was washed with diethyl ether to yield **1** as white solid.

Yield: 92%. 1H NMR ($DMSO-d_6$) δ 8.66 (s, 10 H), 8.38 (s, 10 H), 7.88 (s, 20 H), 7.56 (s, 10 H), 7.25 (d, $J = 6.4$ Hz, 30 H), 7.17 (s, 10 H), 6.93 (s, 30 H), 6.67 (s, 20 H),

4.68 (s, 10 H), 4.51 (s, 10 H), 4.34 (s, 10 H), 4.20 (s, 10 H), 3.19 (s, 20 H), 3.07 (s, 10 H), 2.80 (s, 40 H), 2.58 (s, 10 H). ^{13}C NMR (DMSO- d_6) δ 172.1, 170.7, 168.2, 159.0, 158.7, 158.3, 158.0, 149.1, 138.1, 136.8, 130.1, 129.7, 129.5, 128.5, 128.2, 126.8, 126.6, 122.0, 119.1, 116.1, 114.6, 113.1, 67.7, 54.7, 53.5, 38.7, 38.2, 36.9, 29.0, 27.0, 25.5. HRMS: $\text{C}_{255}\text{H}_{293}\text{N}_{40}\text{O}_{40}$ $[\text{M}+3\text{H}]^{3+}$: 1519.0724, found 1519.0792.

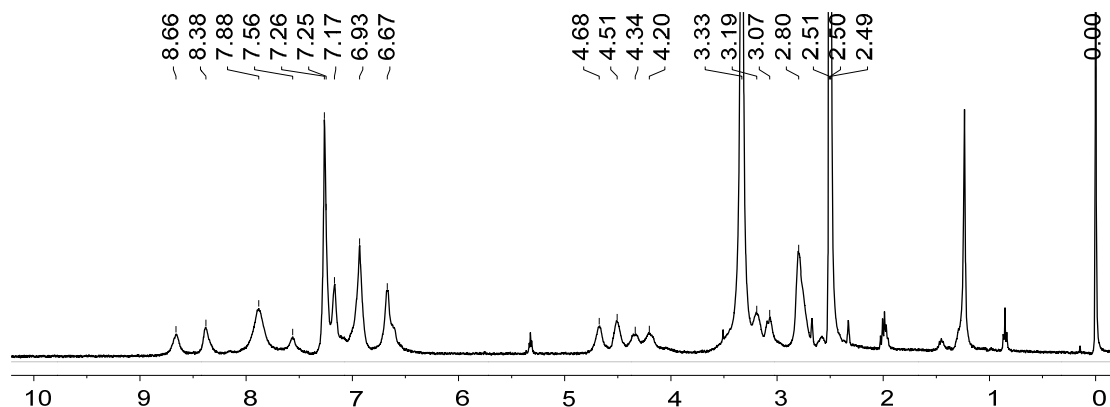


Figure S7. ^1H NMR spectrum of **1** in DMSO- d_6 .

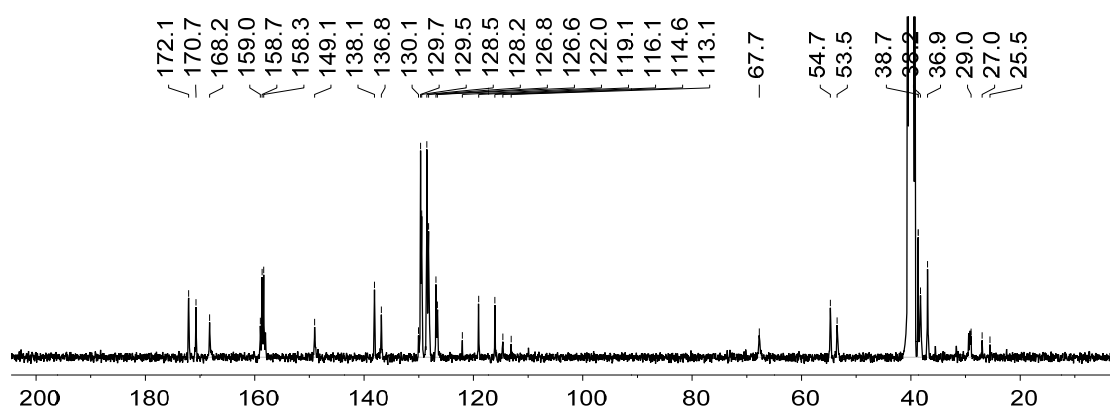


Figure S8. ^{13}C NMR spectrum of **1** in DMSO- d_6 .

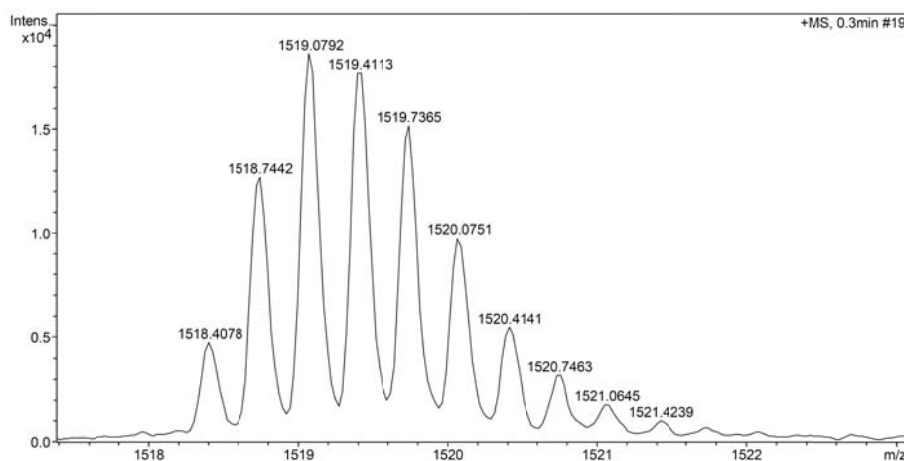


Figure S9. HR-MS of **1**.

Synthetic procedure for compound **2**:

To a solution of **5** (0.1 g, 0.2 mmol) in methanol (20 mL) was added H₂O (1 mL) and NaOH (0.1 g, 5 mmol). The mixture was stirred at 25 °C for 12 h. After removing of the solvent, the crude product was acidified with aqueous HCl solution (2%, 50 mL) and then filtered to yield **2** as white solid.

Yield: 90%. ¹H NMR (DMSO-*d*₆) δ 12.69 (s, 10 H), 8.70 (s, 10 H), 8.47 (s, 10 H), 7.50 (s, 10 H), 7.33-6.61 (m, 120 H), 4.66 (s, 20 H), 4.23 (s, 20 H), 3.82-3.68 (m, 20 H), 3.10 (d, *J* = 12.0 Hz, 10 H), 2.76 - 2.67 (m, 20 H). ¹³C NMR (DMSO-*d*₆) δ 172.1, 171.5, 170.8, 168.2, 149.0, 138.3, 136.9, 129.8, 129.6, 129.5, 128.5, 128.4, 128.2, 126.8, 126.6, 114.6, 67.7, 54.5, 53.4, 41.2, 38.3, 31.7, 29.5, 29.0, 27.0. HRMS: C₂₅₅H₂₆₂N₃₀O₆₀ [M+2H]²⁺: 2352.9214, found 2352.9212.

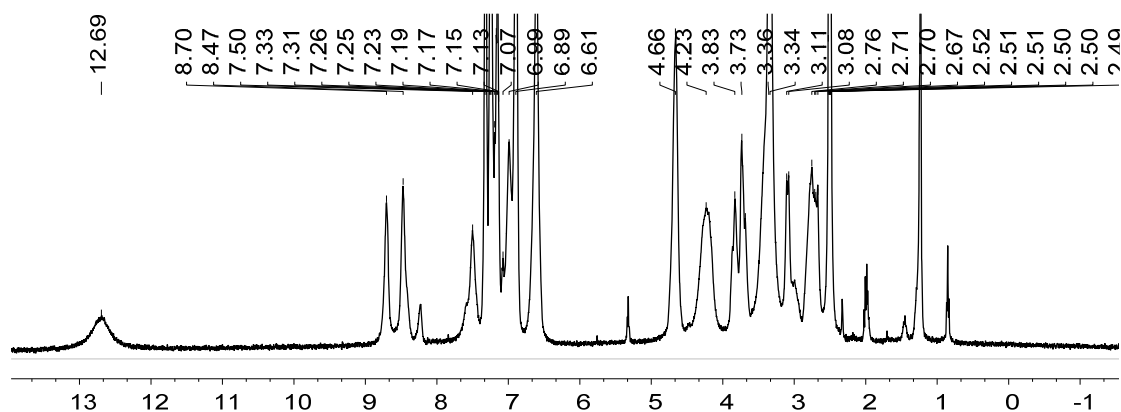


Figure S10. ¹H NMR spectrum of **2** in DMSO-*d*₆.

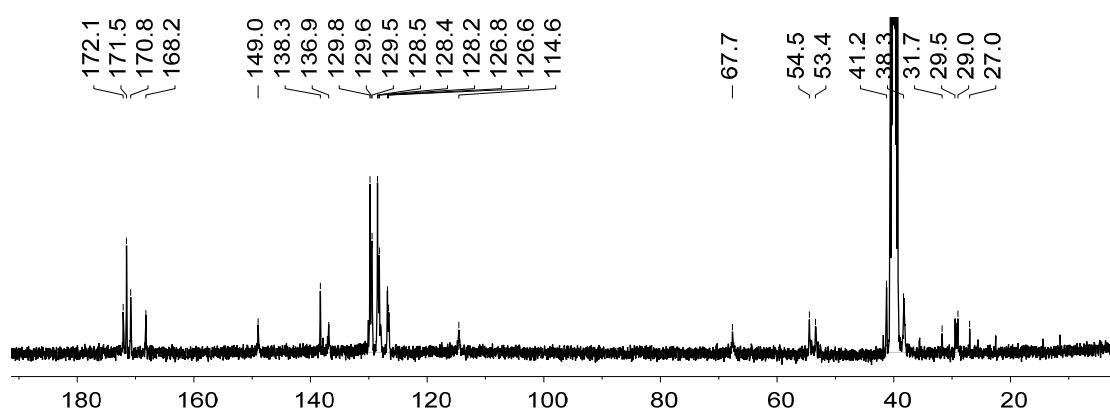


Figure S11. ¹³C NMR spectrum of **2** in DMSO-*d*₆.

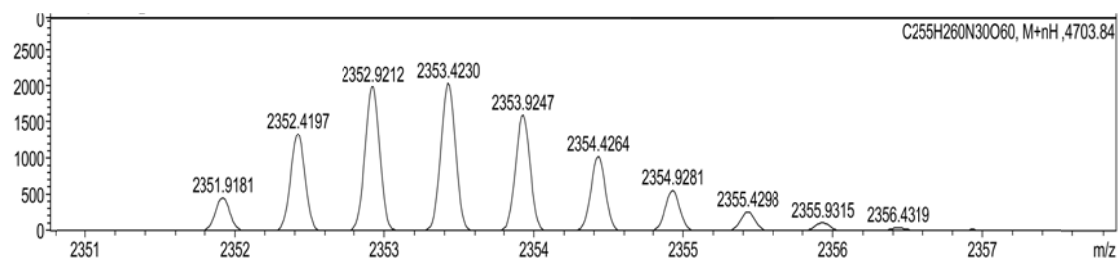


Figure S12. HR-MS of **2**.

3. References:

- [1] (a) X.-B. Hu, L. Chen, W. Si, Y. Yu, J.-L. Hou, *Chem. Commun.* **2011**, *47*, 4694-4696. (b) L. Chen, W. Si, L. Zhang, G. Tang, Z.-T. Li, J.-L. Hou, *J. Am. Chem. Soc.* **2013**, *135*, 2152-2155