

General procedure, illustrated with compound **P9**.

In a flame-dried 25ml round-bottom flask equipped with a septum and stirbar, anhydrous K_2CO_3 (1.22g, 8.9mmol, 1.5 eqv.) and hex-5-yn-1-amine (579mg, 5.9mmol, 1.0 eqv.) was slurried in dry THF and cooled to 0°C. *Per*-fluoropentanoyl chloride (2.5g, 8.9mmol, 1.5 eqv.) was added drop-wise to the rapidly stirred solution. The reaction was allowed to warm to room temperature. After 2 hours, the reaction was quenched by careful addition of MeOH before filtering. The solvent was carefully removed under reduced pressure (the product is slightly volatile). Chromatography on silica gel with 1:5 EtOAc:Hex as eluent gives 273mg product (40%) as a clear, colorless oil.

P3:

MS - m/z calculated for $C_{13}H_{14}O_2$ = 202.1; found 202.0; 1H - (300 MHz; $CDCl_3$): δ 8.01 (s, 2H), 7.42 (s, 4H), 4.34 (s, 2H), 2.27 (d, J = 2.7, 2H), 1.95 (s, 1H), 1.92-1.84 (m, 2H), 1.71-1.66 (m, 2H); ^{13}C -NMR (75MHz; $CDCl_3$): δ 166.6, 132.9, 130.6, 129.5, 128.3, 83.9, 64.4, 27.8, 25.1, 18.1.

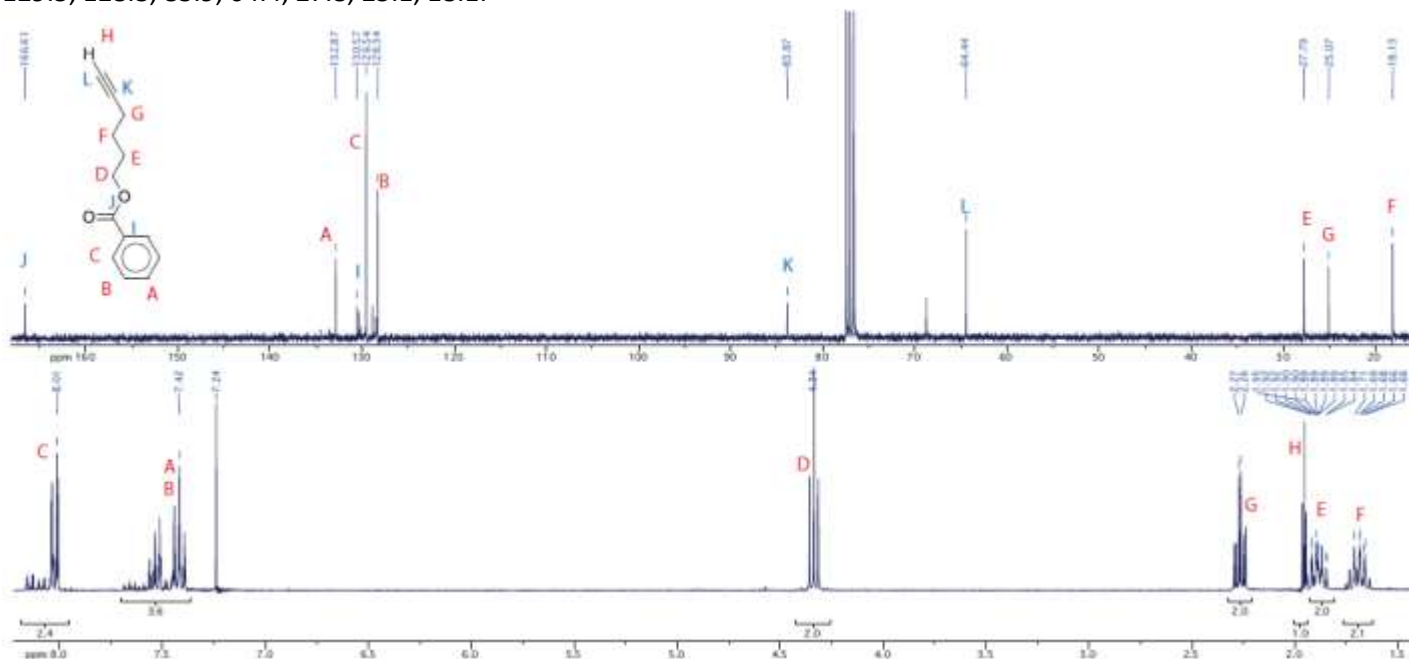


Fig. S1: 1H -NMR and ^{13}C - spectra of **P3**

P4

$^1\text{H-NMR}$ (300 MHz; CDCl_3): δ 4.03 (t, $J = 6.4$, 2H), 2.21 (t, $J = 7.4$, 3H), 2.17 (td, $J = 7.2, 2.4$, 3H), 1.89 (t, $J = 2.7$, 1H), 1.72-1.51 (m, 7H), 0.88 (t, $J = 7.4$, 3H); $^{13}\text{C-NMR}$ (126MHz; CDCl_3): δ 173.5, 83.8, 69.1, 63.8, 36.3, 27.5, 25.3, 18.8, 17.4, 13.8.

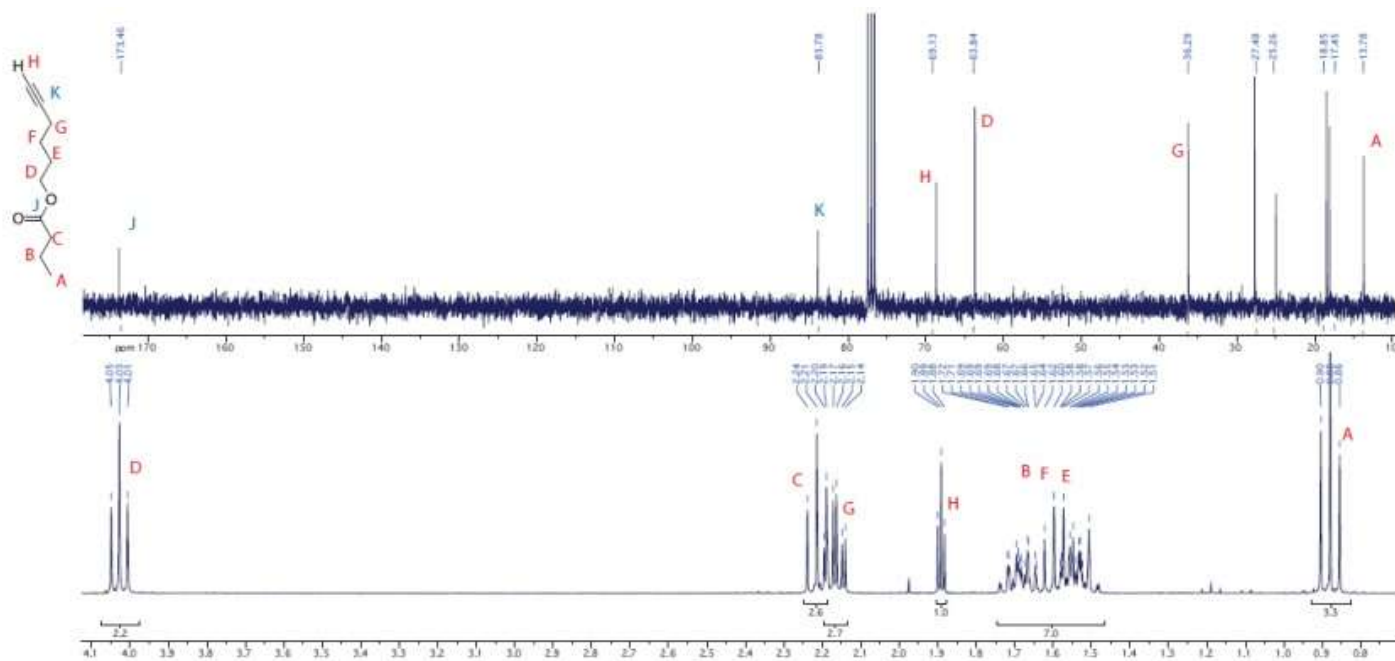


Fig. S2: $^1\text{H-NMR}$ and $^{13}\text{C-}$ spectra of **P4**

P5

MS - m/z calculated for $C_{10}H_{17}NO$ = 167.1; found 168.0; 1H -NMR (300 MHz; $CDCl_3$): δ 5.52 (s, 1H), 3.25 (q, J = 6.4, 2H), 2.19 (td, J = 6.7, 2.7, 2H), 2.11 (t, J = 7.5, 2H), 1.93 (t, J = 2.7, 1H), 1.67-1.52 (m, 6H), 0.91 (t, J = 7.4, 3H); ^{13}C -NMR (75MHz; $CDCl_3$): δ 173.4, 84.0, 68.7, 38.86, 38.78, 28.7, 25.7, 19.2, 18.1, 13.8

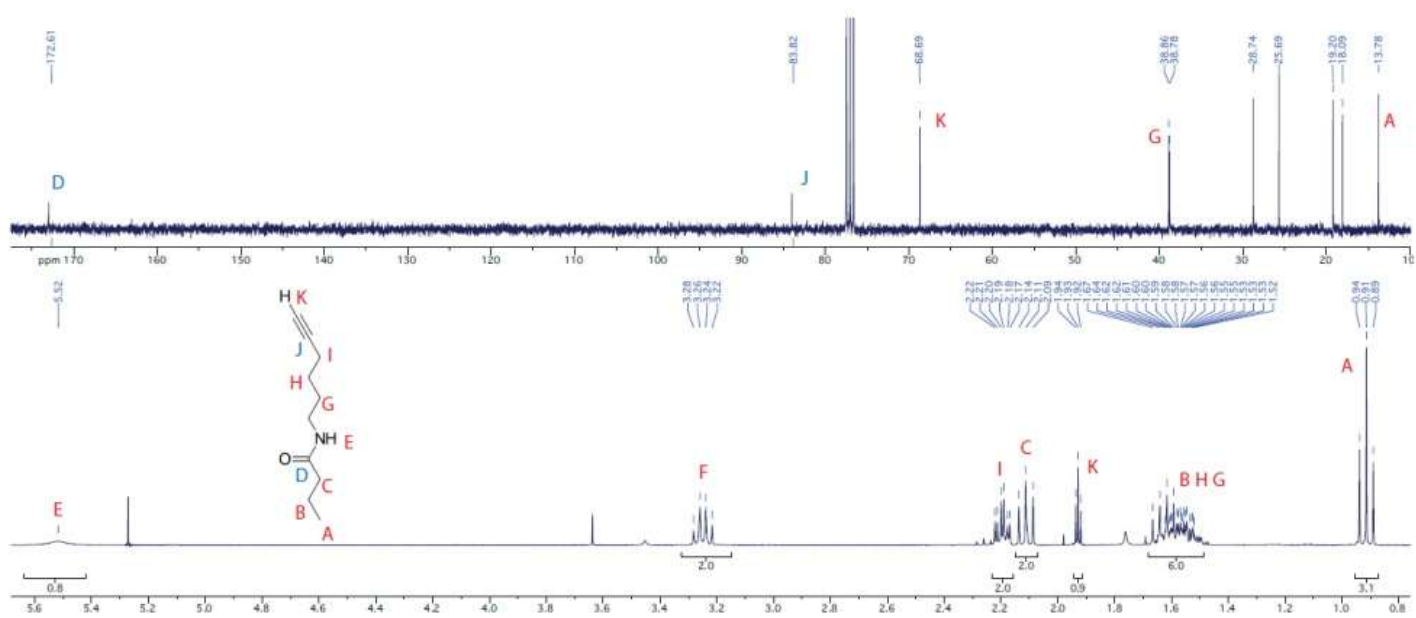


Fig. S3: 1H -NMR and ^{13}C - spectra of **P5**

P6

MS - m/z calculated for $C_{10}H_9F_7O_2 = 294.0$; found 293.8. 1H -NMR (300 MHz; $CDCl_3$): δ 4.40 (t, $J = 6.4$, 2H), 2.24 (td, $J = 6.9$, 2.7, 2H), 1.96 (t, $J = 2.7$, 1H), 1.92-1.83 (m, 2H), 1.66-1.56 (m, 2H); ^{19}F (282 MHz; $CDCl_3$): δ -119.39 (q, $J = 8.6$, 1F), -127.02 (s, 1F). The terminal CF_3 is characteristically at higher chemical shift (*ca.* -80ppm) than the range probed here (-100 to 200ppm). The observed 9 Hz coupling is for $^4J_{F-F^3}$; ^{13}C -NMR (126MHz; $CDCl_3$): δ 82.9, 69.3, 68.2, 27.2, 24.4, 18.0. Insufficient signal intensity for quaternary carbon detection.

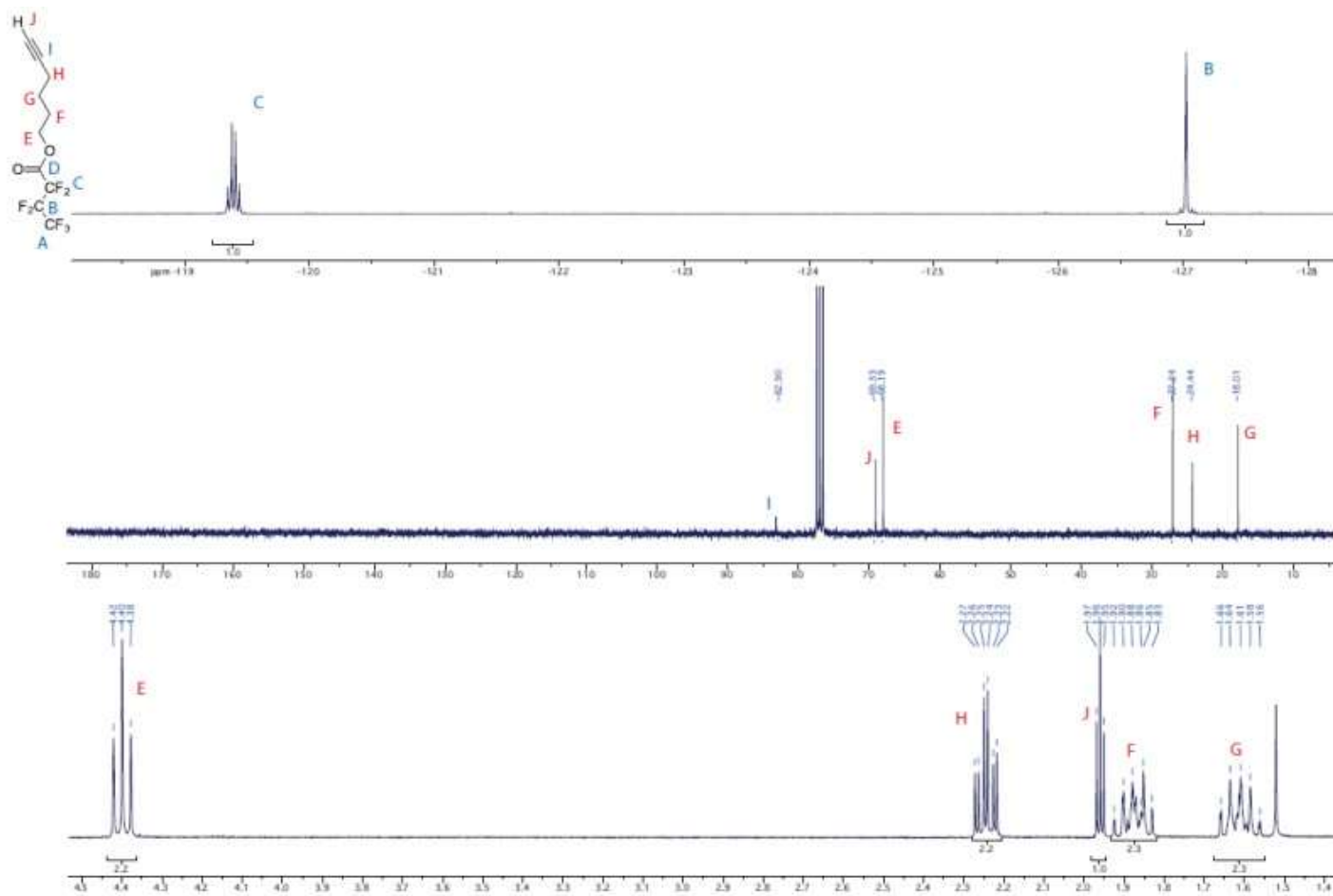


Fig. S4: Partial ^{19}F -NMR, 1H -NMR and ^{13}C -NMR spectra of **P6**

P7

MS - m/z calculated for $C_{10}H_{10}F_7NO$ = 293.0; found 293.0; 1H -NMR (300 MHz; $CDCl_3$): δ 6.36 (s, br, 1H), 3.37 (dd, J = 6.8, 0.7, 2H), 2.19 (td, J = 6.7, 2.7, 2H), 1.92 (t, J = 2.7, 1H), 1.72-1.62 (m, 2H), 1.56-1.46 (m, 2H); ^{19}F -NMR - (282 MHz; $CDCl_3$): δ -120.77 (q, J = 8.8, 2F), -127.03 (s, 2F). CF_3 fluorines were out of probed range; ^{13}C -NMR (126MHz; $CDCl_3$): δ 157.7 (t), 118.8 (qt), 108.5 (tt), 83.7, 68.4, 39.4, 28.3, 25.5, 17.6.

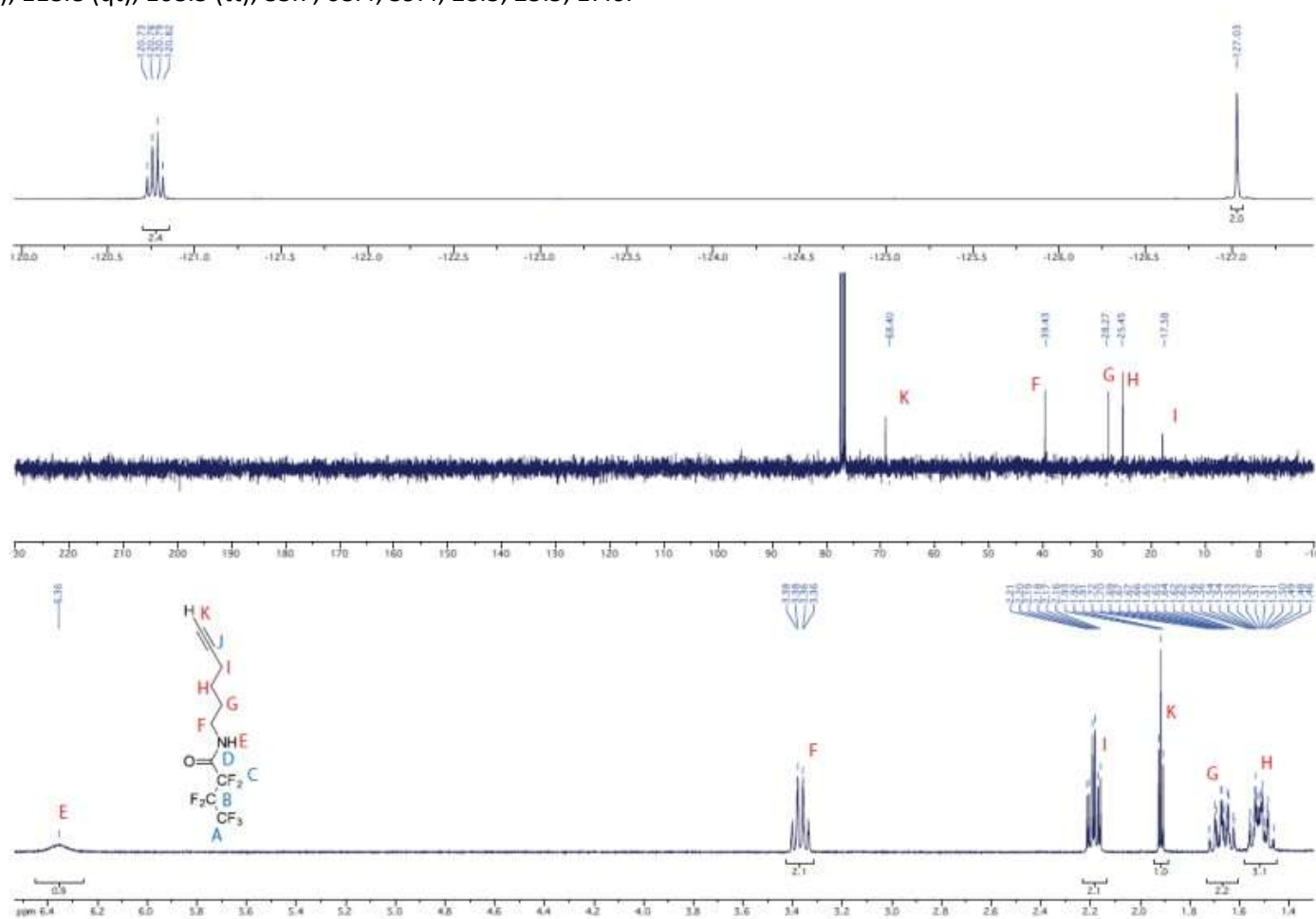


Fig. S5: 1H -NMR and ^{13}C -NMR spectra of **P7**

P8

MS - m/z calculated for $C_{11}H_{10}F_9NO$ = 343.0; found 342.9; 1H -NMR (300 MHz; $CDCl_3$): δ 6.33 (s, A), 3.37 (q, J = 6.5 Hz, B), 2.19 (td, J = 6.7, 2.7 Hz, C), 1.91 (t, J = 2.7 Hz, D), 1.72-1.62 (m, E), 1.56-1.48 (m, F); ^{19}F -NMR - (282 MHz; $CDCl_3$): δ -119.94 (td, J = 12.0, 2.3 Hz, A), -123.42--123.55 (m, B), -125.90 (dtd, J = 12.0, 7.7, 4.2 Hz, C); ^{13}C -NMR (126MHz; $CDCl_3$): δ 157.73 (t, J = 25.7 Hz, A), 83.73 (s, B), 69.33 (s, C), 39.88 (s, D), 28.16 (s, E), 25.52 (s, F), 18.17 (s, G).

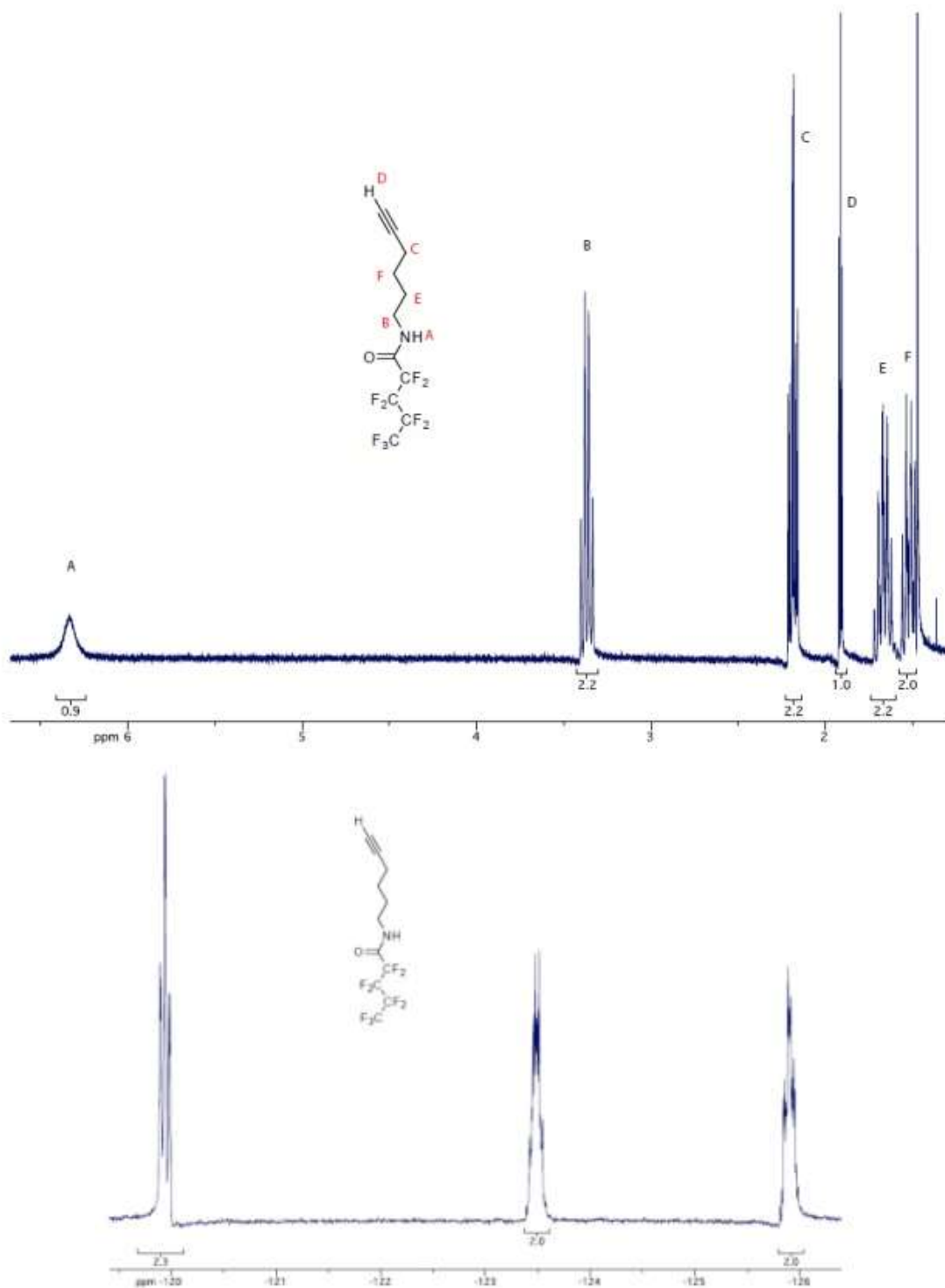


Fig. S6: 1H -NMR and Partial ^{19}F -NMR spectrum of **P8**

P9

MS - m/z calculated for $C_{14}H_{22}O_4 + H^+$ = 255.15909; found 255.15912; 1H -NMR (500 MHz; $CDCl_3$): δ 4.10 (q, J = 7.1, 2H), 4.08 (q, J = 6.8, 2H), 2.30-2.28 (m, 4H), 2.21 (td, J = 6.9, 2.7, 2H), 1.94 (t, J = 2.7, 1H), 1.74-1.54 (m, 8H), 1.23 (t, J = 7.1, 3H); ^{13}C -NMR (126MHz; $CDCl_3$): δ 173.3, 83.8, 68.7, 63.8, 60.3, 34.0, 27.7, 24.9, 24.4, 18.1, 14.2.

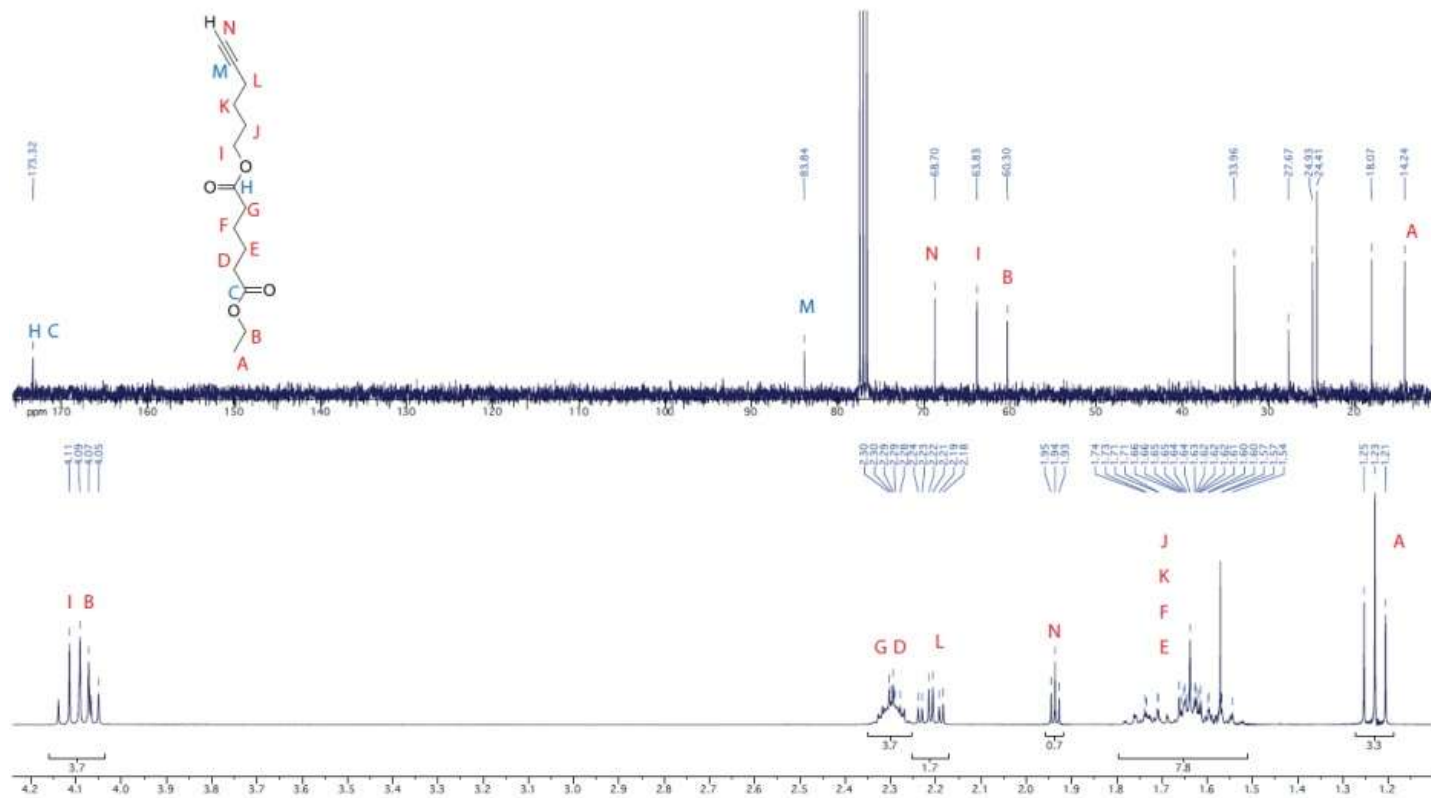


Fig. S7: 1H -NMR and ^{13}C -NMR spectra of **P9**

P10

MS - m/z calculated for $C_{14}H_{24}O_2 = 224.2$; found 224.2; 1H -NMR (300 MHz; $CDCl_3$): δ 4.02 (t, $J = 6.4$, 2H), 2.23 (septet, $J = 7.4$, 2H), 2.16 (td, $J = 7.0$, 2.7, 2H), 1.88 (t, $J = 2.7$, 1H), 1.68 (dd, $J = 8.1$, 0.9, 2H), 1.58-1.50 (m, 5H), 1.26-1.18 (m, 14H), 0.83-0.79 (m, 5H); ^{13}C -NMR (75MHz; $CDCl_3$): δ 68.6, 63.7, 34.3, 31.6, 29.1, 28.9, 27.8, 24.9, 24.7, 22.6, 18.0. Neither of the quaternary carbons had enough intensity to be resolved from the baseline.

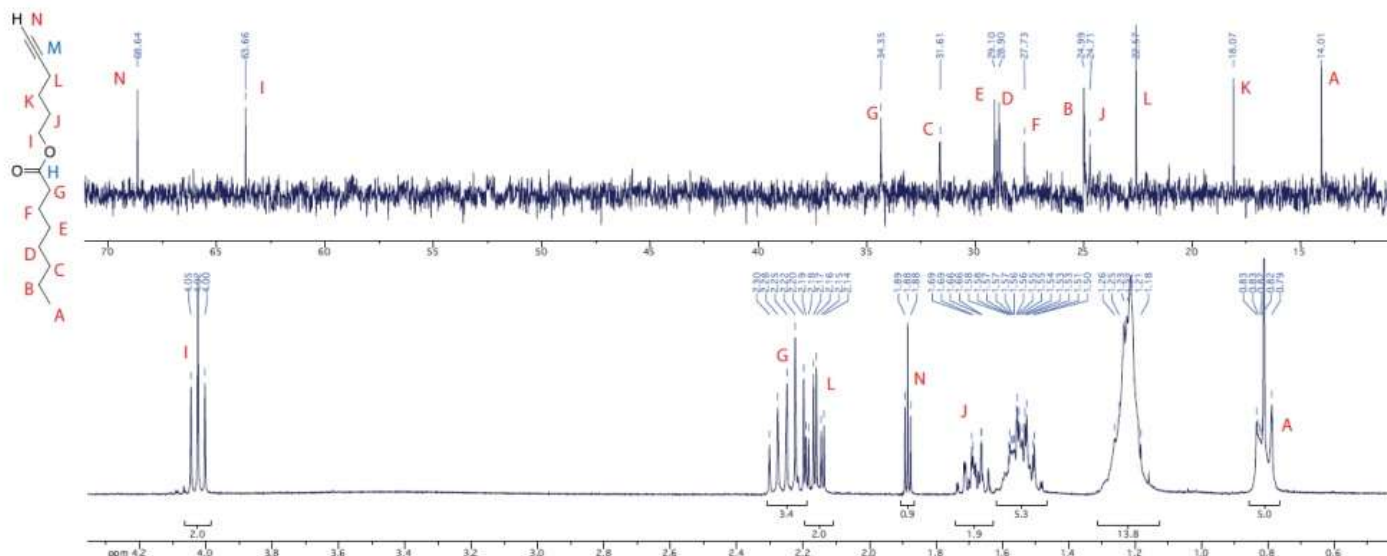


Fig. S8: 1H -NMR and ^{13}C -NMR spectra of **P10**

P11

MS - m/z calculated for C₁₄H₂₅NO = 223.2; found 223.0; ¹H-NMR (300 MHz; CDCl₃): δ 5.40 (s, 1H), 3.21 (q, J = 6.4, 2H), 2.16 (td, J = 6.7, 2.7, 2H), 2.08 (t, J = 7.6, 2H), 1.88 (t, J = 2.7, 1H), 1.61-1.43 (m, 7H), 1.23 (t, J = 6.9, 8H), 0.81 (t, J = 6.8, 3H); ¹³C-NMR (126MHz; CDCl₃): δ 172.8, 83.8, 68.5, 39.1, 37.3, 31.7, 29.3, 29.0, 28.7, 25.83, 25.74, 22.5, 18.1, 14.1.

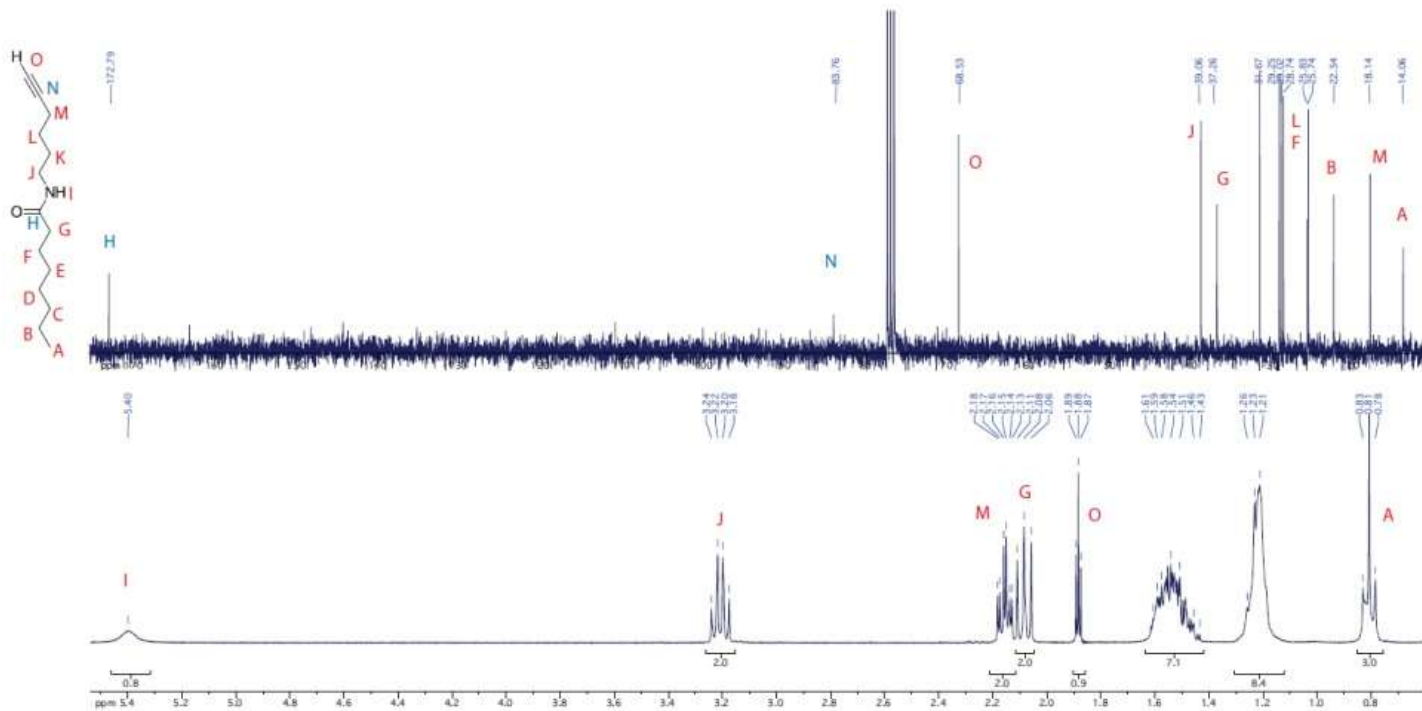
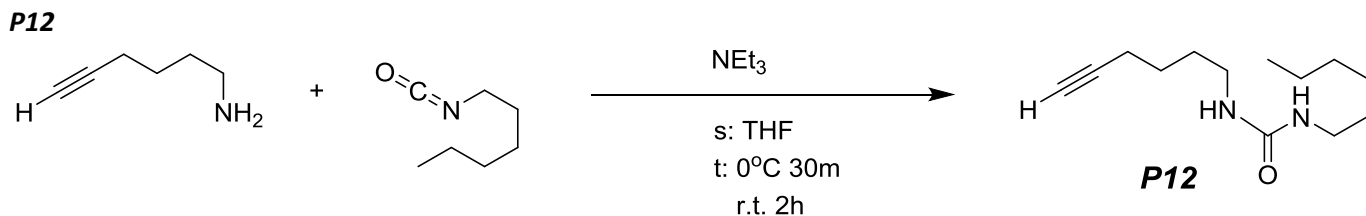


Fig. S9: ¹H-NMR and ¹³C-NMR spectra of **P11**



In a flame-dried 50 mL flask equipped with a stir bar, 10 mL of dry CH_2Cl_2 was added, into which 5-aminohex-1-yne (500 mg, 5.15mmol, 1.0eqv) was dissolved. Hexylisocyanate (656mg, 5.15 mmol, 1.0 eqv) was then added, and the reaction mixture stirred at room temperature. After 1 hour, the solvent was removed under vacuum to give white needles. This was further purified by chromatography on silica gel (30 g, EtOAc:Hex 1:1) to give 990 mg of a white solid (85%).

MS (EI) - m/z calculated for $\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}$ = 224.2; found 224.0; $^1\text{H-NMR}$ (300 MHz; CDCl_3): δ 4.13 (s, 2H), 3.13 (q, J = 6.3, 2H), 3.08 (dd, J = 12.8, 7.1, 2H), 2.16 (td, J = 6.7, 2.7, 2H), 1.88 (t, J = 2.7, 1H), 1.57-1.40 (m, 12H), 1.26-1.21 (m, 7H), 0.82 (t, J = 6.7, 3H); $^{13}\text{C-NMR}$ (126MHz; CDCl_3): δ 84.0, 68.7, 40.9, 40.1, 31.4, 30.0, 29.1, 26.4, 25.6, 22.4, 18.0, 14.1

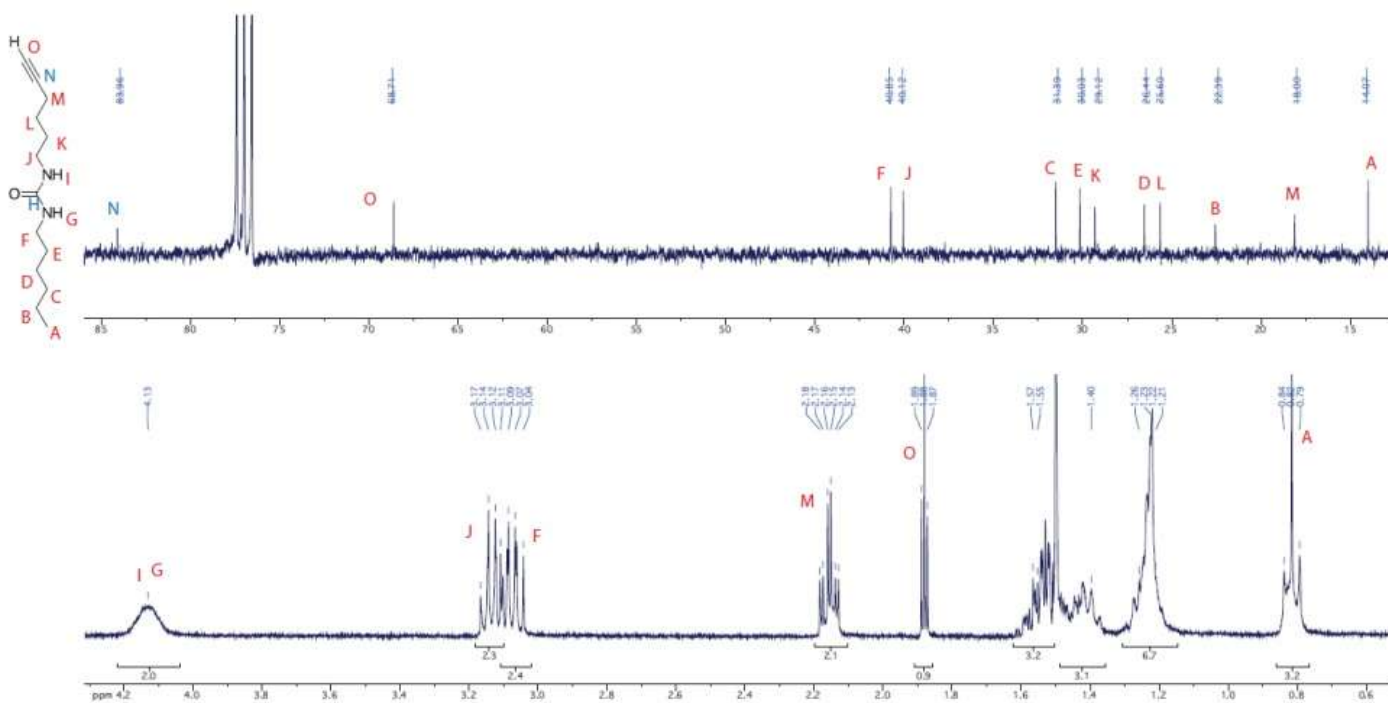
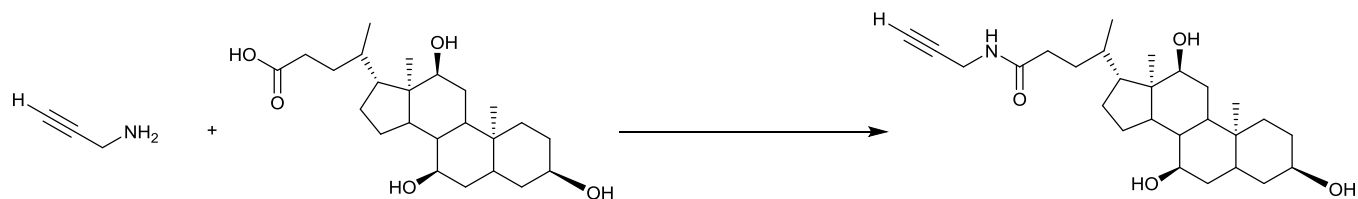


Fig. S10: $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra of **P12**

P2**P2**

Coupling of propargyl amine to cholic acid follows a procedure modified from ref². Cholic acid (4.94 g, 12.1mmol, 1.0 eqv.), propargyl amine (1.0 g, 18.2mmol, 1.5 eqv.), and dimethylaminopyridine (0.148 g, 1.21mmol, 0.1 eqv.) were combined in 50 mL of dichloromethane, and this light yellow heterogenous solution was stirred at room temperature for 30 minutes, after which dicyclohexylcarbodiimide (2.75 g, 13.3mmol, 1.1 eqv.) was added and the solution stirred for a further 24 hours. Directly applying the concentrated solution to a silica gel column, using 10% MeOH in CH₂Cl₂ as an eluent gives 5.4 g as a clear glass (34%).

MS - m/z calculated for C₂₇H₄₃NO₄+H⁺ = 446.327, C₂₇H₄₃NO₄+Na⁺ = 468.309; found 446.31, 468.24; ¹H-NMR (300 MHz; CDCl₃): δ 6.99 (s, 1H), 3.95 (s, br, 2H), 3.88 (s, br, 1H), 3.76 (s, br, 1H), 3.36 (s, br, 1H), 2.20 (t, J = 2.4, 1H), 2.21-2.01 (m, 5H), 1.82-1.19 (m, 19H), 0.94 (s, br, 5H), 0.82 (s, 3H), 0.60 (s, 3H). Signals are in general broad for this compound²; ¹³C-NMR (126MHz; CDCl₃): δ 174.1, 80.2, 73.2, 72.1, 71.3, 68.3, 46.7, 46.1, 41.7, 39.2, 35.7, 34.6, 33.1, 31.4, 30.7, 28.8, 28.3, 27.7, 26.1, 23.2, 22.6, 17.7, 12.5.

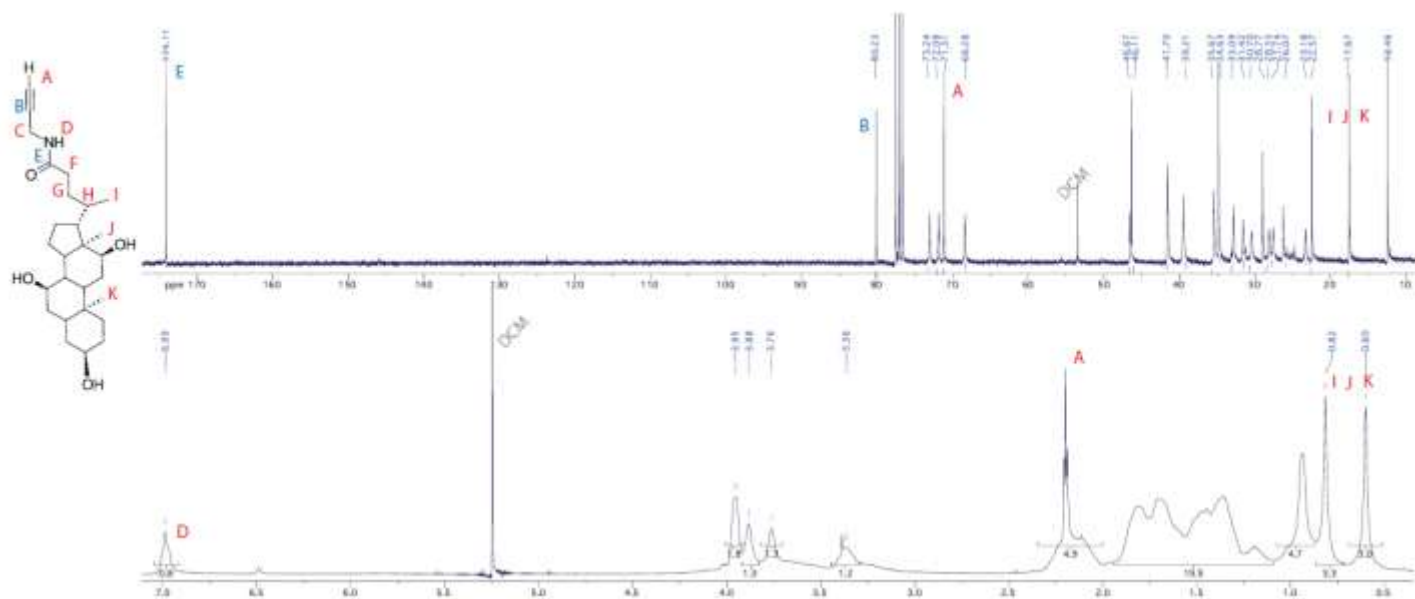
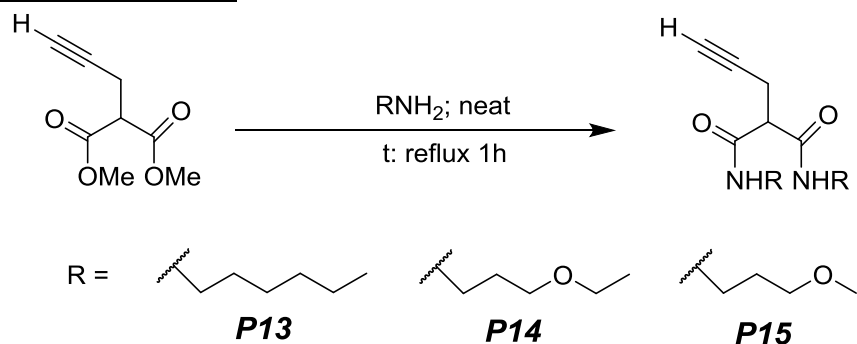


Fig. S11: ¹H-NMR and ¹³C-NMR spectra of **P2**

Cyclodextrin Channel Precursors- twin tailed



General Procedure, illustrated with **P14**

In a 5mL flask equipped with a reflux condenser, the propargyl malonate ester (1.0 g, 5.88 mmol, 1.0 eqv) and 1-amino-3-ethoxypropane (1.4 g, 1.6 mL, 13.5mmol, 2.3 eqv) was combined. The solution was heated to 100 °C for 4hours. On cooling, this mixture was directly chromatographed on silica gel (EtOAc:Hex 1:4, gradient to 4:1) to give 1.305 g of white needles (71%).

MS - m/z calculated for $\text{C}_{16}\text{H}_{28}\text{N}_2\text{O}_4 + \text{Na}^+$ = 335.1948; found 335.209; $^1\text{H-NMR}$ (300 MHz; CDCl_3): δ 7.13 (s, br, 2H), 3.48-3.43 (m, 8H), 3.34 (q, $J = 6.0$, 4H), 3.08 (t, $J = 7.6$, 1H), 2.71 (dd, $J = 7.6, 2.7$, 2H), 2.03 (t, $J = 2.6$, 1H), 1.75 (quintet, $J = 6.2$, 4H), 1.18 (t, $J = 7.0$, 6H); $^{13}\text{C-NMR}$ (75MHz; CDCl_3): δ 168.8, 80.6, 71.4, 69.2, 66.7, 53.7, 38.3, 29.1, 21.3, 15.4

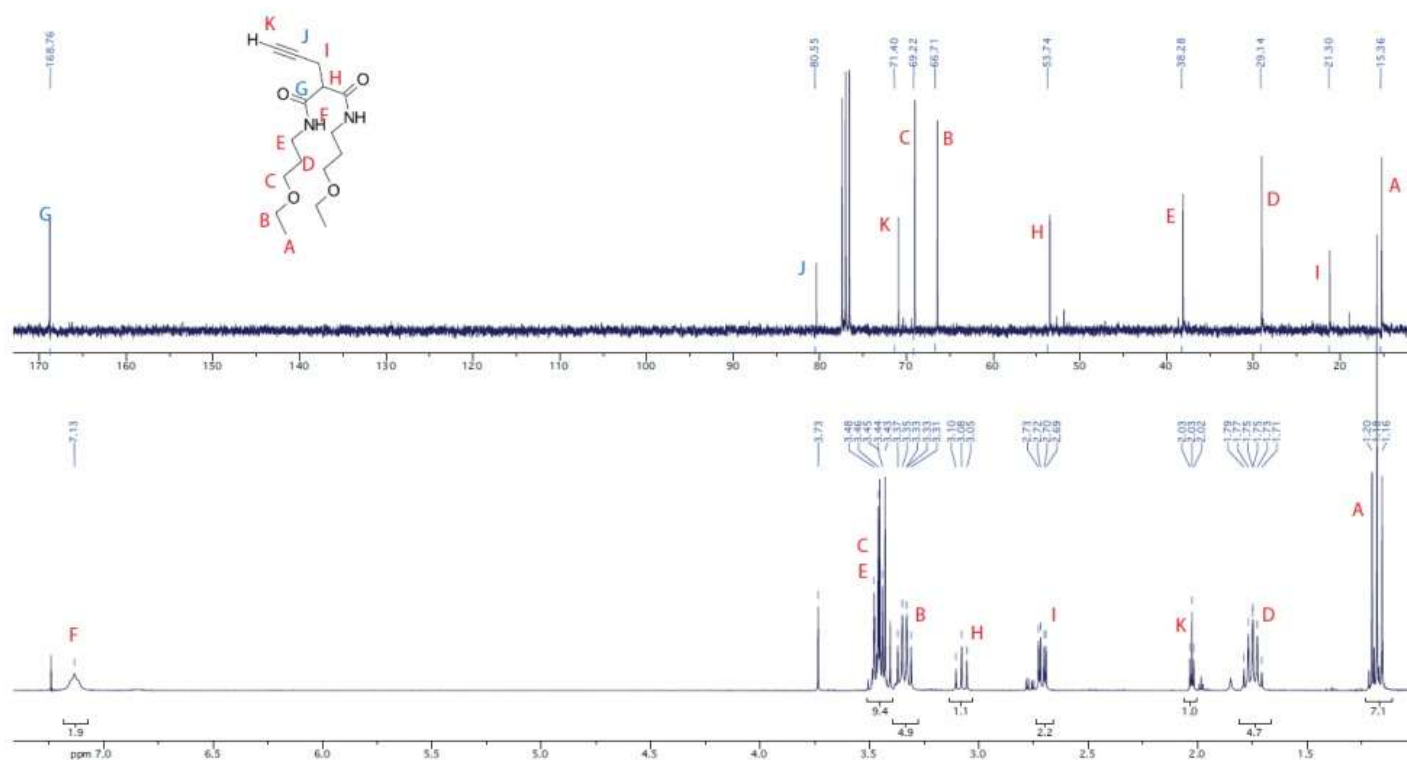


Fig. S12: $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra of **P14**

P13

MS - m/z calculated for $C_{18}H_{32}N_2O_2 + Na^+$ = 331.2358; found 331.63; 1H -NMR (300 MHz; $CDCl_3$): δ 6.91 (s,br, 2H), 3.22 (q, $J = 6.4, 4H$), 3.15 (t, $J = 7.6, 1H$), 2.72 (dd, $J = 7.6, 2.7, 2H$), 2.03 (t, $J = 2.6, 1H$), 1.50-1.45 (m, 4H), 1.31-1.22 (m, 12H), 0.85 (t, $J = 6.8, 6H$); ^{13}C -NMR (75MHz; $CDCl_3$): delta 169.1, 80.4, 71.1, 53.3, 39.8, 31.4, 29.3, 26.5, 22.5, 21.5, 14.0.

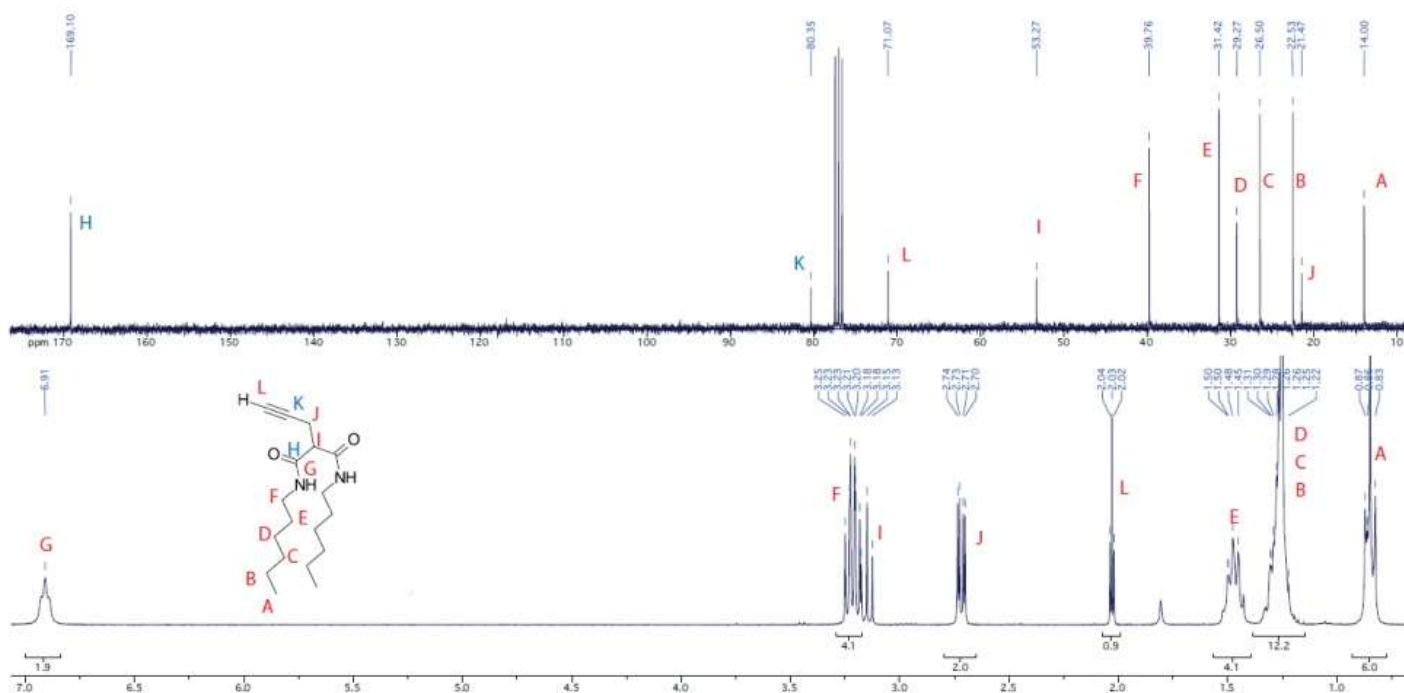


Fig. S13: 1H -NMR and ^{13}C -NMR spectra of **P13**

P15

MS - m/z calculated for $C_{14}H_{24}N_2O_4 + Na^+$ = 307.163; found 307.16; 1H -NMR (300 MHz; $CDCl_3$): δ 6.98 (s, 2H), 3.44 (t, J = 5.9, 4H), 3.36 (q, J = 6.0, 4H), 3.32 (s, 6H), 3.09 (t, J = 7.5, 1H), 2.73 (dd, J = 7.5, 2.7, 2H), 2.04 (t, J = 2.7, 1H), 1.76 (qd, J = 6.4, 5.9, 4H); ^{13}C -NMR (126MHz; $CDCl_3$): δ 169.0, 80.6, 71.0, 70.9, 58.7, 52.9, 37.8, 29.0, 20.8.

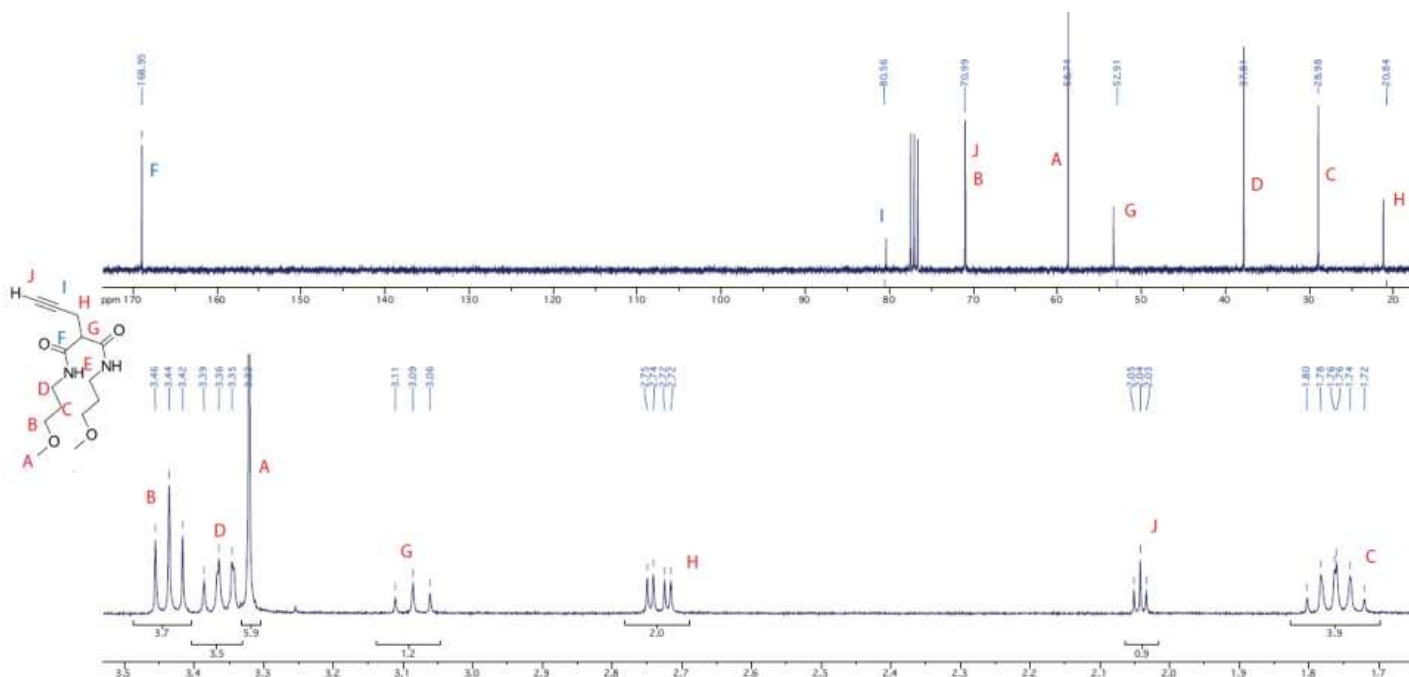
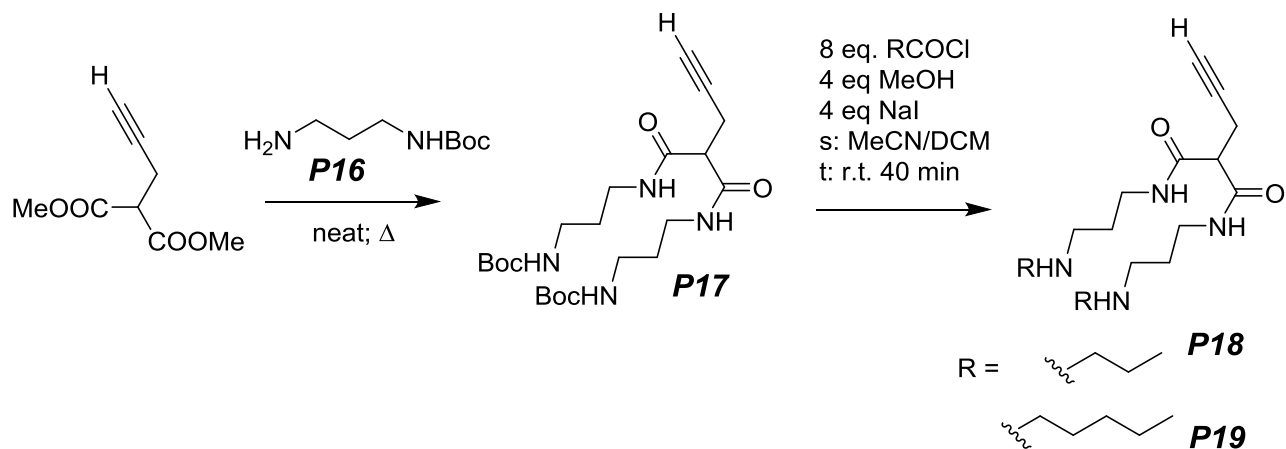


Fig. S14: 1H -NMR and ^{13}C -NMR spectra of **P15**



The monoprotected propylene diamine (**P16**) was prepared and purified as described⁴. In a 25 mL flask equipped with a reflux condenser, **P16** (6.0 g, 34.5 mmol, 2.5 eqv.) and dimethylpropargylmalonate (2.34 g, 13.8 mmol, 1.0 eqv.) was combined. The viscous, light-yellow oil was heated to reflux for 80 minutes; on cooling it solidifies to a brown-red solid. This solid is soluble in hot EtOAc and only sparingly soluble when cold. The product was first recrystallized from ethyl acetate (30 mL) to give a white powder, and then chromatographed (silica gel, 10% MeOH in dichloromethane) to give 1.43 g of a crystalline white solid (25%).

MS - m/z calculated for $C_{22}H_{38}N_4O_6+H]^+$ = 455.3, found 455.3; 1H -NMR (300 MHz; $CDCl_3$): δ 3.26 (dt, $J = 3.3, 1.6, 2H$), 3.19-3.16 (m, 4H), 3.02 (t, $J = 6.7, 4H$), 2.66 (dd, $J = 7.7, 2.7, 2H$), 2.32 (t, $J = 2.7, 1H$), 1.60 (quintet, $J = 6.7, 4H$), 1.39 (s, 18H); ^{13}C -NMR (175 MHz; $CDCl_3$): δ 169.2, 156.7, 80.3, 79.1, 69.8, 52.2, 37.9, 36.3, 29.2, 26.4, 19.2

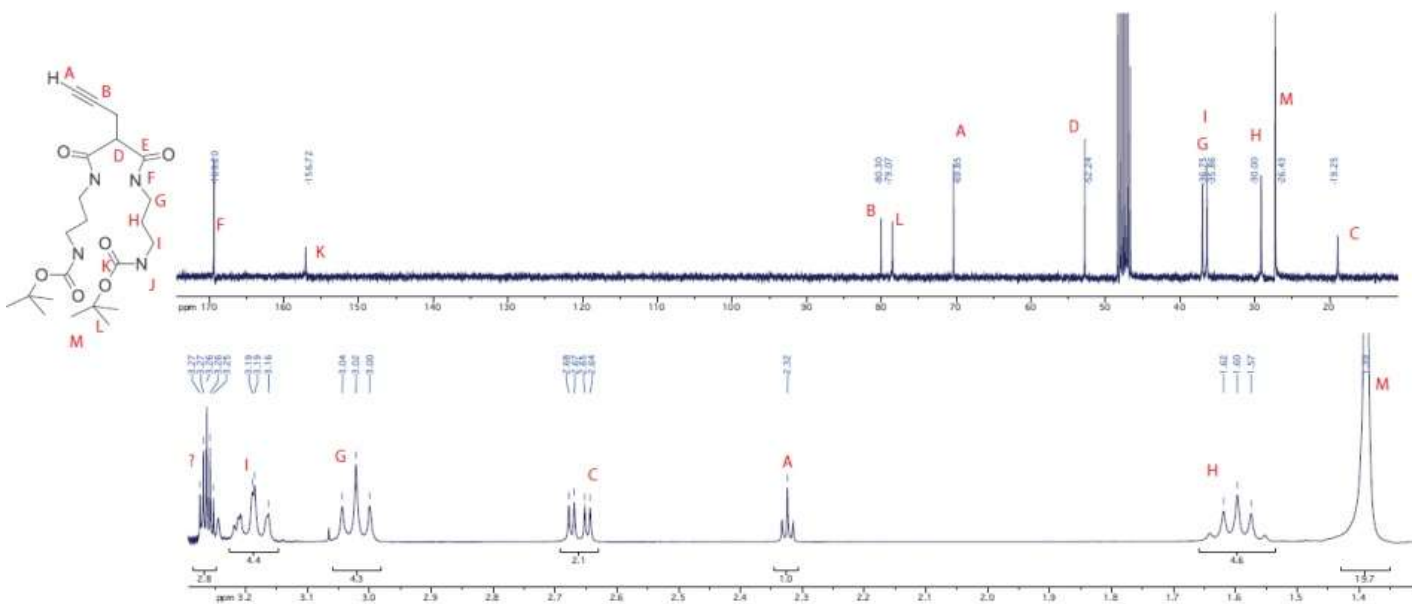


Fig. S15: 1H -NMR and ^{13}C -NMR spectra of **P17**

A one-pot deprotection--coupling procedure was used in the preparation of bis-amides **P18** and **P19**. *General procedure* illustrated for bis-butylamide **P18**. Carbamate **P16** (200 mg, 0.44mmol, 1.0 eqv.) was stirred in 4 mL acetonitrile and 4 mL dichloromethane. Methanol (70 μ L, 1.76mmol, 4.0 eqv.) was added, followed by NaI (263 mg, 1.76mmol, 4.0 eqv.), upon the addition of which the solution becomes homogenous. Butyryl chloride (249 μ L, 3.52mmol, 8.0 eqv.) was added and the reaction vessel capped immediately, and stirred vigorously at room temperature for 40 minutes. Anhydrous K_2CO_3 (1.21 g, 8.8mmol, 20 eqv.) was added and let stir overnight, during which the color of the solution turns substantially lighter. The heterogenous solution was filtered, solvent evaporated, and chromatographed (silica gel, gradient from 5% MeOH in CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to yield 116 mg of a white powder (67%).

1H -NMR (300 MHz; $CDCl_3$): δ .27-3.17 (m, 8H), 2.71 (dd, J = 7.7, 2.7, 2H), 2.37 (t, J = 2.7, 1H), 2.16 (t, J = 7.4, 4H), 1.72-1.57 (m, 8H), 0.94 (t, J = 7.4, 6H); ^{13}C -NMR (75MHz; MeOD- d_4): δ 176.29, 176.20, 170.8, 81.6, 71.9, 54.2, 39.18, 39.13, 38.1, 37.78, 37.66, 30.3, 20.45, 20.40, 14.1. Slow amide rotation observed in methanol, resulting in double sets of certain peaks .

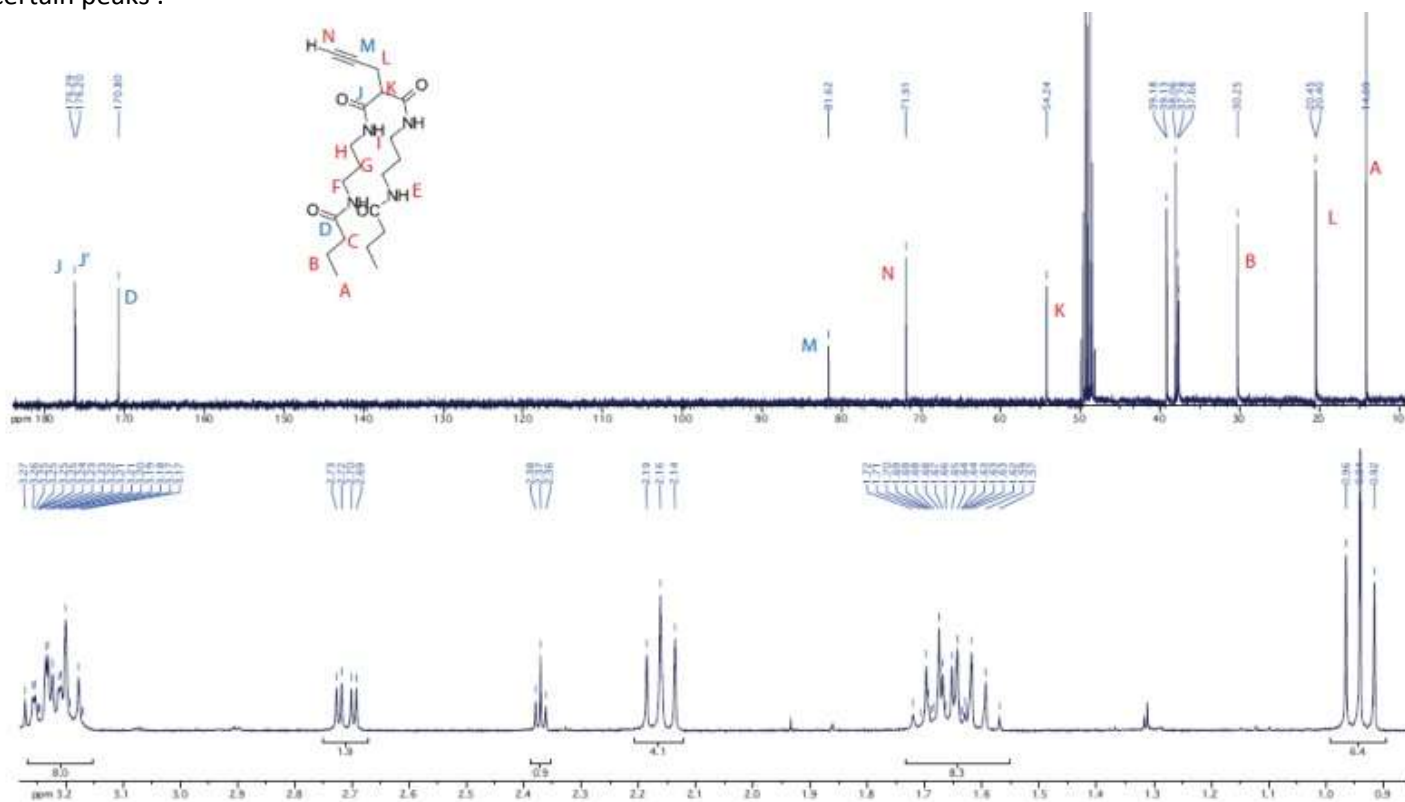


Fig. S16: 1H -NMR and ^{13}C -NMR spectra of **P18**

P19

$^1\text{H-NMR}$ (500 MHz; MeOH-d_4): δ 3.24 (dt, $J = 6.7, 3.4, 4\text{H}$), 3.20 (t, $J = 6.8, 4\text{H}$), 2.71 (dd, $J = 7.7, 2.7, 2\text{H}$), 2.37 (t, $J = 2.6, 1\text{H}$), 2.18 (t, $J = 7.6, 4\text{H}$), 1.68 (quintet, $J = 6.8, 4\text{H}$), 1.61 (dt, $J = 15.0, 7.5, 4\text{H}$), 1.36-1.29 (m, 9H), 0.92 (t, $J = 7.1, 7\text{H}$);
 $^{13}\text{C-NMR}$ (126MHz; CDCl_3): δ 81.7, 72.0, 54.5, 38.2, 37.8, 37.3, 32.7, 30.3, 26.9, 23.6, 20.6, 14.5

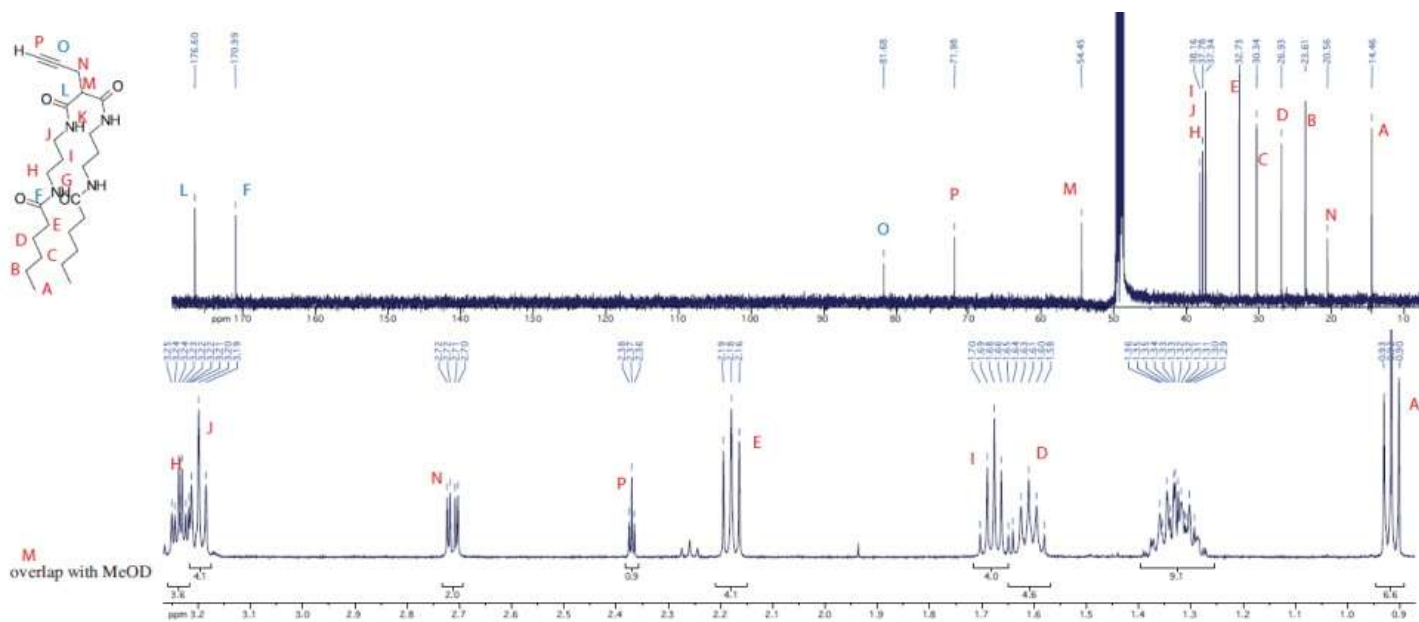
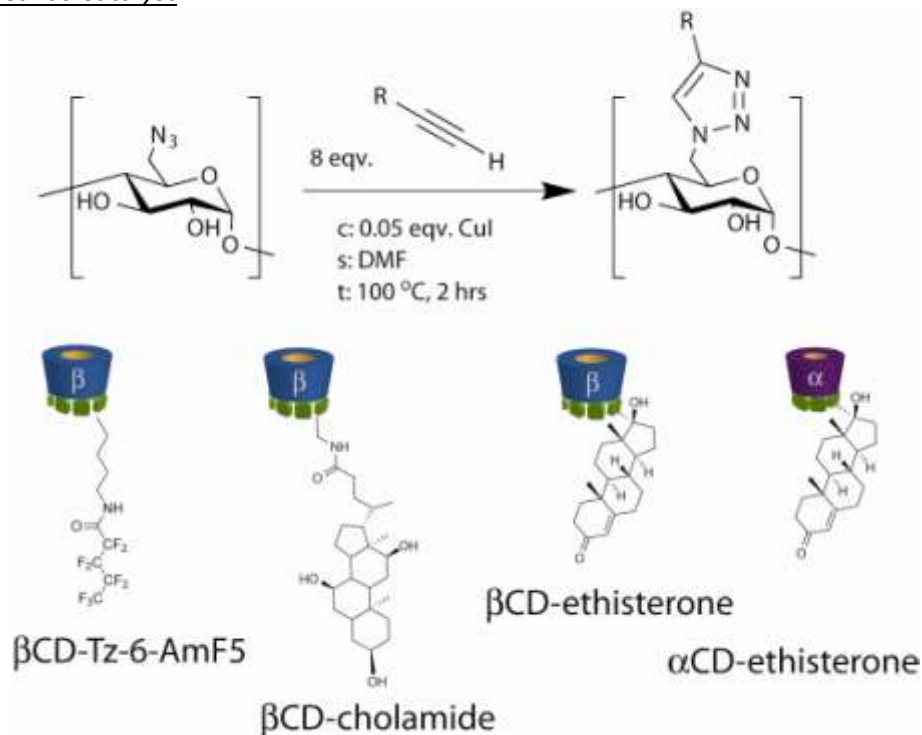


Fig. S17: $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra of **P19**



General procedure. In a sample vial equipped with a stir-bar, alkyne (8.0 eqv., 1.15 eqv. per azide), *per*-6-azido α - or β -cyclodextrin (1.0 eqv.), and CuI (2.1 eqv., 0.3 eqv. per azide) were dissolved in 1:1 DMF:water. The sample vial was capped, sealed with teflon tape, and heated to 100°C. The solution remains heterogenous throughout. After 2 hours, the dark green-to-orange reaction mixture was cooled to room temperature, and directed applied on a silica gel column, using 10:2:1 acetonitrile:water:NH₄OH(aq) as eluent. The copper salt is retained as a thin blue band on top of the column. Evaporation of solvent with a stream of air gives desired products in 20-75% yields. Air evaporation is preferable to the usual procedure of rotary evaporation; some amphiphilic products foam under vacuum

βCD-Tz-6AmF5 from P8

MS (MALDI-TOF) - m/z calculated for $C_{119}H_{133}N_{28}F_{63}O_{35}+2H]^{2+} = 1856.9336$. Found 1856.9341; ¹H-NMR (500 MHz; MeOH-d₄): δ 7.68 (s, A), 5.12 (d, J = 3.5 Hz, B), 4.54 (d, J = 12.3 Hz, C), 4.31 (dd, J = 14.4, 6.1 Hz, D), 4.14 (ddd, J = 9.5, 6.1, 3.2 Hz, E), 3.87 (t, J = 9.3 Hz, F), 3.43 (dd, J = 9.8, 3.4 Hz, G), 3.28 (t, J = 9.3 Hz, H), 2.58-2.51 (m, I), 1.59 (d, J = 4.8 Hz, J).

¹³C-NMR (126 MHz; MeOH-d₄): δ 159.26 (t, J = 25.8 Hz, A), 148.75 (s, B), 125.42 (s, C), 118.88 (qt, J = 287.9, 33.2 Hz, D), 114-106 (m, E, F, G'), 104.00 (s, G), 84.93 (s, H), 74.22 (s, I), 74.04 (s, J), 71.62 (s, K), 51.64 (s, L), 40.87 (s, M), 29.43 (s, N), 27.47 (s, O), 25.73 (s, P); ¹⁹F-NMR] - (282 MHz; MeOH-d₄): δ -120.06--121.01 (m, A), -124.15--124.73 (m, B), -126.93--127.36 (m, C); Elemental Analysis - Expected C 38.50, H 3.61, N 10.56. Found C 37.59, H 3.73, N 10.40. Analysis for oxygen unavailable due to interference by fluorine.

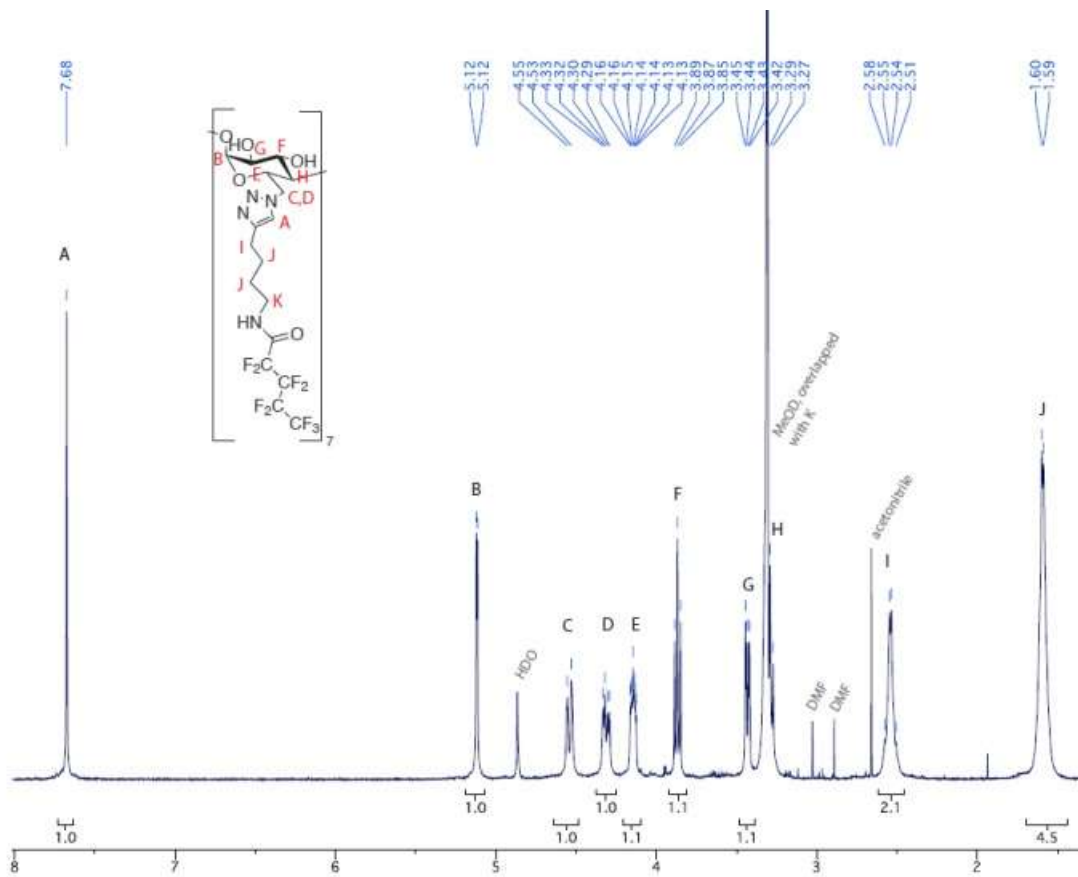


Fig. S18: $^1\text{H-NMR}$ spectrum of β CD-Tz-6AmF5

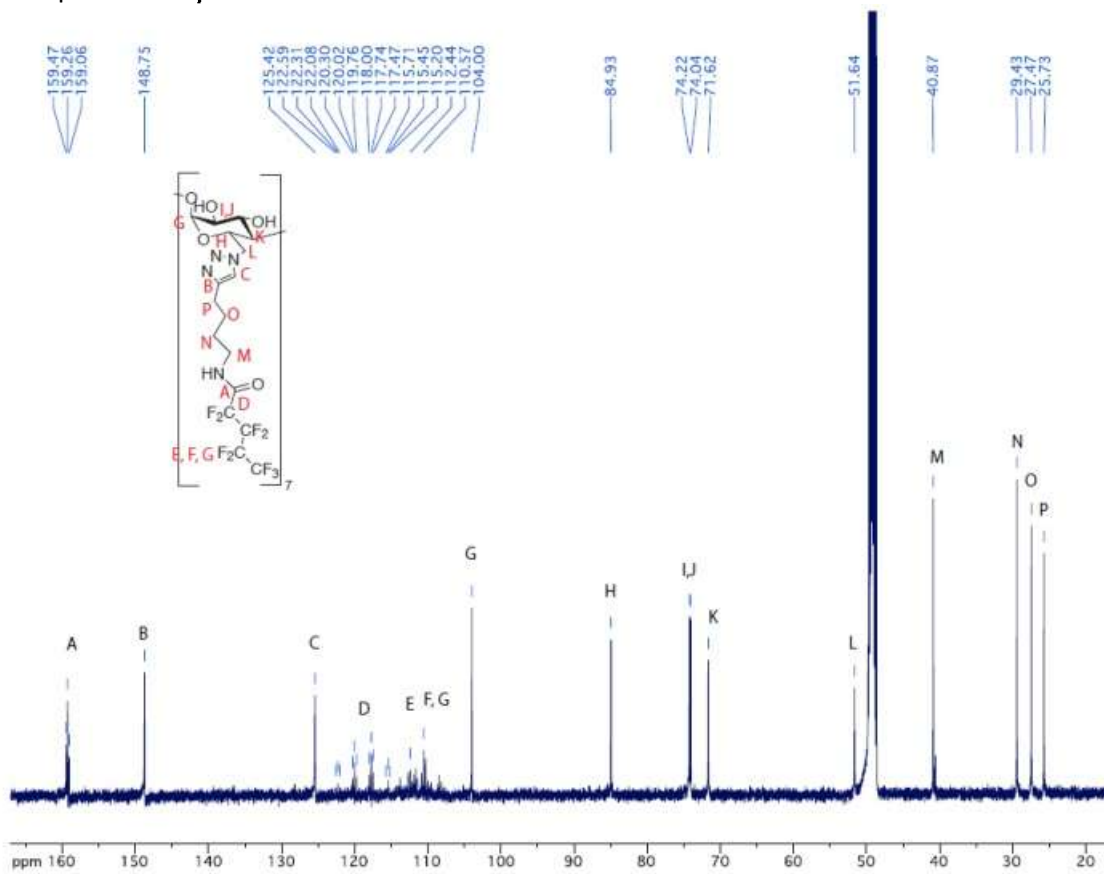


Fig. S19 $^{13}\text{C-NMR}$ spectrum of β CD-Tz-6AmF5

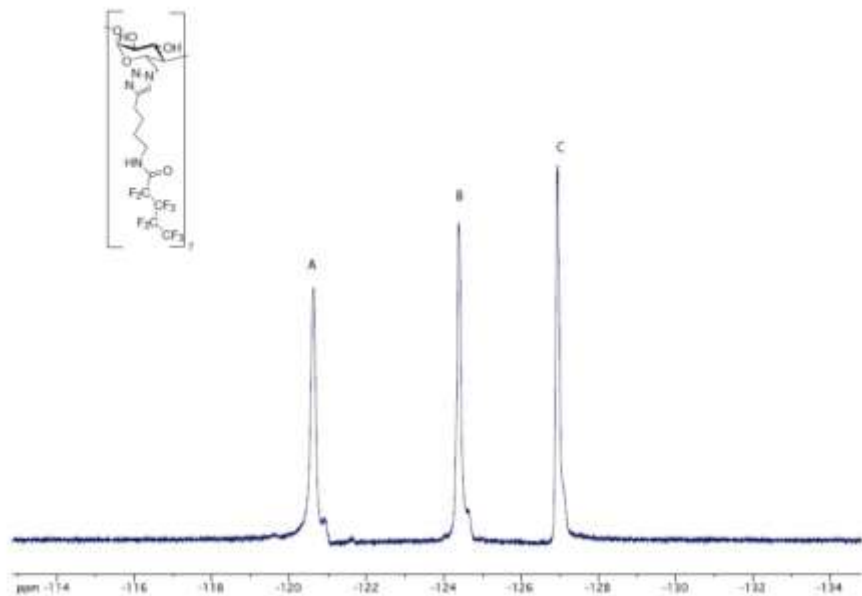


Fig. S20: ^{19}F -NMR spectrum of $\beta\text{CD-Tz-6AmF5}$

β CD-Tz-Cholamide from P2

MS - m/z calculated for $C_{231}H_{364}N_{28}O_{56}+3Na^{3+} = 1498$, $C_{231}H_{364}N_{28}O_{56}+2Na+K^{3+} = 1504$; found 1497.7, 1504.8; 1H -NMR (500 MHz; DMSO- d_6): δ 8.15 (s, 1H), 7.71 (s, 1H), 5.07 (s, 1H), 4.44-4.01 (m, 7H), 3.77-3.61 (m, 3H), 3.27 (d, $J = 59.3$, 8H), 2.27-2.09 (m, 2H), 1.95 (s, 2H), 1.67 (t, $J = 19.7$, 5H), 1.39-1.14 (m, 10H), 0.89 (d, $J = 5.3$, 4H), 0.80 (s, 4H), 0.56 (s, 3H); ^{13}C -NMR (500 MHz; DMSO- d_6): δ 172.5, 144.4, 124.3, 101.5, 82.7, 72.3, 71.9, 71.1, 70.5, 66.4, 46.3, 45.8, 41.6, 41.4, 35.5, 34.9, 34.5, 33.8, 32.5, 31.7, 30.4, 28.6, 27.4, 26.3, 22.9, 22.7, 17.2, 12.4.

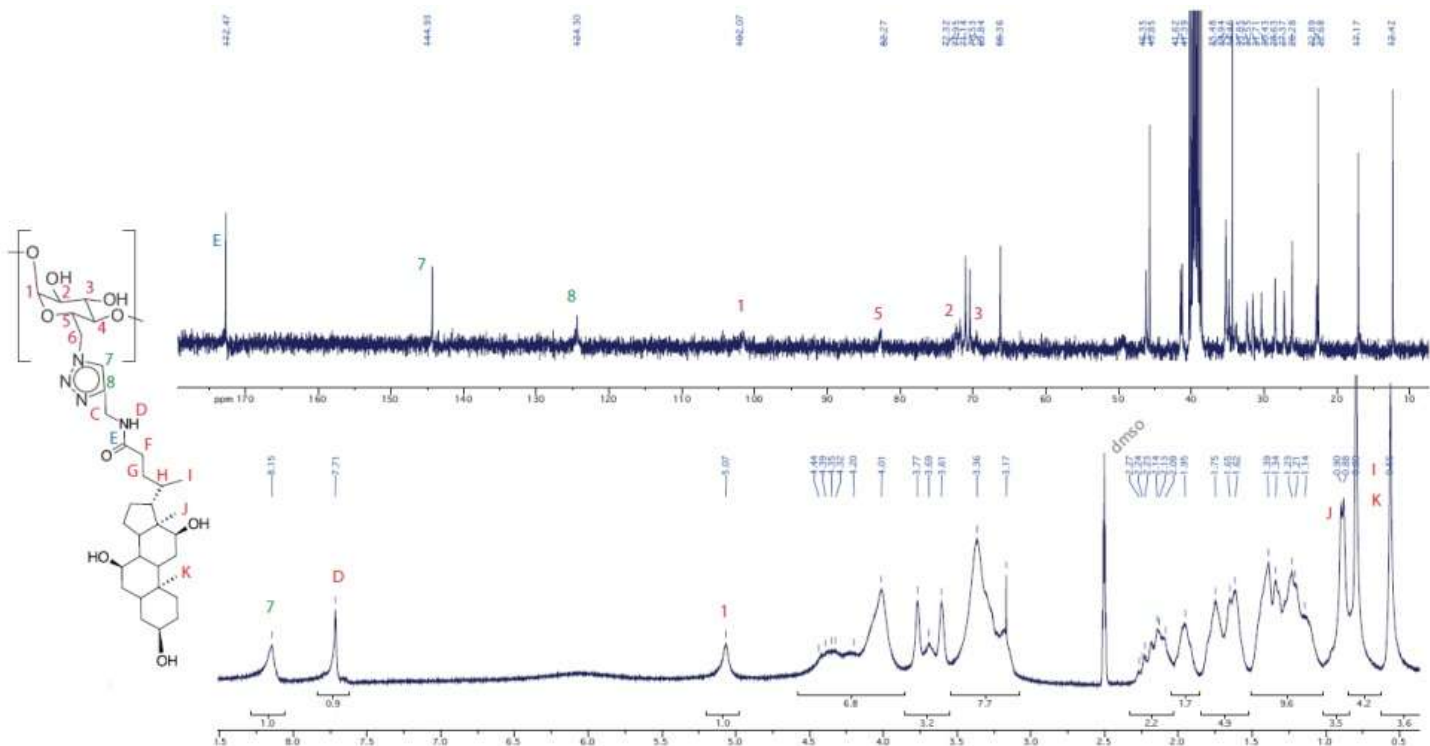


Fig. S21: 1H -NMR and ^{13}C -NMR spectra of β CD-Tz-Cholamide

β CD-Tz-Ethisterone from P1

MS - m/z calculated for $C_{189}H_{259}N_{21}O_{42}+2H^{2+} = 1749.4478$; found 1749.4511; 1H -NMR (500 MHz; MeOH- d_4): δ 7.81 (s, V), 5.70 (s, U), 5.15 (d, J = 3.4 Hz, T), 4.77 (d, J = 12.8 Hz, S), 4.60 (s, R), 4.52 (d, J = 15.1 Hz, Q), 4.18-4.16 (m, P), 3.88 (t, J = 9.3 Hz, O), 3.40 (dd, J = 9.8, 3.3 Hz, N), 3.19 (t, J = 9.3 Hz, M), 2.52-2.44 (m, L), 2.26 (m, K), 2.14 (s, J), 2.00 (dd, J = 9.5, 3.3 Hz, I), 1.94-1.88 (m, H), 1.82-1.78 (m, G), 1.67-1.55 (m, F), 1.46-1.36 (m, E), 1.30-1.23 (m, D), 1.03-0.99 (m, C), 0.71-0.65 (m, B), 0.58-0.53 (m, A); ^{13}C -NMR (126 MHz; MeOH- d_4): δ 202.15 (A), 175.07 (B), 154.73 (C), 126.50 (D), 124.35 (E), 103.73 (F), 84.25 (G), 83.00 (H), 74.36 (I), 73.86 (J), 71.75 (K), 55.43 (L), 51.61 (M), 40.17 (N), 38.05 (O), 37.60 (P), 37.14 (Q), 34.94 (R), 34.31 (S), 34.02 (T), 33.35 (U), 25.08 (V), 21.96 (W), 17.86 (X), 15.15 (Y).

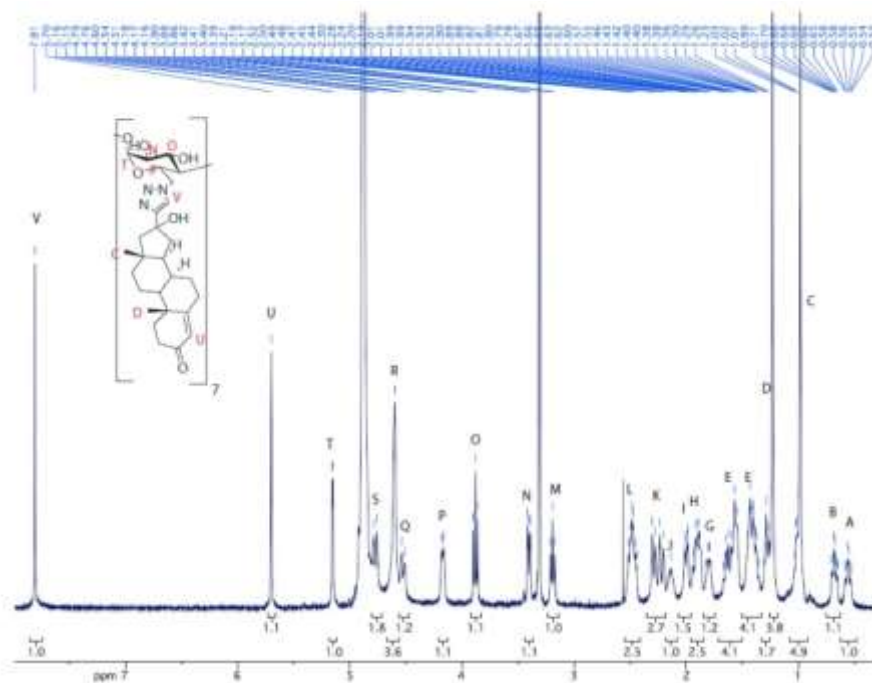


Fig. S22: 1H -NMR spectrum of β CD-Tz-Ethisterone

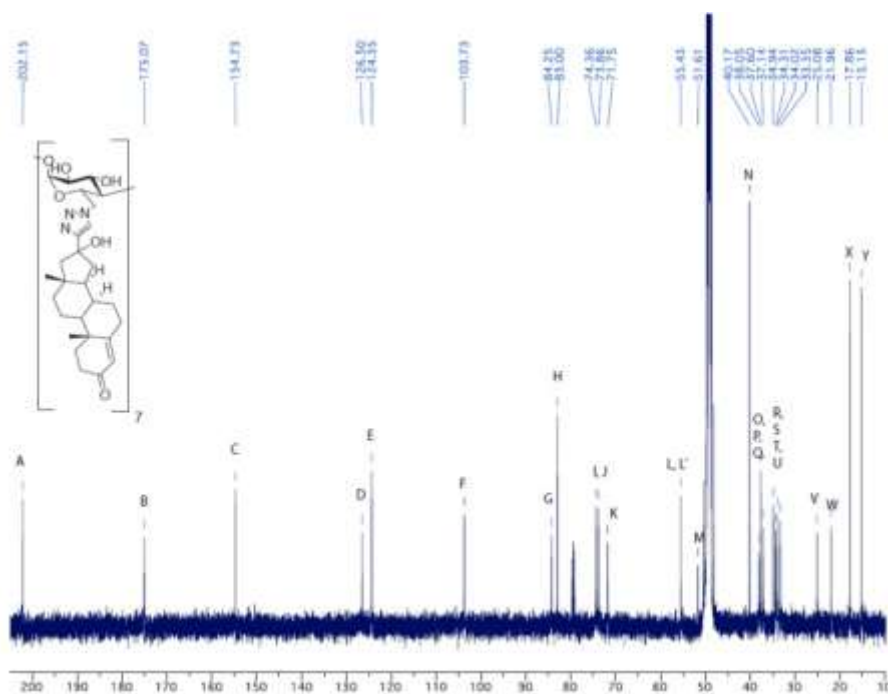


Fig. S23: ^{13}C -NMR spectrum of β CD-Tz-Ethisterone

α CD-Tz-Ethisterone from P1

MS - m/z calculated for $C_{162}H_{222}N_{18}O_{36}+2H^{2+} = 1499.8153$; found 1499.8164; 1H -NMR (500 MHz; MeOD- d_4 /CDCl $_3$): δ 7.76 (s, 1H), 5.69 (s, 1H), 5.10 (s, 1H), 4.54 (s, 1H), 4.40 (s, 1H), 4.08 (s, 1H), 3.95 (t, $J = 9.2$, 1H), 3.40-3.38 (m, 1H), 3.17 (s, 1H), 2.45 (m, 3H), 2.29-2.21 (m, 3H), 1.99-1.38 (m, 17H), 1.25-1.19 (m, 6H), 1.06-0.99 (m, 6H), 0.72-0.60 (m, 3H); ^{13}C -NMR (126MHz; MeOD- d_4 /CDCl $_3$): δ 201.9, 174.8, 154.7, 125.9, 124.1, 103.3, 82.6, 74.3, 73.1, 54.9, 39.9, 37.2, 36.7, 34.7, 34.1, 33.8, 32.9, 24.8, 21.6, 17.9, 15.0.

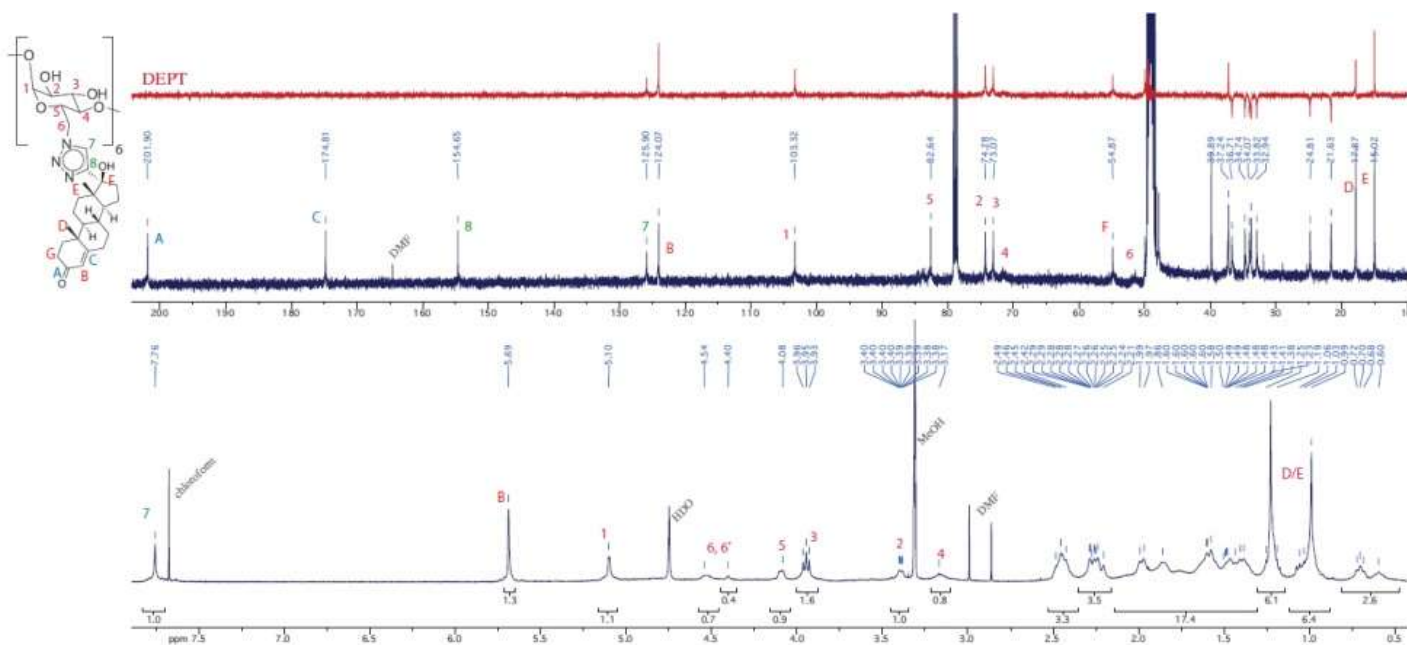
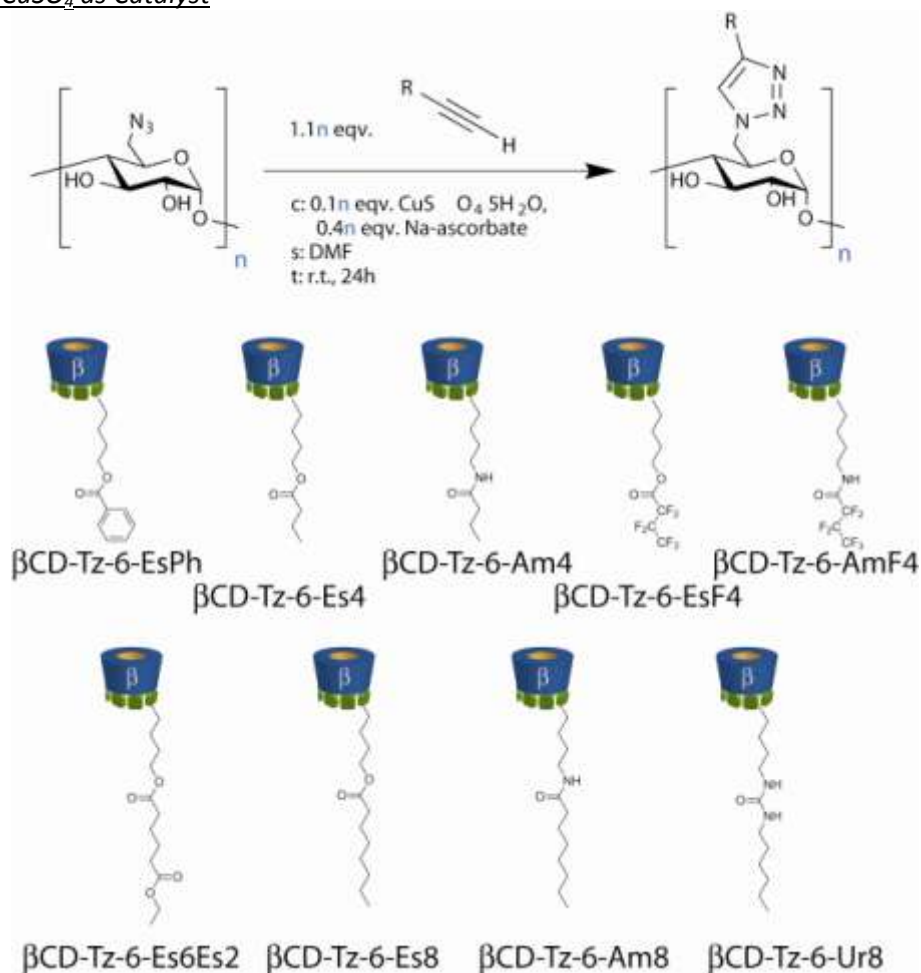


Fig. S24: 1H -NMR and ^{13}C -NMR spectrum of α CD-Tz-Ethisterone



General procedure illustrated with compound $\beta\text{CD-Tz-6AmF4}$. In a 1 dram sample vial equipped with a small stir-bar, alkyne **P5** (250 mg, 0.814mmol, 7.7 eqv.), *per*-6-azido- β -cyclodextrin (139 mg, 0.106mmol, 1.0 eqv.), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (21.3mg, 0.085mmol, 0.8 eqv.), sodium ascorbate (68 mg, 0.34mmol, 3.2 eqv.) were combined and dissolved in 2 mL DMSO. The resulting light-brown solution was left to stir at room-temperature for 24 hours. At the end of the reaction, the mixture was quenched into 100 mL ice-cold water; filtration gives a light green powder that was redissolved in methanol. Solid-liquid extraction by addition of Chelex-100 for a minimum of three times gives a clear, colorless solution, which was evaporated by a stream of air, chromatographed (silica gel, 20% MeOH: chloroform) to give 119 mg of a white powder (33%).

β CD-Tz-6EsPh from P3

MS - m/z calculated for $C_{133}H_{161}N_{21}O_{42}+Na+H^{2+} = 1374.5553$; found 1374.5525; 1H -NMR (500 MHz; DMSO- d_6): δ 7.84 (dd, $J = 6.1, 2.2, 3H$), 7.61-7.51 (m, 2H), 7.42-7.38 (m, 3H), 5.01 (s, 1H), 4.24-3.95 (m, 5H), 3.64 (s, 1H), 2.32 (s, 2H), 1.55 (t, $J = 46.9, 5H$). Possibly related to aggregate formation, the signals for β bCD-Tz-6EsPh are extremely broad in both methanol- d_4 as well as DMSO- d_6 ; ^{13}C -NMR (126MHz; DMSO- d_6): δ 166.3, 146.9, 133.8, 130.4, 129.7, 129.3, 123.9, 102.4, 83.6, 73.0, 72.6, 70.3, 65.0, 50.5, 28.5, 25.9, 25.0.

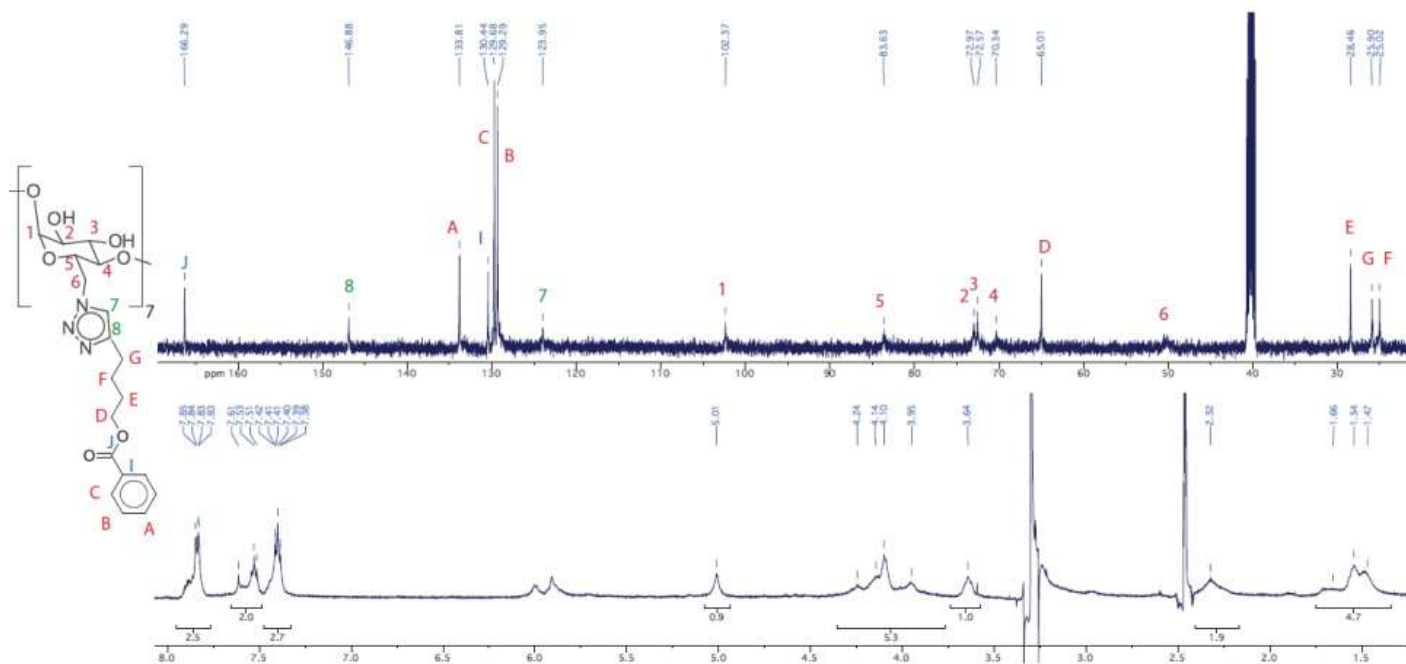


Fig. S25: 1H -NMR and ^{13}C -NMR spectrum of β CD-Tz-6EsPh

β CD-Tz-6Es4 from P4

MS - m/z calculated for $C_{112}H_{175}N_{21}O_{42}+2H^{2+} = 1244.6191$, found 1244.6167; 1H -NMR (500 MHz; MeOD- d_4): δ 7.73 (s, 1H), 5.16 (d, $J = 3.6$, 1H), 4.57-4.54 (m, 1H), 4.39 (dd, $J = 14.5$, 5.7, 1H), 4.17 (ddd, $J = 9.4$, 5.6, 3.6, 1H), 4.08-4.02 (m, 2H), 3.90 (t, $J = 9.3$, 1H), 3.44 (dd, $J = 9.8$, 3.4, 1H), 2.60-2.48 (m, 2H), 2.27 (t, $J = 7.3$, 2H), 1.65-1.59 (m, 6H), 0.93 (t, $J = 7.3$, 3H); ^{13}C -NMR (126MHz; MeOD- d_4): δ 175.4, 148.7, 125.6, 103.7, 84.6, 74.3, 73.9, 71.8, 65.3, 51.5, 37.2, 29.4, 26.9, 25.9, 19.7, 14.2.

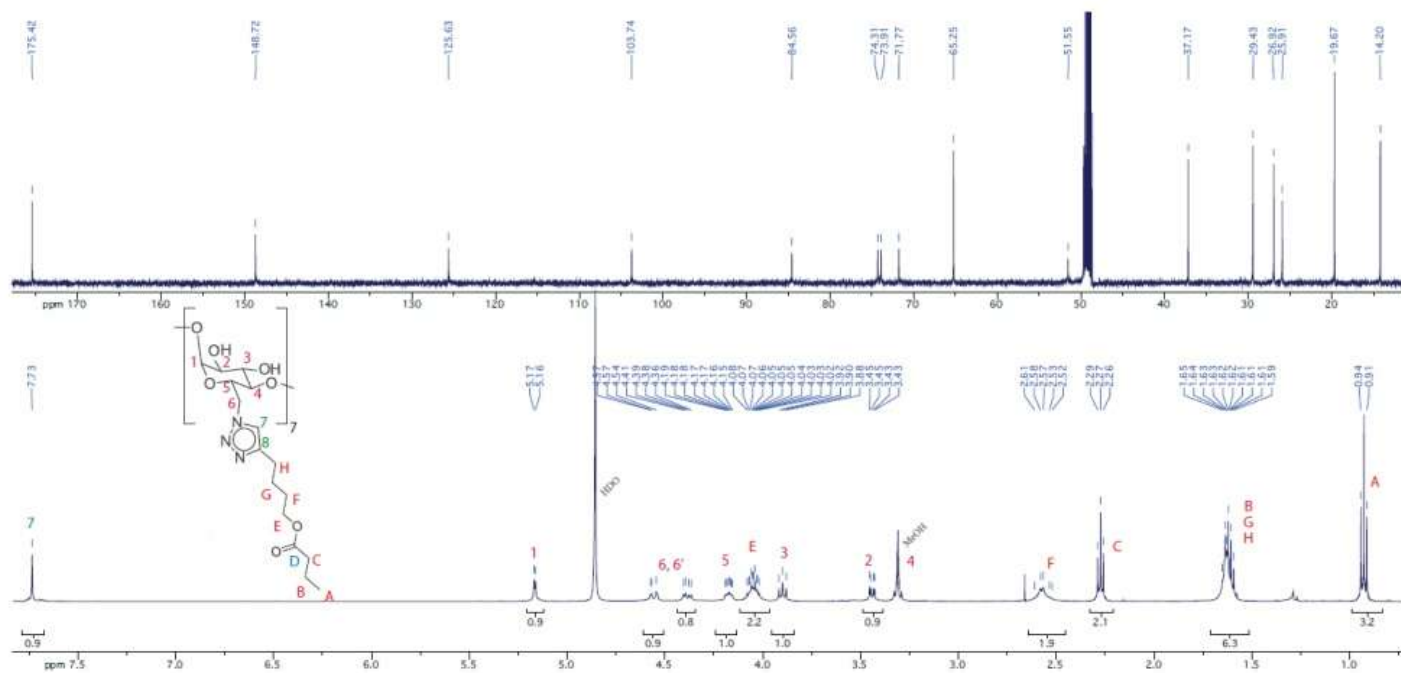


Fig. S26: 1H -NMR and ^{13}C -NMR spectrum of β CD-Tz-6Es4

β CD-Tz-6Am4 from P5

MS - m/z calculated for $C_{112}H_{182}N_{28}O_{35}+Na^+$ = 2503.3, found 2503.4; 1H -NMR (500 MHz; MeOD- d_4): δ 7.75 (s, 1H), 5.17 (d, J = 3.6, 1H), 4.57 (d, J = 14.2, 1H), 4.43-4.41 (s, br, 1H), 4.22-4.19 (s, br, 1H), 3.90 (d, J = 8.3, 2H), 3.45 (d, J = 9.5, 1H), 3.14 (t, J = 6.3, 2H), 2.57 (s,br, 2H), 2.14 (t, J = 7.4, 2H), 1.61 (7, J = 7.4, 6H), 1.50 (6, J = 7.1, 2H), 0.92 (t, J = 7.4, 3H); ^{13}C -NMR (126MHz; $CDCl_3$): δ 176.1, 148.9, 125.7, 103.7, 84.5, 74.3, 73.9, 71.6, 51.6, 40.6, 40.1, 39.2, 30.2, 27.9, 26.0, 20.6, 14.2

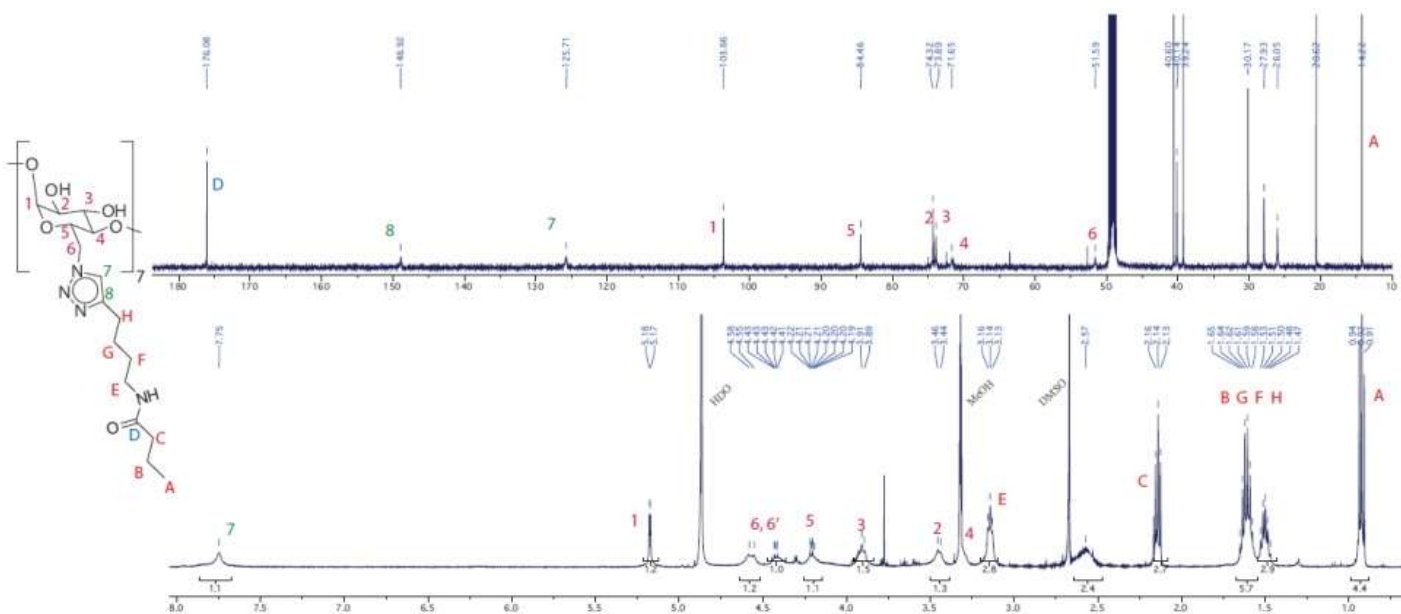


Fig. S27: 1H -NMR and ^{13}C -NMR spectrum of β CD-Tz-6Am4

β CD-Tz-6EsF4 from P6

MS - m/z calculated for $C_{112}H_{126}N_{21}F_{49}O_{42}+2Na^{2+} = 1707.4$; found 1707; 1H -NMR (500 MHz; MeOD- d_4): δ 7.74 (s, 1H), 5.17 (s, br, 1H), 4.55 (d, J = 12.9, 1H), 4.42-4.39 (m, 1H), 4.20 (s, br, 1H), 3.93 (t, J = 8.7, 1H), 3.53 (t, J = 6.4, 2H), 3.46-3.44 (m, 1H), 3.33-3.25 (m, 1H), 2.59-2.51 (m, 2H), 1.64-1.50 (m, 4H); ^{13}C -NMR (126MHz; MeOD- d_4): δ 163.1 (t, J = 24), 149.0, 125.6, 119.6 (qt, J = 286.81, 34.39), 110.4 (m, 112.75-107.96), 103.7, 84.5, 74.2, 73.9, 71.6, 62.7, 51.5, 33.3, 26.9, 26.1.

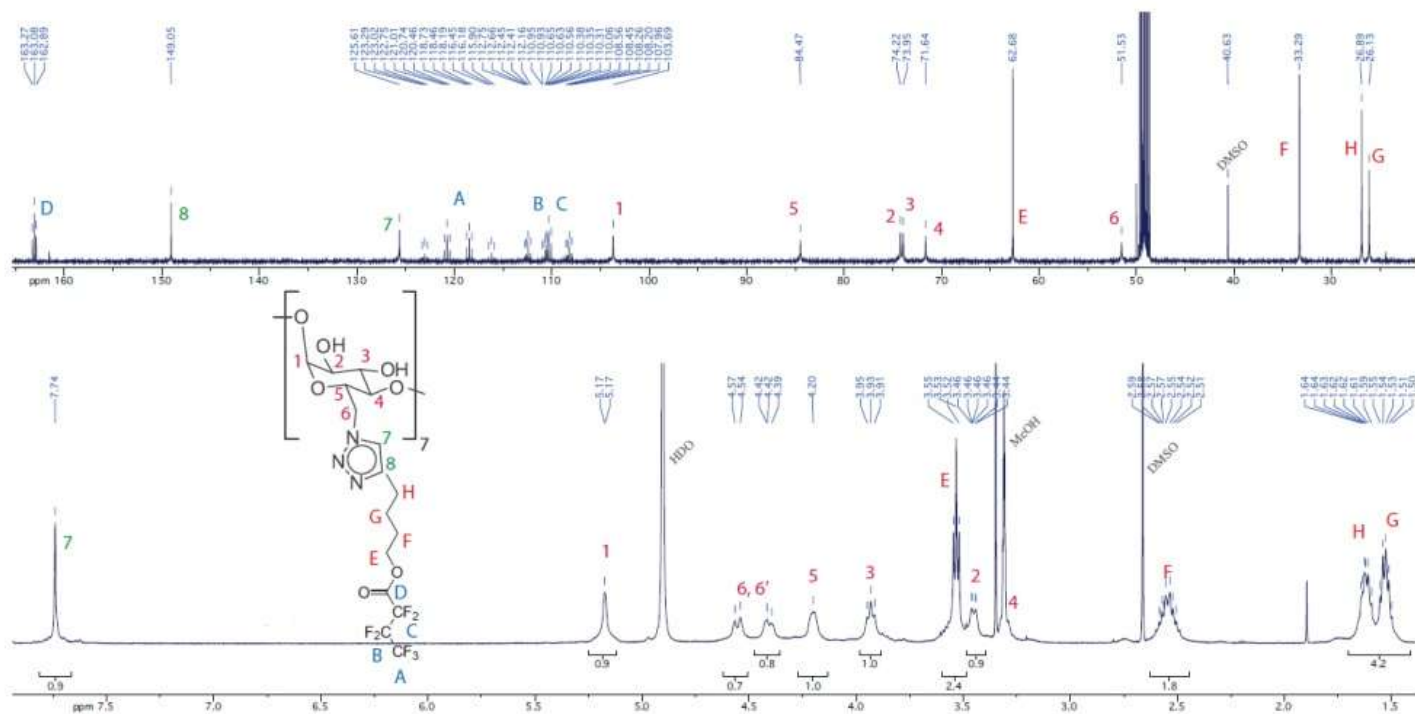


Fig. S28: 1H -NMR and ^{13}C -NMR spectrum of β CD-Tz-6EsF4

β CD-Tz-6Es6Es2 from P9

MS - m/z calculated for $C_{147}H_{231}N_{21}O_{56}$ = 3186.5876; found $[M+H]^+$; 1H -NMR (500 MHz; $CDCl_3$): δ 7.74 (s, 1H), 5.17 (s, 1H), 4.57-4.39 (m, 2H), 4.19 (s, 1H), 4.10 (q, J = 7.1, 4H), 4.04 (s, 2H), 3.93-3.89 (m, 2H), 3.46-3.44 (m, 1H), 2.56 (s, 2H), 2.32 (s, 6H), 1.63-1.61 (m, 11H), 1.23 (t, J = 7.1, 4H); ^{13}C -NMR (126MHz; $CDCl_3$): δ 175.21, 175.16, 148.7, 125.6, 103.7, 84.5, 74.3, 73.9, 71.7, 65.3, 61.6, 34.9, 29.4, 26.9, 26.0, 25.6, 14.8.

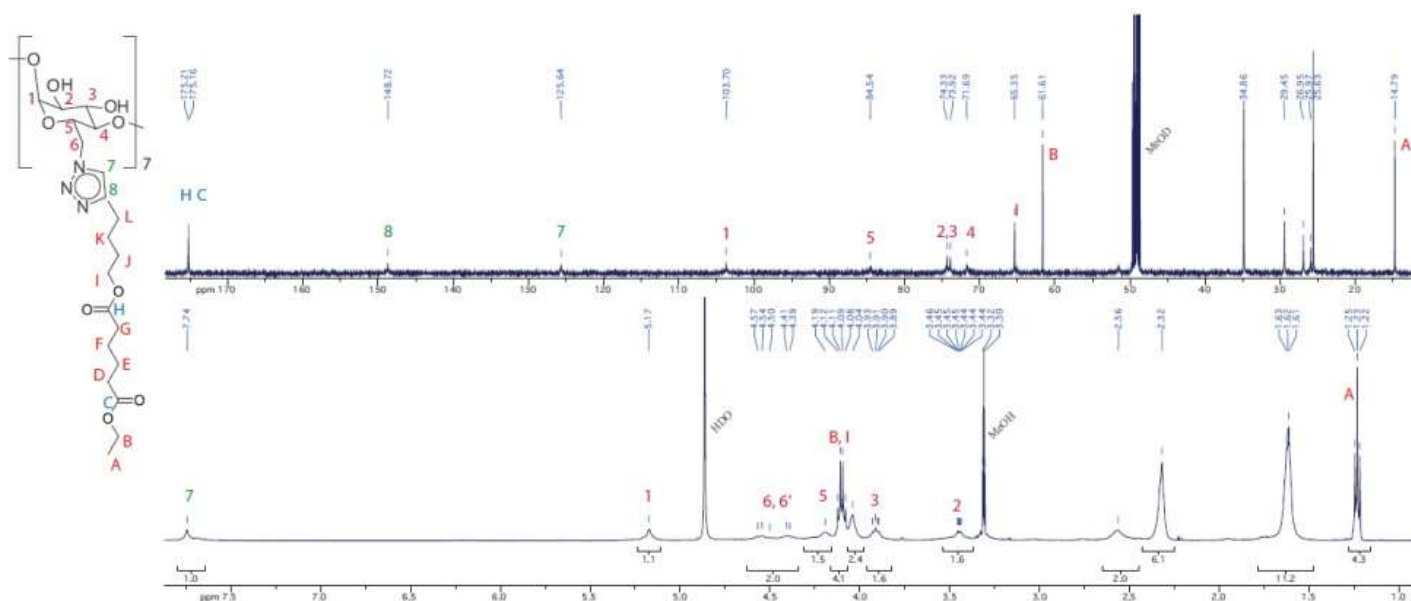


Fig. S29: 1H -NMR and ^{13}C -NMR spectrum of β CD-Tz-6Es6Es2

β CD-Tz-6Es8 from P10

MS - m/z calculated for $C_{140}H_{231}N_{21}O_{42}+2H^{2+} = 1440.8388$; found 1440.8376; 1H -NMR (500 MHz; MeOD- d_4): δ 7.73 (s, 1H), 5.16 (d, J = 3.6, 1H), 4.57-4.54 (m, 1H), 4.39 (t, J = 13.3, 1H), 4.17 (s, 1H), 4.03 (s, br, 2H), 3.91 (m, 1H), 3.45 (s, br, 1H), 2.57 (s, br, 2H), 2.27 (t, J = 7.7, 6H), 1.63-1.58 (m, 13H), 1.35-1.30 (m, 32H), 0.90 (d, J = 14.1, 11H); ^{13}C -NMR (126MHz; MeOD- d_4): δ 178.5, 175.5, 148.7, 125.6, 103.7, 84.6, 74.3, 73.9, 71.7, 65.3, 51.6, 35.5, 35.3, 33.0, 30.41, 30.26, 26.4, 23.8, 14.6.

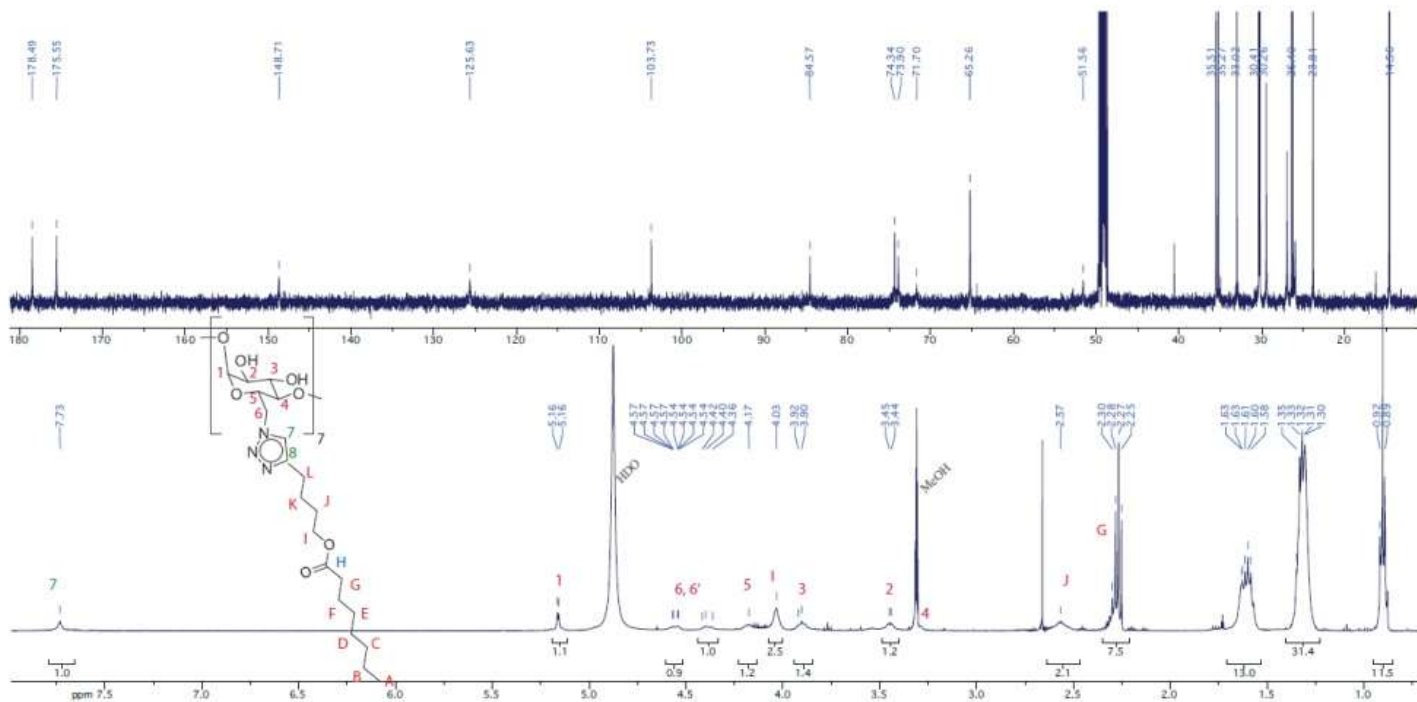


Fig. S30: 1H -NMR and ^{13}C -NMR spectrum of β CD-Tz-6Es8

β CD-Tz-6Am8 from P11

MS - m/z calculated for $C_{140}H_{238}N_{28}O_{35}+2H^{2+} = 1437.3947$; found 1437.3942; 1H -NMR (500 MHz; MeOD- d_8): δ 7.73 (s, 1H), 5.16 (d, J = 3.6, 1H), 4.57-4.54 (m, 1H), 4.41 (dd, J = 14.4, 5.4, 1H), 4.19-4.17 (m, 1H), 3.91 (t, J = 9.3, 1H), 3.44 (dd, J = 9.8, 3.3, 1H), 3.14 (t, J = 6.9, 2H), 2.57-2.52 (m, 2H), 2.16 (t, J = 7.6, 2H), 1.59 (dt, J = 14.3, 7.2, 5H), 1.49 (t, J = 7.2, 2H), 1.33-1.29 (m, 10H), 0.90 (q, J = 4.4, 3H); ^{13}C -NMR (126MHz; $CDCl_3$): δ 176.3, 148.9, 125.6, 103.7, 84.5, 74.3, 73.9, 71.7, 51.6, 40.2, 37.4, 33.1, 30.5, 30.29, 30.15, 27.9, 27.3, 26.0, 23.8, 14.7.

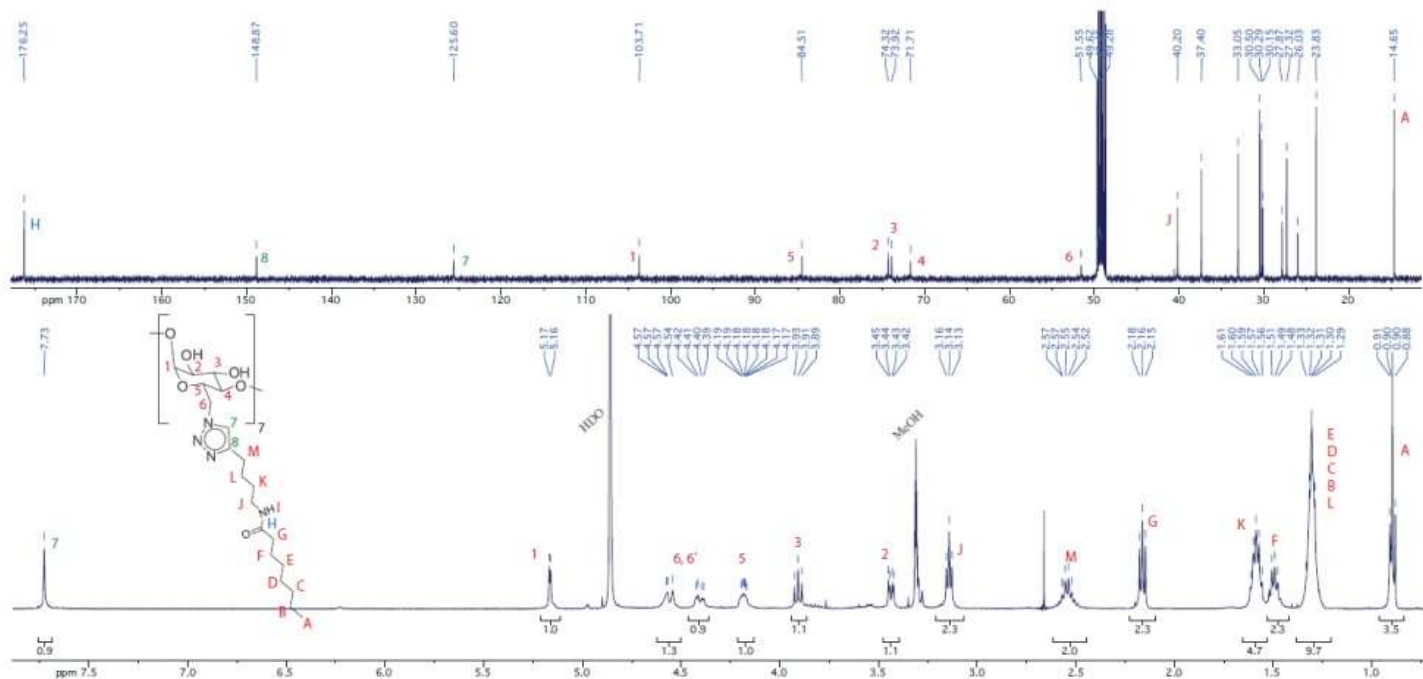


Fig. S31: 1H -NMR and ^{13}C -NMR spectrum of β CD-Tz-6Am8

β CD-Tz-6Ur8 from P12

MS - m/z calculated for $C_{133}H_{231}N_{35}O_{35}+2H^{2+} = 1440.8781$; found 1440.8781; 1H -NMR (500 MHz; MeOD- d_4): δ 7.73 (s, 1H), 5.17 (s, 1H), 4.53 (d, J = 12.2, 1H), 4.40-4.38 (m, 1H), 4.19-4.17 (m, 1H), 3.91 (t, J = 9.1, 1H), 3.47-3.45 (m, 1H), 3.09 (t, J = 7.0, 4H), 2.52 (10, J = 8.0, 2H), 1.62-1.55 (m, 2H), 1.46 (q, J = 6.9, 4H), 1.35-1.31 (m, 6H), 0.90 (t, J = 6.9, 3H); ^{13}C -NMR (126MHz; MeOD- d_4): δ 161.4, 148.9, 125.6, 103.7, 84.5, 74.3, 73.9, 71.7, 51.5, 41.3, 40.9, 32.9, 31.5, 31.1, 27.8, 26.1, 23.8, 14.6.

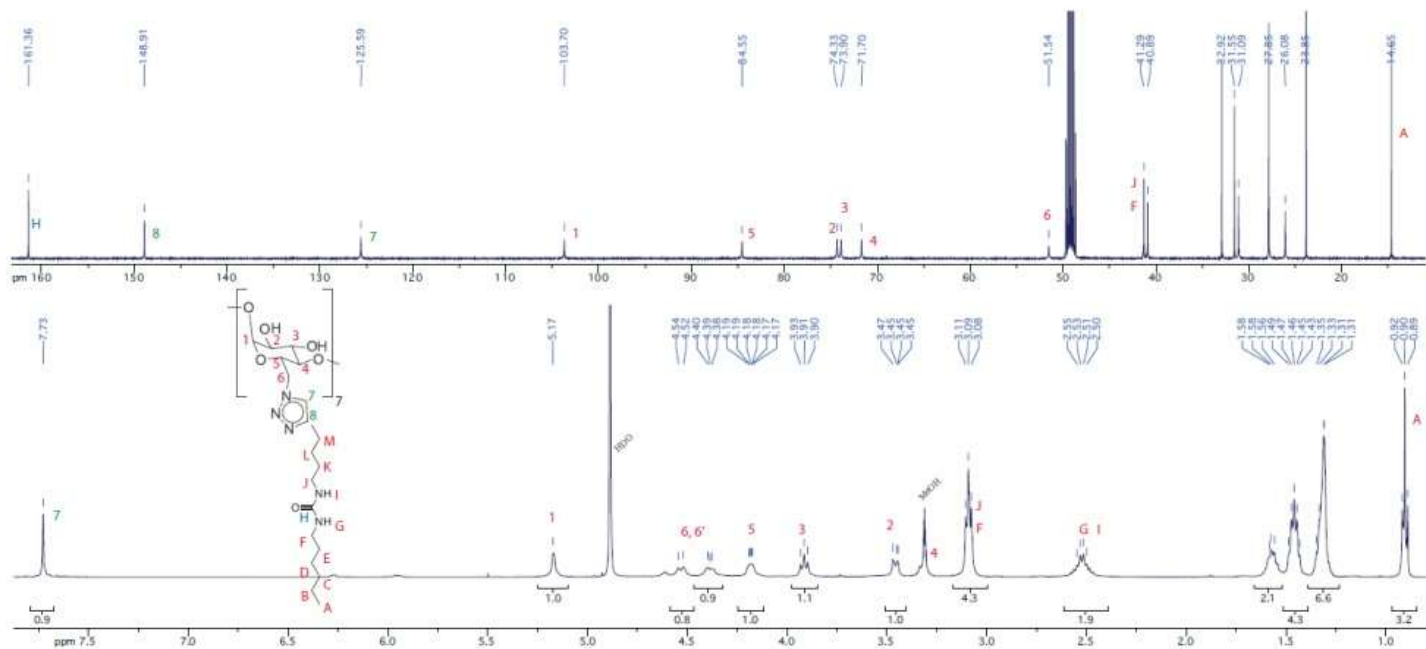
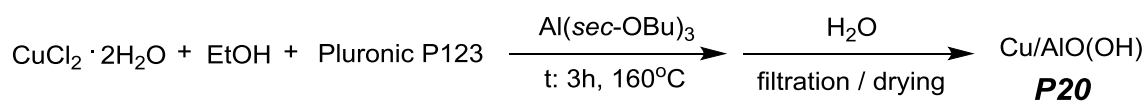
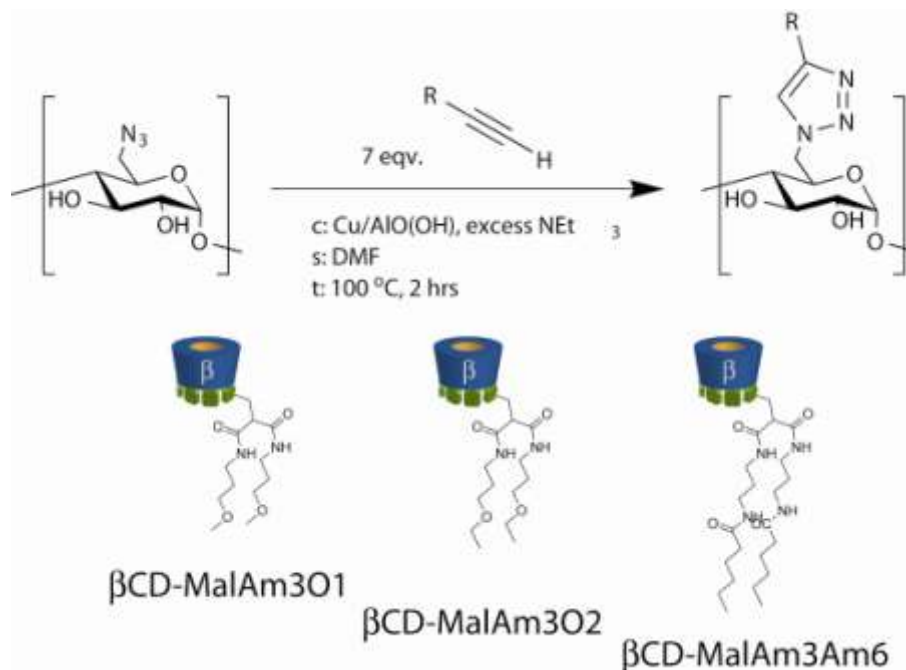


Fig. S32: 1H -NMR and ^{13}C -NMR spectrum of β CD-Tz-6Ur8

Click Chemistry using Cu/AIO(OH) as Catalyst



The preparation of catalyst **P20** proceeded as described Park *et al*⁵. Briefly: CuCl₂·2H₂O (400 mg), EtOH (8.0 g), and pluronic P123 (4.0 g) were combined, the mixture was stirred at room temperature for 30 minutes, after which Al(sec-OBu)₃ (9.1 g, 37 mmole{) was added slowly. The heterogenous solution was heated to 160 °C (reflux) for 3 h, and gelation was effected by dropwise addition of water (3.0 mL) through the top of the condenser. The reaction was stirred for another 30 minutes, cooled and kept at room temperature overnight. The baby-blue solid was filtered, washed with acetone, and dried in an oven overnight to give **P20** as a green solid. This insoluble solid is kept in the oven (120 °C) as it absorbs moisture readily to return to the blue color, and used as is without further characterization.



General procedure illustrated with compound β CD-Tz-MalAm3Am6. In a 1 dram sample vial, alkyne **P19** (93 mg, 0.206mmol, 8.0 eqv.), *per*-6-azido- β -cyclodextrin (33.7 mg, 0.0257mmol, 1.0 eqv.), Cu/AIO(OH) (**P20**, 60mg), triethylamine (86 μ L, 0.62mmol, 24 eqv.) was combined in 1 mL DMF to give a heterogenous solution. The sample vial was capped, sealed with teflon tape, and further wrapped with parafilm to prevent evaporation of triethylamine. The reaction was then heated to 80 °C in an oil bath, and the previously light-green heterogenous solution turns to a dark-brown almost immediately at this temperature. This is allowed to stir for 24 hours. For workup, the reaction is first cooled to room temperature, and then centrifuged. The light brown solution, now free of solid catalyst, was chromatographed (silica gel, using dichloromethane:MeOH 9:1 gradient to 1:1 as eluent) to give 45 mg of a light-yellow crystalline material (39%).

β CD-Tz-MalAm3Am6 from P19

MS - m/z calculated for $C_{210}H_{357}N_{49}O_{56} = 4461.6593$; found $[M+H]^+$; 1H -NMR (300 MHz; $CDCl_3$): δ 7.73 (s, 1H), 5.11 (s, 1H), 4.59 (s, 1H), 4.30 (s, 1H), 4.11 (s, 1H), 3.87-3.84 (m, 2H), 3.48-3.44 (m, 2H), 3.25-3.03 (m, 15H), 2.19 (t, $J = 6.7$, 6H), 1.69-1.68 (m, 5H), 1.61 (t, $J = 7.1$, 7H), 1.35-1.29 (m, 14H), 0.91 (t, $J = 6.5$, 10H); ^{13}C -NMR (126MHz; $CDCl_3$): δ 176.4, 171.6, 145.8, 126.4, 103.8, 84.6, 74.4, 73.9, 71.9, 38.5, 38.0, 37.4, 32.8, 30.48, 30.43, 27.0, 23.6, 14.6.

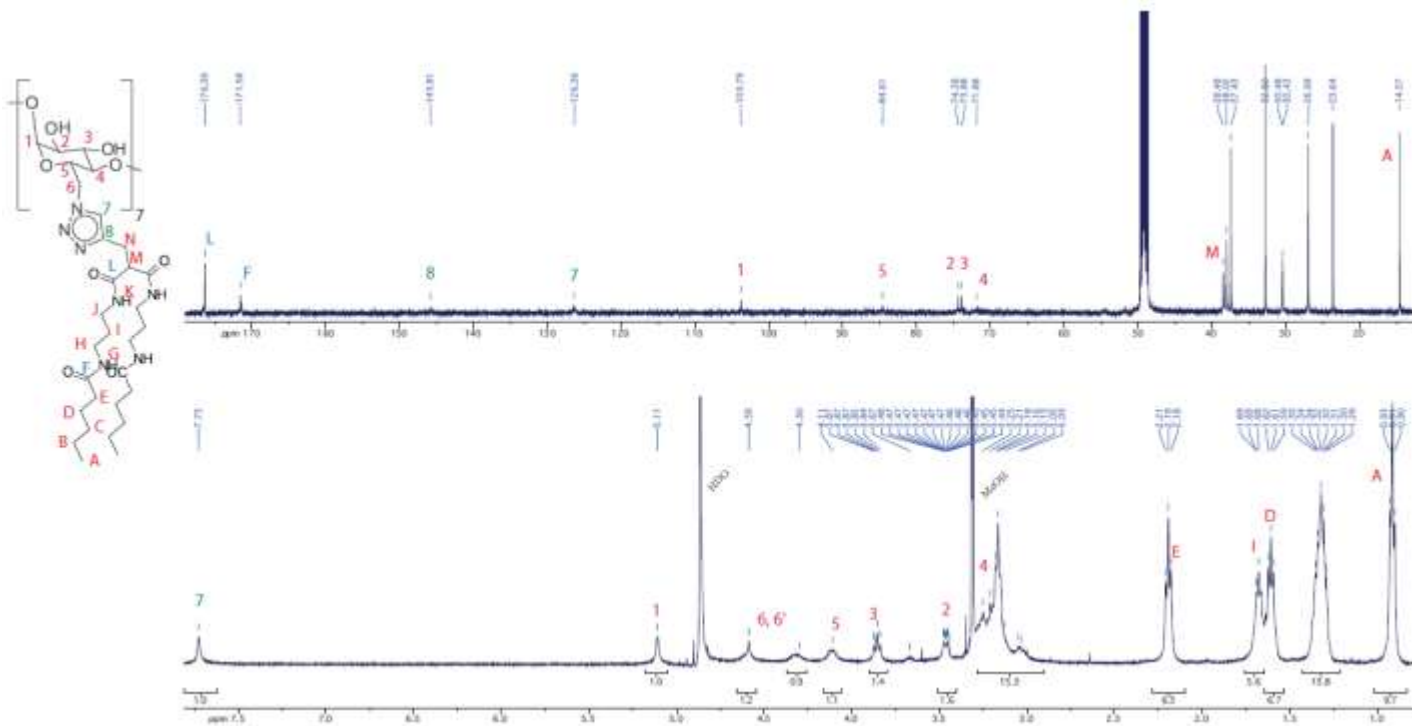


Fig. S33: 1H -NMR and ^{13}C -NMR spectrum of β CD-Tz-MalAm3Am6

β CD-Tz-MalAm3O1 from P15

MS - m/z calculated for $C_{140}H_{231}N_{35}O_{56}+H+Na^{2+} = 1661.3$; found 1661.7; 1H -NMR (300 MHz; $CDCl_3$): δ 7.69 (s, 1H), 5.11 (d, $J = 3.3$, 1H), 4.55 (d, $J = 9.0$, 1H), 4.38 (d, $J = 9.2$, 1H), 4.14 (t, $J = 4.1$, 1H), 3.86 (t, $J = 9.2$, 1H), 3.64 (t, $J = 7.6$, 1H), 3.47-3.44 (m, 2H), 3.41-3.36 (m, 6H), 3.30 (s, 6H), 3.28-3.07 (m, 7H), 1.76-1.69 (m, 5H), 1.31 (t, $J = 7.3$, 2H).

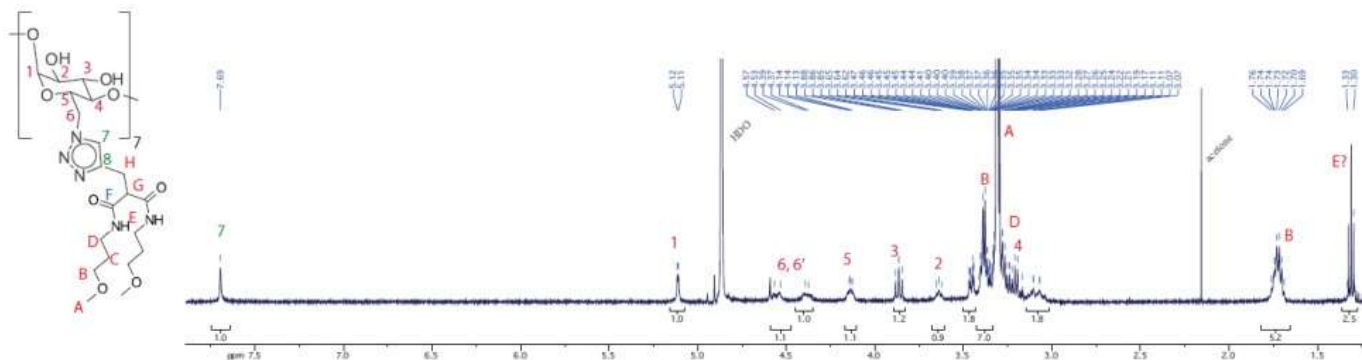


Fig. S34: 1H -NMR spectrum of β CD-Tz-MalAm3O1

β CD-Tz-MalAm3O2 from P14

MS - m/z calculated for $C_{154}H_{259}N_{35}O_{56}$ = 3494.849; found $[M+H]^+$; 1H -NMR (500 MHz; MeOD): δ 7.70 (s, 1H), 5.11 (d, J = 3.3, 1H), 4.57 (d, J = 14.0, 1H), 4.39 (d, J = 8.8, 1H), 4.13 (s, 1H), 3.87 (t, J = 9.2, 1H), 3.67-3.60 (m, 2H), 3.51-3.41 (m, 12H), 3.27 (d, J = 11.9, 5H), 3.07 (s, 2H), 1.92 (s, 1H), 1.73 (dt, J = 17.0, 8.9, 4H), 1.17 (m, 6H); ^{13}C -NMR (126MHz; $CDCl_3$): δ 171.3, 145.8, 126.0, 103.8, 84.6, 74.4, 73.9, 72.0, 69.3, 67.4, 55.0, 51.6, 38.44, 38.38, 38.30, 30.7, 15.8

Upon conjugation, the alkyl tails appear to have broken symmetry due to slow amide rotation. This is manifested in non-equivalent amide carbons (171 ppm), as well as overlapping terminal methyl proton triplets at 1.17 ppm.

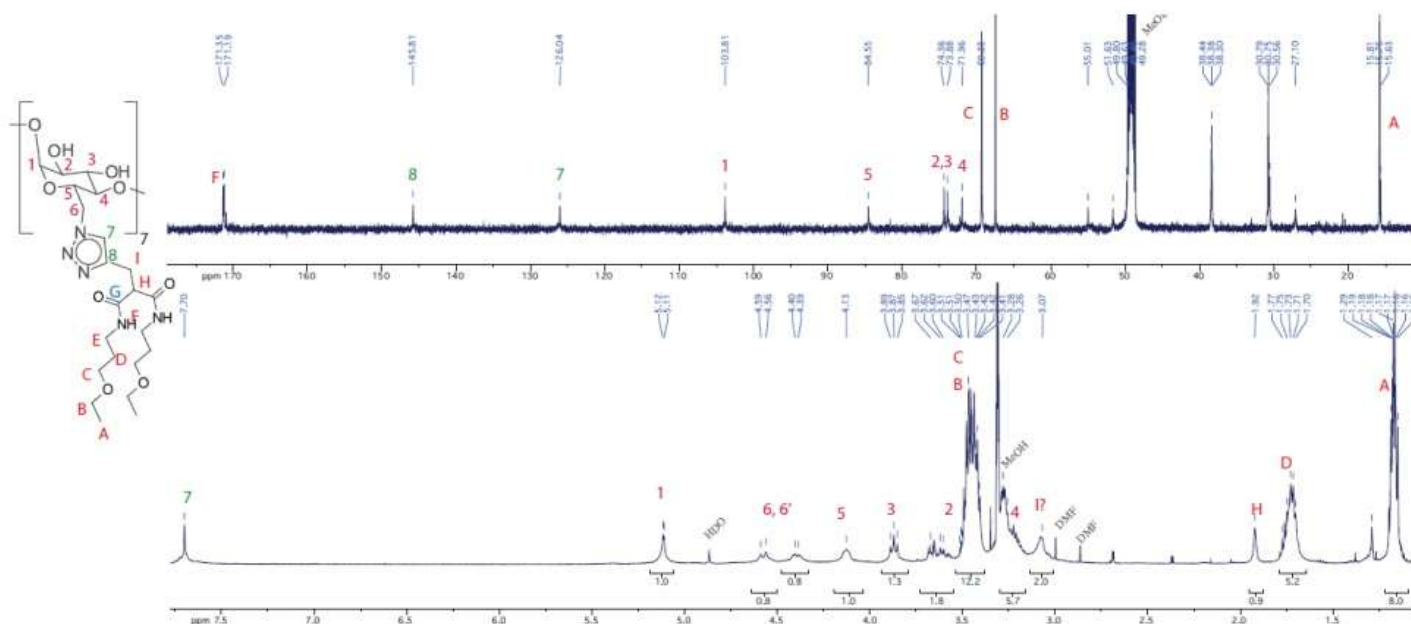


Fig. S35: 1H -NMR and ^{13}C -NMR spectrum of β CD-Tz-MalAm3O2

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