Electronic Supporting Information of the Manuscript:

Proline-Coated Gold Nanoparticle as a Highly Efficient Nanocatalyst for the Enantioselective Direct Aldol Reaction in Water.

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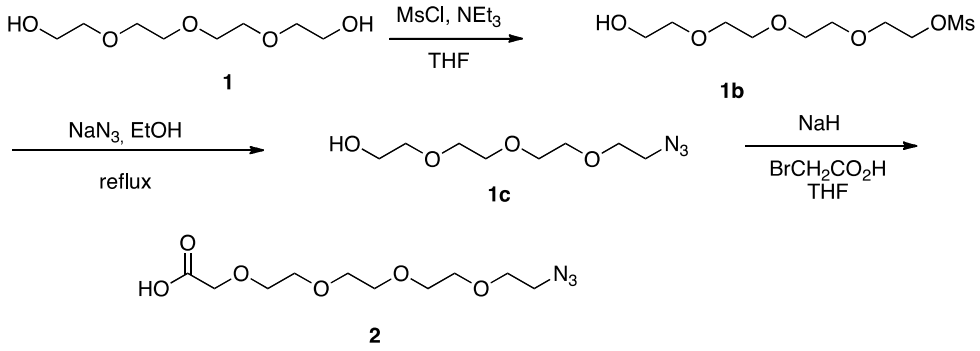
General Methods

If not indicated, all reactions were run under an atmosphere of dry argon using oven-dried glassware and freshly distilled and dried solvents. Toluene, CH_2Cl_2 and diethyl ether were dried on an Innovative technology drying system. The precursor chemicals were obtained from Sigma-Aldrich and used without further purification. TLC was performed on Silica Gel GF254 (Merck) with detection by charring with phosphomolybdic acid/EtOH. For flash chromatography, silica Gel (Merck 230-400 mesh) was used. Chromatographic columns were eluted with positive air pressure and eluents are given as volume to volume ratios (v/v). NMR spectra were recorded with a Bruker Avance DPX400 (^{1}H, 400 MHz) and Bruker Avance DRX500 (^{1}H, 500 MHz), spectrometers. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. Routine spectra were referenced to the residual proton or carbon signals of the solvent. High Resolution mass spectra (HRMS) were recorded in "Centro de Investigación, Tecnología e Innovación de la Universidad de Sevilla" with a Kratos MS-80RFA 241-MC apparatus. Optical rotations were determined with a Perkin-Elmer 341 polarimeter. Elemental analyses were measured in a LECO TruSpec® CHNS-932 apparatus. Melting points were measured in STUART SMP3 apparatus in open end capillary tubes. Enantiomeric excesses were measured on a Waters alliance 2695 and Agilent Technologies 1200 series apparatus with stationary chiral phase using Chiralpack AD column. TEM images of the gold nanoparticles were recorded in "Centro de Investigación, Tecnología e Innovación de la Universidad de Sevilla" using a Philips CM-200 electronic microscope.

14-azido-3,6,9,12-tetraoxatetradecanoic acid (2).

Synthesis of the hydrophilic spacer **2**, has been done in three steps following the scheme:



To a solution of tetraethylene glycol **1** (22.7 mL, 140 mmol) and Et_3N (15 mL) in THF (100 mL) at 0ºC was added dropwise a solution of methanesulfonyl chloride (10.8 mL, 140 mmol). The reaction mixture was then allowed to warm to room temperature and stirred vigorously overnight. The mixture was diluted with CH_2Cl_2 (250 mL) and washed with saturated NH_4Cl aqueous solution (50 mL) and brine (20 mL). The organic solution was dried over Na_2SO_4 and concentrated in vacuum to give the crude product. The oily residue was purified by flash column chromatography, eluting with dichlorometane/methanol (20:1) to give 12.9 g of the mesylated compound **1a** as an oil (37% yield): R_f = 0.5 in dichlorometane/methanol (9:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.41- 4.35 (m, 2H), 3.81-3.60 (m, 14H), 3.09 (s, 3H), 2.97 (s, 1H). ^{13}C NMR (125.6 MHz, $CDCl_3$) δ: 72.5, 70.4, 70.3, 70.1, 69.4, 68.9, 61.4, 37.4. HRMS Calcd. for $C_9H_{20}O_7SNa$ $[M+Na]^+$: m/z 273.1008. Found: 273.0997.

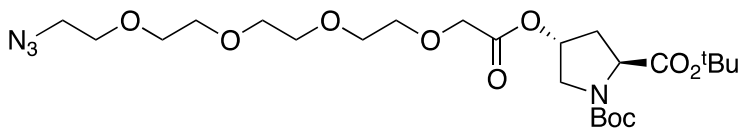
A mixture of mesylated compound **1a** (9.1 g, 33.4 mmol) and sodium azide **(**2.4 g., 36.8 mmol) in ethanol (50 mL) was heated at reflux overnight, then cooled to room temperature and concentrated in vacuo. The residue was diluted with ether (250 mL), washed with brine (50 mL), and dried over Na_2SO_4. The solvent was removed under vacuum to yield the crude product, which was purified by flash column chromatography, eluting with a gradient of hexane/ethyl acetate (1:1) to give 6.4 g of the azide **1b** as an oil (97% yield): R_f = 0.18 in hexane/ethyl acetate (1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.58 (t, 2H, J = 4.8 Hz), 3.57-3.51 (m, 10H), 3.46 (t, 2H, J = 4.8 Hz), 3.26 (t, 2H, J = 4.8 Hz), 3.10 (brs, 1H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 72.5, 70.6, 70.5, 70.4, 70.2, 69.9, 61.5, 50.5. HRMS calcd for $C_8H_{17}N_3O_4Na$ $[M+Na]^+$: m/z 220.1297. Found: 220.1288.

To a suspension of NaH (660 mg, 27.40 mmol) in dry THF (22 mL) under argon, was added dropwise during 30 min a solution of **1b** (1.00 g, 4.60 mmol) in THF (23 mL). Once the addition finished the mixture was stirred another 1 h, then a solution of acetic acid bromide (1.30 g, 9.20 mmol) in THF (23 mL) was added dropwise during 1 h and stirred overnight. The excess of NaH was destroyed by a slow addition of water, THF was evaporated at vacuum and the mixture washed with HCl 1M (50 mL) and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent evaporated. The crude mixture was purified by column chromatography (CH_2Cl_2/MeOH, 9:1) affording **2** (980 mg, 77%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42 (bs, 1H), 4.16 (s, 2H), 3.76-3.62 (m, 14H), 3.40 (t, 2H, $^3J_{H,H}$ = 5.2). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 172.8, 71.1, 70.6, 70.5, 70.4, 70.3, 70.2, 70.0, 68.8, 50.6. HRMS: Calcd. for $C_{10}H_{19}N_3ONa$ $[M+Na]^+$: 300.1172 Found: 300.1157.

***tert*-Butyl *N*-*tert*-Butoxycarbonyl-4-hydroxy-L-proline (3)**

To a solution of *N*-Boc-4-hydroxy-L-proline (4 g, 17.29 mmol), triethylbenzylamonium chloride (3.9 g, 17.29 mmol), and K_2CO_3 (40g, 449 mmol) in DMF (80 mL) was added 2-bromo-2-methylpropane (19 mL, 172.9 mmol), and the reaction heated (60°C) under reflux for 12 hours. The solvent was evaporated, added water and extracted with ether (3 x 200 mL). The organic layer was dried over Na_2SO_4, and the solvent evaporated. The crude mixture was purified by column chromatography (AcOEt : Hex, 1:1) affording **3** (2.4 g, 49 %) as a colourless oil .$[\alpha]_D^{20}$: -56.6 (*c.* 1, $CHCl_3$).^{1}H NMR (500 MHz , $CDCl_3$) δ: 4.45 (s, 1H), 4.32-4.25 (m, 1H), 3.60 (m, 1H), 3.43-3.41 (m, 1H), 2.31-2.23 (m, 1H), 2.04-2.00 (m, 1H), 1.46 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.2, 154.2, 81.2, 80.2, 69.2, 58.5, 54.7, 39.2, 28.3, 28.0. HRMS: Calcd for $C_{14}H_{25}NO_5$: [M + Na] 310.1630 Found: 310.1639 (2.8 ppm).

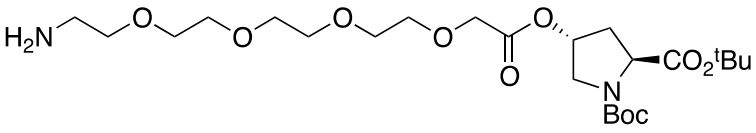
tert-Butyl 4-(14-azido-3,6,9,12-tetraoxatetradecanoyl)-*N*-Boc-L-proline (4)



To a solution of **2** (900 mg, 3.86 mmol) and diisopropylcarbodiimide (488.39 mg, 3.87 mmol) in CH_2Cl_2 (45 mL), a solution of **3** (1.1 g, 3.86 mmol) and DMAP (cat.) in CH_2Cl_2 (40 mL) was canulated and stirred for 6 hours. The mixture was nuetralized with 1M HCl and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent evaporated. The crude mixture was purified by column chromatography (AcOEt : Hex, 4 : 1) affording **4** (1.5 g, 71 %) as a yellow oil. ^{1}H NMR (500 MHz , $CDCl_3$) δ: 5.34 (s, 1H), 4.30-4.21 (m, 1H), 4.15 (s, 2H), 3.73-3.67 (m, 15H), 3.54-3.52 (m, 1H),

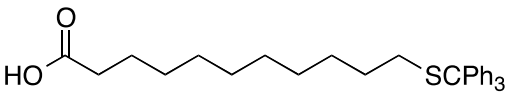
3.40-3.38 (m, 2H), 2.43-2.39 (m, 1H), 2.23-2.17(m, 1H), 1.48 (s, 9H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.4, 170.0, 154.0, 81.4, 80.2, 72.3, 70.9, 70.7, 70.6, 70.1, 70.0, 68.5, 58.8, 58.4, 58.3, 57.0, 51.8, 50.7, 28.5, 28.3, 28.0, 27.9 ppm. HRMS: Calcd. for $C_{24}H_{42}N_4O_{10}Na$ [M+Na] 569.2799. Found 569.2810 (2.5 ppm).

***tert*-Butyl 4-(14-amino-3,6,9,12-tetraoxatetradecanoyl)-*N*-Boc-L-proline (5)**



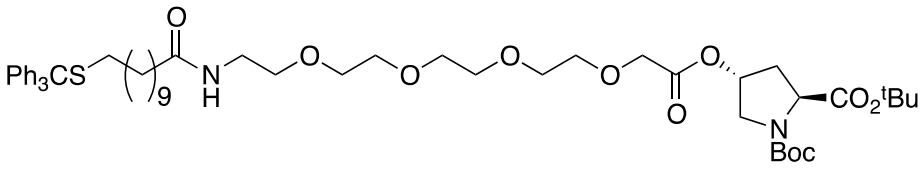
Into a Fisher-Porter **4** (1 g, 1.8 mmol), Pd (100 mg) and CH_2Cl_2 (20 mL) was added and hydrogenated at 1 atm of H_2 for 12 hours. The mixture was filtered through Celite and the crude was purified by column chromatography (Cl_2CH_2 : MeOH, from 15 : 1 to 5 :1) affording **5** (440 mg, 47 %) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.26 (s, 1H), 4.22-4.07 (m, 3H), 3.81 (t, 2H, *J* = 5 Hz), 3.66-3.44 (m, 14H), 3.22-3.15 (m, 2H), 2.35-2.33 (m, 1H), 2.13-2.08 (m, 1H), 1.39 (s, 9H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.4, 170.4, 153.9, 81.4, 80.3, 73.7, 72.8, 70.5, 70.0, 69.9, 69.7, 69.5, 68.3, 66.6, 58.2, 51.7, 39.8, 36.4, 28.2, 27.9. HRMS: Calcd. for $C_{24}H_{44}N_2O_{10}Na$ [M+Na] 543.2894 Found 543.2897 (0.6 ppm).

11-tritylsulfenylundecanoic acid (6)



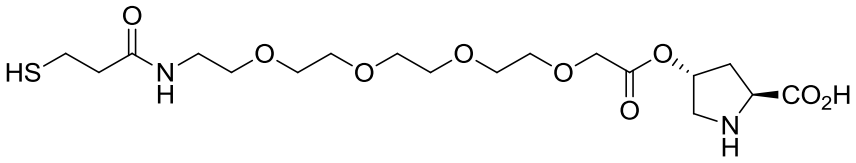
To a solution of 11-mercaptoundecanoic acid (2g, 9.09 mmol) and DIPEA (4.8 mL, 27.42 mmol) in toluene (60 mL), trityl chloride (5.12 g, 18.41 mmol) was added and stirred for 24 hours. The solvent was evaporated and the crude was purified by column chromatography (AcOEt : Hex, 1:9) affording **6** (3.6 g, 90%) as a white solid. ^{1}H NMR (300 MHz , $CDCl_3$) δ: 7.48-7.34 (m, 6H), 7.31-7.21 (m, 9H), 2.38 (t, 2H, *J* = 8.2 Hz), 2.18 (t, 2H, *J* = 7.5 Hz), 1.71-1.61 (m, 2H), 1.47-1.22 (m, 12H), 0.95-0.88 (m, 2H).

***tert*-Butyl 4-[N-(11-tritylsulfenyl)undecanoyl)-14-amino-3,6,9,12-tetraoxatetradecanoyl]-N-Boc-L-proline (7).**



To a solution of **5** (796 mg, 1.53 mmol) and DIPEA (533 μL, 3.06 mmol) in DMF (10 mL/mmol amina), a solution of **6** (774 mg, 1.68 mmol), TBTU (539.4 mg, 1.68 mmol) and DIPEA (266 μL, 3.06 mmol) in DMF was added and stirred overnight. DMF was evaporated and the mixture was neutralized with saturated $NaHCO_3$ aq. solution and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The crude was purified by column chromatography (AcOEt : Hex, 1 : 1) affording **7** (1.4 g, 95%) as a colorless oil. $[\alpha]_D^{20}$: -12.8 (*c.* 1.6, $CHCl_3$). ^{1}H NMR (500 MHz , $CDCl_3$) δ: 7.38-7.37 (m, 6H), 7.25-7.22 (m, 6H), 7.17-7.14 (m, 3H), 6.29 (s, 1H), 5.3 (s, 1H), 4.25 (dt, 1H, *J* = 7.5 and 24.0 Hz), 4.11 (s, 2H), 3.72-3.62 (m, 14H), 3.54 (t, 2H, *J* = 5.0 Hz), 3.44-3.43 (m, 3H) 2.51-2.38 (m, 1H), 2.22-2.11 (m, 5H), 1.61 (m, 2H), 1.47 (s, 9H), 1.44 (s, 9H), 1.40 (m, 2H), 1.25-1.20 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.3, 171,4, 169.9, 153.7, 145.1, 129.6, 127.8, 126.5, 81.5, 80.4, 80.2, 73.3, 72.4, 70.9, 70.6, 70.5, 70.2, 69.9, 68.5, 66.3, 58.3, 51.9, 39.1, 36.6, 35.4, 32.0. HRMS: Calcd. for $C_{54}H_{78}N_2O_{11}SNa$ [M+Na] 985.5220. Found: 985.5231 (1.3 ppm)

4-[N-(11-mercaptoundecanoyl)-14-amino-3,6,9,12-tetraoxatetradecanoyl]-L-proline (8).



To a solution of **7** (788 mg, 0.81 mmol) in CH_2Cl_2 (20 mL) under argon atmosphere, TFA (2.33 mL, 32.4 mmol) and Et_3SiH (386 μL, 2.43 mmol) were added and stirred for 24. The mixture was stopped by adding water (7 mL), extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude was purified by column chromatography (CH_2Cl_2 : MeOH, 5 : 1) affording **8** (80 mg, 15 % yield) as a colorless oil. ^{1}H NMR (500 MHz , $CDCl_3$) δ: 6.35 (bs, 1H), 5.40 (bs, 1H), 4.28 (s, 1H), 4.28-4.13 (m, 2H), 3.79-3.43 (m, 16H), 2.54-2.50 (m, 2H), 2.46-2.44 (m, 1H), 2.35-2.34 (m, 1H), 2.19-2.16 (m, 2H) 1.69-1.59 (m, 4H), 1.38-1.26 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.4, 172.5, 169.9, 82.21, 73.6, 70.9, 70.4, 70.4, 70.4, 70.4, 70.1, 69.9, 68.3, 60.1, 50.4, 41.7, 39.2, 39.1,

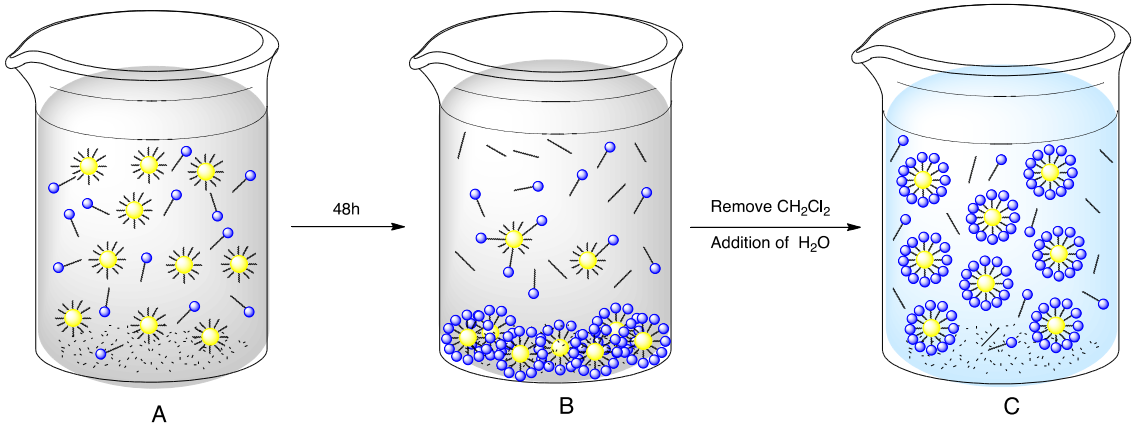
36.6, 35.1, 34.0, 31.0, 29.8, 29.4, 29.4, 29.4, 29.3, 29.3, 29.3, 29.3, 29.1, 29.0, 28.4, 28.3, 28.3, 25.7, 24.6, 22.9.

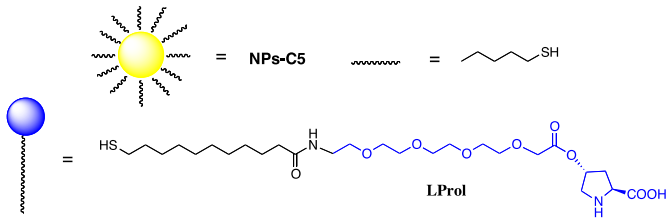
Synthesis of pentanethiolate stabilized gold nanoparticles (9)

To a solution of $HAuCl_4$ (326 mg, 0.82 mmol) in water (30 mL), a solution of TOAB (496 mg, 0.90 mmol) in toluene (20 mL) was added and stirred for 5 min. Then, pentanothiol (0.165 mmol) was added and stirred for 15 min. After a freshly $NaBH_4$ (343.30 mg, 9.07 mmol) aqueous solution (20 mL) was added, the reaction became dark. After stirring for 5 hours, the organic layer was separated and the solvent evaporated to 5 mL. The particles were precipitated by adding ethanol (40 mL) and put in the fridge for 12 hours. The black solid nanoparticles were filtered and washed three times with EtOH. The crude was dissolved in toluene and EtOH was added and put in the fridge again. The process was repeated for three times, affording NPs-C5 as a black solid.^{1}H NMR (500 MHz , $CDCl_3$) δ: 1.3 (bs, 5H), 0.8 (bs, 6H). Anal. Calc. for $(C_5H_{11}S)_{97}Au_{250}$: C, 9.83; H, 1.82; S, 5.25. Found: C, 9.52; H, 2.00; S, 5.51.

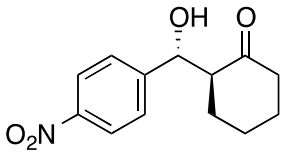
Sythesis of proline-coated gold nanoparticles (I)

To a solution of **9** (20 mg) in CH_2Cl_2 (1.5 mL), a solution of **8** (35 mg) in CH_2Cl_2 (1.5 mL) was added and stirred for 48 hours. The solvent was evaporated and the crude was dissolved in water. The proline functionalized nanoparticles were purified by dialysis (10.000 MWCO, SnakeSkin) for 48 hours. The solution was lyophilized affording **I** (44 mg) as a black solid. Anal. Calc. for $(C_{24}H_{43}N_2O_8S)_{92}Au_{250}$: C. 27.48, H. 4.30, S. 3.00. found C. 27.45%, H. 4.39%, S. 2.62%.

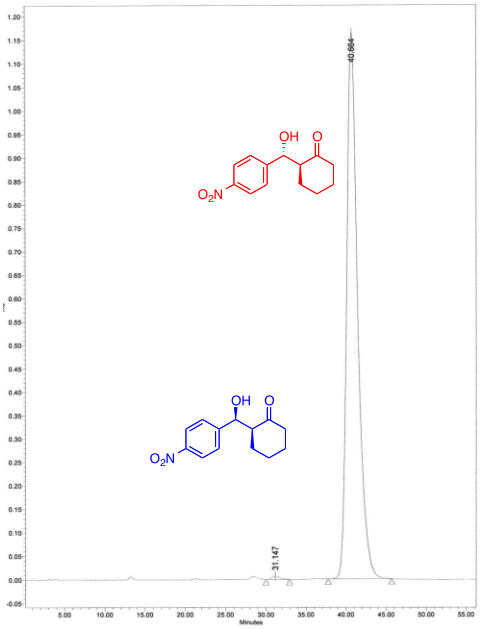




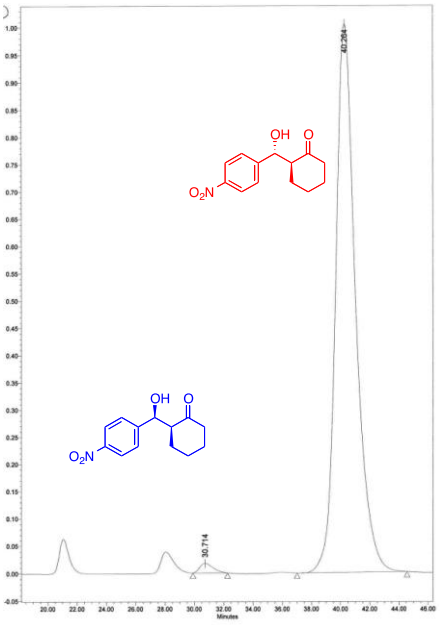
Direct aldol reaction. (2*S*)-2-[(1*R*)-1-Hydroxy-1-(4-nitrophenyl)methyl]cyclohexanone. (12)



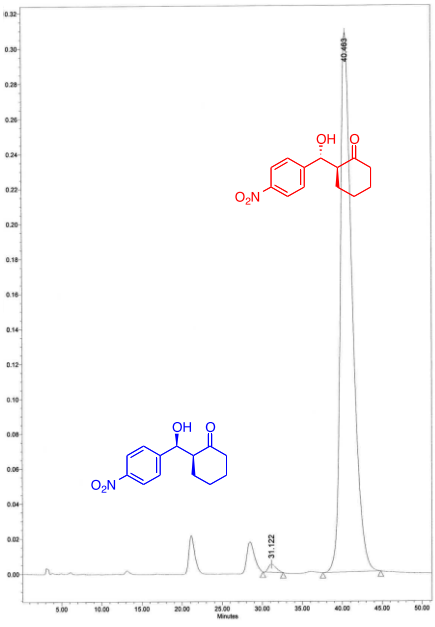
To a suspension of *p*-nitrobenzaldehyde (65 mg, 0.44 mmoles) in cyclohexanone (207 μL, 1.9 mmol), a solution of **I** (24 mg, 2.5 mol%) in water (600 μL) was added and stirred for 48 hours. Then the product was extracted with CH_2Cl_2 and the nanoparticles **I** remained in water were put in reaction again. The organic layer was dried over Na_2SO_4 and the crude was purified by column chromatography (AcOEt/Hex, 1:3) affording **12** as a colorless oil, and the enantiomeric excess was determined by HPLC: Chiracel AD, 1 mL/min, Hexanes : 2-propanol, 92:8; 30°C, t_{Rminor} = 31.14 min, **(*S*)**, t_{Rmayor} = 40.6 min, **(*R*).** Spectroscopy data of mayor isomer *anti* 2*S*,1'*R*. ^{1}H NMR (500 MHz , $CDCl_3$) δ: 8.23 (d, 2H, *J* = 8.5 Hz), 7.53 (d, 2H, *J* = 8.5 Hz), 4.92 (d, 1H, *J* = 8.5 Hz), 4.10 (bs, 1H), 2.64-2.59 (m, 1H), 2.42-2.36 (m, 1H), 2.16-2.1 (m, 1H), 1.71-1.57 (m, 4H), 1.44-1-22 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 148.4, 147.6, 127.9, 123.6, 57.2, 42.7, 30.8, 27.6, 24.7.



1st cycle

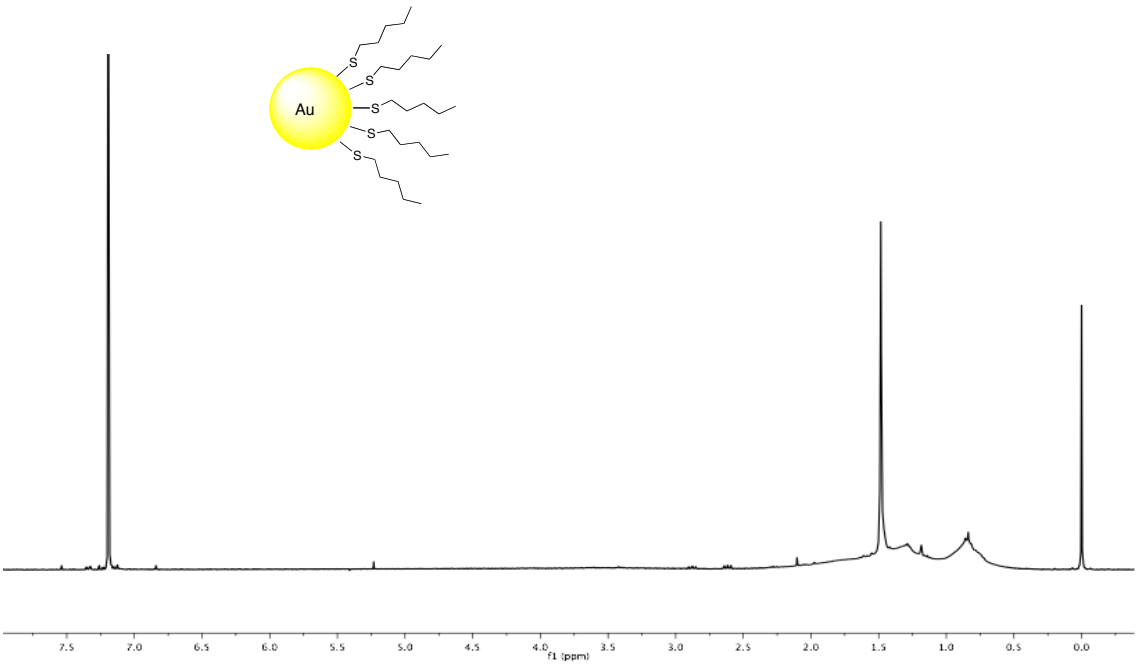


2nd cycle

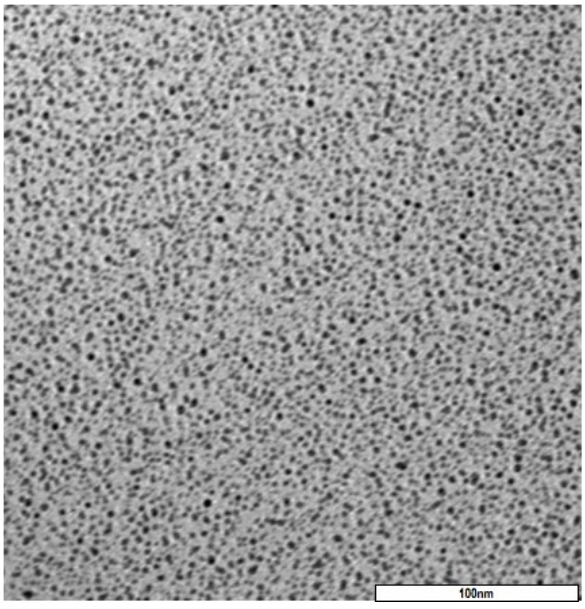


3rd cycle

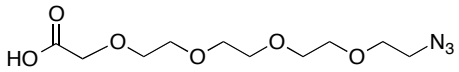
^{1}H-NMR (500MHz, $CDCl_3$)

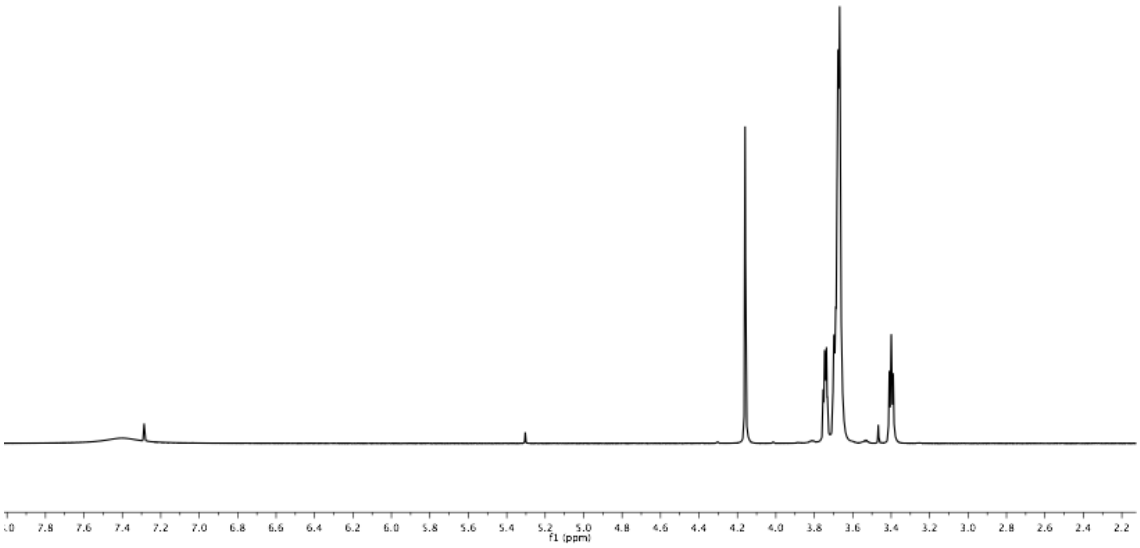


TEM image of NPs-C5



^{1}H-NMR (500MHz, $CDCl_3$)





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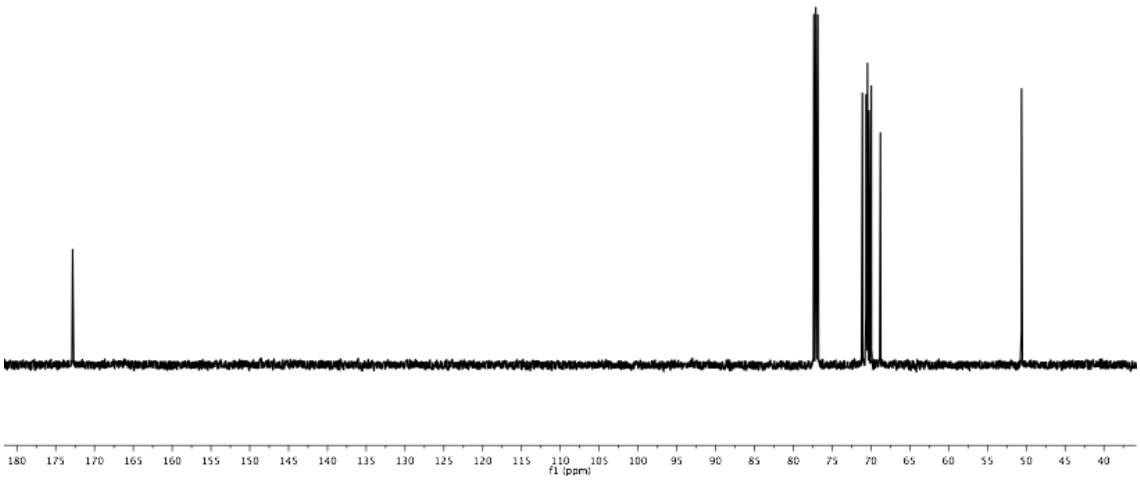
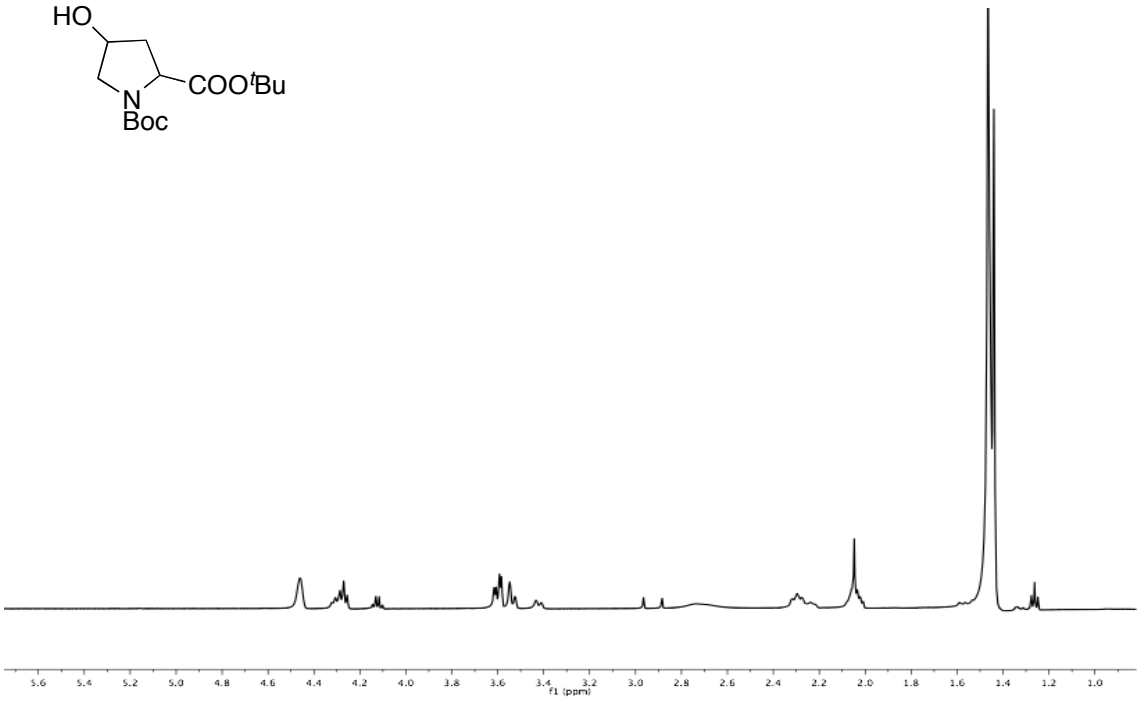
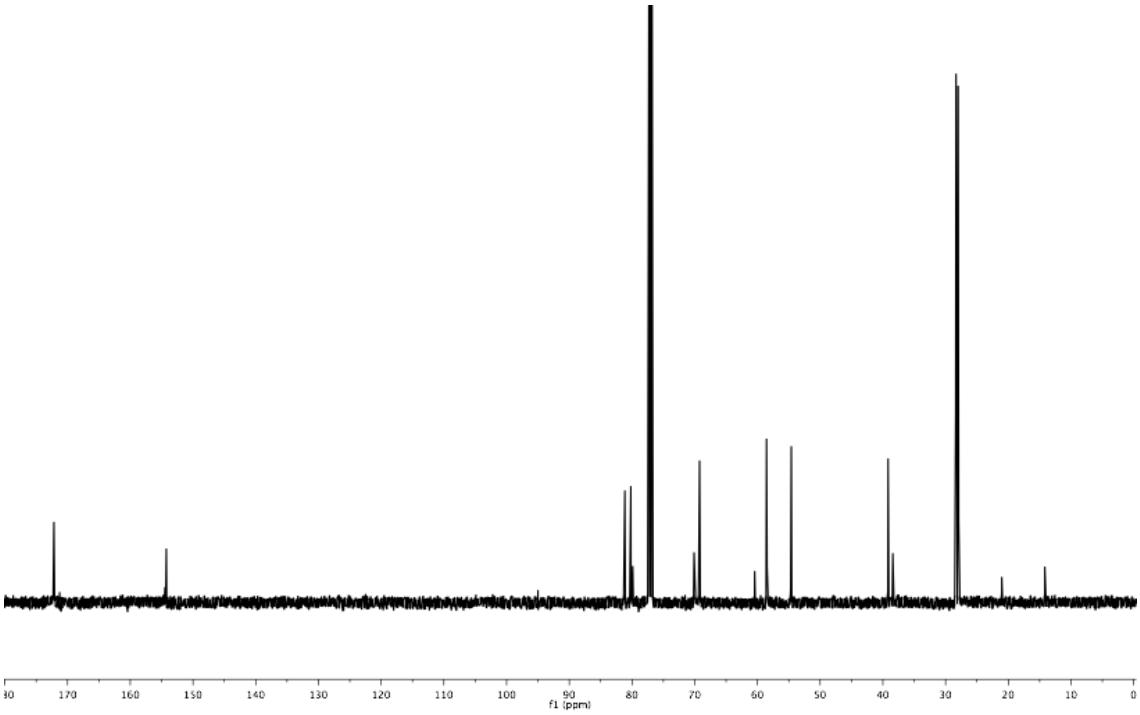


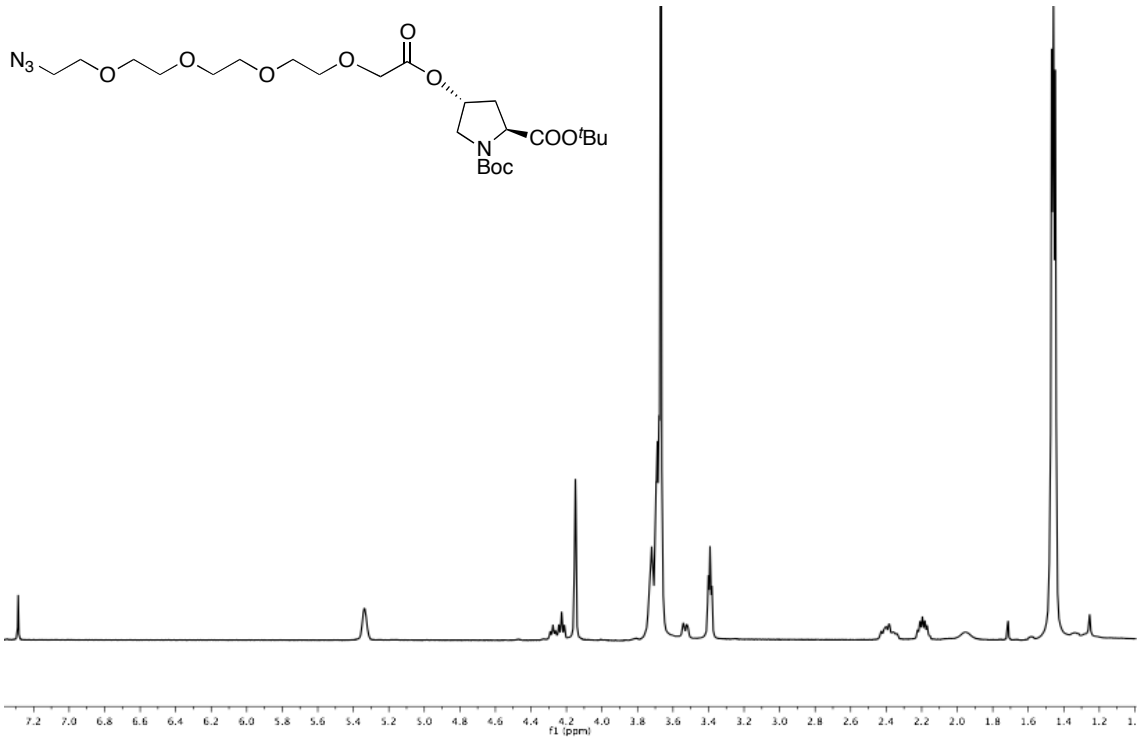
^{1}H-NMR (500MHz, $CDCl_3$)



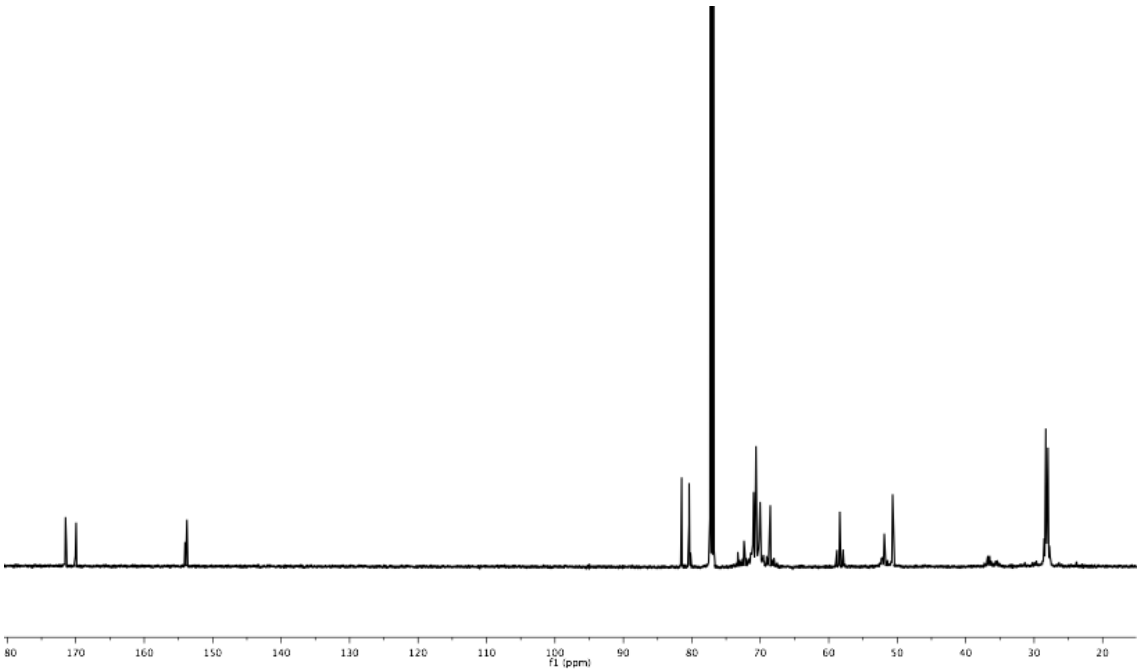
^{13}C-NMR (125MHz, $CDCl_3$)



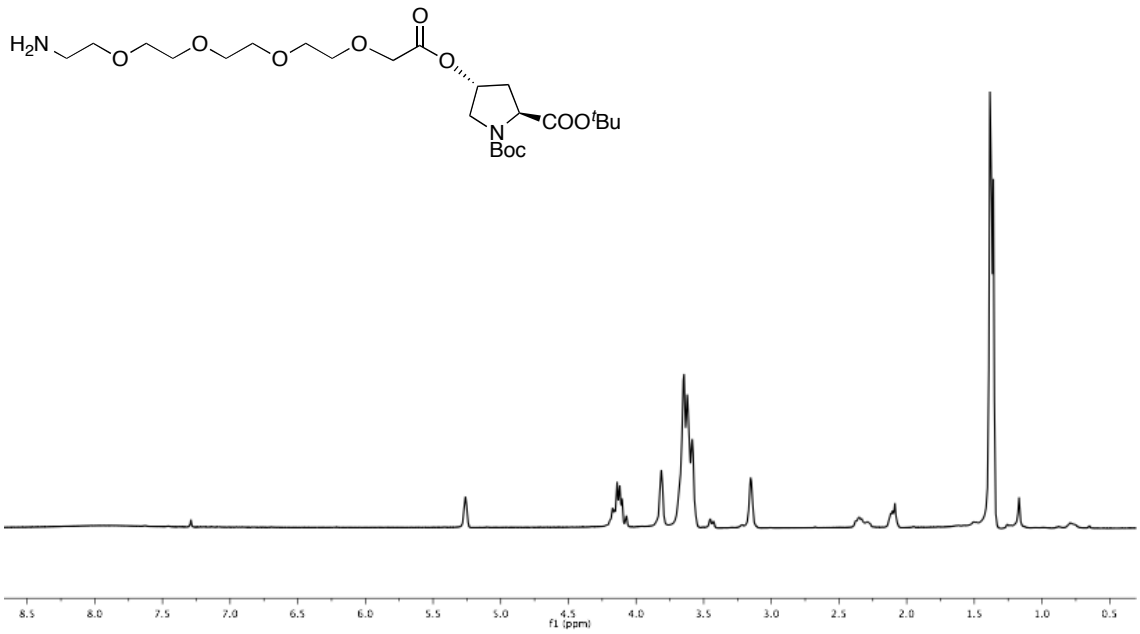
^{1}H-NMR (500MHz, $CDCl_3$)



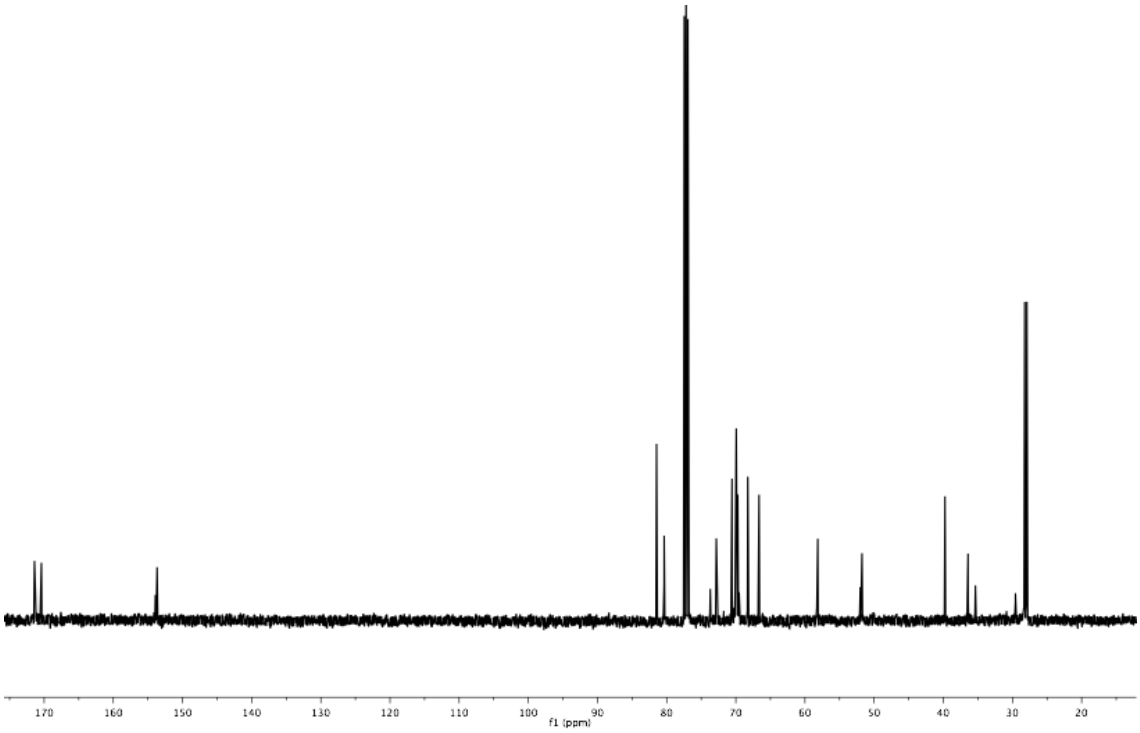
^{13}C-NMR (125MHz, $CDCl_3$)



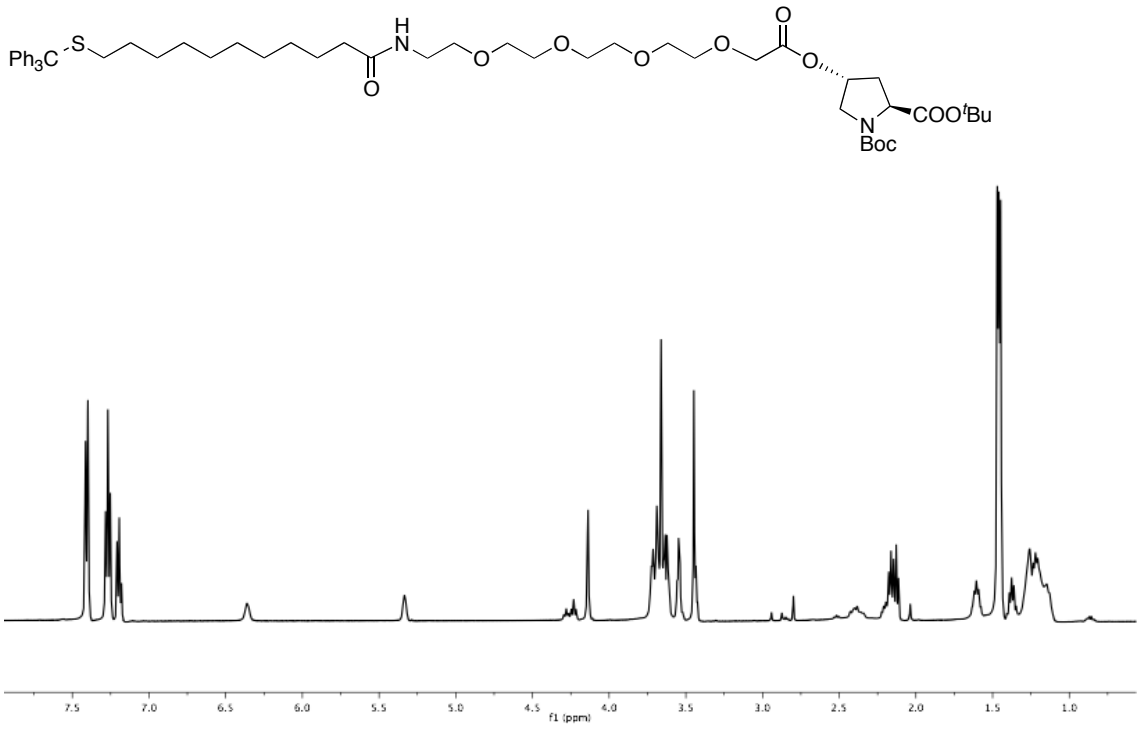
^{1}H-NMR (500MHz, $CDCl_3$)



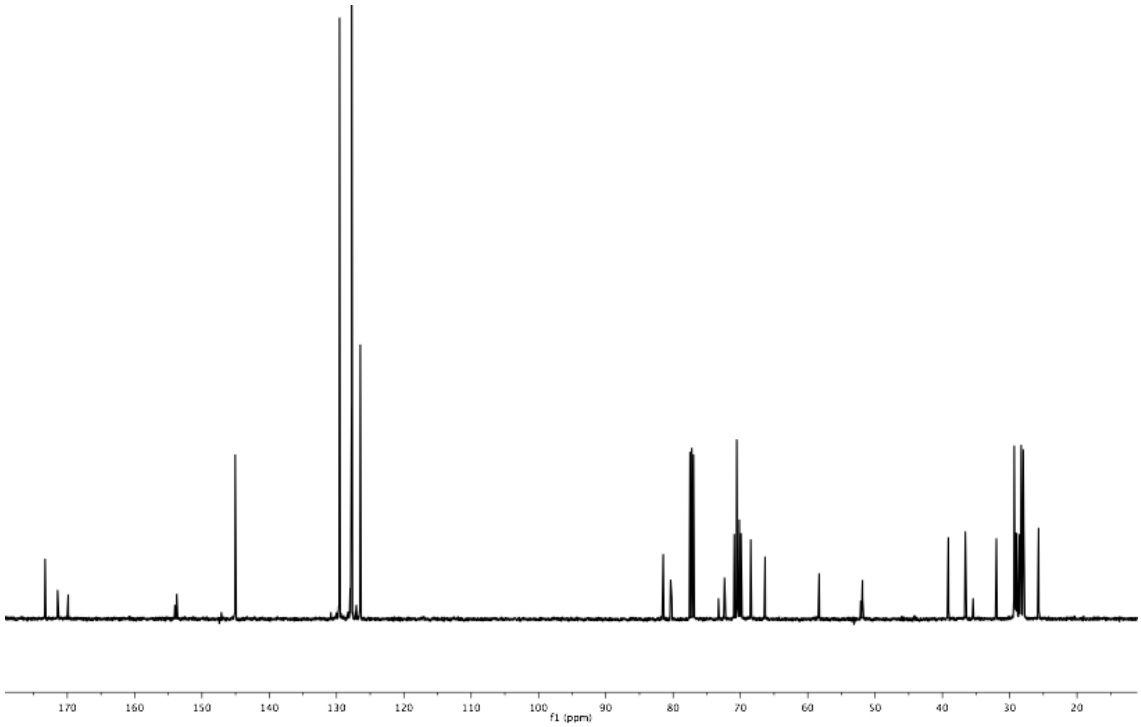
^{13}C-NMR (125MHz, $CDCl_3$)



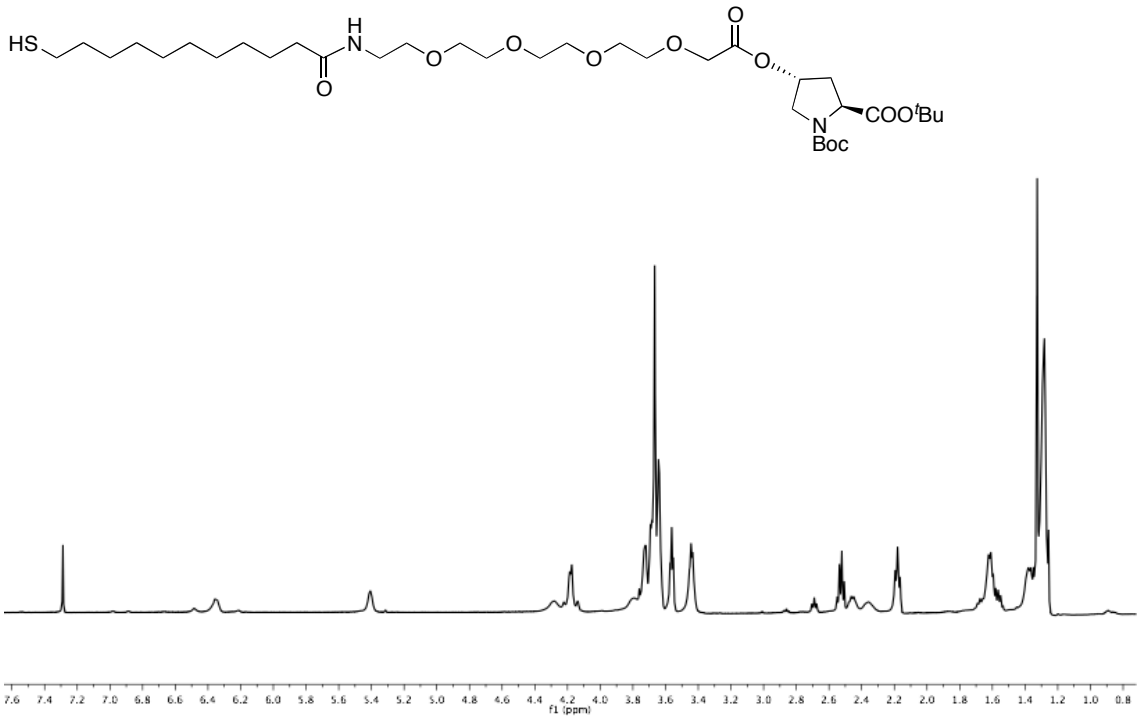
^{1}H-NMR (500MHz, $CDCl_3$)



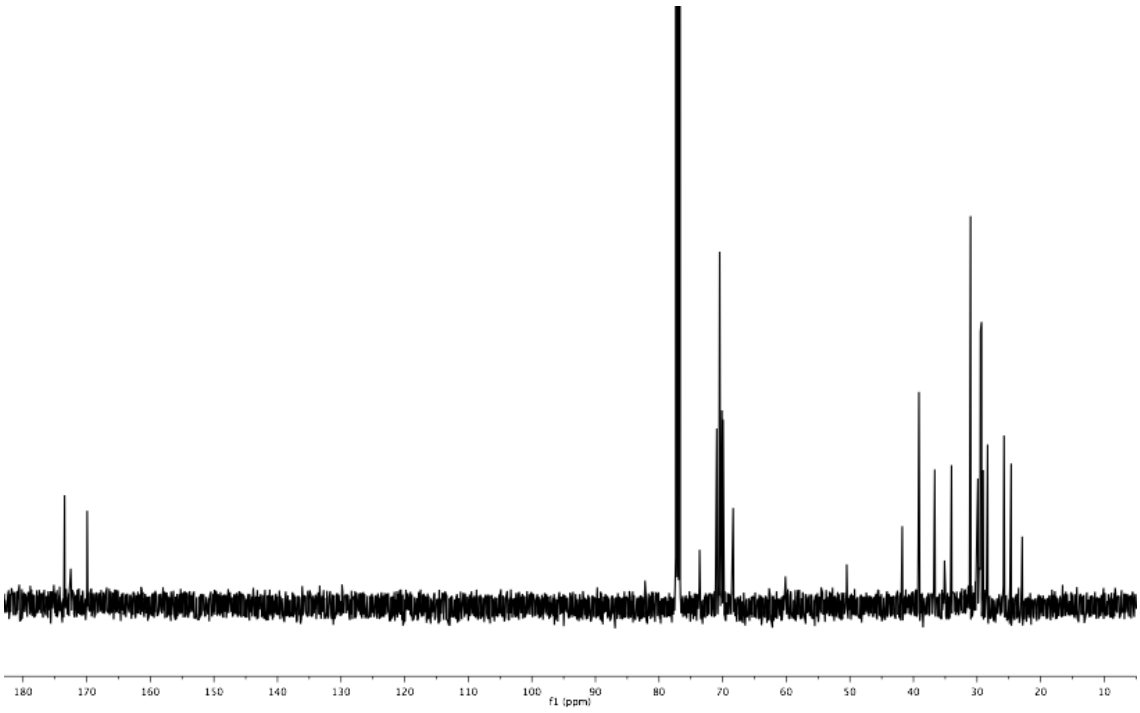
^{13}C-NMR (125MHz, $CDCl_3$)



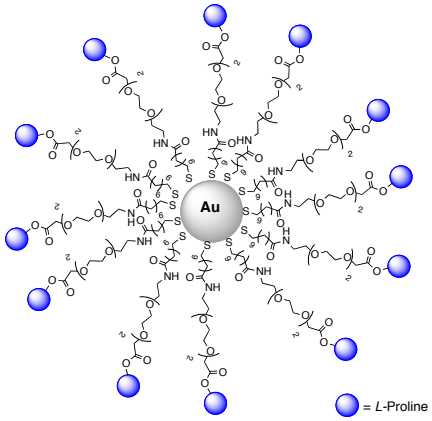
^{1}H-NMR (500MHz, $CDCl_3$)

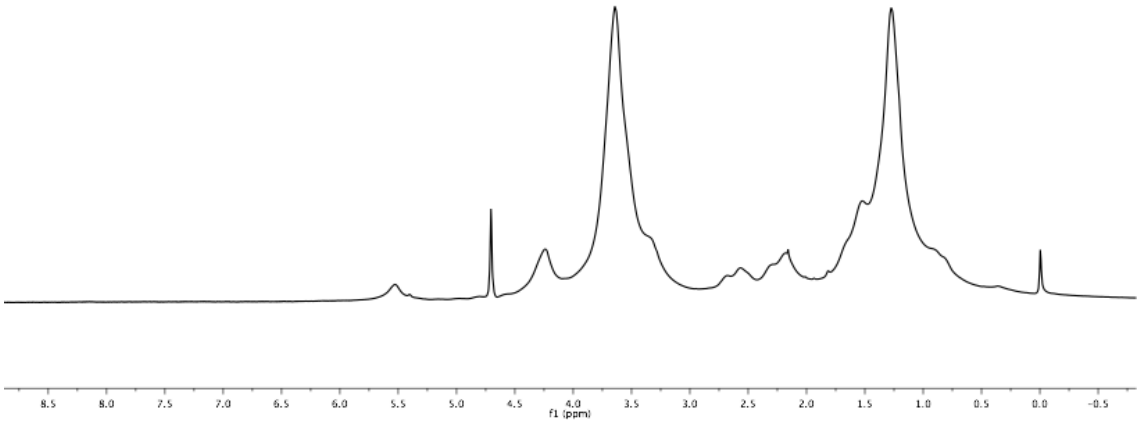


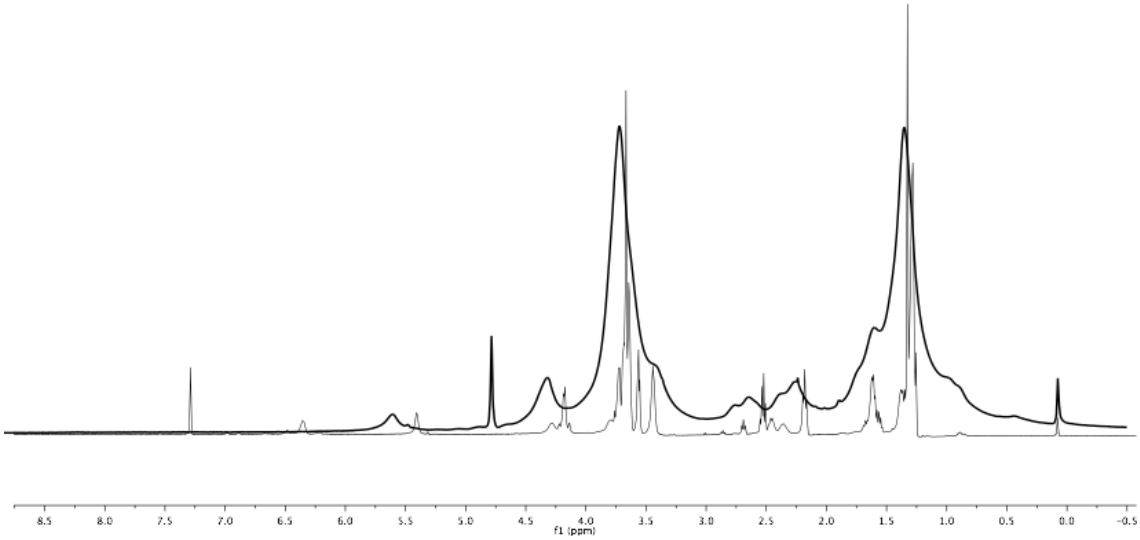
^{13}C-NMR (125MHz, $CDCl_3$)



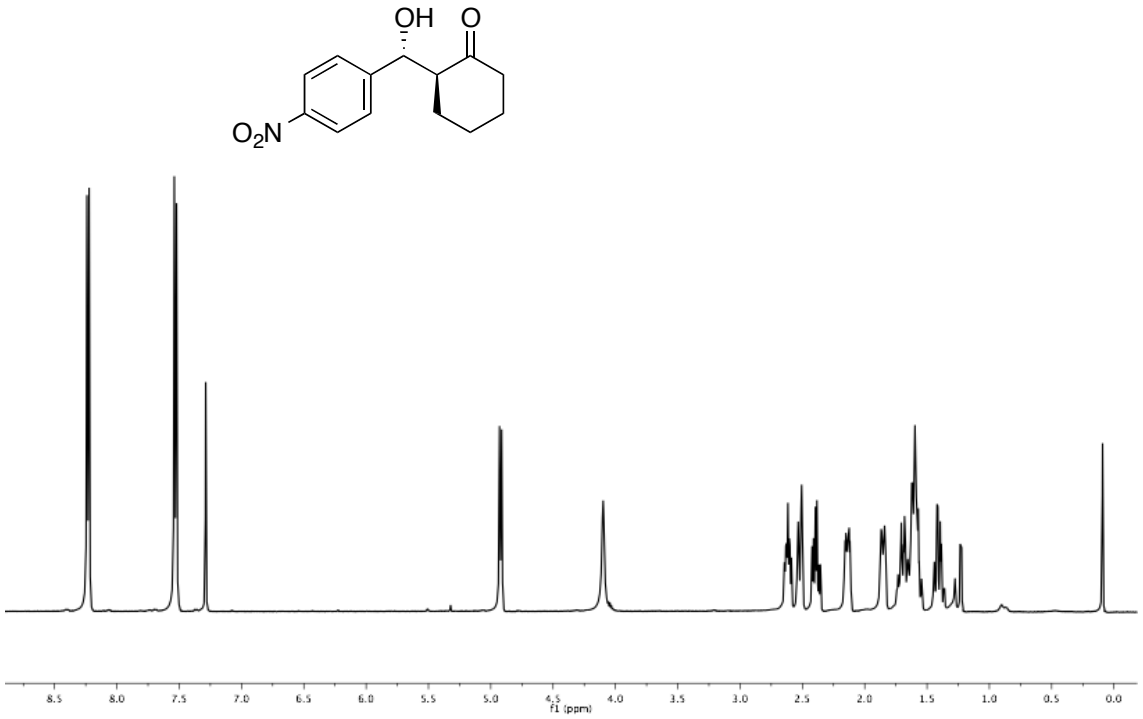
^{1}H-NMR (500MHz, D_2O)







^{1}H-NMR (500MHz, $CDCl_3$)



^{13}C-NMR (125MHz, $CDCl_3$)