Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Positive Variation of MRI Signal via Intramolecular Inclusion Complexation of a C-2 functionalized β-Cyclodextrin

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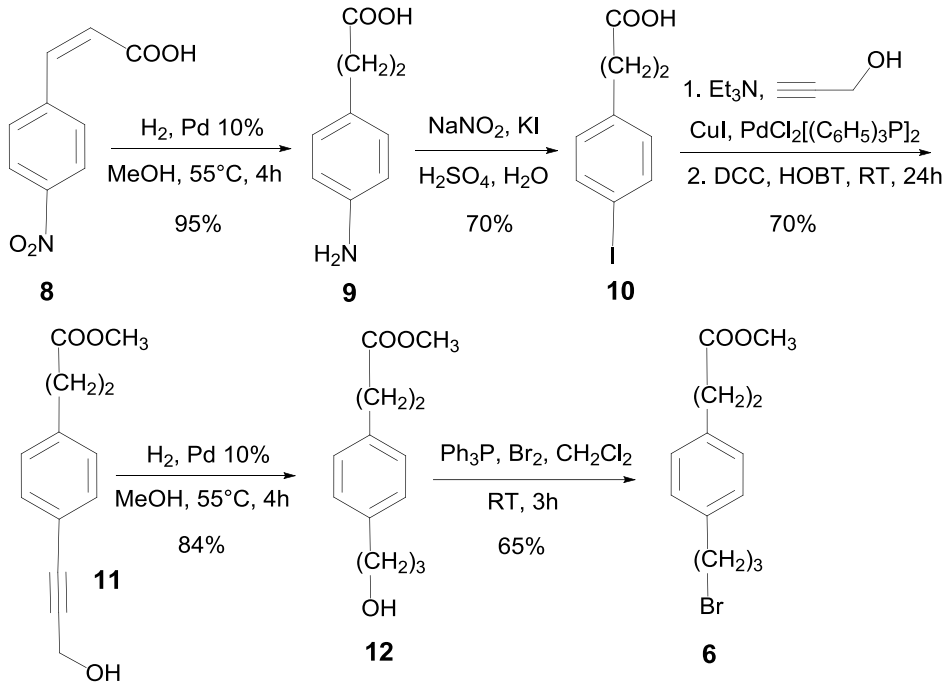
Supporting Information available

1. General

All solvents and reagents were purchased from commercial sources and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) on a plate of silica gel 60 F_{254} (E. Merck, Darmstadt, Germany) and detection by charring with sulfuric acid. Column chromatographies were performed on silica gel 60 (0.063-0.200 mm, E. Merck). ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on Bruker AVANCE 300. Chemical shifts in NMR spectra are reported in parts per million from TMS. IR spectra were recorded on a Perkin-Elmer IRFT 1650 spectrometer. ESI-MS data were acquired using a HCT Ultra Ion Trap mass spectrometer (Bruker Daltonics, Bremen, Germany) or using a LCT Premier XE (Waters, Manchester, UK) for the complexes. Accurate mass measurements (HR-MS) were realized using a Synapt G2 HDMS (Waters, Manchester, UK) equipped with a lockspray electrospray (ESI) source. Experiments were achieved in positive or negative ion mode using protonated or deprotonated molecule of bombesine as internal reference (*m/z* 1619.8229 and 1617.8073 respectively). Circular dichroism spectral measurements were performed in a conventional quartz cell (light path 0.1) on a DC III Jobin Yvon spectropolarimeter equipped with a temperature controller. The temperature of the cell was kept constant at 25°C. Equimolar solutions of gadolinium complexes and guest were prepared in water. Circular dichroism spectra were measured at 0.2 μmol/dm^{-3}.

2. General procedure for the synthesis of compounds 6,7,3

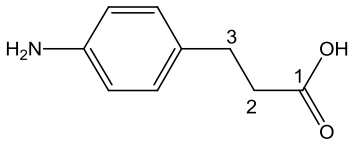
Compound **6** was synthetized according to the following:



Scheme 1 Synthesis of functionalized flexible spacer arm **6**

1 Q. Chen, P. Rao, E. Knaus, *Bioorg. Med. Chem.*, 2006, **14**, 7898-7909.
2 F. Balavoine, D. Madec, C. Mioskowski, *Tetrahedron Lett.*, 1999, **40**, 8351-8354.

3-(4-aminophenyl)propanoic acid 9

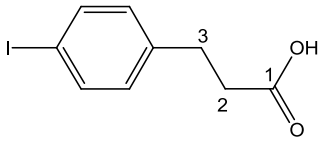


Pd/C 10% (100 mg) was added to a solution of 4-nitrocinnamic acid **8** (700 mg, 3.63 mmol) in methanol (40 mL), and the reaction mixture was stirred under hydrogen atmosphere (1 atm) at 55°C for 4 hours. The catalyst was filtered through celite and the filtrate was concentrated to give a brown solid (580 mg, 95% yield).

^{1}H NMR (300 MHz, MeOD) δ: 6.99 (d, *J* = 9 Hz, 2 H, H-Ar), 6.68 (d, *J* = 9 Hz, 2 H, H-Ar), 2.78 (t, *J* = 6 Hz, 2 H, H-3), 2.52 (t, *J* = 6 Hz, 2 H, H-2). ^{13}C NMR (75 MHz, MeOD) δ: 177.2 (C=O),

146.0 (C-Ar), 132.4 (C-Ar), 129.9 (2C, C-Ar), 117.2 (2C, C-Ar), 37.4 (C-3), 31.4 (C-2). HRMS (ESI, *m/z*) calcd for $C_9H_{10}NO_2$ $[M-H]^-$: 164.0706; found: 164.0720.

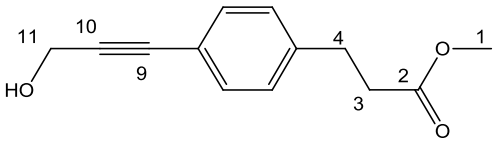
3-(4-iodophenyl)propanoic acid 10



To a solution of 3-(4-aminophenyl)propanoic acid **9** (1.63 g, 10 mmol) in 10 mL of water and 2 mL of concentrated sulfuric acid, a solution of sodium nitrite (828 mg, 12 mmol) in water (3 mL) was added dropwise under stirring at 0°C. The reaction mixture was stirred for 30 minutes prior to the addition of a cooled solution of potassium iodide (3.32 g, 20 mmol) in water (12 mL). The reaction was maintained under stirring for 3 hours at 0°C. The dark brown mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with 5% aqueous HCl (20 mL), then with saturated aqueous sodium thiosulfate solution (50 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/acetone, 3/1, v/v) to give a white powder (1.93 g, 70% yield).

Rf = 0.28. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 6 Hz, 2 H, H-Ar), 6.97 (d, *J* = 9 Hz, 2 H, H-Ar), 2.89 (t, *J* = 7.5 Hz, 2 H, H-3), 2.65 (t, *J* = 7.5 Hz, 2 H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.1 (C=O), 139.8 (C-Ar), 137.7 (2 C, C-Ar), 130.5 (2 C, C-Ar), 91.7 (C-Ar), 35.4 (C-3), 30.1 (C-2). IR (ATR-D) ν_{max} (cm^{-1}): 3400 (O-H), 1732 (C=O). HRMS (ESI, *m/z*) calcd for $C_9H_8O_2I$ $[M-H]^-$: 274.9563; found: 274.9573.

Methyl 3-(4-(3-hydroxyprop-1-ynyl)phenyl)propanoate 11

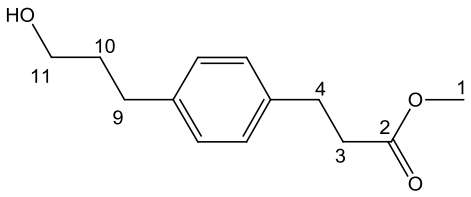


Cuprous iodide (15 mg, 0.08 mmol) and dichlorobis(triphenylphosphine)palladium (27 mg, 0.04 mmol) were added under nitrogen atmosphere to a solution of 3-(4-iodophenyl)propanoic acid **10**

(356 mg, 1.29 mmol) and propargyl alcohol (108 mg, 1.93 mmol) in trimethylamine (8 mL). The reaction was stirred for 18 hours at 50°C. After cooling to 25°C, triethylamine was removed under reduced pressure to give a black oil. The crude product was dissolved in a mixture of methanol (5 mL) and tetrahydrofuran (5 mL). *N*,*N*'-Dicyclohexylcarbodiimide (0.48 g, 2.34 mmol) and 1-hydroxybenzotriazol hydrate (0.32 g, 2.34 mmol) were then added. The mixture was stirred at room temperature for 24 hours. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 9/1, v/v) to give a yellow oil (196 mg, 70% yield).

Rf = 0.18. ^{1}H NMR (300 Hz, $CDCl_3$) δ: 7.31 (d, *J* = 9 Hz, 2 H, H-Ar), 7.07 (d, *J* = 9 Hz, 2 H, H-Ar), 4.45 (s, 2 H, H-11), 3.62 (s, 3 H, H-1), 2.88 (t, *J* = 7.5 Hz, 3 H, H-4), 2.57 (t, *J* = 7.5 Hz, 3 H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.4 (C=O), 140.9 (C-5, C-Ar), 131.8 (2 C, C-Ar), 128.3 (2 C, C-Ar), 120.6 (C-8, C-Ar), 87.3, 85.2, 51.8, 51.3, 35.3 (C-4), 30.7 (C-3). IR (ATR-D) ν_{max} (cm^{-1}): 3400 (O-H), 2200 (C-alcyne). Elemental analysis: Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 70.91; H, 6.24.

Methyl 3-(4-(3-hydroxypropyl)phenyl)propanoate 12

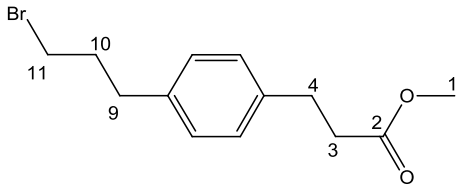


120 mg of Pd/C (10%) were added to a solution of methyl 3-(4-(3-hydroxyprop-1-ynyl)phenyl)propanoate **11** (775 mg, 3.55 mmol) in methanol (40 mL), and the reaction mixture was stirred under hydrogen atmosphere (1 atm) at 55°C for 4 hours. The catalyst was filtered through celite, and the filtrate was concentrated to give a white solid (2.98 mmol, 84% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.12 (s, 4 H, H-Ar), 3.66 (m, 5 H, C$\underline{H}_2$OH, OC$\underline{H}_3$), 2.92 (t, *J* = 7.5 Hz, 2 H, H-4), 2.64 (m, 4 H, H-3, H-9), 1.87 (m, 2 H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.5 (C=O), 139.8 (C-5, C-Ar), 137.9 (C-Ar), 128.6 (2 C, C-Ar), 128.3 (2 C, C-Ar), 62.2 (C-11), 51.7 (C-1), 35.8 (C-4), 34.2 (C-9), 31.6 (C-10), 30.5

(C-3). IR (ATR-D) ν_{max} (cm^{-1}): 3400 (O-H), 1732 (C=O), 1509 (C=C). HRMS (ESI, *m/z*) calcd for $C_{13}H_{18}O_3Na$ $[M+Na]^+$: 245.1148; found: 245.1149.

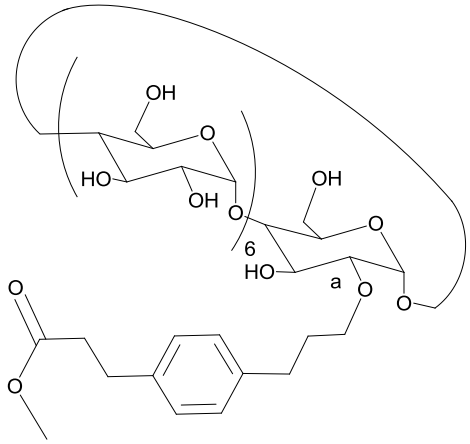
Methyl 3-(4-(3-bromopropyl)phenyl)propanoate 6



A solution of bromine (0.18 mL, 3.51 mmol) in dry methylene chloride (4 mL) was added dropwise under stirring at 0°C under nitrogen atmosphere to a solution of triphenylphosphine (920 mg, 3.51 mmol) in methylene chloride (5 mL). The reaction mixture was stirred for 30 minutes prior to the addition of methyl 3-(4-(3-hydroxypropyl)phenyl)propanoate **12** (650 mg, 2.93 mmol) in methylene chloride (5 mL). The reaction mixture was stirred for 3 hours at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 95/5, v/v) to give a yellow oil (537 mg, 65% yield).

Rf= 0.14. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.13 (s, 4 H, H-Ar), 3.67 (s, 3 H, H-1), 3.39 (t, *J* = 6.5 Hz, 2 H, H-11), 2.93 (t, *J* = 7.5 Hz, 2 H, H-4), 2.77 (t, *J* = 7 Hz, 2 H, H-9), 2.62 (t, *J* = 7.5 Hz, 2 H, H-3), 2.15 (m, 2 H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.4 (C=O), 138.5 (2 C, C-Ar), 128.7 (2 C, C-Ar), 128.4 (2 C, C-Ar), 51.7 (C-1), 35.7 (C-4), 34.2 (C-11), 33.5 (C-9), 33.2 (C-10), 30.5 (C-3). IR (ATR-D) ν_{max} (cm^{-1}): 2952, 1729 (C=O), 1433 (C=C). Elemental analysis: Anal. Calcd for $C_{13}H_{17}BrO_2$: C, 54.75; H, 6.01; found: C, 55.17; H, 6.24.

2^{I}-*O*-methyl 3-(4-(3-propyl)phenyl)propanoate-β-cyclodextrin 7

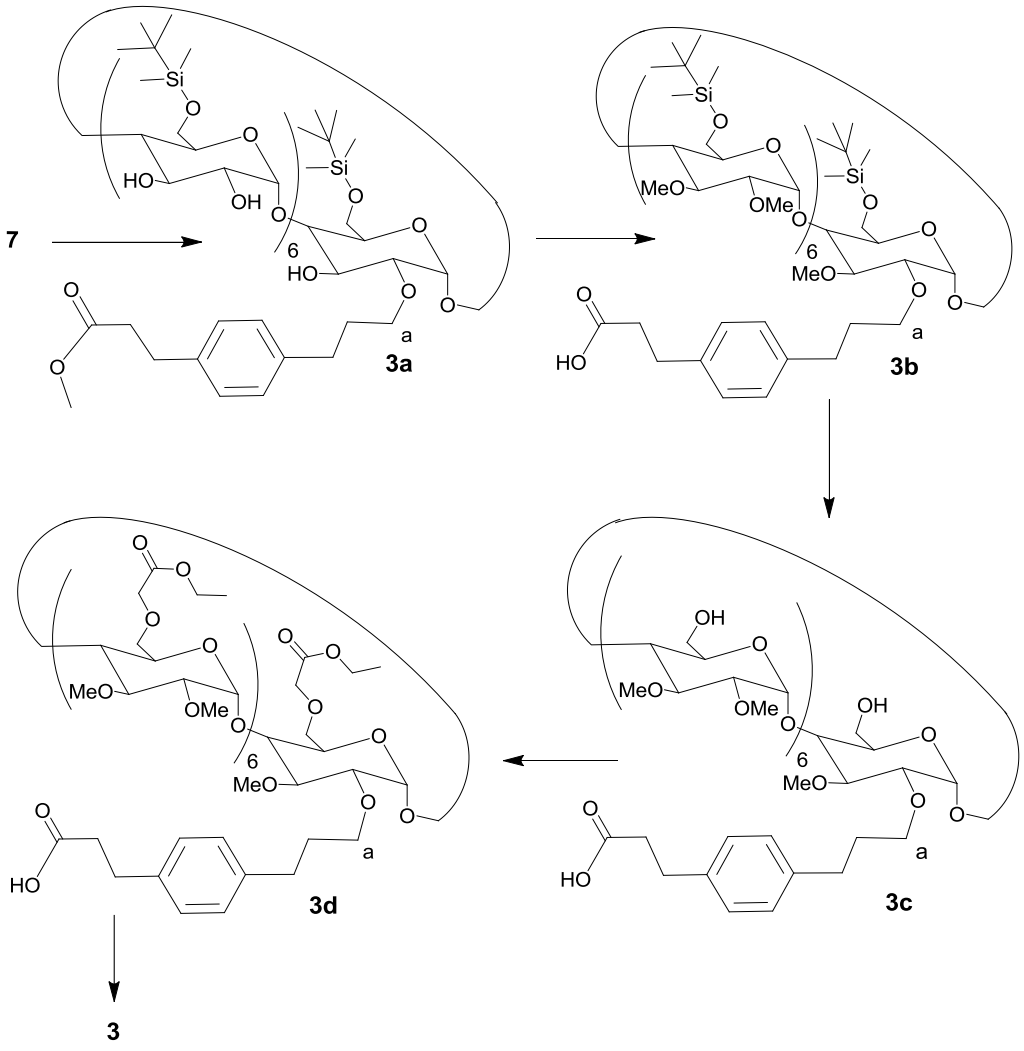


Sodium hydride (35 mg, 0.88 mmol, 60% in mineral oil) was added under nitrogen atmosphere, to a solution of β-cyclodextrin (1 g, 0.88 mmol) in anhydrous dimethyl sulfoxide (5 mL). The mixture was stirred for 14 hours at room temperature and a solution of electrophile reagent **6** (0.88 mmol) in anhydrous dimethyl sulfoxide (3 mL) was added. The solution was stirred at room temperature for 9 hours. The crude product was then precipitated in acetone (1000 mL), filtered off and chromatographed. The residue was purified by flash chromatography on silica gel (ethyl acetate/isopropanol/water, 12/7/4, v/v/v) to give a white powder (211 mg, 18% yield).

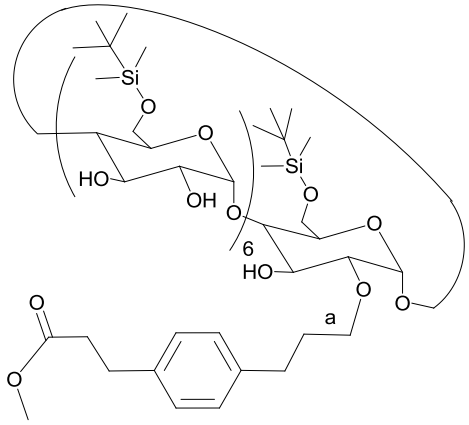
m.p. >260°C. Rf = 0.3. ^{1}H NMR (300 MHz, D_2O) δ: 7.00 (s, 4 H, H-Ar), 4.97 (s, 7 H, H-1), 3.73-3.52 (m, 47 H, H-6, H-4, H-5, H-3, H-2, OCH_3, 1 x C$\underline{H}_2$), 2.79 (m, 2 H, 1 x C$\underline{H}_2$), 2.67-2.55 (m, 4 H, 2 x C$\underline{H}_2$), 1.86 (2 H, 1 x C$\underline{H}_2$). ^{13}C NMR (75 MHz, D_2O) δ: 175.3 (C=O), 139.6 (C-Ar), 138.3 (C-Ar), 128.1 (C-Ar), 127.9 (C-Ar), 102.0 (6 x C-1), 100.9 (C'-1), 82.5 (7 x C-4), 82.1 (C'-2), 72.9, 73.3 (C-3, 6 x C-2), 71.8 (7 x C-5), 71.4 ($OCH_2CH_2CH_2$), 59.8 (C-6), 52.3 (O-CH_3), 38.7, 35.9, 31.5, 30.1 (4 CH_2-Ar). HRMS (ESI, *m/z*) calcd for $C_{55}H_{86}O_{37}Na$ $[M+Na]^+$: 1361.4740; found: 1361.4733.

2^{I}-*O*-methyl-3-(4-(3-propyl)phenyl)propanoate-heptakis-(6-*O*-carboxymethyl-2,3-di-*O*-methyl)-β-cyclodextrin 3

Compound **3** was synthetized according to the following pathway:



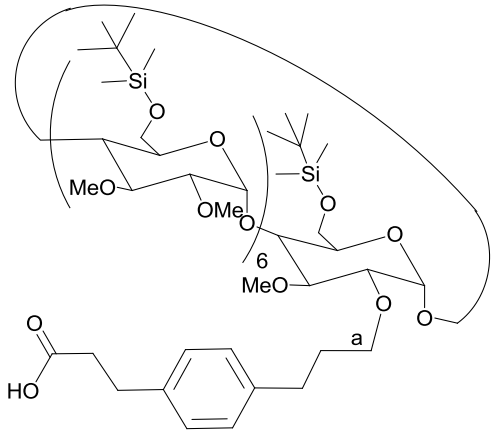
2^{I}-*O*-methyl-3-(4-(3-propyl)phenyl)propanoate-heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin 3a



Under nitrogen atmosphere, a solution of 2^{I}-*O*-methyl-3-(4-(3-propyl)phenyl)propanoate-β-cyclodextrin **7** (1.606 g, 0.001 mol) was dissolved in 7 mL of anhydrous pyridine and *tert*-butyldimethylsilyl chloride (2.3 g, 0.015 mmol) was added. The solution was stirred at room temperature for 5 hours. The reaction was quenched with 3 mL of water and the solution was evaporated under reduced pressure. The compound was purified by flash chromatography on silica gel (methylene chloride/methanol, 95/5, v/v) to give a white powder (641 mg, 30% yield).

m.p. >260°C. Rf = 0.14. ^{1}H NMR (300 MHz, C_6D_6) δ: 7.38-7.21 (m, 4 H, H-Ar), 5.12 (m, 7 H, H-1), 4.57-3.82 (m, 47 H, H-6, H-4, H-5, H-3, H-2, CH_3, CH_2), 3.00 (t, *J* = 9 Hz, 2 H, CH_2), 2.81 (t, *J* = 6 Hz, 2 H, CH_2), 2.56 (t, *J* = 6 Hz, 2 H, CH_2), 2.16 (m, 2 H, CH_2), 1.12 (s, 63 H, $(C\underline{H}_3)_3$-C), 0.17 (s, 42 H, $(C\underline{H}_3)_2$-Si). ^{13}C NMR (75 MHz, C_6D_6) δ: 171.2 (C=O), 138.6 (C-Ar), 137.1 (C-Ar), 127.6 (C-Ar), 126.6 (C-Ar), 101.4 (C-1), 81.3 (C-4), 72.8 (C-3), 72.7, 72.3 (C-2, C-5), 71.5 (C-a), 61.1 (C-6), 51.9 (CH_3), 34.6, 30.4, 29.6, 28.8 (4 CH_2), 24.8 $(\underline{C}H_3)_3$-C), 17.3 $(CH_3)_3$-$\underline{C}$), -6.1 $(\underline{C}H_3)_2$-Si). HRMS (ESI, *m/z*) calcd for $C_{97}H_{184}O_{37}Si_7Na$ $[M+Na]^+$: 2160.0793; found: 2160.0762.

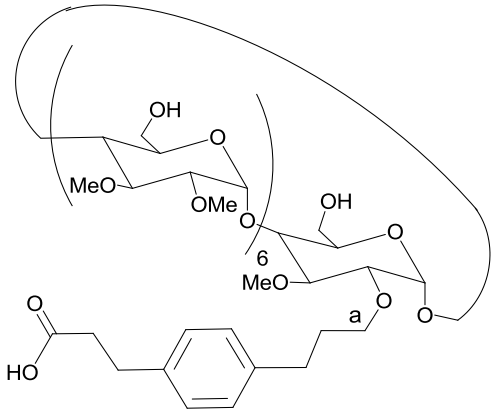
2^{I}-*O*-methyl-3-(4-(3-propyl)phenyl)propanoate-heptakis-(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)-β-cyclodextrin 3b



Under nitrogen atmosphere, 2^{I}-*O*-methyl-3-(4-(3-propyl)phenyl)propanoate-heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin **3a** (560 mg, 0.26 mmol) was dissolved in anhydrous tetrahydrofuran (12 mL). Sodium hydride dispersed in mineral oil (60%) (280 mg, 7.02 mmol) was slowly added at 0˚C. Iodomethane (1 mL, 15.23 mmol) was added dropwise over 1 hour period and the reaction mixture was further stirred for 18 hours at room temperature. The excess of sodium hydride was decomposed by addition of methanol (7 mL). Solvents were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (methylene chloride/methanol, 99/1, v/v) to give a white powder (507 mg, 85% yield).

m.p. >260°C. Rf = 0.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.06 (m, 4 H, H-Ar), 5.19 (d, *J* = 9 Hz, 7 H, H-1), 4.24-3.35 (m, 82 H, H-6, H-4, H-5, H-3, ^{2}O-CH_3, ^{3}O-CH_3, CO_2CH_3, CH_2), 3.05 (dd, *J* = 9 Hz, *J* = 3 Hz, 7 H, H-2), 2.84 (m, 2 H, CH_2), 2.66 (m, 2 H, CH_2), 2.51 (m, 2 H, CH_2), 1.89 (m, 2 H, CH_2), 0.85 (s, 63 H, $(CH_3)_3$-C), 0.01 (s, 42 H, $(CH_3)_2$-Si). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.9 (C-Ar), 138.7 (C-Ar), 128.4 (C-Ar), 128.2 (C-Ar), 98.1 (C-1), 82.1, 72.3, 72.0, 71.2 (C-4, C-3, C-2, C-5), 71.5 (CH_2-a), 66.4, 62.3, 61.4, 58.5 (O-$\underline{C}H_2$-CO, C-6, ^{2}O-CH_3,^{3}O-CH_3), 31.9, 31.6, 29.7, 22.7 (4 CH_2), 24.8 ($\underline{C}H_3)_3$-C), 18.2 $(CH_3)_3$-$\underline{C}$), - 5.2 $(CH_3)_2$-Si). HRMS (ESI, *m/z*) calcd for $C_{109}H_{208}O_{37}Si_7Na$ $[M+Na]^+$: 2328.2671; found: 2328.2554.

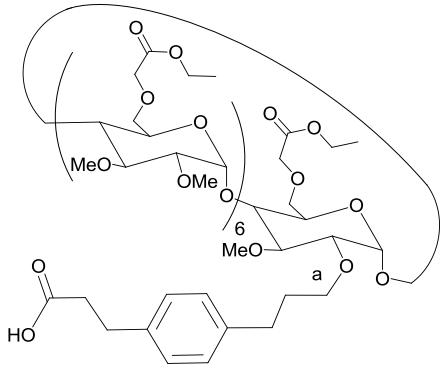
2^{I}-*O*-methyl-3-(4-(3-propyl)phenyl)propanoate-heptakis-(2,3-di-*O*-methyl)-β-cyclodextrin 3c



Under nitrogen atmosphere, ammonium fluoride (216 mg, 5.85 mmol) was added at room temperature to a solution of 2^{I}-*O*-methyl-3-(4-(3-propyl)phenyl)propanoate-heptakis-(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)-β-cyclodextrin **3b** (507 mg, 0.22 mmol) in 16 mL of methanol. The mixture was stirred at 75°C for 24 hours. Further addition of ammonium fluoride (0.86 g, 23 mmol) was then added, and the mixture was stirred at 75°C for 24 hours. The solvent was evaporated under reduced pressure and the residue was dissolved in 100 mL of methylene chloride. The white precipitate obtained was filtered off and discarded. The solvent from the residual filtrate was evaporated under reduced pressure to give the desired compound as a white powder (316 mg, 95 % yield).

m.p. >260°C. ^{1}H NMR (300 MHz, MeOD) δ: 7.00 (s, 4 H, H-Ar), 5.13 (s, 7 H, H-1), 3.83-3.23 (m, 82 H, H-6, H-4, H-5, H-3, ^{2}O-CH_3, ^{3}O-CH_3, CO_2CH_3, CH_2), 3.10 (d, *J* = 12 Hz, 7 H, H-2), 2.80 (t, *J* = 9 Hz, 2 H, CH_2), 2.66 (t, *J* = 12 Hz, 2 H, CH_2), 2.48 (t, *J* = 6 Hz, 2 H, CH_2), 1.89 (m, 2 H, CH_2). ^{13}C NMR (75 MHz, MeOD) δ: 176.0 (C=O), 139.6 (C-Ar), 138.2 (C-Ar), 128.1 (C-Ar), 127.7 (C-Ar), 98.0 (C-1), 82.8 (C-4), 79.1, 71.9, 72.0, (C-2, C-3, C-5), 71.5 (CH_2-a), 69.5, 60.6, 60.3, 57.4 (O-$\underline{C}H_2$-CO, C-6, ^{2}O-CH_3, ^{3}O-CH_3), 31.6, 31.2, 30.4, 29.2 (4 CH_2). HRMS (ESI, *m/z*) calcd for $C_{67}H_{109}O_{37}$ $[M-H]^-$: 1505.6642; found: 1505.6610.

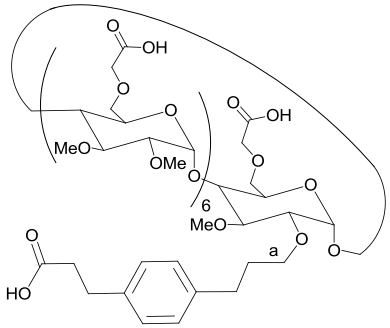
2^{I}-*O*-methyl-3-(4-(3-propyl)phenyl)propanoate-heptakis-(6-*O*-ethoxycarboxymethyl -2,3-di-*O*-methyl)-β-cyclodextrin 3d



Under nitrogen atmosphere, 2^{I}-*O*-methyl-3-(4-(3-propyl)phenyl)propanoate-heptakis-(2,3-di-*O*-methyl)-β-cyclodextrin **3c** (140 mg, 0.093 mmol) was dissolved in 18 mL of dry methylene chloride and ethyl diazoacetate (105 mg, 0.929 mmol) was added. A solution of HBF_4 54% ethereal was diluted in methylene chloride (5 µL dissolved in 0.5 mL of methylene chloride) and added. Bubbles of N_2 were observed. The reaction mixture was stirred at room temperature for 24 hours, 0.3 mL of 5% aqueous $NaHCO_3$ was added and the mixture was stirred for 5 minutes. The organic phase was separated, dried over Na_2SO_4 and it was evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (ethyl acetate/methylene chloride/methanol, 50/50/4, v/v/v) to give a white powder (70 mg, 36% yield).

m.p. >260°C. Rf = 0.21. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.12 (s, 4 H, H-Ar), 5.17 (s, 7 H, H-1), 4.19-4.15 (m, 28 H, O-C$\underline{H}_2$-CO, O-C$\underline{H}_2$-CH_3), 3.94-3.35 (m, 82 H, H-6, H-4, H-5, H-3, ^{2}O-CH_3, ^{3}O-CH_3, CO_2CH_3, CH_2), 2.91 (t, *J* = 9 Hz, 2 H, CH_2), 2.70 (m, 4 H, $2CH_2$), 1.92 (m, 2 H, CH_2), 1.25 (t, *J* = 6 Hz, 21 H, O-CH_2-C$\underline{H}_3$). ^{13}C NMR (75 MHz, MeOD) δ: 175.7 (C=O), 169.2 (C=O), 139.2 (C-Ar), 136.6 (C-Ar), 127.6 (C-Ar), 128.2 (C-Ar), 98.1 (C-1), 81.0 (C-4), 79.1 (C'-2), 69.8, 69.4, 69.1 (C-3, C-2, C-5), 68.8 (CH_2-a), 67.5, 60.8, 60.3, 59.4 (O-C$\underline{H}_2$-CO, C-6, ^{2}O-CH_3, ^{3}O-CH_3), 57.3 (O-C$\underline{H}_2$-CH_3) 34.4, 30.7, 29.3, 28.4 (4 CH_2), 13.2 (O-CH_2-C$\underline{H}_3$). LRMS (ESI): *m/z* 2107.8 $[M-H]^-$.

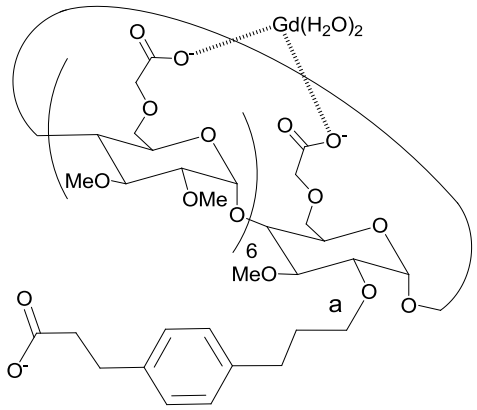
2^{I}-*O*-methyl-3-(4-(3-propyl)phenyl)propanoate-heptakis-(6-*O*-carboxymethyl-2,3-di-*O*-methyl)-β-cyclodextrin 3



Under nitrogen atmosphere, 2^{I}-*O*-methyl-3-(4-(3-propyl)phenyl)propanoate-heptakis-(6-*O*-ethoxycarboxymethyl-2,3-di-*O*-methyl)-β-cyclodextrin **3d** (60 mg, 0.028 mmol) was dissolved in methanol (5 mL) and a solution of sodium hydroxide (0.6 mL, 0.570 mmol) was added. The reaction mixture was stirred for 18 hours at room temperature. Solvents were evaporated, water (3 mL) was added, and the solution was filtered on Dowex 50WX8-100 (H^+). Lyophilization of the solution gave the desired product as a white powder (50 mg, 92% yield).

m.p. >260°C. ^{1}H NMR (300 MHz, D_2O) δ: 7.13 (dd, *J* = 6 Hz, *J* = 9 Hz, 4 H, H-Ar), 5.18 (s, 7 H, H-1), 4.18 (dd, *J* = 18 Hz, *J* = 6 Hz, 14 H, O-C$\underline{H}_2$-CO), 3.77-3.18 (m, 86 H, H-6, H-4, H-5, H-3, H-2, ^{2}O-CH_3, ^{3}O-CH_3, CH_2), 2.82 (t, *J* = 9 Hz, 2 H, CH_2), 2.70 (m, 4 H, 2CH_2), 1.62 (m, 2 H, CH_2). ^{13}C NMR (75 MHz, D_2O) δ: 174.7 (C=O), 173.8 (C=O), 140.6 (C-Ar), 137.6 (C-Ar), 128.6 (C-Ar), 128.1 (C-Ar), 98.6 (C-1), 81.4 (C-4), 79.6 (C'-2), 70.9, 69.6, 67.8 (C-3, C-2, C-5), 67.9 (CH_2-a), 60.7, 59.1, 58.1, 57.8 (O-$\underline{C}H_2$-CO, C-6, ^{2}O-CH_3, ^{3}O-CH_3), 36.2, 31.6, 31.4, 30.8 (4 CH_2). HRMS (ESI, *m/z*) calcd for $C_{81}H_{123}O_{51}$ $[M-H]^-$: 1911.7026; found: 1911.7043.

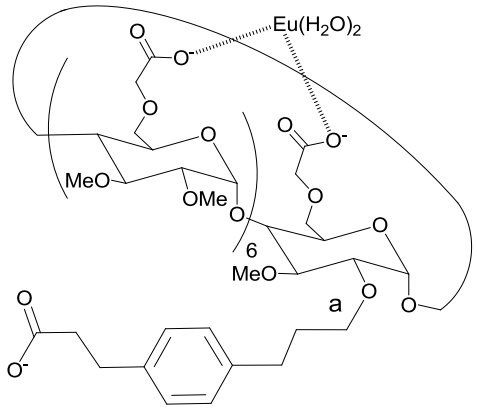
2^{I}-*O*-methyl-3-(4-(3-propyl)phenyl)propanoate-heptakis-(6-*O*-carboxymethyl-2,3-di-*O*-methyl)-β-cyclodextrin gadolinium 3(Gd)



To a solution of 2^{I}-*O*-methyl-3-(4-(3-propyl)phenyl)propanoate-heptakis-(6-*O*-carboxymethyl -2,3-di-*O*-methyl)-β-cyclodextrin **3** (25 mg, 0.013 mmol) in 1.7 mL of deionized water (7.64 mM), a solution of $GdCl_3.6.H_2O$ (3.42 mg, 0.013 mmol) in 0.43 mL of deionized water (30.23 mM) was added in three portions. The pH was adjusted to 7.0 after each addition using a 1 M sodium hydroxide solution. The reaction mixture was stirred at room temperature for 18 hours. The pH was then adjusted to 8.5. The residual lanthanide was precipitated, centrifuged and filtered through a 0.2 μm membrane. The resulting solution was lyophilized to give quantitatively the desired product as a light yellow product (98% yield).

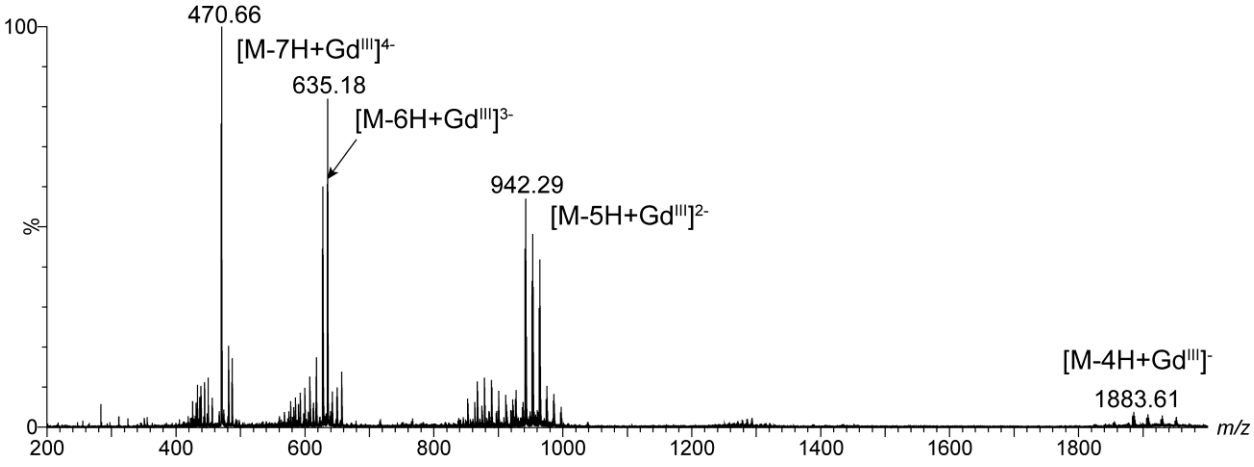
LRMS (ESI, *m/z*) 1031.2 $[M-5H+Gd]^{2-}$.

2^{I}-*O*-methyl-3-(4-(3-propyl)phenyl)propanoate-heptakis-(6-*O*-carboxymethyl-2,3-di-*O*-methyl)-β-cyclodextrin europium 3(Eu)



To a solution of 2^{I}-*O*-methyl-3-(4-(3-propyl)phenyl)propanoate-heptakis-(6-*O*-carboxymethyl -2,3-di-*O*-methyl)-β-cyclodextrin **3** (25 mg, 0.013 mmol) in 1.7 mL of deionized water (7.64 mM), a solution of $EuCl_3.6.H_2O$ (3.35 mg, 0.013 mmol) in 0.43 mL of deionized water (30.23 mM) was added in three portions. The pH was adjusted to 7.0 after each addition using a 1 M sodium hydroxide solution. The reaction mixture was stirred at room temperature for 18 hours. The pH was then adjusted to 8.5. The residual lanthanide was precipitated, centrifuged and filtered through a 0.2 μm membrane. The resulting solution was lyophilized to give quantitatively the desired product as a light yellow product (98% yield).

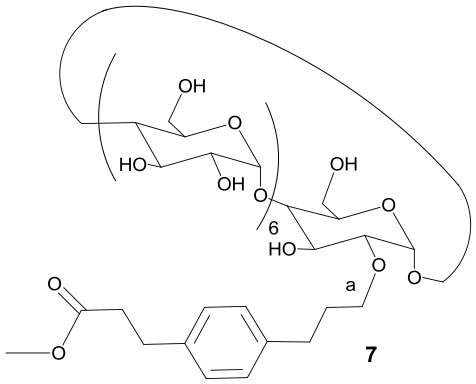
HRMS (ESI, *m/z*) calcd for $C_{70}H_{106}O_{49}Eu$ $[M-4H+Eu]^-$: 1883.5009; found: 1883.5078. LRMS (ESI, *m/z*) 1883.61 $[M-4H+Eu]^-$.

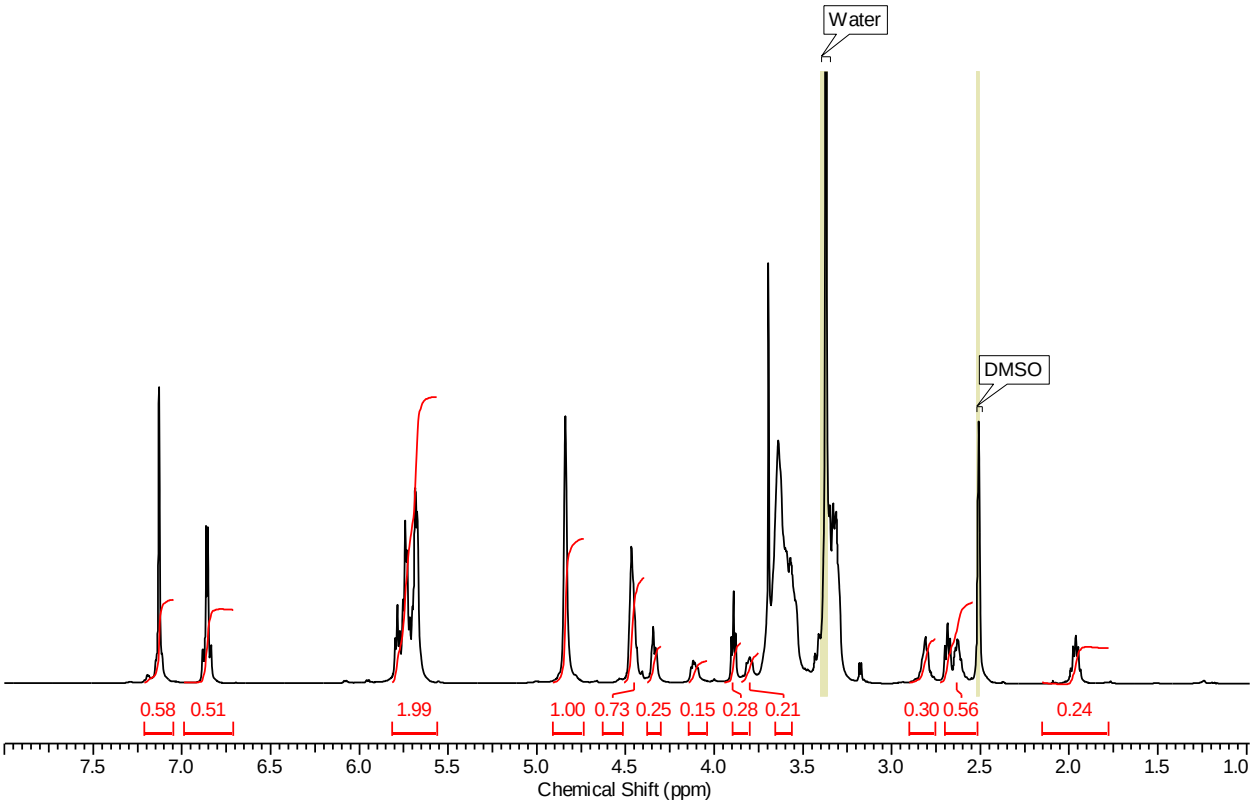


ESI mass spectrum in negative ion mode of **3(Eu)**

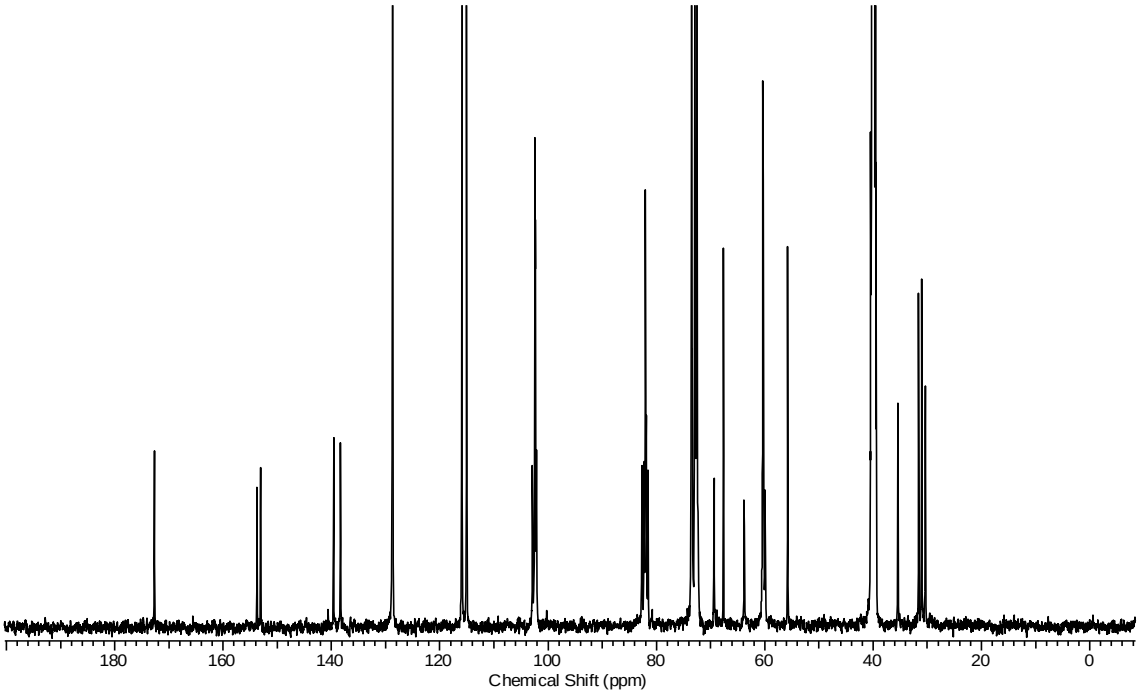
3. Routine NMR analysis

3.1. ^{1}H NMR spectrum of **7**

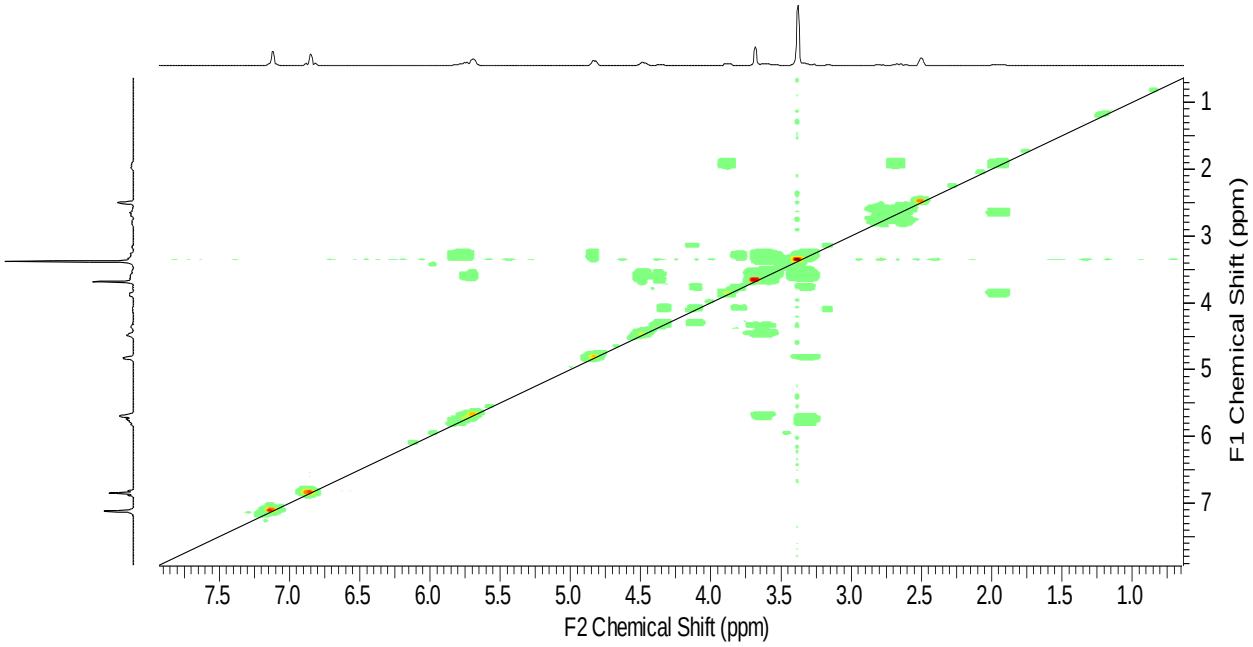




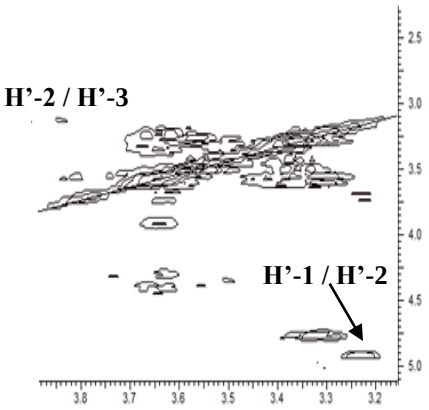
3.2 ^{13}C NMR spectrum of **7**



3.3 COSY NMR spectrum of **7**

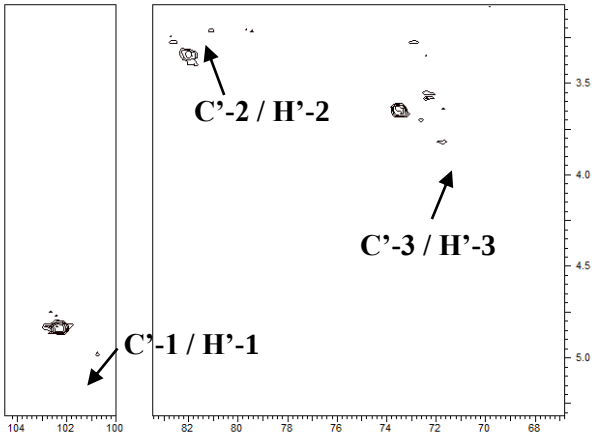


^{1}H NMR showed four pics at 4.98 ppm (H'-1), 3.81 ppm (H'-3), and 3.22 ppm (H'-2) attributed on the basis of COSY NMR analysis.



COSY ^{1}H-^{1}H spectrum of **7**

The corresponding carbons (C'-1, C'-2 and C'-3) were designed thanks to NMR HMQC analysis.



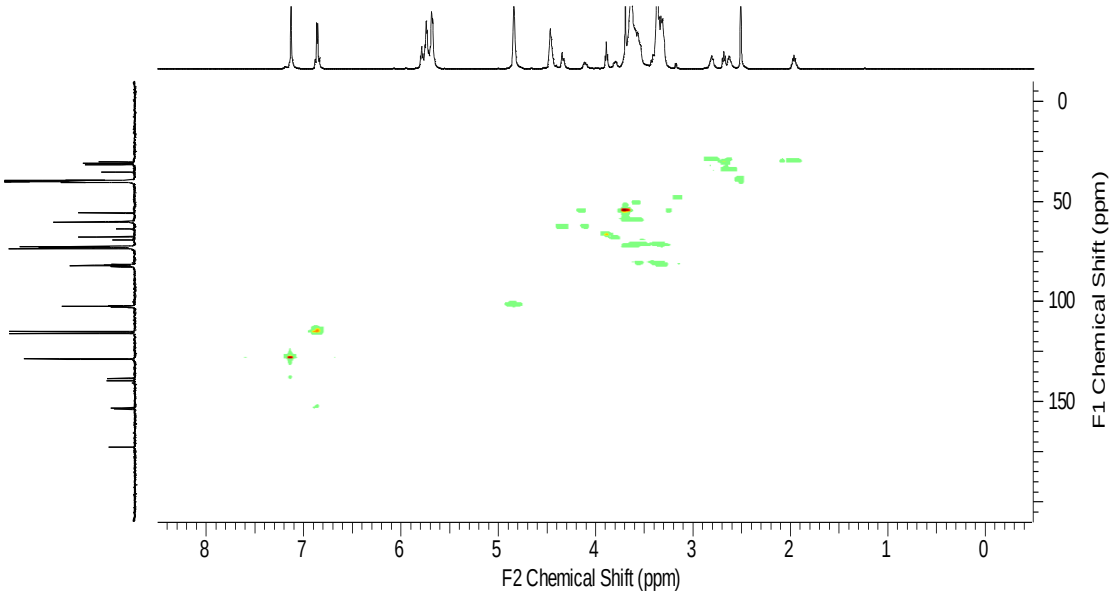
HMQC of compound **7**

	2-*O*-benzyl-β-cyclodextrin	**3-*O*-benzyl-β-cyclodextrin**
ΔC-1	-1.6 ppm	-0.7 ppm
ΔC-2	+7.3 ppm	+6.2 ppm
ΔC-3	-0.6 ppm	+7.0 ppm

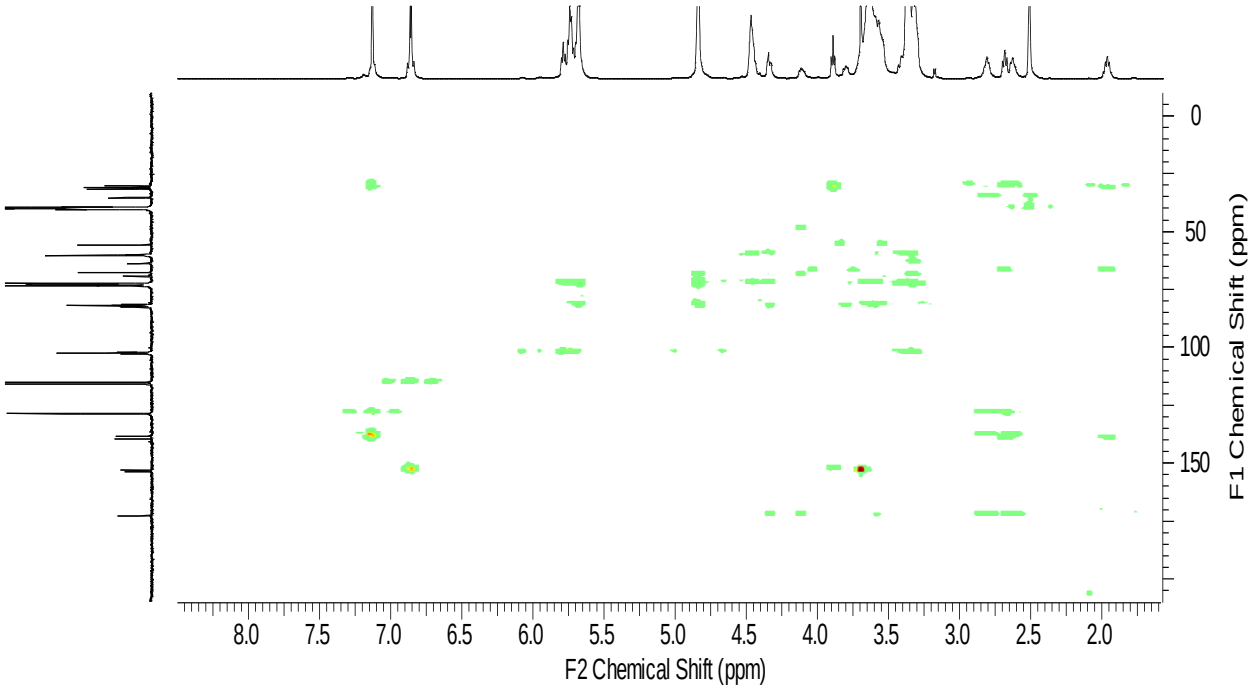
Variations of shift in function of the substitution position.[a]

[a] N. Masurier, O, Lafont, R. Le Provost, D. Lesur, P. Masson, F. Djedaini-Pilard, F. Estour, *Chem. Commun.* 2009, 589-591.

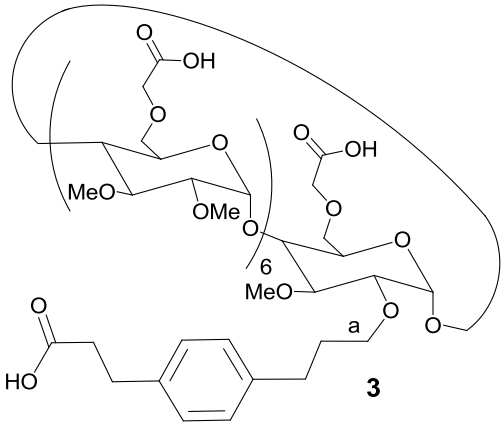
3.4 HMQC NMR spectrum of **7**



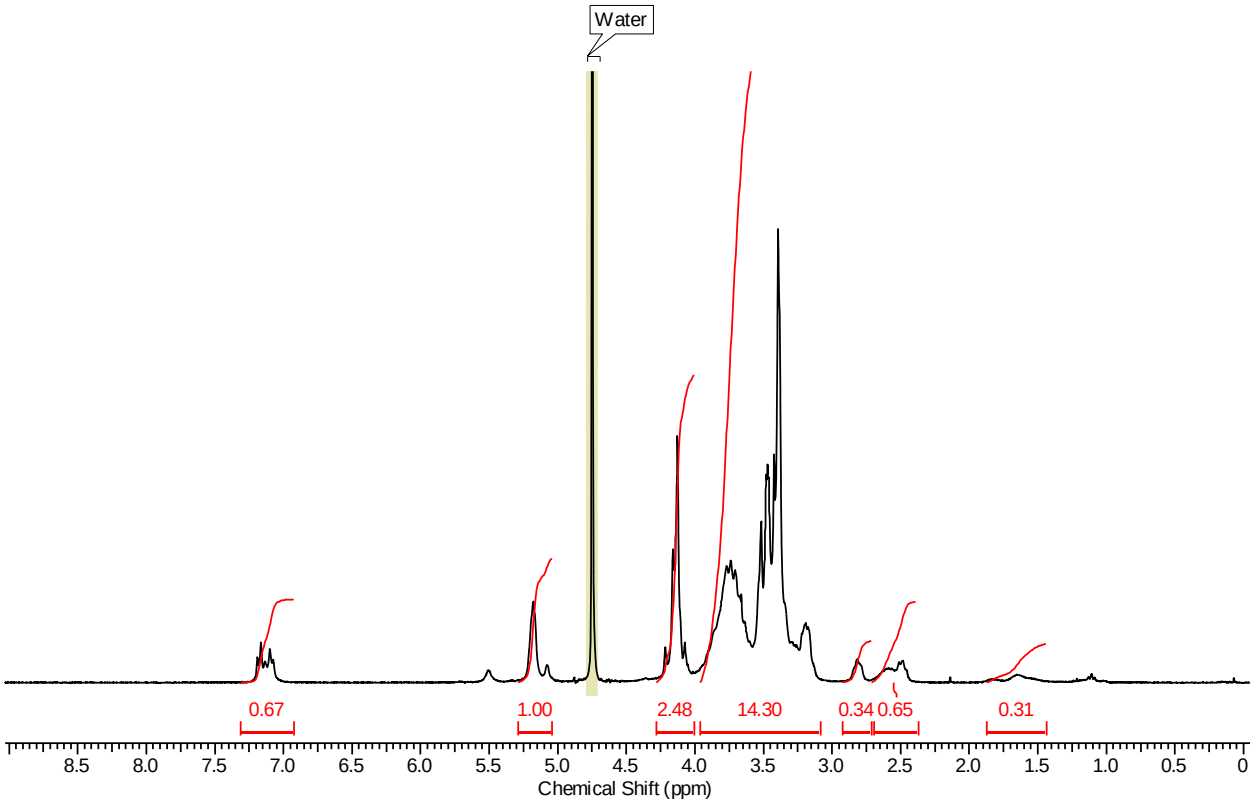
3.5 HMBC NMR spectrum of **7**



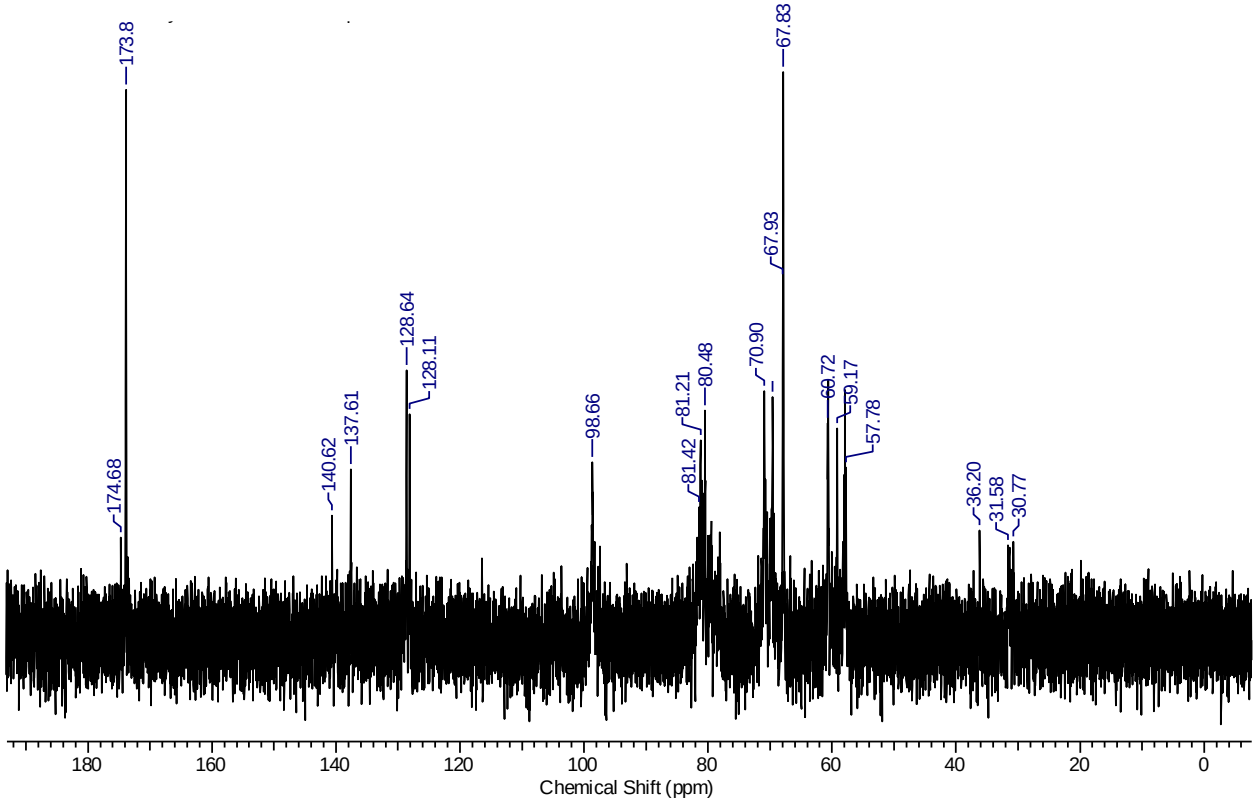
3.6 ^{1}H NMR spectrum of **3**



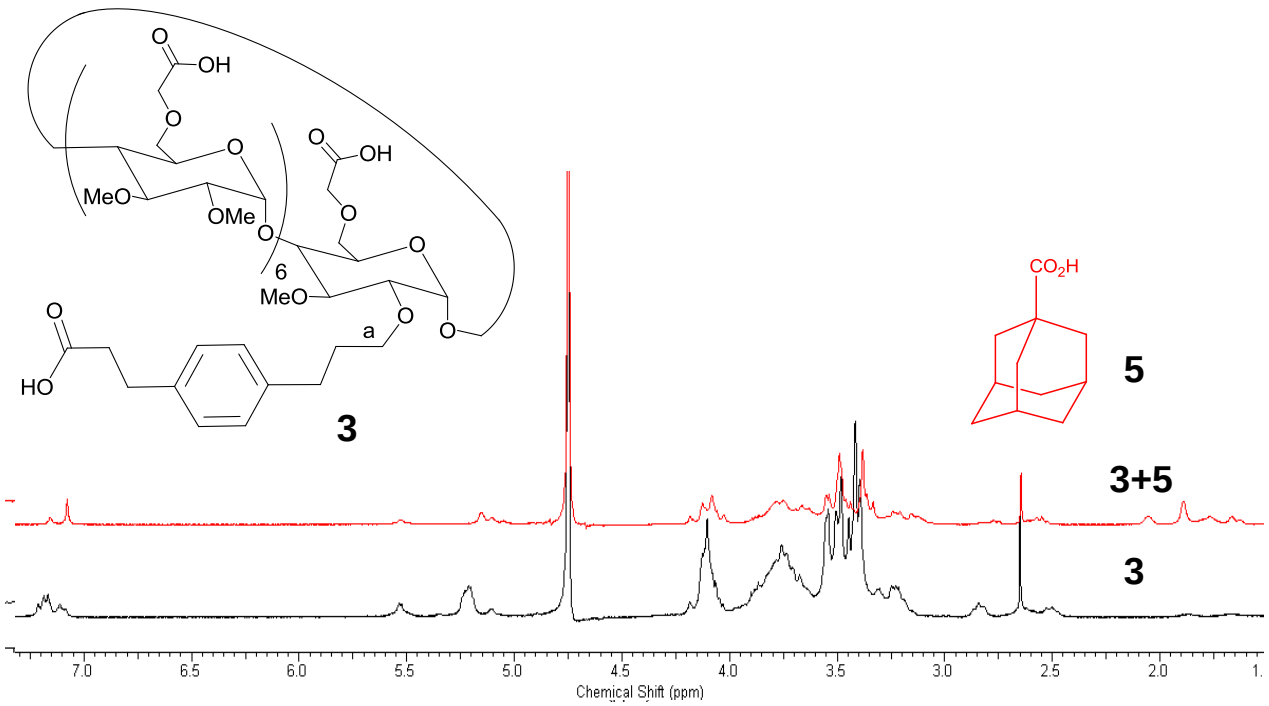
3

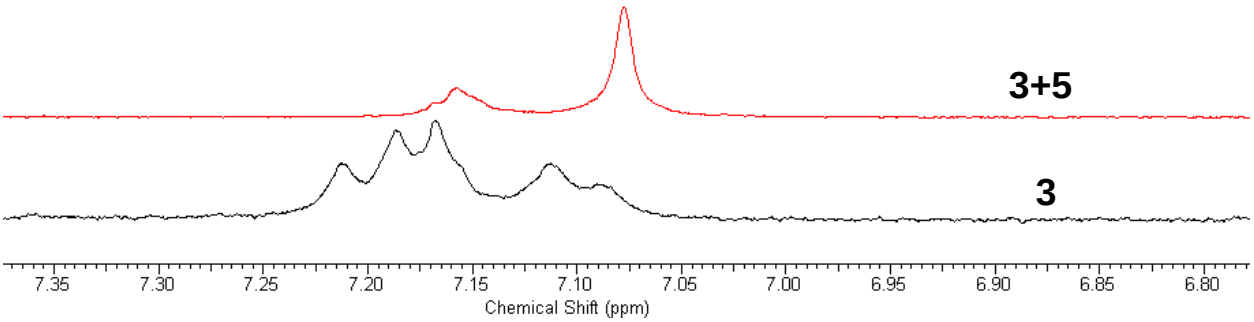


3.7 ^{13}C NMR spectrum of **3**



3.8 ^{1}H NMR spectrum of **3+5**

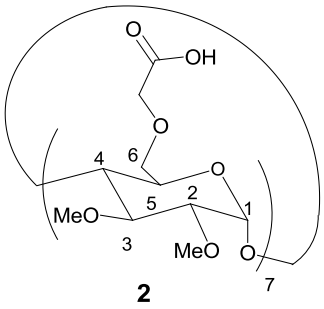




Zoom of the aromatic part

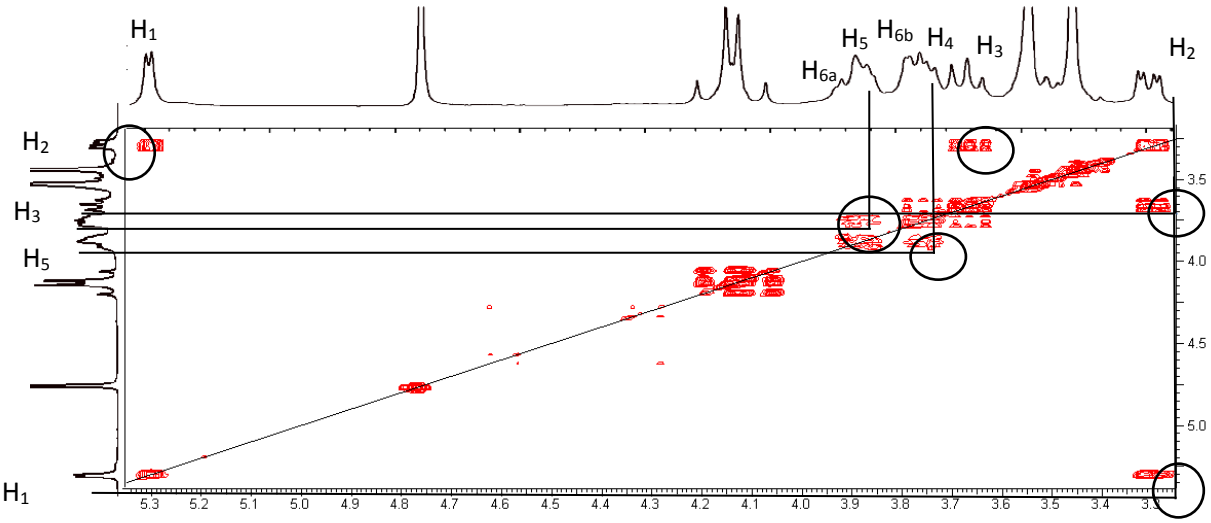
3.9. COSY NMR spectrum of **2**

Internal protons (H_3 and H_5) of oligosaccharide **2** were attributed by a COSY ^1H-^1H NMR.[b]



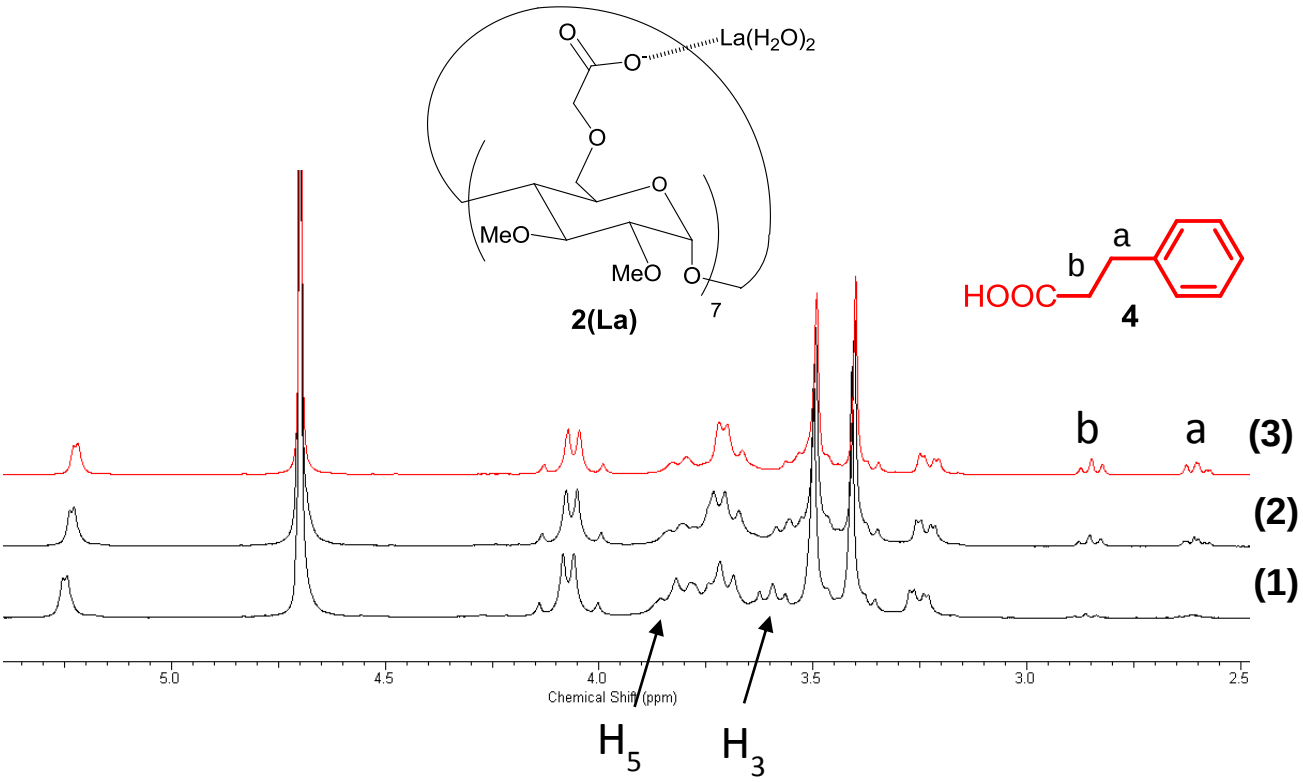
2

[b] H. Idriss, F. Estour, I. Zgani, C. Barbot, A. Biscotti, S. Petit, C. Galaup, M. Hubert-Roux, L. Nicol, P. Mulder, G. Gouhier, *RSC Adv*. 2013, **3**, 4531-4534.



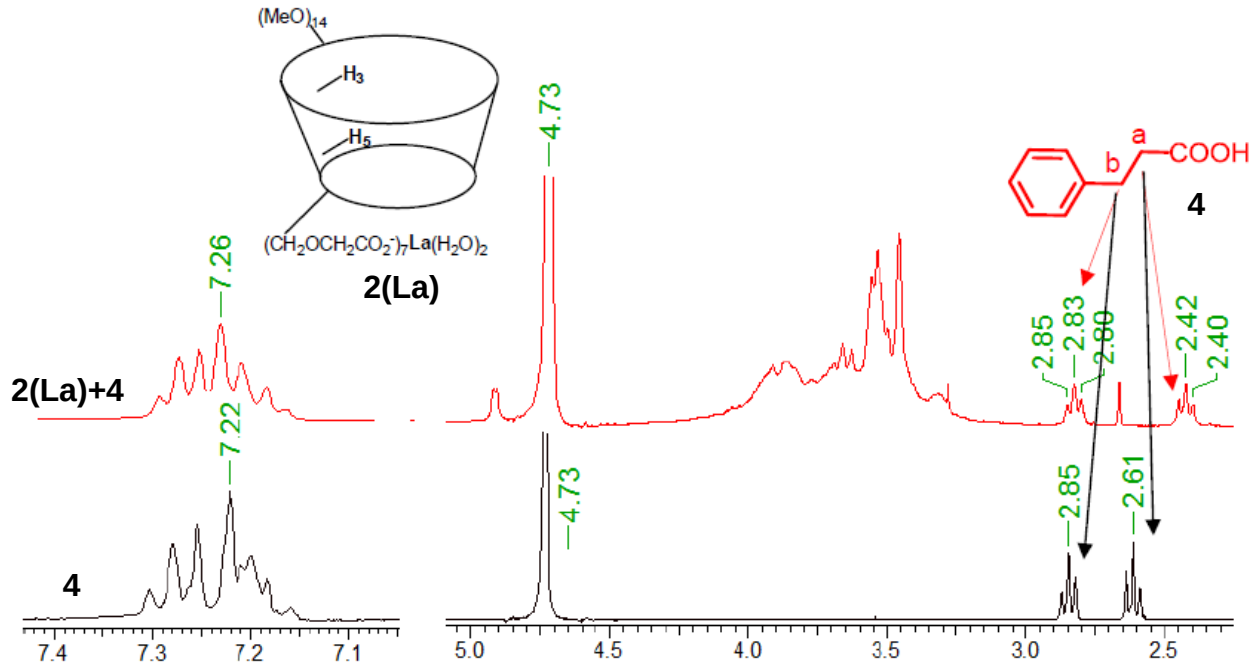
COSY ^1H-^1H NMR of compound **2**, 25°C, D_2O

3.10. ^{1}H NMR spectrum of **2(La)+4**

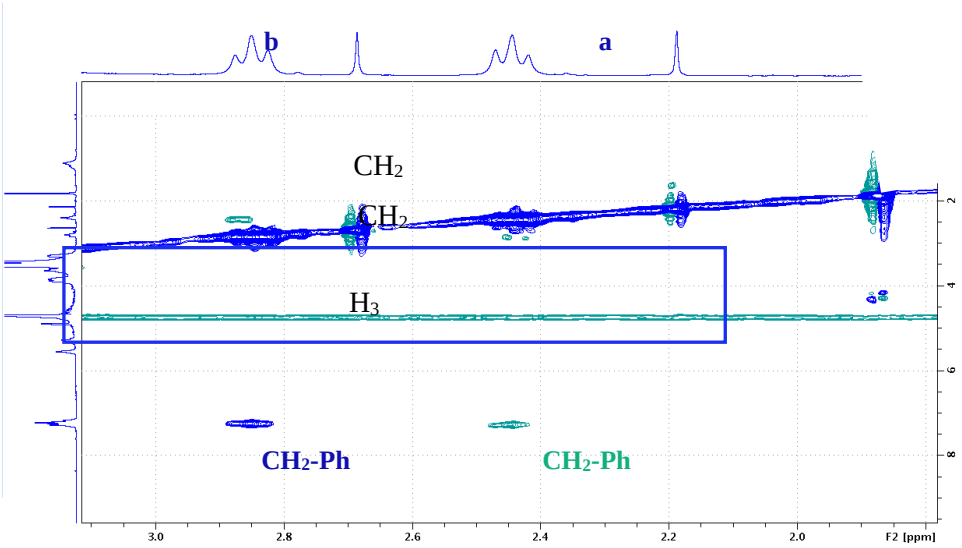


^{1}H NMR of compound **2(La)** in presence of 0.12 (spectrum a), 1 (spectrum 2) and 1.5 equivalents (spectrum 3) of hydrocinnamic acid **4**, PBS, 25˚C, pH 7.4

3.11 ^{1}H NMR spectrum of **2(La)+4**

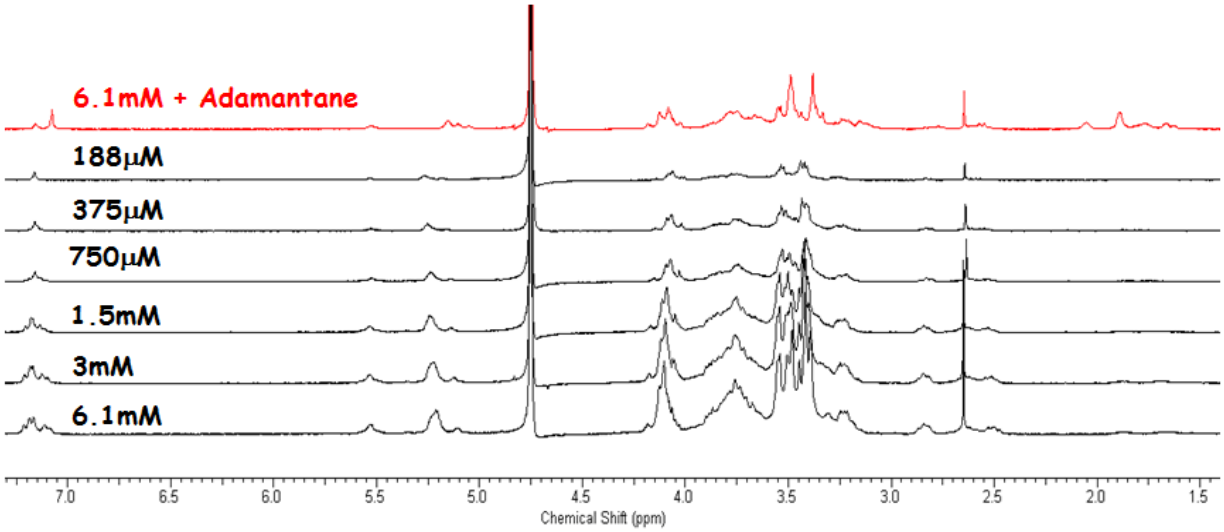


3.12 ROESY NMR spectrum of **2(La)+4**



Zoom of methyl proton area of NMR ROESY spectrum of inclusion complex **2(La)**+**4**, 25˚C, pH 7.4, D_2O

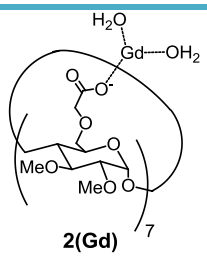
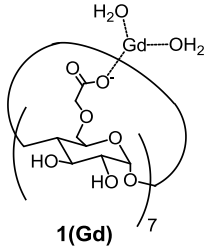
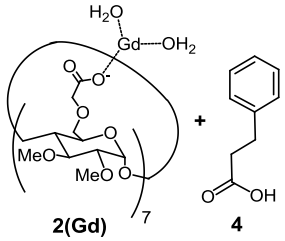
3.13 ^{1}H NMR study of **3** function of the concentration

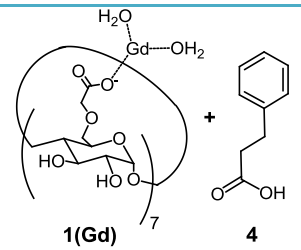
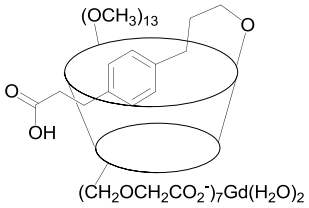


^{1}H NMR of **3** without and with adamantane carboxylic acid **5** in various concentrations, 25˚C, pH 7.4

4. Relaxivity measurements

Contrast agents **1(Gd)**, **2(Gd)** or **3(Gd)** were diluted (1, 0.5, 0.25, 0.125, 0.0625 mM) in TRIS buffer (10 mM TRIS, 154 mM NaCl, pH 7.4). **2(Gd)**+**4** and **1(Gd)**+**4** were prepared in TRIS buffer. The guest was completely soluble in TRIS buffer after the addition of contrast agents and stirred for 30 min. Water proton relaxation times (T_1, T_2) were measured on a minispec mq20 (Bruker, Germany) spectrometer operating at 20 MHz and the relaxivity values were calculated by plotting the curves of 1/T as function of the concentration. Relaxation values were measured three times and the average has been calculated. The temperature was kept at 37°C with a Julabo ED Heating Immersion Circulators (uncertainty ± 0.1°C).

Structures	r_1 ($mM^{-1}.s^{-1}$)	r_2 ($mM^{-1}.s^{-1}$)
 **2(Gd)**	**4.74**[b]	**5.86**[b]
 **1(Gd)**	**6.53**[b]	**8.09**[b]
 **2(Gd)** + **4**	**5.72**	**7.05**

 **1(Gd)** **4**	**10.26**	**12.47**
 **3(Gd)**	**5.92**	**6.96**

Relaxivity measurements realized at 0.5 T in a TRIS buffer (pH 7.4, 37°C).