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Multivalent thioglycopeptoids via photoclick chemistry: potent affinities towards LecA and BC2L-A lectins

C. Caumes,[ab] E. Gillon,[c] B. Legeret,[ab] C. Taillefumier,[ab] A. Imberty*[c] and S. Faure*[ab]

[a] *CNRS, UMR6296, ICCF, BP 80026, 63171 Aubière, France*
[b] *Clermont Université, Université Blaise Pascal, Institut de Chimie de Clermont-Ferrand, BP 10448, 63000 Clermont-Ferrand, France*
[c] *CERMAV, UPR5301,CNRS and Université Grenoble Alpes, BP 53, 38041 Grenoble, France.*

Email: sophie.faure@univ-bpclermont.fr

Contents

General experimental information for synthesis

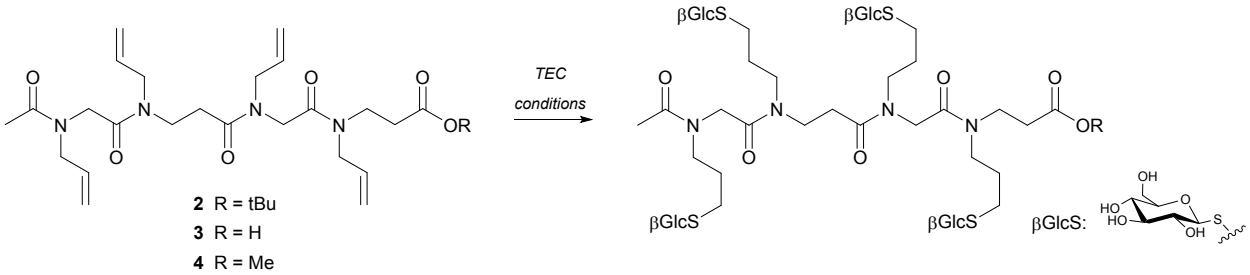
CH_2Cl_2 was distilled under N_2 from CaH_2 and stored over 4Å molecular sieves. CH_2Cl_2 and MeOH for column chromatography were distilled before use. DMF and DIPEA were dried over 4Å molecular sieves. All other solvents and chemicals obtained from commercial sources were used as received.

Melting points were determined on a on a Stuart SMP3 melting point apparatus and are uncorrected. NMR spectra were recorded on a 400 MHz Bruker AC 400 spectrometer. Chemical shifts are referenced to the residual solvent peak and *J* values are given in Hz. The following multiplicity abbreviations are used: (s) singlet, (d) doublet, (m) multiplet, (ls) large singlet and (br) broad. Where applicable, assignments were based on COSY, HMBC, HSQC and *J*-mod-experiments. TLC was performed on Merck TLC aluminium sheets, silicagel 60, F_{254}. Progression of reactions was, when applicable, followed by HPLC and/or TLC. Visualizing of spots was effected with UV-light and/or ninhydrin in EtOH/AcOH. Flash chromatography was performed with Merck silica gel 60, 40-63 μm. HRMS were recorded on a Micromass Q-Tof Micro (3000V) apparatus.

Optimization of the photo-induced TEC reaction conditions

The linear α,β-peptoid **2** acetylated at the *N*-terminus was chosen as a model since preliminary studies of photoinduced TEC reactions on peptoids in our group had revealed problems associated with the presence of a free terminal secondary amine. The commercially available sodium salt of 1-thio-β-D-glucose (βGlcSNa) was employed first as thiol partner. We started from well-established photoTEC conditions using 2,2-dimethoxy-2-phenylacetophenone (DPAP) as photoinitiator but switching the organic solvent for water since the starting materials and expected glycopeptoids were soluble in aqueous media (Table S1). Irradiation of the allyl-functionalized scaffold **2** and βGlcSNa (1 equiv. per alkene group) in equimolar quantities in presence of HCl during 1 h led to a low conversion as anticipated in protic solvent (entry 1). Increasing the irradiation time to 5 h (entry 2) resulted in the complete alkenes conversion as shown by NMR but together with a partial hydrolysis of the tertbutyl ester. Our attempts to avoid the ester cleavage or to drive it to completion were unsuccessful and starting from the free acid peptoid **S2** (obtained from **2** by TFA deprotection) the photoTEC process never reached the 100% conversion even with an excess of 1-thio-β-D-glucose (1.2 equiv. per alkene moiety, entry 4). We thus decided to use the linear α,β-peptoid **3** with a terminal methyl ester as a model which led to a reproducible 100% conversion after overnight irradiation using 1.1 excess of thiosugar (entries 5, 6). We were able to decrease the DPAP amount to 20% while maintaining complete TEC conversion (entries 7, 8). The optimized conditions (Entry 7) were then used for the synthesis of thioglycoclusters.

Table S1 Optimization of photo-induced TEC with 1-thio-β-D-glucose



2 R = tBu
3 R = H
4 R = Me

Entry	Scaffold	βGlcSH/alkene [a]	Time (h)	DPAP (%/sugar)	Conversion (%)[b]
1	**2**	1.0/1.0	1	30	–[c]
2	**2**	1.0/1.0	5	30	100[d]
3	**S2**	1.0/1.0	5	30	77
4	**S2**	1.2/1.0	5	30	85
5	**3**	1.0/1.0	5	30	100[e]
6	**3**	1.1/1.0	15	30	100
7	**3**	1.1/1.0	15	20	100
8	**3**	1.1/1.0	15	10	91

[a] Experimental conditions: βGlcSNa/HCl 1M, DPAP, H_2O, hν pyrex. [b] Determined by integration of residual allyl proton from ^1H NMR spectra in D_2O. [c] Low conversion. [d] Partial *tert*butyl ester hydrolysis ~ 30%. [e] non-reproducible reaction.

General experimental synthetic procedures

General procedure A: α-peptoid residues synthesis: Acylation step.

To a solution of the crude secondary amine (1.0 equiv, 0.2 M) in THF at 0 °C under Ar was added Et_3N (1.2 equiv) and then bromoacetyl bromide (1.2 equiv). After stirring for 1 h at 0°C the resulting mixture was diluted with EtOAc (10 mL per mmol starting material) and filtered, washing the solids with EtOAc. The filtrate was then concentrated and dried *in vacuo*, yielding the crude bromoacetyl amide.

General procedure B: α-peptoid residues synthesis: Substitution step.

To a solution of *tert*-butyl bromoacetate or the crude bromoacetyl amide (1.0 equiv, 0.2 M) in THF at 0 °C under Ar was added Et_3N (2.0 equiv) followed by the chosen primary amine (4.0 equiv). After stirring overnight at r.t., the resulting mixture was diluted with EtOAc (10 mL per mmol starting material) and filtered, washing the solids with EtOAc. The filtrate was then concentrated under reduced pressure. EtOAc was added to the residue, which was then concentrated under reduced pressure. This was repeated twice and the residue was dried *in vacuo*, yielding the desired crude secondary amine.

General procedure C: β-peptoid residues synthesis: Acylation step.

To a solution of the crude secondary amine (1.0 equiv, 0.2 M) in THF at 0 °C under Ar was added Et_3N (2.2 equiv) and then acryloyl chloride (1.2 equiv). After stirring for 1 h at 0 °C the resulting mixture was diluted with EtOAc (10 mL per mmol starting material) and filtered, washing the solids with EtOAc. The filtrate was then concentrated and dried *in vacuo*, yielding the crude acrylamide.

General procedure D: β-peptoid residues synthesis: aza-Michael step.

To a solution of *tert*-butyl acrylate or the crude acrylamide (1.0 equiv, 0.4 M) in MeOH at r.t. under Ar was added the chosen primary amine (2.0 equiv). After stirring overnight at 50 °C, the mixture was concentrated under reduced pressure. EtOAc was added to the residue, which was then concentrated under reduced pressure. This was repeated twice and the residue was dried *in vacuo*, yielding the desired crude secondary amine.

General procedure E: Acetylation of *N*-terminal peptoid.

To a solution of a peptoid (1 equiv) and Et_3N (1.4 equiv) in THF or EtOAc (0.2 M) at 0°C under Ar, was added AcCl (1.2 equiv). After stirring for 1 hour at 0°C, the mixture was filtered washing the solids with EtOAc. The filtrate was then concentrated and dried *in vacuo*, yielding the crude *N*-acylated compound.

General procedure F: *tert*-butyl ester removal.

The protected compound (1 equiv) was dissolved into DCM (0.1-0.3 M) at 0°C under argon atmosphere and TFA (equal volume of that of DCM) was added. After stirring 1h30 at r.t. the mixture

is concentrated under reduced pressure. The residue was dissolved and concentrated from Et_2O or DCM (three times) to allow evaporation of TFA and furnish the trifluoroacetate salt.

General procedure G: Macrocyclisation using EDCI as coupling reagent

To a solution of the resulting unprotected linear peptoid in DCM (10 mL) was added Et_3N (6 equiv). The mixture was stirred at room temperature for 5 minutes and added to a solution of EDCI (6 equiv) and HOBt (6 equiv) in DCM (5 mM in peptoid). The reaction mixture was stirred at room temperature for 3 days, then washed successively with satd. aq. $NaHCO_3$ (2×1/5 the volume of DCM), satd. aq. NH_4Cl (2×1/5 the volume of DCM) and brine (1/5 the volume of DCM). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure.

General procedure H: Multivalent TEC considering n alkenes

In a Pyrex tube were introduced successively 1-thio-β-D-glucose (n×1.1 equiv), DPAP (n×0.2 equiv) and a solution of HCl 1M in H_2O (n×1.1 equiv). A solution of the peptoid bearing n alkenes (1 equiv) in H_2O (0.05 M) was prepared then added in the Pyrex tube. The tube was irradiated with a 400 W medium-pressure Hg lamp fitted with a Pyrex filter refrigerated by water circulation. The aqueous solution was irradiated overnight at rt under Ar bubbling then washed with DCM (3×5 mL) yielding the crude conjugated peptoid in aqueous solution.

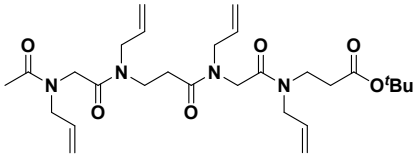
Purification using a Waters Sep-Pak® Vac C18 cartridge

The cartridge was rinsed with one volume of MeOH, and then equilibrated with one volume of distilled H_2O. The crude peptoid in aqueous solution was adsorbed through the cartridge then washed with one volume of distilled H_2O and eluted with one volume of MeOH. Evaporation of MeOH yielded the peptoid glycocluster in pure form.

Experimental procedures and characterisation data of peptoids and thioglycopeptoids

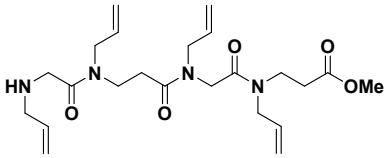
Synthesis and characterisation data for peptoids **1**, **4** and **8** have been previously reported.[S1]

α,β-tetrapeptoid 2



α,β-peptoid **2** was synthesised starting from α,β-peptoid **1** (588 mg, 1.20 mmol, 1.0 equiv) by application of the **General procedure E** using AcOEt as solvent. Flash chromatography on silica gel of the crude product using AcOEt/MeOH 93:7 as solvent yielded peptoid **2** (447 mg, 0.84 mmol**,** 70 %**)** as a yellow oil: R_f = 0.39 (AcOEt/MeOH 93:7); IR (ATR) $\bar{\nu}$ (cm^{-1}): 3080 (NH), 2980, 2931, 1725 (C=O ester), 1652, 1645 (C=O amide), 1472, 1415, 1214, 1152; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.26 (s, 9H, ^{t}Bu), 1.82/1.95 (2×s, 3H, NAc), 2.32-2.39 (m, 2H, NCH_2CH_2C=OO), 2.51-2.58 (m, 2H, NCH_2CH_2C=ON), 3.34-3.46 (m, 4H, 2×NCH_2CH_2C=O), 3.80-4.07 (m, 12H, 4×CH_2CH=CH_2 and 2×NCH_2C=O), 4.91-5.07 (m, 8H, 4×CH_2CH=CH_2), 5.54-5.65 (m, 4H, 4×CH_2CH=CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.6, 21.0 (CH_3, NAc), 27.6 ($3CH_3$, ^{t}Bu), 30.8, 33.6, 34.1 (CH_2, NCH_2CH_2C=OO), 31.2 (CH_2, NCH_2CH_2C=ON), 41.5, 41.9, 42.5, 42.7, 43.0, 43.2, 43.5, 43.8 ($2CH_2$, 2×NCH_2CH_2C=O), 45.8, 46.0, 46.2, 46.5, 47.5, 47.6, 47.8, 48.0, 48.2, 48.3, 48.6, 48.7, 48.9, 49.6, 49.8, 50.2, 50.3, 50.7 ($6CH_2$, 4×CH_2CH=CH_2 and 2×NCH_2C=O), 80.1, 80.7 (C, ^{t}Bu), 116.4, 116.5, 116.7, 116.9, 117.0, 117.1, 117.2, 117.3, 117.5 ($4CH_2$, 4×CH_2CH=CH_2), 132.3, 132.4, 132.5, 132.7, 133.0, 133.1, 133.4 (4CH, 4×CH_2CH=CH_2), 167.3, 167.6, 167.7, 168.2, 169.8, 170.5, 170.6, 170.8, 171.4, 171.5 (5C, 5×C=O). HRMS (TOF MS ES+): calcd for $C_{28}H_{45}N_4O_6$ $[M + H]^+$ *m/z* 533.3339, found 533.3322.

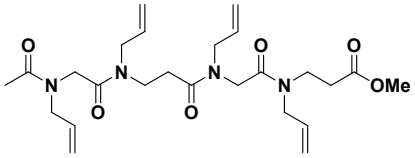
α,β-tetrapeptoid S3



α,β-Peptoid S**3** was synthesised starting from methyl acrylate (517 mg, 6.00 mmol, 1.0 equiv) by application of the **General procedure D** using allylamine as primary amine, then **General procedures A** and **B** using allylamine as primary amine, then **General procedures C** and **D** using allylamine as primary amine, then **General procedures A** and **B** using allylamine as primary amine. Flash chromatography on silica gel of the crude product using EtOAc to EtOAc/MeOH 90:10 to 80:20 as solvent yielded peptoid **S3** (1.49 g, 3.32 mmol, 55 %) as a yellowish oil: R_f = 0.13 (DCM/MeOH 80:20); **^{1}H** NMR (400 MHz, $CDCl_3$) δ (ppm): 2.15-2.77 (m, 4H, 2×NCH_2CH_2C=O), 2.86-3.31 (m, 3H, $NHCH_2CH$=CH_2 and 0.5×$NHCH_2C$=O), 3.31-3.46 (m, 4H, 2×NCH_2CH_2C=O), 3.43/3.46 (2×s, 3H, OCH_3), 3.55-4.20 (m, 9H, 3×NCH_2CH=CH_2, NCH_2C=O and 0.5×$NHCH_2C$=O), 4.70-5.27 (m, 8H, 4×CH_2CH=CH_2), 5.36-5.93 (m, 4H, 4×CH_2CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 30.0, 30.8, 31.0, 31.2, 32.0, 32.2, 32.3, 32.7, 34.3, 34.7 ($2CH_2$, 2×NCH_2CH_2C=O), 41.3, 41.7, 42.1, 42.4, 42.7, 43.1, 43.2 ($2CH_2$, 2×NCH_2CH_2C=O), 45.9, 46.0, 46.2, 46.3, 47.6, 47.7, 48.0, 48.3, 48.7, 48.8, 48.8, 49.0, 49.8, 49.9, 50.2, 50.7, 50.9, 51.1, 51.2, 54.7 ($6CH_2$, 2×NCH_2C=O and 4×CH_2CH=CH_2), 51.2, 51.3, 51.4, 51.5 (CH_3, OCH_3), 115.4, 116.1, 116.3, 116.4, 116.6, 116.8, 116.9, 117.0, 117.1, 117.2, 117.3, 117.5, 117.8, 118.1, 118.7 ($4CH_2$, 4×CH_2CH=CH_2), 132.1, 132.2, 132.3, 132.4, 132.5, 132.8, 132.9, 133.0, 133.5, 133.8, 134.0, 134.5, 134.6, 134.7, 134.9

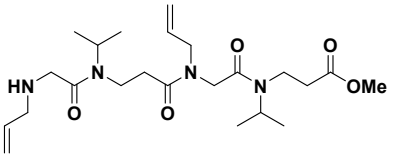
(4CH, 4×$CH_2CH=CH_2$), 167.1, 167.3, 167.6, 167.7, 167.8, 169.2, 170.0, 170.2, 170.3, 170.5, 170.9, 171.3, 171.5, 171.7 (4C, 4×*C*=O); HRMS (TOF MS ES+): calcd for $C_{23}H_{37}N_4O_5$ $[M + H]^+$ *m/z* 449.2764, found 449.2768.

α,β-tetrapeptoid 3



α,β-Peptoid **3** was synthesised from α,β-Peptoid **S3** (1.00 g, 2.24 mmol, 1.0 equiv) by application of the **General procedure E** using THF as solvent. Flash chromatography on silica gel of the crude product using AcOEt/MeOH 95:5 to 90:10 as solvent yielded peptoid **3** (682 mg, 1.39 mmol, 62 %) as a yellow oil: R_f = 0.29 (EtOAc/MeOH 90:10); IR (ATR) $\bar{\nu}$ (cm^{-1}): 2985, 2953, 1735 (C=O ester), 1645 (C=O amide), 1473, 1436, 1419, 1201, 990, 922; **1**H NMR (400 MHz, MeOD) δ (ppm): 1.84-2.10 (m, 3H, NAc), 2.26-2.73 (m, 4H, 2×NCH_2CH_2C=O), 3.40-3.80 (m, 7H, 2×NCH_2CH_2C=O and OCH_3), 3.80-4.31 (m, 12H, 4×$NCH_2CH=CH_2$ and 2×NCH_2C=O), 4.95-5.26 (m, 8H, 4×$CH_2CH=CH_2$), 5.55-5.85 (m, 4H, 4×$CH_2CH=CH_2$); ^{13}C NMR (100 MHz, MeOD) δ (ppm): 20.9, 21.3 (CH_3, NAc), 31.1, 31.3, 31.5, 32.5, 33.0, 34.9 ($2CH_2$, 2×NCH_2CH_2C=O), 41.6, 41.8, 42.0, 42.8, 43.0, 43.3, 43.5, 43.9, 44.1, 44.5 ($2CH_2$, 2×NCH_2CH_2C=O), 46.1, 46.1, 46.3, 46.4, 46.5, 46.7, 47.8, 47.9, 48.1, 48.4, 48.6, 48.7, 48.9, 49.0, 50.1, 50.3, 50.5, 50.6, 51.0, 51.2, 51.3, 51.7, 52.1, 52.4 ($6CH_2$, 2×NCH_2C=O and 4×$CH_2CH=CH_2$), 51.8, 51.6 (CH_3, OCH_3), 115.8, 116.0, 116.3, 116.5, 116.7, 116.9, 117.0, 117.2, 117.4, 117.6, 117.7, 117.9 ($4CH_2$, 4×$CH_2CH=CH_2$), 131.7, 132.4, 132.5, 132.5, 132.6, 132.7, 132.9, 133.2, 133.3, 133.6, 134.1 (4CH, 4×$CH_2CH=CH_2$), 167.7, 167.9, 168.2, 168.5, 167.0, 170.5, 170.8, 171.1, 171.2, 171.8, 171.9, 172.1, 172.2, 172.7 (5C, 5×*C*=O); HRMS (TOF MS ES+): calcd for $C_{25}H_{38}N_4O_6Na$ $[M + Na]^+$ *m/z* 513.2689, found 513.2675.

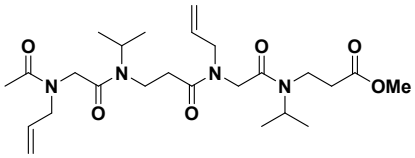
α,β-tetrapeptoid S5



α,β-Peptoid S**5** was synthesised starting from methyl acrylate (515 mg, 6.00 mmol, 1.0 equiv) by application of the **General procedure D** using isopropylamine as primary amine, then **General procedures A** and **B** using allylamine as primary amine, then **General procedures C** and **D** using isopropylamine as primary amine, then **General procedures A** and **B** using allylamine as primary amine. Flash chromatography on silica gel of the crude product using DCM/MeOH 90:10 as solvent yielded peptoid **S5** (1.00 g, 2.21 mmol, 36 %) as a yellowish oil: R_f = 0.37 (DCM/MeOH 90:10); IR (ATR) ν (cm^{-1}): 2975, 1734 (C=O ester), 1641 (C=O amide), 1436, 1420, 1120, 1128, 1084, 996, 928; **1**H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.81-1.42 (m, 12H, 2×$CH(CH_3)_2$), 2.33-2.76 (m, 4H, 2×NCH_2CH_2C=O), 2.95-3.29 (m, 4H, 2×$CH_2CH=CH_2$), 3.29-3.52 (m, 4H, 2×NCH_2CH_2C=O), 3.52-3.72 (m, 3H, OCH_3), 3.72-4.62 (m, 6H, 2×$COCH_2N$ and 2×$CH(CH_3)_2$), 4.95-5.37 (m, 4H, 2×$CH_2CH=CH_2$), 5.56-5.95 (m, 2H, 2×$CH_2CH=CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.1, 20.8, 20.9, 22.6 ($4CH_3$, NAc and 2×$CH(CH_3)_2$), 32.3, 33.6, 33.1, 35.2 ($2CH_2$, 2×NCH_2CH_2C=O), 36.7, 36.8, 37.5, 37.8, 38.0, 38.3 ($2CH_2$, 2×NCH_2CH_2C=O), 41.1, 41.7, 46.1, 46.5, 46.6, 47.1, 48.1, 48.3, 48.7, 49.3, 49.4, 50.7, 51.1, 51.3, 51.3, 51.7, 51.8, 52.1 ($4CH_2$, 2×N_2CH_2C=O and 2×$CH_2CH=CH_2$), 46.1, 46.3, 46.9, 47.3, 47.5, 47.6 (2CH, 2×$CH(CH_3)_2$), 51.5

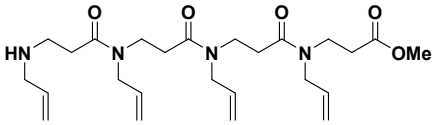
(CH_3, O*C*H_3), 115.8, 116.6, 116.7, 116.8, 116.9, 117.3, 117.4, 117.9 (2CH_2, 2×CH_2CH=*C*H_2), 132.5, 132.7, 132.8, 133.5, 134.1, 135.5, 135.6, 135.7 (2CH, 2×CH_2*C*H=CH_2), 167.0, 167.1, 167.3, 167.7, 169.6, 169.9, 170.7, 171.2, 171.7, 172.0, 172.1 (4C, 4×*C*=O); HRMS (TOF MS ES+): calcd for $C_{23}H_{41}N_4O_5$ $[M + H]^+$ *m/z* 453.3077, found 453.3087.

α,β-tetrapeptoid 5



α,β-Peptoid **6** was synthesised from α,β-Peptoid **S5** (934 mg, 2.19 mmol, 1.0 equiv) by application of the **General procedure E** using THF as solvent. Flash chromatography of the crude product in EtOAc/MeOH 90:10 yielded peptoid **5** (747 mg, 1.51 mmol, 69 %) as a yellow oil: TLC R_f = 0.34 (EtOAc/MeOH 90:10); IR (ATR) $\bar{\nu}$ (cm^{-1}): 2975, 1736 (C=O ester), 1642 (C=O amide), 1469, 1436, 1419, 1369, 1303, 1246, 1200, 1173, 1084, 991, 923; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.89-1.26 (m, 12H, 2×CH(C*H*$_3$)$_2$), 1.80-2.06 (m, 3H, NAc), 2.30-2.74 (m, 4H, 2×NCH_2C*H*$_2$C=O), 3.28-3.49 (m, 4H, 2×NC*H*$_2$CH_2C=O), 3.53/3.58 (2×s, 3H, OC*H*$_3$), 3.70-4.57 (m , 10H, 2×COC*H*$_2$N, 2×C*H*$_2$CH=CH_2 and 2×C*H*(CH_3)$_2$), 4.93-5.16 (m, 4H, 2×CH_2CH=C*H*$_2$), 5.53-5.82 (m, 2H, 2×CH_2C*H*=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.0, 20.7, 20.8, 21.2 (5CH_3, 2×CH(*C*H$_3$)$_2$), 32.3, 33.0, 33.3, 33.5, 34.8 (2CH_2, 2×NCH_2*C*H_2C=O), 35.2, 36.6, 36.8, 36.9, 37.5, 37.7, 38.0, 38.2, 38.5, 38.6, 38.7 (2CH_2, 2×N*C*H_2CH_2C=O), 45.7, 45.9, 47.3, 47.5, 47.7 (2CH, 2×*C*H(CH_3)$_2$), 46.0, 46.1, 46.2, 46.2, 46.4, 46.5, 46.8, 46.9, 48.0, 48.1, 48.3, 48.5, 48.7, 48.8, 49.0, 50.6, 50.8, 51.2, 51.4, 51.6, 52.1, 52.4 (4CH_2, 2×N$_2$*C*H_2C=O and 2×*C*H_2CH=CH_2), 51.3, 51.6 (CH_3, O*C*H_3), 116.5, 116.7, 116.8, 117.2, 117.7 (2CH_2, 2×CH_2CH=*C*H_2), 132.4, 132.7, 132.8, 133.4, 133.5, 133.7 (2CH, 2×CH_2*C*H=CH_2), 166.6, 166.8, 167.1, 167.2, 167.3, 167.7, 167.9, 170.8, 170.9, 171.1, 171.4, 171.6, 171.7, 171.9, 172.0 (5C, 5×*C*=O); HRMS (TOF MS ES+): calcd for $C_{25}H_{42}N_4O_6Na$ $[M + Na]^+$ *m/z* 517.3002, found 517.3011.

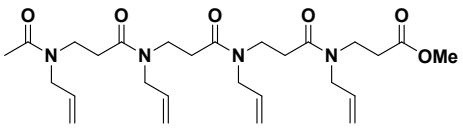
β-tetrapeptoid S6



β-Peptoid **S6** was synthesised starting from methyl acrylate (515 mg, 6.00 mmol, 1.0 equiv) by application of the **General procedure D** using allylamine as primary amine, then three times repetition of **General procedures C** and **D** using allylamine as primary amine. Flash chromatography on silica gel of the crude product using DCM/MeOH 90:10 as solvent yielded peptoid **S6** (1.13 g, 2.36 mmol, 39%) as yellowish oil: TLC R_f = 0.44 (EtOAc/MeOH 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.49-2.83 (m, 8H, 4×NCH_2C*H*$_2$C=O), 2.88-3.00 (m, 2H, NC*H*$_2$CH_2C=O), 3.28-3.41 (m, 2H, NC*H*$_2$CH=CH_2), 3.50-3.63 (m, 6H, 3×NC*H*$_2$CH_2C=O), 3.66 (ls, 3H, OC*H*$_3$), 3.90-4.08 (m, 6H, 3×NC*H*$_2$CH=CH_2), 5.04-5.31 (m, 4H, 4×CH_2CH=C*H*$_2$), 5.68-5.81 (m, 3H, 3×CH_2C*H*=CH_2), 5.82-5.99 (m, 1H, CH_2C*H*=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 31.4, 31.6, 31.8, 32.0, 32.1, 32.3, 32.6, 33.1, 33.3 (4CH_2, 4×NCH_2*C*H_2C=O), 41.8, 42.6, 42.7, 42.8, 43.3, 43.4, 43.5, 44.4 (4CH_2, 4×N*C*H_2CH_2C=O), 47.8, 48.0, 48.1 (CH_2, *C*H_2CH=CH_2), 51.0, 51.1, 51.51.6, 51.8, 51.9, 53.4 (3CH_2, 3×*C*H_2CH=CH_2), 51.9 (CH_3, O*C*H_3), 116.4, 116.6, 117.1, 117.2, 117.6, 117.9 (4CH_2, 4×CH_2CH=*C*H_2), 132.7, 132.9, 133.0, 133.1, 133.2 (3CH, 3×CH_2*C*H=CH_2), 134.2, 134.7, 135.0 (CH,

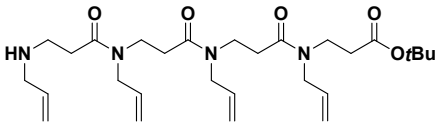
$CH_2CH=CH_2$), 170.6, 170.8, 172.0, 172.3 (4C, 4×*C*=O); HRMS (TOF MS ES+): calcd for $C_{25}H_{41}N_4O_5$ $[M + H]^+$ *m/z* 477.3077, found 477.3073.

β-tetrapeptoid 6



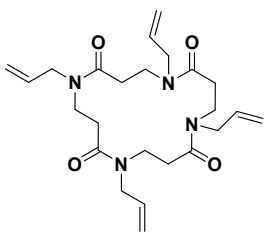
β-Peptoid **6** was synthesised starting from β-peptoid **S6** (805 mg, 1.69 mmol, 1.0 equiv) by application of the **General procedure E** using AcOEt as solvent. Flash chromatography of the crude product in DCM/MeOH 95:5 yielded peptoid **6** (723 mg, 1.39 mmol, 82%) as a yellow oil: R_f = 0.18 (DCM/MeOH 95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.84, 1.92 and 1.96 (3s, 3H, NAc), 2.30-2.69 (m, 8H, 4×NCH_2CH_2C=O), 3.32-3.44 (m, 8H, 4×NCH_2CH_2C=O), 3.45 and 3.47 (2s, 3H, OCH_3), 3.72-3.92 (m, 8H, 4×$NCH_2CH=CH_2$), 4.88-5.03 (m, 8H, 4×$CH_2CH=CH_2$), 5.51-5.69 (m, 4H, 4×$CH_2CH=CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.1 (CH_3, NAc), 31.1, 31.3, 31.6, 32.3, 32.8, 33.0 (4CH_2, 4×NCH_2CH_2C=O), 42.3, 42.5, 43.0, 43.1, 43.4, 44.0 (4CH_2, 4×NCH_2CH_2C=O), 47.5, 47.6, 47.7 (CH_2, $CH_2CH=CH_2$), 50.7, 50.9, 51.3, 51.9 (3CH_2, 3×$CH_2CH=CH_2$), 51.5, 51.8 (CH_3, OCH_3), 116.1, 116.3, 116.7, 116.9, 117.2 (4CH_2, 4×$CH_2CH=CH_2$), 132.7, 132.8, 133.0, 133.2 (4CH, 4×$CH_2CH=CH_2$), 169.6, 169.9, 170.3, 170.5, 170.6, 171.1, 171.2, 172.0 (5C, 5×*C*=O); HRMS (TOF MS ES+): calcd for $C_{27}H_{42}N_4O_6Na$ $[M + Na]^+$ *m/z* 541.3002, found 541.2985.

β-tetrapeptoid 7



β-Peptoid **7** was synthesised starting from tertbutyl acrylate (385 mg, 3.00 mmol, 1.0 equiv) by application of the **General procedure D** using allylamine as primary amine, then three times repetition of **General procedures C** and **D** using allylamine as primary amine. Flash chromatography on silica gel of the crude product using AcOEt/MeOH 90:10 as solvent yielded peptoid **8** (625 mg, 1.20 mmol, 40%) as a yellowish oil: R_f = 0.18 (AcOEt/MeOH 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.18 (ls, 9H, *t*Bu), 2.18-2.48 (m, 9H, 4×NCH_2CH_2C=O and N*H*), 2.56-2.69 (m, 2H, NCH_2CH_2C=O), 2.95-3.06 (m, 2H, $NCH_2CH=CH_2$), 3.25-3.42 (m, 6H, 3×NCH_2CH_2C=O), 3.70-3.79 (m, 6H, 3×$NCH_2CH=CH_2$), 4.80-5.00 (m, 8H, 4×$CH_2CH=CH_2$), 5.46-5.72 (m, 4H, 4×$CH_2CH=CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 27.6 (3CH_3, *t*Bu), 31.0, 31.2, 31.5, 31.6, 32.2, 32.5, 32.8, 33.6, 34.0, 34.2 (4CH_2, 4×NCH_2CH_2C=O), 42.1, 42.4, 42.5, 42.9, 43.0, 43.2, 44.2, 44.3 (4CH_2, 4×NCH_2CH_2C=O), 47.2, 47.3, 47.5, 47.6, 47.7 (CH_2, $CH_2CH=CH_2$), 50.4, 50.7, 50.8, 51.8 (3CH_2, 3×$CH_2CH=CH_2$), 80.0, 80.1, 80.6, 80.7 (C, *t*Bu), 115.0, 115.6, 115.7, 115.9, 116.0, 116.2, 116.5, 116.7, 116.8, 116.9 (4CH_2, 4×$CH_2CH=CH_2$), 132.6, 132.7, 132.8, 132.9 (3CH, 3×$CH_2CH=CH_2$), 135.8, 135.9, 136.0 (CH, $CH_2CH=CH_2$), 169.5, 169.6, 169.8, 170.0, 170.2, 170.3, 170.4, 170.6, 170.8, 170.9, 171.1 (4C, 4×*C*=O); HRMS (TOF MS ES+): calcd for $C_{28}H_{47}N_4O_5$ $[M + H]^+$ *m/z* 519.3546, found 519.3534.

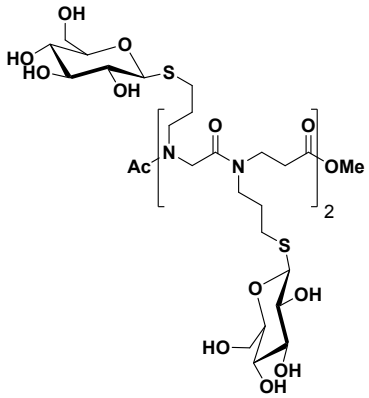
β-cyclotetrapeptoid 9



Cyclic β-Peptoid **9** was synthesised starting from β-Peptoid **7** (130 mg, 0.25 mmol, 1.0 equiv) by application of the macrocyclisation procedure**.** Flash chromatography on silica gel of the crude product using DCM/MeOH 95:5 as

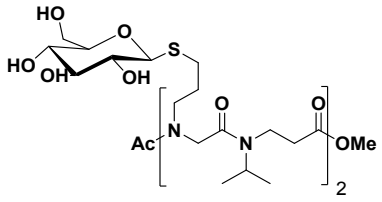
solvent yielded peptoid **9** (89 mg, 0.20 mmol, 80%) as a yellowish oil: R_f = 0.40 (DCM/MeOH 95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.34-2.85 (m, 8H, 4×$NCH_2CH_2CH_2C$=O), 3.39-3.73 (m, 8H, 4×$NCH_2CH_2CH_2C$=O), 3.80-4.05 (m, 8H, 4×NCH_2CH=CH_2), 4.94-5.15 (m, 8H, 4×CH_2CH=CH_2), 5.61-5.74 (m, 4H, 4×CH_2CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 29.6, 30.7, 31.2, 31.7, 31.8, 32.1, 32.7, 32.9, 33.0 (4CH_2, 4×$NCH_2CH_2CH_2C$=O), 41.7, 41.9, 42.2, 42.9, 43.3, 43.5, 43.9, 44.2, 44.4, 45.3 (4CH_2, 4×$NCH_2CH_2CH_2C$=O), 47.8, 47.9, 48.1, 48.4, 48.6, 48.7, 50.4, 51.4, 52.0, 52.4, 53.0 (4CH_2, 4×CH_2CH=CH_2), 115.9, 116.1, 116.3, 116.4, 116.6, 117.2, 117.3, 117.5, 117.6, 118.1 (4CH_2, 4×CH_2CH=CH_2), 132.4, 132.7, 132.8, 132.9, 133.0, 133.3 (4CH, 4×CH_2CH=CH_2), 168.9, 169.5, 170.0, 170.2, 170.5, 170.8, 170.9, 171.1, 171.2, 171.3, 171.5, 171.6, 172.3 (4C, 4×C=O); HRMS (TOF MS ES+): calcd for $C_{24}H_{36}N_4O_4Na$ $[M + Na]^+$ *m/z* 467.2634, found 467.2628.

Thioglycocluster 10



The thioglycopeptoid **10** was synthesised starting from **3** (29 mg, 59 µmol, 1.0 equiv) by application of the **General procedure H** using the sodium salt of 1-thio-β-D-glucose. Purification using **General procedure I** of the crude product yielded thioglycopeptoid **10** (67 mg, 53 µmol**,** 90 %**)** as white foam: IR (ATR) $\bar{\nu}$ (cm^{-1}): 3353 (O-H), 2930, 2865, 2503, 1729 (C=O ester), 1635 (C=O amide), 1489, 1436, 1368, 1271, 1064, 1031; ^{1}H NMR (400 MHz, D_2O) δ (ppm): 1.76-2.28 (m, 11H, 4×$CH_2CH_2CH_2S$ and NAc), 2.44-3.00 (m, 12H, 4×$CH_2CH_2CH_2S$ and 2×$NCH_2CH_2CH_2C$=O), 3.20-4.13 (m, 39H, 12×C*H*OH, 4×C*H*CH_2OH, 2×$NCH_2CH_2CH_2C$=O, 4×$CH_2CH_2CH_2S$ and OCH_3), 4.18-4.36 (m, 2H, $NCH_2CH_2CH_2C$=O), 4.38-4.64 (m, 6H, $NCH_2CH_2CH_2C$=O and 4×OC*H*S); ^{13}C NMR (100 MHz, D_2O) δ (ppm): 20.4, 20.9 (CH_3, NAc), 27.1, 27.4, 28.1, 30.6, 31.2, 32.2, 32.7 (10CH_2, 4×$CH_2CH_2CH_2S$, and 2×$NCH_2CH_2CH_2C$=O), 42.5, 42.8, 43.1, 43.4, 45.0, 45.2, 46.3, 46.6, 46.8, 47.0, 48.0, 48.5, 49.3, 50.3, 50.9 (8CH_2, 2×$NCH_2CH_2CH_2C$=O, 2×$NCH_2CH_2CH_2C$=O and 4×$CH_2CH_2CH_2S$), 52.4 (CH_3, OCH_3), 60.9, 61.3 (4CH_2, 4×CHCH_2OH), 69.2, 69.5, 71.2, 71.4, 72.3, 73.5, 73.7, 75.7, 77.0, 77.2, 79.9, 80.2 (16CH, 4×*C*HCH_2OH and 12×*C*HOH), 85.5, 85.6, 89.4 (4CH, 4×OC*H*S), 169.4, 169.7, 169.8, 173.2, 173.6, 173.8, 174.0, 174.4, 174.8, 175.2 (5C, 5×*C*=O); HRMS (TOF MS ES+): calcd for $C_{49}H_{86}N_4O_{26}S_4Na_2$ $[M + 2Na]^{2+}$ *m/z* 660.2104, found 660.2109; OR: $[\alpha]_D^{24} = -32.1$ (*c* 1.12, H_2O).

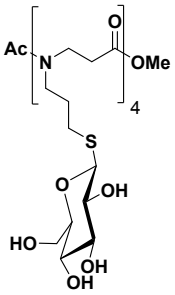
Thioglycocluster 11



The thioglycopeptoid **11** was synthesised starting from **5** (30 mg, 60 µmol, 1.0 equiv) by application of the **General procedure H** using the sodium salt of 1-thio-β-D-glucose. Purification using **General procedure I** of the crude product yielded thioglycopeptoid **11** (48 mg, 54 µmol, 90 %) as white foam: IR (ATR) $\bar{\nu}$ (cm^{-1}): 3399 (O-H), 2978, 2917, 2509, 1731 (C=O ester), 1630 (C=O amide), 1438, 1434, 1370, 1267, 1208, 1075, 1067, 1036; ^{1}H NMR (400 MHz, D_2O) δ (ppm): 1.01-1.26 (m, 12H, 2×$CH(CH_3)_2$), 1.68-1.99 (m, 5H, 2×$CH_2CH_2CH_2S$, 1/3×NAc), 2.04-2.19 (m, 2H, 2/3×NAc), 2.33-2.92 (m, 8H, 2×$NCH_2CH_2CH_2C$=O and 2×$CH_2CH_2CH_2S$), 3.16-3.57 (m, 16H, 6×C*H*OH, 2×C*H*CH_2OH, 2×$NCH_2CH_2CH_2C$=O and

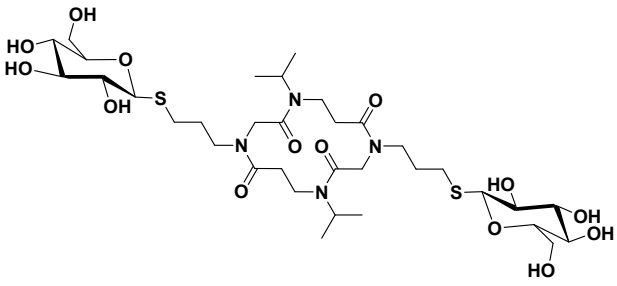
2×CH_2CH$_2$CH$_2$S), 3.57-3.70 (m, 5H, OCH_3 and CHCH_2OH), 3.76-3.86 (m, 2H, CHCH_2OH), 3.89-4.52 (m, 8H, 2×NCH_2C=O, 2×CH(CH$_3$)$_2$ and 2×OCHS); ^{13}C NMR (100 MHz, D$_2$O) δ (ppm): 19.2, 19.3, 19.8, 19.9, 19.9, 20.4, 20.8 (5CH$_3$, NAc and 2×CH(*C*H$_3$)$_2$), 27.1, 27.4, 28.0, 28.2, 32.0, 32.5, 33.7, 34.6 8 (6CH$_2$, 2×NCH$_2$*C*H$_2$C=O and 2×CH$_2$*C*H$_2$*C*H$_2$S), 37.0, 37.2, 37.5, 38.5, 39.2, 46.8, 46.9, 47.3, 47.5, 47.6, 48.0, 48.4, 49.2, 49.4, 50.4, 50.9 (6CH$_2$, 2×*C*H$_2$CH$_2$CH$_2$S, 2×N*C*H$_2$CH$_2$C=O and 2×N*C*H$_2$C=O), 48.5, 48.6, 48.9 (2CH, 2×*C*H(CH$_3$)$_2$), 52.3 (CH$_3$, O*C*H$_3$), 60.9 (2CH$_2$, 2×CH*C*H$_2$OH), 69.5, 72.3, 77.2, 79.9 (8CH, 2×*C*HCH$_2$OH and 6×*C*HOH), 85.5, 85.6, 89.4 (2CH, 2×OC*H*S), 168.9, 169.0, 169.6, 169.7, 174.0, 174.3, 174.4, 174.8, 174.9 (5C, 5×*C*=O); HRMS (TOF MS ES+): calcd for $C_{37}H_{66}N_4O_{16}S_2Na$ $[M + Na]^+$ *m/z* 909.3813, found 909.3804; OR: $[\alpha]_D^{24} = -27.7$ (*c* 1.07, H$_2$O).

Thioglycocluster 12



The thioglycopeptoid **12** was synthesised starting from **6** (29 mg, 55 µmol, 1.0 equiv) by application of the **General procedure H** using the sodium salt of 1-thio-β-D-glucose. Purification using **General procedure I** of the crude product yielded thioglycopeptoid **12** (58 mg, 45 µmol, 81 %) as white foam: IR (ATR) $\bar{\nu}$ (cm^{-1}): 3377 (O-H), 2922, 2490, 1733 (C=O ester), 1616 (C=O amide), 1429, 1373, 1273, 1067, 1027; ^{1}H NMR (400 MHz, D$_2$O) δ (ppm): 1.81-2.07 (m, 8H, 4×CH$_2$C*H*$_2$CH$_2$S), 2.11-2.21 (m, 3H, NAc), 2.52-2.91 (m, 16H, 4×CH$_2$CH$_2$C*H*$_2$S and 4×NCH$_2$C*H*$_2$C=O), 3.26-3.55 (m, 24H, 12×C*H*OH, 4×C*H*CH$_2$OH and 4×C*H*$_2$CH$_2$CH$_2$S), 3.55-3.96 (m, 19H, 4×NC*H*$_2$CH$_2$C=O, 4×CHC*H*$_2$OH and OC*H*$_3$), 4.48-4.63 (m, 4H, 4×OC*H*S); ^{13}C NMR (100 MHz, D$_2$O) δ (ppm): 20.7 (CH$_3$, NAc), 27.0, 27.4, 28.3, 28.4, 31.0, 31.7, 32.3, 32.9 (12CH$_2$, 4×CH$_2$*C*H$_2$*C*H$_2$S, and 4×NCH$_2$*C*H$_2$C=O), 42.3, 42.8, 43.0, 43.1, 43.9, 44.5, 44.8, 45.2, 45.3, 47.4, 48.3 (8CH$_2$, 4×N*C*H$_2$CH$_2$C=O and 4×*C*H$_2$CH$_2$CH$_2$S), 52.4 (CH$_3$, O*C*H$_3$), 60.6, 60.8, 60.9 (4CH$_2$, 4×CH*C*H$_2$OH), 69.1, 69.5, 69.7, 71.0, 71.1, 72.2, 73.7, 77.0, 77.2, 79.9, 80.2 (16CH, 4×*C*HCH$_2$OH and 12×*C*HOH), 85.5, 85.5, 85.6, 89.4 (4CH, 4×OC*H*S), 172.7, 172.9, 173.4, 174.0, 174.7 (5C, 5×*C*=O); HRMS (TOF MS ES+): calcd for $C_{51}H_{90}N_4O_{26}S_4Na_2$ $[M + 2Na]^{2+}$ *m/z* 674.2261, found 674.2270; OR $[\alpha]_D^{24} = -21.7$ (*c* 0.69, H$_2$O).

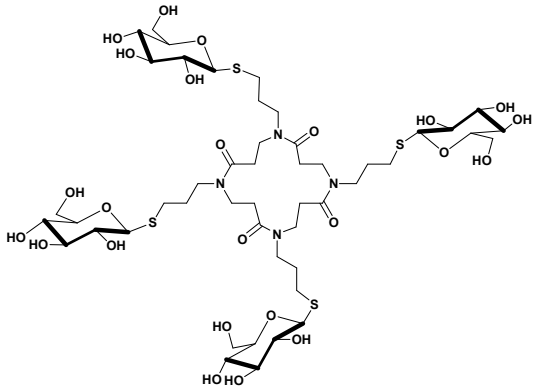
Thioglycocluster 13



The thioglycopeptoid **13** was synthesised starting from **8** (32 mg, 76 µmol, 1.0 equiv) by application of the **General procedure H** using the sodium salt of 1-thio-β-D-glucose. Purification using **General procedure I** of the crude product yielded thioglycopeptoid **13** (42 mg, 52 µmol, 68 %) as white foam: IR (ATR) $\bar{\nu}$ (cm^{-1}): 3367 (O-H), 2916, 1648 (C=O amide), 1639(C=O amide), 1463, 1445, 1427, 1368, 1331, 1289, 1216, 1072, 1028; ^{1}H NMR (400 MHz, D$_2$O) δ (ppm): 1.03-1.22 (m, 12H, 2×CH(C*H*$_3$)$_2$), 1.72-1.90 (m, 4H, 2×CH$_2$C*H*$_2$CH$_2$S), 2.52-2.79 (m, 4H, 2×CH$_2$CH$_2$C*H*$_2$S), 2.82-3.52 (m, 16H, 6×C*H*OH, 2×C*H*CH$_2$OH, 2×NCH$_2$C*H*$_2$C=O and 2×C*H*$_2$CH$_2$CH$_2$S), 3.55-4.31 (m, 14H, 2×NC*H*$_2$CH$_2$C=O, 2×C*H*(CH$_3$)$_2$, 2×NC*H*$_2$C=O and 2×CHC*H*$_2$OH), 4.42-4.49 (m, 2H, 2×OC*H*S); ^{13}C

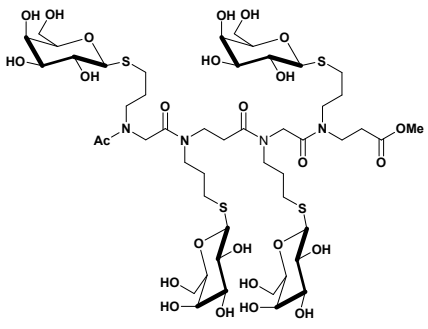
NMR (100 MHz, D_2O) δ (ppm): 19.2, 20.0 ($4CH_3$, *i*Pr), 27.0, 27.4, 30.8 ($6CH_2$, $2\times CH_2CH_2CH_2S$, and $2\times NCH_2CH_2C{=}O$), 35.6, 36.4, 37.3, 38.0, 39.6 ($2CH_2$, $2\times CH_2CH_2CH_2S$), 47.6, 48.0 ($2CH_2$, $2\times NCH_2CH_2C{=}O$), 48.2, 48.3 (2CH, *i*Pr), 50.5, 50.9, 51.3 ($2CH_2$, $2\times NCH_2C{=}O$), 60.9 ($2CH_2$, $2\times CHCH_2OH$), 69.5 (2CH, $2\times CHCH_2OH$), 72.2, 77.2, 79.8 (6CH, $6\times CHOH$), 85.5 (2CH, $2\times OCHS$), 169.4, 169.5, 169.7, 174.4, 174.6 (4C, $4\times C{=}O$); HRMS (TOF MS ES+): calcd for $C_{34}H_{60}N_4O_{14}S_2Na$ $[M + Na]^+$ *m/z* 835.3445, found 835.3439.

Thioglycocluster 14



The thioglycopeptoid **14** was synthesised starting from **9** (30 mg, 67 µmol, 1.0 equiv) by application of the **General procedure H** using the sodium salt of 1-thio-β-D-glucose. Purification using **General procedure I** of the crude product yielded thioglycopeptoid **14** (60 mg, 49 µmol, 73 %) as white foam: IR (ATR) $\bar{\nu}$ (cm^{-1}): 3362 (O-H), 2922, 2855, 1619 (C=O amide), 1461, 1432, 1367, 1272, 1218, 1097, 1065, 1024; ^{1}H NMR (400 MHz, D_2O+H_2O) δ (ppm): 1.70-1.92 (m, 8H, $4\times CH_2CH_2CH_2S$), 2.45-2.76 (m, 16H, $4\times CH_2CH_2CH_2S$ and $4\times NCH_2CH_2C{=}O$), 3.14-3.80 (m, 32H, $12\times CHOH$, $4\times CHCH_2OH$, $4\times CH_2CH_2CH_2S$, $4\times NCH_2CH_2C{=}O$), 3.78 (dd, 4H, J_{AB} = 12.4 Hz, *J* = 5.6 Hz, $4/2\times CHCH_2OH$), 3.78 (d, 4H, J_{AB} = 12.4 Hz, $4/2\times CHCH_2OH$), 4.42 (ld, 4H, *J* = 8 Hz, $4\times OCHS$); ^{13}C NMR (100 MHz, D_2O+H_2O) δ (ppm): 27.0, 27.4, 28.4 ($8CH_2$, $4\times CH_2CH_2CH_2S$), 31.6 ($4CH_2$, $4\times NCH_2CH_2C{=}O$), 44.2, 45.1, 45.4 ($8CH_2$, $4\times NCH_2CH_2C{=}O$ and $4\times CH_2CH_2CH_2S$), 60.8, 60.9 ($4CH_2$, $4\times CHCH_2OH$), 69.5, 72.2, 77.1, 79.8 (16CH, $4\times CHCH_2OH$ and $12\times CHOH$), 89.3 (4CH, $4\times OCHS$), 172.4, 172.6, 173.2, 173.4 (4C, $4\times C{=}O$); HRMS (TOF MS ES+): calcd for $C_{48}H_{84}N_4O_{24}S_4Na_2$ $[M + 2Na]^{2+}$ *m/z* 637.2077, found 637.2070.

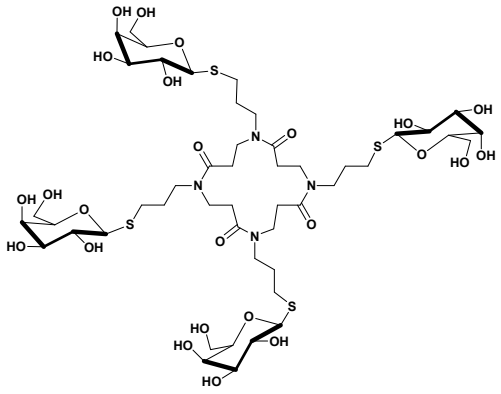
Thioglycocluster 15



The thioglycopeptoid **15** was synthesised starting from **3** (30 mg, 61 µmol, 1.0 equiv) by application of the **General procedure H** using the sodium salt of 1-thio-β-D-galactose.[S2] Purification using **General procedure I** of the crude product yielded thioglycopeptoid **15** (59 mg, 46 µmol, 76 %) as white foam: IR (ATR) $\bar{\nu}$ (cm^{-1}): 3385 (O-H), 2929, 1724 (C=O ester), 1639, 1623, 1615 (C=O amide), 1437, 1369, 1265, 1139, 1080, 1052, 1039; ^{1}H NMR (400 MHz, D_2O) δ (ppm): 1.71-1.98 (m, 8H, $4\times CH_2CH_2CH_2S$), 1.91, 2.10, 2.11 (m, 3H, NAc), 2.38-2.85 (m, 12H, $4\times CH_2CH_2CH_2S$ and $2\times NCH_2CH_2C{=}O$), 3.24-3.49 (m, 12H, $4\times CHCH_2OH$ and $4\times CH_2CH_2CH_2S$), 3.50-3.69 (m, 23H, $2\times NCH_2CH_2C{=}O$, $8\times CHOH$, $4\times CHCH_2OH$ and OCH_3), 3.87 (d, 4H, $4\times CHOH$), 4.11-4.41 (m, 8H, $2\times NCH_2C{=}O$, $4\times OCHS$); ^{13}C NMR (100 MHz, D_2O) δ (ppm): 20.3, 20.9 (CH_3, NAc), 26.5, 26.6, 27.0, 27.3, 27.4, 28.0, 28.1, 29.7, 30.5, 31.1, 31.8, 31.9, 32.2, 32.6, 33.0 ($10CH_2$, $2\times NCH_2CH_2C{=}O$ and $4\times CH_2CH_2CH_2S$), 42.5, 42.8, 43.2, 44.8, 46.3, 46.5, 46.7, 46.9, 47.9, 48.0, 48.4, 49.3, 50.1, 50.8 ($8CH_2$, $4\times CH_2CH_2CH_2S$, $2\times NCH_2CH_2C{=}O$

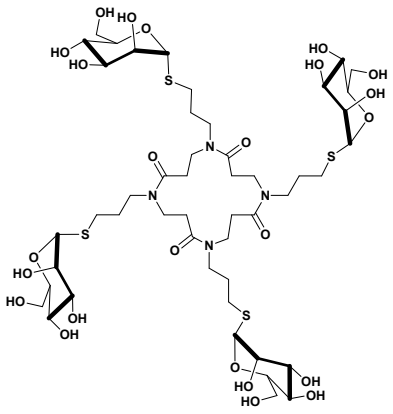
and 2×N*C*H$_2$C=O), 52.4 (CH$_3$, O*C*H$_3$), 61.1 (4CH$_2$, 4×CH*C*H$_2$OH), 68.8 (4CH, 4×*C*HCH$_2$OH), 69.6 (4CH, 4×*C*HOH), 73.9 (4CH, 4×*C*HOH), 78.9 (4CH, 4×*C*HOH), 85.9 (4CH, 4×OC*H*S), 169.6, 174.0, 174.3, 174.8 (5C, 5×*C*=O); HRMS (TOF MS ES+): calcd for $C_{49}H_{87}N_4O_{26}S_4K$ [M + H + K] $^{2+}$ *m/z* 657.2064, found 657.2048.

Thioglycocluster 16



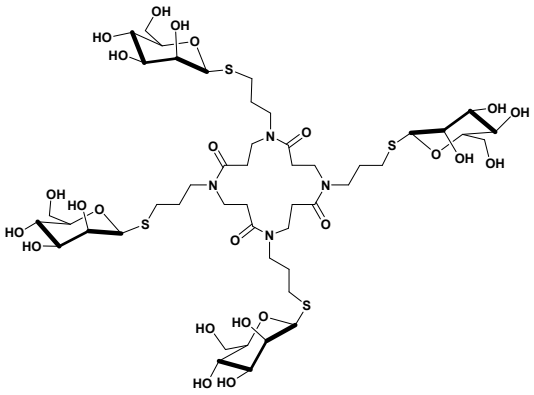
The thioglycopeptoid **16** was synthesised starting from **9** (31 mg, 70 µmol, 1.0 equiv) by application of the **General procedure H** using the sodium salt of 1-thio-β-D-galactose. Purification using **General procedure I** of the crude product yielded thioglycopeptoid **16** (57 mg, 46 µmol, 66 %) as white foam: IR (ATR) $\bar{\nu}$ (cm^{-1}): 3399 (O-H), 2916, 2856, 1613 (C=O amide), 1459, 1364, 1257, 1140, 1077, 1055, 1039; ^{1}H NMR (400 MHz, D$_2$O) δ (ppm): 1.74-1.95 (m, 8H, 4×CH$_2$C*H*$_2$CH$_2$S), 2.45-2.80 (m, 16H, 4×CH$_2$CH$_2$C*H*$_2$S and 4×NCH$_2$C*H*$_2$C=O), 3.30-3.71 (m, 36H, 8×C*H*OH, 4×C*H*CH$_2$OH, 4×C*H*$_2$CH$_2$CH$_2$S, 4×NC*H*$_2$CH$_2$C=O and 4×CHC*H*$_2$OH), 3.89 (d, 4H, *J* = 2.0 Hz, 4×C*H*OH), 4.39 (d, 4H, *J* = 9.6 Hz, 4×OC*H*S); ^{13}C NMR (100 MHz, D$_2$O) δ (ppm): 27.0, 27.2, 27.4, 27.6, 28.0, 28.2, 28.6 (8CH$_2$, 4×CH$_2$*C*H$_2$*C*H$_2$S), 30.1, 31.6, 31.8, 32.0, 32.3 (4CH$_2$, 4×NCH$_2$*C*H$_2$C=O), 41.7, 42.6, 43.8, 44.2, 45.0, 45.4, 46.1, 47.3, 47.9, 48.3, 49.9 (8CH$_2$, 4×N*C*H$_2$CH$_2$C=O and 4×*C*H$_2$CH$_2$CH$_2$S), 61.1 (4CH$_2$, 4×CH*C*H$_2$OH), 68.8, 69.6, 73.9, 78.9 (16CH, 4×*C*HCH$_2$OH and 12×*C*HOH), 86.0 (4CH, 4×OC*H*S), 172.3, 172.4, 172.6, 172.8, 173.2, 1473.4, 173.6, 173.8 (4C, 4×*C*=O); HRMS (TOF MS ES+): calcd for $C_{48}H_{84}N_4O_{24}S_4Na_2$ [M + 2Na] $^{2+}$ *m/z* 637.2077, found 637.2094.

Thioglycocluster 17



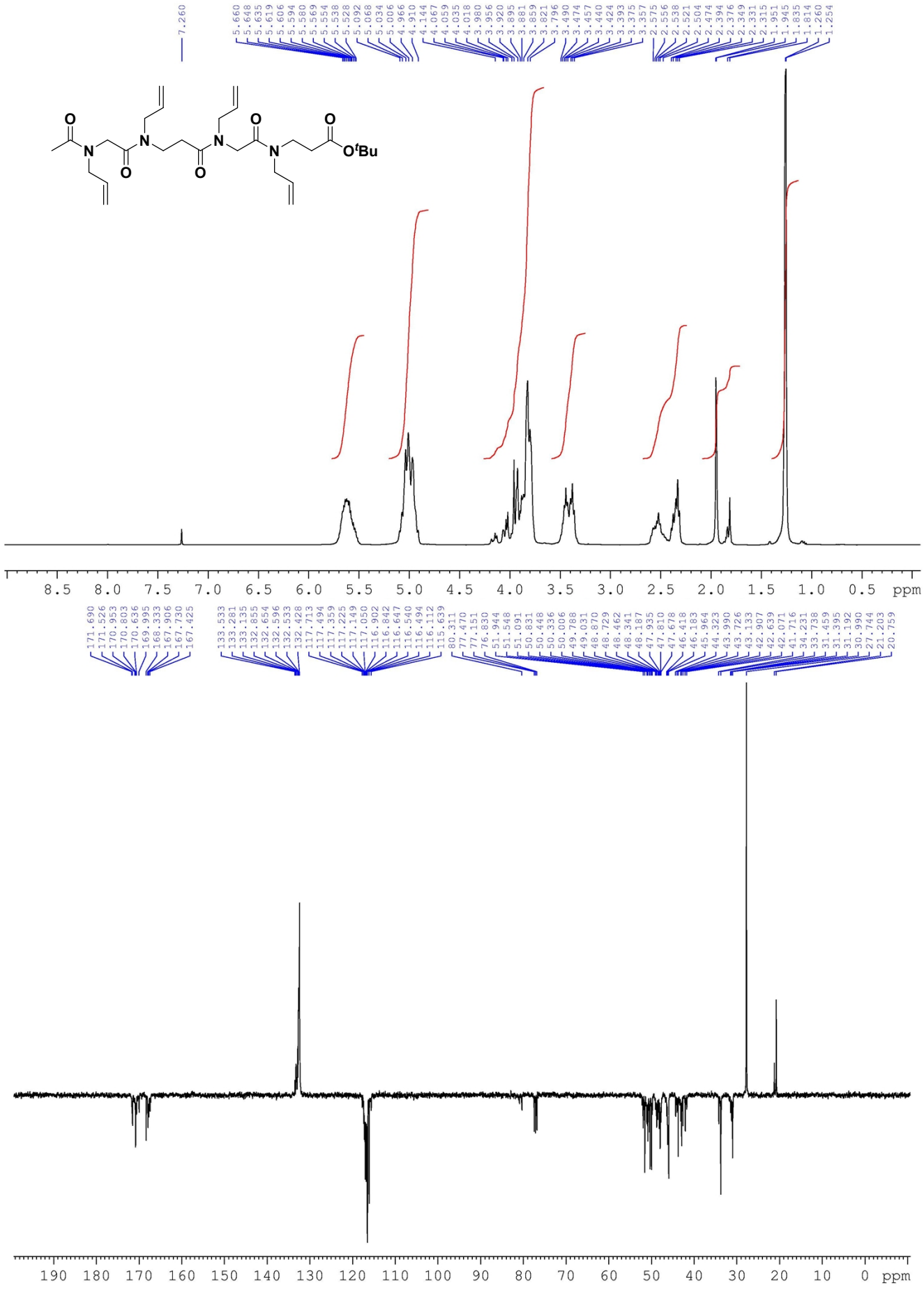
The thioglycopeptoid **17** was synthesised starting from **9** (27 mg, 61 µmol, 1.0 equiv) by application of the **General procedure H** using the sodium salt of 1-thio-α-D-mannose.[S3] Purification using **General procedure I** of the crude product yielded thioglycopeptoid **17** (51 mg, 41 µmol, 67 %) as white foam: IR (ATR) $\bar{\nu}$ (cm^{-1}): 3399 (O-H), 2929, 2863, 1614 (C=O amide), 1459, 1419, 1250, 1199, 1092, 1067, 1043; ^{1}H NMR (400 MHz, D$_2$O+H$_2$O) δ (ppm): 1.72-1.93 (m, 8H, 4×CH$_2$C*H*$_2$CH$_2$S), 2.49-2.78 (m, 16H, 4×CH$_2$CH$_2$C*H*$_2$S and 4×NCH$_2$C*H*$_2$C=O), 3.27-3.80 (m, 32H, 4×NC*H*$_2$CH$_2$C=O, 4×C*H*OH, 4×C*H*CH$_2$OH, 4×CHC*H*$_2$OH and 4×C*H*$_2$CH$_2$CH$_2$S), 3.89 (m, 4H, 4×C*H*OH), 4.00, 3.96 (ls, 4H, 4×C*H*OH), 5.22 (ls, 4H, 4×OC*H*S); ^{13}C NMR (100 MHz, D$_2$O+H$_2$O) δ (ppm): 26.7, 26.9, 27.6, 27.9, 28.1 (8CH$_2$, 4×CH$_2$*C*H$_2$*C*H$_2$S), 31.6, 32.1 (4CH$_2$, 4×NCH$_2$*C*H$_2$C=O), 41.7, 44.3, 45.0, 45.5, 50.1 (8CH$_2$, 4×*C*H$_2$CH$_2$CH$_2$S, 4×N*C*H$_2$CH$_2$C=O), 60.9 (4CH$_2$, 4×CH*C*H$_2$OH), 67.1 (4CH, 4×*C*HCH$_2$OH), 71.1 (4CH, 4×*C*HOH), 71.7 (4CH, 4×*C*HOH), 73.1, 73.3 (4CH, 4×*C*HOH), 84.9 (4CH, 4×OC*H*S), 172.6, 173.1, 173.5, 173.7 (4C, 4×*C*=O); HRMS (TOF MS ES+): calcd for $C_{48}H_{84}N_4O_{24}S_4Na_2$ [M + 2Na] $^{2+}$ *m/z* 637.2077, found 637.2068.

Thioglycocluster 18

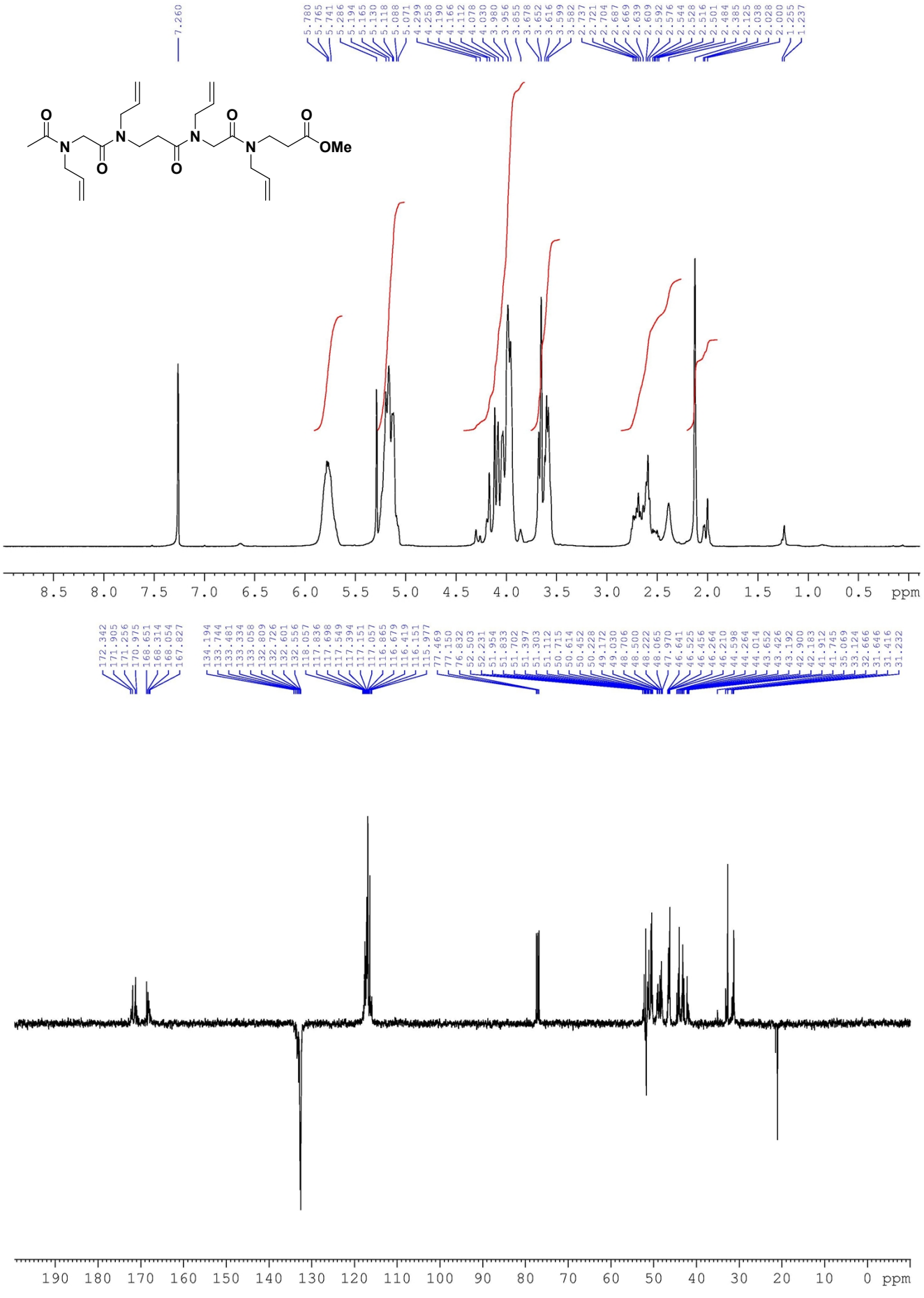


The thioglycopeptoid **18** was synthesised starting from **9** (31 mg, 70 µmol, 1.0 equiv) by application of the **General procedure H** using the sodium salt of 1-thio-β-D-mannose.[S4] Purification using **General procedure I** of the crude product yielded thioglycopeptoid **18** (57 mg, 46 µmol, 66 %) as white foam: IR (ATR) $\bar{\nu}$ (cm^{-1}): 3400 (O-H), 2938, 2869, 1627 and 1611 (C=O amide), 1451, 1425, 1371, 1244, 1063, 1054, 1045; ^{1}H NMR (400 MHz, D_2O+H_2O) δ (ppm): 1.73-1.92 (m, 8H, 4×CH_2CH_2*CH_2*CH_2S), 2.48-2.79 (m, 16H, 4×$CH_2CH_2CH_2$*CH_2*S and 4×NCH_2CH_2*CH_2*C=O), 3.23-3.82 (m, 36H, 4×NC*H*$_2CH_2C$=O, 8×C*H*OH, 4×C*H*CH_2OH, 4×CHC*H*$_2$OH and 4×C*H*$_2CH_2CH_2$S), 3.96, 3.94 (ls, 4H, 4×C*H*OH), 4.76 (ls, 4H, 4×OC*H*S); ^{13}C NMR (100 MHz, D_2O) δ (ppm): 27.4, 27.9, 28.1, 28.3 (8CH_2, 4×CH_2*C*H_2*C*H_2S), 30.7, 31.5 (4CH_2, 4×NCH_2*C*H_2C=O), 44.3, 44.9, 45.4, 50.0 (8CH_2, 4×*C*$H_2CH_2CH_2$S, 4×N*C*H_2CH_2C=O), 61.1 (4CH_2, 4×CH*C*H_2OH), 66.6 (4CH, 4×*C*HOH), 72.2 (4CH, 4×*C*HOH), 73.8 (4CH, 4×*C*HOH), 80.3 (4CH, 4×*C*HOH), 84.6 (4CH, 4×OC*H*S), 172.4, 172.6, 172.8, 173.2, 173.4, 173.6, 173.8 (4C, 4×*C*=O); HRMS (TOF MS ES+): calcd for $C_{48}H_{84}N_4O_{24}S_4Na_2$ [M + 2Na]$^{2+}$ *m/z* 637.2077, found 637.2081.

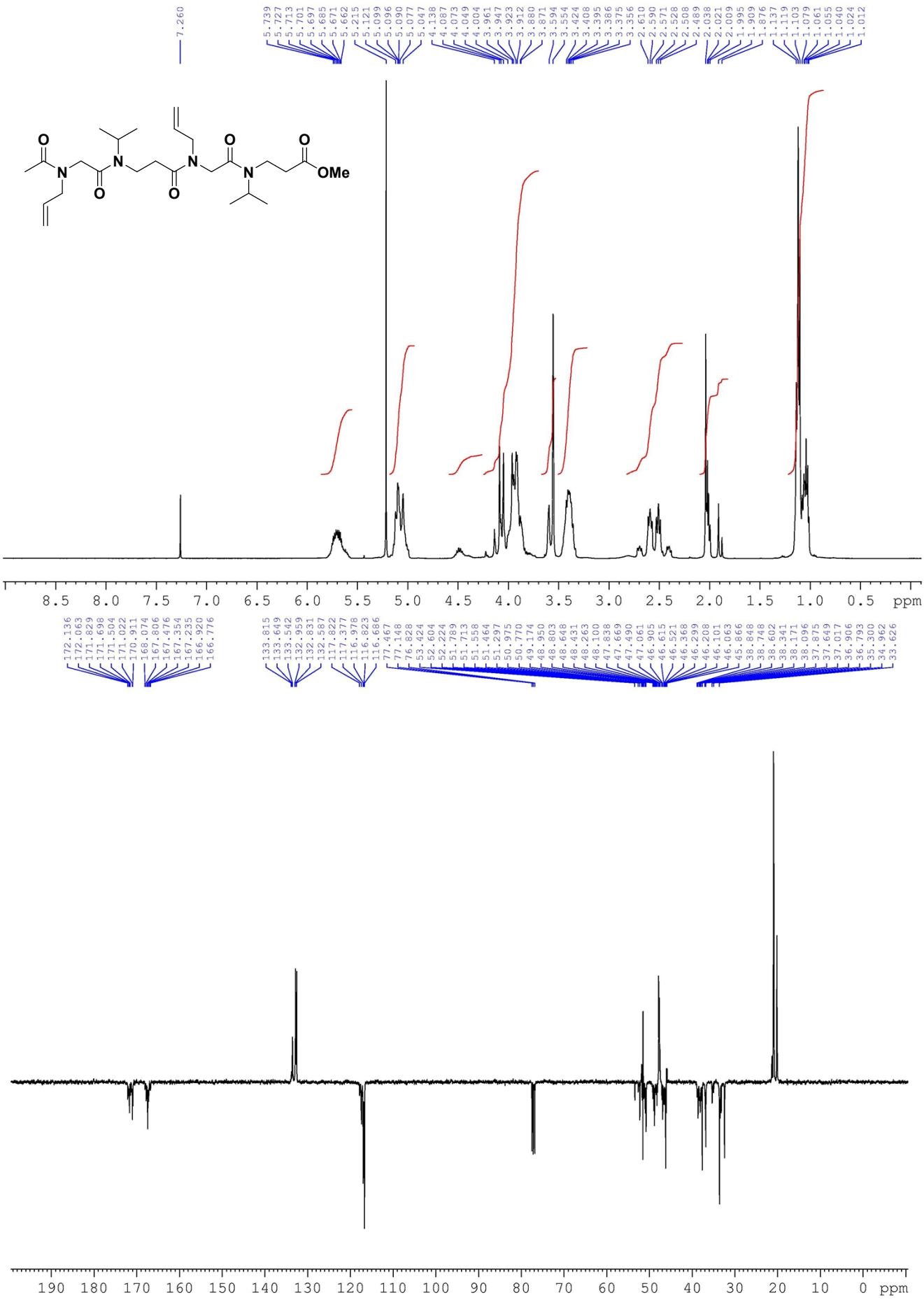
NMR spectra of 2 ($CDCl_3$)



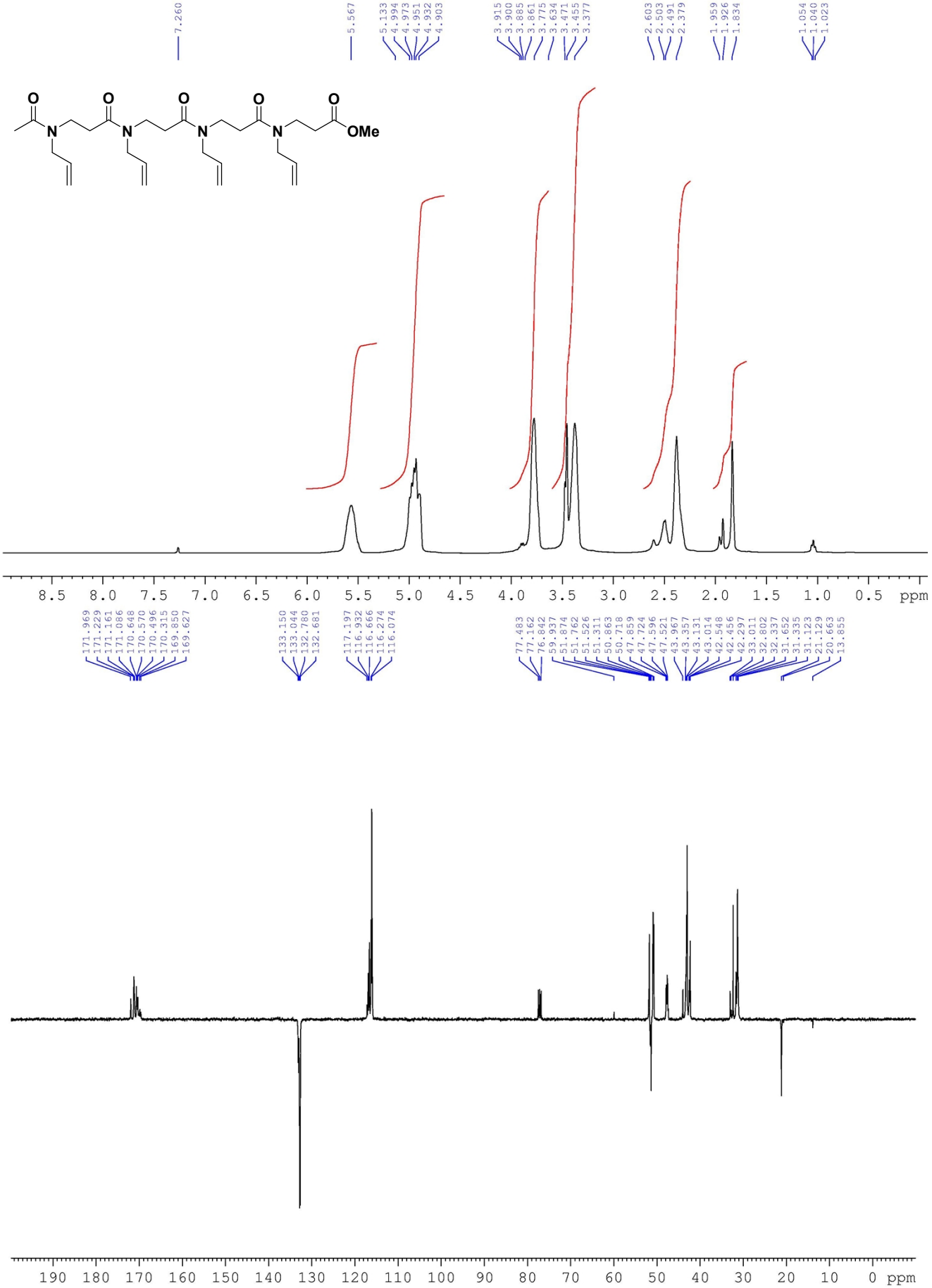
NMR spectra of 3 ($CDCl_3$)



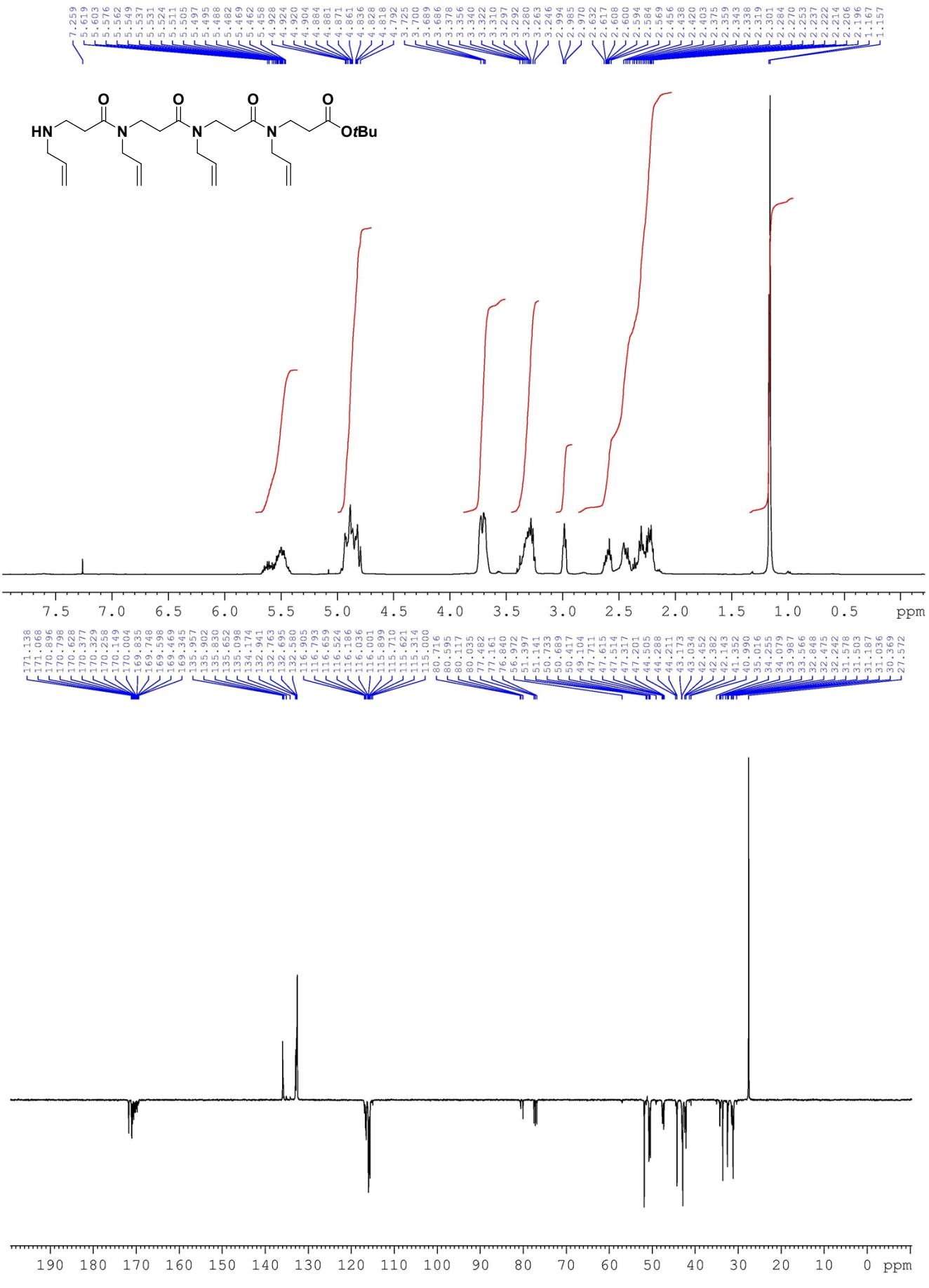
NMR spectra of 5 ($CDCl_3$)



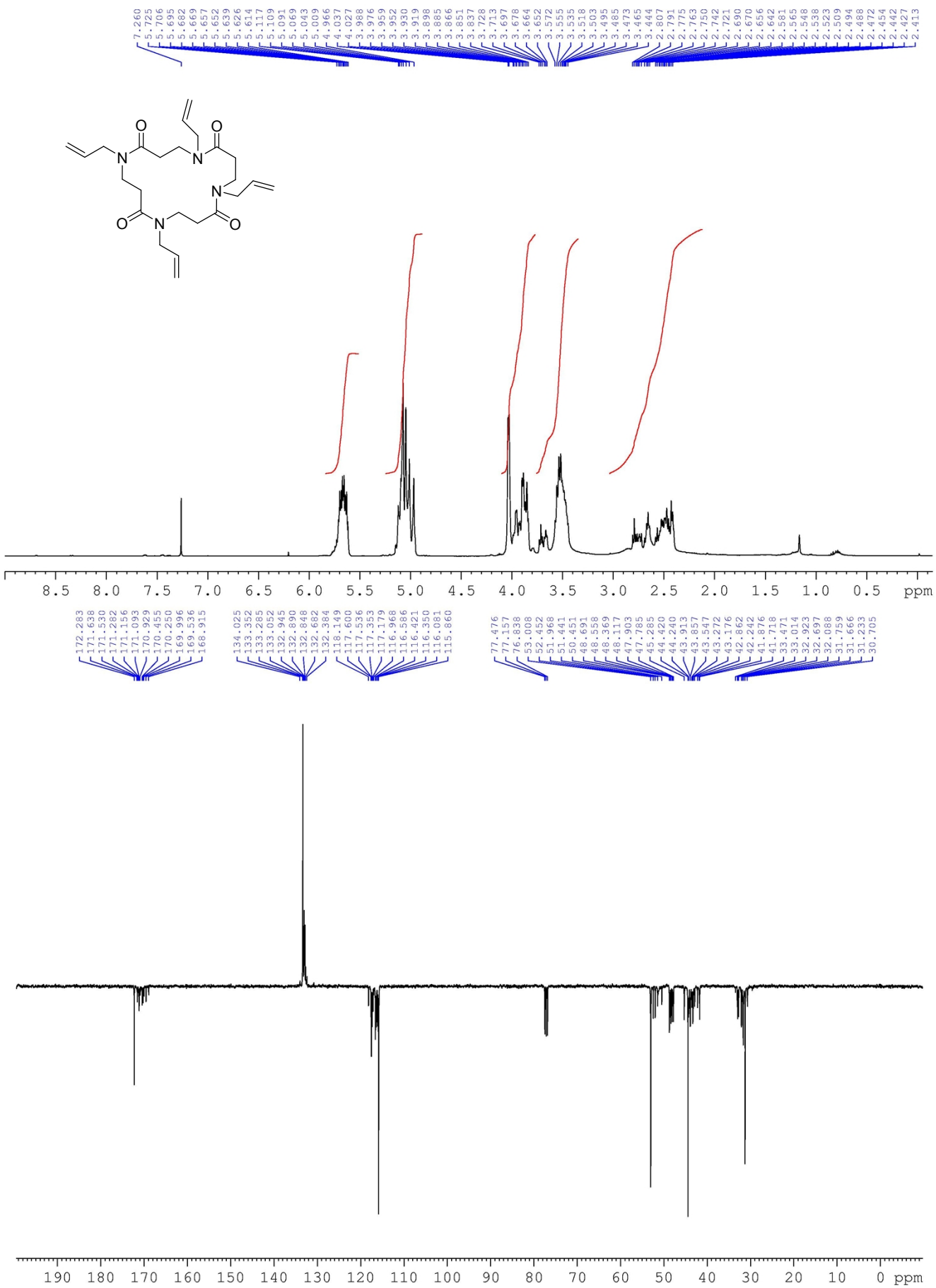
NMR spectra of 6 ($CDCl_3$)



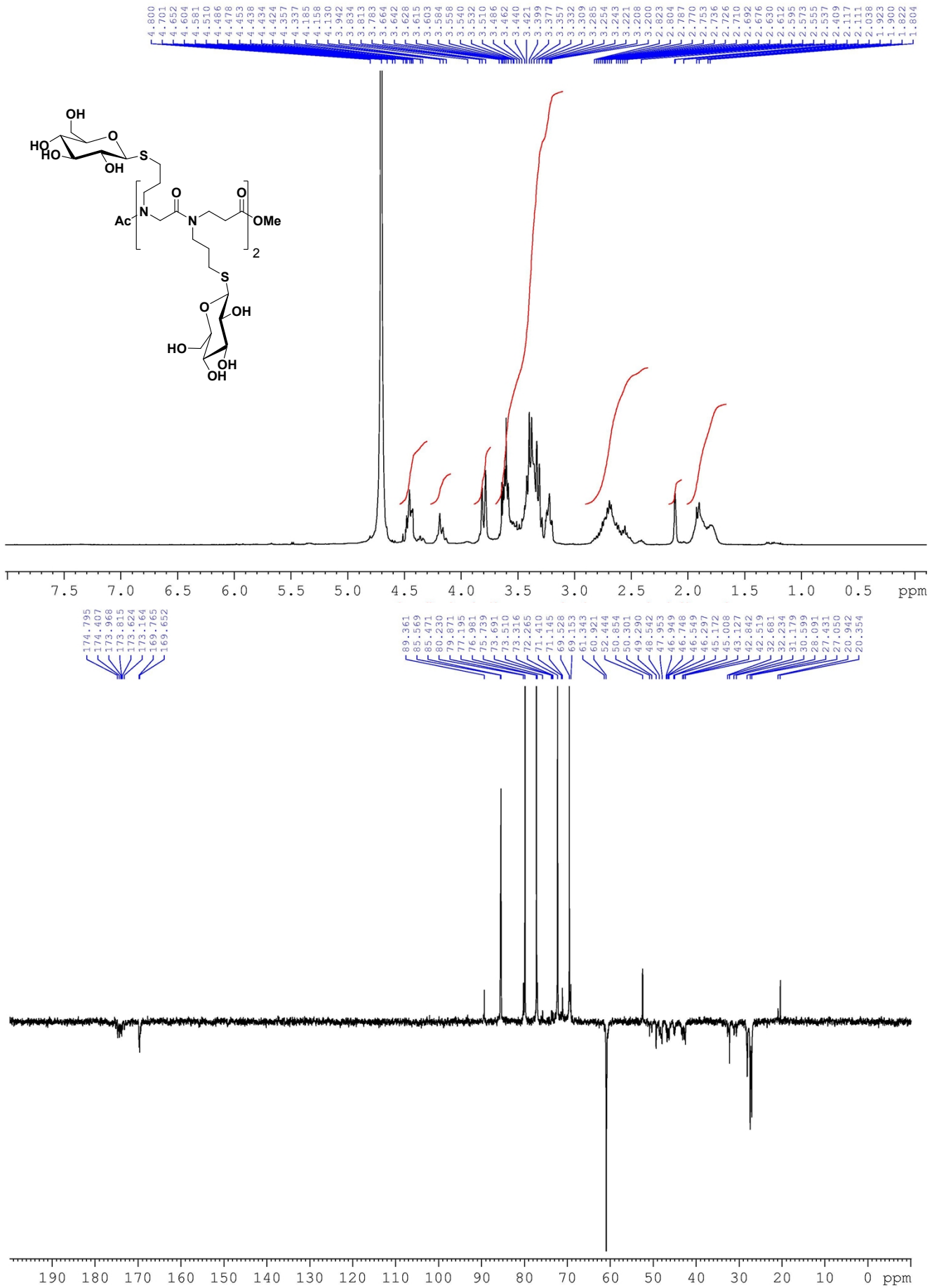
NMR spectra of 7 ($CDCl_3$)



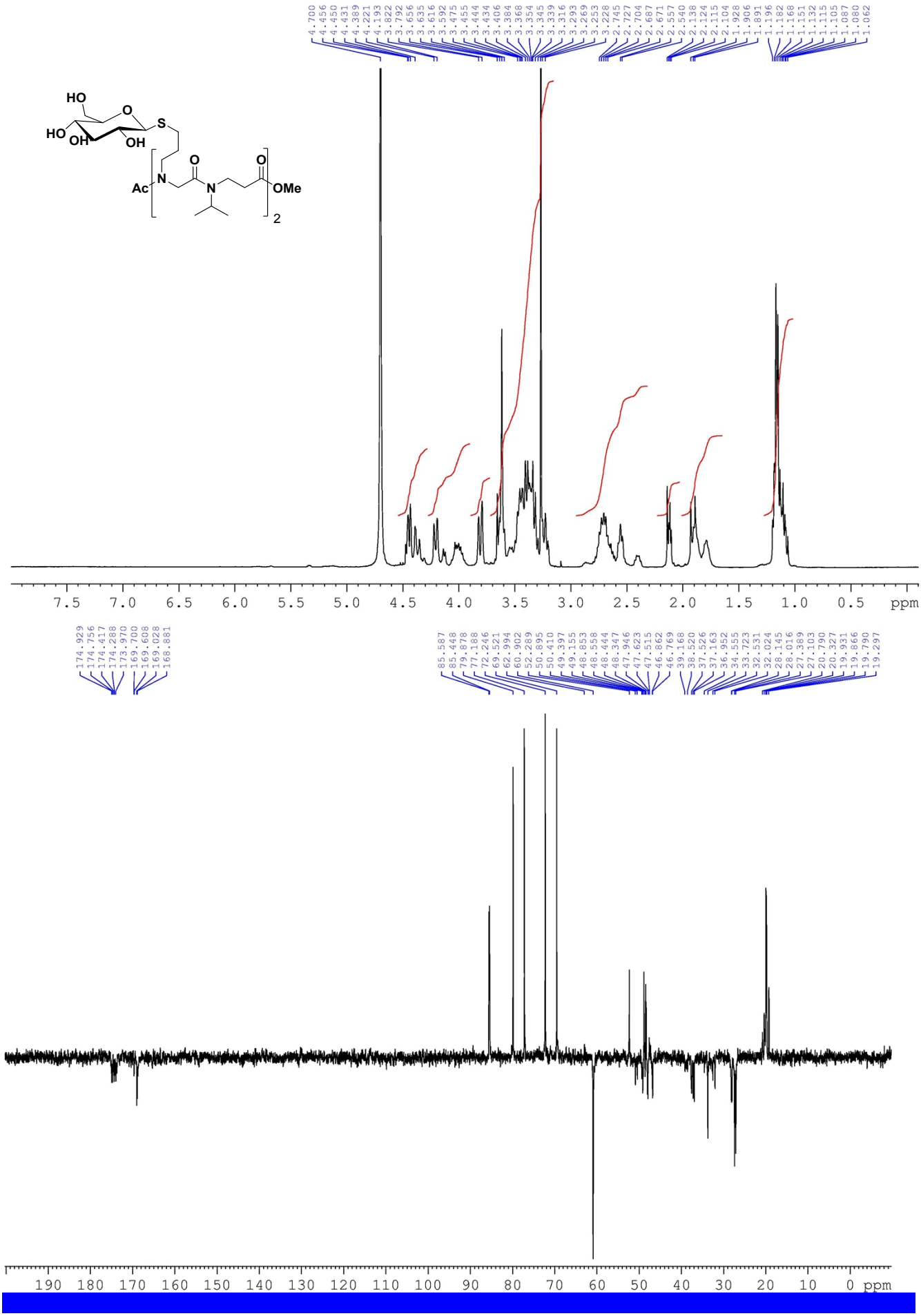
NMR spectra of 9 ($CDCl_3$)



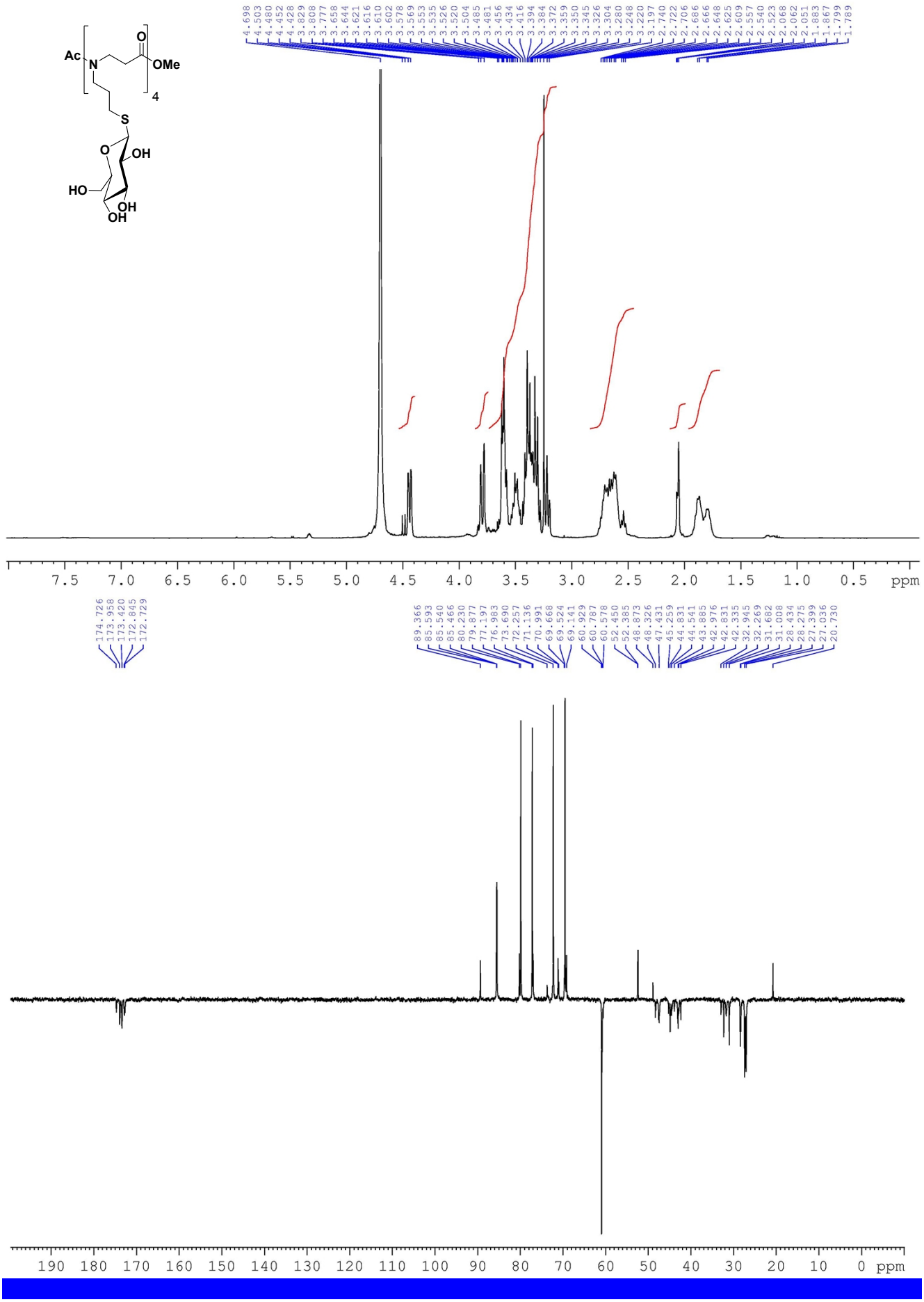
NMR spectra of 10 (D_2O)



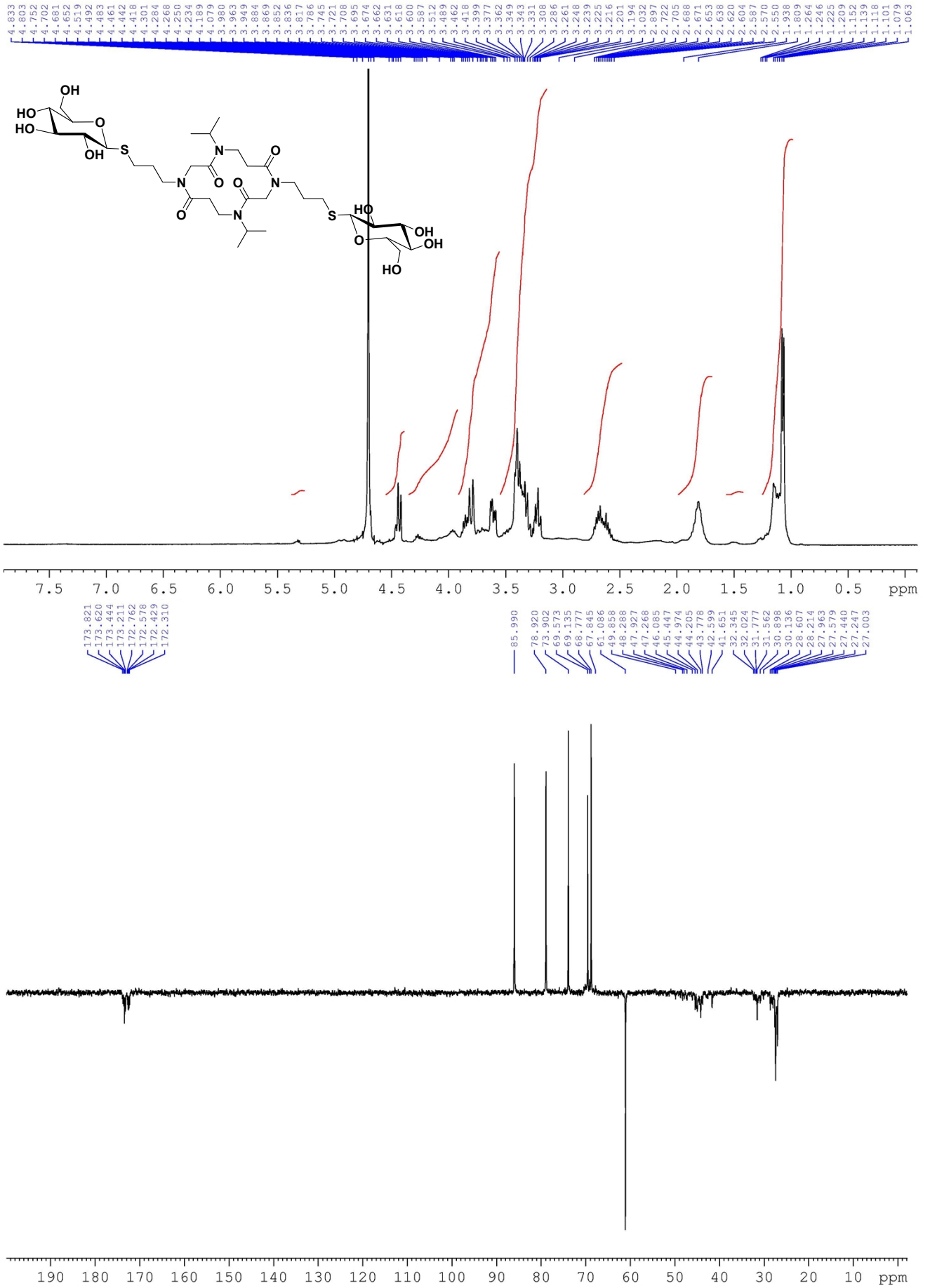
NMR spectra of 11 (D_2O)



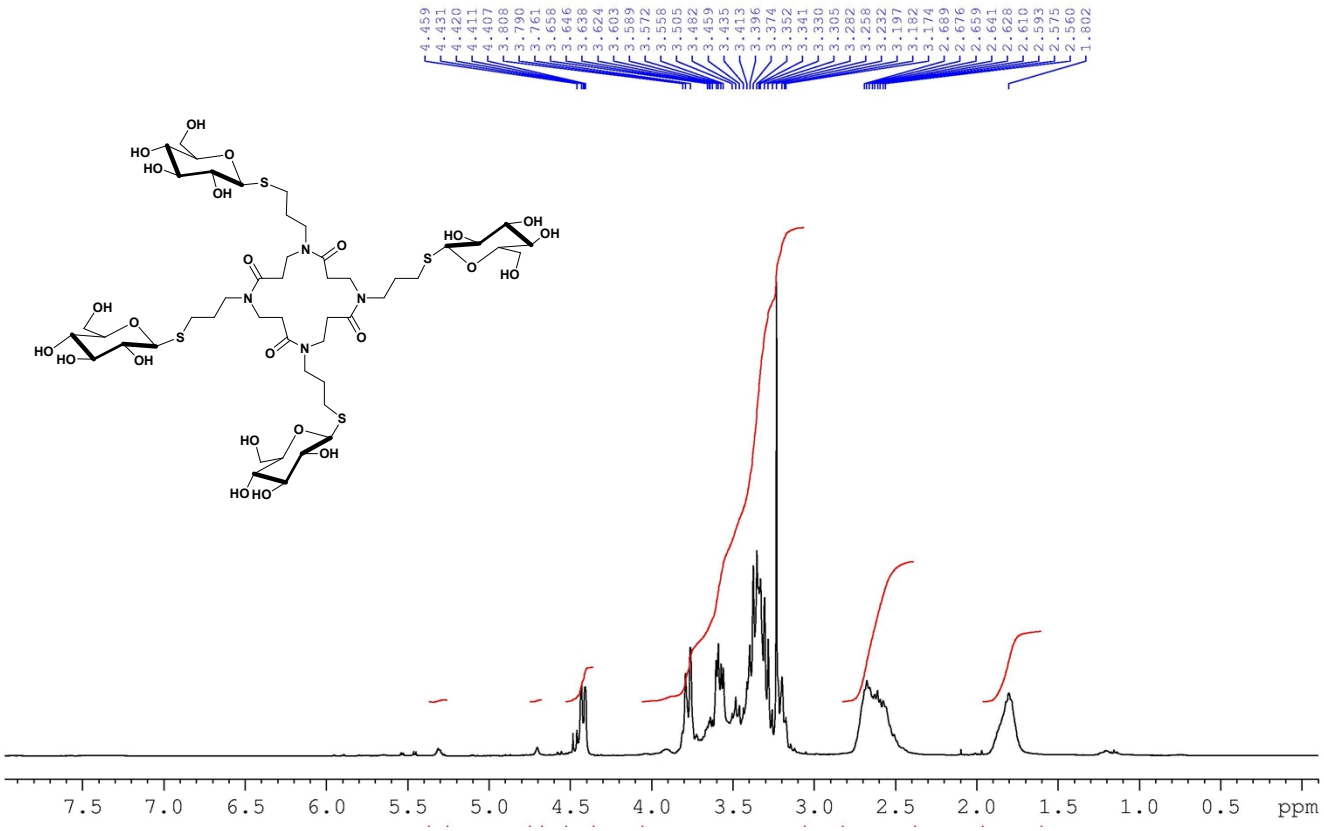
NMR spectra of 12 (D_2O)

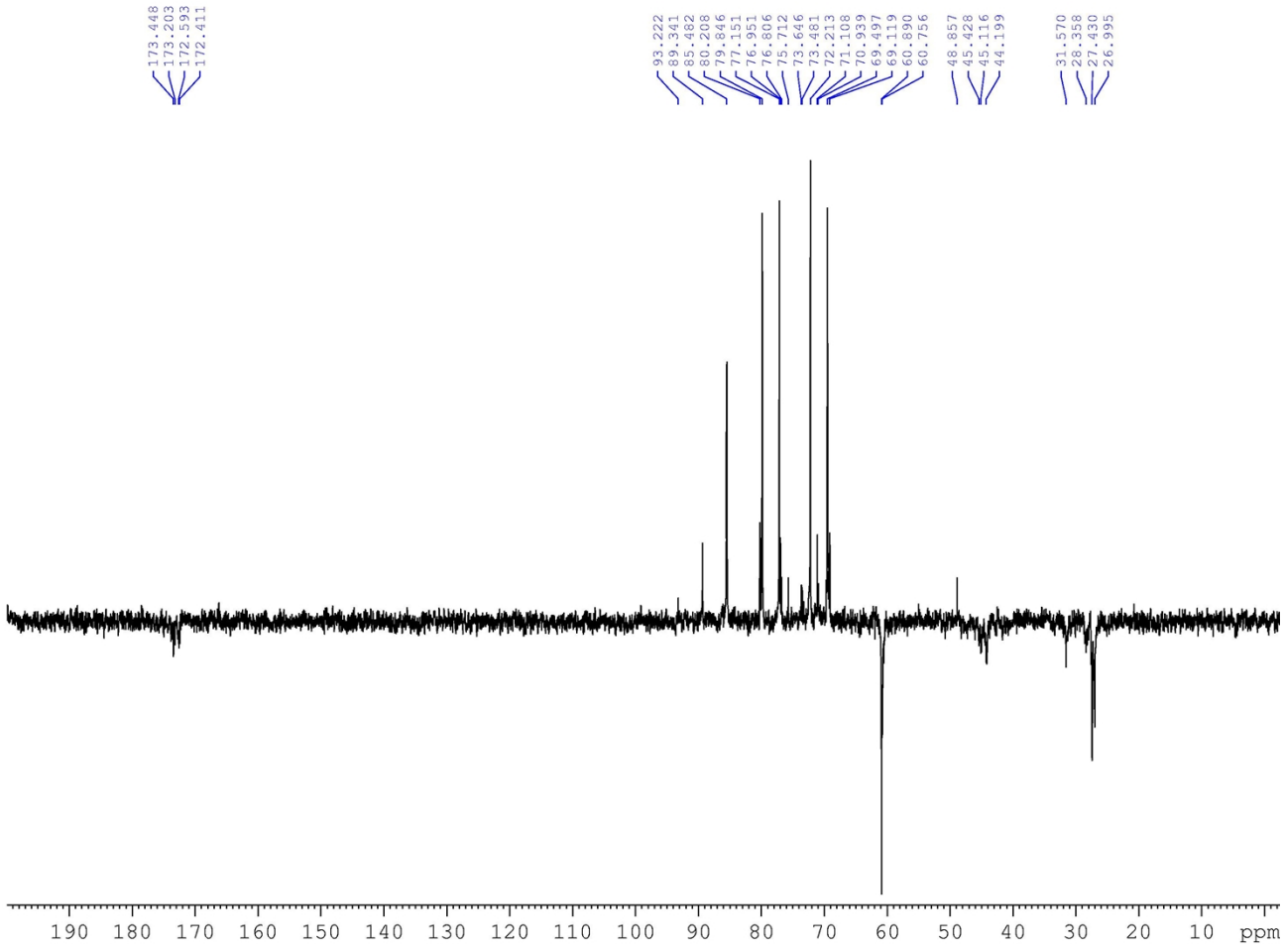


NMR spectra of 13 (D_2O)

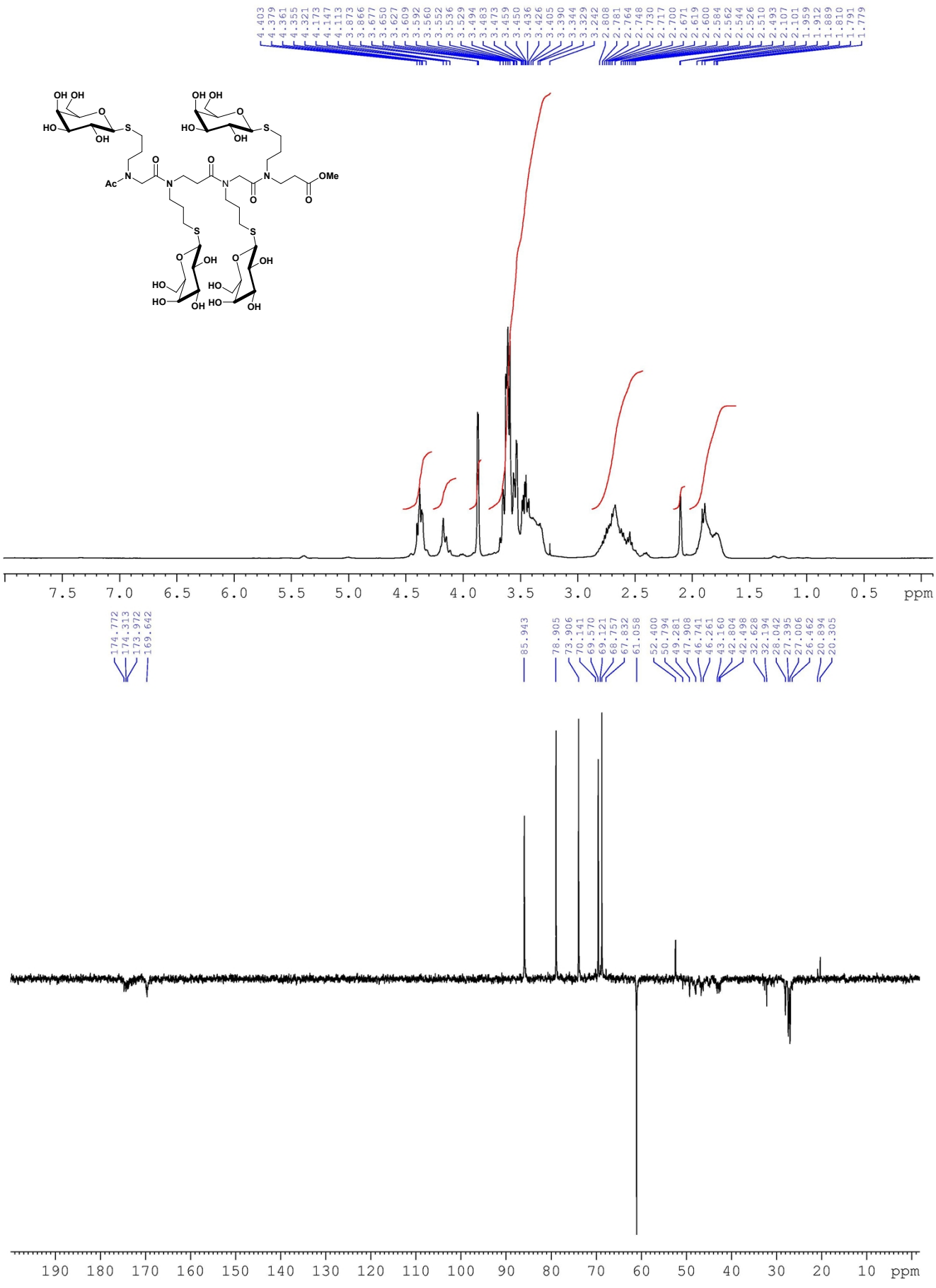


NMR spectra of 14 (D_2O)

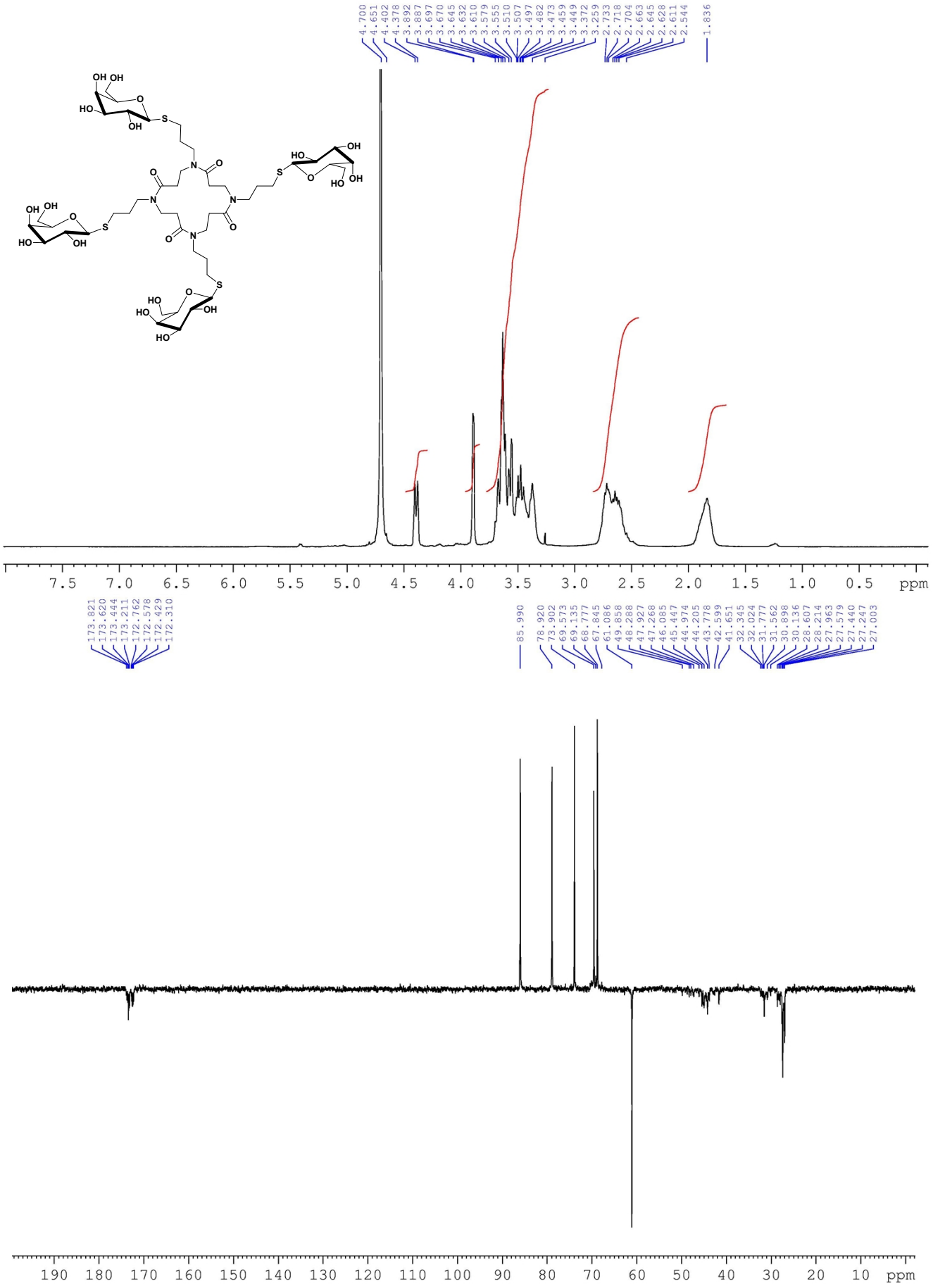




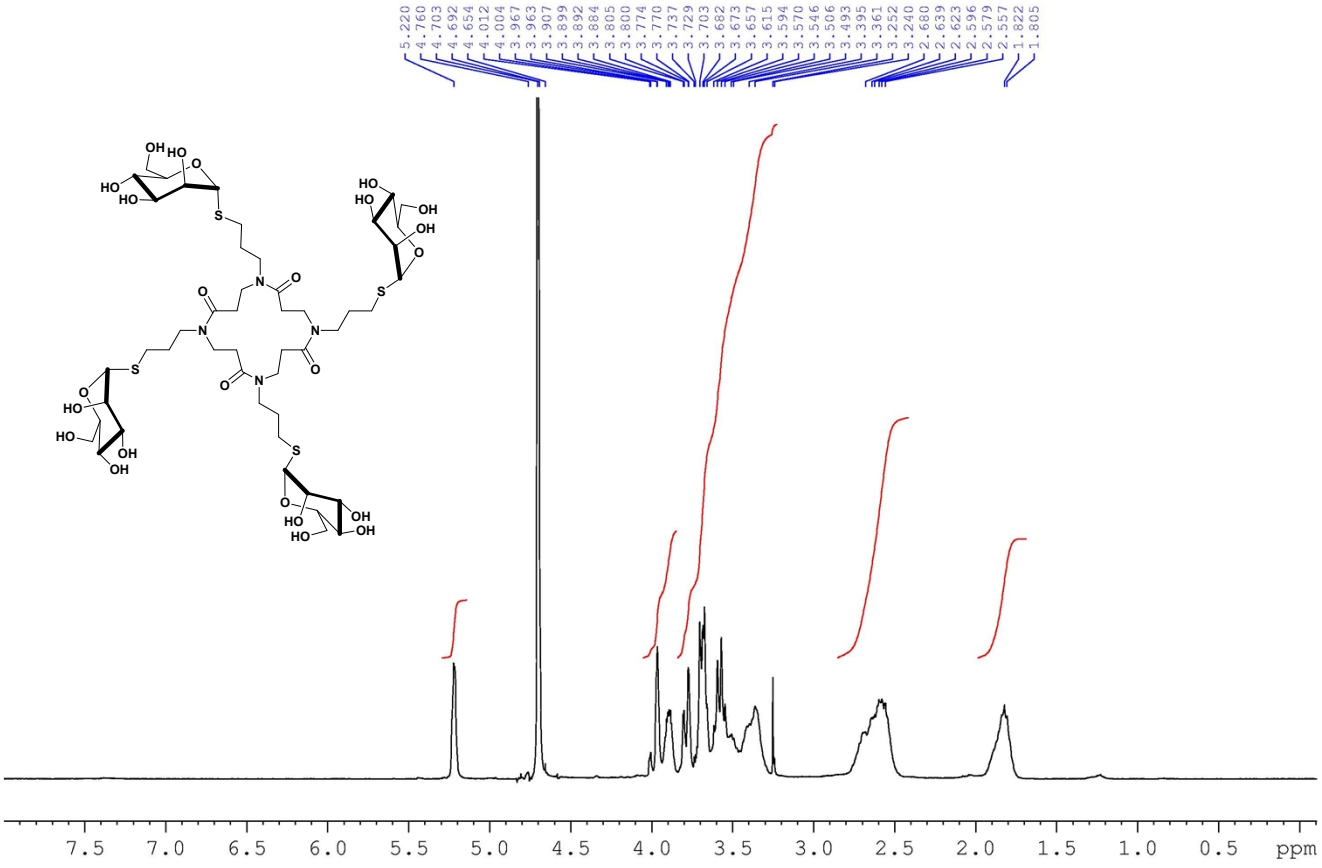
NMR spectra of 15 (D_2O)

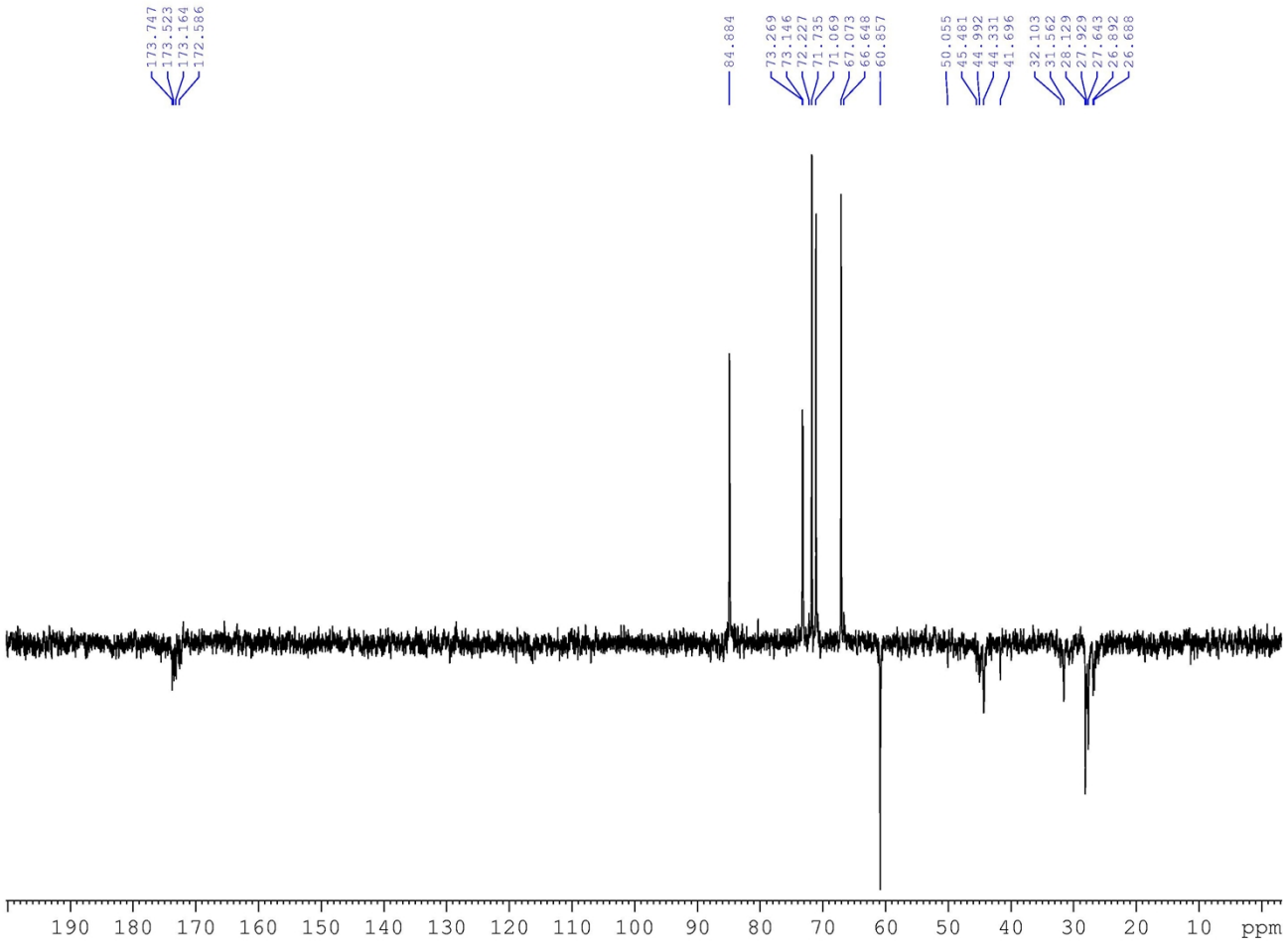


NMR spectra of 16 (D_2O)

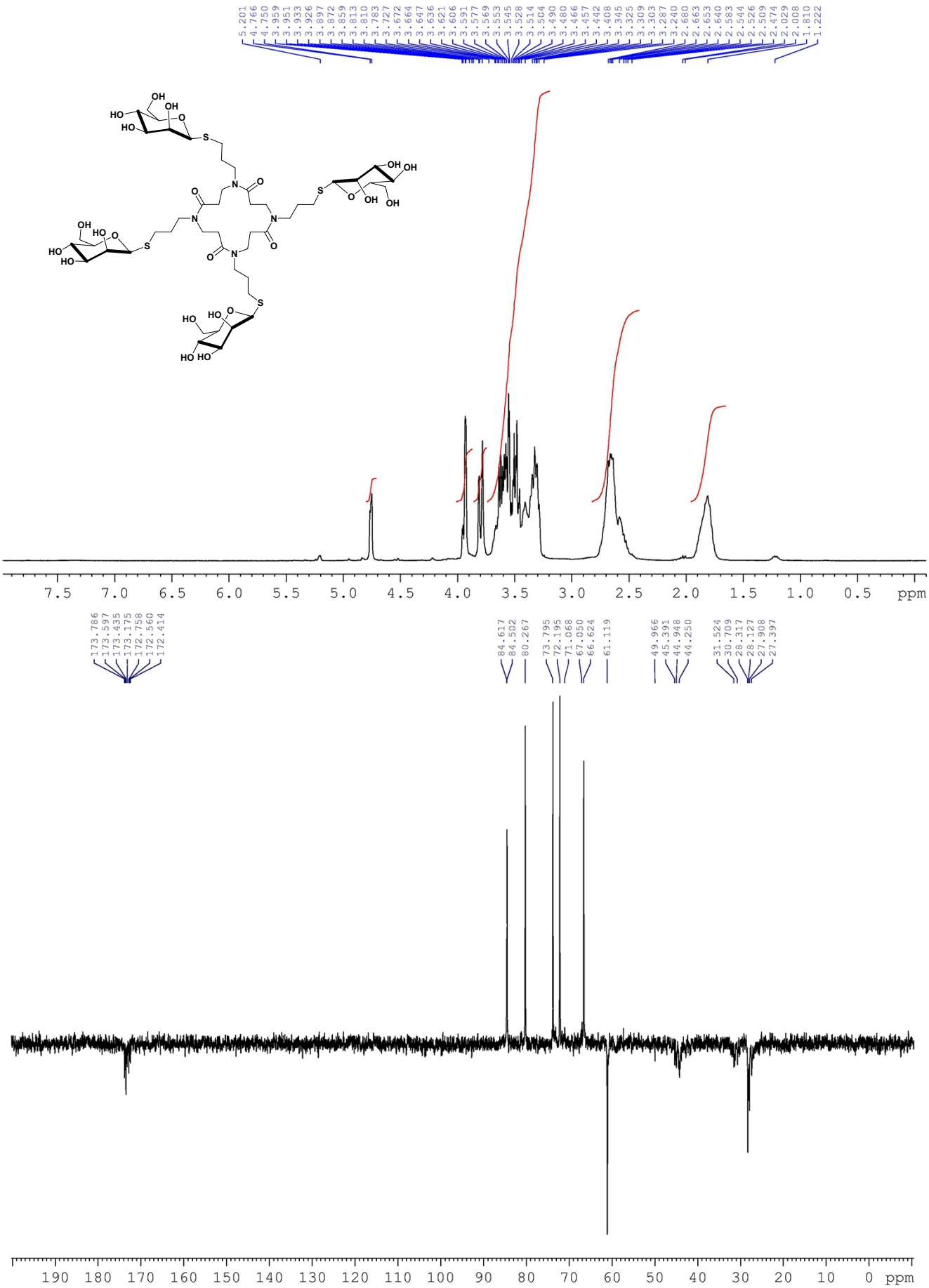


NMR spectra of 17 (D_2O)





NMR spectra of 18 (D_2O)



Isothermal Titration Microcalorimetry (ITC)

General experimental information

LecA and BC2L-A were produced in *Escherichia coli* and purified on affinity columns as previously described.[S5] Lyophilized LecA and BC2L-A were dissolved in buffer (20 mM Tris-HCl, 0.1 M NaCl pH 7.5 with 100 µM $CaCl_2$). For monovalent compounds, titration was performed using ITC200 microcalorimeter (Malvern Instruments, UK). Lectins (50 to 150 µM) were placed in the 200 µl sample cell operating at 25°C. Titrations were performed with 20 injections of 2 µl sugar derivatives (1.5 to 5 mM) every 120 s. For tetravalent compounds **15-18**, titration was performed using VP-ITC microcalorimeter (Malvern Instruments, UK) the lectins (80 to100 µM) were placed into the 1.4478-mL sample cell, at 25°C, using 10-µL injections of glycocluster (250 to 400 µM every 300 s).
The experimental data were fitted to a theoretical titration curve using the supplied Origin software, with ΔH (enthalpy change), Ka (association constant) and n (number of binding sites per monomer) as adjustable parameters. Free energy change (ΔG) and entropy contributions (TΔS) were derived from the equation $\Delta G = \Delta H - T\Delta S = - RT \ln Ka$ (with T as the absolute temperature and R = 8.314 J mol^{-1} K^{-1}). Two or three independent titrations were performed for each tested ligand.

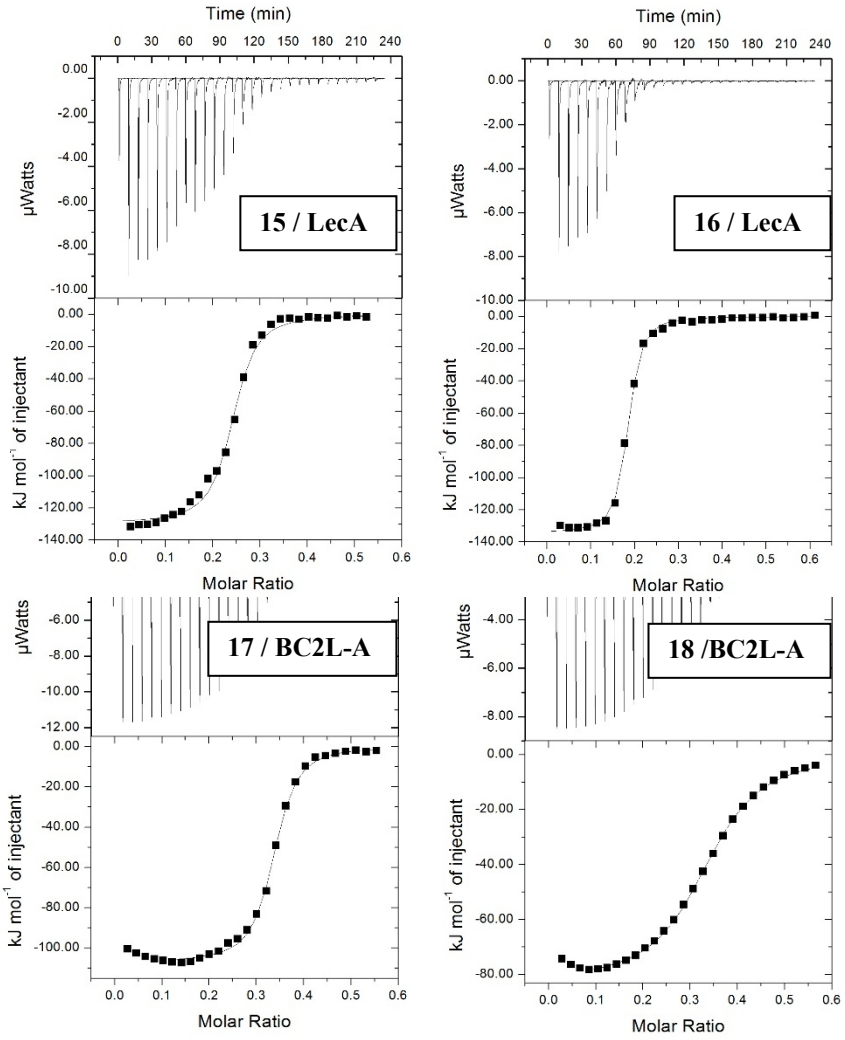


Fig. S1. Raw ITC data (top) obtained by injections of glycosylated peptoids in a solution of lectin and the respective integrated titration curve (bottom).

Model building

The crystal structure of β-peptoid[S6] was used as starting structure. The attached linkers decorated with mannose and galactose were built in their extended conformation using the molecular editor from the Sybyl-X suite (Certara, www.certara.com), and structures were optimized for removing any steric conflict with the Tripos force field.[S7]

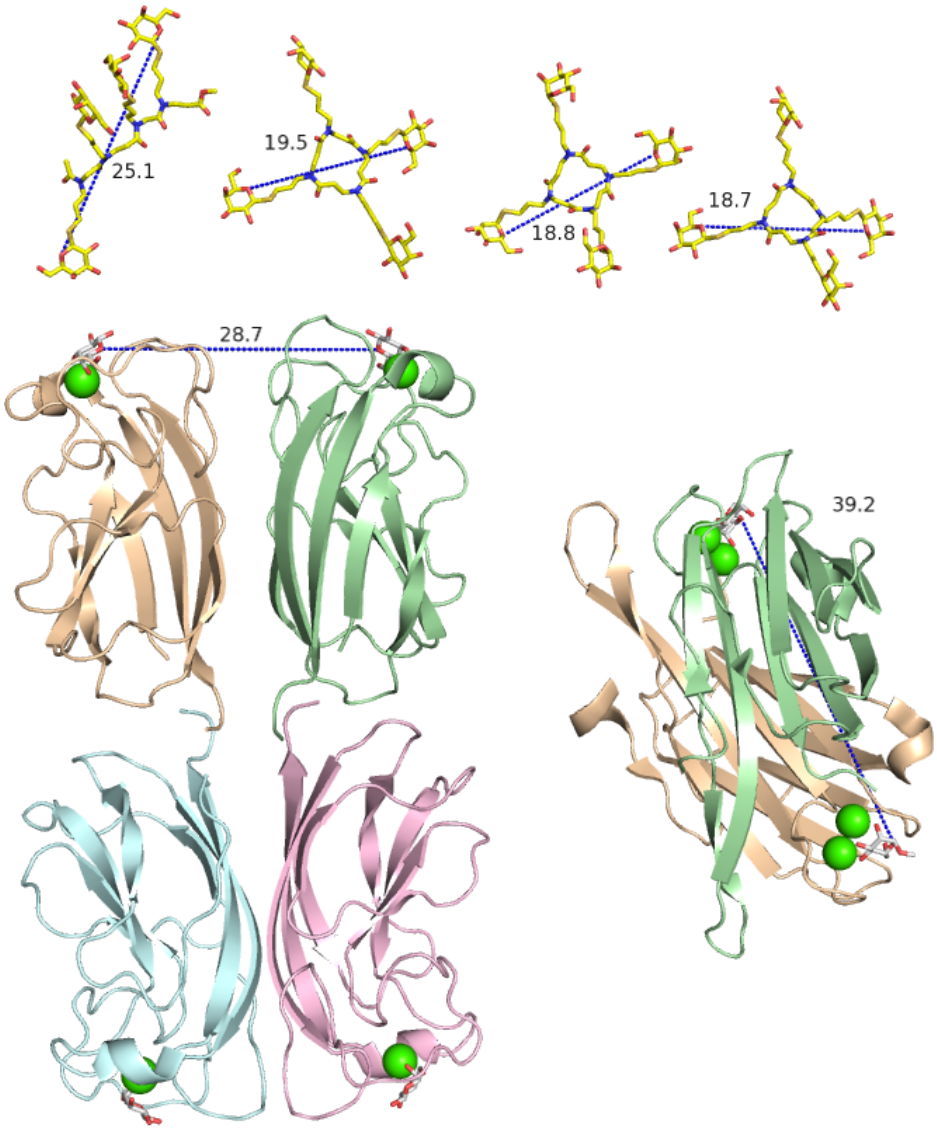


Fig. S2 Top: models of compounds **15** to **18** built in extended conformation. Bottom: Crystal structure of LecA/galactose complex (PDB code 1OKO)[S8] and BC2LA/mannoside complex (PDB code 2VNV)[S9]. Dashed lines represent the distances between sugar ring oxygen atoms.

References

[S1] C. Caumes, C. Fernandes, O. Roy, T. Hjelmgaard, E. Wenger, C. Didierjean, C. Taillefumier, S. Faure, *Org. Lett.*, 2013, **15**, 3626.

[S2] Sodium salt of 1-thio-β-D-galactose was prepared according literature procedure: A. Kozikowski, J. Lee, *J. Org. Chem*. **1990**, *55*, 863; Z. Pei, H. Dong, R. Caraballo, O. Ramström *Eur. J. Org. Chem.* **2007**, 4927.

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