Supporting Information for:

A Bio-inspired Approach to Ligand Design: Folding Single-Chain Peptoids to Chelate a Multimetallic Cluster

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General considerations.
N,*N*'-diisopropylcarbodiimide, Fmoc-L-alanine-OH, Fmoc-methionine-OH, L-alanine *tert*-butyl ester hydrochloride, glycine *tert*-butyl ester hydrochloride, *β*-alanine *tert*-butyl ester hydrochloride, 2-chlorotrityl chloride resin, HCTU were purchased from Chem-Impex. *N*-Boc ethylenediamine was purchased from CNH Technologies, Inc. Bromoacetic acid, (*R*)-(+)-α-methylbenzylamine, ethanolamine, tert-butyl dimethylsilyl chloride, 2,4,6-trimethylpyridine, trifluoroacetic acid, formic acid, tosyl chloride, triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, sodium acetate trihydrate, hydrogen peroxide, triisopropylsilane, cyanogen bromide were purchased from Sigma-Aldrich. 4-methylpiperidine, chloroacetyl chloride was purchased from TCI. Methylamine (40% in water), cobalt(II) nitrate hexahydrate was purchased from Alfa Aesar. Cluster **1** was synthesized by previously reported methods.[1] Deuterated methanol (CD_3OD) was purchased from Sigma-Aldrich, and deuterated chloroform ($CDCl_3$) was purchased from Cambridge Isotopes.

HPLC. Preparative HPLC was performed on a Waters Prep 150 HPLC, equipped with C18 (Xbridge™ BEH300 5 μm, 19 x 100 mm) or C4 (Symmetry300™ 5 μm, 19 x 100 mm) columns

Column chromatography. Silica chromatography was performed on a Biotage SP1 flash chromatography system, equipped with a dual wavelength detector.

Electrospray ionization mass spectrometry. Data were acquired on Bruker MICROTOF-Q spectrometer, either by direct sample injection or *via* a C18 liquid chromatography column at 25ºC.

MALDI-TOF. Data was acquired on an AB SCIEX TF4800 MALDI TOF-TOF mass spectrometer.

NMR spectroscopy. Data was collected on a Bruker Avance II 500 MHz at 25º C, unless otherwise noted. Parameters for 2D NMR are listed:
TOCSY. "MLEVPHSW" parameter file, "mlevph" pulse program
HSQC. "HSQCEDETGP" parameter file, "hsqcedetgp" pulse program
HMBC. "HMBCGPND" parameter file, "hmbcgpndqf" pulse program, CNST13 = 7 Hz
ROESY. "ROESYPHSW" parameter file, "roesyph" pulse program, p15 mixing time = 300 ms.

Organic Syntheses.

***O*-protection of ethanolamine: 2-((*tert*-butyldimethylsilyl)oxy)ethan-1-amine.** Ethanolamine (3.75 g, 61.4 mmol) was dissolved in 100 mL of MeCN. To this solution was added *tert*-butyldimethylsilyl chloride (9.25 g, 61.4 mmol) as a solution in 50 mL MeCN. Finally, DBU (9.34 g, 61.4 mmol) was added, and the reaction mixture was stirred for 16 h. Volatiles were removed by rotary evaporator, and the residue was partitioned between 100 mL of water and 100 mL of diethyl ether. The organic layer was extracted 2 x 100 mL water, and then dried with $MgSO_4$. The slurry was filtered, and the filtrate was dried under vacuum to yield a colorless oil (8.6 g, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.60 (2H, t, CH_2), 2.74 (2H, t, CH_2), 0.88 (9H, s, CH_3), 0.04 (6H, s, CH_3).

Solid phase synthesis. Peptoids were synthesized by the submonomer method[2] using bromoacetic acid and *N*,*N*'-diisopropylcarbodiimide (DIC). Polystyrene-supported MBHA Fmoc-protected Rink amide (0.64 mmol/g loading, Protein Technologies) or 2-chlorotrityl chloride (1.5 mmol/g loading, Chem-Impex) resins were used as the solid support. Manual syntheses were performed in a fritted glass vessel equipped with a T-junction leading to either vacuum or positive N_2 flow. During the swelling, reaction, or wash steps, the T-junction is turned to allow N_2 to bubble through the frit to agitate the resin slurry. The vessel is drained into a receiving flask by turning the T-junction to vacuum. Automated peptoid syntheses were performed by the Symphony X (Protein Technologies).

Manual synthesis procedures

Swelling step: 0.2 g of MBHA Rink amide resin (for C-terminal NH_2) was swollen for 10 minutes with 1 mL *N*-methylpyrrolidone (NMP), and then drained. For 2-chlorotrityl chloride resin (for C-terminal OH), DCM was used for the swelling step, instead.

First step after swelling:

a) ***Rink Resin***: 1 mL of 20% 4-methylpiperidine in NMP was added to the swollen resin and allowed to react for 20 min, followed by draining.
b) ***2-chlorotrityl chloride loading***: 1.1 equivs of Fmoc-L-alanine-OH was dissolved in a 20% 2,4,6-trimethylpyridine solution in DCM to obtain a 0.1 M concentration. This mixture was added to swollen 2-chlorotrityl chloride resin and allowed to react for 1 hr. The mixture is then drained.

***Wash steps*:** 2 mL of NMP was added to the resin, agitated for 15 s with N_2, and the drained. The wash is repeated two more times.

***Bromoacetylation*:** 0.5 mL of 2 M DIC in NMP was added to the washed resin quickly followed by 0.5 mL of 2 M bromoacetic acid in NMP. The mixtures is agitated for 10 min, drained, and washed three times.

***Displacement*:** In general, 0.5 mL of 1 M amine solution in NMP was added to the washed resin, and agitated with N_2 for 10 min. For poorly nucleophilic amines such as alanine *tert*-butyl ester and glycine *tert*-butyl ester, the displacement time was extended to 2 h. The reaction mixture is drained and then washed three times. Hydrochloride amine salts are free-based *in situ* with 1 equiv DIPEA.

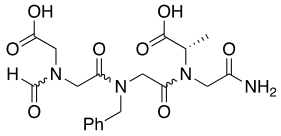
Formylation: 0.5 mL of 2 M DIC in NMP was added to the washed resin quickly followed by 0.5 mL of 2 M formic acid in NMP. The mixture is agitated for 10 min, drained, and washed three times.

Final wash: 2 mL of DCM was added to the resin, agitated for 15 s with N_2, and the drained. The wash is repeated two more times.

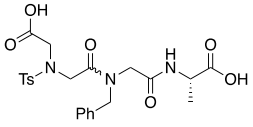
***Cleavage and global deprotection*:** 4 mL of the deprotection cocktail (95% trifluoroacetic acid, 2.5% water, and 2.5% triisopropylsilane) was added to the resin. After 15 min, the slurry was filtered and the resin was washed three times with DCM. The filtrate was concentrated *in vacuo* until an oily residue remained. 10 ml of diethyl ether was added to the residue to precipitate the peptoid as a white powder. The peptoid was collected by vacuum filtration and washed three times with diethyl ether.

***Purification*:** The peptoid solid was dissolved in ~5 mL of acetonitrile/water mixture and purified by HPLC (C_{18} column, the gradient depended on the sequence, 0.1% trifluoroacetic acid added to water and acetonitrile). The pure fractions were dried under vacuum, redissolved in water with a minimal amount of acetonitrile, and lyophilized.

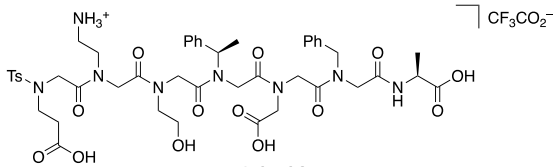
Chart S1. Peptoids used in this study



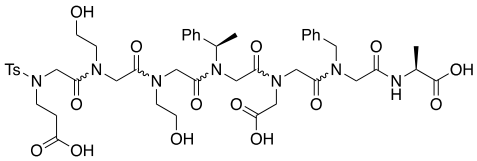
H_2A



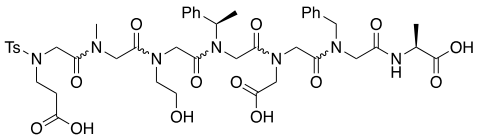
H_2B



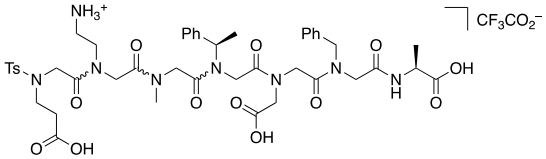
H_3C·CF_3CO_2H



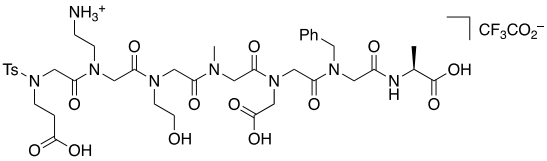
H_3C-Nae2Nhe



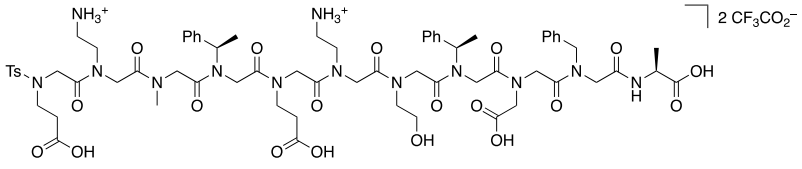
H_3C-Nae2Sar



H_3C-Nhe3Sar·CF_3CO_2H



H_3C-Nrpe4Sar·CF_3CO_2H



H_4D·$2CF_3CO_2H$

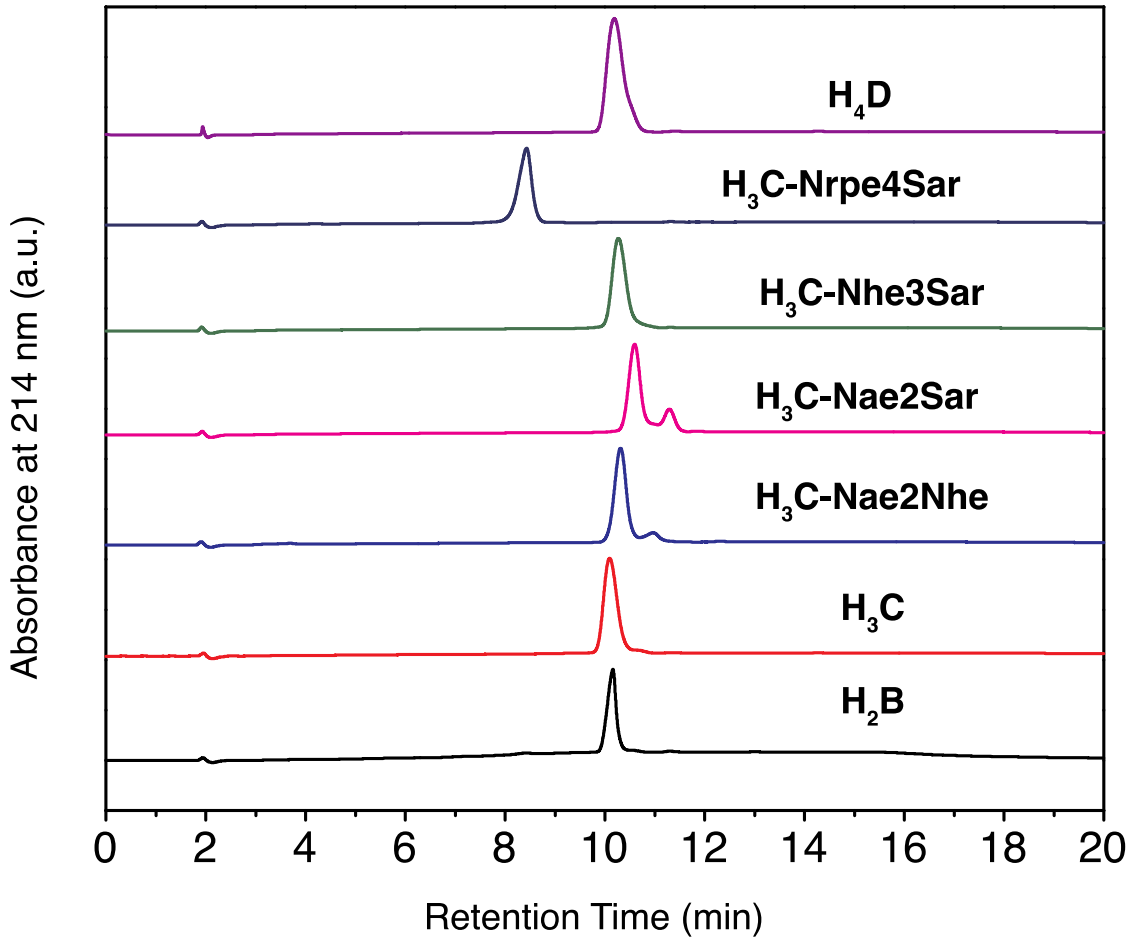
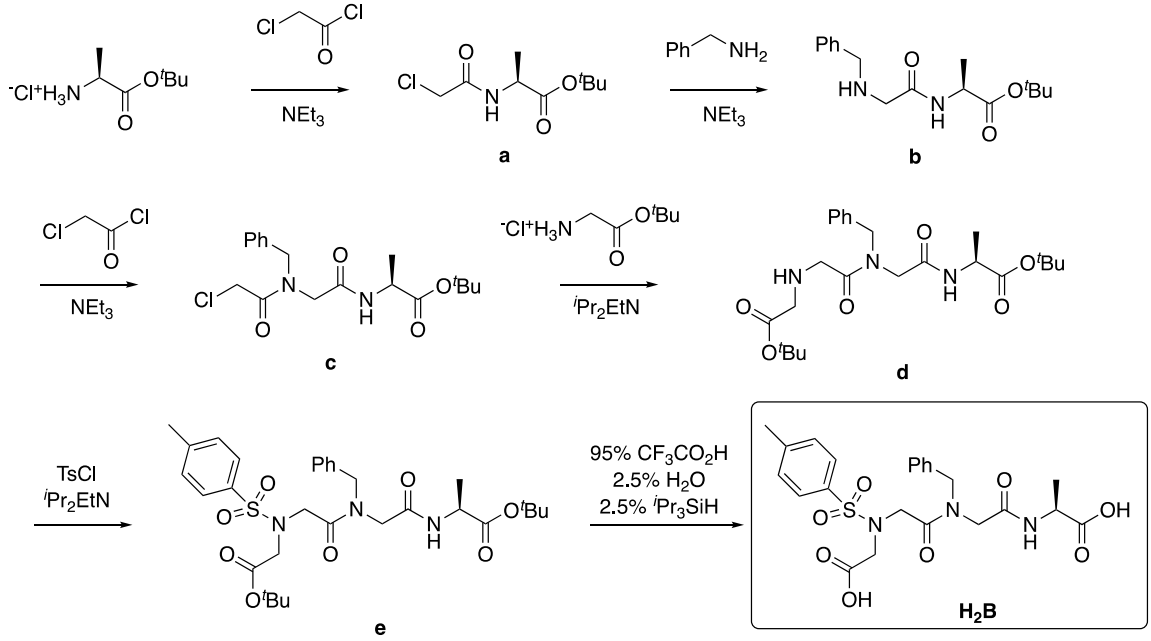


Figure S1. HPLC traces for purified peptoids at 25ºC. Gradient: 5-95% acetonitrile/water with 0.1% trifluoroacetic acid over 20 min.

Table S1. High resolution ESI-MS data

Peptoid	Calculated	Found
H_2A	435.15 $[M-H]^-$	435.2 $[M-H]^-$
H_2B	506.16 $[M+H]^+$	506.2 $[M+H]^+$
H_3C	997.40 $[M+H]^+$	997.4 $[M+H]^+$
H_3C-Nae2Nhe	998.38 $[M+H]^+$	998.4 $[M+H]^+$
H_3C-Nae2Sar	968.37 $[M+H]^+$	968.4 $[M+H]^+$
H_3C-Nhe3Sar	967.39 $[M+H]^+$	967.4 $[M+H]^+$
H_3C-Nrpe4Sar	907.35 $[M+H]^+$	907.4 $[M+H]^+$
H_4D	1459.63 $[M+H]^+$	1459.6 $[M+H]^+$

Scheme S1. Solution phase synthesis of H_2B.



Compound a. Chloroacetyl chloride (6.5 g, 57.6 mmol) was dissolved in 50 mL of DCM and cooled to 0ºC. To this solution was slowly added a 100 mL DCM solution containing alanine *tert*-butyl ester hydrochloride (10.0 g, 55.0 mmol) and triethylamine (15.6 mL, 112 mmol). The mixture was removed from the ice bath and stirred at 25ºC for 1 h. The mixture was then extracted with water, and the organic layer was collected. The aqueous layer was extracted 2 x 100 mL of DCM. The combined organic extracts were dried by $MgSO_4$, and dried *in vacuo* to yield 12.0 g (98%, crude) of pale yellow oil. The material was used directly in the next step.

Compound b. Benzylamine (23.2 g, 216.5 mmol) was dissolved in 100 mL of NMP and heated to 60ºC. To this solution was added dropwise by addition funnel (~1 drop/sec) compound **a** (12.0 g, 54.1 mmol) in 50 mL of NMP. After 2 h, 2 equiv of HCl (9 mL of 12 M) was added and the mixture was partitioned between 200 mL of water and 200 mL of DCM. The DCM layer was extracted 2 x 200 mL with water. The organic layer is then dried with $MgSO_4$, and volatiles were removed *in vacuo* to yield 10.56 g of a red oil (67%). The material was used directly in the next step.

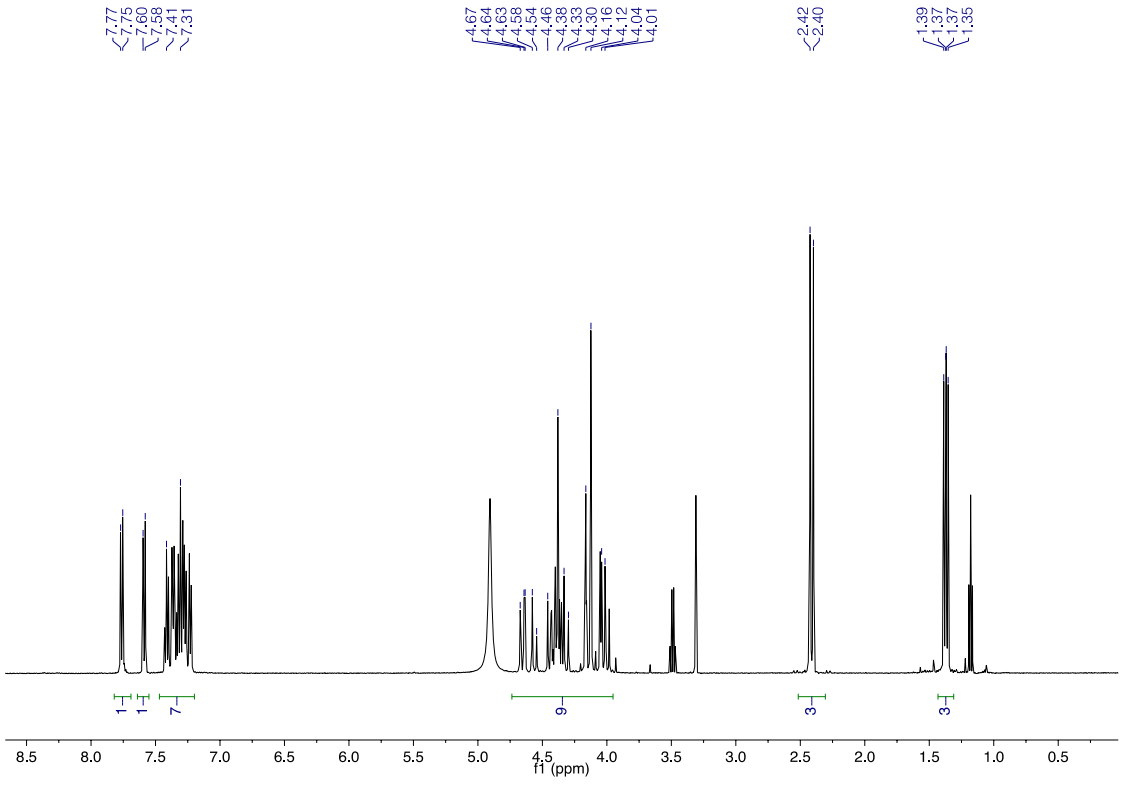
Compound c. Chloroacetyl chloride (4.28 g, 37.9 mmol) was dissolved in 50 mL of DCM and cooled to 0ºC. To this solution was slowly added a 100 mL DCM solution containing compound **b** (10.56 g, 36.1 mmol) and triethylamine (5.54 mL, 40 mmol). The mixture was stirred at 25ºC for 16 h. The mixture was then extracted with water, and the organic layer was collected. The aqueous layer was extracted 2 x 100 mL of DCM. The combined organic extracts were dried by $MgSO_4$, and volatiles were removed *in vacuo*. The residue was dissolved in a minimal amount of DCM and loaded onto a silica plug, and eluted with EtOAc. The solution was dried *in vacuo* to yield 10.54 g of a dark oil (79%). The material was used directly in the next step.

Compound d. Glycine *tert*-butyl ester hydrochloride (9.09 g, 54.2 mmol) and *N*,*N*-diisopropylethylamine (7.01 g, 54.2 mmol) were dissolved in 50 mL of NMP and heated to 70ºC. To this solution was added dropwise by addition funnel (~1 drop/sec) compound **c** (5.0 g, 13.6 mmol) in 50 mL of NMP. After 3 h, the mixture was partitioned between 200 mL of water and 200 mL of DCM. The DCM layer was extracted 2 x 200 mL with water, and once with brine. The organic layer is then dried with $MgSO_4$, and volatiles were removed *in vacuo*. The residue was purified by silica chromatography (0-10% gradient of methanol in DCM with 1% triethylamine) to yield 5.37 g (85%) of a red oil. The material was used directly in the next step.

Compound e. Compound **d** (5.37 g, 11.6 mmol) and *N*,*N*-diisopropylethylamine (2.05 mL, 11.6 mmol) were dissolved in 50 mL DCM. To this solution was added *p*-toluenesulfonyl chloride (2.209 g, 11.6 mmol) as a solution in 20 mL DCM. The reaction mixture was stirred at room temperature for 16 h. The mixture was extracted with water, and the aqueous layer was extracted with 2 x 100 mL DCM. The combined organic layers were dried by $MgSO_4$, and volatiles were removed *in vacuo*. The residue was purified by silica chromatography (0-5% gradient of methanol in DCM). The reside was dried *in vacuo* and triturated with diethyl ether to yield 3.57 g (50 %).

H_2B. To compound **e** (3.57 g, 5.77 mmol) was added 0.5 mL of water, 0.5 mL of triisopropylsilane, and 20 mL of trifluoroacetic acid. After 20 min, the volatiles were removed *in vacuo* to yield an oil. Diethyl ether (~100 mL) was added to the oil, and after agitating the mixture, a white solid precipitated. The solid was collected by filtration washed 2 x 50 mL with diethyl ether to yield 2.50 g (86 %). Purity was assessed by HPLC, while ESI-MS and ^{1}H NMR spectroscopy (Figure S2) confirmed the material was identical to the pure material obtained by solid-phase synthesis.

Figures S2. ^{1}H NMR spectrum of **H_2B** (CD_3OD, 500 MHz). Two amide isomers (*cis* and *trans*) are present in an approximate 1:1 ratio.



One-bead-one-compound screening.
Rappe Tentagel NH2 Macrobead (MB300002) amino functionalized resins (280-320 μm diameter, 0.27 mmol/g, ~65500 beads/g) were used for on-bead screening.

Peptoid library generation by split-and-pool synthesis.
The resin (1.0 g, 0.27 mmol) was swollen in DCM for 30 min. HCTU (0.502 g, 1.2 mmol) was dissolved in 2 mL of 20% *N*-methylmorpholine/DMF, followed by addition of Fmoc-Met-OH (0.500 g, 1.3 mmol) to the solution. The solution was quickly added to the swollen resin and allowed to react for 1 h, after which, the solution was drained and resin was rinsed thoroughly with DCM three times. Fmoc deprotection was effected by addition of 5 mL of a 20% 4-methylpiperidine/NMP solution, and agitated for 10 min. The resin was drained and washed three times with NMP.
Peptoid synthesis was performed as described earlier for resides Nala, Nbn, and Ncm.

For the tripeptoid benchmark, the sequence is capped at this point with a tosyl group by addition of 1 mL of 1 M *p*-toluenesulfonyl chloride/NEt_3. After 30 min, the resin is drained, washed three times with NMP, and washed three times with DCM.

The library was generated by the split-pool method. The 0.8 g of resin was bromoacetylated and washed (as described earlier), and suspended in DCM. The resin was distributed as evenly as possible by pipette into five 6 mL polypropylene cartridges (Applied Separations) equipped with a 20μ PE frit ("split" step). The resin in each vessel was drained of DCM and capped at the outlet. To each vessel was added a different amine solution in NMP (1 M 2-((*tert*-butyldimethylsilyl)oxy)ethan-1-amine, 1 M *N*-Boc-ethylenediamine, 2 M *p*-anisidine, 2 M (*R*)-(+)-α-methlylbenzylamine, 2 M methylamine), and swirled on an orbital shaker for 30 min. Each vessel was drained and washed three times with NMP, and then consolidated into the glass vessel ("pool" step). The pooled resin was bromoacetylated as described before. The "split" and "pool" cycles were repeated three times to generate a library of 5^3 sequences.

For the final constant residue (Nce), 4 mL of 1 M β-alanine *tert*-butyl ester/DIPEA in NMP was added to the pooled and bromoacetylated resin, and agitated for 10 min. The resin was drained and washed. The sequence is capped with a tosyl group by addition of 4 mL of 1 M *p*-toluenesulfonyl chloride/NEt_3. After 30 min, the resin is drained, washed three times with NMP, and washed three times with DCM.

The side chain protecting groups were removed by 20 mL of 95% trifluoroacetic acid: 2.5% water: 2.5% triisopropylsilane for 15 min. The resin was collected by filtration and very thoroughly washed with DCM (10 washes, 15 sec each) and methanol (4 washes, 1 min per wash). ***Note***: it is critical for the following metallation procedure that the resin is completely free of residual trifluoroacetic acid. The resin is dried under vacuum for 16 h.

Library metallation.
0.100 g (0.027 mmol) of the resin library was suspended in 20 mL of methanol with 0.023 g (0.027 mmol) of dissolved **1**. The mixture was heated at 50º C for 20 h. The resin was collected by filtration and washed five times with methanol. The dark green resin was dried under vacuum for 16 h.

Library screening.
To glass dram vials containing 0.025 g of the metallated library was added 675 μL of 0.5 M, 1.0 M, 3.0 M, and 10 M acetic acid in methanol. The capped vials were heated at 50º C for 20 h. The supernatant of each vial were decanted, and the resin was washed with methanol three times. The resins were stored under methanol.

The resin beads were analyzed on a petri dish under an optical microscope (Scheme S2, Figure S3). In all screens, beads were either colorless or olive green. Hits were defined as beads that retained the olive green color of the $[Co_4O_4]$ cluster, and were isolated using a micropipette tip. The isolated bead was transferred into an Eppendorf tube.

Scheme S2. On bead screening strategy

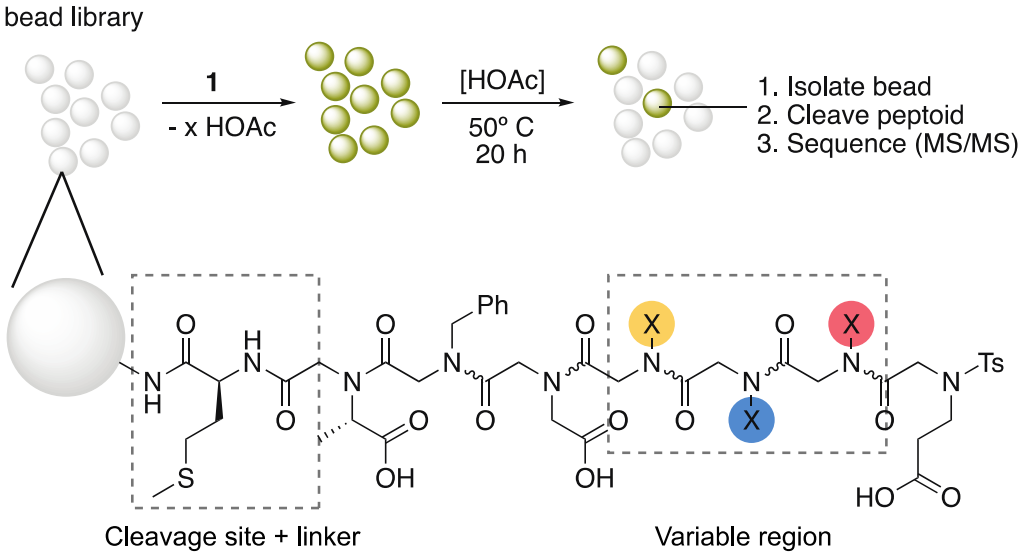
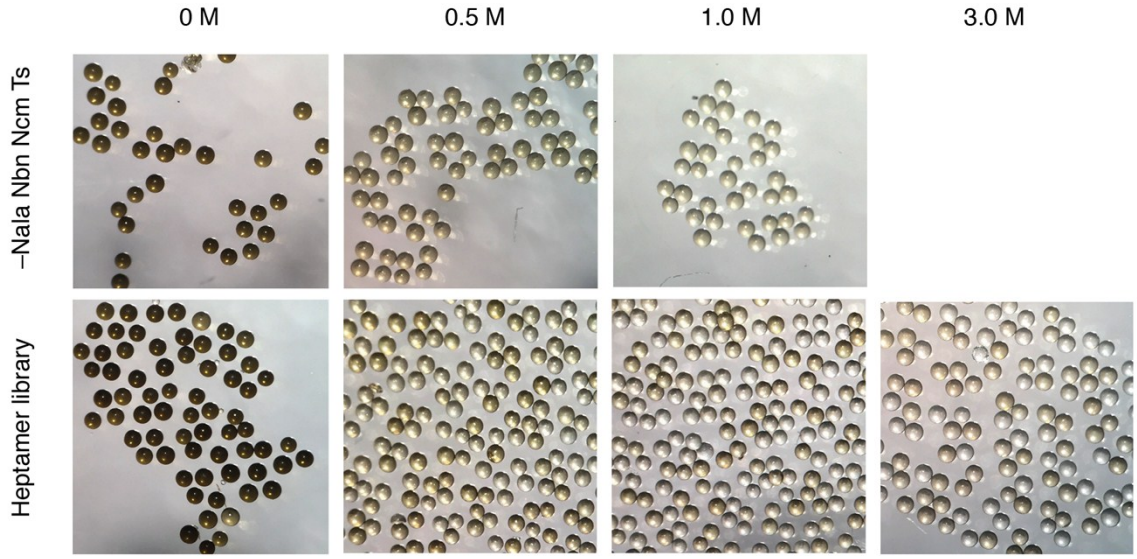


Figure S3. Results of on bead screening at different acetic acid concentrations.



Hit sequencing.
To the isolated bead was added 10 µL of a 4 mg/mL BrCN solution in MeCN and 10 µL of 0.25 M $HCl_{(aq)}$. After 16 h, 10 µL of the solution was mixed with 10 µL of MALDI matrix solution (α-cyano-4-hydroxycinnamic acid, 10 mg/mL in MeCN), and spotted onto a MALDI plate. A representative MS/MS spectrum is shown in Figure S4.

Figure S4. A representative MALDI TOF-TOF MS/MS spectrum.

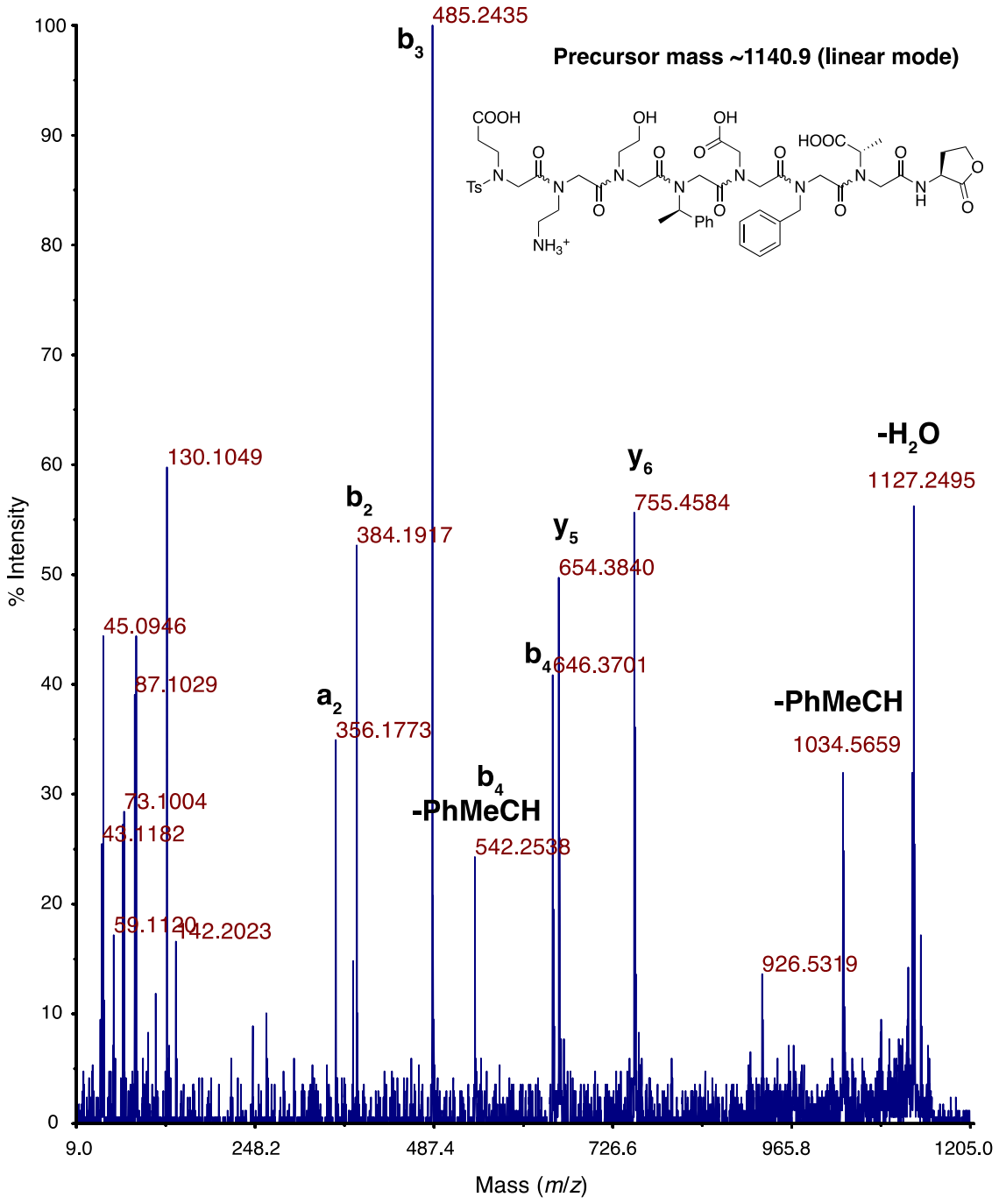


Table S2. Summary of hits identified from one-bead-one-compound screening

Residue Position			Number of
2	3	4	times identified
Nae	Nhe	Nae	2
Nae	Nae	Nae	3
Nhe	Nae	Nae	3
Nrpe	Nae	Nrpe	1
Nrpe	Nrpe	Nae	2
Nae	Nhe	Nrpe	2
Nae	Nrpe	Nae	2
Nae	Nrpe	Nhe	1
Nhe	Nanis	Nae	2
Nae	Nanis	Nae	1

Synthesis and characterization of metal complexes.

1-A. 0.050 g of **1** (0.0587 mmol) and 0.026 g of **H_2A** (0.0596 mmol) were dissolved in 10 mL of methanol in a scintillation vial and heated to 60º C for 2.5 h. The solution was filtered and dried by rotary evaporator. The residue was redissolved in a minimal amount of DCM and loaded onto a silica column. The product was eluted with 0-10% methanol:DCM, and the pure fractions were dried *in vacuo* to yield 0.026 g (38%) of a dark green solid.

Figure S5. High-resolution positive mode ESI-MS of **1-A**.

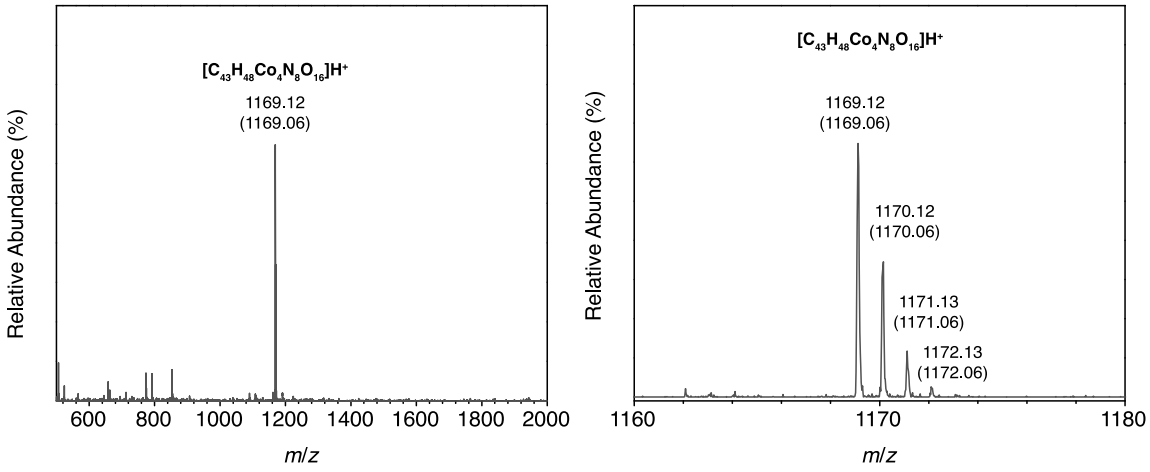


Figure S6. ^{1}H NMR (500 MHz, CD_3OD) of **1-A**. Inset: close-up of the formyl protons.

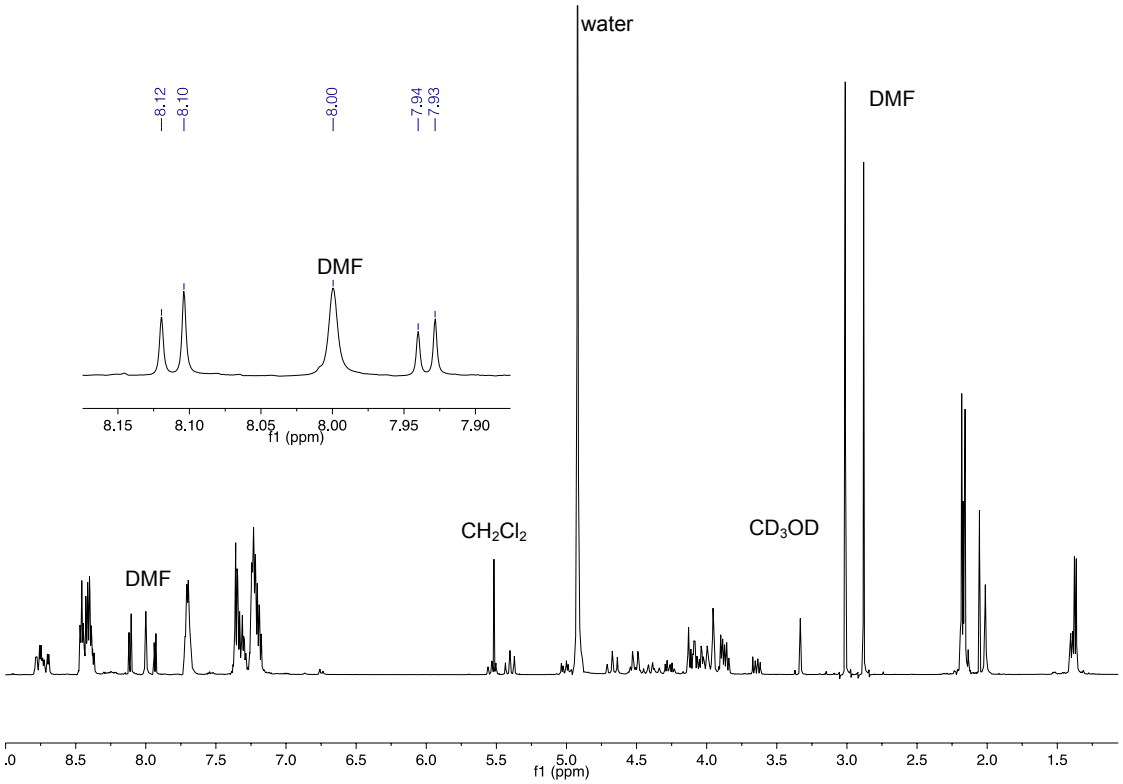


Figure S7. TOCSY spectrum of **1-A**.

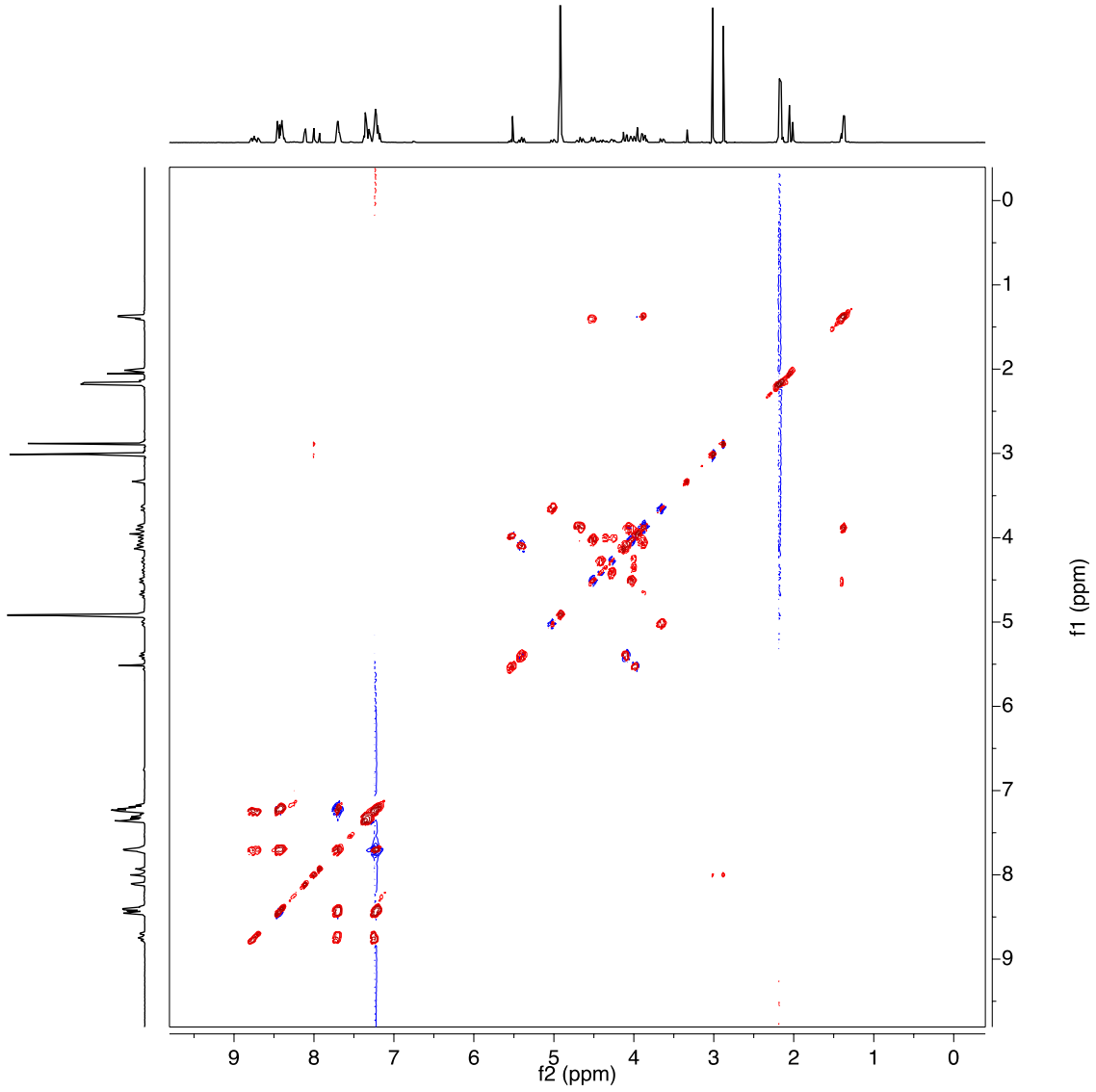


Figure S8. $^{1}H–^{13}C$ HSQC multiplicity-edited spectrum of **1-A**.

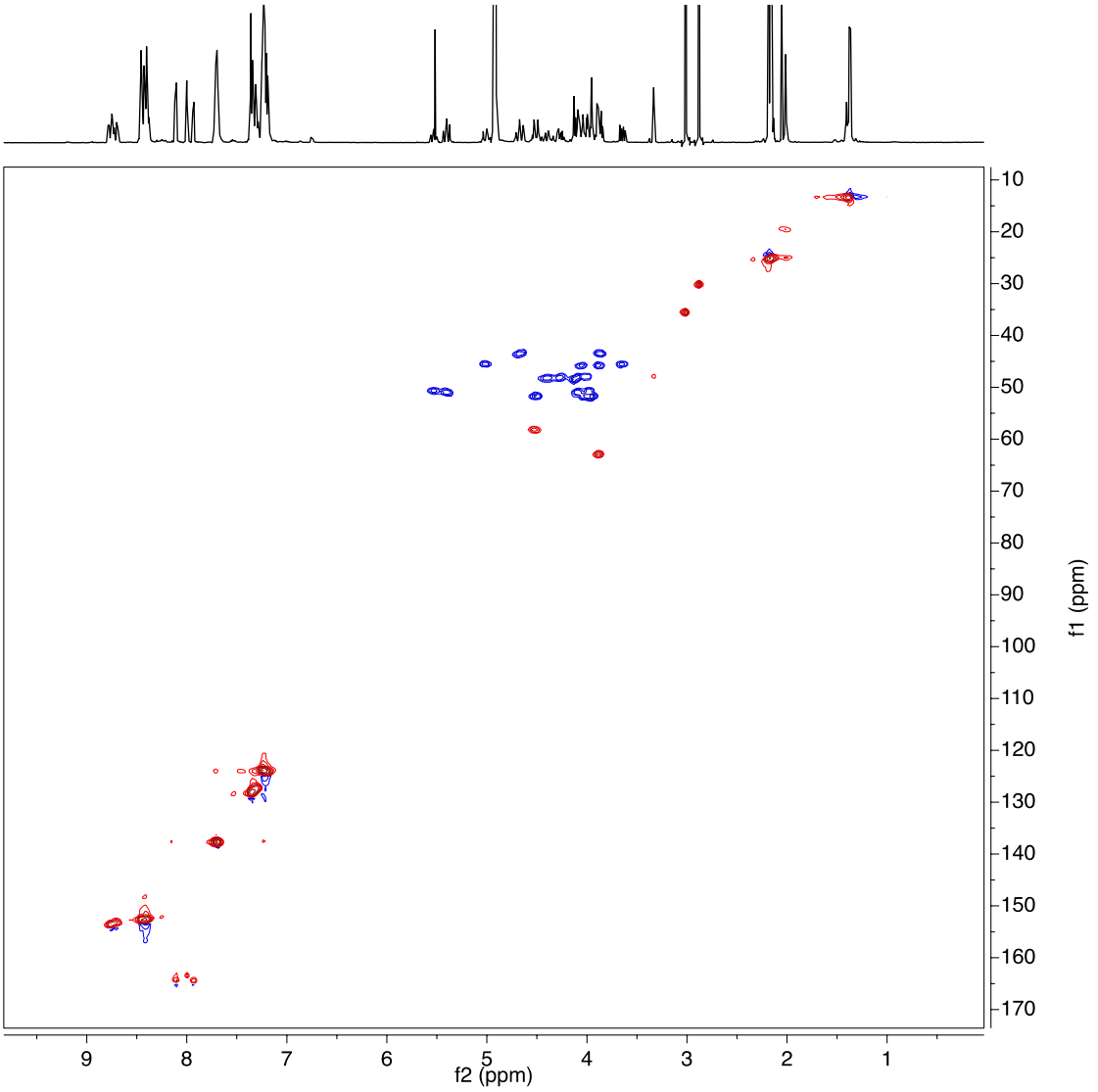


Figure S9. HMBC spectrum of **1-A**.

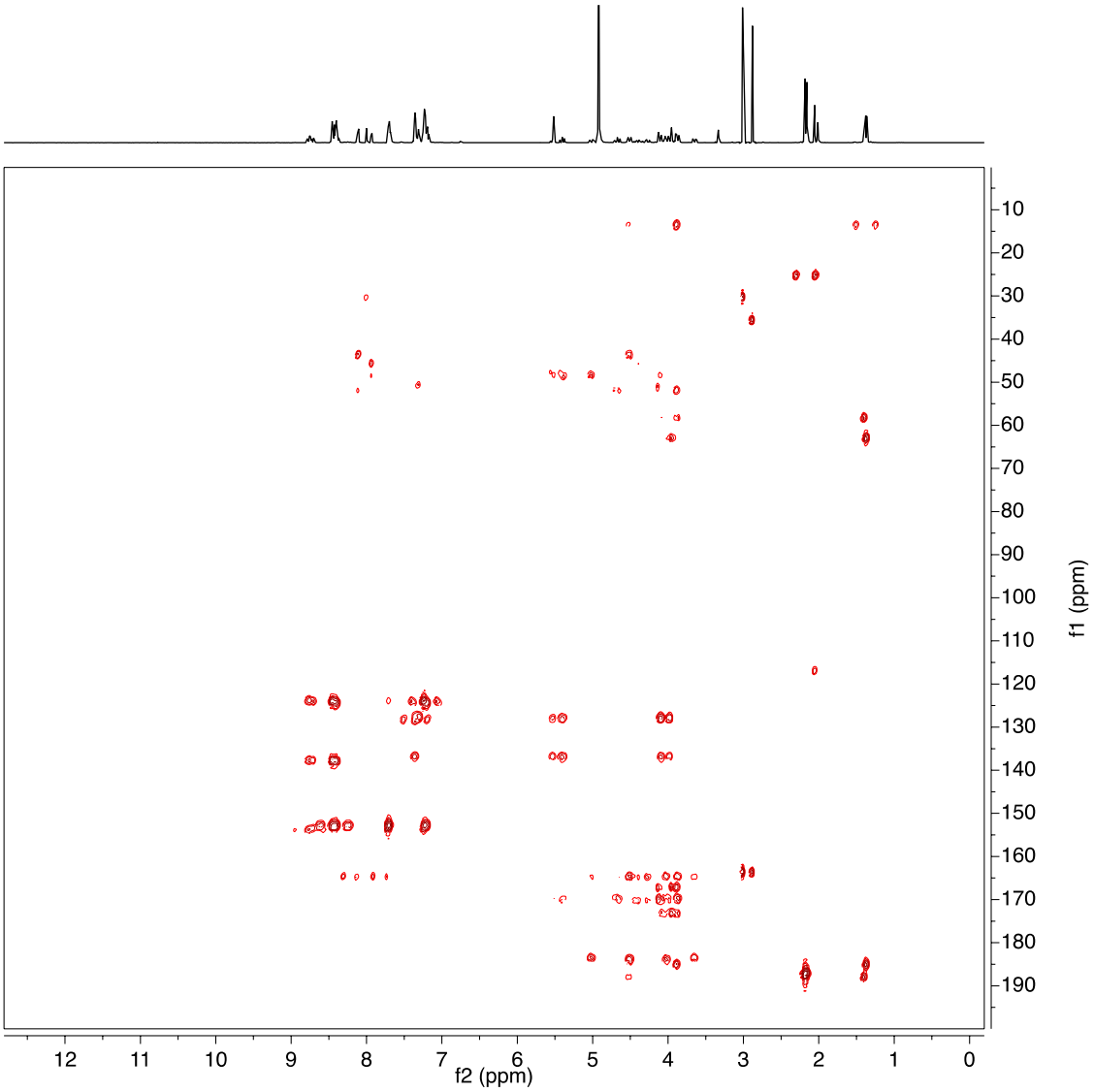
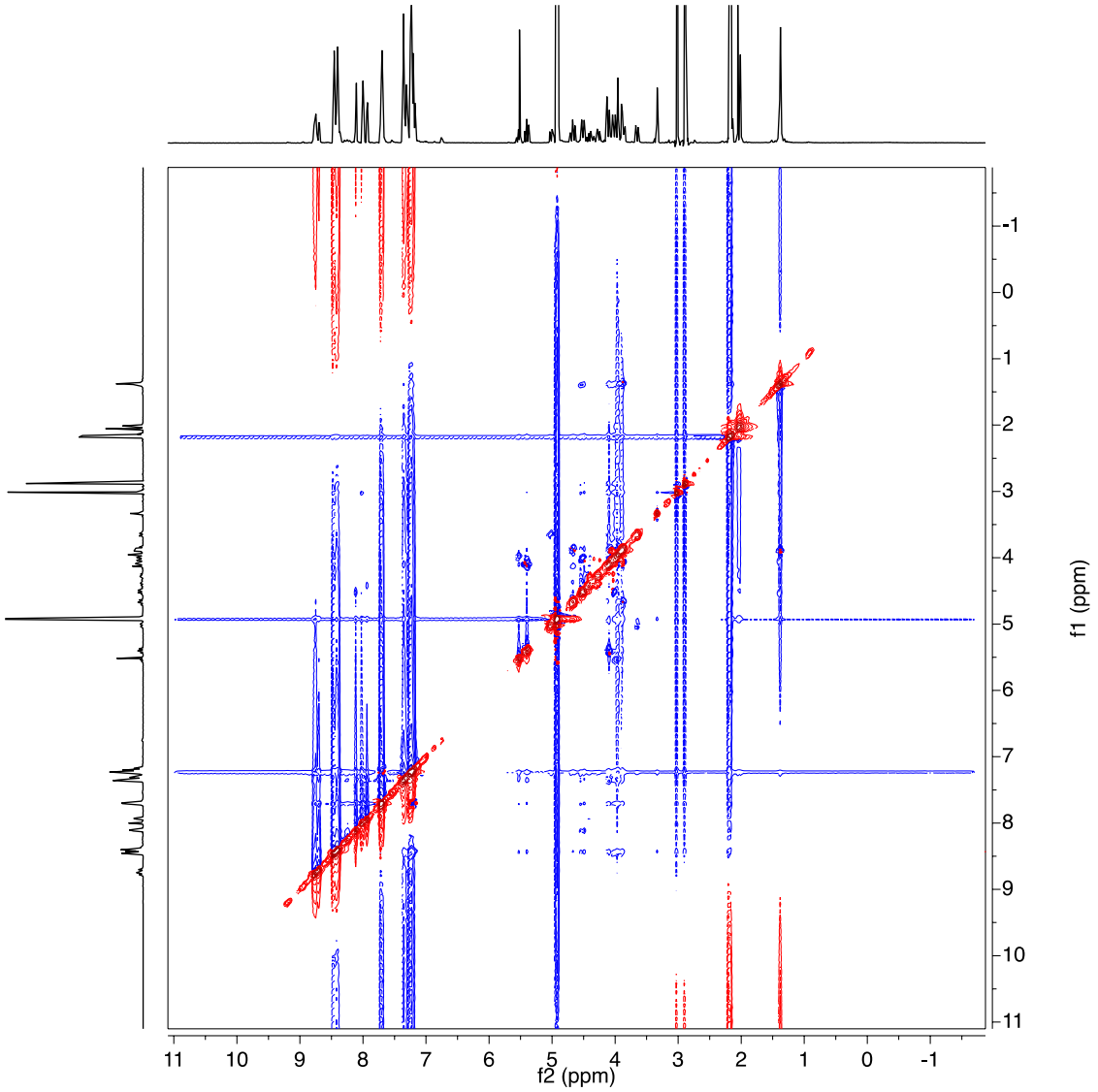


Figure S10. NOESY spectrum of **1-A**.



1-B. 0.100 g of **1** (0.117 mmol) and 0.060 g of $\mathbf{H_2B}$ (0.119 mmol) were dissolved in 10 mL of methanol and heated for 16 h. Volatiles were removed on a rotary evaporator in a 25ºC water bath. The residue was dissolved in a minimal amount of DCM and loaded onto a silica column. The product was eluted with 0-5% methanol:DCM, and the pure fractions were dried *in vacuo* to yield 0.025 g (17%) of dark green solid.

Figure S11. High-resolution positive mode ESI-MS of **1-B**.

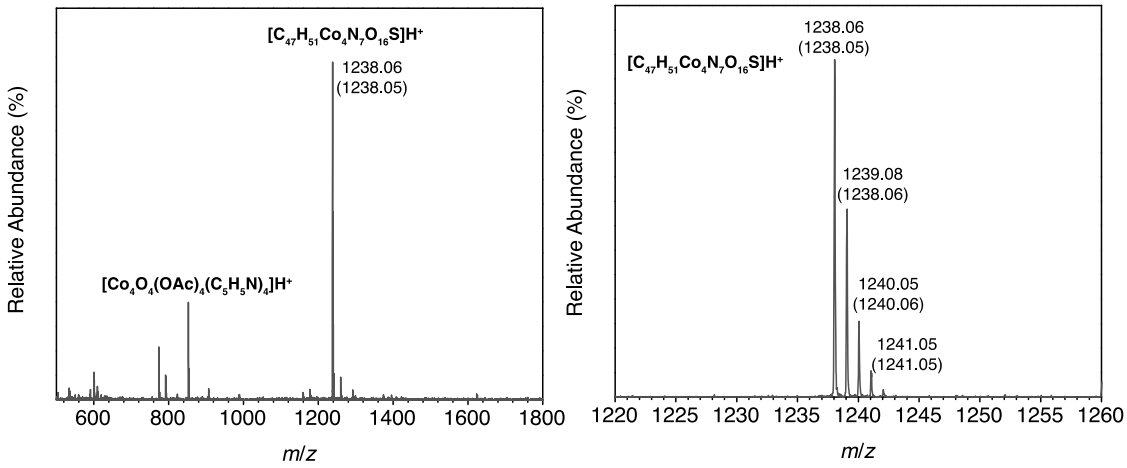
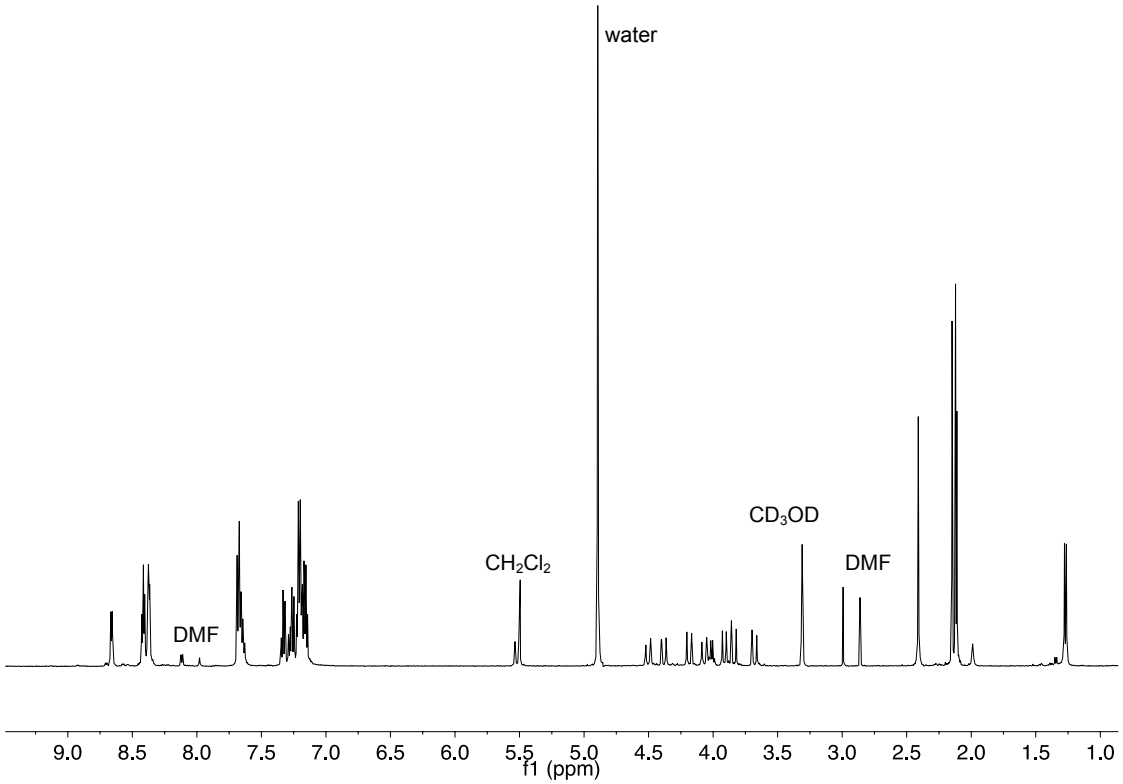


Table S3.

δ (ppm)	Integration	Multiplicity	Type	Residue
1.27	3	d	C*H*$_3$	Ala
2.12	3	s	C*H*$_3$	Acetate
2.15	3	s	C*H*$_3$	Acetate
2.41	3	s	C*H*$_3$	Tosyl
3.68	1	d	C*H*$_2$	*unassigned*
3.84	1	d	C*H*$_2$	*unassigned*
3.92	1	d	C*H*$_2$	*unassigned*
4.01	1	q	C*H*	*unassigned*
4.07	1	d	C*H*$_2$	*unassigned*
4.19	1	d	C*H*$_2$	*unassigned*
4.38	1	d	C*H*$_2$	*unassigned*
4.50	1	d	C*H*$_2$	*unassigned*
5.52	1	d	C*H*$_2$	*unassigned*
7.14-7.35	15	m	Ar-C*H*	Pyridine + Tosyl + Nbn
7.63-7.69	6	m	Ar-C*H*	Tosyl + pyridine
8.37-8.43	8	m	Ar-C*H*	Pyridine
8.67	2	dd	Ar-C*H*	Pyridine

Figure S12. ^{1}H NMR (500 MHz, CD_3OD) of **1-B**.



1-2B. 0.050 g of **1** (0.0587 mmol) and 0.060 g of $\mathbf{H_2B}$ (0.119 mmol) were dissolved in 20 mL of 1:9 methanol:toluene and heated to 50º C for 3 h. Volatiles were removed on a rotary evaporator. The residue was redissolved in 20 mL of 1:9 methanol:toluene, heated for 16 h, and dried by rotary evaporator. The residue was dissolved in a minimal amount of DCM and loaded onto a silica column. The product was eluted with 0-5% methanol:DCM, and the pure fractions were dried *in vacuo* to yield 0.0246 g (26%) of dark green solid.

Figure S13. High-resolution positive mode ESI-MS of **1-2B**.

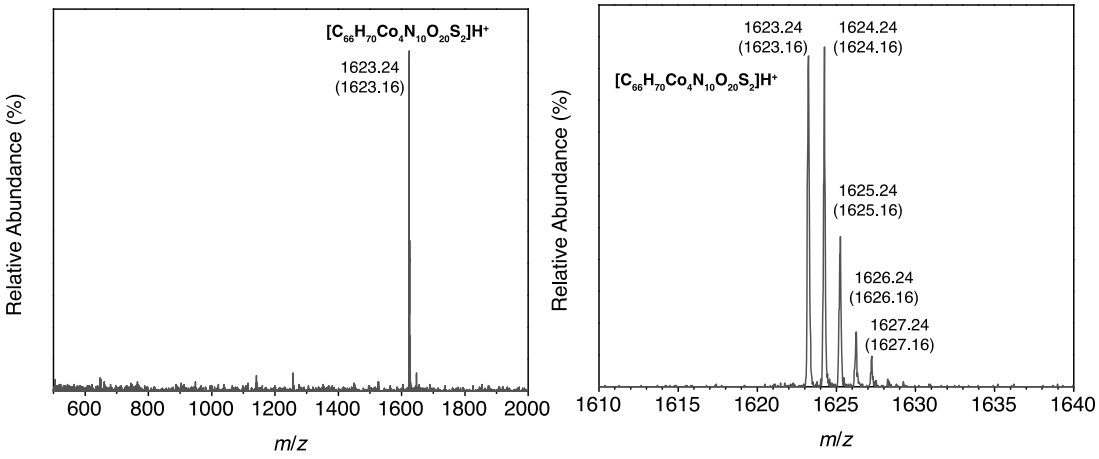


Table S4.

δ (ppm)	Integration	Multiplicity	Type	Residue
1.25	6	d	CH_3	Ala
2.41	6	s	CH_3	Tosyl
3.66	2	d	CH_2	Nbn bb
3.86	2	d	CH_2	Nbn sc
3.90	2	d	CH_2	Ncm sc
4.00	2	q	CH	Ala
4.07	2	d	CH_2	Nbn bb
4.17	2	d	CH_2	Ncm bb
4.42	2	d	CH_2	Ncm sc
4.50	2	d	CH_2	Ncm bb
5.53	2	d	CH_2	Nbn sc
7.13-7.17	8	m	Ar-CH	pyridine
7.18-7.21	4	m	Ar-CH	Nbn sc
7.26-7.27	6	m	Ar-CH	Tosyl + Nbn sc
7.30-7.33	4	m	Ar-CH	Nbn sc
7.61	2	tt	Ar-CH	pyridine
7.65	2	tt	Ar-CH	pyridine
7.70	4	d	Ar-CH	tosyl
8.35	4	dd	Ar-CH	pyridine
8.58	4	dd	Ar-CH	pyridine

Figure S14. ^{1}H NMR (500 MHz, CD_3OD) of **1-2B**.

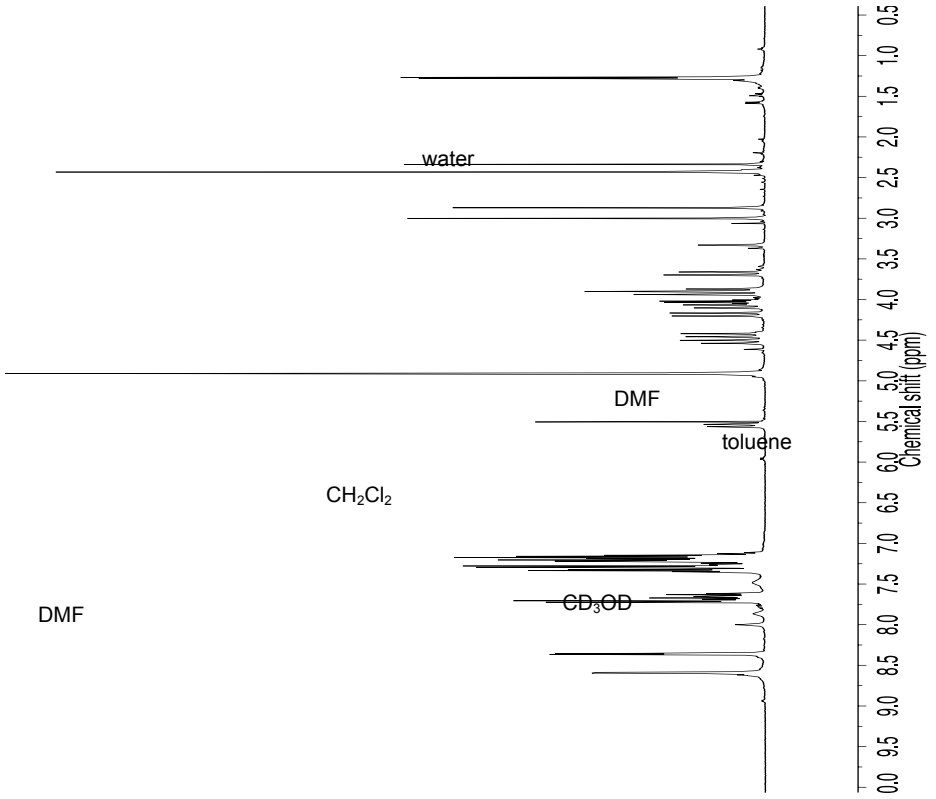


Figure S15. $^{1}H–^{13}C$ HSQC multiplicity-edited spectrum of **1-2B**.

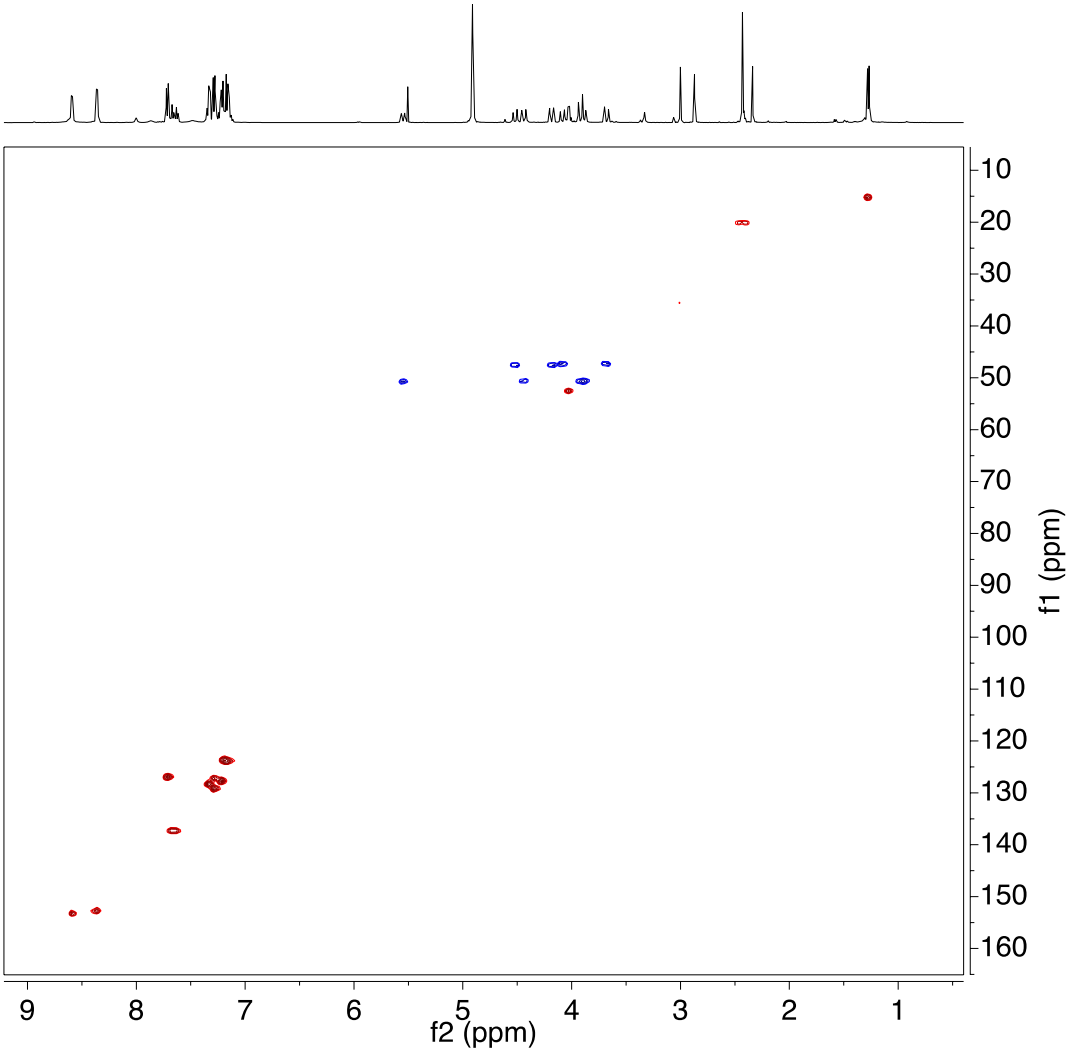
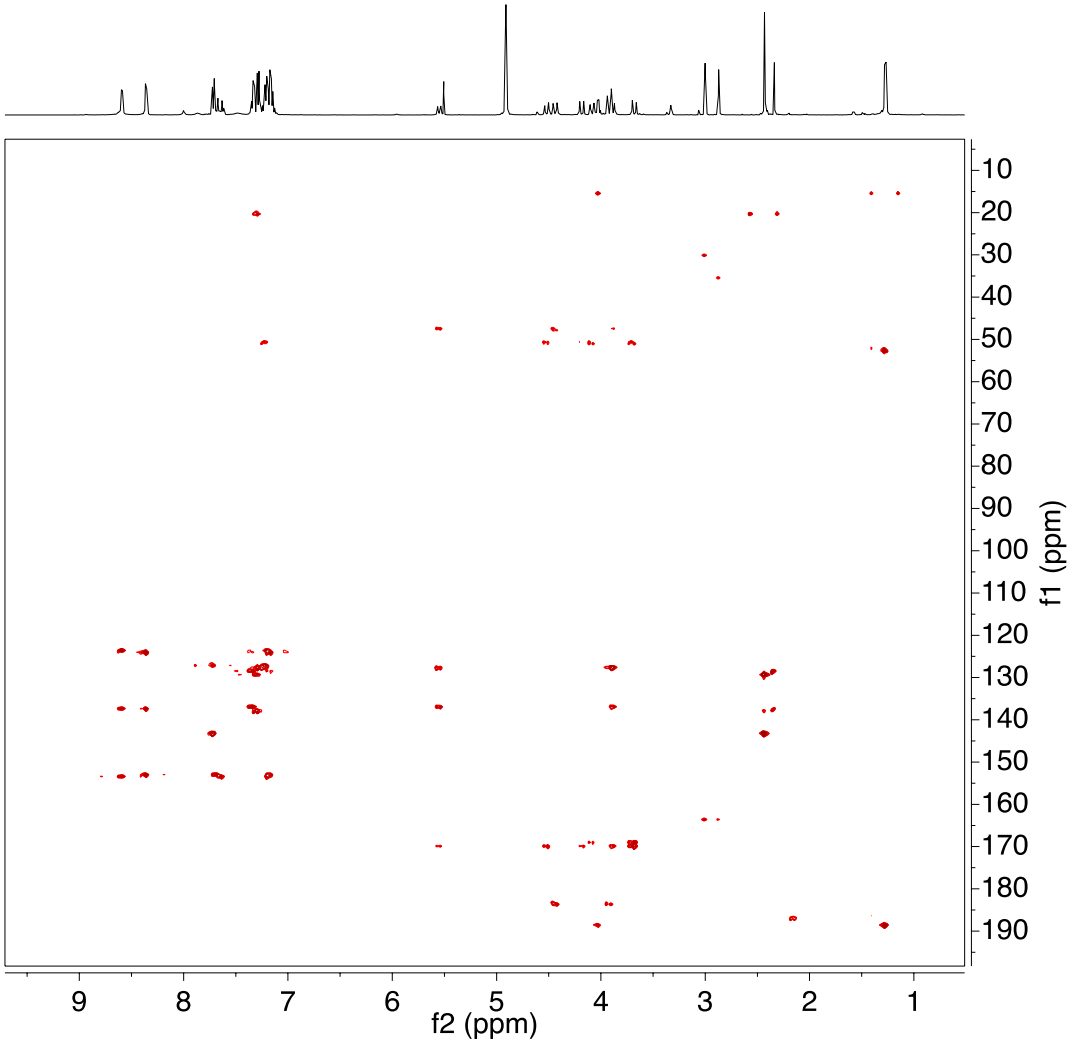


Figure S16. Full HMBC spectrum of **1-2B**.



1-C. 0.0379 g (0.0445 mmol) of **1** and 0.0495 g (0.0445 mmol) of **H_3C** were dissolved in 20 mL of methanol and heated to 50º C for 16 h. Volatiles were removed on a rotary evaporator with a 25ºC water bath. The residue was rinsed three times with diethyl ether to remove remaining acetic acid byproduct. The product was dissolved in 2 mL of 30% MeCN in water, and purified by HPLC on C18 column (30-90% gradient of pure MeCN:water over 30 min). The pure fractions were immediately frozen and lyophilized to yield 0.0106 g (13%) of a dark green solid.

Figure S17. High-resolution positive mode ESI-MS of **1-C.**

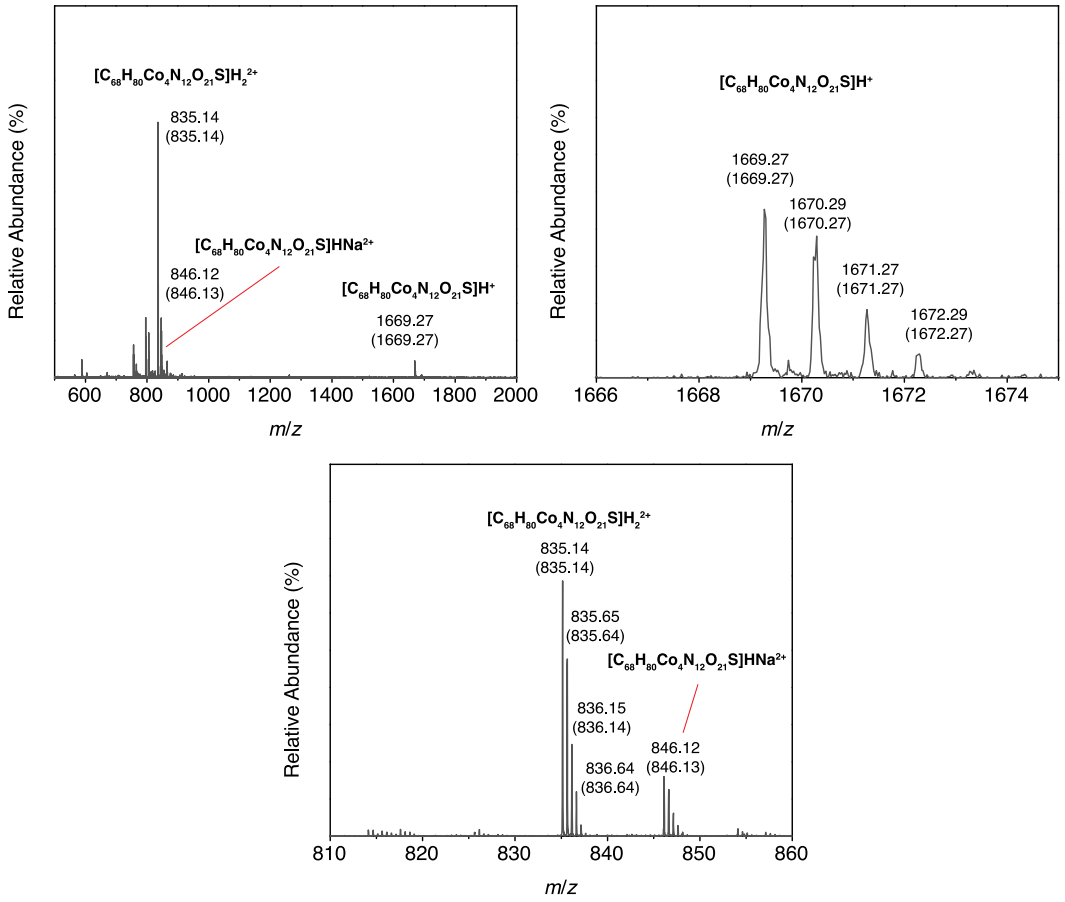


Figure S18. ^{1}H NMR (500 MHz, CD_3OD) of **1-C**.

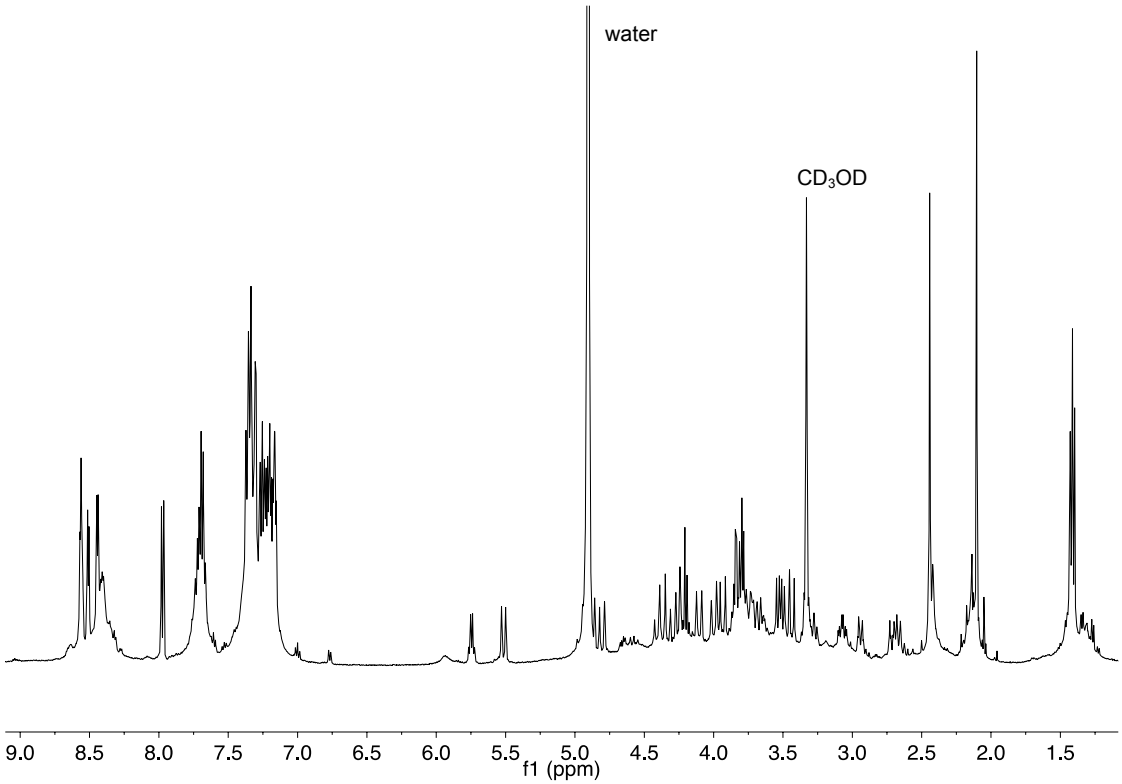


Figure S19. TOCSY of **1-C.**

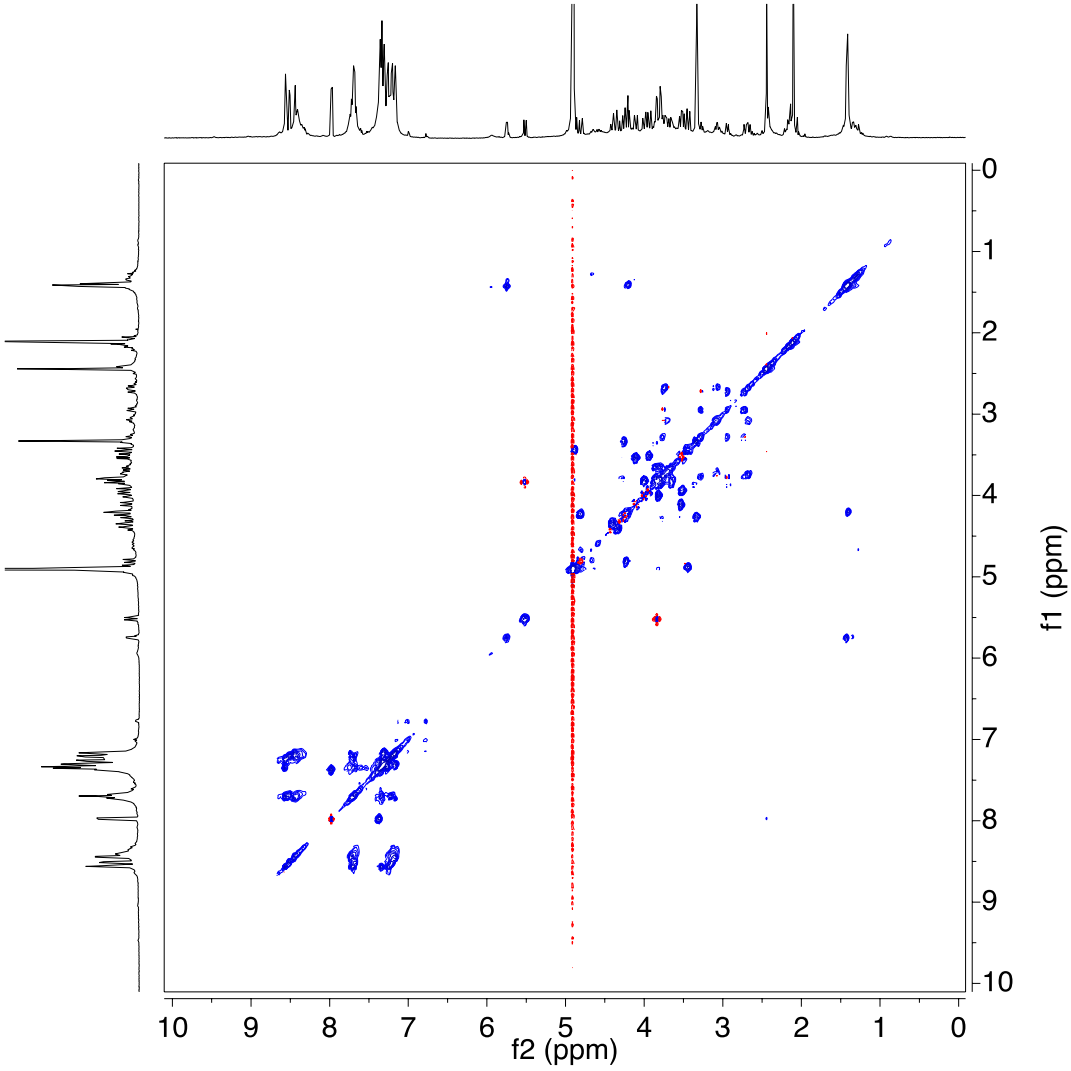


Figure S20. $^{1}H–^{13}C$ HSQC multiplicity-edited spectrum of **1-C.**

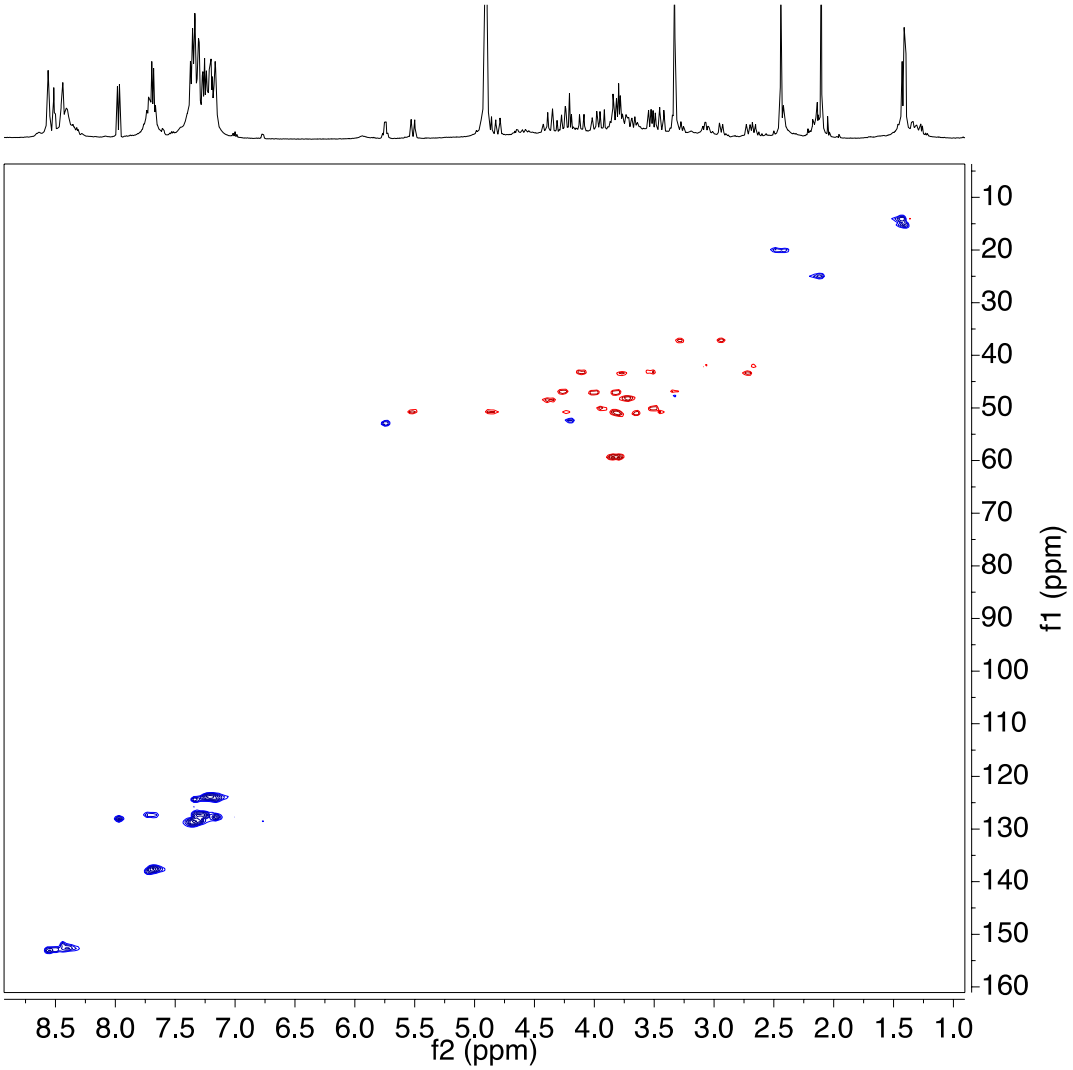


Figure S21. Expansion of the $^{1}H–^{13}C$ HSQC multiplicity-edited spectrum of **1-C.**

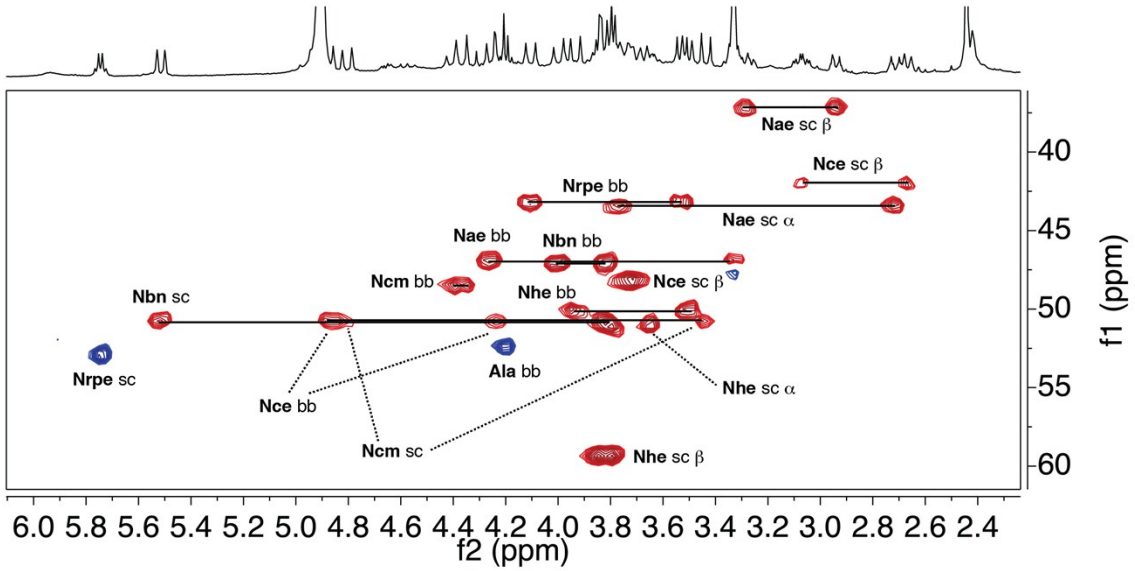


Figure S22. Full HMBC spectrum of **1-C.**

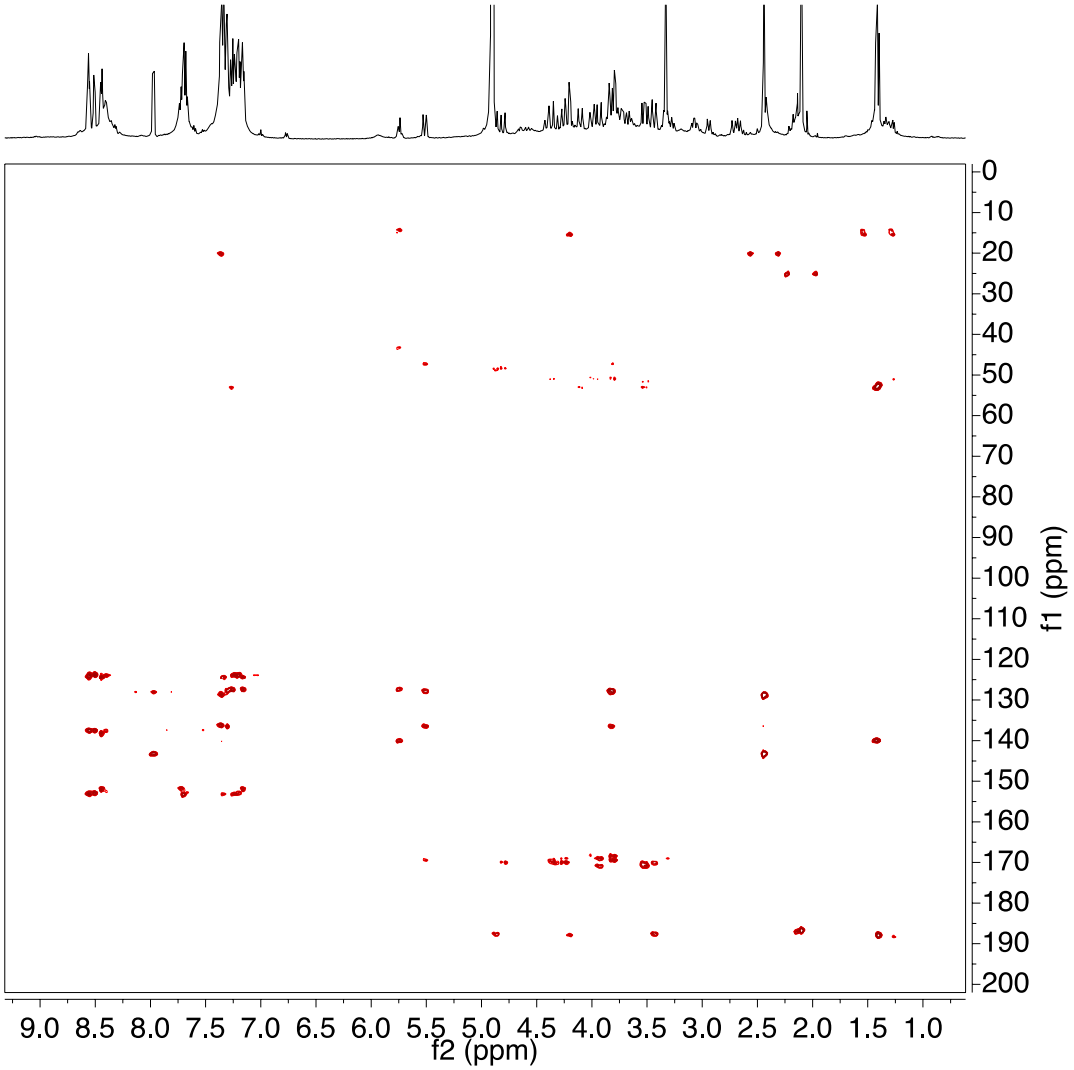
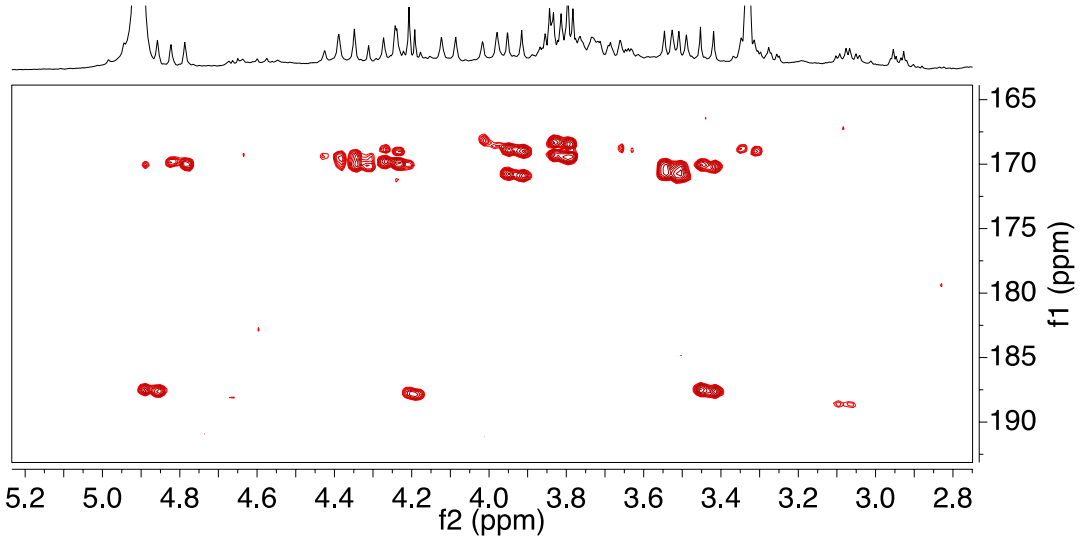


Figure S23. Expansion of the HMBC spectrum of **1-C.**



1-C-Nhe3Sar. 0.0140 g (0.0164 mmol) of **1** and 0.01775 g (0.0164 mmol) of **H_3C-Nhe3Sar** were dissolved in 20 mL of methanol (0.8 mM) and heated to 50º C for 16 h. Volatiles were removed on a rotary evaporator with a 25ºC water bath. The residue was rinsed three times with diethyl ether to remove remaining acetic acid byproduct. The product was dissolved in 4 mL of water and the insoluble material was filtered. The filtrate was purified by HPLC on C18 column (5-95% gradient of pure MeCN:water over 30 min). The pure fractions were immediately frozen and lyophilized to yield 0.0077 g (27%) of a dark green solid.

Figure S24. ^{1}H NMR (500 MHz, CD_3OD) of **1-C-Nhe3Sar**.

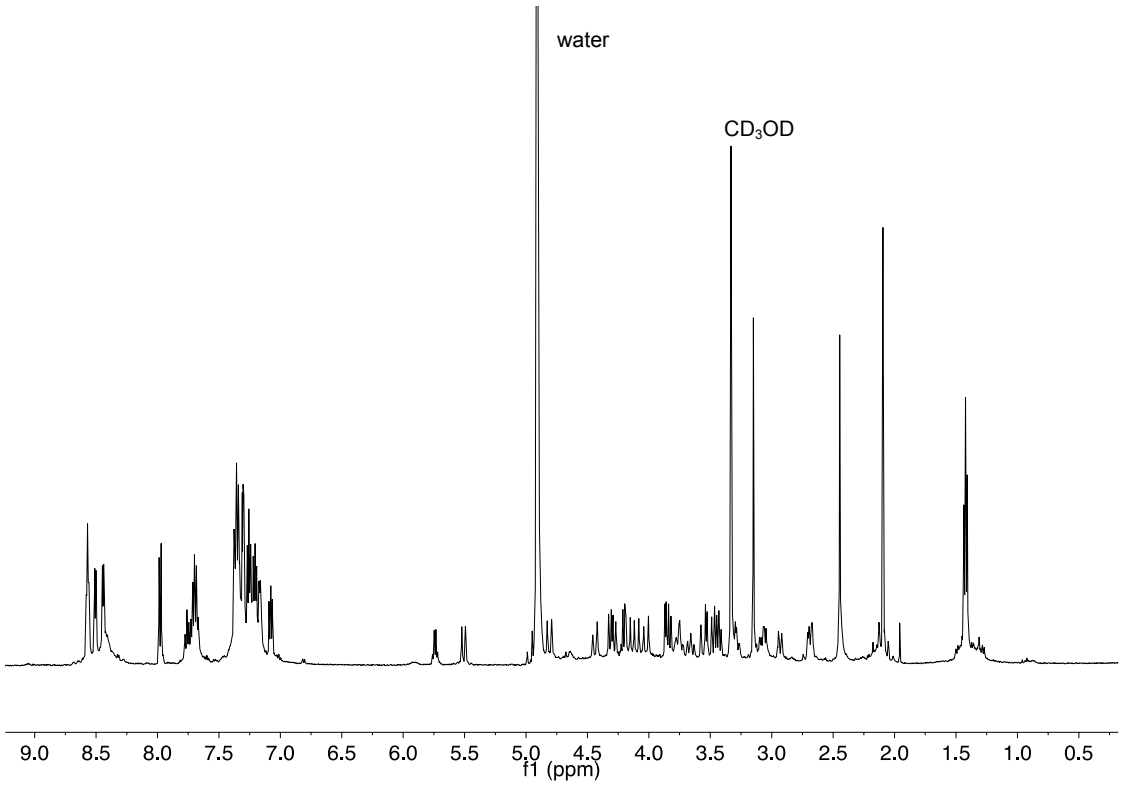


Figure S25. TOCSY of **1-C-Nhe3Sar**.

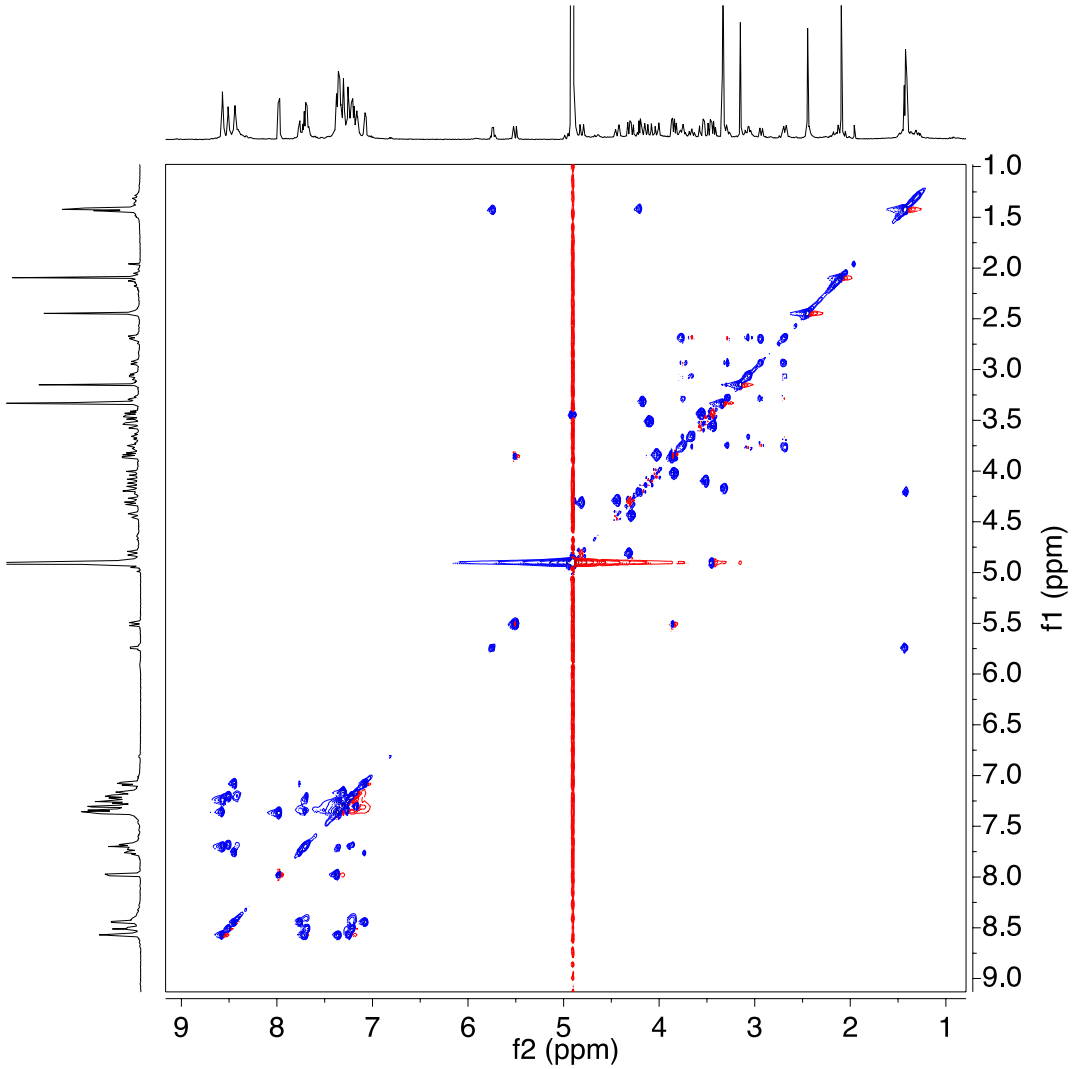


Figure S26. $^{1}H–^{13}C$ HSQC multiplicity-edited spectrum of **1-C-Nhe3Sar**.

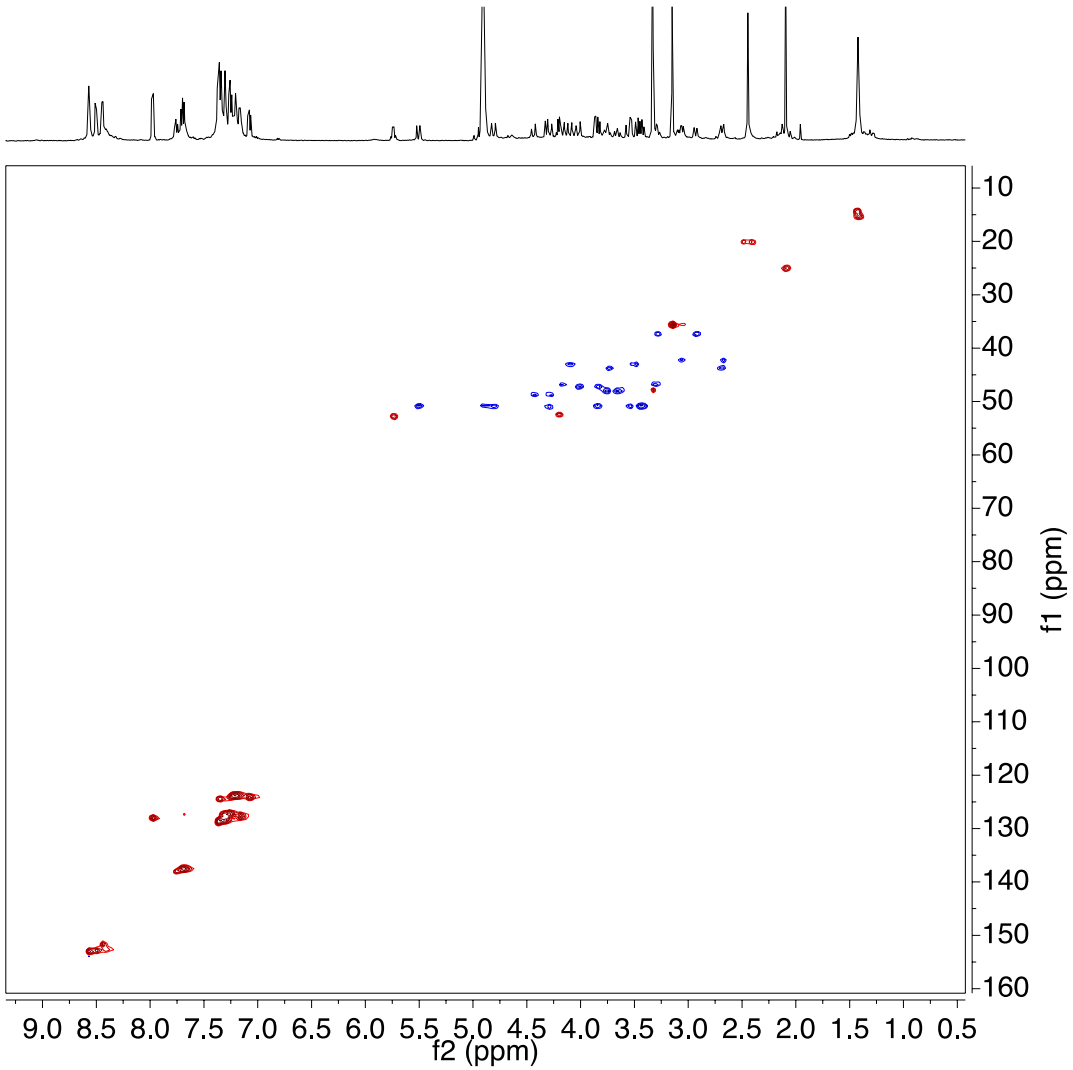


Figure S27. Expansion of the $^{1}H–^{13}C$ HSQC multiplicity-edited spectrum of **1-C-Nhe3Sar** and crosspeak assignment:

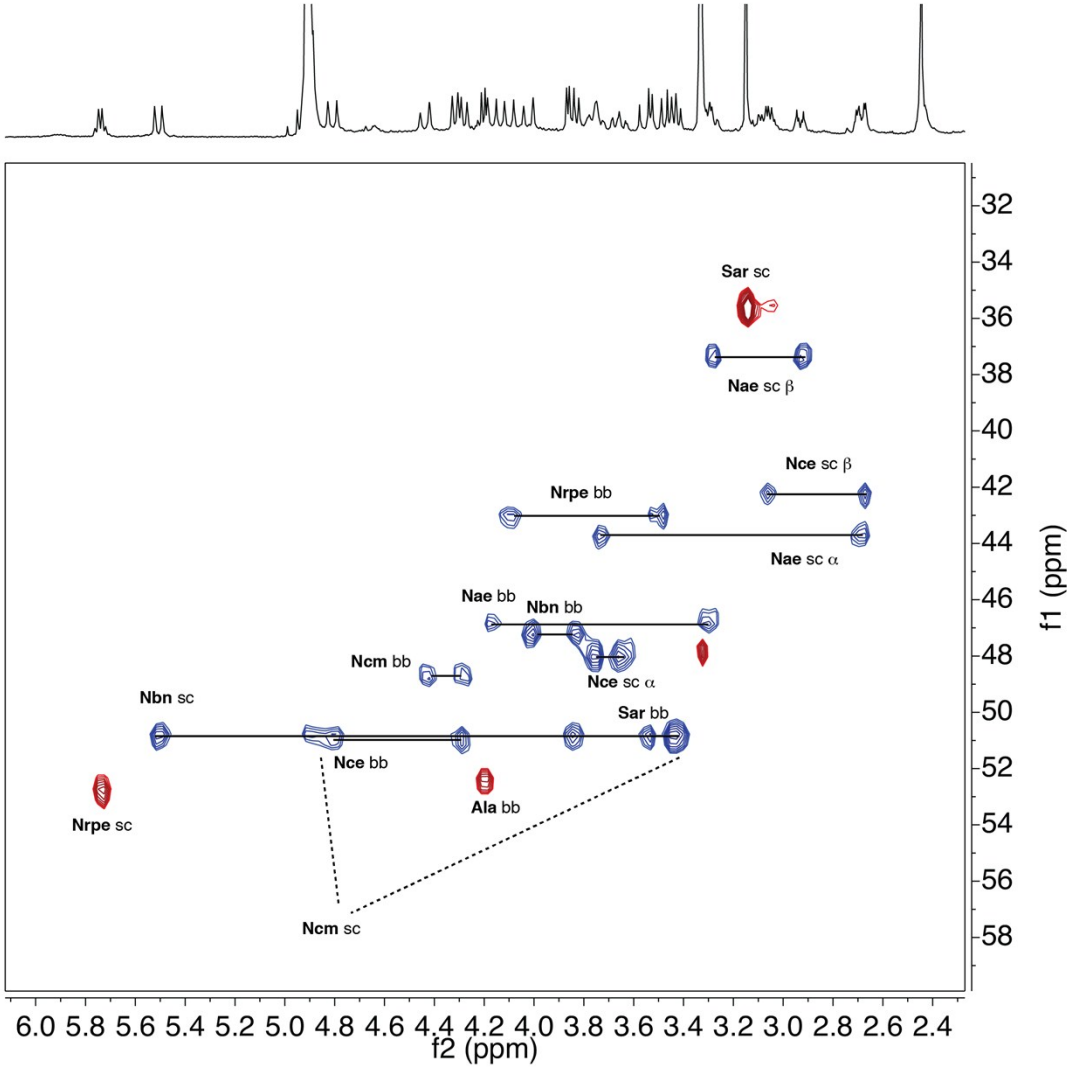
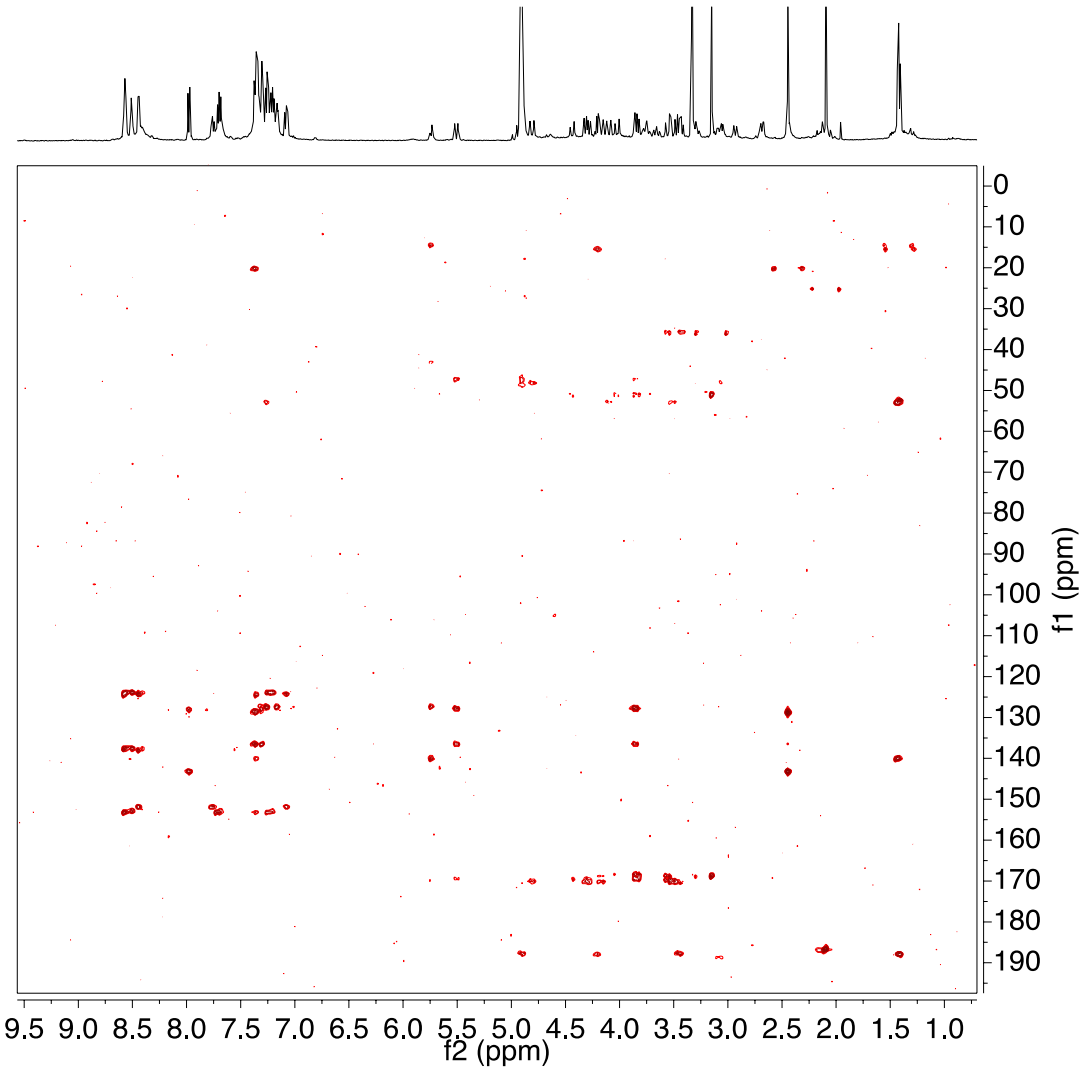
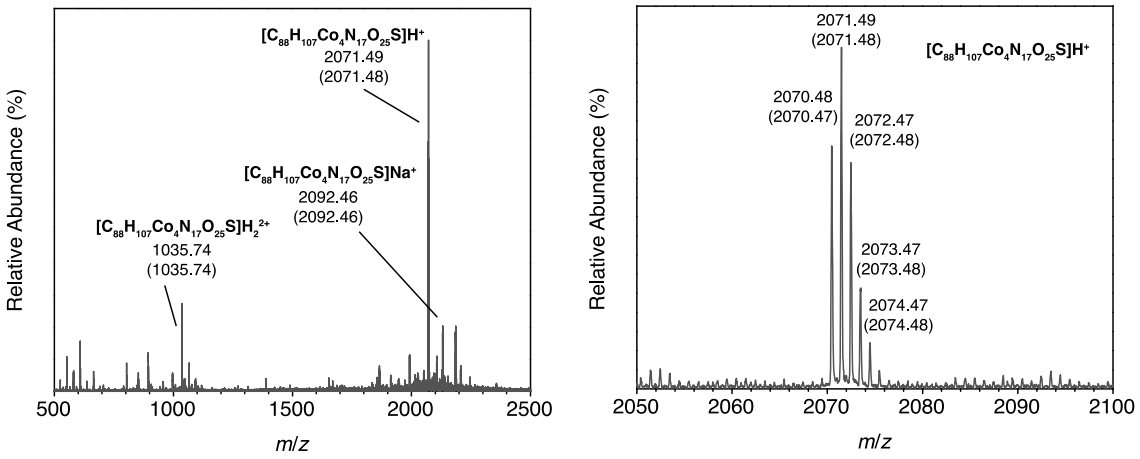


Figure S28. Full HMBC spectrum of **1-C-Nhe3Sar**.



1-D. 0.0108 g (0.0127 mmol) of **1** and 0.0214 g (0.0127 mmol) of **H_4D** were dissolved in 20 mL of methanol (~0.6 mM) and heated to 50º C for 16 h. Volatiles were removed on a rotary evaporator with a 25ºC water bath. The residue was rinsed three times with diethyl ether to remove remaining acetic acid byproduct. The residue was redissolved in 20 mL methanol, heated at 50ºC for 2 h, dried, and washed with diethyl ether three times. This process was repeated once more. The crude product was dissolved in 3 mL of 1:1 methanol: water and purified by HPLC on C4 column (5-95% gradient of pure acetonitrile:water over 30 min). The purest fractions were lyophilized to yield 0.0068 g (~23%).

Figure S29. HR-ESI MS spectrum of **1-D**.



NMR titration of 1-2B by DOAc.

To a 444 μL solution of **1-2B (**11.4 mM CD_3OD) in a standard NMR tube was added various amounts of neat d_3-acetic acid *via* micropipette. The tubes were capped and wrapped with Parafilm. Each mixture was equilibrated fully for at least 7 days at 25º C. Table S5 shows the concentration of reagents for each titration experiment.

Table S5.

Equiv DOAc	DOAc added (μL)	Final Volume (μL)	[**1-2B**]$_f$ (mM)	[DOAc]$_f$ (mM)
10	2.8	447	11.3	113.0
30	8.7	453	11.2	334.5
40	11.6	456	11.0	443.2
60	17.3	462	11.0	656.5
70	20.2	465	10.9	761.2
90	26.0	470	10.7	966.6
120	34.7	479	10.6	1265.5

Figure S30. ^{1}H NMR titration of **1-2B** with DOAc. Labels: **a** is **1-2B**, **b** is **1-B**, **c** is **1**, and **P** is **H_2B**.

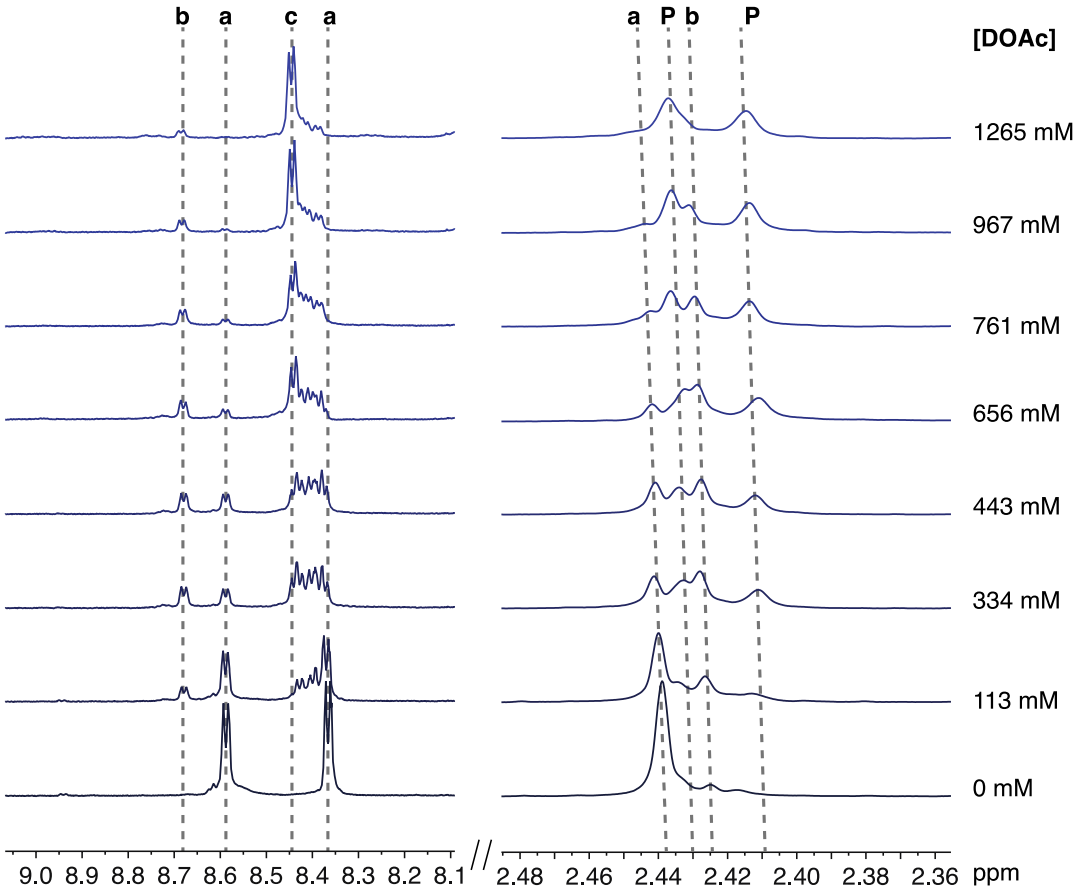


Figure S31. An example fitting of the tosyl CH_3 resonances to extract relative concentrations of species during the titration. The black line is the experimental NMR spectrum, blue is the fitted peaks, magenta is the sum of the fitted peaks, and red is the residual of the fit. Note that the free peptoid **H_2B** (**P**) has two tosyl CH_3 resonances due to the *cis* and *trans* amide isomers. Labels: **a** is **1-2B**, **b** is **1-B**, **c** is **1**, and **P** is **H_2B**.

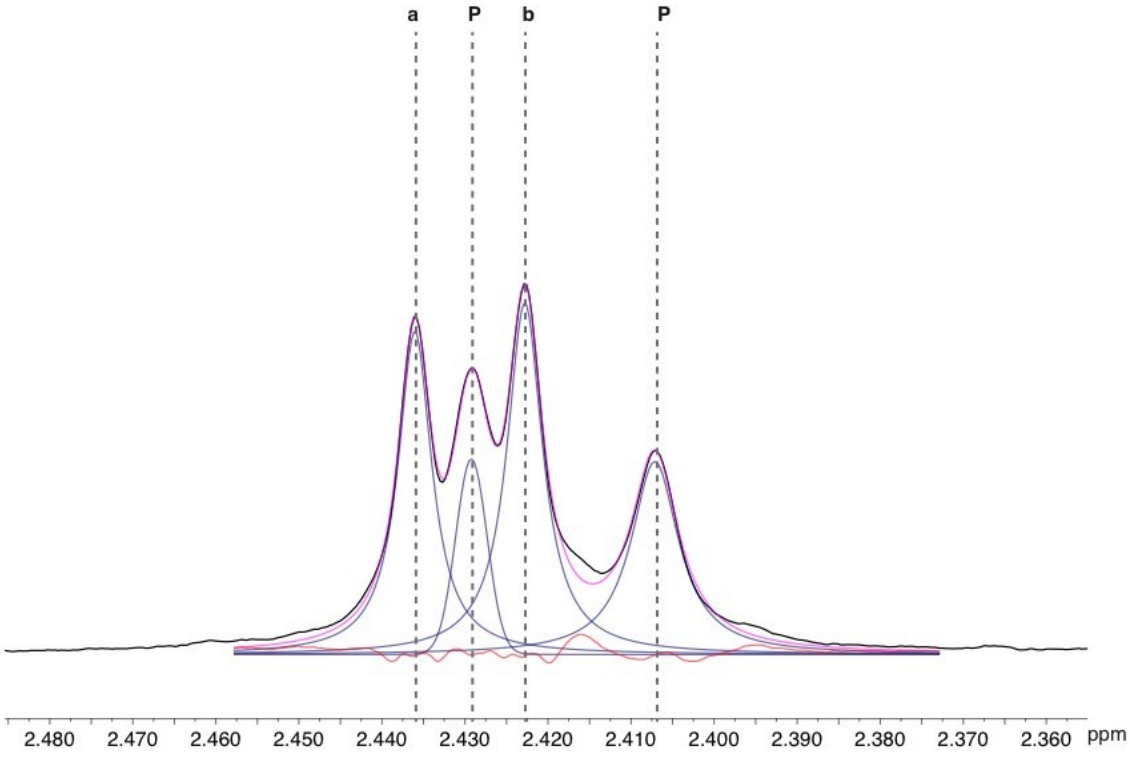
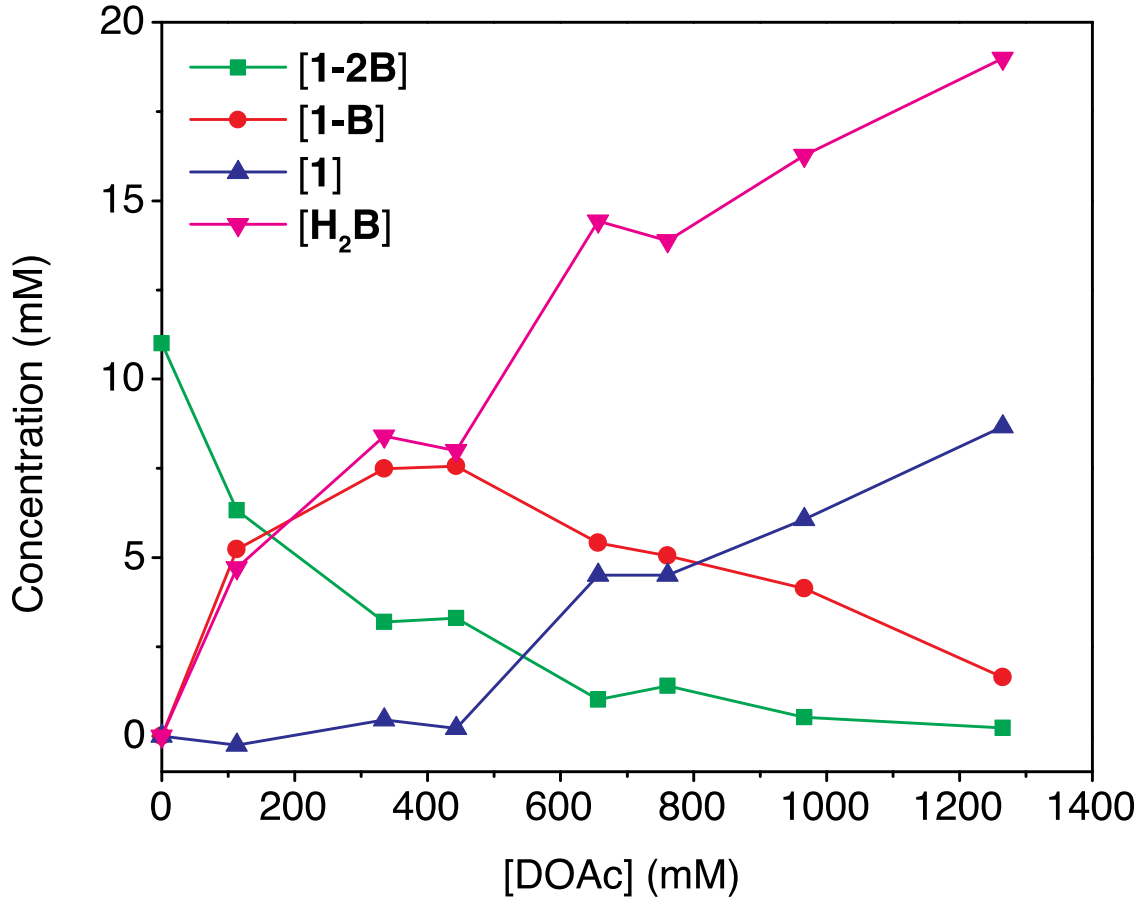


Figure S32. Concentration of species versus the amount of DOAc added. Because resonances belonging to **1** could not be integrated accurately, its concentration of **1** was determined indirectly using mass balance: [**1**] = [**1-2B**]$_0$ – [**1-2B**] – [**1-B**]



Determination of equilibrium constants. The stepwise equilibrium constants K_1 and K_2 were determined with equations S1 and S2 at each titration point:

$$K_1 = \frac{[1-B][DOAc]^2}{[1][H_2B]} \quad \text{(S1)}$$

$$K_2 = \frac{[1-2B][DOAc]^2}{[1-B][H_2B]} \quad \text{(S2)}$$

The total stability constant β is defined by equation S3:

$$\beta = K_1K_2 = \frac{[1-2B][DOAc]^4}{[1][H_2B]^2} \quad \text{(S3)}$$

The equilibrium constants derived at each value is then averaged to obtain the values reported in the main text.

Electrochemistry.
Cyclic voltammetry was performed using an AMETEK VersaSTAT 3 Potentiostat (Princeton Applied Research), wherein glassy carbon acts as the working electrode, a platinum-coated titanium rod acts as the counter electrode, and a silver wire acts as the pseudo-reference electrode, respectively. Samples were prepared as 1 mM solutions in methanol with tetra-*n*-butylammonium hexafluorophosphate (0.1 M) as the electrolyte at a scan rate of 100 mVs^{-1}, using the ferrocene/ferronium (Fc^{+}/Fc) redox couple as an internal standard.

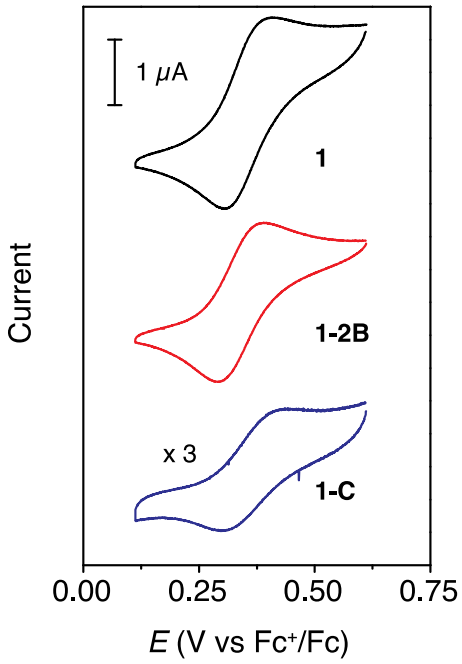


Figure S33. Cyclic voltammograms of **1, 1-2B,** and **1-C (**100 mV/s scan rate in methanol solvent with 0.1 M $[^{n}Bu_4N]PF_6$ supporting electrolyte). All analytes are at ~1 mM concentration except for **1-C**, which is less soluble in the presence of PF_6^{-}.

Data used in NMR structure determination.

Figure S34. Full ROESY spectrum of bidentate **1-2B**.

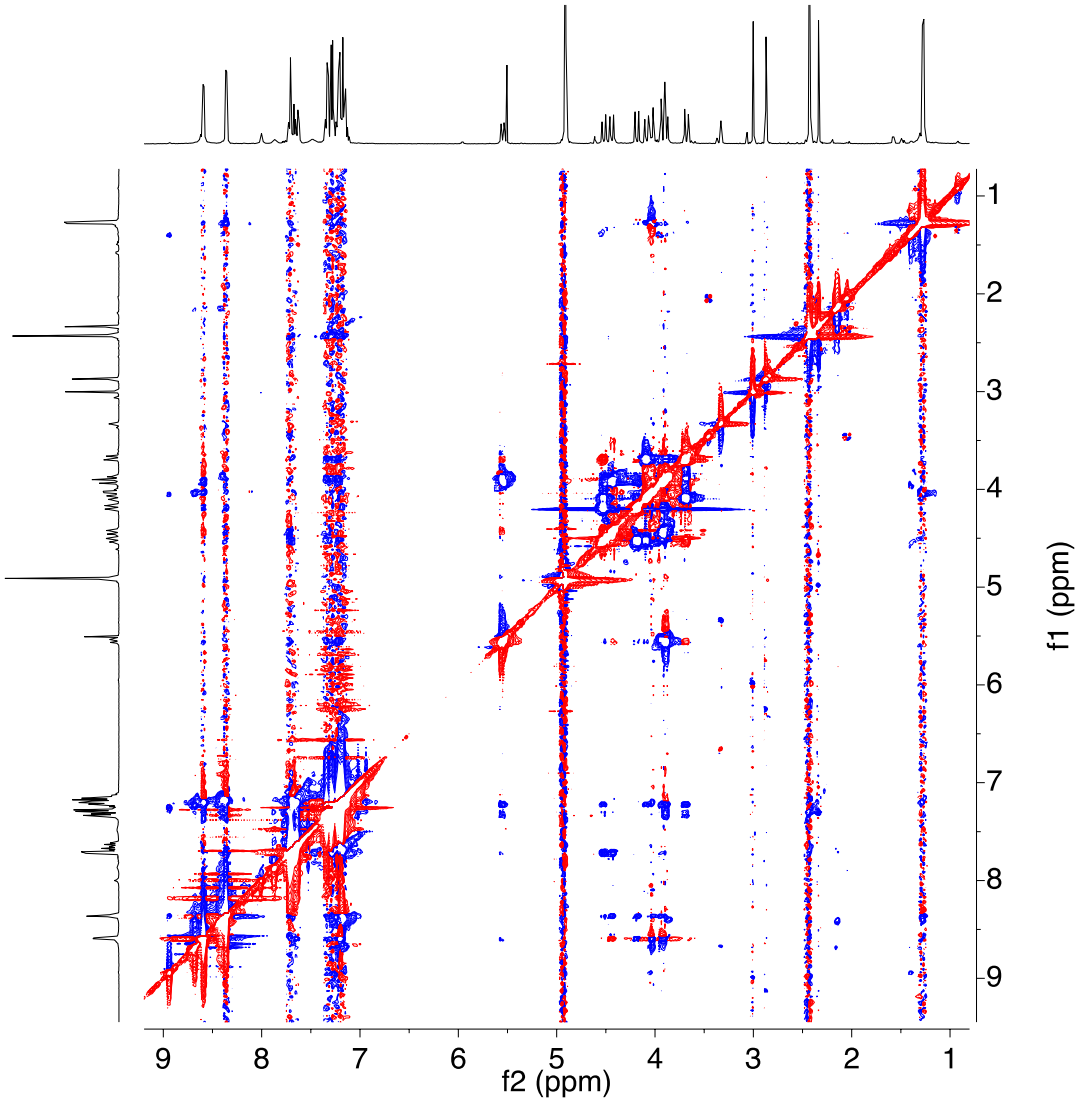


Figure S35. Enlarged ROESY spectrum of **1-2B** showing backbone methylene correlations. NOE crosspeaks below the diagonal are labeled, while crosspeaks are due to 2-bond correlations (COSY-type) of geminal methylene protons are unlabeled. The labels "bb" and "sc" refer to "backbone" and "side chain", respectively.

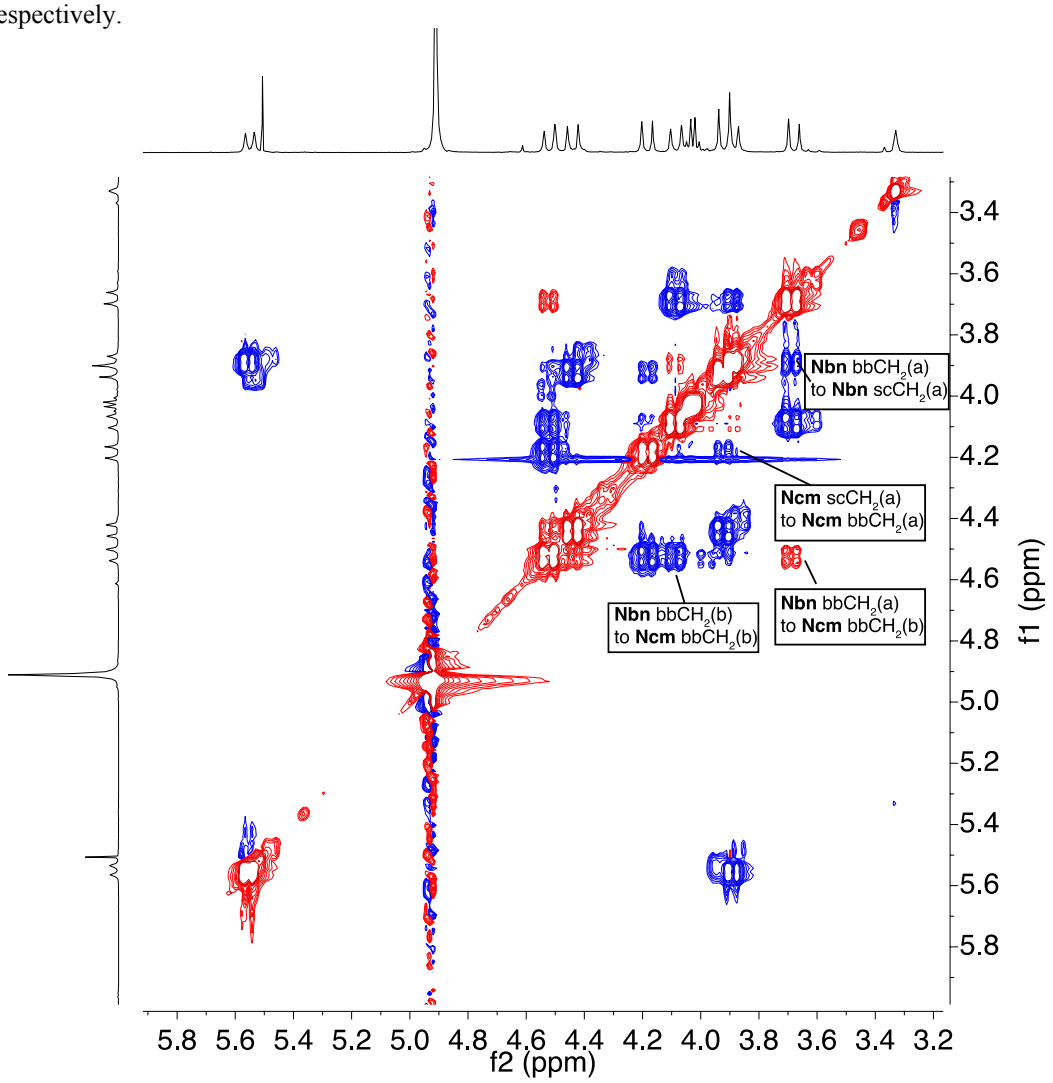


Figure S36. Full ROESY spectrum of bidentate **1-C**.

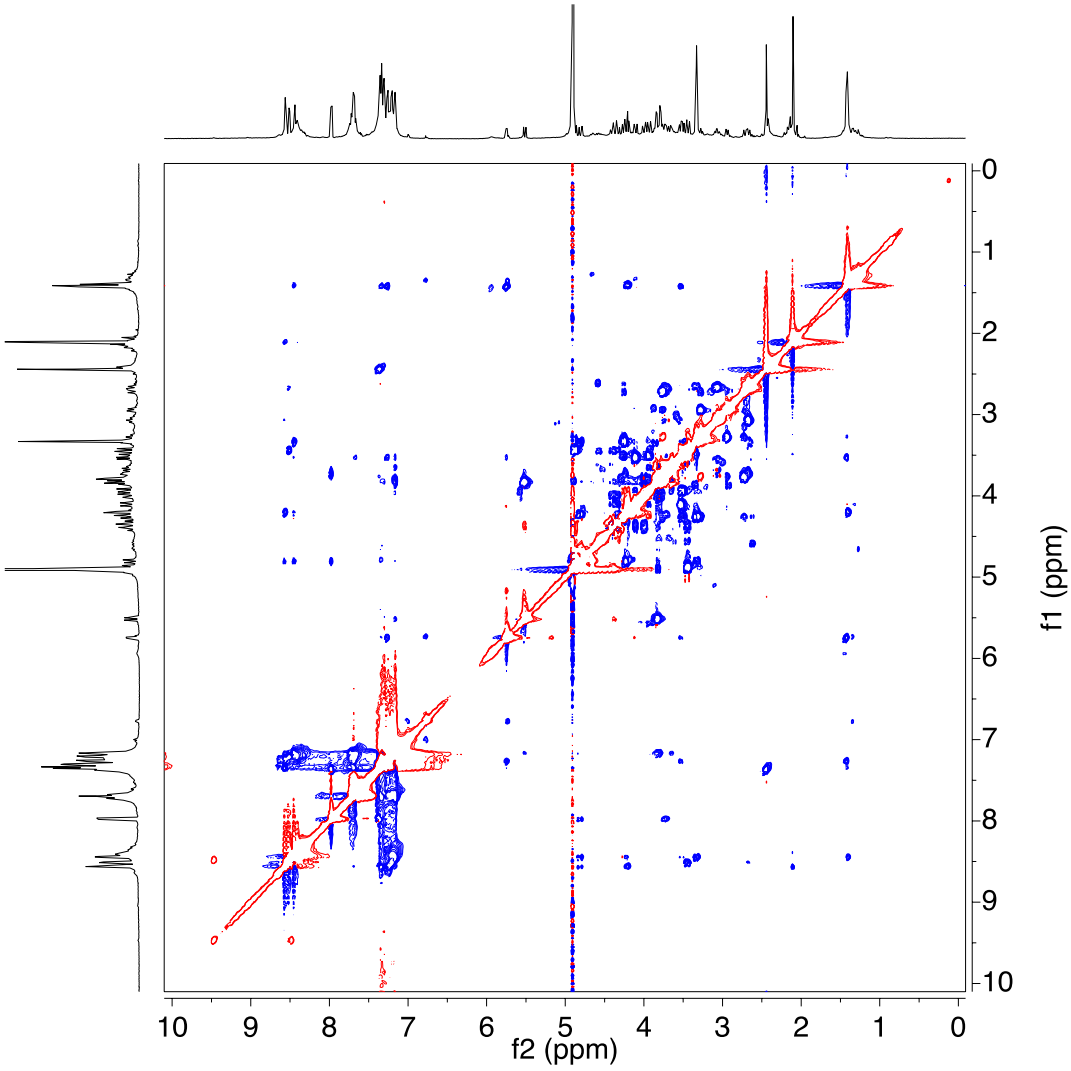


Figure S37. Enlarged ROESY spectrum of **1-C** showing backbone methylene correlations. NOE crosspeaks below the diagonal are labeled, while crosspeaks are due to 2-bond correlations (COSY-type) of geminal methylene protons are unlabeled. The labels "bb" and "sc" refer to "backbone" and "side chain", respectively.

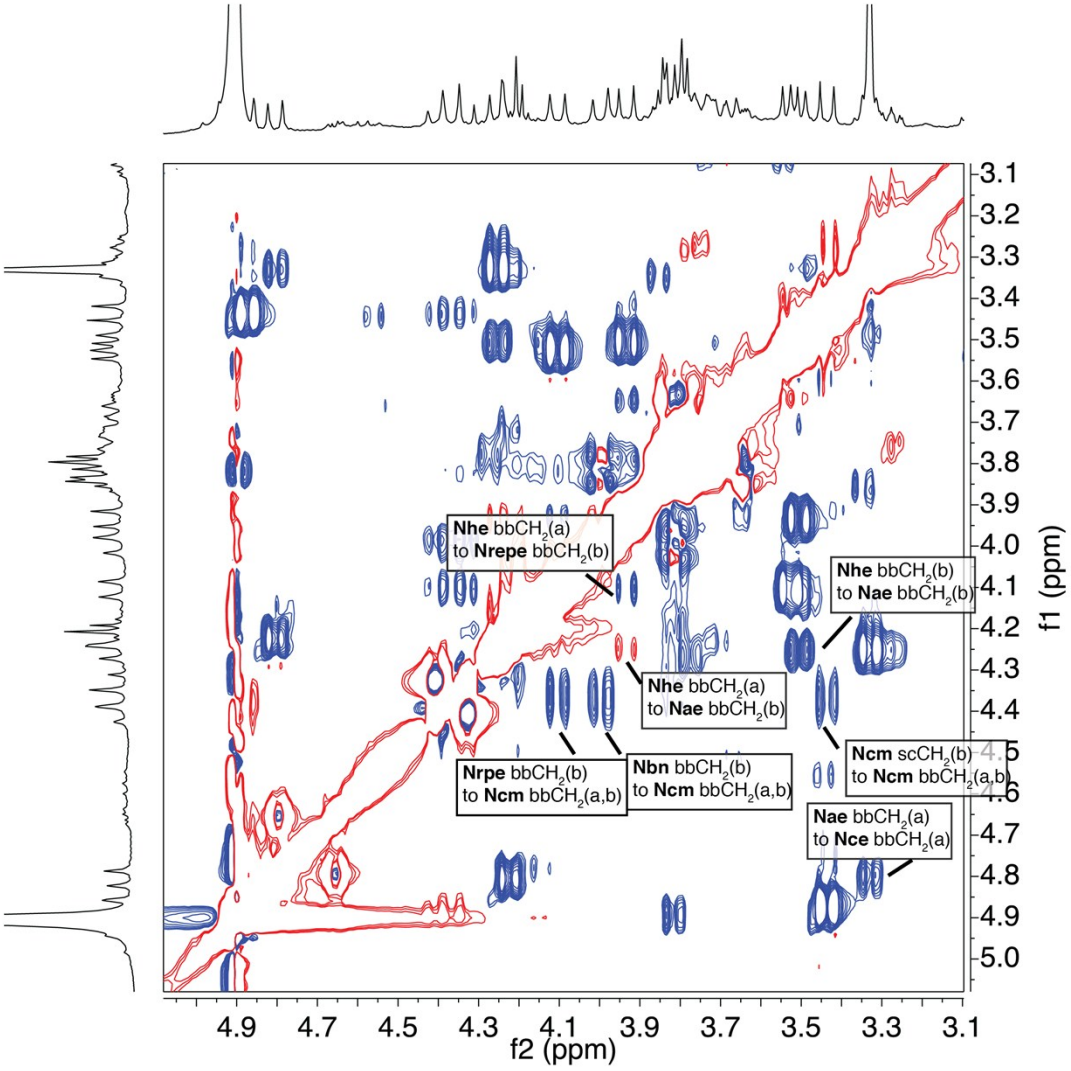


Figure S38. Enlarged ROESY spectrum of **1-C** showing aromatic correlations.

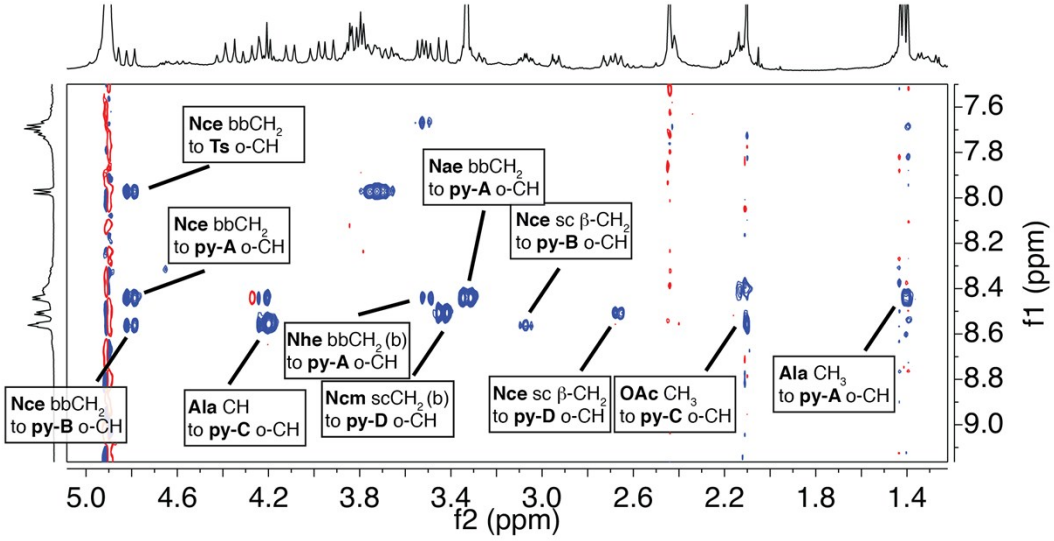


Figure S39. Coupling scheme for Nce1 and Nae2 side-chains of **1-C**.

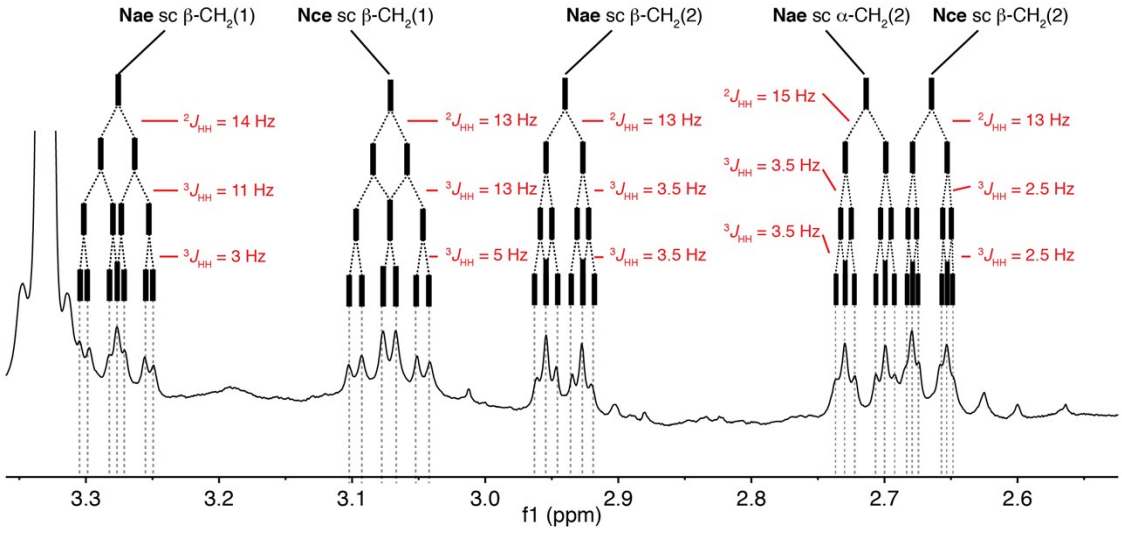


Figure S40. Full ROESY spectrum of **1-C-Nhe3Sar**.

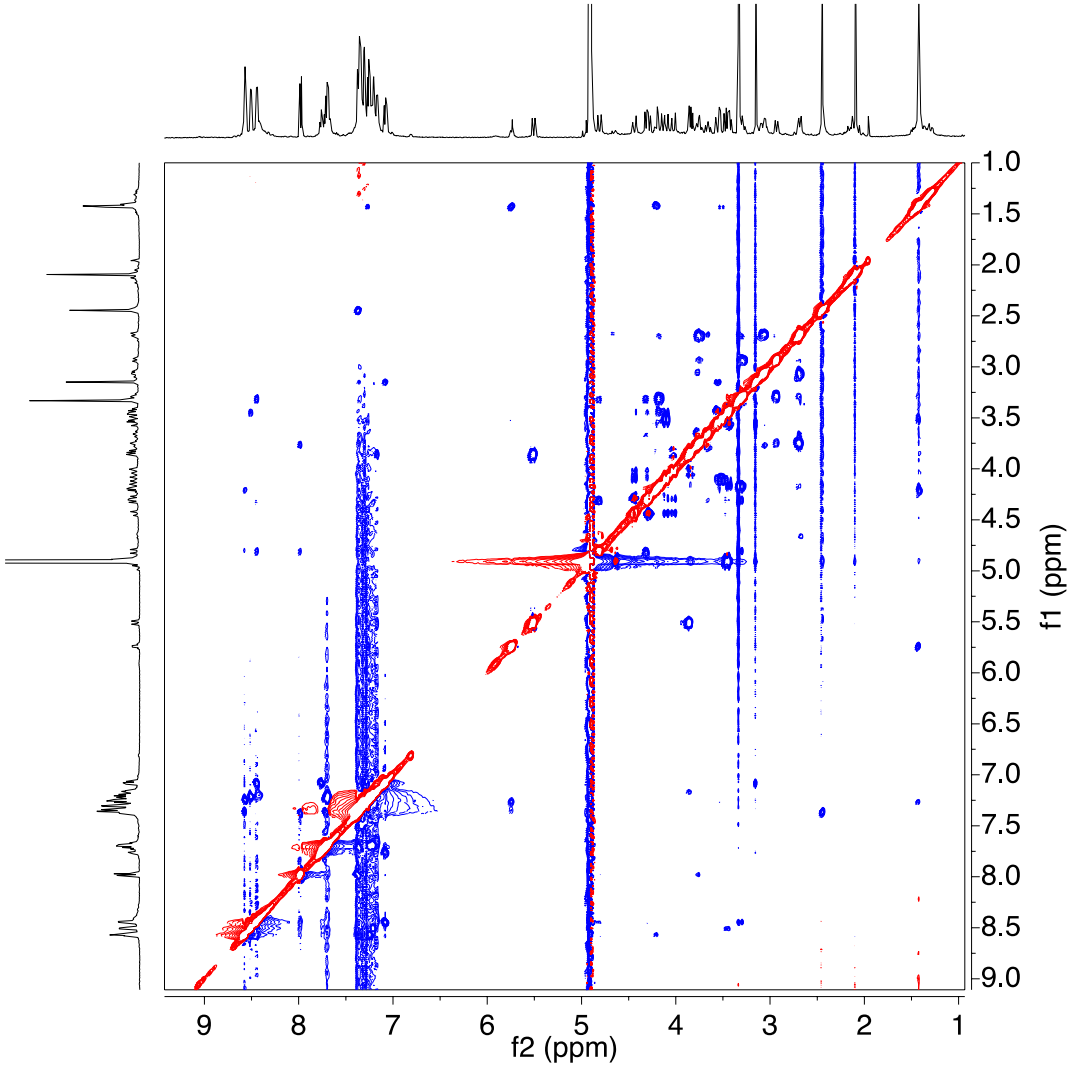


Figure S41. Enlarged ROESY spectrum of **1-C-Nhe3Sar** showing backbone methylene correlations. NOE crosspeaks below the diagonal are labeled, while crosspeaks are due to 2-bond correlations (COSY-type) of geminal methylene protons are unlabeled. The labels "bb" and "sc" refer to "backbone" and "side chain", respectively.

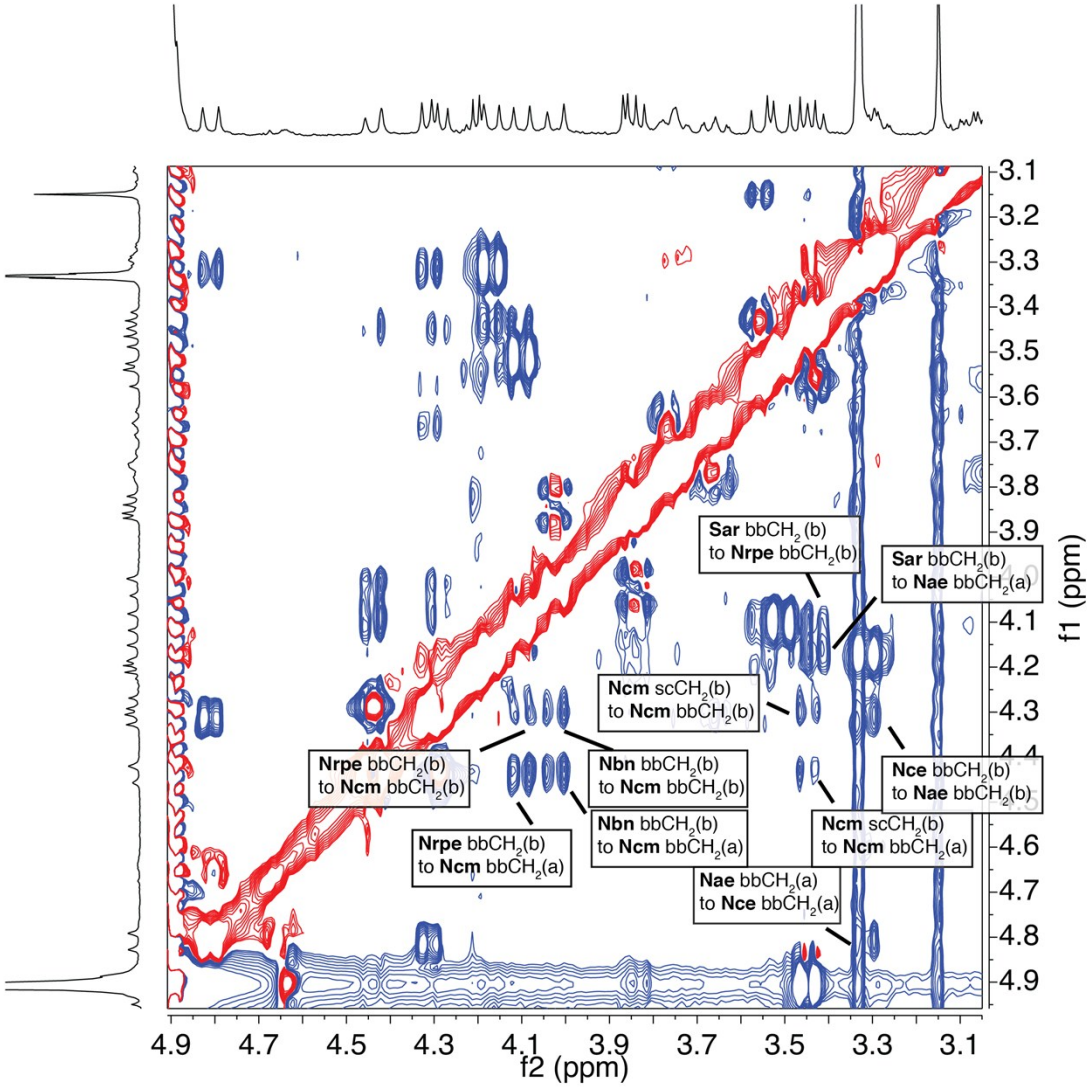


Table S6. NOE table for **1-2B**

ROESY crosspeak					
δ_i	δ_j	δ_i *assignment*	δ_j *assignment*	*Volume Integral* [a]	*Bin* [b]
5.55	8.59	Nbn-sc(CH_2)	*o*-pyridine A	0.01	Weak
5.55	7.72	Nbn-sc(CH_2)	Tosyl-2	0.01	Weak
5.55	7.30	Nbn-sc(CH_2)	Tosyl-1	0.01	Weak
3.92	7.72	Ncm-sc	Tosyl-2	0.01	Weak
1.27	7.19	Ala-CH_3	*m*-pyridine B	0.02	Weak
4.03	7.20	Ala-CH	*m*-pyridine A	0.02	Weak
3.88	7.30	Nbn-sc(CH_2)	Tosyl-1	0.02	Weak
3.69	5.55	Nbn-bb	Nbn-sc	0.02	Weak
4.18	8.59	Ncm-bb	*o*-pyridine A	0.02	Weak
4.18	8.37	Ncm-bb	*o*-pyridine B	0.02	Weak
4.52	7.22	Ncm-bb	Nbn-sc(Ar)	0.02	Weak
4.44	8.59	Ncm-bb	*o*-pyridine A	0.02	Weak
4.44	8.37	Ncm-bb	*o*-pyridine B	0.02	Weak
4.52	7.72	Ncm-bb	Tosyl-2	0.06	Weak
4.44	7.72	Ncm-sc	Tosyl-2	0.07	Medium
1.27	8.37	Ala-CH_3	*o*-pyridine B	0.13	Medium
4.03	8.59	Ala-CH	*o*-pyridine A	0.16	Medium
3.92	8.59	Ncm-sc	*o*-pyridine A	0.21	Medium
4.52	3.69	Ncm-bb	Nbn-bb	0.22	Medium
4.18	3.92	Ncm-bb	Ncm-sc	0.26	Medium
3.88	3.69	Nbn-sc(CH_2)	Nbn-bb	0.41	Strong
4.52	4.08	Ncm-bb	Nbn-bb	0.84	Strong

[a] Volume integrals (V_{ij}) are calibrated against the (Tosyl-1,Tosyl-2) crosspeak, defined as 1.00, with a H–H distance of 2.5 Å.

[b] Bins are defined according to upper limit distance, *r*, obtained from the NOE relationship: $r = 2.5\text{Å} \times V_{ij}^{-1/6}$

strong = $r < 3.0$ Å, *medium* = 3.0 Å < $r < 4.0$ Å, *weak* = 4.0 Å < $r < 5.5$ Å

Table S7. NOE table for **1-C**

ROESY crosspeak					
δ_i	δ_j	δ_i *assignment*	δ_j *assignment*	*Volume Integral* [a]	*Bin* [b]
3.07	8.57	Nce-sc β	*o*-pyridine B	0.02	Weak
2.67	8.51	Nce-sc β	*o*-pyridine D	0.03	Weak
3.51	8.44	Nhe-bb	*o*-pyridine A	0.03	Weak
3.53	5.75	Nrpe-bb	Nrpe-sc(CH)	0.04	Weak
1.42	3.28	Nrpe-sc(CH_3)	Nae-sc β	0.03	Weak
4.81	7.97	Nce-bb	Tosyl-1	0.06	Weak
4.81	8.57	Nce-bb	*o*-pyridine B	0.06	Weak
3.93	4.10	Nhe-bb	Nrpe-bb	0.07	Medium
1.40	8.44	Ala-CH_3	*o*-pyridine A	0.08	Medium
4.81	8.44	Nce-bb	*o*-pyridine A	0.10	Medium
1.42	3.53	Nrpe-sc(CH_3)	Nrpe-bb	0.12	Medium
3.72	7.97	Nce-sc α	Tosyl-1	0.16	Medium
3.44	4.37	Ncm-sc	Ncm-bb	0.17	Medium
4.20	8.56	Ala-CH	*o*-pyridine C	0.18	Medium
3.44	8.51	Ncm-sc	*o*-pyridine D	0.19	Medium
3.33	8.44	Nae-bb	*o*-pyridine A	0.21	Medium
3.33	4.81	Nae-bb	Nce-bb	0.24	Medium
4.10	4.37	Nrpe-bb	Ncm-bb	0.28	Medium
4.00	4.37	Nbn-bb	Ncm-bb	0.32	Medium
3.50	4.25	Nhe-bb	Nae-bb	0.46	Strong

[a] Volume integrals (V_{ij}) are calibrated against the (Tosyl-1,Tosyl-2) crosspeak, defined as 1.00, with a H–H distance of 2.5 Å.

[b] Bins are defined according to upper limit distance, r, obtained from the NOE relationship: $r = 2.5\text{Å} \times V_{ij}^{-1/6}$

strong = r < 3.0 Å, *medium* = 3.0 Å < r < 4.0 Å, *weak* = 4.0 Å < r < 5.5 Å

Replica-Exchange Molecular Dynamics (REMD) Simulation Setup.

Initial coordinates for replica-exchange molecular dynamic simulations (REMD) were derived from the $Co_4O_4(OAc)_4(py)_4$ cubane X-ray crystal structure previously reported.[3] Carboxylate atoms (C, O, O^-) interacting with the cluster were placed according to the acetate locations in the cubane crystal structure. Residues Ala-Nbn-Gly(Tos) were modeled using PyMOL. Topology information and .psf generation were performed using autopsf in VMD.[4] The coordinates for the carboxylate (C, O, O^-) and pyridines (N and C4) were frozen during the simulations, since the Co–$O_{carboxylate}$ and Co–$N_{pyridine}$ distances do not significantly change with different carboxylate or pyridyl ligands.[5] The [Co_4O_4] moiety was excluded during the REMD calculation. NOE constraints derived from NMR data (Tables S6 and S7) were applied using the collective variable (colvars) distanceInv option in NAMD.[6] REMD simulations were run in NAMD with parameters similar to MFTOID[7] and with generalized Born implicit solvent (GBIS) in conditions optimized for methanol (solvent dielectric = 33). For **1-C**, charges was addressed by adding an ion concentration value of 0.2 M, and reducing the negative charges on the carboxylate O atoms to -0.51 (the same charge as the amide carbonyl O atoms). Simulations were run on 32 replicas with a temperature range of 300-600K for 20 ns (a total of 640 ns of simulation time). Replicas were sorted and 20 lowest energy structures were selected for statistical analysis. Full models of the peptoid-cubane complex were constructed by first aligning the carboxylate atoms of the REMD peptoid structures with the acetate ligands from crystal structure of $Co_4O_4(OAc)_4(py)_4$, and subsequently removing the acetate and pyridine ligands.

Table S8. Average RMSD of the 20 lowest energy structures from the average structure **1-2B**

RMSD (all atoms) / Å	RMSD (backbone) / Å
1.022	0.112

Table S9. 1-2B backbone dihedral angles for the lowest energy structure

Residues	ψ / °	ϕ / °	ω / °
1-2 (Chain A)	137.0	76.9	-9.9
2-3 (Chain A)	-162.4	N/A	174.4
1-2 (Chain B)	157.3	88.6	29.9
2-3 (Chain B)	-142.2	N/A	162.2

Figure S42. Important H–H distances (dashed lines) from the REMD model for **1-2B** that are also consistent with experimental NOE correlations. Since the molecule has C_2 symmetry by NMR spectroscopy, only the asymmetric set of NOE distances are shown.

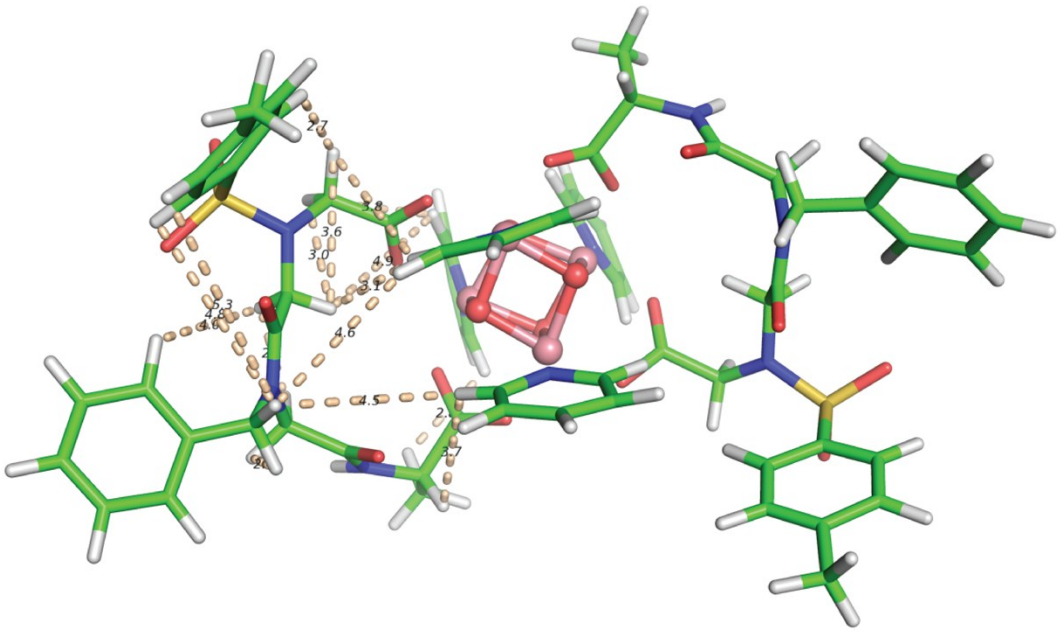


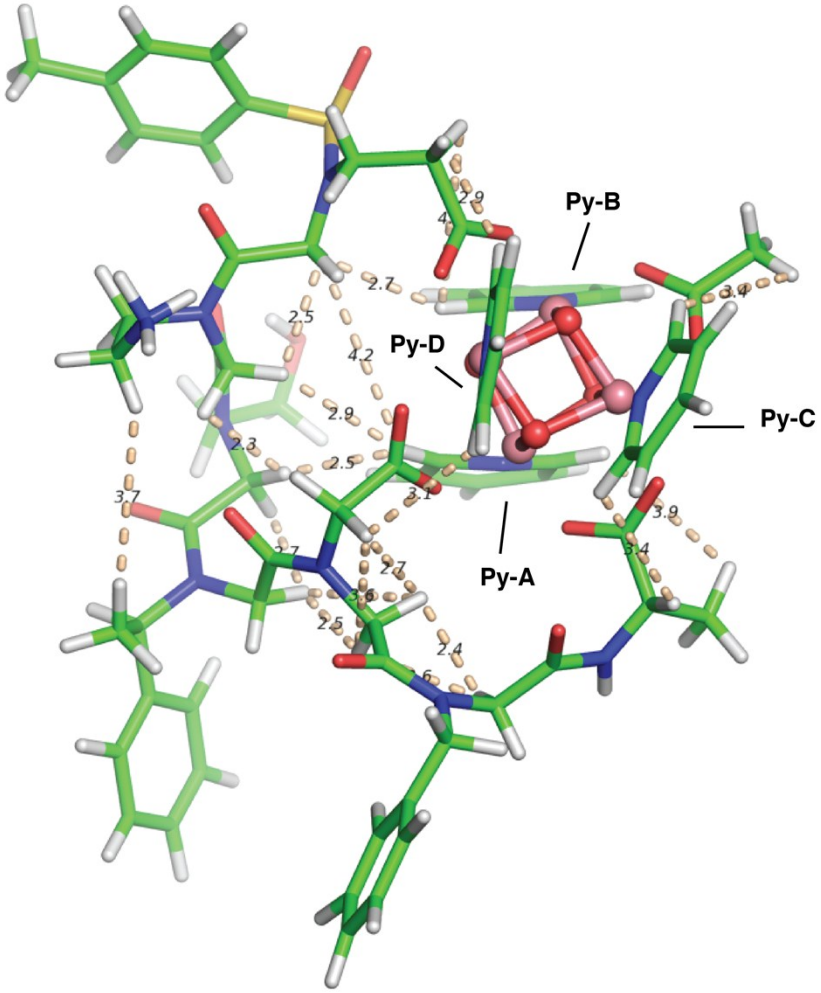
Table S10. Average RMSD of the 20 lowest energy structures from the average structure **1-C**

RMSD (all atoms) / Å	RMSD (backbone) / Å
1.539	0.0822

Table S11. 1-C backbone dihedral angles for the lowest energy structure

Residues	ψ / °	ϕ / °	ω / °
1-2	152.8	-90.4	14.6
2-3	-162.8	97.4	-10.1
3-4	-176.6	78.0	-2.8
4-5	-146.3	-92.8	-36.3
5-6	174.0	89.7	15.3
6-7	-173.9	N/A	171.8

Figure S43. Important H–H distances from REMD model for **1-C** (dashed lines) that are consistent with experimental NOE correlations.



Analysis of binding by peptoid mutants.
500 μL of 1.0 mM peptoid in methanol and 500 μL of 1.0 mM **1** in methanol were combined in a dram vial. The solution was capped and heated at 50º C for 20 h. An ~100 μL aliquot of the solution was analyzed by LCMS (gradient: 5-95% acetonitrile/water with 10 mM NH_4OAc/HOAc buffer, pH ~ 5.2).

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