Electronic Supplementary Material (ESI) for RSC Advances.

Ctr-1 Mets7 motif inspiring new peptide ligands for Cu(I)-catalyzed asymmetric Henry reaction.

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SUPPORTING INFORMATION

Computational Methods

Mets7 and S1 peptides were built with the *tLEaP* module of AMBER 14,[1] and REMD simulations were performed by starting from an extended conformation (φ = ψ = ω = 180°). The parameters for scaffold X were obtained as described in previous articles for other non-natural aminoacids.[2] Simulations were conducted by using the ff99SBildn forcefield,[3] coupled with the GB-Neck2 (igb = 8) implicit solvation model for water and the *mbondi3* sets of radii.[4] The number of replicas (20) and the temperature range (from 260.0 to 673.9 K) were selected through the T-REMD server.[5] Each simulation was run for 100 ns, for a total of 2 μs. The trajectories at 302.8 K of the REMD simulations were extracted and analyzed over steps of 25 ns. Cluster analyses were conducted with *cpptraj*, sampling one every two frames by using the average-linkage algorithm and requesting five clusters; the pairwise mass-weighted RMSD on backbone heavy atoms was used as a metric. We considered a simulation converged when the population of the principal cluster differed less than 5% from that obtained in the previous 25 ns section of trajectory. Both simulations were already converged between 50 and 75 ns, so the discussion is based on the analysis of the subsequent 75-100 ns section. Clustering was also repeated by requesting 10 clusters, but no significant variation was observed in the quality and composition of principal clusters.

An H-bond analysis was also performed with *cpptraj*, setting a donor-acceptor distance threshold of 4.0 Å and an angle cutoff of 120°.

Table TS1. Values of ψ and φ Dihedrals (deg.) for each Representative Geometry Obtained from the Cluster Analysis of the 75-100 ns section of the 302.8 K REMD trajectory for Mets7 and S1

Mets7	**pop%**	**ψ1**	**φ1**	**ψ2**	**φ2**	**ψ3**	**φ3**	**ψ4**	**φ4**	**ψ5**	**φ5**	**ψ6**	**φ6**	**ψ7**	**φ7**
#1	131.5	-54.4	-37.4	-65.1	-11.6	-95.9	-17.2	-131.2	-2.6	-119.4	23.5	-103.6	9.1	-122.1	131.5
#2	110.9	-93.8	-21.4	-78.8	54.7	-102.8	147.3	-171.9	128.1	75.5	160.2	-112.7	144.3	-154.8	110.9
#3	-25.6	-112.0	5.6	-77.3	-149.9	-72.8	-20.2	-86.6	161.5	-82.5	158.5	-62.5	136.3	-128.4	-25.6
#4	42.6	-65.8	-51.0	-48.4	-40.4	-84.1	-25.5	-95.9	-22.5	98.3	50.4	-136.9	133.8	50.9	42.6
#5	-5.5	-89.8	-3.3	74.0	-9.3	-59.6	118.8	-71.9	131.9	91.3	-9.7	-121.6	27.3	-71.3	-5.5
S1	**pop%**	**ψ1**	**φ1**	**ψ2**	**φ2**	**ψ3**	**φ3**	**ψ4**	**φ4***	**ψ5***	**φ5***	**ψ6**	**φ6**	**ψ7**	**φ7**
#1	168.7	-93.6	165.3	79.7	-145.9	-58.8	148.4	-106.3	-179.0	-66.4	135.3	-81.1	177.2	-56.9	168.7
#2	169.3	-92.3	163.6	86.1	-154.5	-57.1	157.3	-105.2	176.9	-61.2	151.0	-91.8	171.1	-63.4	169.3

#3	156.0	-80.4	164.9	63.3	-144.2	-86.9	155.9	-115.6	175.0	-73.2	-40.1	-60.9	-166.8	-66.9	156.0
#4	-175.7	-115.0	-175.2	74.3	-173.2	-116.5	160.0	-111.7	173.9	-85.5	-44.7	-65.2	165.0	-52.7	-175.7
#5	169.3	-67.2	170.9	133.5	-168.0	-68.6	152.1	117.3	177.4	-86.8	166.7	-65.0	-150.3	-80.1	169.3

Table TS2. Results from H-Bond Analysis of the 75-100 ns Section of the 302.8 K REMD Trajectory of Mets7 and S1

Mets7				
#Acceptor[a]	**Donor[a]**	**Occupancy %**	**Avg. Dist. (Å)**	**Avg. Ang. (deg.)**
MET_2@O	MET_5@N	33.43	3.3	151.1
ACE_1@O	GLY_4@N	30.35	3.3	152.3
THR_3@O	LYS_6@N	24.6	3.4	150.9
GLY_4@O	GLY_7@N	17.8	3.4	150.4
MET_2@O	LYS_6@N	16.82	3.1	153.6
MET_5@O	MET_8@N	16.53	3.3	153.2
THR_3@O	GLY_7@N	10.78	3.2	145.8
THR_3@O	MET_5@N	10.12	3.2	134.8
LYS_6@O	SER_9@N	9.4	3.5	150.5
MET_8@O	SER_9@OG	8.42	3.0	149.3
LYS_6@O	MET_8@N	7.92	3.1	135.5
GLY_4@O	LYS_6@N	7.21	3.2	135.3
ACE_1@O	THR_3@N	6.55	3.3	133.9
ACE_1@O	MET_5@N	6.36	3.4	146.4
MET_5@O	GLY_7@N	6.31	3.2	135.4
GLY_7@O	NHE_10@N	6.18	3.5	154.9
GLY_7@O	SER_9@N	5.96	3.3	134.5
MET_2@O	GLY_4@N	5.35	3.3	134.0
MET_5@O	SER_9@N	5.31	3.2	149.0
S1				
#Acceptor[a]	**Donor[a]**	**Occupancy %**	**AvgDist**	**AvgAng**
THR_3@OG1	GLY_4@N	75.8	2.9	128.7
X_6@O	X_6@N2	33.23	3.6	146.7

[a] Numbering includes the N-terminal acetyl cap (ACE, residue 1) and the C-terminal NH_2 cap (NHE, residue 10 or residue 9 for Mets7 and S1 peptides, respectively)

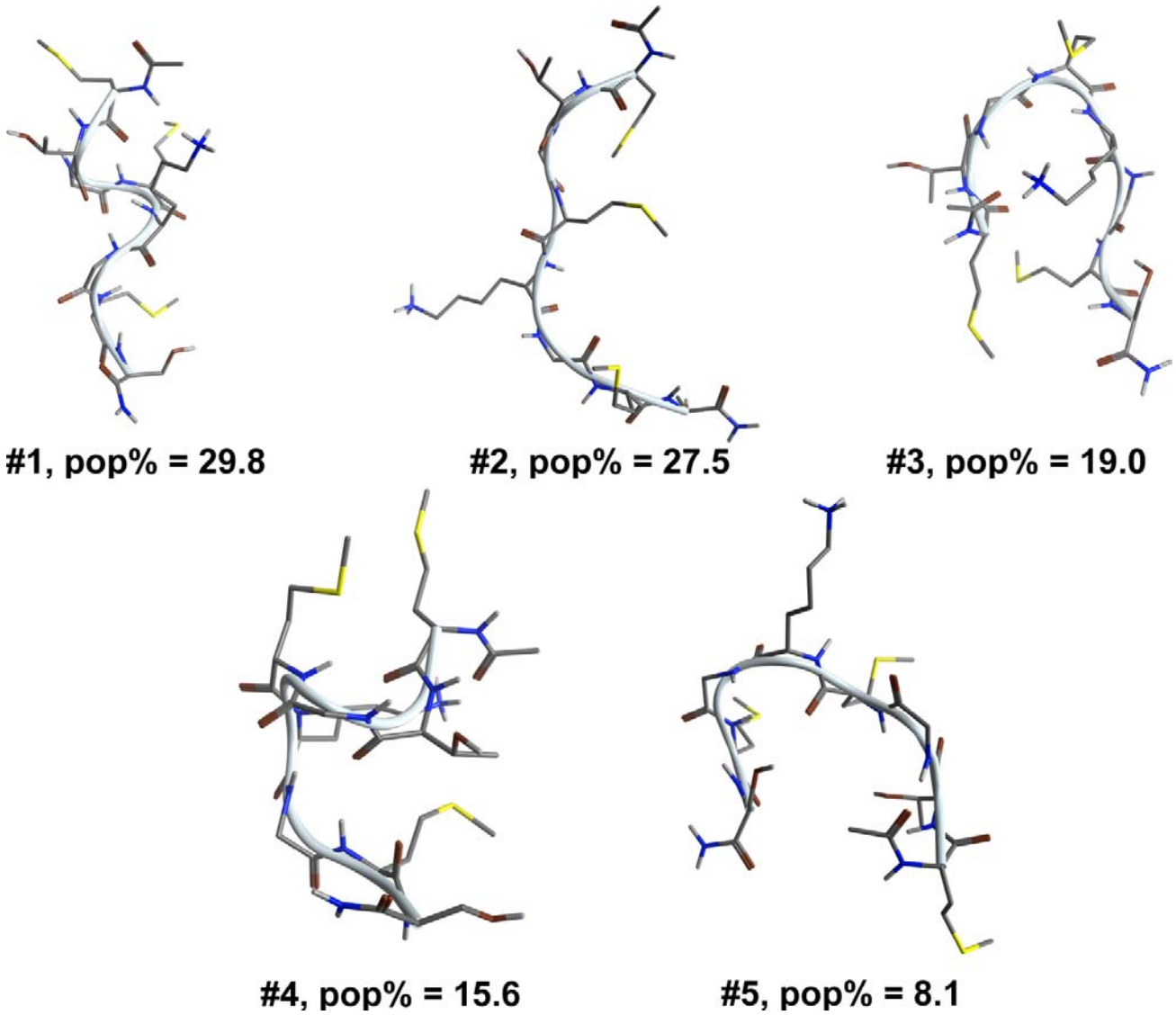


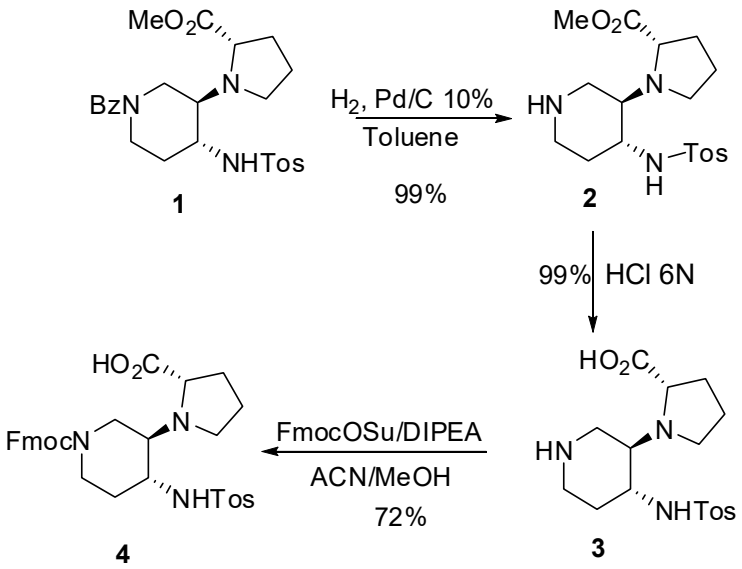
Figure FS1. Geometries of the most representative structures obtained from the cluster analysis of the 75-100 ns section of the 302.8 K REMD trajectory of Mets7

Experimental Materials and Methods

Solvents, reagents were purchased from commercial sources. All peptides were purified using RP-HPLC and a C-18 column (10 μm, 250 22 mm). ESI mass spectra were recorded on a LCQ Advantage spectrometer.

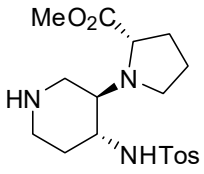
Synthesis of Fmoc-protected scaffold 4

The Fmoc-protected compound **4** was synthesized in solution starting from the known compound **1**.[6] (Scheme S1). Hydrogenolysis of **1** was performed in toluene affording free amino compound **2** (99%). The ester function was hydrolyzed in acidic conditions yielding compound **3** (99%). Finally, the Fmoc group was introduced using Fmoc-OSu, in the presence of DIPEA and MeOH/ACN affording **4** (72%).



Scheme S1. Synthesis of Fmoc scaffold 4

Methyl 1-[(3R,4R)-4-(4-methylphenylsulfonamido)piperidin-3-yl]-pyrrolidine-2-(S)-carboxylate (2)

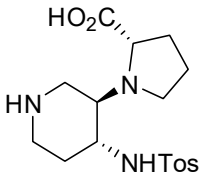


2

Compound **1** (0.1 g; 0.212 mmol) was dissolved in toluene (20 ml) and Pd/C (10% 0.1 g) was added. The reaction was kept overnight under stirring in hydrogen atmosphere (TLC: CH_2Cl_2/MeOH 20:1). The catalyst was filtered over a celite pad, and the solvent removed under vacuum, affording compound **2** as a a white powder (80 mg, 99%).

$[\alpha]^{25}_D$: -82,14° (*c* 0.28 $CHCl_3$); mp = 122-124°C; IR ν max (KBr): 3436, 3212, 1730cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 1.35-1.75 (m, 3H), 1.76-2.25 (m, 4H), 2.42 (s, 3H), 2.30-2.75 (m, 5H), 2.40 (s, 3H), 3.40-3.52 (m, 1H), 3.76 (s, 3H), 6.70 (bs, 1H, exch), 7.27 (d, *J* 2.5, 2H), 7.78 (d, *J* 2.5, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ ppm: 21.7, 24.6, 30.0, 35.3, 44.4, 44.9, 45.1, 52.5, 54.2, 59.9, 62.3, 127.5, 129.6 , 137.7, 143.0, 176.1; $C_{18}H_{27}N_3O_4S$: 381.17 ESI-MS: m/z: 382.2 $[M+H]^+$

1-[(3R,4R)-4-(4-Methylphenylsulfonamido)piperidin-3-yl]-pyrrolidine-2-(S)-carboxylic Acid (3)

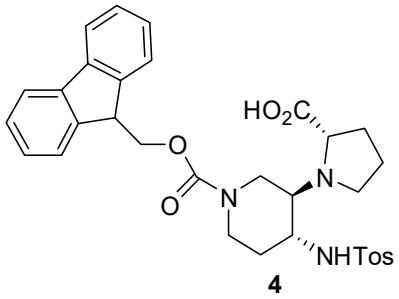


3

Operating in a sealed tube, compound **2** (0.1 g; 0.262 mmol) was dissolved in 6M HCl (10 mL) and heated at 110°C under stirring. After 4 h, the solvent was removed. The crude precipitated was taken up with acetone and a white solid was filtered (95 mg, 99 %).

$[\alpha]^{25}_D$: -2,8°(*c* 1 H_2O); m.p: 170-172 °C; IR ν_{max} (KBr): 3412, 1731 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ ppm: 1.56-1.70 (m, 2H), 2.06-2.46 (m, 4H), 2.39 (s, 3H), 2.93-3.40 (m, 4H), 3.71-3.87 (m, 4H), 4.36-4.44 (m,1H), 7.45 (d, *J* 7.8, 2H), 7.80 (d, *J* 8.3, 2H) ^{13}C NMR (125 MHz, D_2O) δ ppm: 21.1, 24.1, 27.4, 28.8, 41.0), 43.1), 50.0, 50.3, 60.3, 67.4, 127.2, 130.9, 135.6, 146.4, 172.0 $C_{17}H_{25}N_3O_4S$: 367.46 ESI-MS: m/z: 368.16$[M+H]^+$

1-[(3R,4R)-1-(((9H-Fluoren-9-yl)methoxy)carbonyl)-4-(4-methylphenylsulfonamido)piperidin-3-yl]-pyrrolidine-2-(S)-carboxylic Acid (4)



4

Compound **3** (0.12 g, 0.3 mmol) was dissolved in ACN/MeOH (4:1, 10 mL). Fmoc-OSu (0.12 mg, 0.33 mmol) and DIPEA (114 µl, 0.6 mmol) were added to the solution (pH<8). The reaction was left under stirring for 3h, (TLC: DCM : AcOEt, 1:1). The solvent was removed under vacuum. The crude was resuspended in DCM (30 mL) and washed with H_2O (3 x 30 mL). The organic layer was anhydrified over Na_2SO_4 and the solvent removed. The crude was precipitated with AcOEt/Hexane affording compound **4** (0.125 g, 70%) as a white solid.

$[\alpha]^{25}_D$: 29.7°(*c* 1 MeOH); m.p.: 122-127 °C; IR ν_{max}(KBr): 3247, 1740 cm^{-1} ^1H NMR (CD_3OD, 200 MHz) δ 1.56-1.67 (m, 2H), 2.06-2.14 (m, 4H), 2.39 (s,3H), 2.66-2.74 (m, 4H), 3.19-3.29 (m, 2H), 3.67-3.71 (m, 2H), 4.19-4.22 (m, 1H), 4.39-4.80 (m, 3H), 7.20−7.40 (m, 6H), 7.54-7.57 (m, 2H), 7.65-7.80 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.3, 24.4, 25.1, 29.7, 31.1, 41.2, 41.6, 52.1, 54.6, 60.8, 66.3, 67.1, 119.8, 124.5, 127.1, 127.2, 127.7, 129.7, 137.5, 141.5, 144.0, 155.2, 174.7 $C_{32}H_{35}N_3O_6S$: 589.7 ESI-MS: m/z: 590.8 $[M+H]^+$

Synthesis of Peptides Mets7, A, B, B1, C, S1

Peptides **Mets7, A, B, B1, C** and **AlaScan**[7] were synthesized on Rink-amide resin (0.72 loading) using standard conditions[8] (AA/HOBT/HBTU/DIPEA, 5:5:5:10); 1 h coupling and then 20% piperidine in DMF for Fmoc deprotection).

Regarding peptide **S1**, the coupling of **4** (1.5 eq) was performed on the peptide growing chain linked to rink-amide resin using HOBT and HBTU (1.5 eq) and DIPEA (3 eq), and standing the mixture under shaking overnight.

Compounds **Mets7, A, B, B1, C, S1** and **AlaScan** were finally acetylated on resin using Ac_2O (10 eq) and DIPEA (10 eq). The cleavage was then performed using reagent K[14] (trifluoroacetic acid/phenol/water/thioanisole/1,2-ethanedithiol; 82.5:5:5:5:2.5) for 180 min. After the cleavage, the peptides were precipitated and washed using ice-cold anhydrous ethyl ether. The peptides was purified by RP-HPLC using a gradient elution of 95–30% solvent A (solvent A: water/acetonitrile/trifluoroacetic acid 95 : 5 : 0.1; solvent B: water/acetonitrile/trifluoroacetic acid 5 : 95 : 0.1) over 20 min at a flow rate of 20 mL/min^{-1}. The purified peptides were freeze-dried and stored at 0 °C.

Mets7: IR (KBr): 3430, 3067, 2918, 1651, 1534, 1437, 1384, 1239, 1168, 1121, 1077, 1030, 595 cm^{-1}; ESI-MS for $C_{34}H_{62}N_{10}O_{11}S_3$: calcd 882.365 found 883.6 $[M+H]^+$; peptide A: IR (KBr): 3306, 1673, 1435, 1338, 1200, 1073, 1044, 838, 800, 723, 665 cm^{-1}; ESI-MS for $C_{31}H_{56}N_{10}O_9S$: calcd 744.348 found 745.4 $[M+H]^+$; peptide B: IR (KBr): 3307, 3073, 2928, 1665, 1538, 1441, 1202, 1179, 1133, 835, 800, 721, 598 cm^{-1}; ESI-MS for $C_{30}H_{53}N_9O_9S_2$: calcd 747.330 found 748.4 $[M+H]^+$; peptide C: IR (KBr): 3400, 3076, 2927, 1661, 1534, 1441, 1202, 1179, 1133, 835, 800, 721, 597 cm^{-1}; ESI-MS for $C_{30}H_{53}N_9O_9S_2$: calcd 747.330 found 748.4 $[M+H]^+$; peptide B1: IR (KBr): 3319, 3078, 2936, 2560, 1782, 1665, 1537, 1442, 1203, 1178, 1140, 837, 800, 721, 705 597, 518 cm^{-1}; ESI-MS for $C_{34}H_{60}N_{10}O_{11}S_2$: calcd 848.378 found 849.4 $[M+H]^+$; peptide S1: IR (KBr): 3401, 3063, 2974, 2919, 1657, 1535, 1444, 1327, 1306, 1159, 1089, 907, 816, 667, 575, 552 cm^{-1}; ESI-MS for $C_{43}H_{70}N_{10}O_{12}S_4$: calcd 1046.699 found 1047.3 $[M+H]^+$; 1069.6 $[M+Na]^+$.

Synthesis of Cu(I) complexes. In a Schlenk tube containing 4-8 mg of purified, lyophilized peptide in 2 mL of MeOH, solid $Cu(OAc)_2$ (1 eq.) was added. Ascorbic acid (2 eq.) was introduce for *in situ* reduction of Cu(II) to Cu(I).[9] The solution was stirred for 4 h at room temperature and a formation of precipitate was evinced. The precipitated complex was filtered and the solid was dried *in vacuo*. The solid was washed three times with diethyl ether and analysed by ESI-MS.

Copper(I) complex of Mets7: Pale yellow powder. 3.3 mg, yield 48 %. IR (KBr): 3429, 2919, 1657, 1536, 1429, 1261, 1092, 1026, 587 cm^{-1}. ESI-MS for $[C_{34}H_{62}N_{10}O_{11}S_3Cu]^+$: calcd 945.31 found 945.3 $[Cu(pep)]^+$. Copper(I) complex of A: Pale green powder. 2.1 mg, yield 34 %. IR (KBr): 3322, 3077, 2950, 1661, 1541, 1445, 1251, 1202, 1169, 1030, 639 cm^{-1}. ESI-MS for $C_{31}H_{56}N_{10}O_9SCu]^+$: calcd 807.32 found 806.3 $[Cu(pep)]^+$. Copper(I) complex of B: pale brown powder. 3.1 mg, yield 44 %. IR (KBr): 3436, 2963, 2926, 1640, 1543, 1441, 1261, 1097, 1033, 802, 642 cm^{-1}. ESI-MS for $[C_{30}H_{53}N_9O_9S_2Cu]^+$: calcd 810.27 found 810.3 $[Cu(pep)]^+$. Copper(I) complex of B1: pale brown powder. 3.0 mg, yield 38 %. IR (KBr): 3427, 2958, 1802, 1671, 1552, 1439, 1204, 1138, 1086, 1023, 836, 725, 676, 616 cm^{-1}. ESI-MS for $[C_{34}H_{60}N_{10}O_{11}S_2Cu]^+$: calcd 911.32 found 911.4 $[Cu(pep)]^+$. Copper(I) complex of C: pale violet powder. 2.7 mg, yield 33 %. IR (KBr): 3423, 2963, 2918, 2850, 1632, 1442, 1384, 1261, 1095, 1023, 873, 799, 669 cm^{-1}. ESI-MS for $[C_{30}H_{53}N_9O_9S_2Cu]^+$: calcd 810.27 found 810.2 $[Cu(pep)]^+$. Copper(I) complex of S1: pale lilac powder. 4.5 mg, yield 68 %. IR (KBr): 3421, 2960, 1794, 1632, 1554, 1435, 1261, 1078, 1023, 800, 610, 575 cm^{-1}. ESI-MS for $[C_{43}H_{70}N_{10}O_{12}S_4Cu]^+$: calcd 1109.34 found 1108.3$[Cu(pep)]^+$.

General procedure for Henry reaction.[8] A mixture of peptide-Cu(I) complex (5 mol %, 0.05 eq), *t*-BuOH (1 mL) and either CH_3NO_2 (1 mL) in a screw capped vial-2 mL was stirred at room temperature for 1.5 h. Then aldehyde (1 eq) was added to the above solution. The resulting reaction mixture was stirred for 12 h at 40 °C. Afterwards, 1N HCl was added to quench the reaction and then the volatiles were evaporated by rotavapor to get crude product. The conversion was determined by ^{1}H-NMR and the enantiomeric excess by HPLC analysis.[10]

1-Phenyl-2-nitroethanol: Chiralcel OD-H column: 90:10/ hexane:isopropanol, flow: 1.0 mL/min, λ = 216 nm, t (*R*)= 15.1 min, t (*S*)= 18.5 min.

1-(4-Nitrophenyl)-2-nitroethanol: Chiralcel OD-H column: 80:20/ hexane:isopropanol, flow: 0.5 mL/min, λ = 254 nm, t (*R*)= 26.9 min, t (*S*)= 33.5 min.

1-(4-Chlorophenyl)-2-nitroethanol: Chiralcel OD-H column: 90:10/ hexane:isopropanol, flow: 1.0 mL/min, λ = 216 nm, t (*R*)= 15.6 min, t (*S*)= 19.0 min.

Table TS3: Evaluation of different solvents in Henry catalyzed reaction by Mets7-copper (I) complex using benzaldehyde as substrate.

Solvent	**Conversion (%)**[a]	**e.e. (%)**[b]
MeOH/CH_3NO_2: 5/5	82	23
2-propanol/ CH_3NO_2: 8/2	75	18
t-BuOH/ CH_3NO_2: 8/2	50	45
t-BuOH/ CH_3NO_2: 5/5	54	48
6 % NaCl in H_2O/ CH_3NO_2: 8/2	79	10
MOPS, pH = 7.0, 0.2 M/ CH_3NO_2: 8/2	80	8
H_2O/ CH_3NO_2: 8/2	20	30
DMSO/ H_2O/ CH_3NO_2: 5/2/5	85	12

All reactions were carried out for 12 h using 5 mol % complex in 2 mL of mixture solvent. [a]Conversion was obtained by ^{1}H-NMR analysis. [b]Data were compared by taking the average of three independent experiments. Enantiomeric excess was determined using HPLC equipped with chiral OD-H column. Eluent: hexane/2-propanol=90/10 flow=1.0 mL/min, λ = 215 nm. $[sub]_f$ = 10 mM, $[cat]_f$ = 0.45 mM.

NMR data and discussion for peptide S1

All experiments (^{1}H, COSY, TOCSY, and ROESY) were recorded in H_2O/D_2O 90:10 (9.6 mM) at 500 MHz.

Compound **S1** is present in solution as a mixture of *cis/trans* rotamers of the tertiary amide on the piperidine ring. In particular, the signals of Met-1 and Met-4 are double, while Met-6 are single (Figure FS3), confirming the higher mobility of the peptide chain linked to the piperidine ring due to the rotation of the tertiary amide bond.

Table TS4 ^{1}H NMR chemical shifts of S1

Residue	**NH**	**α-H**	**β-H**	**Other**	**Roesy[a]**
MeCO	-	-	-	2.05[b]	-
Met-1[d]	9.00	4.60 [b]	2.53[c]	2.08[c]	-
Thr-2	8.08	4.30	4.19		NH: α-H Met-1, α-H Gly-3 α-H: α-H Gly-3
Gly-3	8.36c	3.85	-	-	NH: α-H Thr-2 α-H: α-H Thr-2 α-H: H5 scaffold
Met-4[d]	8.07	4.52 [b]	2.53[b]	2.07[c]	NH: α-H Gly-3
Piperidine	7.78[c]	-	H-2: 4.19 [c] , H-2': 3.54 H-3: 2.36 [c] ; H-4: 2.49 [c] H-5: 2.36 [c] , 1.86 [c] H-6: 3.21, 3.16 Arom: 7.79*o*, 7.46*m*; Me: 2.40		H6: α-H Gly-3, α-H Met-4
Pro-5	-	4.17	H-5, H-5': 3.59, 3.48; H-4, H-4': 1.61, 1.44; H-3, H-3': 2.54 [c]		α-H: α-H Gly-3
Met-6	8.35 [c]	4.90[b]	2.50 [c]	2.00	
Ser-7	8.35 [c]	4.42	3.88		

NH_2	7.60 7.09	-	-	-	7.60: α-H Ser-7

[a]most significative; [b]overlapped with solvent signals; [c] overlapped

ROESY experiments confirmed the presence of a turn structure. Spatial proximity was indeed observed between the piperidine moiety (H-6 protons) and α-H of Met-4 and of Gly-3 (Figures FS4-6) as already reported for model sequences.[6b] No NH-NH spatial proximity were observed, while a complete set of NH/α-H were present, indicating that the two peptidic arms are almost extended, although not in a β hairpin conformation (no intrastrand ROEs observed). This lack of a stable hairpin conformation is also confirmed by the temperature dependence chemical shift variations experiments, in which no NH protons appeared to be involved in H-bonds (Figure FS7).

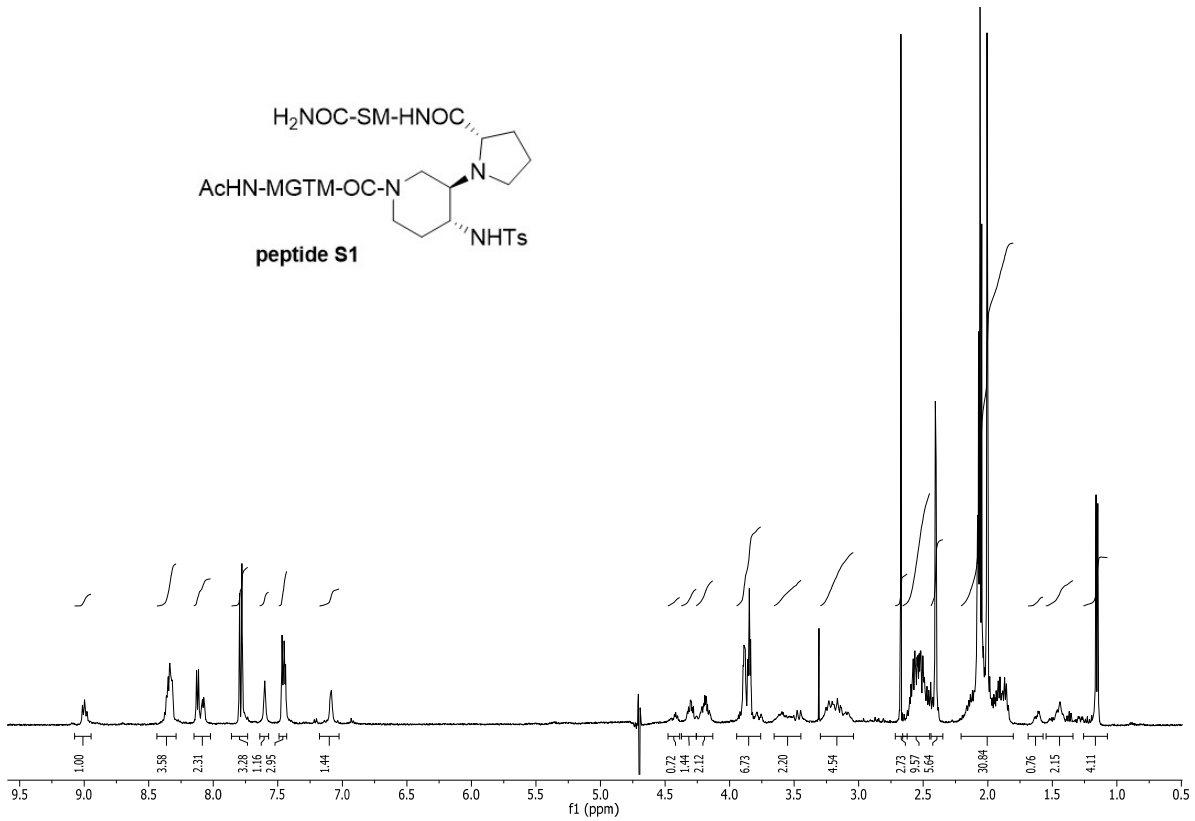


FIGURE FS2. [1]H-NMR spectra of peptide **S1**.

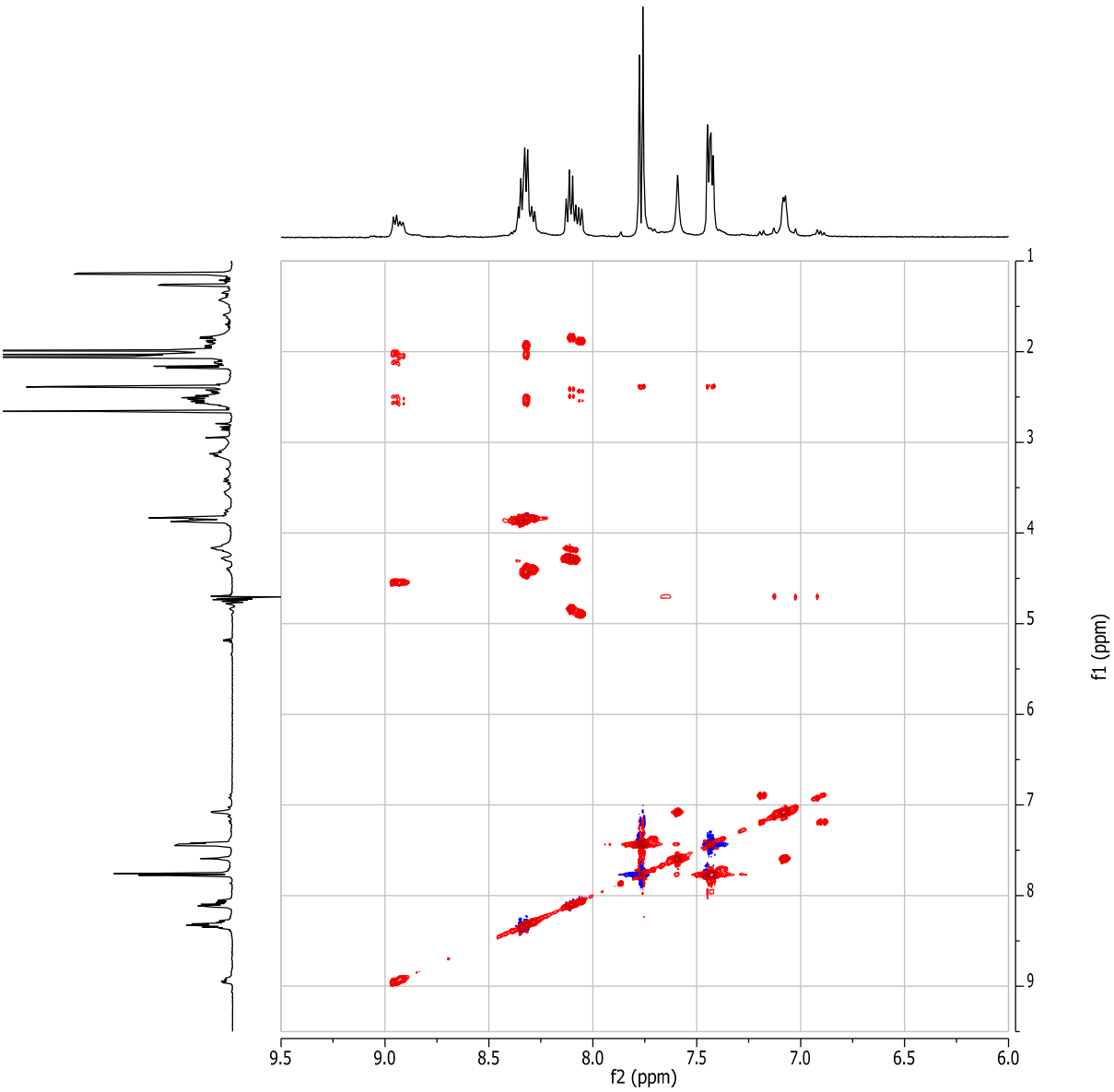


FIGURE FS3: NH/CH region in the TOCSY experiment (500MHZ, 60 ms)

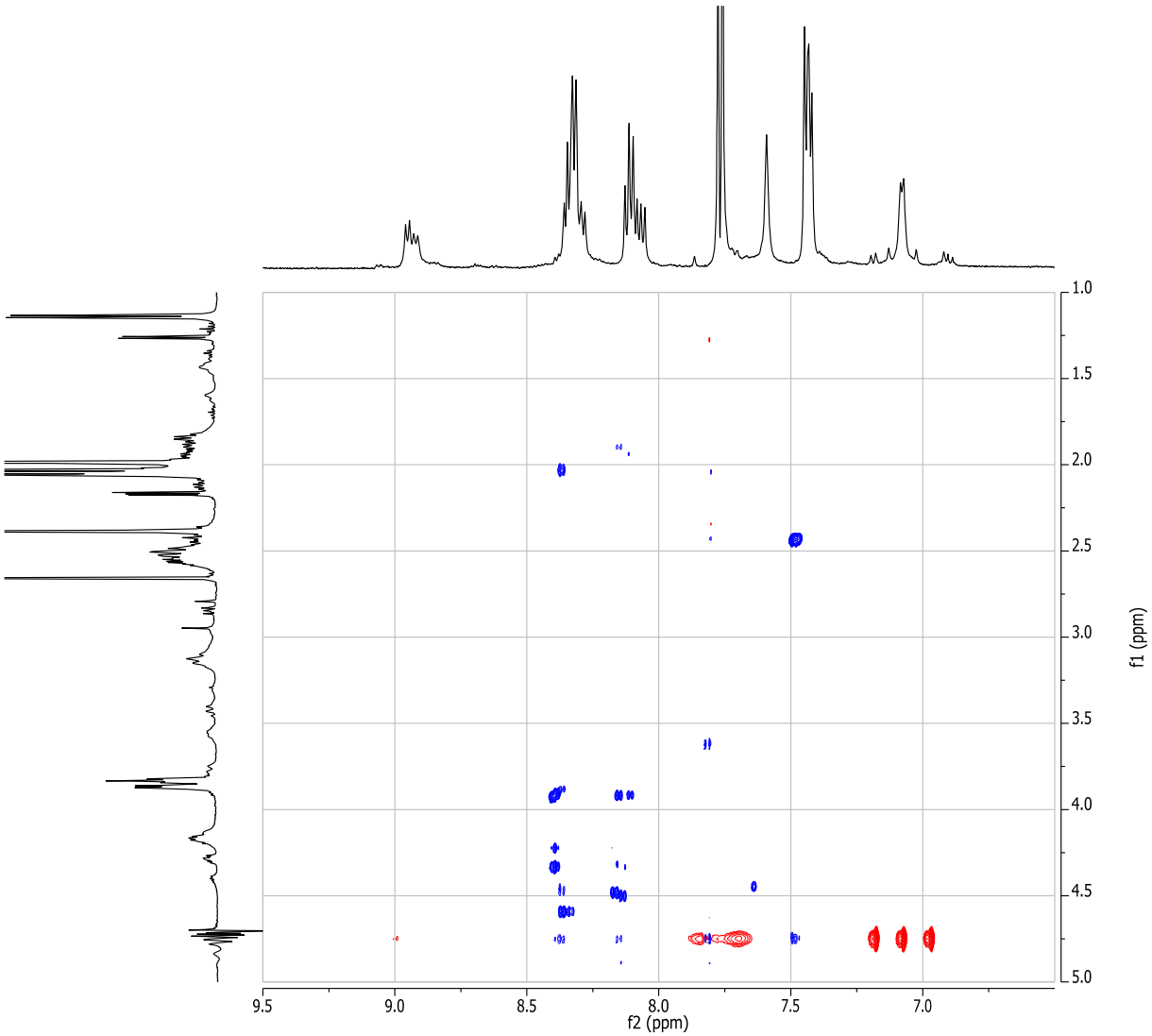


FIGURE FS4: NH/CH region in the ROESY experiment (500MHZ, 200 ms)

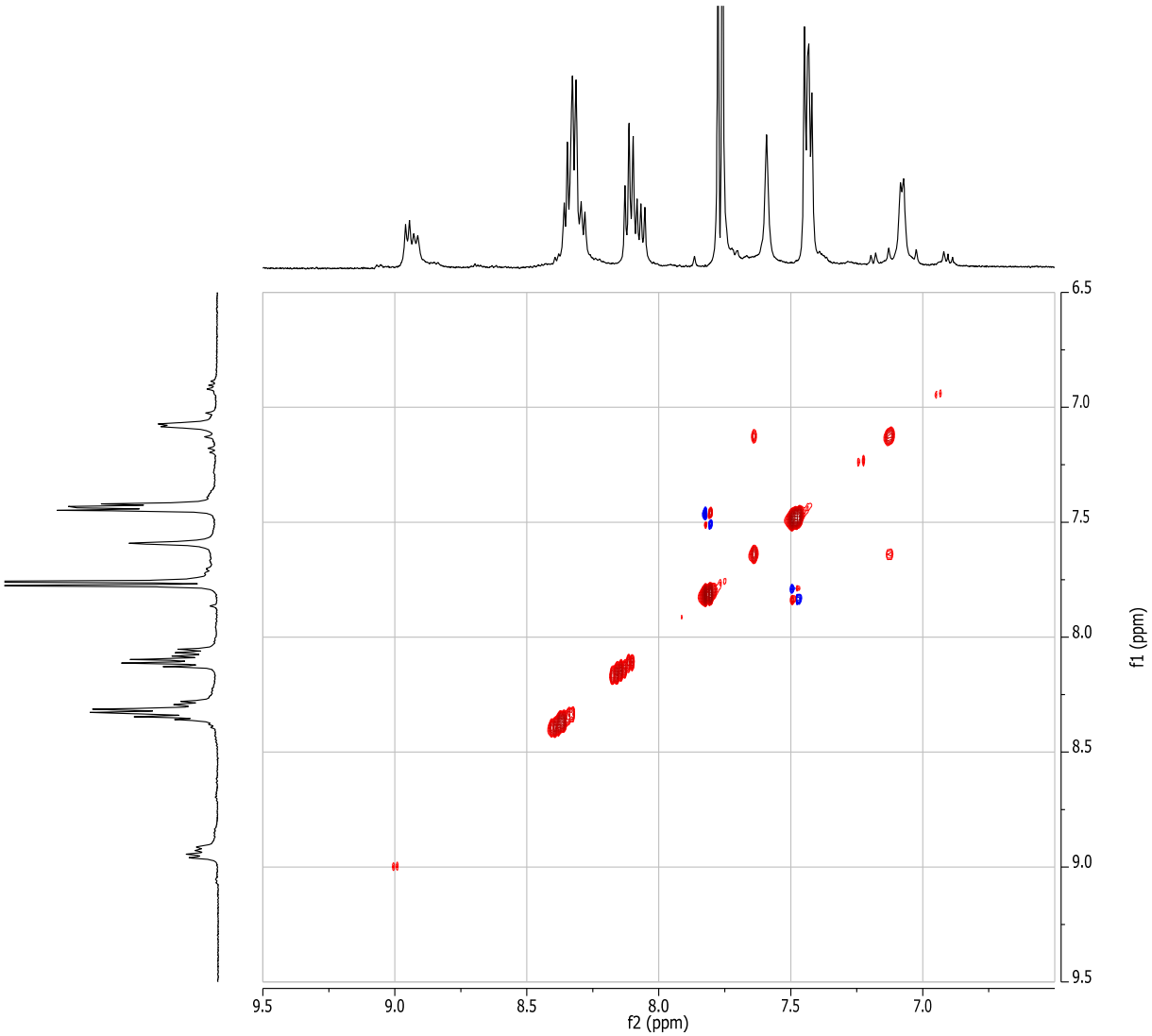


FIGURE FS5: NH/NH region in the ROESY experiment (500MHZ, 200 ms)

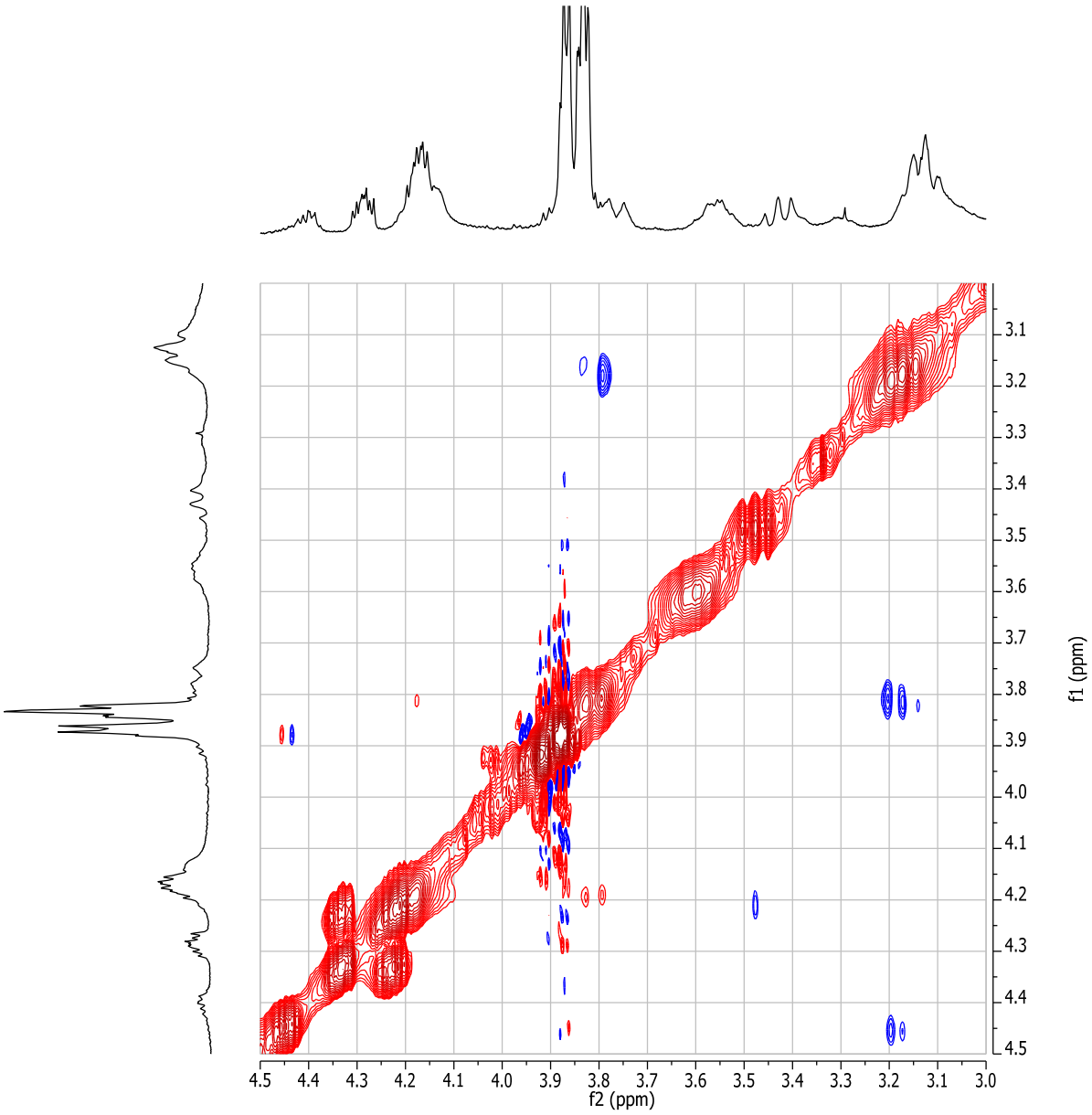


FIGURE FS6: CH/CH region in the ROESY experiment (500MHZ, 200 ms)

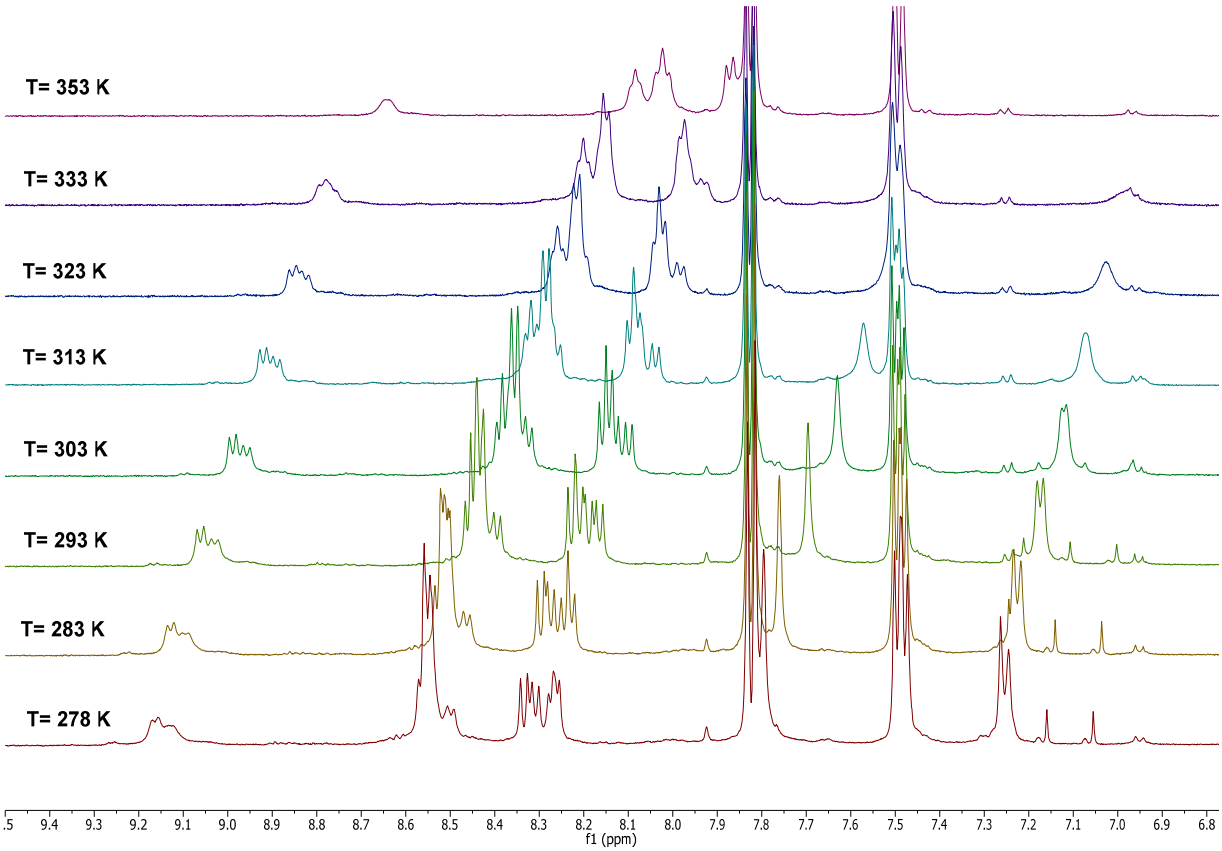


FIGURE FS7: ^{1}H-NMR spectra of peptide **S1** at different temperatures

ESI-MS spectra of peptides and corresponding Cu-(I) complexes

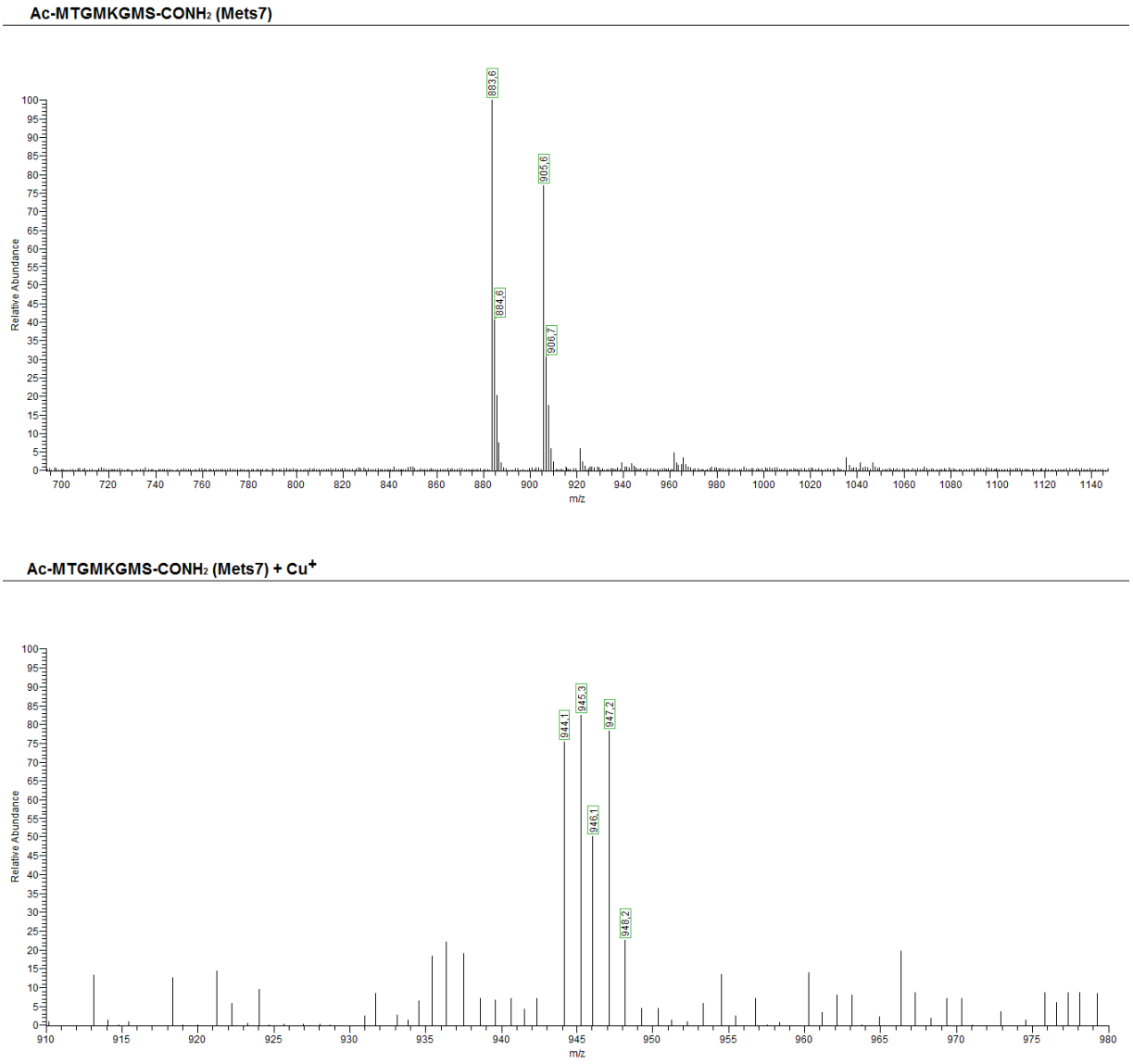


FIGURE FS8. ESI-MS of peptide Mets7 and of its corresponding Cu(I)-complex.

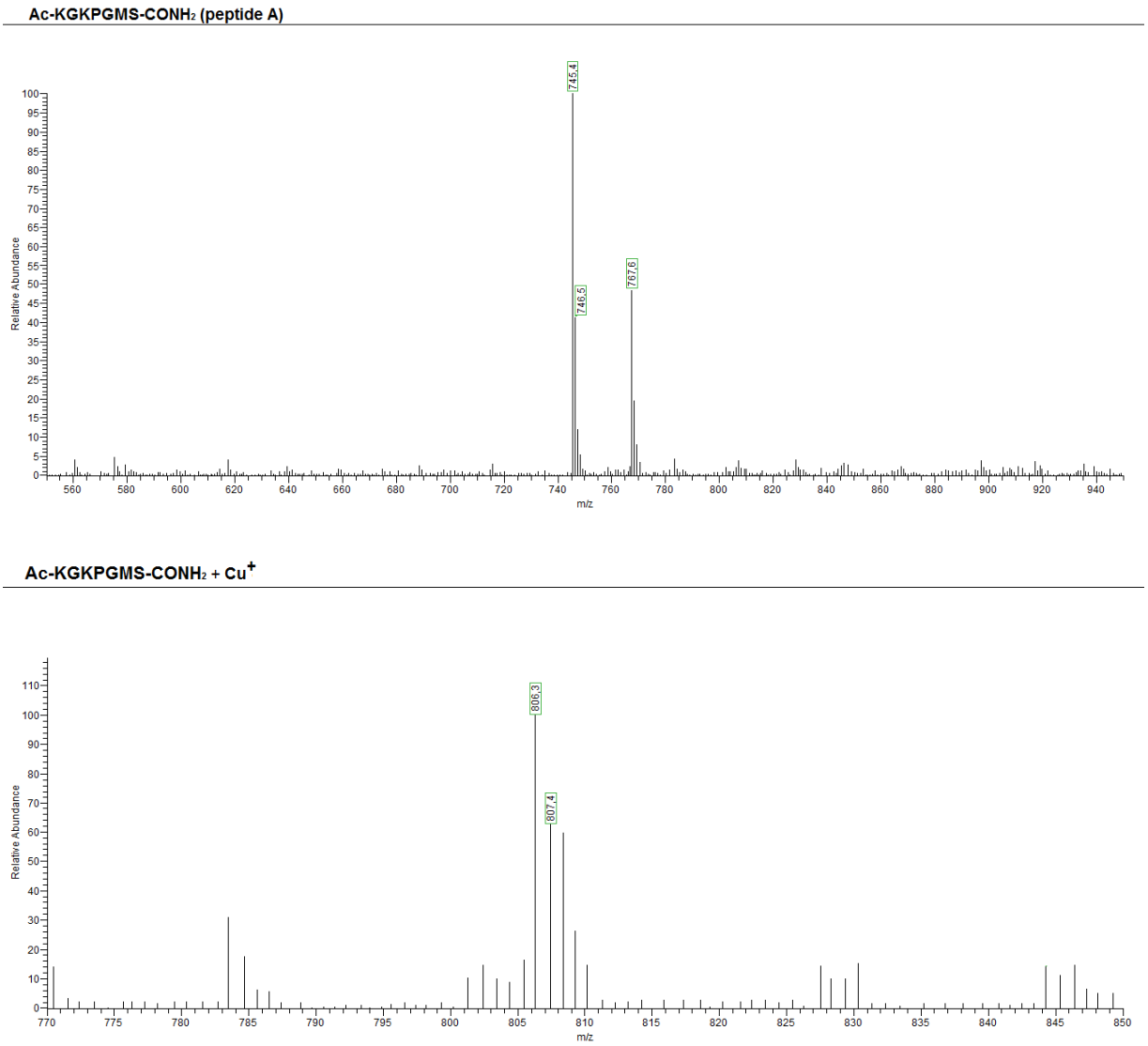


FIGURE FS9. ESI-MS of peptide A and of its corresponding Cu(I)-complex.

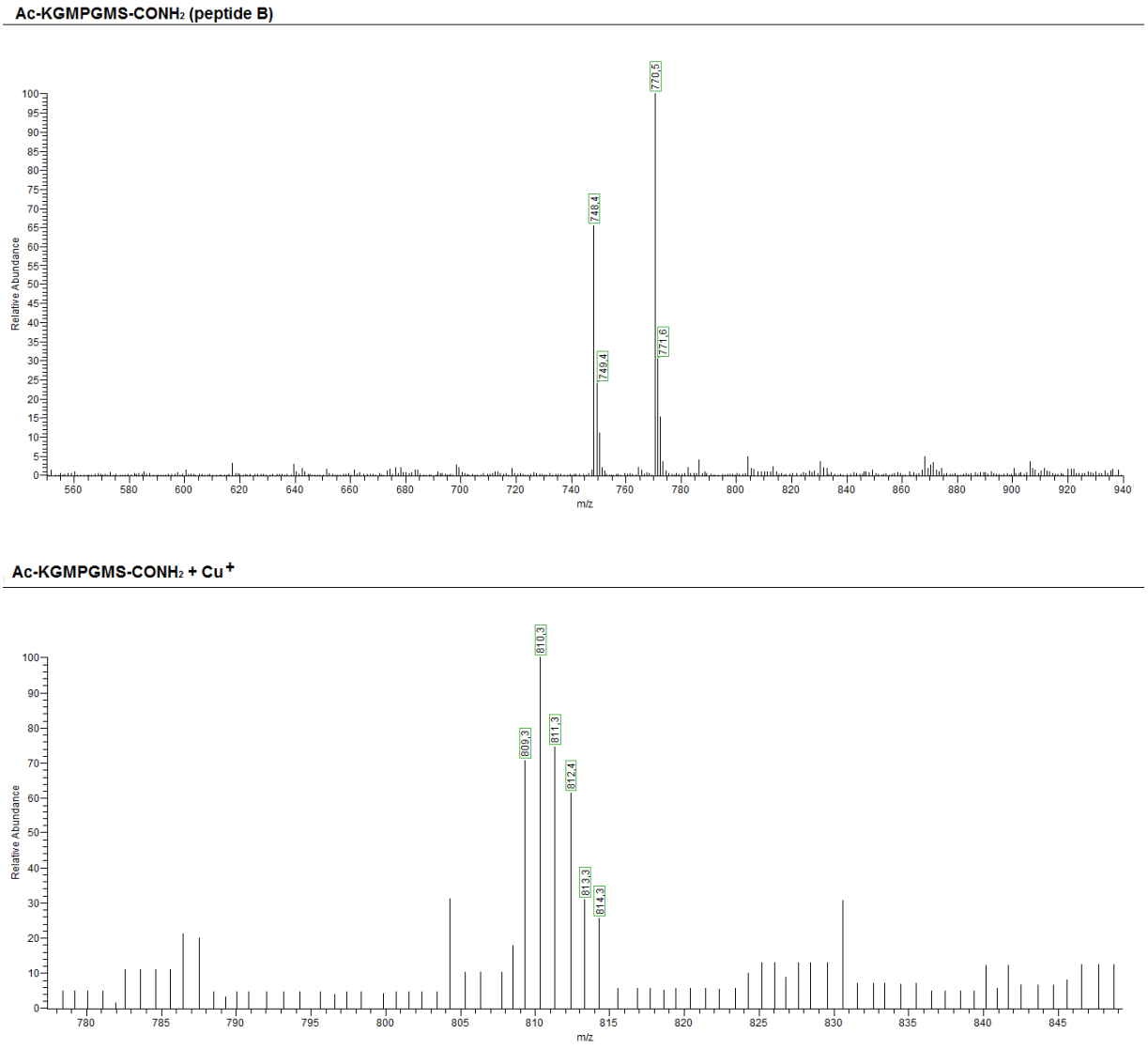


FIGURE FS10. ESI-MS of peptide B and of its corresponding Cu(I)-complex.

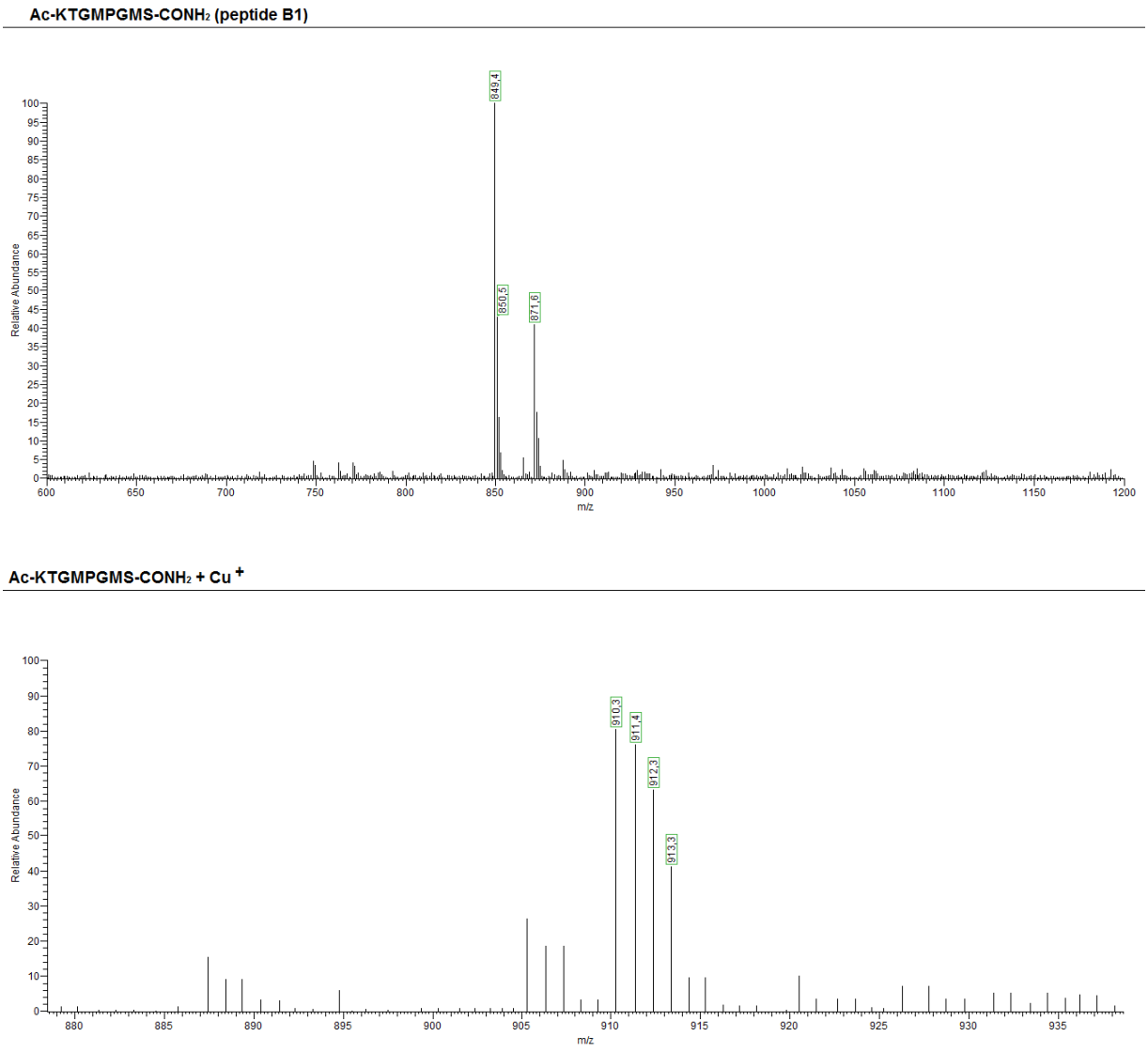


FIGURE FS11. ESI-MS of peptide B1 and of its corresponding Cu(I)-complex.

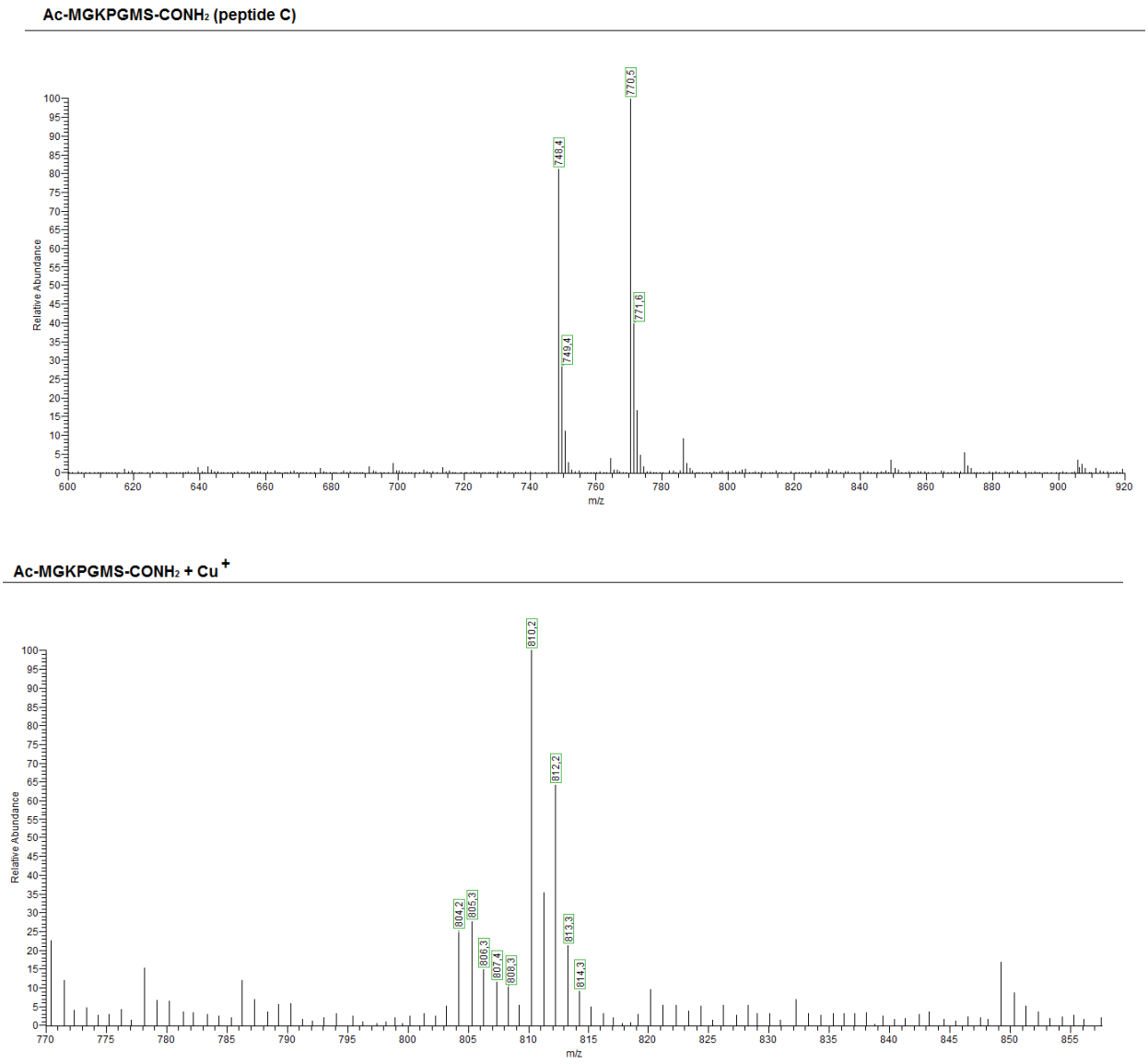


FIGURE FS12. ESI-MS of peptide C and of its corresponding Cu(I)-complex.

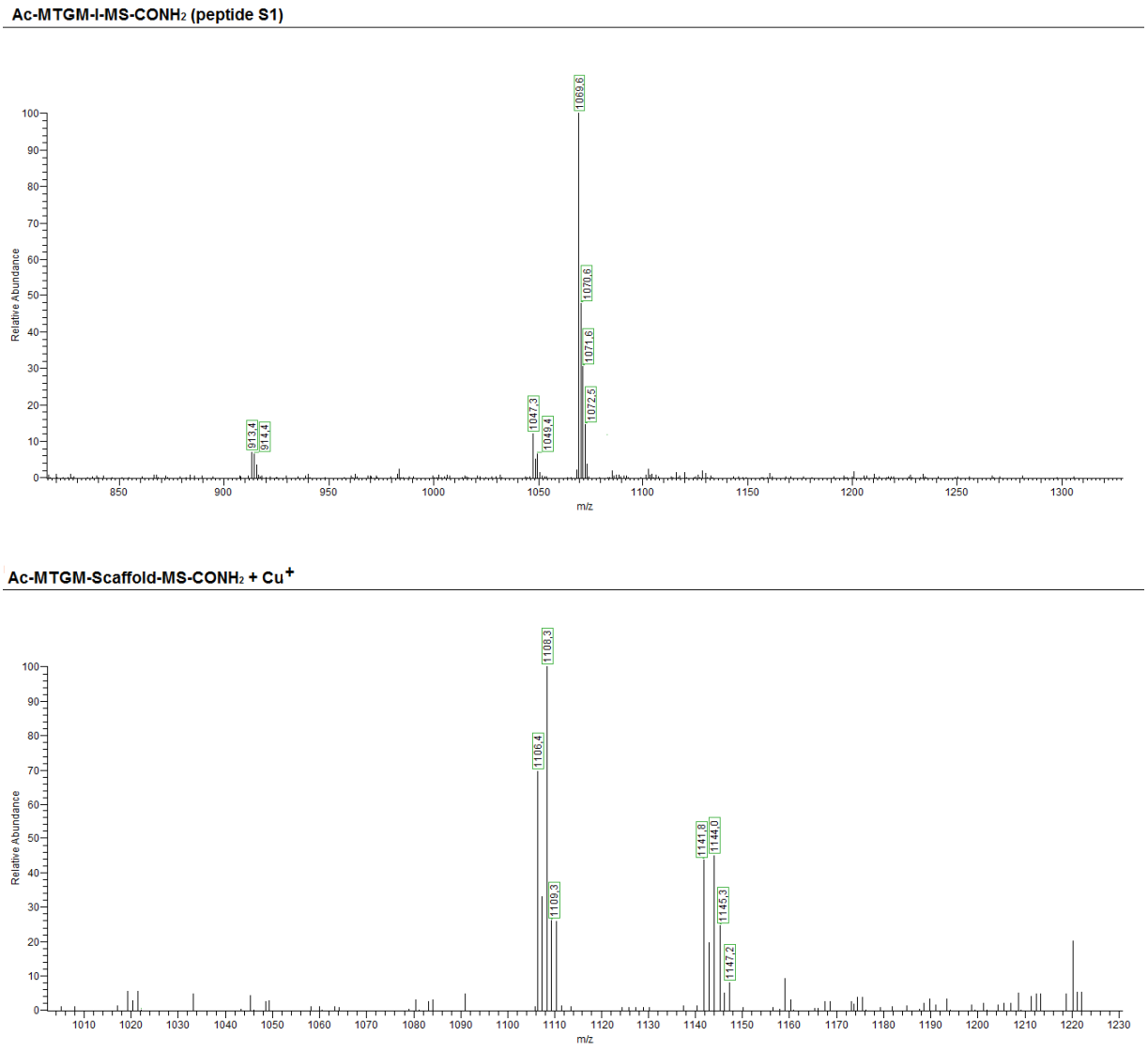


FIGURE FS13. ESI-MS of Cu(I)-complex with peptide S1.

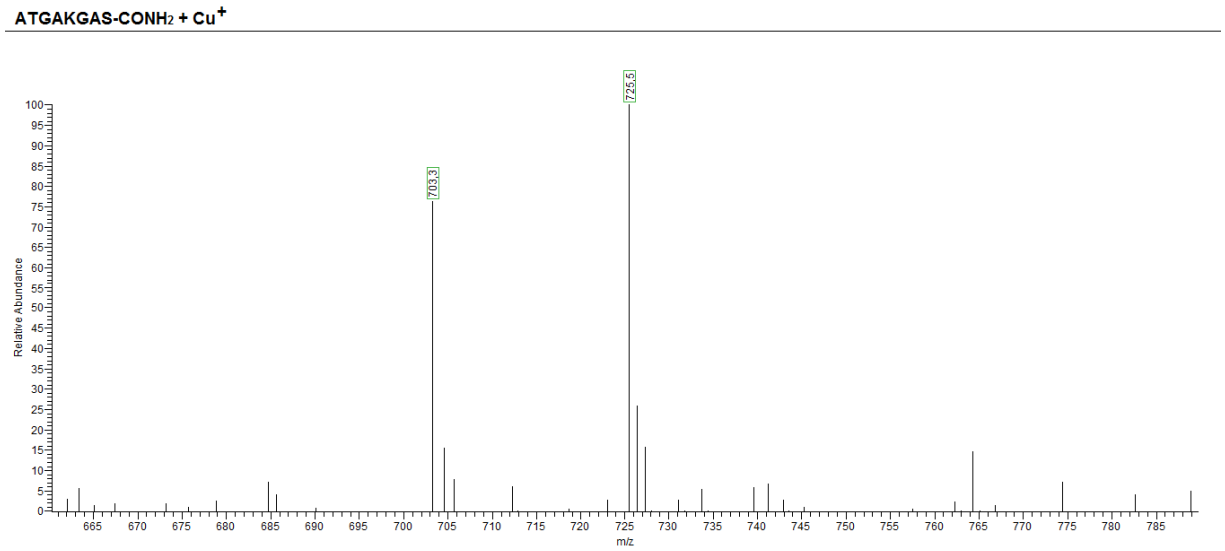


FIGURE FS14. ESI-MS of Cu(I)-complex with Ala-Scan in which the lack of coordination was evinced.

Circular Dichroism and UV experiments

Solutions of peptides **Mets7, A, B, B1, C, S1** and their Cu(I) complexes were prepared in H_2O (100 μM, 1.5 mL). CD spectra were obtained from 195 to 250 nm with a 0.1 nm step and 1 s collection time per step, taking three averages. The spectrum of the solvent was subtracted to eliminate interference from cell, solvent, and optical equipment. The CD spectra were plotted as mean residue ellipticity θ (degree x cm^2 x $dmol^{-1}$) versus wave length λ (nm). Noise-reduction was obtained using a Fourier-transform filter program.

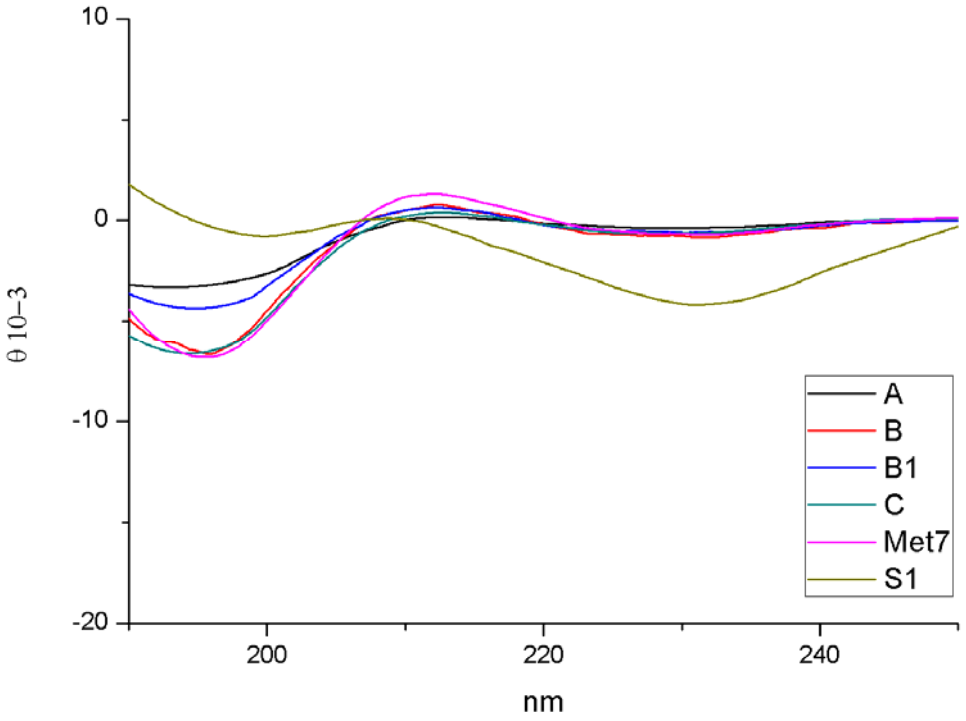


FIGURE FS15. CD spectra of peptides alone

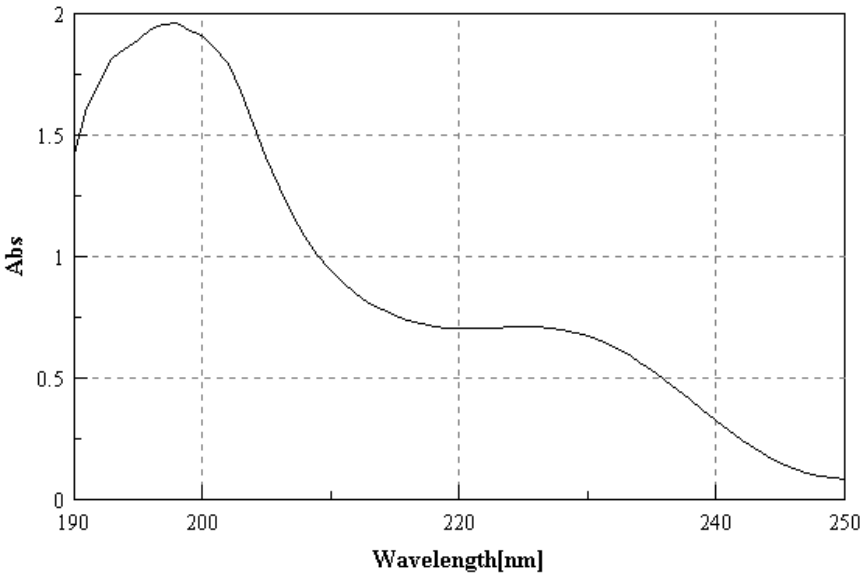


FIGURE FS16. UV spectra in water of peptide **S1**. [peptide] = 0.3 mM.

HPLC spectra of products from Henry reactions

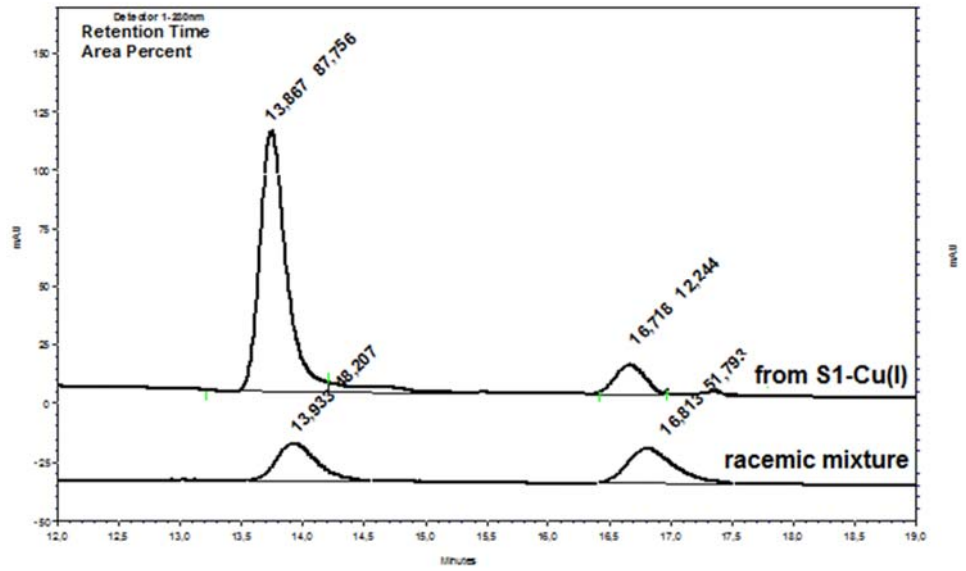


FIGURE FS17: HPLC spectra of standard racemic mixture of 2-nitro-1-phenylethan-1-ol vs result obtained by Henry condensation catalyzed by S1-Cu(I) complex.

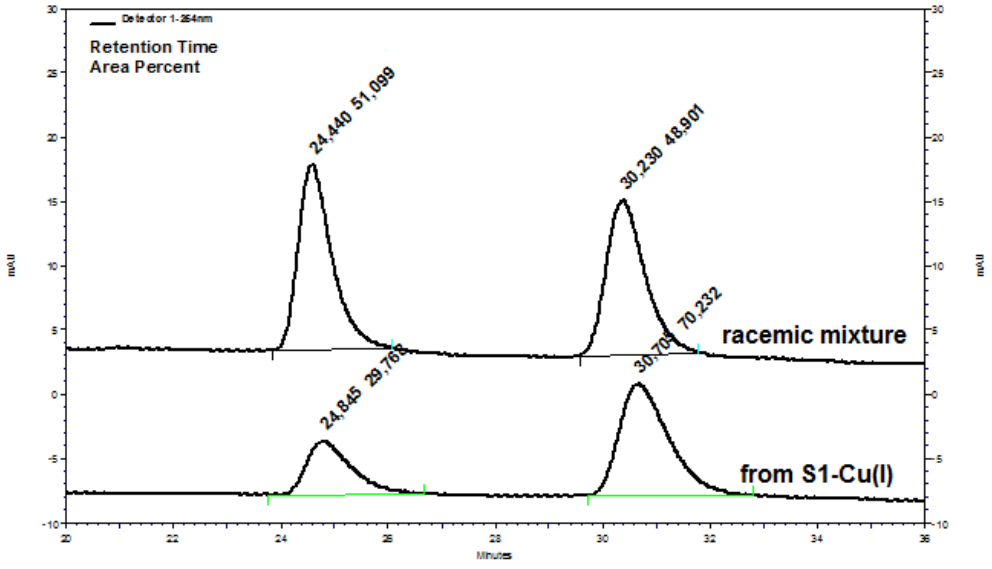


FIGURE FS18: HPLC spectra of standard racemic mixture of 2-nitro-1-(4-nitrophenyl)ethan-1-ol vs result obtained by Henry condensation catalyzed by S1-Cu(I) complex.

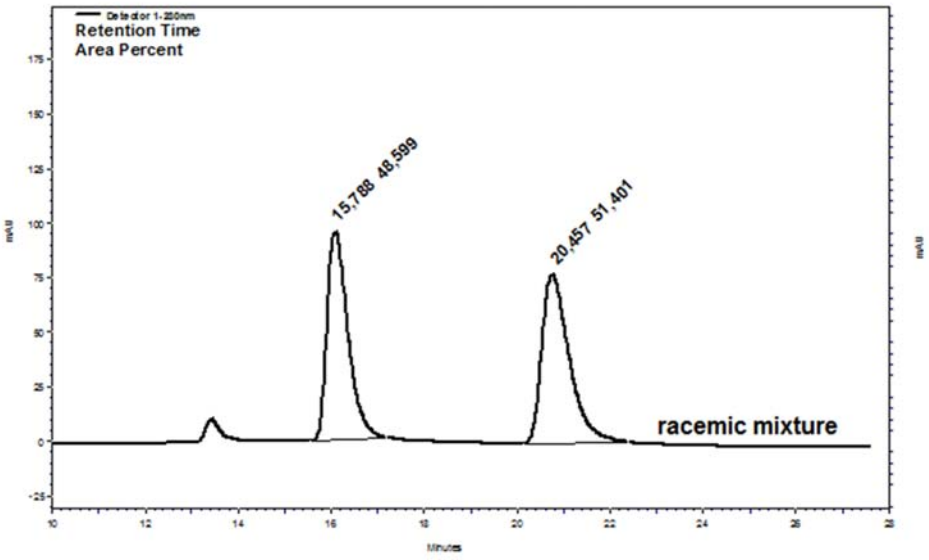


FIGURE FS19: HPLC spectra of standard racemic mixture of 1-(4-chlorophenyl)-2-nitroethan-1-ol.

Bibliography

(1) Case, D. A. B., V.; Berryman, J. T.; Betz, R. M.; Cai, Q.; Cerutti, D. S.; T.E. Cheatham, I.; Darden, T. A.; Duke, R. E.; Gohlke, H.; Goetz, A. W.; Gusarov, S.; Homeyer, N.; Janowski, P.; Kaus, J.; Kolossváry, I.; Kovalenko, A.; Lee, T. S.; LeGrand, S.; Luchko, T.; Luo, R.; Madej, B.; Merz, K. M.; Paesani, F.; Roe, D. R.; Roitberg, A.; Sagui, C.; Salomon-Ferrer, R.; Seabra, G.; Simmerling, C. L.; Smith, W.; Swails, J.; Walker, R. C.; Wang, J.; Wolf, R. M.; Wu, X.; Kollman, P. A. AMBER 14; University of California, San Francisco, 2014.
(2) (a) Ruffoni, A.; Contini, A.; Soave, R.; Lo Presti, L.; Esposto, I.; Maffucci, I.; Nava, D.; Pellegrino, S.; Gelmi, M. L.; Clerici, F., *RSC Advances* **2015,** *5* (41), 32643-32656; (b) Pellegrino, S.; Contini, A.; Clerici, F.; Gori, A.; Nava, D.; Gelmi, M. L., *Chem. Eur. J.* **2012,** *18* (28), 8705-8715; (c) Maffucci, I.; Clayden, J.; Contini, A., *J. Phys. Chem. B* **2015,** *119* (44), 14003-14013; (d) Maffucci, I.; Pellegrino, S.; Clayden, J.; Contini, A., *J. Phys. Chem. B* **2015,** *119* (4), 1350-1361.
(3) Lindorff-Larsen, K.; Piana, S.; Palmo, K.; Maragakis, P.; Klepeis, J. L.; Dror, R. O.; Shaw, D. E., *Proteins: Structure, Function, and Bioinformatics* **2010,** *78* (8), 1950-1958.
(4) Nguyen, H.; Roe, D. R.; Simmerling, C., *J. Chem. Theory Comput.* **2013,** *9* (4), 2020-2034.
(5) Patriksson, A.; van der Spoel, D., *Physical Chemistry Chemical Physics* **2008,** *10* (15), 2073-2077.
(6) (a) Pellegrino, S.; Annoni, C.; Contini, A.; Clerici, F.; Gelmi, M. L., *Amino Acids* **2012,** *43* (5), 1995-2003; (b) Pellegrino, S.; Contini, A.; Gelmi, M. L.; Lo Presti, L.; Soave, R.; Erba, E., *J. Org. Chem.* **2014,** *79* (7), 3094-3102.
(7) Ferri, N.; Facchetti, G.; Pellegrino, S.; Pini, E.; Ricci, C.; Curigliano, G.; Rimoldi, I., *Bioorg Med Chem* **2015,** *23*, 2538-47.
(8) Boobalan, R.; Lee, G.-H.; Chen, C., *Adv. Synth. Catal.* **2012,** *354* (13), 2511-2520.
(9) Jiang, J.; Nadas, I. A.; Kim, M. A.; Franz, K. J., *Inorg. Chem.* **2005,** *44* (26), 9787-9794.
(10) Lai, G.; Guo, F.; Zheng, Y.; Fang, Y.; Song, H.; Xu, K.; Wang, S.; Zha, Z.; Wang, Z., *Chem. Eur. J.* **2011,** *17* (4), 1114-1117.