Supplimentary Information

Ni(II)-Mediated Asymmetric Synthesis of a Conjugated Diyne-Containing Non-Proteinogenic Amino Acid via Glaser Heterocoupling

Emma A. Khachatryan*

Institute of Pharmacy, Yerevan State University, 1 Alex Manoogian Str., 0025 Yerevan, Armenia

**email: emma.khachatryan@ysu.am Tel.: +374 77 444 370; +374 41 444 370*

Contents

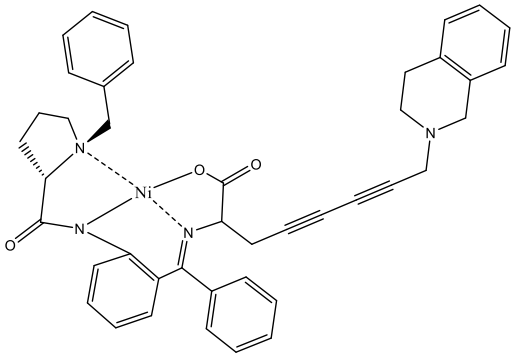
Materials

All initial reagents were obtained from commercial sources and used without further purification. TLC analyses were performed on glass plates coated with silica gel 60 F254. Column chromatography was performed on silica gel (60×120 mesh) on a glass column. Melting points (mp) were determined by Electrothermal. ^{1}H and ^{13}C NMR spectra (Mercury-300 Varian 300 MHz and 75 MHz, respectively) were recorded using TMS as an internal standard (0 ppm). Elemental analyses were done by elemental analyzer EURO EA 3000. The enantiomeric purity of the amino acids was determined by HPLC (Waters Alliance 2695 HPLC System) on the chiral phase Diaspher-110- Chirasel-E-PA 6.0 μm 4.0×250 mm, and a mixture of 20% MeOH and 80% 0.1 M aqueous solution $NaH_2PO_4 \cdot 2H_2O$ was used as the eluent. The optical rotation was measured on a Perkin Elmer-341 polarimeter. LCMS analysis was done by Shimadzu LCMS 2020 with prominence-I LC-2030C 3D. The CD analyses were carried out by Chirascan™ V100.

Procedure for synthesis of complex 3

Copper iodide (0.71 g, 3.73 mmol) and 2-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline 1.27 g (7.4 mmol) were added to a mixture of 1,4-dioxane (5 mL) and triethylamine (5 mL). After 15 minutes 2 g (3.73 mmol) **complex 1** was added and stirred at 70°C. The progress of the reaction was monitored by TLC on silica using a 3:1 $CH_3COOC_2H_5$/ $CHCl_3$ mixture as a mobile phase. After the reaction was complete, the mixture was extracted with chloroform and distilled water. The organic phase was dried over anhydrous $MgSO_4$ to remove residual moisture and filtered through filter paper. Complex 3 was purified using silica gel column chromatography (SiO2, $CH_3COOC_2H_5$/ $CHCl_3$ = 3/1). The reaction duration was 24 h.

Complex 3



3

Yield 72% (1.87 g), Mp +149°C, $[\alpha]_D^{20}$ +1845 (c=0.15, CH_3OH). ESI-MS (m/z): 705.05 (found), 705.24 (calculated for $[C_{42}H_{38}N_4NiO_3 + H]^+$).

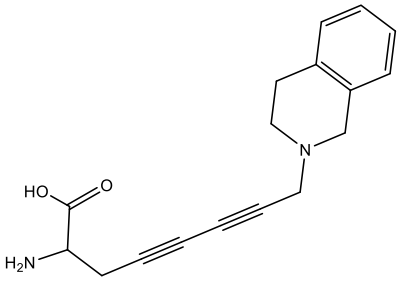
^{1}H NMR: ($CDCl_3$) δ=2.0–2.16 (2H, m, α, β- H_a Pro); 2.18 (1H, s); 2.33 (1H, dd, J=17.17); 2.41–2.55 (1H, m); 2.77 (1H, dd, J=17.7); 2.85 (2H, dd, J=6.3); 2.90–3.01 (3H, m); 3.44 (1H, dd, J=10.4); 3.65 (5H, d, J=15.4); 3.78 (2H, s); 4.01 (1H, dd, J=6.6); 4.45 (1H, d, J=12.6); 6.61–6.69 (2H, m); 7.00–7.06 (2H, m); 7.09–7.27 (8H, m); 7.36 (2H, t, J=7.6); 7.45–7.55 (3H, m); 8.04 (2H, dd, J=7.1); 8.26 (1H, d, J=8.7).

^{13}C NMR: ($CDCl_3$) δ=23.55 (CH_2); 24.361 (β-CH_2 Pro); 29.311; 30.945 (γ -CH_2 Pro); 47.535 (CH_2); 49.905 (NCH_2); 54.516 (NCH_2); 57.323 (CH_2N); 63.381 (δ-CH_2 Pro); 67.660 (≡C); 70.127 (C≡); 70.572; 73.541; 73.897(≡C); 77.670 (C≡); 120.707 (Ar); 123.878 (Ar); 125.787 (Ar); 126.288 (Ar); 126.652 (Ar); 126.733 (Ar); 127.760 (Ar); 128.731 (Ar); 128.941 (Ar); 129.006 (Ar); 129.200 (Ar); 129.232 (Ar); 130.074 (Ar); 131.740 (Ar); 132.646 (Ar); 133.253 (Ar); 133.536 (Ar); 133.697 (Ar); 134.150 (Ar); 134.150 (Ar); 134.353 (Ar); 143.161 (Ar); 172.176 (C=O); 178.429 (Ar); 180.572 (C=O).

Procedure for isolation of amino acid

A suspension of the complex in CH_3OH was slowly added to a vigorously stirred 2 M aqueous HCl solution at 50°C. After the complexes were decomposed (10–20 min), the free amino acids were purified using a cation-exchange column (Dowex-8 (H+ form)).

2-amino-8-(3,4-dihydroisoquinolin-2(1H)-yl)octa-4,6-diynoic acid 4



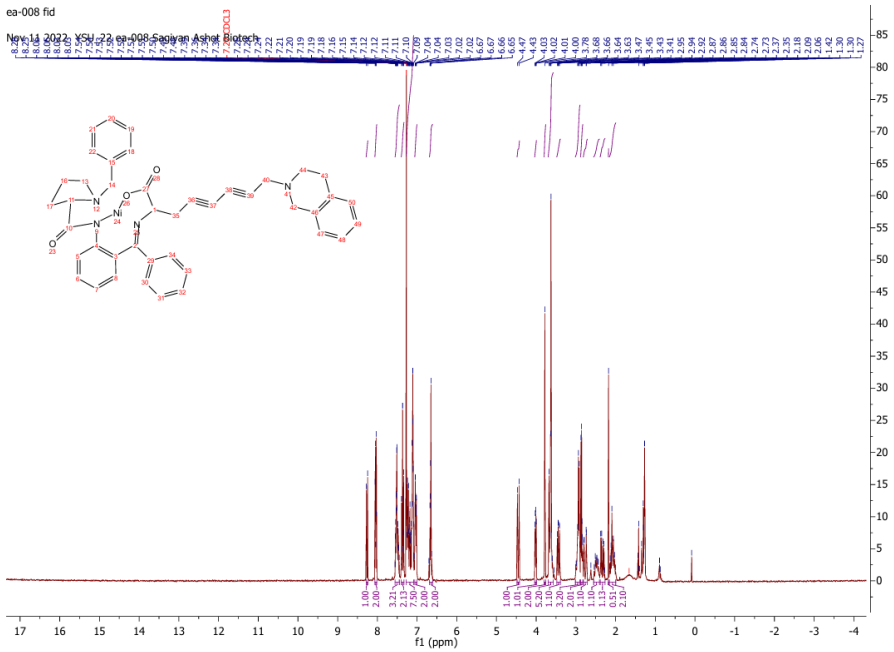
Yield 43.8% (0.46 g), Mp +212°C, $[\alpha]_D^{20}$ -10° (c=0.2, 6 N HCl). ESI-MS (m/z): 282.95 (found), 283.14 (calculated for $[C_{17}H_{18}N_2O_2 +H]^+$).

^{1}H NMR: (DMSO/CCl_4/CF_3COOD) δ= 3.54 (2H, t, *J* = 6.3; CH_2); 4.10 (1H, t, *J* = 5.5); 4.40 (4H, d, *J* = 13.6, Ar); 7.21 (4H, m; Ar).

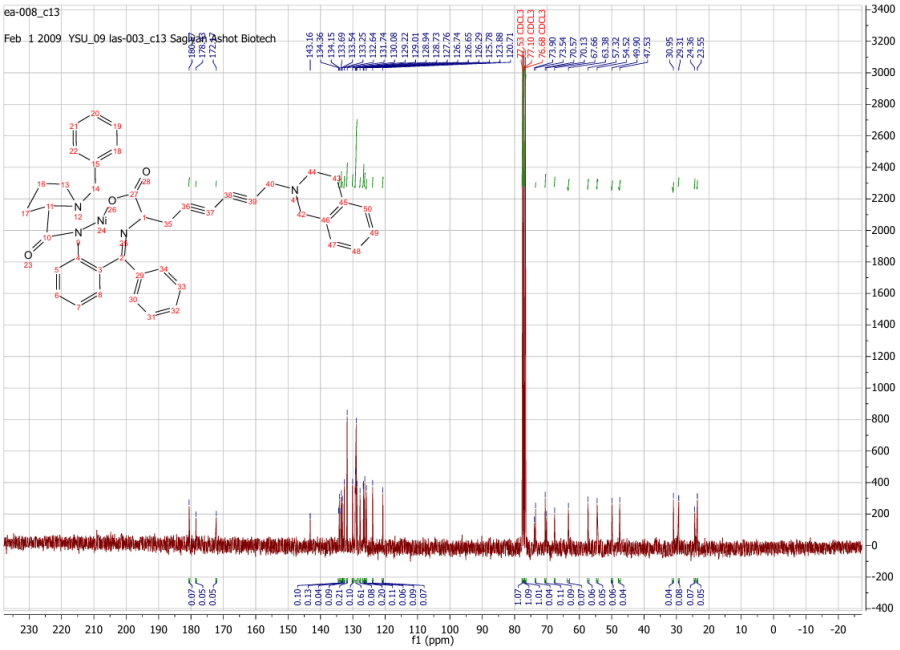
^{13}C NMR: (DMSO/CCl_4/CF_3COOD) δ=20.686 (CH_2); 25.215 (CH_2); 38.667; 40.333; 44.855; 48.349; 50.193; 51.496; 66.913; 67.188 (CH_2N); 73.327 (≡C); 75.600 (C≡); 126.414 (Ar); 126.454 (Ar); 127.457 (Ar); 128.096 (Ar); 130.846 (Ar); 158.777 (Ar); 168.694 (C=O).

NMR spectra

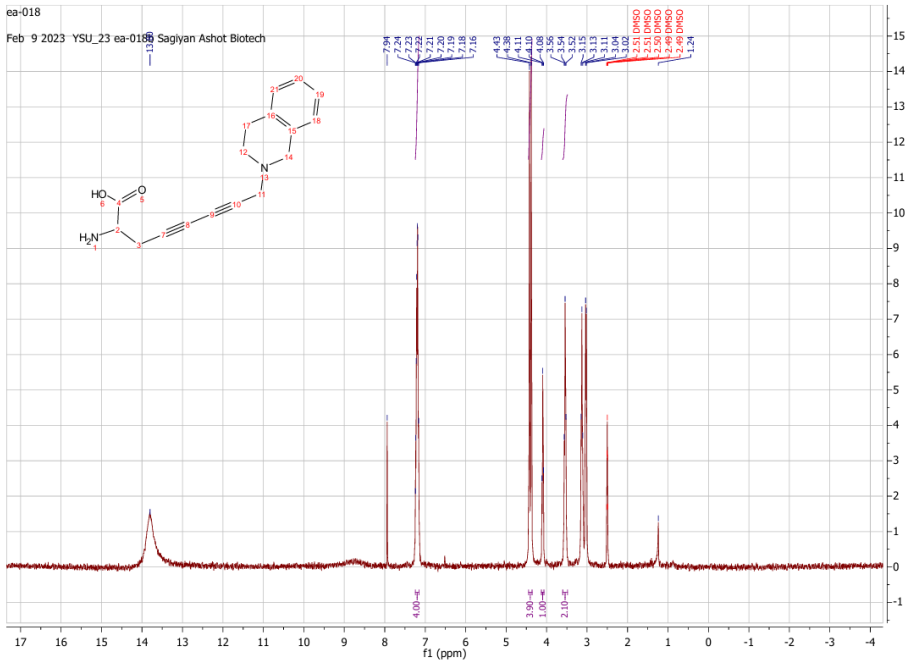
^{1}H NMR Complex 3



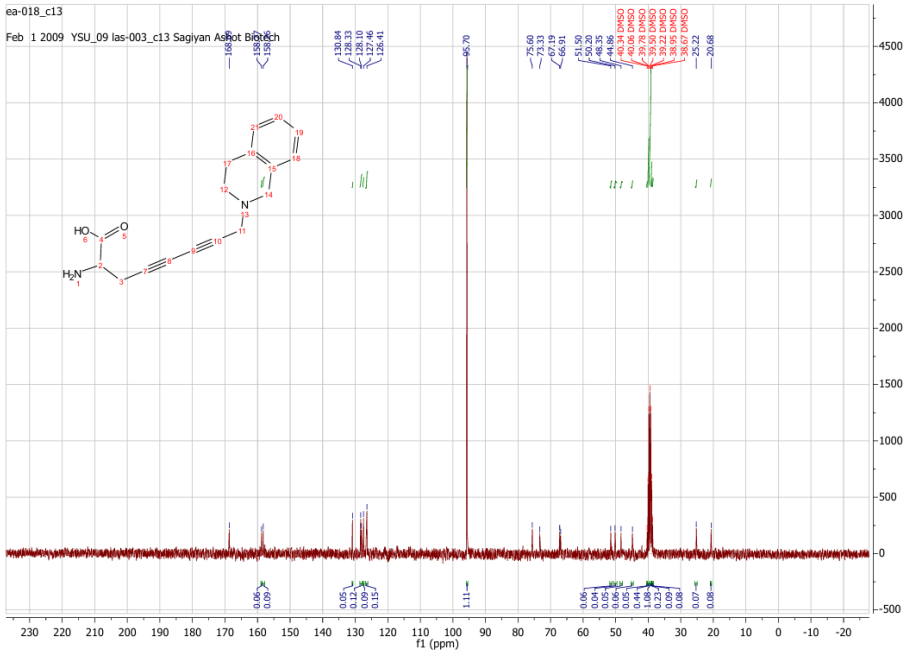
^{13}C NMR Complex 3



^{1}H NMR 2-amino-8-(3,4-dihydroisoquinolin-2(1H)-yl)octa-4,6-diynoic acid 4



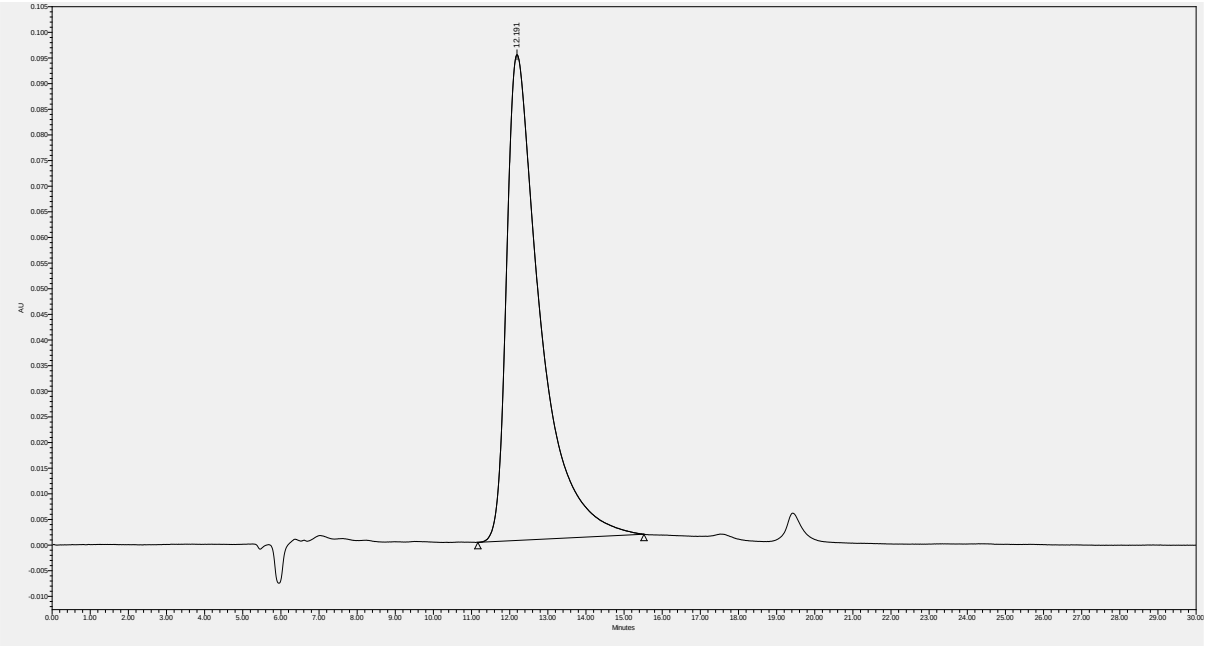
^{13}C NMR 2-amino-8-(3,4-dihydroisoquinolin-2(1H)-yl)octa-4,6-diynoic acid 4



HPLC analysis

HPLC analysis: The separation of chiral amino acids was carried out on the Waters Alliance 2695 HPLC system on the chiral phase Diaspher-110- Chirasel-E-PA 6.0 μm 4.0×250 mm, and a mixture of 20% MeOH and 80% 0.1 M aqueous solution $NaH_2PO_4 \cdot 2H_2O$ was used as the eluent. Analysis was carried out at a flow rate of 0.5 mL/min, and the column temperature was set to 40°C. The fluorescence excitation and emission wavelengths were 350 and 450 nm, respectively, and the injection volume was 10 μL.

HPLC analysis of **2-amino-8-(3,4-dihydroisoquinolin-2(1H)-yl)octa-4,6-diynoic acid 4**



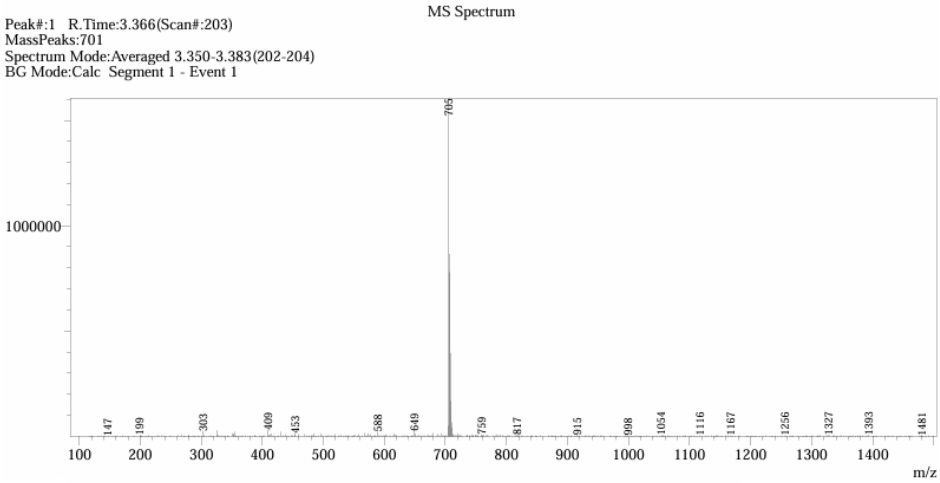
	Name	Retention Time	Area	% Area	Height
1		12.191	5846979	100.00	94729

MS spectra

LC-MS: Compounds were analyzed using a Prominence I LC-2030C 3D Plus (Shimadzu Corporation, Kyoto, Japan) LC system connected to a simple quadrupole MS system (LC-MS-2020, Shimadzu Corporation, Kyoto, Japan) equipped with electrospray ionization (ESI) source. The mobile phase contained 0.1 % formic acid in water and 0.1 % formic acid in methanol (20/80 v/v) at a flow rate of 0.2 mL/min. The mass spectrometer was operated in the positive electrospray ionization mode. The interface settings were as follows. Nebulizing-gas flow rate: 1.5 L/min; drying-gas flow rate: 15.0 L/min; interface temperature: 350°C; heat

block temperature: 200°C, DL temperature: 250°C. All the peak analyses for the LC-MS were performed using LabSolutions ver. 5.99 SP2 (Shimadzu, Japan).

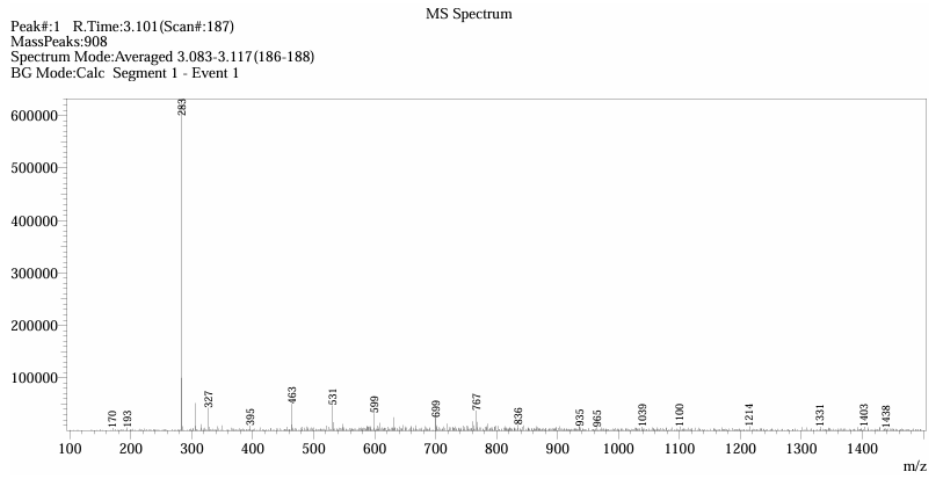
Complex 3



MASS Peak Table TIC

Peak#	Ret. Time	Area	Base Peak m/z
1	3.366	98685850	705.05
Total		98685850	

2-amino-8-(3,4-dihydroisoquinolin-2(1H)-yl)octa-4,6-diynoic acid 4



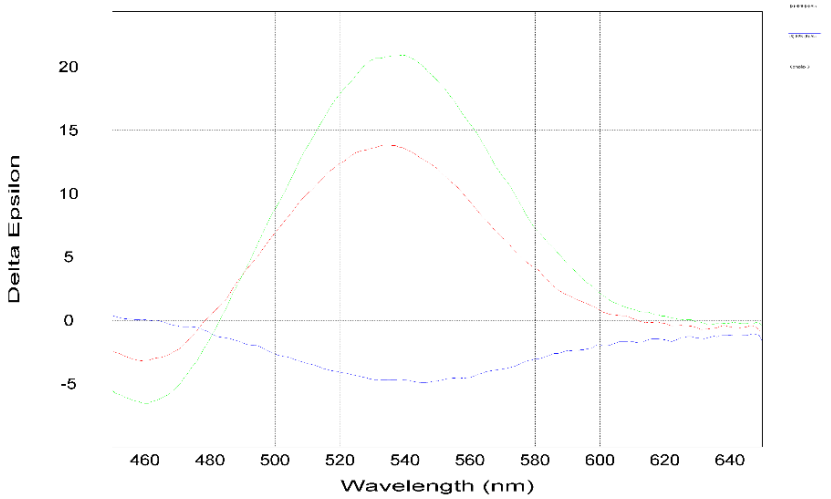
MASS Peak Table TIC

Peak#	Ret. Time	Area	Base Peak m/z
1	3.101	59192223	282.95
Total		59192223	

CD analysis

CD spectra of complex 3 and the reference (*S*,*S*)- and (*S*,*R*)-diastereomeric alanine complexes.

Complex 3: C: 0.2 mg/mL. $\Delta\varepsilon_{max}$ (λ_{max}): -13.36 (413); -4.56 (439); -6.56 (461); +20.92 (539).



Complex 3 exhibits a CD profile with the same sign and similar shape as the (*S*,*S*)-diastereomer, whereas the (*S*,*R*)-diastereomer shows the opposite CD response, supporting assignment of the (*S*,*S*) configuration to complex 3.