Supporting Information

Convenient Asymmetric Synthesis of Fmoc-(*S*)-6,6,6-trifluoro-Norleucine

Haibo Mei, Zizhen Yin, Toshio Miwa, Hiroki Moriwaki,* Hidenori Abe, Jianlin Han,* and Vadim A. Soloshonok*

1. General Methods. All reagents and solvents were used as received. Reactions were magnetically stirred and monitored by thin layer chromatography on Merck silica gel 60-F_{254} coated 0.25 mm plates, detected by UV. Flash chromatography was performed with the indicated solvents on silica gel (particle size 0.064-0.210 mm). Yields reported are for isolated, spectroscopically pure compounds. HPLC was performed on a SHIMADZU LC-2010CHT chromatograph with a CLASS-VP™ analysis data system using the Inertsil™ ODS-3 column (particle size 3 μm, 150 x 4.6 mm i.d.) operated at 1.0 mL/min, 30 ºC and monitored at wavelength of 254 nm with a linear gradient of 10 mM aqueous ammonium formate containing 0.1% formic acid (eluent A) and acetonitrile (eluent B) from A: B = 95:5 to 20:80 (0 to 15 min) and 20:80 (15 min to 25 min), unless otherwise stated. ^{1}H-, ^{19}F- and ^{13}C-NMR spectra were recorded on Brüker AVANCE III-400 spectrometer. Chemical shifts are given in ppm (*d*), referenced to tetramethylsilane (TMS) for ^{1}H-NMR and the ^{13}C-resonances of $CDCl_3$ (*d* = 77.0 ppm) for ^{13}C-NMR as internal standards. The letters s, d, t, q, m, and br stand for singlet, doublet, triplet, quartet, multiplet, and broad, respectively. Optical rotations were recorded on a DIP-370 polarimeter (Jasco, Inc.). Melting points were recorded on a Mettler Toledo MP70 Melting Point System and are not corrected. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. All physicochemical data reported for

the Ni(II) complexes are due to the single diastereomers after purification by chromatography or crystallization.

Alkylation of Glycine Complex (*S*)-4 with $ICH_2CH_2CH_2CF_3$. To a solution of the Ni-Glycine complex (*S*)-**4** (20.0 g, 33.2 mmol, 1.0 equiv.) and 1,1,1-trifluoro-4-iodobutane (7.90 g, 33.2 mmol, 1.0 equiv.) in deoxygenated *N*,*N*-dimethyl-formamide (DMF) (140 mL, 7 v/w) was added 10 % KOH methanol solution (18.6 mL, 33.2 mmol, 1.0 equiv.) at room temperature under an argon atmosphere. The mixture was stirred at same temperature for 2 h, and then was poured water (46 mL) at same temperature to give precipitate. After 0.5 h, the mixture was added water (24 mL), and was stirred for 15 h. After that, the precipitate was filtered, washed with DMF-H_2O (36 mL, 2:1 v/v), washed with water (40 mL) and dried *in vacuo* at 60 °C for 7 h to afford crude Ni complex (20.8 g, 87.9%, a red solid) as a mixture of (*S*,2*S*)-**6** and (*S*,2*R*)-**7**, the diastereomeric ratio of which was determined to be (98.7 %*de*) by HPLC analysis in which the major (*S*,2*S*)-**6** was eluted at a retention time (t_R) of 20.3 min and the minor (*S*,2*R*)-**7** at 21.5 min under the conditions described in the general methods.

(*S*,2*S*)-**6 (major isomer)**: M.p. 229-231 °C. $[\alpha]^{25}_D$= +2616 (c = 0.2, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89 (d, *J* = 1.6 Hz, 1H), 8.09 (d, *J* = 9.2 Hz, 1H), 7.77 (dd, *J* = 1.7, 8.1 Hz, 1H), 7.49-7.58 (m, 3H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.29-7.30 (m, 1H), 7.11

(dd, J = 2.4, 9.2 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 6.59 (d, J = 2.4 Hz, 1H), 4.34 (d, J = 12.6 Hz, 1H), 3.87 (dd, J = 8.0, 3.4 Hz, 1H), 3.51-3.57 (m, 2H), 3.35-3.39 (m, 1H), 3.21 (d, J = 12.6 Hz, 1H), 2.59-2.71 (m, 2H), 2.35-2.37 (m, 1H), 2.24-2.25 (m, 1H), 1.84-2.08 (m, 3H), 1.82-1.84 (m, 2H), 1.60-1.66 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0, 23.5, 30.8 32.6 (J = 29.0 Hz, q), 34.1, 58.3, 63.0, 69.7, 71.3, 124.1, 125.3 (J = 276.6 Hz, q), 125.7, 127.0, 127.1, 127.2, 129.3, 129.4, 129.8, 130.3, 132.1, 132.4, 132.7, 133.3, 133.5, 133.6, 134.8, 140.5, 170.4, 178.3, 179.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -66.8 (CF_3). IR (KBr): ν = 2977, 1674, 1650, 1535, 1463, 1398, 1251, 1188, 1077, 826 cm^{-1}. MS (ESI): m/z = 710.1 $[M + H]^+$.

The additional minor products were isolated by preparative thin layer chromatography on Merck silica gel 60-F_{254} coated 1 mm plates.

(*S*,2*R*)-**7 (minor isomer)**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, J = 9.2 Hz, 1H), 8.37 (d, J = 2.0 Hz, 1H), 7.74 (dd, J = 2.0, 8.0 Hz, 1H), 7.03-7.23 (m, 4H), 7.20-7.23 (m, 2H), 7.00-7.03 (m, 1H), 6.72 (d, J = 2.4, 1H), 4.24-4.30 (m, 2H), 3.71 (dd, J = 10.0, 3.2 Hz, 1H), 3.55 (dd, J = 8.8, 4.4 Hz, 1H), 3.35-3.38 (m, 1H), 2.62-2.67 (m, 2H), 2.25-2.30 (m, 2H), 1.80-2.00 (m, 2H), 1.64-1.79 (m, 3H), 1.25-1.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 23.1, 30.3 32.2 (J = 29.0 Hz, q), 35.1, 59.5, 60.5, 69.2, 69.7, 125.0, 125.4 (J = 276.6 Hz, q), 125.7, 126.6, 126.7, 127.6, 129.1, 129.5, 130.2, 130.5, 132.3, 132.5, 133.2, 133.3, 133.4, 133.8, 133.9, 141.3, 170.9, 178.9, 181.5. ^{19}F NMR

(376 MHz, $CDCl_3$): δ = -66.6 (CF_3). IR (KBr): ν = 2945, 1676, 1644, 1584, 1464, 1395, 1247, 1135, 1029, 823 cm^{-1}.

Preparation of Fmoc-(*S*)-2-amino-6,6,6-trifluorohexanoic acid (*S*)-9. To a solution of Ni complex (*S*,2*S*)-**6** (20.0 g, 28.1 mmol, 1.0 equiv.) in dimethoxyethane (DME) (100 mL, 5 v/w) was added HCl (3 N, 46.8 mL, 5.0 equiv.), and the resulting mixture was heated at 50-60 °C for 2 h. Then, the reaction mixture was cooled to room temperature, and the the reaction mixture was evaporated to remove DME. Water (400 mL) was added, and white precipitate (HCl salt) appeared. The precipitate was filtered, washed with water (20 mL × 2). The filtrate was total 80 mL.

To the above L-6,6,6-trifluoro-Norleucine HCl green solution were added ethylenediaminetetraacetic acid disodium salt hydrate (10.5 g, 1.0 equiv) and acetonitrile (60 mL) and the mixture was stirred for 0.5 h at room temperature. 48% NaOH (9.5 g, 4.1 equiv) was added. Then, sodium carbonate (3.87 g, 1.3 equiv) and Fmoc-OSu (9.48 g, 1.0 equiv.) were added to the resulting mixture. The mixture was stirred for 3 h at room temperature, and then was concentrated. To the residue was added ethyl acetate (100 mL) and HCl (6N, 20.0 mL), and the phases were separated. Water layer was washed with ethyl acetate (40 mL) and the combined organic layer was

washed with water (40 mL) and 10 % brine (40 mL). The combined organic solution was dried with Na_2SO_4, and then the filtrate was concentrated to dryness and dried *in vacuo* at 50 °C to afford (*S*)-**9** (11.45 g, a white powder).

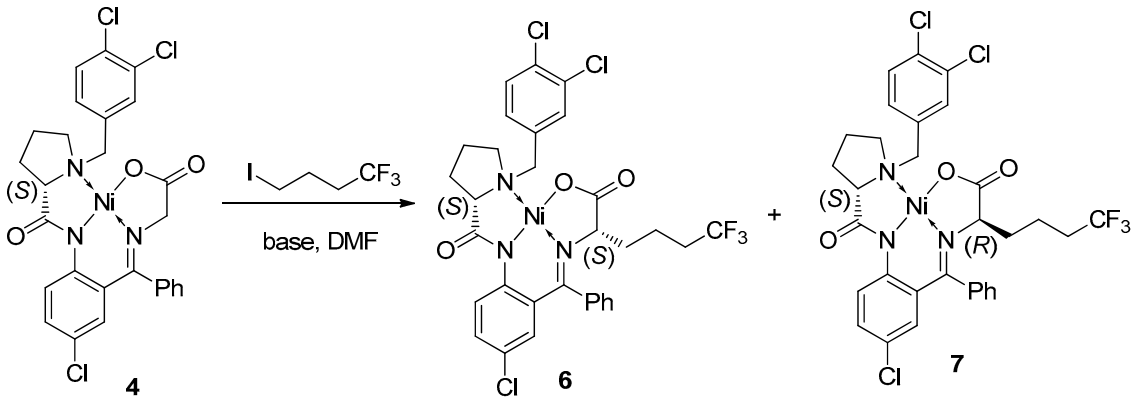
Fmoc amino acid (*S*)-**9** (11.45 g) was dissolved in ethyl acetate (100 mL) and toluene (200 mL). The solution was concentrated. Toluene (100 mL) was added to the solution and then concentrated. The solution was adjusted to 200 mL and left to stand for overnight. The precipitate was filtered, washed with toluene (60 mL) and dried *in vacuo* at 50 °C to afford (*S*)-**9** (10.7 g, 93.7 %, a white powder, 99.0% ee).

(*S*)-**9**: M.p. 152-154 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.77-7.79 (m, 2H), 7.64-7.69 (m, 2H), 7.32-7.40 (m, 2H), 7.28-7.30 (m, 2H), 4.36-4.37 (m, 2H), 4.18-4.24 (m, 2H), 2.18-2.23 (m, 2H), 1.92-1.95 (m, 1H), 1.64-1.77 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -67.6 (CF_3). IR (KBr): ν = 3265, 3067, 2926, 2858, 1654, 1476, 1445, 1049 cm^{-1}. MS (ESI): m/z = 431.1 $[M + Na]^+$.

2. Synthesis of Fmoc-L-6,6,6-trifluoro-Norleucine 9 (> 5 g)

2.1. Preparation of (*S,S*)- 6

Alkylation of **4** with 1,1,1-trifluoro-4-iodobutane



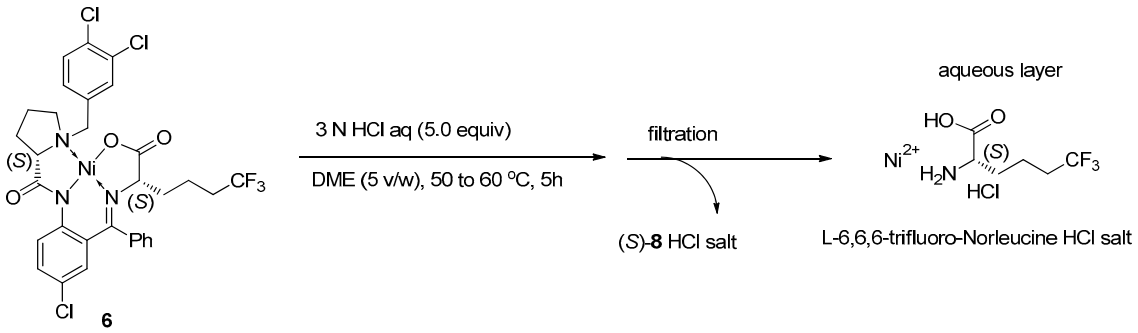
Entry	Scale	Conditions	Yield	HPLC results
1	20.0 g	1,1,1-Trifluoro-4-iodobutane (1.0 eq., 7.90 g) DMF (7 v/w, 140 mL) 10%KOH/MeOH* (1.0 eq., 18.6 mL) r.t. 2h	20.8 g, 87.9% yield	98.44% purity 98.7% *de*

HPLC Analyses of alkylation of (*S*)-4

sample	18.1 min	20.3 min	21.5 min	27.3 min
	(*S*)-4	**(*S,S*)-6**	**(*S,R*)-7**	**(*S*)-8**
Reaction 5 min	1.56	92.33	3.43	0.09
Reaction 1 h	1.06	93.29	3.41	0.10
Reaction 2 h	0.84	92.67	3.36	0.09
dry	0.62	98.44	0.56	0.02

2.2. Disassembly of (*S,S*)-6

Disassembly of **(*S,S*)-6**



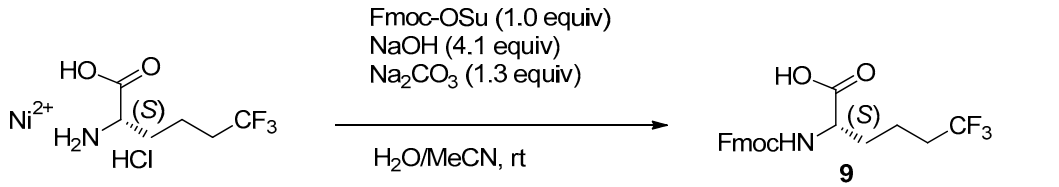
Entry	**(*S,S*)-6**	Conditions	Results
1	20.0 g 98.44% purity 98.7% *de*	3 N HCl (5.0 equiv, 46.8 mL), DME (5 v, 100 mL) 50 to 60 °C, 2 h	Starting material completely converted to TM though TM was not detected by HPLC

HPLC Analyses of Disassembly of (*S,S*)-6

sample	**(*S*)-4**	**(*S,S*)-6**	**(*S,R*)-7**	**(*S*)-8**
Reaction 1 h	n.d.	0.17	n.d.	99.64
Reaction 2 h	n.d.	0.01	n.d.	99.86

2.3. Fmoc-protection of L-6,6,6-trifluoro-Norleucine 9

Fmoc-protection of L-6,6,6-trifluoro-Norleucine **9**



L-6,6,6-trifluoro-Norleucine HCl salt

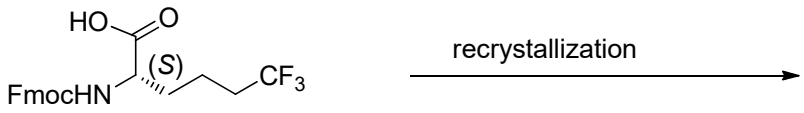
Fmoc-L-6,6,6-trifluoro-Norleucine

Entry	**Scale**	Conditions	Results
1	7.37 g	MeCN (60 mL), EDTA (1.0 equiv, 10.5 g), 48% NaOH (4.1 equiv, 9.5 g), Na2CO3 (1.3 eq, 3.87 g) Fmoc-OSu (1.0 equiv, 9.48 g), rt, 16.5 h	-

Fmoc-L-6,6,6-trifluoro-Norleucine AcOEt solution (theoretical yield 11.45 g)

2.4. Crystallization of Fmoc-L-6,6,6-trifluoro-Norleucine 9

Exp. # 1371-109 Crystallization of Fmoc-L-6,6,6-trifluoro-Norleucine **9**



Fmoc-L-6,6,6-trifluoro-Norleucine

Entry	**Scale**	Conditions	Yield	Results
1	11.45 g	Toluene (300 mL)	93.7% (from (S,S)-**6**)	98.79% purity 99.0% ee

Fmoc-L-6,6,6-trifluoro-Norleucine (10.73 g, 93.7% yield)

3. HPLC analysis data

3-1. General conditions for HPLC analysis of Ni(II) complexes

<HPLC conditions : for the Ni(II) complex>

Insturument: SHIMADZU LC-2010CHT chromatography system and a CLASS-VP^{TM} analysis data system (SHIMADZU CORPORATION, Kyoto, Japan).

Column: Inertsil ODS-3, S-3 μm, ϕ4.6 mm×150 mm

Eluent: A = 0.01 M $HCOONH_4$ in 0.1% HCOOH aq

B = acetonitrile

Gradient:

Time(min)	0.0	15.00	20.00	23.00	30.00	30.01	37.00
A (%)	95	20	20	0	0	95	95
B (%)	5	80	80	100	100	5	5

Flow rate: 1.0 mL/min.

Column temperature: 30 °C

Detector: UV 254 nm

3-2. General conditions for Chiral HPLC analysis of Fmoc amino acid

General conditions for Chiral HPLC analysis of Fmoc amino acid

<Chiral HPLC conditions : for Fmoc amino acid>

Insturument: SHIMADZU LC-2010CHT chromatography system and a CLASS-VP^{TM} analysis data system (SHIMADZU CORPORATION, Kyoto, Japan).

Column: CHIRALPAK IC (DAICEL CHEMICAL), S-5 μm, φ 4.6 mm×150 mm

Eluent: A = 0.1% H_3PO_4 in H_2O

B = 0.1% H_3PO_4 in MeCN

Flow rate: 0.5 mL/min.

Gradient: Isocratic (A : B = 6 : 4)

Column temperature: 30 °C

Detector: UV 254 nm

Major isomer

サンプル名 : 1371-09113_major_miwa
サンプルID :
トレイ番号 : 1
バイアル番号 : 42
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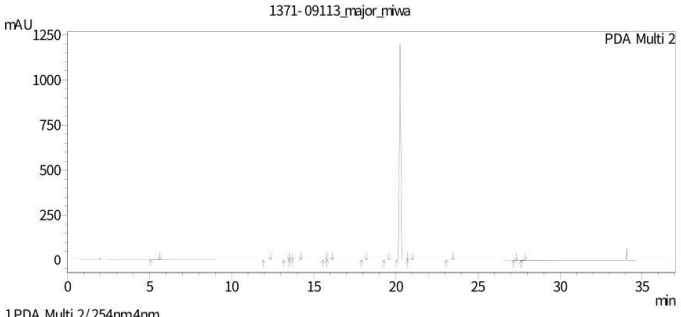

1PDA Multi 2/254nm,4nm

<ピークテーブル>

PDA Ch2 254nm

ピーク#	保持時間	面積	面積%	マーク	理論段数(USP)	化合物名
1	5.6	1167	0.015		295	
2	12.1	1266	0.016		19196	
3	13.2	1003	0.013		274	
4	13.6	1311	0.017	V	19507	
5	13.8	2182	0.028	V	21901	
6	15.7	1439	0.018		52044	
7	15.9	1167	0.015	V	16950	
8	18.0	1369	0.017		139125	
9	19.4	6878	0.087		185617	
10	20.2	7889763	99.659		178006	
11	20.9	2693	0.034	V	79699	
12	23.3	1647	0.021	V	81466	
13	27.2	1869	0.024		479312	
14	27.7	3021	0.038		405602	
合計		7916775	100.000			

Minor isomer

サンプル名 : 1371-09115_minor_miwa
サンプルID :
トレイ番号 : 1
バイアル番号 : 43
注入量 : 10 uL
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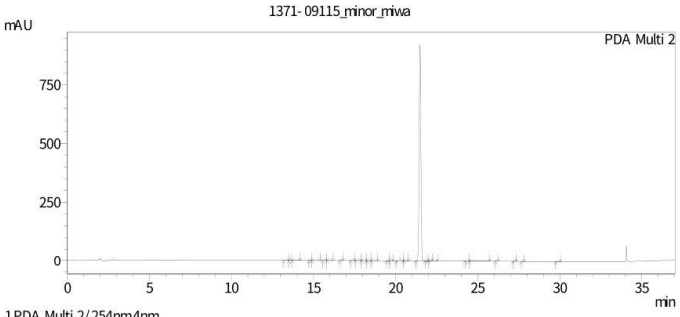


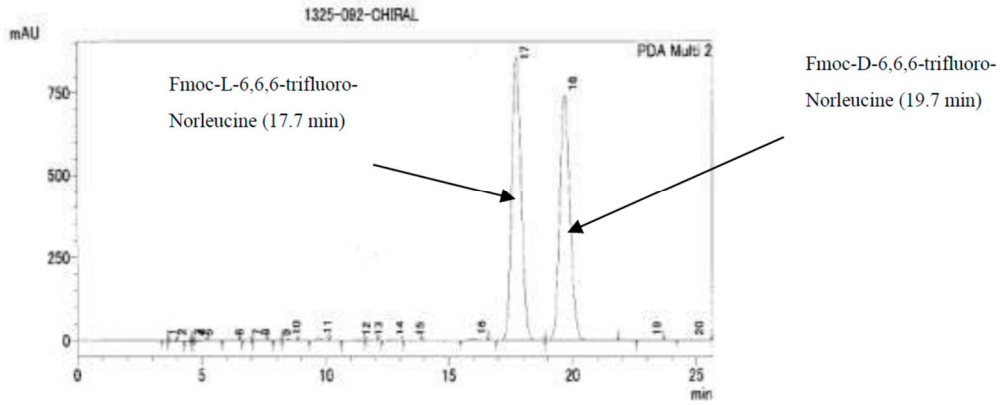
1PDA Multi 2/254nm,4nm

<ピークテーブル>

PDA Ch2 254nm

ピーク#	保持時間	面積	面積%	マーク	理論段数(USP)	化合物名
1	13.2	1122	0.016		182437	
2	13.6	1544	0.022	V	946	
3	13.8	2558	0.036	V	10979	
4	14.8	1853	0.026		38253	
5	15.0	3292	0.046	V	17205	
6	15.6	3647	0.052		43481	
7	15.9	4203	0.059	V	10233	
8	16.7	1010	0.014		106851	
9	17.3	3911	0.055		161677	
10	17.7	3392	0.048		142849	
11	18.0	1389	0.020		138210	
12	18.3	1388	0.020		100083	
13	18.6	11060	0.156		116365	
14	19.5	2660	0.038		227130	
15	19.7	4348	0.061		188191	
16	20.2	115728	1.635		169165	
17	20.5	2285	0.032	V	53281	
18	21.5	6889050	97.301	SV	160892	
19	21.9	1894	0.027	T	306520	
20	22.1	1876	0.026	T	147534	
21	24.3	1045	0.015		31374	
22	24.6	8873	0.125	V	6303	
23	26.1	1173	0.017		415833	
24	27.2	8302	0.117		454295	
25	27.7	1302	0.018		509973	
26	29.9	1256	0.018		355772	
合計		7080159	100.000			

Chiral HPLC chart of mixture of (*S*)- and (*R*)-**Fmoc-amino acid**



Chiral HPLC chart of (*S*)-**Fmoc-amino acid**

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バイアル番号	: 11
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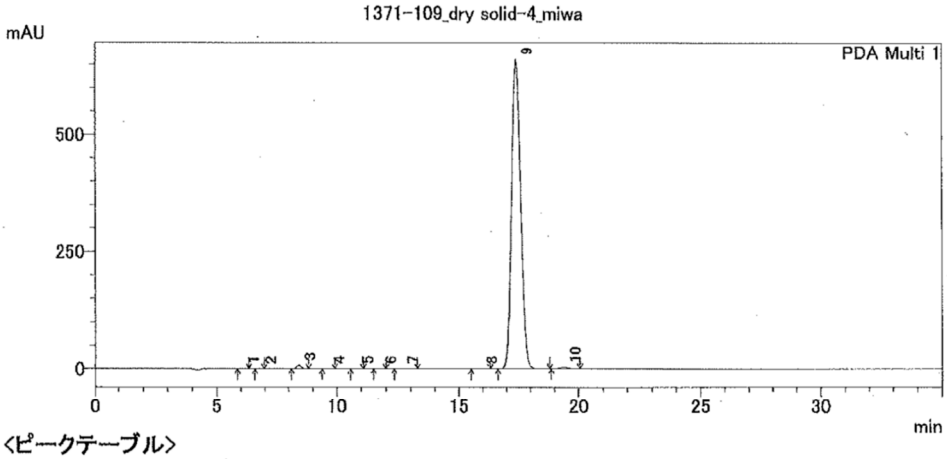
〈クロマトグラム〉



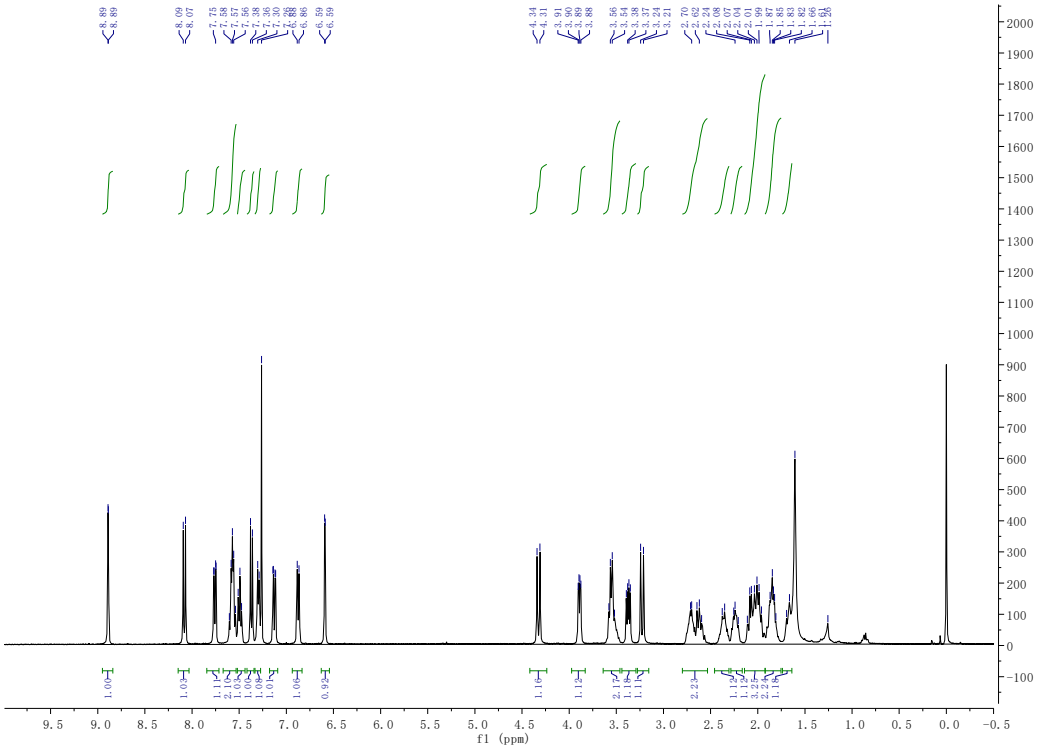
〈ピークテーブル〉

PDA Ch1 254nm 4nm

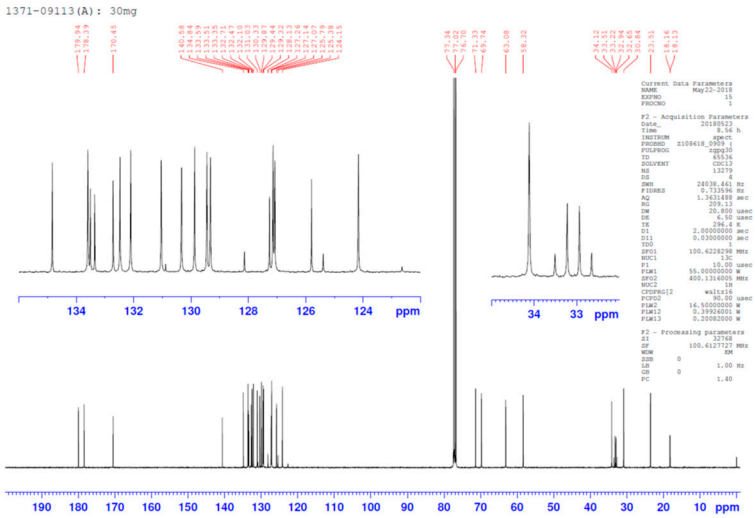
ピーク#	保持時間	面積	面積%	マーク
1	6.054	10254	0.058	
2	6.774	1505	0.008	
3	8.400	102697	0.579	
4	9.626	4870	0.027	
5	10.789	3284	0.019	
6	11.720	3440	0.019	
7	12.614	13248	0.075	
8	15.903	11871	0.067	
9	17.408	17503569	98.657	SME
10	19.396	87024	0.491	RE
合計		17741762	100.000	

4. Copies of ^{1}H, ^{13}C and ^{19}F-NMR spectra

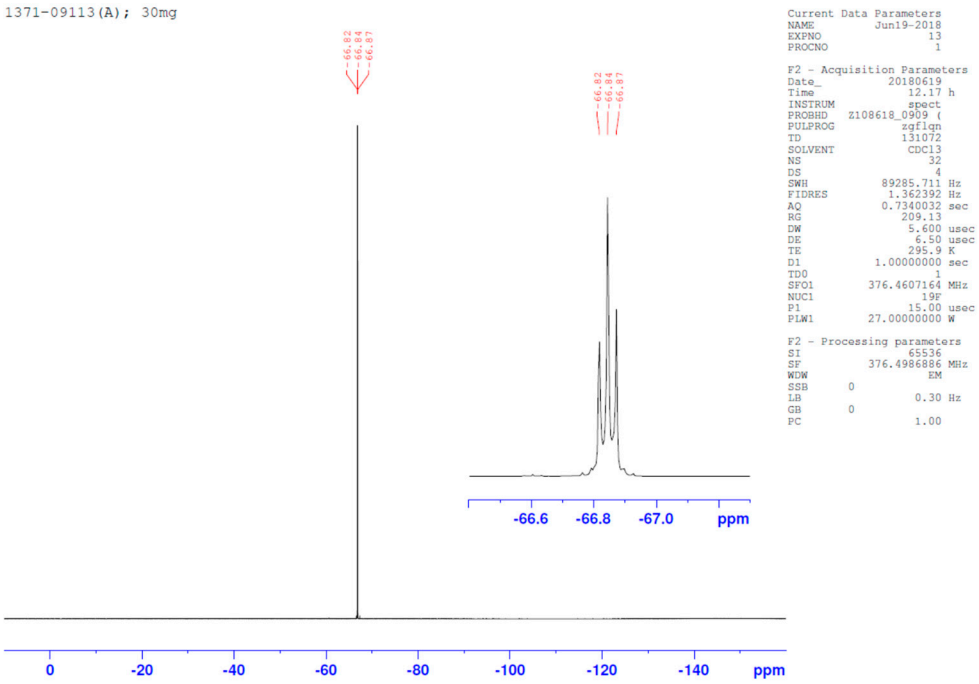
^{1}H-NMR (400 MHz, $CDCl_3$) of (*S*,2*S*)-**Ni-complex 6 (major isomer)**



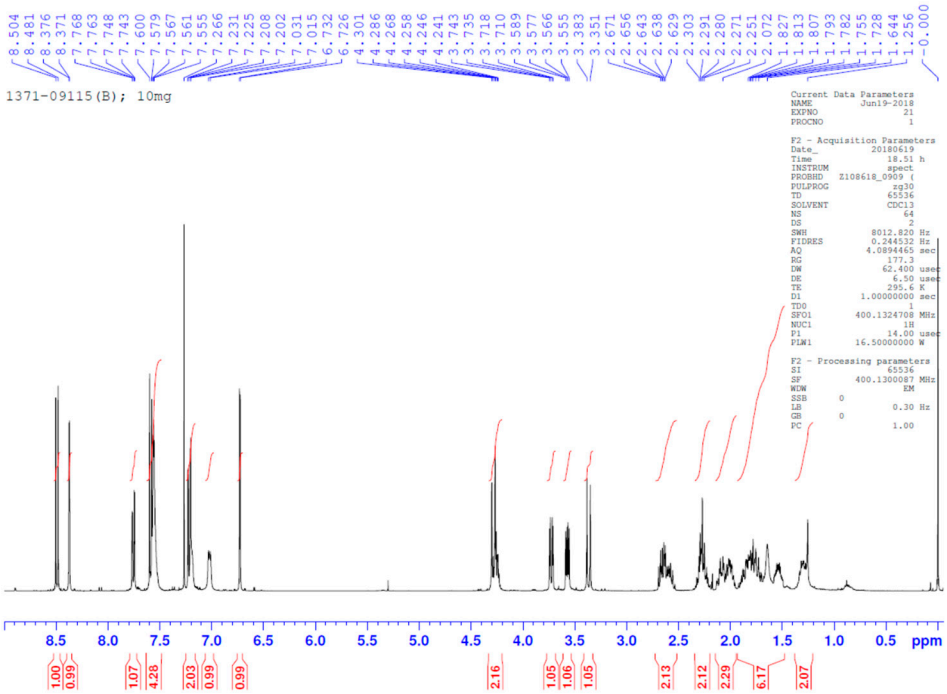
^{13}C-NMR (100 MHz, $CDCl_3$) of (*S*,2*S*)-**Ni-complex 6 (major isomer)**



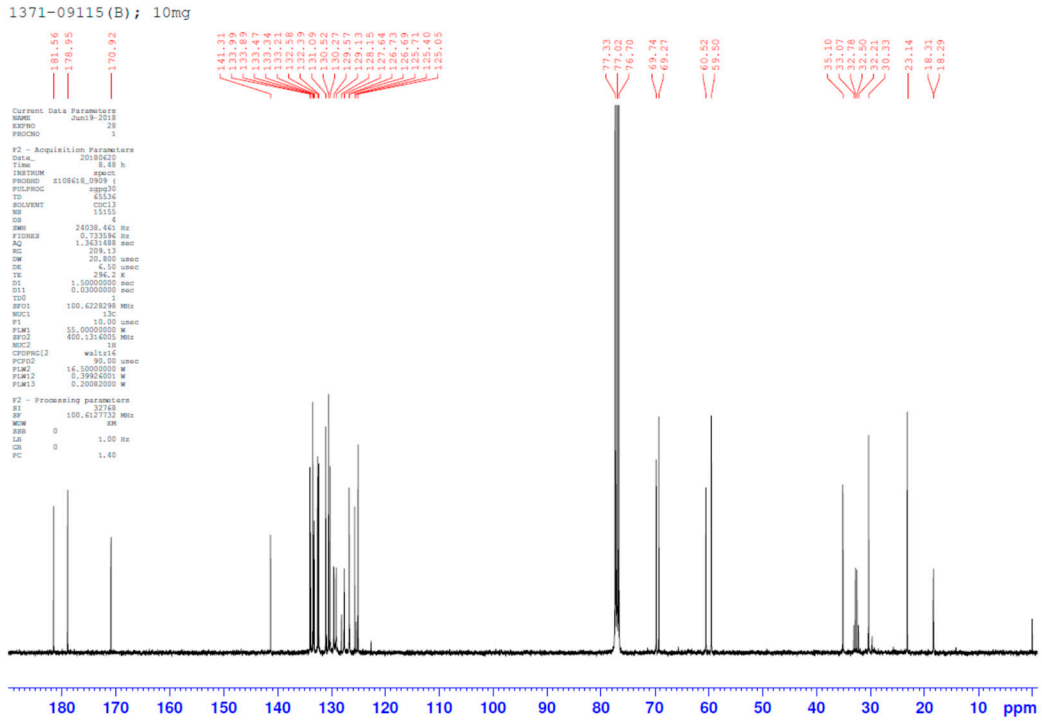
^{19}F-NMR (376 MHz, $CDCl_3$) of (*S*,2*S*)-**Ni-complex 6**



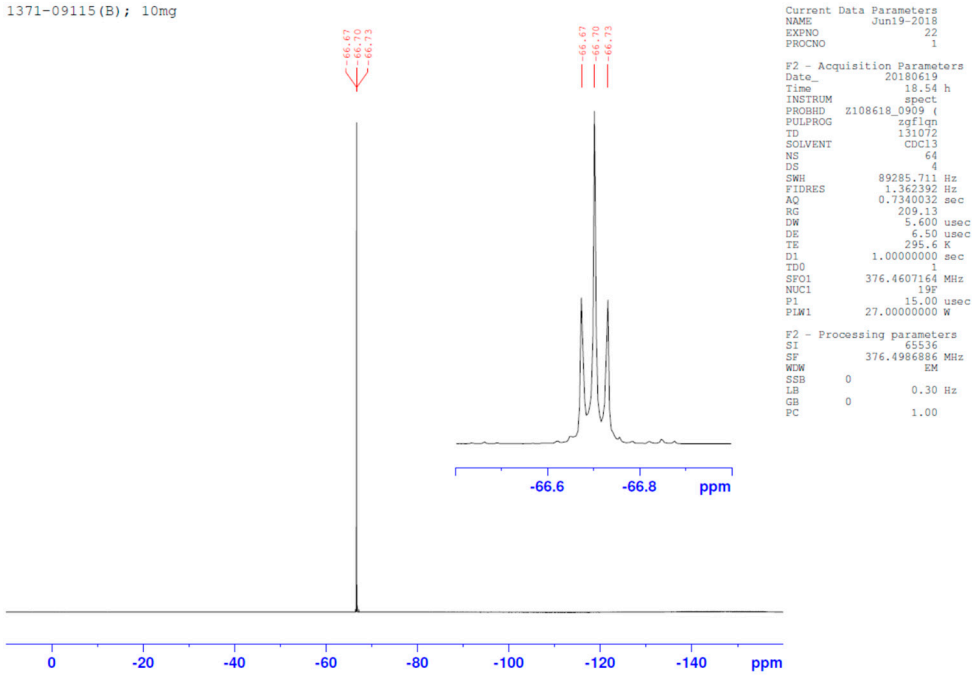
^{1}H-NMR (400 MHz, $CDCl_3$) of (*S*,2*R*)-**Ni-complex 7 (minor isomer)**



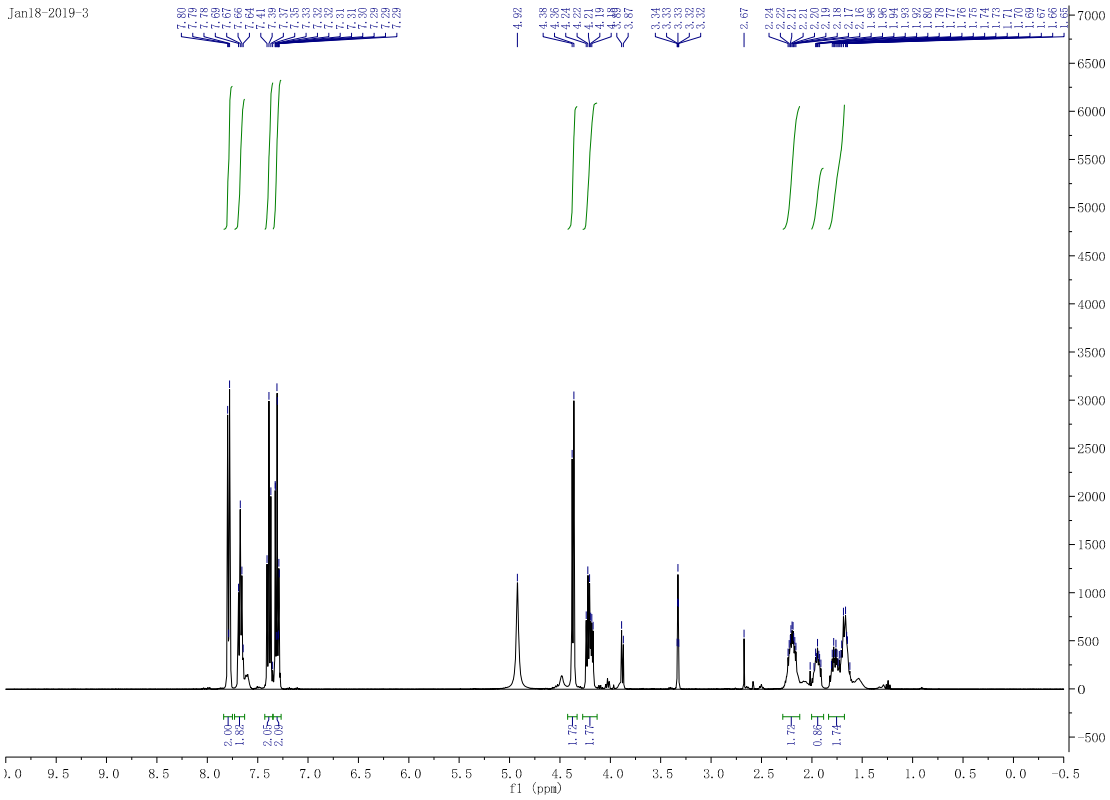
^{13}C-NMR (100 MHz, $CDCl_3$) of (*S*,2*R*)-**Ni-complex 7 (minor isomer)**



^{19}F-NMR (376 MHz, $CDCl_3$) of (*S*,2*R*)-**Ni-complex 7 (minor isomer)**



^{1}H-NMR (400 MHz, CD_3OD) of (*S*)-**Fmoc-amino acid 9**



^{19}F-NMR (376 MHz, CD_3OD) of (*S*)-**Fmoc-amino acid 9**