

Supporting Information

Enantioselective Total Syntheses of Grayanane Diterpenoids: (–)-Grayanotoxin III, (+)-Principinol E, and (–)-Rhodomollein XX

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I. Supplementary Figures and Tables

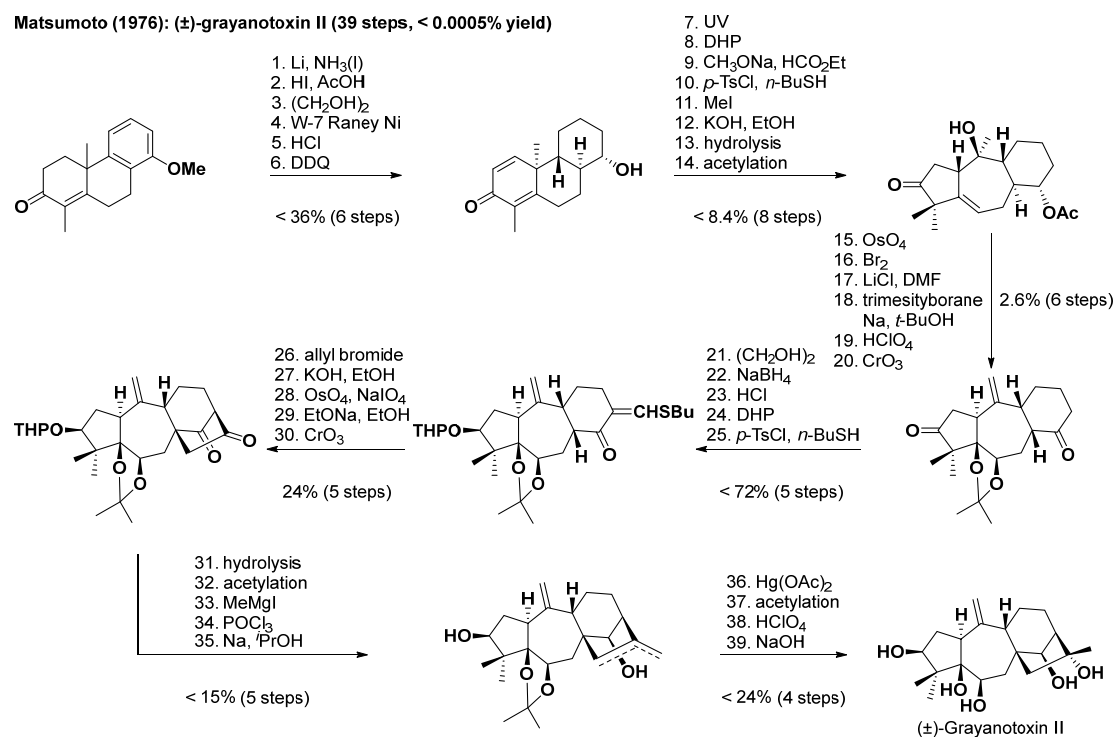
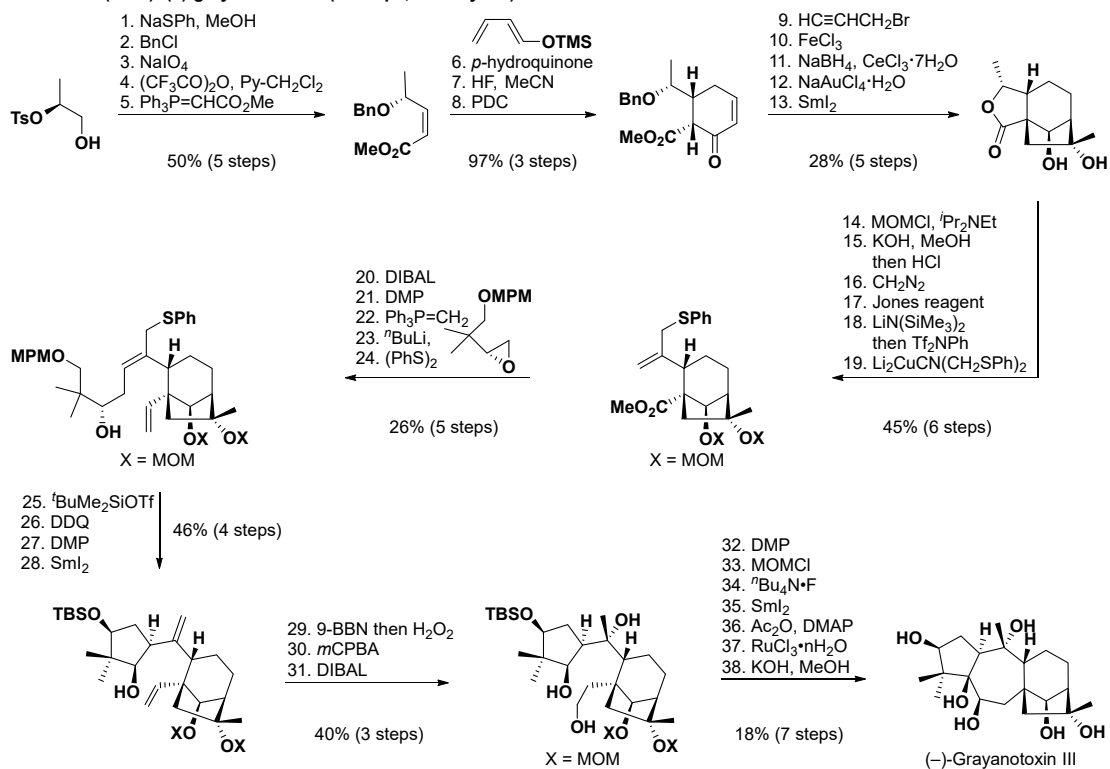


Figure S1. Relay total synthesis of grayanotoxin II.^[1]

Shirahama (1994): (–)-grayanotoxin III (38 steps, 0.05% yield)



Newhouse (2019): principinol D (19 steps, 1% yield)

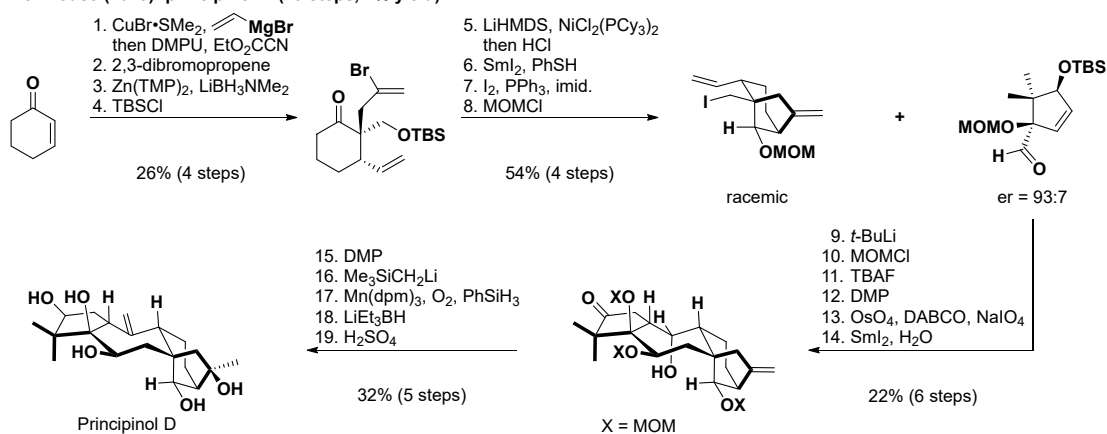
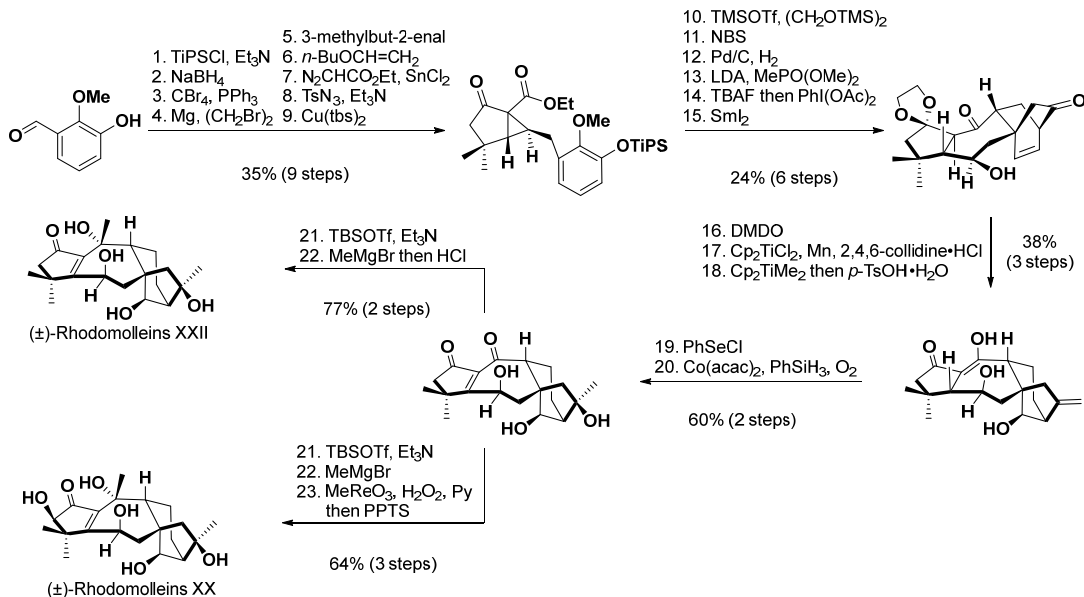


Figure S2. Reported total syntheses of grayanane diterpenoids.^[2,3]

Ding (2019): (±)-rhodomolleins XX and XXII (23 steps, 1.2% yield; 22 steps, 1.4% yield)



Ding (2020): (–)-rhodomollanol A (30 steps, 0.07% yield)

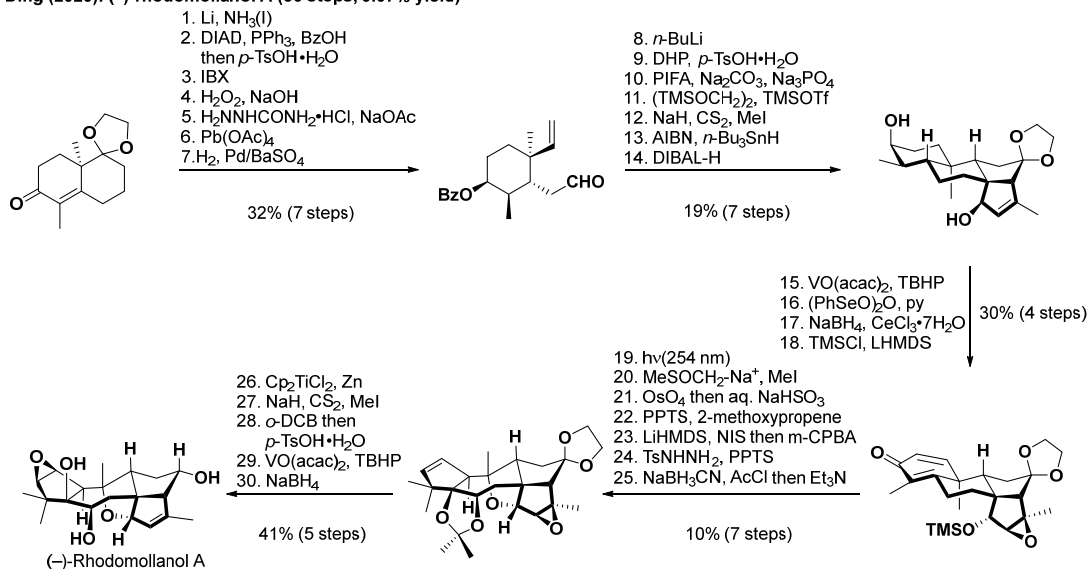


Figure S2. Reported total syntheses of grayanane diterpenoids (continued).^[4]

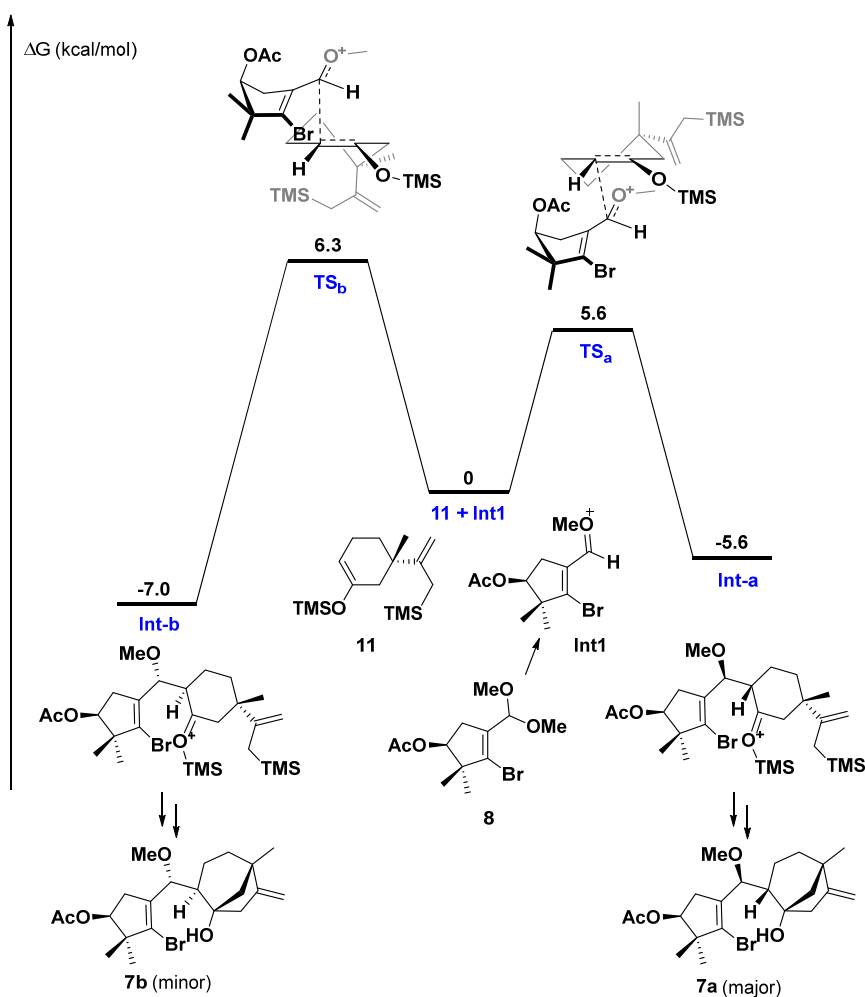
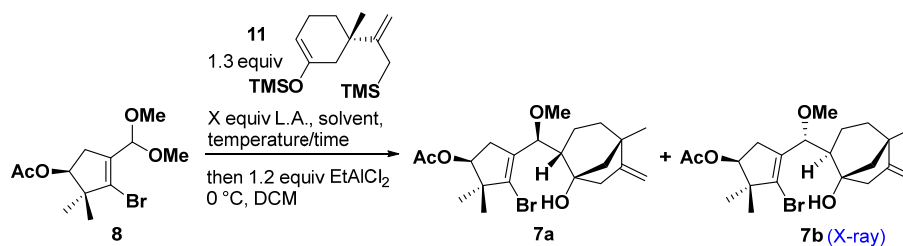


Figure S3. DFT calculated potential energy surface (PES) for Mukaiyama aldol reaction. Energies were obtained at B3LYP/6-31G(d,p) level of theory.

The intermolecular Mukaiyama aldol reaction between **8** and **11** catalyzed by 0.1 equiv TMSOTf in DCM was followed by the EtAlCl₂-mediated Sakurai reaction in the same reaction flask, affording two major products, **7a** and **7b**, as a 2:1 mixture. In order to rationalize the diastereoselectivity, we performed preliminary density functional theory (DFT) calculations and located two competing synclinal open transition states **TS_a** and **TS_b** with minimized gauche interactions between the OTMS moiety and the substituents on the oxocarbenium (Figure S3);^[5] the facial selectivity of silyl enol ether was dictated by the Fürst–Plattner rule.^[6] In agreement with the experimentally observed diastereoselectivity (assuming the similar efficiency of intramolecular Sakurai cyclizations), **TS_a** is favored over **TS_b** by 0.7 kcal/mol, which could be expected from the pseudo-axial occupation of the bulky propenyl group in **TS_b**.

Table S1. Optimization of the Mukaiyama Adol Reaction Followed by Cyclization.



entry	X	L.A.	solvent	temperature/time	yield (ratio) ^a
1	1	EtAlCl ₂	DCM	−78 °C, 3 h ^b	31% (1:1)
2	1	TiCl ₄	DCM	−78 °C, 10 min ^c	44% (2:1)
3	0.10	TMSOTf	DCM	−78 °C, 6 h then −40 °C, 1 h ^c	<67% (2:1) ^d
4	0.15	TMSOTf	DCM	−78 °C, 2 h then −40 °C, 1 h ^c	<62% (1.7:1) ^d
5	0.10	TMSOTf	^t BuOMe	−78 °C, 6 h ^c	– ^e
6	0.10	TMSOTf + (–)- A	DCM	−78 °C, 5 h then −40 °C, 2 h ^c	67% (3.2:1) ^d
7	0.10	TMSOTf + (–)- A	^t BuOMe	−78 °C, 1 h ^{c,f}	65% (1:2.5)
8	0.10	TMSOTf + (+)- A	DCM	−78 °C, 5 h then −40 °C, 2 h ^c	<15% (9:1)
9	0.10	TMSOTf + (+)- A	^t BuOMe	−78 °C, 1 h ^{c,f}	60% (9:1)
10	0.15	TMSOTf + (+)- A	^t BuOMe	−78 °C, 3 h ^{f,g}	58% (8.7:1)
11	0.15	TMSOTf + (+)- A	^t BuOMe	−78 °C, 3 h ^{g,h}	58%

^aIsolated yield after flash chromatography. ^b[**8**] = 0.114 M (0.057 mmol). ^c[**8**] = 0.114 M (0.114 mmol).

^dThe products were contaminated by a small amount of unidentified impurity. ^eTrace amount of Mukaiyama aldol products were observed via TLC, and subsequent cyclization was not executed. ^fThe Mukaiyama aldol reaction was quenched by NaHCO₃ (aq.), and the reaction mixture was extracted with EtOAc and concentrated *in vacuo* to give a residue that was subsequently dissolved in DCM (1 mL), followed by the addition of EtAlCl₂. ^g3 g scale. ^hThe Mukaiyama aldol reaction was quenched by MeOH/TEA, and the reaction mixture was diluted by DCM followed by the addition of 2 equiv EtAlCl₂; **7a** was isolated in 58% yield as a single diastereomer.

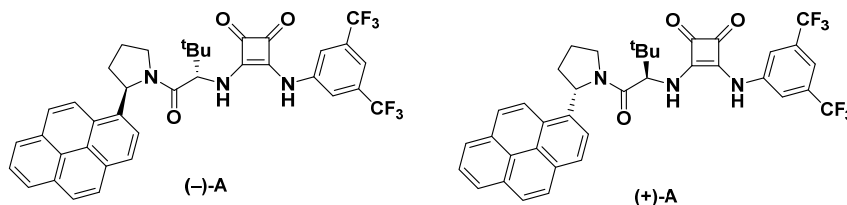
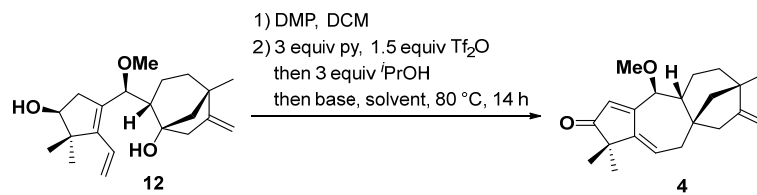


Table S2. Optimization of the Cyclization to Afford **4**.^a



entry	base	solvent	yield (%) ^b
1	1.5 equiv py	DCE	32
2	1.5 equiv Et ₃ N	DCE	25
3	1.5 equiv PhNEt ₂	DCE	34
4	6 equiv PhNEt ₂	DCE	9
5	1.5 equiv PhNEt ₂	DCE	16 ^c
6	1.5 equiv PhNMe ₂	DCE	33
7	1.5 equiv 2-Br-py	DCE	7
8	1.5 equiv 4-Ph-py	DCE	39
9	1.5 equiv 4-Ph-py	DCE:HMPA=4:1	0
10	1.5 equiv 4-Ph-py	DCE:THF=4:1	21
11	1.5 equiv 4-Ph-py	DCE:1,4-dioxane=4:1	29
12	1.5 equiv 4-Ph-py	DCE	44 ^d

^aReaction performed on 0.06 mmol scale; after triflation in DCM, 3 equiv ⁱPrOH was added and the volatiles were removed under vacuo, followed by the addition of solvent and base to the same flask. ^bNMR yield determined using 1,4-dinitrobenzene as the internal control. ^cT = 70 °C.

^dReaction performed on 12 mmol scale, isolated yield.

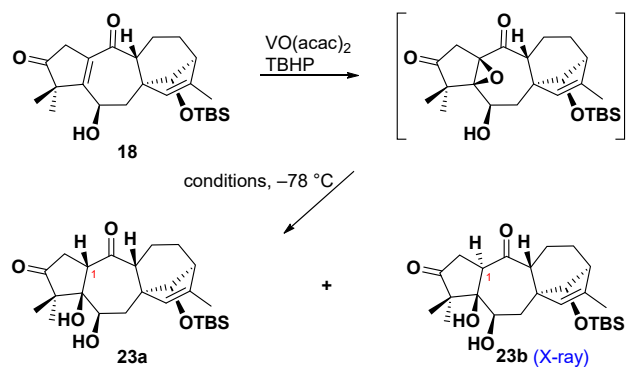
Table S3. Optimization of the MHAT Hydrogenation.^a

$\Delta^{1,2}$ -GTX (**22a**) $\xrightarrow{\text{conditions}}$ (-)-Grayanotoxin III (**1**) + 1-*epi*-GTX (**23**)

entry	conditions	conversion (%) ^b	yield (%) ^b	
			1	23
1	0.2 equiv Fe(acac) ₃ , 0.2 equiv <i>p</i> -MePhSH 2 equiv PhSiH ₃ , EtOH, 44 h	79 (79) ^c	-	70 (61) ^c
2	0.2 equiv Mn(dpm) ₃ , 1.5 equiv TBHP, 2.5 equiv PhSiH ₃ , ^t PrOH, 44 h	96	15	40
3	0.2 equiv Mn(dpm) ₃ , 1.5 equiv TBHP, 2.5 equiv Ph(ⁱ PrO)SiH ₂ , ^t PrOH, 44 h	88	21	19
4	0.2 equiv Mn(dpm) ₃ , 1.5 equiv TBHP, 2.5 equiv Ph(ⁱ PrO)SiH ₂ , EA, 18 h	89	25	5
5	0.2 equiv Mn(dpm) ₃ , 1.5 equiv TBHP, 2.5 equiv Ph(ⁱ PrO)SiH ₂ , DCM, 18 h	79	53	-
6	0.2 equiv Mn(dpm) ₃ , 1.5 equiv TBHP, 2.5 equiv Ph(ⁱ PrO)SiH ₂ , DCM, 27 h	80	51 ^d	-

^aReaction performed on 0.022 mmol scale in the glove box at room temperature, [**22a**] = 0.043 M. ^bNMR yield and conversion determined using 1,4-dinitrobenzene as the internal control. ^cYield in parentheses is isolated yield after flash chromatography. ^dIsolated yields for the reaction performed on 0.043 mmol scale, [**22a**] = 0.043 M.

Table S4. Optimization of the Epoxide Reduction.^a

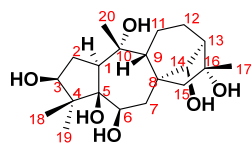


entry	reductant	solvent	yield (ratio) ^b
1	2.5 equiv SmI_2	THF/MeOH = 4:1	59% (2:1)
2	2.5 equiv SmI_2	THF/MeOH = 1:1	65% (3:1)
3	2.5 equiv SmI_2	THF/glycol = 10:1	67% (1.3:1)
4	2.5 equiv SmI_2	THF/ H_2O = 10:1	70% (1:1)
5	2.5 equiv SmI_2	THF/L-valinol = 20:1	52% (10:1)
6	2.5 equiv SmI_2	THF/D-valinol = 20:1	65% (20:1)
7	excess Li/Naphthalene	THF	40% (1:1.5)
8	2.5 equiv SmI_2	THF/D-valinol = 20:1	76% (8.5:1) ^c

^aReaction performed on 0.012 mmol scale. ^bIsolated yield over 2 steps after flash chromatography; the ratio (**23a**:**23b**) was determined by ^1H -NMR.

^cReaction performed on 0.046 mmol scale (20 mg).

Table S5. Comparison of the ^1H and ^{13}C NMR Data for Natural and Synthesized Grayanotoxin III (**1**)



Grayanotoxin III (**1**)

Position	Natural product 1 ^{a,b}		Synthesized 1 ^e	
	δ_{H} (m, J[Hz]) ^c	δ_{C} ^{a,d}	δ_{H} (m, J[Hz]) ^c	δ_{C} ^d
1	3.20 (m, 1H) ^a	51.6	3.19 (dd, 11.8, 4.6, 1H)	51.9
2	-	35.7	2.64-2.57 (m, 1H); 2.55-2.48 (m, 1H)	36.0
3	3.87 (s, 1H) ^a / 3.89 (d, 2.5, 1H) ^b	82.6	3.88 (d, 4.6, 1H)	82.8
4	-	51.7	-	52.1
5	-	84.6	-	84.9
6	4.55 (dd, 11, 4, 1H) ^a / 4.52 (dd, 10.5, 4.0, 1H) ^b	74.0	4.56 (dd, 11.2, 4.2, 1H)	74.4
7	-	44.2	2.89 (dd, 13.5, 4.2, 1H); 2.55-2.48 (m, 1H)	44.5
8	-	52.4	-	52.8
9	-	55.1	2.18 (d, 6.9, 1H)	55.5
10	-	78.1	-	78.4
11	-	22.4	2.04 (dd, 14.1, 6.1, 1H); 1.64-1.58 (m, 1H)	22.8
12	-	27.0	2.64-2.57 (m, 1H); 1.69-1.65 (m, 1H)	27.3
13	-	56.3	2.55-2.48 (m, 1H)	56.5
14	5.00 (s, 1H) ^a / 5.00 (s, 1H) ^b	79.3	5.05 (s, 1H)	79.5
15	-	60.3	2.27 (d, 14.6, 1H); 2.09 (d, 14.5, 1H)	60.5
16	-	79.8	-	80.0
17	1.51 (s, 3H) ^a / 1.51 (s, 3H) ^b	23.8	1.51 (s, 3H)	24.0
18	1.67 (s, 3H) ^a / 1.65 (s, 3H) ^b	19.7	1.70 (s, 3H)	20.1
19	1.17 (s, 3H) ^a / 1.12 (s, 3H) ^b	23.3	1.13 (s, 3H)	23.5
20	1.87 (s, 3H) ^a / 1.84 (s, 3H) ^b	28.3	1.87 (s, 3H)	28.5
OH	-		-	

^a Chemical shifts and coupling constants are reported by El-Naggar *et al.* (in $\text{C}_5\text{D}_5\text{N}$, D_2O exchanged)^[7]

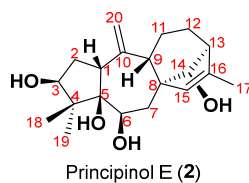
^b Chemical shifts and coupling constants are reported by Kan *et al.* (250 MHz in $\text{C}_5\text{D}_5\text{N}$)^[2]

^c TMS was used as internal standard: δ_{H} in ppm, J values (Hz) are in parentheses.

^d TMS was used as internal standard.

^e 600 MHz NMR spectrometer ($\text{C}_5\text{D}_5\text{N}$, D_2O exchanged).

Table S6. Comparison of the ^1H and ^{13}C NMR Data for Natural and Synthesized Principinol E (**2**).



Position	Natural product 2 ^a		Synthesized 2 ^d	
	δ_{H} (m, J [Hz]) ^b	δ_{C} ^c	δ_{H} (m, J [Hz]) ^b	δ_{C} ^c
1	2.80 (t, 9.2, 1H)	56.2	2.81 (t, 9.3, 1H)	56.5
2	2.24 (m, 1H); 1.95 (dd, 14.7, 9.2, 1 H)	36.2	2.25 (ddd, 14.6, 9.3, 5.1 1H); 1.99-1.93 (m, 1 H)	36.4
3	3.74 (d, 5.2, 1H)	84.2	3.75 (dd, 7.3, 5.0, 1H)	84.4
4	-	50.5	-	50.7
5	-	86.5	-	86.6
6	3.77 (d, 10.3, 1H)	69.5	3.80 (dd, 10.1, 5.8, 1H)	69.8
7	2.46 (1H); 1.64 (1H)	37.6	2.51-2.45 (m, 1H); 1.67-1.62 (m, 1H)	37.9
8	-	54.1	-	54.3
9	2.16 (d, 7.1, 1H)	50.0	2.17 (d, 7.1, 1H)	50.3
10	-	152.5	-	152.8
11	1.74 (1H); 1.56 (dd, 13.1, 5.0, 1H)	26.5	1.75-1.71 (m, 1H); 1.59-1.54 (m, 1H)	26.7
12	1.81 (m, 1H); 1.64 (1H)	24.1	1.86-1.78 (m, 1H); 1.67-1.62 (m, 1H)	24.3
13	2.46 (1H)	54.0	2.53-2.51 (m, 1H)	54.3
14	4.05 (s, 1H)	79.5	4.04 (d, 8.9, 1H)	79.6
15	5.08 (s, 1H)	129.4	5.10-5.08 (m, 1H)	129.7
16	-	138.9	-	139.1
17	1.74 (s, 3H)	15.4	1.75 (d, 1.5, 3H)	15.6
18	0.97 (s, 3H)	22.3	0.98 (s, 3H)	22.5
19	1.24 (s, 3H)	19.8	1.24 (s, 3H)	20.0
20	5.26 (s, 1H); 5.15 (s, 1H)	111.8	5.26 (s, 1H); 5.15 (d, 0.9, 1H)	111.9
OH	-		3.41 (br s, 1H), 2.92 (d, 7.5, 1H) 2.02 (d, 10.0, 1H), 1.99 - 1.93 (m, 1H)	

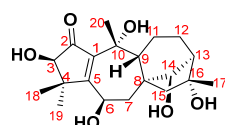
^a Chemical shifts and coupling constants are reported by Liu *et al.* (400 MHz in CDCl_3)^[6]

^b TMS was used as internal standard: δ_{H} in ppm, J values (Hz) are in parentheses.

^c TMS was used as internal standard.

^d 500 MHz NMR spectrometer (CDCl_3).

Table S7. Comparison of the ^1H NMR Data for Natural and Synthesized Rhodomollein XX (3).



Rhodomollein XX (3)

Position	Natural product 3 ^a	Synthesized 3 by Ding ^b	Synthesized 3 by us ^d
	δ_{H} (m, J [Hz]) ^c	δ_{H} (m, J [Hz]) ^c	δ_{H} (m, J [Hz]) ^c
1	-	-	-
2	-	-	-
3	4.29 (s, 1H)	4.23 (d, 3.9, 1H)	4.18 (d, 4.1, 1H)
4	-	-	-
5	-	-	-
6	5.51 (dd, 5.4, 3.1, 1H)	5.51 (dd, 5.4, 3.1, 1H)	5.46-5.42 (m, 1H)
7	3.35 (dd, 14.8, 3.1, 1H); 2.40 (dd, 14.8, 5.4, 1H)	3.35 (dd, 14.8, 3.4, 1H); 2.40 (dd, 14.8, 6.1, 1H)	3.32 (dd, 14.8, 3.3, 1H); 2.34 (dd, 14.9, 6.3, 1H)
8	-	-	-
9	2.78 (d, 6.9, 1H)	2.78 (d, 6.8, 1H)	2.74 (d, 6.9, 1H)
10	-	-	-
11	2.18-2.06 (m, 1H); 1.64-1.58 (m, 1H)	2.12 (dd, 14.9, 5.7, 1H); 1.65-1.61 (m, 1H)	2.08 (dd, 14.5, 5.7, 1H); 1.60-1.56 (m, 1H)
12	2.58-2.44 (m, 1H); 1.76-1.68 (m, 1H)	2.58-2.52 (m, 1H); 1.76-1.70 (m, 1H)	2.50-2.44 (m, 1H); 1.70-1.65 (m, 1H)
13	2.53 (d, 6.6, 1H)	2.53 (d, 7.0, 1H)	2.50-2.44 (m, 1H)
14	5.14 (d, 6.6, 1H)	5.14 (d, 8.3, 1H)	5.08 (d, 7.8, 1H)
15	2.37 (d, 15.0, 1H); 2.32 (d, 15.0, 1H)	2.35 (d, 15.0, 1H); 2.32 (d, 15.0, 1H)	2.31 (d, 14.8, 1H); 2.27 (d, 14.7, 1H)
16	-	-	-
17	1.62 (s, 3H)	1.60 (s, 3H)	1.54 (s, 3H)
18	1.62 (s, 3H)	1.60 (s, 3H)	1.55 (s, 3H)
19	1.68 (s, 3H)	1.67 (s, 3H)	1.61 (s, 3H)
20	2.02 (s, 3H)	2.02 (s, 3H)	1.96 (s, 3H)
OH	-	-	-

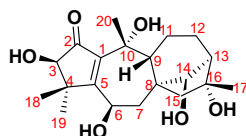
^a Chemical shifts and coupling constants are reported by Li *et al.* (400 MHz in $\text{C}_5\text{D}_5\text{N}$)^[9]

^b Chemical shifts and coupling constants are reported by Ding's group (400 MHz in $\text{C}_5\text{D}_5\text{N}$)^[4a]

^c TMS was used as internal standard: δ_{H} in ppm, J values (Hz) are in parentheses.

^d 600 MHz NMR spectrometer ($\text{C}_5\text{D}_5\text{N}$).

Table S8. Comparison of the ^{13}C NMR Data for Natural and Synthesized Rhodomollein XX (3).



Rhodomollein XX (3)

Position	Natural product 3 ^a	Synthesized 3 by Ding ^b	Synthesized 3 by us ^d
	$\delta_{\text{C}}^{\text{c}}$	$\delta_{\text{C}}^{\text{c}}$	$\delta_{\text{C}}^{\text{c}}$
1	141.2	141.2	141.4
2	209.7	209.7	209.9
3	82.2	82.2	82.4
4	45.2	45.1	45.3
5	178.4	178.2	178.5
6	65.8	65.7	65.9
7	44.2	44.2	44.4
8	52.9	52.8	53.0
9	52.1	52.2	52.3
10	75.9	75.9	76.0
11	21.0	21.0	21.2
12	26.8	26.8	27.0
13	55.9	56.0	56.2
14	79.5	79.4	79.6
15	60.4	60.5	60.7
16	80.0	79.9	80.1
17	24.1	24.2	24.4
18	24.9	24.9	25.2
19	23.8	23.8	24.0
20	32.2	32.2	32.4

^a Chemical shifts and coupling constants are reported by Li *et al.* (400 MHz in $\text{C}_5\text{D}_5\text{N}$)^[9]

^b Chemical shifts and coupling constants are reported by Ding's group (400 MHz in $\text{C}_5\text{D}_5\text{N}$)^[4a]

^c TMS was used as internal standard

^d 600 MHz NMR spectrometer ($\text{C}_5\text{D}_5\text{N}$).

II. Experimental Procedures and Spectroscopic Data

General Information

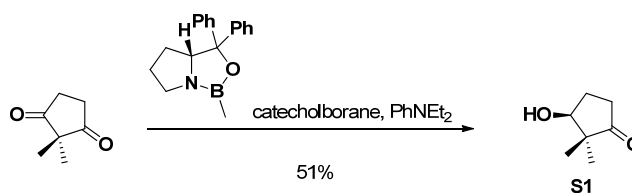
Unless otherwise mentioned, all reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions. All the chemicals were purchased commercially, and used without further purification. Anhydrous THF and ether were distilled from sodium-benzophenone, toluene was distilled from sodium, and dichloromethane was distilled from calcium hydride. Yields refer to chromatographically. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated.

Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254), using UV light as the visualizing agent and an ethanolic solution of ammonium molybdate and heat, or KMnO₄ and heat as developing agents. If not specially mentioned, flash column chromatography uses silica gel (200-300 mesh) supplied by Tsingtao Haiyang Chemicals (China).

NMR spectra were recorded on Brüker Advance 400 (¹H 400 MHz, ¹³C 100 MHz), Brüker Advance 500 (¹H 500 MHz, ¹³C 125 MHz) or Brüker Advance 600 (¹H 600 MHz, ¹³C 150 MHz). TMS was used as internal standard for ¹H NMR (0.00 ppm), and solvent signal was used as reference for ¹H NMR (CDCl₃, 7.26 ppm, CD₃OD, 3.31 ppm, C₅D₅N, 8.74, 7.58, 7.22 ppm, CD₃COCD₃, 2.05 ppm), ¹³C NMR (CDCl₃, 77.16 ppm, CD₃OD, 49.00 ppm, C₅D₅N, 150.35, 135.91, 123.87 ppm, CD₃COCD₃, 206.26, 29.84 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

Mass spectrometric data were obtained using Brüker Apex IV FTMS using ESI (electrospray ionization) and Waters GCT (GC-MS) using EI (electron impact ionization). Infrared spectra were recorded on a Thermo Nicolet iS5 spectrometer. Optical rotations were measured on a InsMark IP-digi300 digital polarimeter with a LED light source at ambient temperature and are reported as follows: [α]_λ (c g/100 mL).

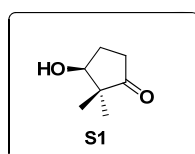
Synthesis of compound S1



The procedure was modified from the reported protocol.^[10, 11]

To a solution of 2,2-dimethylcyclopentan-1-one (10.0 g, 79.2 mmol, 1.00 equiv) in toluene (160 mL) was added (*R*)-oxazaborolidine (31.7 mL, 1 M in toluene, 31.7 mmol, 0.40 equiv) and PhNEt₂ (6.30 mL, 39.6 mmol, 0.50 equiv). The reaction mixture was cooled to −60 °C, then a solution of catecholborane (111 mL, 1 M in toluene, 111 mmol, 1.40 equiv) was added with syring pump over 2 h. The reaction was stirred for 30 min at the same temperature, and then quenched with MeOH (30 mL). The mixture was allowed to warm to room temperature and diluted with Et₂O (200 mL). Then saturated aq. NaHCO₃ (100 mL) and 3 M NaOH aqueous solution (100 mL) were added to the flask. The mixture was stirred vigorously for 1 h. The layers were separated and the aqueous phase was extracted with Et₂O (3×250 mL). The combined organic layers were washed with H₂O (200 mL), 0.5 M HCl aqueous solution (80 mL) and brine, and dried over Na₂SO₄. Then Et₂O was removed under vacuum. The resulting solution was loaded onto a silica gel and flushed with PE to remove toluene, and then purified by flash column chromatography on silica gel (Et₂O/PE = 1/5 to 2/1) to give compound **S1** (5.14 g, 40.1 mmol, 83% ee) as a colorless oil in 51% yield.

The characterization data are consistent with those reported in the literature.^[10, 11]



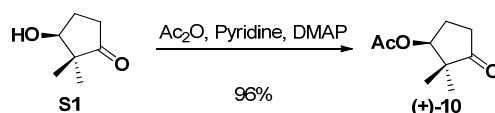
R_f = 0.5 (EtOAc/PE = 1/1)

[α]_D²⁹ +12.3 (*c* 1.0 CHCl₃) [Lit.¹⁰: enantiomer **[α]_D²⁵** −14.0 (*c* 1.0 CHCl₃), 94% ee]

¹H NMR (400 MHz, CDCl₃) δ 4.08 – 4.02 (m, 1H), 2.53 – 2.41 (m, 1H), 2.32 – 2.18 (m, 2H), 1.97 – 1.85 (m, 1H), 1.68 (br s, 1H), 1.03 (s, 6H).

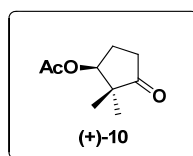
¹³C NMR (100 MHz, CDCl₃) δ 221.4, 78.3, 50.2, 34.3, 27.8, 22.3, 16.9.

Synthesis of compound (+)-10



To a solution of compound **S1** (15.0 g, 117 mmol, 1.00 equiv) in DCM (540 mL) was added pyridine (12.0 g, 152 mmol, 1.30 equiv), DMAP (4.40 g, 35.1 mmol, 0.30 equiv) and Ac₂O (17.9 g, 175 mmol, 1.50 equiv) sequentially at 0 °C. The reaction mixture was stirred for 1 h at the same temperature and then quenched with saturated aq. NaHCO₃ (400 mL). The layers were separated and the aqueous phase was extracted with DCM (3×300 mL). The combined organic layers were washed with 0.5 M HCl aqueous solution (3×150 mL) and brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1/50 to 1/5) to give compound **(+)-10** (19.0 g, 112 mmol) as a pale yellow oil in 96% yield.

The H-NMR data are consistent with that reported in the literature.^[12]



R_f = 0.5 (EtOAc/PE = 1/3)

[α]_D¹⁷ +68.2 (*c* 1.0 CHCl₃)

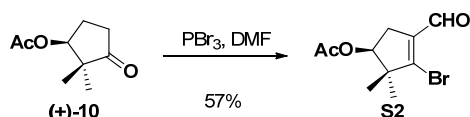
HRMS-ESI (*m/z*) calc. for C₉H₁₅O₃ [M+H⁺]: 171.1016; Found: 171.1014.

IR (neat, cm⁻¹): 2973, 1735, 1470, 1373, 1239, 1076, 1048, 1026.

¹H NMR (400 MHz, CDCl₃) δ 5.13 (t, *J* = 4.3 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.40 – 2.25 (m, 2H), 2.07 (s, 3H), 2.03 – 1.93 (m, 1H), 1.07 (s, 3H), 1.02 (s, 3H).

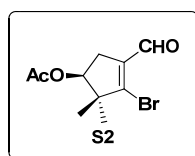
¹³C NMR (100 MHz, CDCl₃) δ 219.8, 170.5, 79.8, 49.2, 34.2, 25.5, 22.7, 21.2, 17.7.

Synthesis of compound S2



A flame-dried 1 L round-bottom flask equipped with a stir bar was charged with CHCl_3 (400 mL) and phosphorus tribromide (118 g, 436 mmol, 3.90 equiv) under N_2 . The mixture was cooled to 0 °C. DMF (63.7 g, 873 mmol, 7.80 equiv) was added to the flask and then the mixture was stirred for 1 h at 0 °C. Then compound (+)-10 (19.0 g, 112 mmol, 1.00 equiv) in CHCl_3 (40 mL) was added to the flask at 0 °C. The reaction mixture was allowed to heat to 50 °C and stirred for 40 h.

The mixture was slowly added into saturated aq. NaOAc (400 mL), and then 2 M NaOH aqueous solution (700 mL) and saturated aq. NaHCO_3 (450 mL) were added slowly at 0 °C. The layers were separated and the aqueous phase was extracted with Et_2O (3×400 mL). The combined organic layers were washed with saturated aq. NaHCO_3 and brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel ($\text{Et}_2\text{O}/\text{PE} = 1/20$ to $1/5$) to give compound S2 (16.7 g, 64.0 mmol) as a pale yellow oil in 57% yield.



$R_f = 0.65$ ($\text{EtOAc}/\text{PE} = 1/3$)

$[\alpha]_D^{29} +29.4$ (c 1.0 CHCl_3)

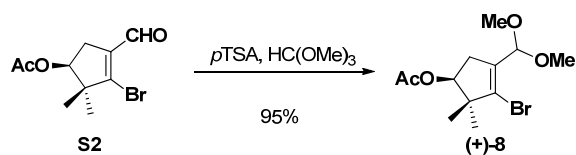
HRMS-ESI (m/z) calc. for $\text{C}_{10}\text{H}_{14}\text{BrO}_3$ $[\text{M}+\text{H}^+]$: 261.0121; Found: 261.0121.

IR (neat, cm^{-1}): 2968, 1746, 1677, 1605, 1464, 1373, 1236, 1042.

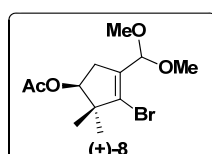
^1H NMR (400 MHz, CDCl_3) δ 9.88 (s, 1H), 5.16 (dd, $J = 6.9, 3.8$ Hz, 1H), 2.94 (dd, $J = 16.8, 6.9$ Hz, 1H), 2.49 (dd, $J = 16.8, 3.8$ Hz, 1H), 2.07 (s, 3H), 1.20 (s, 3H), 1.13 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 189.6, 170.6, 150.1, 135.4, 77.3, 53.3, 34.9, 24.8, 21.1, 19.7.

Synthesis of compound (+)-8



To a solution of compound **S2** (10.2 g, 39.0 mmol, 1.00 equiv) in MeOH (160 mL) was added HC(OMe)₃ (41.4 g, 390 mmol, 10.0 equiv) and *p*TSA (742 mg, 3.90 mmol, 0.10 equiv) at room temperature. The reaction mixture was stirred for 1 h at the same temperature and then quenched with saturated aq. NaHCO₃ (200 mL). MeOH was removed under vacuum and the mixture was extracted with EtOAc (3×200 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1/100 to 1/20) to give compound **(+)-8** (11.3 g, 36.8 mmol) as a colorless oil in 95% yield.



R_f = 0.65 (EtOAc/PE = 1/3)

[α]_D²⁹ +16.0 (*c* 1.0 CHCl₃)

HRMS-ESI (*m/z*) calc. for C₁₂H₁₉BrNaO₄ [M+Na⁺]: 329.0359;

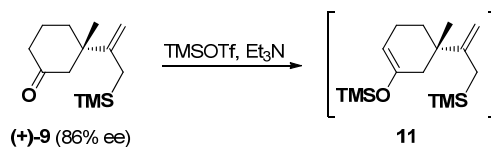
Found: 329.0355.

IR (neat, cm⁻¹): 2968, 2829, 1743, 1464, 1371, 1238, 1106, 1070.

¹H NMR (400 MHz, CDCl₃) δ 5.11 (dd, *J* = 7.0, 4.3 Hz, 1H), 4.99 (s, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 2.84 (dd, *J* = 16.7, 7.1 Hz, 1H), 2.36 (dd, *J* = 16.7, 4.3 Hz, 1H), 2.06 (s, 3H), 1.13 (s, 3H), 1.05 (s, 3H).

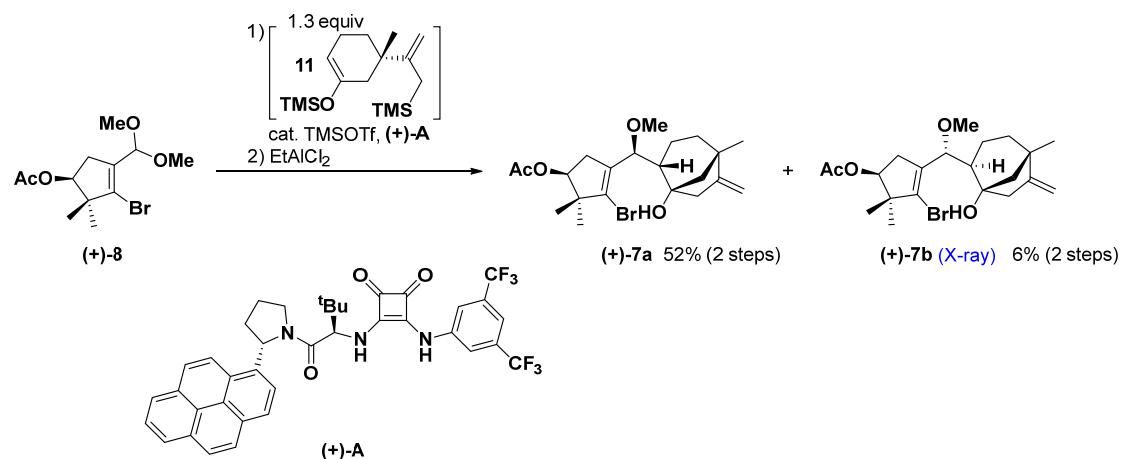
¹³C NMR (100 MHz, CDCl₃) δ 170.8, 133.5, 130.5, 101.8, 78.0, 54.6, 54.5, 51.3, 35.6, 25.3, 21.2, 20.0.

Preparation of compound 11



To a solution of (+)-**9**^[13] (16.5 g, 73.6 mmol, 1.00 equiv) in DCM (360 mL) at 0 °C was added Et₃N (15.3 mL, 110 mmol, 1.50 equiv) followed by TMSOTf (16.6 mL, 92.0 mmol, 1.25 equiv). After being stirred at the same temperature for 30 min, the reaction mixture was quenched with saturated aq. NaHCO₃ (150 mL) and brine (150 mL). The layers were separated and the aqueous phase was extracted with DCM (3×200 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to afford crude silyl enol ether **11** (20.6 g, quantitative) that could be used without further purification.

Two-step synthesis of compound (+)-7a



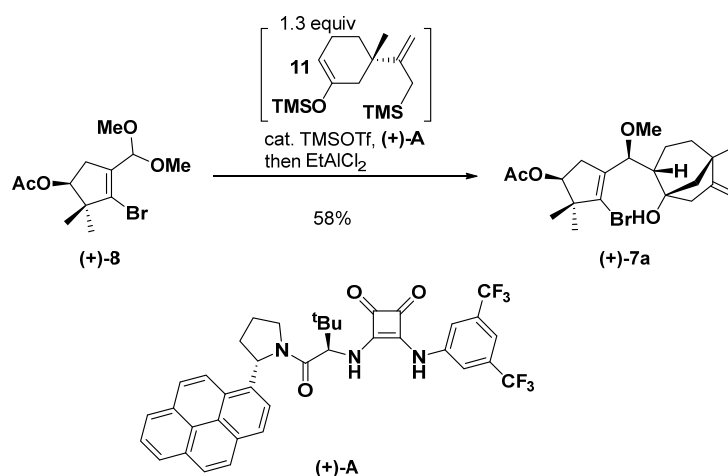
To a solution of compound (+)-**8** (3.15 g, 10.3 mmol, 1.00 equiv), compound **11** (3.97 g, 13.4 mmol, 1.30 equiv) and (+)-**A**^[14] (1.07 g, 1.55 mmol, 0.15 equiv) in ^tBuOMe (100 mL) was added TMSOTf (0.28 mL, 1.55 mmol, 0.15 equiv) at -78 °C. The reaction mixture was stirred for 3 h at the same temperature, then the reaction mixture was quenched with saturated aq. NaHCO₃ (40 mL). The layers were separated and the aqueous phase was then extracted with Et₂O (3×50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*.

The residue was dissolved in DCM (90 mL), and EtAlCl₂ (6.90 mL, 1.8 M in toluene, 12.4 mmol, 1.20 equiv) was added at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was quenched with saturated aq. NaHCO₃ (20 mL) and saturated aq. Rochelle's salt (60 mL) diluted with EtOAc (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×50 mL).

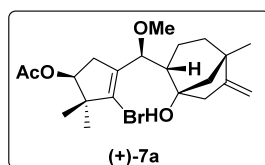
The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1/30 to 1/1 to pure EtOAc) to give compound (+)-**7a** (2.29 g, 5.37 mmol) as a pale yellow oil in 52% yield and (+)-**7b** (0.273 g, 0.641 mmol) as a white solid in 6% yield over 2 steps, also recover (+)-**A** (1.02 g, 1.48 mmol).

Following the procedure reported by Jacobsen's group,^[14] we prepared both ligands (+)-**A** and its enantiomer, (–)-**A**.

One-pot synthesis of compound (+)-**7a**



To a solution of compound (+)-**8** (3.15 g, 10.3 mmol, 1.00 equiv), compound **11** (3.97 g, 13.4 mmol, 1.30 equiv) and (+)-**A** (1.07 g, 1.55 mmol, 0.15 equiv) in *t*BuOMe (100 mL) was added TMSOTf (0.28 mL, 1.55 mmol, 0.15 equiv) at –78 °C. The reaction mixture was stirred for 3 h at the same temperature. Et₃N (0.64 mL, 4.64 mmol, 0.45 equiv) and MeOH (0.25 mL, 6.23 mmol, 0.60 equiv) was added slowly to the flask and the reaction mixture was stirred for 5 min at –78 °C, then the mixture was allowed to warm to 0 °C. After diluting with DCM (200 mL), EtAlCl₂ (11.4 mL, 1.8 M in toluene, 20.6 mmol, 2.00 equiv) was added at 0 °C. The reaction mixture was stirred at the same temperature for 1 h, and then was quenched with saturated aq. NaHCO₃ (30 mL) and saturated aq. Rochelle's salt (150 mL) diluted with EtOAc (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1/30 to 1/1 to pure EtOAc) to give compound (+)-**7a** (2.57 g, 6.01 mmol) as a pale yellow oil in 58% yield and recover (+)-**A** (1.00 g, 1.45 mmol).



$R_f = 0.46$ (EtOAc/PE = 1/5)

$[\alpha]_D^{18} +6.2$ (c 0.5 CHCl₃)

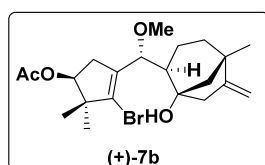
HRMS-ESI (m/z) calc. for C₂₁H₃₅BrNO₄ [M+NH₄⁺]:

444.1744; Found: 444.1747.

IR (neat, cm⁻¹): 2930, 1742, 1724, 1459, 1372, 1239, 1090, 1046.

¹H NMR (400 MHz, CDCl₃) δ 5.12 (dd, J = 7.0, 4.6 Hz, 1H), 4.76 (s, 1H), 4.70 (t, J = 2.3 Hz, 1H), 4.21 (d, J = 6.2 Hz, 1H), 3.20 (s, 3H), 2.92 (dd, J = 16.7, 2.0 Hz, 1H), 2.79 (dd, J = 16.4, 7.0 Hz, 1H), 2.46 (dd, J = 16.4, 4.5 Hz, 1H), 2.31 – 2.23 (m, 1H), 2.26 (br s, 1H), 2.07 (s, 3H), 2.02 – 1.94 (m, 1H), 1.87 – 1.80 (m, 1H), 1.78 (dd, J = 10.7, 1.6 Hz, 1H), 1.46 – 1.30 (m, 4H), 1.14 (s, 3H), 1.09 (s, 3H), 1.03 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 170.9, 157.1, 136.9, 130.2, 103.1, 79.9, 78.1, 77.7, 56.8, 54.9, 51.1, 49.2, 45.3, 42.7, 40.4, 36.4, 25.3, 24.4, 23.6, 21.2, 19.8.



$R_f = 0.42$ (EtOAc/PE = 1/5)

$[\alpha]_D^{18} +87.7$ (c 0.5 CHCl₃)

Melting point: 130-132 °C

HRMS-ESI (m/z) calc. for C₂₁H₃₂BrO₄ [M+H⁺]: 427.1478; Found: 427.1485.

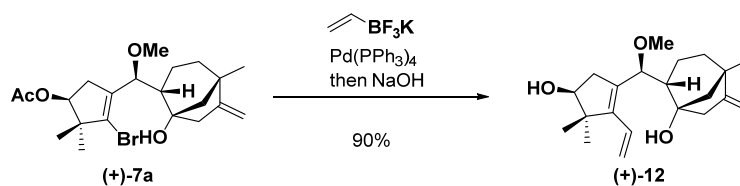
IR (neat, cm⁻¹): 2960, 2927, 1743, 1720, 1372, 1241, 1085, 1045.

¹H NMR (400 MHz, CDCl₃) δ 5.11 (dd, J = 6.7, 4.0 Hz, 1H), 4.77 (s, 1H), 4.71 (t, J = 2.3 Hz, 1H), 4.27 (d, J = 8.1 Hz, 1H), 3.22 (s, 3H), 2.89 (dd, J = 16.3, 6.7 Hz, 1H), 2.55 (dd, J = 16.8, 2.0 Hz, 1H), 2.42 (dt, J = 16.8, 2.7 Hz, 1H), 2.30 (dd, J = 16.3, 4.0 Hz, 1H), 2.06 (s, 3H), 2.03 – 1.97 (m, 1H), 1.91 – 1.83 (m, 2H), 1.64 (br s, 1H), 1.59 – 1.47 (m, 3H), 1.19 – 1.13 (m, 1H), 1.11 (s, 3H), 1.08 (s, 3H), 1.08 (s, 3H).

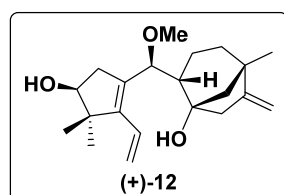
¹³C NMR (100 MHz, CDCl₃) δ 170.7, 156.1, 137.8, 129.5, 103.0, 78.3, 77.8, 77.1, 56.0, 51.0, 48.5, 48.3, 47.5, 46.7, 37.5, 35.9, 24.6, 23.7, 22.2, 21.2, 20.3.

CCDC 2144563 contains the supplementary crystallographic data for compound (+)-7b and is available free of charge from The Cambridge Crystallographic Data Centre via <https://www.ccdc.cam.ac.uk/structures/>

Synthesis of compound (+)-12



To the solution of compound (+)-7a (4.15 g, 9.71 mmol, 1.00 equiv) in EtOH (83 mL), H₂O (125 mL) and toluene (250 mL), Pd(PPh₃)₄ (2.80 g, 2.43 mmol, 0.25 equiv), potassium vinyltrifluoroborate (9.11 g, 68.0 mmol, 7.00 equiv) and Na₂CO₃ (10.3 g, 97.1 mmol, 10.0 equiv) were added sequentially at room temperature. The reaction mixture was allowed to reflux for 72 h under air atmosphere, and then the mixture was allowed to cool to room temperature. EtOH and toluene were removed under reduced pressure, then MeOH (125 mL) and NaOH (4.15 g, 104 mmol, 10.7 equiv) were added to the flask and the reaction mixture was stirred for 30 min at 50 °C. MeOH was removed under reduced pressure and the mixture was quenched with saturated aq. NH₄Cl (200 mL). The mixture was subsequently extracted with EtOAc (4×150 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1/30 to 1/1) to give compound (+)-12 (2.92 g, 8.78 mmol) as a light yellow foam in 90% yield.



$R_f = 0.4$ (EtOAc/PE = 1/1)

$[\alpha]_D^{24} +10.2$ (*c* 0.5 CHCl₃)

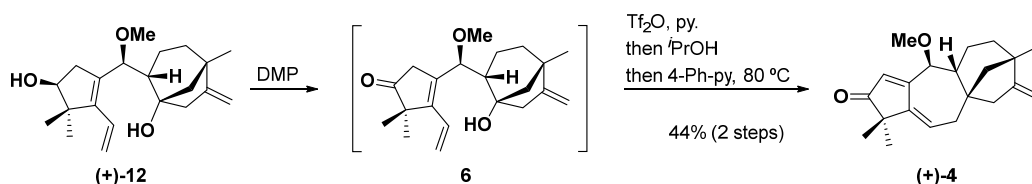
HRMS-ESI (m/z) calc. for C₂₁H₃₃O₃ [M+H⁺]: 333.2424;
Found: 333.2424.

IR (neat, cm⁻¹): 2953, 2928, 1655, 1456, 1362, 1190, 1086, 1048.

¹H NMR (400 MHz, CDCl₃) δ 6.41 (dd, *J* = 17.9, 11.7 Hz, 1H), 5.36 (d, *J* = 17.9 Hz, 1H), 5.22 (d, *J* = 11.7 Hz, 1H), 4.77 (s, 1H), 4.70 (t, *J* = 2.2 Hz, 1H), 4.17 (d, *J* = 7.4 Hz, 1H), 3.83 (t, *J* = 5.0 Hz, 1H), 3.13 (s, 3H), 2.81 (dd, *J* = 16.7, 1.9 Hz, 1H), 2.70 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.36 (dd, *J* = 16.9, 4.3 Hz, 1H), 2.25 (d, *J* = 16.7 Hz, 1H), 2.06 – 1.98 (m, 1H), 1.98 – 1.92 (m, 1H), 1.75 (dd, *J* = 10.7, 1.6 Hz, 1H), 1.62 (br s, 1H), 1.41 (dd, *J* = 10.7, 2.4 Hz, 1H), 1.38 – 1.29 (m, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H).

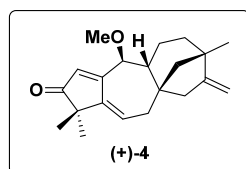
¹³C NMR (100 MHz, CDCl₃) δ 157.1, 144.9, 137.6, 129.4, 116.9, 103.3, 80.0, 78.0, 78.0, 56.03, 54.9, 50.4, 48.9, 45.2, 42.9, 40.5, 38.1, 25.1, 25.0, 23.6, 19.5.

Synthesis of compound (+)-4



To a solution of compound (+)-12 (4.00 g, 12.0 mmol, 1.00 equiv) in DCM (240 mL) was added NaHCO_3 (10.1 g, 120 mmol, 10.0 equiv) and DMP (10.2 g, 24.0 mmol, 2.00 equiv) at 0 °C. The reaction mixture was allowed to stir for 4 h at the same temperature, then was quenched with saturated aq. Na_2SO_3 (400 mL) diluted with H_2O (200 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×200 mL). The combined organic layers were washed with 0.5 M NaOH aqueous solution (3×240 mL), H_2O (150 mL) and brine, dried over Na_2SO_4 , and concentrated *in vacuo* to obtain crude **6** that was used without purification.

The residue of crude **6** was dissolved in DCM (320 mL). Pyridine (2.84 mL, 36.0 mmol, 3.00 equiv) and Tf_2O (3.00 mL, 18.0 mmol, 1.50 equiv) were added sequentially at 0 °C. The reaction mixture was stirred for 0.5 h at 0 °C and then allowed to warm to room temperature with stirring for 1.5 h. Subsequently, $i\text{'PrOH}$ (2.76 mL, 36 mmol, 3.00 equiv) was added to the flask and the solution was concentrated *in vacuo* and azeotroped with toluene (3×30 mL). The residue was dissolved in DCE (400 mL) and 4-Ph-pyridine (2.80 g, 18.0 mmol, 1.50 equiv) was added. The reaction mixture was allowed to stir for 14 h at 80 °C under N_2 atmosphere. DCE was removed under vacuum, the residue was diluted with H_2O (400 mL), and the mixture was extracted with Et_2O (3×200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1/50 to 1/5) to give compound (+)-4 (1.65 g, 5.28 mmol) as a light yellow oil in 44% yield over 2 steps.



$R_f = 0.5$ (EtOAc/PE = 1/5)

$[\alpha]_D^{24} +56.9$ (c 0.5 CHCl_3)

HRMS-ESI (m/z) calc. for $\text{C}_{21}\text{H}_{29}\text{O}_2$ $[\text{M}+\text{H}^+]$: 313.2162;

Found: 313.2161.

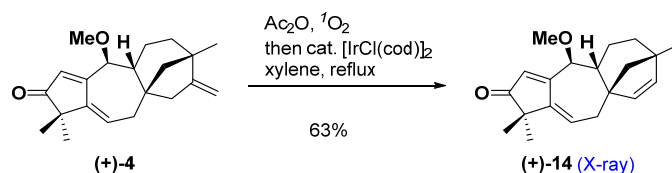
IR (neat, cm^{-1}): 2924, 1701, 1570, 1455, 1114, 1094, 1071, 873.

^1H NMR (400 MHz, CDCl_3) δ 6.08 (s, 1H), 5.84 (ddd, $J = 7.2, 5.7, 1.4$ Hz, 1H), 4.69 (s, 1H), 4.64 (t, $J = 2.2$ Hz, 1H), 3.90 (d, $J = 4.4$ Hz, 1H), 3.30 (s, 3H), 2.56 (dd, $J = 16.1, 5.7$ Hz, 1H), 2.32 (dd, $J = 17.4, 2.0$ Hz, 1H), 2.23 (dd, $J = 16.1, 7.3$ Hz, 1H),

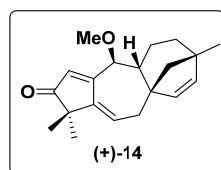
2.03 – 1.90 (m, 2H), 1.79 – 1.68 (m, 1H), 1.47 – 1.31 (m, 5H), 1.13 (s, 3H), 1.13 (s, 3H), 1.06 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 211.0, 171.1, 157.6, 147.9, 128.0, 125.6, 102.2, 83.0, 58.2, 55.3, 52.1, 47.9, 46.0, 44.8, 42.2, 40.5, 38.4, 25.2, 25.0, 23.6, 22.8.

Synthesis of compound (+)-14



To a solution of compound (+)-4 (3.25 g, 10.4 mmol, 1.00 equiv) in CDCl_3 (150 mL) was added TPP (3.5 mg, 5.7 μmol , 0.00055 equiv), pyridine (0.42 mL, 5.20 mmol, 0.50 equiv), DMAP (76.2 mg, 0.620 mmol, 0.06 equiv) and Ac_2O (1.20 mL, 12.5 mmol, 1.20 equiv). The solution was degassed by O_2 over 15 min. The reaction mixture was allowed to stir for 36 h under O_2 (1 atm) with the irradiation of three fluorescent lamps (Essential 65 W, PHILIPS®, distance ~2 cm) at 0 °C (complete consumption of the starting material was indicated by TLC). The reaction was stopped by removing the light source and then allowed to warm to room temperature with stirring for 5 h. The reaction mixture was concentrated *in vacuo* and azeotroped with toluene (3×30 mL). The residue was dissolved in xylene (53 mL), and $[\text{IrCl}(\text{cod})]_2$ (698 mg, 1.04 mmol, 0.10 equiv) and PPh_3 (546 mg, 2.08 mmol, 0.20 equiv) were added. The reaction mixture was degassed by a freeze-pump-thaw method for two times, and then allowed to reflux for 2.5 h. Subsequently, the reaction mixture was cooled to room temperature and quenched with brine (100 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×70 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1/30 to 1/3) to give compound (+)-14 (1.95 g, 6.53 mmol) as a light yellow oil in 63% yield. This compound solidified during storage in the refrigerator (−20 °C).



R_f = 0.6 (EtOAc/PE = 1/3)

$[\alpha]_D^{17} +211.4$ (c 0.5 CHCl_3)

Melting point: 84–86 °C

HRMS-ESI (m/z) calc. $\text{C}_{20}\text{H}_{27}\text{O}_2$ $[\text{M}+\text{H}^+]$: 299.2006; Found: 299.2004.

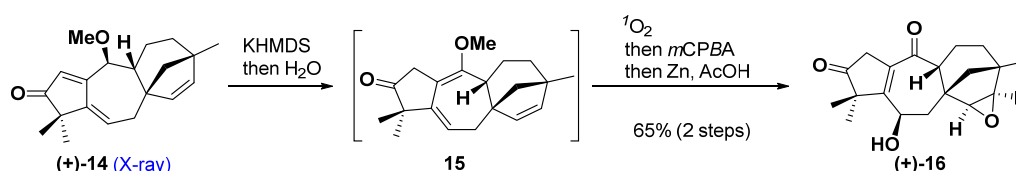
IR (neat, cm^{-1}): 2923, 2861, 1702, 1571, 1454, 1357, 1118, 1082.

^1H NMR (400 MHz, CDCl_3) δ 6.04 (s, 1H), 5.90 (ddd, $J = 7.6, 5.0, 1.4$ Hz, 1H), 5.53 (d, $J = 5.7$ Hz, 1H), 5.42 (d, $J = 5.7$ Hz, 1H), 3.79 (d, $J = 3.5$ Hz, 1H), 3.23 (s, 3H), 2.70 (dd, $J = 16.4, 5.0$ Hz, 1H), 2.29 (dd, $J = 16.4, 7.7$ Hz, 1H), 1.88 (dt, $J = 8.7, 4.1$ Hz, 1H), 1.73 – 1.66 (m, 1H), 1.50 (d, $J = 9.8$ Hz, 1H), 1.31 (d, $J = 9.9$ Hz, 1H), 1.29 – 1.23 (m, 1H), 1.22 – 1.17 (m, 2H), 1.16 (s, 3H), 1.14 (s, 3H), 1.05 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 211.1, 170.3, 147.4, 138.8, 132.4, 129.1, 126.2, 83.8, 60.2, 57.9, 53.3, 48.3, 48.2, 46.5, 36.9, 31.6, 25.8, 25.3, 24.5, 22.6.

CCDC 2144671 contains the supplementary crystallographic data for compound (+)-**14** and is available free of charge from The Cambridge Crystallographic Data Centre via <https://www.ccdc.cam.ac.uk/structures/>

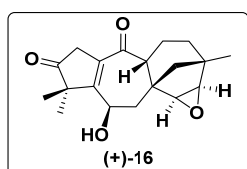
Synthesis of compound (+)-**16**



To a solution of compound (+)-**14** (1.02 g, 3.42 mmol, 1.00 equiv) in THF (80 mL) was added KHMDS (8.55 mL, 1 M in THF, 8.55 mmol, 2.50 equiv) within 15 s at room temperature. The reaction mixture was allowed to stir for 5 min at the same temperature and then quenched with H_2O (80 mL). The mixture was diluted with saturated aq. NH_4Cl (20 mL) and Et_2O (80 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×80 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was briefly purified by passing through a short column of silica gel ($\text{EtOAc/PE} = 1/20$) to give crude **15**.

The residue obtained was dissolved in DCM (55 mL) and then TPP (1 mg, 1.6 μmol , 0.00047 equiv) was added. The solution was degassed by O_2 over 5 min. The reaction mixture was allowed to stir for 20 min under O_2 (1 atm) with the irradiation of three fluorescent lamps (Essential 65 W, PHILIPS®, distance ~ 2 cm) at 0°C (complete consumption of the starting material was indicated by TLC). The reaction was stopped by removing the light source, then *m*CPBA (70% wt/wt, 1.10 g, 4.45 mmol, 1.30 equiv) was added to the flask at 0°C , and the reaction mixture was allowed to stir for 3.5 h at the same temperature. Subsequently, the reaction mixture was concentrated *in vacuo* and the residue was dissolved in Et_2O (100 mL), then Zn (5.59 g, 85.5 mmol, 25.0 equiv) and AcOH (9.80 mL, 171 mmol, 50.0 equiv) were added sequentially at room temperature. The reaction mixture was stirred vigorously

for 1 h at the same temperature, and was quenched with saturated aq. NaHCO₃ (200 mL). The layers were separated and the aqueous phase was extracted with EtOAc (4×80 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1/15 to 1/1) to give compound (+)-**16** (707 mg, 2.23 mmol) as a white solid in 65% yield over 2 steps.



R_f = 0.4 (EtOAc/PE = 1/1)

[α]_D¹⁷ +72.3 (*c* 0.5 CHCl₃)

Melting point: 180-182 °C

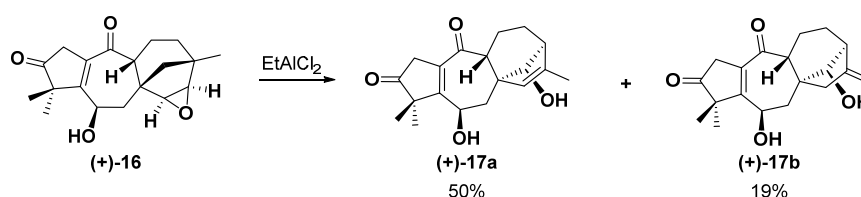
HRMS-ESI (*m/z*) calc. for C₁₉H₂₅O₄ [M+H⁺]: 317.1747; Found: 317.1743.

IR (neat, cm⁻¹): 2967, 1749, 1662, 1457, 1383, 1209, 1078, 916.

¹H NMR (400 MHz, CDCl₃) δ 4.79 – 4.74 (m, 1H), 3.52 (dd, *J* = 12.5, 5.1 Hz, 1H), 3.43 (d, *J* = 23.2 Hz, 1H), 3.06 (d, *J* = 23.2 Hz, 1H), 3.04 (d, *J* = 3.0 Hz, 1H), 3.01 (d, *J* = 3.0 Hz, 1H), 2.30 (dd, *J* = 15.2, 6.6 Hz, 1H), 2.27 – 2.17 (m, 1H), 2.14 (d, *J* = 15.5 Hz, 1H), 1.74 – 1.69 (m, 1H), 1.74 (br s, 1H), 1.52 (dt, *J* = 11.7, 5.6 Hz, 1H), 1.44 (dd, *J* = 13.1, 6.2 Hz, 1H), 1.37 (s, 2H), 1.29 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H).

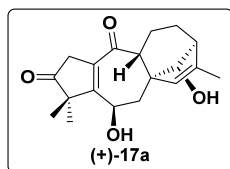
¹³C NMR (100 MHz, CDCl₃) δ 217.4, 199.6, 159.1, 137.5, 65.0, 58.8, 58.4, 54.7, 53.8, 47.1, 42.7, 42.5, 41.6, 41.0, 34.0, 22.6, 22.5, 21.4, 20.4.

Synthesis of compound (+)-**17a**



To a solution of compound (+)-**16** (1.38 g, 4.36 mmol, 1.00 equiv) in DCM (140 mL) was added EtAlCl₂ (1.94 mL, 0.9 M in heptane, 1.74 mmol, 0.40 equiv) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, and then was quenched with saturated aq. NaHCO₃ (20 mL) and saturated aq. Rochelle's salt (150 mL) diluted with EtOAc (200 mL). The mixture was stirred for 30 min, then the layers were separated and the aqueous phase was extracted with EtOAc (4×200 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified carefully by flash column chromatography on silica gel (EtOAc/PE = 1/15 to 3/1) to give compound (+)-**17a**

(690 mg, 2.18 mmol) as a white solid in 50% yield and compound **(+)-17b** (269 mg, 0.850 mmol) as a white solid in 19% yield.



R_f = 0.3 (EtOAc/PE = 2/1)

[α]_D¹⁷ +75.7 (*c* 0.5 CHCl₃)

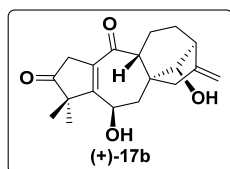
Melting point: 179-181 °C

HRMS-ESI (*m/z*) calc. for C₁₉H₂₅O₄ [M+H⁺]: 317.1747; Found: 317.1741.

IR (neat, cm⁻¹): 3517, 2927, 1752, 1658, 1198, 1045, 904, 729.

¹H NMR (400 MHz, CDCl₃) δ 5.40 (s, 1H), 4.78 (t, *J* = 5.2 Hz, 1H), 3.66 (d, *J* = 6.6 Hz, 1H), 3.52 (d, *J* = 10.1 Hz, 1H), 3.39 (d, *J* = 23.3 Hz, 1H), 3.05 (d, *J* = 23.3 Hz, 1H), 2.50 (s, 1H), 2.32 (dd, *J* = 15.5, 6.5 Hz, 1H), 2.12 (dd, *J* = 15.4, 1.1 Hz, 1H), 1.94 (dd, *J* = 13.5, 5.9 Hz, 1H), 1.90 – 1.82 (m, 1H), 1.79 (d, *J* = 1.3 Hz, 3H), 1.75 (d, *J* = 4.4 Hz, OH-1H), 1.64 (d, *J* = 10.3 Hz, OH-1H), 1.57 – 1.50 (m, 1H), 1.47 – 1.35 (m, 1H), 1.28 (s, 3H), 1.17 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 217.6, 201.6, 159.8, 140.9, 136.8, 129.0, 83.6, 65.2, 54.9, 53.7, 51.6, 51.0, 41.6, 39.5, 22.6, 22.4, 22.0, 20.8, 15.6.



R_f = 0.4 (EtOAc/PE = 2/1)

[α]_D¹⁷ +42.0 (*c* 0.2 CHCl₃)

Melting point: 199-201 °C

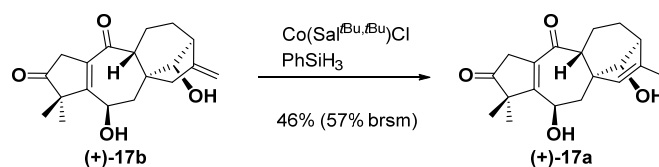
HRMS-ESI (*m/z*) calc. for C₁₉H₂₅O₄ [M+H⁺]: 317.1747; Found: 317.1740.

IR (neat, cm⁻¹): 3521, 2919, 2850, 1751, 1664, 1403, 1037, 862.

¹H NMR (400 MHz, CDCl₃) δ 5.02 – 4.98 (m, 2H), 4.82 – 4.77 (m, 1H), 3.72 (d, *J* = 6.1 Hz, 1H), 3.58 (d, *J* = 4.7 Hz, 1H), 3.39 (d, *J* = 23.2 Hz, 1H), 3.06 (d, *J* = 23.2 Hz, 1H), 2.72 (d, *J* = 17.2 Hz, 1H), 2.66 – 2.59 (m, 2H), 2.43 (dd, *J* = 15.4, 6.9 Hz, 1H), 2.21 (dd, *J* = 15.3, 1.0 Hz, 1H), 2.09 – 1.99 (m, 1H), 1.85 (dd, *J* = 13.7, 5.5 Hz, 1H), 1.67 (d, *J* = 4.3 Hz, OH-1H), 1.65 – 1.53 (m, 2H), 1.29 (s, 3H), 1.18 (s, 3H).

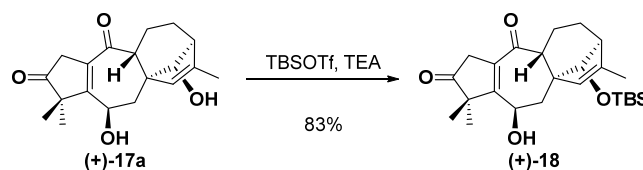
¹³C NMR (125 MHz, CDCl₃) δ 217.5, 201.4, 159.9, 153.1, 137.0, 107.4, 81.2, 65.3, 55.6, 54.9, 52.1, 46.4, 45.9, 43.2, 41.6, 31.1, 22.6, 22.5, 20.4.

Isomerization of compound (+)-17b to compound (+)-17a

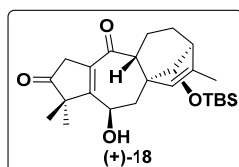


To the solution of compound **(+)-17b** (50.0 mg, 0.158 mmol, 1.00 equiv) and $\text{Co(Sal}^{\text{tBu,tBu}}\text{)Cl}^{[15]}$ (5.1 mg, 0.00790 mmol, 0.05 equiv) in acetone (1.8 mL) was degassed by bubbling N_2 through the solution for 10 min. PhSiH_3 (2 μL , 0.0158 mmol, 0.10 equiv) was added at room temperature. The mixture was degassed by bubbling N_2 through the solution for 1 min again and stirred for 27 h at room temperature. The mixture was concentrated *in vacuo*. The residue was purified carefully by flash column chromatography on silica gel ($\text{EtOAc/PE} = 1/15$ to $3/1$) to give compound **(+)-17a** (23.0 mg, 0.0727 mmol) as a white solid in 46% yield (57% brsm) and recover compound **(+)-17b** (9.7 mg, 0.0306 mmol) as a white solid.

Synthesis of compound (+)-18



To a solution of compound **(+)-17a** (1.00 g, 3.16 mmol, 1.00 equiv) in THF (200 mL) was added Et_3N (1.10 mL, 7.90 mmol, 2.50 equiv) followed by TBSOTf (1.02 mL, 4.42 mmol, 1.40 equiv) at 0 °C. The reaction mixture was stirred at the same temperature for 5 min, and then was quenched with saturated aq. NaHCO_3 (50 mL) diluted with EtOAc (50 mL). The layers were separated and the aqueous phase was then extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel ($\text{EtOAc/PE} = 1/15$ to $1/2$) to give compound **(+)-18** (1.13 g, 2.62 mmol) as a white solid in 83% yield.



$R_f = 0.5$ ($\text{EtOAc/PE} = 1/2$)

$[\alpha]_D^{17} +71.0$ (c 0.5 CHCl_3)

Melting point: 178-180 °C

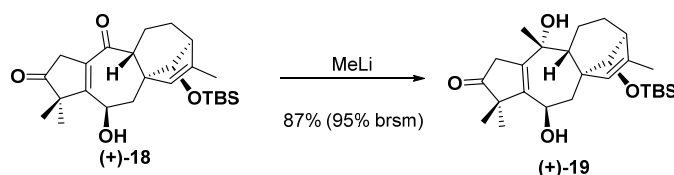
HRMS-ESI (m/z) calc. for $\text{C}_{25}\text{H}_{39}\text{O}_4\text{Si}$ $[\text{M}+\text{H}^+]$: 431.2612; Found: 431.2608.

IR (neat, cm^{-1}): 3666, 2958, 2928, 1753, 1653, 1393, 1253, 1068.

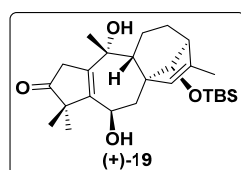
^1H NMR (400 MHz, CDCl_3) δ 5.33 (s, 1H), 4.75 (t, $J = 5.1$ Hz, 1H), 3.64 (d, $J = 6.6$ Hz, 1H), 3.59 (s, 1H), 3.39 (d, $J = 23.3$ Hz, 1H), 3.05 (d, $J = 23.3$ Hz, 1H), 2.40 – 2.36 (m, 1H), 2.31 (dd, $J = 15.7, 6.4$ Hz, 1H), 2.00 – 1.87 (m, 2H), 1.83 – 1.76 (m, 1H), 1.75 (d, $J = 1.4$ Hz, 3H), 1.69 (d, $J = 4.2$ Hz, OH-1H), 1.56 – 1.37 (m, 2H), 1.28 (s, 3H), 1.17 (s, 3H), 0.82 (s, 9H), -0.02 (s, 3H), -0.04 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 217.8, 201.9, 159.9, 139.7, 136.8, 128.9, 84.7, 65.5, 54.9, 53.5, 51.6, 51.3, 41.6, 39.6, 25.9, 22.6, 22.3, 22.1, 20.9, 18.3, 15.6, -4.0, -4.7.

Synthesis of compound (+)-19



To the solution of compound (+)-18 (1.12 g, 2.60 mmol, 1.00 equiv) in THF (350 mL) was added MeLi (24.4 mL, 1.6 M in Et_2O , 39.0 mmol, 15.0 equiv) at -40 °C. The reaction mixture was stirred for 20 min at -40 °C and then allowed to warm to 0 °C with stirring for 40 min. After quenching the reaction with saturated aq. NH_4Cl (100 mL) diluted with EtOAc (200 mL), the layers were separated and the aqueous phase was extracted with EtOAc (3×200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1/15 to 1/1) to give compound (+)-19 (1.01 g, 2.26 mmol) as a white foam in 87% yield (95% brsm) and recover compound (+)-18 (0.105 g, 0.244 mmol) as a white solid.



$R_f = 0.4$ (EtOAc/PE = 1/2)

$[\alpha]_D^{17} +21.5$ (c 0.5 CHCl_3)

HRMS-ESI (m/z) calc. for $\text{C}_{26}\text{H}_{43}\text{O}_4\text{Si}$ $[\text{M}+\text{H}^+]$: 447.2925;

Found: 447.2922.

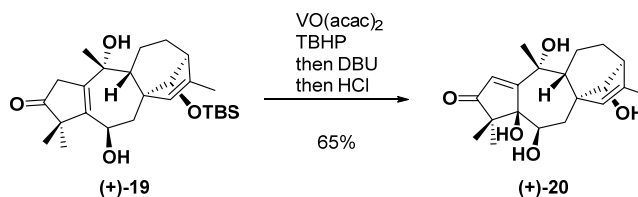
IR (neat, cm^{-1}): 3675, 2987, 2970, 1736, 1405, 1393, 1250, 1066.

^1H NMR (400 MHz, CDCl_3) δ 5.20 (s, 1H), 4.64 – 4.58 (m, 2H), 3.20 (d, $J = 23.0$ Hz, 1H), 3.05 (d, $J = 23.0$ Hz, 1H), 2.43 (t, $J = 4.0$ Hz, 1H), 2.40 – 2.36 (m, 1H), 2.28 (dd, $J = 15.0, 2.3$ Hz, 1H), 1.97 (dd, $J = 15.0, 6.8$ Hz, 1H), 1.71 (d, $J = 1.3$ Hz, 3H), 1.70 –

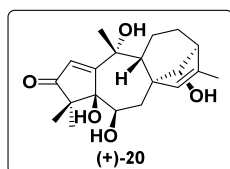
1.63 (m, 3H), 1.44 (s, 3H), 1.34 – 1.29 (m, 2H), 1.20 (s, 3H), 1.14 (s, 3H), 0.85 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 220.5, 145.4, 139.5, 138.3, 131.8, 82.4, 76.9, 66.1, 55.3, 53.9, 53.7, 44.8, 43.2, 40.0, 31.6, 26.1, 23.8, 23.4, 22.7, 21.5, 18.4, 15.5, -3.8, -4.3.

Synthesis of compound (+)-20



To the solution of compound (+)-19 (200 mg, 0.448 mmol, 1.00 equiv) in DCM (24 mL) was added VO(acac)_3 (17.8 mg, 0.0671 mmol, 0.15 equiv) and TBHP (5.5 M in decane, 0.20 mL, 1.12 mmol, 2.50 equiv) sequentially at $-20\text{ }^\circ\text{C}$. Then the reaction mixture was stirred for 1.5 h at the same temperature. Subsequently, the reaction mixture was concentrated *in vacuo* and the residue was dissolved in DCM (20 mL), and DBU (0.10 mL, 0.672 mmol, 1.50 equiv) was added at $0\text{ }^\circ\text{C}$. The mixture was allowed to warm to room temperature with stirring for 15 min. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in THF (8 mL) and MeOH (8 mL) followed by the addition of 2 M HCl aqueous solution (12 mL). The reaction mixture was stirred for 20 min at room temperature, and was quenched with saturated aq. NaHCO_3 diluted with EtOAc (30 mL). The layers were separated and the aqueous phase was extracted with EtOAc (contains 15% THF, $6 \times 30\text{ mL}$). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/DCM = 1/5 to pure EtOAc) to give compound (+)-20 (101 mg, 0.290 mmol) as a white solid in 65% yield.



$R_f = 0.5$ (EtOAc)

$[\alpha]_D^{15} +70.2$ (c 0.3 MeOH)

Melting point: 199-201 $^\circ\text{C}$

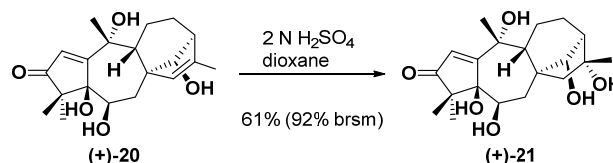
HRMS-ESI (m/z) calc. for $\text{C}_{20}\text{H}_{27}\text{O}_5$ $[\text{M}-\text{H}]^-$: 347.1864; Found: 347.1863.

IR (neat, cm^{-1}): 3358, 2960, 2919, 2850, 1693, 1258, 1016, 797.

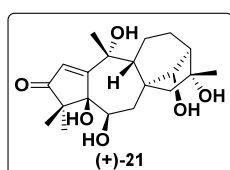
¹H NMR (400 MHz, CD₃OD) δ 6.26 (s, 1H), 5.16 (s, 1H), 4.21 (s, 1H), 3.76 (dd, J = 7.2, 5.0 Hz, 1H), 2.32 (t, J = 2.8 Hz, 1H), 2.22 (d, J = 7.3 Hz, 1H), 2.02 – 1.95 (m, 1H), 1.93 (d, J = 3.6 Hz, 1H), 1.92 (s, 1H), 1.77 (dd, J = 14.0, 5.9 Hz, 1H), 1.72 (d, J = 1.4 Hz, 3H), 1.61 – 1.52 (m, 1H), 1.51 (s, 3H), 1.47 – 1.39 (m, 1H), 1.14 (s, 3H), 1.10 (s, 3H).

¹³C NMR (125 MHz, CD₃OD) δ 213.3, 190.4, 139.6, 131.4, 127.0, 85.7, 81.0, 78.8, 73.5, 58.5, 55.9, 55.1, 45.8, 40.6, 31.9, 27.9, 24.6, 21.4, 18.8 15.4.

Synthesis of compound (+)-21



To the solution of compound (+)-20 (158 mg, 0.454 mmol, 1.00 equiv) in 1,4-dioxane (2.4 mL) followed by the addition of 2 M H₂SO₄ aqueous solution (3.2 mL). The reaction mixture was stirred for 24 h at 30 °C, and was quenched with saturated aq. NaHCO₃ diluted with EtOAc (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (contains 15% THF, 6×20 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (MeOH/DCM = 1/30 to 1/10) to give compound (+)-21 (102 mg, 0.278 mmol) as a white solid in 61% yield (92% brsm) and recover compound (+)-20 (53.0 mg, 0.152 mmol) as a white solid.



R_f = 0.2 (DCM/MeOH = 1/10)

[α]_D¹⁵ +24.6 (c 0.3 MeOH)

Melting point: 130-132 °C

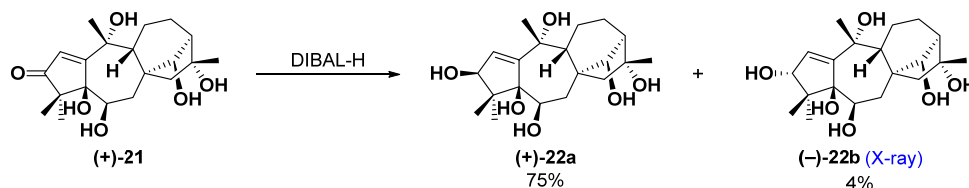
HRMS-ESI (m/z) calc. for C₂₀H₂₉O₆ [$\text{M}-\text{H}$]⁻ : 365.1970; Found: 365.1973.

IR (neat, cm⁻¹): 3358, 2963, 2921, 1687, 1259, 1091, 1018, 798.

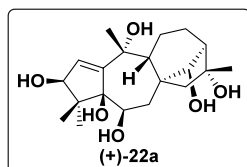
¹H NMR (400 MHz, CD₃OD) δ 6.23 (s, 1H), 4.24 (s, 1H), 3.79 (dd, J = 8.3, 3.7 Hz, 1H), 2.27 (d, J = 7.0 Hz, 1H), 2.15 – 2.05 (m, 2H), 2.04 – 1.96 (m, 2H), 1.94 (s, 1H), 1.88 (d, J = 14.9 Hz, 1H), 1.81 – 1.72 (m, 1H), 1.62 – 1.53 (m, 2H), 1.50 (s, 3H), 1.31 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H).

¹³C NMR (125 MHz, CD₃OD) δ 213.3, 190.4, 126.7, 85.3, 82.2, 81.1, 78.2, 73.3, 59.1, 58.4, 55.3, 52.9, 51.8, 44.4, 31.8, 27.8, 26.9, 23.4, 20.7, 18.7.

Syntheses of compound (+)-22a and (–)-22b



To the solution of compound (+)-21 (100 mg, 0.273 mmol, 1.00 equiv) in THF (40 mL) was added DIBAL-H (2.73 mL, 1.0 M in hexane, 2.73 mmol, 10.0 equiv) at –78 °C. The reaction mixture was stirred for 1 h at the same temperature and then allowed to warm to –20 °C over 2 h. Subsequently, the reaction mixture was quenched with saturated aq. Rochelle's salt (80 mL) diluted with EtOAc (80 mL). The mixture was stirred for 30 min, then the layers were separated and the aqueous phase was extracted with EtOAc (contains 15% THF, 6×100 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (MeOH/DCM = 1/20 to 1/5 to MeOH/EtOAc = 1/3) to give compound (–)-22b (4 mg, 0.0108 mmol) as a white solid in 4% yield and compound (+)-22a contaminated by a small amount of silica gel. Afterwards, this sample of compound (+)-22a was dissolved in EtOAc (100 mL) and then filtered through a short pad of cotton, and the combined solution was concentrated *in vacuo* to give pure compound (+)-22a (76 mg, 0.206 mmol) as a white solid in 75% yield.



$R_f = 0.32$ (DCM/MeOH = 1/5)

$[\alpha]_D^{16} +24.0$ (c 0.3 MeOH)

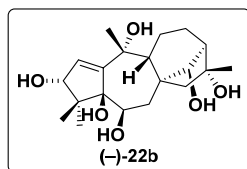
Melting point: 203–205 °C

HRMS-ESI (m/z) calc. for C₂₀H₃₁O₆ [M–H][–]: 367.2126; Found: 367.2127.

IR (neat, cm^{–1}): 3358, 2960, 2919, 2850, 1259, 1088, 1016, 796.

¹H NMR (400 MHz, CD₃OD) δ 5.73 (d, J = 1.2 Hz, 1H), 4.27 – 4.23 (m, 2H), 3.90 (dd, J = 8.9, 3.9 Hz, 1H), 2.14 – 2.04 (m, 2H), 2.00 (d, J = 7.0 Hz, 1H), 1.97 – 1.85 (m, 3H), 1.81 (d, J = 14.8 Hz, 1H), 1.71 (dd, J = 14.0, 6.3 Hz, 1H), 1.58 – 1.44 (m, 2H), 1.41 (s, 3H), 1.29 (s, 3H), 1.15 (s, 3H), 0.89 (s, 3H).

¹³C NMR (150 MHz, CD₃OD) δ 156.3, 127.7, 86.5, 82.1, 80.8, 80.3, 76.8, 70.6, 59.2, 56.0, 55.5, 53.1, 52.2, 44.8, 32.8, 27.0, 23.5, 21.5, 21.0, 19.5.



R_f = 0.4 (DCM/MeOH = 1/5)

[α]_D¹⁶ -10.3 (*c* 0.15 MeOH)

Melting point: 193-195 °C

HRMS-ESI (*m/z*) calc. for C₂₀H₃₂NaO₆ [M+Na⁺]: 391.2091; Found: 391.2096.

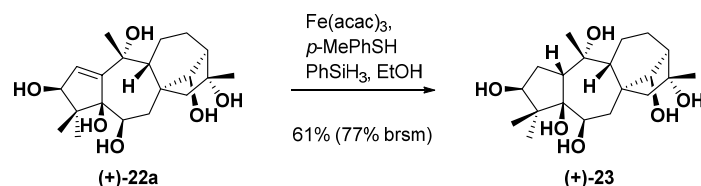
IR (neat, cm⁻¹): 3357, 2957, 2920, 2851, 1469, 1258, 1011, 798.

¹H NMR (400 MHz, CD₃OD) δ 5.90 (d, *J* = 3.2 Hz, 1H), 4.36 (s, 1H), 4.17 (dd, *J* = 7.7, 3.2 Hz, 1H), 3.99 (d, *J* = 3.2 Hz, 1H), 2.26 (dd, *J* = 14.8, 3.3 Hz, 1H), 2.13 (d, *J* = 7.8 Hz, 1H), 2.07 – 2.00 (m, 1H), 1.96 (d, *J* = 15.4 Hz, 1H), 1.92 – 1.84 (m, 3H), 1.73 (dd, *J* = 14.3, 6.5 Hz, 1H), 1.61 – 1.53 (m, 1H), 1.52 – 1.44 (m, 1H), 1.37 (s, 3H), 1.30 (s, 3H), 1.08 (s, 3H), 0.95 (s, 3H).

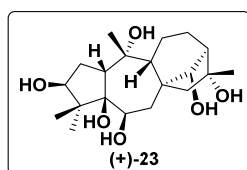
¹³C NMR (150 MHz, CD₃OD) δ 161.1, 125.4, 86.7, 82.6, 81.6, 81.2, 77.2, 72.6, 59.4, 54.9, 53.1, 51.0, 50.6, 43.4, 32.4, 27.1, 27.0, 23.4, 20.4, 18.5.

CCDC 2144673 contains the supplementary crystallographic data for compound **(-)-22b** and is available free of charge from The Cambridge Crystallographic Data Centre via <https://www.ccdc.cam.ac.uk/structures/>

Synthesis of (+)-1-*epi*-grayanotoxin III (**23**)



The solution of compound **(+)-22a** (8.0 mg, 0.0217 mmol, 1.00 equiv), Fe(acac)_3 (1.5 mg, 0.00434 mmol, 0.20 equiv) and $p\text{-MePhSH}$ (0.54 mg, 0.00434 mmol, 0.20 equiv) in EtOH (0.5 mL) was degassed by bubbling N_2 through the solution for 10 min. PhSiH_3 (5.4 μL , 0.0434 mmol, 2.00 equiv) was added at room temperature. The mixture was degassed again by bubbling N_2 through the solution for 1 min. Then the flask was moved into a glove box and the reaction mixture was stirred for 44 h at room temperature in the glove box under N_2 atmosphere. The flask was removed from the glove box and the mixture was concentrated *in vacuo*. The residue was purified by preparative Thin-Layer Chromatography on silica gel (DCM/MeOH = 1/7) to give **(+)-1-*epi*-grayanotoxin III 23** (4.9 mg, 0.0132 mmol) as a white solid in 61% yield (77% brsm) and recover compound **(+)-22a** (1.7 mg, 0.00461 mmol) as a white solid.



$R_f = 0.5$ (DCM/MeOH = 1/5)

$[\alpha]_D^{16} +7.9$ (c 0.3 MeOH)

Melting point: 157-159 °C

HRMS-ESI (m/z) calc. for $\text{C}_{20}\text{H}_{34}\text{NaO}_6$ $[\text{M}+\text{Na}^+]$: 393.2248; Found: 393.2248.

IR (neat, cm^{-1}): 3675, 2970, 2901, 1396, 1259, 1066, 1027, 879.

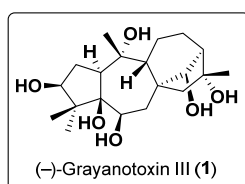
^1H NMR (600 MHz, acetone- d_6 D_2O exchanged) 5.05 (s, 1H), 4.30 (d, $J = 9.9$ Hz, 1H), 3.44 (d, $J = 4.2$ Hz, 1H), 2.37 (dd, $J = 13.8, 10.3$ Hz, 1H), 2.16 (dd, $J = 10.4, 9.0$ Hz, 1H), 2.08 – 2.02 (m, 1H), 1.97 – 1.91 (m, 3H), 1.89 (dd, $J = 13.3, 8.8$ Hz, 1H), 1.78 (d, $J = 14.7$ Hz, 1H), 1.74 (d, $J = 14.4$ Hz, 1H), 1.76 – 1.70 (m, 1H), 1.54 – 1.45 (m, 2H), 1.40 (d, $J = 7.9$ Hz, 1H), 1.29 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H), 1.02 (s, 3H).

^{13}C NMR (150 MHz, acetone- d_6 D_2O exchanged) δ 86.5, 81.7, 79.6, 77.5, 77.2, 68.8, 60.8, 57.5, 55.6, 53.0, 52.7, 49.1, 40.8, 36.3, 29.4, 25.0, 22.4, 21.1, 21.0, 19.7.

Synthesis of (–)-grayanotoxin III (1)



The solution of compound **(+)-22a** (16.0 mg, 0.0434 mmol, 1.00 equiv) and Mn(dpm)_3 (5.2 mg, 0.00869 mmol, 0.20 equiv) in DCM (1.2 mL) was degassed by bubbling N_2 through the solution for 10 min. TBHP (12 μL , 5.5 M in decane, 0.0651 mmol, 1.50 equiv) and $\text{Ph}(i\text{PrO})\text{SiH}_2$ (19.5 μL , 0.108 mmol, 2.50 equiv) were added sequentially at room temperature. The mixture was degassed again by bubbling N_2 through the solution for 1 min. Then the flask was moved into a glove box and the reaction mixture was stirred for 27 h at room temperature in the glove box under N_2 atmosphere. The flask was removed from the glove box and the mixture was concentrated *in vacuo*. The residue was purified by preparative Thin-Layer Chromatography on silica gel (DCM/MeOH = 1/7) to give (–)-grayanotoxin III (**1**) (8.2 mg, 0.0221 mmol) as a white solid in 51% yield (64% brsm) and recover compound **(+)-22a** (3.2 mg, 0.00869 mmol) as a white solid.



$R_f = 0.4$ (DCM/MeOH = 1/5)

$[\alpha]_D^{14} -12.6$ (*c* 0.2 MeOH) [Lit.⁷: $[\alpha]_D^{24} -16$ (*c* 0.45 MeOH), Lit.²: $[\alpha]_D^{25} -17.5$ (*c* 0.4 MeOH)]

Melting point: 244–246 °C [Lit.¹⁶: mp = 218 °C, Lit.⁷: mp = 218–222 °C, Lit.²: mp = 213–214 °C]

HRMS-ESI (*m/z*) calc. for $\text{C}_{20}\text{H}_{34}\text{NaO}_6$ [$\text{M}+\text{Na}^+$]: 393.2248; Found: 393.2250.

IR (neat, cm^{-1}): 3339, 2920, 1466, 1410, 1121, 1044, 933, 876. [Lit.⁷: IR: 3280, 1453, 1373, 1030, 870, 710.]

¹H NMR (600 MHz, pyridine-*d*₅ D₂O exchanged) δ 5.05 (s, 1H), 4.56 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.88 (d, *J* = 4.6 Hz, 1H), 3.19 (dd, *J* = 11.8, 4.6 Hz, 1H), 2.89 (dd, *J* = 13.5, 4.2 Hz, 1H), 2.64 – 2.57 (m, 2H), 2.55 – 2.48 (m, 3H), 2.27 (d, *J* = 14.6 Hz, 1H), 2.18 (d, *J* = 6.9 Hz, 1H), 2.09 (d, *J* = 14.5 Hz, 1H), 2.04 (dd, *J* = 14.1, 6.1 Hz, 1H), 1.87 (s, 3H), 1.70 (s, 3H), 1.69 – 1.65 (m, 1H), 1.64 – 1.58 (m, 1H), 1.51 (s, 3H), 1.13 (s, 3H).

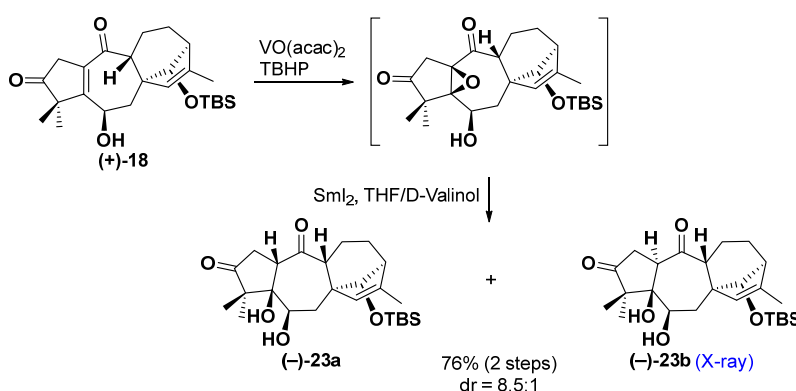
¹H NMR (600 MHz, acetone-*d*₆ D₂O exchanged) δ 4.27 (s, 1H), 3.88 (dd, *J* = 11.1, 4.3 Hz, 1H), 3.54 (d, *J* = 4.8 Hz, 1H), 2.62 (dd, *J* = 11.9, 4.7 Hz, 1H), 2.18 (ddd, *J* = 15.1, 11.9, 4.8 Hz, 1H), 2.12 (dd, *J* = 13.6, 4.4 Hz, 1H), 2.07 (dd, *J* = 6.4, 3.2 Hz, 1H),

2.02 (dd, $J = 15.2, 4.8$ Hz, 1H), 1.97 (s, 1H), 1.89 (d, $J = 14.7$ Hz, 1H), 1.83 – 1.76 (m, 2H), 1.74 (d, $J = 7.4$ Hz, 1H), 1.68 (dd, $J = 13.2, 6.1$ Hz, 1H), 1.50 – 1.42 (m, 2H), 1.34 (s, 3H), 1.25 (s, 3H), 1.17 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (150 MHz, pyridine- d_5 D $_2$ O exchanged) δ 84.9, 82.8, 80.0, 79.5, 78.4, 74.4, 60.5, 56.5, 55.5, 52.8, 52.1, 51.9, 44.5, 36.0, 28.5, 27.3, 24.0, 23.5, 22.8, 20.1.

^{13}C NMR (150 MHz, acetone- d_6 D $_2$ O exchanged) δ 83.7, 82.1, 79.3, 78.5, 77.4, 73.0, 59.2, 55.2, 54.6, 51.5, 51.0, 50.2, 43.1, 34.6, 27.1, 26.2, 22.7, 22.5, 21.5, 18.4.

Syntheses of compounds (–)-23a and (–)-23b

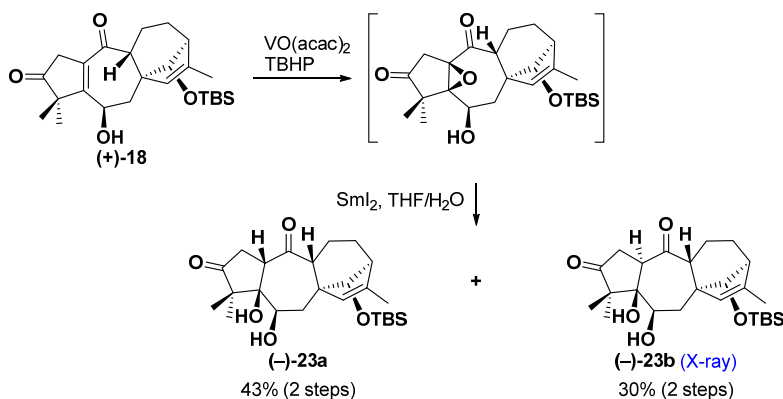


To a solution of compound (+)-18 (20.0 mg, 0.0464 mmol, 1.00 equiv) in DCM (1.2 mL) was added VO(acac) $_2$ (6.2 mg, 0.0232 mmol, 0.50 equiv) and TBHP (5.5 M in decane, 25.3 μL , 0.139 mmol, 3.00 equiv) sequentially at 0 °C. The resulting dark-brown solution was stirred for 3 h at 0 °C before additional TBHP (5.5 M in decane, 12.6 μL , 0.0696 mmol, 1.50 equiv) was added to the reaction mixture. The reaction mixture was allowed to warm to room temperature with stirring for 20 min (complete consumption of the starting material was observed by TLC). The mixture was diluted with EtOAc (3 mL) and quenched with the saturated aq. Na $_2$ S $_2$ O $_3$ (3 mL). The layers were separated, and the organic layer was washed with saturated aq. Na $_2$ S $_2$ O $_3$ (2 \times 3 mL) and saturated aq. NaHCO $_3$ (3 mL). The combined aqueous layers were extracted with EtOAc (3 \times 5 mL), and the combined organic layers were washed with brine, dried over Na $_2$ SO $_4$, and concentrated *in vacuo*.

The residue was dissolved in degassed THF (1.5 mL, contains 0.08 mL D-valinol), and then SmI $_2$ (1.16 mL, 0.1 M in THF, 0.116 mmol, 2.50 equiv) was added at –78 °C. The reaction mixture was stirred for 5 min at the same temperature, and then was quenched with saturated aq. NaHCO $_3$ (5 mL) diluted with EtOAc (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 \times 5 mL). The combined organic layers were washed with brine, dried over Na $_2$ SO $_4$, and concentrated *in vacuo*. The residue was purified by preparative Thin-Layer

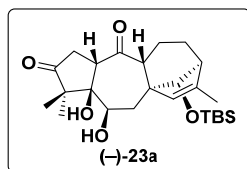
Chromatography on silica gel (EtOAc/PE = 1/3) to give a mixture of (–)-**23a** and (–)-**23b** (15.9 mg, 0.0354 mmol, ¹H-NMR ratio **23a**:**23b** = 8.5:1) in 76% yield over 2 steps.

Syntheses of compounds (–)-**23a** and (–)-**23b**



To a solution of compound (+)-**18** (20.0 mg, 0.0464 mmol, 1.00 equiv) in DCM (1.2 mL) was added VO(acac)₂ (6.2 mg, 0.0232 mmol, 0.50 equiv) and TBHP (5.5 M in decane, 25.3 μL, 0.139 mmol, 3.00 equiv) sequentially at 0 °C. The resulting dark-brown solution was stirred for 3 h at 0 °C before additional TBHP (5.5 M in decane, 12.6 μL, 0.0696 mmol, 1.50 equiv) was added to the reaction mixture. The reaction mixture was allowed to warm to room temperature with stirring for 20 min (complete consumption of the starting material was observed by TLC). The mixture was diluted with EtOAc (3 mL) and quenched with the saturated aq. Na₂S₂O₃ (3 mL). The layers were separated, and the organic layer was washed with saturated aq. Na₂S₂O₃ (2×3 mL) and saturated aq. NaHCO₃ (3 mL). The combined aqueous layers were extracted with EtOAc (3×5 mL), and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*.

The residue was dissolved in degassed THF (0.8 mL) and H₂O (0.1 mL), then SmI₂ (1.16 mL, 0.1 M in THF, 0.116 mmol, 2.50 equiv) was added at –78 °C. The reaction mixture was stirred for 5 min at the same temperature, then the mixture was quenched with saturated aq. NaHCO₃ (5 mL) diluted with EtOAc (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by preparative Thin-Layer Chromatography on silica gel (acetone/toluene = 1/10 for 2 times) to give compound (–)-**23a** (9.0 mg, 0.0201 mmol) as a white solid in 43% yield and compound (–)-**23b** (6.2 mg, 0.0138 mmol) as a white solid in 30% yield over 2 steps.



$R_f = 0.5$ (Acetone/Toluene = 1/10 for 2 times)

$[\alpha]_D^{28} -13.2$ (c 1.0 CHCl₃)

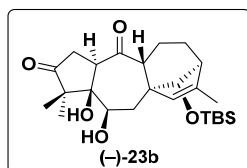
Melting point: 160-162 °C

HRMS-ESI (m/z) calc. for C₂₅H₄₁O₅Si [M+H⁺]: 449.2718; Found: 449.2717.

IR (neat, cm⁻¹): 3503, 2929, 2856, 1736, 1702, 1379, 1255, 1101.

¹H NMR (400 MHz, CDCl₃) δ 5.08 (s, 1H), 3.86 (dd, J = 10.1, 1.6 Hz, 1H), 3.83 (s, 1H), 3.39 (dd, J = 10.1, 4.6 Hz, 1H), 3.02 (dd, J = 19.2, 4.6 Hz, 1H), 2.98 (br s, 1H), 2.78 (d, J = 6.8 Hz, 1H), 2.57 (dd, J = 14.1, 10.3 Hz, 1H), 2.40 (dd, J = 19.2, 10.1 Hz, 1H), 2.41 (s, 1H), 1.86 (d, J = 14.0 Hz, 1H), 1.83 – 1.76 (m, 1H), 1.73 (d, J = 1.5 Hz, 3H), 1.68 (dd, J = 14.0, 6.2 Hz, 1H), 1.63 (br s, 1H), 1.60 – 1.52 (m, 1H), 1.37 (ddd, J = 19.6, 14.0, 7.1 Hz, 1H), 1.14 (s, 3H), 1.02 (s, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 220.1, 213.7, 140.0, 126.8, 81.9, 80.6, 69.3, 56.6, 55.0, 54.7, 53.4, 53.0, 37.9, 36.5, 25.9, 22.6, 21.9, 21.7, 18.8, 18.1, 15.6, -3.7, -4.6.



$R_f = 0.4$ (Acetone/Toluene = 1/10 for 2 times)

$[\alpha]_D^{27} -124.5$ (c 0.5 CHCl₃)

Melting point: 220-222 °C

HRMS-ESI (m/z) calc. for C₂₅H₄₁O₅Si [M+H⁺]: 449.2718; Found: 449.2719.

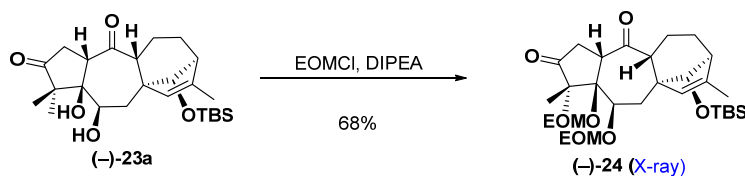
IR (neat, cm⁻¹): 3486, 2950, 2928, 2855, 1727, 1684, 1257, 1105.

¹H NMR (400 MHz, CDCl₃) δ 5.09 – 5.05 (m, 1H), 4.39 – 4.33 (m, 1H), 3.85 (s, 1H), 3.34 – 3.25 (m, 1H), 3.08 (dd, J = 19.9, 10.3 Hz, 1H), 2.58 (dd, J = 19.9, 9.1 Hz, 1H), 2.51 – 2.45 (m, 1H), 2.47 (br s, 1H), 2.26 (br s, 1H), 2.18 – 2.03 (m, 3H), 1.72 (d, J = 1.6 Hz, 3H), 1.58 – 1.51 (m, 1H), 1.50 – 1.41 (m, 1H), 1.36 – 1.24 (m, 2H), 1.20 (s, 3H), 1.15 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

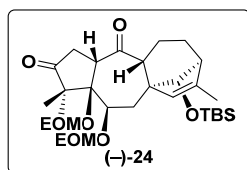
¹³C NMR (100 MHz, CDCl₃) δ 219.1, 209.7, 137.8, 129.1, 83.4, 82.6, 72.2, 57.3, 53.7, 53.4, 51.9, 51.2, 39.3, 37.0, 25.9, 22.9, 22.7, 22.1, 18.2, 17.8, 15.3, -3.3, -4.5.

CCDC 2144675 contains the supplementary crystallographic data for compound (-)-23b and is available free of charge from The Cambridge Crystallographic Data Centre via <https://www.ccdc.cam.ac.uk/structures/>

Synthesis of compound (–)-24



To a solution of compound (–)-23a (21.0 mg, 0.0468 mmol, 1.00 equiv) in DCE (0.5 mL) was added *N,N*-diisopropylethylamine (90.7 mg, 0.702 mmol, 15.0 equiv), DMAP (12.6 mg, 0.103 mmol, 2.20 equiv) and chloromethyl ethyl ether (44.2 mg, 0.468 mmol, 10.0 equiv) sequentially. The reaction vial was capped and heated to 80 °C for 18 h. The reaction mixture was cooled to 23 °C and quenched with saturated aq. NaHCO₃ (1 mL) diluted with EtOAc (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×3 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by preparative Thin-Layer Chromatography on silica gel (EtOAc/PE = 1/3) to give compound (–)-24 (18.0 mg, 0.0319 mmol) as a white solid in 68% yield.



$R_f = 0.7$ (EtOAc/PE = 1/2)

$[\alpha]_D^{28} -44.0$ (*c* 0.5 CHCl₃)

Melting point: 122–124 °C

HRMS-ESI (*m/z*) calc. for C₃₁H₅₃O₇Si $[M+H]^+$: 565.3555; Found: 565.3557.

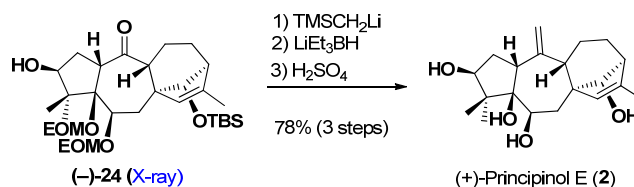
IR (neat, cm^{–1}): 2929, 2857, 1741, 1704, 1473, 1257, 1098, 1021.

¹H NMR (500 MHz, CDCl₃) δ 5.09 (s, 1H), 4.99 (d, *J* = 7.0 Hz, 1H), 4.96 (d, *J* = 8.4 Hz, 1H), 4.63 (d, *J* = 7.0 Hz, 1H), 4.56 (d, *J* = 8.4 Hz, 1H), 4.13 (dd, *J* = 10.0, 5.9 Hz, 1H), 4.10 (s, 1H), 3.88 – 3.81 (m, 1H), 3.79 – 3.70 (m, 2H), 3.60 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.50 (dq, *J* = 14.2, 7.0 Hz, 1H), 3.23 (dd, *J* = 19.2, 5.9 Hz, 1H), 2.79 (d, *J* = 5.9 Hz, 1H), 2.56 (s, 1H), 2.44 (dd, *J* = 14.7, 10.2 Hz, 1H), 2.32 (dd, *J* = 19.2, 10.2 Hz, 1H), 2.21 (d, *J* = 14.7 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.75 (d, *J* = 1.2 Hz, 3H), 1.63 (dd, *J* = 14.0, 6.1 Hz, 1H), 1.59 – 1.53 (m, 1H), 1.40 (ddd, *J* = 20.6, 13.9, 7.1 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.19 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 3H), 1.09 (s, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 220.3, 213.4, 140.2, 127.7, 93.1, 91.4, 88.0, 81.1, 75.6, 65.1, 64.3, 55.0, 53.5, 53.3, 52.4, 36.7, 36.6, 33.5, 26.5, 22.4, 22.2, 22.2, 18.9, 18.8, 15.6, 15.4, 15.2, –2.4, –3.3.

CCDC 2144676 contains the supplementary crystallographic data for compound (–)-**24** and is available free of charge from The Cambridge Crystallographic Data Centre via <https://www.ccdc.cam.ac.uk/structures/>

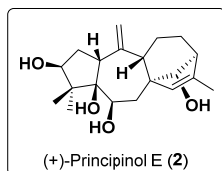
Synthesis of (+)-principinol E (**2**)



To a solution of compound (–)-**24** (8.0 mg, 0.0142 mmol, 1.00 equiv) in THF (1.4 mL) was added (trimethylsilyl)methyl lithium solution (0.26 mL, 0.55 M in hexane, 0.142 mmol, 10.0 equiv) at 0 °C and then stirred for 10 min at the same temperature. The reaction mixture was quenched with saturated aq. NaHCO₃ (2 mL) diluted with EtOAc (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×3 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*.

The residue was dissolved in THF (1.2 mL), and then LiEt₃BH (0.20 mL, 1.0 M in THF, 0.198 mmol, 14.0 equiv) was added at 0 °C. The reaction mixture was stirred for 1 h at the same temperature, and quenched with saturated aq. NaHCO₃ (2 mL) diluted with EtOAc (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×3 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was briefly purified by flash column chromatography on silica gel (EtOAc/PE = 1/10 to 1/2) to give crude product.

The residue of the crude product above was dissolved in 1,4-dioxane (1.0 mL) followed by the addition of 2 M H₂SO₄ aqueous solution (0.6 mL). The reaction mixture was stirred for 20 h at room temperature, and quenched with saturated aq. NaHCO₃ (2 mL) diluted with EtOAc (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (5×4 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by preparative Thin-Layer Chromatography on silica gel (EtOAc) to give (+)-principinol E (**2**) (3.7 mg, 0.0111 mmol) as a white solid in 78% yield over 3 steps.



$R_f = 0.4$ (EtOAc)

$[\alpha]_D^{26} +51.8$ (*c* 0.27 MeOH) [Lit.⁸: $[\alpha]_D^{20} +34.5$ (*c* 0.51 MeOH)]

Melting point: 173-175 °C

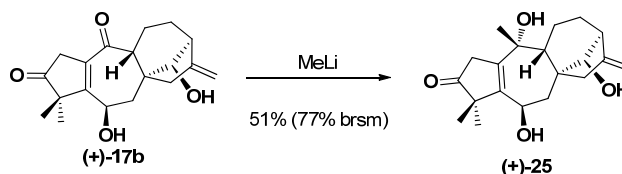
HRMS-ESI (*m/z*) calc. for $C_{20}H_{30}NaO_4$ $[M+Na^+]$: 357.2036; Found: 357.2032.

IR (neat, cm^{-1}): 3384, 2933, 2865, 2173, 1633, 1441, 1049, 1020. [Lit.⁸: IR: 3403, 2942, 1633, 1458, 1047.]

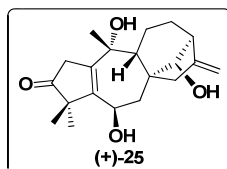
1H NMR (500 MHz, $CDCl_3$) δ 5.26 (s, 1H), 5.15 (d, *J* = 0.9 Hz, 1H), 5.10 – 5.08 (m, 1H), 4.04 (d, *J* = 8.9 Hz, 1H), 3.80 (dd, *J* = 10.1, 5.8 Hz, 1H), 3.75 (dd, *J* = 7.3, 5.0 Hz, 1H), 3.41 (br s, 1H), 2.92 (d, *J* = 7.5 Hz, OH-1H), 2.81 (t, *J* = 9.3 Hz, 1H), 2.53 – 2.51 (m, 1H), 2.51 – 2.45 (m, 1H), 2.25 (ddd, *J* = 14.6, 9.3, 5.1 Hz, 1H), 2.17 (d, *J* = 7.1 Hz, 1H), 2.02 (d, *J* = 10.0 Hz, OH-1H), 1.99 – 1.93 (m, 2H), 1.86 – 1.78 (m, 1H), 1.75 (d, *J* = 1.5 Hz, 3H), 1.75 – 1.71 (m, 1H), 1.67 – 1.62 (m, 2H), 1.59 – 1.54 (m, 1H), 1.24 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 139.1, 129.7, 111.9, 86.6, 84.4, 79.6, 69.8, 56.5, 54.3, 54.3, 50.7, 50.3, 37.9, 36.4, 26.7, 24.3, 22.5, 20.0, 15.6.

Synthesis of compound (+)-25



To the solution of compound (+)-**17b** (225 mg, 0.711 mmol, 1.00 equiv) in THF (100 mL) was added MeLi (6.7 mL, 1.6 M in Et_2O , 10.7 mmol, 15.0 equiv) at -40 °C. The reaction mixture was stirred for 15 min at -40 °C and then allowed to warm to 0 °C with stirring for 30 min. The reaction mixture was quenched with saturated aq. NH_4Cl (60 mL) diluted with EtOAc (60 mL). The layers were separated and the aqueous phase was extracted with EtOAc (5×80 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (Acetone/PE = 1/10 to 1/1) to give compound (+)-**25** (120 mg, 0.361 mmol) as a white foam in 51% yield (77% brsm) and recover compound (+)-**17b** (76 mg, 0.240 mmol) as a white solid.



$R_f = 0.5$ (Acetone /PE = 1/1)

$[\alpha]_D^{13} +19.6$ (*c* 0.5 MeOH)

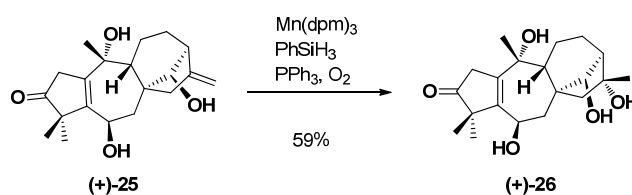
HRMS-ESI (*m/z*) calc. for $C_{20}H_{29}O_4$ $[M+H]^+$: 333.2060; Found: 333.2060.

IR (neat, cm^{-1}): 3431, 2923, 2850, 1735, 1656, 1459, 1121, 1020.

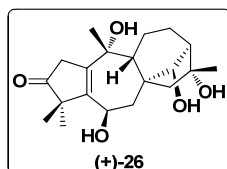
1H NMR (400 MHz, CD_3OD) δ 4.87 – 4.84 (m, 2H overlap), 4.65 (d, *J* = 7.3 Hz, 1H), 4.61 (s, 1H), 3.17 (dd, *J* = 23.0, 1.1 Hz, 1H), 3.06 (d, *J* = 23.1 Hz, 1H), 2.57 – 2.53 (m, 1H), 2.49 (s, 1H), 2.47 – 2.45 (m, 1H), 2.44 – 2.35 (m, 2H), 2.06 (dd, *J* = 14.5, 7.8 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.85 – 1.75 (m, 1H), 1.74 – 1.59 (m, 1H), 1.51 – 1.42 (m, 1H), 1.40 (s, 3H), 1.19 (s, 3H), 1.13 (s, 3H).

^{13}C NMR (100 MHz, CD_3OD) δ 223.5, 157.1, 146.7, 141.7, 105.3, 80.1, 75.5, 66.2, 55.0, 52.7, 52.3, 51.5, 48.9, 44.0, 43.4, 32.2, 30.3, 23.7, 23.1, 21.7.

Synthesis of compound (+)-26



To the solution of compound (+)-25 (53.0 mg, 0.159 mmol, 1.00 equiv), $Mn(dpm)_3$ (14.5 mg, 0.0239 mmol, 0.15 equiv) and PPh_3 (62.6 mg, 0.238 mmol, 1.50 equiv) in EtOH (8 mL) at 0 °C was placed under an O_2 atmosphere (balloon). After the dropwise addition of $PhSiH_3$ (43.2 μ L, 0.350 mmol, 2.20 equiv), the reaction mixture was then stirred under an oxygen atmosphere at 0 °C for 1 h and then the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 1/30 to 1/10) to give compound (+)-26 (33.2 mg, 0.0947 mmol) as a white foam in 59% yield.



$R_f = 0.2$ (DCM/MeOH = 1/10)

$[\alpha]_D^{13} +18.1$ (*c* 0.5 MeOH)

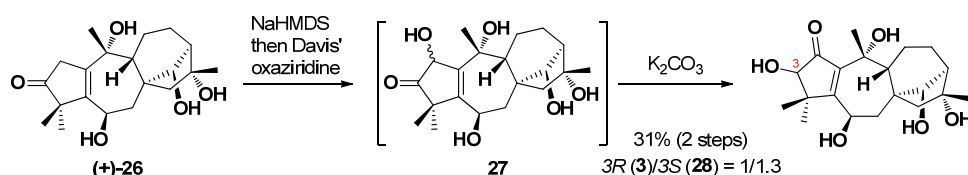
HRMS-ESI (*m/z*) calc. for $C_{20}H_{34}NO_5$ $[M+NH_4]^+$: 368.2431; Found: 368.2428.

IR (neat, cm^{-1}): 3387, 2918, 2852, 1736, 1465, 1378, 1112, 1040.

^1H NMR (400 MHz, CD_3OD) δ 4.63 – 4.59 (m, 1H), 4.58 (s, 1H), 3.19 (d, J = 23.1 Hz, 1H), 3.08 (d, J = 23.0 Hz, 1H), 2.54 (dd, J = 14.6, 2.5 Hz, 1H), 2.36 (d, J = 7.1 Hz, 1H), 2.12 (d, J = 14.9 Hz, 1H), 2.03 (dd, J = 14.6, 7.2 Hz, 1H), 2.00 – 1.91 (m, 2H), 1.91 – 1.77 (m, 2H), 1.64 – 1.52 (m, 2H), 1.39 (s, 3H), 1.34 (s, 3H), 1.18 (s, 3H), 1.13 (s, 3H).

^{13}C NMR (125 MHz, CD_3OD) δ 223.6, 146.1, 141.0, 82.2, 81.8, 76.0, 66.2, 60.0, 55.0, 54.9, 53.1, 53.0, 44.9, 44.1, 30.7, 26.5, 23.6, 23.5, 23.0, 21.7.

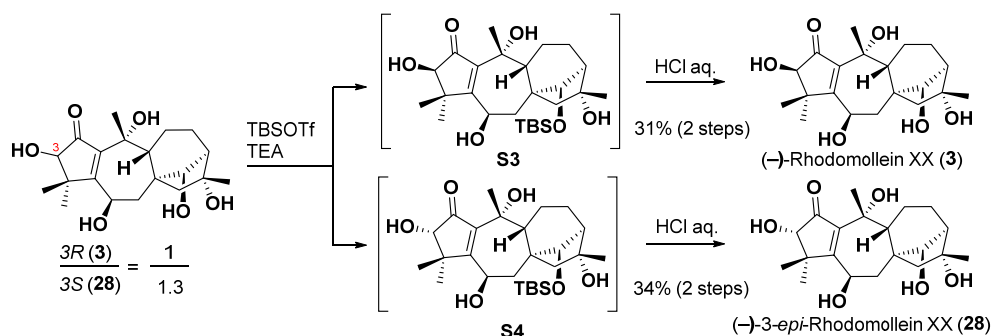
Syntheses of (–)-rhodomollein XX (**3**) and (–)-3-*epi*-rhodomollein XX (**28**)



To the solution of compound (+)-**26** (18.0 mg, 0.0514 mmol, 1.00 equiv) in THF (5.6 mL) was added NaHMDS (2.0 M in THF, 0.28 mL, 0.56 mmol, 11.0 equiv) at –78 °C, and stirring was continued at the same temperature for 2.5 h. Subsequently, to the reaction mixture was added a solution of (±)-trans-2-(phenylsulfonyl)-3-phenyloxaziridine (161 mg, 0.619 mmol, 12.0 equiv) in THF (1 mL) at the same temperature, and stirring was continued for further 2 h. The reaction mixture was quenched with saturated aq. NH_4Cl (5 mL) diluted with EtOAc (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (6×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was briefly purified by passing through a short column of silica gel (eluted by DCM/MeOH = 1/30 to 1/7) to give crude **27** (10.0 mg, 0.0273 mmol) as a white foam.

The residue obtained above was dissolved in MeOH (1.8 mL) and K_2CO_3 (3.8 mg, 0.0273 mmol, 1.00 equiv) was added in one portion at room temperature. The reaction mixture was stirred for 1.5 h at the same temperature, and then quenched with saturated aq. NH_4Cl (3 mL) diluted with EtOAc (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (6×5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by preparative Thin-Layer Chromatography on silica gel (DCM/MeOH = 1/7) to give a mixture of (–)-rhodomollein XX (**3**) and (–)-3-*epi*-rhodomollein XX (**28**) (5.8 mg, 0.0158 mmol, ^1H -NMR ratio **3**:**28** = 1:1.3) in 31% yield over 2 steps.

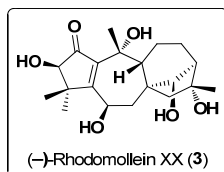
Protection followed by deprotection to afford pure (–)-rhodomollein XX (3) and (–)-3-*epi*-rhodomollein XX (28)



To a solution of the mixture of (–)-rhodomollein XX (3) and (–)-3-*epi*-rhodomollein III (28) (5.8 mg, 0.0158 mmol, ¹H-NMR ratio **3:28** = 1:1.3, 1.00 equiv) in THF (1.5 mL) was added Et₃N (4.4 μL, 0.0316 mmol, 2.00 equiv) followed by TBSOTf (4.7 μL, 0.0205 mmol, 1.30 equiv) at –40 °C. The reaction mixture was stirred at the same temperature for 10 min, and then was quenched with saturated aq. NaHCO₃ (2 mL) diluted with EtOAc (2 mL). The layers were separated and the aqueous phase was then extracted with EtOAc (4×5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by preparative Thin-Layer Chromatography on silica gel (hexane/EtOAc = 1/1) to give compound **S3** (~3 mg) as a white foam and give compound **S4** (~3 mg) as a white foam.

To a solution of compound **S3** in THF (0.15 mL) and MeOH (0.15 mL) was added 2 M HCl aqueous solution (75 μL). The reaction mixture was stirred for 10 min at 15 °C, and was quenched with saturated aq. NaHCO₃ diluted with EtOAc (3 mL). The layers were separated and the aqueous phase was extracted with EtOAc (6×3 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by preparative Thin-Layer Chromatography on silica gel (DCM/MeOH = 1/7) to give (–)-rhodomollein XX (3) (1.8 mg, 0.00491 mmol) as a white solid in 31% yield over 2 steps.

To a solution of compound **S4** in THF (0.15 mL) and MeOH (0.15 mL) was added 2 M HCl aqueous solution (75 μL). The reaction mixture was stirred for 10 min at 15 °C, and was quenched with saturated aq. NaHCO₃ diluted with EtOAc (3 mL). The layers were separated and the aqueous phase was extracted with EtOAc (6×3 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by preparative Thin-Layer Chromatography on silica gel (DCM/MeOH = 1/7) to give (–)-3-*epi*-rhodomollein XX (28) (2.0 mg, 0.00546 mmol) as a white solid in 34% yield over 2 steps.



R_f = 0.4 (DCM/MeOH = 1/7)

[α]_D¹⁷ -45.7 (*c* 0.1 EtOH); **[α]_D¹⁷** -44.8 (*c* 0.2 EtOH)

Melting point: 210-212 °C

HRMS-ESI (*m/z*) calc. for C₂₀H₂₉O₆ [M-H]⁻: 365.1970; Found: 365.1968.

IR (neat, cm⁻¹): 3469, 3356, 1680, 1644, 1470, 1419, 1367, 1106. [Lit.⁹: IR: 3415, 1676, 1630, 1363.]

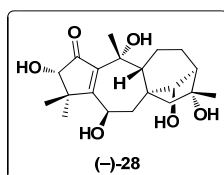
¹H NMR (600 MHz, CD₃OD) δ 4.84 (dd, *J* = 6.1, 3.6 Hz, 1H), 4.35 (s, 1H), 3.86 (s, 1H), 2.69 (dd, *J* = 15.1, 3.6 Hz, 1H), 2.33 (d, *J* = 6.6 Hz, 1H), 2.14 – 2.06 (m, 2H), 1.99 (s, 1H), 1.86 (dd, *J* = 15.2, 6.1 Hz, 1H), 1.82 (dd, *J* = 14.0, 6.0 Hz, 1H), 1.78 (d, *J* = 15.0 Hz, 1H), 1.52 (s, 3H), 1.51 – 1.42 (m, 2H), 1.32 (s, 3H), 1.30 (s, 3H), 1.14 (s, 3H).

¹³C NMR (150 MHz, CD₃OD) δ 209.4, 177.9, 141.7, 82.5, 81.1, 80.0, 76.2, 66.1, 59.9, 56.0, 52.9, 52.8, 45.6, 43.4, 31.6, 26.8, 24.3, 23.3, 23.2, 21.1.

¹H NMR (600 MHz, pyridine-*d*₅) δ 5.46 – 5.42 (m, 1H), 5.08 (d, *J* = 7.8 Hz, 1H), 4.18 (d, *J* = 4.1 Hz, 1H), 3.32 (dd, *J* = 14.8, 3.3 Hz, 1H), 2.74 (d, *J* = 6.9 Hz, 1H), 2.50 – 2.44 (m, 2H), 2.34 (dd, *J* = 14.9, 6.3 Hz, 1H), 2.31 (d, *J* = 14.8 Hz, 1H), 2.27 (d, *J* = 14.7 Hz, 1H), 2.08 (dd, *J* = 14.5, 5.7 Hz, 1H), 1.96 (s, 3H), 1.70 – 1.65 (m, 1H), 1.61 (s, 3H), 1.60 – 1.56 (m, 1H), 1.55 (s, 3H), 1.54 (s, 3H).

¹³C NMR (150 MHz, pyridine-*d*₅) δ 209.9, 178.5, 141.4, 82.4, 80.1, 79.6, 76.0, 65.9, 60.7, 56.2, 53.0, 52.3, 45.3, 44.4, 32.4, 27.0, 25.2, 24.4, 24.0, 21.2.

There has been only one reported isolation of rhodomollein XX by Li *et al.*,^[9] which reported the optical rotation: **[α]_D²⁵** +8.6 (*c* 0.1 EtOH). However, the sign of our optical rotation was opposite to that reported by Li *et al.*: **[α]_D¹⁷** -45.7 (*c* 0.1 EtOH). We determine absolute configuration based on the established stereochemistry of **9**,^[13] as well as the X-ray crystallography of synthetic intermediate **14**, which is further supported by the X-ray crystallography of other related compounds (such as **22b** and **23b**). The discrepancy in the sign of the optical rotation may have been a tabulation error, or due to a minor impurity.



R_f = 0.4 (DCM/MeOH = 1/7)

[α]_D¹⁷ -2.7 (*c* 0.1 EtOH)

Melting point: 202-204 °C

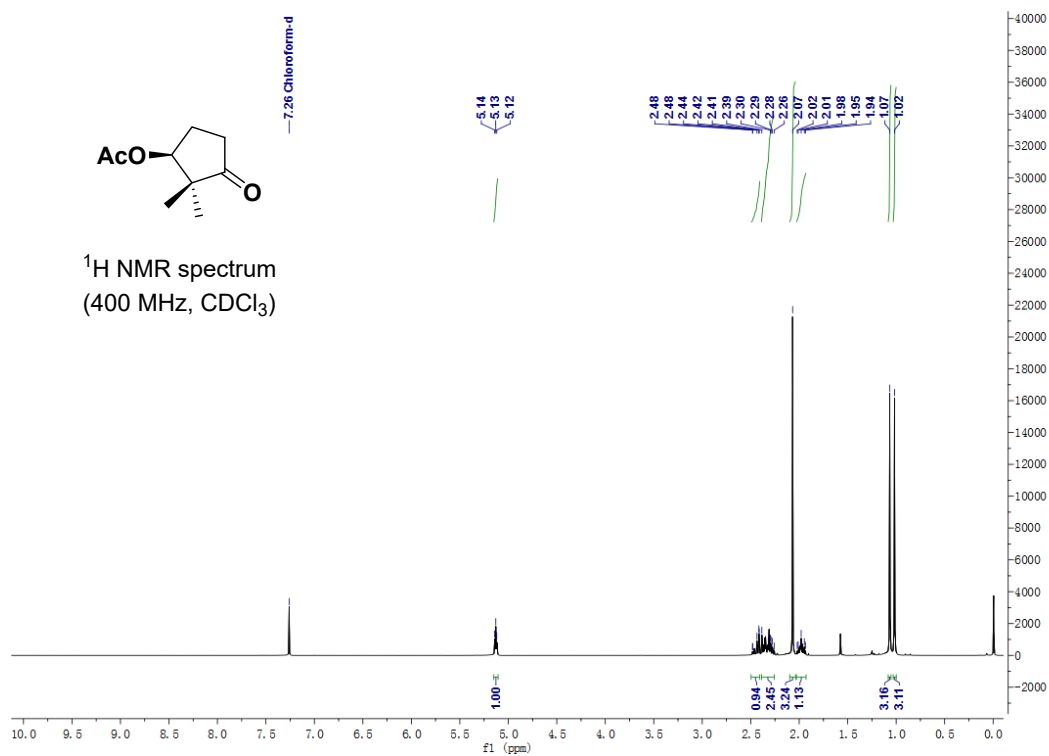
HRMS-ESI (*m/z*) calc. for C₂₀H₂₉O₆ [M-H]⁻: 365.1970; Found: 365.1972.

IR (neat, cm^{-1}): 3429, 3355, 2920, 1683, 1635, 1456, 1419, 1367.

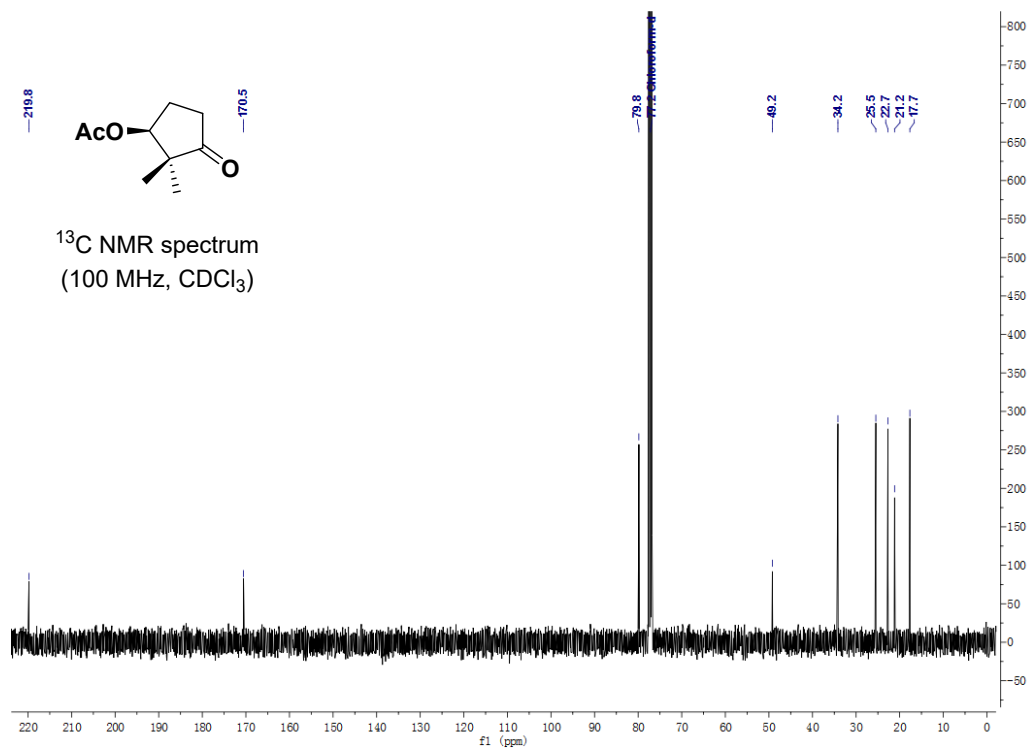
^1H NMR (600 MHz, CD_3OD) δ 4.66 (dd, $J = 5.8, 2.3$ Hz, 1H), 4.49 (s, 1H), 3.89 (s, 1H), 2.60 (d, $J = 7.3$ Hz, 1H), 2.56 (dd, $J = 15.6, 2.2$ Hz, 1H), 2.21 (d, $J = 15.0$ Hz, 1H), 2.11 (dd, $J = 15.6, 5.8$ Hz, 1H), 2.06 – 1.98 (m, 1H), 1.96 (s, 1H), 1.92 (d, $J = 15.1$ Hz, 1H), 1.90 – 1.84 (m, 1H), 1.56 – 1.49 (m, 2H), 1.48 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H), 1.05 (s, 3H).

^{13}C NMR (150 MHz, CD_3OD) δ 210.7, 176.9, 141.8, 82.8, 82.1, 81.6, 76.7, 65.3, 61.0, 55.3, 53.2, 50.9, 45.7, 43.5, 30.4, 26.8, 23.7, 23.5, 23.3, 20.

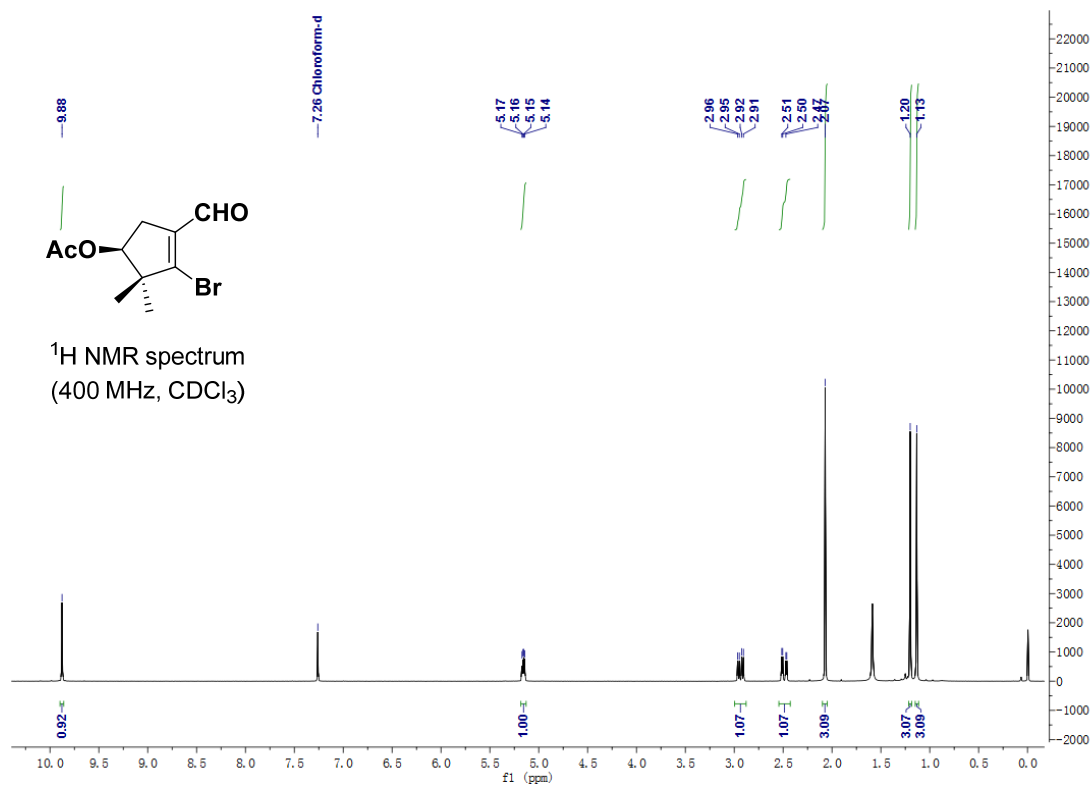
III. NMR Spectra



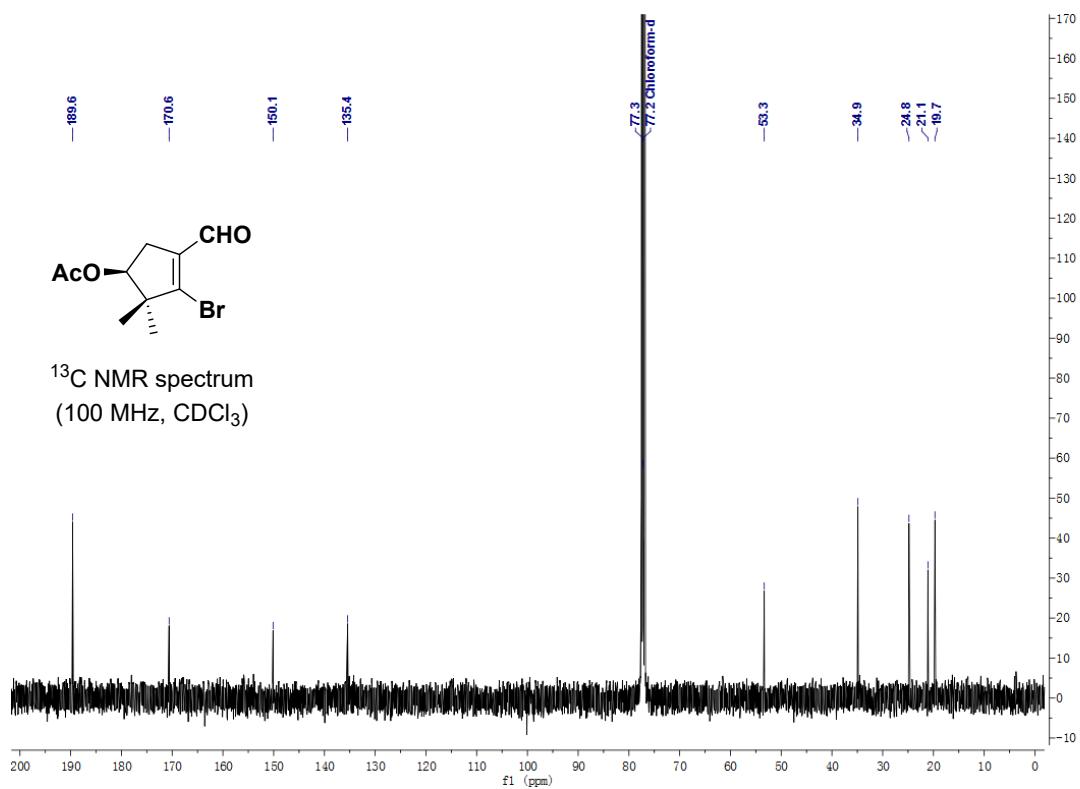
¹H NMR of compound (+)-10



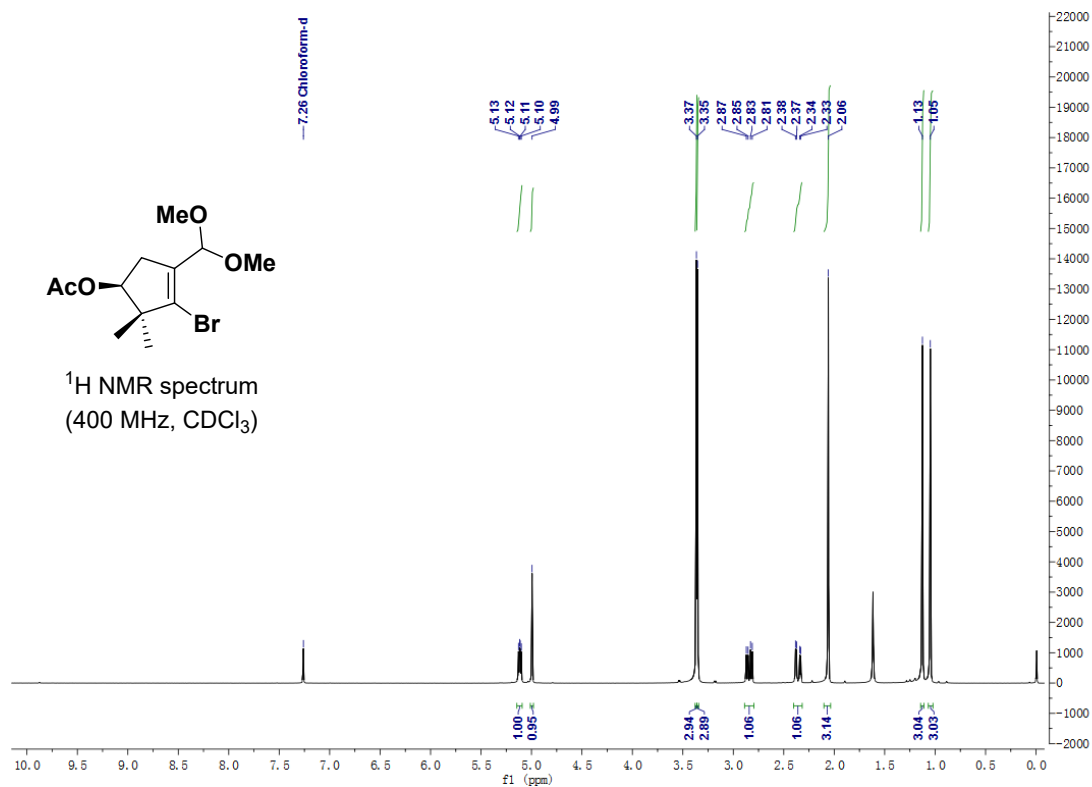
¹³C NMR of compound (+)-10



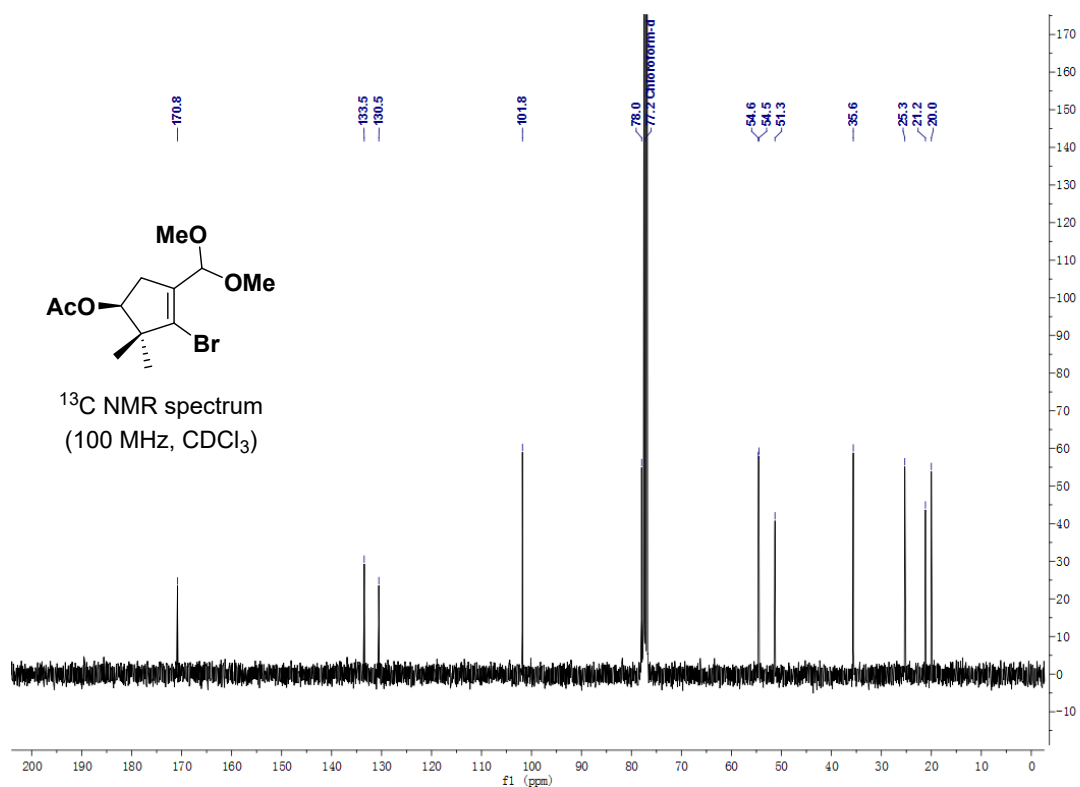
¹H NMR of compound S2



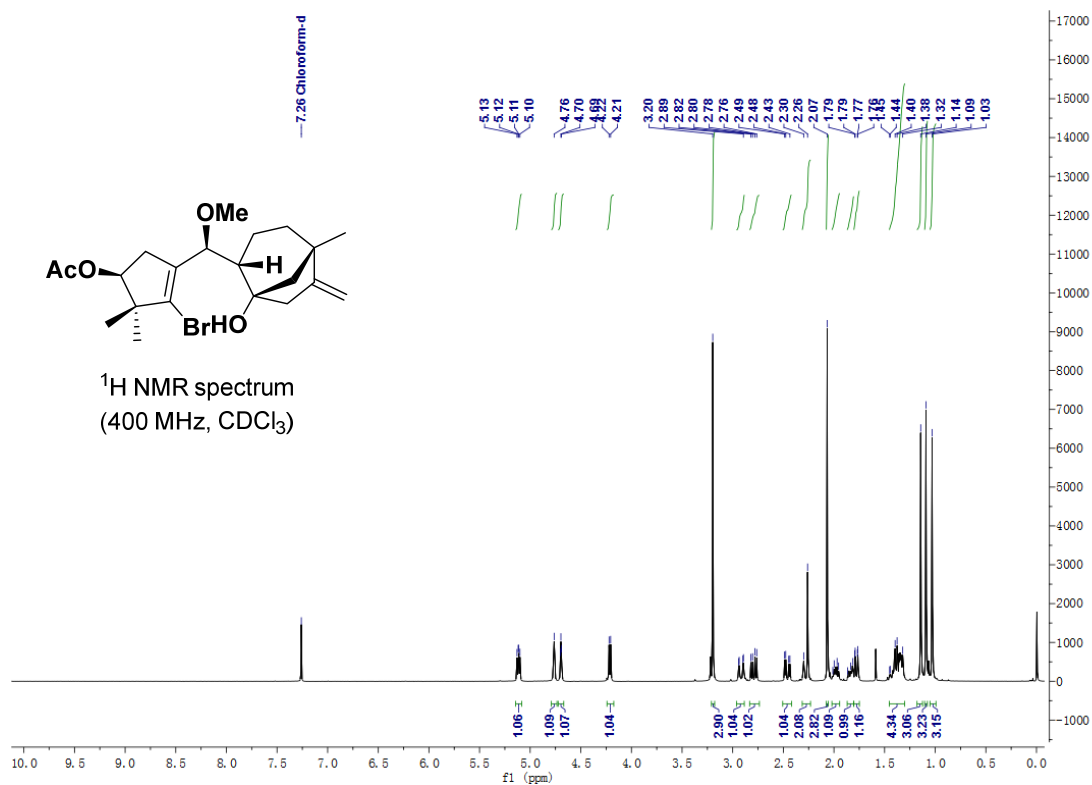
¹³C NMR of compound S2



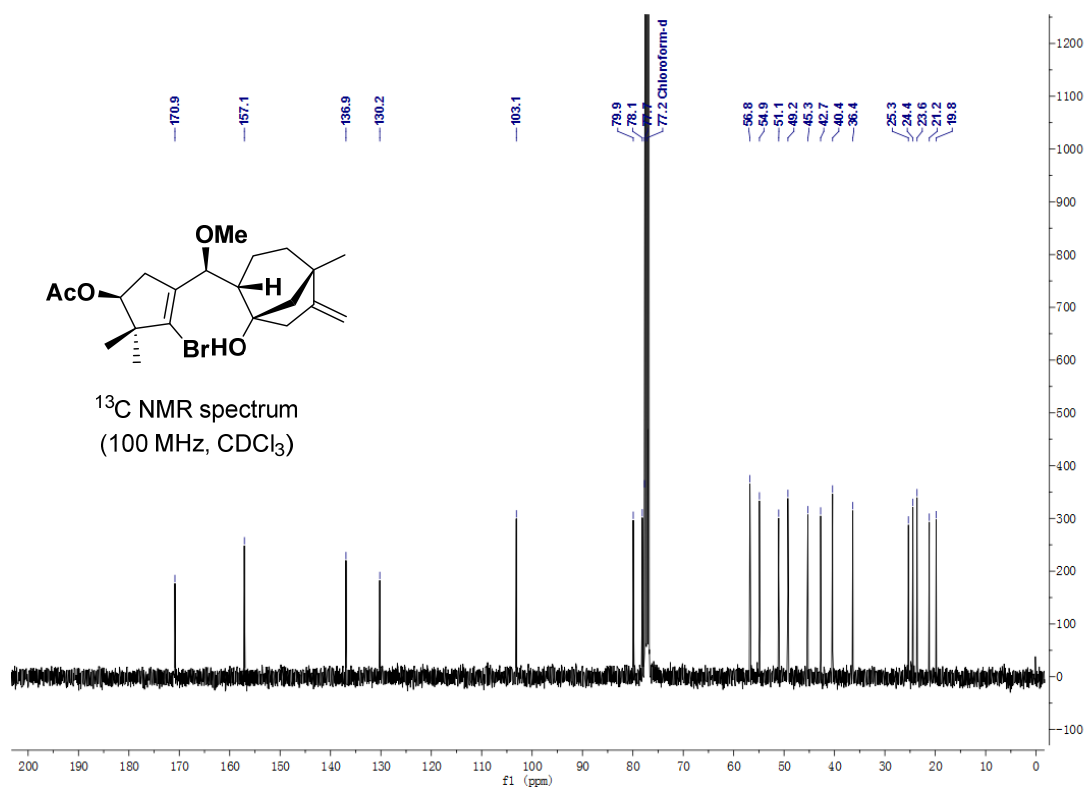
¹H NMR of compound (+)-8



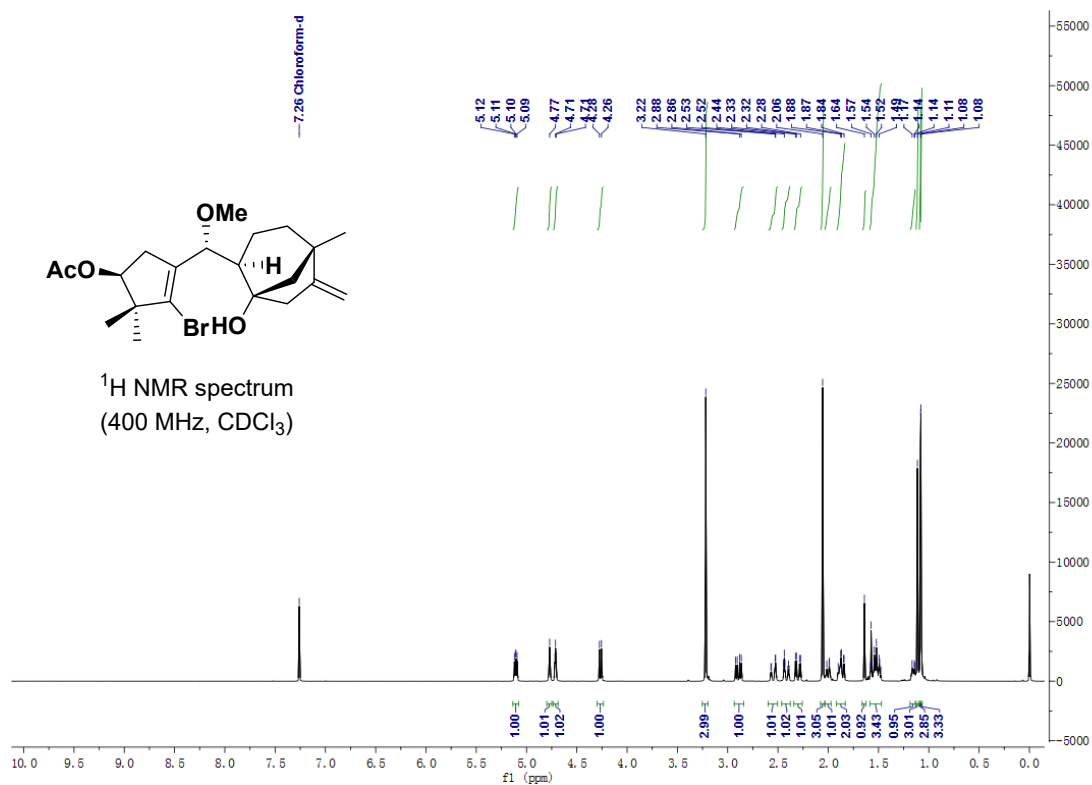
¹³C NMR of compound (+)-8



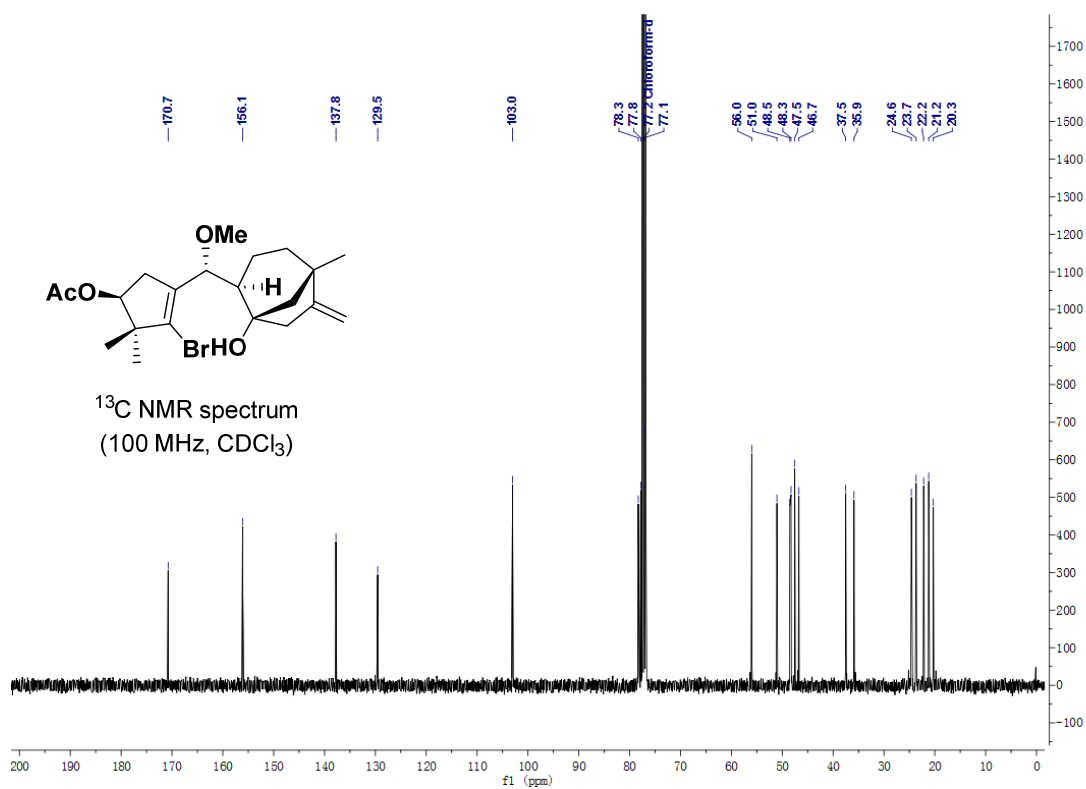
¹H NMR of compound (+)-7a



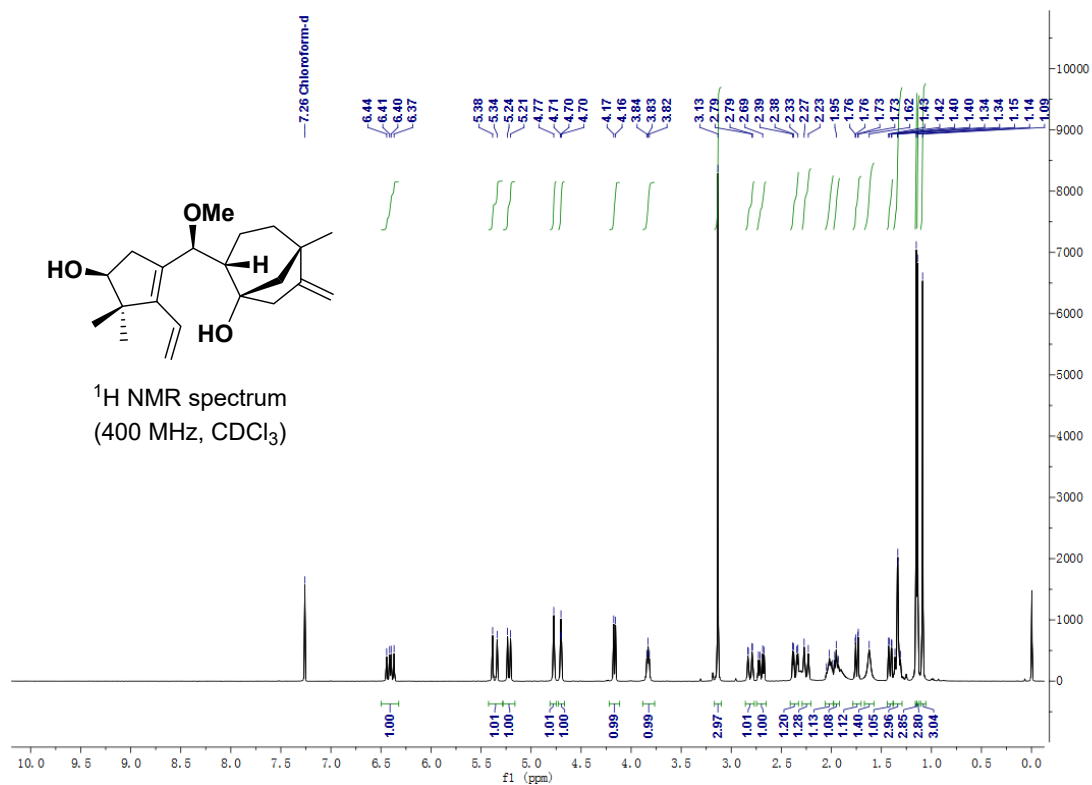
¹³C NMR of compound (+)-7a



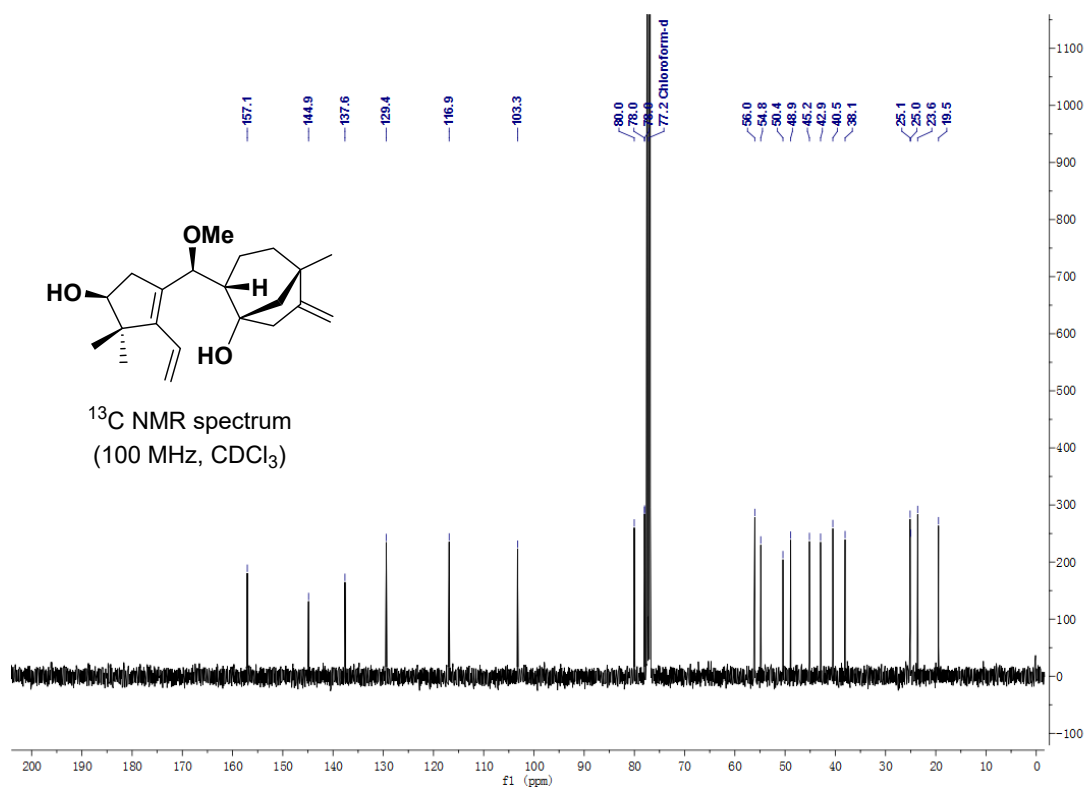
¹H NMR of compound (+)-7b



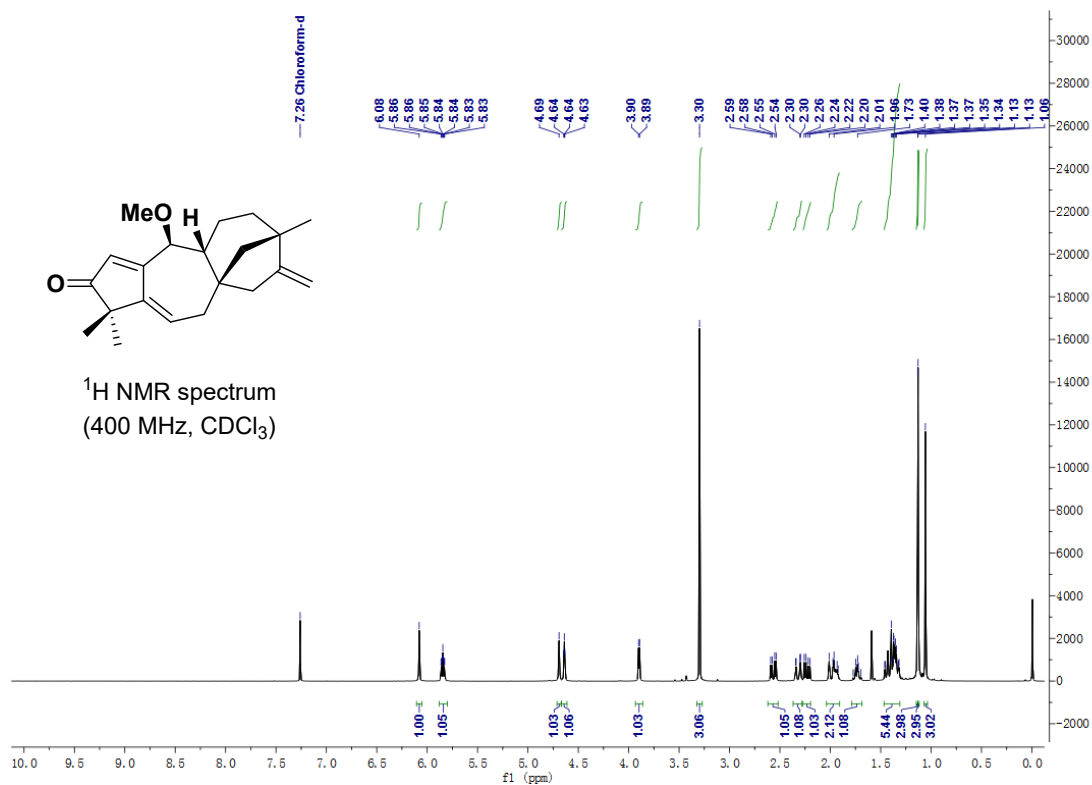
¹³C NMR of compound (+)-7b



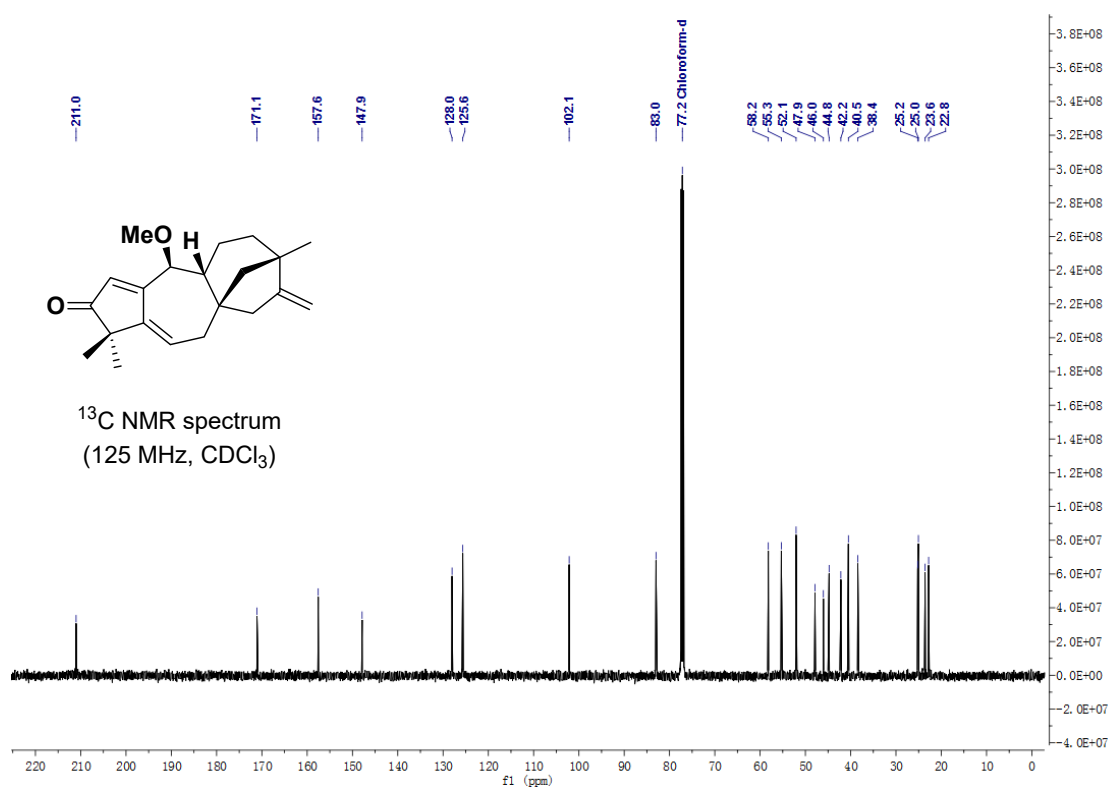
¹H NMR of compound (+)-12



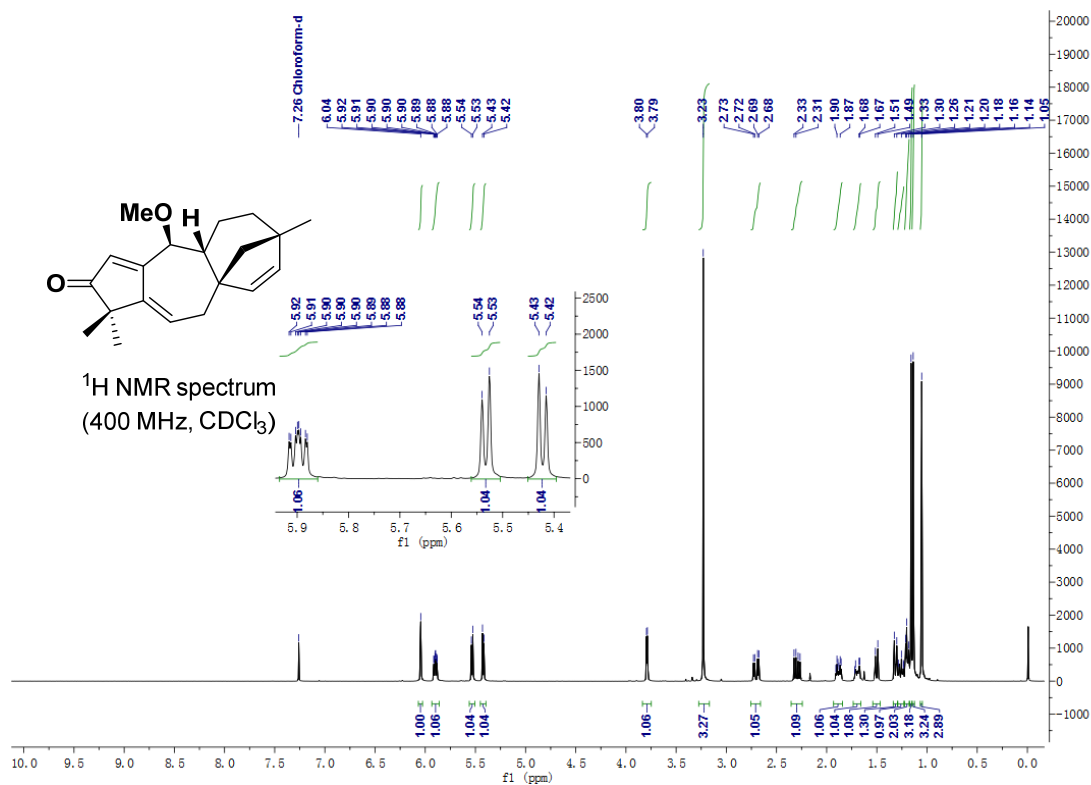
¹³C NMR of compound (+)-12



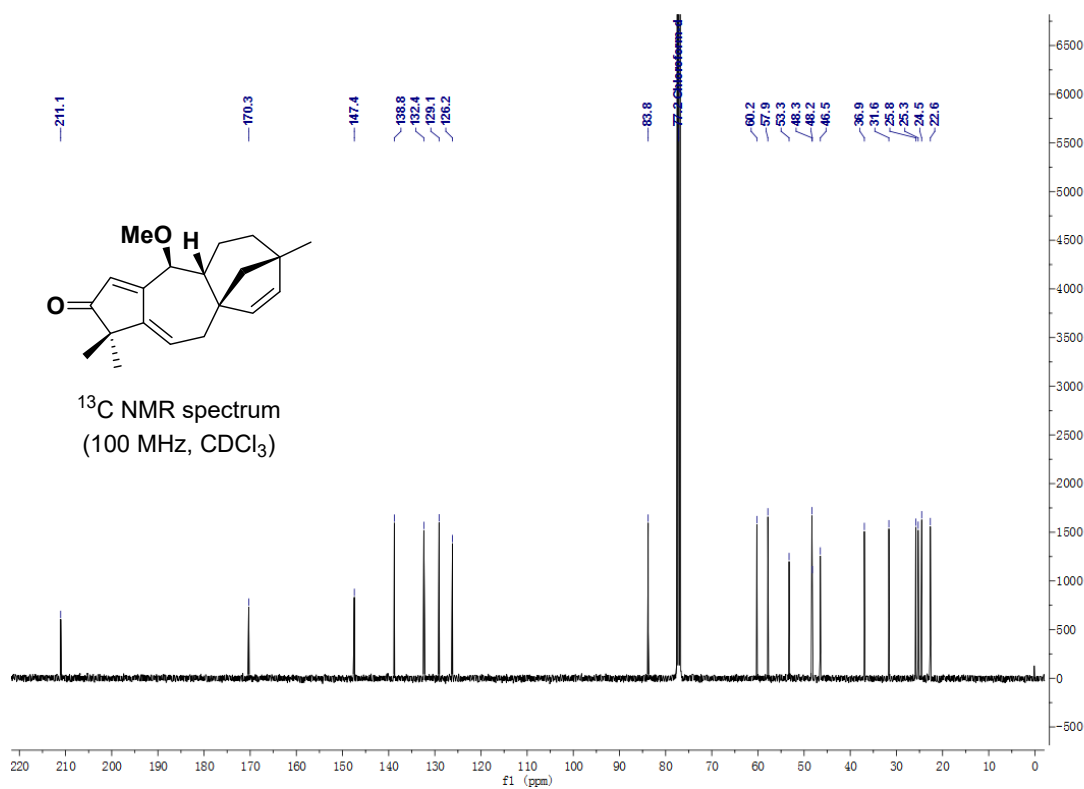
¹H NMR of compound (+)-4



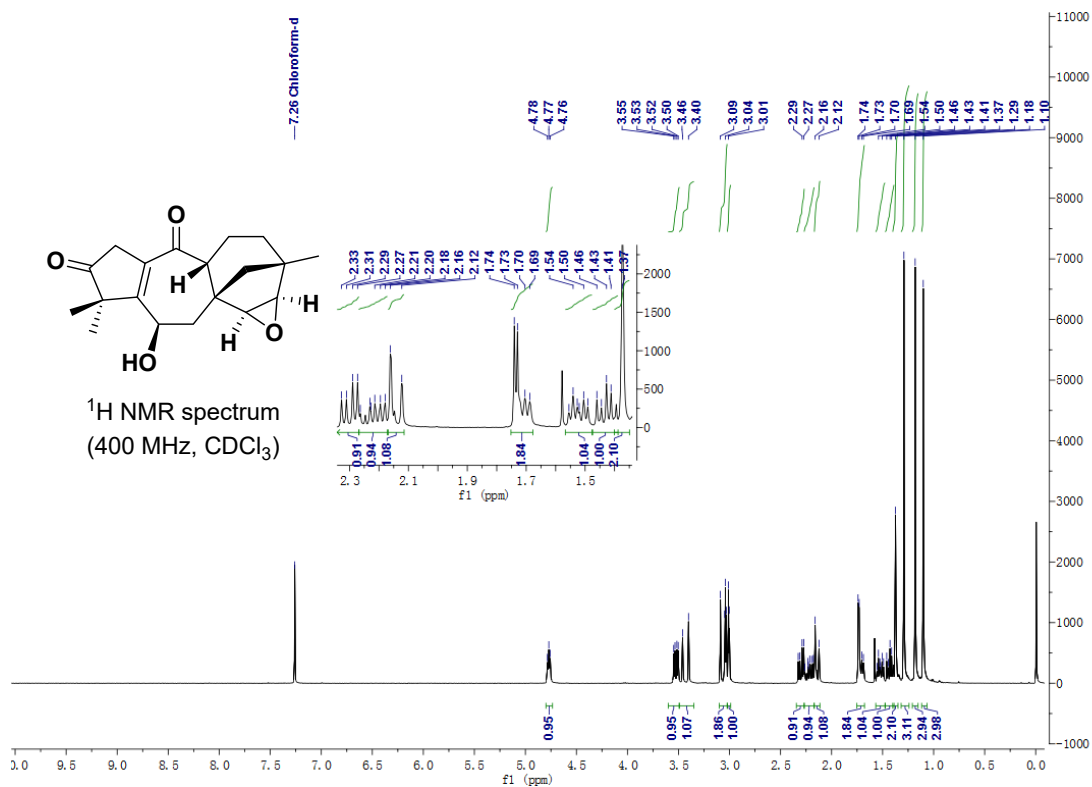
¹³C NMR of compound (+)-4



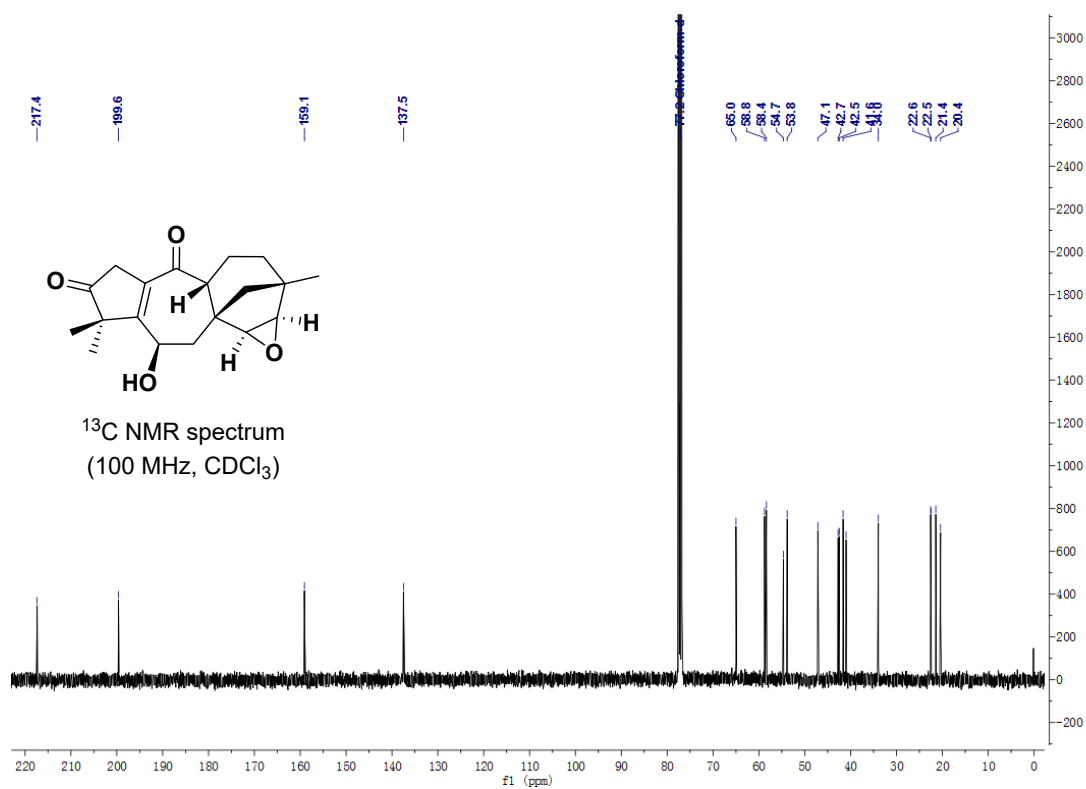
¹H NMR of compound (+)-14



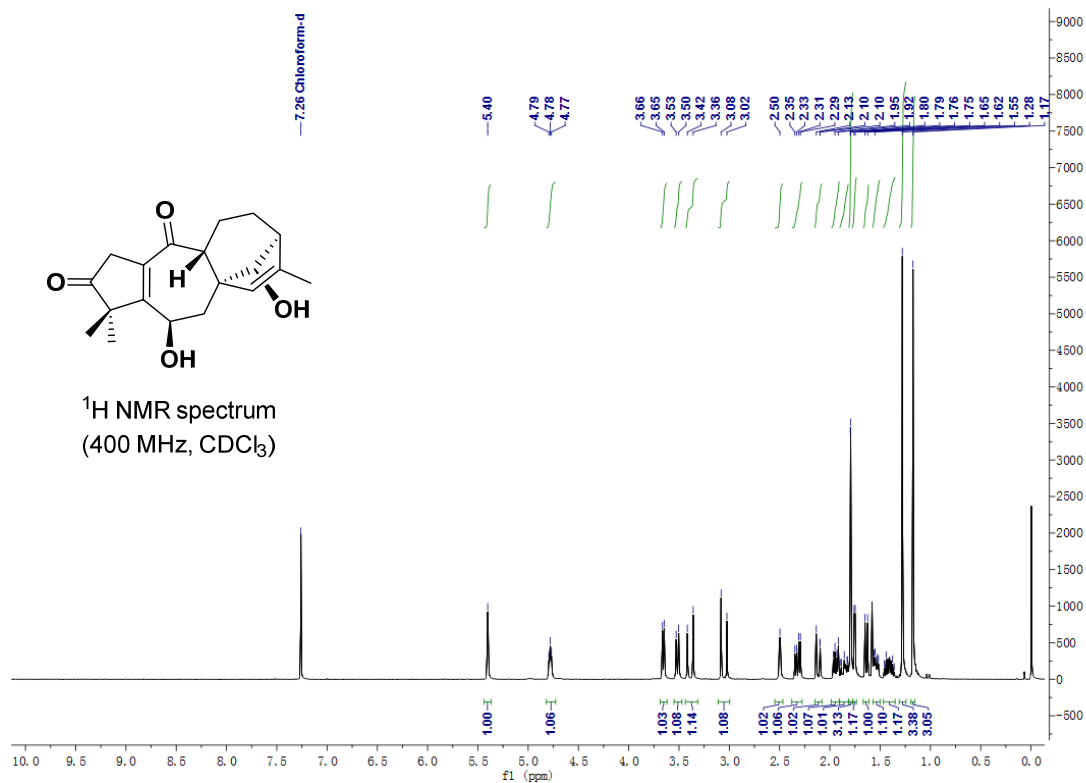
¹³C NMR of compound (+)-14



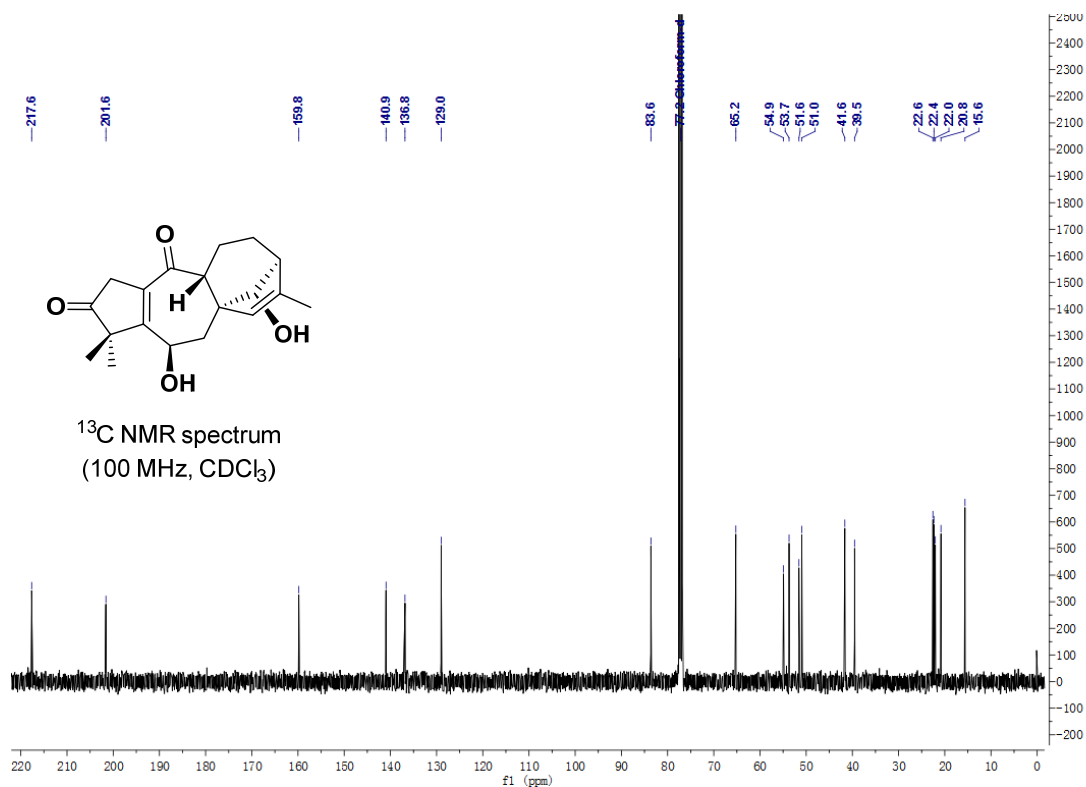
¹H NMR of compound (+)-16



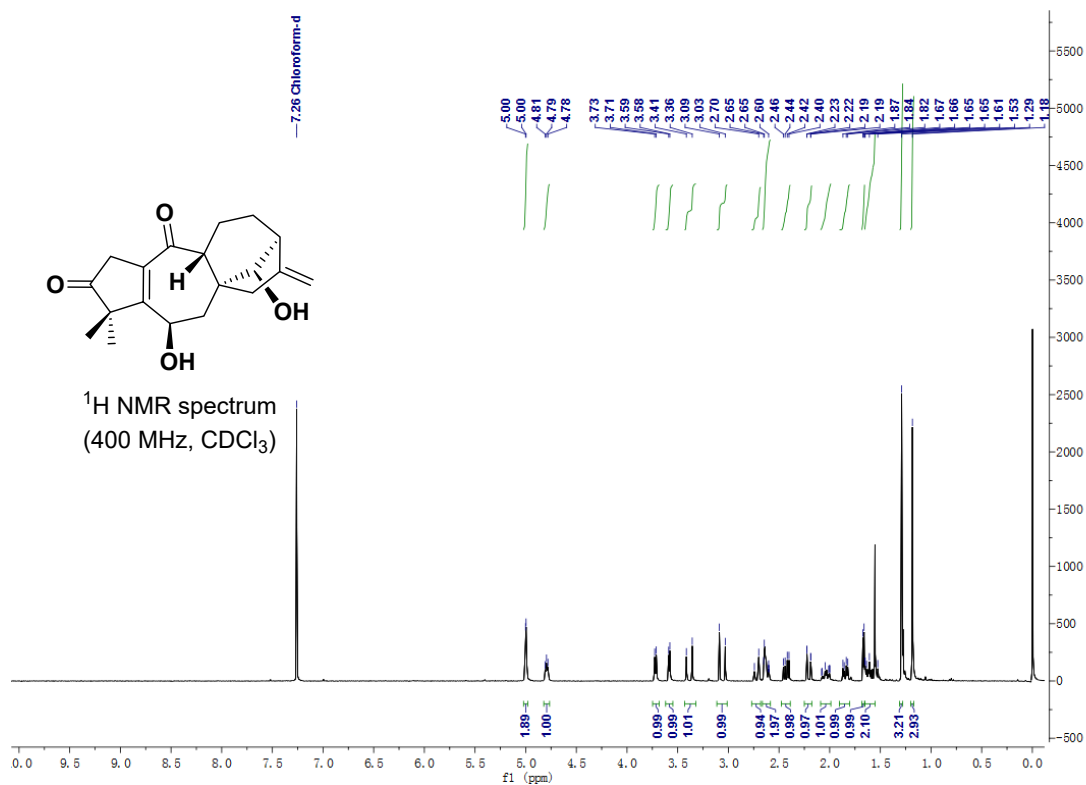
¹³C NMR of compound (+)-16



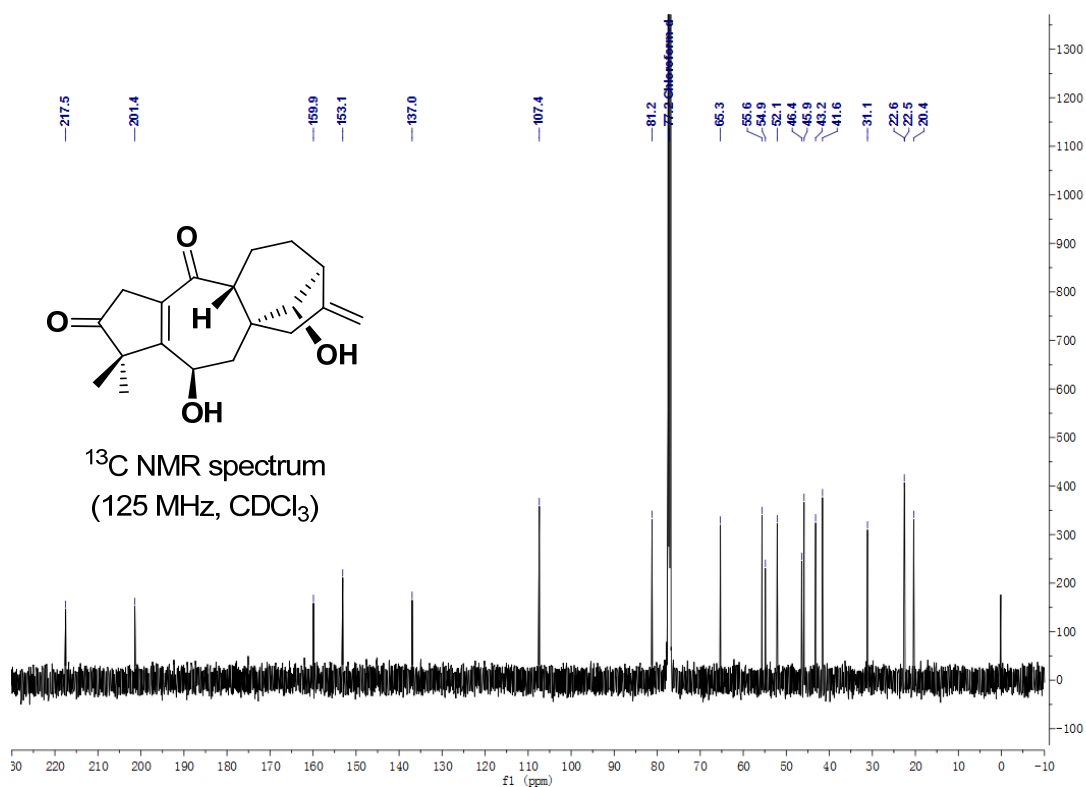
¹H NMR of compound (+)-17a



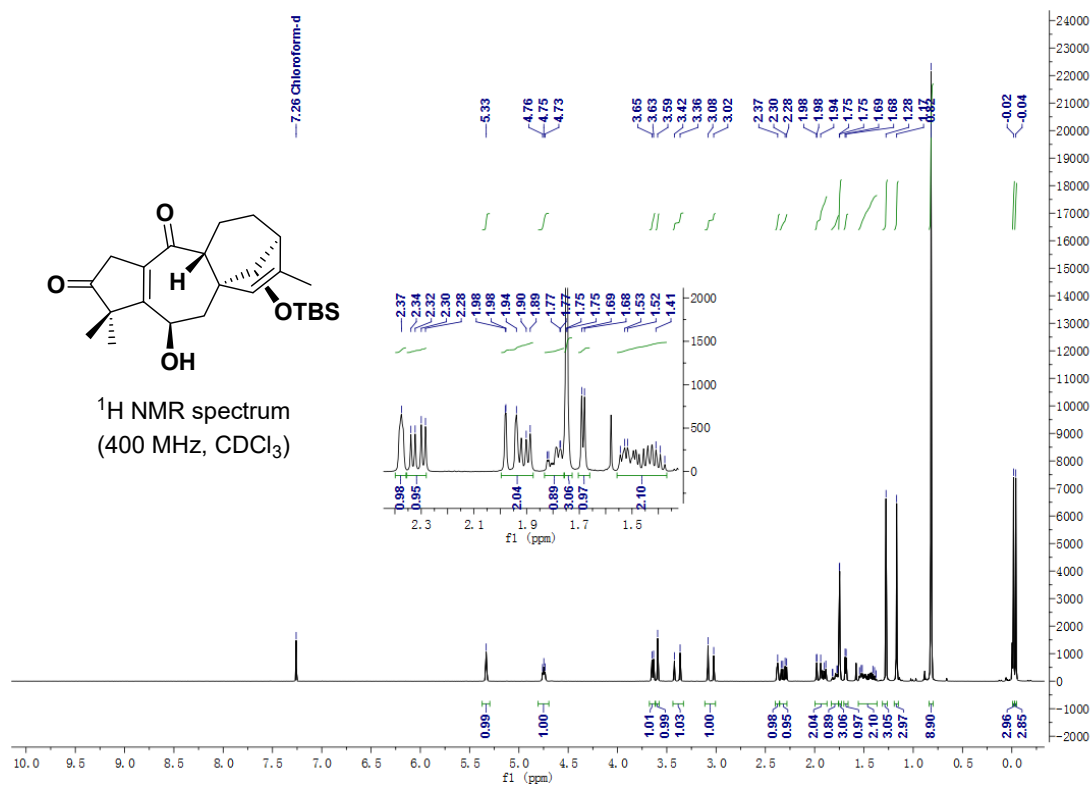
¹³C NMR of compound (+)-17a



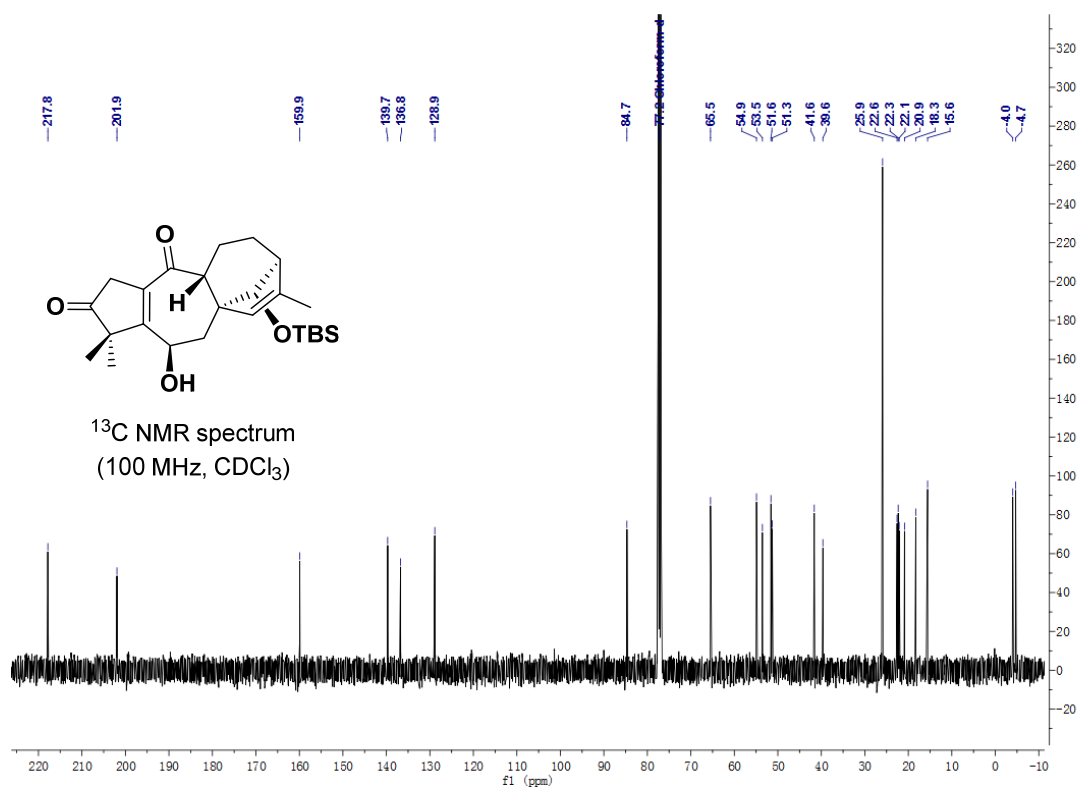
¹H NMR of compound (+)-17b



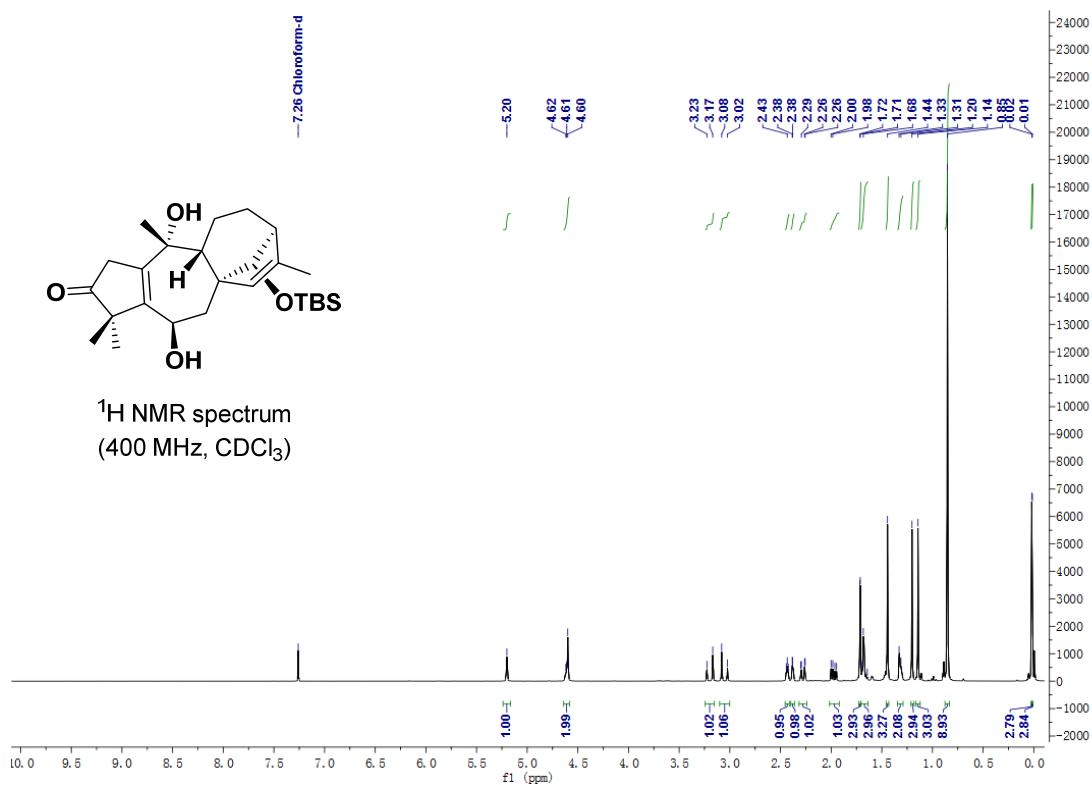
¹³C NMR of compound (+)-17b



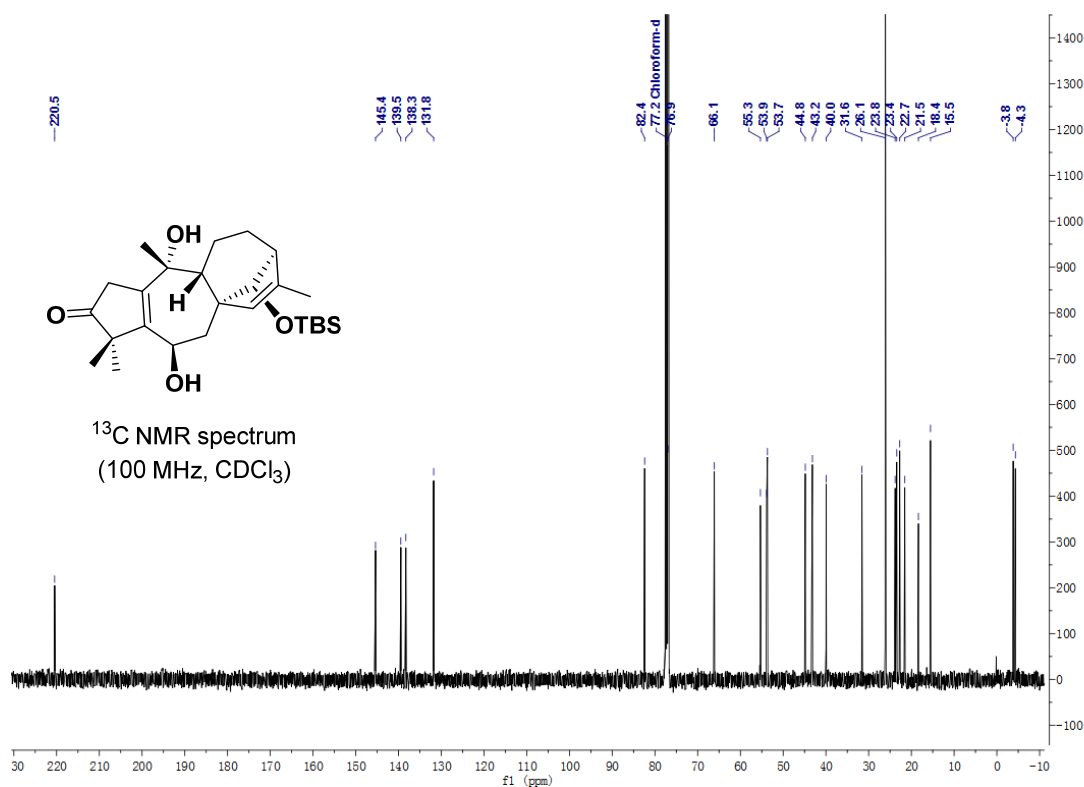
¹H NMR of compound (+)-18



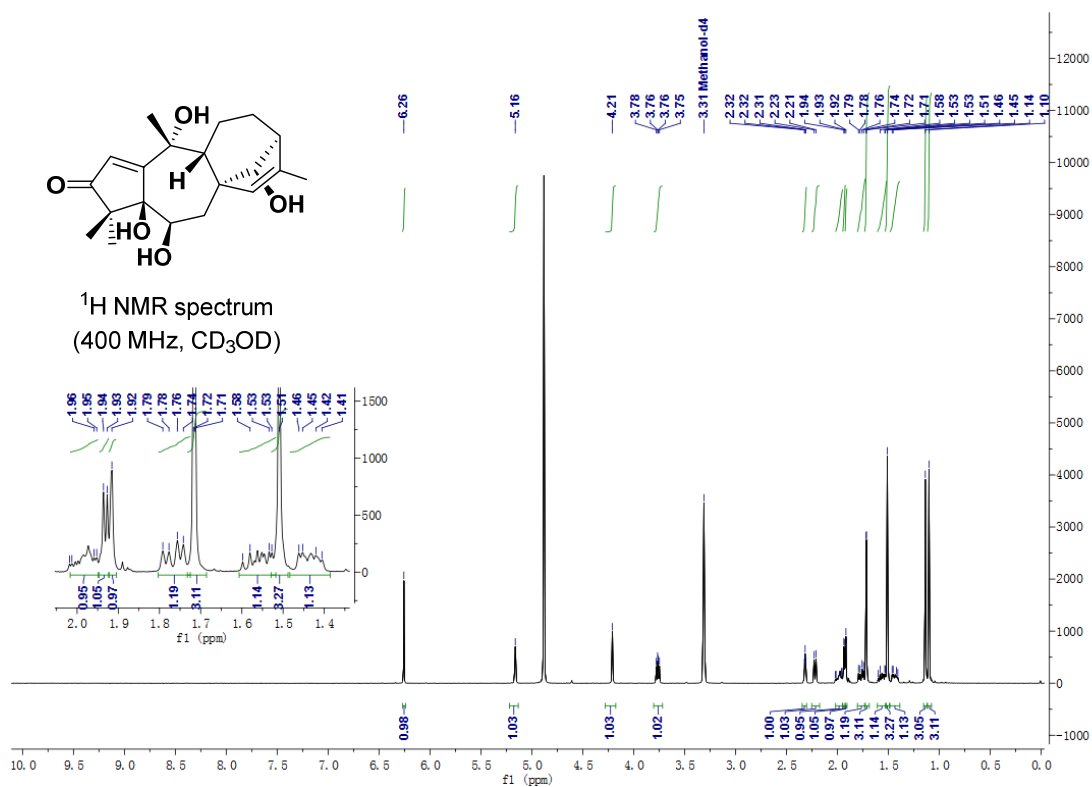
¹³C NMR of compound (+)-18



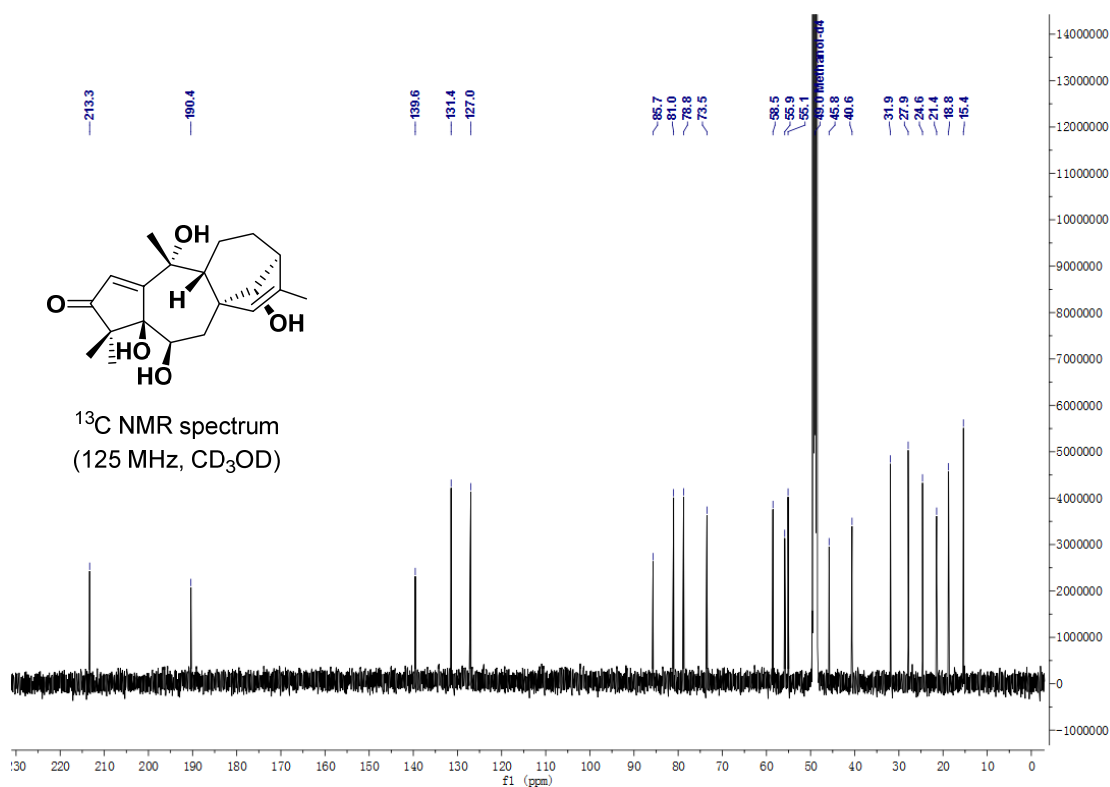
¹H NMR of compound (+)-19



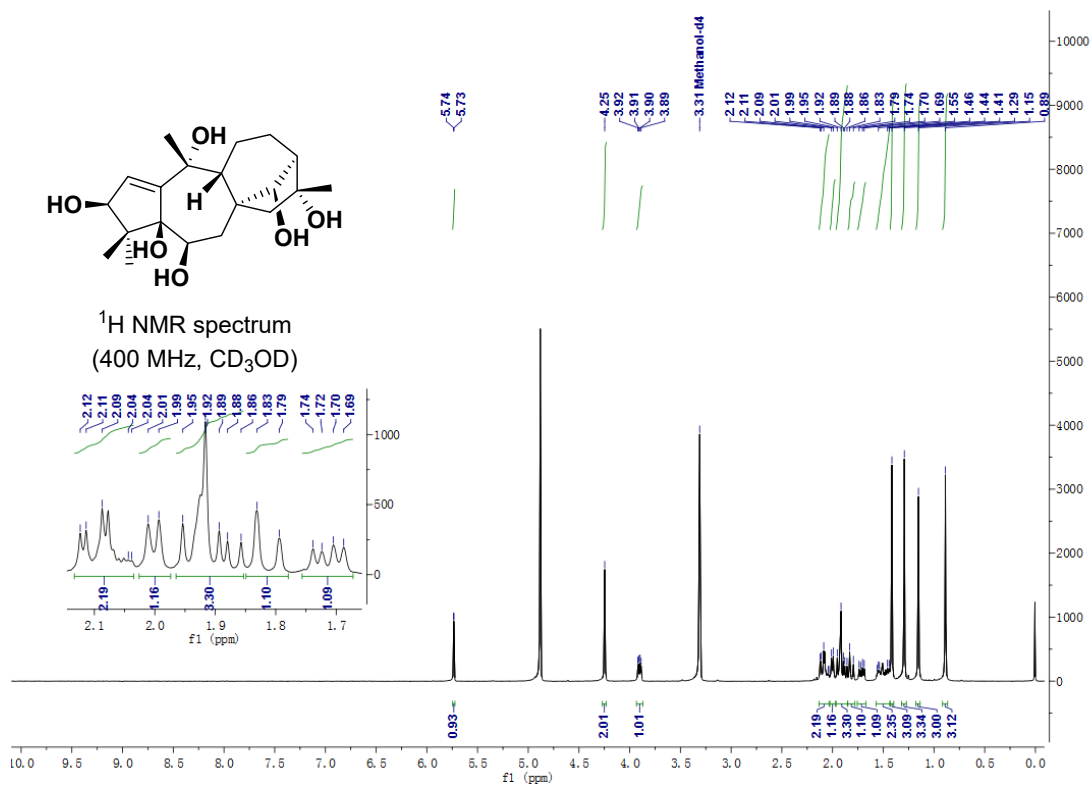
¹³C NMR of compound (+)-19



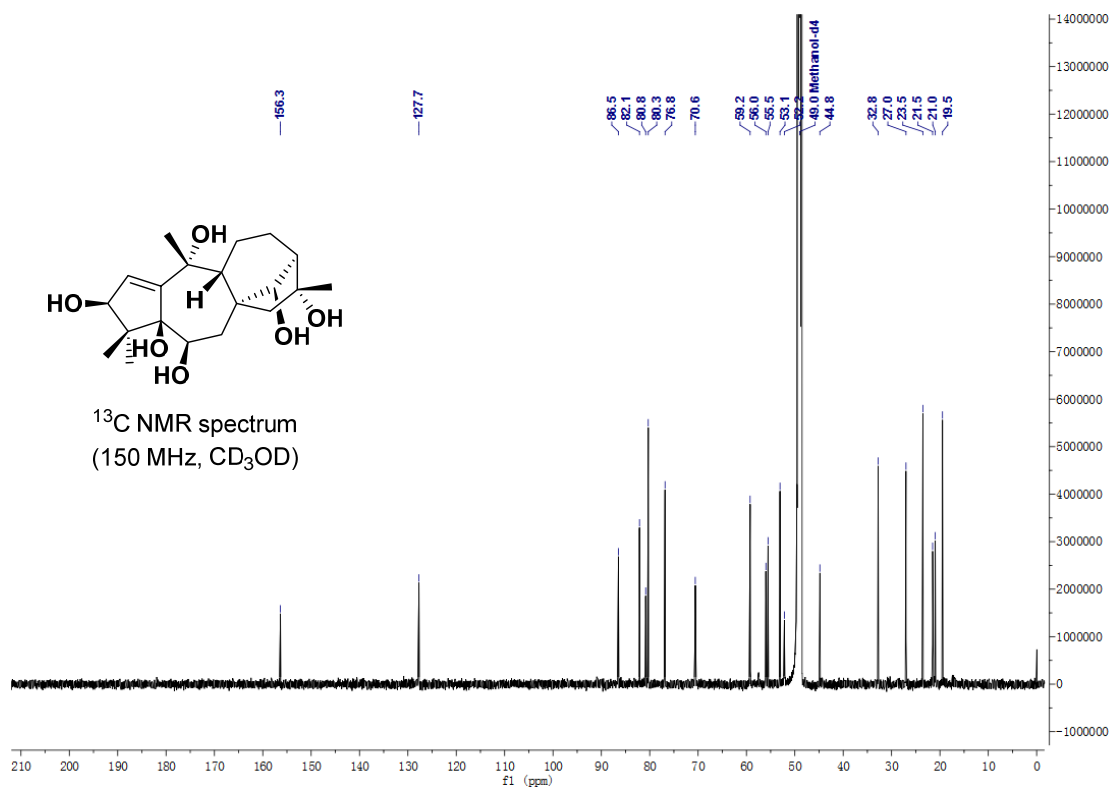
¹H NMR of compound (+)-20



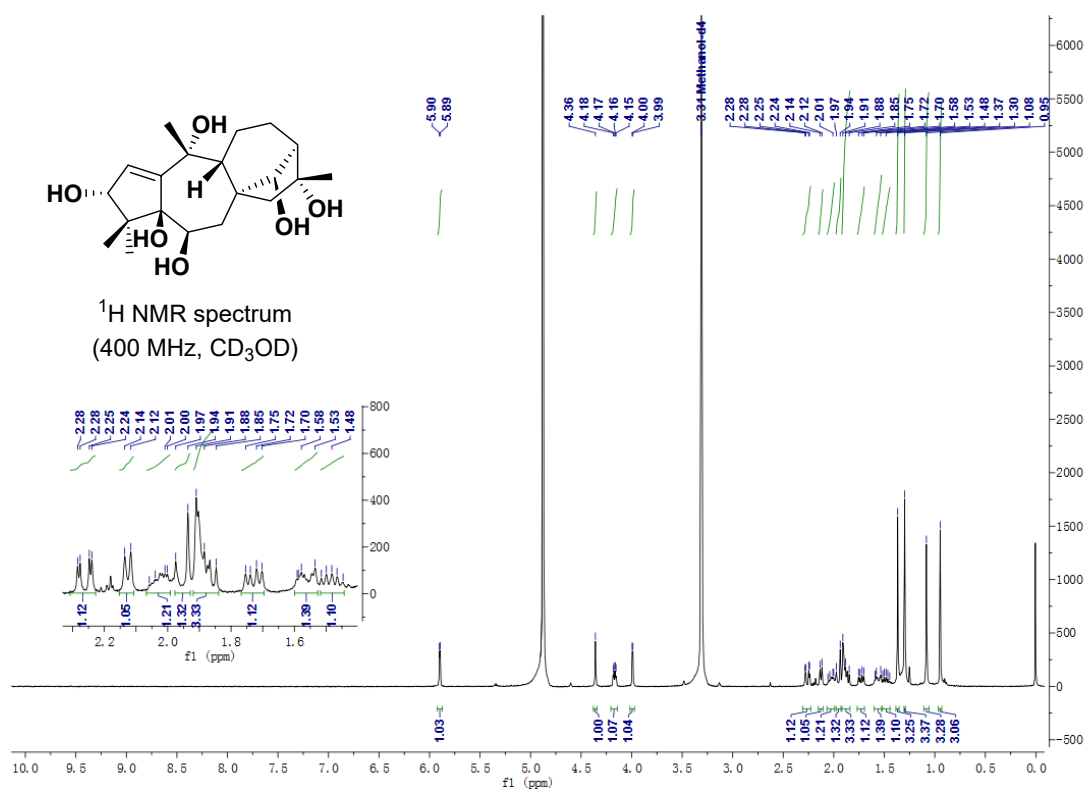
¹³C NMR of compound (+)-20



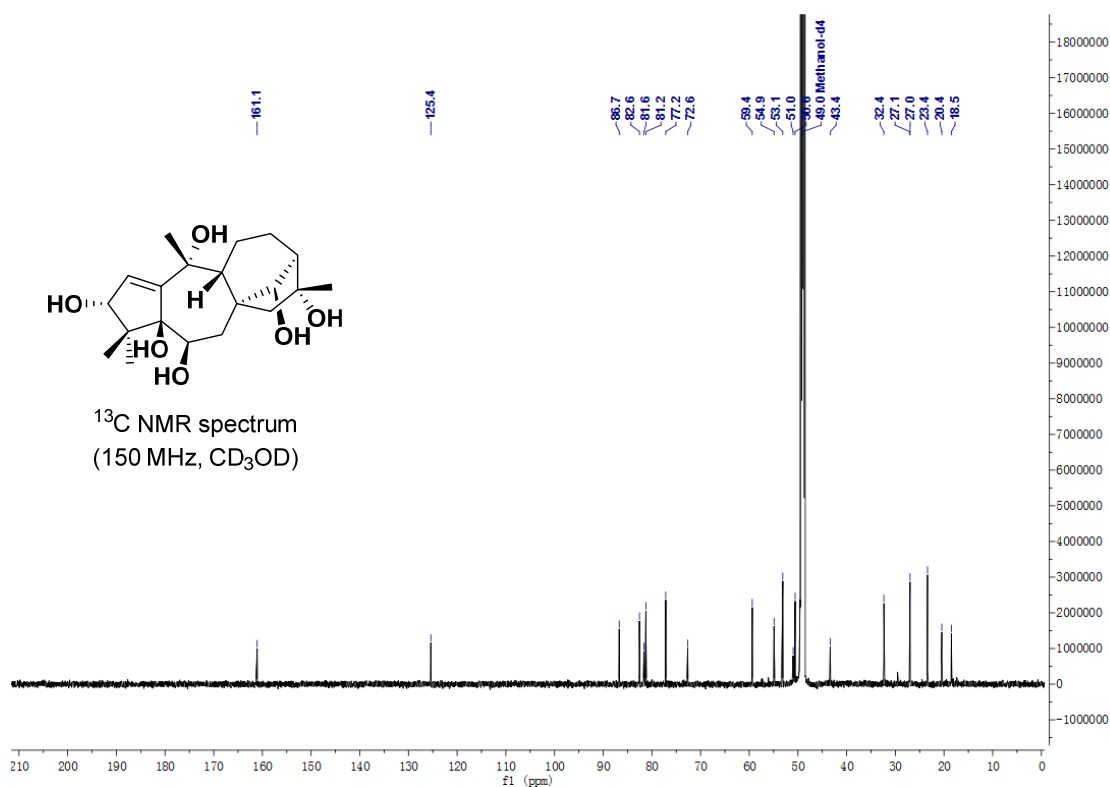
¹H NMR of compound (+)-22a



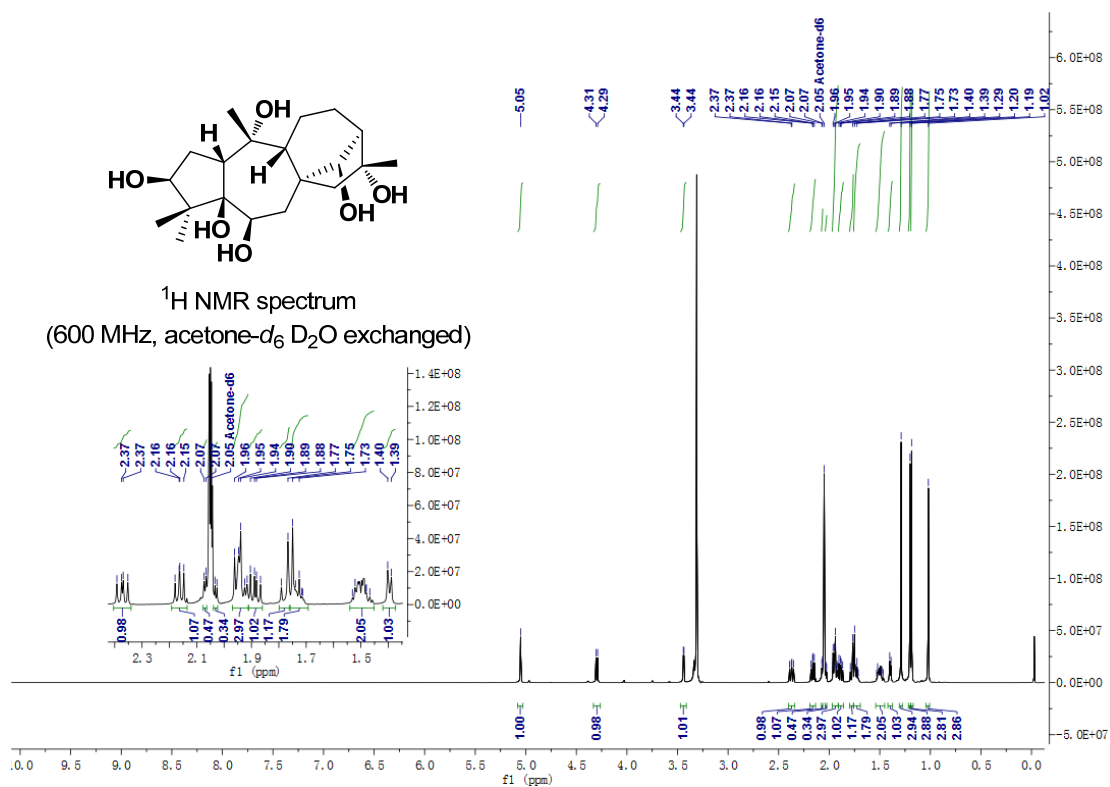
¹³C NMR of compound (+)-22a



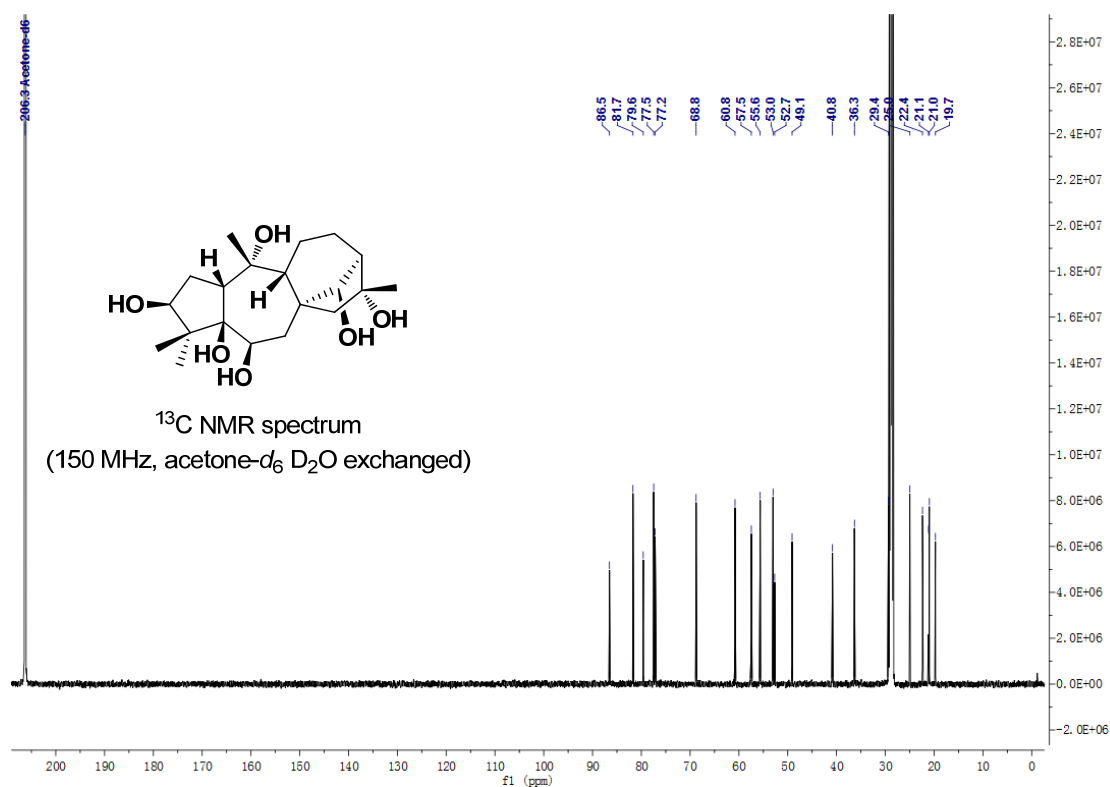
¹H NMR of compound (-)-22b



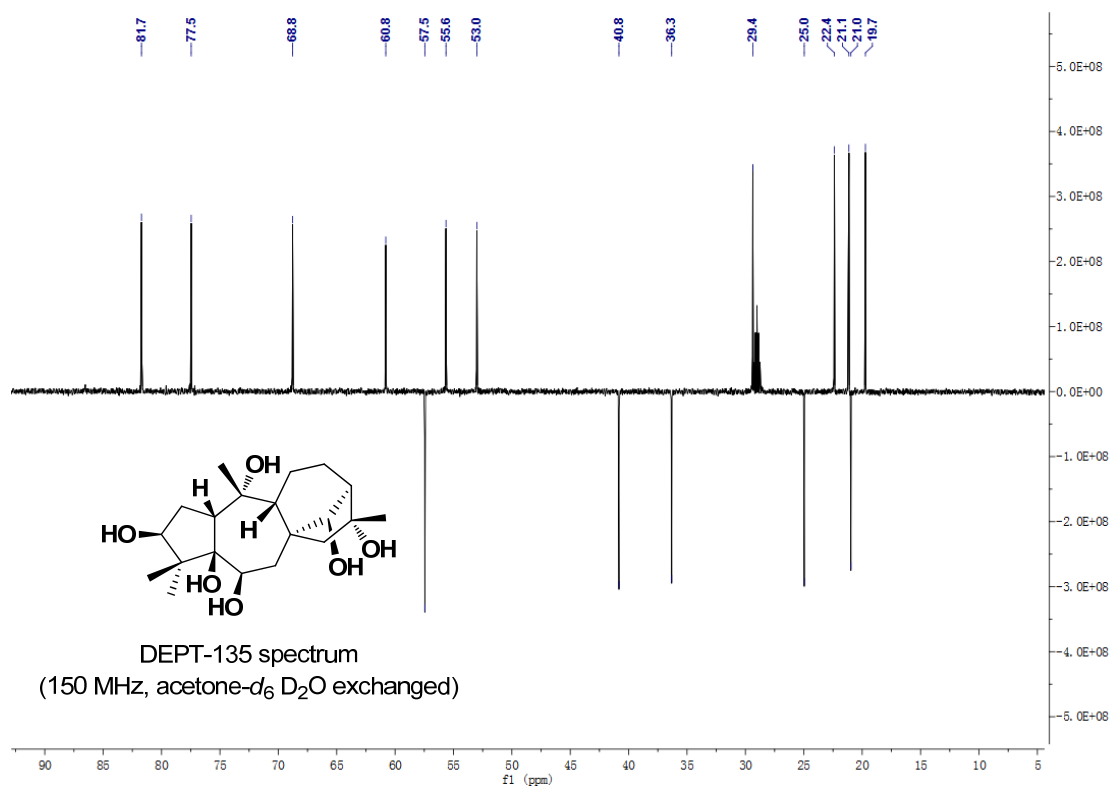
¹³C NMR of compound (-)-22b



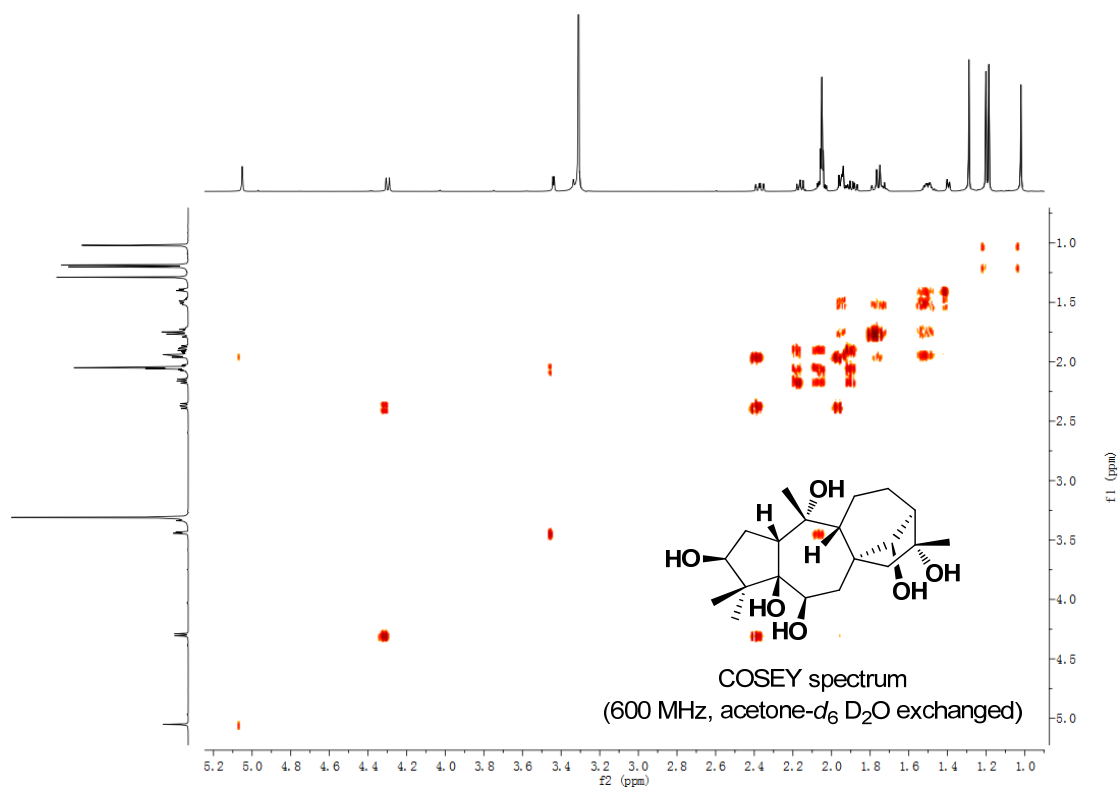
¹H NMR of compound (+)-23



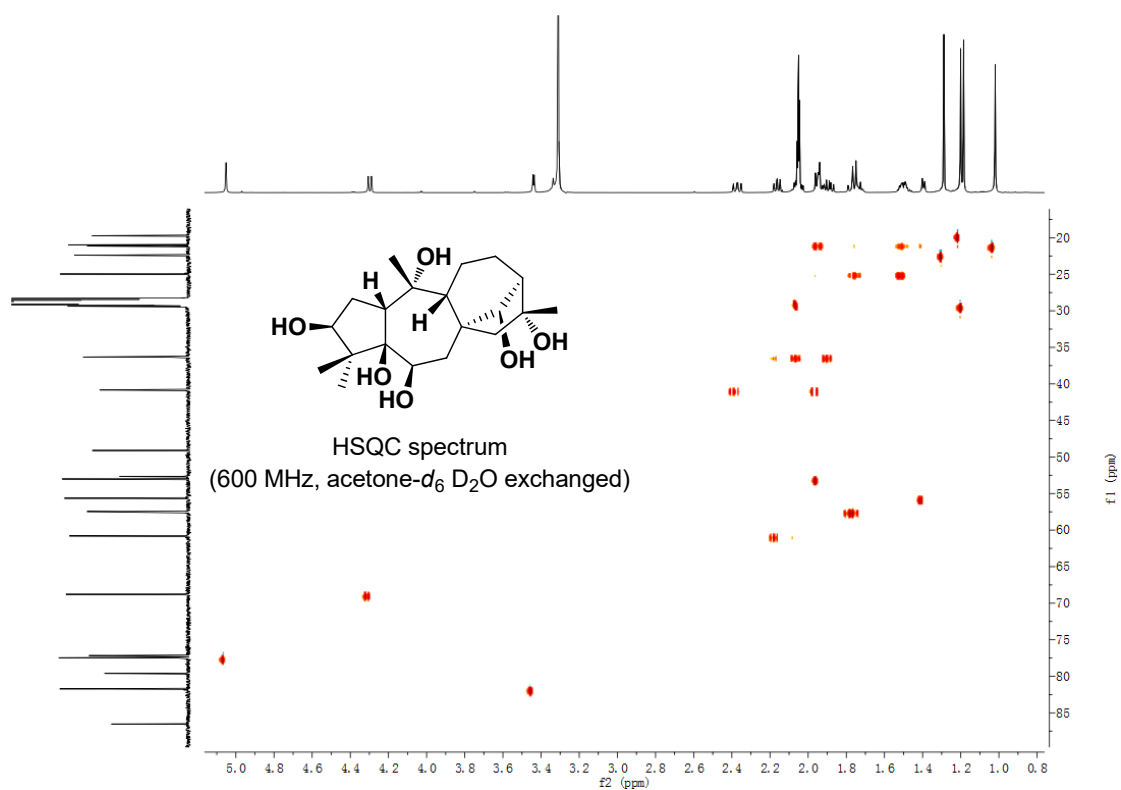
¹³C NMR of compound (+)-23



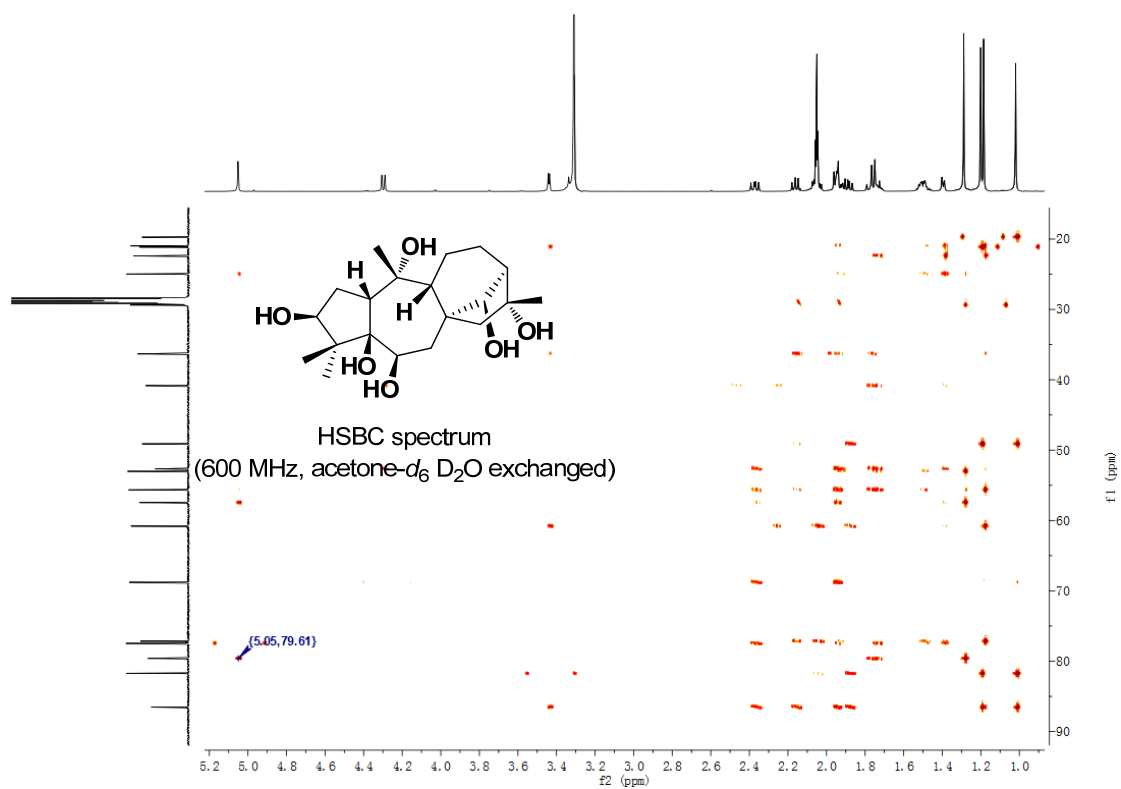
DEPT-135 of compound (+)-23



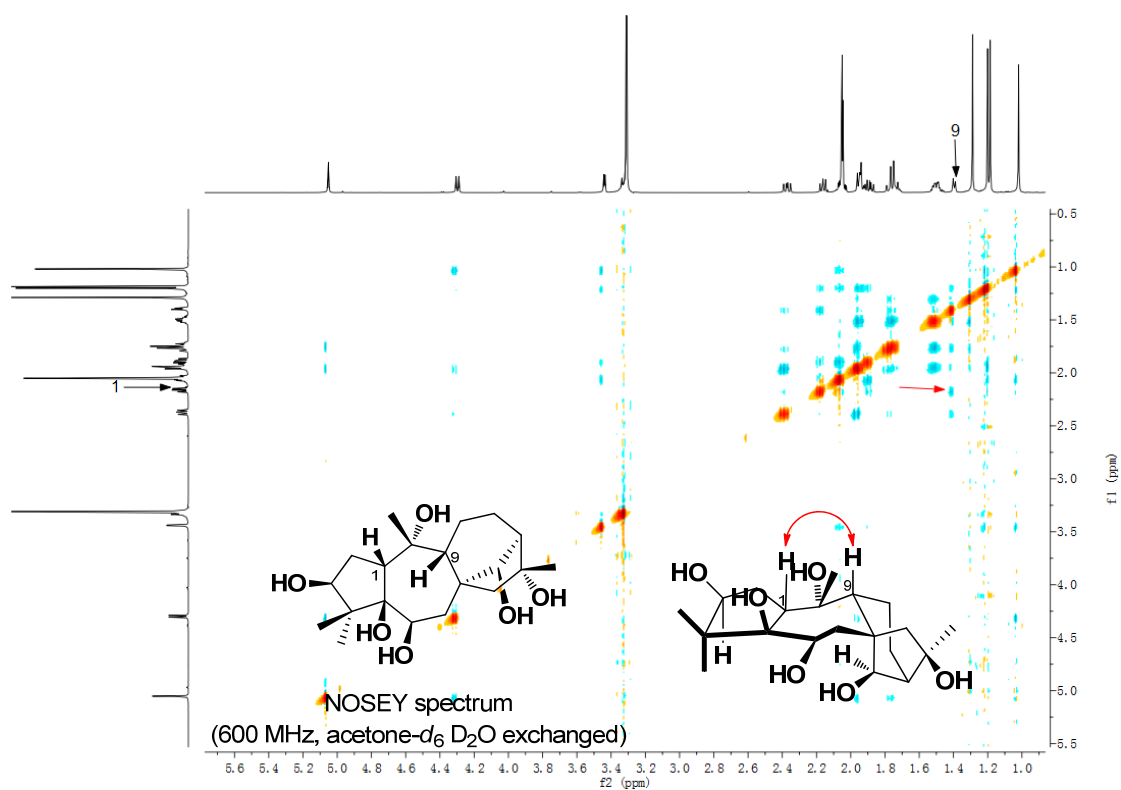
H-H COSEY NMR of compound (+)-23



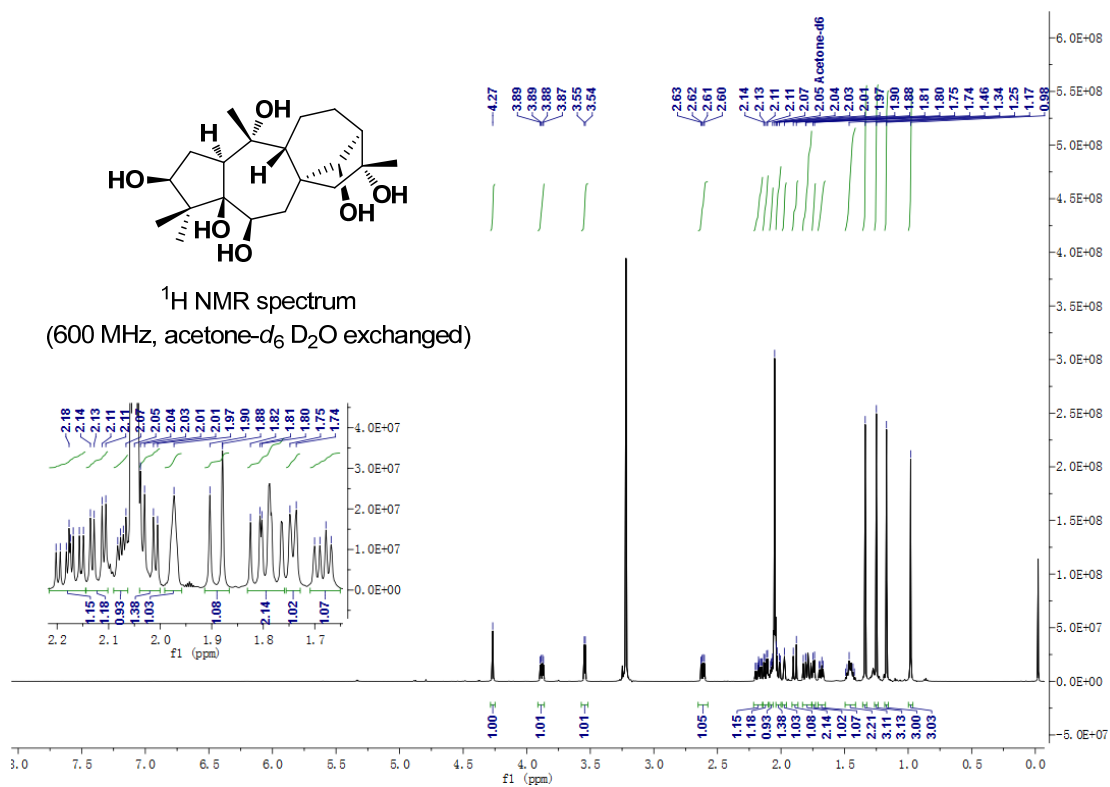
C-H HSQC NMR of compound (+)-23



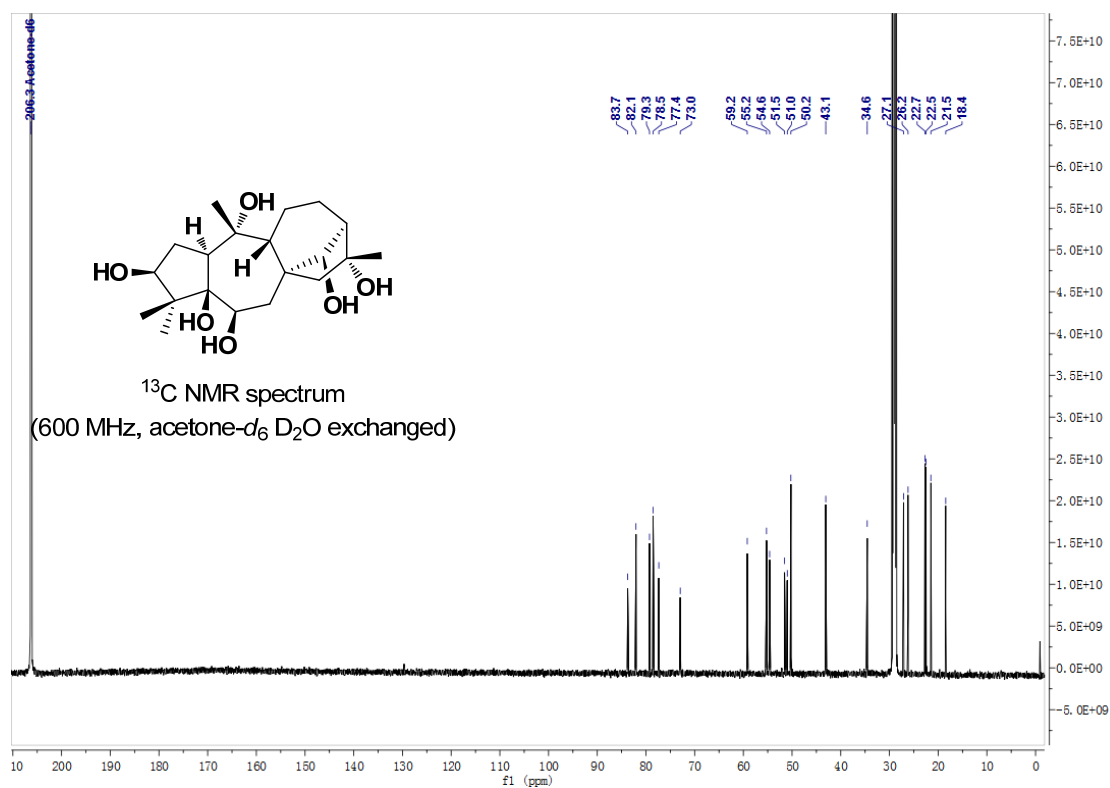
C-H HSBC NMR of compound (+)-23



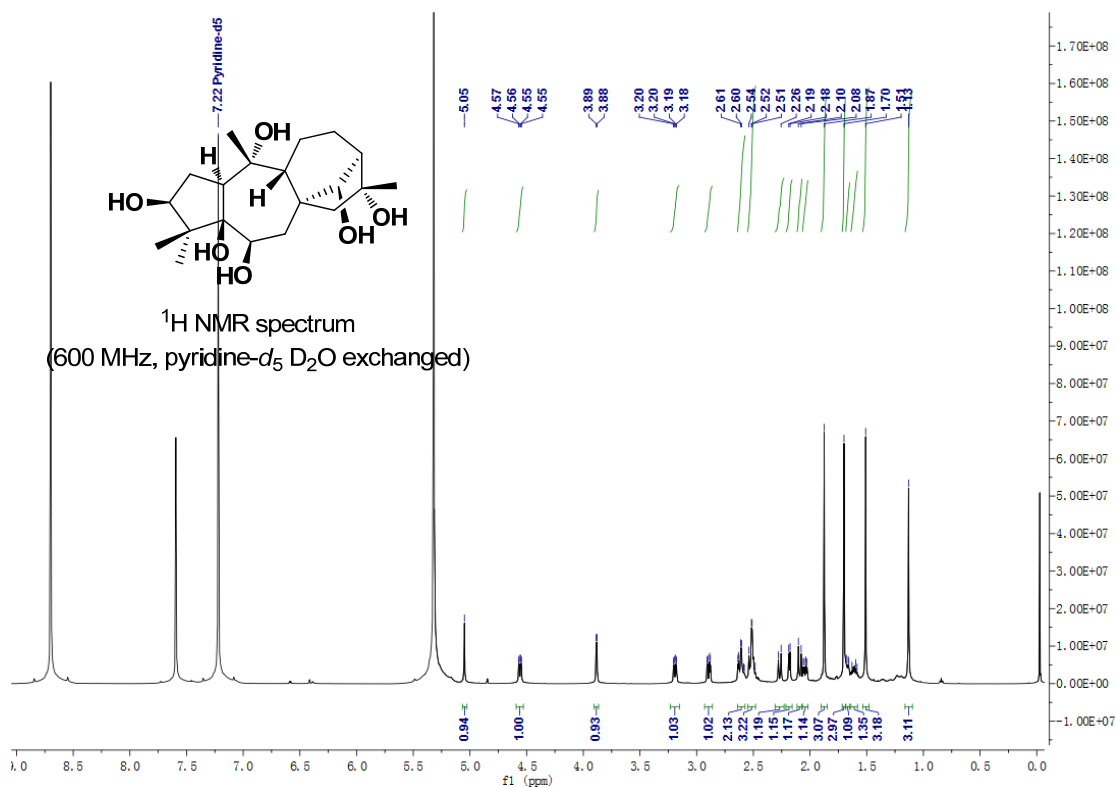
H-H NOSEY NMR of compound (+)-23



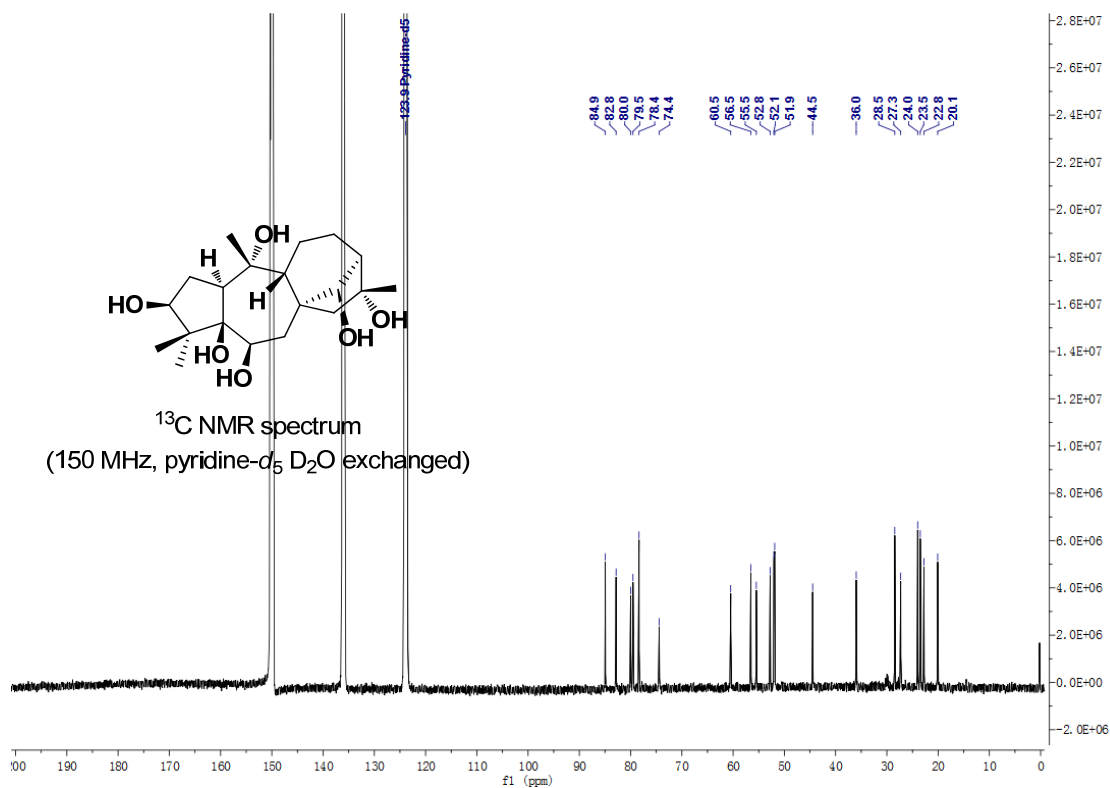
¹H NMR of synthesized (-)-grayanotoxin III (1)



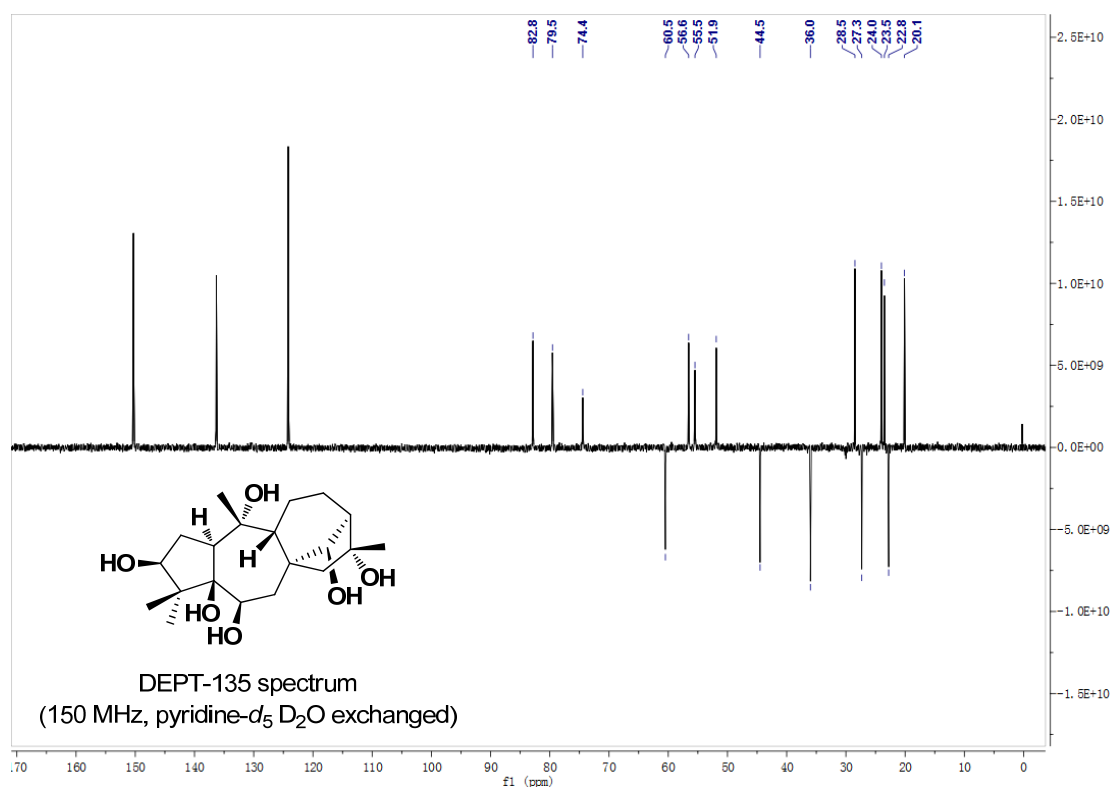
¹³C NMR of synthesized (-)-grayanotoxin III (1)



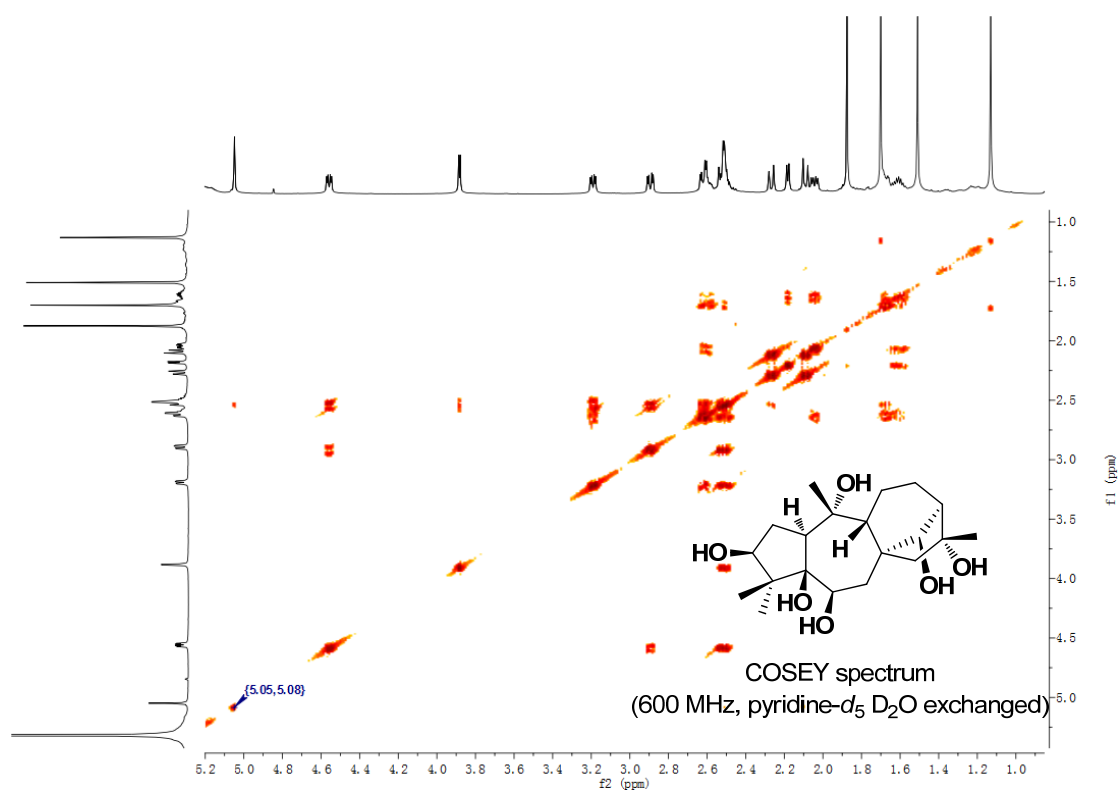
¹H NMR of synthesized (-)-grayanotoxin III (1)



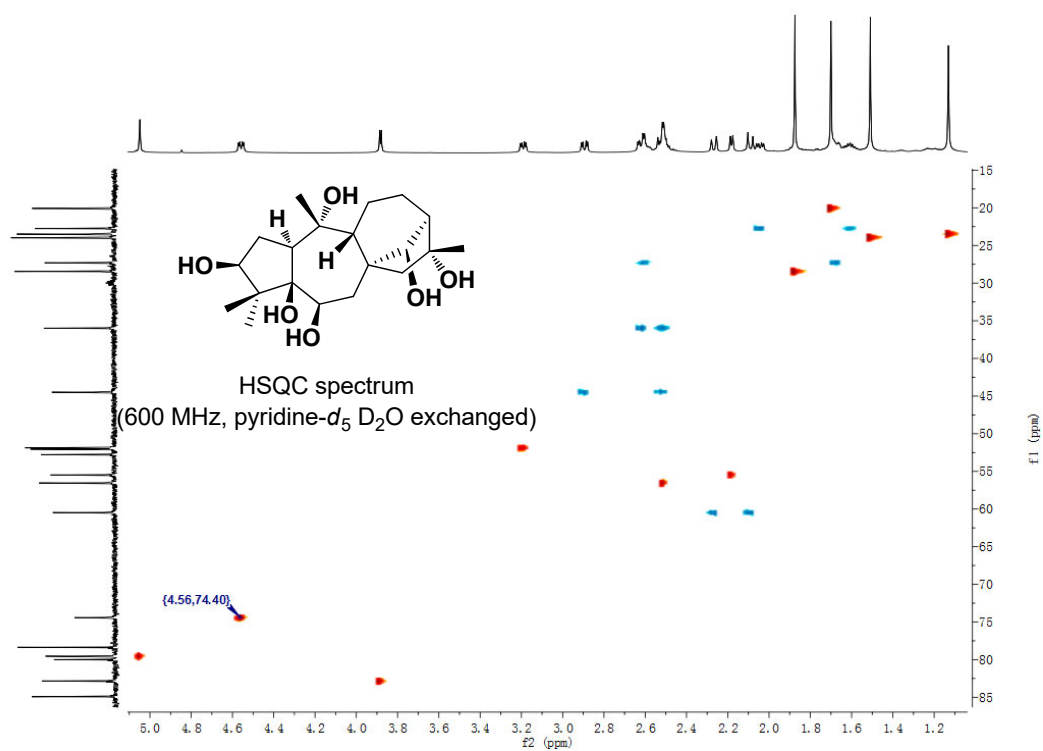
¹³C NMR of synthesized (-)-grayanotoxin III (1)



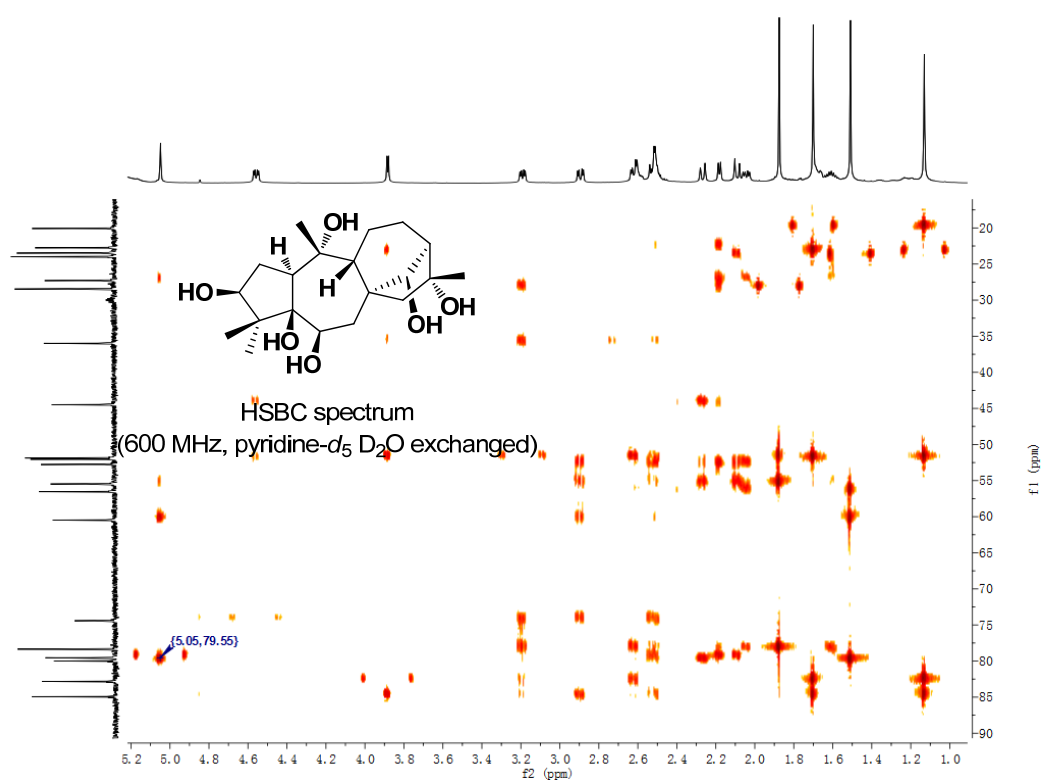
DEPT-135 of synthesized (-)-grayanotoxin III (**1**)



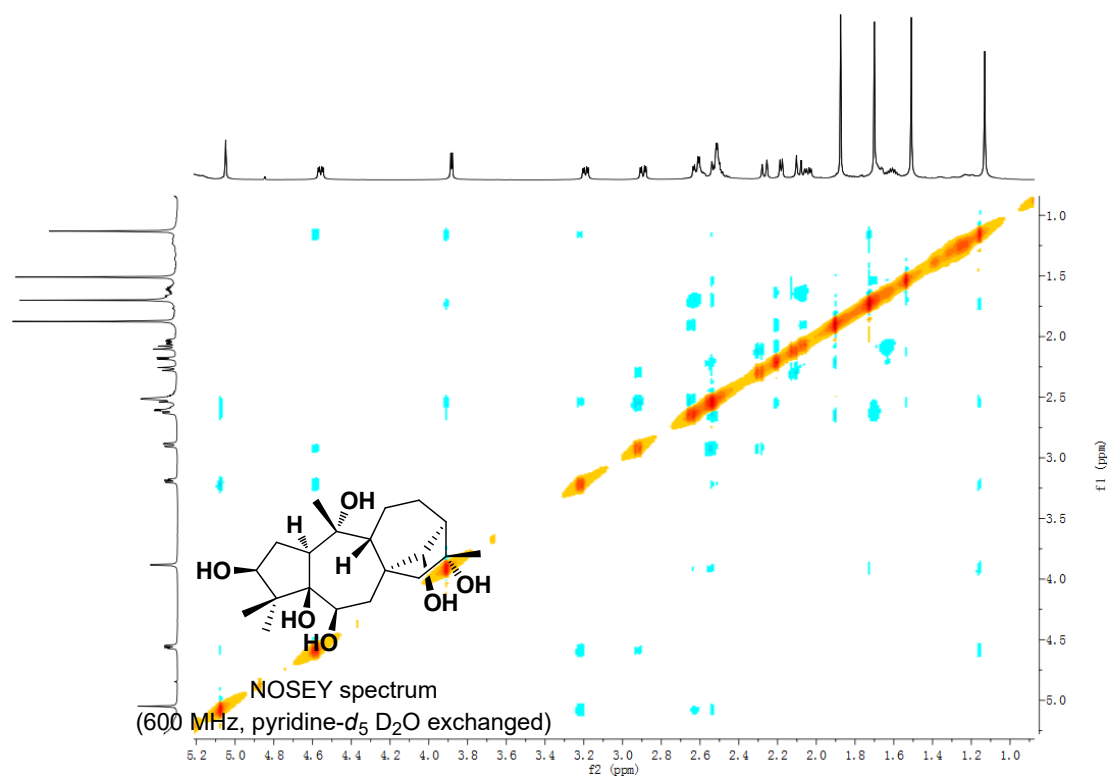
H-H COSEY NMR of synthesized (-)-grayanotoxin III (**1**)



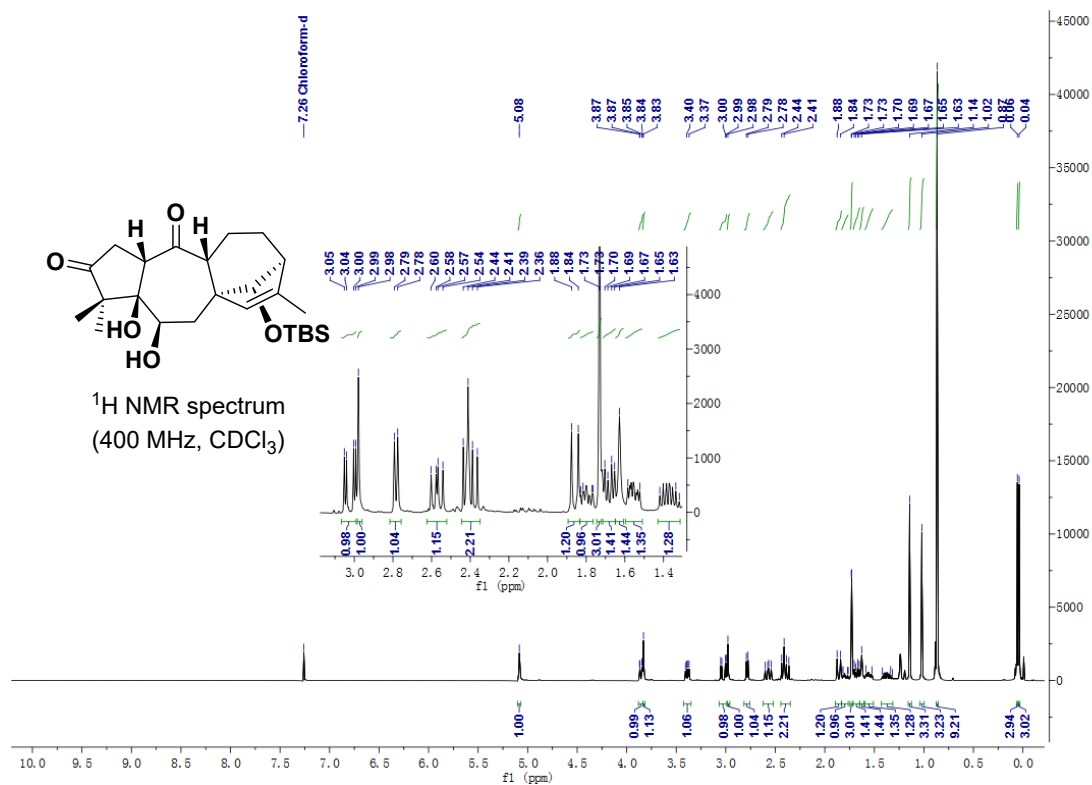
C-H HSQC NMR of synthesized (–)-grayanotoxin III (**1**)



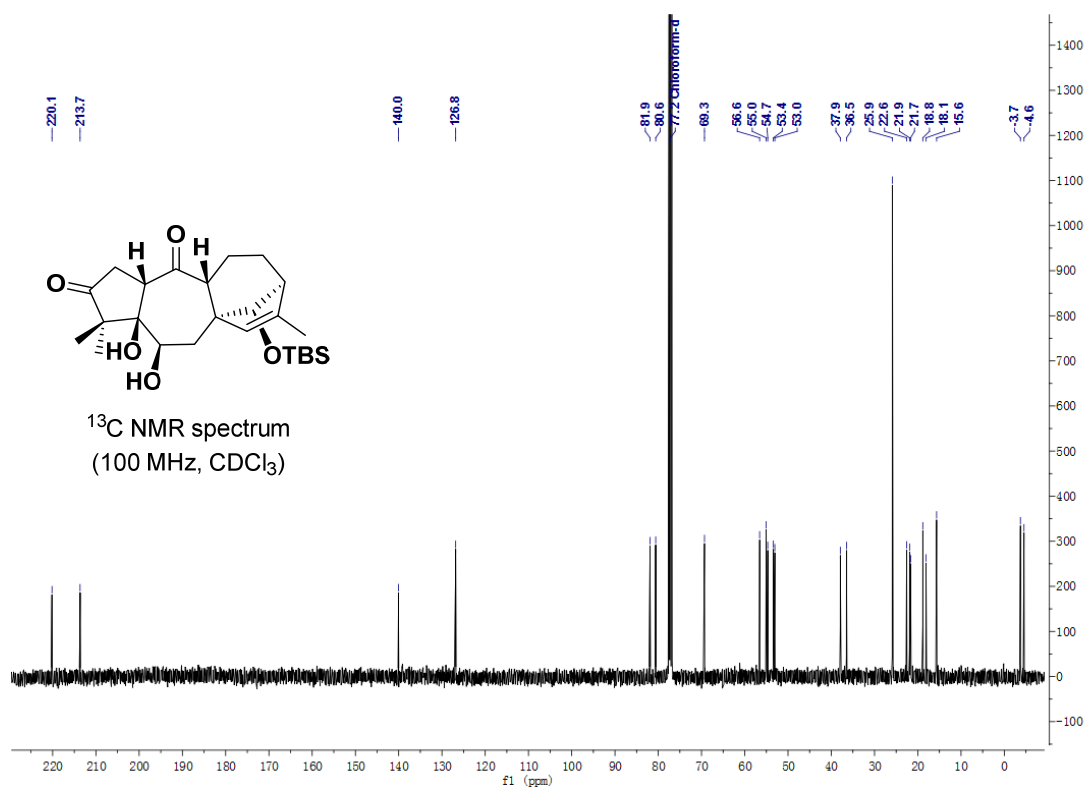
C-H HSBC NMR of synthesized (–)-grayanotoxin III (**1**)

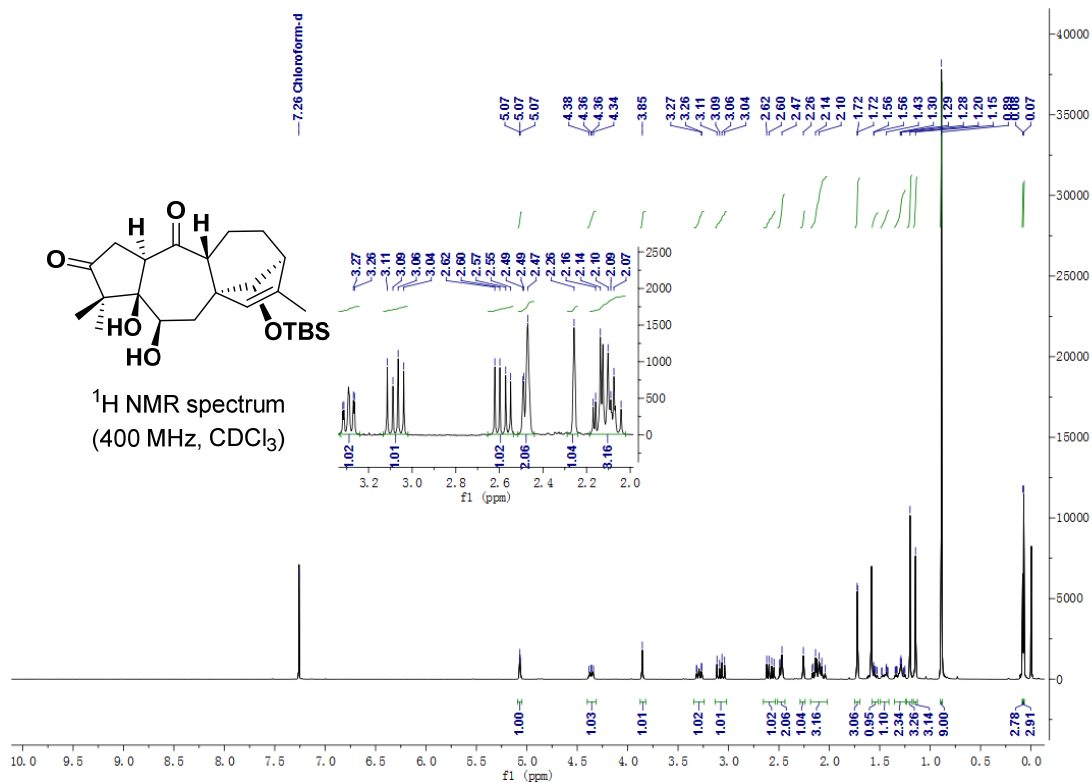


H-H NOSEY NMR of synthesized (–)-grayanotoxin III (**1**)

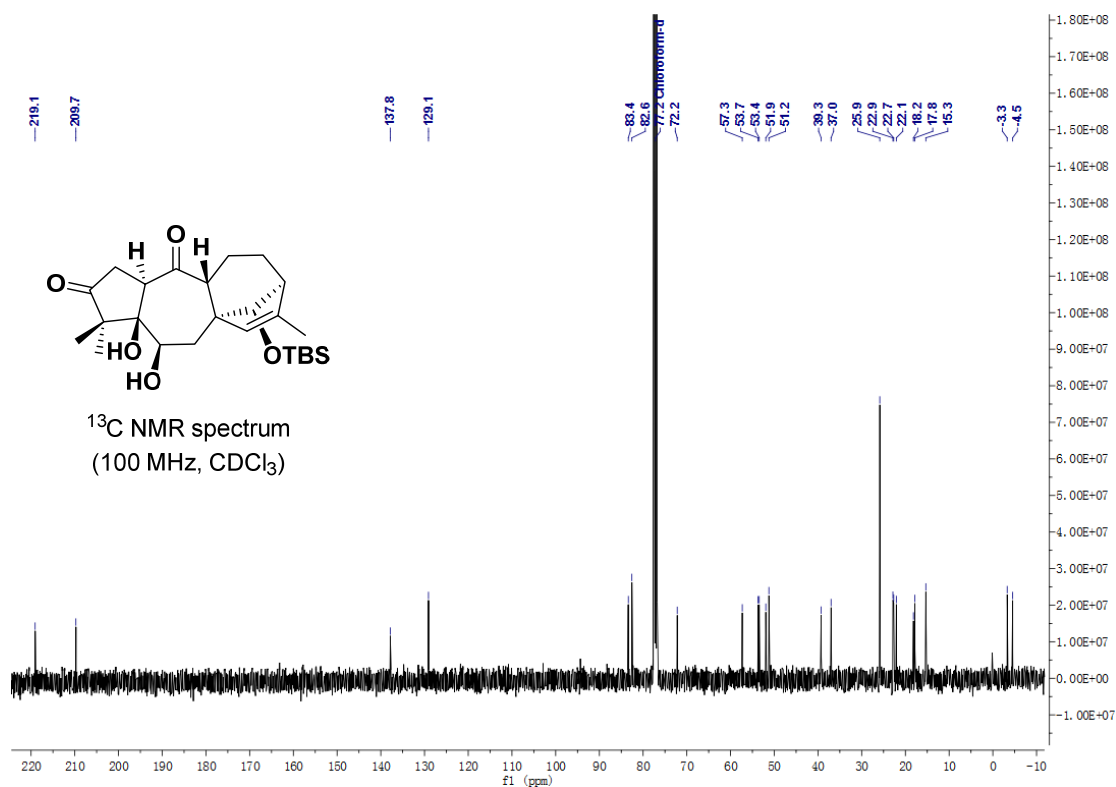


¹H NMR of compound (–)-**23a**

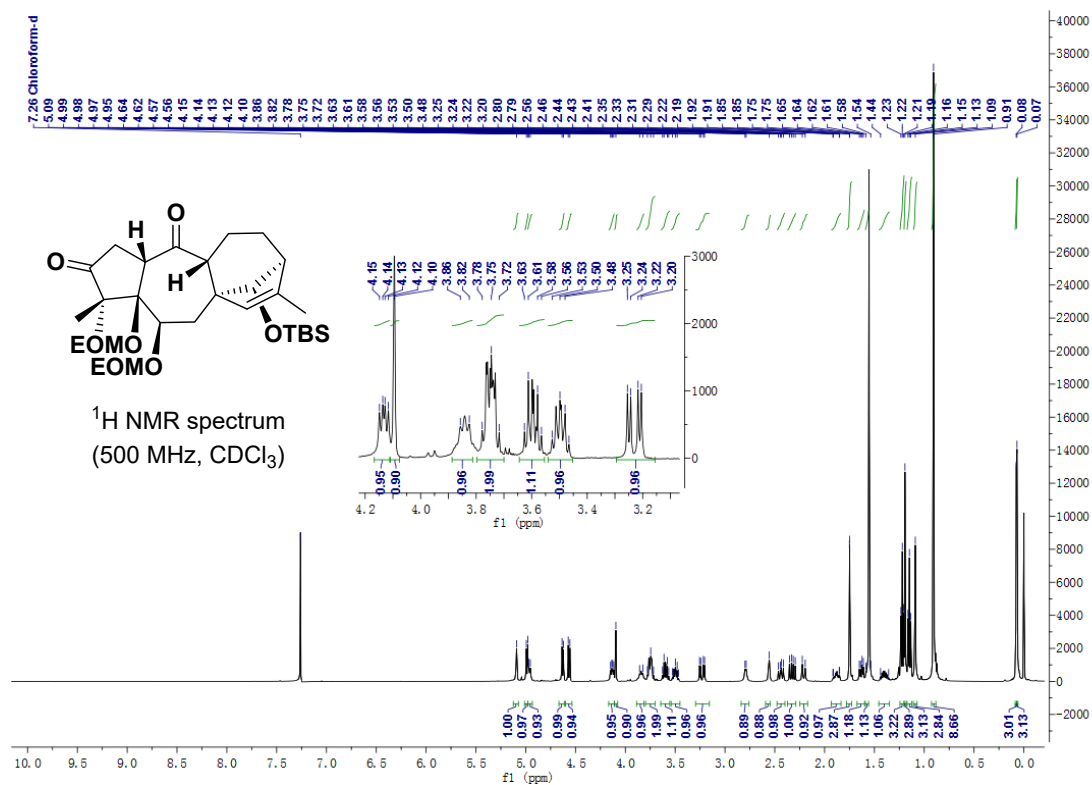
 ^{13}C NMR of compound (-)-**23a**



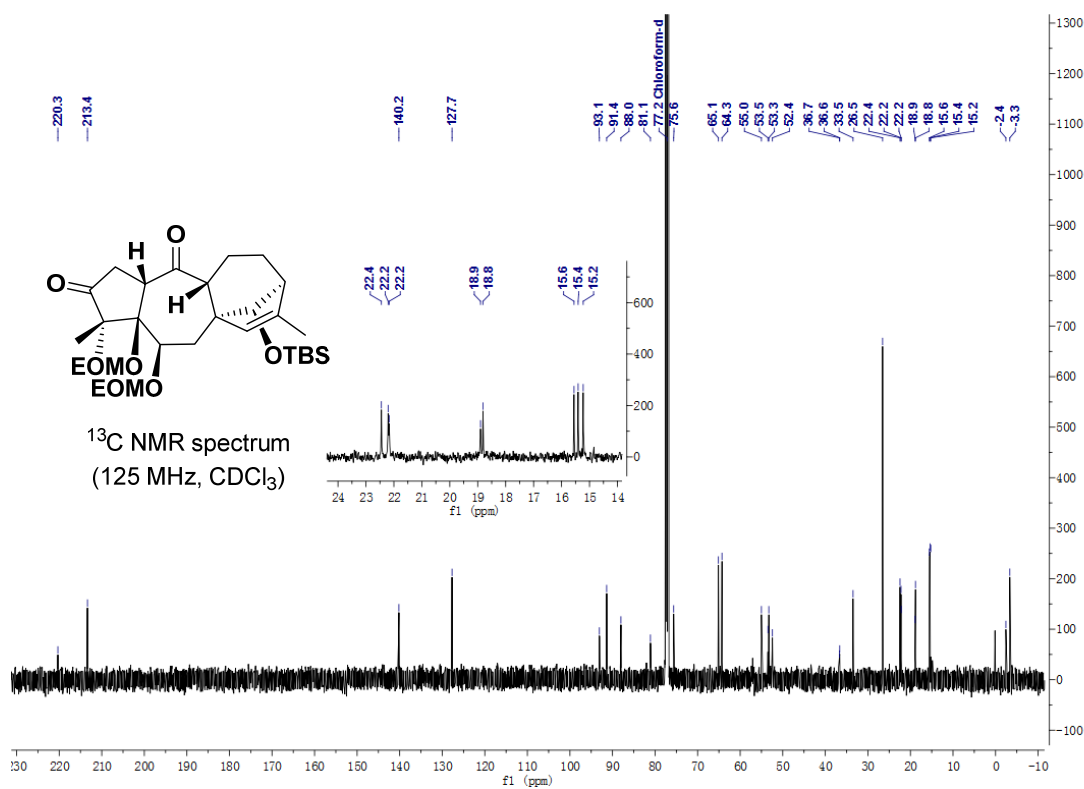
¹H NMR of compound (-)-23b



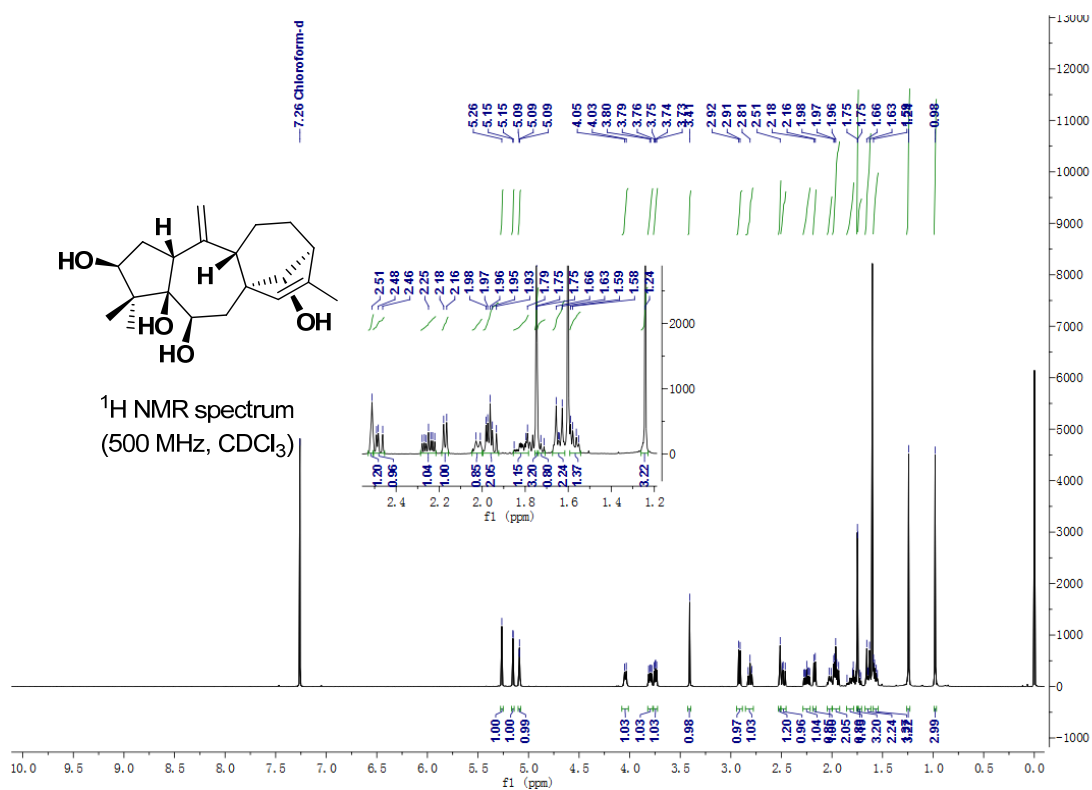
¹³C NMR of compound (-)-23b



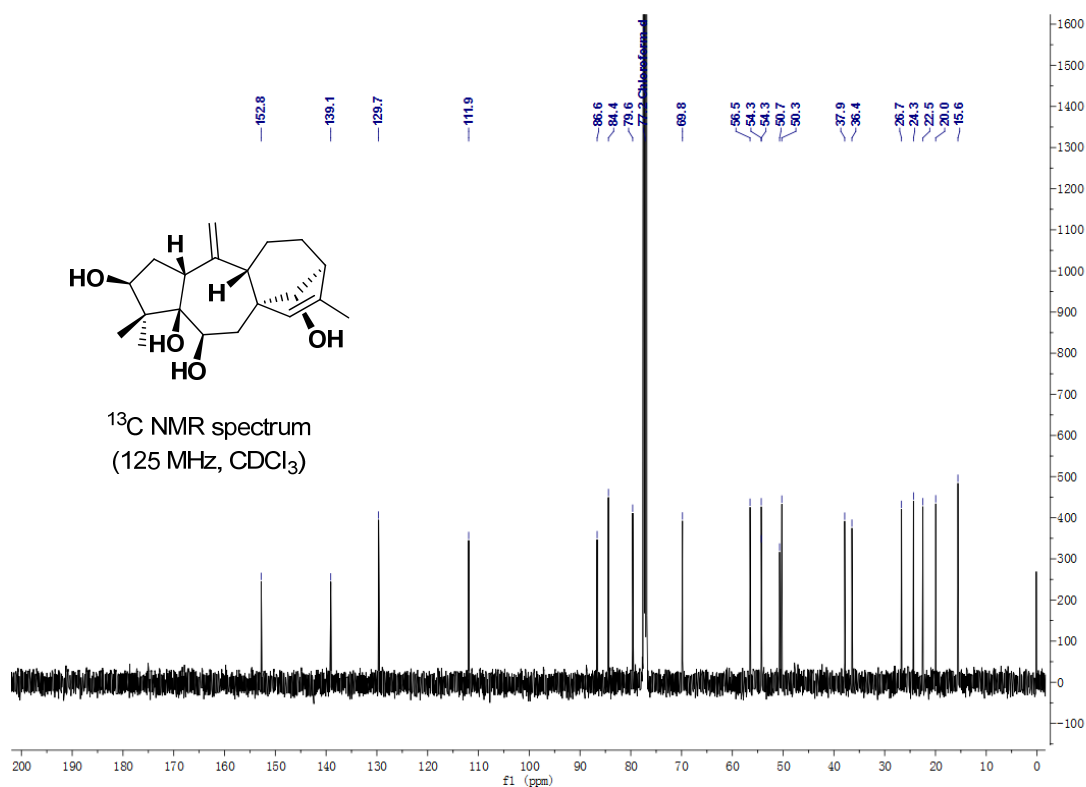
¹H NMR of compound (-)-24



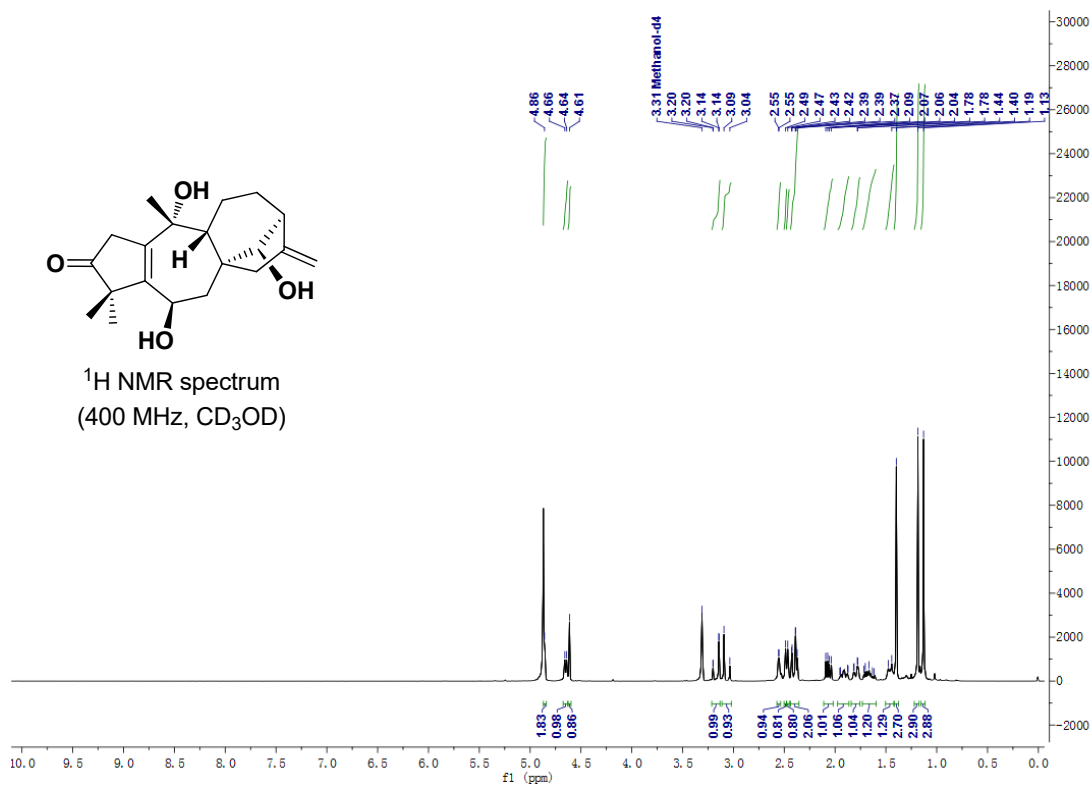
¹³C NMR of compound (-)-24



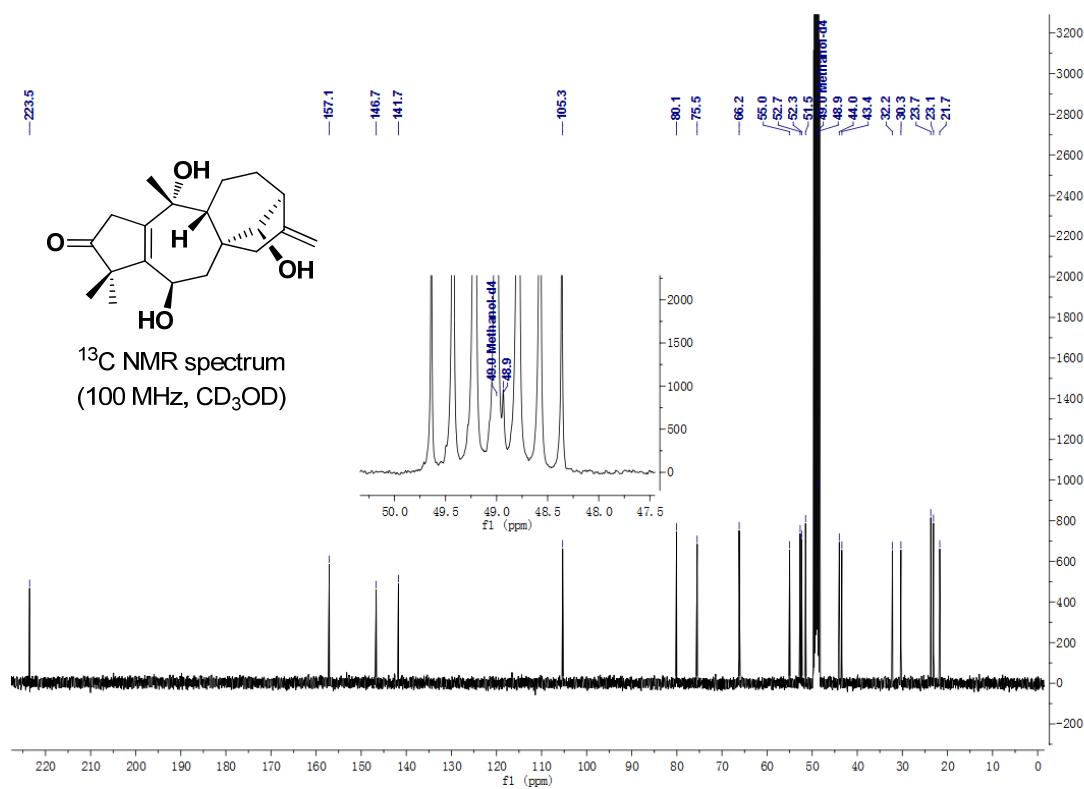
¹H NMR of (+)-principinol E (2)



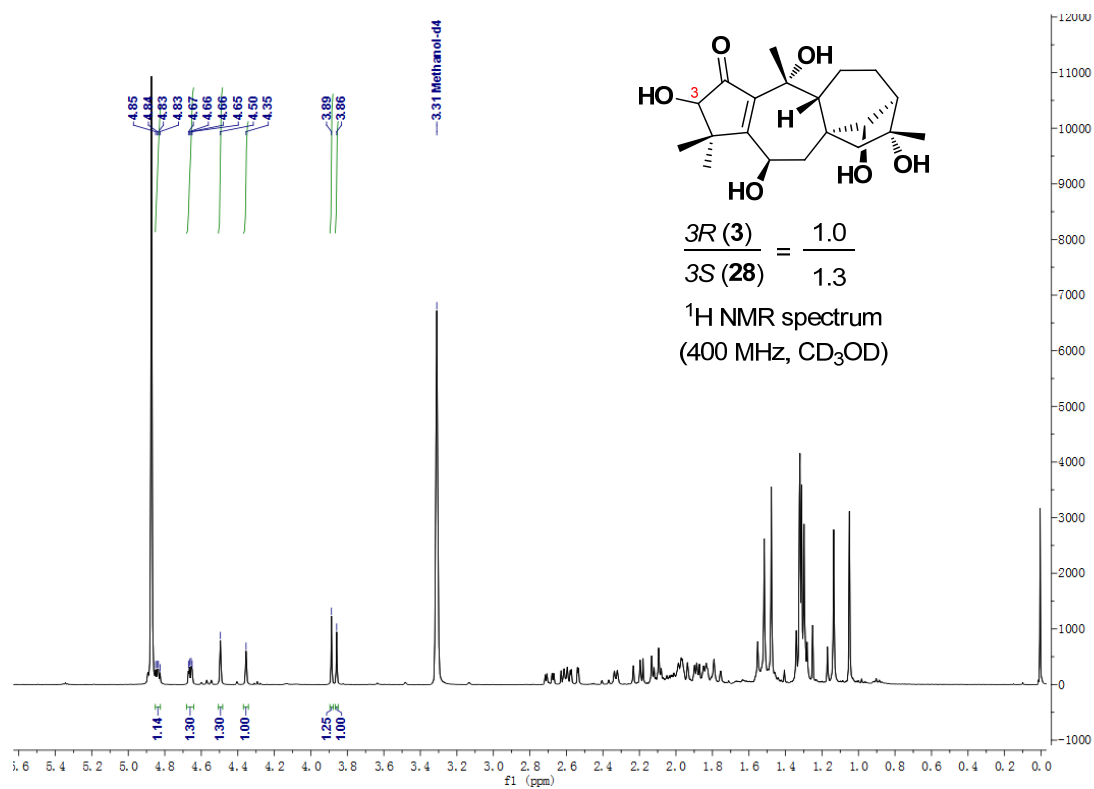
¹³C NMR of (+)-principinol E (2)



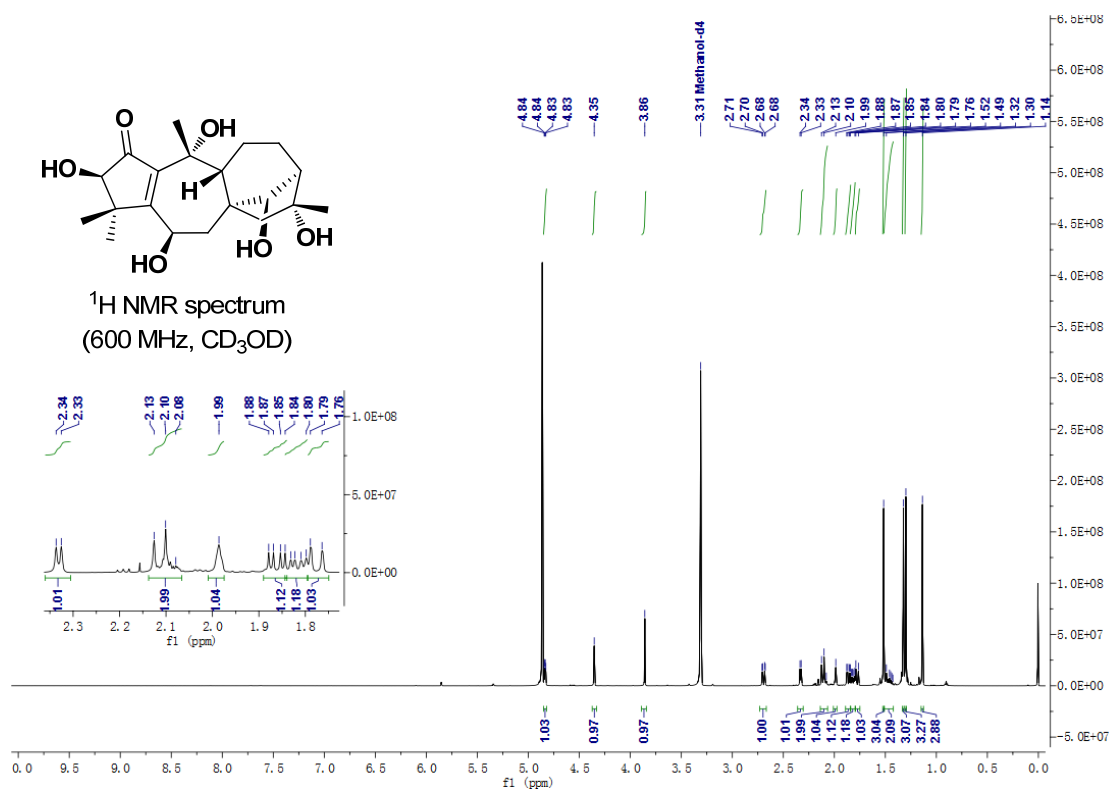
^1H NMR of compound (+)-25



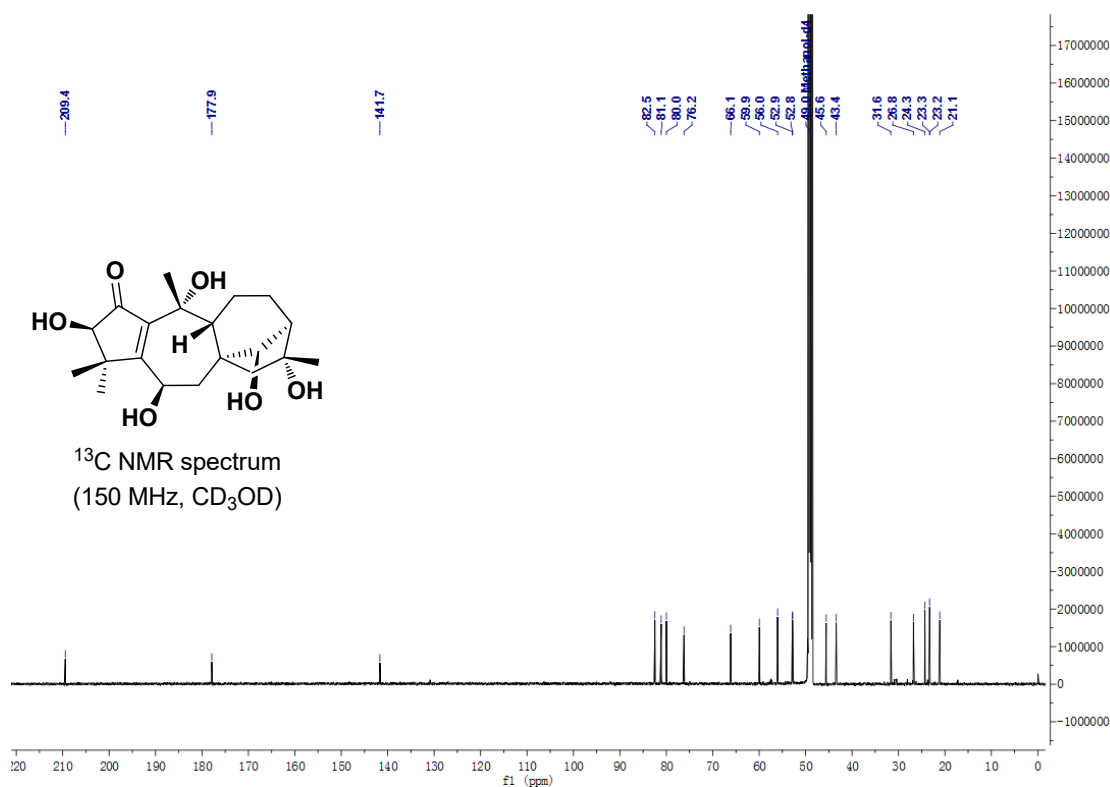
^{13}C NMR of compound (+)-25



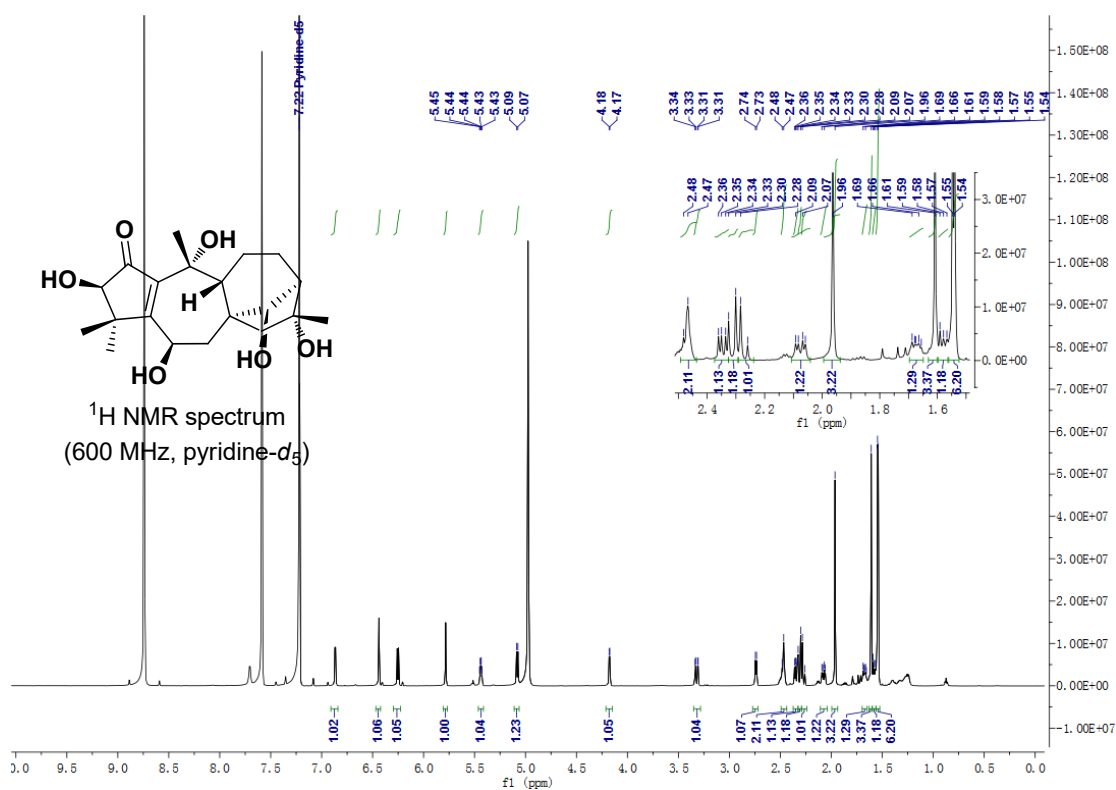
^1H NMR of the mixture of (–)-rhodomollein XX (**3**) and (–)-3-*epi*-rhodomollein XX (**28**)



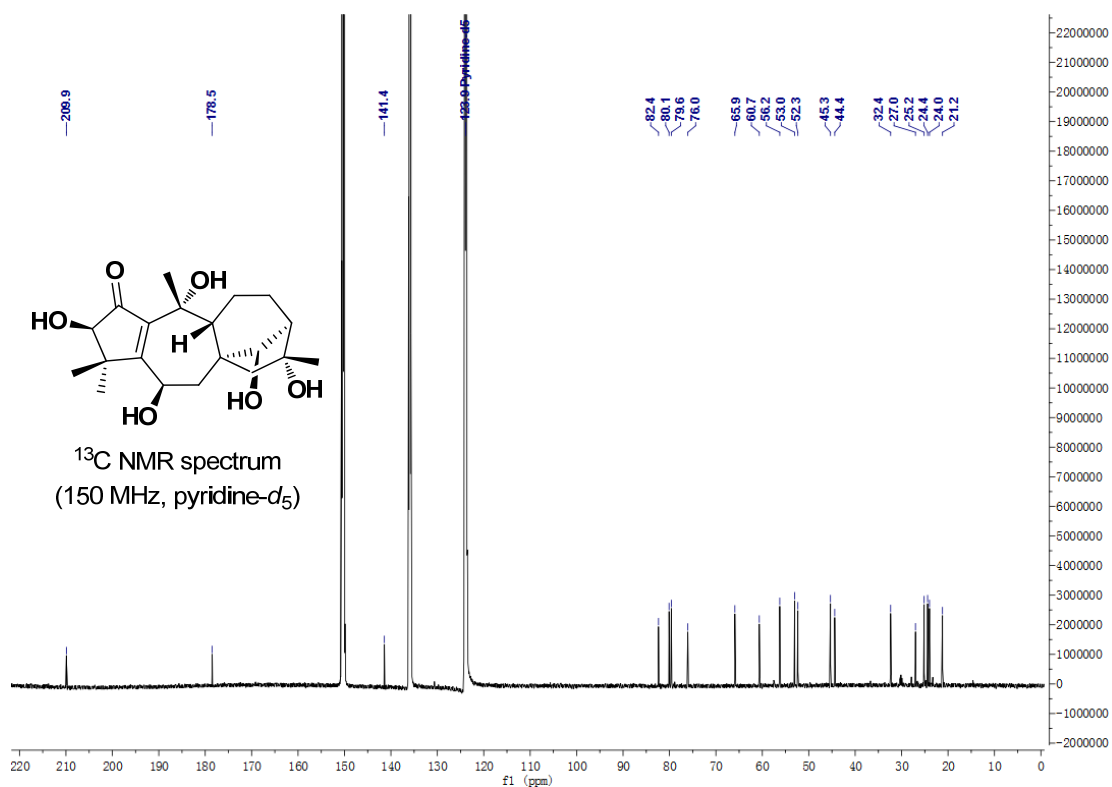
¹H NMR of (–)-rhodomollein XX (3)



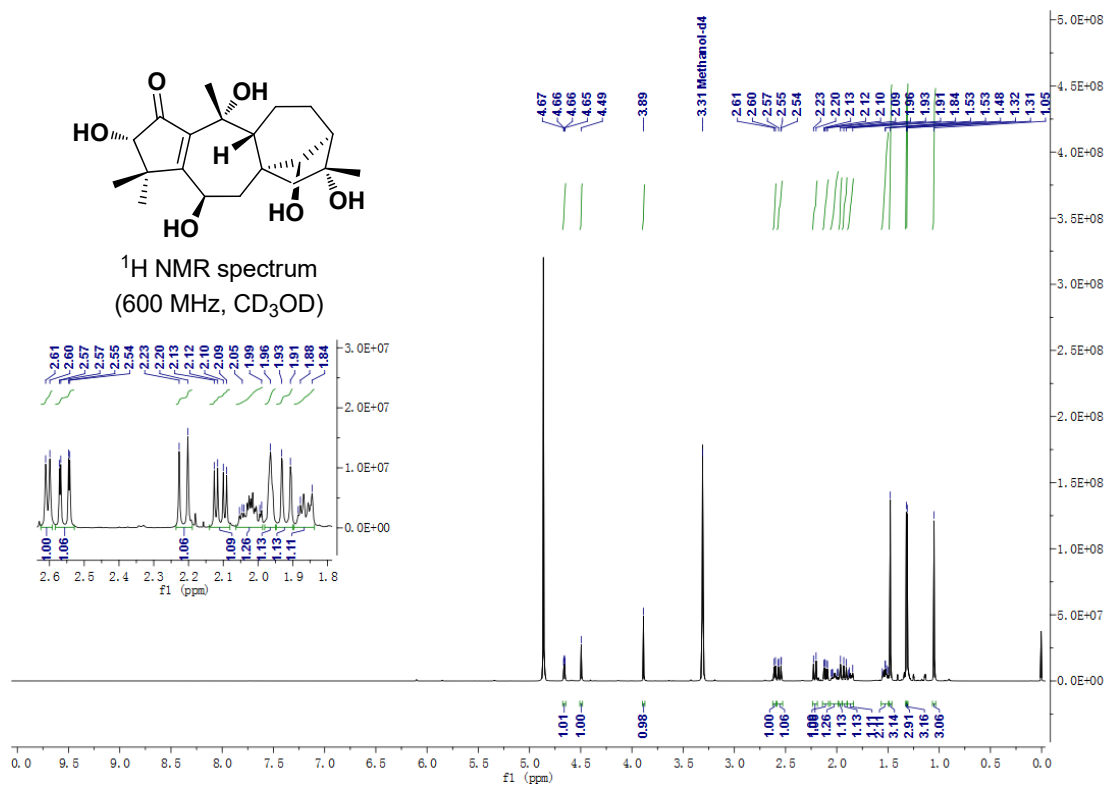
¹³C NMR of (–)-rhodomollein XX (3)



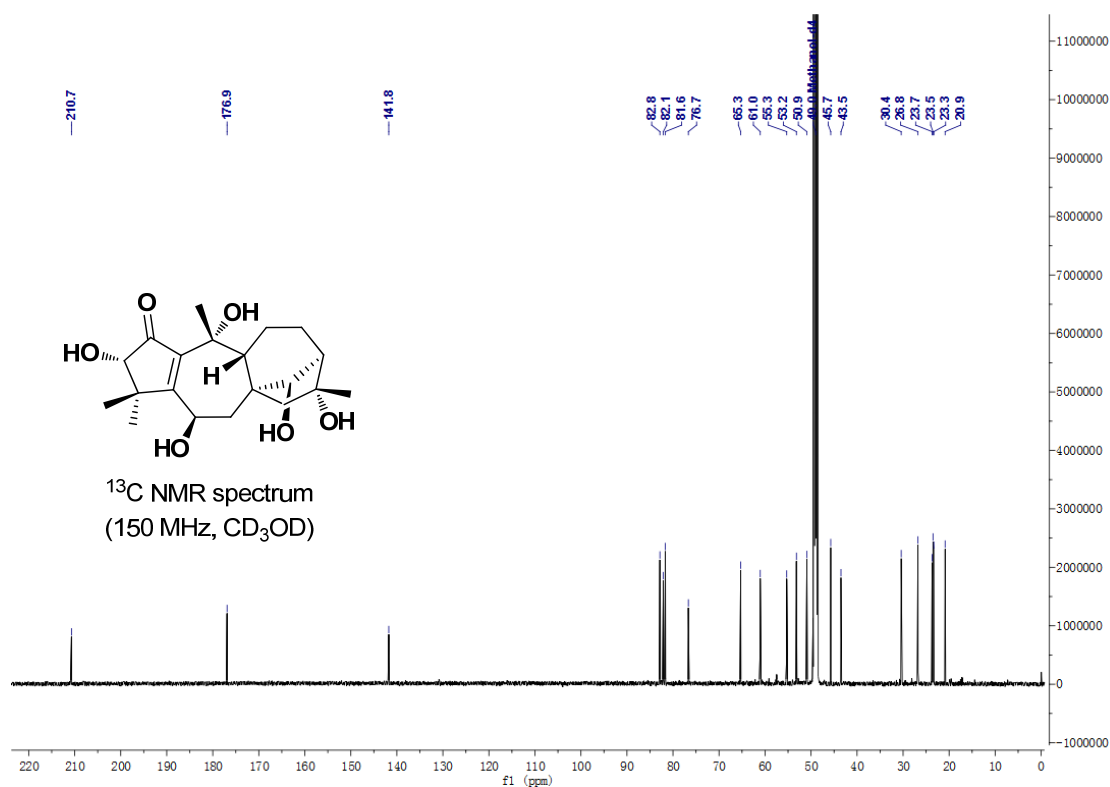
¹H NMR of (–)-rhodomollein XX (3)



¹³C NMR of (–)-rhodomollein XX (3)



^1H NMR of compound (-)-28



^{13}C NMR of compound (-)-28

IV. DFT Calculation

Density functional theory (DFT) calculations was carried out using Gaussian 09 D.01 software package.^[17] Geometry optimizations were performed with B3LYP functional using 6-31G(d,p) basis set for all atoms. Vibrational frequencies were computed at the same level of theory as geometry optimizations, and to make sure no imaginary frequency was found on the minima of potential energy surface.

Int1

Thermal Correction for Gibbs free energy: 0.208065 Eh

Thermal Correction for enthalpy: 0.273647 Eh

E_{B3LYP/6-31G(D,P)} = -3225.949608 Eh

Coordinate:

O	2.50968300	2.62449700	-0.04367200
C	3.85677600	3.17885000	-0.12141200
H	4.59565200	2.37781000	-0.18585900
H	3.88203700	3.81170800	-1.00826400
H	3.99960700	3.77703100	0.77827800
C	-1.32749700	0.57702400	-0.28963300
H	-1.53382200	0.58501500	-1.36292400
C	-0.25546500	1.62548400	0.07117800
H	-0.42016300	2.00337800	1.08683800
H	-0.25844300	2.48397400	-0.60483200
C	1.03007000	0.82965500	0.00219300
C	0.74834400	-0.52548500	0.00839500
O	-2.52723500	0.88454900	0.41253300
C	-3.71712000	0.62593600	-0.23786400
C	-4.88155500	1.11021900	0.57899100
H	-4.83361200	2.19844100	0.68278400
H	-5.81011700	0.82772600	0.08541200
H	-4.84410200	0.68516900	1.58574400
O	-3.76285100	0.08708300	-1.31650900
C	-0.72056900	-0.82871800	0.08062000
C	-1.04192600	-1.23067300	1.54948400
H	-2.11609100	-1.40599000	1.63411200
H	-0.51476500	-2.15083500	1.81204300
H	-0.76770100	-0.44967800	2.26297900
C	-1.16041400	-1.94434900	-0.88643600
H	-2.24853000	-2.02627200	-0.86520000
H	-0.86604000	-1.71931800	-1.91527700
H	-0.72903000	-2.90689300	-0.60166700
C	2.32236500	1.34826000	-0.05276200
H	3.19292300	0.69210400	-0.11257600
Br	2.01135300	-1.88998900	0.00265900

Compound 11

Thermal Correction for Gibbs free energy: 0.386698 Eh

Thermal Correction for enthalpy: 0.471556 Eh

E_{B3LYP/6-31G(D,P)} = -1283.321311 Eh

Coordinate:

C	-1.57466300	0.55870000	0.08139200
C	-2.14132400	1.74403600	-0.18041400
H	-3.22319700	1.84038100	-0.20643500
C	-0.08389100	0.34339200	0.16830100
H	0.09801500	-0.33987100	1.00547000
H	0.23751400	-0.19353800	-0.73327400
C	-1.32496300	2.98606400	-0.42227100
H	-1.72227700	3.52836800	-1.29086000
H	-1.43690000	3.68014600	0.42461800
C	0.16251100	2.68510700	-0.66400500
H	0.72833700	3.62071000	-0.60277500
H	0.28900700	2.30083600	-1.68354500
C	0.74260700	1.64955100	0.32664100
C	0.60221200	2.18835000	1.77317600
H	1.06222400	1.51329600	2.50019800
H	1.09165900	3.16327600	1.86762300
H	-0.44951500	2.29956000	2.05041600
Si	3.60826800	-1.26500900	-0.03070100
C	5.15550600	-0.79721400	-1.01895600
H	5.62637600	-1.69431100	-1.43698500
H	4.91730600	-0.13077400	-1.85364100
H	5.90071100	-0.29581000	-0.39145000
C	2.35534500	-2.06249900	-1.20348300
H	2.80250400	-2.92954100	-1.70309700
H	1.46124200	-2.41000300	-0.67584600
H	2.03618100	-1.36200100	-1.98206700
C	4.09581100	-2.51426100	1.31084600
H	4.82978500	-2.08926300	2.00469900
H	3.22729800	-2.82853600	1.90043300
H	4.54001300	-3.41510100	0.87295400
O	-2.25418500	-0.61362000	0.29543400
Si	-3.84808700	-1.06713500	-0.04189300
C	-5.05784600	-0.17782800	1.09996900
H	-5.10719000	0.89867000	0.91061200
H	-6.06880700	-0.58261600	0.97356400

H	-4.77428600	-0.31745600	2.14856300
C	-4.24734900	-0.73256400	-1.85295100
H	-3.58931600	-1.31148200	-2.50947500
H	-5.28069900	-1.01694200	-2.08173000
H	-4.12549000	0.32385200	-2.10887500
C	-3.86831300	-2.91106200	0.31889800
H	-3.60034300	-3.11138700	1.36131900
H	-4.86225100	-3.33670100	0.14117500
H	-3.15588500	-3.44564100	-0.31742200
C	2.23339300	1.35989900	0.06390300
C	2.96535300	2.07310100	-0.80353200
H	4.02617600	1.87914400	-0.93029200
H	2.55717400	2.87753100	-1.40236700
C	2.88977400	0.25692700	0.88625900
H	2.20187400	-0.13440900	1.64319300
H	3.72874000	0.68037700	1.45549200

TS_a

Thermal Correction for Gibbs free energy: 0.619868 Eh

Thermal Correction for enthalpy: 0.746672 Eh

E_{B3LYP/6-31G(D,P)} = -4509.287035 Eh

Coordinate:

O	-0.62895000	0.23941500	2.48678500
C	-0.07486200	1.25103400	3.36553500
H	-0.87367200	1.64744500	3.99824800
H	0.66523700	0.74125500	3.98011400
H	0.39027400	2.05382300	2.79209000
C	-3.68567600	-2.26577000	0.70184700
H	-4.31504400	-2.97698800	1.23715800
C	-2.54735500	-1.67945900	1.56198600
H	-1.63096900	-2.26245700	1.44312800
H	-2.80080500	-1.69113900	2.62846700
C	-2.42291300	-0.24972900	1.07159400
C	-3.50741300	0.06980600	0.32820000
O	-3.05387800	-2.95814700	-0.39408500
C	-3.67308300	-4.09869600	-0.84281200
C	-2.86325000	-4.75160100	-1.93118000
H	-1.86544000	-5.00128900	-1.55930700
H	-3.37198400	-5.65467800	-2.26501700
H	-2.73824800	-4.06340600	-2.77229700
O	-4.72402400	-4.49505000	-0.39962300
C	-4.53067600	-1.04125800	0.20207000
C	-5.08182100	-1.20009600	-1.22328500
H	-5.73310600	-2.07587600	-1.27029600
H	-5.66952600	-0.32204700	-1.50257200
H	-4.27961800	-1.32343700	-1.95398700
C	-5.69278400	-0.77286900	1.18975100
H	-6.42864200	-1.57855300	1.11867400
H	-5.34249300	-0.71640900	2.22508500
H	-6.19050900	0.17046500	0.94895500
C	-1.36773200	0.65442100	1.45966700
H	-1.54238900	1.72659500	1.37786400
Br	-3.83050000	1.77235400	-0.41785100
C	0.85271400	1.40139200	0.09361600
C	-0.23277900	0.71056100	-0.43364300
H	-1.01534100	1.30316700	-0.90059900
C	2.07685000	0.68565300	0.58731400

H	2.90927200	1.39404800	0.58381700
H	1.90224700	0.42158700	1.64146900
C	-0.04512000	-0.69983100	-0.94898700
H	-0.97642900	-1.26693000	-0.85134900
H	0.13334200	-0.63231900	-2.03075800
C	1.10616500	-1.44837900	-0.26370100
H	1.29102900	-2.38740500	-0.79434700
H	0.79933500	-1.71383700	0.75415300
C	2.41270000	-0.62460000	-0.18959100
C	2.89241500	-0.27122300	-1.61585800
H	3.82969300	0.28892100	-1.59990900
H	3.05980500	-1.17997900	-2.20045600
H	2.15871400	0.34145700	-2.15043300
Si	6.42625700	-1.43297100	-0.08764700
C	6.16123300	-1.77206600	-1.92948100
H	7.06226900	-2.22634400	-2.35635300
H	5.33364700	-2.46850300	-2.09934800
H	5.95830100	-0.85822200	-2.49750500
C	6.88439700	-3.04697600	0.78299600
H	7.83254000	-3.42894100	0.38847100
H	7.01302100	-2.90697300	1.86189700
H	6.13112200	-3.82615400	0.63075400
C	7.82076100	-0.17384100	0.13760800
H	7.60098000	0.77224400	-0.36954400
H	7.99568700	0.04925300	1.19586400
H	8.76085300	-0.55506600	-0.27561000
O	0.81462200	2.70374400	0.33537500
Si	0.63762400	4.16661600	-0.60002600
C	2.31409200	4.47788800	-1.37406700
H	2.60394300	3.67210000	-2.05661100
H	2.29739300	5.40711100	-1.95454800
H	3.09445900	4.57696600	-0.61322400
C	-0.70000300	3.94325800	-1.89579700
H	-1.66676800	3.67812700	-1.45773500
H	-0.83287500	4.88720600	-2.43714500
H	-0.43898800	3.18191700	-2.63780100
C	0.18355300	5.43093600	0.70001300
H	0.94111800	5.48036500	1.48830000
H	0.11037300	6.42741000	0.25097700
H	-0.78159100	5.21009400	1.16693000
C	3.53012200	-1.35795000	0.58127100
C	3.33433200	-2.55747100	1.14630800
H	4.12489500	-3.03906200	1.71252600

H	2.40409300	-3.10739300	1.07918800
C	4.86736100	-0.64755300	0.73116000
H	5.11634900	-0.57179700	1.79796100
H	4.81806100	0.38703500	0.37403900

TS_b

Thermal Correction for Gibbs free energy: 0.617671 Eh

Thermal Correction for enthalpy: 0.746543 Eh

E_{B3LYP/6-31G(D,P)} = -4509.283823 Eh

Coordinate:

O	0.69857000	-0.51651000	2.11725300
C	-0.32925100	0.07358200	2.93815600
H	-1.22002400	0.26266100	2.33674100
H	-0.55009100	-0.65913200	3.71221000
H	0.03433600	1.00240300	3.38540300
C	4.29378700	-1.71291300	0.03567600
H	4.01464900	-2.14896700	-0.92642500
C	3.07048600	-1.63895900	0.97159000
H	3.37622800	-1.75616700	2.01814100
H	2.33547500	-2.42049500	0.76093500
C	2.54325900	-0.24015000	0.72600200
C	3.47712700	0.49583500	0.07582100
O	5.29044700	-2.54335500	0.63699300
C	6.03409200	-3.33714800	-0.19972000
C	6.97733500	-4.20159900	0.59244900
H	6.41040500	-4.86191500	1.25531800
H	7.58403500	-4.79393300	-0.09077800
H	7.61948200	-3.58066700	1.22342800
O	5.91684600	-3.32025100	-1.40223200
C	4.76961100	-0.23475500	-0.21501000
C	5.84419200	0.22087100	0.79875900
H	6.77994000	-0.31178000	0.61516700
H	6.03205900	1.29235600	0.68774200
H	5.53992600	0.02751400	1.83086500
C	5.26721800	-0.02164600	-1.65547400
H	6.12333300	-0.67129500	-1.84824900
H	4.49190900	-0.27031400	-2.38635800
H	5.57182200	1.01592700	-1.81621000
C	1.28909400	0.25951900	1.22403300
H	1.12530700	1.33398400	1.29385400
Br	3.26069100	2.30864800	-0.39147000
C	-1.01417700	1.09799900	-0.28099500
C	0.06639900	0.32704500	-0.68021400
H	0.91682200	0.90478500	-1.02779400
C	-2.44008400	0.61670100	-0.30425900

H	-2.92905900	0.87539000	0.64108200
H	-2.94141000	1.23518500	-1.06441400
C	-0.14993000	-1.06508500	-1.23708200
H	0.53726400	-1.22338800	-2.07414600
H	0.10729600	-1.82807100	-0.49199200
C	-1.59483900	-1.27188000	-1.72390300
H	-1.73188700	-2.31684300	-2.01821700
H	-1.74591400	-0.66475200	-2.62368400
C	-2.65681900	-0.88650000	-0.66837000
C	-2.48209200	-1.77635900	0.58313700
H	-3.20155200	-1.52087700	1.36521500
H	-2.63883800	-2.82652300	0.32296400
H	-1.47953900	-1.68978500	1.01134500
Si	-6.48868400	-2.01086300	0.27179500
C	-5.62013300	-3.50661300	1.03793200
H	-6.36441900	-4.24892000	1.34696200
H	-4.95057000	-3.99639800	0.32345000
H	-5.03585900	-3.24392600	1.92612300
C	-7.51865000	-2.58172500	-1.20588200
H	-8.30885000	-3.26299500	-0.87093800
H	-8.00668000	-1.74266200	-1.71361600
H	-6.91717900	-3.11996400	-1.94496900
C	-7.61623600	-1.19847100	1.55605900
H	-7.05735400	-0.86591700	2.43801700
H	-8.13554000	-0.32649400	1.14334500
H	-8.38252000	-1.90117000	1.90064900
O	-0.76868500	2.34147400	0.11535400
Si	-1.58375200	3.88186500	0.07583600
C	-1.89772300	4.27854000	-1.72882700
H	-2.59130500	3.57546300	-2.20109000
H	-2.33935100	5.27747300	-1.81840500
H	-0.96732300	4.27640900	-2.30516100
C	-3.16416000	3.81512500	1.08676800
H	-2.98416200	3.45032300	2.10340800
H	-3.57262300	4.82849000	1.17712000
H	-3.93968900	3.19362300	0.62969700
C	-0.30042900	4.99813100	0.85432500
H	0.67243400	4.87707100	0.36757000
H	-0.59300900	6.04940900	0.76151500
H	-0.17282200	4.78629000	1.92080600
C	-4.09816900	-1.02617600	-1.20447800
C	-4.35588400	-1.41610600	-2.46014200
H	-5.37656000	-1.47227200	-2.82399100

H	-3.58777900	-1.68709000	-3.17322800
C	-5.23517000	-0.64702700	-0.26597400
H	-5.85108100	0.12749600	-0.74232600
H	-4.86036700	-0.18853500	0.65635400

Int-a

Thermal Correction for Gibbs free energy: 0.624489 Eh

Thermal Correction for enthalpy: 0.749237 Eh

E_{B3LYP/6-31G(D,P)} = -4509.309561 Eh

Coordinate:

O	-0.16750000	-0.38587500	2.20328800
C	-0.55089600	-0.22246900	3.57101800
H	-1.55625800	-0.61475500	3.76104500
H	0.17092900	-0.78365200	4.16526500
H	-0.52175600	0.83551700	3.86400000
C	-3.75430200	-2.28966400	0.47436700
H	-4.36301300	-3.05687100	0.95356600
C	-2.46680400	-1.94469200	1.25041800
H	-1.63008700	-2.56167700	0.91301600
H	-2.59250900	-2.14366800	2.32207400
C	-2.27847900	-0.45924600	1.00039200
C	-3.41612300	0.04816200	0.51560600
O	-3.32503800	-2.79488200	-0.80974000
C	-4.08762900	-3.78580200	-1.36842200
C	-3.48182700	-4.25720500	-2.66504600
H	-2.46546800	-4.62382900	-2.49511700
H	-4.09837200	-5.05209900	-3.08209800
H	-3.41802800	-3.42668000	-3.37424700
O	-5.10276200	-4.20569300	-0.86555700
C	-4.55171600	-0.94515800	0.33319400
C	-5.28090800	-0.79320000	-1.00921500
H	-6.01399000	-1.59437400	-1.13051100
H	-5.81181400	0.16185500	-1.04383800
H	-4.58533300	-0.82773800	-1.85085400
C	-5.55740900	-0.80881100	1.49822600
H	-6.37188700	-1.52899800	1.37943600
H	-5.08080700	-0.98523100	2.46787800
H	-5.98865100	0.19632100	1.51515900
C	-1.00193400	0.29477800	1.28740200
H	-1.26144100	1.28738600	1.68846300
Br	-3.68357600	1.90009200	0.14252100
C	1.01882800	1.34991000	0.17019600
C	-0.22276200	0.55475500	-0.06704900
H	-0.91964900	1.15598300	-0.65484700
C	2.22416600	0.67563100	0.69463100

H	3.03389200	1.39772100	0.79964000
H	1.94388900	0.27489000	1.67733000
C	0.15603500	-0.72131500	-0.87414400
H	-0.71631900	-1.37972500	-0.89697800
H	0.32318500	-0.41637500	-1.91270200
C	1.38449900	-1.46290600	-0.33155000
H	1.61129900	-2.30116200	-0.99859500
H	1.13582300	-1.88228600	0.64604800
C	2.64135200	-0.57019300	-0.19602400
C	3.10202800	-0.06876900	-1.58294700
H	3.96820100	0.59227700	-1.50871800
H	3.38375300	-0.91515700	-2.21457200
H	2.31560600	0.48879500	-2.10372900
Si	6.71962200	-1.11501500	-0.06610700
C	6.49602600	-1.40607200	-1.92159400
H	7.43144700	-1.77430900	-2.35713300
H	5.72501400	-2.15651100	-2.12500700
H	6.22845800	-0.48913600	-2.45730400
C	7.30073400	-2.71343700	0.75775800
H	8.29186800	-2.98805200	0.37986800
H	7.38501500	-2.60495400	1.84458100
H	6.63195000	-3.55501700	0.55255200
C	7.99829600	0.24841800	0.22368300
H	7.70857500	1.18759900	-0.26074700
H	8.13441300	0.45331200	1.29125300
H	8.97450300	-0.04008200	-0.18056300
O	1.10245400	2.59201900	-0.08414000
Si	0.15879700	3.98775700	-0.75431000
C	-0.85554700	3.39024500	-2.20888500
H	-1.77428800	2.88072500	-1.90606900
H	-1.14816200	4.26752700	-2.79863900
H	-0.28603400	2.73645000	-2.87712800
C	-0.84313000	4.59588900	0.69950600
H	-0.22518100	4.72900800	1.59263900
H	-1.27272900	5.57390200	0.45246900
H	-1.67335700	3.92380000	0.93455900
C	1.56170700	5.11183500	-1.24507600
H	2.19052100	4.66046300	-2.01869800
H	1.16529700	6.05034100	-1.64841800
H	2.19621600	5.35912200	-0.38890900
C	3.80768900	-1.27614400	0.52309800
C	3.70081900	-2.53597200	0.96731900
H	4.52855100	-3.01078700	1.48317700

H	2.81252300	-3.14257300	0.84691800
C	5.08728400	-0.48348100	0.74522100
H	5.29615500	-0.43302300	1.82217400
H	4.97813900	0.55904000	0.42660500

Int-b

Thermal Correction for Gibbs free energy: 0.618968 Eh

Thermal Correction for enthalpy: 0.748444 Eh

E_{B3LYP/6-31G(D,P)} = -4509.306216 Eh

Coordinate:

O	0.89225200	0.70270100	2.05651800
C	1.51263400	1.60556400	2.96594300
H	1.29751700	2.64936800	2.69667800
H	1.09738100	1.39295900	3.95242900
H	2.60020300	1.47248100	3.00218600
C	4.44292100	-1.38670500	0.41105700
H	4.08252900	-2.27904700	-0.10608300
C	3.34025300	-0.81369700	1.32398400
H	3.78924200	-0.33844300	2.20542900
H	2.66081800	-1.58694400	1.69504700
C	2.66343300	0.20813300	0.43184100
C	3.44375200	0.45831200	-0.62447100
O	5.57577600	-1.75642800	1.20833500
C	6.24072200	-2.90190800	0.86582500
C	7.37304200	-3.16094800	1.82480500
H	6.99295100	-3.22520600	2.84822500
H	7.87293500	-4.08917300	1.55195500
H	8.08589000	-2.33163800	1.79399800
O	5.93839000	-3.59124500	-0.08050800
C	4.76381100	-0.28976500	-0.66608200
C	5.90686900	0.65086500	-0.23376900
H	6.86354400	0.12268600	-0.24293800
H	5.97596900	1.49468300	-0.92664300
H	5.74758000	1.04698100	0.77307500
C	5.06951200	-0.90700400	-2.03985600
H	5.95668900	-1.54177400	-1.97920500
H	4.24008300	-1.52910400	-2.39041700
H	5.25086700	-0.12871000	-2.78650400
C	1.32102200	0.85086700	0.71092100
H	1.39427900	1.91796100	0.45603700
Br	3.00142200	1.72752300	-1.98027500
C	-1.06941600	1.00727500	-0.13846300
C	0.20980800	0.22979800	-0.16717500
H	0.53409300	0.33154500	-1.21973400
C	-2.29386300	0.41765300	-0.74773800

H	-3.15810500	1.05817900	-0.57170300
H	-2.11800800	0.38798900	-1.83293600
C	-0.02256200	-1.28131400	0.10960700
H	0.86522200	-1.81693200	-0.23567200
H	-0.07635600	-1.42145600	1.19156800
C	-1.26399000	-1.84901500	-0.58415500
H	-1.39406100	-2.89212500	-0.27944300
H	-1.09726300	-1.85646700	-1.66744200
C	-2.55590500	-1.06242900	-0.27369100
C	-2.82582900	-1.06655100	1.24817400
H	-3.73751200	-0.52259600	1.50323300
H	-2.94566000	-2.09258500	1.60512100
H	-2.00491100	-0.61135700	1.81338300
Si	-6.53865200	-1.96179400	-0.00555500
C	-6.00153600	-2.72051000	1.64101500
H	-6.82692900	-3.30107400	2.06760500
H	-5.15557300	-3.40439000	1.51632100
H	-5.72168700	-1.96389800	2.38153700
C	-7.06630800	-3.33666100	-1.18761300
H	-7.93776100	-3.86380200	-0.78365600
H	-7.34922700	-2.94624600	-2.17124600
H	-6.27609100	-4.07960600	-1.33271900
C	-7.97581800	-0.76426700	0.27361400
H	-7.70935500	0.03919700	0.96946200
H	-8.30204200	-0.29986700	-0.66338800
H	-8.84041200	-1.28700000	0.69662600
O	-1.05213400	2.17313100	0.35454800
Si	-2.18478800	3.58222700	0.54317100
C	-2.73741100	4.02854300	-1.18566300
H	-3.40004200	3.28507800	-1.63715200
H	-3.29064900	4.97419800	-1.14440100
H	-1.88359700	4.18463300	-1.85267300
C	-3.53844300	3.00692600	1.69566700
H	-3.12661700	2.56154900	2.60651800
H	-4.13471300	3.87538100	1.99922500
H	-4.22250700	2.28816600	1.23634000
C	-1.03501800	4.83257600	1.30545100
H	-0.18067800	5.04457900	0.65552500
H	-1.56630100	5.77639300	1.47140700
H	-0.65606100	4.49241100	2.27384400
C	-3.78273800	-1.58109500	-1.05053400
C	-3.67747900	-2.56712700	-1.95224300
H	-4.54698600	-2.90150100	-2.50821300

H	-2.75171700	-3.07996900	-2.17904000
C	-5.12432200	-0.90966600	-0.79814800
H	-5.53424600	-0.55514900	-1.75294200
H	-5.02144800	-0.01212100	-0.17658500

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