Supporting Information

Synthesis of Four Illudalane Sesquiterpenes Utilizing a One-Pot Diels-Alder/Oxidative Aromatization Sequence

Miao-Miao Xun, Yunli Bai, Yanhong Wang, Zhiyong Hu, Kai Fu, Wenbing Ma, Changchun Yuan*

National Demonstration Center for Experimental Chemical Engineering Comprehensive Education, School of Chemical Engineering and Technology, North University of China, Taiyuan 030000, P.R. China

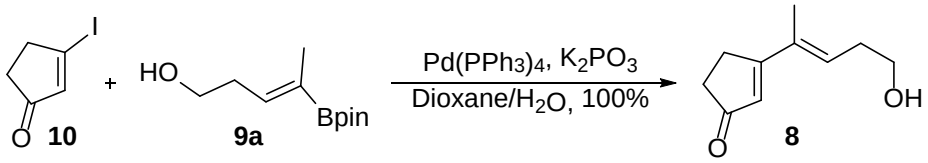
Table of Contents

General Information

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dichloromethane (DCM) and toluene were distilled from calcium hydride under argon; Tetrahydrofuran was distilled from sodium-benzophenone. All the chemicals were purchased commercially and used without further purification, unless otherwise stated. Flash chromatography was performed using silica gel (200-300 mesh). Reactions were monitored by thin layer chromatography (TLC). Visualization was achieved under a UV lamp (254 nm and 365 nm), I_2 and by developing the plates with *p*-anisaldehyde or phosphomolybdic acid. ^{1}H and ^{13}C NMR were recorded on Bruker DRX-400 MHz and Bruker DRX-600 MHz NMR spectrometer with TMS as the internal standard and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: ^{1}H NMR = 7.26, ^{13}C NMR = 77.16; C_6D_6: ^{1}H NMR = 7.28, ^{13}C NMR = 127.82). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. Coupling constants (*J*) are reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a FTMS-7 spectrometers and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M + Na]^+$, $[M + H]^+$. Infrared (IR) spectra were recorded on a NEXUS 670 FT-IR Fourier transform infrared spectrophotometer and are reported in wavenumbers (cm^{-1}). Single-crystal structure of compound were measured on Bruker D8 venture.

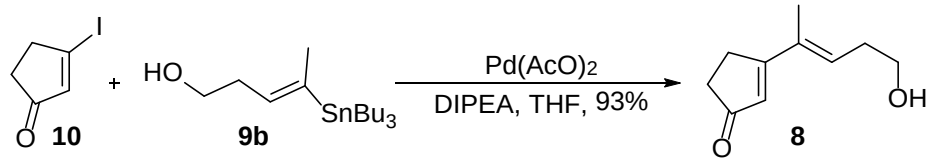
Experimental Procedures

Method A for the Preparation of Compound 8



Known compound **10** can be commercially acquired or be prepared in one step from commercially available 1,3-cyclopentanedione on the basis of known literature.[1] To a solution of compound **10** (1.95 g, 9.40 mmol) and compound **9a** (a known compound,[2] 4.00 g, 18.86 mmol) in dioxane (75 mL) and water (15 mL) was added $Pd(PPh_3)_4$ (543 mg, 0.47 mmol) and K_3PO_4 (6.00 g, 28.27 mmol) in order at rt. Then the reaction was allowed to heat to 60 °C stirring for 5 h and 80 °C stirring for 2 h, before it was filtered through a pad of Celite and washed with EtOAc. The layers were diluted with H_2O (50 mL) and separated. Then the aqueous layer was extracted with EtOAc (3 × 60 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1 : 1 petroleum ether-EtOAc) to furnish compound **8** (1.56 g, 100%) as a pale yellow solid.

Method B for the Preparation of Compound 8



To a solution of compound **10** (500 mg, 2.40 mmol) and compound **9b** (a known

compound,[3] 1.60 g, 4.25 mmol) in THF (25 mL) was added $Pd(AcO)_2$ (162 mg, 0.72 mmol) and DIPEA (0.21 mL, 162 mg, 1.25 mmol) in order at rt. Then the reaction was allowed to stir for 5 h at this temperature, before it was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1 : 1 petroleum ether-EtOAc) to furnish compound **8** (445.2 mg, 93%) as a pale yellow solid.

Mp = 72.3 – 73.5 °C;

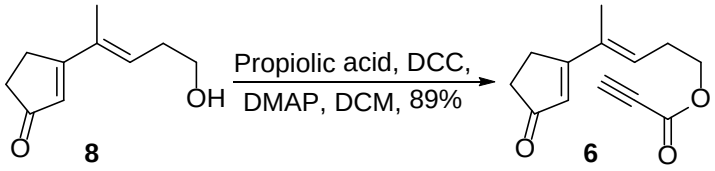
IR (thin film): 3418, 2925, 1672, 1626, 1574, 1441, 1298, 1195, 1048, 838 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 6.18 (t, *J* = 7.2 Hz, 1H), 6.06 (s, 1H), 3.77 (dd, *J* = 12.0, 6.6 Hz, 2H), 2.79 – 2.78 (m, 2H), 2.52 (q, *J* = 7.2 Hz, 2H), 2.48 – 2.37 (m, 2H), 1.93 (s, 3H), 1.88 (t, *J* = 5.4 Hz, 1H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 210.2, 175.8, 134.0, 132.4, 127.4, 61.8, 35.1, 32.4, 27.7, 14.6;

HRMS (ESI): m/z calcd for $C_{10}H_{14}NaO_2$ $[M+Na]^+$ 189.0886 found 189.0880.

Procedure for the Preparation of Compound 6



To a solution of compound **8** (3.50 g, 21.07 mmol) in dry DCM (35 mL) was added propiolic acid (2.00 mL, 2.28 g, 32.50 mmol) at 0 °C and the resulting mixture was stirred for 30 min at the same temperature. The mixture of DCC (8.70 g, 42.17 mmol) and DMAP (51 mg, 0.42 mmol) in DCM (35 mL) was added to the above solution at

0 °C. After stirring for another 1.5 h at 0 °C, it was filtered through a pad of Celite to remove the solid and washed with DCM. The organic layer were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (2 : 1 petroleum ether-EtOAc) to furnish compound **6** (4.07 g, 89%) as a white solid.

Mp = 95.1 – 96.8 °C;

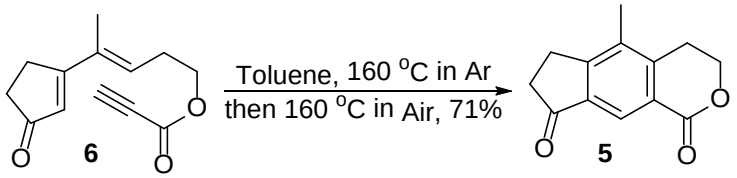
IR (thin film): 3153, 3063, 2923, 2844, 2103, 1708, 1632, 1576, 1475, 1429, 1241, 1200, 1076, 989, 643 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.10 (s, 1H), 6.08 (t, *J* = 7.2 Hz, 1H), 4.31 (t, *J* = 6.6 Hz, 2H), 2.91 (s, 1H), 2.81 – 2.75 (m, 2H), 2.65 (q, *J* = 6.6 Hz, 2H), 2.48 – 2.46 (m, 2H), 1.94 (s, 3H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 209.8, 175.0, 152.7, 134.8, 129.8, 128.1, 75.3, 74.6, 64.8, 35.1, 28.2, 27.7, 14.6;

HRMS (ESI): m/z calcd for $C_{13}H_{14}NaO_3$ $[M+Na]^+$ 241.0835 found 241.0835.

Procedure for the Preparation of Compound 5



A solution of compound **6** (170 mg, 0.78 mmol) in toluene (4.0 mL) was heated at 160 °C in a 15 mL sealed-tube for 15 h under argon atmosphere. Then the reaction was cooled to room temperature and toluene (2.0 mL) was added, before it was fully contacted with air. Adherence the mixture was heated to 160 °C again and stirred for another 15 h in this

sealed-tube, before it was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1 : 1 petroleum ether-EtOAc) to furnish compound **5** (119.6 mg, 71%) as a pale yellow solid.

Mp = 203.9 – 204.5 °C;

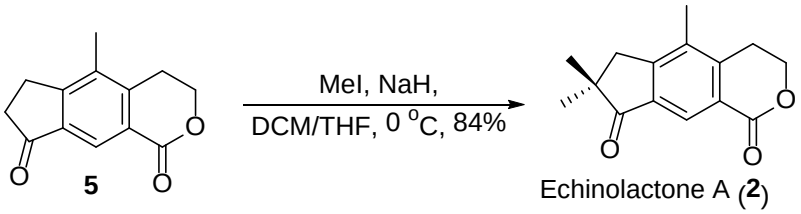
IR (thin film): 2923, 1723, 1606, 1432, 1402, 1290, 1259, 1197, 1158, 1100, 957, 780 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (s, 1H), 4.54 (t, *J* = 6.0 Hz, 2H), 3.11 (t, *J* = 12.0 Hz, 2H), 3.08 (t, *J* = 6.0 Hz, 2H), 2.76 – 2.74 (m, 2H), 2.34 (s, 3H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 205.8, 165.0, 158.7, 143.8, 136.2, 133.2, 125.4, 124.5, 66.4, 36.3, 25.9, 25.7, 14.3;

HRMS (ESI): m/z calcd for $C_{13}H_{12}NaO_3$ $[M+Na]^+$ 239.0679 found 239.0677.

Procedure for the Preparation of Natural product Echinolactone A (2)



5 Echinolactone A (**2**)

To a suspension of NaH (60% suspension in mineral oil, 110.4 mg, 2.76 mmol) in dry THF (2 mL) was added the solution of compound **5** (50 mg, 0.23 mmol) in dry DCM (1 mL) at 0 °C. Then the mixture was allowed to stir at room temperature for 20 min, followed re-coolling to 0 °C and by addition of excess MeI drop by drop. This mixture was then stirred for a further 2 h and diluted with dry THF (10 mL). Then the reaction mixture was droply added to the solution of HCl (5 mL, 1 M in H_2O) and H_2O (10 mL) at

0 ^{o}C, followed by concentration under reduced pressure in order to remove THF. The aqueous layer was extracted with DCM (10 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (2 : 1 petroleum ether-EtOAc) to furnish natural product echinolactone A (**2**) (47.3 mg, 84%) as a white solid.

Mp = 218.5 – 218.6 °C;

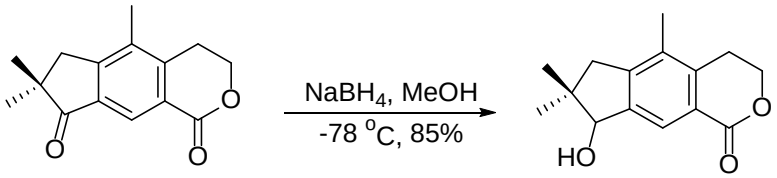
IR (thin film): 2925, 1720, 1599, 1468, 1386, 1266, 1292, 1211, 1174, 1087, 790 773 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (s, 1H), 4.53 (t, *J* = 6.0 Hz, 2H), 3.07 (t, *J* = 6.0 Hz, 2H), 2.96 (s, 2H), 2.30 (s, 3H), 1.25 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2, 165.0, 155.9, 144.0, 134.4, 133.2, 125.5, 125.0, 66.4, 45.7, 42.6, 25.9, 25.4, 14.3;

HRMS (ESI): m/z calcd for $C_{15}H_{16}NaO_3$ $[M+Na]^+$ 267.0992 found 267.0990.

Procedure for the Preparation of Natural product (±)-Radulactone (3)



Echinolactone A (**2**) (±)-Radulactone (**3**)

To a solution of echinolactone A (**2**) (10 mg, 0.04 mmol) in MeOH (1 mL)was added $NaBH_4$ (2.3 mg, 0.06 mmol) at -78 °C. After stirring for 5 h at -78 °C, the resulting mixture was diluted with MeOH (5 mL) at this temperature. Then the reaction mixture was droply added to the saturated aqueous NH_4Cl (10 mL) at 0 ^{o}C, followed by

concentration under reduced pressure in order to remove MeOH. The aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (2 : 1 petroleum ether-EtOAc) to furnish natural product (±)-radulactone (**3**) (8.4 mg, 85%) as a white solid.

Mp = 218.0 – 218.4 °C;

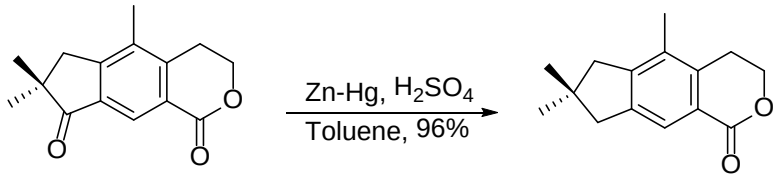
IR (thin film): 3325, 2962, 2927, 1720, 1601, 1460, 1391, 1292, 1211, 1173, 1089, 1028, 967, 791, 769 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 8.01 (s, 1H), 4.70 (s, 1H), 4.50 (t, *J* = 6.0 Hz, 2H), 2.97 (t, *J* = 6.0 Hz, 2H), 2.80 (d, *J* = 16.2 Hz, 1H), 2.63 (d, *J* = 16.2 Hz, 1H), 2.20 (s, 3H), 1.18 (s, 3H), 1.06 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 147.6, 143.9, 138.3, 131.4, 124.4, 83.2, 66.8, 44.4, 44.3, 26.9, 25.4, 21.6, 15.1.

HRMS (ESI): m/z calcd for $C_{15}H_{18}NaO_3$ $[M+Na]^+$ 269.1148 found 269.1150.

Procedure for the Preparation of Natural product Granulolactone (1)



Echinolactone A (**2**) Granulolactone (**1**)

5 g of zinc powder was washed with HCl (6 M in water, 2 × 4.45 mL). Then $HgCl_2$ (214.5 mg, 0.79 mmol), water (3.4 mL), and concentrated HCl (0.6 mL) were added to the washed Zn dust, and the resulting mixture was stirred vigorously for 1 h at room

temperature. To this mixture was added echinolactone A (**2**) (42.9 mg, 0.18 mmol) in toluene (2.0 mL) followed by addition of concentrated HCl (3.2 mL). After stirring overnight at room temperature, it was filtered through a pad of Celite to remove the solid and washed with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (8 : 1 petroleum ether-EtOAc) to furnish natural product granulolactone (**1**) (39.6 mg, 96%) as a white solid.

Mp = 117.8 – 119.2 °C;

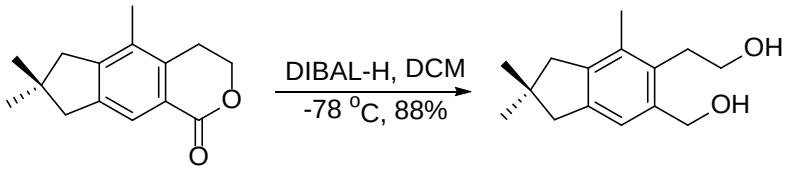
IR (thin film): 2964, 2924, 1722, 1610, 1467, 1446, 1396, 1332, 1285, 1264, 1185, 1156, 1085, 1035, 936, 795 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 7.78 (s, 1H), 4.49 (t, *J* = 6.0 Hz, 2H), 2.94 (t, *J* = 6.0 Hz, 2H), 2.76 (s, 2H), 2.71 (s, 2H), 2.18 (s, 3H), 1.15 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 149.5, 142.6, 136.3, 130.9, 124.3, 123.6, 66.9, 47.6, 47.3, 39.8, 29.0, 25.2, 15.4;

HRMS (ESI): m/z calcd for $C_{15}H_{18}NaO_2$ $[M+Na]^+$ 253.1199 found 253.1200.

Procedure for the Preparation of Natural product Riparol (4)



Granulolactone (**1**) Riparol B (**4**)

To a solution of granulolactone (**1**) (24 mg, 0.104 mmol) in DCM (1 mL) was slowly added DIBAL-H (0.3 mL, 0.45 mmol, 1.5 M in toluene) at -78 °C. Then the reaction was

stirred for 1 h at this temperature, before it was slowly added to saturated Rochelle salt (10 mL) at 0 °C. After stirred for another 1 h, the layers were separated and the aqueous layer was extracted with DCM (10 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1 : 1, petroleum ether-EtOAc) to furnish natural product riparol **(4)** (21.4 mg, 88%) as a white solid.

Mp = 154.2 – 154.8 °C;

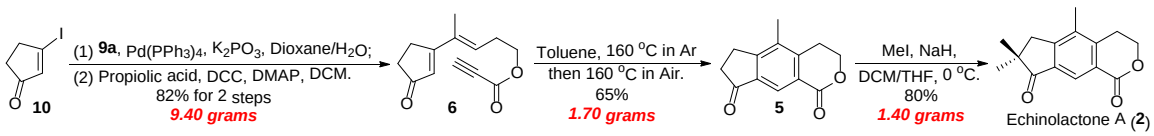
IR (thin film): 3225, 2961, 2926, 1460, 1429, 1384, 1368, 1261, 1023, 900, 866, 754 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 7.01 (s, 1H), 4.61 (s, 2H), 3.86 (t, *J* = 6.0 Hz, 2H), 3.02 (t, *J* = 6.0 Hz, 2H), 2.96 (b s, 2H), 2.72 (s, 2H), 2.67 (s, 2H), 2.20 (s, 3H), 1.15 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 141.7, 138.1, 133.4, 133.2, 124.2, 64.5, 61.8, 48.0, 47.4, 39.5, 31.8, 29.4, 16.2;

HRMS (ESI): m/z calcd for $C_{15}H_{23}O_2$ $[M+H]^+$ 235.1693 found 235.1695.

Gram-scale synthesis of echinolactone A (2)



To a solution of compound **10** (9.40 g, 45.20 mmol) and compound **9a** (19.2 g, 90.40 mmol) in dioxane (375 mL) and water (75 mL) was added $Pd(PPh_3)_4$ (2.60 g, 2.26 mmol) and K_3PO_4 (29.0 g, 135.6 mmol) in order at rt. Then the reaction was allowed to heat to

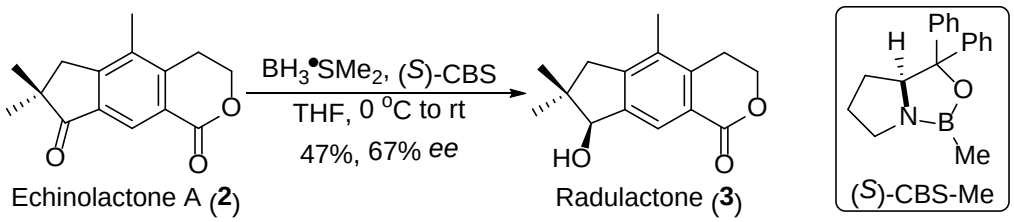
70 °C stirring for 4 h, before it was filtered through a pad of Celite and washed with EtOAc. The layers were diluted with H_2O (150 mL) and separated. Then the aqueous layer was extracted with EtOAc (8 × 200 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1 : 1 petroleum ether-EtOAc) to furnish crude compound **8** as a pale yellow solid. To a solution of the above crude compound **8** in dry DCM (85 mL) was added propiolic acid (4.70 mL, 5.35 g, 76.7 mmol) at 0 °C and the resulting mixture was stirred for 30 min at the same temperature. The mixture of DCC (21.0 g, 102.3 mmol) and DMAP (122 mg, 1.00 mmol) in DCM (85 mL) was added to the above solution at 0 °C. After stirring for another 4 h at 0 °C, it was filtered through a pad of Celite to remove the solid and washed with DCM. The organic layer were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (2 : 1 petroleum ether-EtOAc) to furnish compound **6** (8.0 g, 82% for two steps) as a white solid.

A solution of compound **6** (1.70 g, 7.79 mmol) in toluene (40 mL) was heated at 160 °C in a 150 mL sealed-tube for 15 h under argon atmosphere. Then the reaction was cooled to room temperature and toluene (20 mL) was added, before it was fully contacted with air. Adherence the mixture was heated to 160 °C again and stirred for another 15 h in this sealed-tube, before it was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1 : 1 petroleum ether-EtOAc) to furnish compound **5** (1.09 g, 65%) as a brown solid.

To a suspension of NaH (60% suspension in mineral oil, 5.18 g, 129.49 mmol) in dry THF (60 mL) was added the solution of compound **5** (1.4 g, 6.47 mmol) in dry DCM (20 mL) at 0 ^{o}C. Then the mixture was allowed to stir at room temperature for 20 min, followed re-coolling to 0 ^{o}C and by addition of excess MeI (4 mL, 9.2 g, 64.7 mmol) drop by drop. This mixture was then stirred for a further 4 h and diluted with dry THF (20 mL). Then the reaction mixture was droply added to the solution of HCl (150 mL, 1 M in H_2O) at 0 ^{o}C, followed by concentration under reduced pressure in order to remove THF. The aqueous layer was extracted with DCM (5 × 120 mL) and EtOAc (5 × 120 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (2 : 1 petroleum ether-EtOAc) to furnish natural product echinolactone A (**2**) (1.27 g, 80.3%) as a white solid.

Asymmetric synthesis of radulactone (3)

Method A (CBS reduction):

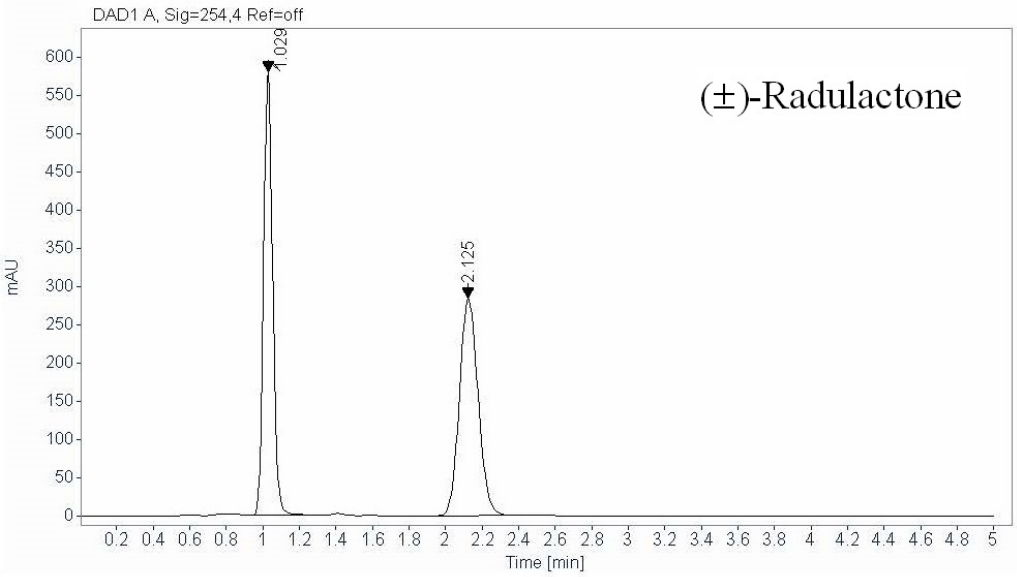


(+)-Radulactone (**3**) can be synthesized according to the known procedure.[4] To a solution of BH_3•SMe_2 (0.27 mL, 2 M in THF, 0.533 mmol) and (*S*)-CBS-Me (0.12 mL, 1 M in toluene, 0.123 mmol) in THF (4 mL) at 0 °C was added echinolactone A (**2**) (100 mg, 0.41 mmol) in THF (6 mL). The reaction mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with H_2O (10 mL) carefully, then diluted with EtOAc (30 mL), washed with 1 N HCl aqueous solution (15 mL), and extracted with EtOAc (5 × 30 mL). The combined organic layer was washed with brine (30 mL), dried over $NaSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (2 : 1 petroleum ether-EtOAc) to recycle echinolactone A (**2**) (9.45 mg, 9%) and furnish (+)-radulactone (**3**) (47.6 mg, 47% yield, 52% brsm, *ee* = 67%) as a colorless oil. $[\alpha]_D^{26}$ +17.5 (c 0.3, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis on Chiralpak IG-3 column (MTBE(0.1%DEA):EtOH=50:50, flow rate = 1 mL/min, λ = 254 nm), t_R = 1.03 min (*minor*), t_R = 2.11 min (*major*).

HPLC charts for Method A

HPLC Report

Sample Name	**RS**
Injection date:	8/19/2019 4:27:45 PM
Injection Volume	1.000
Acq. method:	Chiral.M
Column name:	CHIRALPAK IG-3 4.6*50mm 3um
Method Comment:	Mobile phase :MTBE(0.1%DEA):EtOH=50:50 Flow :1.0mL/min Temperature :25
Instrument:	1260



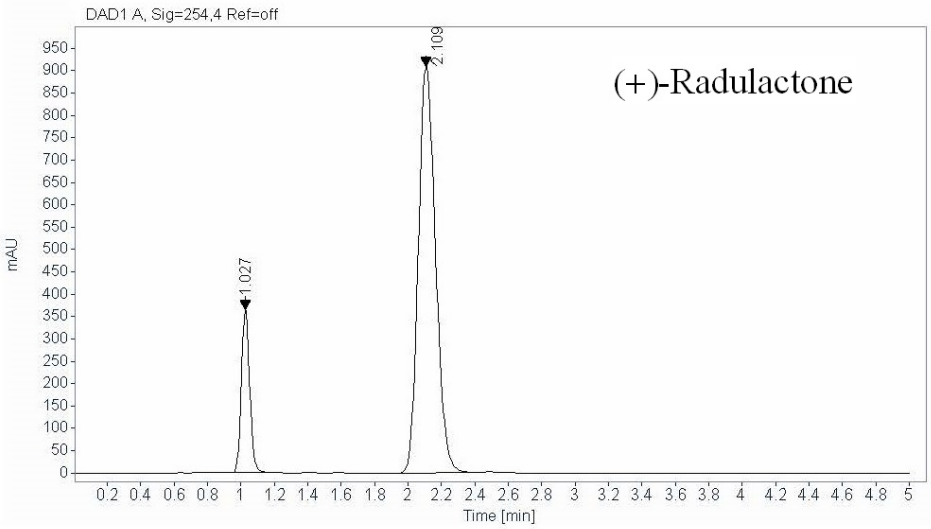
Signal: DAD1 A, Sig=254,4 Ref=off

RT [min]	Area	Height	Area%
1.03	2019.45	584.83	49.94
2.12	2024.12	284.73	50.06

HPLC charts for Method A

HPLC Report

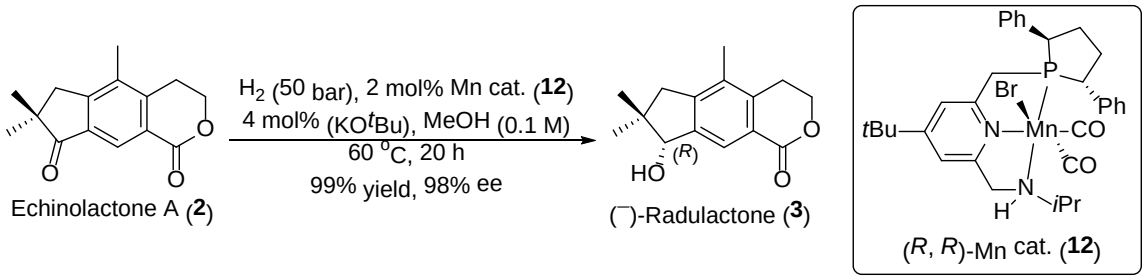
Sample Name	**D**
Injection date:	8/19/2019 4:21:58 PM
Injection Volume	1.000
Acq. method:	Chiral.M
Column name:	CHIRALPAK IG-3 4.6*50mm 3um
Method Comment:	Mobile phase :MTBE(0.1%DEA):EtOH=50:50 Flow :1.0mL/min Temperature :25
Instrument:	1260



Signal: DAD1 A, Sig=254,4 Ref=off

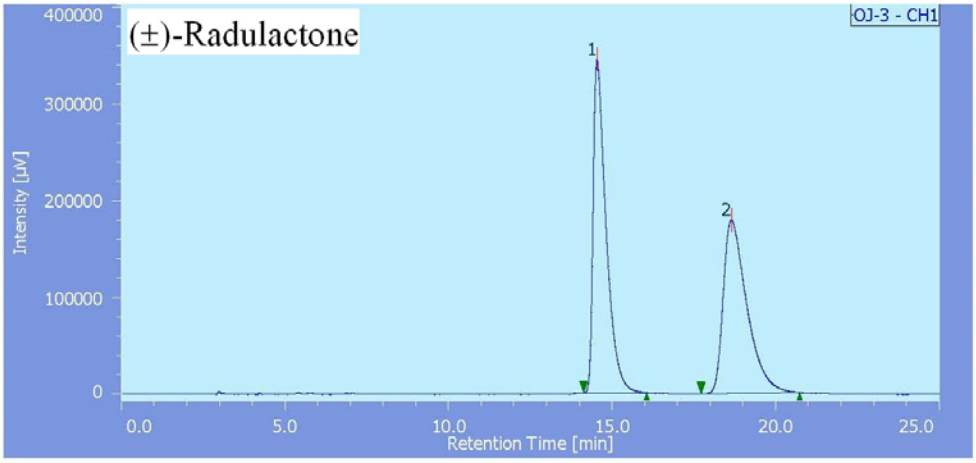
RT [min]	Area	Height	Area%
1.03	1275.47	369.90	16.36
2.11	6518.86	910.76	83.64

Method B (asymmetric hydrogenation):



According to the known reference,[5] in a glove box, a 125-mL Parr autoclave was charged with Mn complex (**12**, 2.6 mg, 0.004 mmol,), KO*t*Bu (0.9 mg, 0.008 mmol), MeOH (2 mL) and echinolactone A (**2**, 48.8 mg, 0.2 mmol). The reaction vessel was sealed and then purged three times with hydrogen gas. The pressure of H_2 in the autoclave was finally adjusted to 50 bar and the vessel was stirred at 60 ºC for 20 h. The residual H_2 was released carefully in a hood and the reaction mixture was concentrated and the residue was purified by column chromatography on silica gel to afford the pure chiral (-)-radulactone (**3**) as a white solid (49.0 mg, 99% yield, 98% ee). $[\alpha]_D^{25}$ -30 (c 0.5, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis on Chiralpak OJ-3 column (hexane : isopropanol = 85 : 15, flow rate = 1 mL/min, λ = 254 nm), t_R = 14.1 min (*major*), t_R = 18.4 min (*minor*).

HPLC charts for Method B



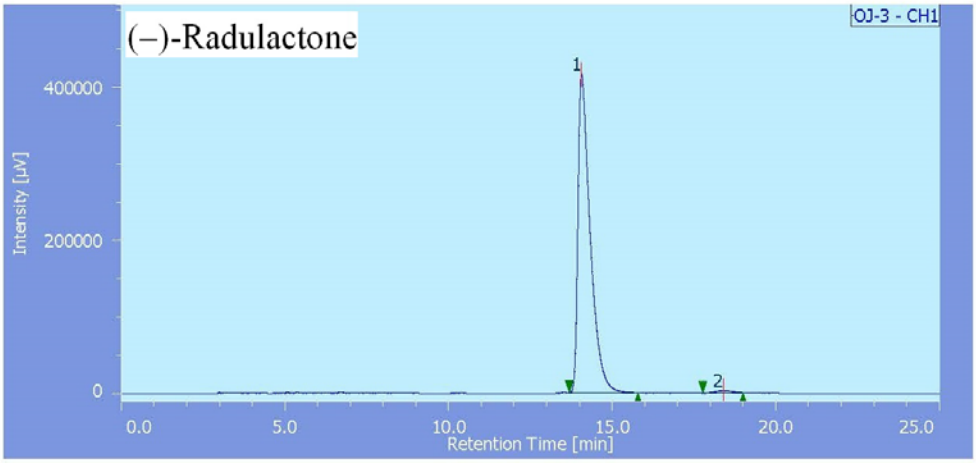
Chromatogram Information	
User Name	Administrator
Date Modified	2019/8/16 13:09:57
Description	
HPLC System Name	HPLC
Injection Date	2019/8/16 12:36:03
Volume	1.00 [μL]
Sample Number	1
Project Name	zhanglinli
Acquisition Time	59.0 [min]
Acquisition Sequence	zll805-16-105-rac-OJ-3-2
Control Method	85 15 1 ml min 254
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	OJ-3-CH1
Sample Name	
Channel Name	CH1
Sampling Interval	500 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	14.542	9455547	344465	51.230	65.775	N/A	7186	4.196	2.037	
2	Unknown	1	18.650	9001415	179239	48.770	34.225	N/A	3410	N/A	1.733	

HPLC charts for Method B



Chromatogram Information

User Name	Administrator
Date Modified	2019/8/15 17:07:37
Description	
HPLC System Name	HPLC
Injection Date	2019/8/15 16:38:47
Volume	1.00 [μL]
Sample Number	1
Project Name	zhanglinli
Acquisition Time	59.0 [min]
Acquisition Sequence	zll805-16-105
Control Method	85 15 1 ml min 254
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	OJ-3-CH1
Sample Name	
Channel Name	CH1
Sampling Interval	500 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	14.067	10787544	415725	99.005	99.320	N/A	7556	5.068	2.068	
2	Unknown	1	18.400	108393	2848	0.995	0.680	N/A	4755	N/A	0.998	

Table S1. Comparison of ^{1}H NMR data of natural granulolactone (1)[6] (400 MHz) with those of synthetic granulolactone (1) (600 MHz)

Position	Natural, 400 MHz, $CDCl_3$, δ_H (mult. *J* in Hz)	Synthetic, 600 MHz, $CDCl_3$, δ_H (mult. *J* in Hz)	$\Delta\delta^*$ (ppm)
1	2.72 (s)	2.71 (s)	0.01
2	--	--	--
3	--	--	--
4	4.48 (t, 6.13)	4.49 (t, 6.0)	-0.01
5	2.94 (t, 6.0)	2.94 (t, 6.0)	0.00
6	--	--	--
7	--	--	--
8	7.79 (s)	7.78 (s)	0.01
9	--	--	--
10	2.77 (s)	2.76 (s)	0.01
11	--	--	--
12	1.16 (s)	1.15 (s)	0.01
13	1.16 (s)	1.15 (s)	0.01
14	--	--	--
15	2.18 (s)	2.18 (s)	0.00

*The chemical shift of natural product minus the chemical shift of synthetic product.

Table S2. Comparison of ^{13}C NMR data of natural granulolactone (1)[6] (100 MHz) with those of synthetic granulolactone (1) (100 MHz)

Position	Natural, 100 MHz, $CDCl_3$, δ_C (ppm)	Synthetic, 100 MHz, $CDCl_3$, δ_C (ppm)	$\Delta\delta^*$ (ppm)
1	47.3	47.3	0.0
2	149.3	149.5	-0.2
3	130.7	130.9	-0.2
4	66.7	66.9	-0.2
5	25.2	25.2	0.0
6	136.2	136.3	-0.1
7	123.6	123.6	0.0
8	124.2	124.3	-0.1
9	142.5	142.6	-0.1
10	47.6	47.6	0.0
11	39.7	39.8	-0.1
12	28.9	29.0	-0.1
13	28.9	29.0	-0.1
14	166.2	166.4	-0.2
15	15.3	15.4	-0.1

*The chemical shift of natural product minus the chemical shift of synthetic product.

Table S3. Comparison of ^{1}H NMR data of natural echinolactone A (2)[7] (400 MHz) with those of synthetic echinolactone A (2) (600 MHz)

Position	Natural, 400 MHz, $CDCl_3$, δ_H (mult. *J* in Hz)	Synthetic, 600 MHz, $CDCl_3$, δ_H (mult. *J* in Hz)	$\Delta\delta^*$ (ppm)
1	2.96 (s)	2.96 (s)	0.00
2	--	--	--
3	--	--	--
4	--	--	--
5	3.08 (t, 5.9)	3.07 (t, 6.0)	0.01
6	4.52 (t, 5.9)	4.53 (t, 6.0)	-0.01
7	--	--	--
8	--	--	--
9	8.42 (s)	8.41 (s)	0.01
10	--	--	--
11	--	--	--
12	--	--	--
13	2.30 (s)	2.30 (s)	0.00
14	1.25 (s)	1.25 (s)	0.00
15	1.25 (s)	1.25 (s)	0.00

*The chemical shift of natural product minus the chemical shift of synthetic product.

Table S4. Comparison of ^{13}C NMR data of natural echinolactone A (2)[7] (100 MHz) with those of synthetic echinolactone A (2) (100 MHz)

Position	Natural, 100 MHz, $CDCl_3$, δ_C (ppm)	Synthetic, 100 MHz, $CDCl_3$, δ_C (ppm)	$\Delta\delta^*$ (ppm)
1	42.6	42.6	0.0
2	155.8	155.9	-0.1
3	133.1	133.2	-0.1
4	143.7	144.0	-0.3
5	25.3	25.9	-0.6
6	66.2	66.4	-0.2
7	165.0	165.0	0.0
8	125.5	125.5	0.0
9	125.1	125.0	0.1
10	134.2	134.4	-0.2
11	209.8	210.2	-0.4
12	45.2	45.7	-0.5
13	14.8	14.3	-0.5
14	25.1	25.4	-0.3
15	25.1	25.4	-0.3

*The chemical shift of natural product minus the chemical shift of synthetic product.

Table S5. Comparison of ^{1}H NMR data of natural (±)-radulactone (3)[8] (500 MHz) with those of synthetic (±)-radulactone (3) (600 MHz)

Position	Natural, 500 MHz, $CDCl_3$, δ_H (mult. *J* in Hz)	Synthetic, 600 MHz, $CDCl_3$, δ_H (mult. *J* in Hz)	$\Delta\delta^*$ (ppm)
1α	2.62 (d, 16.3)	2.63 (d, 16.2)	-0.01
1β	2.79 (d, 16.3)	2.80 (d, 16.2)	-0.01
2	--	--	--
3	--	--	--
4	4.48 (t, 5.9)	4.50 (t, 6.0)	-0.02
5	2.96 (d, 5.9)	2.97 (d, 6.0)	-0.01
6	--	--	--
7	--	--	--
8	7.99 (s)	8.01 (s)	-0.02
9	--	--	--
10	4.69 (s)	4.70 (s)	-0.01
11	--	--	--
12	2.18 (s)	2.20 (s)	-0.02
13	--	--	--
14	1.05 (s)	1.06 (s)	-0.01
15	1.17 (s)	1.18 (s)	-0.01

*The chemical shift of natural product minus the chemical shift of synthetic product.

Table S6. Comparison of ^{13}C NMR data of natural (±)-radulactone (3)[8] (100 MHz) with those of synthetic (±)-radulactone (3) (100 MHz)

Position	Natural, 125 MHz, $CDCl_3$, δ_C (ppm)	Synthetic, 100 MHz, $CDCl_3$, δ_C (ppm)	$\Delta\delta^*$ (ppm)
1	44.2	44.4	-0.2
2	147.4	147.6	-0.2
3	131.3	131.4	-0.1
4	66.6	66.8	-0.2
5	25.2	25.4	-0.2
6	138.2	138.3	-0.1
7	124.2	124.4	-0.2
8	124.2	124.4	-0.2
9	143.8	143.9	-0.1
10	83.0	83.2	-0.2
11	44.1	44.3	-0.2
12	14.9	15.1	-0.2
13	165.9	166.0	-0.1
14	21.5	21.6	-0.1
15	26.8	26.9	-0.1

*The chemical shift of natural product minus the chemical shift of synthetic product.

Table S7. Comparison of ^{1}H NMR data of natural riparol B (4)[9] (500 MHz) with those of synthetic riparol B (4) (600 MHz)

Position	Natural, 500 MHz, $CDCl_3$, δ_H (mult. *J* in Hz)	Synthetic, 600 MHz, $CDCl_3$, δ_H (mult. *J* in Hz)	$\Delta\delta^*$ (ppm)
1α	2.68 (s)	2.67 (s)	0.01
1β	2.68 (s)	2.67 (s)	0.01
2	--	--	--
3	--	--	--
4α	3.86 (t, 5.9)	3.86 (t, 6.0)	0.00
4β	3.86 (t, 5.9)	3.86 (t, 6.0)	0.00
5α	3.03 (t, 5.9)	3.02 (t, 6.0)	0.01
5β	3.03 (t, 5.9)	3.02 (t, 6.0)	0.01
6	--	--	--
7	--	--	--
8	7.01 (s)	7.01 (s)	0.00
9	--	--	--
10α	2.73 (s)	2.72 (s)	0.01
10β	2.73 (s)	2.72 (s)	0.01
11	--	--	--
12	1.16 (s)	1.15 (s)	0.01
13	1.16 (s)	1.15 (s)	0.01
14	4.62 (s)	4.61 (s)	0.01
15	2.21 (s)	2.20 (s)	0.01

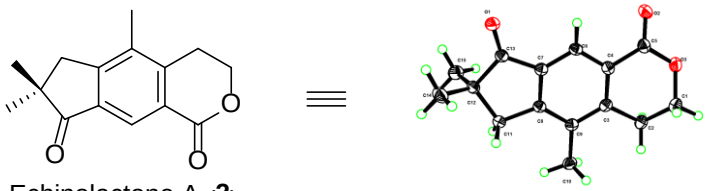
*The chemical shift of natural product minus the chemical shift of synthetic product.

Table S8. Comparison of ^{13}C NMR data of natural riparol B (4)[9] (125 MHz) with those of synthetic riparol B (4) (100 MHz)

Position	Natural, 125 MHz, $CDCl_3$, δ_C (ppm)	Synthetic, 100 MHz, $CDCl_3$, δ_C (ppm)	$\Delta\delta^*$ (ppm)
1	47.3	47.4	-0.1
2	143.4	143.6	-0.2
3	133.1	133.2	-0.1
4	61.7	61.8	-0.1
5	31.6	31.8	-0.2
6	133.3	133.4	-0.1
7	137.9	138.1	-0.2
8	124.0	124.2	-0.2
9	141.6	141.7	-0.1
10	47.8	48.0	-0.2
11	39.3	39.5	-0.2
12	29.2	29.4	-0.2
13	29.2	29.4	-0.2
14	64.3	64.5	-0.2
15	16.0	16.2	-0.2

*The chemical shift of natural product minus the chemical shift of synthetic product.

X-Ray Crystallographic Data for echinolactone A (2)



Echinolactone A (**2**)

Table S9. Crystal data and structure refinement for echinolactone A (CCDC 1940530).

Identification code	0613ZBDX1_0m
Empirical formula	$C_{15}H_{16}O_3$
Formula weight	244.28
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	8.9313(4)
b/Å	11.1597(5)
c/Å	12.1608(6)
α/°	90
β/°	97.7090(10)
γ/°	90
Volume/Å^3	1201.12(10)
Z	4
ρ_{calc}g/cm^3	1.351
μ/mm^{-1}	0.756
F(000)	520.0
Crystal size/mm^3	0.19 × 0.15 × 0.12

Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/ ^{o}	9.994 to 149.322
Index ranges	$-11 \leq h \leq 10$, $-13 \leq k \leq 13$, $-15 \leq l \leq 15$
Reflections collected	14173
Independent reflections	2427 [R_{int} = 0.0496, R_{sigma} = 0.0315]
Data/restraints/parameters	2427/0/166
Goodness-of-fit on F^2	1.108
Final R indexes [I>=2σ (I)]	R_1 = 0.0435, wR_2 = 0.1249
Final R indexes [all data]	R_1 = 0.0445, wR_2 = 0.1260
Largest diff. peak/hole / e $Å^{-3}$	0.51/-0.42

Table S10. Bond Lengths for echinolactone A (CCDC 1940530).

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C13	1.2190(15)	C12	C11	1.5432(17)
O3	C1	1.4554(15)	C12	C15	1.5351(18)
O3	C5	1.3472(16)	C12	C14	1.5271(17)
O2	C5	1.2095(16)	C9	C8	1.3982(17)
C13	C12	1.5322(16)	C9	C3	1.4048(17)
C13	C7	1.4762(17)	C9	C10	1.5085(16)
C4	C6	1.3880(18)	C8	C7	1.3947(16)
C4	C3	1.4098(17)	C8	C11	1.5125(17)
C4	C5	1.4913(17)	C3	C2	1.5067(17)
C6	C7	1.3873(17)	C1	C2	1.5096(18)

Table S11. Bond Angles for echinolactone A (CCDC 1940530).

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C5	O3	C1	117.00(10)	C3	C9	C10	121.32(11)
O1	C13	C12	125.31(11)	C9	C8	C11	128.17(11)
O1	C13	C7	126.61(11)	C7	C8	C9	120.94(11)
C7	C13	C12	108.07(10)	C7	C8	C11	110.87(11)
C6	C4	C3	121.16(11)	C4	C3	C2	117.22(11)
C6	C4	C5	117.77(11)	C9	C3	C4	120.73(11)
C3	C4	C5	120.98(11)	C9	C3	C2	122.05(11)
C7	C6	C4	117.80(11)	C6	C7	C13	128.50(11)
C13	C12	C11	104.42(10)	C6	C7	C8	121.86(11)
C13	C12	C15	107.07(10)	C8	C7	C13	109.64(10)
C15	C12	C11	110.37(10)	O3	C1	C2	111.74(10)
C14	C12	C13	110.48(10)	C8	C11	C12	105.32(9)
C14	C12	C11	114.34(10)	O3	C5	C4	118.11(11)
C14	C12	C15	109.81(11)	O2	C5	O3	118.80(11)
C8	C9	C3	117.51(11)	O2	C5	C4	123.02(12)
C8	C9	C10	121.15(11)	C3	C2	C1	109.53(10)

References:

[1] (a) Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 210−223; (b) Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.; Fensterbank L.; Malacria, Max. *J. Am. Chem. Soc*. **2009**, *131*, 2993–3006.

[2] (a) Hesse, M. J.; Butts, C. P.; Willis, C. L.; Aggarwal. V. K. *Angew. Chem. Int. Ed.* **2012**, *124*, 12612 –12616; (b) Brown, C. A.; Aggarwal, V. K. *Chem. Eur. J.* **2015**, *21*, 13900−13903.

[3] Amans, D.; Bellosta, V.; Cossy, Janine. *Chem. Eur. J.* **2009**, *15*, 3457−3473.

[4] Zeng, Y.; Zhao, Y.; Zhang, Y. *Chem. Commun*. **2019**, *55*, 4250−4253.

[5] Zhang, L.; Tang, Y.; Han, Z.; Ding, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 4973−4977.

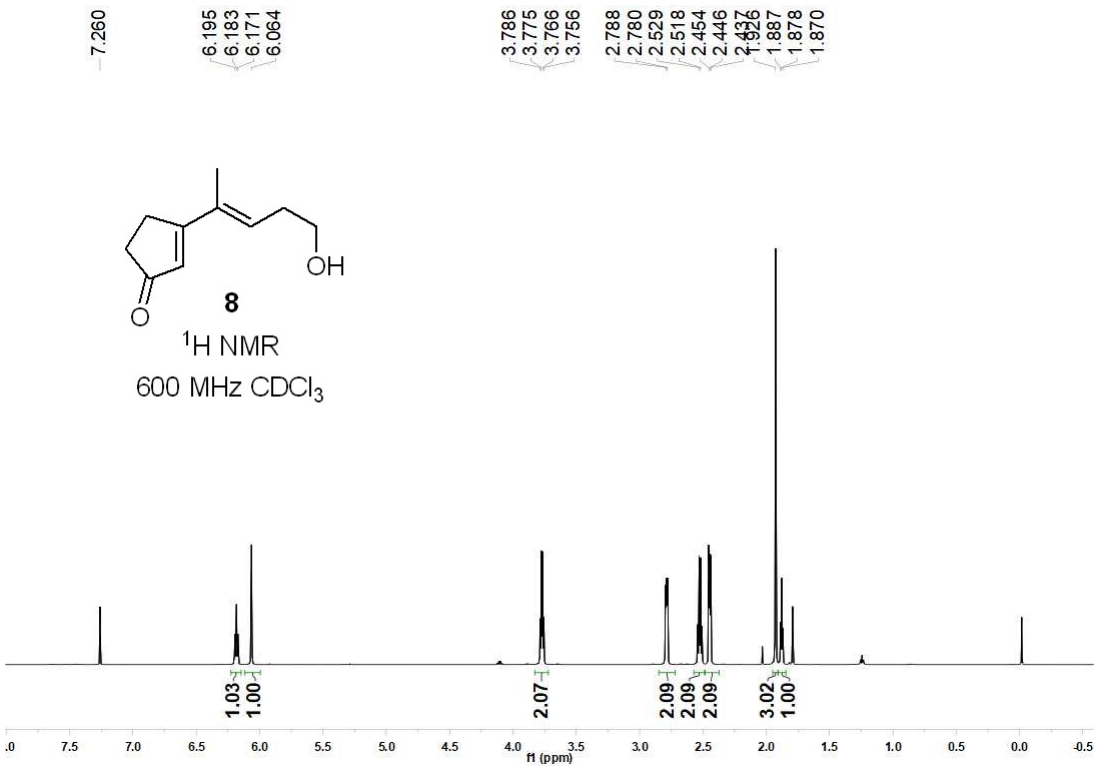
[6] Kokubun, T.; Scott-Brown, A.; Kite, G. C.; Simmonds, M. S. J. *J. Nat. Prod.* **2016**, *79*, 1698−1701.

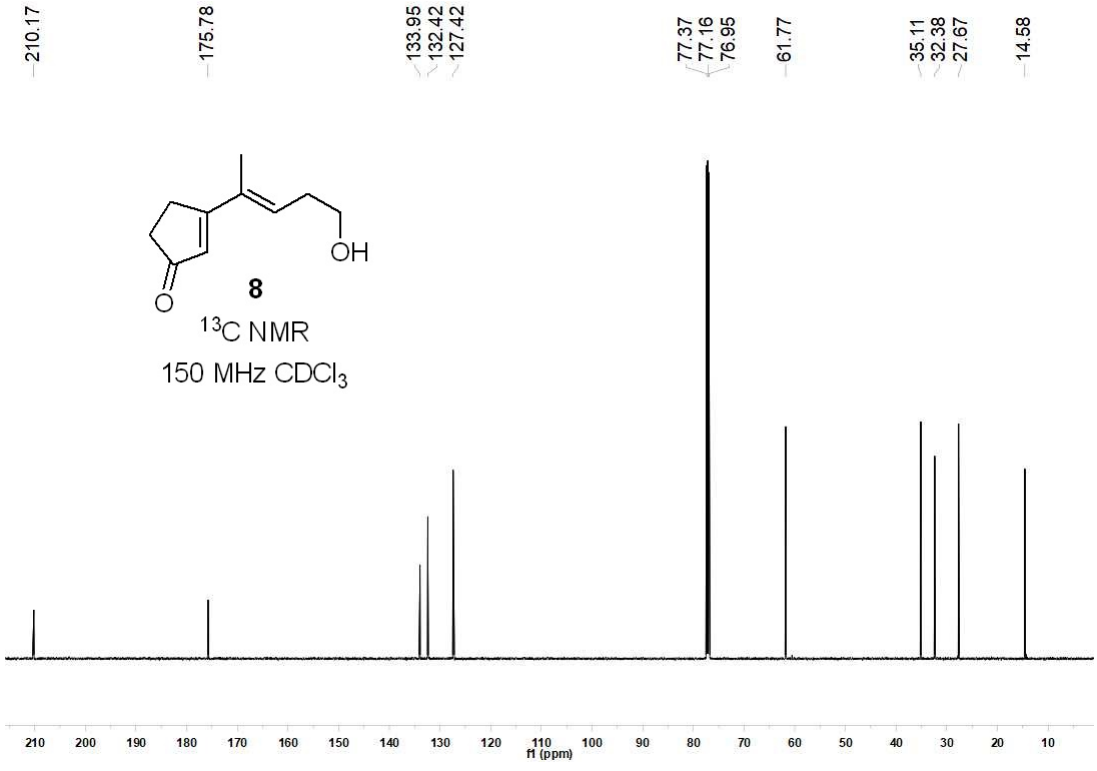
[7] Suzuki, S.; Murayama, T.; Shiono, Y. *Phytochemistry* **2005**, *66*, 2329−2333.

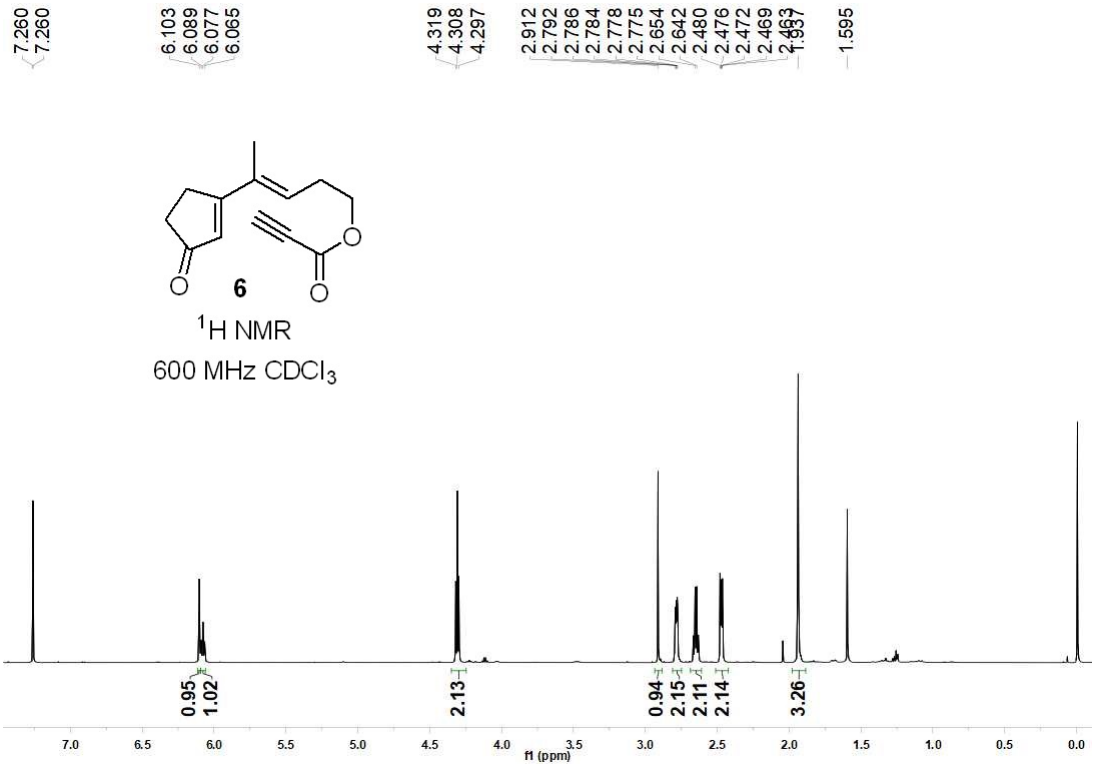
[8] Fabian, K.; Lorenzen, K.; Anke, T.; Johansson, M.; Sterner, O. *Z. Naturforsch.* **1998**, *53c*, 939−945.

[9] Weber, D.; Erosa, G.; Sterner, O.; Anke, T. *Z. Naturforsch., C: J. Biosci.* **2006**, *61*, 663−669.

Spectra for Compounds

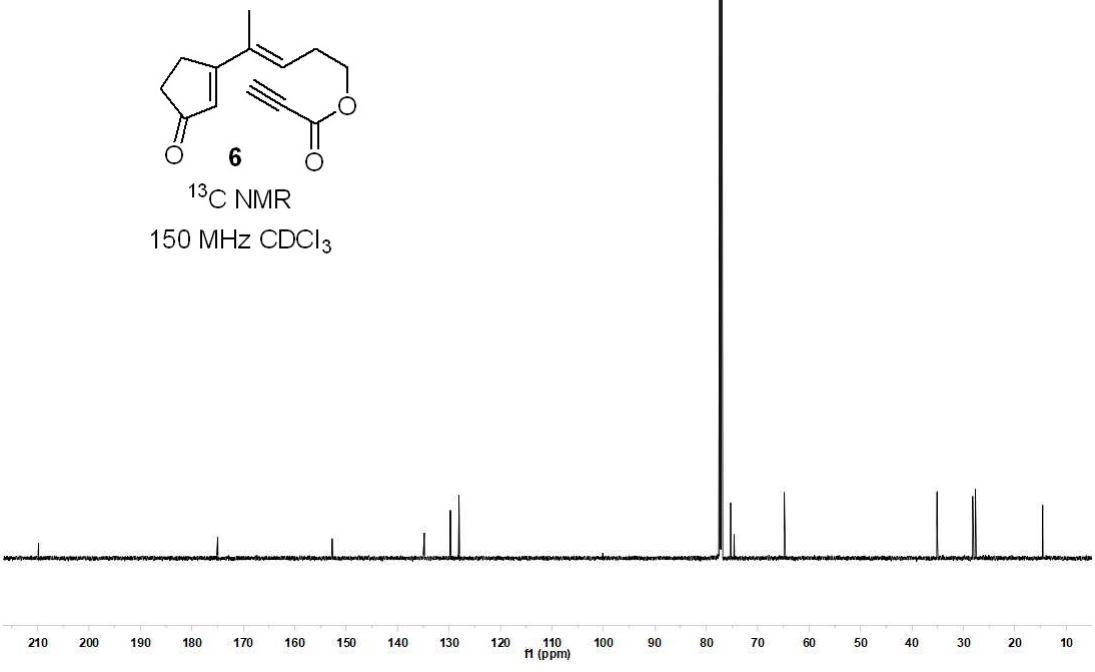






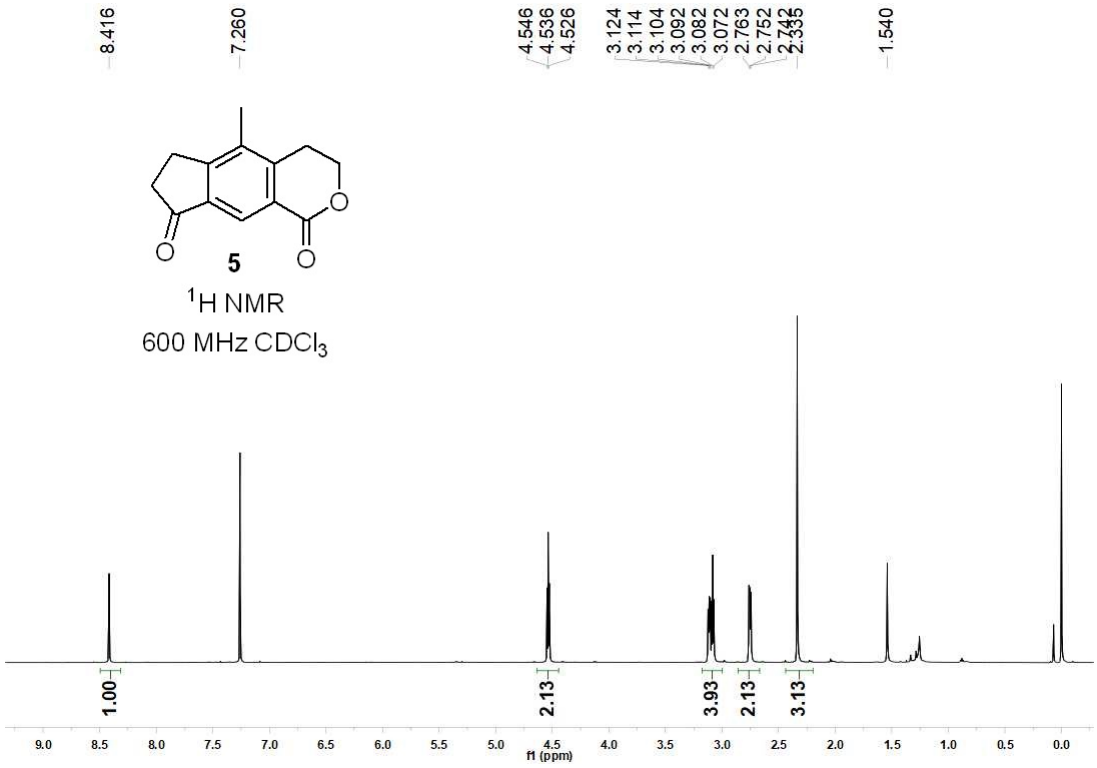
^{1}H NMR

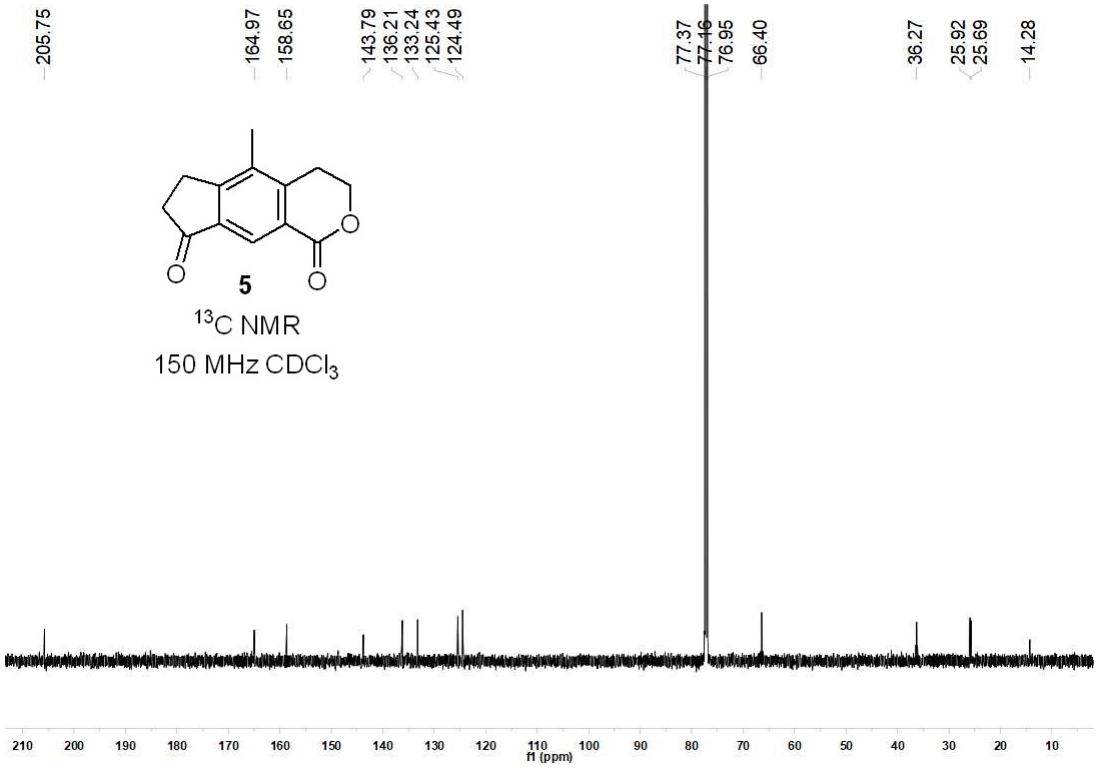
600 MHz $CDCl_3$

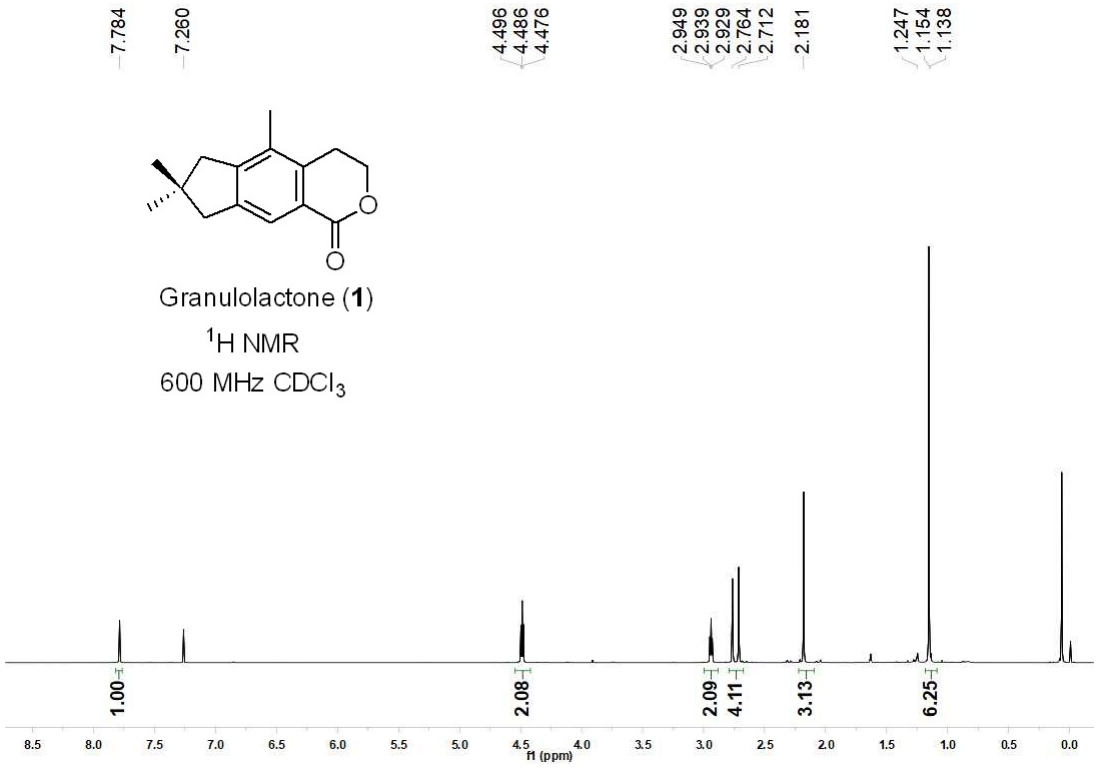


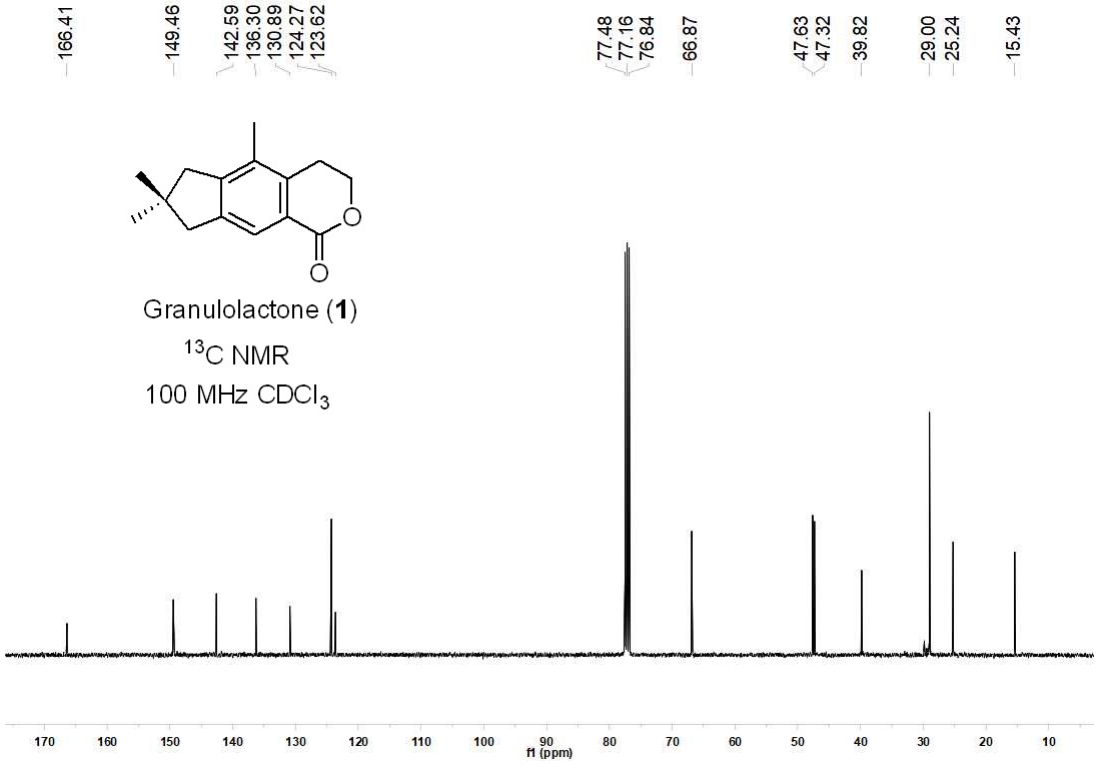
^{13}C NMR

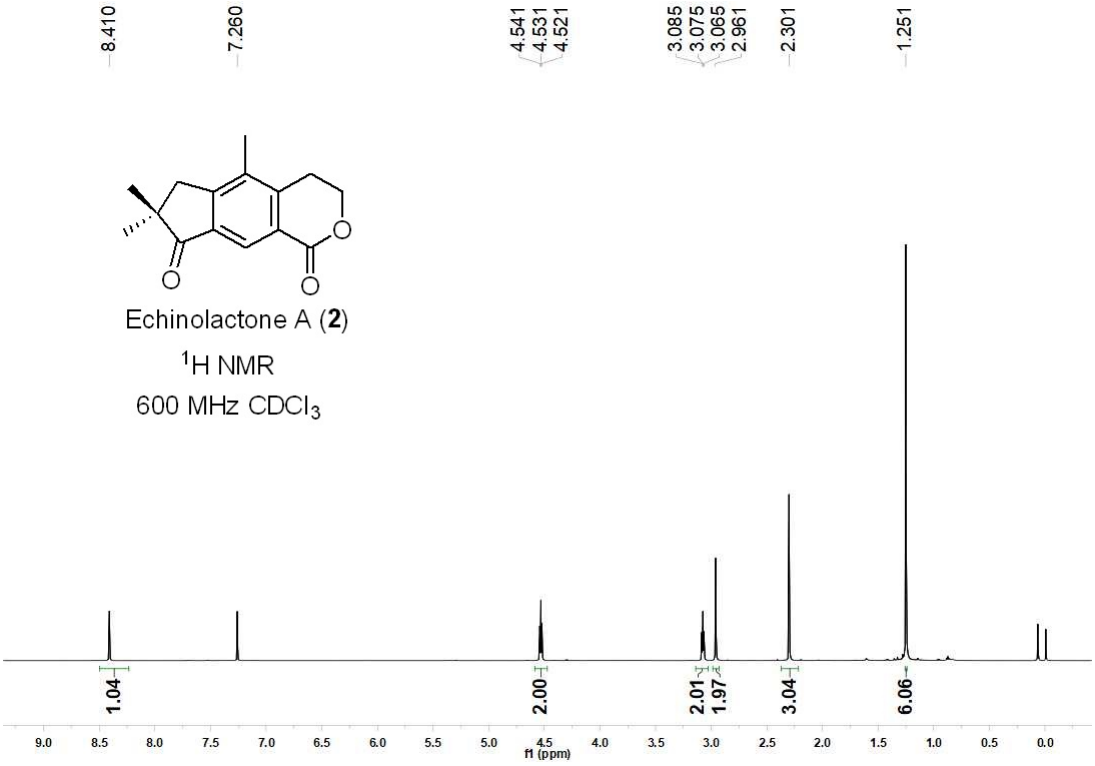
150 MHz $CDCl_3$

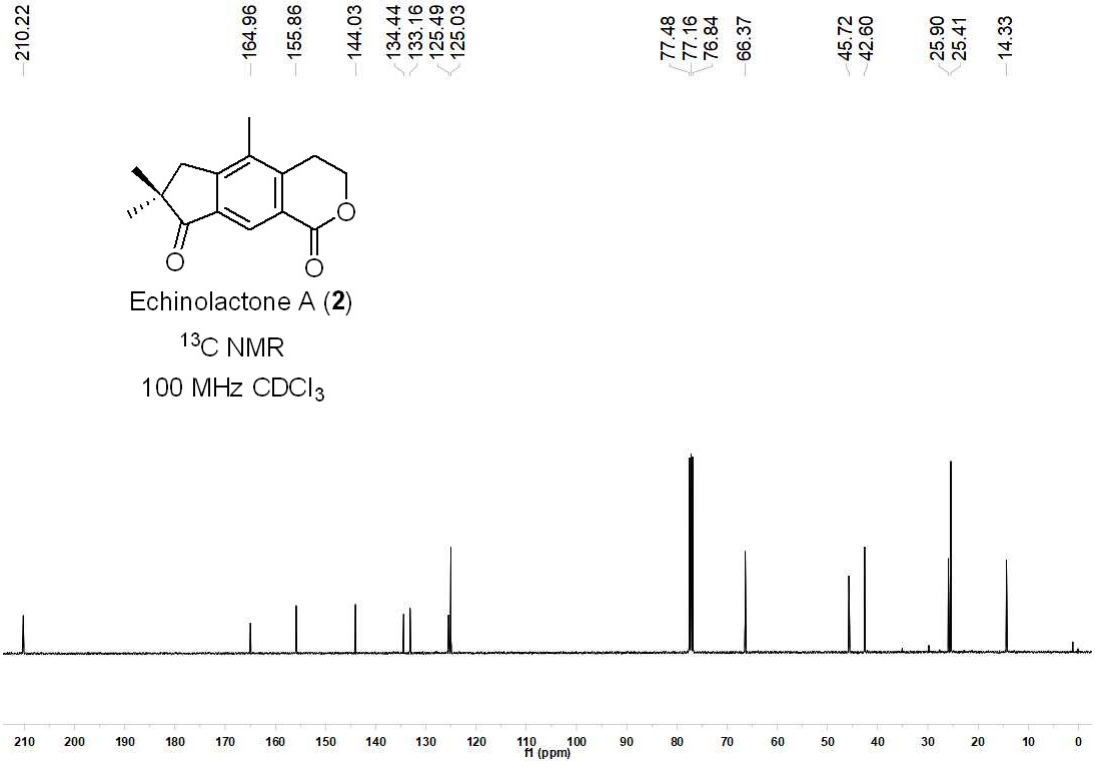

8.416
7.260
4.546
4.536
4.526
3.124
3.114
3.104
3.092
3.082
3.072
2.763
2.752
2.335
1.540
5
1H NMR
600 MHz CDCl3
1.00
2.13
3.93
2.13
3.13
f1 (ppm)

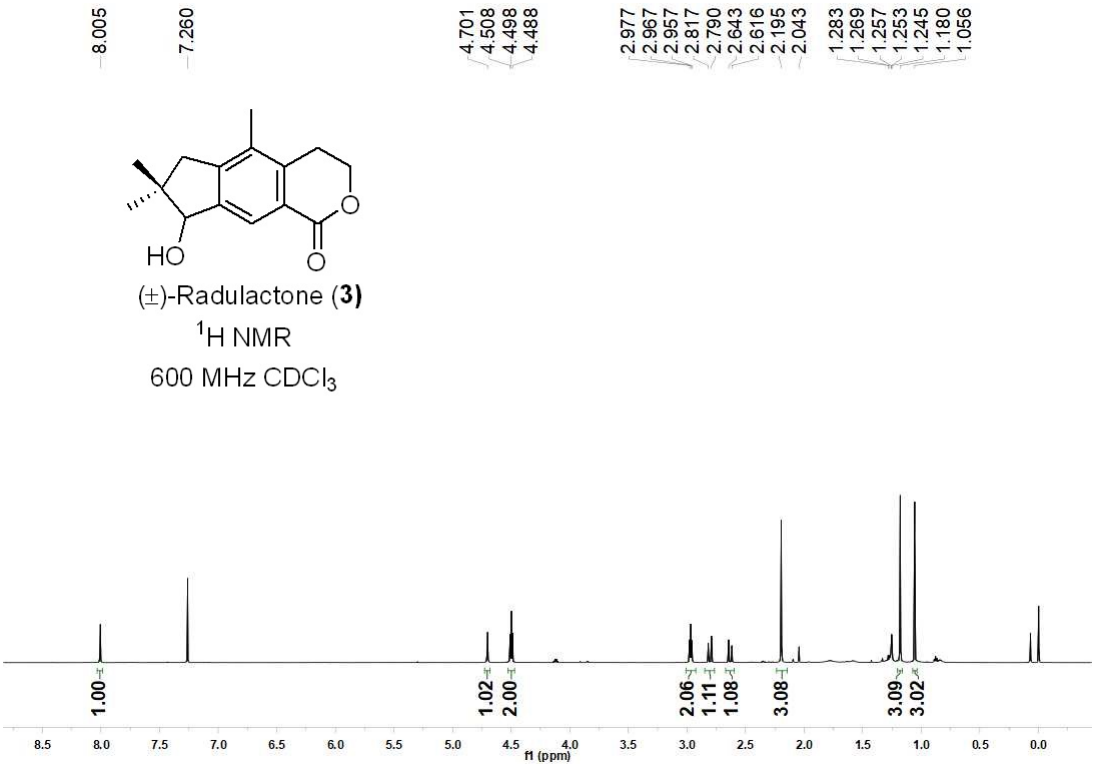

205.75
164.97
158.65
143.79
136.21
133.24
125.43
124.49
77.37
77.16
76.95
66.40
36.27
25.92
25.69
14.28
5
13C NMR
150 MHz CDCl3
f1 (ppm)

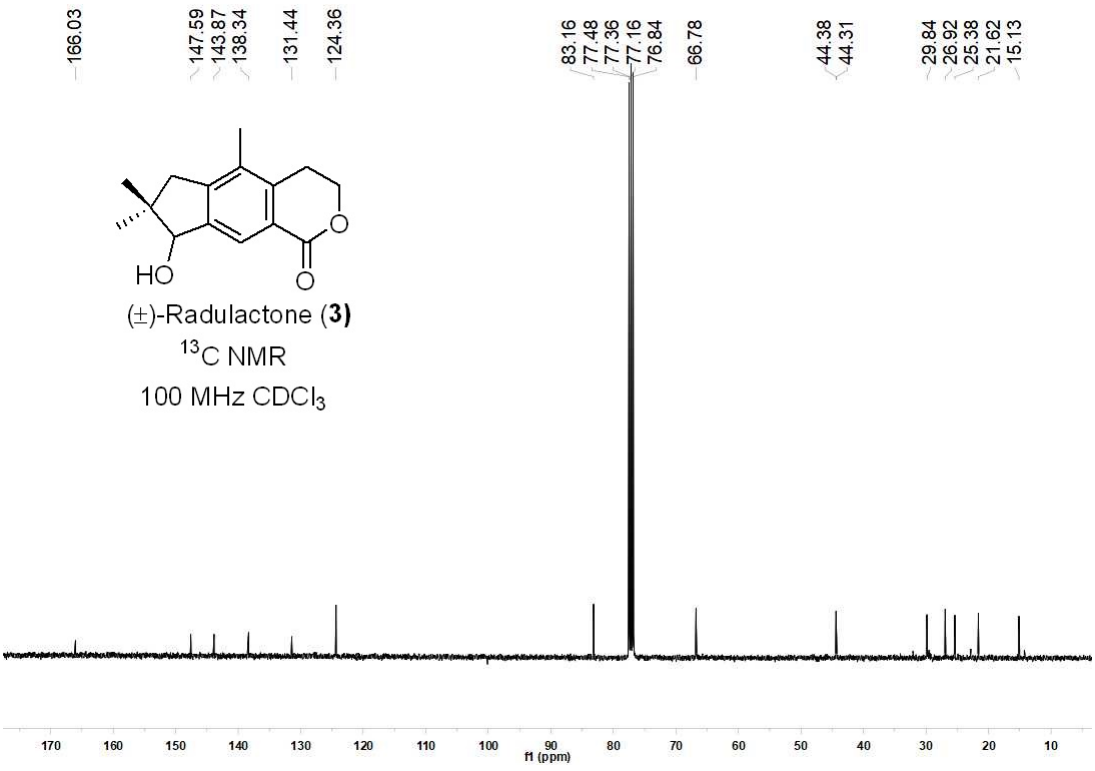

7.784
7.260
4.496
4.486
4.476
2.949
2.939
2.929
2.764
2.712
2.181
1.247
1.154
1.138
Granulolactone (1)
1H NMR
600 MHz CDCl3
1.00
2.08
2.09
4.11
3.13
6.25
f1 (ppm)

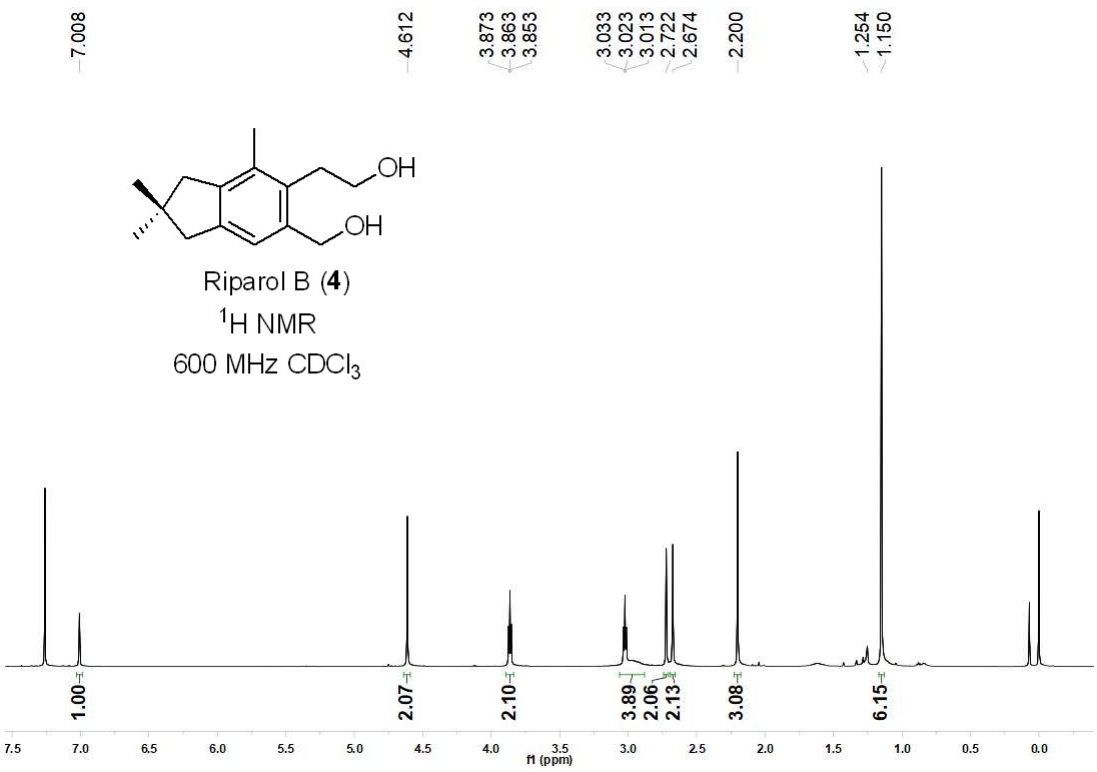

166.41
149.46
142.59
136.30
130.89
124.27
123.62
77.48
77.16
76.84
66.87
47.63
47.32
39.82
29.00
25.24
15.43
Granulolactone (1)
13C NMR
100 MHz CDCl3
f1 (ppm)

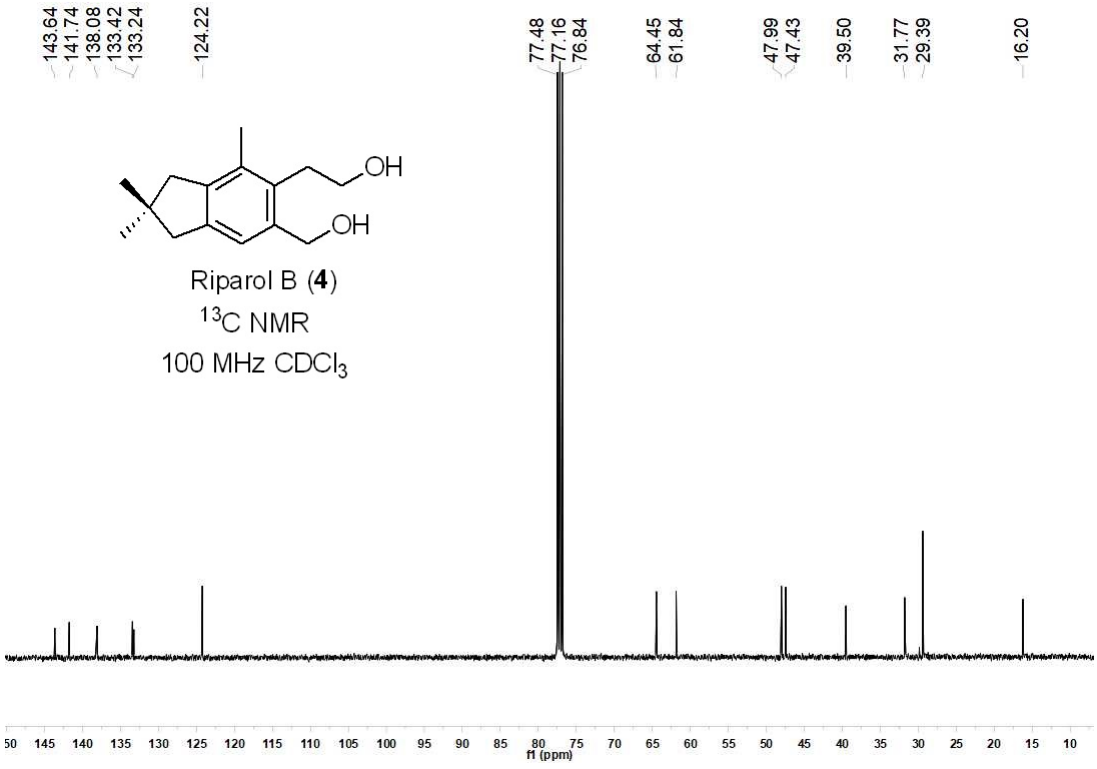

8.410
7.260
4.541
4.531
4.521
3.085
3.075
3.065
2.961
2.301
1.251
Echinolactone A (2)
1H NMR
600 MHz CDCl3
1.04
2.00
2.01
1.97
3.04
6.06
f1 (ppm)


210.22
164.96
155.86
144.03
134.44
133.16
125.49
125.03
77.48
77.16
76.84
66.37
45.72
42.60
25.90
25.41
14.33
Echinolactone A (2)
13C NMR
100 MHz CDCl3
f1 (ppm)


8.005
7.260
4.701
4.508
4.498
4.488
2.977
2.967
2.957
2.817
2.790
2.643
2.616
2.195
2.043
1.283
1.269
1.257
1.253
1.245
1.180
1.056
HO
O
O
(±)-Radulactone (3)
1H NMR
600 MHz CDCl3
1.00
1.02
2.00
2.06
1.11
1.08
3.08
3.09
3.02
f1 (ppm)


166.03
147.59
143.87
138.34
131.44
124.36
83.16
77.48
77.36
77.16
76.84
66.78
44.38
44.31
29.84
26.92
25.38
21.62
15.13
HO
O
O
(±)-Radulactone (3)
13C NMR
100 MHz CDCl3
f1 (ppm)


7.008
4.612
3.873
3.863
3.853
3.033
3.023
3.013
2.722
2.674
2.200
1.254
1.150
OH
OH
Riparol B (4)
1H NMR
600 MHz CDCl3
1.00
2.07
2.10
3.89
2.06
2.13
3.08
6.15
f1 (ppm)


143.64
141.74
138.08
133.42
133.24
124.22
77.48
77.16
76.84
64.45
61.84
47.99
47.43
39.50
31.77
29.39
16.20
OH
OH
Riparol B (4)
13C NMR
100 MHz CDCl3
f1 (ppm)