Supporting Information

Total Synthesis of Clovan-2,9-dione via [3 + 2 + 1] Cycloaddition and Hydroformylation/Aldol Reaction

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1. General Information

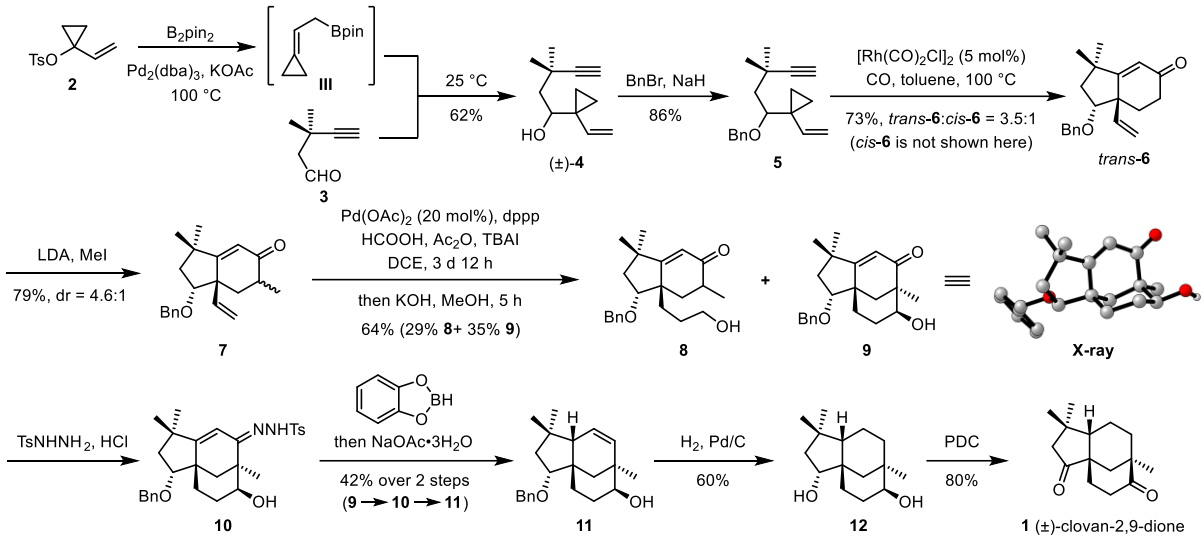
All chemicals were used as received without further purification. DCE (with molecular sieves, water ≤30 ppm) was purchased from J&K. Reactions were stirred using Teflon-coated magnetic stir bars. Elevated temperatures were maintained using Thermostat-controlled silicone oil baths. Analytical TLCs were performed with 0.25 mm silica gel HSGF254. The TLC plates were visualized by ultraviolet light and treatment with anisaldehyde-H_2SO_4 or phosphomolybdic acid stain followed by gentle heating. Purification of products was accomplished by flash chromatography on silica gel (240-370 mesh) and the purified compounds show a single spot by analytical TLC. Organic solutions were concentrated using a Büchi or Eyela rotary evaporator with a desktop vacuum pump. Nuclear magnetic resonance (NMR) spectra were measured on Bruker ARX 400 (^{1}H at 400 MHz; ^{13}C at 101 MHz), Bruker-600M Hz (^{1}H at 600 MHz; ^{13}C at 151 MHz) NMR spectrometers. Data for ^{1}H NMR spectra are reported as follows: chemical shift δ (ppm) referenced to either $CHCl_3$ (7.26 ppm) or $CHDCl_2$ (5.32 ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets), coupling constant J (Hz), and integration. Data for ^{13}C{^{1}H} NMR spectra are reported in terms of chemical shift δ (ppm) referenced to either $CDCl_3$ (77.16 ppm) or CD_2Cl_2 (53.84 ppm). High-resolution mass spectra (HRMS) were recorded on Bruker Solarix XR Fourier transform ion cyclotron resonance (FTICR) mass spectrometer (electrospray ionization, ESI) and Hybrid Quadrupole-Orbitrap GC-MS/MS System (Q Exactive GC). Single crystal X-ray diffractometer was measured on XtaLAB PRO 007HF(Mo). The enantiomeric excess (ee) of the products were determined by chiral HPLC analysis using UltiMate 3000 Pump. Optical rotations were measured on PerkinElmer model 341LC Polarimeter at 20 °C with visible light (λ = 589 nm) and 100 mm length cuvette.

Abbreviations:

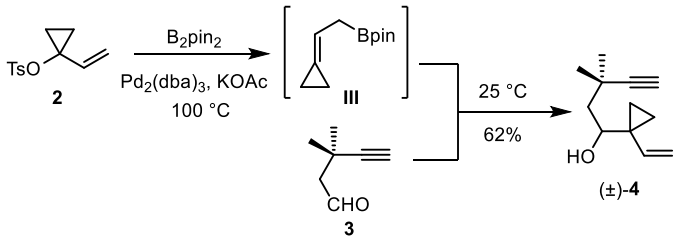
BnBr = benzyl bromide
CBS = Corey-Bakshi-Shibata reagent
dba = dibenzylideneacetone
dppp = 1,3-Bis(diphenylphosphino)propane
DCE = dichloroethane
DMF = *N*,*N*-dimethylformamide
DMSO = dimethyl sulfoxide
DCM = dichloromethane
EA = ethyl acetate
ee = enantiomeric excess
HMPA = hexamethylphosphoramide
^{i}PrOH = isopropanol
LDA = lithium diisopropylamide
*n*BuLi = *n*-butyllithium
PDC = pyridinium dichromate
PE = petroleum ether
TBAI = tetra-*n*-butylammonium iodide
$TsNHNH_2$ = 4-methylbenzenesulfonohydrazide
THF = tetrahydrofuran

2. Total Synthesis of Clovan-2,9-dione

Scheme S1. Total Synthesis of Clovan-2,9-dione.



Detailed synthesis procedures:



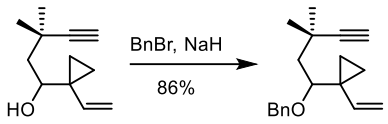
Preparation of (±)-4: Substrate **2**[1] (7.15 g, 30 mmol), B_2pin_2 (15.23 g, 60 mmol), $Pd_2(dba)_3$ (686.8 mg, 0.75 mmol) and KOAc (5.89 g, 60 mmol) were added in a 200 mL reaction flask, DMSO (90 mL) was added under Ar atmosphere. After stirring at 100 °C in an oil bath for 5 hours, the reaction mixture was cooled down by a 25 °C oil bath. Substrate **3**[2] (991.4 mg, 9 mmol) was added, then the reaction mixture was stirred in the 25 °C oil bath for 13 h. When TLC indicated the absence of substrate **3**, the reaction system was quenched by water at room temperature and extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation. Purification of the crude product by flash column chromatography (silica gel, PE/EA = 30:1) afforded the title compound (±)-**4** as a colorless oil. Run 1: (±)-**4** (1013.4 mg, 63%); Run 2: (±)-**4** (955.2 mg, 60%). The average yield of two runs was 62%.

TLC (10:1 PE/EA, R_f): 0.4.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (dd, J = 17.2, 10.7 Hz, 1H), 5.03 – 4.92 (m, 2H), 3.38 (dd, J = 9.0, 2.0 Hz, 1H), 2.20 (s, 1H), 1.76 – 1.68 (m, 2H), 1.29 (s, 3H), 1.26 (s, 3H), 1.22 (brs, 1H), 0.81 – 0.72 (m, 1H), 0.71 – 0.64 (m, 2H), 0.62 – 0.57 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.6, 113.4, 92.0, 75.2, 69.5, 48.2, 30.4, 29.9, 29.3, 29.0, 13.6, 10.7.

HRMS (ESI−FTICR, *m/z*): $[M + H]^+$ calculated for $C_{12}H_{19}O^+$:179.1430; found: 179.1432.



(±)-**4** **5**

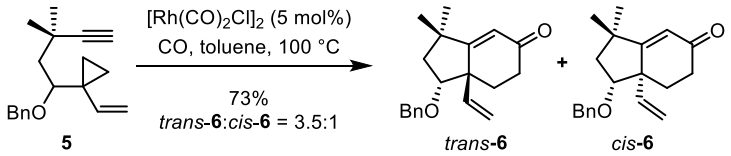
Preparation of 5: To a solution of substrate (±)-**4** (890.7 mg, 5.0 mmol) in DMF (20 mL) was added TBAI (369.4 mg, 1.0 mmol) and NaH (800.0 mg, 60% weight in mineral oil, 15.0 mmol) at 0 °C. After stirred for 20 min, BnBr (2.57 g, 15 mmol) was added under an argon atmosphere. The reaction mixture was then stirred for 13 h in a 25°C oil bath. The reaction was quenched by saturated aqueous ammonium chloride solution and water, extracted with diethyl ether. The combined organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered, concentrated and purified by column chromatography (PE/EA =100:0 ~ 100:1) to give a mixture consisting of desired product **5** and ether Bn_2O. Ratio of the product to Bn_2O was determined by ^{1}H NMR analysis and they could not be separated by column chromatography,[3] but this ether could be removed after the [3 + 2 + 1] reaction by column chromatography. Run 1: mixture (1.4354 g, Ratio of the product to Bn_2O=1:0.375), the calculated mass of desired product **5** was 1.1246 g (84% yield) as a colorless oil; Run 2: mixture (1.5799 g, Ratio of the product to Bn_2O=1:0.485), the calculated mass of desired product **5** was 1.1622 g (87% yield) as a colorless oil. The average yield of two runs was 86%.

TLC (10:1 PE/EA, R_f): 0.9.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H), 6.14 (dd, J = 17.3, 10.7 Hz, 1H), 5.08 – 4.94 (m, 2H), 4.83 (d, J = 11.1 Hz, 1H), 4.42 (d, J = 11.1 Hz, 1H), 3.15 (dd, J = 6.1, 4.0 Hz, 1H), 2.10 (s, 1H), 1.83 (d, J = 2.1 Hz, 1H), 1.82 (s, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 0.97 – 0.85 (m, 2H), 0.66 (ddd, J = 9.1, 6.1, 4.5 Hz, 1H), 0.54 – 0.46 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 138.9, 128.4, 127.9, 127.4, 112.7, 92.4, 83.6, 70.9, 68.2, 47.5, 31.15, 31.13, 28.9, 25.7, 17.4, 9.4.

HRMS (ESI−FTICR, m/z): $[M + H]^+$ calculated for $C_{19}H_{25}O^+$: 269.1900; found: 269.1900.



5 *trans*-**6** *cis*-**6**

Preparation of 6: A solution (in 150 mL round bottomed flask) of the compound **5** (with unseparated Bn_2O but the real mass of substrate **5** is 228.1 mg, 0.85 mmol) and $[Rh(CO)_2Cl]_2$ (16.5 mg, 0.0425 mmol) in anhydrous toluene (17 mL) was bubbled by CO (0.2 atm) for 5 min. The reaction mixture was stirred at 100 °C under balloon pressure mixed gas of CO and N_2 (the ratio of two gases was 1/4 and 0.2 atm CO was estimated) for 1.5 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. Purification of the residue through column chromatography on silica gel (PE/EA 15:1) afforded the product **6** (*trans*-**6** and *cis*-**6**) as a yellow oil. The diastereoselectivity of *trans*-**6** and *cis*-**6** was determined by the crude ^{1}H NMR of reaction mixture as 3.5:1. The mixture was columned again on silica gel (PE/EA 10:1) but only the major isomer *trans*-**6** could be separated as the pure diastereomer for characterization. Run 1: **6** (177.1 mg, 70% combined yield); Run 2: **6** (188.6 mg, 75% combined yield). The average yield of two runs was 73%.

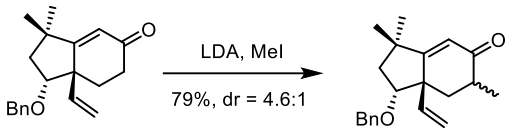
TLC (10:1 PE/EA, R_f): 0.30 (*trans*-**6**), 0.28 (*cis*-**6**).

trans-**6**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 – 7.27 (m, 5H), 6.04 (s, 1H), 5.70 (dd, J = 17.3, 10.4 Hz, 1H), 5.23 (d, J = 10.7 Hz, 1H), 5.06 (d, J = 17.4 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.41 (d, J = 12.0 Hz, 1H),

3.83 (d, *J* = 3.8 Hz, 1H), 2.61 (ddd, *J* = 13.4, 13.2, 4.9 Hz, 1H), 2.44 (ddd, *J* = 17.5, 13.9, 4.9 Hz, 1H), 2.31 (ddd, *J* = 17.5, 4.9, 2.1 Hz, 1H), 1.95 (d, *J* = 14.0 Hz, 1H), 1.80 (dd, *J* = 14.0, 3.9 Hz, 1H), 1.72 (ddd, *J* = 12.7, 5.0, 2.1 Hz, 1H), 1.29 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.5, 180.6, 138.7, 138.5, 128.5, 127.6, 127.3, 123.9, 117.7, 85.4, 70.8, 57.5, 42.4, 42.0, 33.0, 31.6, 30.0, 27.6.

HRMS (ESI−FTICR, *m*/*z*): $[M + H]^+$ calculated for $C_{20}H_{25}O_2^+$: 297.1849; found: 297.1847.



trans-**6** **7**

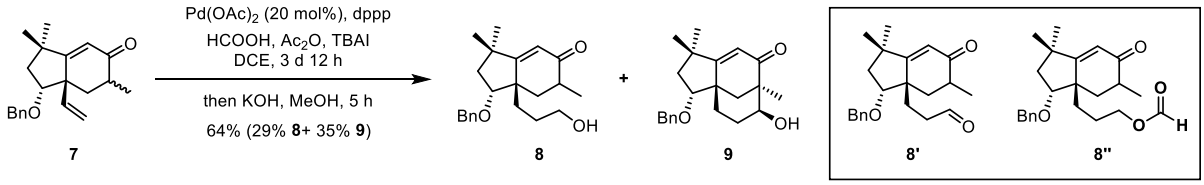
Preparation of 7: To a solution of diisopropylamine (0.90 mL, 6.4 mmol) in anhydrous THF (6 mL) at -78 °C under an argon atmosphere was added ^{n}BuLi (2.7 mL, 2.4 M in hexanes, 6.4 mmol) and the solution was stirred at 0 °C for 30 min. Then the freshly prepared LDA was cooled to -78 °C and a solution of *trans*-**6** (237.1 mg, 0.8 mmol) in anhydrous THF (8 mL) was added. After stirred for 1 h, HMPA (1.2 mL) was added and stirred for another 40 min at -78 °C. Then MeI (0.80 mL, 12.8 mmol) was added to the reaction mixture. The mixture was warmed up naturally and stirred in a 25 °C oil bath for 20 h. The reaction was quenched by saturated aqueous ammonium chloride solution and water, extracted with diethyl ether. The combined organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered, concentrated, and purified by column chromatography (PE/EA 20:1) to give the product **7** as a brown oil. The diastereoselectivity was determined by the crude ^{1}H NMR as 4.6:1. Run 1: **7** (191.4 mg, 77%); Run 2: 7 (199.2 mg, 80%). The average yield of two runs was 79%. The major single diastereomer **7-1** was separated to characterize.

TLC (10:1 PE/EA, R_f): 0.44 (**7-1***)*, 0.38 (**7-2**).

7-1: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 5H), 6.03 (s, 1H), 5.73 (dd, *J* = 17.4, 10.4 Hz, 1H), 5.21 (dd, *J* = 10.4, 1.0 Hz, 1H), 5.07 (dd, *J* = 17.4, 1.1 Hz, 1H), 4.63 (d, *J* = 12.1 Hz, 1H), 4.41 (d, *J* = 12.1 Hz, 1H), 3.80 (d, *J* = 3.8 Hz, 1H), 2.52 – 2.42 (m, 1H), 2.36 (apparent t, *J* = 12.9 Hz, 1H), 1.93 (d, *J* = 14.0 Hz, 1H), 1.82 – 1.72 (m, 2H), 1.28 (s, 3H), 1.21 (s, 3H), 1.13 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.8, 179.6, 139.2, 138.5, 128.5, 127.6, 127.4, 123.7, 117.4, 85.4, 70.8, 58.0, 42.3, 42.0, 36.5, 36.4, 31.8, 29.9, 15.8.

HRMS (ESI−FTICR, *m*/*z*): $[M + H]^+$ calculated for $C_{21}H_{27}O_2^+$: 311.2006; found: 311.2002.



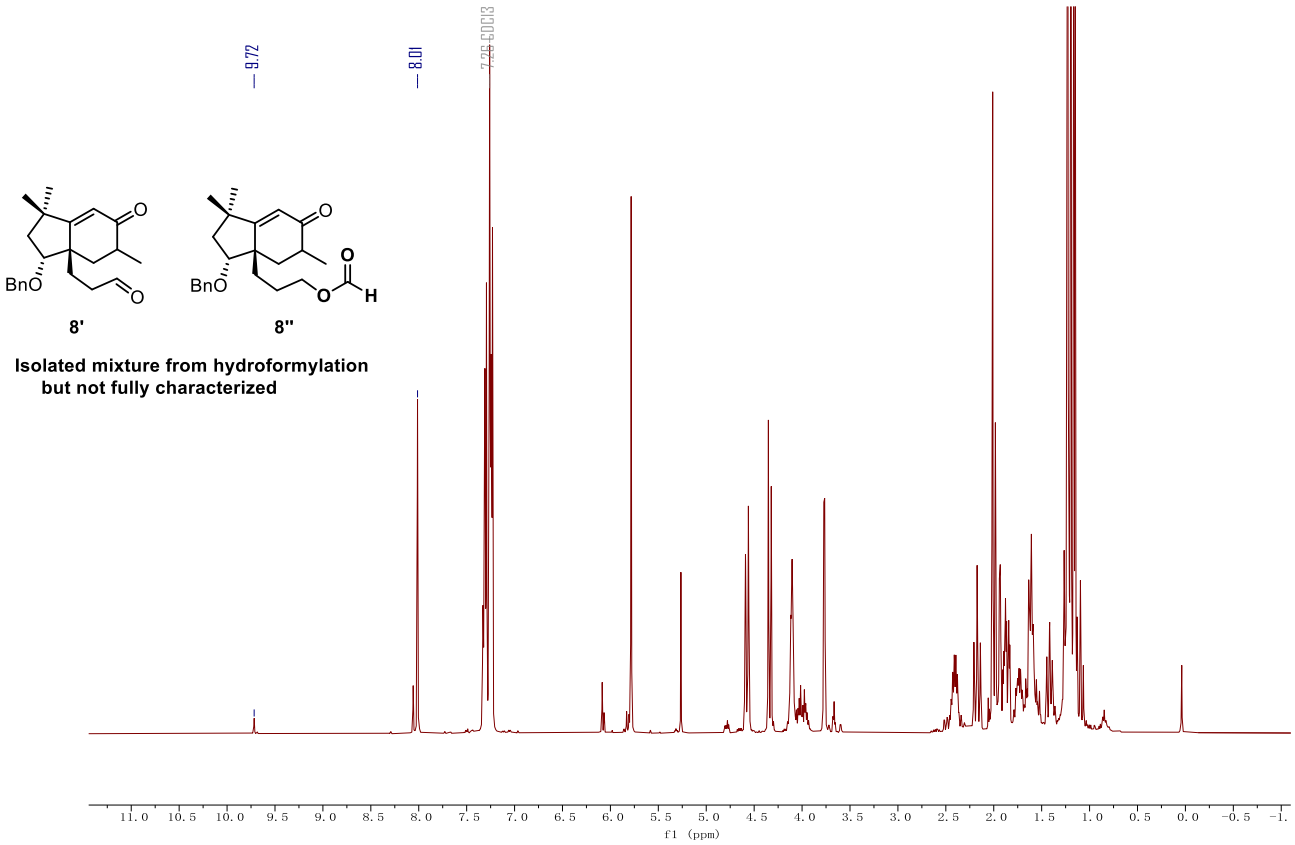
7 **8** **9** **8'** **8''**

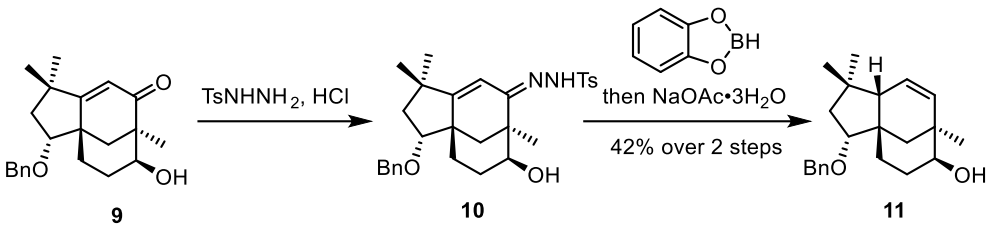
Preparation of 8, 9: To a mixture of $Pd(OAc)_2$ (11.2 mg, 0.025 mmol, 0.05 mmol), dppp (41.2 mg, 0.10 mmol), Bu_4NI (2.3 mg, 0.0063 mmol), 4 Å molecular sieves (20 mg), and 1,2-dichloroethane (DCE) (0.50 mL) in a Schlenk flask (5.0 mL) were added **7** (77.6 mg, 0.25 mmol) dissolved in DCE (0.50 mL) under argon atmosphere, Ac_2O (118.0 μL, 1.25 mmol), and HCOOH (61.3 μL, 1.63 mmol) successively via syringe. The Schlenk flask was tightly sealed. The reaction mixture was stirred at 80 °C for 3 d 12 h and cooled to room temperature, then filtered through silica gel by washing with EA and followed by removal of solvent. The crude product was added KOH (14.6 mg), MeOH (2 ml) and the yellow solution gradually turned brown

after stirring several minutes (pH test strip indicated the basic environment, if not, add more KOH to neutralize the residual acid). After stirring at room temperature for 5 hours, the reaction mixture was concentrated in vacuo, purified by flash chromatography (PE/EA = 5/1~3/1) to give single diastereomer **8** as a yellow oil and single diastereomer **9** as a yellow oil. Run 1: **8** (22.9 mg, 27% yield), **9** (31.4 mg, 37%); Run2: **8** (26.8 mg, 31% yield), **9** (27.0 mg, 32%). The average yield of two runs was 64% (29% **8**+ 35% **9**).
TLC (5:1 PE/EA, R_f): 0.08 (**8**), 0.16 (**9**).
The crystal compound **9** was obtained by adding *n*-hexane to their dichloromethane solutions and then stilling for several days below 8 °C (**9** melts at room temperature).
8: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 5H), 5.80 (s, 1H), 4.60 (d, *J* = 12.1 Hz, 1H), 4.37 (d, *J* = 12.1 Hz, 1H), 3.82 (d, *J* = 3.5 Hz, 1H), 3.62 (ddd, *J* = 5.9, 5.9, 4.2 Hz, 2H), 2.46 (ddd, *J* = 13.7, 6.8, 2.2 Hz, 1H), 2.19 (apparent t, *J* = 13.4 Hz, 1H), 1.99 (dd, *J* = 5.2, 2.5 Hz, 2H), 1.92 (dd, *J* = 13.3, 4.7 Hz, 1H), 1.68 – 1.59 (m, 3H), 1.57 – 1.43 (m, 2H), 1.26 (s, 3H), 1.22 (s, 3H), 1.18 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.4, 185.9, 138.6, 128.5, 127.6, 127.3, 121.0, 83.1, 70.7, 62.9, 52.8, 42.7, 41.5, 36.4, 33.8, 31.8, 31.4, 31.1, 28.9, 16.7.
HRMS (ESI−FTICR, *m*/*z*): $[M + H]^+$ calculated for $C_{22}H_{31}O_3^+$: 343.2268; found: 343.2271

9: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.38 – 7.19 (m, 5H), 6.04 (s, 1H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.36 (d, *J* = 11.9 Hz, 1H), 3.71 (d, *J* = 4.1 Hz, 1H), 3.33 (dd, *J* = 11.9, 5.3 Hz, 1H), 2.42 (dd, *J* = 12.9, 3.0 Hz, 1H), 2.06 (d, *J* = 14.4 Hz, 1H), 1.98 – 1.85 (m, 3H), 1.67 – 1.59 (m, 1H), 1.58 – 1.51 (m, 1H), 1.48 (d, *J* = 12.9 Hz, 1H), 1.37 – 1.30 (m, 1H), 1.30 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H).
^{13}C NMR (101 MHz, CD_2Cl_2) δ 203.1, 182.9, 139.1, 128.7, 127.8, 127.7, 124.3, 86.7, 75.5, 71.0, 51.6, 47.8, 42.8, 42.4, 41.7, 32.3, 31.2, 31.0, 29.2, 21.8.
HRMS (ESI−FTICR, *m*/*z*): $[M + H]^+$ calculated for $C_{22}H_{29}O_3^+$: 341.2111; found: 341.2109.

Note: The hydroformylation reaction gave a mixture of aldehyde **8'** (characteristic peak δ 9.72), formylate **8"** (characteristic peak δ 8.01), and **9** according to the ^{1}H NMR of the isolated mixture shown below. The formation of **8"** was proposed to be formed by the reduction of the in situ formed aldehyde **8'** and then esterification by $Pd(OAc)_2$/HCOOH.[4] We did not isolate both **8'** and **8"** for full characterization because we aimed to get the aldol products**.** Therefore, we added KOH after the hydroformylation reaction to convert **8'** to **9** and hydrolyze **8"** to **8**. It is interesting to note that, in the present reaction system, the aldol reaction of **8'** only gave **9**, while in the transformation of **8** to **9**, both **9** and **9'** were observed after stepwise oxidation and aldol reaction (see the experiment later). This suggested that the reaction conditions for these aldol reactions were different, affecting the reaction's stereochemistry.





Preparation of 11: To a solution of **9** (34.0 mg, 0.1 mmol) in MeOH (2 mL) was added $TsNHNH_2$ (55.9 mg, 0.3 mmol) and a drop of concentrated HCl (12.0 mol/L). The reaction mixture was refluxed at 67 °C for 24 h and then concentrated. Purification of the residue through column chromatography on silica gel (PE/EA=2.5:1) afforded the product **10** as a white solid. m.p.: 187.1-189.2 °C. **TLC** (5:1 PE/EA, R_f):0.16, which is the same as that of **9**.

To a solution of **10** in $CHCl_3$ (1 mL) was added catecholborane (17.7 mg, 0.147 mmol) at 0 °C under argon atmosphere. The reaction was stirred at room temperature for 3 hours and cooled to 0 °C. Sodium acetate trihydrate (36.3 mg, 0.442 mmol) was added and the reaction mixture was brought to a gentle reflux for 13 h. The reaction mixture was purified by flash chromatography (PE/EA = 6/1) to give compound **11** as a colorless oil. Run 1: **11** (13.0 mg, 40%); Run 2: **11** (13.9 mg, 43%). The average yield of two runs was 42% over 2 steps.

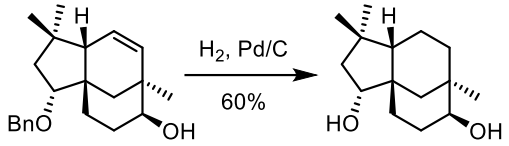
TLC (2:1 PE/EA, R_f): 0.32

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 5H), 6.04 (dd, J = 10.0, 2.1 Hz, 1H), 5.32 (ddd, J = 10.0, 3.6, 1.5 Hz, 1H), 4.52 (d, J = 12.4 Hz, 1H), 4.40 (d, J = 12.4 Hz, 1H), 3.37 (dd, J = 10.3, 5.1 Hz, 1H), 3.33 (d, J = 5.0 Hz, 1H), 2.85 (apparent t, J = 2.9 Hz, 1H), 2.04 – 1.90 (m, 2H), 1.89 – 1.81 (m, 1H), 1.77 (d, J = 14.8 Hz, 1H), 1.75 – 1.59 (m, 2H), 1.42 (dd, J = 12.3, 1.5 Hz, 2H), 1.34 – 1.26 (m, 1H), 1.17 (s, 3H), 1.13 (s, 3H),

1.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5, 130.1, 129.5, 128.4, 127.3, 127.2, 87.2, 78.5, 70.9, 54.1, 48.2, 46.1, 43.3, 41.0, 36.5, 34.1, 33.5, 30.3, 26.4, 24.8.

HRMS (ESI−FTICR, *m*/*z*): $[M + H]^+$ calculated for $C_{22}H_{31}O_2^+$: 327.2319; found: 327.2317.



11 **12**

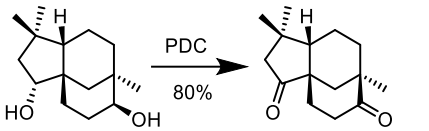
Preparation of 12: To a solution of **11** (10.5 mg, 0.032 mmol) in MeOH (2.1 mL) was added Pd/C (34.2 mg, 10% on dry basis, 0.032 mmol) and bubbled by H_2 (1.0 atm) for 10 min. The reaction mixture was stirred at 60 °C under balloon pressure gas of H_2 (1.0 atm) for 24 h. The mixture was filtered through silica gel by washing with EA and followed by removal of eluent. The crude product mixture was dissolved in MeOH (2.1 mL), and Pd/C (68.4 mg, 10% on dry basis, 0.064 mmol) was added. The reaction mixture was bubbled by H_2 (1.0 atm) for 10 min and stirred for 3 d at 60 °C and then filtered through silica gel by washing with EA, concentrated, and purified by column chromatography (PE/EA = 3:1) to give the product **12** as a colorless oil. Run 1: (4.6 mg, 60% yield); Run 2: (4.6 mg, 60%). The average yield of two runs was 60%.

TLC (2:1 PE/EA, R_f): 0.30

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.87 (dd, *J* = 9.7, 6.2 Hz, 1H), 3.25 (dd, *J* = 10.8, 5.3 Hz, 1H), 1.80 – 1.76 (m, 1H), 1.71 (dd, *J* = 12.3, 6.2 Hz, 1H), 1.61 – 1.53 (m, 5H), 1.37 (dd, *J* = 13.0, 3.2 Hz, 1H), 1.34 – 1.25 (m, 5H), 1.22 – 1.17 (m, 1H), 1.02 (s, 3H), 0.97 (s, 6H), 0.82 (d, *J* = 13.0 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 79.9, 78.1, 51.4, 47.0, 44.8, 38.0, 37.9, 35.3, 34.2, 32.4, 29.7, 29.4, 27.4, 25.9, 22.0.

HRMS (ESI−FTICR, *m*/*z*): $[M + NH_4]^+$ calculated for $C_{15}H_{30}NO_2^+$: 256.2271; found: 256.2269.



12 **1** (±)-clovan-2,9-dione

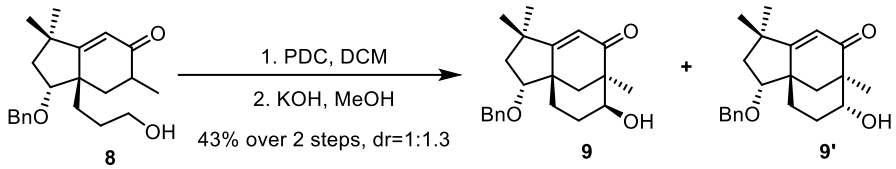
Preparation of clovan-2,9-dione: To a solution of **12** (4.0 mg, 0.0168 mmol) in DCM (1.0 mL) was added 4 Å MS (75.8 mg) and PDC (37.9 mg, 0.101 mmol). After stirred for 5 h at room temperature, the reaction mixture was filtered through silica-gel by washing with EA, concentrated and purified by column chromatography (PE/EA = 5:1) to give the product **1** as a light yellow oil. Run 1: (3.1mg, 79% yield); Run 2: (3.2 mg, 81% yield). The average yield of two runs was 80%.

TLC (2:1 PE/EA, R_f): 0.5

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 – 2.49 (m, 2H), 2.40 (d, *J* = 17.4 Hz, 1H), 2.23 (d, *J* = 17.4 Hz, 1H), 2.22 – 2.13 (m, 1H), 1.97 (dd, *J* = 6.9 Hz, 6.9 Hz, 1H), 1.80 – 1.72 (m, 2H), 1.70 – 1.61 (m, 4H), 1.48 (ddd, *J* = 14.5, 7.5 Hz, 7.5 Hz, 1H), 1.16 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 220.7, 214.6, 52.5, 50.1, 49.0, 44.1, 39.2, 37.2, 36.4, 35.3, 34.6, 30.8, 25.0, 24.9, 20.2.

HRMS (ESI−FTICR, *m*/*z*): $[M + H]^+$ calculated for $C_{15}H_{23}O_2^+$: 235.1693; found: 235.1686.



Transformation of alcohol 8 to **9** and **9'**: To a solution of **8** (22.9 mg, 0.067 mmol) in DCM (2.0 mL) was added 4 Å MS (226.4 mg) and PDC (75.5 mg, 0.2 mmol). After stirred for 5 h at room temperature, the reaction mixture was filtered through silica-gel by washing with EA and followed by removal of solvent. The crude product was dissolved in MeOH (1.0 mL), and then KOH (11.3 mg, 0.201 mmol) was added. The reaction mixture was stirred for 17 h at rt and then concentrated in vacuo. Purification of the residue through column chromatography on silica gel (PE/EA = 3:1) afforded the product **9** and **9'**, the diastereomer radio was determined by the crude ^{1}H NMR of reaction mixture as 1:1.3. The two diastereomers were further separated to characterize respectively. Run1: **9**+**9'** (9.7 mg, 43%); Run2: **9**+**9'** (9.5 mg, 42%). The average yield of two runs was 43%.

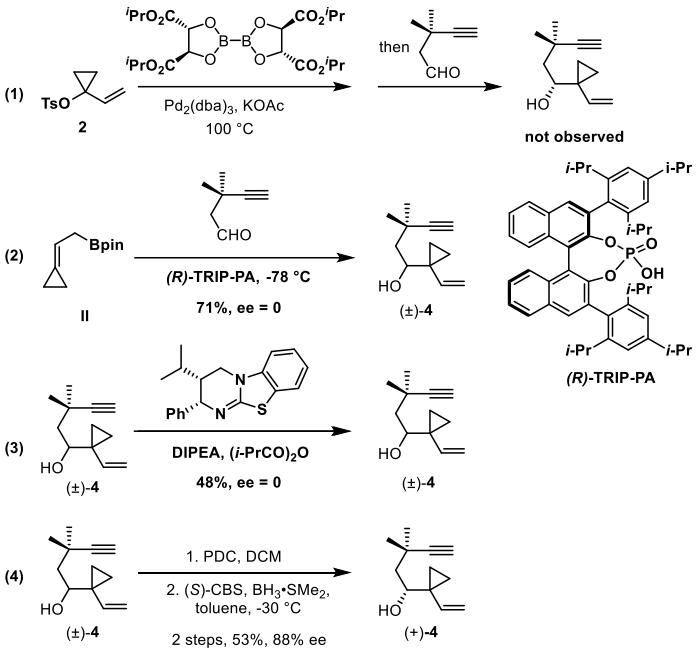
TLC (5:1 PE/EA, R_f): 0.16 (**9**), 0.18(**9'**).

9'. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 5H), 5.97 (s, 1H), 4.61 (d, J = 12.1 Hz, 1H), 4.41 (d, J = 12.1 Hz, 1H), 3.71 (d, J = 4.2 Hz, 1H), 3.59 (dd, J = 3.0 Hz, 1H), 2.14 (ddd, J = 12.7, 2.5, 1.2 Hz, 1H), 2.03 (d, J = 14.4 Hz, 1H), 1.96 (d, J = 12.7 Hz, 1H), 1.91 (dd, J = 14.4, 4.3 Hz, 1H), 1.87 – 1.80 (m, 1H), 1.77 – 1.71 (m, 2H), 1.30 (s, 3H), 1.25 – 1.24 (m, 1H), 1.23 – 1.22 (m, 1H), 1.17 (s, 3H), 1.14 (s, 3H).

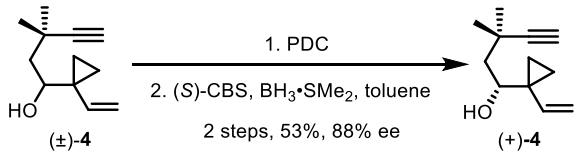
^{13}C NMR (151 MHz, $CDCl_3$) δ 203.7, 181.8, 138.7, 128.5, 127.6, 127.4, 122.6, 86.5, 70.8, 70.4, 51.6, 48.1, 42.8, 42.2, 35.5, 31.1, 30.9, 27.2, 25.1, 21.3.

HRMS (ESI−FTICR, m/z)**:** $[M + H]^+$ calculated for $C_{22}H_{29}O_3^+$: 341.2111; found: 341.2107.

3. Synthesis of Enantiomerically Enriched Substrate (+)-4



To achieve the asymmetric total synthesis of clovan-2,9-dione by using chiral substrate **4**, we tried several asymmetric conditions. The Roush allylation was tested firstly but afforded no desired product, possibly due to using a different organoboron agent (entry 1).[5] Then we tested the asymmetric allyboration using chiral phosphoric acids (*R*)-TRIP-PA,[6] the desired product **4** was obtained in 71% yield but gave poor enantioselectivity (entry 2). Then we examined the kinetic resolution of alcohol (±)-**4** using chiral isothiourea catalysts,[7] which unfortunately did not work either (entry 3). Finally, we performed oxidation of (±)-**4** using PDC, followed by (*S*)-CBS (Corey–Bakshi–Shibata) reduction, giving the enantiomerically enriched substrate (+)-**4** in 88% ee (entry 4).[8]

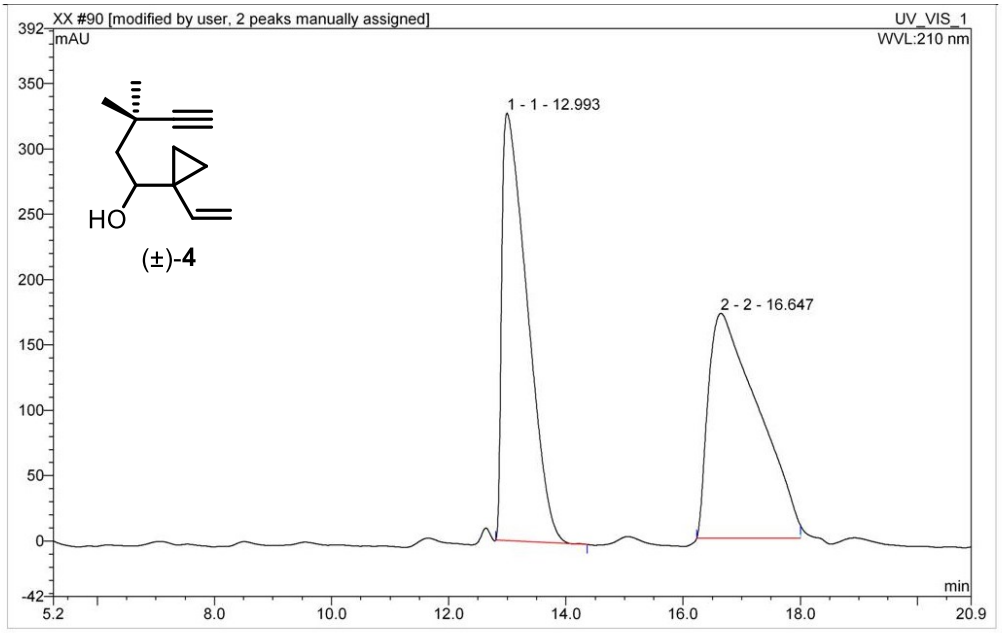


Preparation of chiral substrate 4: To a solution of (±)-**4** (35.6 mg, 0.2 mmol) in DCM (4 mL) was added 4 Å MS (677.2 mg) and PDC (225.7 mg, 0.6 mmol). After stirred for 13 h at room temperature, TLC indicated the absence of substrate. Then the reaction mixture was filtered through silica-gel by washing with DCM. The elute was monitored by TLC and concentrated in vacuo to afford the crude product (29.0 mg). The crude product was dissolved in toluene (2 mL) under argon atmosphere. (*S*)-CBS (0.165 mL, 1M in toluene, 0.165 mmol) was added. The solution was cooled to -30 °C, and then borane dimethyl sulfide complex (0.33 mL, 2 M in THF, 0.658 mmol) was added. The reaction mixture was stirred for 4 h. It was quenched by 0.5 mL methanol at -30 °C. The mixture was warmed to room temperature and then saturated aqueous ammonium chloride solution and water was added. It was extracted with diethyl ether (3 × 20 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered, concentrated and purified by column chromatography (PE/EA = 15:1) to give (+)-**4** as a colorless oil. ee = 88%. HPLC (AD-H,

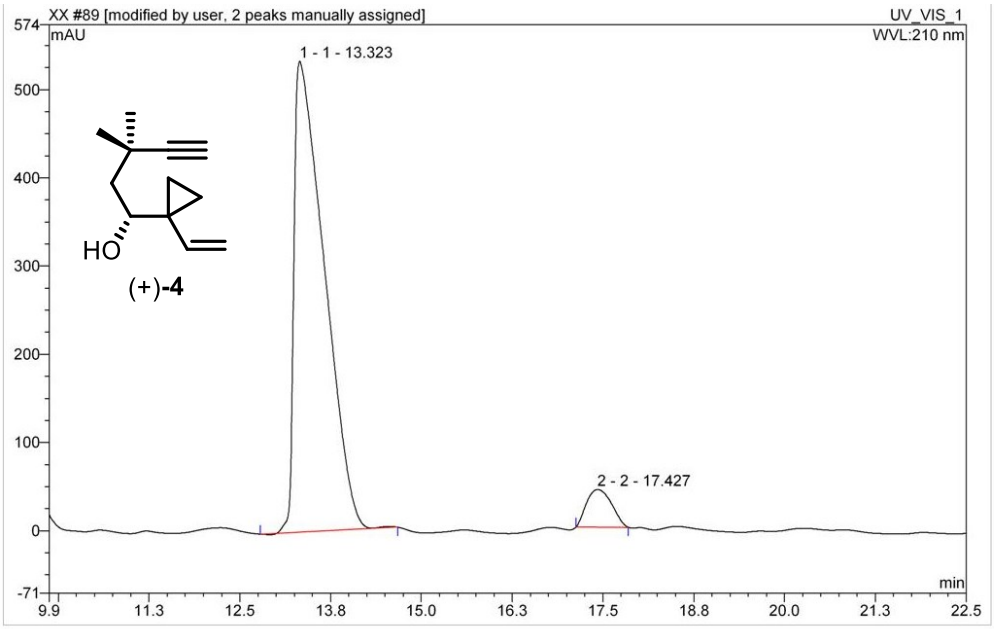
hexanes:^{i}PrOH = 499:1, flow rate = 1.0 mL/min, l = 205 nm) tR = 13.3 min (major), 17.4 min (minor). Run1: (+)-**4** (19.7 mg, 55%); Run2: **(+)-4** (18.2 mg, 51%). The average yield of two runs was 53%.

(+)-4. **Specific Rotation: $[\alpha]^{20}_{D}$ = +15.4 (*c* 0.52 $CDCl_3$).** The absolute configuration of (+)-**4** was proposed according to the Corey's analysis model[7] and the optical rotation direction of (+)-**4** agrees with the previous literature report.[3]

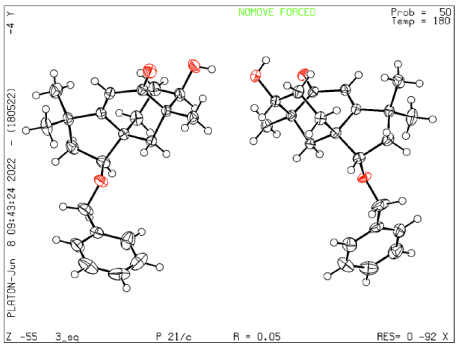
4. HPLC and X-ray data.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area(ident.) %	Amount mg/l	Type
2	12.99	1	327.070	163.661	49.01	n.a.	BMB*^
2	16.65	2	172.035	170.302	50.99	n.a.	BM *^
Total:			499.104	333.963	100.00	0.000	

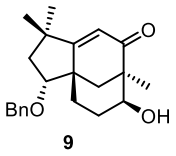


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area(ident.) %	Amount mg/l	Type
2	13.32	1	533.883	257.253	93.78	n.a.	BMB*^
2	17.43	2	42.563	17.061	6.22	n.a.	BMB*^
Total:			576.446	274.313	100.00	0.000	



Ellipsoids are drawn at 50% probability

≡



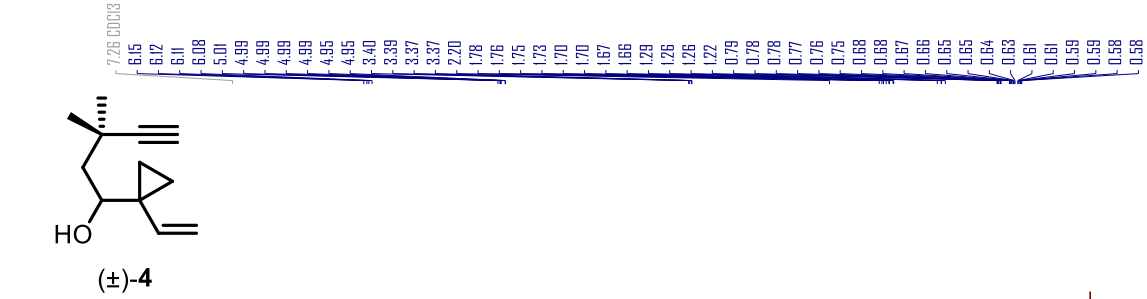
9

CCDC number:2180760

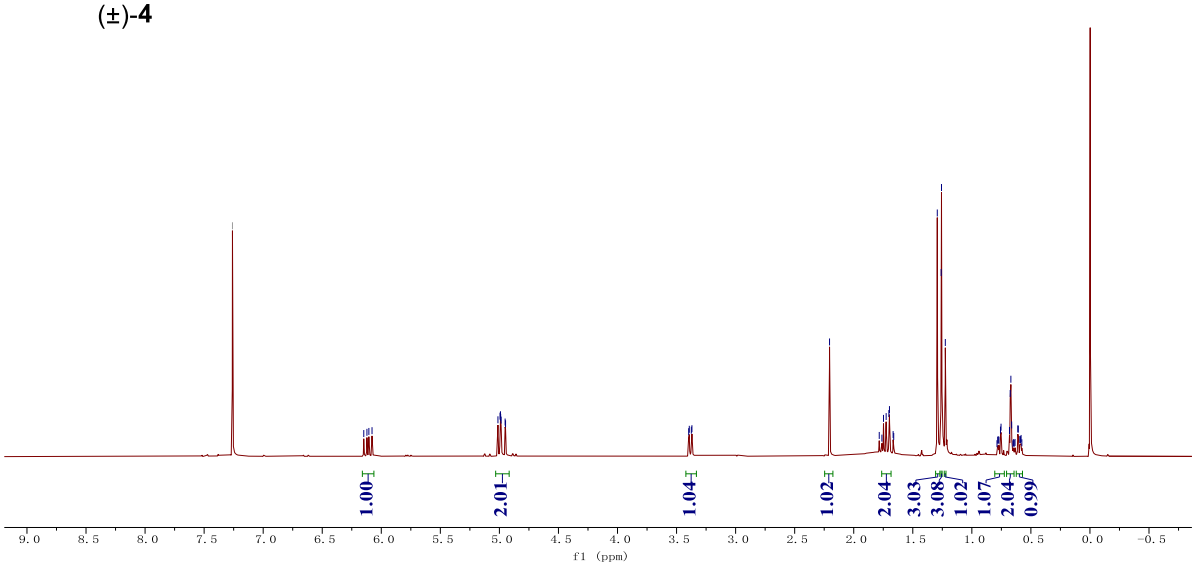
Crystal data	
Chemical formula	$C_{22}H_{28}O_3$
M_r	340.44
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	180
a, b, c (Å)	19.3430 (4), 11.2227 (2), 19.4908 (4)
β (°)	104.175 (2)
V (Å^3)	4102.25 (14)
Z	8
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.07
Crystal size (mm)	0.22 × 0.08 × 0.06
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.051, 0.158, 1.05
No. of reflections	10313
No. of parameters	459
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.37, -0.53

5. NMR spectra of New Compounds.

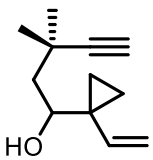
^{1}H NMR (400 MHz, $CDCl_3$):



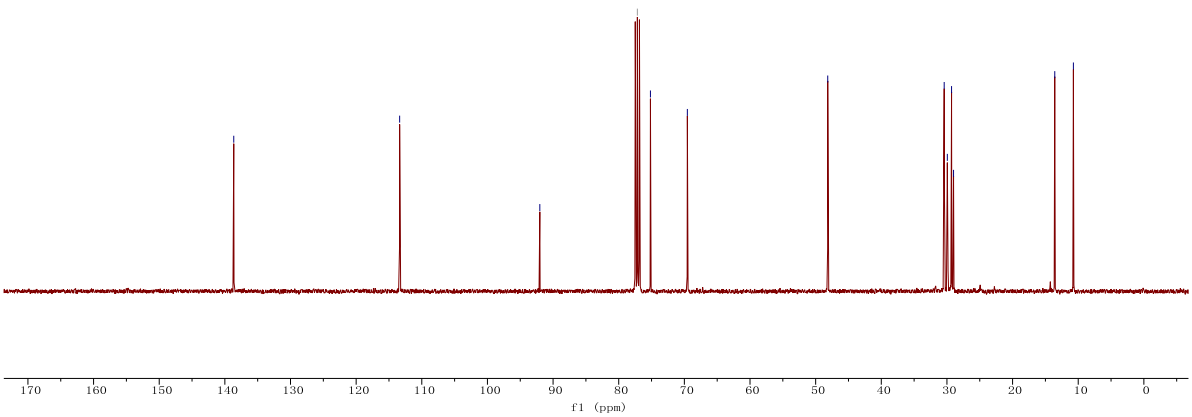
(±)-**4**



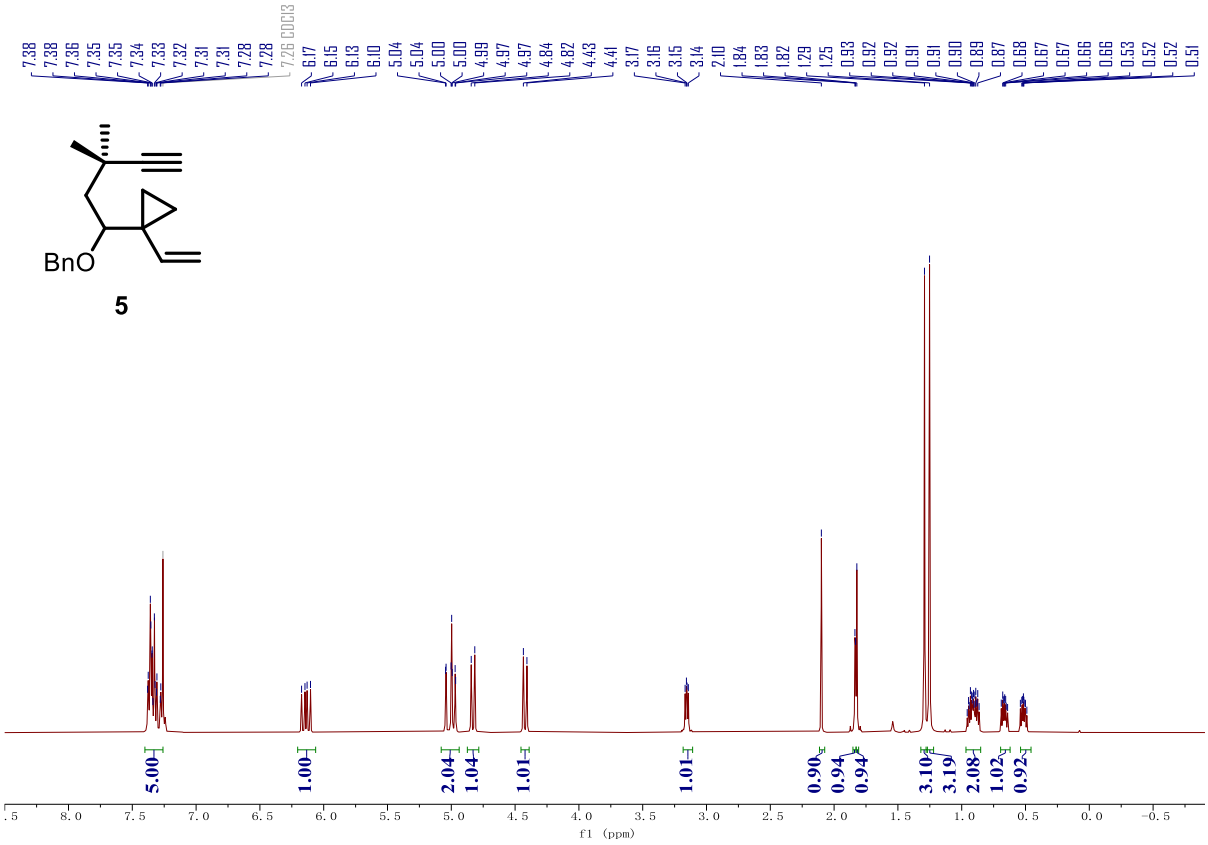
^{13}C NMR (101 MHz, $CDCl_3$):



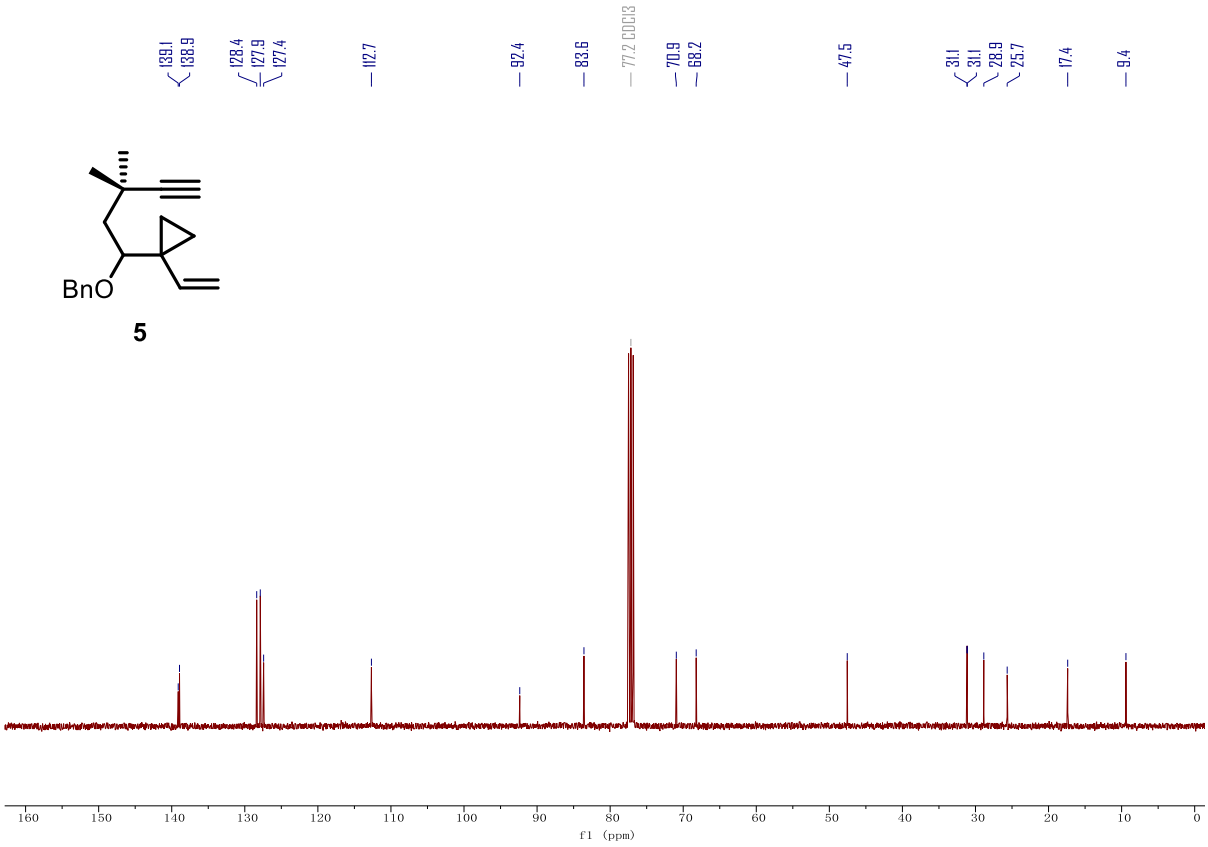
(±)-**4**



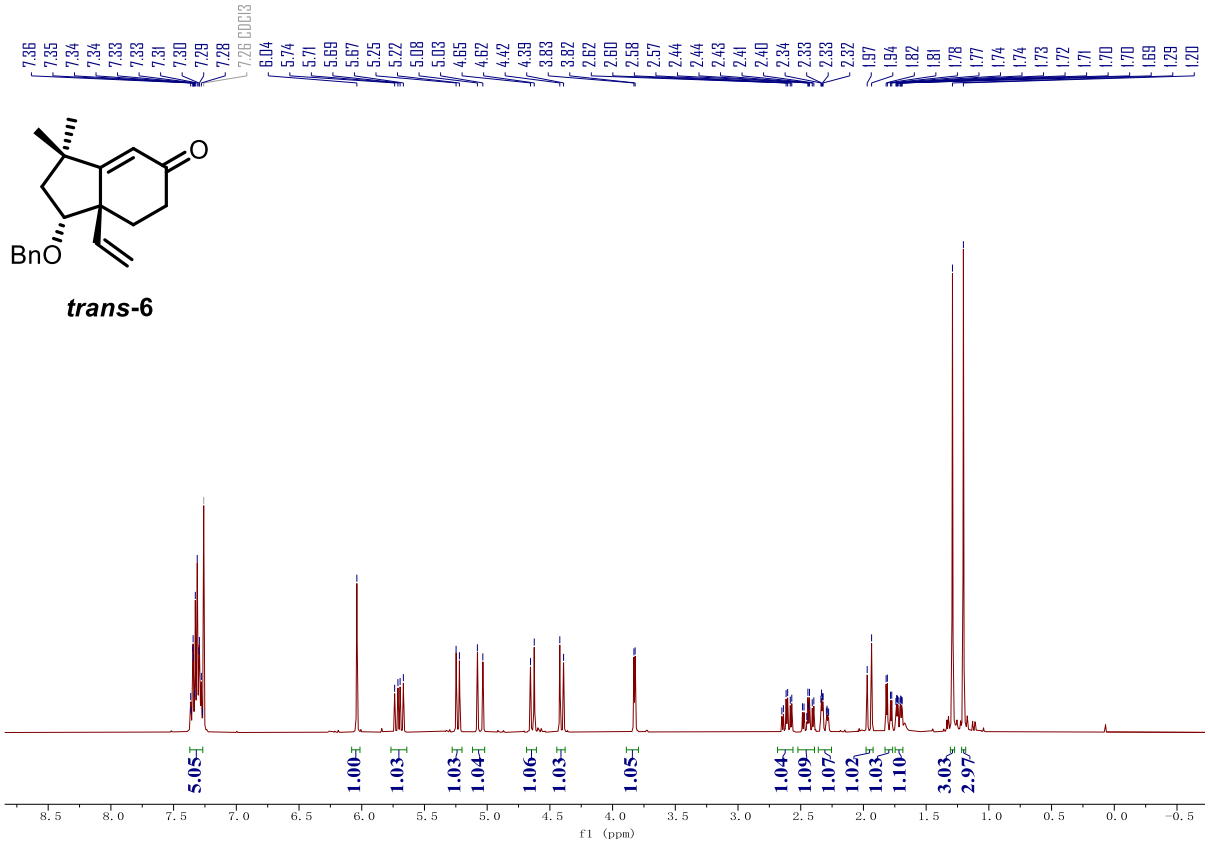
^{1}H NMR (400 MHz, $CDCl_3$):



^{13}C NMR (101 MHz, $CDCl_3$):

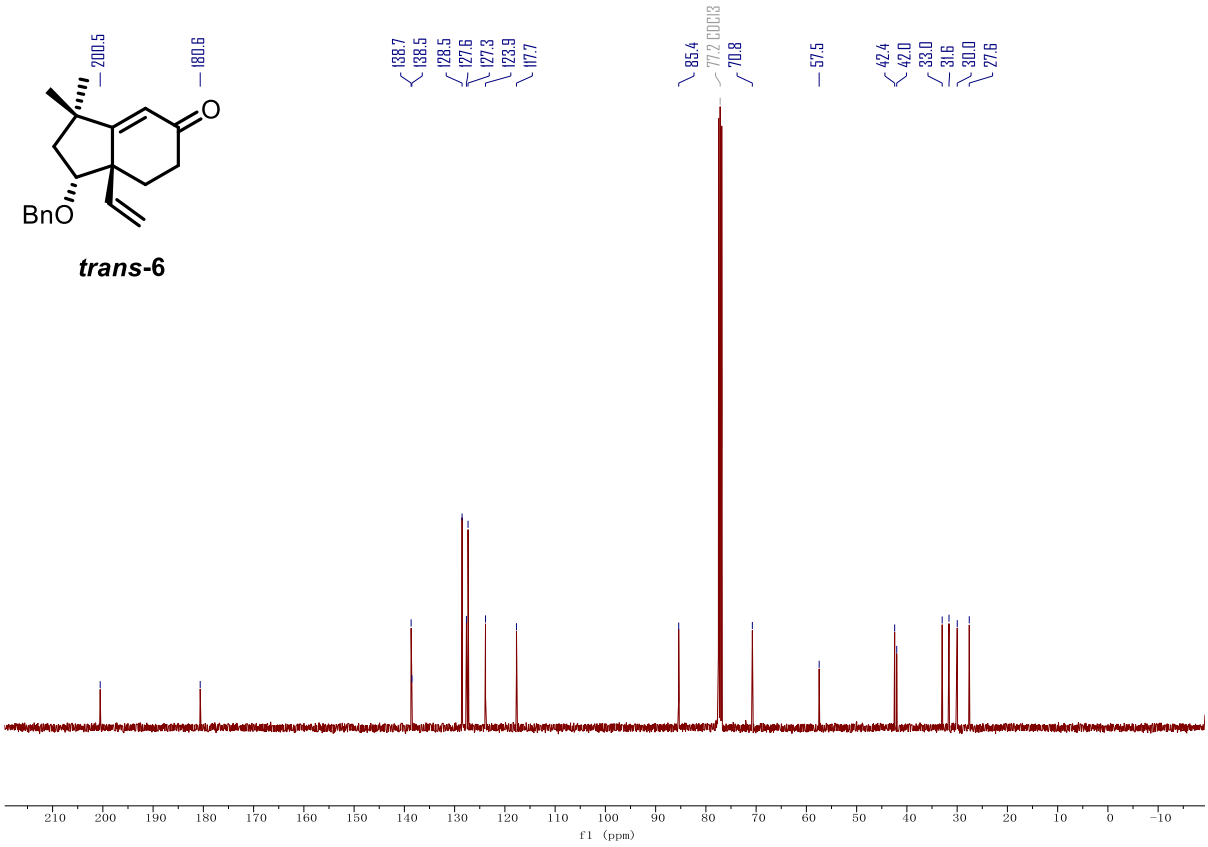


^{1}H NMR (400 MHz, $CDCl_3$):



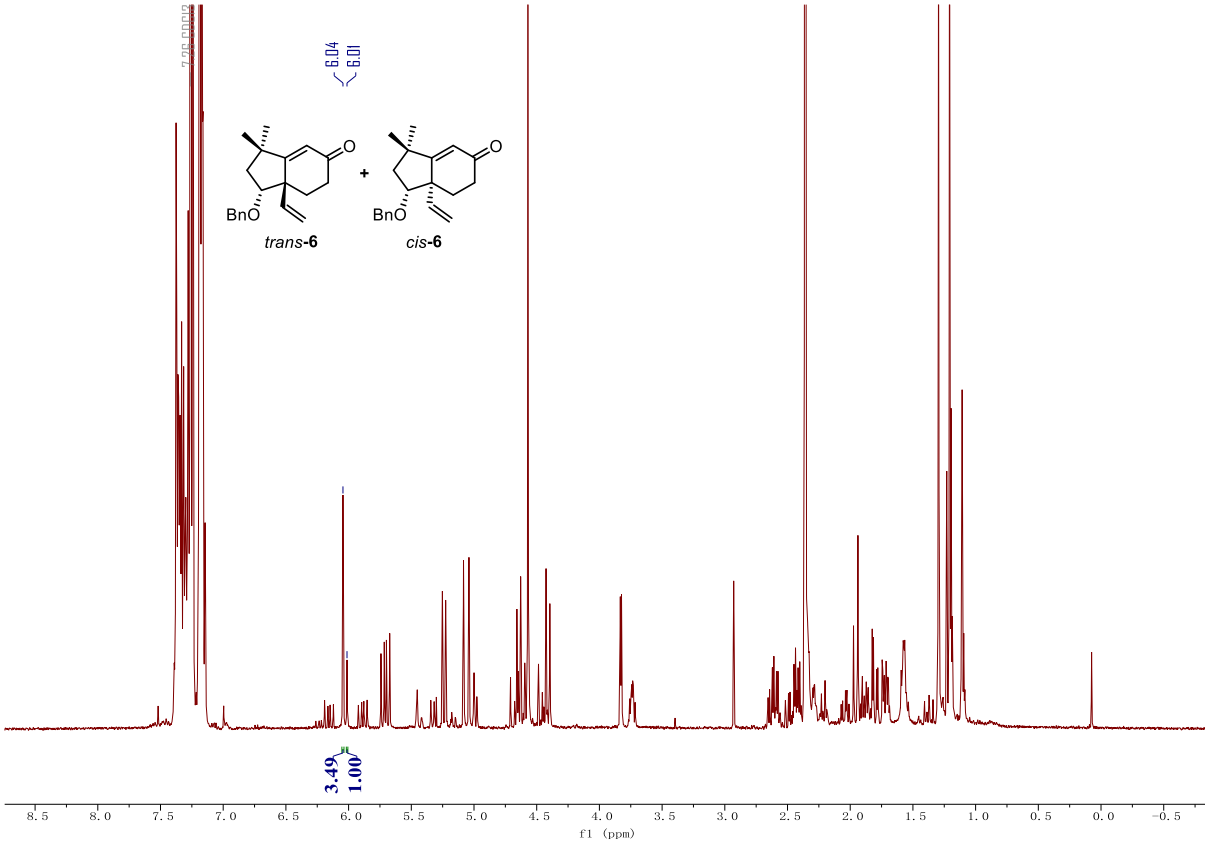
***trans*-6**

^{13}C NMR (101 MHz, $CDCl_3$):

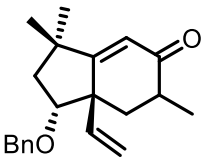


***trans*-6**

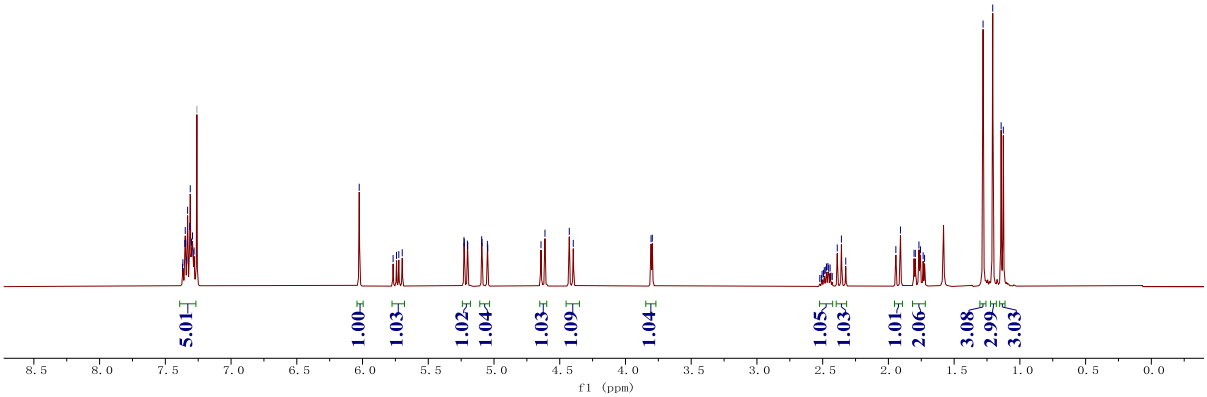
Crude ^{1}H NMR of reaction system (400 MHz, $CDCl_3$):



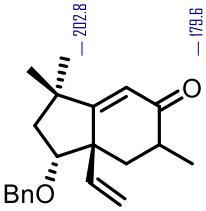
^{1}H NMR (400 MHz, $CDCl_3$):



7-1

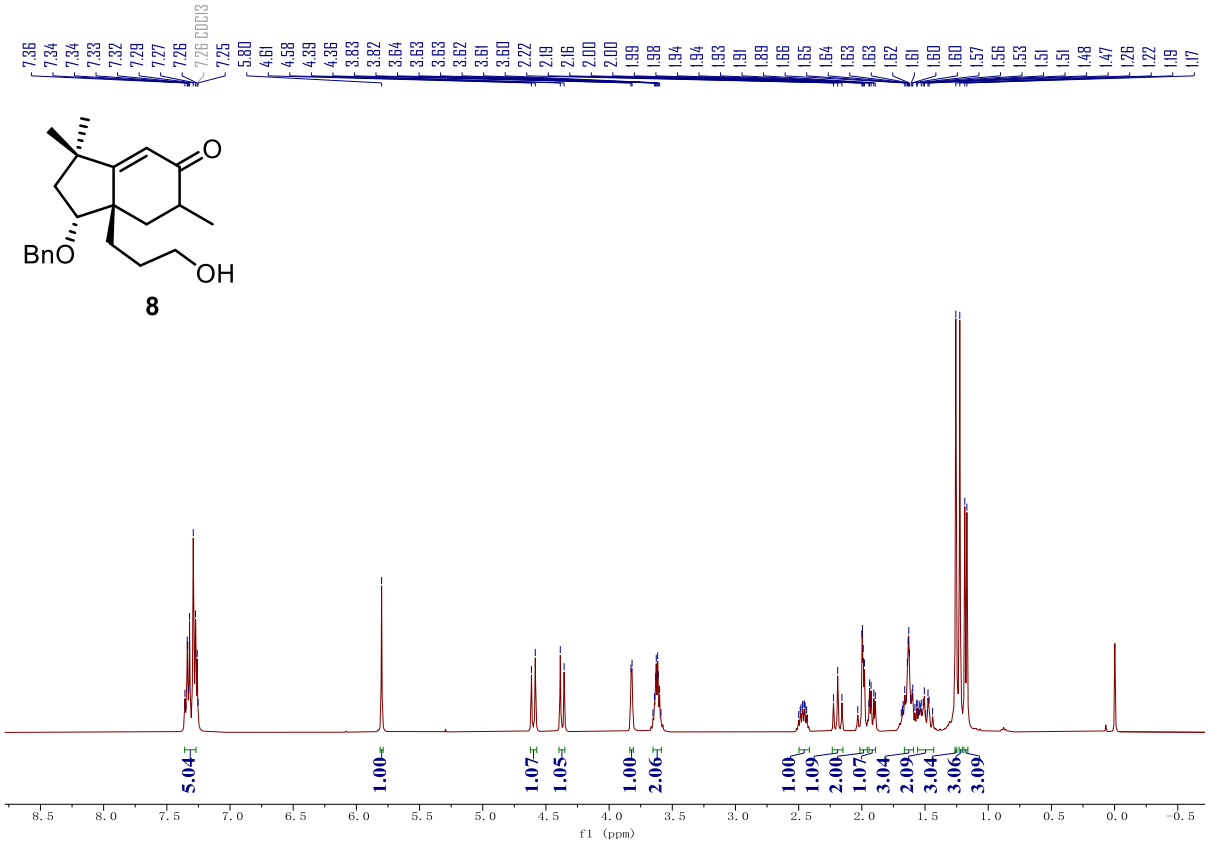


^{13}C NMR (101 MHz, $CDCl_3$):

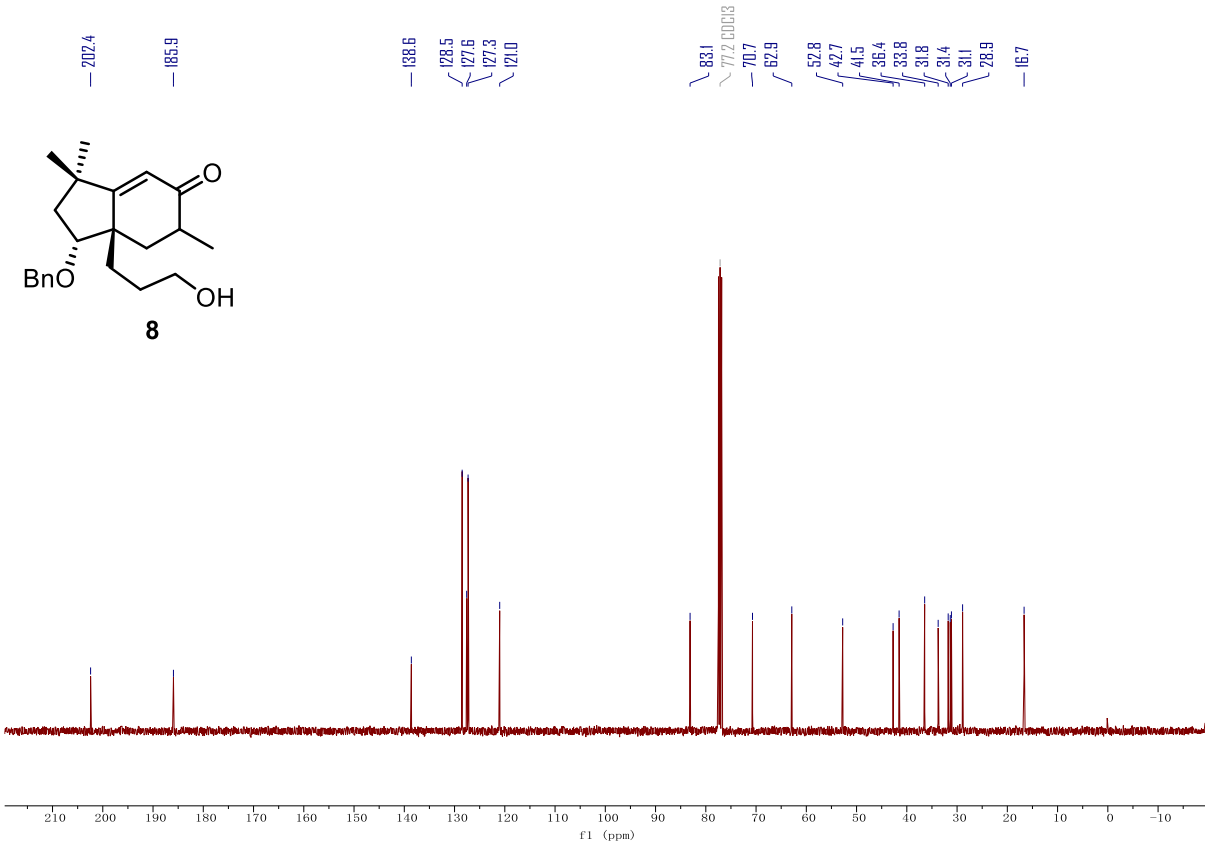


7-1

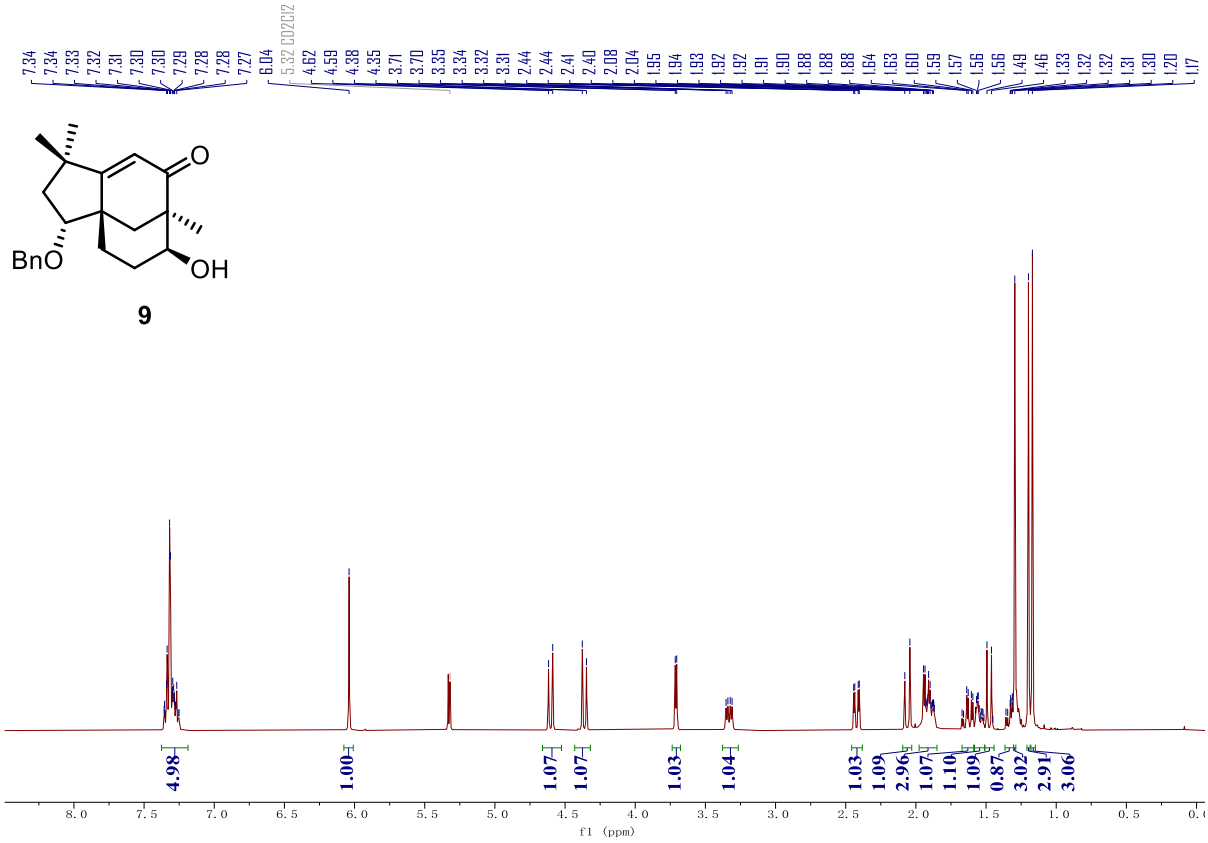
^{1}H NMR (400 MHz, $CDCl_3$):



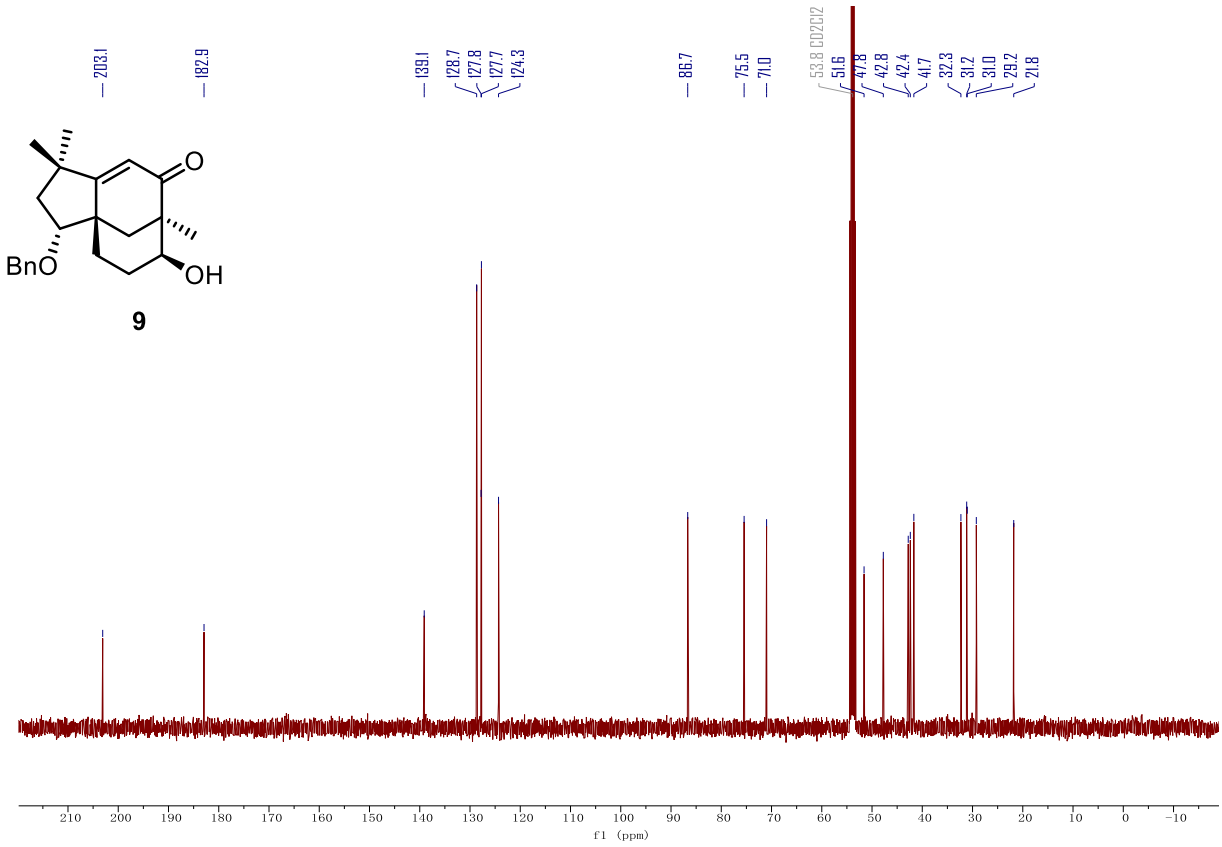
^{13}C NMR (101 MHz, $CDCl_3$):



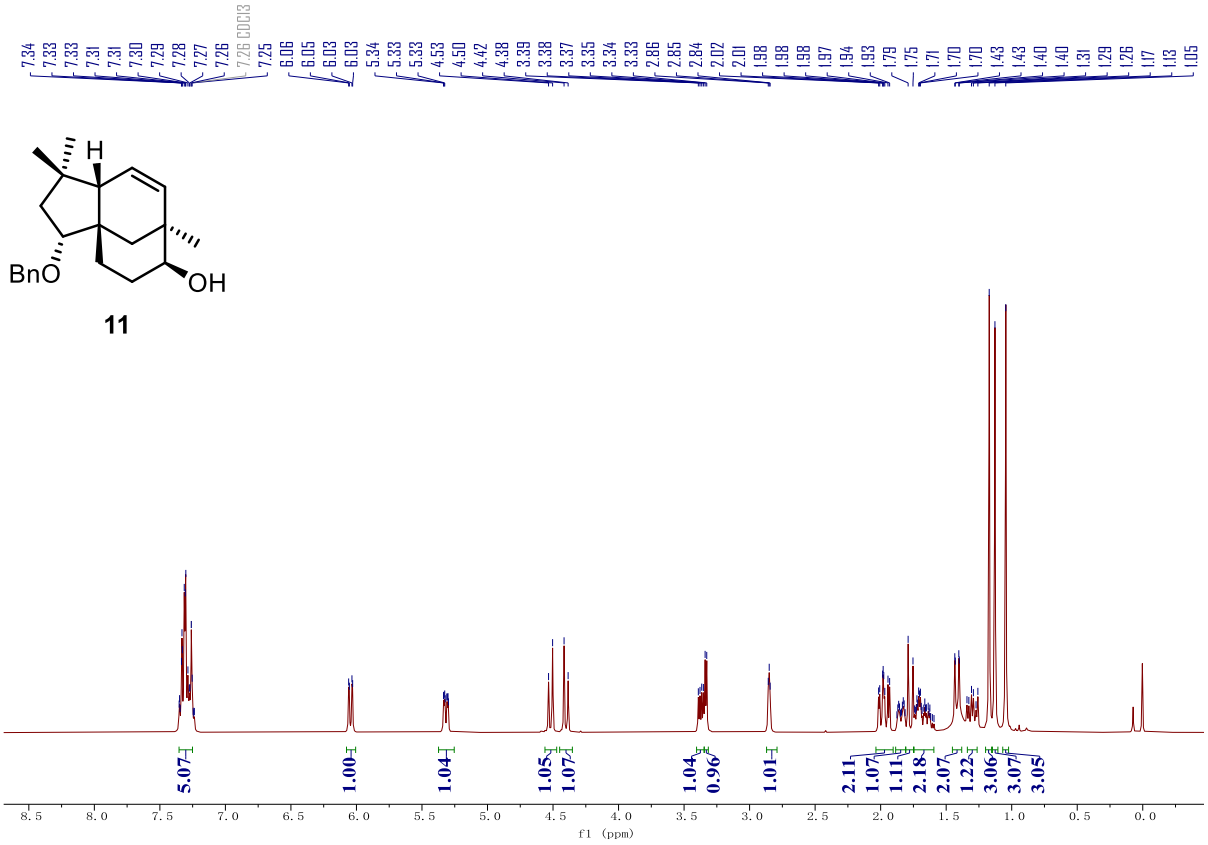
^{1}H NMR (400 MHz, CD_2Cl_2):



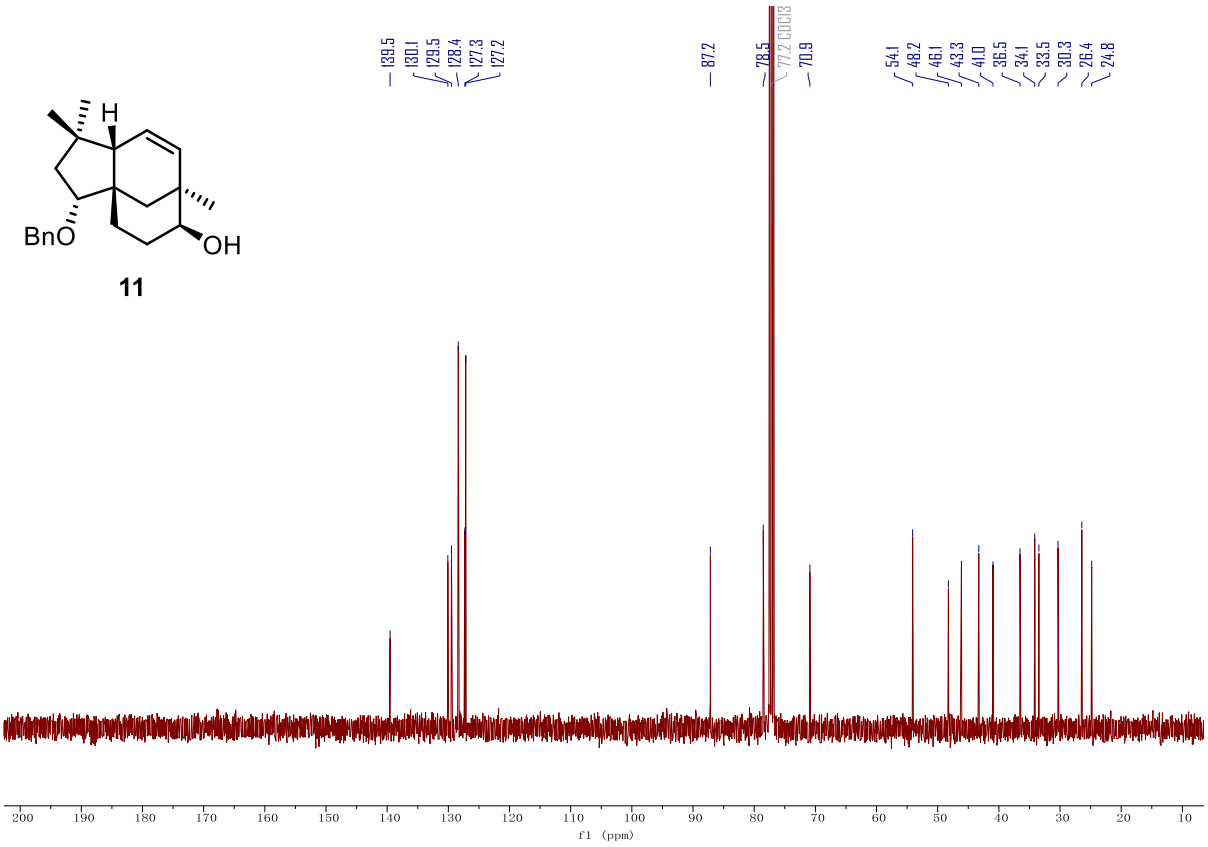
^{13}C NMR (101 MHz, CD_2Cl_2):



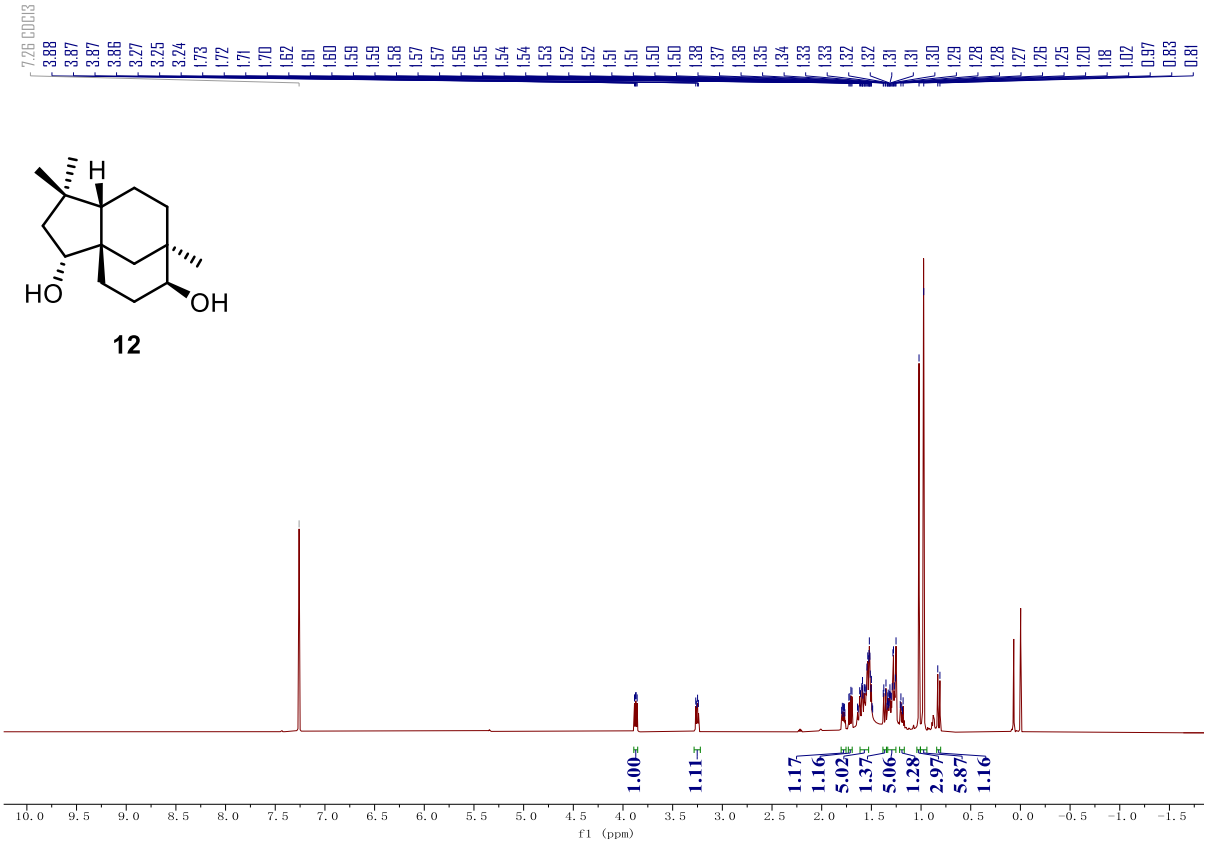
^{1}H NMR (400 MHz, $CDCl_3$):



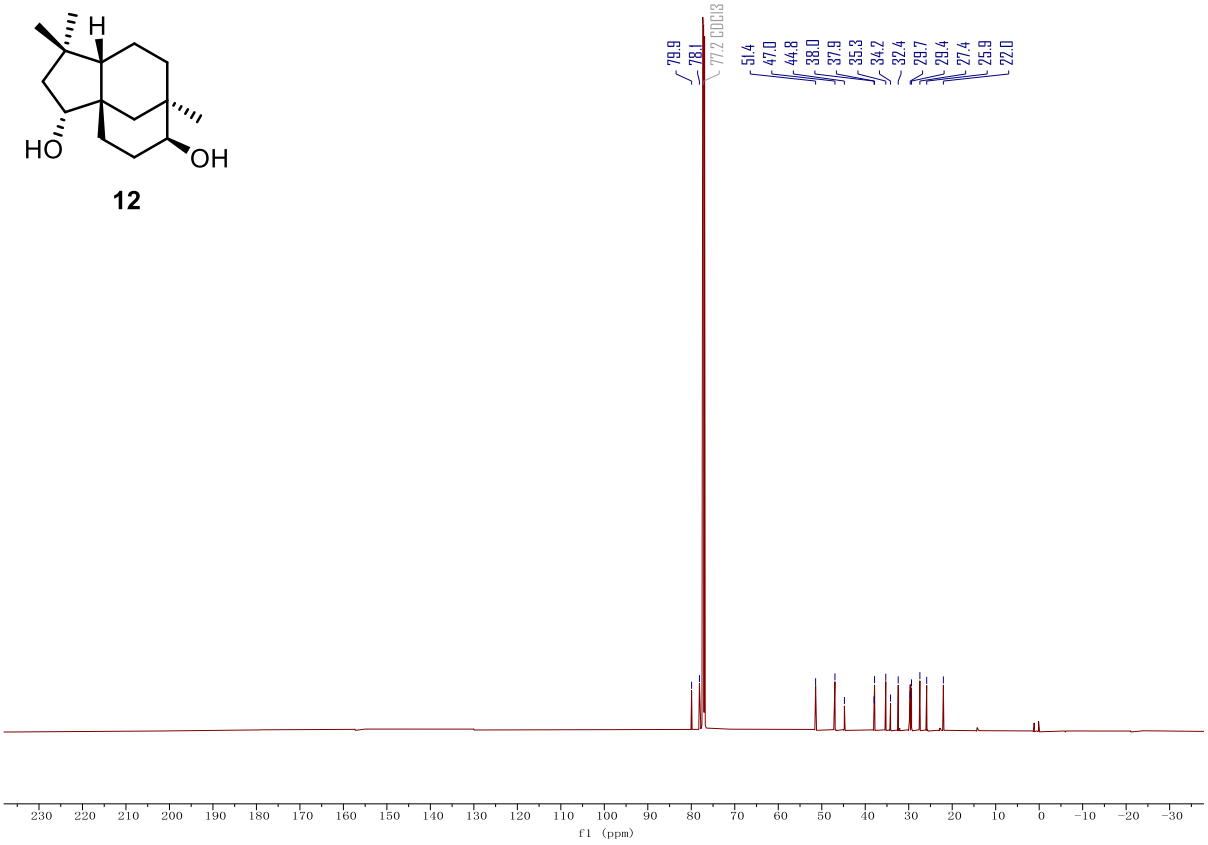
^{13}C NMR (101 MHz, $CDCl_3$):



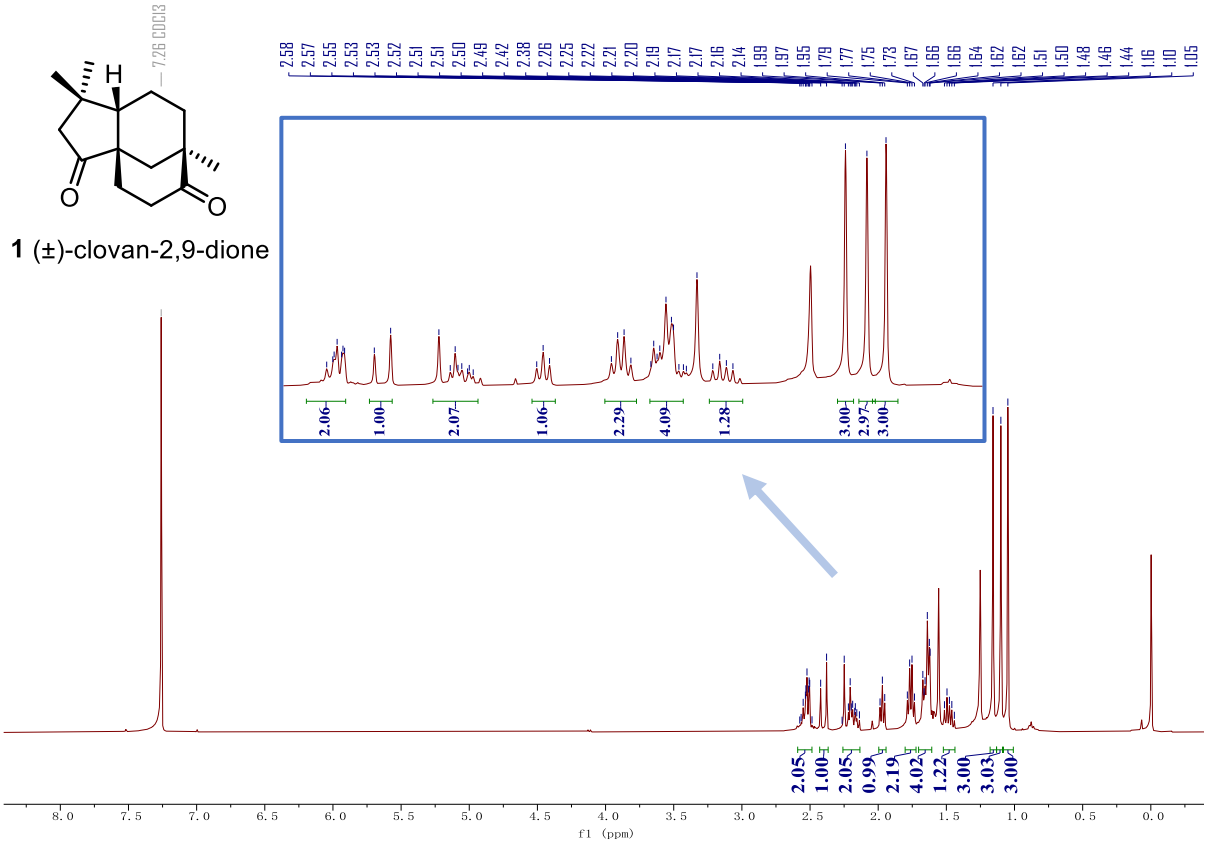
^{1}H NMR (600 MHz, $CDCl_3$):



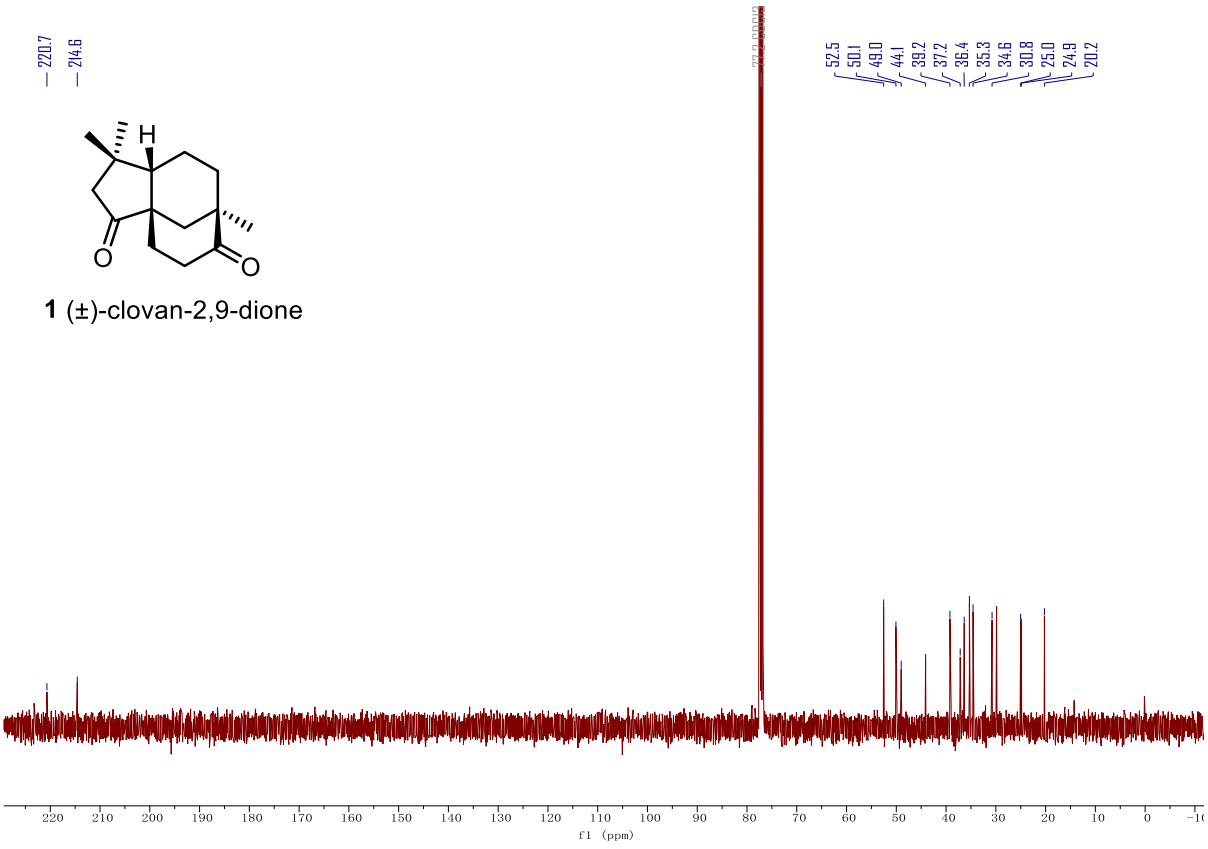
^{13}C NMR (151 MHz, $CDCl_3$):



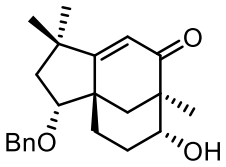
^{1}H NMR (400 MHz, $CDCl_3$):



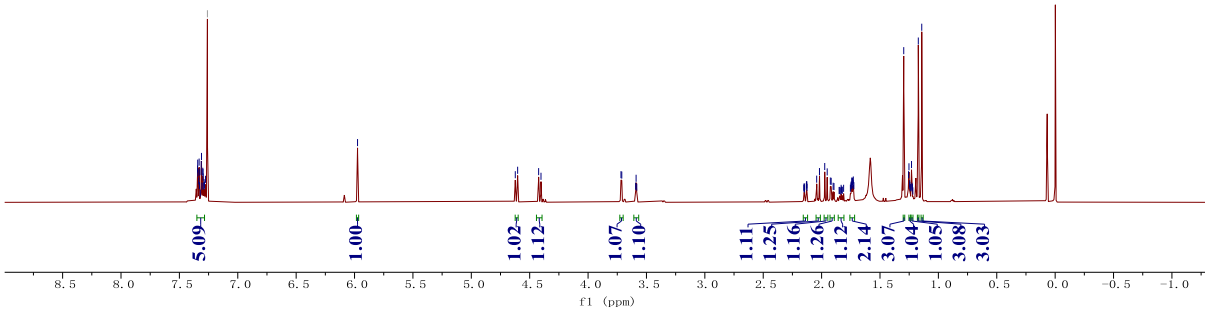
^{13}C NMR (101 MHz, $CDCl_3$):



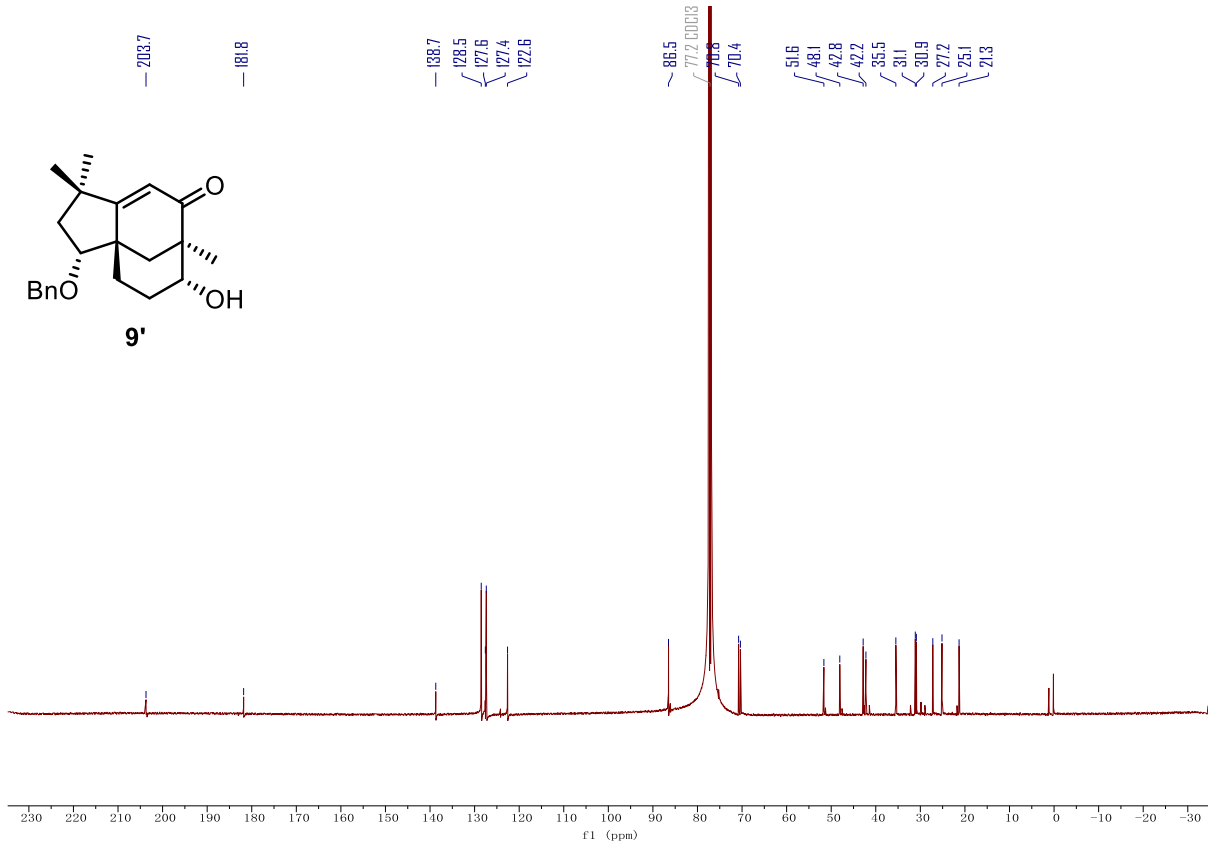
^{1}H NMR (600 MHz, $CDCl_3$):



9'



^{13}C NMR (151 MHz, $CDCl_3$):



9'

6. References

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