Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Biomimetic total syntheses of baefrutones A–D, baeckenon B, and frutescones A, D–F

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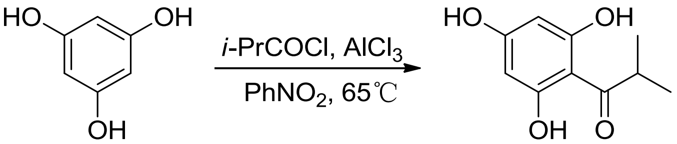
General experimental methods

Optical rotation was measured on a Rudolph Autopol IV polarimeter. The CD spectra were obtained on a JASCO J-810 spectropolarimeter. Diffraction data were collected on a Rigaku Oxford CCD diffractometer diffractometer ($\lambda = 1.54184$). NMR spectra were recorded on 600, 500, 400 and 300 MHz (^{1}H) NMR spectrometers in $CDCl_3$ (δ 7.26 for ^{1}H NMR and 77.2 for ^{13}C NMR), CD_3OD (δ 4.87, 3.31 for ^{1}H NMR and 49.0 for ^{13}C NMR), and DMSO-d_6 (δ 2.50 for ^{1}H NMR and 39.5 for ^{13}C NMR). HRESIMS data were acquired on an Agilent 6520 Q/TOF mass spectrometer with an ESI source in negative mode. Column chromatography was performed using silica gel (100–200 and 200–300 mesh). Preparative HPLC was performed using YMC-pack C18 column (250 × 20 mm, 5 μm). Chiral HPLC separation was conducted on a semipreparative chiral OD-H column (250 × 10 mm, 5 μm) (Daicel Chiral Technologies Co., Ltd., China).



12 **13**

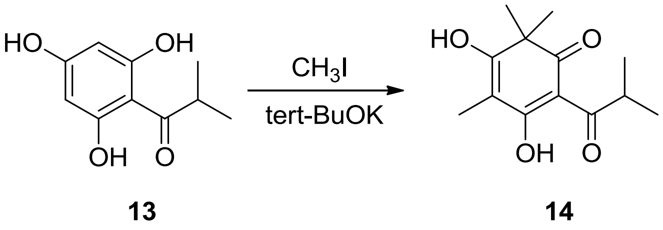
Isobutyrylphloroglucinol (**13**). Aluminium trichloride (42.2 g, 0.32 mol, 4 equiv) was added to a stirred suspension of phloroglucinol (**12**) (10.0 g, 0.079 mol, 1 equiv) in nitrobenzene (100 mL), and the mixture was stirred at room temperature. After 30 min, isobutyryl chloride (9.8 mL, 0.095 mol, 1.2 equiv) was added slowly and the resulting mixture was stirred at 65 ℃ for 18 h. Afterwards, the mixture was cooled down to room temperature and poured into ice-water and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (petroleum ether-acetone, 100:0 → 60:10, v/v) to afford isobutyrylphloroglucinol (**13**, 14.1 g, 91.0%) as yellowish oil.

R_f = 0.40 (petroleum ether/acetone, 2:1).

^{1}H NMR (400 MHz, CD_3OD) δ: 5.81 (2H, s), 3.97 (1H, hept, J = 6.8 Hz), 1.12 (6H, d, J = 6.7 Hz).

^{13}C NMR (100 MHz, CD_3OD) δ: 211.7, 165.8, 165.7, 104.6, 95.8, 39.9, 19.6.

HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{10}H_{13}O_4$, 197.0814; found, 197.0804.



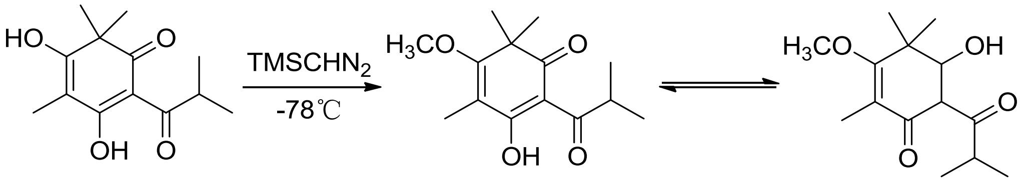
2-Isobutyryl-3,5-dihydroxy-4,6,6-trimethylcyclohexa-2,4-dienone (**14**). To a solution of *tert*-BuOK (21.1 g, 0.189 mol, 3.7 equiv.) and **13** (10 g, 0.051 mol, 1 equiv.) in anhydrous MeOH (150 mL), iodomethane (9.5 mL, 0.15 mol, 3 equiv.) was added and the resulting mixture was refluxed for 7 h. Then the mixture was cooled down to room temperature and concentrated under reduced pressure. The residue was dissolved in water and acidified with 2 M HCl before it was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium sulfite solution (2 × 200 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (petroleum ether-acetone, 100:0 → 90:10, v/v) to afford **14** (8.1 g, 67%).

R_f = 0.43 (petroleum ether/acetone, 4:1).

^{1}H NMR (400 MHz, CD_3OD) δ: 4.09 (1H, m, *J* = 7.1 Hz), 1.83 (3H, s), 1.34 (6H, s), 1.10 (6H, d, *J* = 7.1 Hz).

^{13}C NMR (100 MHz, CD_3OD) δ: 209.3, 198.7, 190.8, 176.6, 105.1, 103.5, 61.5, 36.9, 24.9, 19.4, 7.2.

HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{18}O_4$, 239.1283; found, 239.1286.



14 **15**

2-Isobutyryl-3-dihydroxy-5-methoxy-4,6,6-trimethylcyclohexa-2,4-dienone (**15**). To a solution of **14** (5.0 g, 0.021 mol, 1 equiv.) in a mixture of anhydrous MeOH (12 mL) and EtOAc (60 mL), $TMSCHN_2$ (73.5 mL, 0.147 mol, 2 M in diethyl ether) was added slowly at –78 ℃ under nitrogen atmosphere, and the resulting mixture was stirred for 3 h. Then acetic acid was added to destroy the excess $TMSCHN_2$. The mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (petroleum ether-EtOAc, 100:0 → 97:3, v/v) to afford **15** (4.76 g, 90%).

R_f = 0.54 (petroleum ether/EtOAc, 95:5).

2:1 mixture of tautomers in $CDCl_3$

Data for major tautomer **15**:

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.10 (1H, hept, J = 6.8 Hz), 3.90 (3H, s), 1.93 (3H, s), 1.29 (6H, s), 1.10 (6H, d, J = 7.0 Hz).

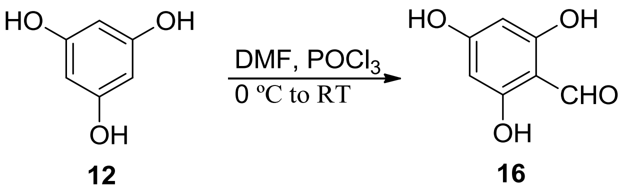
^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.7, 197.1, 190.7, 176.6, 112.4, 105.9, 62.2, 50.6, 35.6, 24.4, 19.0, 9.70.

Data for major tautomer **15**:

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.95 (1H, hept, J = 6.8 Hz), 3.83 (3H, s), 1.87 (3H, s), 1.41 (3H, s), 1.12 (3H, d, J = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.3, 198.1, 185.5, 170.3, 118.3, 108.4, 62.0, 45.2, 36.6, 29.8, 19.0, 10.1.

HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{14}H_{21}O_4$, 253.1440; found, 253.1438.



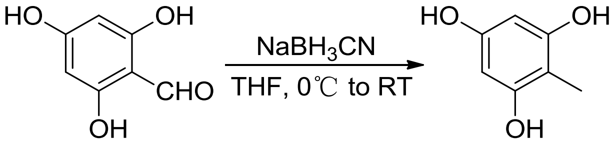
*2, 4, 6-trihydroxybenzaldehyde (**16**).* To a solution of phloroglucinol (10.0 g, 0.079 mol, 1 equiv) in anhydrous acetonitrile (200 ml) was added DMF (6.7 ml, 0.087 mol, 1.1 equiv) and $POCl_3$ (8.7 ml, 0.087 mol, 1.1 equiv) at 0 ℃ in an ice bath. Remove ice bath and the solution was stirred for 2 h. To the reaction mixture was added water and then refluxed for 30 min. When the solution cooled down, EtOAc (3 × 100 mL) was added to extract. The combined organic layers were washed with brine, dried over Na_2SO_4, filtration and then concentration in vacuo. The residue was purified by silica gel column chromatography (petroleum ether-acetone, 4:1, v/v) to yield **16** (11.0 g, 90%) as a white solid.

R_f = 0.36 (petroleum ether/acetone, 2:1).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.40 (1H, br s), 10.75 (1H, br s), 9.93 (1H, s), 5.79 (2H, s).

^{13}C NMR (75 MHz, DMSO-d_6) δ: 190.9 , 167.2 , 164.0, 104.5, 94. 1.

HRMS-ESI (*m/z*) [M − H]$^-$ calcd for $C_7H_5O_4$, 153.0188; found, 153.0197.



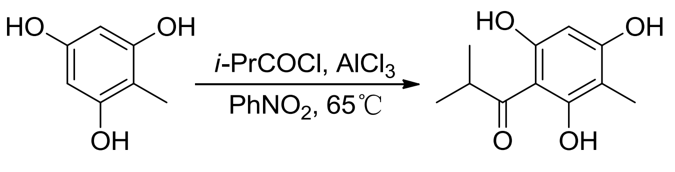
*1,3,5-trihydroxy-2-methylbenzene (**17**)*. To a solution of **16** (10.0 g, 0.065 mol, 1 equiv) in THF (200 ml) was added sodium cyanoborohydride (12.3 g, 0.19 mol, 3 equiv) and methyl orange as PH indicator at 0 ℃ in an ice bath, and 3 M HCl was added to keep the reaction mixture red (acidic environment). Remove ice bath and the solution was stirred until consumption of the starting material. THF was removed under reduced pressure to give the residue, which was disolved in H_2O and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtration and concentration in vacuo to gave a residue, which was purified by silica gel column chromatography (petroleum ether-acetone, 6:1, v/v) to yield **17** (5.0 g, 55%) as a white solid.

R_f = 0.26 (petroleum ether/acetone, 2:1).

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.79 (2H, s), 8.66 (s, 1H), 5.77 (2H, s), 1.81 (3H, s).

^{13}C NMR (75 MHz, DMSO-d_6) δ 156.4, 155.4, 100.7, 94.0, 7.9.

HRMS-ESI (*m/z*) $[M - H]^-$ calcd for $C_7H_7O_3$, 139.0395; found, 139.0398.



17 **11**

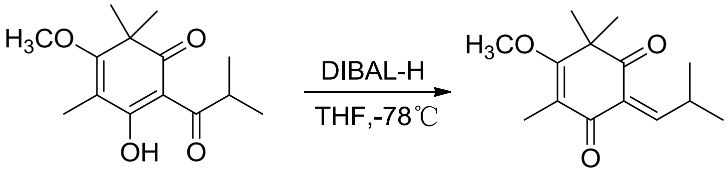
*2, 4, 6-trihydroxy-3-methylisobutyrophenone (**11**)*. To a stirred suspension of **17** (5.0 g, 0.036 mol, 1 equiv) in nitrobenzene (80 mL) was added aluminium trichloride (19.0 g, 0.143 mol, 4 equiv), and the mixture was stirred at room temperature for 30 min. Then isobutyryl chloride (4.4 mL, 0.043 mol, 1.2 equiv) was added slowly and the resulting mixture was stirred at 65 ℃ for 12 h. Afterwards, the mixture was cooled down to room temperature, poured into iced HCl solution, and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (petroleum ether-acetone, 10:1, v/v) to afford isobutyrylphloroglucinol (**11**, 6.2 g, 83.0%) as brown powder.

R_f = 0.23 (petroleum ether/acetone, 4:1).

^{1}H NMR (300 MHz, CD_3OD) δ: 5.90 (1H, s), 4.00 (1H, hept, *J* = 6.7 Hz), 1.92 (3H, s), 1.13 (6H, d, *J* = 6.8 Hz).

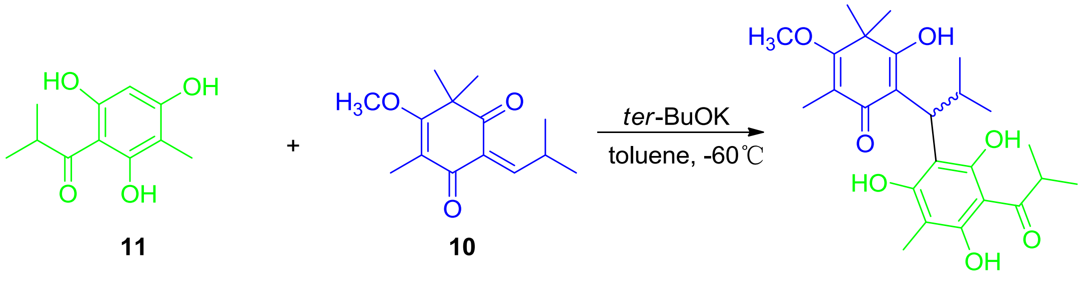
^{13}C NMR (75 MHz, CD_3OD) δ: 211.8, 165.2, 163.6, 160.9, 104.5, 103.7, 95.0, 39.9, 19.7, 7.3.

HRMS-ESI (*m/z*) $[M – H]^-$ calcd for $C_{11}H_{13}O_4$, 209.0814; found, 209.0825.



15 **10**

*Compound **10***. To a solution of **15** (500 mg, 1.98 mmol, 1 equiv) in THF (10 mL) at –78 ℃ under nitrogen atmosphere, DIBAL-H (4.0 mL, 2 equiv, 1 M in hexane) was added dropwise, and the resulting solution was stirred at room temperature for 1 h. Then 2 M HCl (10 mL) was added to destroy the excess DIBAL-H. The mixture was diluted in water and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude compound **4** was unstable and used immediately for the next step.



11 **10** (±)-**5**: baeckenon **B**

Baeckenon B (5). To a solution of **11** (2.0 g, 9.5 mmol, 1.0 equiv) in toluene (50 mL) was added *ter*-BuOK (2.13 g, 19.0 mmol, 2 equiv), and the resulting solution was stirred at room temperature for 15 min. Then a solution of Michael acceptor **10** (2.69 g, 11.4 mmol, 1.2 equiv,) was added to a suspension of **11**. The resulting mixture was stirred at −60 ℃ under nitrogen atmosphere until consumption of the starting material. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (petroleum ether-acetone, 100:0→70:30, v/v) to afford baeckenon B (**5**, 3.5 g, 83%), which could be resolved into (+)-**5** (180 mg) and (−)-**5** (165 mg) on a semipreparative chiral OD-H column (250 × 10 mm, 5 μm).

$R_f = 0.56$ (petroleum ether/EtOAc, 4:1).

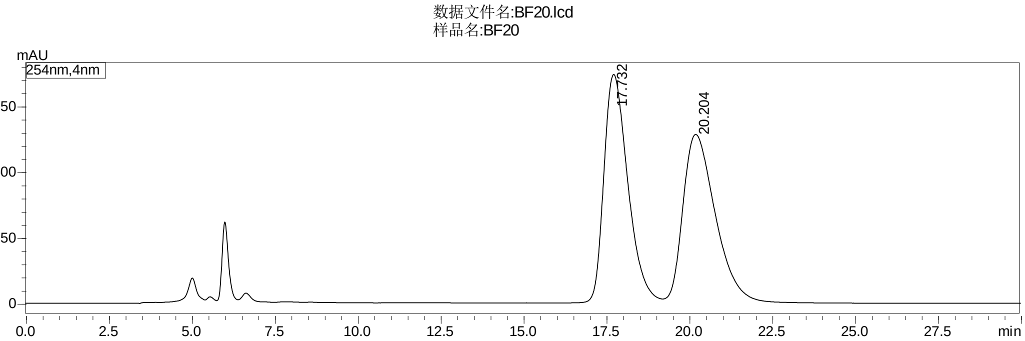
(±)-**5**: $[\alpha]_D^{20} = 0$ (*c* 0.1, MeOH)

(+)-*R*-**5**: $[\alpha]_D^{20} = +38.3$ (*c* 0.4, MeOH)

(−)-*S*-**5**: $[\alpha]_D^{20} = -49.8$ (*c* 0.3, MeOH)

^{1}H and ^{13} NMR see Table S1.

HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{25}H_{35}O_7$, 447.2383; found, 447.2383.

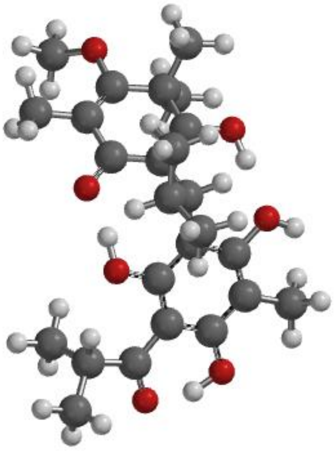


Chiral HPLC chromatogram of (±)-**5**

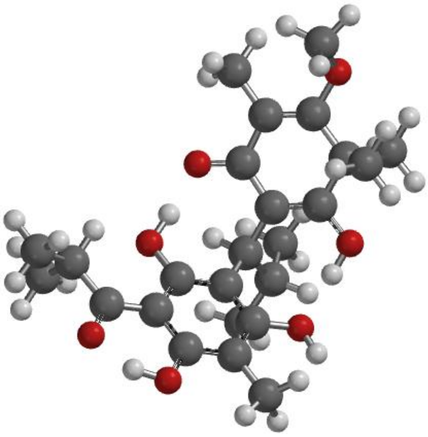
[Chiral HPLC separation of (±)-**5** was carried out on a Daicel Chiralcel OD-H (250 × 10 mm, 5 μm), using *n*-hexane:2-propanol (80:20, v/v) as mobile phase at a flow rate of 4 mL/min at room temperature with UV detection at 254 nm.]

Quantum chemical ECD calculation for **5**

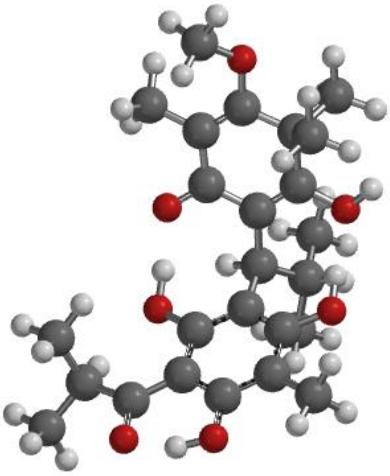
The systematic random conformational analysis of the enantiomers of (7*S*)-**5** was performed in the SYBYL 8.1 program by using the Monte Carlo protocol at the MMFF94s level. Considering a cutoff of 10 kcal/mol, 6 minimum energy conformers for (7*S*)-**5** were inferred to the global minima. All the obtained conformers were optimized using DFT at the B3LYP/6-31+G(d) level in gas phase, and 3 conformers were selected. All of the optimized stable conformers were used for TDDFT computation of the excited stats at the same levels, with the consideration of the first 50 excitations. The overall ECD curves of (7*S*)-**5** were weighted by Boltzmann distribution of each conformer (with a half-bandwidth of 0.3eV) derived from their relative free energy values. The ECD spectra were produced by SpecDis 1.6 software.



Conf. 1
Δε (kcal/mol)=0
(62.5%)

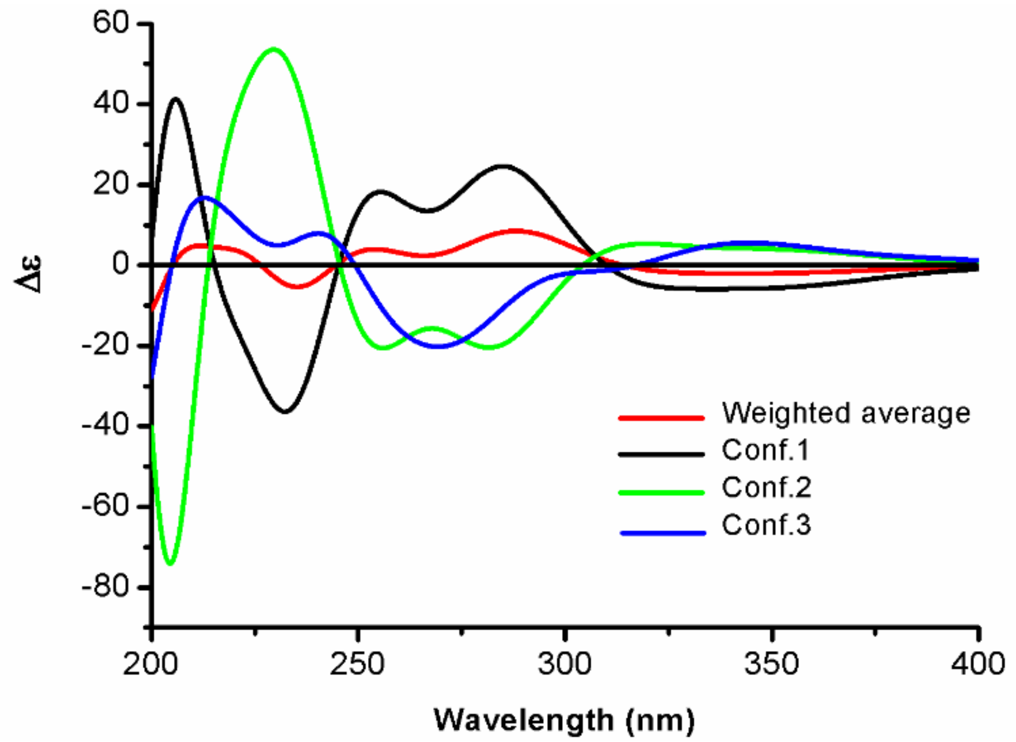


Conf. 2
Δε (kcal/mol)=+0.58
(34.8%)

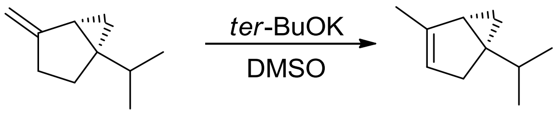


Conf. 3
Δε (kcal/mol)=+3.13
(2.7%)

DFT-optimized structures for low-energy conformers of (7*S*)-**5** at B3LYP/6-31+G(d) level in methanol (PCM), with zero-point corrected free energies calculated at the same level (and Boltzmann population at 298K estimated thereof).



TDDFT-calculated spectra at B3LYP/6-31+G(d) level in methanol (PCM) for the low energy structures of (7*S*)-**5**, and the weighted average using Boltzmann populations at 298K. Gaussian band-shape with 0.3 eV applied to generate the spectra.



18: (-)-sabinene **19**: (+)-thujene

(+)-α-thujene (19). To a solution of **18** (1000 mg, 7.35 mmol, 1.0 equiv) in DMSO (4 mL) was added *ter*-BuOK (823 mg, 7.35 mmol, 1 equiv), and the resulting solution was stirred at 90 ℃ for 6 h. Afterwards, the mixture was cooled down to room temperature and poured into ice-water and extracted with n-hexane (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium sulfite solution (3 × 20 mL) and concentrated in vacuo to afford the crude product **19** (900.7 mg, 90%) as light yellow oil.

Compound **18** (partially characterised)

$[\alpha]_D^{20} = -67.6$ (c 1.0, MeOH)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.80 (1H, s), 4.62 (1H, s), 0.95 (3H, d, J = 6.8 Hz), 0.88 (3H, d, J = 6.9 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.7, 101.7, 37.8, 32.7, 30.2, 29.1, 27.6, 19.9, 19.8, 16.2.

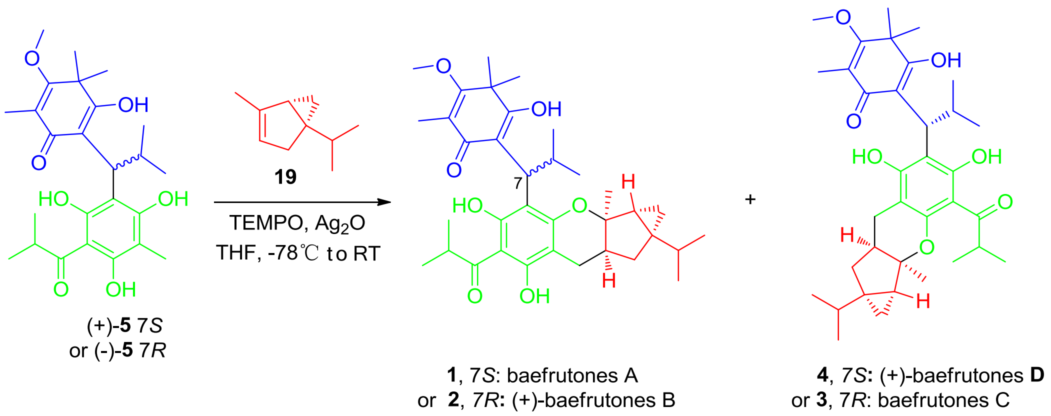
Compound **19** (partially characterised)

$[\alpha]_D^{20} = +40.3$ (c 1.0, MeOH)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.98 (1H, s), 0.97 (3H, d, J = 6.8 Hz), 0.92 (3H, d, J = 6.9 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.3, 121.1, 36.7, 34.2, 33.0, 31.5, 21.6, 20.3, 20.0, 16.5.

HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{10}H_{17}$, 137.1330; found, 137.1333.



Compounds1‒4. To a solution of (+)-**5** or (−)-**5** (100 mg, 0.22 mmol, 1.0 equiv) and **19** (152 µL, 0.67 mmol, 3 equiv) in THF (5 mL) at −78 ℃ was added Ag_2O (56.1 mg, 0.242 mmol, 1.1 equiv,) and TEMPO (41.2 mg, 0.264 mmol, 1.2 equiv). The resulting mixture was stirred at −78 ℃ for 1 h, then warmed to room temperature and stirred for another 2 h. The reaction solution was filtered and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (petroleum ether-acetone, 90:10, v/v) to afford the meroterpenoids-rich fraction. This fraction was separated by recycled preparative HPLC (MeOH-H_2O, 92:8, v/v) to yield **1** (52 mg, 40%), and **4** (44 mg, 34%), or **2** (49 mg, 37%), and **3** (46 mg, 35%), respectively.

Baefrutone A [**1**, yellowish crystals (MeOH)]:

R_f = 0.43 (petroleum ether/EtOAc 95:5). $[\alpha]_D^{20}$ = −123.5 (*c* 1.3, MeOH). ^1H and ^{13} NMR see Table S2. HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{35}H_{49}O_7$, 581.3478; found, 581.3472.

(+)-Baefrutone B (**2**, light yellow oil):

R_f = 0.44 (petroleum ether/EtOAc 95:5). $[\alpha]_D^{20}$ +26.7 (c 0.6, MeOH). ^1H and ^{13} NMR see Table S3. HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{35}H_{49}O_7$, 581.3478; found, 581.3473.

Baefrutone C (**3**, light yellow oil):

R_f = 0.41 (petroleum ether/EtOAc 95:5). $[\alpha]_D^{20}$ −16.7 (c 0.1, MeOH). ^1H and ^{13} NMR see Table S4. HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{35}H_{49}O_7$, 581.3478; found, 581.3478.

(+)-Baefrutone D (**4**, light yellow oil)

R_f = 0.42 (petroleum ether/EtOAc 95:5). $[\alpha]_D^{20}$ +23.2 (c 0.4, MeOH). ^{1}H and ^{13} NMR see Table S5. HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{35}H_{49}O_7$, 581.3478; found, 581.3479.

Table S1. Comparison of ^{1}H, ^{13}C NMR data for the synthetic and isolated natural baeckenon B (**5**).

no.	^{1}H					^{13}C				
	natural[a]		synthetic[b]		error, $\Delta\delta$ (nat.-syn.)	natural[a]		synthetic[b]		error, $\Delta\delta$ (nat.-syn.)
	major	minor	major	minor		major	minor	major	minor	
1	–	–	–	–	–	191.8	192.4	191.8	192.4	0/0
2	–	–	–	–	–	116.7	116.2	116.7	116.1	0/0.1
3	–	–	–	–	–	174.4	174.5	174.3	174.4	0.1/0.1
4	–	–	–	–	–	44.0	44.2	44.1	44.2	-0.1/0
5	–	–	–	–	–	175.8	174.5	175.8	174.5	0/0
6	–	–	–	–	–	113.9	114.1	114.0	114.1	-0.1/0
7	3.77, d (10.9)	3.95, m	3.78 , d (11.0)	3.95, m	-0.01/0	39.2	40.3	39.3	40.3	-0.1/0
8	3.13, m	3.13, m	3.13, m	3.13, m	0/0	26.2	26.5	26.3	26.5	-0.1/0
9	0.79, d (6.4)	0.75, d (6.4)	0.80, d (6.4)	0.75, d (6.4)	-0.1/0	22.2	22.1	22.2	22.0	0/0.1
10	0.85, d (6.4)	0.83, d (6.4)	0.84, d (6.4)	0.83, d (6.4)	0.1/0	22.0	22.0	22.1	22.0	-0.1/0
11	1.90, s	1.91, s	1.90, s	1.91, s	0/0	10.0	10.4	10.0	10.4	0/0
1'	–	–	–	–	–	109.3	109.4	109.4	109.5	-0.1/-0.1
2'	–	–	–	–	–	161.3	161.2	161.4	161.3	-0.1/-0.1
3'	–	–	–	–	–	102.8	102.9	102.8	102.9	0/0
4'	–	–	–	–	–	155.6	155.5	155.6	155.5	0/0
5'	–	–	–	–	–	102.6	102.7	102.7	102.8	-0.1/-0.1
6'	–	–	–	–	–	162.2	162.5	162.2	162.5	0/0
7'	–	–	–	–	–	211.0	211.6	211.0	211.6	0/0
8'	4.00-3.91, m	4.00-3.91, m	4.00-3.91, m	4.00-3.91, m	0/0	39.1	39.2	39.1	39.2	0/0
9'	1.21, d (6.7)	1.21, d (6.7)	1.21, d (7.0)	1.21, d (7.0)	0/0	19.6	19.5	19.7	19.5	0.1/0
10'	1.18, d (6.7)	1.18, d (6.7)	1.18, d (7.0)	1.18, d (7.0)	0/0	19.5	19.6	19.5	19.6	0/0

3-OMe	3.87, s	3.86, s	3.87, s	3.87, s	0/-0.1	62.1	62.0	62.1	62.0	0/0
5-OH	9.69	9.69	9.67	9.67	0.02/0.02	−	−	−	−	−
2'-OH	10.50	10.50	10.49	10.49	0.01/0.01	−	−	−	−	−
4'-OH	11.31	11.31	11.29	11.29	0.02/0.02	−	−	−	−	−
6'-OH	12.38	12.38	12.37	12.37	0.01/0.01	−	−	−	−	−

^{a}Recorded at 400 (^{1}H) and 100 (^{13}C) MHz. ^{b}Recorded at 300 (^{1}H) and 75 (^{13}C) MHz.

Table S2. Comparison of ^{1}H, ^{13}C NMR data for the synthetic and isolated natural baefrutone A (**1**) in $CDCl_3$.

no.	^{1}H					^{13}C				
	natural[a]		synthetic[a]		error, $\Delta\delta$ (nat.-syn.)	natural[a]		synthetic[a]		error, $\Delta\delta$ (nat.-syn.)
	major	minor	major	minor		major	minor	major	minor	
1	–	–	–	–	–	191.4	192.6	191.4	192.5	0/0.1
2	–	–	–	–	–	117.0	116.3	116.9	116.2	0.1/0.1
3	–	–	–	–	–	174.3	174.1	174.3	174.1	0/0
4	–	–	–	–	–	43.7	44.0	43.7	43.9	0/0.1
5	–	–	–	–	–	174.3	173.6	174.3	173.6	0/0
6	–	–	–	–	–	114.5	114.3	114.4	114.2	0.1/0.1
7	3.58, d (10.7)	3.99, d (11.2)	3.58, d (10.8)	3.98, d (11.4)	0/0.01	40.2	40.0	40.1	39.9	0.1/0.1
8	3.15, m	3.05, m	3.14, m	3.05, m	0.01/0	26.4	27.4	26.4	27.3	0/0.1
9	0.79, d (6.2)	0.87, d (6.4)	0.79, d (6.2)	0.86, d (6.4)	0/0.01	22.4	22.3	22.4	22.3	0/0
10	0.75, d (6.2)	0.74, d (6.4)	0.74, d (6.2)	0.74, d (6.4)	0.01/0	21.7	21.7	21.7	21.7	0/0
11	1.91, s	1.93, s	1.90, s	1.92, s	0.01/0.01	10.1	10.5	10.1	10.5	0/0
12	1.45, s	1.40, s	1.44, s	1.40, s	0.01/0	23.9	24.0	23.9	24.0	0/0
13	1.36, s	1.30, s	1.35, s	1.29, s	0.01/0.01	24.0	23.7	24.0	23.7	0/0
1'	–	–	–	–	–	106.8	107.0	106.7	107.0	0.1/0
2'	–	–	–	–	–	158.4	158.5	158.4	158.5	0/0
3'	–	–	–	–	–	106.0	106.3	105.9	106.2	0/0
4'	–	–	–	–	–	163.2	162.9	163.1	162.9	0.1/0
5'	–	–	–	–	–	98.5	99.5	98.4	99.4	0.1/0.1
6'	–	–	–	–	–	155.3	155.1	155.3	155.0	0/0.1
7'	–	–	–	–	–	212.4	212.5	212.3	212.5	0.1/0
8'	4.20, m[b]	4.16, m[b]	4.20, m[b]	4.15, m[b]	0/0.01	39.6	39.6	39.6	39.6	0/0

9'	1.22, d (6.8)	1.21, d (6.9)	1.21, d (6.8)	1.20, d (6.9)	0.01/0.01	20.0	20.1	20.0	20.1	0/0
10'	1.16, d (6.8)	1.15, d (6.9)	1.15, d (6.8)	1.14, d (6.9)	0.01/0.01	19.1	19.3	19.1	19.3	0/0
11'a	2.71, d (17.2)	2.66–2.58, m	2.70, d (17.2)	2.66–2.58, m	0.01/0	17.4	17.5	17.3	17.4	0.1/0.1
11'b	2.47, dd (17.2, 6.8)		2.46, dd (17.2, 6.8)		0.01					
1"	–	–	–	–	–	89.1	89.1	89.0	89.0	0.1/0.1
2"	1.91–1.85, m[b]	1.91–1.85, m[b]	1.91–1.85, m[b]	1.91–1.85, m[b]	0/0	34.8	34.4	34.7	34.3	0.1/0.1
3"a	1.72, dd (12.3, 7.2)	1.93, m[b]	–[c]	–[c]	–[c]	31.3	36.1	31.1	36.0	0.2/0.1
3"b	1.53, m[b]	1.42, m[b]	–[c]	–[c]	–[c]					
4"	–	–	–	–	–	32.7	32.7	32.7	32.7	0/0
5"a	0.65, m[b]	0.63, m[b]	0.65, m[b]	0.63, m[b]	0/0	14.1	8.6	14.1	10.1	0/-1.5
5"b	0.59, dd (8.3, 5.7)	0.48, dd (5.8, 3.3)	0.58, dd (8.3, 5.7)	0.47, dd (5.8, 3.3)	0.01/0.01					
6"	1.48, dd (8.3, 3.2)	1.66, dd (8.6, 3.2)	1.48, dd (8.3, 3.2)	1.65, dd (8.6, 3.2)	0/0.01	33.5	31.7	33.4	31.5	0.1/0.2
7"	1.32, s	1.42, s	1.32, s	1.41, s	0/0.01	21.1	21.4	21.1	21.4	0/0
8"	1.40, m[b]	1.82, m[b]	–[c]	–[c]	–[c]	32.6	30.5	32.6	30.4	0/0.1
9"	0.95, d (7.0)	0.93, d (7.6)	0.95, d (7.0)	0.94, d (7.6)	0/-0.01	20.2	21.3	20.2	21.3	0/0
10"	0.92, d (7.0)	0.79, d (7.6)	0.92, d (7.0)	0.78, d (7.6)	0/0.01	20.1	18.6	20.1	18.5	0/0.1
3-OMe	3.89, s	3.88, s	3.88, s	3.87, s	0.01/0.01	62.1	62.1	62.1	62.0	0/0.1
5-OH	9.05, s	9.82, s	9.06, s	9.83, s	-0.01/-0.01	–	–	–	–	–
2'-OH	12.11, s	12.11, s	12.14, s	11.13, s	-0.03/0.98	–	–	–	–	–
4'-OH	14.21, s	14.10, s	14.24, s	14.13, s	-0.03/-0.03	–	–	–	–	–

[a]Recorded at 500 (^{1}H) and 125 (^{13}C) MHz. [b]Overlapped signals without designating multiplicity. [c]Unassigned signals.

Table S3. Comparison of ^{1}H, ^{13}C NMR data for the synthetic **2** and isolated natural baefrutone B in $CDCl_3$.

	^{1}H					^{13}C				
no.	natural[a]		synthetic[a]		error, Δδ (nat.-syn.)	natural[a]		synthetic[a]		error, Δδ (nat.-syn.)
	major	minor	major	minor		major	minor	major	minor	
1	–	–	–	–	–	192.0	192.4	191.9	192.4	0.1/0
2	–	–	–	–	–	116.8	116.5	116.7	116.5	0.1/0
3	–	–	–	–	–	174.2	174.3	174.2	174.3	0/0
4	–	–	–	–	–	43.9	43.8	43.9	43.8	0/0
5	–	–	–	–	–	175.1	173.2	175.1	173.1	0/0.1
6	–	–	–	–	–	113.9	114.0	113.9	114.0	0/0
7	3.99, m	3.73, d (10.8)	3.98, m	3.73, d (10.8)	0.01/0	40.1	39.8	40.1	39.7	0/0.1
8	2.95, dp (12.6, 6.4)	3.18, dp (10.8, 6.4)	2.95, dp (12.6, 6.4)	3.18, dp (10.8, 6.4)	0/0	27.6	26.3	27.6	26.3	0/0
9	0.74, d (6.2)	0.71, d (6.3)	0.74, d (6.2)	0.71, d (6.3)	0/0	21.9	22.2	21.8	22.2	0.1/0
10	0.85, d (5.8)	0.79, d (6.4)	0.85, d (5.8)	0.79, d (6.4)	0/0	19.6	22.2	19.5	22.2	0.1/0
11	1.92, s	1.91, s	1.92, s	1.91, s	0/0	10.1	10.5	10.1	10.5	0/0
12	1.39, s	1.45, s	1.39, s	1.45, s	0/0	23.9	23.6	23.9	23.6	0/0
13	1.29, s	1.36, s	1.29, s	1.36, s	0/0	22.8	24.3	22.8	24.3	0/0
1'	–	–	–	–	–	107.3	107.9	107.3	107.9	0/0
2'	–	–	–	–	–	158.4	157.9	158.3	157.8	0.1/0.1
3'	–	–	–	–	–	106.0	106.1	106.0	106.1	0/0
4'	–	–	–	–	–	163.0	163.0	163.0	162.9	0/0.1
5'	–	–	–	–	–	99.1	99.3	99.1	99.3	0/0
6'	–	–	–	–	–	154.8	155.1	154.8	155.1	0/0
7'	–	–	–	–	–	212.6	212.4	212.5	212.3	0.1/0.1
8'	4.17, m[b]	4.17, m[b]	4.17, m[b]	4.17, m[b]	0/0	39.7	39.6	39.7	39.7	0/-0.1

9'	1.14, d (6.7)	1.15, d (6.6)	1.14, d (6.7)	1.15, d (6.6)	0/0	19.1	18.3	19.1	18.8	0/-0.5
10'	1.20, d (6.7)	1.21, d (6.8)	1.20, d (6.7)	1.21, d (6.8)	0/0	20.1	19.9	20.1	19.9	0/0
11'a	2.58, m[b]	2.68, d (17.5)	2.58, m[b]	2.68, d (17.5)	0/0	17.9	17.2	17.8	17.2	0.1/0
11'b		2.49, dd (17.5, 4.9)		2.49, dd (17.5, 4.9)	0/0					
1"	–	–	–	–	–	88.6	89.1	88.6	89.1	0/0
2"	1.96–1.88, m[b]	1.88–1.80, m[b]	1.96–1.88, m[b]	1.88–1.80, m[b]	0/0	34.3	34.6	34.3	34.6	0/0
3"a	1.90, m[b]	1.85, m[b]	–[c]	–[c]	–[c]	35.5	33.4	35.5	33.3	0/0.1
3"b	1.45, m[b]	1.55, m[b]	–[c]	–[c]	–[c]					
4"	–	–	–	–	–	32.8	32.8	32.8	32.8	0/0
5"a	0.61, dd (8.4, 5.8)	0.57, d (5.8)	0.61, dd (8.4, 5.8)	0.57, d (5.8)	0/0	9.4	11.8	9.3	11.7	0.1/0.1
5"b	0.52, dd (5.8, 3.3)		0.52, dd (5.8, 3.3)		0/0					
6"	1.57, m	1.63, dd (8.5, 3.2)	1.57, m	1.63, dd (8.5, 3.2)	0/0	32.5	31.8	32.5	31.7	0/0.1
7"	1.36, s	1.32, s	1.36, s	1.32, s	0/0	21.0	23.8	21.0	23.8	0/0
8"	1.57, m[b]	1.72, m[b]	–[c]	–[c]	–[c]	31.9	31.0	31.9	31.0	0/0
9"	0.93, d (6.4)	0.94, d (6.4)	0.92, d (6.4)	0.94, d (6.4)	0.01/0	20.9	20.3	20.9	20.3	0/0
10"	0.83, d (6.9)	0.81, d (6.9)	0.83, d (6.9)	0.81, d (6.9)	0/0	19.3	21.3	19.3	21.3	0/0
3-OMe	3.88, s	3.87, s	3.88, s	3.87, s	0/0	62.1	62.0	62.1	62.0	0/0
5-OH	9.64, s	9.13, s	9.65, s	9.13, s	-0.01/0	–	–	–	–	–
2'-OH	11.18, s	12.14, s	11.20, s	12.16, s	-0.02/-0.02	–	–	–	–	–
4'-OH	14.14, s	14.11, s	14.16, s	14.15, s	-0.02/-0.04	–	–	–	–	–

[a]Recorded at 500 (^{1}H) and 125 (^{13}C) MHz. [b]Overlapped signals without designating multiplicity. [c]Unassigned signals.

Table S4. Comparison of ^{1}H, ^{13}C NMR data for the synthetic and isolated natural baefrutone C (**3**) in $CDCl_3$.

	^{1}H					^{13}C				
no.	natural[a]		synthetic[b]		error, Δδ (nat.-syn.)	natural[a]		synthetic[b]		error, Δδ (nat.-syn.)
	major	minor	major	minor		major	minor	major	minor	
1	–	–	–	–	–	191.8	192.4	191.8	192.4	0/0
2	–	–	–	–	–	116.8	116.2	116.8	116.3	0/-0.1
3	–	–	–	–	–	174.4	174.2	174.4	174.2	0/0
4	–	–	–	–	–	44.0	44.1	44.0	44.1	0/0
5	–	–	–	–	–	174.4	175.6	174.4	175.6	0/0
6	–	–	–	–	–	114.0	114.2	114.1	114.3	-0.1/-0.1
7	3.76, d (10.9)	3.85, m[c]	3.77, m	3.85, m[c]	-0.1/0	40.0	38.9	40.1	38.9	-0.1/0
8	3.16–3.10, m[c]	3.16–3.10, m[c]	3.16–3.10, m[c]	3.16–3.10, m[c]	0/0	26.3	26.5	26.3	26.5	0/0
9	0.85, d (6.5)	0.83, d (6.7)	0.85, d (6.5)	0.83, d (6.7)	0/0	22.2	22.1	22.2	22.1	0/0
10	0.78, d (6.5)	0.77, d (6.7)	0.78, d (6.5)	0.77, d (6.7)	0/0	22.2	22.3	22.1	22.3	0.1/0
11	1.90, s	1.92, s	1.90, s	1.92, s	0/0	10.0	10.4	9.9	10.4	0.1/0
12	1.40, s	1.41, s	1.40, s	1.41, s	0/0	23.9	24.0	23.9	24.0	0/0
13	1.30, s	1.32, s	1.31, s	1.32, s	-0.01/0	24.2	23.8	24.2	23.9	0/-0.1
1'	–	–	–	–	–	108.1	108.0	108.2	108.0	-0.1/0
2'	–	–	–	–	–	162.0	161.9	162.0	162.1	0/-0.2
3'	–	–	–	–	–	103.5	103.6	103.6	103.7	-0.1/-0.1
4'	–	–	–	–	–	154.8	154.7	154.9	154.7	-0.1/0
5'	–	–	–	–	–	100.6	100.3	100.7	100.4	-0.1/-0.1
6'	–	–	–	–	–	162.6	163.0	162.7	163.1	-0.1/-0.1
7'	–	–	–	–	–	211.1	210.7	211.1	210.7	0/0
8'	4.02, p (6.9)	4.02, p (6.9)	4.02, p (6.9)	4.02, p (6.9)	0/0	39.0	38.8	39.1	38.8	-0.1/0

9'	0.88, d (6.8)	0.86, d (6.6)	0.87, d (6.8)	0.85, d (6.6)	0.1/0.1	19.9	20.1	19.9	20.1	0/0
10'	0.81, d (6.8)	0.79, d (6.6)	0.80, d (6.8)	0.79, d (6.6)	0.1/0	20.0	20.0	20.0	20.0	0/0
11'a	2.70, dd (17.2)	2.69, d (17.5)	2.71, m	2.67, m	-0.1/0.2	18.0	18.1	18.0	18.2	0/-0.1
11'b	2.46, dd (17.2, 6.8)	2.53, dd (17.5, 7.3)	2.46, dd (17.2, 6.8)	2.53, dd (17.5, 7.3)	0/0					
1"	–	–	–	–	–	86.5	86.2	86.6	86.2	-0.1/0
2"	1.87–1.79, m[c]	1.87–1.79, m[c]	–[d]	–[d]	–[d]	33.8	35.0	33.9	35.1	-0.1/-0.1
3"a	1.80, m[c]	1.80, m[c]	–[d]	–[d]	–[d]	32.5	32.4	32.6	32.2	-0.1/0.2
3"b	1.45, m[c]	1.45, m[c]	–[d]	–[d]	–[d]					
4"	–	–	–	–	–	32.1	32.7	32.1	32.9	0/-0.2
5"	0.50, m[c]	0.89, m[c]	0.49, m[c]	0.89, m[c]	0.1/0	12.9	14.3	12.9	14.3	0/0
6"	1.50–1.25, m[c]	1.50–1.25, m[c]	–[d]	–[d]	–[d]	32.2	32.1	32.2	32.1	0/0
7"	1.33, s	1.34, s	1.33, s	1.34, s	0/0	22.8	21.6	22.8	21.6	0/0
8"	1.50–1.25, m[c]	1.50–1.25, m[c]	–[d]	–[d]	–[d]	34.0	33.4	34.2	33.5	-0.2/-0.1
9"	0.88, d (6.8)	0.86, d (6.6)	0.87, d (6.8)	0.86, d (6.6)	0.1/0	19.9	20.1	19.9	20.1	0/0
10"	0.81, d (6.8)	0.79, d (6.6)	0.80, d (6.8)	0.79, d (6.6)	0.1/0	20.0	20.0	20.0	20.0	0/0
3-OMe	3.86, s	3.86, s	3.86, s	3.86, s	0/0	62.1	62.0	62.0	61.9	0.1/0.1
5-OH	10.62, s	9.76, s	10.62, s	9.74, s	0/0.02	–	–	–	–	–
2'-OH	16.35, s	16.58, s	16.35, s	16.55, s	0/0.03	–	–	–	–	–
6'-OH	12.23, s	12.23, s	12.21, s	11.08, s	0.02/1.15	–	–	–	–	–

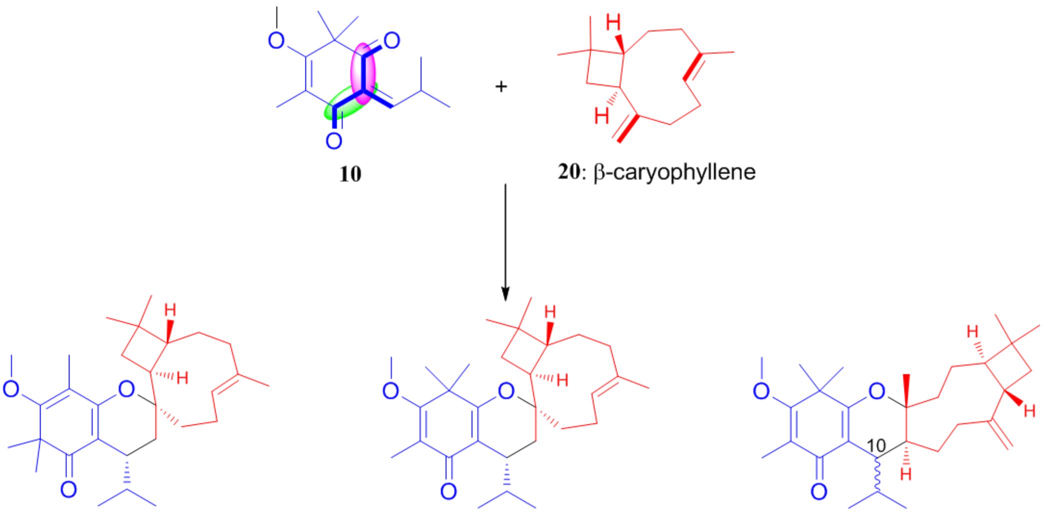
[a]Recorded at 500 (^{1}H) and 125 (^{13}C) MHz. [b]Recorded at 300 (^{1}H) and 75 (^{13}C) MHz. [c]Overlapped signals without designating multiplicity. [d]Unassigned signals.

Table S5. Comparison of ^{1}H, ^{13}C NMR data for the synthetic **4** and isolated natural baefrutone D in $CDCl_3$.

no.	^{1}H					^{13}C				
	natural[a]		synthetic[b]		error, Δδ (nat.-syn.)	natural[a]		synthetic[b]		error, Δδ (nat.-syn.)
	major	minor	major	minor		major	minor	major	minor	
1	–	–	–	–	–	191.8	192.3	191.7	192.3	0.1/0
2	–	–	–	–	–	116.8	116.3	116.8	116.3	0/0
3	–	–	–	–	–	174.2	174.3	174.2	174.4	0/-0.1
4	–	–	–	–	–	44.0	44.1	44.0	44.1	0/0
5	–	–	–	–	–	175.6	174.4	175.6	174.4	0/0
6	–	–	–	–	–	114.1	114.3	114.1	114.3	0/0
7	3.75, d (10.8)	3.87, d (10.8)	3.75, d (10.8)	3.87, m	0/0	39.2	40.0	39.2	40.0	0/0
8	3.11, m[c]	3.11, m[c]	3.11, m[c]	3.11, m[c]	0/0	26.3	26.6	26.3	26.6	0/0
9	0.84, d (6.5)	0.80, d (6.5)	0.84, d (6.5)	0.80, d (6.5)	0/0	22.2	22.1	22.2	22.1	0/0
10	0.78, d (6.5)	0.75, d (6.5)	0.78, d (6.5)	0.75, d (6.5)	0/0	22.1	22.0	22.1	22.0	0/0
11	1.91, s	1.91, s	1.91, s	1.91, s	0/0	10.0	10.4	10.0	10.4	0/0
12	1.41, s	1.33, s	1.41, s	1.33, s	0/0	24.3	24.0	24.3	23.9	0/0.1
13	1.32, s	1.31, s	1.33, s	1.31, s	-0.1/0	24.0	23.9	23.9	23.9	0.1/0
1'	–	–	–	–	–	108.1	108.2	108.0	108.2	0.1/0
2'	–	–	–	–	–	162.0	162.2	162.0	162.2	0/0
3'	–	–	–	–	–	103.6	103.7	103.6	103.7	0/0
4'	–	–	–	–	–	154.7	154.8	154.8	154.7	-0.1/0.1
5'	–	–	–	–	–	100.4	100.8	100.4	100.8	0/0
6'	–	–	–	–	–	162.7	163.0	162.7	163.0	0/0
7'	–	–	–	–	–	210.7	211.2	210.7	211.2	0/0
8'	4.03, p (6.7)	4.03, p (6.7)	4.03, p (6.7)	4.03, p (6.7)	0/0	38.8	38.9	38.8	38.9	0/0

9'	0.85, d (6.6)	0.85, d (6.5)	0.85, d (6.6)	0.85, d (6.5)	0/0	20.1	20.1	20.0	20.0	0.1/0.1
10'	0.81, d (6.6)	0.84, d (6.5)	0.81, d (6.6)	0.84, d (6.5)	0/0	19.8	19.9	19.9	19.9	-0.1/0
11'a	2.69, d (17.4)	2.70, d (17.4)	2.67, m	2.73, m	0.02/-0.03	17.9	18.3	17.8	18.3	0.1/0
11'b	2.52, dd (17.4, 7.3)	2.50–2.43, m[c]	2.52, dd (17.4, 7.3)	2.50–2.43, m[c]	0/0					
1"	–	–	–	–	–	86.1	86.8	86.1	86.8	0/0
2"	1.85–1.77, m[c]	1.86–1.81, m[c]	–[d]	–[d]	–[d]	34.2	35.5	34.2	35.1	0/0.4
3"a	1.72, m[c]	1.74, m[c]	–[d]	–[d]	–[d]	32.8	32.5	32.8	32.5	0/0
3"b	1.45, m[c]	1.50, m[c]	–[d]	–[d]	–[d]					
4"	–	–	–	–	–	32.6	32.6	32.6	32.6	0/0
5"	0.54–0.46, m[c]	0.51, m[c]	0.54–0.46, m[c]	0.51, m[c]	0/0	12.3	13.0	12.3	13.0	0/0
6"	1.47–1.39, m[c]	1.47–1.39, m[c]	–[d]	–[d]	–[d]	32.1	32.2	32.2	32.2	-0.1/0
7"	1.34, s	1.33, s	1.34, s	1.33, s	0/0	21.6	22.1	21.6	22.1	0/0
8"	1.43–1.39, m[c]	1.44–1.40, m[c]	–[d]	–[d]	–[d]	33.6	33.9	33.5	33.9	0.1/0
9"	0.85, d (6.6)	0.85, d (6.5)	0.85, d (6.6)	0.85, d (6.5)	0/0	20.0	19.9	20.0	19.9	0/0
10"	0.81, d (6.6)	0.84, d, (6.5)	0.81, d (6.6)	0.84, d, (6.5)	0/0	19.8	20.0	19.5	19.6	0.2/0.4
3-OMe	3.87, s	3.86, s	3.87, s	3.86, s	0/0	62.0	61.9	62.0	61.9	0/0
5-OH	9.74, s	10.57, s	9.75, s	10.58, s	-0.01/-0.01	–	–	–	–	–
2'-OH	16.31, s	16.53, s	16.33, s	16.54, s	-0.02/-0.01	–	–	–	–	–
6'-OH	12.17, s	12.17, s	12.18, s	11.11, s	-0.01/1.06	–	–	–	–	–

[a] Recorded at 500 (^{1}H) and 125 (^{13}C) MHz. [b] Recorded at 300 (^{1}H) and 75 (^{13}C) MHz. [c] Overlapped signals without designating multiplicity. [d] Unassigned signals.



10 + **20**: β-caryophyllene

6: frutescone A

7: frutescone D

8, 10*S*: frutescone E
9, 10*R*: frutescone F

*Frutescones A,D–F (**6**–**9**)*. A solution of **10** (200 mg, 0.84 mmol, 1.0 equiv) and **20** (573 μL, 2.54 mmol, 3 equiv) in mixture of toluene (6 mL) and H_2O (3 mL) was refluxed at 110 ℃ for 4 h until consumption of the starting material. Then the mixture was cooled down to room temperature and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (petroleum ether-acetone, 90:10, v/v) to afford the meroterpenoids-rich fraction. This fraction was separated by recycled preparative HPLC (CH_3CN-H_2O, 75:25, v/v) to yield **6** (27 mg, 7%), **7** (70 mg, 19%), **8** (62 mg, 17%), and **9** (81 mg, 22%), respectively.

Due to the flexible nine-membered ring of the caryophyllene unit, the ^1H and ^{13}C NMR spectra of compounds **6** and **7** exhibited broad signals and incomplete signals at room temperature (298K), as can be found in some other caryophyllene-based meroterpenoids with oxa-spiro[5.8] tetradecadiene ring (Liu, C. et al. *Org. Lett.*, 2016, 18, 4004-4007; Liu, H. X. et al. *Org. Biomol. Chem.*, 2016, 14,7354–7360). Thus, the NMR spectra of synthetic compounds **6** and **7** were tested at a lower temperature 278K (600 MHz, $CDCl_3$), which displayed two sets of NMR signals, reveallling two major equilibrating conformers (*βα* and *ββ*), and they proved to be in accordance with those of natural compounds **6** and **7** recorded at 242K (600 MHz, $CDCl_3$).

Synthetic frutescone A (**6**, light yellow oil):

R_f = 0.32 (petroleum ether/EtOAc 95:5). $[\alpha]_D^{20}$ = −86.6 (*c* 0.2, MeOH). ^{1}H and ^{13} NMR see Table S6. HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{29}H_{45}O_3$, 441.3363; found, 441.3367.

Synthetic frutescone D (**7**, light yellow oil):

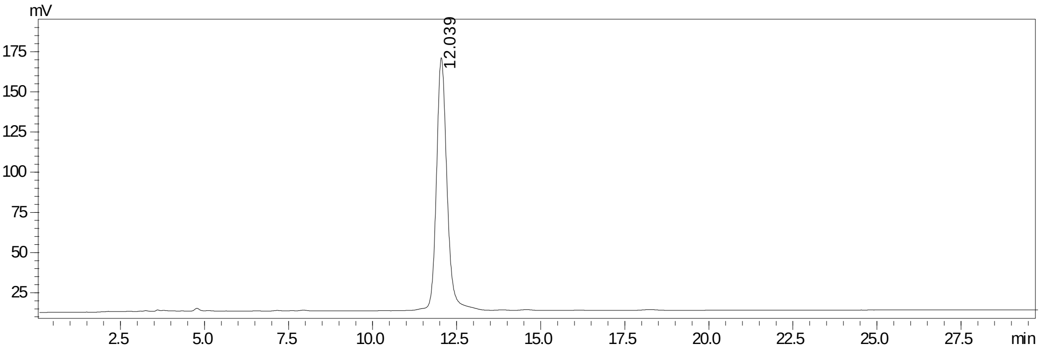
R_f = 0.30 (petroleum ether/EtOAc 95:5). $[\alpha]_D^{20}$ = +76.7 (c 0.1, MeOH). ^{1}H and ^{13} NMR see Table S7. HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{29}H_{45}O_3$, 441.3363; found, 441.3358.

Synthetic frutescone E (**8**, light yellow oil):

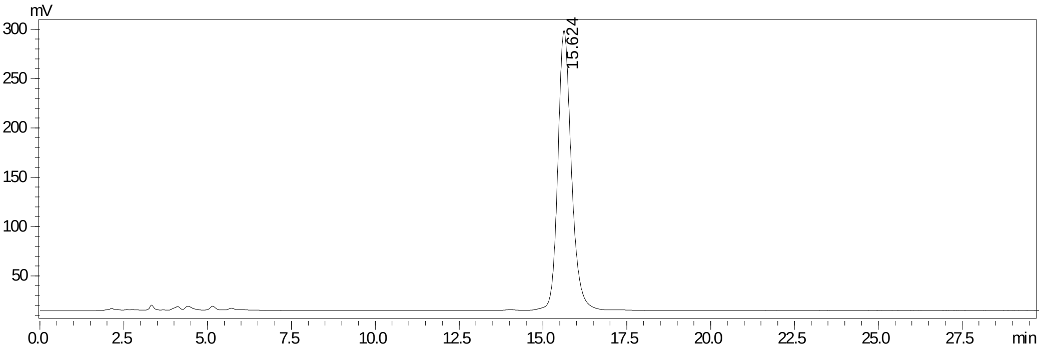
R_f = 0.22 (petroleum ether/EtOAc 95:5). $[\alpha]_D^{20}$ = +114.8 (c 0.1, MeOH). ^{1}H and ^{13} NMR see Table S8. HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{29}H_{45}O_3$, 441.3363; found, 441.3366.

Synthetic frutescone F (**9**, light yellow oil):

R_f = 0.32 (petroleum ether/EtOAc 95:5). $[\alpha]_D^{20}$ = −52.9 (c 0.2, MeOH). ^{1}H and ^{13} NMR see Table S9. HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{29}H_{45}O_3$, 441.3363; found, 441.3359.



HPLC spectrum of synthetic compound **6**



HPLC spectrum of synthetic compound **7**

[The HPLC spectra of synthetic compounds **6** and **7** were carried out on a Shim-pack VP-ODS column (150×4.6 mm, 5 μm), using MeOH-H_2O (92:8, v/v) as mobile phase at a flow rate of 1 mL/min with UV detection at 254 nm.]

Table S6. Comparison of ^{1}H, ^{13}C NMR data for the synthetic and isolated natural frutescone A (**6**) in $CDCl_3$.

	^{1}H					^{13}C				
no.	natural[a]		synthetic[b]		error, Δ*δ* (nat.-syn.)	natural[a]		synthetic[b]		error, Δ*δ* (nat.-syn.)
	major	minor	major	minor		major	minor	major	minor	
1	–	–	–	–	–	106.8	107.3	107.0	107.5	-0.2/-0.2
2	–	–	–	–	–	200.5	200.4	200.3	200.3	0.2/0.1
3	–	–	–	–	–	48.8	48.7	49.0	48.9	-0.2/-0.2
4	–	–	–	–	–	167.2	167.5	167.4	167.7	-0.2/-0.2
5	–	–	–	–	–	112.1	111.9	111.9	111.8	0.2/0.1
6	–	–	–	–	–	166.4	166.4	166.3	166.3	0.1/0.1
7	1.24, s	1.23, s	1.23, s	1.23, s	0.01/0	25.7	25.9	25.6	25.9	0.1/0
8	1.21, s	1.22, s	1.22, s	1.22, s	-0.01/0	22.8	22.7	22.8	22.6	0/0.1
9	1.74, s	1.71, s	1.74, s	1.72, s	0/-0.01	10.1	10.0	9.9	9.8	0.2/0.2
10	2.64, dt (9.0, 4.2)	2.70, dd (10.4, 6.7)	2.66, m	2.72, m	-0.02/-0.02	32.3	32.2	32.5	32.2	-0.2/0
11	2.05	1.60	–[c]	–[c]	–[c]	32.2	32.4	32.4	32.5	-0.2/-0.1
12	1.00, d (6.4)	1.13, d (6.4)	0.98, d (6.5)	1.12, d (6.3)	0.02/0.01	20.8	22.5	20.8	22.5	0/0
13	0.80, d (6.9)	0.75, d (6.9)	0.89, d (6.7)	0.76, d (6.7)	-0.09/-0.01	20.9	21.0	20.9	21.0	0/0
1′	2.50	2.17	–[c]	–[c]	–[c]	54.9	53.3	55.1	53.6	-0.2/-0.3
2′a	1.60	1.95	–[c]	–[c]	–[c]	29.6	30.3	29.7	30.5	-0.1/-0.2
2′b	1.47	1.51	–[c]	–[c]	–[c]					
3′a	2.46	2.07	2.47	–[c]	-0.01/–[c]	36.8	39.9	37.0	40.0	-0.2/-0.1
3′b	1.70	1.95	1.70	1.95	0/0					
4′	–	–	–	–	–	133.2	137.8	133.0	137.5	0.2/0.3
5′	5.07, d (12.1)	5.35, t (7.2)	5.08, d (12.0)	5.34, t (7.2)	-0.01/0.01	125.6	120.0	125.8	120.3	-0.2/-0.3
6′	2.30	2.40	–[c]	–[c]	–[c]	23.7	22.3	23.3	22.4	0.4/-0.1
7′a	2.05	2.01	–[c]	–[c]	–[c]	40.9	43.2	41.1	43.6	-0.2/-0.4

7′b	1.72	1.90	–[c]	–[c]	–[c]					
8′	–	–	–	–	–	85.8	87.9	85.7	87.8	0.1/0.1
9′	1.35	1.57	–[c]	–[c]	–[c]	47.8	46.4	48.1	46.8	-0.3/-0.4
10′	1.28	2.50	–[c]	–[c]	–[c]	35.9	35.1	36.2	35.3	-0.3/-0.2
11′	–	–	–	–	–	31.1	31.1	31.2	31.2	-0.1/-0.1
12′	0.84, s	0.80, s	0.85, s	0.81, s	-0.01/-0.01	29.9	29.7	29.9	29.7	0/0
13′	0.88, s	0.89, s	0.89, s	0.90, s	-0.01/-0.01	24.7	23.1	24.7	23.1	0/0
14′	1.70, s	1.69, s	–[c]	–[c]	–[c]	16.2	16.2	16.1	16.1	0.1/0.1
15′	1.71	1.90	–[c]	–[c]	–[c]	24.6	23.9	24.6	24.1	0/-0.2
OMe	3.74, s	3.74, s	3.73, s	3.73, s	0.01/0.01	62.1	62.1	61.9	61.9	0.2/0.2

[a] Recorded at 242K, 600 (^{1}H) and 150 (^{13}C) MHz. [b] Recorded at 278K, 600 (^{1}H) and 150 (^{13}C) MHz. [c] Unassigned signals.

Table S7. Comparison of ^{1}H, ^{13}C NMR data for the synthetic and isolated natural frutescone D (**7**) in $CDCl_3$.

	^{1}H					^{13}C				
no.	natural[a]		synthetic[b]		error, Δδ (nat.-syn.)	natural[a]		synthetic[b]		error, Δδ (nat.-syn.)
	major	minor	major	minor		major	minor	major	minor	
1	–	–	–	–	–	108.1	108.1	108.4	108.4	-0.3/-0.3
2	–	–	–	–	–	188.7	188.8	188.6	188.6	0.1/0.2
3	–	–	–	–	–	117.2	117.2	117.4	117.2	-0.2/0
4	–	–	–	–	–	171.3	171.2	171.4	171.2	-0.1/0
5	–	–	–	–	–	42.9	42.9	43.0	43.2	-0.1/-0.3
6	–	–	–	–	–	169.4	168.7	169.4	168.7	0/0
7	1.84, s	1.85, s	1.86, s	1.86, s	-0.02/-0.01	10.3	10.2	10.3	10.2	0/0
8	1.25, s	1.23, s	1.27, s	1.24, s	-0.02/-0.01	24.7	24.8	24.8	25.0	-0.1/-0.2
9	1.18, s	1.15, s	1.20, s	1.17, s	-0.02/-0.02	23.0	23.1	22.9	23.2	0.1/-0.1
10	2.64, dq (7.6, 4.2)	2.70, dd (10.4, 6.2)	2.67, m	2.74, m	-0.03/-0.04	31.8	31.7	32.2	32.2	-0.4/-0.5
11	2.05, m	1.59, m	–[c]	–[c]	–[c]	31.8	32.6	32.1	32.5	-0.3/0.1
12	0.81, d (6.4)	1.12, d (6.4)	0.80, d (6.5)	1.11, d (6.3)	0.01/0.01	20.8	21.4	20.8	21.3	0/0.1
13	0.97, d (6.8)	0.77, d (6.8)	0.97, d (6.6)	0.79, d (6.7)	0/-0.02	20.9	22.3	20.9	22.1	0/0.2
1′	2.45	2.13	2.45	2.13	0/0	54.5	52.4	54.7	52.7	-0.2/-0.3
2′a	2.01	1.71	–[c]	–[c]	–[c]	30.5	29.7	30.7	29.8	-0.2/-0.1
2′b	1.52	1.43	–[c]	–[c]	–[c]					
3′a	2.45	2.05	2.45	2.05	0/0	39.8	37.3	40.0	37.7	-0.2/-0.4
3′b	1.60	1.95	–[c]	–[c]	–[c]					
4′	–	–	–	–	–	133.2	137.7	133.1	137.5	0.1/0.2
5′	5.06, d (12.1)	5.34, t (8.1)	5.09, d (12.0)	5.35, t (7.2)	-0.03/-0.01	125.6	119.9	125.9	120.2	-0.3/-0.3
6′	2.26	2.32	2.26	2.32	0/0	23.7	22.4	23.3	22.6	0.4/-0.2
7′a	2.05	1.93	2.05	1.93	0/0	40.3	42.8	40.5	43.0	-0.2/-0.2

7′b	1.75	1.75	–[c]	–[c]	–[c]					
8′	–	–	–	–	–	83.7	85.3	83.8	85.3	-0.1/0
9′	1.37, t (9.4)	1.61	1.41, t (9.6)	–[c]	-0.04/–[c]	47.7	46.2	48.1	46.6	-0.4/-0.4
10′	1.22	2.45	–[c]	–[c]	–[c]	36.6	35.2	37.0	35.5	-0.4/-0.3
11′	–	–	–	–	–	30.9	32.1	31.1	32.1	-0.2/0
12′	0.85, s	0.80, s	0.85, s	0.81, s	0/-0.01	29.9	29.7	30.0	29.9	-0.1/-0.2
13′	0.87, s	0.88, s	0.89, s	0.90, s	-0.02/-0.02	24.9	22.8	25.0	22.9	-0.1/-0.1
14′	1.68, s	1.69, s	–[c]	–[c]	–[c]	16.2	16.2	16.1	16.1	0.1/0.1
15′	1.71	1.89	1.70	1.86	0.01/0.03	24.7	23.9	24.3	24.0	0.4/-0.1
OMe	3.79, s	3.79, s	3.80, s	3.80, s	-0.01/-0.01	62.0	62.0	61.9	61.9	0.1/0.1

[a]Recorded at 242K, 600 (^{1}H) and 150 (^{13}C) MHz. [b]Recorded at 278K, 600 (^{1}H) and 150 (^{13}C) MHz. [c]Unassigned signals.

Table S8. Comparison of ^{1}H, ^{13}C NMR data for the synthetic and isolated natural frutescone E (**8**) in CDCl$_3$.

No.	^{1}H			^{13}C		
	natural[a]	synthetic[a]	error, $\Delta\delta$ (nat.-syn.)	natural[a]	synthetic[a]	error, $\Delta\delta$ (nat.-syn.)
1	–	–	–	114.8	114.8	0
2	–	–	–	187.8	187.7	0.1
3	–	–	–	118.0	117.9	0.1
4	–	–	–	172.1	172.0	0.1
5	–	–	–	42.5	42.5	0
6	–	–	–	169.7	169.6	0.1
7	1.88, s	1.87, s	0.01	10.0	10.0	0
8	1.32, s	1.31, s	0.01	23.6	23.6	0
9	1.23, s	1.22, s	0.01	23.9	23.9	0
10	2.35, d (7.1)	2.34, dd (7.0, 2.6)	0.01	40.4	40.5	-0.1
11	2.05, m[b]	2.05, m[b]	0	31.9	31.9	0
12	0.89, d (7.2)	0.89, d (7.1)	0	20.8	20.8	0
13	0.75, d (7.2)	0.74, d (7.0)	0.01	19.3	19.3	0
1′	2.10, m[b]	2.10, m[b]	0	54.2	54.2	
2′a	2.10, m[b]	2.10, m[b]	0	21.8	21.9	-0.1
2′b	1.42, m[b]	1.42, m[b]	0			
3′a	2.05, m[b]	2.05, m[b]	0	39.2	39.2	0
3′b	1.90, m[b]	1.90, m[b]	0			
4′	–	–	–	82.7	82.6	0.1
5′	2.14, m[b]	2.14, m[b]	0	38.4	38.5	-0.1
6′	1.56, m	1.56, m	0	36.2	36.2	0
7′a	2.45, m[b]	2.45, m[b]	0	35.5	35.5	0
7′b	2.03, m[b]	2.03, m[b]	0			
8′	–	–	–	152.8	152.8	0
9′	2.40, m[b]	2.40, m[b]		42.2	42.2	0
10′a	1.76, t (10.2)	1.75, t (10.5)	0.01	36.0	36.0	0
10′b						
11′	–	–	–	33.7	33.7	0
12′	1.02, s	1.01, s	0.01	30.7	30.7	0
13′	0.99, s	0.98, s	0.01	22.6	22.6	0
14′	0.99, s	0.98, s	0.01	21.3	21.2	0.1
15′	4.94, brs	4.93, brs	0.01	111.2	111.2	0
	4.88, brs	4.87, brs	0.01			
OMe	3.83, s	3.83, s	0	61.8	61.7	0

[a] Recorded at 300 (^{1}H) and 75 (^{13}C) MHz. [b] Overlapped signals without designating multiplicity.

Table S9. Comparison of ^{1}H, ^{13}C NMR data for the synthetic and isolated natural frutescone E (**9**) in $CDCl_3$.

No.	^{1}H natural[a]	^{1}H synthetic[b]	^{1}H error, $\Delta\delta$ (nat.-syn.)	^{13}C natural[a]	^{13}C synthetic[b]	^{13}C error, $\Delta\delta$ (nat.-syn.)
1	–	–	–	112.6	112.6	0
2	–	–	–	188.2	188.2	0
3	–	–	–	117.4	117.4	0
4	–	–	–	171.9	171.9	0
5	–	–	–	42.7	42.6	0.1
6	–	–	–	168.9	168.9	0
7	1.89, s	1.87, s	0.02	10.1	10.1	0
8	1.30, s	1.29, s	0.01	24.4	24.4	0
9	1.28, s	1.27, s	0.01	23.5	23.5	0
10	2.70, m	2.70, m	0	35.8	35.8	0
11	2.03, m[c]	2.03, m[c]	0	26.0	25.9	0.1
12	1.17, d (6.8)	1.15, d (6.8)	0.02	26.8	26.7	0.1
13	0.64, d (7.0)	0.62, d (6.9)	0.02	19.7	19.6	0.1
1′	1.56, m[c]	1.56, m[c]	0	57.1	57.1	0
2′a	1.59, m[c]	1.59, m[c]	0	23.7	23.7	0
2′b	1.33, m[c]	1.33, m[c]	0			
3′a	2.03, m[c]	2.03, m[c]	0	44.5	44.4	0.1
3′b	1.47, m	1.47, m	0			
4′	–	–	–	84.2	84.2	0
5′	1.78, m[c]	1.78, m[c]	0	39.6	39.6	0
6′	1.71–1.81, m[c]	1.71–1.81, m[c]	0	25.1	25.1	0
7′a	2.41, m	2.41, m	0	35.7	35.7	0
7′b	2.16, m	2.16, m	0			
8′	–	–	–	151.3	151.3	0
9′	2.43, m[c]	2.43, m[c]	0	41.7	41.7	0
10′a	1.70, m	1.70, m	0	36.6	36.6	0
10′b	1.58, m[c]	1.58, m[c]	0			
11′	–	–	–	34.4	34.4	0
12′	0.93, s	0.91, s	0.02	29.9	29.9	0
13′	0.96, s	0.95, s	0.01	21.9	21.8	0.1
14′	1.29, s	1.28, s	0.01	23.1	23.1	0
15′	4.88, brs	4.87, brs	0.01	110.9	110.8	0.1
OMe	3.83, s	3.82, s	0.01	61.8	61.7	0.1

[a] Recorded at 500 (^{1}H) and 125 (^{13}C) MHz. [b] Recorded at 300 (^{1}H) and 75 (^{13}C) MHz. [c] Overlapped signals without designating multiplicity.

Antimicrobial activity assay

Determination of the MIC values were conducted by the conventional broth microdilution method. Four pathogenic strains, *Pseudomonas aeruginosa* PA01, *Staphylococcus aureus* Newman, *Samonella paratyphi* ATCC 27853, and *Candida albicans* ATCC 10231, were grown on potato dextrose agar. The inoculum was standardized to approximately 5×10^5 CFU/mL, and the test compounds (100 μg/mL as stock solution in DMSO and serial dilutions) were transferred to a 96-well plate in triplicate, achieving a final volume of 200 μL. The plates were incubated at 37 ° C for 16 h, and MIC values were recorded as the lowest concentration of antibiotic at which no visible growth of bacteria and fungal was observed. Tetracycline, vancomycin, and fluconazole were used as the positive control.

NMR Spectra

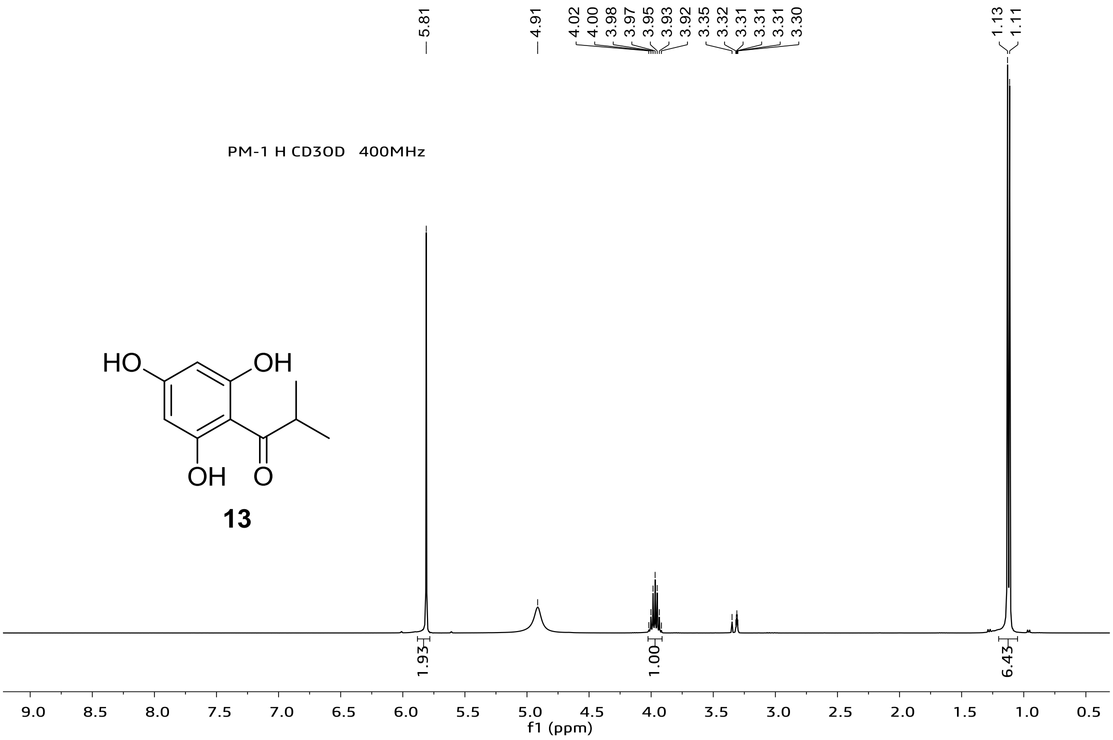


Figure S1-1. ^{1}H NMR of compound **13** (400 MHz, CD_3OD)

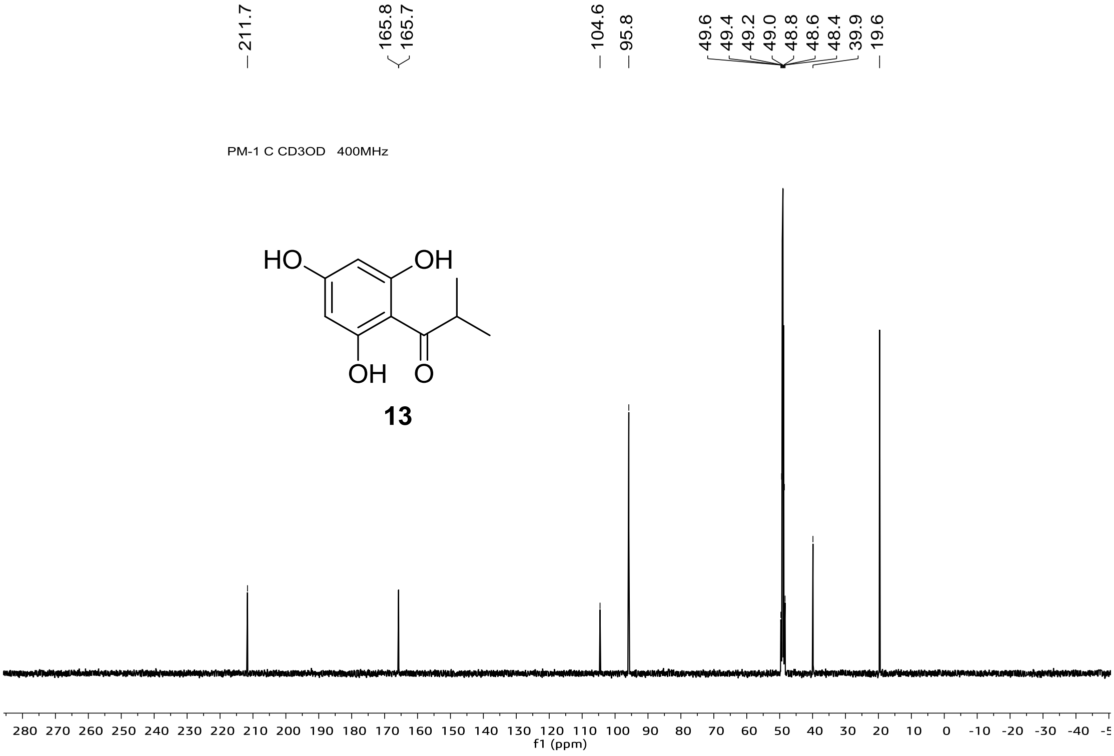


Figure S1-2. ^{13}C NMR of compound **13** (100 MHz, CD_3OD)

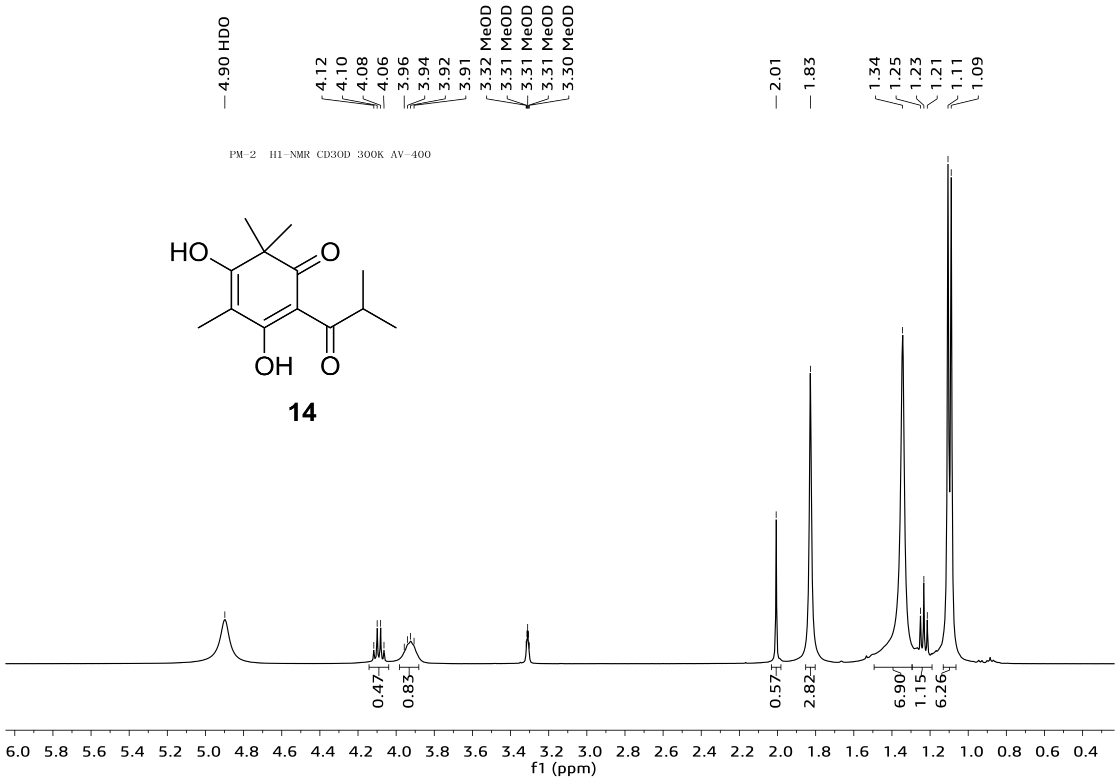


Figure S2-1. ^{1}H NMR of compound **14** (400 MHz, CD_3OD)

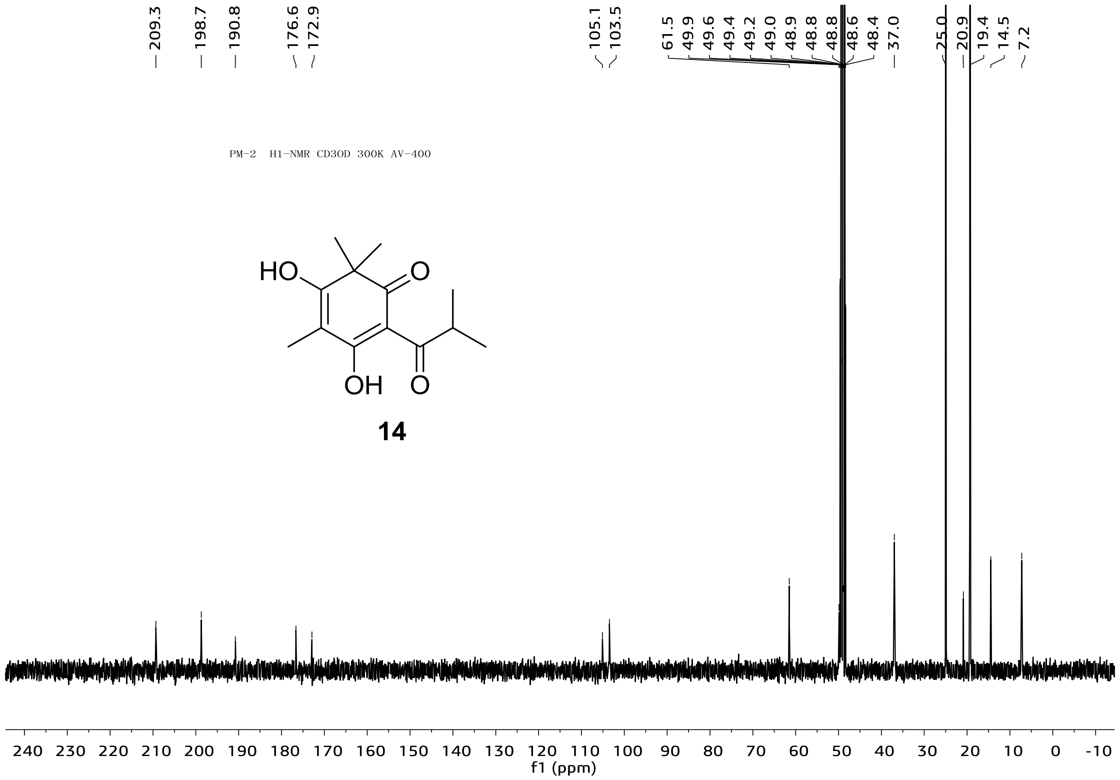


Figure S2-2. ^{13}C NMR of compound **14** (100 MHz, CD_3OD)

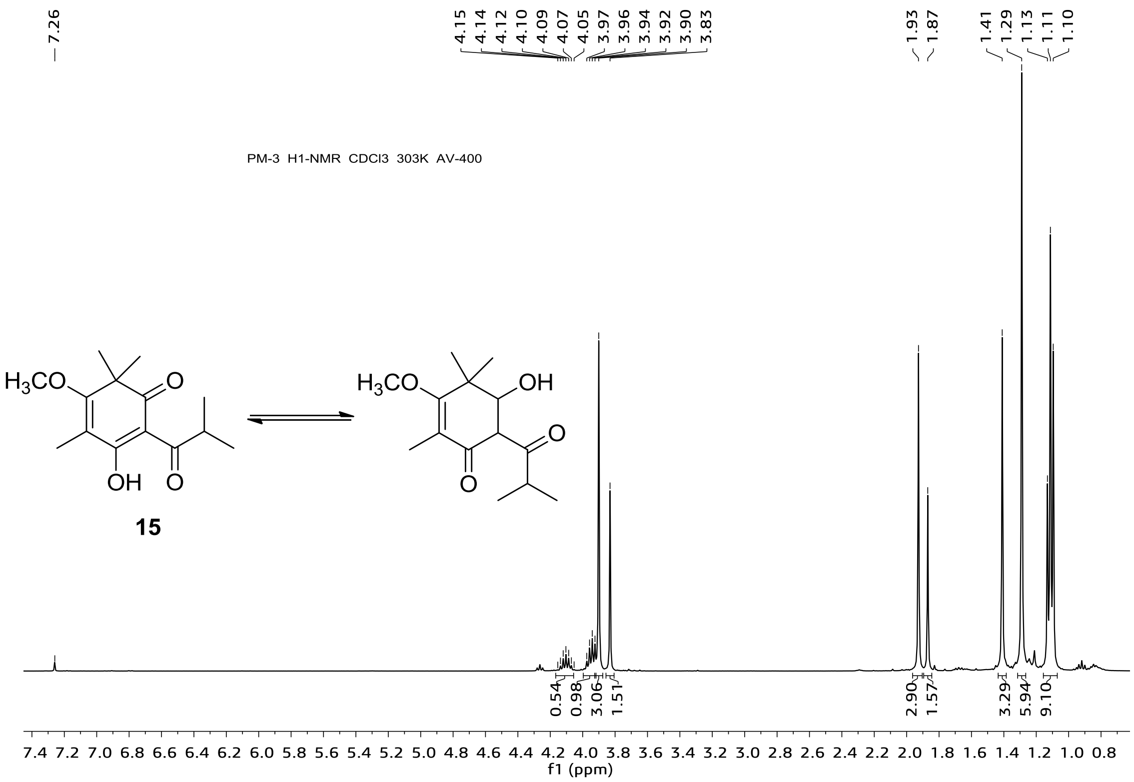


Figure S3-1. ^{1}H NMR of compound **15** (400 MHz, $CDCl_3$)

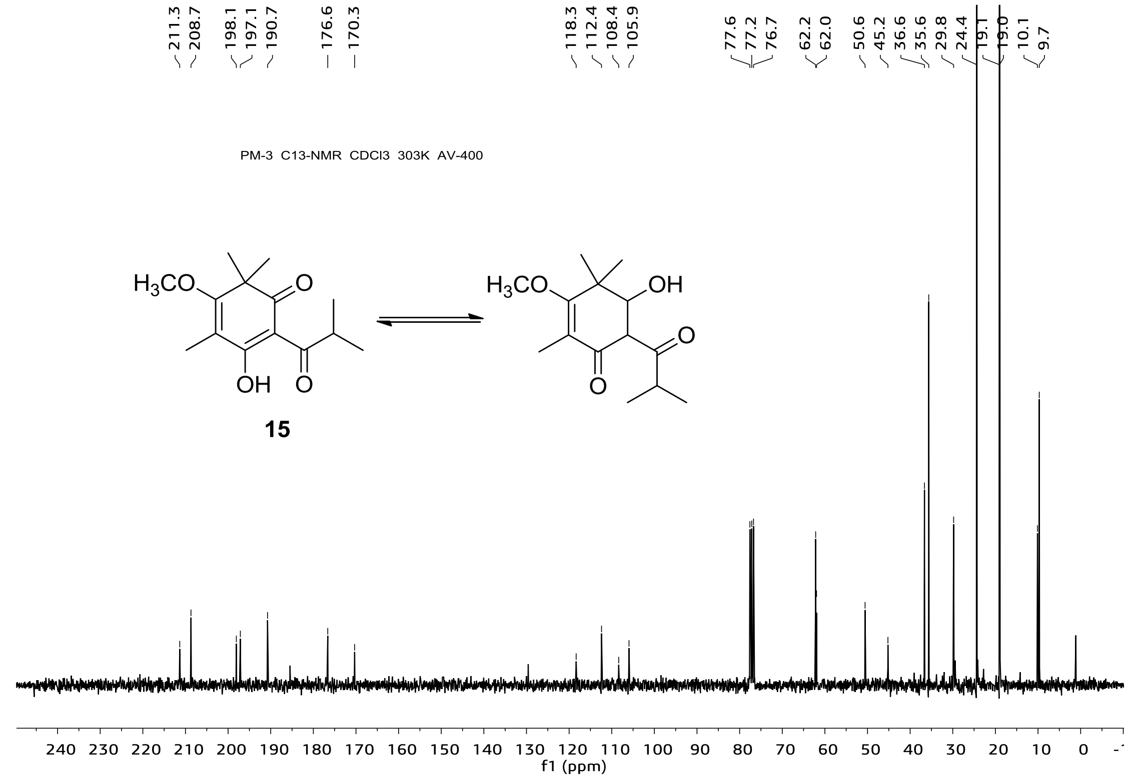


Figure S3-2. ^{13}C NMR of compound **15** (100 MHz, $CDCl_3$)

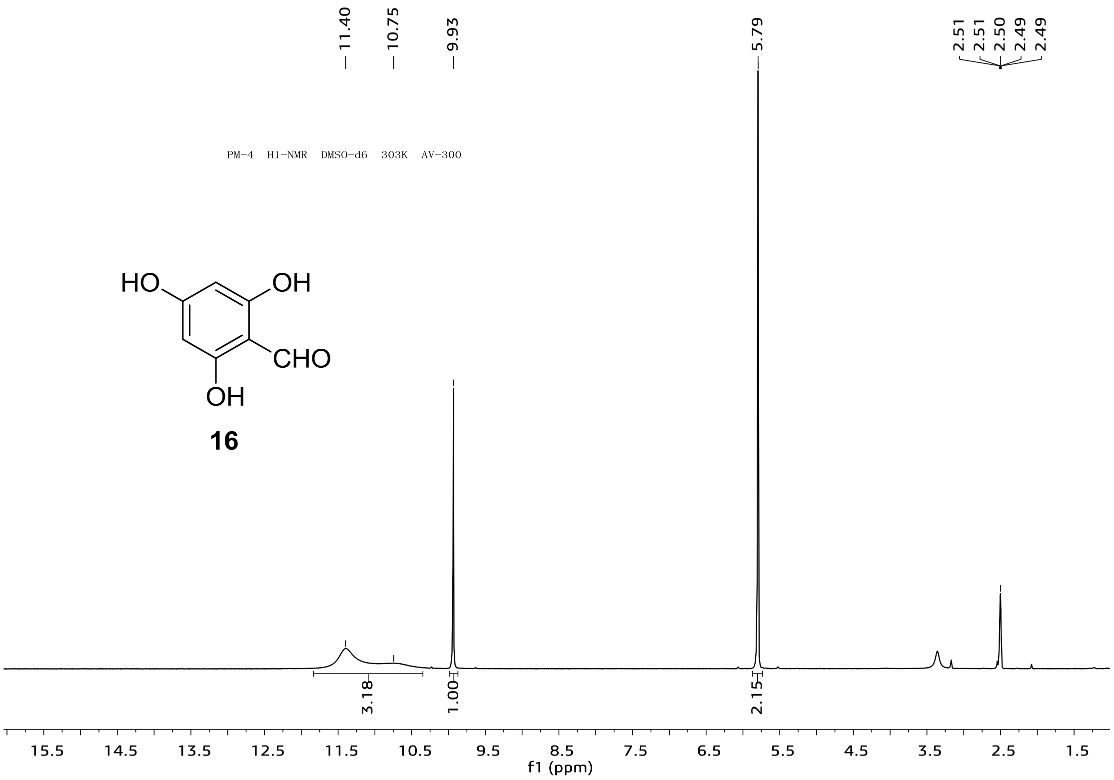


Figure S4-1. ^{1}H NMR of compound **16** (300 MHz, DMSO-d_6)

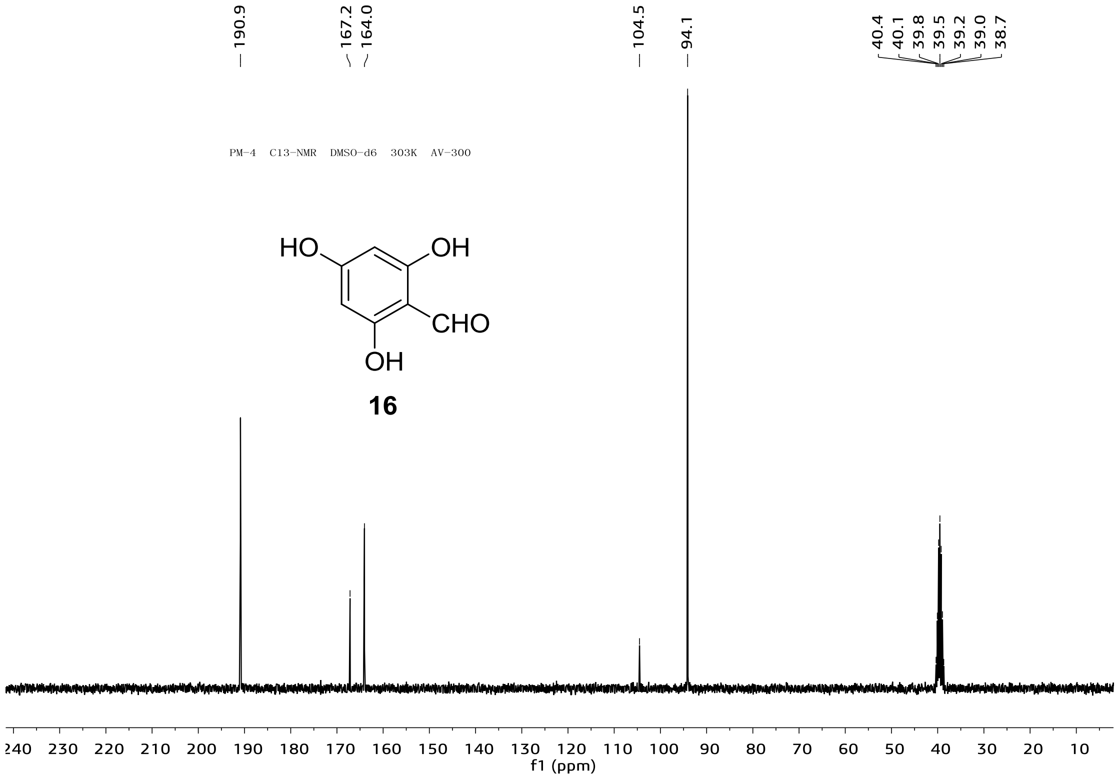


Figure S4-2. ^{13}C NMR of compound **16** (75 MHz, DMSO-d_6)

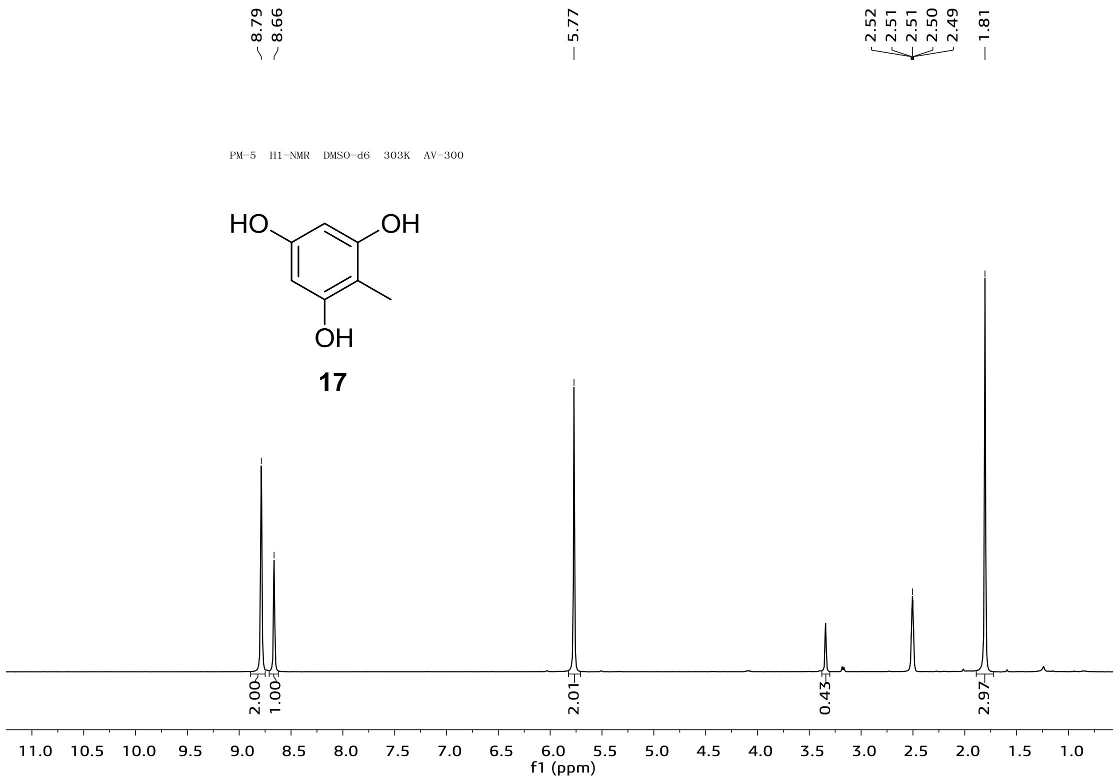


Figure S5-1. ^{1}H NMR of compound **17** (300 MHz, DMSO-d_6)

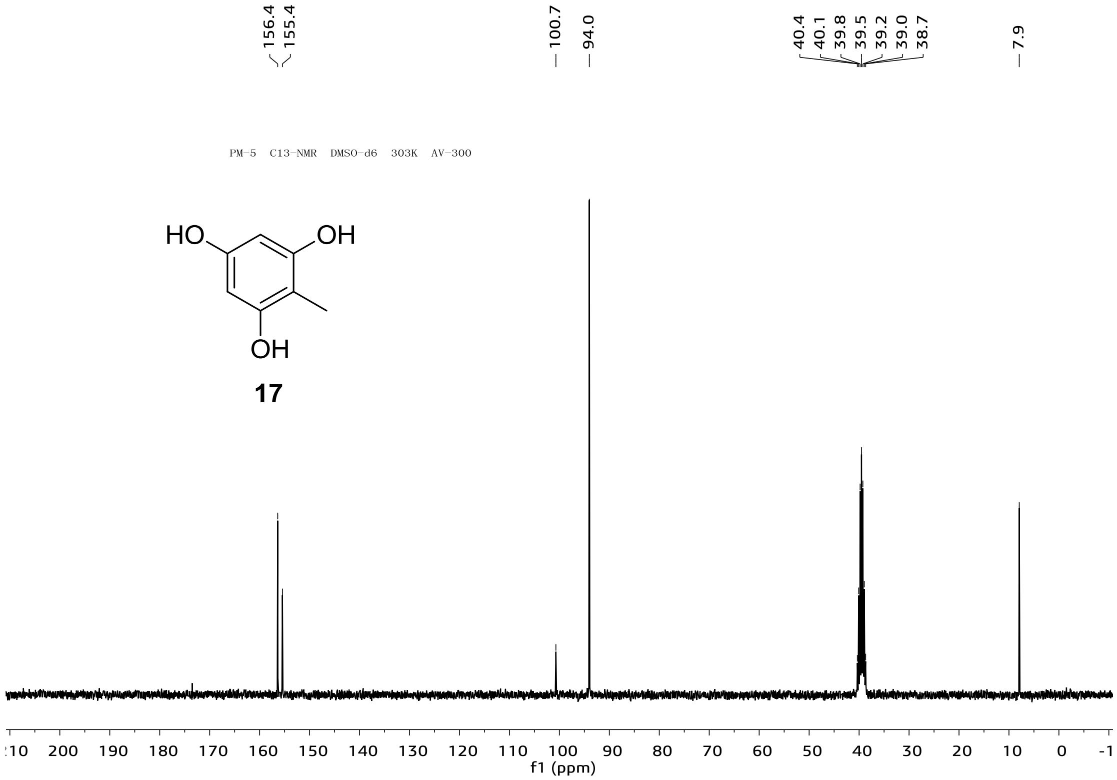


Figure S5-2. ^{13}C NMR of compound **17** (75 MHz, DMSO-d_6)

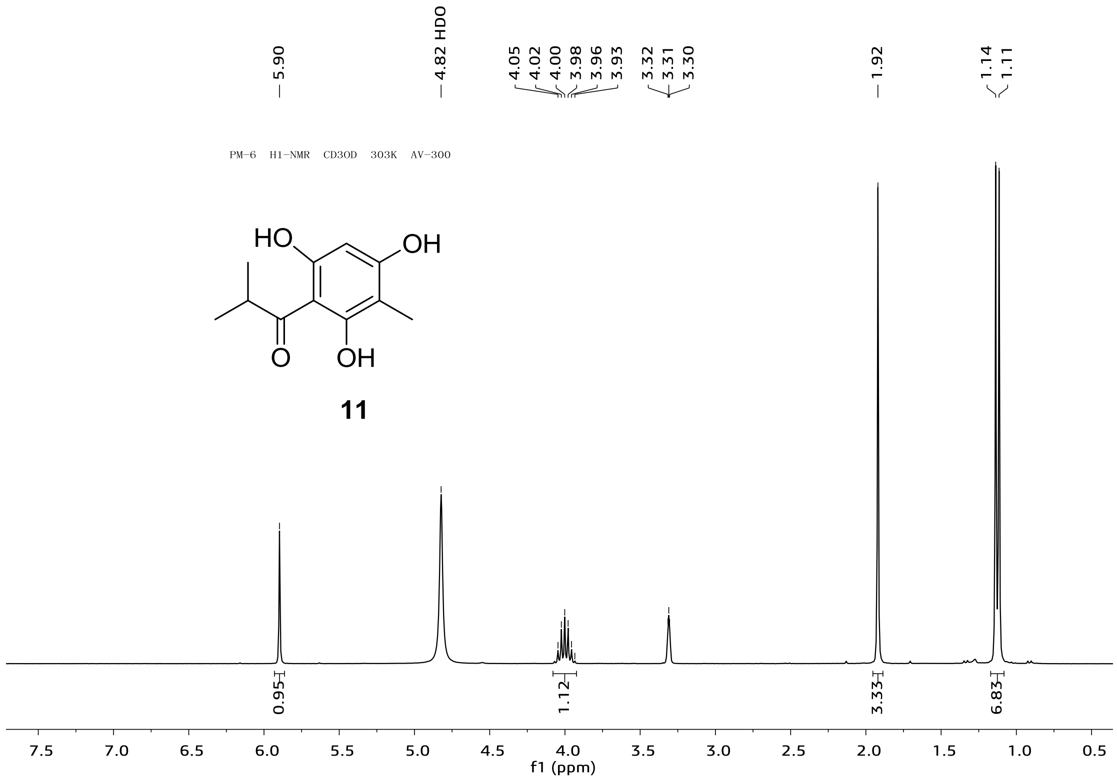


Figure S6-1. ^{1}H NMR of compound **11** (300 MHz, CD_3OD)

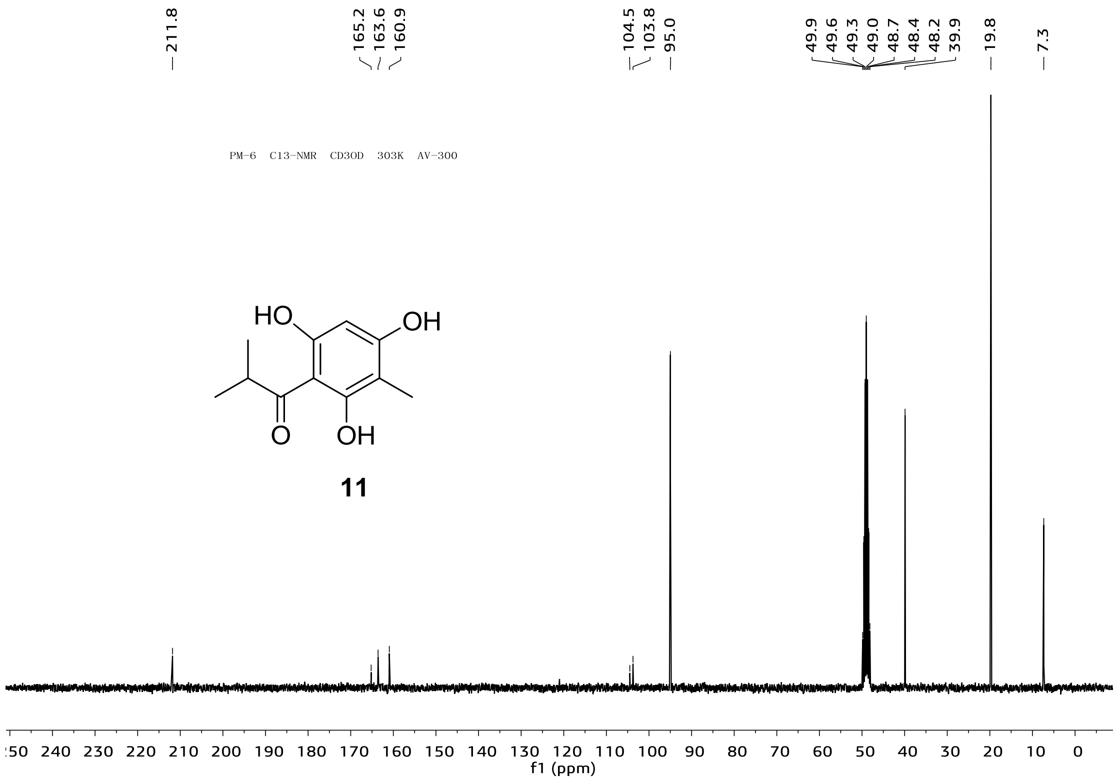


Figure S6-2. ^{13}C NMR of compound **11** (75 MHz, CD_3OD)

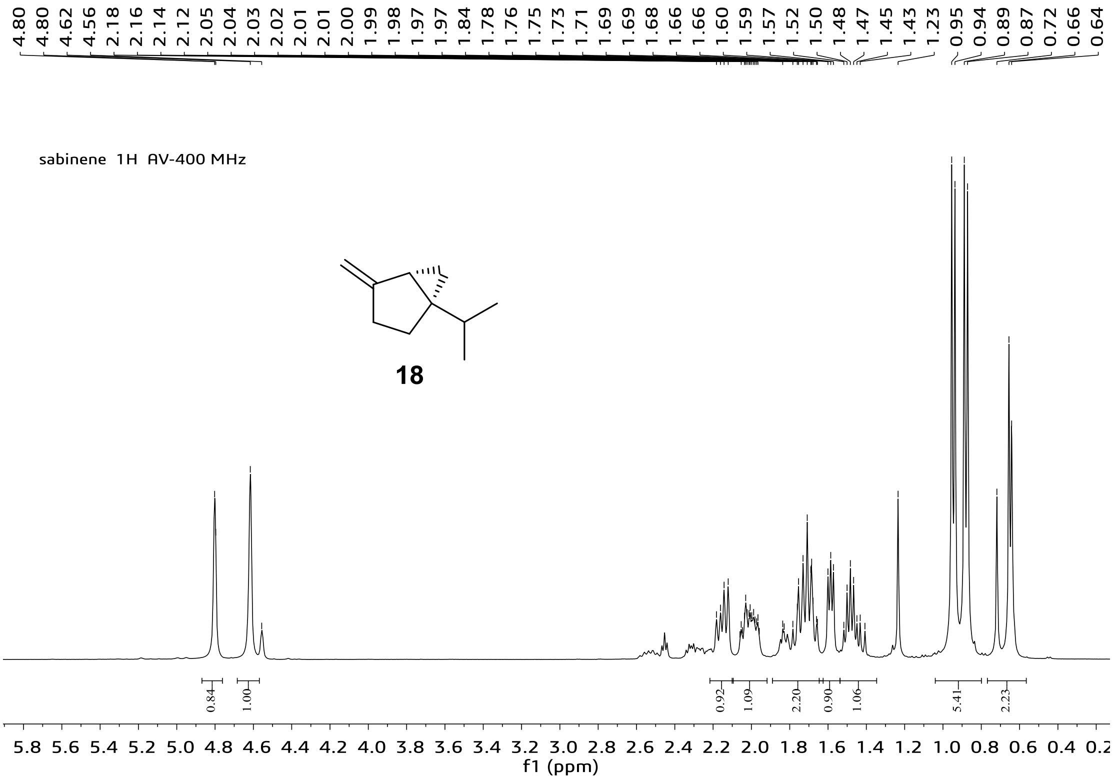


Figure S7-1. ^{1}H NMR of compound **18** (400 MHz, CDCl$_3$)

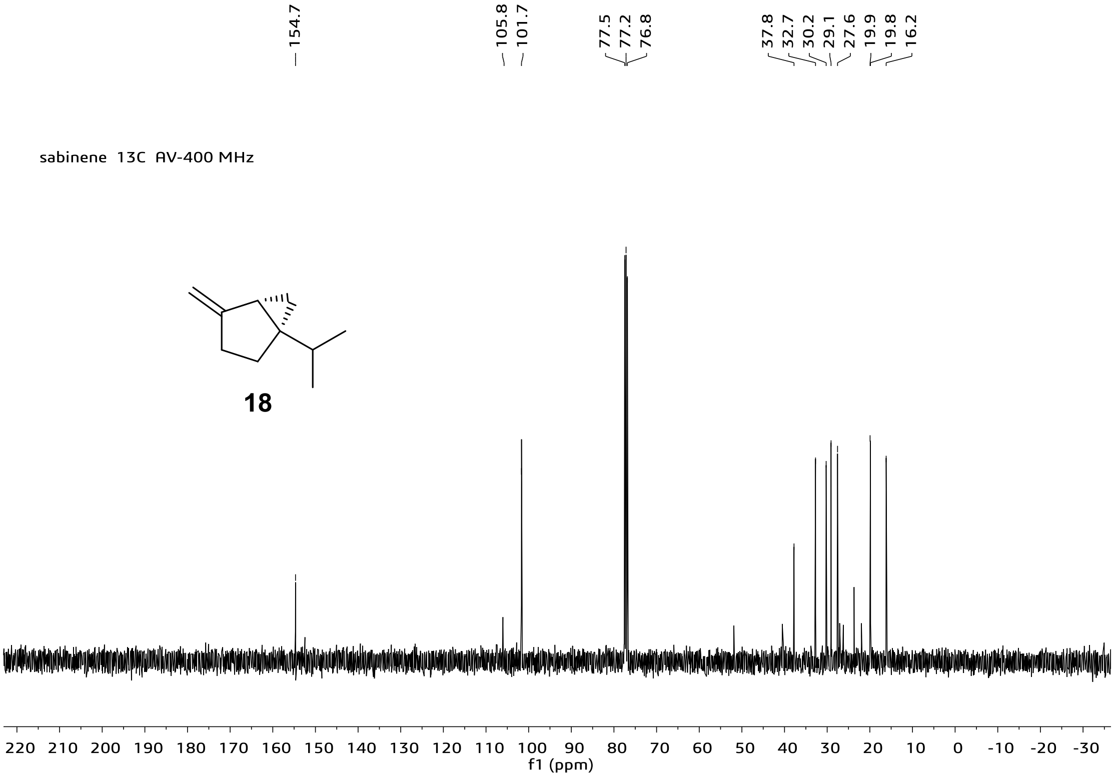


Figure S7-2. ^{13}C NMR of compound **18** (100 MHz, CDCl$_3$)

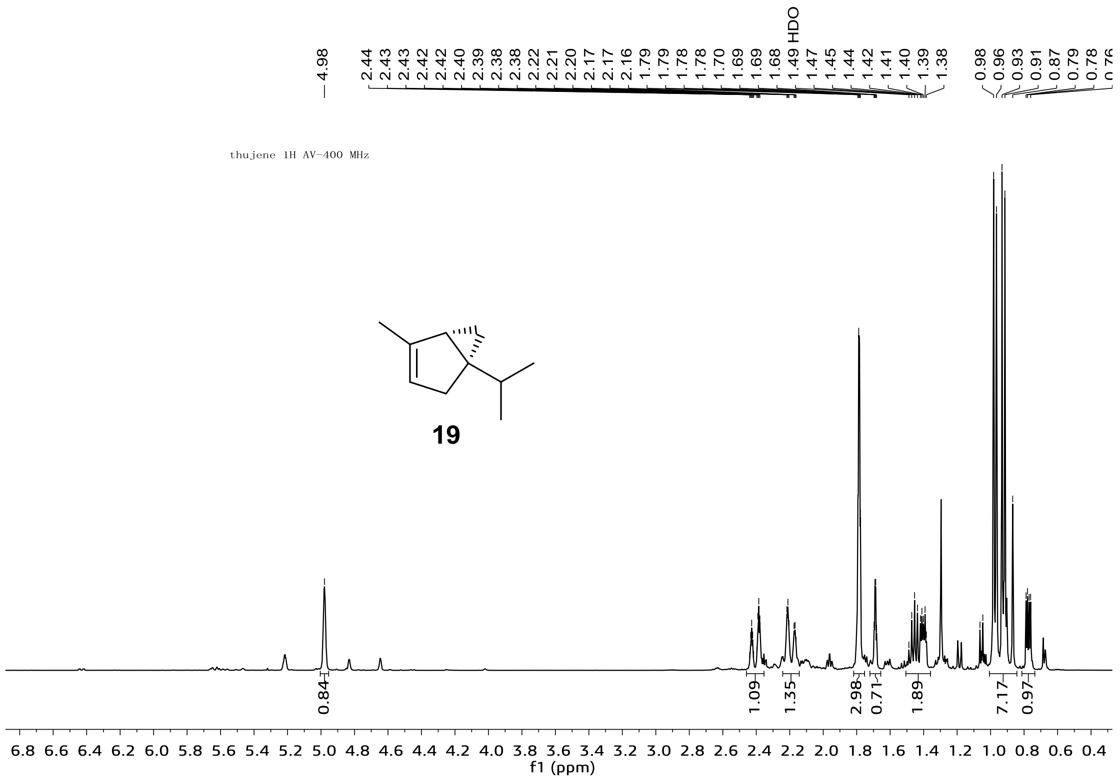


Figure S8-1. ^{1}H NMR of compound **19** (400 MHz, $CDCl_3$)

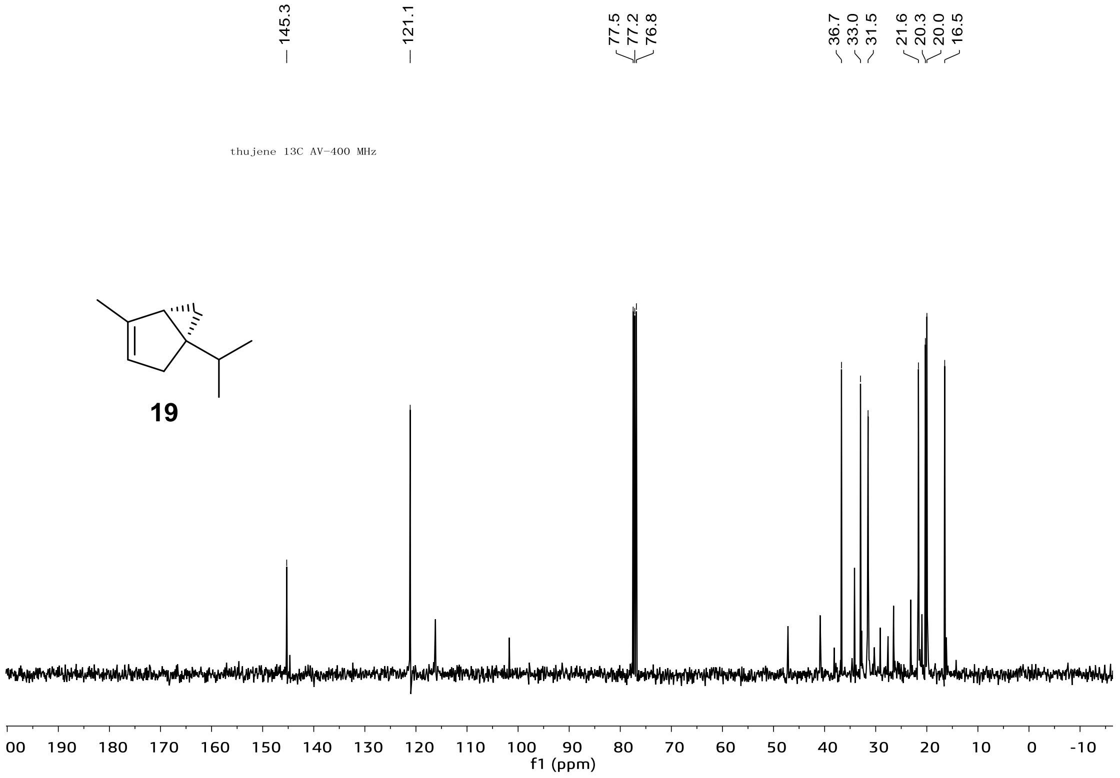


Figure S8-2. ^{13}C NMR of compound **19** (100 MHz, $CDCl_3$)

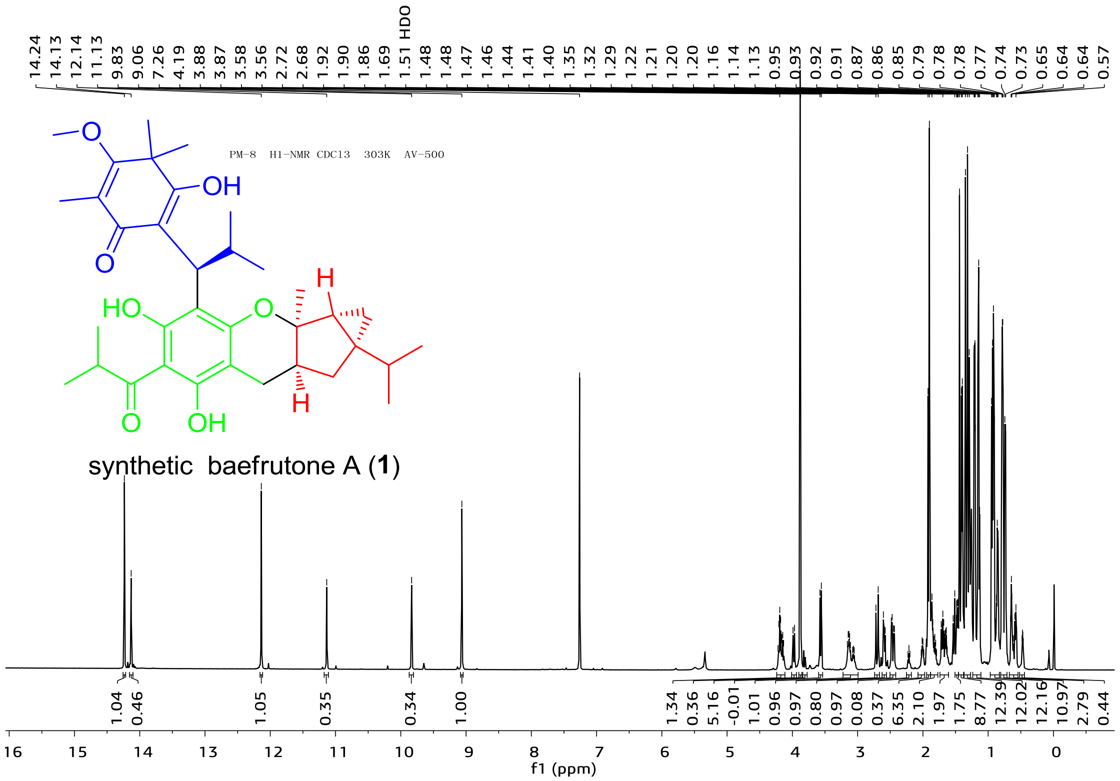


Figure S9-1. ^{1}H NMR of synthetic **1** (500 MHz, $CDCl_3$)

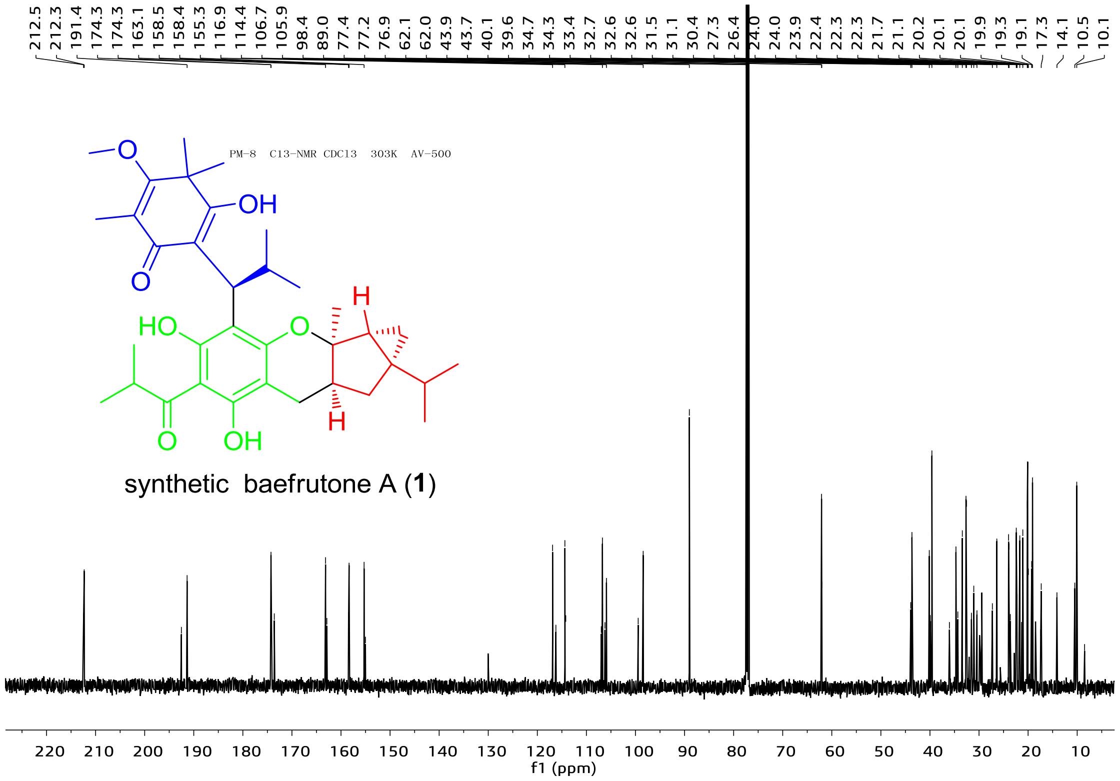


Figure S9-2. ^{13}C NMR of synthetic **1** (125 MHz, $CDCl_3$)

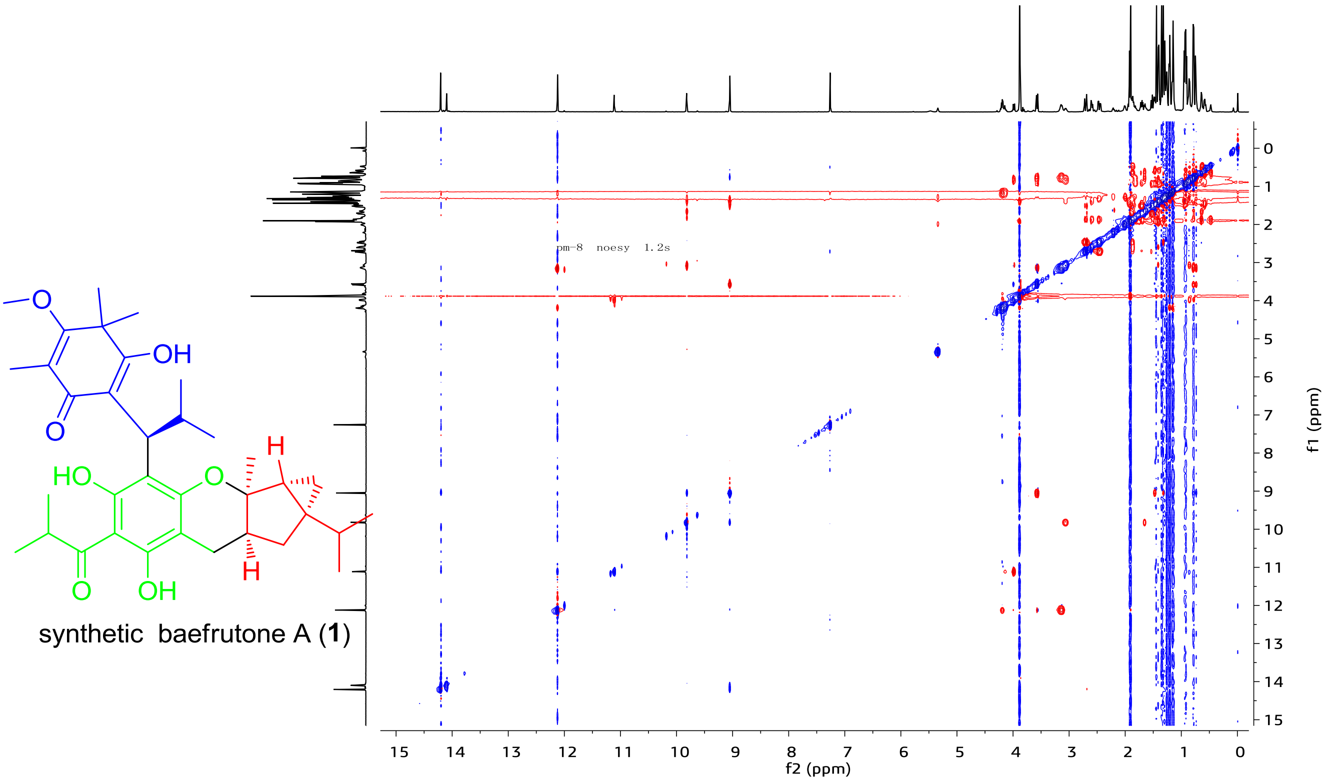


Figure S9-3. NOESY of synthetic **1** (500 MHz, $CDCl_3$)

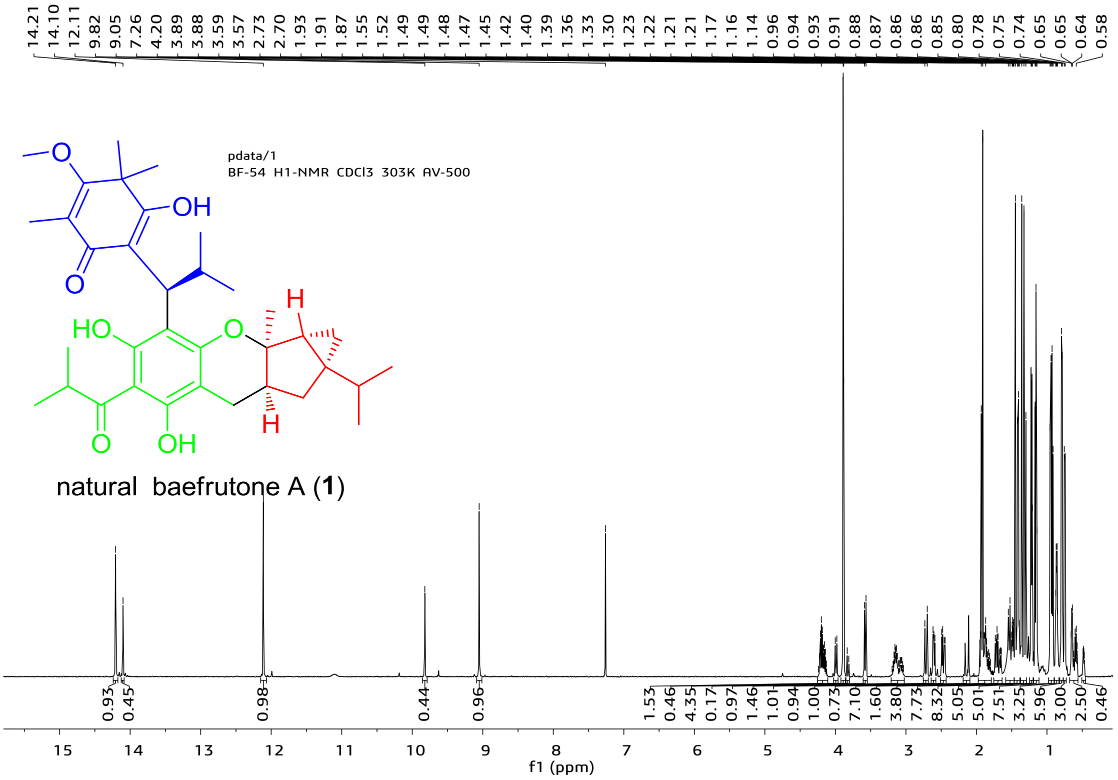


Figure S10-1. ^{1}H NMR of natural **1** (500 MHz, $CDCl_3$)

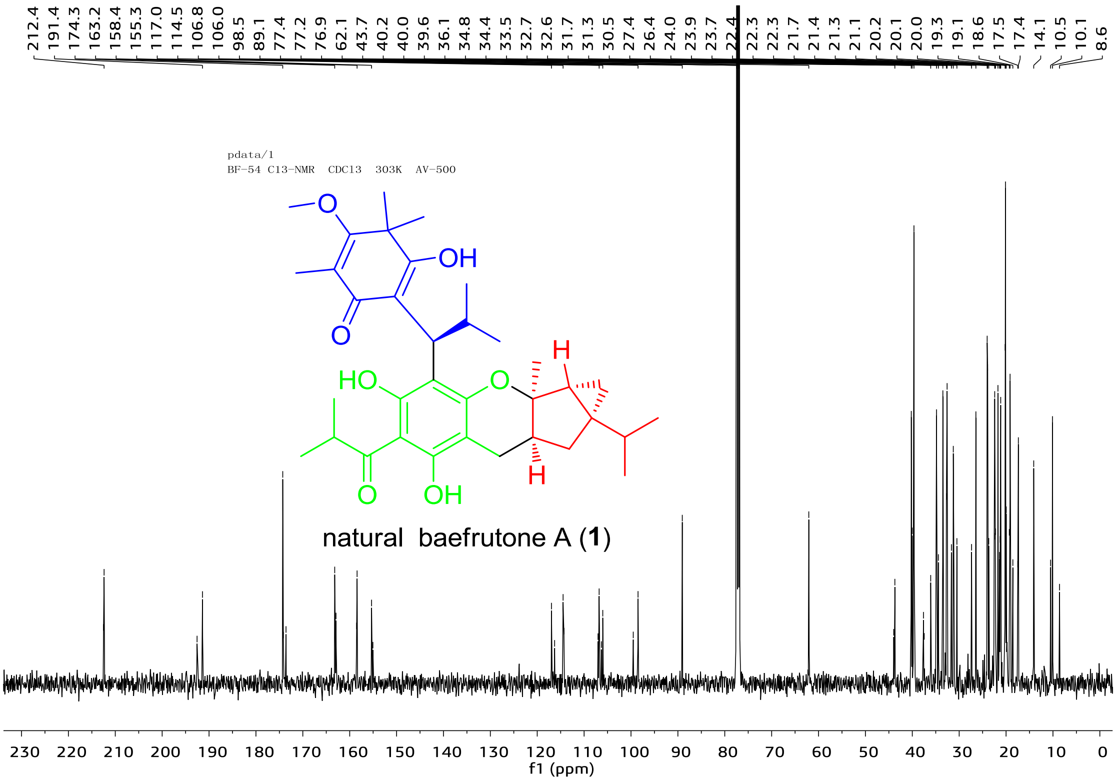


Figure S10-2. ^{13}C NMR of natural **1** (125 MHz, $CDCl_3$)

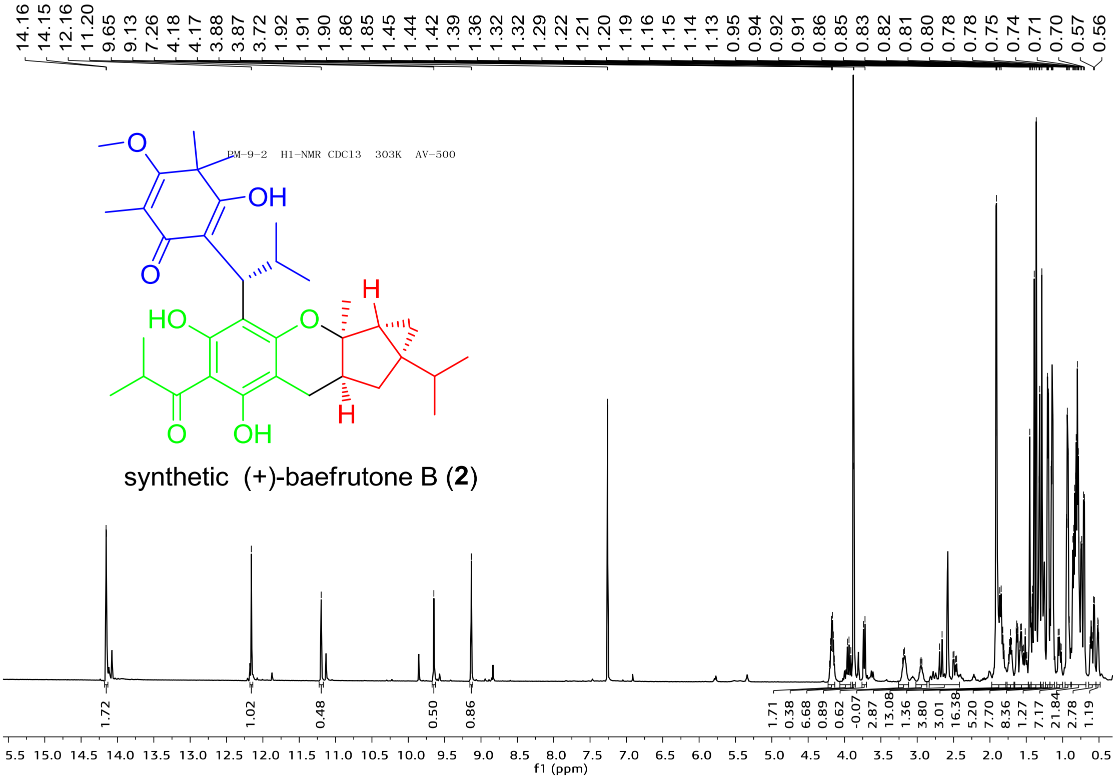


Figure S11-1. ^{1}H NMR of synthetic **2** (500 MHz, $CDCl_3$)

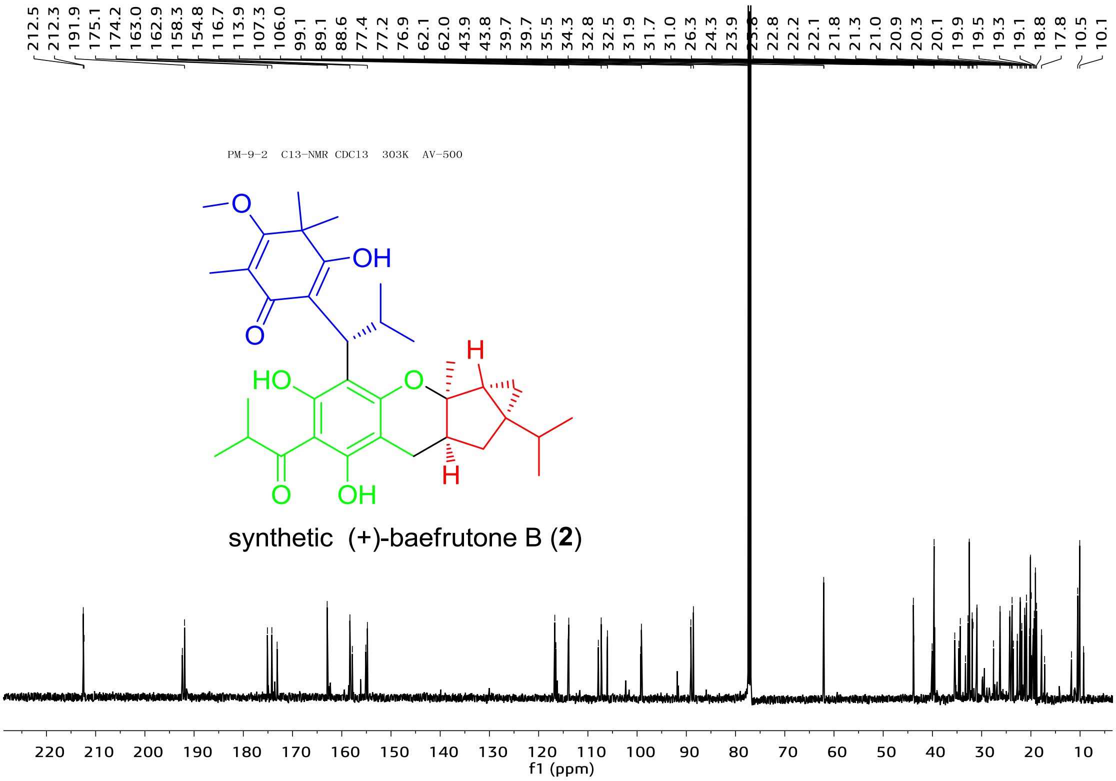


Figure S11-2. ^{13}C NMR of synthetic **2** (125 MHz, CDCl$_3$)

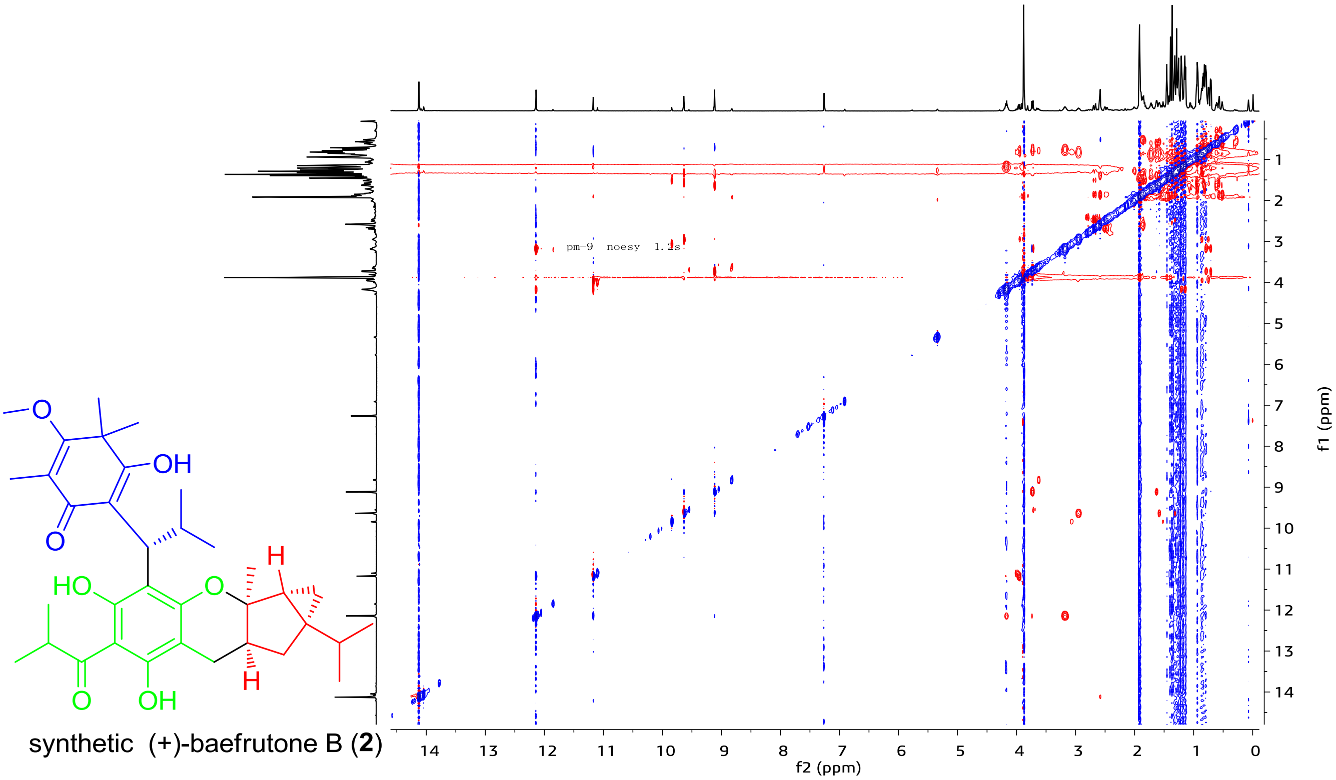


Figure S11-3. NOESY of synthetic **2** (500 MHz, CDCl$_3$)

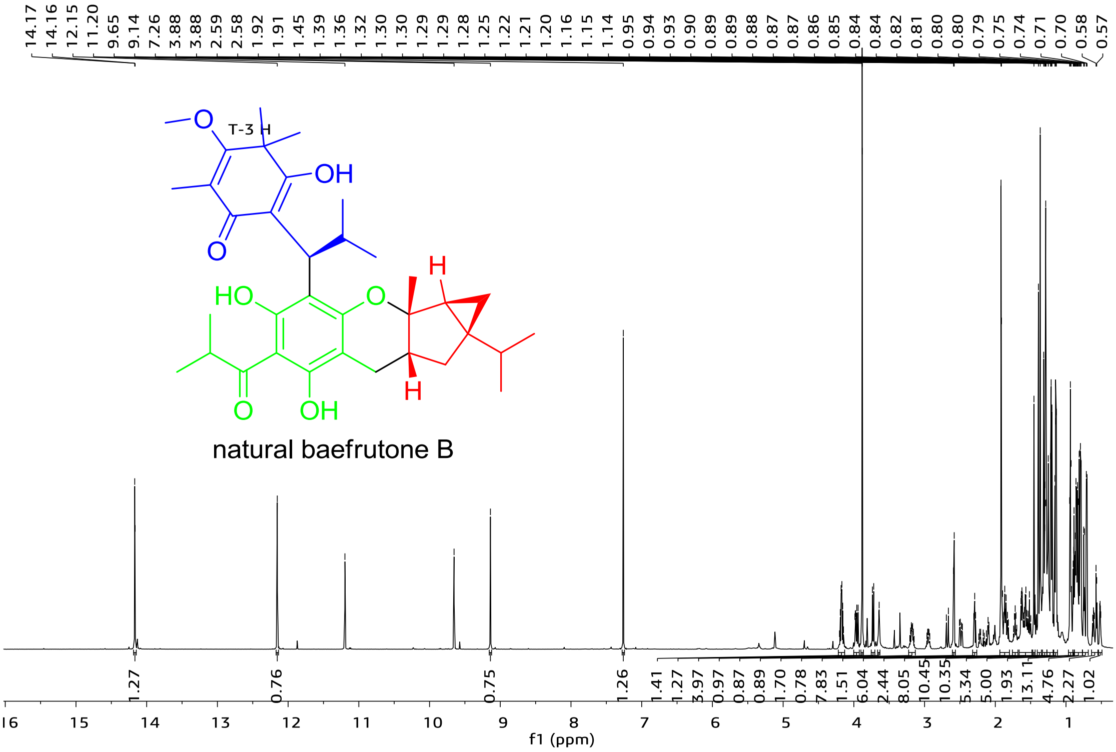


Figure S12-1. ^{1}H NMR of natural baefrutone B (500 MHz, $CDCl_3$)

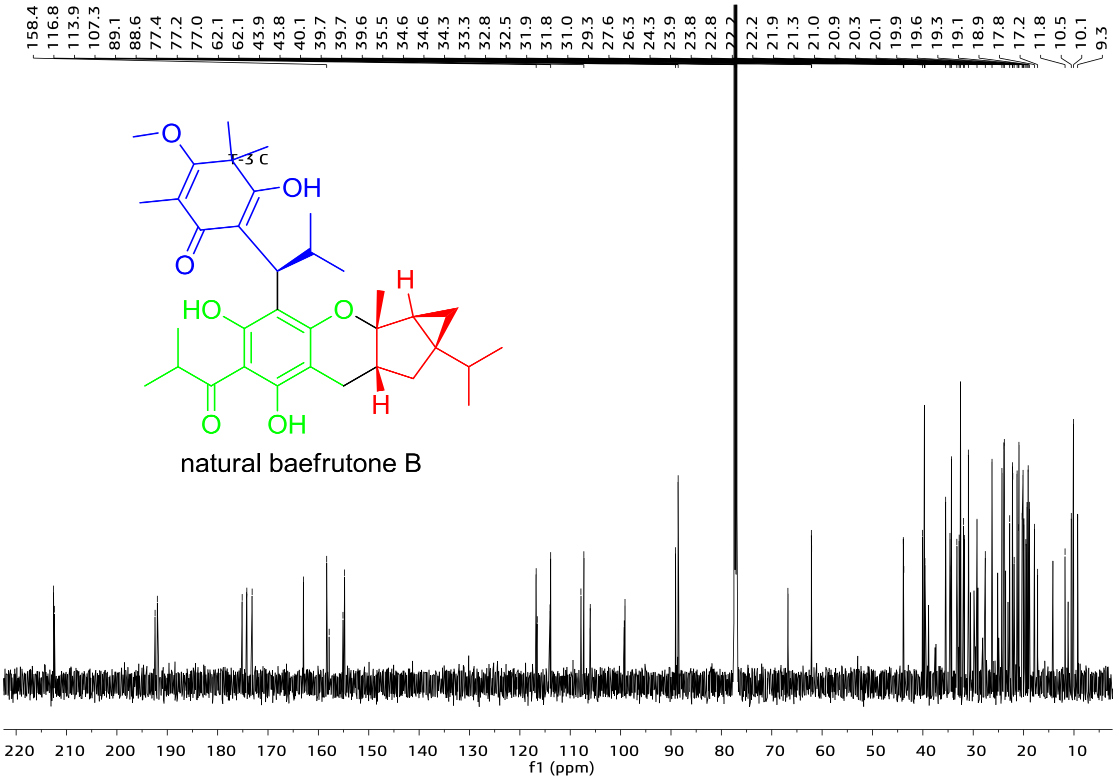


Figure S12-2. ^{13}C NMR of natural baefrutone B (125 MHz, $CDCl_3$)

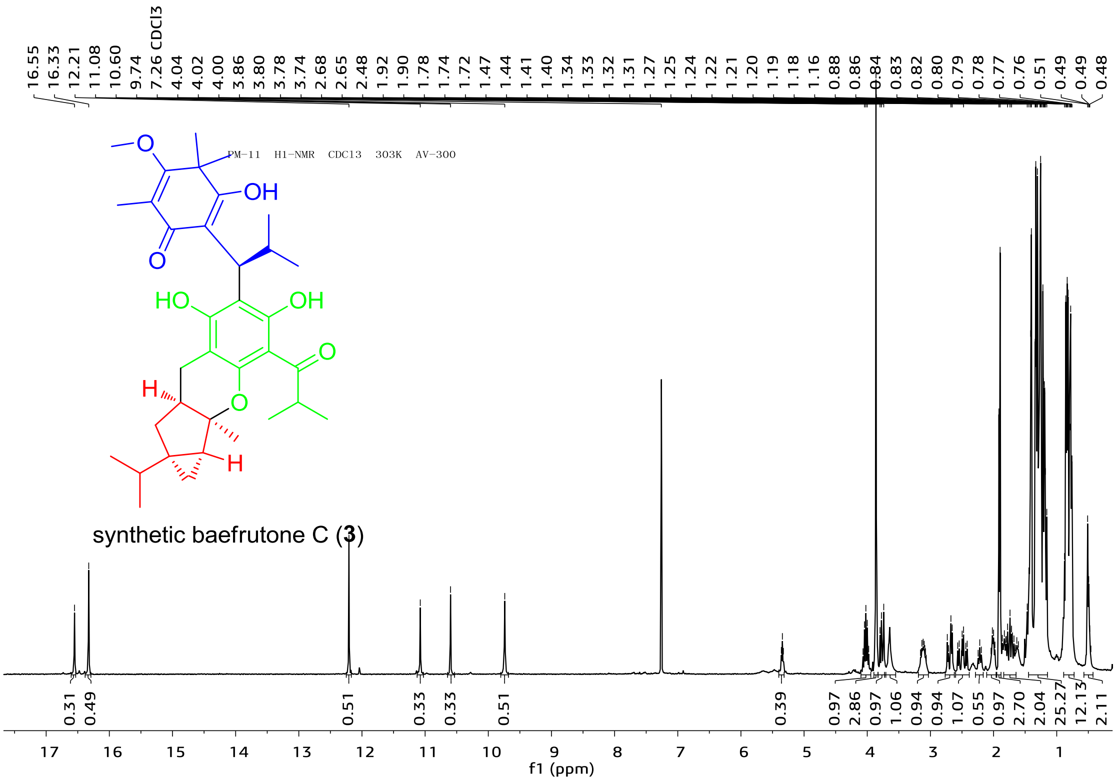


Figure S13-1. ^{1}H NMR of synthetic **3** (300 MHz, $CDCl_3$)

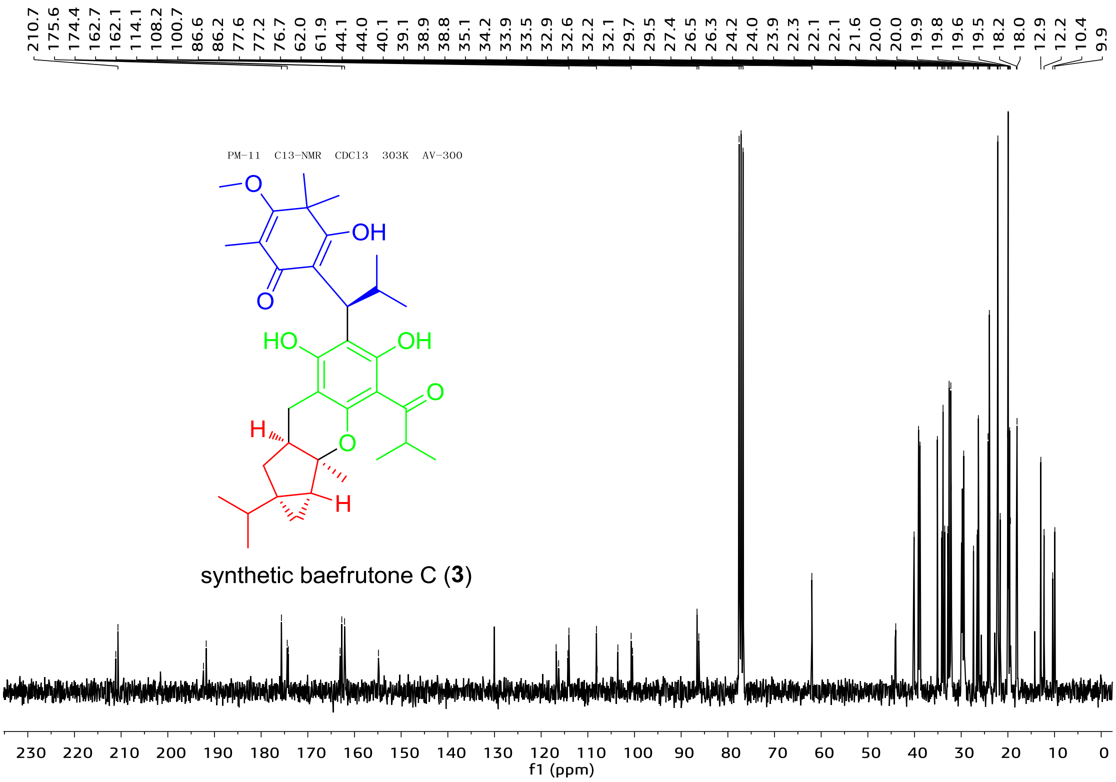


Figure S13-2. ^{13}C NMR of synthetic **3** (75 MHz, $CDCl_3$)

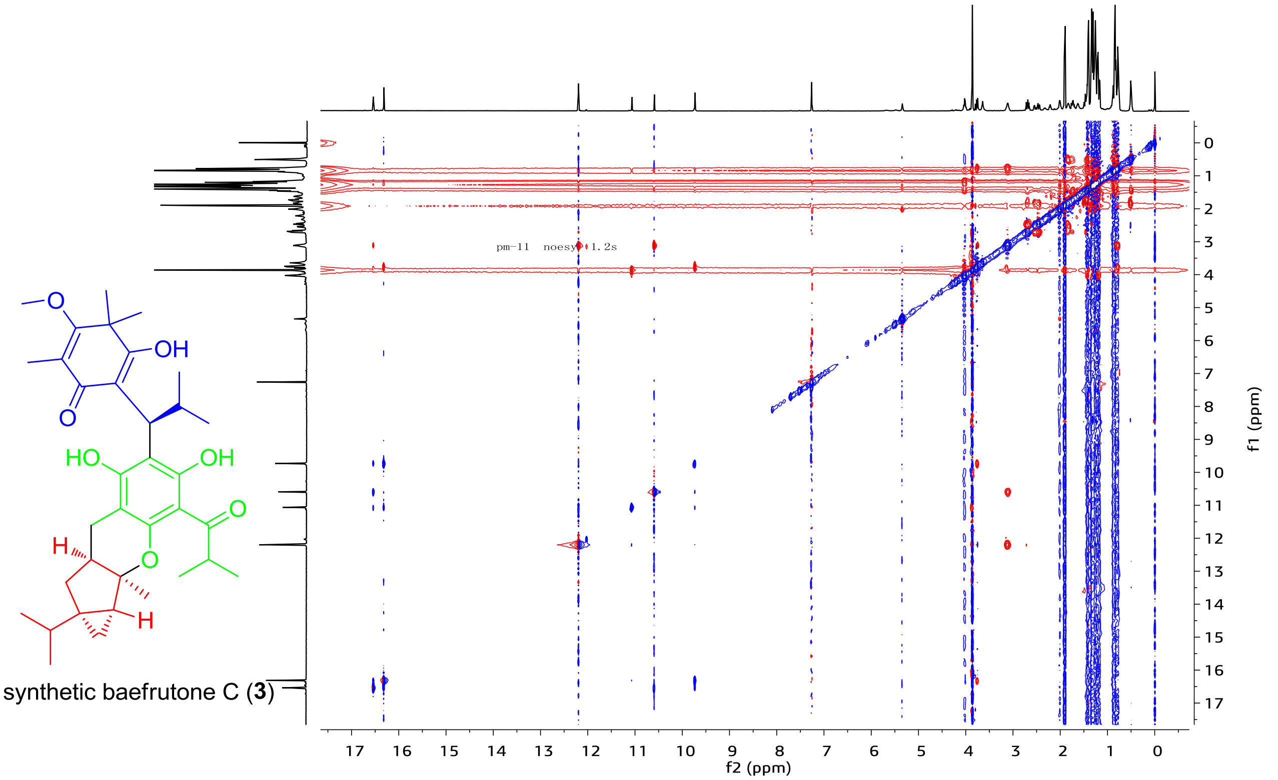


Figure S13-3. NOESY of synthetic **3** (300 MHz, $CDCl_3$)

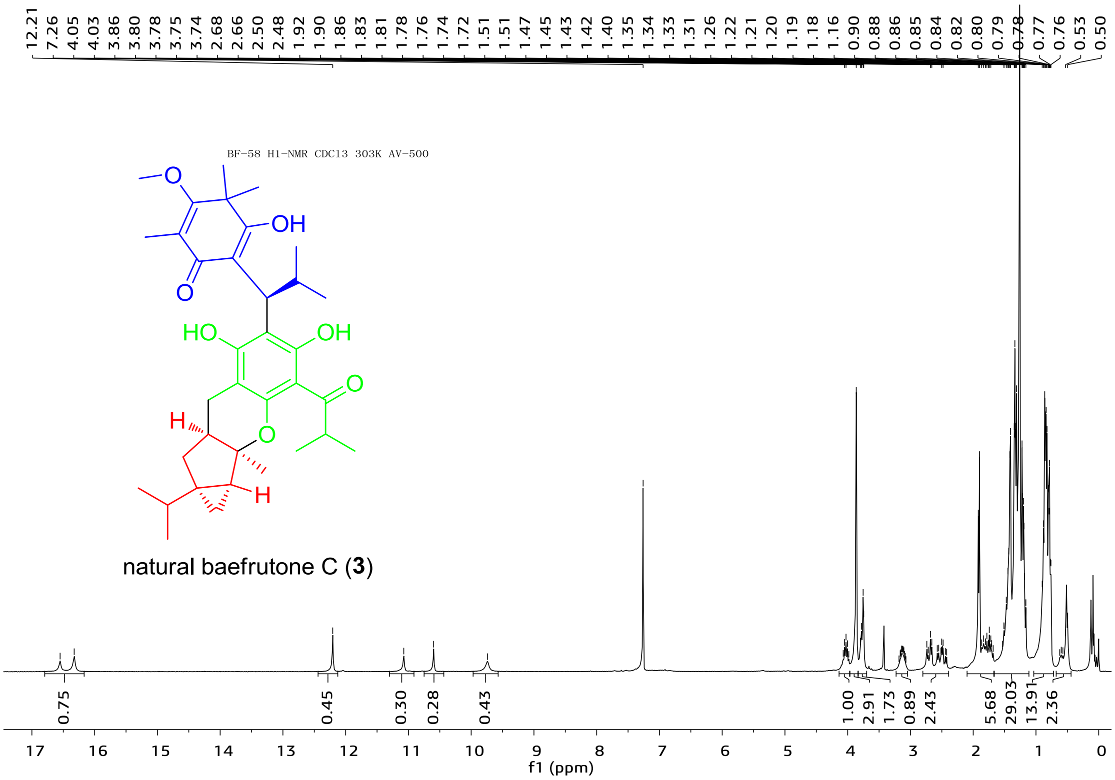


Figure S14-1. ^{1}H NMR of natural **3** (500 MHz, $CDCl_3$)

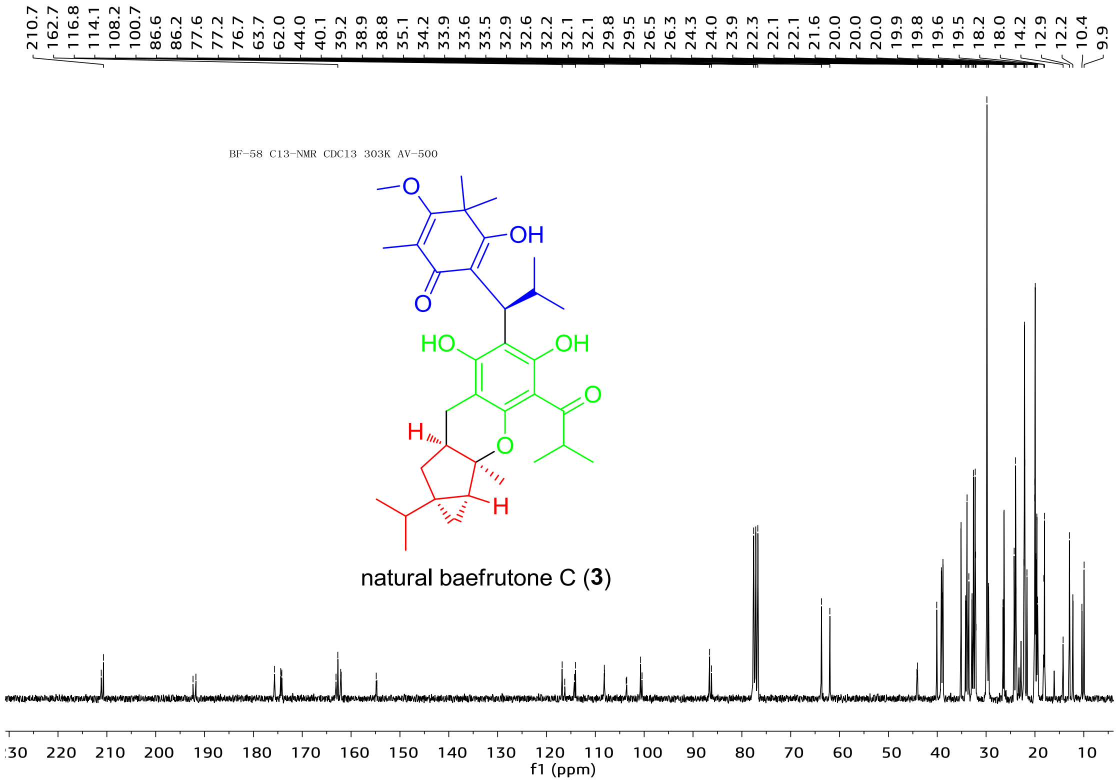


Figure S14-2. ^{13}C NMR of natural **3** (125 MHz, CDCl$_3$)

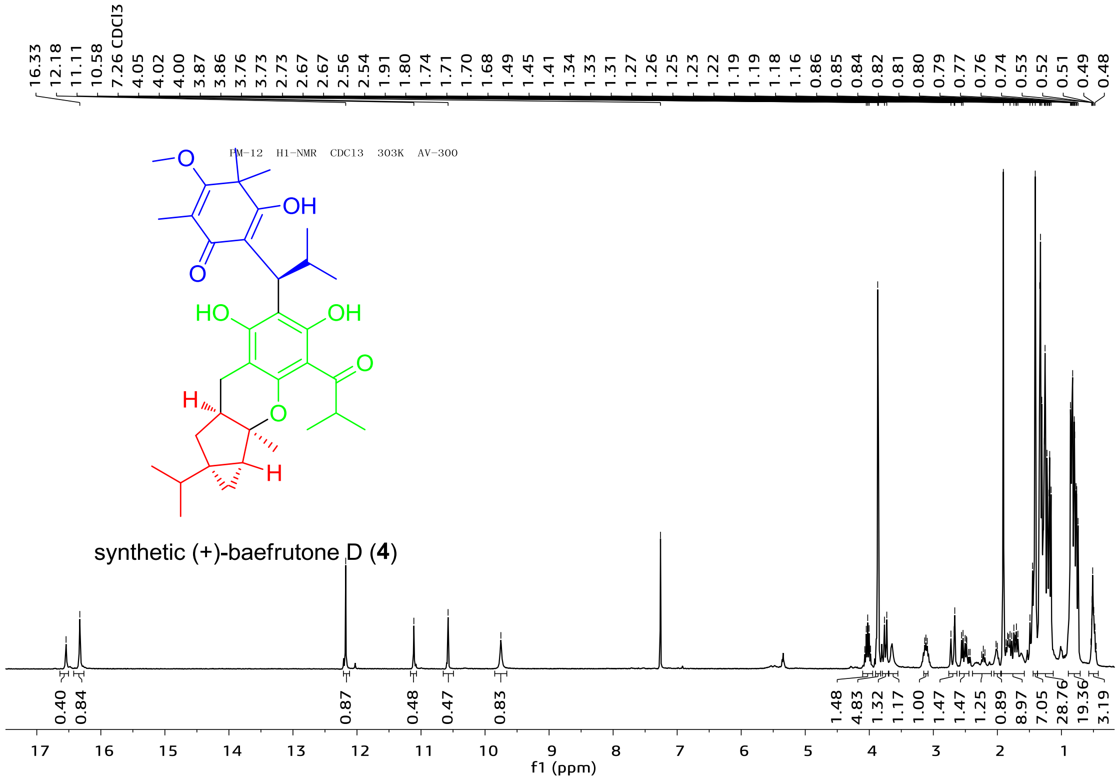


Figure S15-1. ^{1}H NMR of synthetic **4** (300 MHz, CDCl$_3$)

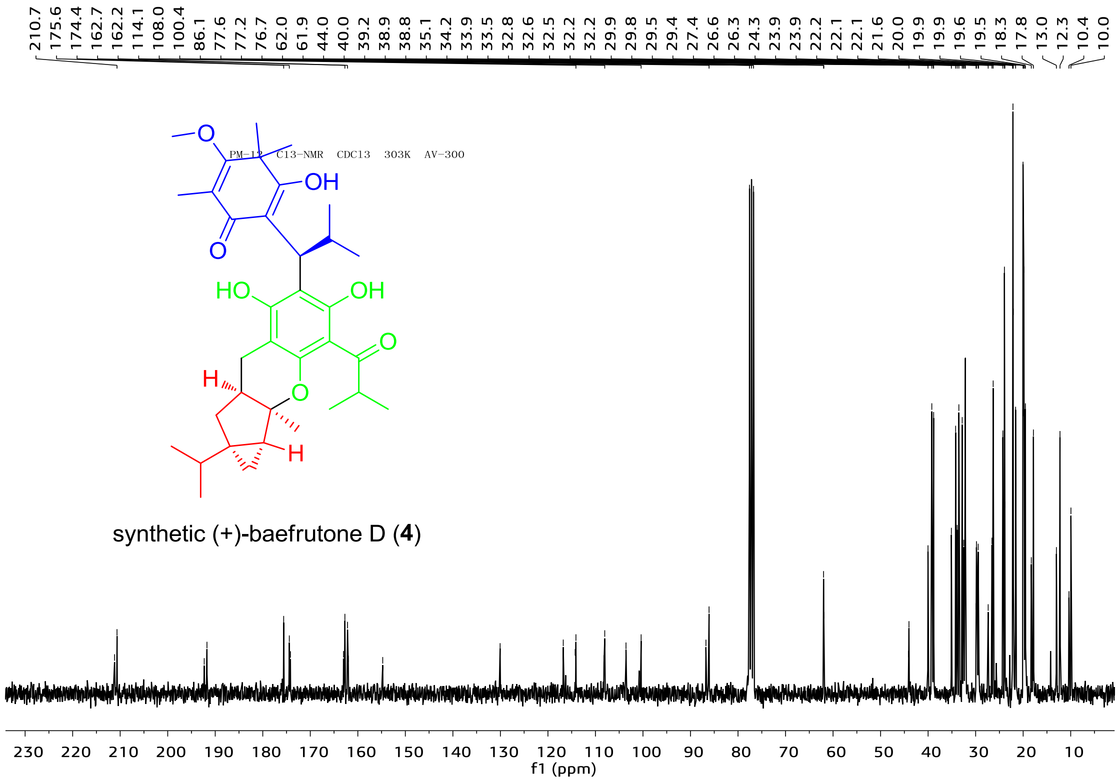


Figure S15-2. ^{13}C NMR of synthetic **4** (75 MHz, CDCl$_3$)

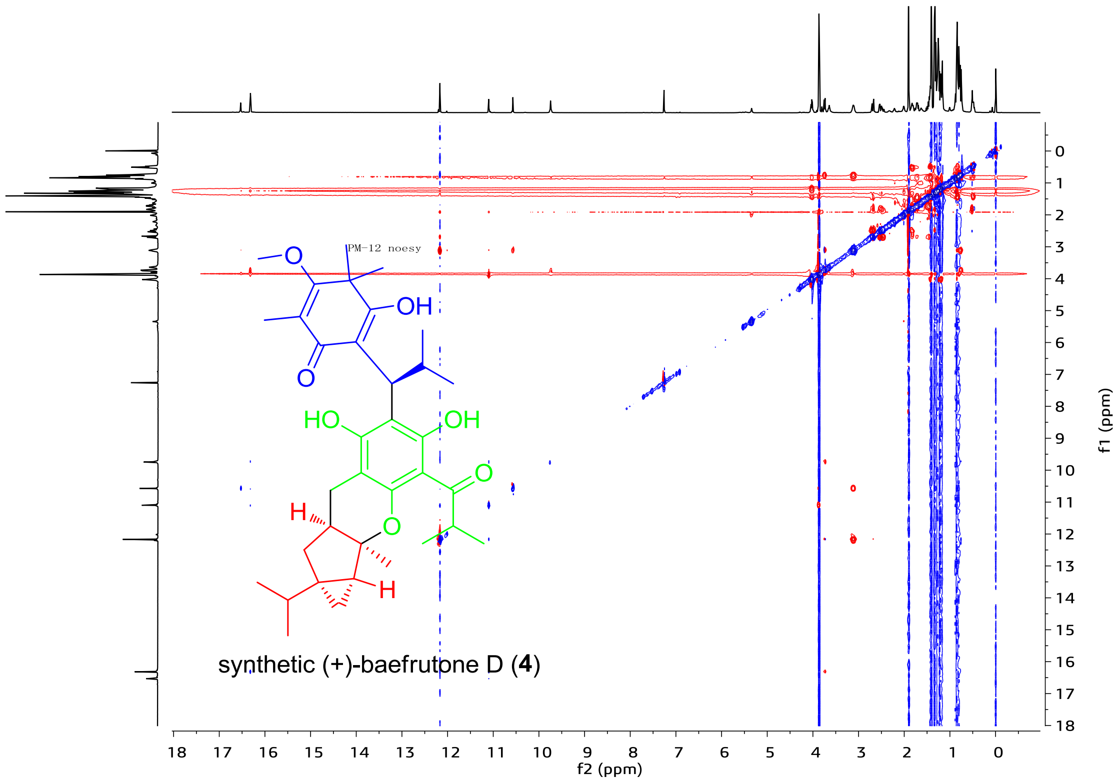


Figure S15-3. NOESY of synthetic **4** (300 MHz, CDCl$_3$)

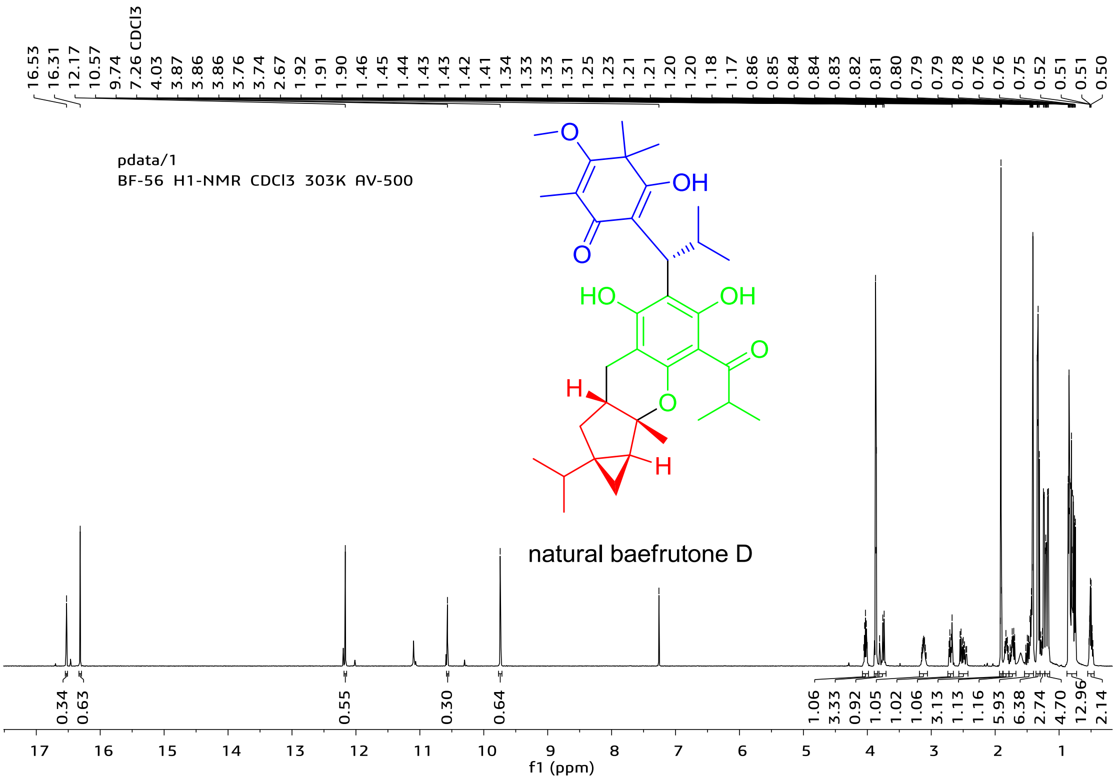


Figure S16-1. ^{1}H NMR of natural baefrutone D (500 MHz, $CDCl_3$)

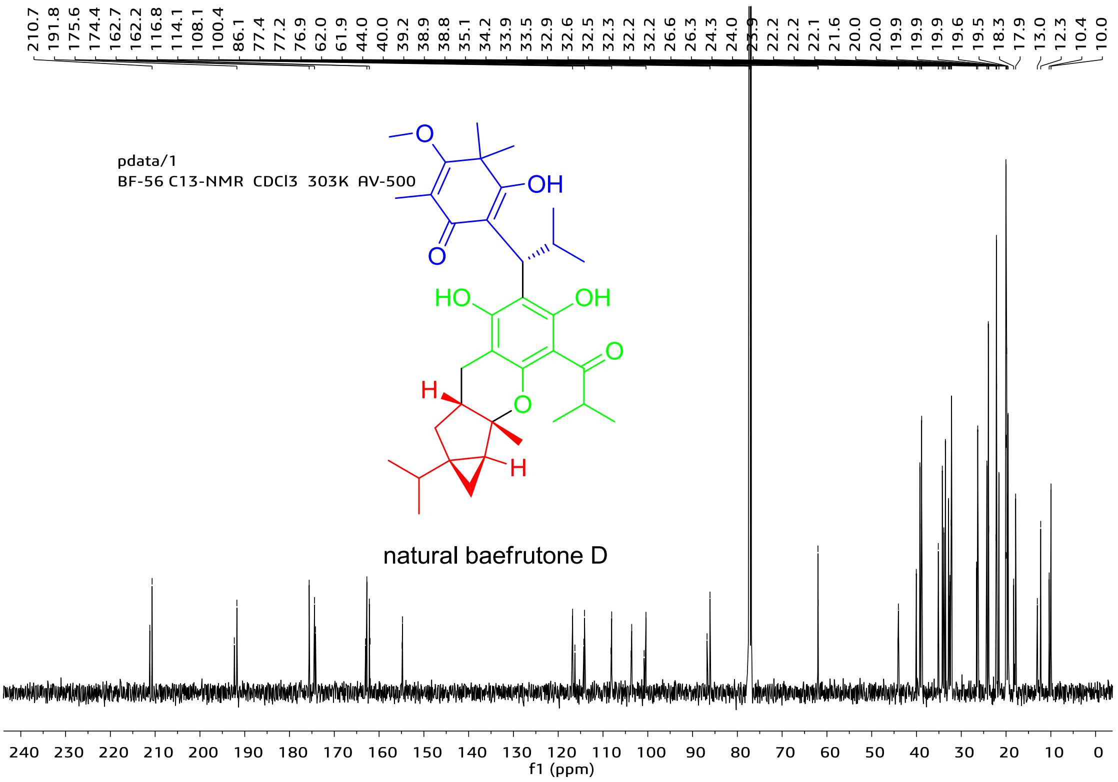


Figure S16-2. ^{13}C NMR of natural baefrutone D (125 MHz, $CDCl_3$)

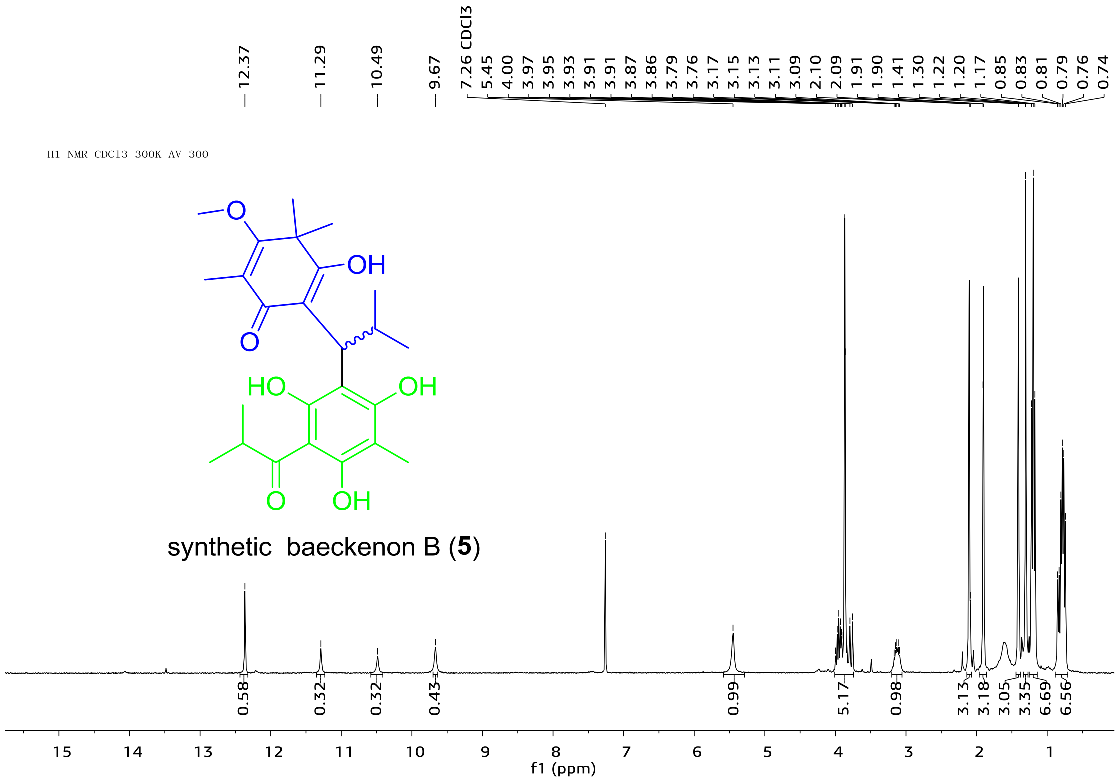


Figure S17-1. ^{1}H NMR of synthetic **5** (300 MHz, $CDCl_3$)

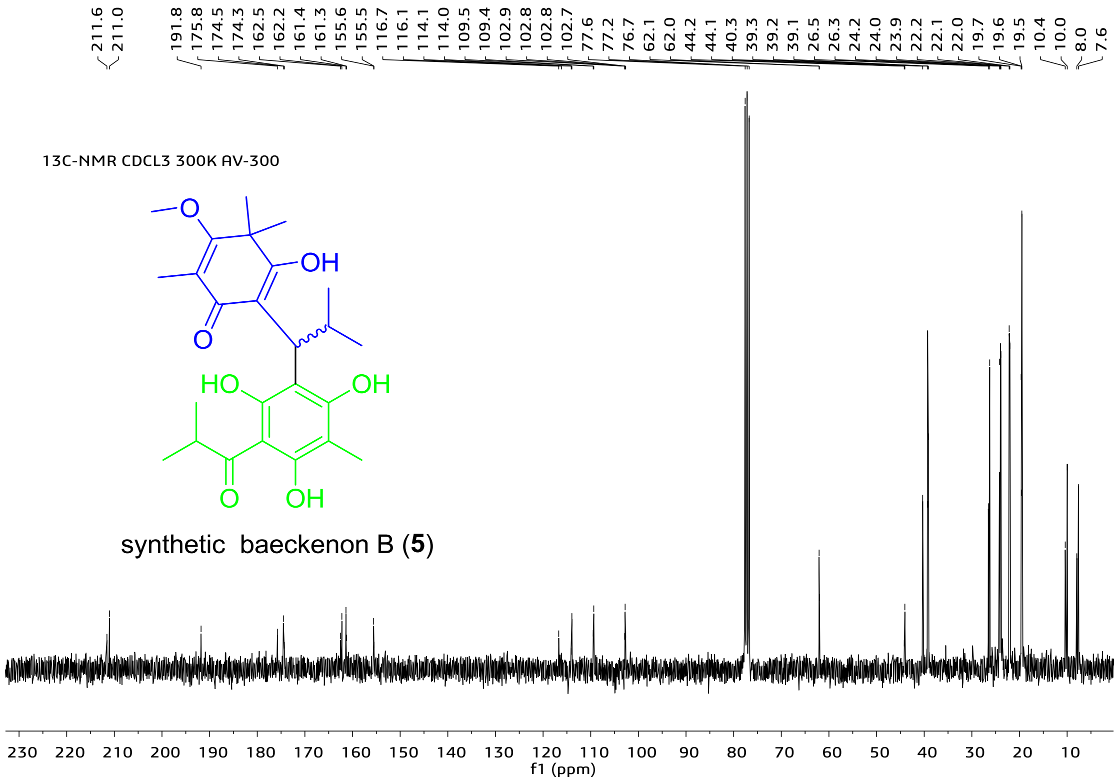


Figure S17-2. ^{13}C NMR of synthetic **5** (75 MHz, $CDCl_3$)

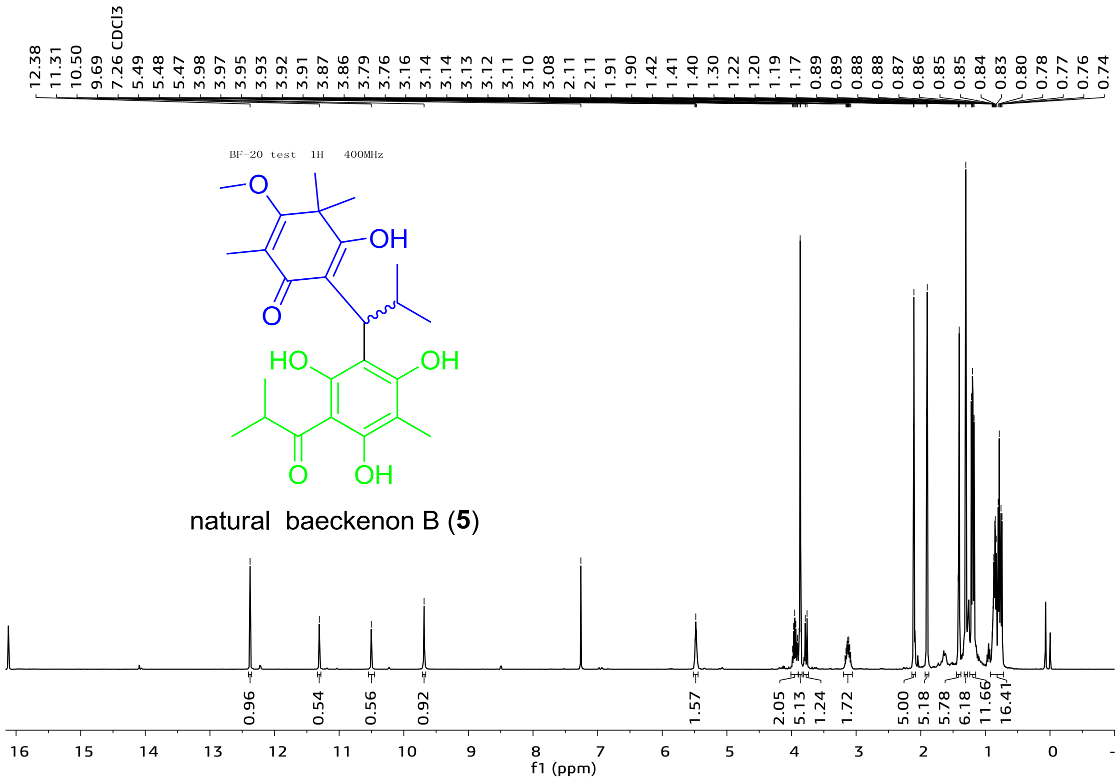


Figure S18-1. ^{1}H NMR of natural **5** (400 MHz, $CDCl_3$)

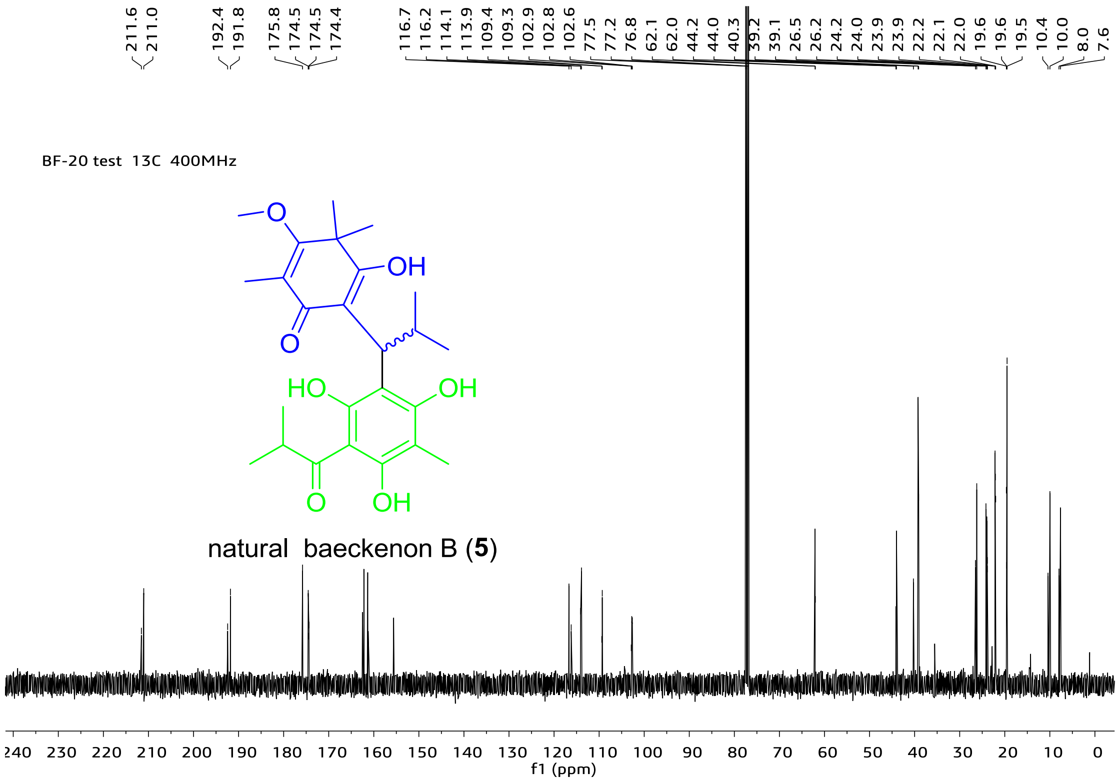


Figure S18-2. ^{13}C NMR of synthetic **5** (100 MHz, $CDCl_3$)

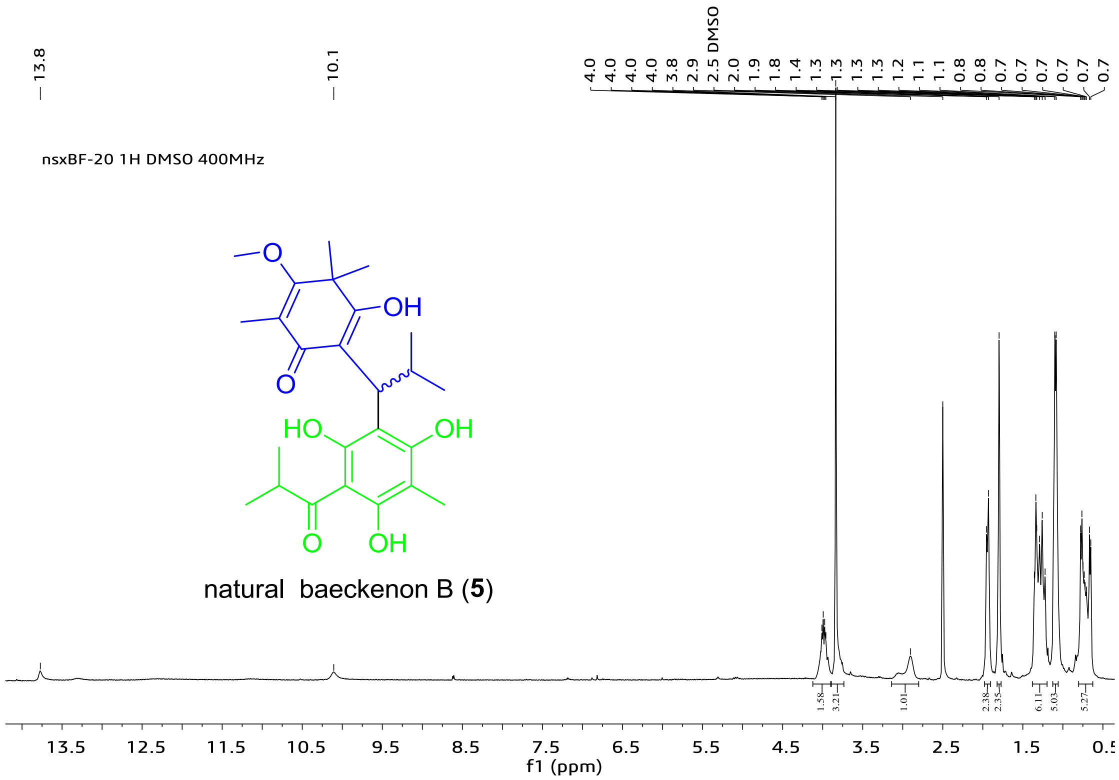


Figure S18-3. ^{1}H NMR of natural **5** (400 MHz, DMSO-d_6)

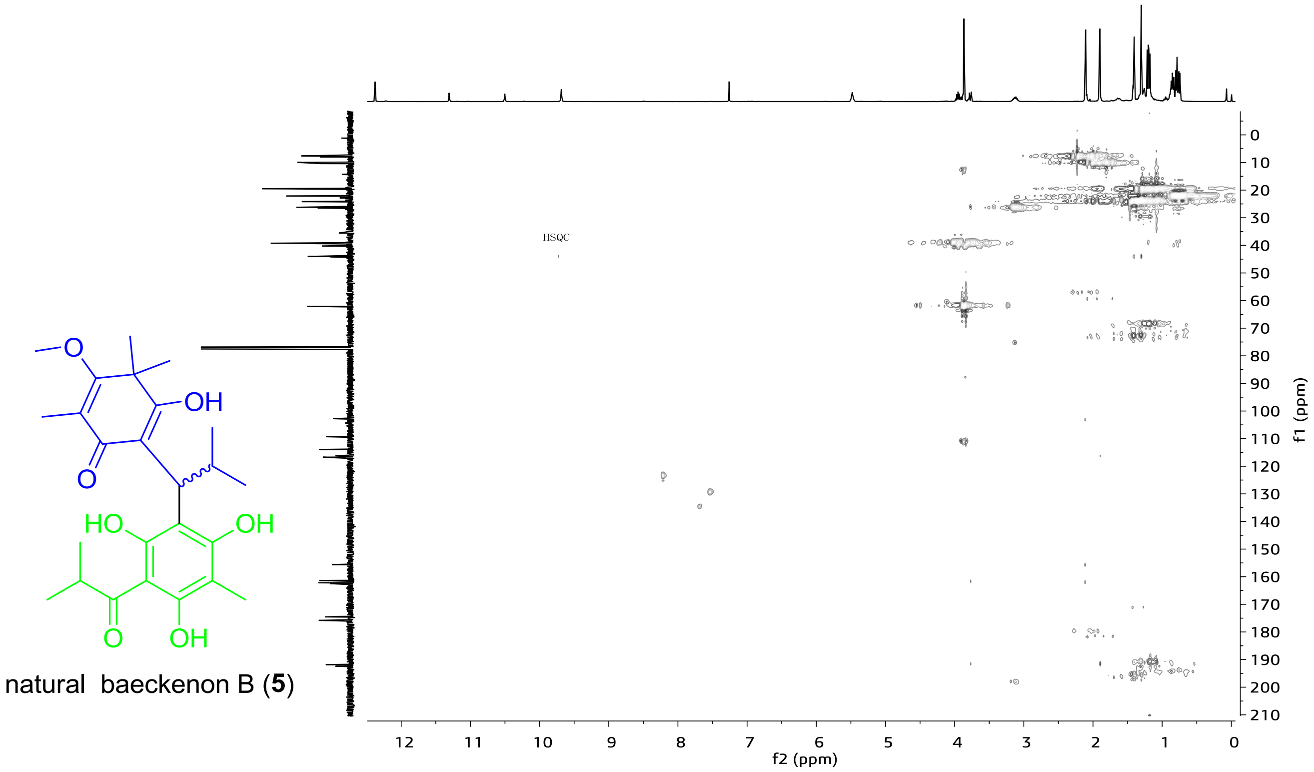
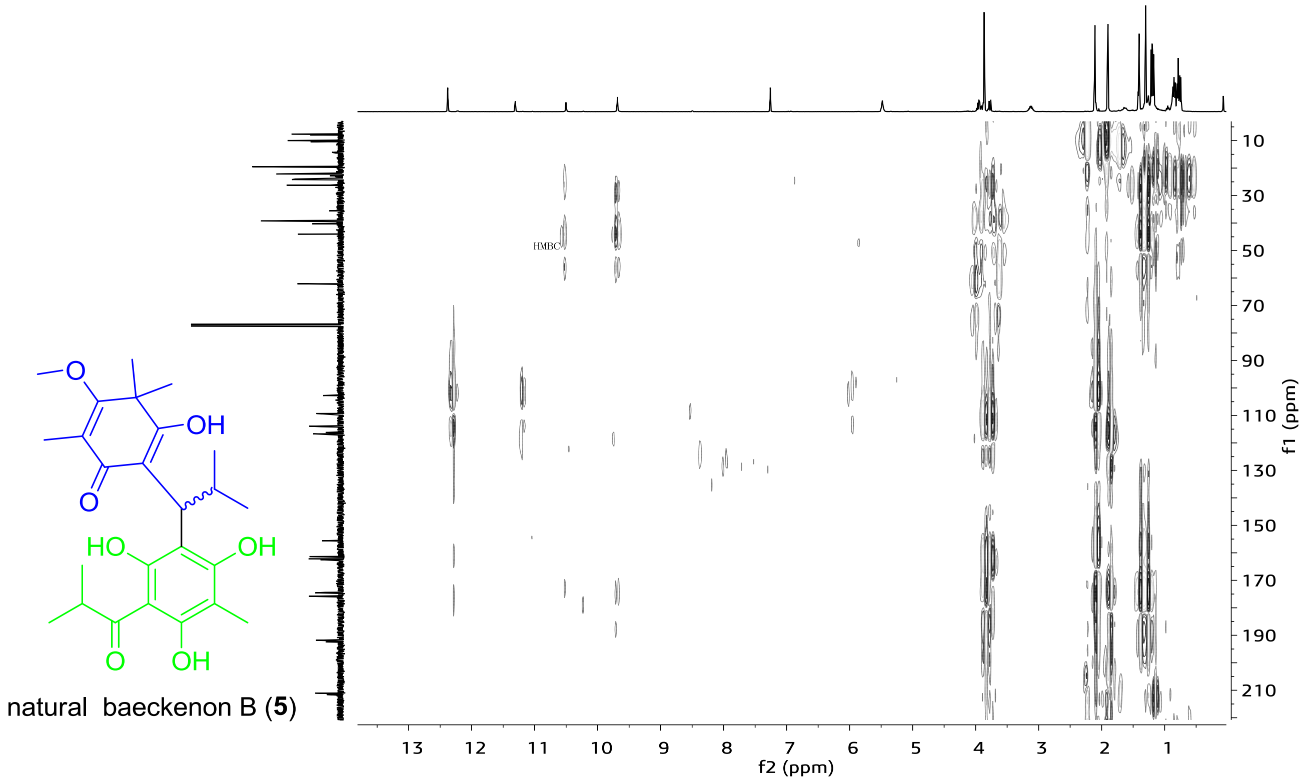
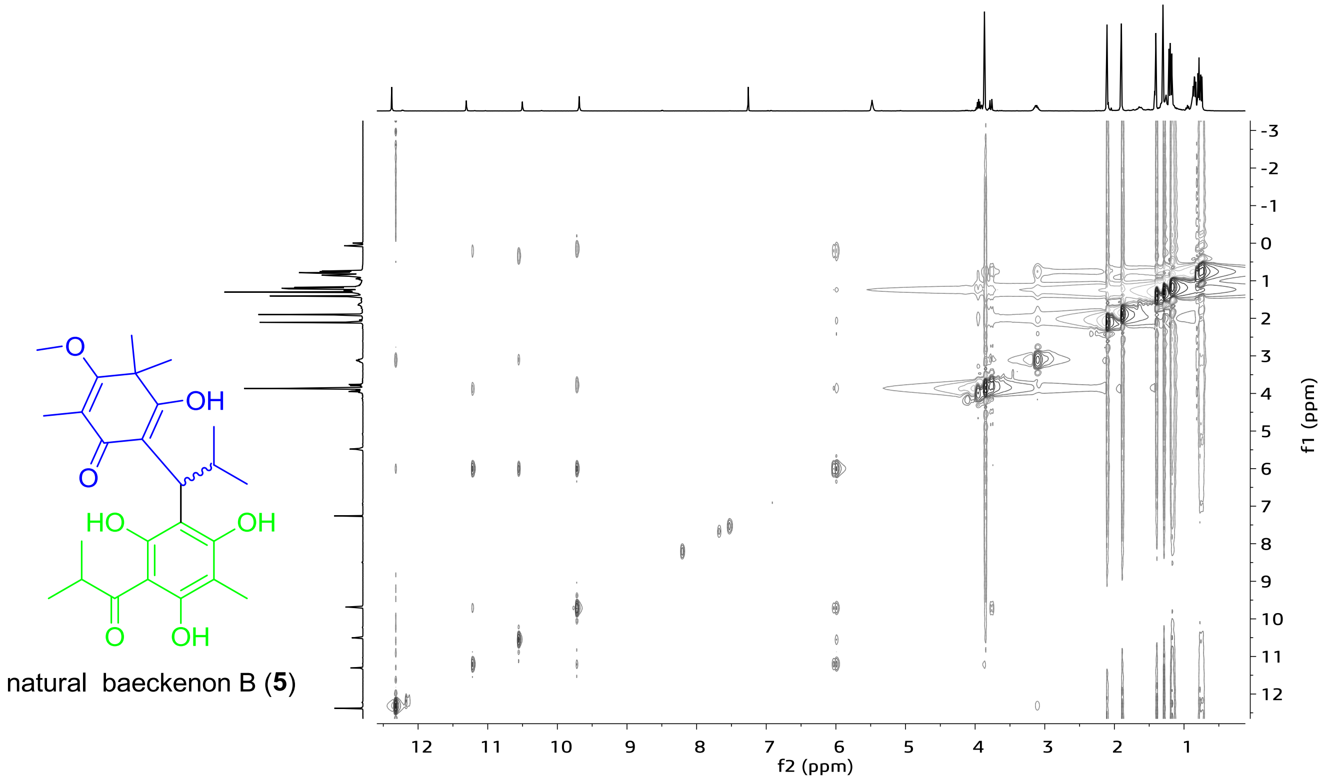


Figure S18-4. HSQC of natural **5** (400 MHz, $CDCl_3$)



natural baeckenon B (**5**)

Figure S18-5. HMBC of natural **5** (400 MHz, $CDCl_3$)



natural baeckenon B (**5**)

Figure S18-6. NOESY of natural **5** (400 MHz, $CDCl_3$)

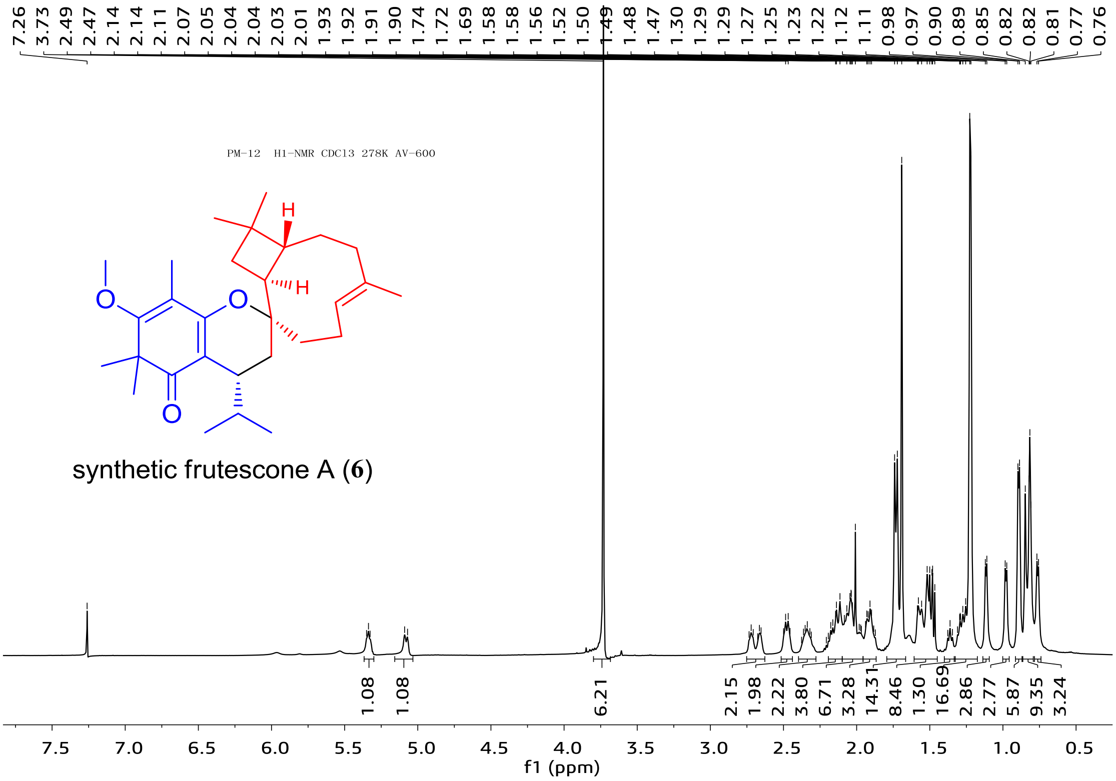


Figure S19-1. ^{1}H NMR of synthetic **6** (278K, 600 MHz, CDCl$_3$)

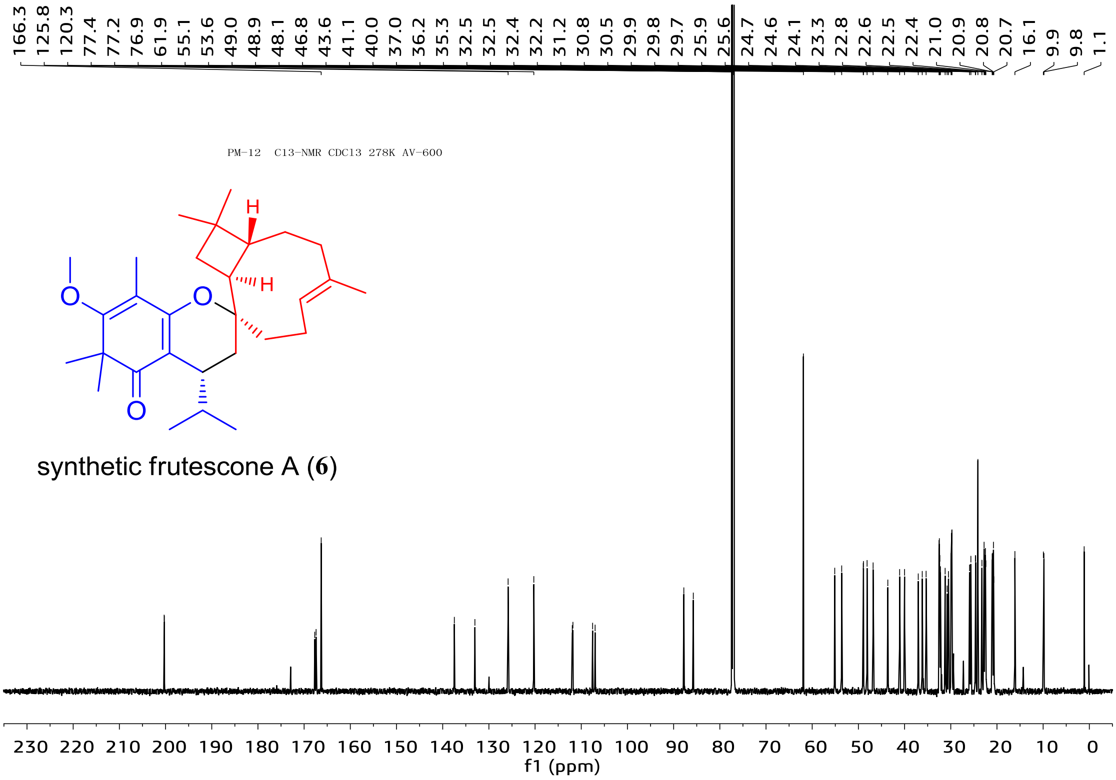


Figure S19-2. ^{13}C NMR of synthetic **6** (278K, 150 MHz, CDCl$_3$)

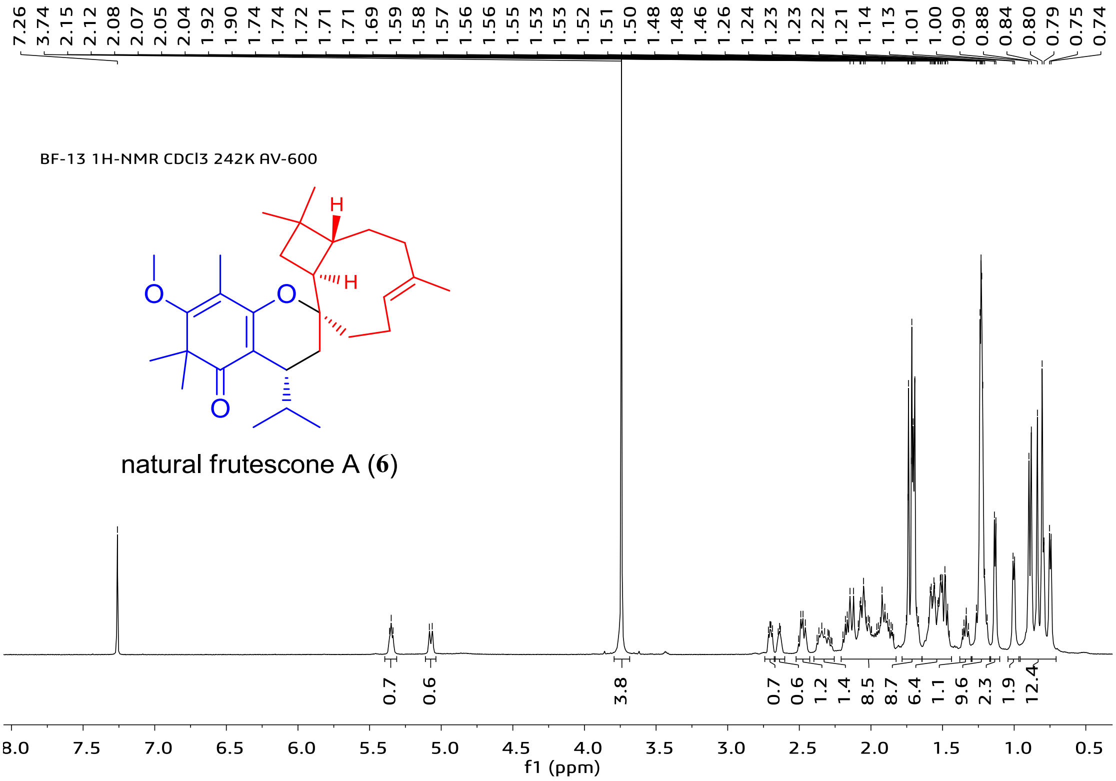


Figure S20-1. ^{1}H NMR of natural **6** (242K, 600 MHz, CDCl$_3$)

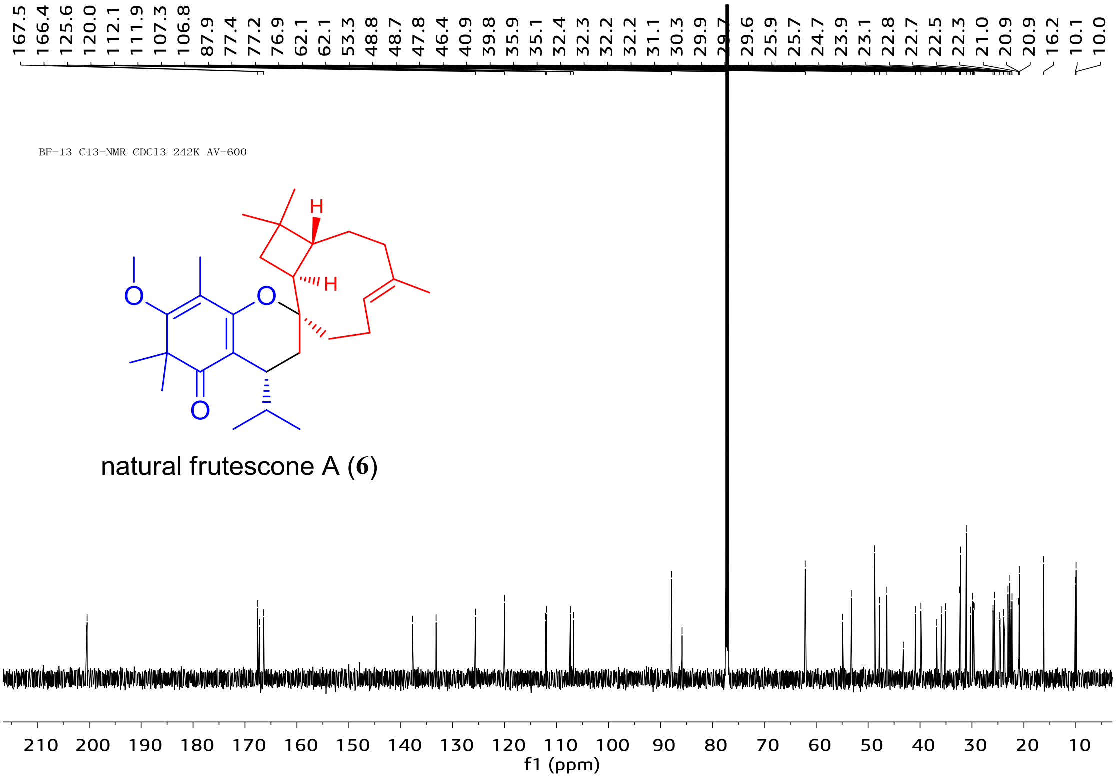


Figure S20-2. ^{13}C NMR of natural **6** (242K, 150 MHz, CDCl$_3$)

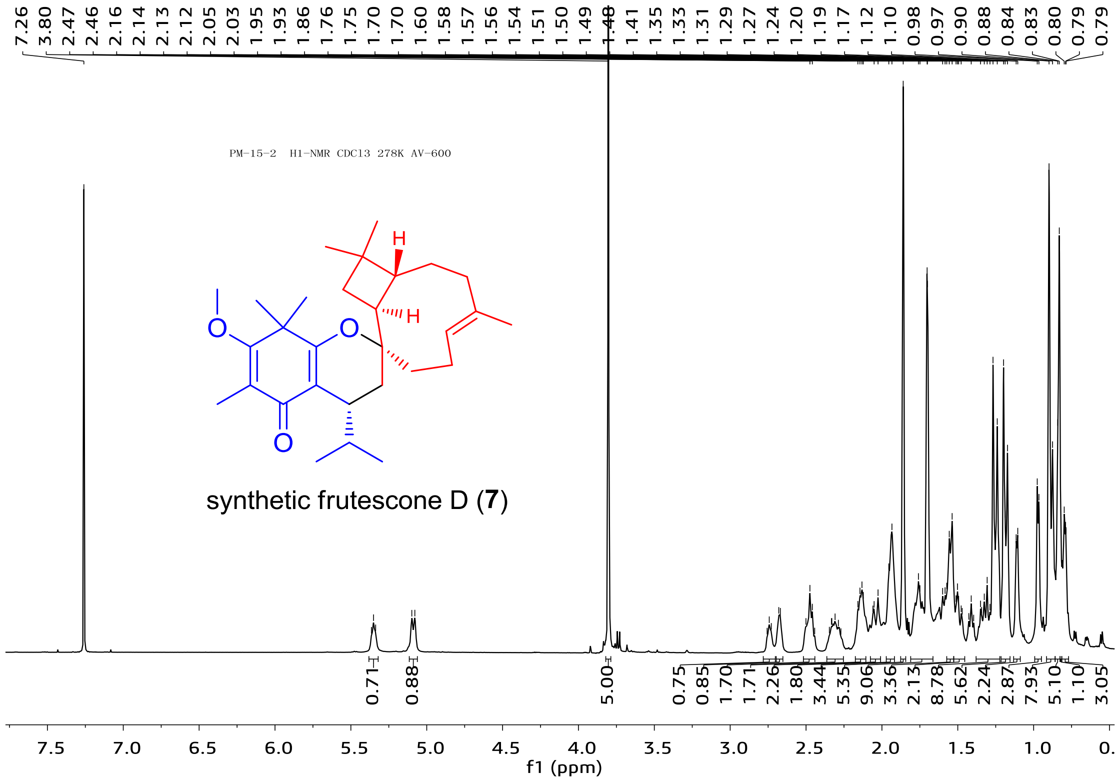


Figure S21-1. ^{1}H NMR of synthetic **7** (278K, 600 MHz, $CDCl_3$)

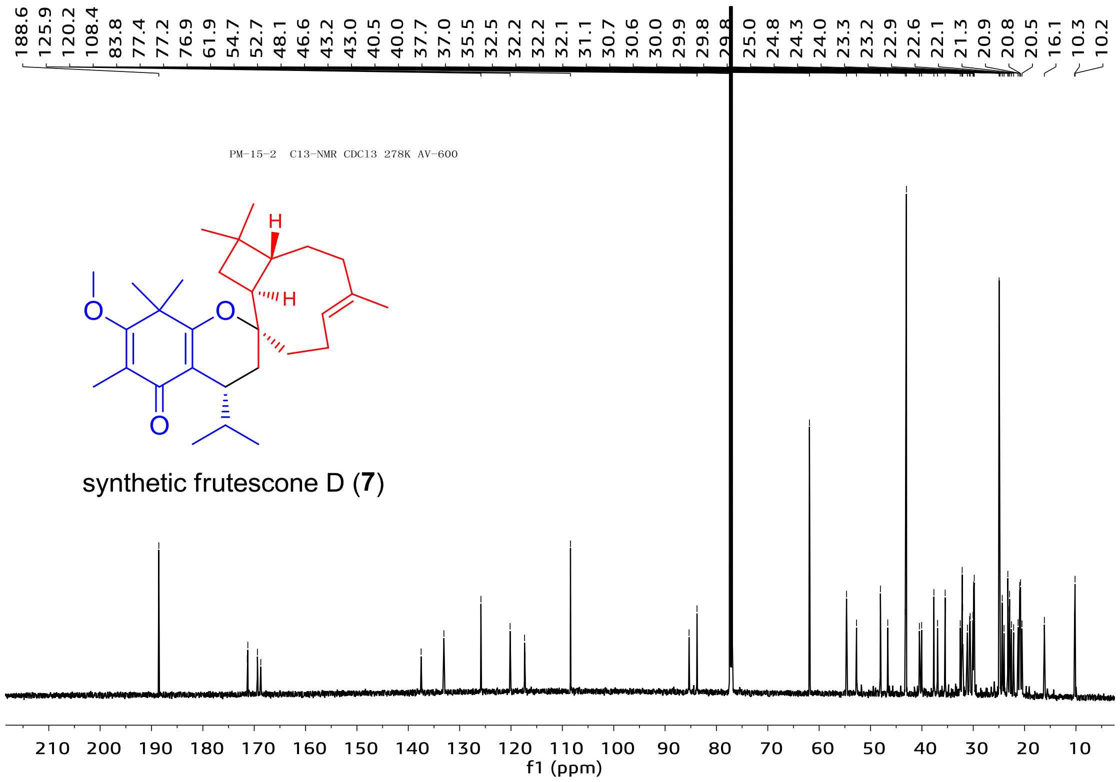


Figure S21-2. ^{13}C NMR of synthetic **7** (278K, 150 MHz, $CDCl_3$)

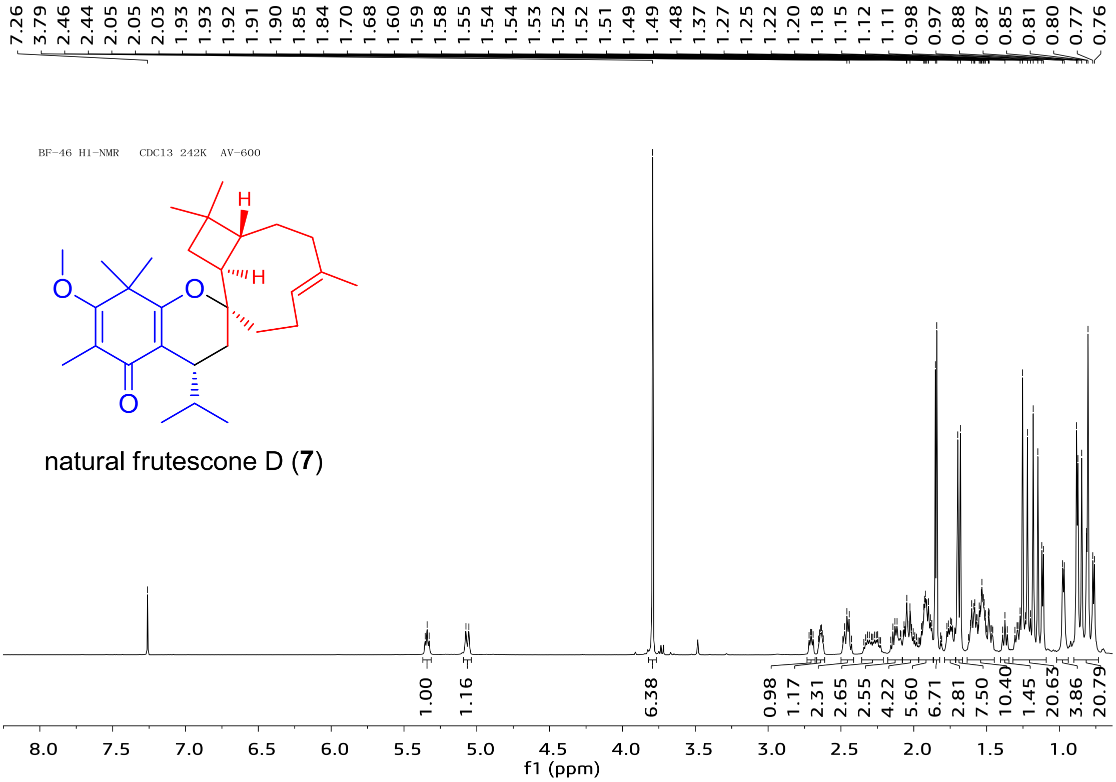


Figure S22-1. ^{1}H NMR of natural **7** (242K, 600 MHz, CDCl$_3$)

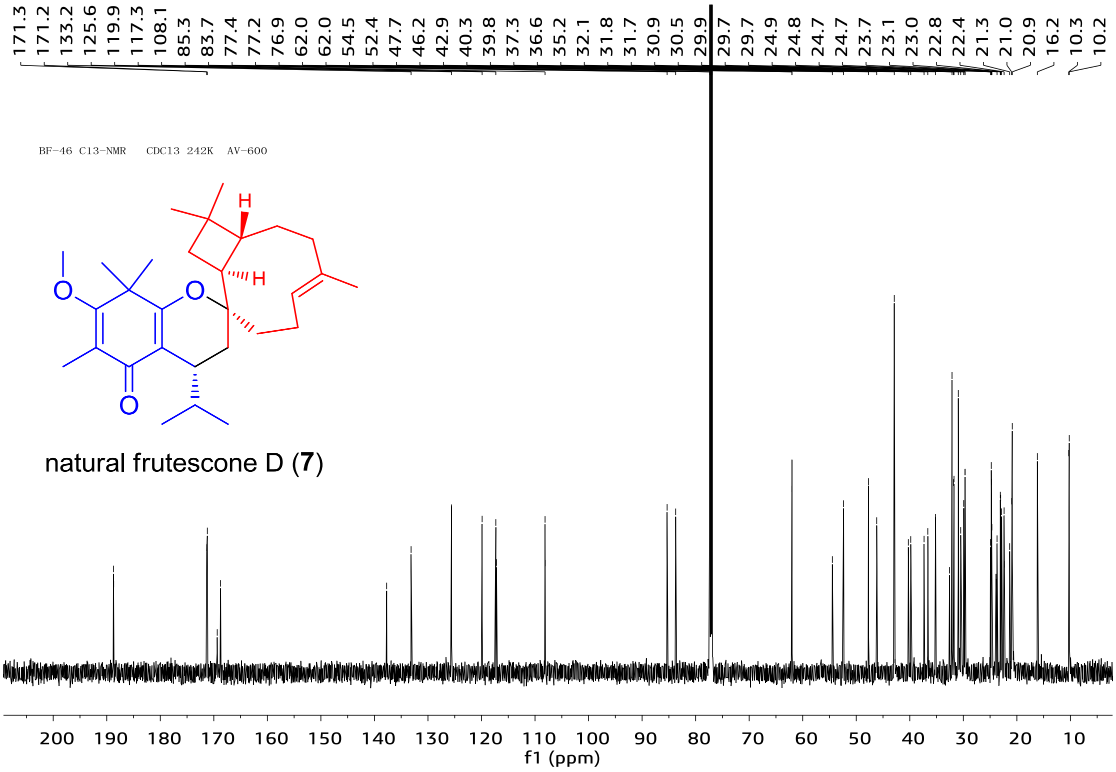


Figure S22-2. ^{13}C NMR of natural **7** (242K, 150 MHz, CDCl$_3$)

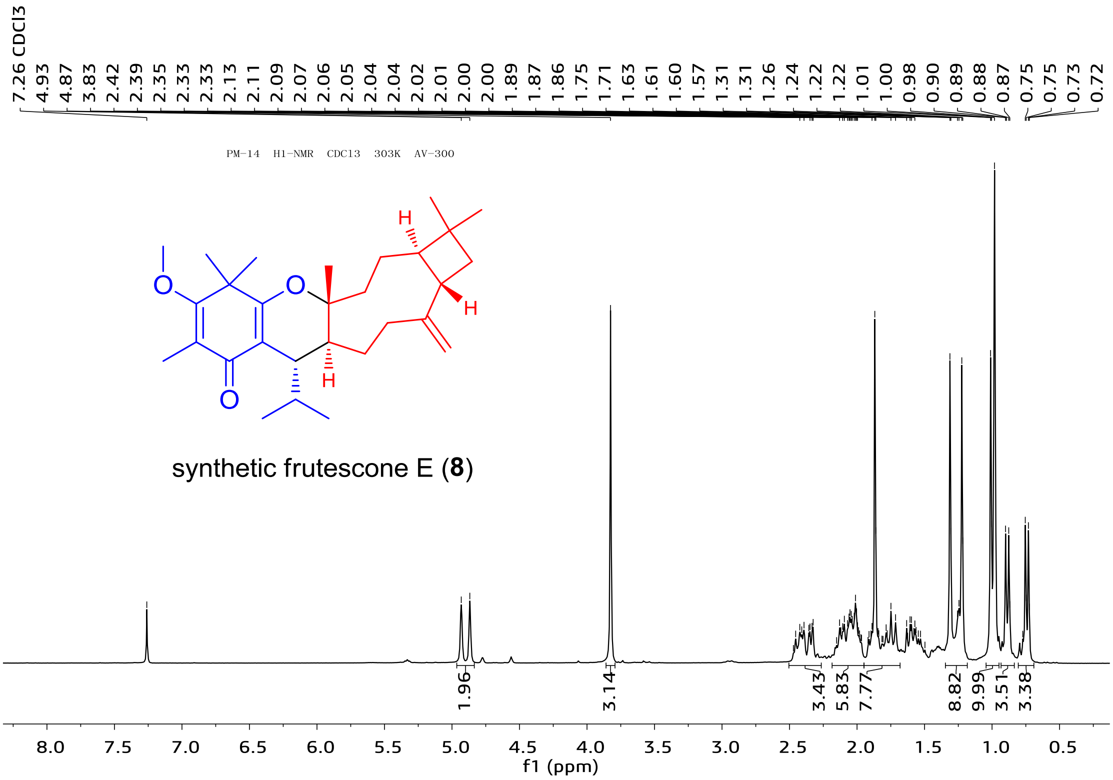


Figure S23-1. ^{1}H NMR of synthetic **8** (300 MHz, $CDCl_3$)

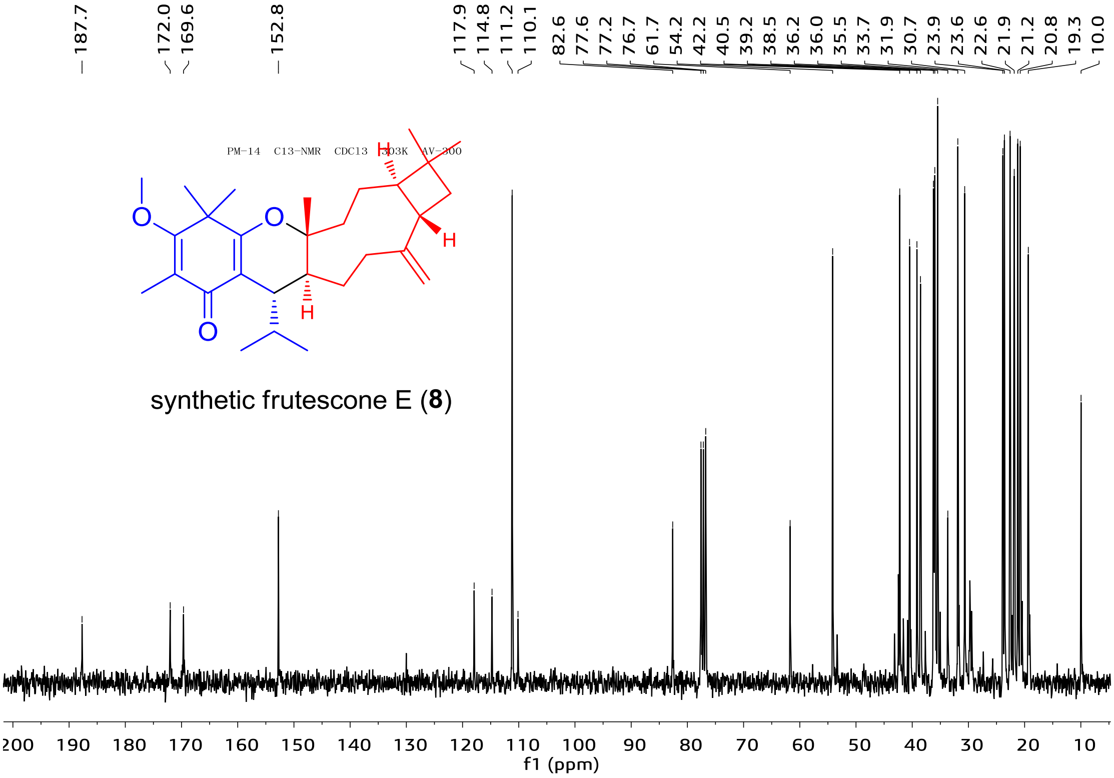


Figure S23-2. ^{13}C NMR of synthetic **8** (75 MHz, $CDCl_3$)

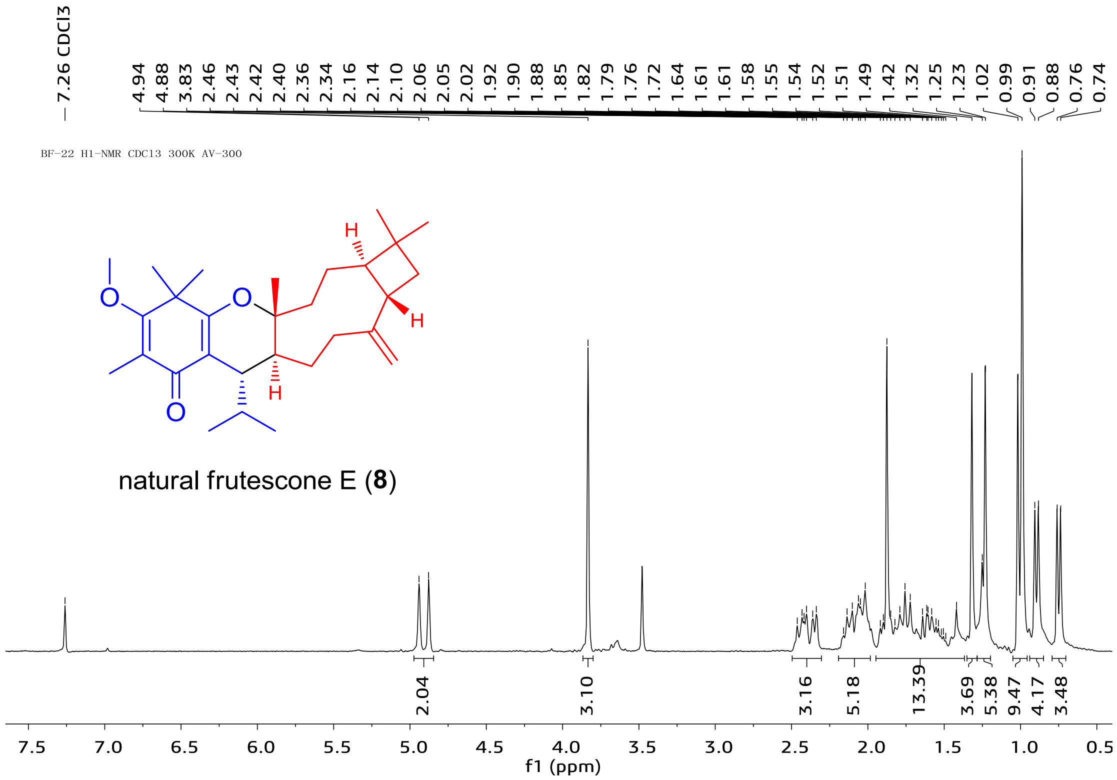


Figure S24-1. ^{1}H NMR of natural **8** (300 MHz, $CDCl_3$)

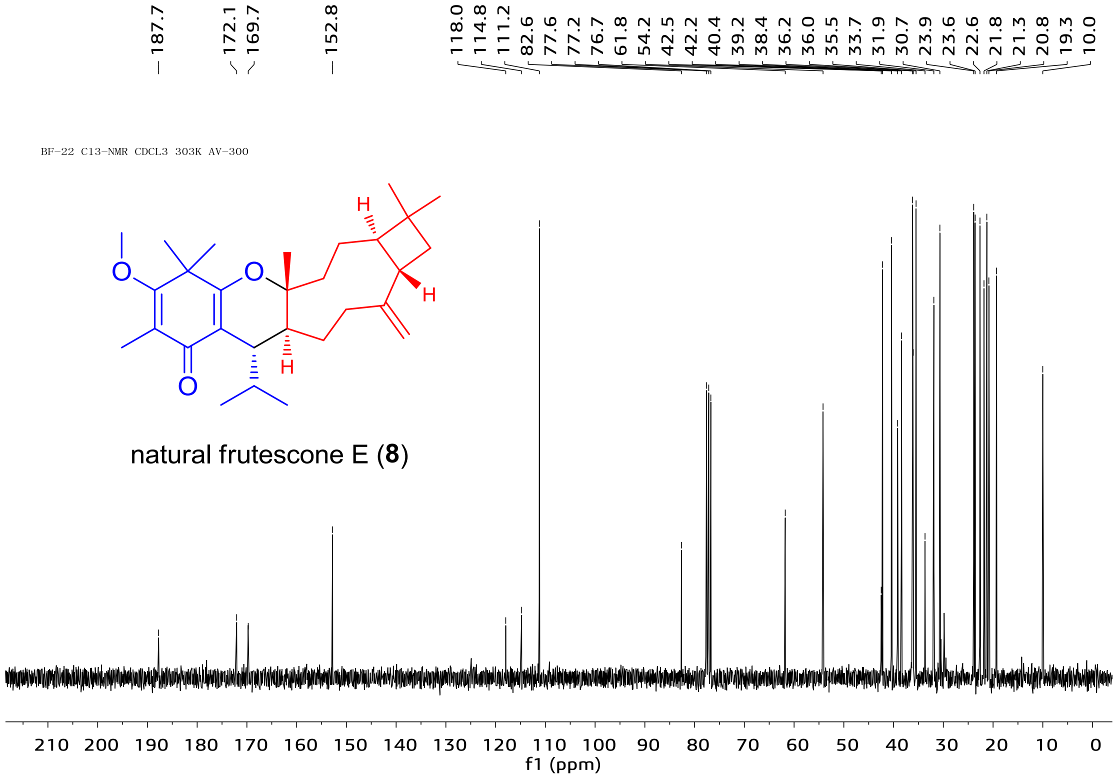


Figure S24-2. ^{13}C NMR of natural **8** (75 MHz, $CDCl_3$)

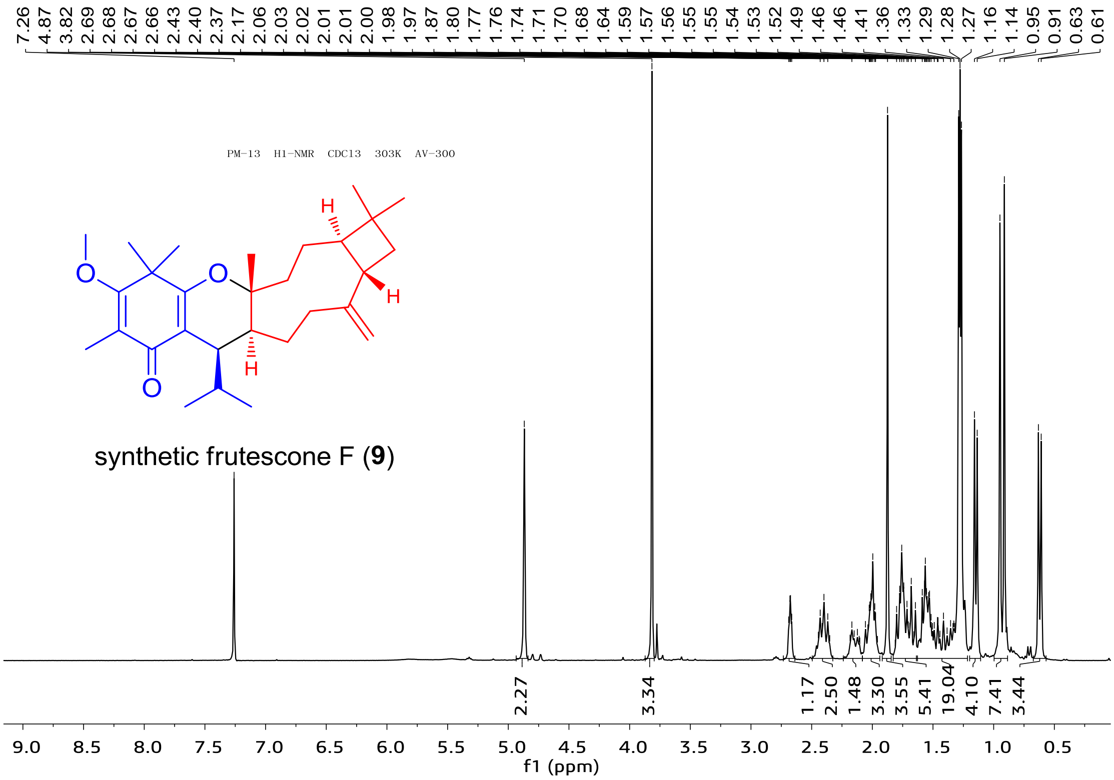


Figure S25-1. ^{1}H NMR of synthetic **9** (300 MHz, CDCl$_3$)

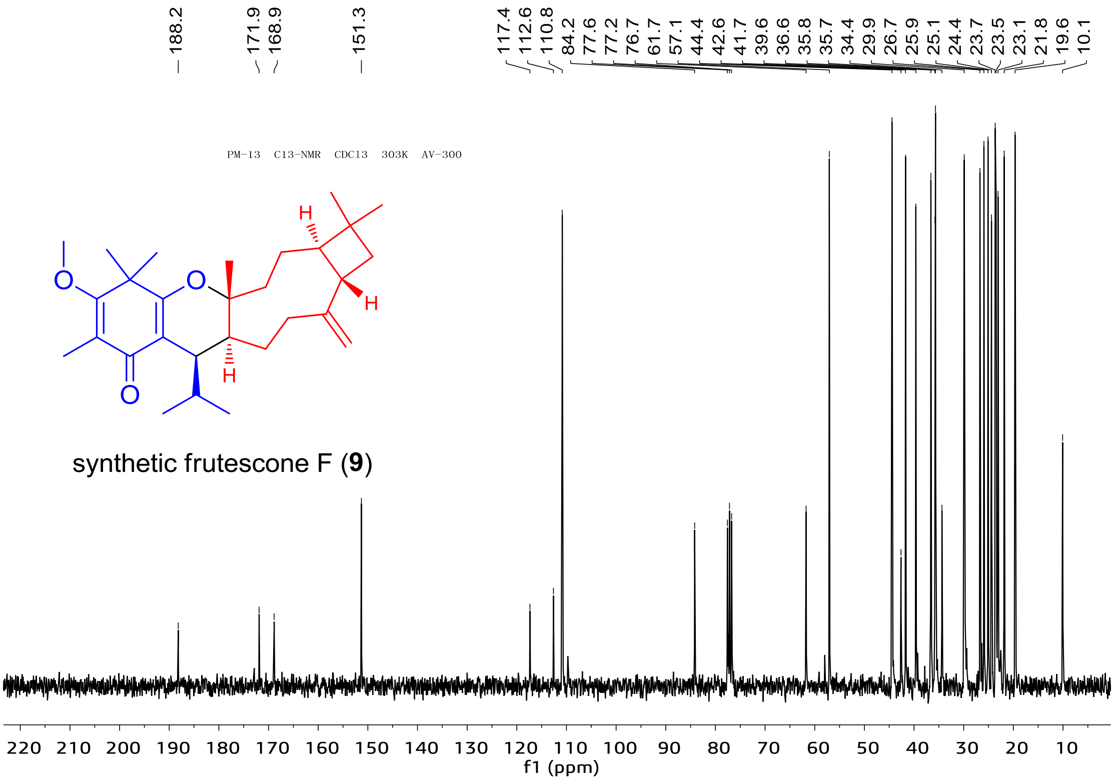


Figure S25-2. ^{13}C NMR of synthetic **9** (75 MHz, CDCl$_3$)

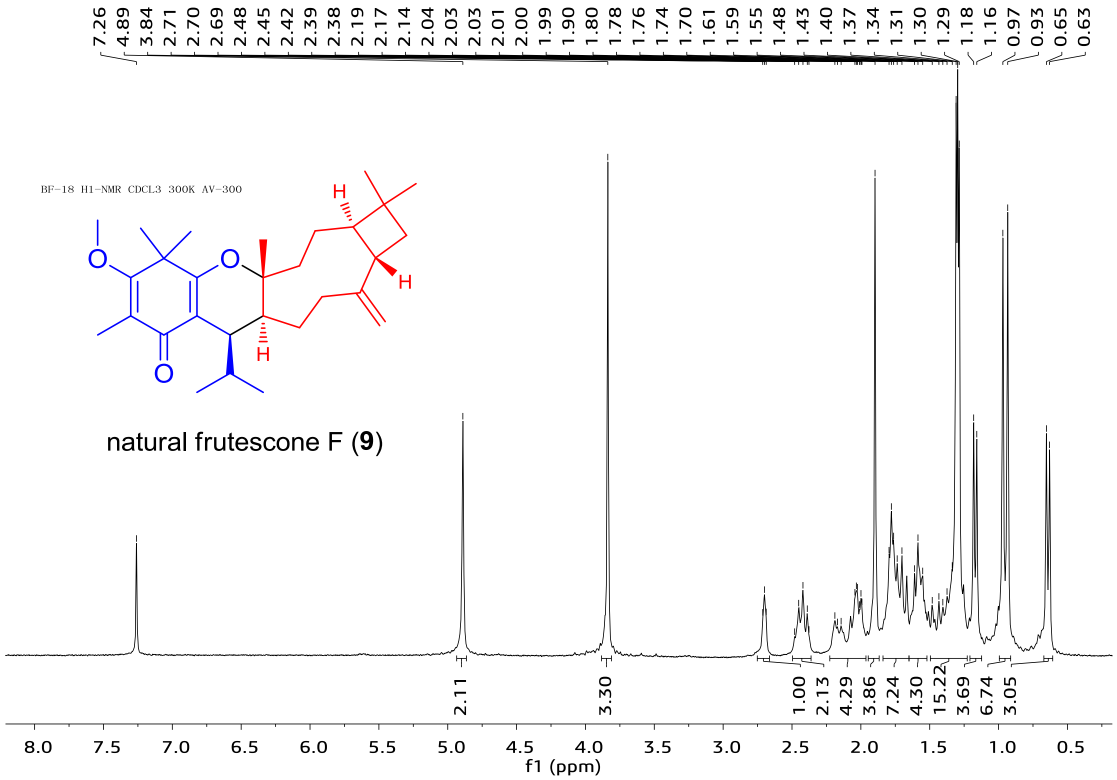


Figure S26-1. ^{1}H NMR of natural **9** (500 MHz, $CDCl_3$)

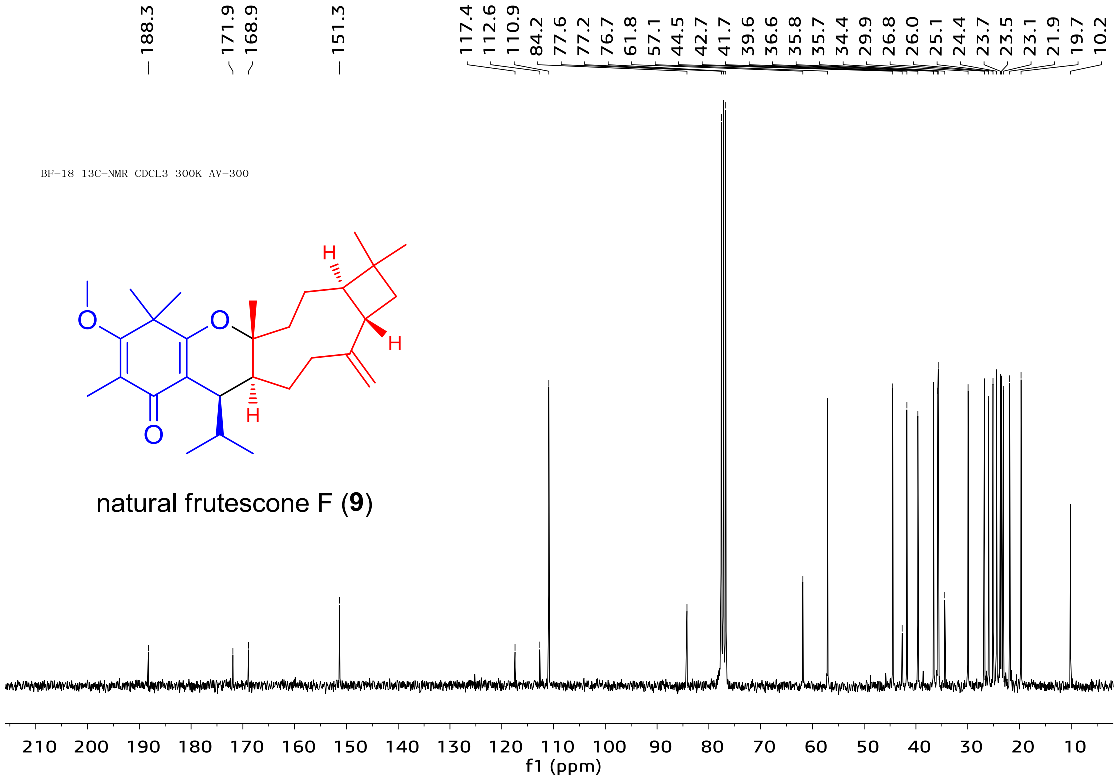


Figure S26-2. ^{13}C NMR of natural **9** (125 MHz, $CDCl_3$)