Asymmetric Total Synthesis of Pedrolide

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Supporting Information

Table of Contents

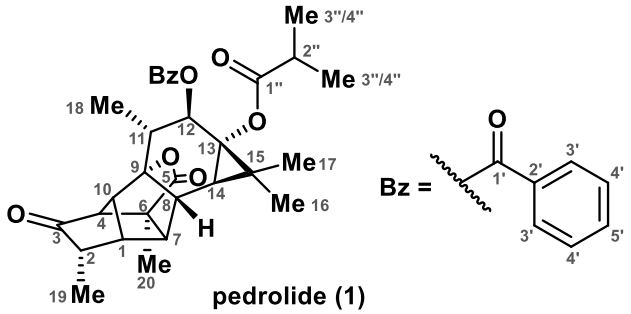
1. General Information

All air and water sensitive reactions were carried out under Argon atmosphere with dry solvents under anhydrous conditions unless otherwise noted. All the chemicals were purchased commercially and used without further purification. Dry acetonitrile (MeCN) and dichloromethane (DCM) were distilled from calcium hydride; Dry diethyl ether (Et_2O), tetrahydrofuran (THF), and toluene (PhMe) were distilled from sodium-benzophenone. Other solvents purification was conducted according to Purification of Laboratory Chemicals (Perrin, D. D.; Armarego, W. L. and Perrins, D. R., Pergamon Press: Oxford, 1980). Yields refer to chromatographically, unless otherwise stated. Lower temperatures were maintained using acetone/CO_2(s) (−78 °C), water/ice (0 °C) baths, and low temperature reactor. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Tsingdao silica gel plates (60F-254) that were analyzed by fluorescence upon 254 nm irradiation or staining with basic aqueous potassium permanganate ($KMnO_4$) or an ethanolic solution of phosphomolybdic acid, and heat as developing agents. If not specially mentioned, flash column chromatography uses silica gel (200-300 mesh) supplied by Tsingtao Haiyang Chemicals (China).

NMR spectra were recorded on either a Brüker Avance 400 (^{1}H: 400 MHz, ^{13}C: 101 MHz), or Brüker Avance 600 (^{1}H: 600 MHz, ^{13}C: 151 MHz), and calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$, δ 7.26 ppm ^{1}H NMR, δ 77.16 ppm ^{13}C NMR). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. High-resolution mass spectra (HRMS) were recorded on a Bruker Apex IV FTMS mass spectrometer using ESI (electrospray ionization). Infrared spectra were recorded on a Shimadzu IR Prestige 21, using thin films of the sample on KBr plates. Optical rotations were recorded on a Perkin-Elmer 351 polarimeter at 589 nm, 100 mm cell at 25 °C. Data were reported as follow: optical rotation (*c*, g/100 mL) in solvent. Melting points were obtained on an MP450-01 micro-melting point apparatus (Hanon Instrument, Shandong, China) without correction.

2. NMR Comparison of (+)-Pedrolide

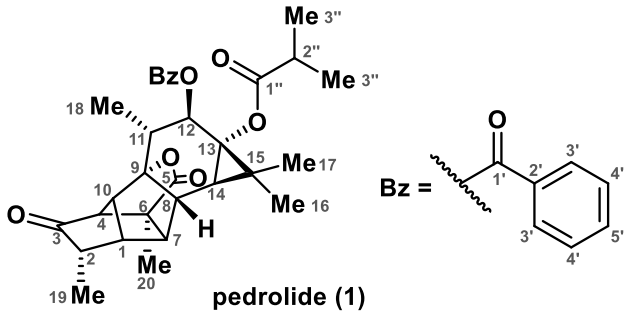
Table S1. ^{1}H Spectrum Comparison in $CDCl_3$ (δ_H in ppm, multiplicity, J in Hz).



pedrolide (1)

C#	Pedrolide (*Nat*) (300 MHz)	Carreira's (500 MHz)	Ours (600 MHz)	Δ (*Nat-Ours*)
1	2.63 (m)	2.65 – 2.62 (m)	2.65 – 2.62 (m)	\
2	2.39 (qd, J = 7.2, 4.7)	2.39 (qd, J = 7.3, 4.8)	2.39 (qd, J = 7.3, 4.4)	0
4	2.61 (br d, J = 2.1)	2.61 (br s)	2.61 (d, J = 2.3)	0
7	2.44 (br s)	2.44 (br s)	2.44 (br s)	0
8	1.75 (br d, J = 5.5)	1.75 (dd, J = 5.7, 0.6)	1.74 (d, J = 5.7)	0.01
10	3.03 (dd, J = 4.5, 2.1)	3.03 (dd, J = 4.4, 2.2)	3.03 (d, J = 2.4)	0
11	1.80 (dq, J = 8.2, 7.0)	1.80 (dq, J = 8.1, 6.7)	1.83 – 1.77 (m)	\
12	5.95 (d, J = 8.2)	5.95 (d, J = 8.2)	5.95 (d, J = 8.2)	0
14	0.96 (d, J = 5.5)	0.96 (d, J = 5.7)	0.96 (d, J = 5.7)	0
16	1.12 (s)	1.12 (s)	1.12 (s)	0
17	1.45 (s)	1.45 (s)	1.45 (s)	0
18	1.18 (d, J = 7.0)	1.19 (d, J = 6.7)	1.18 (d, J = 6.6)	0
19	1.25 (d, J = 7.2)	1.25 (d, J = 7.2)	1.25 (d, J = 7.5)	0
20	1.25 (s)	1.25 (s)	1.25 (s)	0
3'	8.02 (dd, J = 7.2, 1.4)	8.06 – 8.01 (m)	8.06 – 8.03 (m)	\
4'	7.44 (dd, J = 7.2, 1.4)	7.47 – 7.41 (m)	7.44 (t, J = 7.7 Hz)	0
5'	7.55 (dd, J = 7.2, 1.4)	7.54 (ddt, J = 7.9, 6.9, 1.3)	7.54 (t, J = 7.3 Hz)	0.01
2"	2.54 (hept, J = 7.0)	2.54 (hept, J = 7.0)	2.53 (hept, J = 7.0)	0.01
3"	1.12 (d, J = 7.0)	1.12 (d, J = 7.0)	1.12 (d, J = 7.0)	0
4"	1.10 (d, J = 7.0)	1.10 (d, J = 7.0)	1.09 (d, J = 7.0)	0.01

Table S2. ^{13}C Spectrum Comparison in $CDCl_3$ (δ_C in ppm).

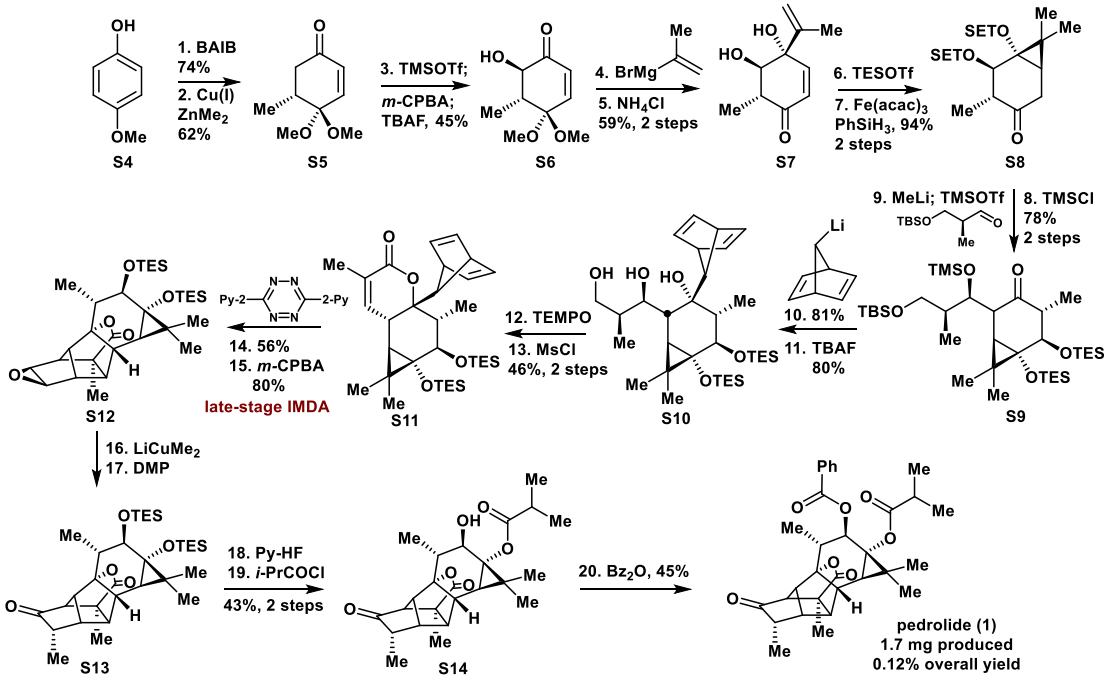


C#	Pedrolide (*Nat*) (75 MHz)	Carreira's (126 MHz)	Ours (151 MHz)	Δ (*Nat-Ours*)
1	55.6 (55.64)	55.6	55.7 (55.65)	-0.01
2	45.0	45.0	45.0	0
3	212.2	212.2	212.2	0
4	63.1	63.1	63.1	0
5	176.8	176.8	176.8	0
6	45.6	45.6	45.6	0
7	46.7	46.7	46.7	0
8	51.0	51.0	51.0	0
9	88.5	88.5	88.5	0
10	50.1	50.1	50.1	0
11	43.4	43.4	43.4	0
12	80.1	80.1	80.1	0
13	66.4	66.4	66.4	0
14	28.2	28.2	28.2	0
15	30.3	30.3	30.3	0
16	23.2	23.2	23.2	0
17	18.0	18.0	18.0	0
18	13.8	13.9	13.8	0
19	12.4	12.4	12.4	0
20	17.4	17.4	17.4	0
1'	166.3	166.3	166.3	0
2'	130.9 (130.92)	130.9	130.9 (130.95)	-0.03
3'	129.8	129.8	129.8	0
4'	128.5	128.5	128.5	0
5'	132.8	132.8	132.8	0
1"	177.3	177.3	177.3	0
2"	33.8	33.8	33.8	0
3"[a]	19.1	18.9	18.9	0.2
4"[a]	18.9	19.1	19.1	-0.2

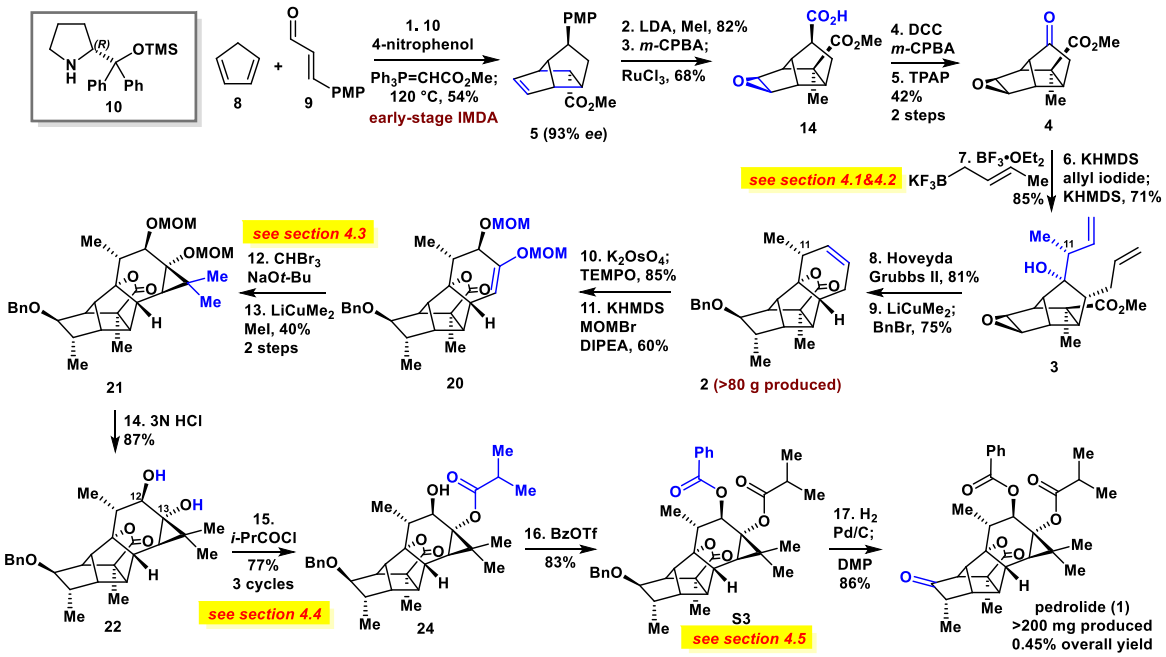
Note: [a]Carreira reported that "Evaluation of the 2D NMR data for synthetic (+)-pedrolide suggests, that the assignment of the ^1H NMR signals to the corresponding ^{13}C NMR signals for 3" and 4" was inverted in the isolation report." Based on HSQC analysis, our NMR was consistent with Carreira's result.

3. Total Synthesis of (+)-Pedrolide

Scheme S1. Carreira's total synthesis of (+)-pedrolide based on a late-stage IMDA reaction (*J. Am. Chem. Soc.* **2023**, *145*, 8332).[1]



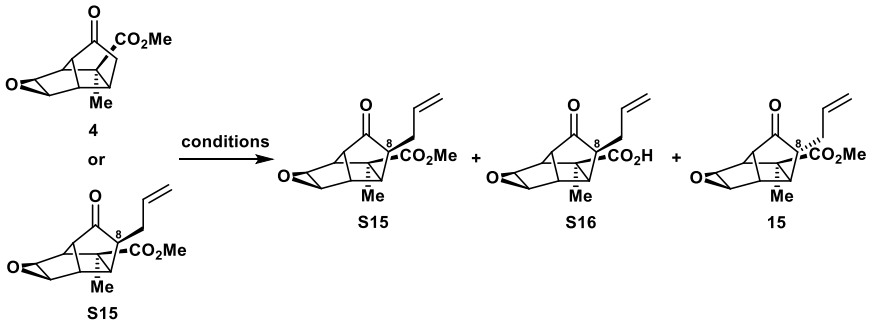
Scheme S2. Our total synthesis of (+)-pedrolide based on an early-stage IMDA reaction.



4. Detailed Optimizations and Unsuccessful Attempts

4.1 C8 Allylation and Epimerization

Table S3. Allylation and epimerization conditions.



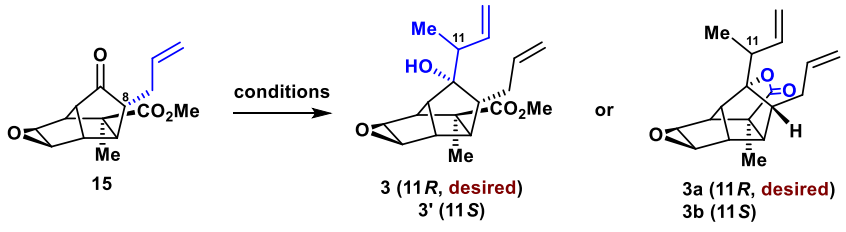
Entry[a]	Substrate	Reagent	Solvent/Temp. (°C)	Products (Yield(%))
1	**4**	KHMDS, allyl iodide	THF/-78	**S15** (90)
2	**S15**	KHMDS	THF/-78	NR
3	**S15**	KHMDS	THF/-60	**15** (20) + **S16** (60)
4	**S15**	KHMDS	THF/-30	**S16** (30)
5	**S15**	NaHMDS	THF/-30	NR
6	**S15**	LDA	THF/-30	decomposed
7	**S15**	LHMDS	THF/-30	NR
8	**S15**	KO*t*-Bu	THF/-30	**S16** (70)
9	**S15**	KHMDS	THF-Et_2O (1:1) -50	**15** (trace)
10	**S15**	KHMDS	Et_2O/-50	**15** (trace)
11	**S15**	KHMDS	CPME-THF (4:1) -50	**15** (74)
12	**4**	KHMDS, allyl iodide; KHMDS	CPME-THF (4:1) -50	**15** (71)

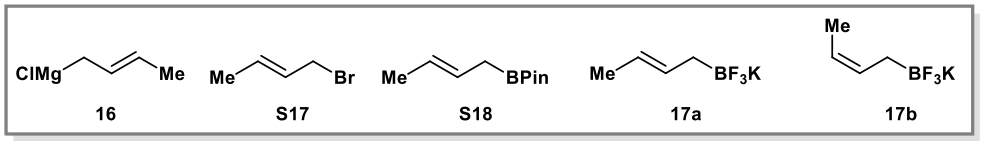
[a] Reactions performed on 0.1 mmol scale. [b] No reaction = NR.

Hydrolysis process was much slower in CPME than in THF. Originally, **4** or **S15** had poor solubility in CPME but its enolate was well dissolved in CPME at -50 °C. It was proposed that this difference in solubility helped to prevent the hydrolysis of methyl ester and promote the epimerization process.

4.2 Optimization of Crotylation

Table S4. Optimization of crotylation using different reagents.



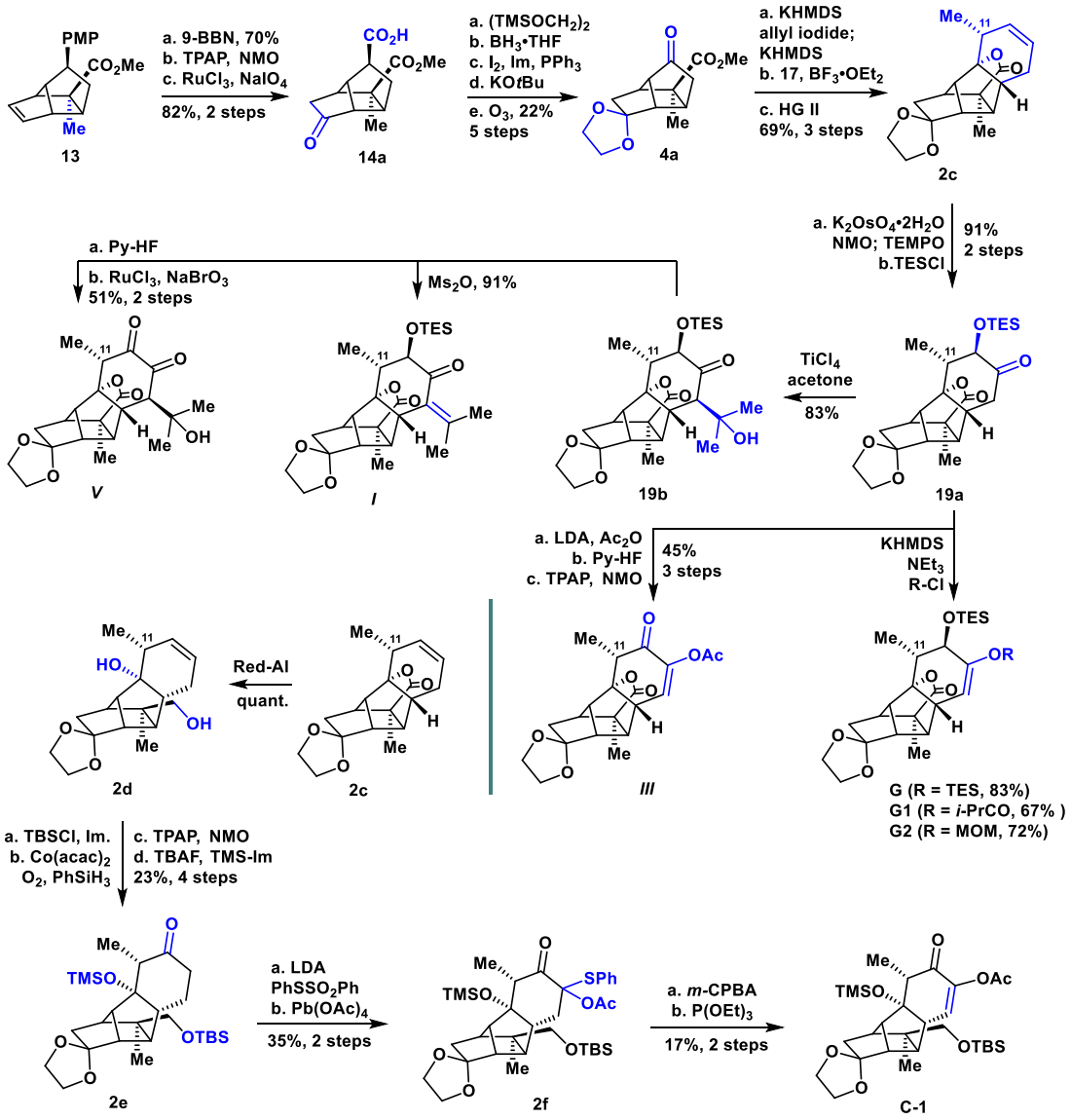


Entry[a]	Reagent	Solvent/Temp. (°C)	*R*:*S*	Yield (%)	Products
1	**16**	THF/-30	1:2.0	70	**3a+3b**
2	**16**, $TiCl_4$	THF/-78	1:2.1	no determined	**3a+3b**
3	**16**, $CeCl_3$	THF/-78	\	NR	\
4	**16**, $ZnBr_2$	THF/-78	\	NR	\
5	**S17** Cp_2TiCl_2	THF/25	\	no desired product	\
6	**S17**, In	THF-H_2O/reflux	\	low conversion	**3a+3b**
7	**S18**, In	THF or DCM/ reflux	\	NR	\
8	**17a** K-catalyst	DCM-H_2O/25	\	NR	\
9	**17a** $BF_3{\cdot}OEt_2$	DCM/-50	*R* only	85	**3**
10	**17a** $BF_3{\cdot}OEt_2$	DCM/-30	\	epoxide-opening side products	\
11	**17b** $BF_3{\cdot}OEt_2$	DCM/-50	*S* only	70	**3'**

[a] Reactions performed on 0.2 mmol scale. K-catalyst (Montmorillonite K10).

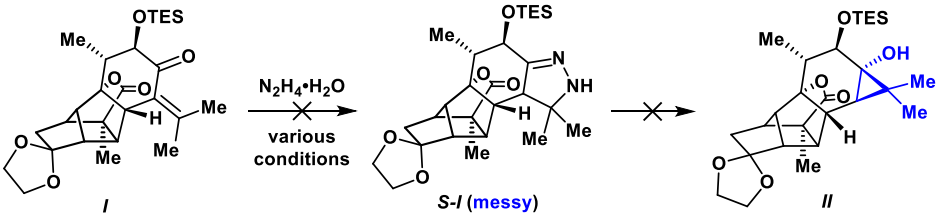
4.3 The Synthesis of Cyclopropane D ring

Scheme S3. Initial synthetic routes for cyclopropanation precursors (***I***, ***III***, ***V***, ***S-II***, **G** and **G1-2**).

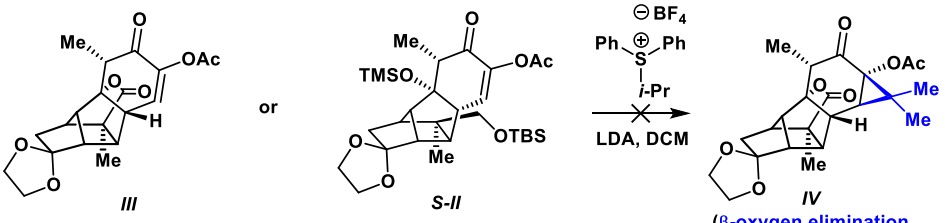


Scheme S4. Unsuccessful attempts to construct the desired cyclopropane ring.

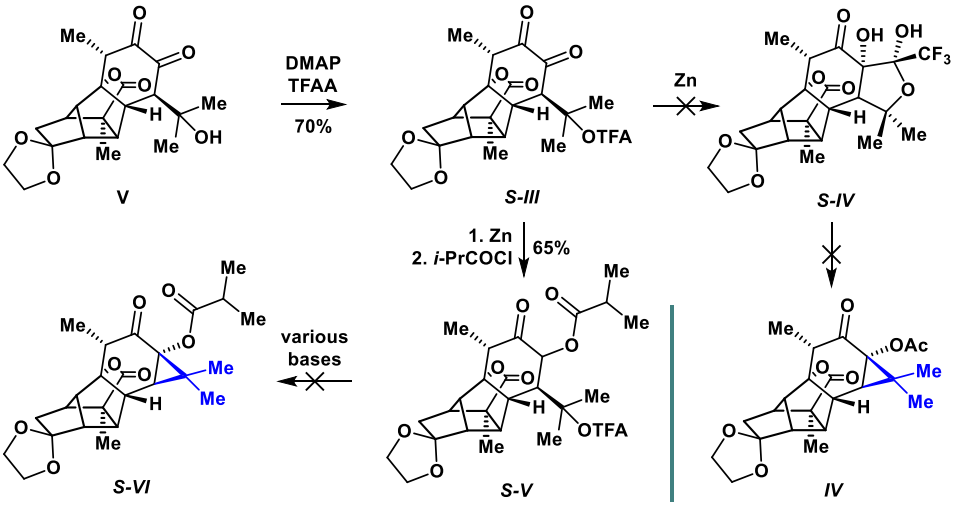
a) Photolysis of cyclic diazene (Wender)



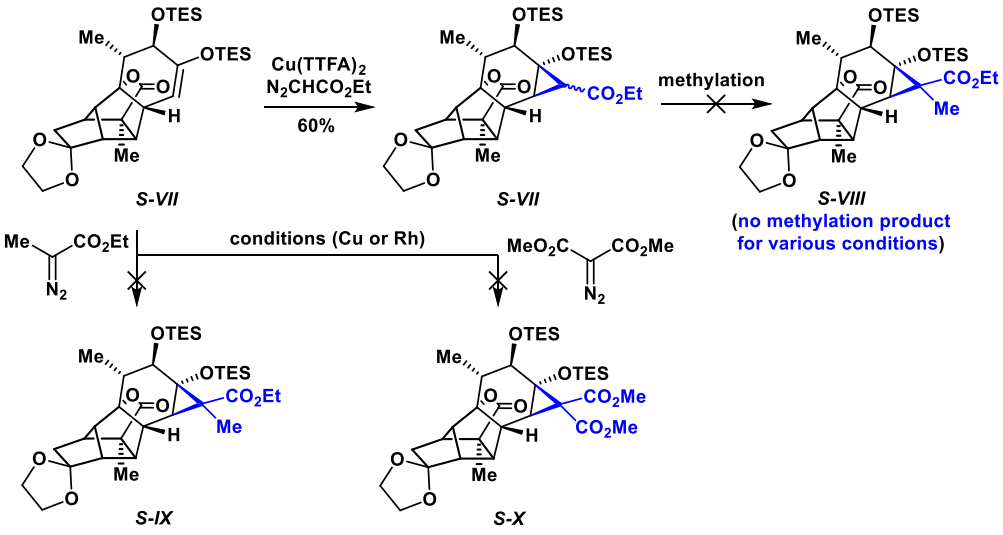
b) Diphenylisopropylsulfonium ylide addition (Wender)



c) Cascade rearrangement (Baran)

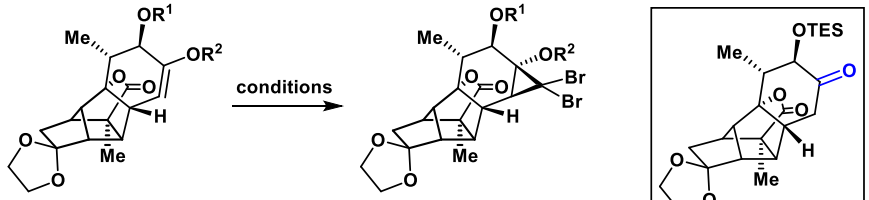


d) Cu-catalyzed carbenoid cyclopropanations



Part II: Optimization of the Free Carbene Cyclopropanation

Table S5. Optimization of the free carbene cyclopropanation with **G**, **G1** and **G2**.



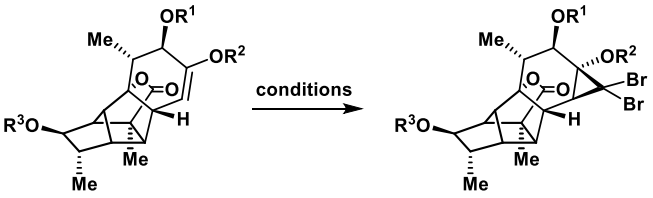
G: (R^1 = TES, R^2 = TES)
G1: (R^1 = TES, R^2 = *i*-PrCO)
G2: (R^1 = TES, R^2 = MOM)

G3: (R^1 = TES, R^2 = TES)
G4: (R^1 = TES, R^2 = *i*-PrCO)
G5: (R^1 = TES, R^2 = MOM)

Entry[a]	Substrate	Reagent	Solvent/Temp. (°C)	Yield (%)	Product
1	**G**	KO*t*-Bu $CHBr_3$	pentane/-30	NR	\
2	**G**	Br_2CMe_2 *n*-BuLi	pentane/-78	NR	\
3	**G**	Br_2CMe_2 *n*-BuLi	pentane/ -78 to 25	decomposed	\
4	**G1**	KO*t*-Bu $CHBr_3$	pentane/-30	\	**19a**
5	**G2**	Br_2CMe_2 *n*-BuLi	pentane/ -78 to 25	NR, slightly decomposed	\
6	**G2**	KO*t*-Bu $CHBr_3$	pentane/-30	20	**G5**
7	**G2**	KO*t*Bu $CHBr_3$	pentane/-40	low conversion	**G5**
8	**G2**	KO*t*-Bu $CHBr_3$	hexane/-30	74	**G5**

[a] Reactions performed on 0.05 mmol scale.

Table S6. Optimizations of the free carbene cyclopropanation with **20a**, **20** and **20b**.



20a: (R^1 = MOM, R^2 = TES, R^3 = TBS)
20: (R^1 = MOM, R^2 = MOM, R^3 = Bn)
20b: (R^1 = MOM, R^2 = MOM, R^3 = TBS)

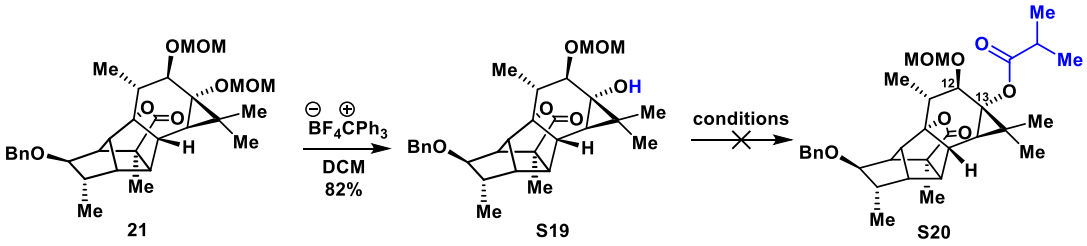
S2a: (R^1 = MOM, R^2 = TES, R^3 = TBS)
S2: (R^1 = MOM, R^2 = MOM, R^3 = Bn)
S2b: (R^1 = MOM, R^2 = MOM, R^3 = TBS)

Entry[a]	Sub-strate	Reagent	Solvent/Temp. (°C)	Yield (%)	Conversion (%)	Product
1	**20a**	KO*t*-Bu $CHBr_3$	hexane/-30 to 25	NR	0	\
2	**20**	KO*t*-Bu $CHBr_3$	hexane/-30	20	50	**S2**
3	**20**	KO*t*-Bu $CHBr_3$	PE/-30	33	60	**S2**
4	**20**	KO*t*-Bu $CHBr_3$	CPME/-30	17	25	**S2**
5	**20**	KO*t*-Bu $CHBr_3$	CPME/0	trace	\	**S2**
6	**20**	KHMDS $CHBr_3$	PE/-30	decom-posed	\	\
7	**20**	NaOH TEBAC $CHBr_3$	DCM-H_2O/25	\	10, slow	**S2**
8	**20**	NaOH TEBAC $CHBr_3$	DCM-H_2O/40	decom-posed	\	\
9	**20**	NaO*t*-Bu $CHBr_3$	PE/-30	NR	0	\
10	**20**	NaO*t*Bu $CHBr_3$	PE/-10	36	60	**S2**
11	**20**	NaO*t*-Bu $CHBr_3$	PE/0	50	80	**S2**
12	**20b**	KO*t*-Bu $CHBr_3$	PE/-30	48	100	**S2b**
13[b]	**20b**	NaO*t*-Bu $CHBr_3$	PE/0	61	90	**S2b**

[a] Reactions performed on 0.05 mmol scale. [b] Although **20b** provided a slightly higher yield, however, TBS group was not compatible when removing MOM group. Therefore, we continued our total synthesis with **S2**; PE (petroleum ether). CPME (cyclopentyl methyl ether); TEBAC (benzyltriethylammonium chloride).

4.4 Optimization of C13 Esterification

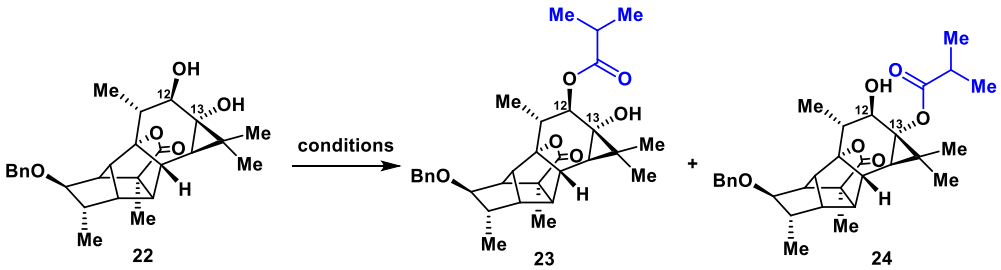
Table S7. Failed C13 esterification with **S19**.



Entry[a]	Reagent	Solvent/Temp. (°C)	Result
1	EDCI, DMAP, *i*-PrCOOH	DCM/40	NR
2	EDCI, DMAP, *i*-PrCOOH	DMF/80	NR
3	DCC, DMAP, *i*-PrCOOH	DCM/40	NR
4	DCC, DMAP, *i*-PrCOOH	THF/80	NR
5	NaH, $(i\text{-PrCO})_2O$	THF/60	slightly decomposed
6	NaH, *i*-PrCOCl	THF/60	slightly decomposed
7	NEt_3, DMAP, *i*-PrCOCl	DCM/40	NR
8	NEt_3, DMAP, *i*-PrCOCl	DMF/80	NR
9	NEt_3, DMAP, $(i\text{-PrCO})_2O$	DCM/40	NR
10	NEt_3, DMAP, $(i\text{-PrCO})_2O$	DMF/80	NR

[a]Reactions performed on 0.1 mmol scale. EDCI (*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride); DCC (dicyclohexy-lcarbodiimide); DMAP (4-dimethylaminopyridine).

Table S8. C13 esterification with **22**.



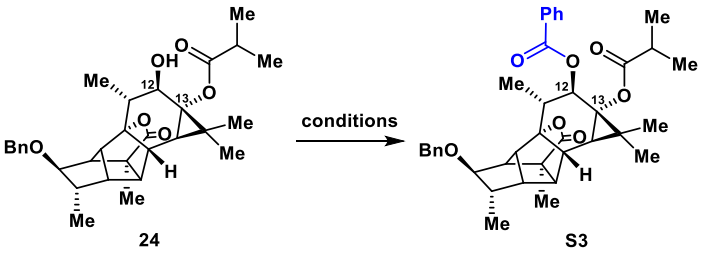
Entry[a]	Reagent	Solvent/Temp. (°C)	23/24	Yield (%)
1	EDCI, DMAP *i*-PrCOOH	DCM/40	**23** only	50 (incomplete reaction)
2	NaH, *i*-PrCOCl	THF/0 to 25	**23** only	20
3	DMAP *i*-PrCOCl	DCM/40	**23** only	90
4	NEt_3, *i*-PrCOCl	DCM/40	1:1	92 (**23** + **24**)
5	NEt_3, *i*-PrCOCl	DCM/50	2:1	90 (**23** + **24**)
6	NEt_3, *i*-PrCOCl	THF/50	\	decomposed
7	NEt_3, DMAP *i*-PrCOCl	DCM/40	1.5:1	90 (**23** + **24**)
8	NEt_3 $(i\text{-PrCO})_2O$	DCM/40	\	NR
9	NaHMDS, NEt_3 *i*-PrCOCl	THF/-20	**23** only	trace
10	NaHMDS *i*-PrCOCl	THF/-20	\	NR

[a] Reactions performed on 0.03 mmol scale.

We tried to explore the possible intramolecular transacylation of both **23** and **24**. However, this transformation was not observed by heating with amine bases (e.g. NEt_3 or DIPEA) in DCM, THF or DMF.

4.5 Optimization of C12 Esterification

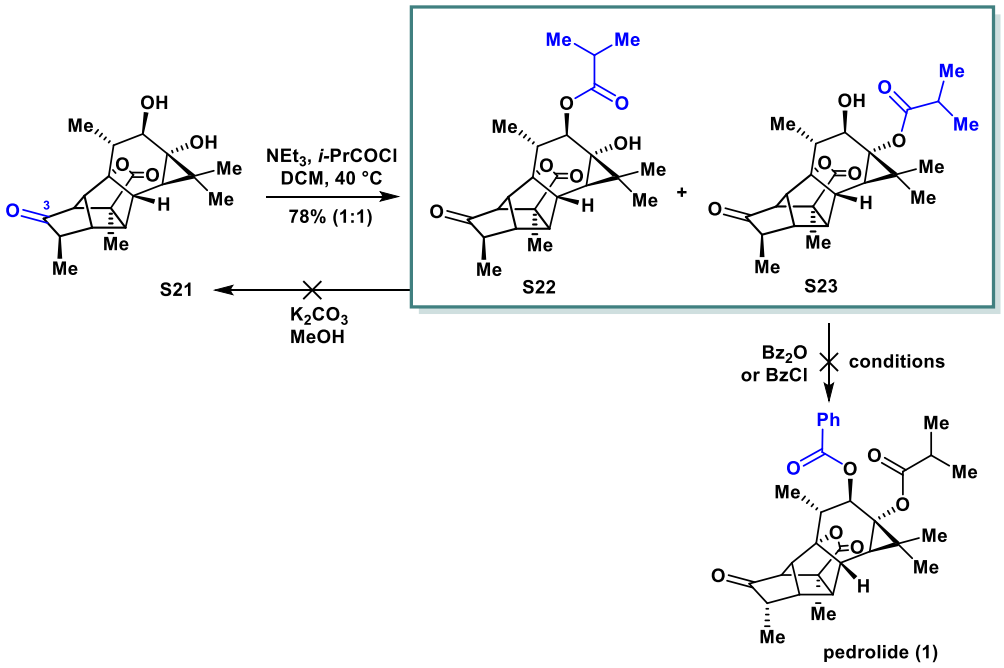
Table S9. C12 esterification with **24**.



Entry[a]	Reagent	Solvent/Temp. (°C)	Yield (%)
1[b]	Py, DMAP, Bz_2O	DCM/40	NR
2	Py, DMAP, Bz_2O	DMF/80	NR
3	Py, DMAP, BzCl	DCM/40	NR
4	Py, DMAP, BzCl	DMF/40	NR
5	Py, DMAP, BzCl	DMF/80	NR
6	EDCI, DMAP, BzOH	DCM/40	NR
7	EDCI, DMAP, BzOH	DMF/40	NR
8	NEt_3, DMAP, BzCl	DCM/40	NR
9	NEt_3, DMAP, Bz_2O	DCM/40	NR
10	2,4,6-trichlorobenzoyl chloride NEt_3, DMAP, BzOH	PhMe/80	20
11	Py, BzOTf	DCM/0 to 25	NR
12	Py, BzOTf	DCM/40	NR
13	Py, BzOTf	DCM/60	83

[a] Reactions performed on 0.05 mmol scale. [b] Inspired by Carreira's elegant work,[1] we tried to adopt their condition (entry 1) for our substrate **24**, but no reaction was observed. Therefore, we turned to screen other benzoylation reagents.

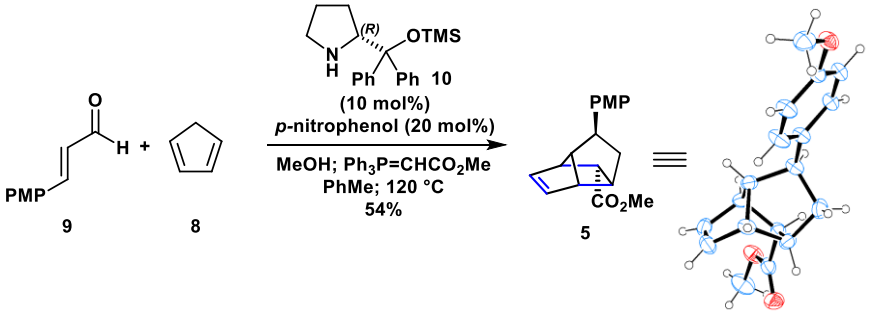
Scheme S5. Attempts toward C12 esterification with **S21** using Bz_2O or BzCl.



Initially (Scheme S5), we have synthesized **S22** and **S23** as a 1:1mixture in our laboratory by treating **S21** with NEt_3 and *i*-PrCOCl. We tried to separate them but failed. Thus, we continued our synthesis with a 1:1 mixture of **S22** and **S23**. Unfortunately, when treating the mixture with pyridine (20 equiv., fresh distilled from anhydrous CaH_2), Bz_2O (10 equiv., Bidepharm and J&K Scientific) and DMAP (1-3 equiv., purchase from Energy Chemical) in DCM (fresh distilled from anhydrous CaH_2) or DMF (Energy Chemical, 99.8%, extra dry, with molecular sieves, water ≤ 50 ppm (by K.F.)), no esterification reaction was observed, and most of substrates were recovered. Additionally, we tried to recover **S21** from **S22** and **S23** with K_2CO_3 and MeOH, but they were decomposed and none of **S21** was obtained. It was possible that C3 ketone group was sensitive to the basic conditions (such as K_2CO_3 and MeOH).

5. Experimental Procedures

Synthesis of compound 5



To a stirred solution of diphenyl prolinol catalyst **10** (10.0 g, 30.8 mmol, 10 mol%) and *p*-nitrophenol (**11**, 8.57 g, 61.6 mmol, 20 mol%) in MeOH (500 ml) was added (*E*)-*p*-methoxycinnamaldehyde (**9**, 50.0 g, 308.3 mmol, 1.0 equiv.) at 25 °C. The solution was stirred for 10 minutes before the addition of cyclopentadiene (**8**, 46.5 ml, 616.6 mmol, 2.0 equiv.). After stirring the reaction mixture for 20 h at 25 °C, MeOH was removed from the reaction mixture under reduced pressure. The resulting mixture was then redissolved by PhMe (500 mL). To the resulting PhMe solution of aldehyde was added methyl (triphenylphosphoranylidene) acetate (**12**, 103.1 g, 308.3 mmol, 1.0 equiv.) at 25 °C and the reaction mixture was stirred for 12 h. The resulting solution was then refluxed at 120 °C for 8 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane = 1/16) to afford alkene **5** as a light yellow solid (47.3 g, 54%).

TLC: R_f = 0.6 (hexane/EtOAc = 10:1);

$[\alpha]_D^{22}$ = +159.5 (*c* = 3.0 in $CHCl_3$);

IR (film) λ_{max} 2951, 2902, 1732, 1514, 1247, 1207, 1037 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.11 (ddd, *J* = 5.8, 3.1, 1.0 Hz, 1H), 5.92 (ddd, *J* = 5.7, 2.8, 0.8 Hz, 1H), 3.78 (s, 3H), 3.62 (s, 3H), 3.04 – 3.02 (m, 2H), 2.72 (t, *J* = 8.0 Hz, 1H), 2.64 (d, *J* = 5.0 Hz, 1H), 2.46 – 2.42 (m, 1H), 2.37 – 2.28 (m, 2H), 1.80 (ddd, *J* = 12.4, 8.0, 3.0 Hz, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 174.1, 157.9, 138.6, 134.1, 133.3, 127.9 (×2), 113.9 (×2), 70.0, 55.3, 51.9, 51.4, 50.0, 49.2, 44.8, 40.3, 39.3 ppm;

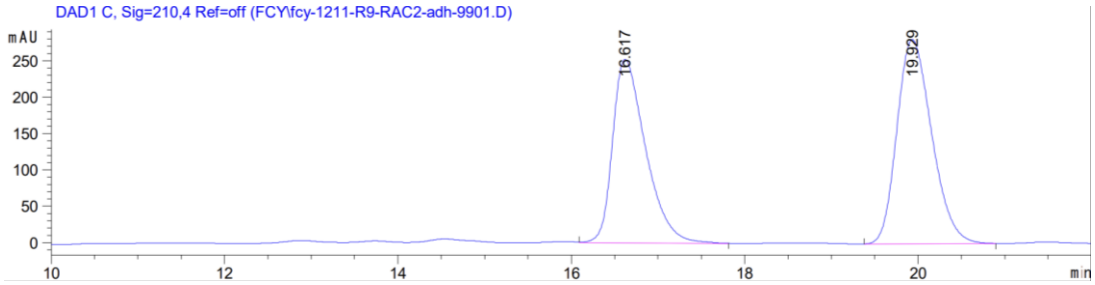
HRMS (ESI) calc'd for $C_{18}H_{21}O_3$ $[M+H]^+$ 285.1485; found 285.1485;

Crystal preparation: Slow evaporation of Et_2O/Hexane (1:1) at 25 °C to yield suitable single crystals for X-ray diffraction;

Melting point = 68 - 75°C;

HPLC analysis T_R(*rac*, minor) = 16.62 min, T_R(*rac*, major) = 19.93 min; T_R(*ent*, minor) = 16.68 min, T_R(*ent*, major) = 20.02 min. 93.4% *ee* shown.

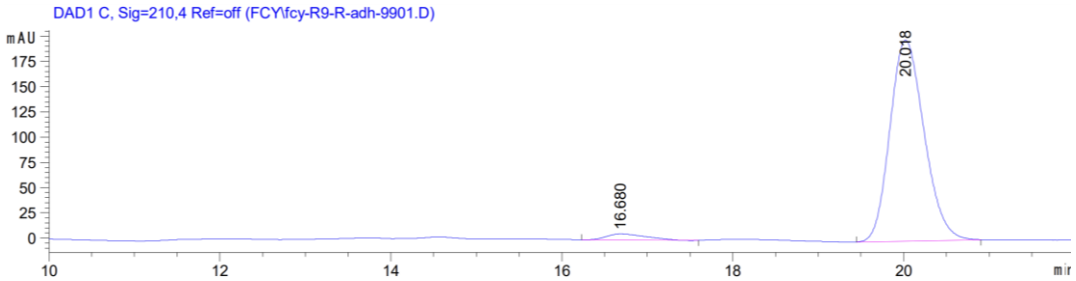
Column	CHIRALPAK AD-H 4.6mmϕ × 250mmL	
Column Temperature	25 °C	
Flow rate	0.7 mL/min	
Injection volume	5 μL	
Detection wavelength	210 nm	
Mobile Phase	A: hexane	B: *i*-PrOH
Gradient	A:B = 99:1	



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.617	VB	0.4033	6693.00635	252.47191	46.0674
2	19.929	BB	0.4333	7835.73389	281.03021	53.9326

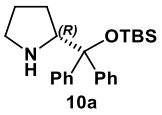
Figure S1. HPLC analysis of racemic **5**.



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.680	BB	0.4483	190.00807	5.98599	3.3121
2	20.018	BB	0.4348	5546.73828	199.23643	96.6879

Figure S2. HPLC analysis of enantioenriched **5**.

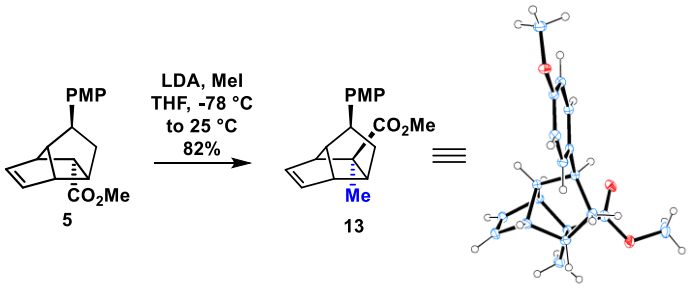


10a

Note: 1. The literature reported that catalyst **10a** gave best enantioselectivity,[2] however, this condition gave low conversion (<30% yield) in gram scale reaction. Thus, we screened several catalysts and found **10** as appropriate catalyst for gram-scale preparation of **5**.

2. According to the above procedure, more than 1000 g of compound **5** was prepared readily after 22 simple parallel operations.

Synthesis of compound 13



To a stirred solution of alkene **5** (50.0 g, 175.8 mmol, 1.0 equiv.) in THF (400 mL) was added LDA (lithium diisopropylamide, 96.8 mL, 2 M in THF, 193.7 mmol, 1.1 equiv.) at -78 °C under Ar. The reaction was stirred for 40 min at this temperature before MeI (24.1 mL, 386.8 mmol, 2.2 equiv.) was added to the solution. The mixture was stirred at -78 °C for 30 min and 25 °C for 1 h before it was quenched with saturated aqueous NH_4Cl (300 mL) and extracted with Et_2O (200 mL × 3). The combined organic phase was washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane = 1/10) to afford compound **13** as light yellow solid (43.0 g, 82%).

TLC: R_f = 0.7 (hexane/EtOAc = 10:1);

$[\alpha]_D^{22}$ = +177.0 (*c* = 2.0 in $CHCl_3$);

IR (film) λ_{max} 2964, 1720, 1514, 1456, 1247, 1222, 1111, 1099 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 – 7.09 (m, 2H), 6.83 – 6.78 (m, 2H), 6.12 (t, *J* =

2.0 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.29 – 3.27 (m, 1H), 3.04 – 3.02 (m, 1H), 2.81 (t, J = 8.1 Hz, 1H), 2.45 – 2.37 (m, 2H), 1.89 – 1.85 (m, 1H), 1.72 (ddd, J = 13.1, 8.2, 3.0 Hz, 1H), 1.09 (s, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.4, 157.8, 139.2, 136.2, 133.3, 128.0 (×2), 113.8 (×2), 72.6, 55.4, 54.4, 52.8, 51.8, 51.6, 47.6, 41.9, 38.1, 24.1 ppm;

HRMS (ESI) calc'd for $C_{19}H_{22}NaO_3$ $[M+Na]^+$ 321.1461; found 321.1461;

Crystal preparation: Slow evaporation of Et_2O/Hexane/DCM (1:3:1) at 25 °C to yield suitable single crystals for X-ray diffraction;

Melting point = 135 – 140 °C.

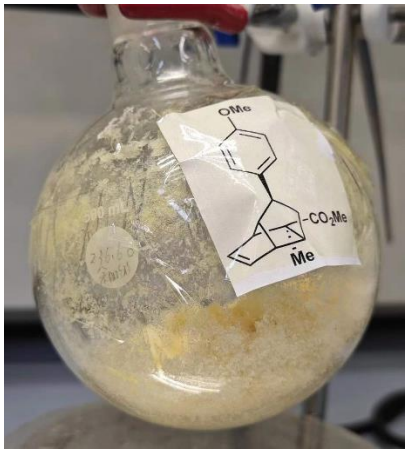
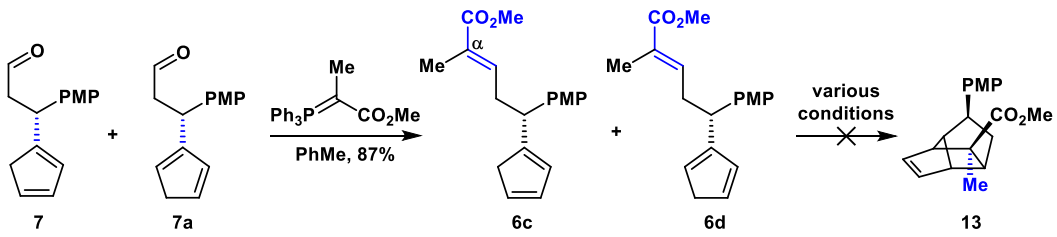


Figure S3. 43.0 g of purified compound **13** was prepared from one pot.

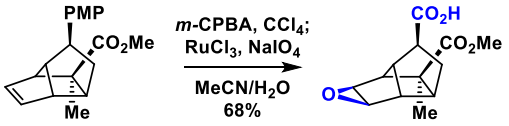
Note: 1. According to the above procedure, more than 800 g of compound **13** was prepared readily after 19 simple parallel operations.

2. It is interesting to note that the direct IMDA reaction of **6**'s analogues (α-methyl α,β-unsaturated esters: **6c** and **6d**) didn't occur to give **13** under heating (up to 200 °C). Additionally, we have screened various transition metal catalysts and Lewis acids, but none of these conditions gave desired **13** (Scheme S6).

Scheme S6. Failed IMDA reaction with **6c** and **6d**.



Synthesis of compound 14



To a stirred solution of alkene **13** (100.0 g, 318.5 mmol, 1.0 equiv.) in CCl_4 (800 mL) was added *m*-CPBA (3-chloroperoxybenzoic acid, 82.2 g, 80 w%, 477.8 mmol, 1.5 equiv.) at 25 °C. After stirring the reaction mixture for 2 h at 25 °C, MeCN (800 mL), H_2O (1200 mL), sodium periodate (1.23 kg, 5.72 mol, 18 equiv.) and a catalytic amount of ruthenium (III) chloride (1.32 g, 6.37 mmol, 0.025 equiv.) were added to the solution. The reaction mixture was allowed to stir at 25 °C under air. After 18 h, DCM (400 mL) was added, and the aqueous and organic layers were separated. The aqueous layer was extracted with dichloromethane (5 × 500 mL), washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated to give crude **14** as a black solid. The residue was purified by flash column chromatography (EtOAc/hexane = 1/2) to afford acid **14** as light yellow solid (54.6 g, 68%).

TLC: R_f = 0.3 (hexane/EtOAc = 1:1);

$[\alpha]_D^{22}$ = +109.3 (*c* = 1.0 in $CHCl_3$);

IR (film) λ_{max} 2962, 1714, 1693, 1259, 1238, 1203, 1116, 802 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.36 (s, 2H), 3.03 (d, *J* = 1.8 Hz, 1H), 2.66 (s, 1H), 2.61 (t, *J* = 8.2 Hz, 1H), 2.30 (q, *J* = 2.1 Hz, 1H), 2.07 – 2.02 (m, 1H), 1.91 – 1.80 (m, 2H), 1.35 (s, 3H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 181.1, 177.0, 52.1, 51.4, 50.8, 50.7, 50.4, 48.5, 44.0, 42.3, 37.2, 34.7, 21.2 ppm;

HRMS (ESI) calc'd for $C_{13}H_{17}O_5$ $[M+H]^+$ 253.1071; found 253.1067;

Melting point = 100 – 108 °C.

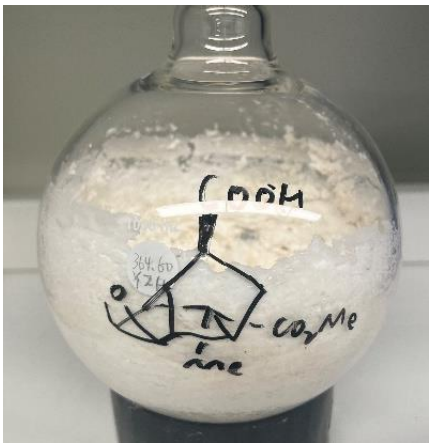
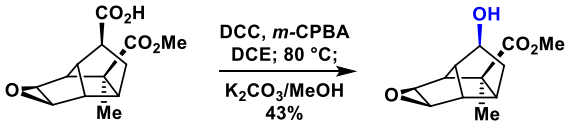


Figure S4. 109 g of purified compound **14** was prepared from two pots.

Note: According to the above procedure, more than 400 g of compound **14** was prepared readily after 8 simple parallel operations.

Synthesis of compound S1



To a stirred solution of acid **14** (30.0 g, 118.9 mmol, 1.0 equiv.) in DCE (1,2-dichloroethane, 600 mL) was added *m*-CPBA (32.8 g, 80 w%, 190.2 mmol, 1.6 equiv.) and DCC (dicyclohexylcarbodiimide, 39.2 g, 190.2 mmol, 1.6 equiv.) at 0 °C under Ar. After stirring the reaction mixture for 30 min, the reaction mixture was then refluxed at 80 °C. After 4 h, DCE was removed from the reaction mixture under reduced pressure. The resulting mixture was then redissolved by MeOH (300 mL). To the resulting MeOH solution was added K_2CO_3 (32.9 g, 237.8 mmol, 2.0 equiv.) at 25 °C. The reaction mixture was stirred for 2 h before the H_2O (300 mL) was added and extracted with DCM (200 mL × 3). The combined organic phase was washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane = 1/2) to afford compound **S1** as white solid (11.6 g, 43%).

TLC: R_f = 0.30 (hexane/EtOAc = 1:1);

$[\alpha]_D^{22}$ = +95.0 (*c* = 1.0 in $CHCl_3$);

IR (film) λ_{max} 2960, 2927, 1726, 1259, 1236, 1205, 1087 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (dd, *J* = 7.0, 4.8 Hz, 1H), 3.70 (s, 3H), 3.36 (s, 2H), 2.94 (t, *J* = 1.7 Hz, 1H), 2.77 (s, 1H), 2.06 (ddd, *J* = 13.6, 7.0, 1.1 Hz, 1H), 2.03 – 1.99 (m, 1H), 1.95 (q, *J* = 2.3 Hz, 1H), 1.40 – 1.34 (m, 1H), 1.33 (s, 3H);

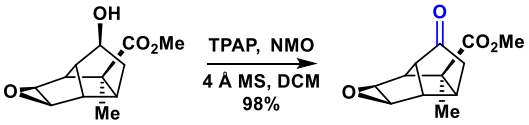
^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 67.6, 51.9, 51.5, 50.7, 50.2, 49.5, 49.0, 47.4, 42.2, 42.0, 20.9 ppm;

HRMS (ESI) calc'd for $C_{12}H_{17}O_4$ $[M+H]^+$ 225.1121; found 225.1121;

Melting point = 105 – 110 °C.

Note: 1. **S1** was formed during the heating process, but there were still some unhydrolyzed ester. Thus, quenching the mixture with K_2CO_3 and MeOH was necessary. 2. According to the above procedure, more than 160 g of compound **S1** was prepared readily after 14 simple parallel operations.

Synthesis of compound 4



S1 **4**

To a mixture of **S1** (11.6 g, 51.7 mmol, 1.0 equiv.), NMO (12.1 g, 103.4 mmol, 2.0 equiv.) and powder 4Å MS (12.0 g) in dry DCM (200 ml). TPAP (909 mg, 2.6 mmol, 5 mol%) was added in one portion and the resulting black mixture was stirring at 25 °C for 1 h. The mixture was passed through a 2-3 cm pad of silica gel (DCM) to afford pure compound **4** as white solid (11.3 g, 98%).

TLC: R_f = 0.30 (hexane/EtOAc = 2:1);

$[\alpha]_D^{22}$ = +114.2 (*c* = 2.0 in $CHCl_3$);

IR (film) λ_{max} 2929, 2854, 1753, 1728, 1261, 1238, 1116, 1097 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.51 – 3.49 (m, 1H), 3.45 (dd, *J* = 3.3, 1.3 Hz, 1H), 3.26 (d, *J* = 1.5 Hz, 1H), 2.89 (dd, *J* = 2.3, 1.2 Hz, 1H), 2.42 – 2.36 (m, 2H), 2.14 – 2.08 (m, 1H), 2.05 (dd, *J* = 17.9, 1.3 Hz, 1H), 1.47 (s, 3H) ppm;

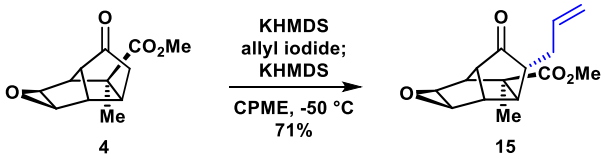
^{13}C NMR (101 MHz, $CDCl_3$) δ 212.9, 175.4, 53.0, 52.1, 51.9, 50.9, 50.2, 49.9, 46.7,

46.6, 44.8, 20.2 ppm;

HRMS (ESI) calc'd for $C_{12}H_{15}O_4$ $[M+H]^+$ 223.0965; found 223.0964;

Melting point = 112 – 122 °C.

Synthesis of compound 15



To a stirred solution of **4** (10.0 g, 45.0 mmol, 1.0 equiv.) in CPME (cyclopentyl methyl ether, 400 mL) was added KHMDS (potassium bis(trimethylsilyl)amide, 49.5 mL, 1 M in THF, 49.5 mmol, 1.1 equiv.) at -50 °C under Ar. The reaction was stirred for 40 min at this temperature before allyl iodide (4.94 mL, 54.0 mmol, 1.2 equiv.) was added to the solution. The reaction was stirred for another 40 min at this temperature before KHMDS (54.0 mL, 1 M in THF, 54.0 mmol, 1.2 equiv.) was added to the solution. Upon the completion of reaction (typically another 2 h), it was quenched with saturated aqueous NH_4Cl (300 mL) and extracted with EtOAc (100 mL × 3). The combined organic phase was washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane = 1/3) to afford compound **15** as colorless oil (8.38 g, 71%).

TLC: R_f = 0.5 (hexane/EtOAc = 2:1);

$[\alpha]_D^{22}$ = +70.2 (*c* = 2.0 in $CHCl_3$);

IR (film) λ_{max} 2962, 2924, 1739, 1712, 1261, 1238, 1120, 1095 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (dddd, *J* = 16.8, 10.2, 7.4, 6.4 Hz, 1H), 5.05 – 4.97 (m, 2H), 3.64 (s, 3H), 3.45 (dd, *J* = 3.4, 1.6 Hz, 1H), 3.41 (dd, *J* = 3.3, 1.3 Hz, 1H), 3.19 (t, *J* = 1.3 Hz, 1H), 2.75 (s, 1H), 2.51 (q, *J* = 2.3 Hz, 1H), 2.46 – 2.44 (m, 1H), 2.35 – 2.27 (m, 1H), 2.20 (ddd, *J* = 8.6, 5.4, 3.1 Hz, 1H), 1.79 – 1.71 (m, 1H), 1.43 (s, 3H) ppm;

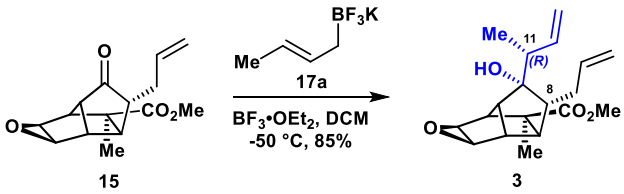
^{13}C NMR (101 MHz, $CDCl_3$) δ 212.6, 175.7, 136.3, 116.6, 59.2, 53.6, 52.4, 52.2, 51.2, 51.1, 49.8, 47.6, 46.1, 28.4, 20.6 ppm;

HRMS (ESI) calc'd for $C_{15}H_{19}O_4$ $[M+H]^+$ 263.1278; found 263.1277.

Note: 1. Compound **4** was not well dissolved in CPME but it did not affect further reaction. Upon the addition of KHMDS, **4** would be gradually dissolved within 5 min. The reaction mixture would become cloudy after the addition of allyl iodide, and it would be redissolved once KHMDS was added.

2. According to the above procedure, more than 120 g of compound **15** was prepared readily after 15 simple parallel operations.

Synthesis of compound 3



To a stirred solution of alkene **15** (8.0 g, 30.5 mmol, 1.0 equiv.) and *E*-potassium crotyltrifluoroborate (**17a**, 24.7 g, 152.5 mmol, 5.0 equiv.) in DCM (400 mL) was added $BF_3{\cdot}OEt_2$ (1.86 ml, 15.2 mmol, 0.5 equiv.) at -50 °C under Ar. After stirring for 36 h, it was quenched with saturated aqueous $NaHCO_3$ (300 mL) and extracted with DCM (100 mL × 3). The combined organic phase was washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane = 1/5) to afford compound **3** as colorless oil (8.25 g, 85%) and recovered starting material **15** (880 mg, 11%).

TLC: R_f = 0.6 (hexane/EtOAc = 5:1);

$[\alpha]_D^{22}$ = +19.8 (*c* = 0.4 in $CHCl_3$);

IR (film) λ_{max} 2962, 2933, 1703, 1456, 1259, 1095, 1024 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.84 – 5.76 (m, 2H), 5.03 – 4.91 (m, 4H), 3.71 (s, 3H), 3.41 (t, *J* = 2.0 Hz, 2H), 3.30 (d, *J* = 3.3 Hz, 1H), 3.10 (t, *J* = 1.6 Hz, 1H), 2.44 (q, *J* = 1.5 Hz, 1H), 2.34 (t, *J* = 1.8 Hz, 1H), 2.26 – 2.22 (m, 1H), 2.10 – 1.98 (m, 2H), 1.77 (ddt, *J* = 12.3, 5.5, 1.7 Hz, 1H), 1.72 – 1.63 (m, 1H), 1.39 (s, 3H), 1.06 (dd, *J* = 6.7, 1.1 Hz, 3H) ppm;

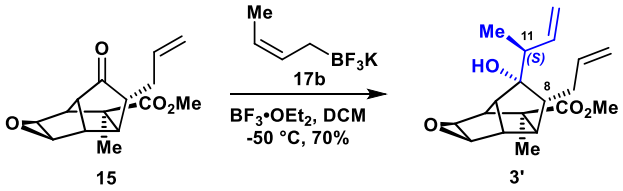
^{13}C NMR (151 MHz, $CDCl_3$) δ 180.9, 140.4, 137.8, 115.5, 115.2, 75.8, 53.4, 52.5 (×2),

52.43, 52.40, 51.2, 50.4, 48.7, 48.5, 41.6, 29.3, 22.8, 16.0 ppm;

HRMS (ESI) calc'd for $C_{19}H_{26}O_4Na$ $[M+Na]^+$ 341.1723; found 341.1722.

Note: 1. The internal temperature of reaction should not be higher than -30 °C. If not, epoxide opening would be the predominantly reaction as reaction temperature raised. 2. Compound **17a** was prepared from *trans*-2-butene.[3]

Synthesis of compound 3'



To a stirred solution of alkene **15** (100 mg, 0.38 mmol, 1.0 equiv.) and *E*-potassium crotyltrifluoroborate (**17b**, 309 mg, 1.91 mmol, 5.0 equiv.) in DCM (10 mL) was added $BF_3{\cdot}OEt_2$ (70 μl, 0.57 mmol, 1.5 equiv.) at -50 °C under Ar. After stirring for 36 h, it was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with DCM (10 mL × 3). The combined organic phase was washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane = 1/5) to afford compound **3'** as colorless oil (85 mg, 70%).

TLC: R_f = 0.55 (hexane/EtOAc = 5:1);

$[\alpha]_D^{22}$ = +31.5 (*c* = 0.2 in $CHCl_3$);

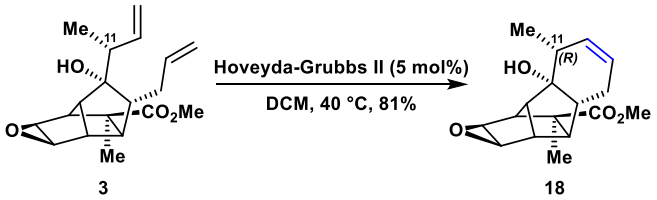
IR (film) λ_{max} 2949, 2933, 1701, 1456, 1276, 908, 856 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.91 – 5.77 (m, 2H), 5.04 – 4.96 (m, 4H), 3.72 (s, 3H), 3.40 (br s, 1H), 3.30 (d, *J* = 3.5 Hz, 1H), 3.10 (s, 1H), 2.47 – 2.43 (s, 1H), 2.38 – 2.35 (m, 1H), 2.25 (d, *J* = 2.5 Hz, 1H), 2.19 – 2.10 (m, 1H), 2.09 – 2.03 (m, 1H), 1.89 – 1.76 (m, 3H), 1.39 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 180.7, 141.8, 137.9, 115.7, 115.4, 75.8, 53.7, 52.5, 52.4, 52.3, 51.8, 51.2, 49.7, 48.6, 48.5, 41.7, 29.9, 23.0, 14.9 ppm;

HRMS (ESI) calc'd for $C_{19}H_{26}O_4Na$ $[M+Na]^+$ 341.1723; found 341.1722.

Synthesis of compound 18



3 18

To a stirred solution of diene **3** (10.0 g, 31.4 mmol, 1.0 equiv.) in DCM (800 mL) was added Hoveyda-Grubbs II catalyst (982.4 mg, 1.57 mmol, 5 mol%) at 25 °C under Ar, the resulting mixture was then heated to 40 °C. Upon complete consumption of starting material by TLC analysis (typically 48 h), the resulting solution was concentrated directly, and the crude material was purified by flash column chromatography (EtOAc /hexane = 1/7) to afford alkene **18** as white foam (7.4 g, 81%).

TLC: R_f = 0.4 (hexane/EtOAc = 3:1);

$[\alpha]_D^{22}$ = +70.0 (*c* = 1.0 in $CHCl_3$);

IR (film) λ_{max} 2962, 2924, 2852, 1737, 1454, 1261, 1095, 800 cm^{-1};

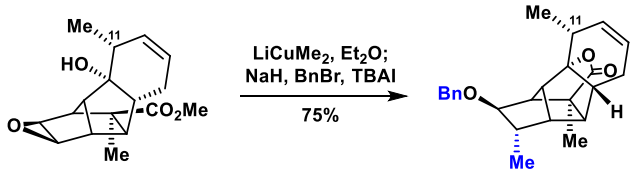
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.73 (ddt, *J* = 9.9, 4.9, 2.3 Hz, 1H), 5.25 (dq, *J* = 10.1, 2.0 Hz, 1H), 3.64 (s, 3H), 3.48 (dd, *J* = 3.6, 1.8 Hz, 1H), 3.35 (dd, *J* = 3.4, 1.3 Hz, 1H), 3.22 (q, *J* = 1.7 Hz, 1H), 2.56 (dddt, *J* = 14.6, 12.5, 4.6, 2.3 Hz, 1H), 2.43 (t, *J* = 1.9 Hz, 1H), 2.34 – 2.30 (m, 1H), 2.25 (q, *J* = 2.1 Hz, 1H), 2.15 (q, *J* = 1.7 Hz, 1H), 2.09 – 2.03 (m, 1H), 1.79 (ddd, *J* = 12.4, 4.6, 2.0 Hz, 1H), 1.47 (s, 1H), 1.33 (s, 3H), 0.94 (d, *J* = 7.2 Hz, 3H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 131.0, 129.6, 73.2, 55.2, 52.32, 52.26, 51.7, 51.4, 50.8, 49.8, 44.4, 43.3, 42.6, 25.4, 24.9, 14.4 ppm;

HRMS (ESI) calc'd for $C_{17}H_{23}O_4$ $[M+H]^+$ 291.1591; found 291.1589.

Note: Over 80 g of **18** was synthesized by repeating this condition for over 12 times.

Synthesis of compound 2



18 2

To a stirred solution of CuCN (3.39 g, 37.8 mmol, 1.1 equiv.) in Et_2O (250 mL) at -78 °C was added MeLi (47.3 mL, 1.6 M in Et_2O, 75.7 mmol, 2.2 equiv.) dropwise. The resulting mixture was warmed to 25 °C overall 15 min, then a solution of the epoxide **18** (10 g, 34.4 mmol, 1.0 equiv.) in Et_2O (200 mL) was added dropwise. The resulting mixture was stirred at 25 °C for 6 h. Et_2O was then removed carefully under vacuum. The resulting slurry was redissolved by THF (400 mL) followed by the addition of NaH (2.75 g, 60% in mineral oil, 69.0 mmol, 2 equiv.), BnBr (10.2 mL, 86.0 mmol, 2.5 equiv.) and TBAI (tetrabutylammonium iodide, 3.82 g, 10.4 mmol, 0.3 equiv.). The reaction was stirred overnight before quenching by saturated aqueous NaCl (200 mL) and extracted with EtOAc (100 mL × 3). The combined organic phase was washed with brine (150 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane = 1/5) to afford compound **2** as colorless oil (9.4 g, 75%).

TLC: R_f = 0.3 (hexane/EtOAc = 5:1);

$[\alpha]_D^{22}$ = +83.8 (*c* = 1.0 in $CHCl_3$);

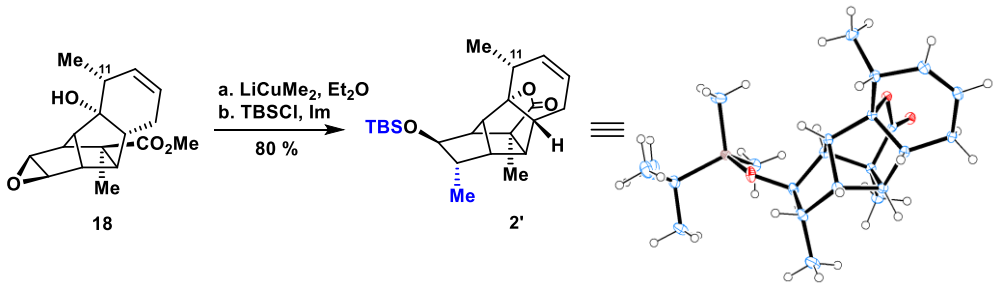
IR (film) λ_{max} 2962, 2933, 1745, 1454, 1207, 1093, 798 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 5H), 5.65 (dq, *J* = 9.7, 3.1 Hz, 1H), 5.44 (dt, *J* = 10.0, 2.0 Hz, 1H), 4.50 – 4.42 (m, 2H), 3.40 (d, *J* = 2.0 Hz, 1H), 2.97 – 2.96 (m, 1H), 2.50 – 2.47 (m, 1H), 2.31 – 2.27 (m, 1H), 2.15 – 2.12 (m, 2H), 1.91 – 1.82 (m, 4H), 1.25 (s, 3H), 1.20 – 1.16 (m, 3H), 1.14 (d, *J* = 7.3 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 180.0, 138.4, 131.4, 128.6 (×2), 127.8, 127.7 (×2), 125.9, 85.5, 81.9, 70.7, 58.4, 54.9, 52.4, 51.4, 44.4, 44.0, 41.5, 37.9, 23.5, 16.3, 16.1, 14.3 ppm;

HRMS (ESI) calc'd for $C_{24}H_{29}O_3$ $[M+H]^+$ 365.2111; found 365.2110.

Synthesis of compound 2'



To a stirred solution of CuCN (123 mg, 1.38 mmol, 4.0 equiv.) in Et_2O (2 mL) at -78 °C was added MeLi (1.7 mL, 1.6 M in Et_2O, 2.75 mmol, 8.0 equiv.) dropwise. The resulting mixture was warmed to 25 °C, then a solution of the epoxide **18** (100 mg, 0.34 mmol, 1.0 equiv.) in Et_2O (3.00 mL) was added dropwise. The reaction was stirred for 4 h before quenching by saturated aqueous NaCl (10 mL) and extracted with EtOAc (5 mL × 3). The combined organic phase was washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated. The residue was directly for next step without further purification.

To a stirred solution of crude product in DCM (15 mL) at 25 °C was added imidazole (Im, 93.8 mg, 1.38 mmol, 4.0 equiv.) and TBSCl (*tert*-butyldimethylsilyl chloride, 103.8 mg, 0.69 mmol, 2.0 equiv.) and the resulting suspension was stirred for 8 h. The reaction was concentrated directly to give the crude as a yellow solid. The residue was purified by flash column chromatography (EtOAc/hexane = 1/10) to afford **2'** as white plate (107.1 mg, 80%).

TLC: R_f = 0.4 (hexane/EtOAc = 10:1);

$[\alpha]_D^{22}$ = +98.3 (*c* = 1.0 in $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (ddd, *J* = 9.8, 4.2, 2.5 Hz, 1H), 5.45 – 5.37 (m, 1H), 3.62 – 3.56 (m, 1H), 2.94 (q, *J* = 2.4 Hz, 1H), 2.47 (dt, *J* = 7.4, 2.5 Hz, 1H), 2.07 (dt, *J* = 4.5, 1.9 Hz, 1H), 1.99 – 1.91 (m, 2H), 1.86 – 1.79 (m, 4H), 1.25 (s, 3H), 1.13 (dd, *J* = 7.5, 6.4 Hz, 6H), 0.84 (s, 9H), 0.01 (d, *J* = 5.9 Hz, 6H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.2, 131.3, 125.9, 85.5, 75.5, 58.4 (×2), 52.0, 51.3, 44.3, 44.0, 43.9, 37.8, 25.9 (×3), 23.5, 18.1, 15.9, 15.6, 14.2, -4.5, -4.6 ppm;

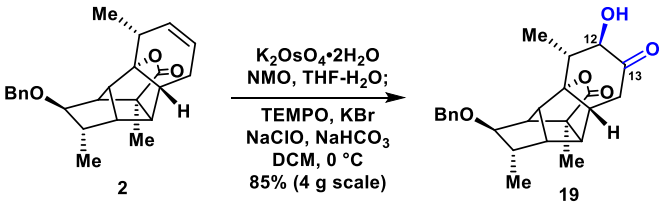
IR (film) λ_{max} 2956, 2933, 1747, 1462, 1257, 1066, 839 cm^{-1};

HRMS (ESI) calc'd for $C_{23}H_{37}O_3Si$ $[M+H]^+$ 389.2506; found 389.2504;

Crystal preparation: Slow evaporation of DCM/Hexane (1:2) at 25 °C to yield suitable single crystals for X-ray diffraction;

Melting point = 115 – 122 °C.

Synthesis of compound 19



To a stirred solution of alkene **2** (4.0 g, 10.97 mmol, 1.0 equiv.) in THF-H_2O (200 mL, 4:1) was added $K_2OsO_4 \cdot 2H_2O$ (34.2 mg, 0.11 mmol, 1 mol%) and NMO (4-methylmorpholine *N*-oxide, 1.93 g, 16.5 mmol, 1.5 equiv.) at 25 °C. The reaction mixture was stirred for 36 h at 25 °C. Then the solvents were then removed under vacuum. The resulting crude diol was redissolved in DCM (100 mL) followed by the addition of 5% aqueous $NaHCO_3$ (40.0 mL), KBr (522 mg, 4.40 mmol, 0.40 equiv.) and TEMPO (2,2,6,6-tetramethylpiperidinooxy, 686 mg, 4.40 mmol, 0.40 equiv.). The biphasic mixture was cooled to 0 °C and bleach (commercial bleach solution, 6% NaClO, 27.9 mL, 22.9 mmol, 2.0 equiv.) was added dropwise to the rapidly stirring mixture. The reaction mixture was stirred for 12 h at 0 °C and then partitioned between saturated aqueous Na_2SO_3 (200 mL) and DCM (200 mL). The aqueous layer was extracted with DCM (200 mL × 3) and the combined organic layers were washed with brine (125 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane = 1/2) to afford hydroxyl ketone **19** as colorless oil (3.70 g, 85%).

TLC: R_f = 0.6 (hexane/EtOAc = 3:2);

$[\alpha]_D^{22}$ = +134.6 (*c* = 0.8 in $CHCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 5H), 4.47 (s, 2H), 4.17 (dd, *J* = 9.8, 2.6

Hz, 1H), 3.52 (d, J = 2.7 Hz, 1H), 3.42 (d, J = 2.3 Hz, 1H), 3.07 – 3.06 (m, 1H), 2.58 (t, J = 14.3 Hz, 1H), 2.42 (dd, J = 14.0, 4.2 Hz, 1H), 2.35 – 2.32 (m, 1H), 2.19 – 2.13 (m, 2H), 1.99 – 1.92 (m, 3H), 1.36 (d, J = 6.5 Hz, 3H), 1.27 (s, 3H), 1.18 (d, J = 7.2 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 208.6, 178.7, 138.1, 128.6 (×2), 127.9, 127.7 (×2), 86.6, 81.3, 78.3, 70.8, 58.8, 54.8, 53.8, 51.6, 46.3, 44.44, 44.37, 41.5, 37.0, 16.2, 15.9, 12.9 ppm;

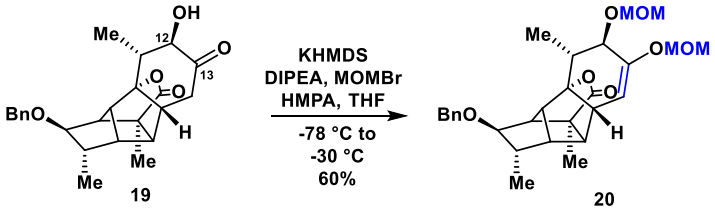
IR (film) λ_{max} 2964, 2933, 1755, 1714, 1261, 1095, 1068, 800 cm^{-1};

HRMS (ESI) calc'd for $C_{24}H_{29}O_5$ $[M+H]^+$ 397.2010; found 397.2008.

Note: 1. The TEMPO oxidation did not proceed in the THF solution, and it was necessary to switch THF into DCM. The pH value was crucial to the successful oxidation, the best pH value was around 10 (adjusted by $NaHCO_3$). The overall yield was higher than a 2-step procedure. It was found that a part of diol would be lost in extraction and during column chromatography process.[4]

2. According to the above procedure, more than 20 g of compound **19** was prepared readily after 6 simple parallel operations.

Synthesis of compound 20



To a stirred solution of hydroxyl ketone **19** (2.0 g, 5.05 mmol, 1.0 equiv.) and HMPA (hexamethyl phosphoramide, 3.95 mL, 22.7 mmol, 6.0 equiv.) in THF (50 mL) was added KHMDS (10.1 mL, 1 M in THF, 10.1 mmol, 2.0 equiv.) at -78 °C under Ar. The reaction was stirred for 1 h at this temperature before DIPEA (*N*,*N*-diisopropylethylamine, 1.76 mL, 10.1 mmol, 2.0 equiv.) and MOMBr (bromomethyl methyl ether, 0.82 mL, 10.1 mmol, 2.0 equiv.) were added to the solution. The reaction mixture was warmed up to -30 °C after another 30 min. KHMDS (20.2 mL, 1 M in THF, 20.2 mmol, 4.0 equiv.) was then added to the reaction mixture. The reaction was stirred

for 1 h at this temperature before DIPEA (3.52 mL, 20.2 mmol, 4.0 equiv.) and MOMBr (1.65 mL, 20.2 mmol, 4.0 equiv.) were added to the solution. It was quenched with saturated aqueous NH_4Cl (200 mL) and extracted with Et_2O (50 mL × 4). The combined organic phase was washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane = 1/5) to afford enol ether **20** as colorless oil (1.47 g, 60%).

TLC: R_f = 0.4 (hexane/EtOAc = 3:1);

$[\alpha]_D^{22}$ = +91.7 (*c* = 1.0 in $CHCl_3$);

IR (film) λ_{max} 2916, 2848, 2360, 1749, 1456, 1261, 1091, 1020, 800 cm^{-1};

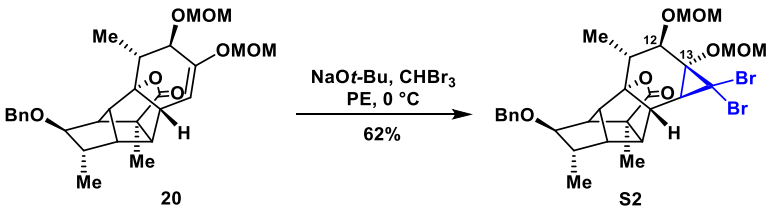
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 5H), 4.95 (d, *J* = 6.2 Hz, 1H), 4.87 (t, *J* = 7.1 Hz, 2H), 4.82 (d, *J* = 1.9 Hz, 1H), 4.72 (d, *J* = 6.7 Hz, 1H), 4.45 (s, 2H), 4.06 (d, *J* = 6.6 Hz, 1H), 3.42 (s, 3H), 3.38 (s, 3H), 3.36 (d, *J* = 2.3 Hz, 1H), 3.03 (d, *J* = 2.6 Hz, 1H), 2.67 (s, 1H), 2.27 – 2.09 (m, 4H), 1.97 (s, 1H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.20 (s, 3H), 1.17 (d, *J* = 7.4 Hz, 3H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 155.7, 138.3, 128.6 (×2), 127.9, 127.7 (×2), 97.8, 95.9, 93.9, 88.4, 82.0, 81.3, 70.7, 58.8, 56.0 (×2), 55.6, 51.9, 51.7, 44.6, 44.2, 44.0, 41.5, 16.3, 15.9, 13.7 ppm;

HRMS (ESI) calc'd for $C_{28}H_{37}O_7$ $[M+H]^+$ 485.2534; found 485.2533.

Note: Compound **20** could be produced by warming up to -30 °C directly without the second addition of KHMDS, HMPA, DIPEA and MOMBr, but the yield would be lower (30-40%). Additionally, DIPEA was necessary for the formation of enol MOM ether.

Synthesis of compound S2



To a stirred solution of enol ether **20** (1.0 g, 2.06 mmol, 1.0 equiv.) in PE (petroleum ether, 100 mL) and NaO*t*-Bu (4.95 g, 51.5 mmol, 25.0 equiv.) at 0 °C was added $CHBr_3$ (5.40 mL, 62.0 mmol, 30.0 equiv.) dropwise over 30 min. The reaction mixture was

allowed to stir for another 10 h. It was then quenched with saturated aqueous NH_4Cl (100 mL) and extracted with Et_2O (80 mL × 3). The combined organic phase was washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane = 1/5) to afford dibromide **S2** as colorless oil (835 mg, 62%).

TLC: R_f = 0.5 (hexane/EtOAc = 5:1);

$[\alpha]_D^{22}$ = +126.8 (*c* = 1.0 in $CHCl_3$);

IR (film) λ_{max} 2964, 2931, 2360, 1751, 1458, 1261, 1097, 1068, 800 cm^{-1};

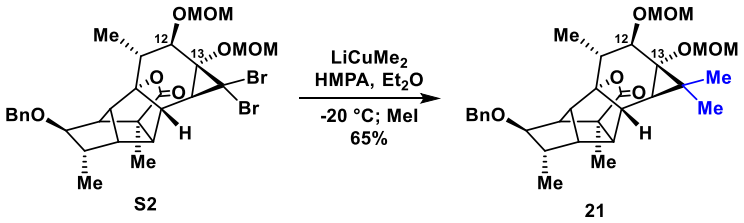
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 5.12 (d, *J* = 6.4 Hz, 1H), 5.07 (d, *J* = 6.8 Hz, 1H), 4.85 (d, *J* = 6.7 Hz, 1H), 4.73 (d, *J* = 6.4 Hz, 1H), 4.45 (s, 2H), 4.38 (d, *J* = 8.7 Hz, 1H), 3.48 (s, 3H), 3.45 (s, 3H), 3.40 (d, *J* = 2.5 Hz, 1H), 3.02 (d, *J* = 2.4 Hz, 1H), 2.35 – 2.30 (m, 2H), 2.27 (dd, *J* = 4.8, 2.3 Hz, 1H), 2.16 – 2.11 (m, 1H), 2.04 (d, *J* = 4.7 Hz, 1H), 1.89 (dd, *J* = 4.7, 1.3 Hz, 1H), 1.77 – 1.74 (m, 1H), 1.28 (s, 3H), 1.23 (d, *J* = 6.7 Hz, 3H), 1.20 (d, *J* = 7.5 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.8, 138.2, 128.6 (×2), 128.0, 127.7 (×2), 96.3, 95.9, 87.5, 82.0, 81.4, 70.8, 66.6, 58.6, 57.3, 56.4, 55.7, 54.2, 51.3, 47.1, 45.0, 44.4, 41.4 (×2), 34.5, 16.2, 15.9, 13.9 ppm;

HRMS (ESI) calc'd for $C_{29}H_{36}Br_2O_7Na$ $[M+Na]^+$ 677.0720; found 677.0718.

Note: According to the above procedure, more than 4 g of compound **S2** was prepared readily after 5 simple parallel operations.

Synthesis of compound 21



To a stirred solution of Cu(SCN) (3.38 g, 27.5 mmol, 15.0 equiv.) in Et_2O (100 mL) at -78 °C was added MeLi (34.4 mL, 1.6 M in Et_2O, 55.0 mmol, 30.0 equiv.). The resulting mixture was warmed to -20 °C before it was added dropwise to a solution of

the dibromide **S2** (1.2 g, 1.83 mmol, 1.00 equiv.) in HMPA (30.0 mL) and Et_2O (20.00 mL). The resulting mixture was stirred at -20 °C for 8 h before it was added MeI (4.56 mL, 73.2 mmol, 40.0 equiv.). The reaction was then warmed to 25 °C and stirred overnight. Then the reaction was quenched by saturated aqueous NH_4Cl (60 mL), and then diluted with Et_2O (100 mL) and brine (300 mL). After the separation of two layers, the organic layer was then washed with brine (100 mL) three times to remove HMPA. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane = 1/7) to afford **21** as colorless oil (625 mg, 65%).

TLC: R_f = 0.6 (hexane/EtOAc = 5:1);

$[\alpha]_D^{22}$ = +65.6 (*c* = 1.0 in $CHCl_3$);

IR (film) λ_{max} 2962, 2935, 1751, 1735, 1454, 1261, 1089, 1068, 800 cm^{-1};

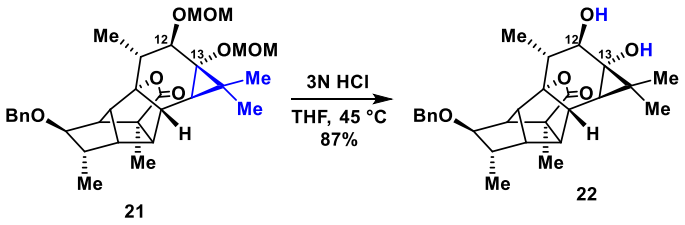
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 5H), 5.04 (d, *J* = 6.2 Hz, 1H), 4.89 (d, *J* = 6.2 Hz, 1H), 4.82 (d, *J* = 6.2 Hz, 1H), 4.61 (d, *J* = 6.2 Hz, 1H), 4.44 (s, 2H), 4.36 (d, *J* = 8.0 Hz, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 3.37 (d, *J* = 2.3 Hz, 1H), 2.98 (d, *J* = 2.5 Hz, 1H), 2.28 (s, 1H), 2.17 – 2.07 (m, 3H), 1.54 (p, *J* = 6.8 Hz, 1H), 1.42 (d, *J* = 5.2 Hz, 1H), 1.25 (d, *J* = 6.2 Hz, 6H), 1.19 (s, 3H), 1.17 (d, *J* = 7.4 Hz, 3H), 1.08 (s, 3H), 0.89 (d, *J* = 5.1 Hz, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 179.7, 138.2, 128.5 (×2), 127.8, 127.6 (×2), 95.8, 95.3, 88.1, 82.8, 81.5, 70.7, 68.5, 58.6, 56.3, 55.9, 55.6, 51.4, 50.3, 47.1, 44.6, 42.9, 41.3, 28.5, 27.0, 23.5, 17.7, 16.2, 16.0, 14.7 ppm;

HRMS (ESI) calc'd for $C_{31}H_{42}O_7Na$ $[M+Na]^+$ 549.2823; found 549.2821.

Note: According to the above procedure, more than 1.5 g of compound **21** was prepared readily after 3 simple parallel operations.

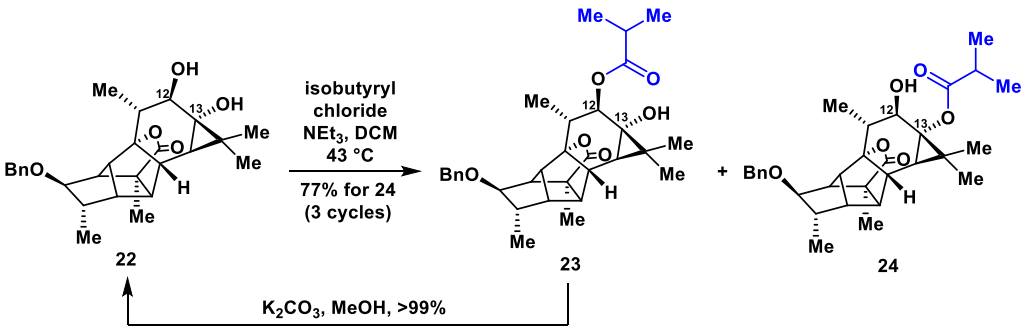
Synthesis of compound 22



To a stirred solution of **21** (625 mg, 1.19 mmol, 1.0 equiv.) in THF (33 mL) at 0 °C was added 3N aqueous HCl (11 mL) over 1 min. The reaction mixture was warmed up to 45 °C and allowed to stir for another 16 h. It was then quenched with saturated aqueous $NaHCO_3$ (10 mL) till CO_2 stopped ceasing and extracted with EtOAc (40 mL × 5). The residue was filtered through a short pad of celite to remove inorganic salts, the crude diol **22** (1.03 mmol, 87%, determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard) was used directly without further purification.

Note: While diol **22** can be isolated in relative pure form for characterization (containing some silicon grease but did not affect NMR analysis), low yields are typically observed due to its polarity and incompatibility with normal phase silica gel column chromatography. As a result, **22** was filtered through a short pad of silica gel before used directly in the subsequent step without further purification.

Synthesis of compounds 23 and 24



To a stirred solution of **22** (crude, 1.0 mmol) in DCM (25 mL) at 43 °C (preheated for 5 min) was added NEt_3 (1.38 mL, 10.0 mmol, 10.0 equiv.) and freshly distilled isobutyryl chloride (0.52 mL, 5.0 mmol, 5.0 equiv.), and the resulting suspension was stirred for 3 h. The reaction was allowed to cool to 25 °C, and then concentrated directly

to give the crude as a brown solid. The residue was purified by flash column chromatography (EtOAc/hexane = 1/5) to afford desired **24** as colorless oil (233 mg, 46%) and **23** as colorless oil (228 mg, 45%).

To a stirred solution of **23** (228 mg, 0.45 mmol, 1.0 equiv.) in MeOH (10 mL) was added K_2CO_3 (186 mg, 1.35 mmol, 3.0 equiv.), the resulting suspension was stirred for 8 h. It was then diluted with saturated aqueous NaCl (10 mL) and extracted with DCM (10 mL × 5). The combined organic phase was dried (Na_2SO_4), filtered and concentrated. The crude diol **22** (>99% purity) was used directly without further purification.

As a result, 391 mg of **24** was obtained after 3 cycles in 77% overall yield.

Data for 23:

TLC: R_f = 0.2 (hexane/EtOAc = 5:1);

$[\alpha]_D^{22}$ = +137.4 (*c* =1.0 in $CHCl_3$);

IR (film) λ_{max} 2964, 2933, 1751, 1735, 1456, 1259, 1089, 1068, 798 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 5H), 5.05 (d, *J* = 8.1 Hz, 1H), 4.49 – 4.42 (m, 2H), 4.37 (s, 1H), 3.38 (d, *J* = 2.4 Hz, 1H), 3.00 (d, *J* = 2.4 Hz, 1H), 2.58 (hept, *J* = 7.0 Hz, 1H), 2.33 (d, *J* = 2.4 Hz, 1H), 2.18 (dt, *J* = 4.3, 1.9 Hz, 1H), 2.12 – 2.08 (m, 2H), 1.73 – 1.68 (m, 1H), 1.41 (d, *J* = 5.6 Hz, 1H), 1.26 (s, 3H), 1.21 – 1.17 (m, 12H), 1.13 (s, 3H), 1.00 (s, 3H), 0.69 (d, *J* = 5.4 Hz, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 179.4, 179.1, 138.2, 128.6 (×2), 127.8, 127.7(×2), 89.0, 88.3, 81.5, 70.8, 62.7, 58.4, 55.7, 51.1, 50.3, 46.6, 44.7, 42.0, 41.5, 34.3, 28.9, 28.6, 22.2, 19.2, 19.0, 17.7, 16.2, 16.1, 14.7 ppm;

HRMS (ESI) calc'd for $C_{31}H_{41}O_6$ $[M+H]^+$ 509.2898; found 509.2896.

Data for 24:

TLC: R_f = 0.4 (hexane/EtOAc = 5:1);

$[\alpha]_D^{22}$ = +60.7 (*c* = 1.0 in $CHCl_3$);

IR (film) λ_{max} 2962, 2931, 1751, 1735, 1458, 1259, 1083, 1074, 798 cm^{-1};

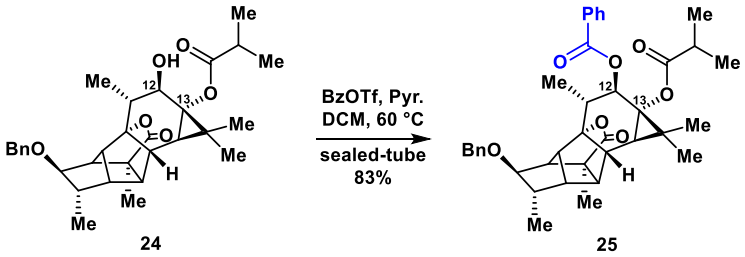
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 5H), 4.48 – 4.42 (m, 2H), 4.35 (s, 1H), 4.10 (d, *J* = 7.8 Hz, 1H), 3.39 (d, *J* = 2.4 Hz, 1H), 3.02 (d, *J* = 2.4 Hz, 1H), 2.64 (hept,

J = 7.0 Hz, 1H), 2.29 – 2.26 (m, 1H), 2.21 (dt, J = 4.5, 2.1 Hz, 1H), 2.16 – 2.09 (m, 2H), 1.56 (dt, J = 7.6, 6.5 Hz, 1H), 1.45 (dd, J = 5.7, 1.4 Hz, 1H), 1.27 (s, 3H), 1.26 (d, J = 7.2 Hz, 3H), 1.21 (s, 3H), 1.19 – 1.15 (m, 9H), 1.08 (s, 3H), 0.85 (d, J = 5.7 Hz, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 181.7, 179.8, 138.2, 128.6 (×2), 127.9, 127.7 (×2), 89.0, 81.5, 80.0, 70.8, 70.1, 58.5, 56.0, 51.1, 49.8, 46.4, 44.8, 43.5, 41.4, 33.9, 29.2, 28.2, 23.0, 19.3, 19.1, 17.4, 16.3, 16.1, 14.6 ppm;

HRMS (ESI) calc'd for $C_{31}H_{41}O_6$ $[M+H]^+$ 509.2898; found 509.2896.

Synthesis of compound 25



To a stirred solution of **24** (100 mg, 0.20 mmol, 1.0 equiv.) in DCM (10 mL) at 0 °C was added pyridine (0.29 mL, 4.0 mmol, 20.0 equiv.) and BzOTf (benzoyl trifluoromethanesulfonate, 0.33 mL, 2.0 mmol, 10.0 equiv.) and the resulting suspension was stirred for 55 h at 60 °C (sealed tube). It was then quenched with saturated aqueous $NaHCO_3$ (40 mL) and extracted with DCM (10 mL × 5). The combined organic phase was dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane = 1/5) to afford **25** (100 mg, 83%) as colorless oil.

TLC: R_f = 0.3 (hexane/EtOAc = 3:1)

$[\alpha]_D^{22}$ = +52.0 (c = 0.5 in $CHCl_3$);

IR (film) λ_{max} 2962, 2926, 1751, 1718, 1261, 1095, 1068, 798 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 – 8.00 (m, 2H), 7.55 – 7.51 (m, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.36 – 7.27 (m, 5H), 5.94 (d, J = 8.2 Hz, 1H), 4.47 (s, 2H), 3.40 (dd, J = 11.5, 2.4 Hz, 1H), 3.03 (m, 1H), 2.57 – 2.51 (m, 1H), 2.35 (d, J = 2.5 Hz, 1H), 2.24 – 2.21 (m, 1H), 2.17 – 2.11 (m, 2H), 1.76 – 1.72 (m, 1H), 1.41 (s, 3H), 1.30 (s, 3H), 1.23

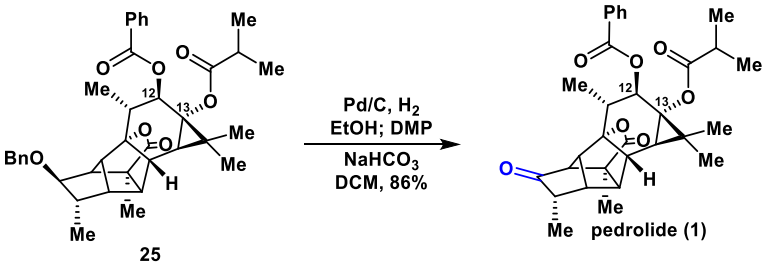
– 1.15 (m, 7H), 1.12 (d, J = 6.9 Hz, 3H), 1.11 – 1.06 (m, 6H), 0.87 (d, J = 5.9 Hz, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 179.3, 177.4, 166.4, 138.2, 132.7, 131.1, 129.8 (×2), 128.6 (×2), 128.4 (×2), 127.9, 127.7 (×2), 88.7, 81.5, 80.4, 70.9, 66.5, 58.6, 55.9, 51.2, 49.9, 46.5, 44.9, 43.7, 41.5, 33.8, 30.1, 28.5, 23.3, 19.2, 18.9, 18.0, 16.3, 16.2, 13.9 ppm;

HRMS (ESI) calc'd for $C_{38}H_{44}O_7Na$ $[M+Na]^+$ 635.2979; found 635.2977.

Note: BzOTf was purchased from TCI chemicals as colorless oil at 25 °C, which would solidify under -20 °C. We have also purchased it from other companies, but the quality was not good enough for this reaction.

Synthesis of pedrolide (1)



To a stirred solution of **25** (150 mg, 0.24 mmol, 1.0 equiv.) in EtOH (10 mL) was added Pd/C (15 mg, dried, 10% Pd (dry basis), reduced, wetted with 55% H_2O). The reaction flask was transferred to a stainless-steel autoclave (Parr 4761). The hydrogenation was performed at 25 °C under 52 bar hydrogen pressure for 8 h. After carefully releasing the hydrogen, the solvent was concentrated under reduced pressure. In the same flask, $NaHCO_3$ (121 mg, 1.44 mmol, 6.0 equiv.) was added followed by quick addition of a solution of DMP (Dess-Martin periodinane, 203 mg, 0.48 mmol, 2.0 equiv.) in DCM (20 mL). The reaction was allowed to stir for 3 h at 25 °C before quenched by saturated aqueous Na_2SO_3 (40 mL) and extracted with DCM (10 mL × 4). The combined organic phase was dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane = 1/2) to afford pedrolide (**1**, 109 mg, 86%) as white solid.

TLC: R_f = 0.5 (hexane/EtOAc = 3:2);

$[\alpha]_D^{22}$ = +70.5 (*c* = 0.75 in $CHCl_3$);

IR (film) λ_{max} 2962, 2924, 1747, 1722, 1710, 1261, 1095, 1024, 800 cm^{-1};

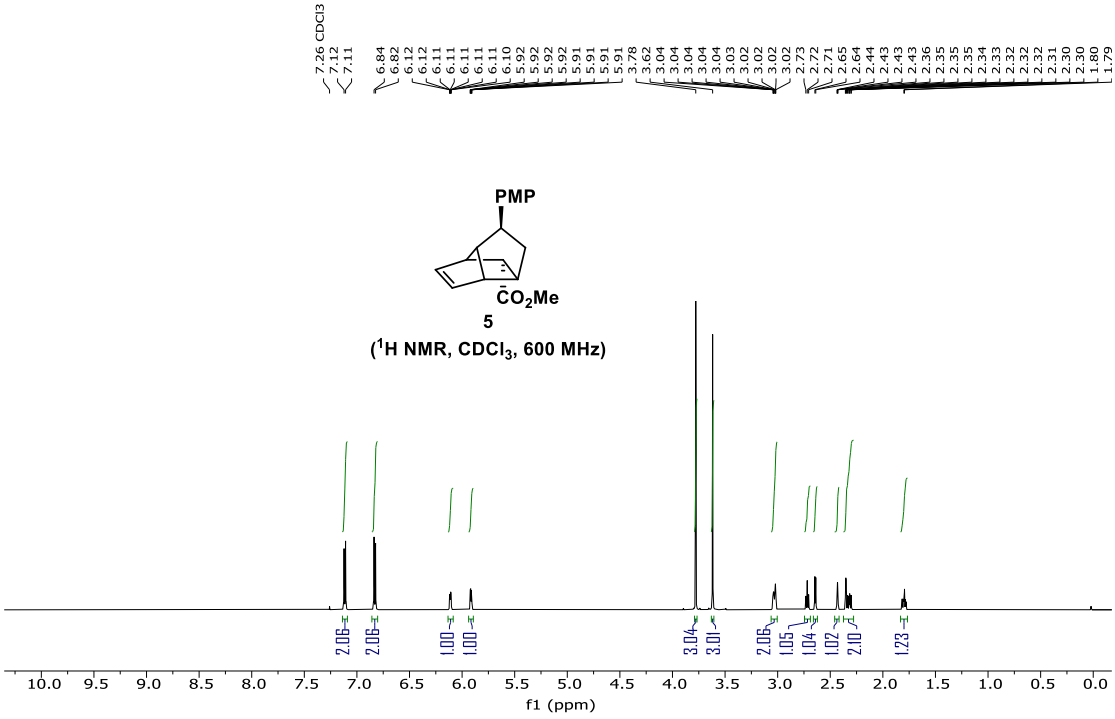
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 – 8.03 (m, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 5.95 (d, *J* = 8.2 Hz, 1H), 3.03 (d, *J* = 2.4 Hz, 1H), 2.65 – 2.62 (m, 1H), 2.61 (d, *J* = 2.3 Hz, 1H), 2.53 (hept, *J* = 7.0 Hz, 1H), 2.44 (br s, 1H), 2.39 (qd, *J* = 7.3, 4.4 Hz, 1H), 1.83 – 1.77 (m, 1H), 1.74 (d, *J* = 5.7 Hz, 1H), 1.45 (s, 3H), 1.25 (d, *J* = 7.5 Hz, 3H) (s, 3H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.12 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 5.7 Hz, 1H) ppm;

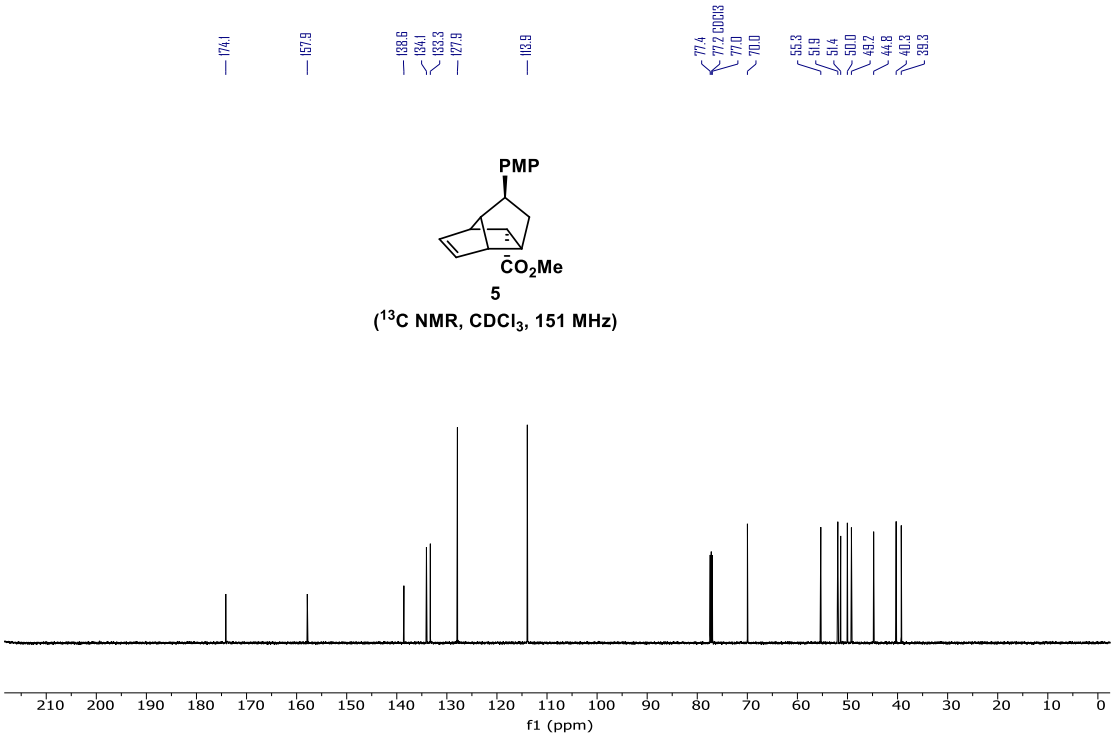
^{13}C NMR (151 MHz, $CDCl_3$) δ 212.2, 177.3, 176.8, 166.3, 132.8, 131.0, 129.8 (×2), 128.5 (×2), 88.5, 80.1, 66.4, 63.1, 55.7, 51.0, 50.1, 46.7, 45.6, 45.0, 43.4, 33.8, 30.3, 28.2, 23.2, 19.1, 18.9, 18.0, 17.4, 13.8, 12.4 ppm;

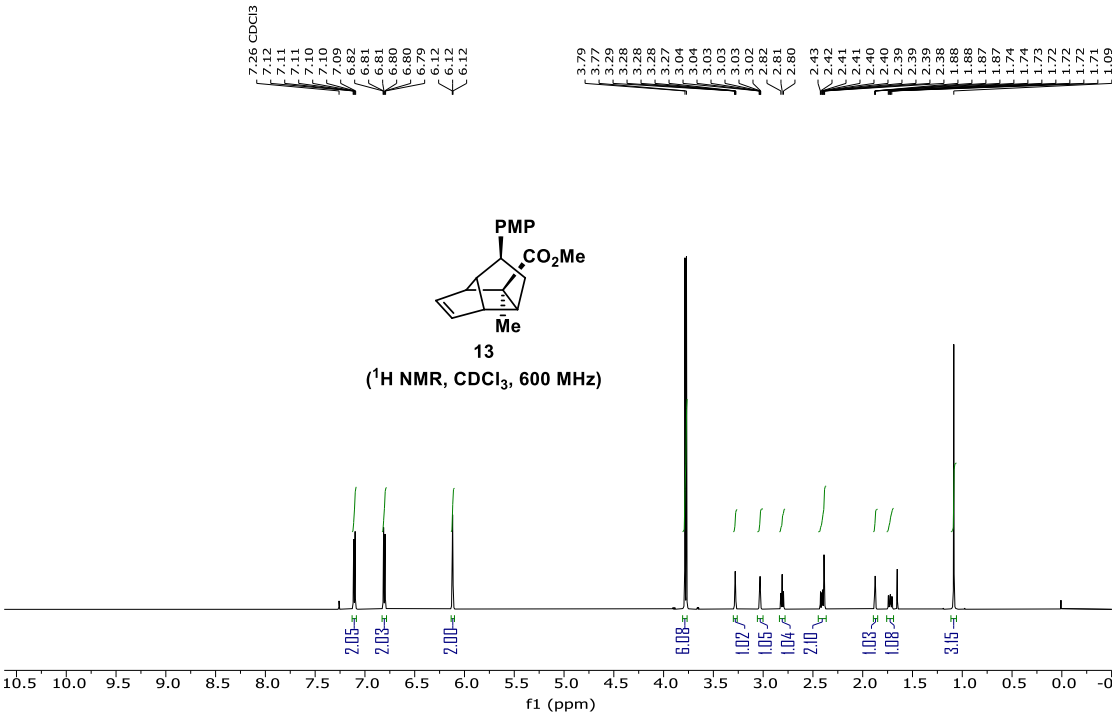
HRMS (ESI) calc'd for $C_{31}H_{36}O_7Na$ $[M+Na]^+$ 543.2353; found 543.2354.

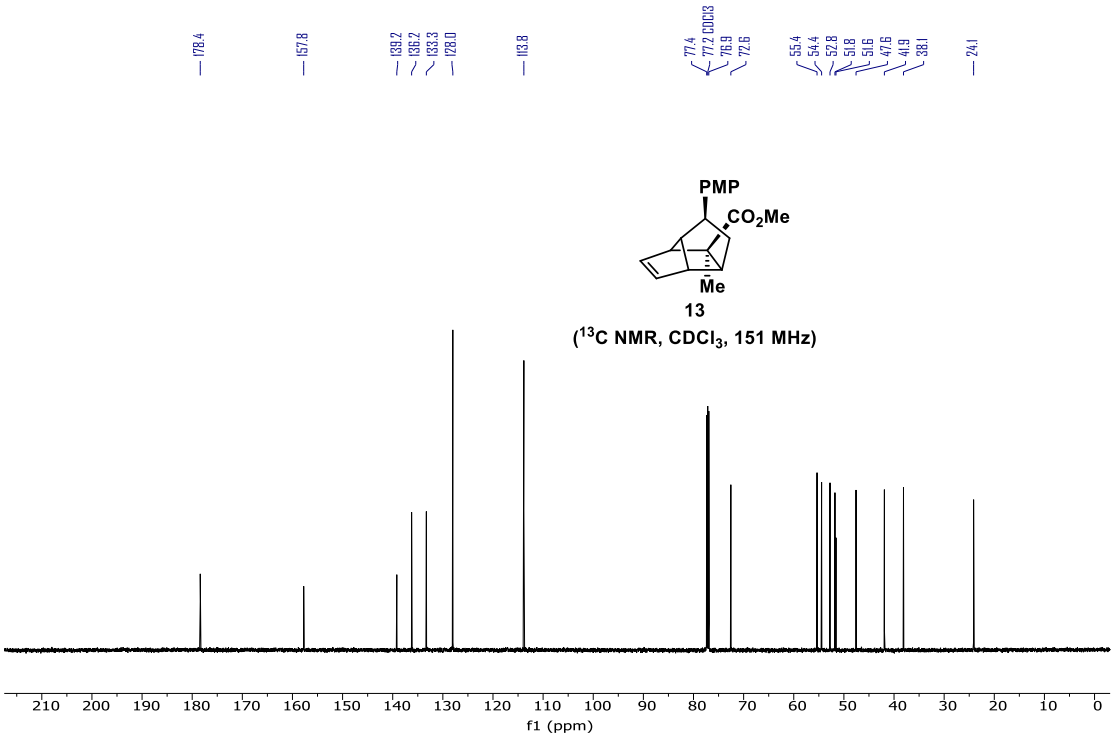
Note: Over 200 mg pedrolide was prepared through 2 parallel reactions.

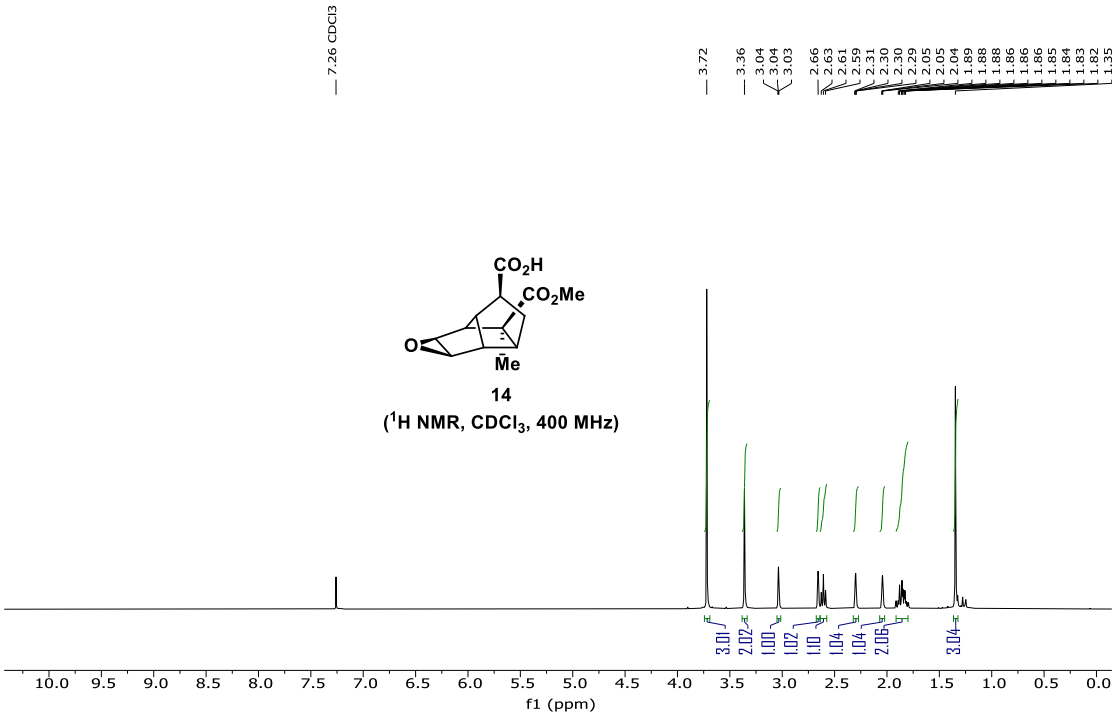
6. NMR Spectra





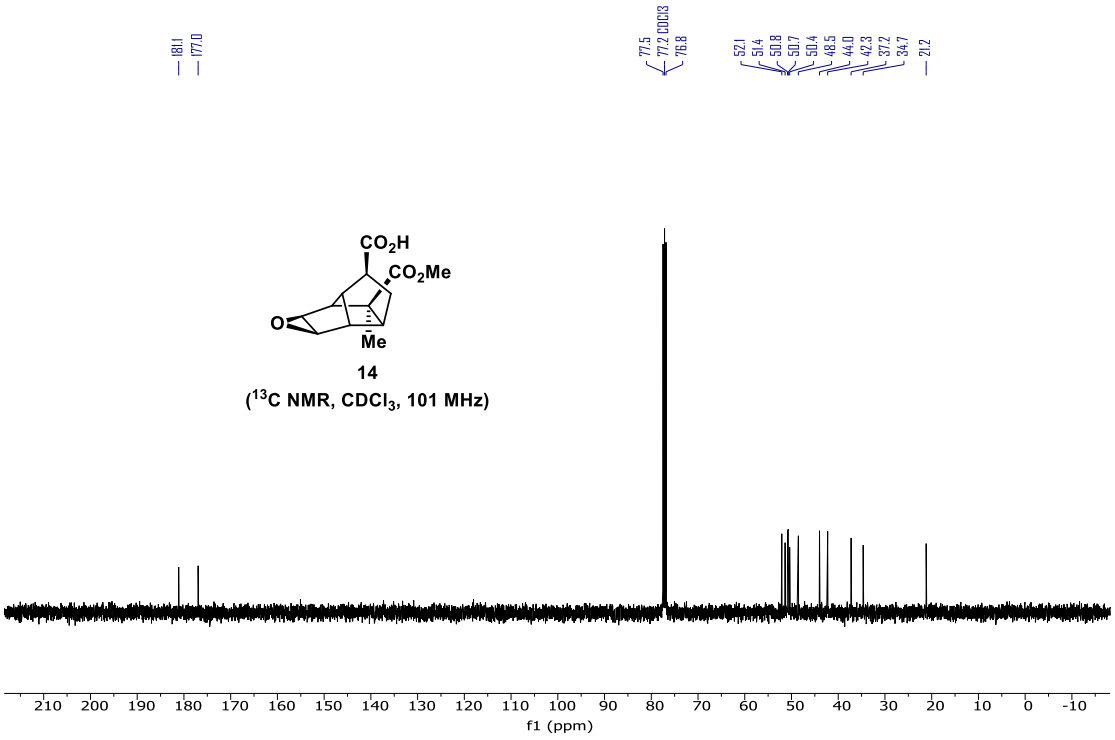

PMP
CO2Me
Me
13
(1H NMR, CDCl3, 600 MHz)
f1 (ppm)


PMP
CO2Me
Me
13
(13C NMR, CDCl3, 151 MHz)
f1 (ppm)



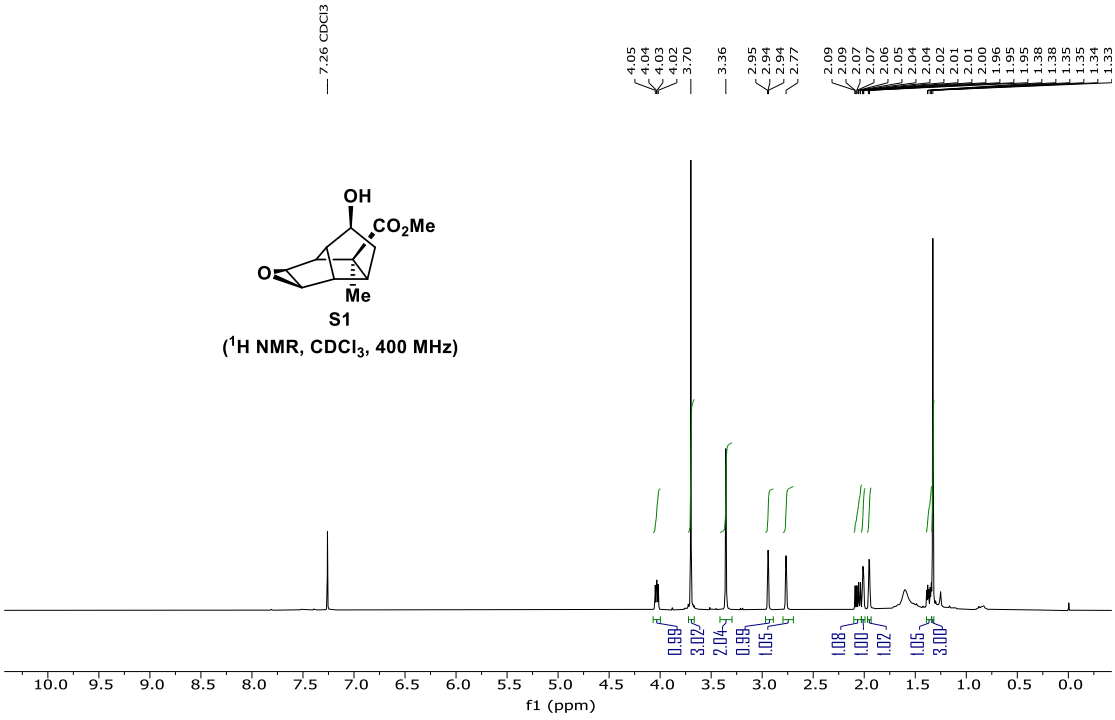
14

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



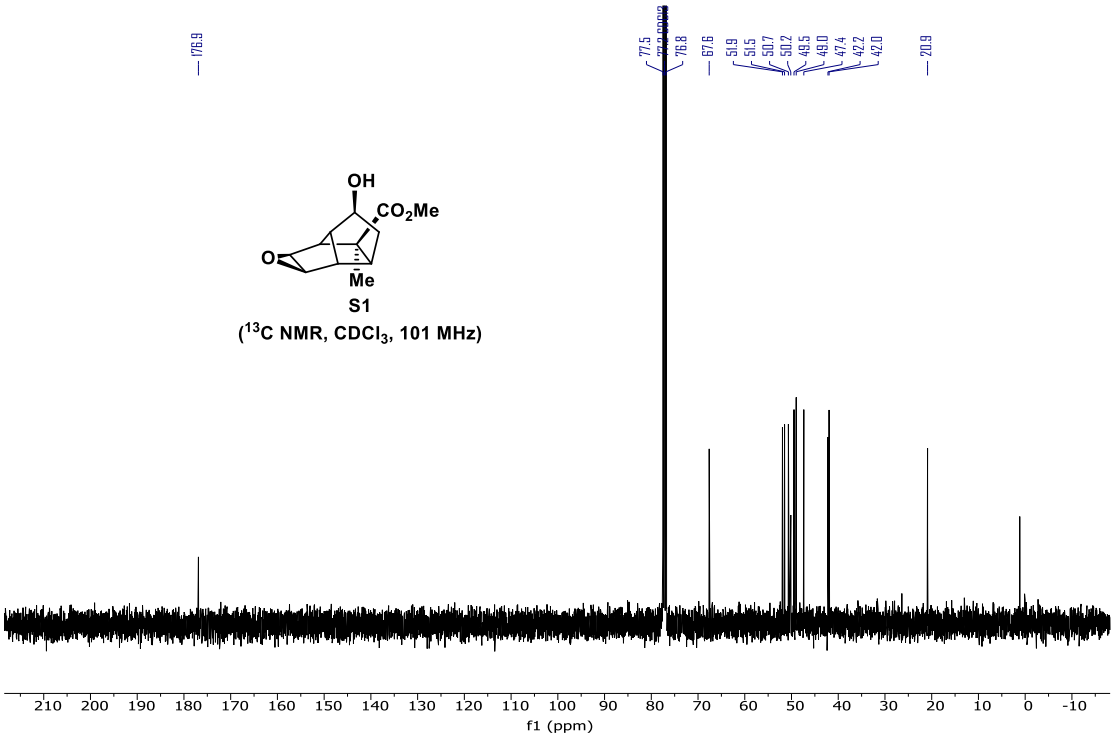
14

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



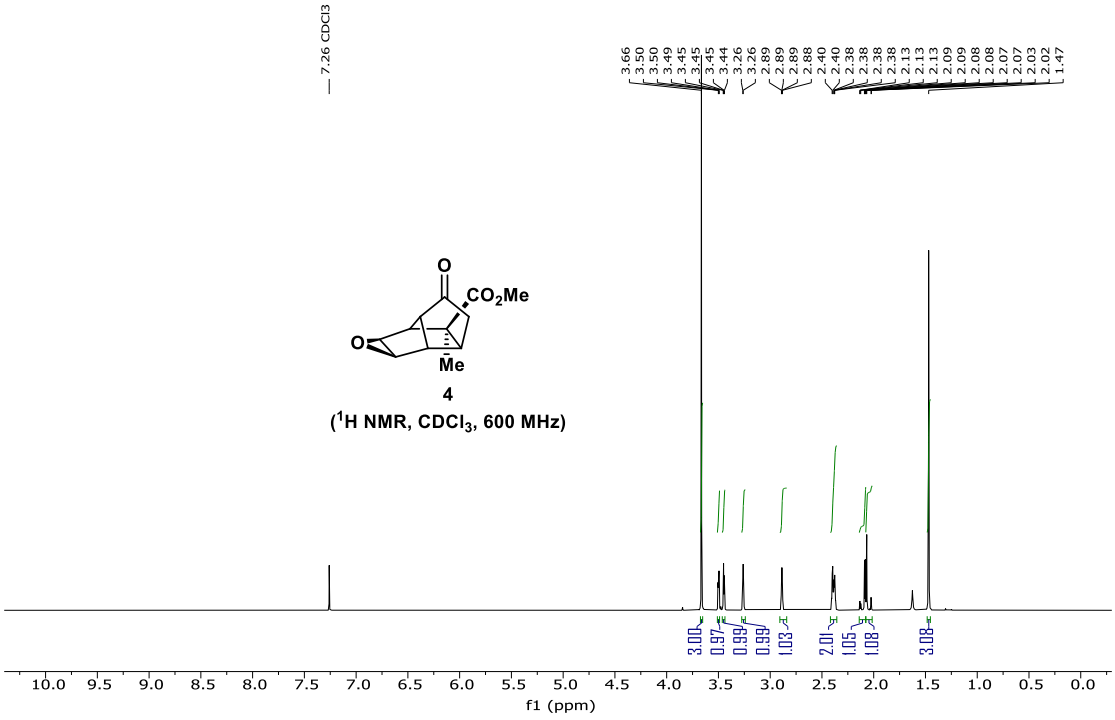
S1

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



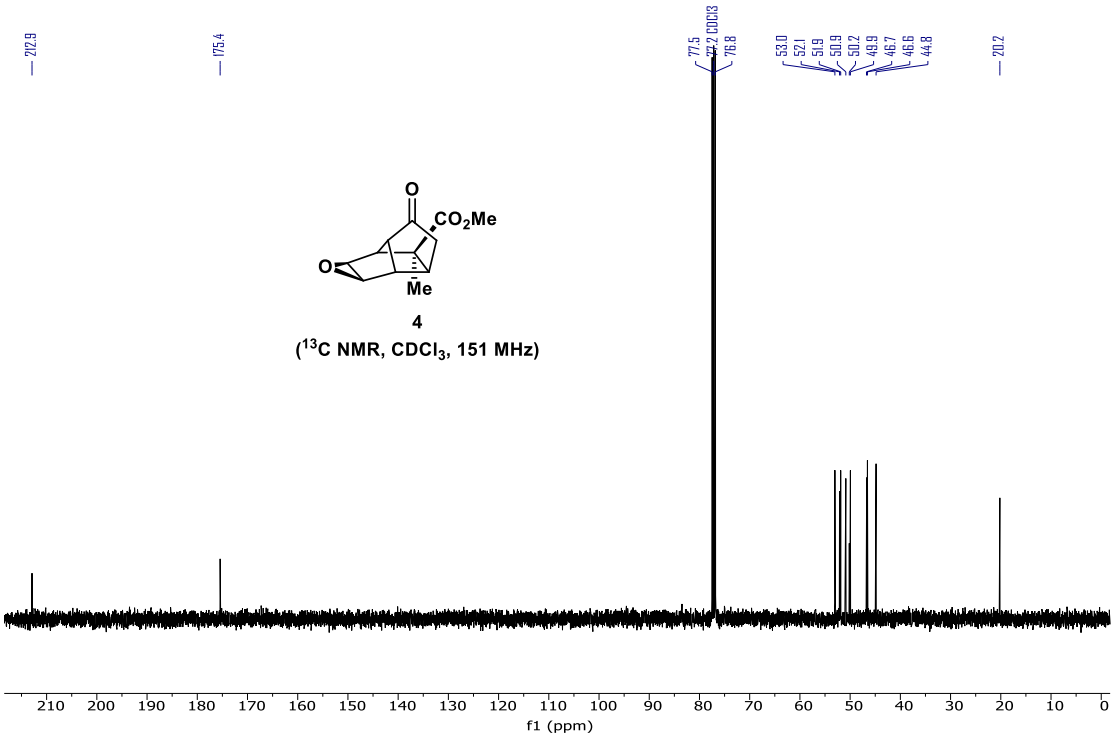
S1

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



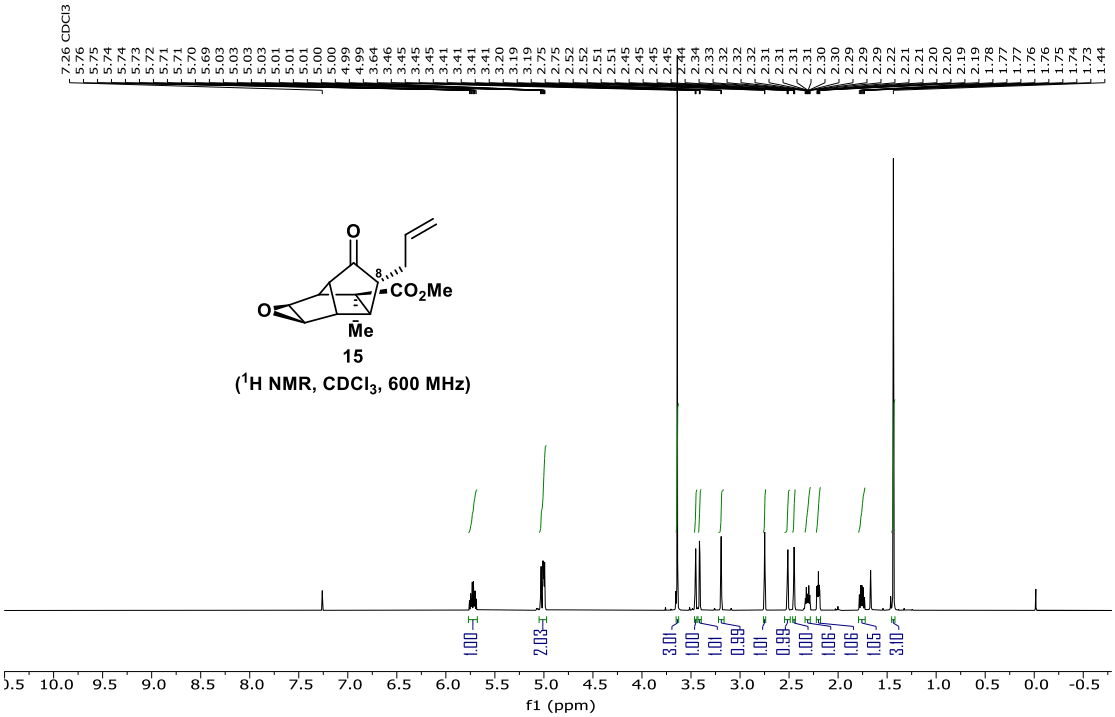
4

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



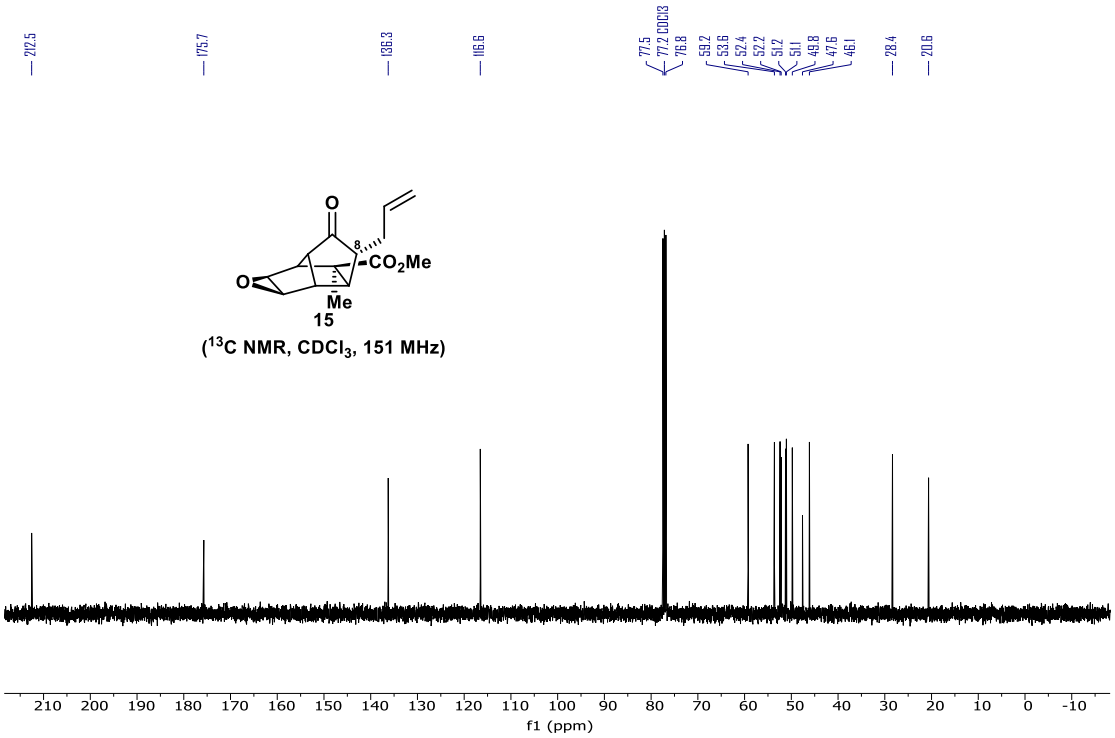
4

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



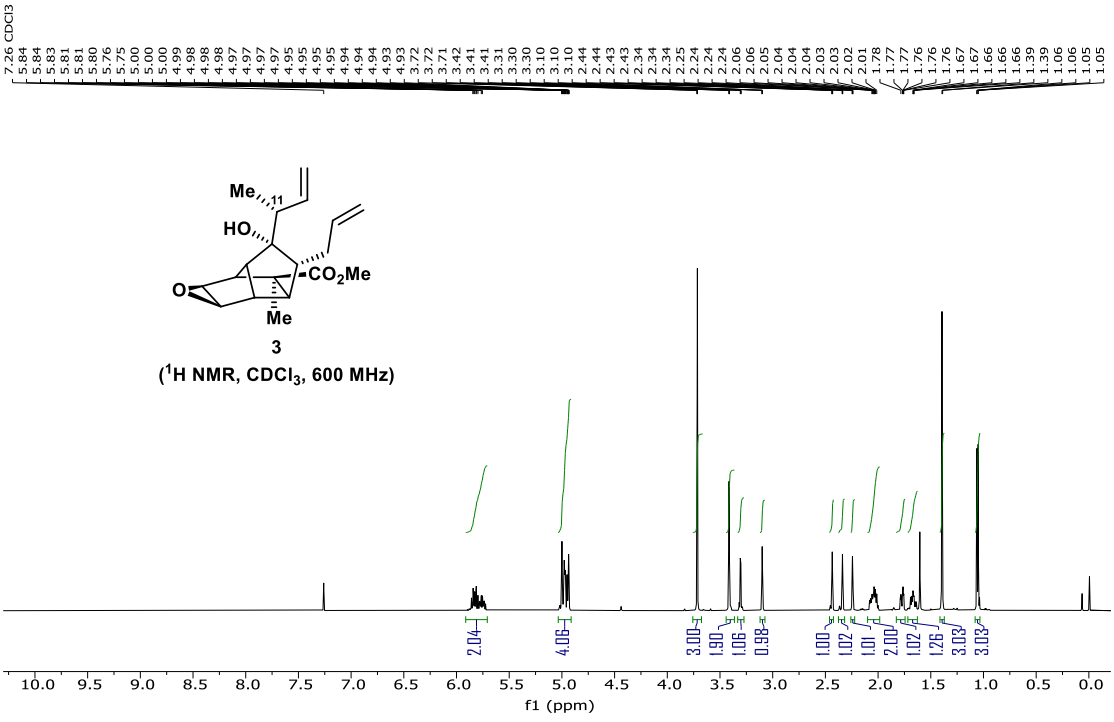
15

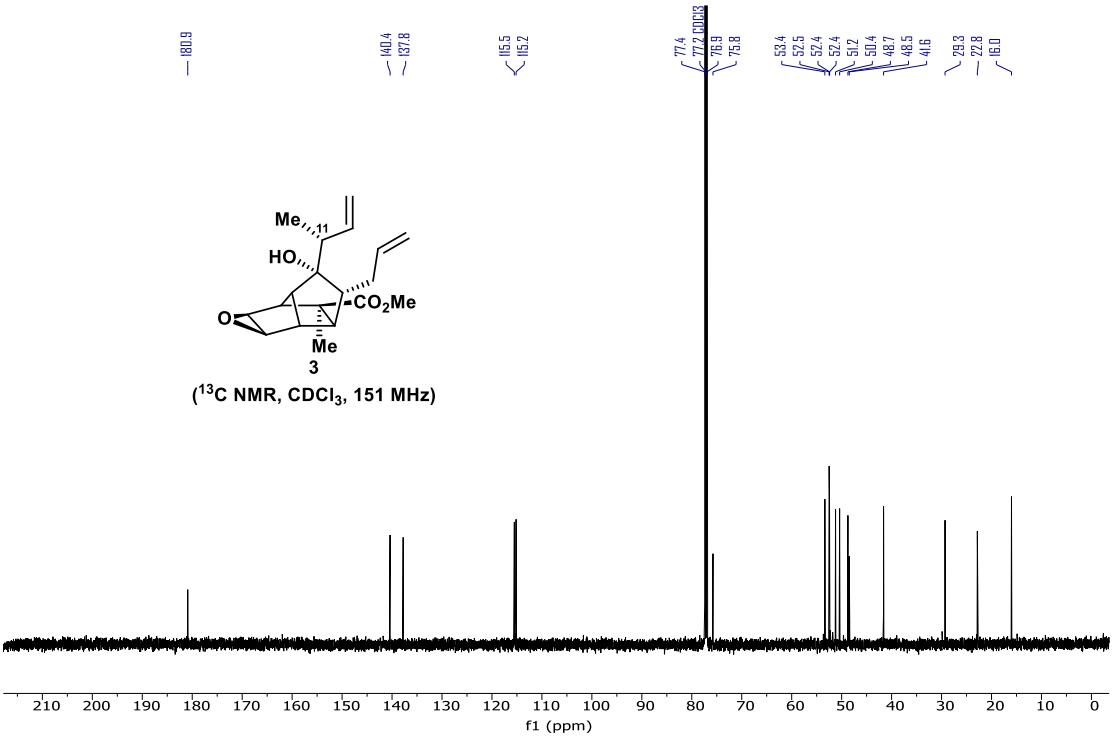
(^{1}H NMR, $CDCl_3$, 600 MHz)

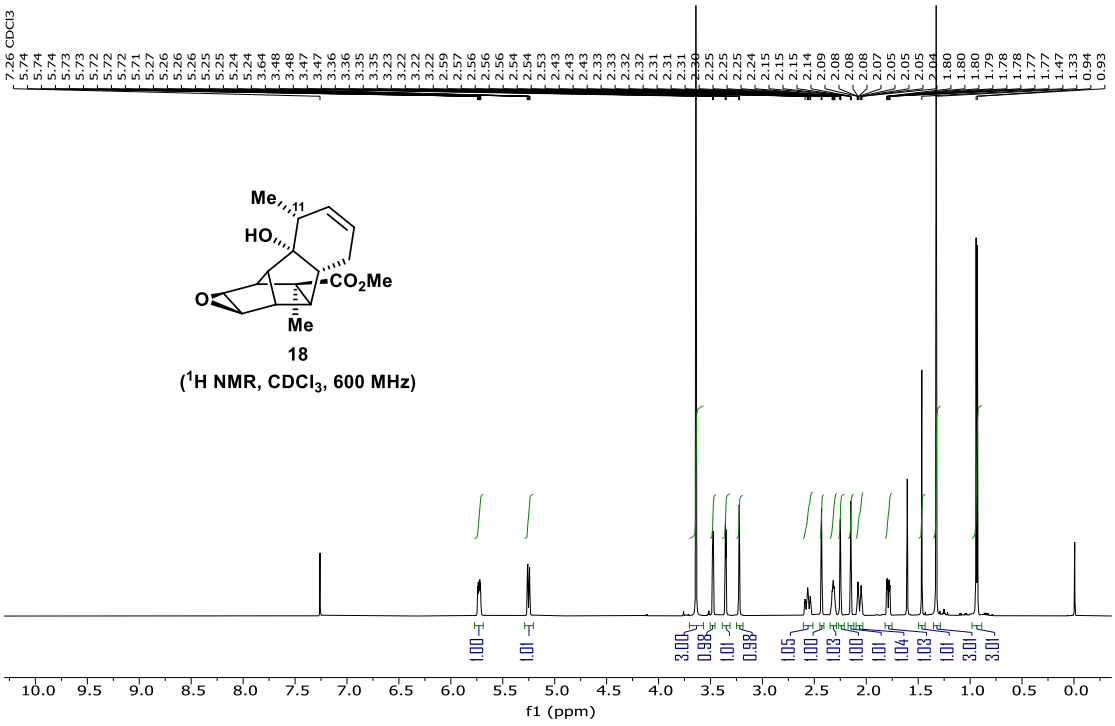


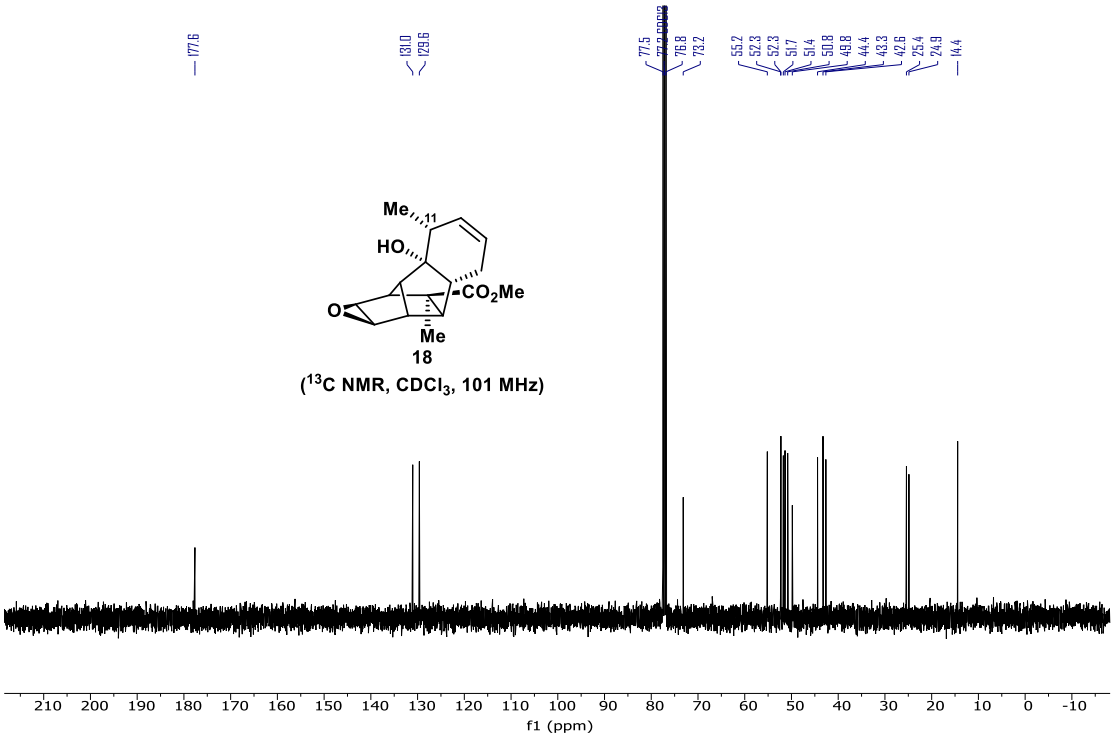
15

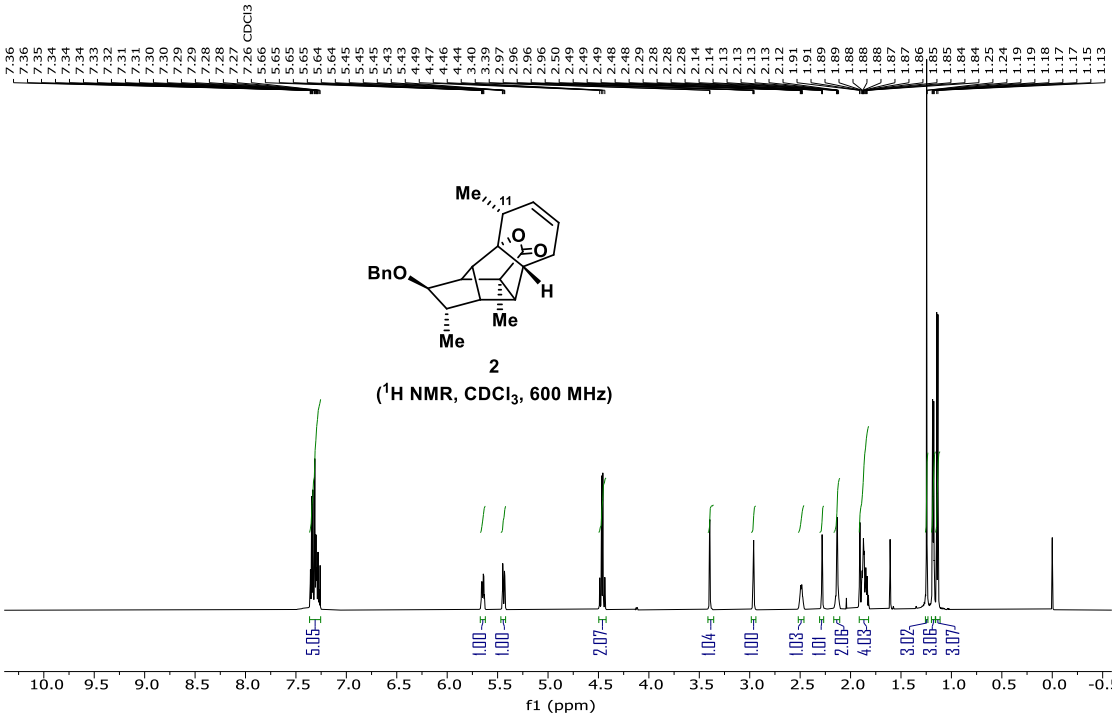
(^{13}C NMR, $CDCl_3$, 151 MHz)

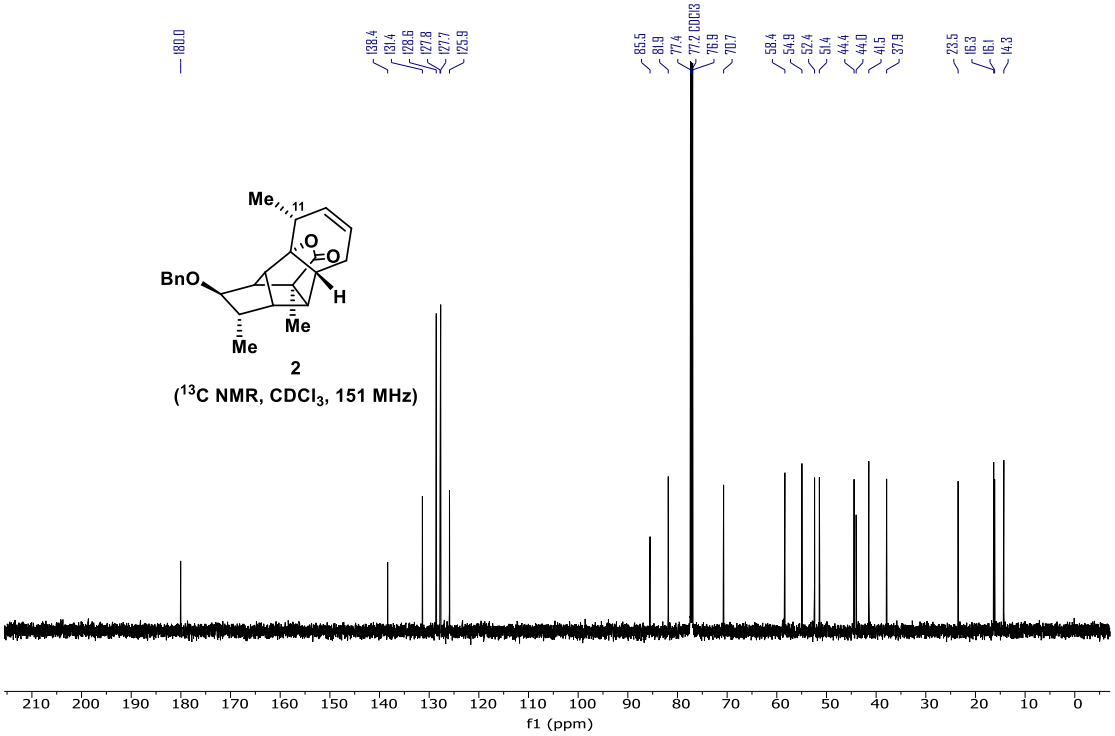

7.26 CDCl3
Me
11
HO
CO2Me
O
Me
3
(1H NMR, CDCl3, 600 MHz)
2.04
4.06
3.00
1.90
1.06
0.98
1.00
1.02
1.01
2.00
1.02
1.26
3.03
3.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

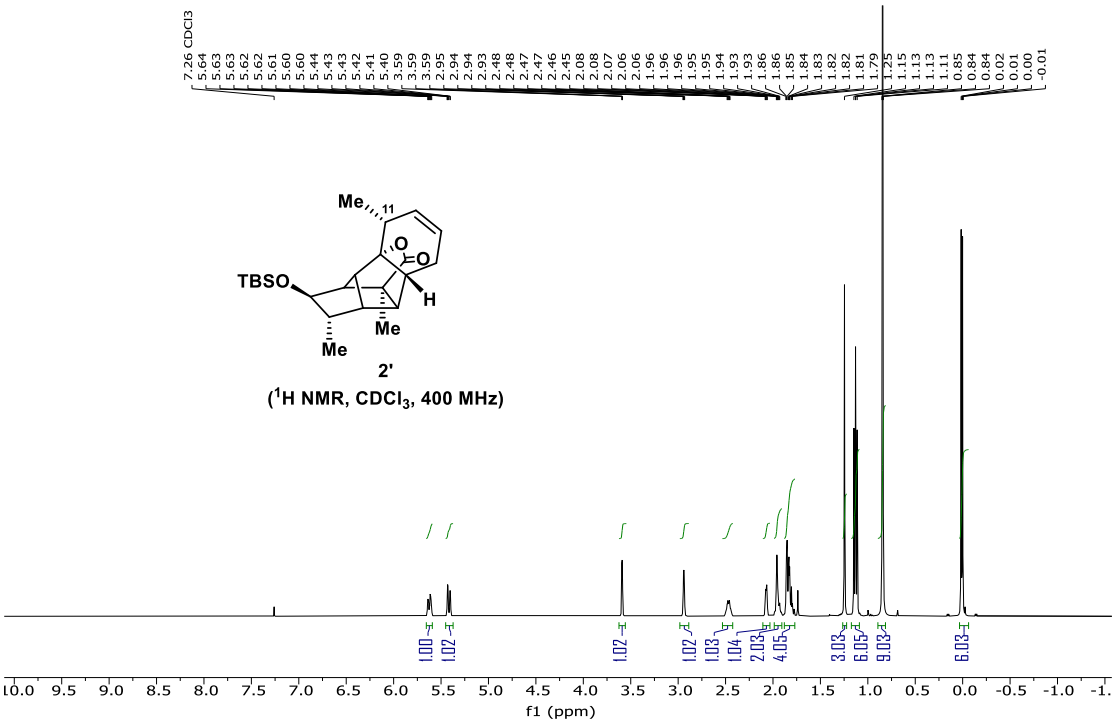

180.9
140.4
137.8
115.5
115.2
77.4
77.2 CDCl3
76.9
75.8
53.4
52.5
52.4
52.4
51.2
50.4
48.7
48.5
41.6
29.3
22.8
16.0
Me
11
HO
CO2Me
O
Me
3
(13C NMR, CDCl3, 151 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
11
HO
CO2Me
O
Me
18
(1H NMR, CDCl3, 600 MHz)
f1 (ppm)


Me
11
HO
CO2Me
O
Me
18
(13C NMR, CDCl3, 101 MHz)
f1 (ppm)

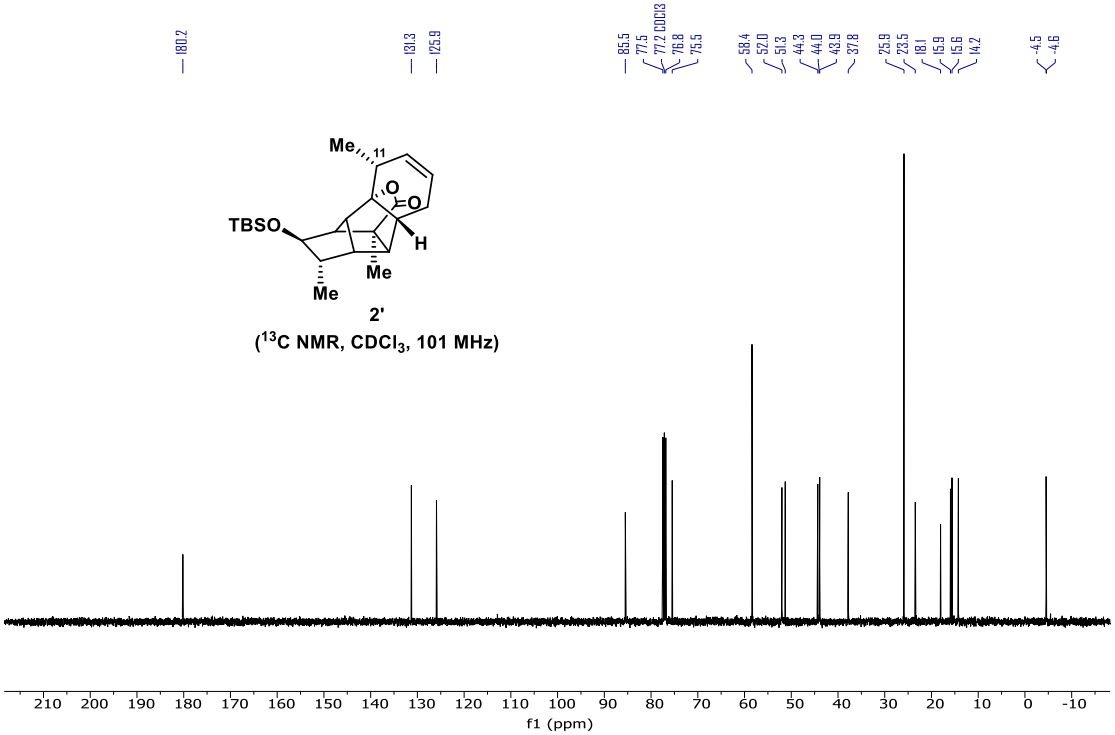

Me
11
O
O
BnO
H
Me
Me
2
(1H NMR, CDCl3, 600 MHz)
f1 (ppm)


Me
11
O
O
BnO
H
Me
Me
2
(13C NMR, CDCl3, 151 MHz)
f1 (ppm)



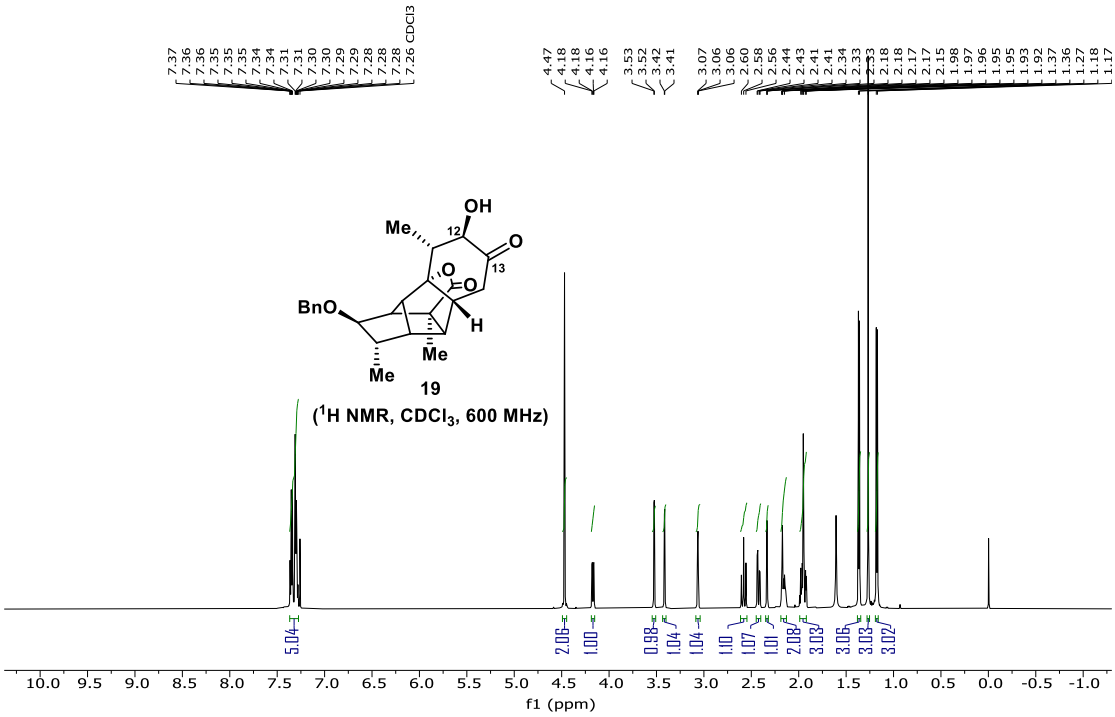
2'

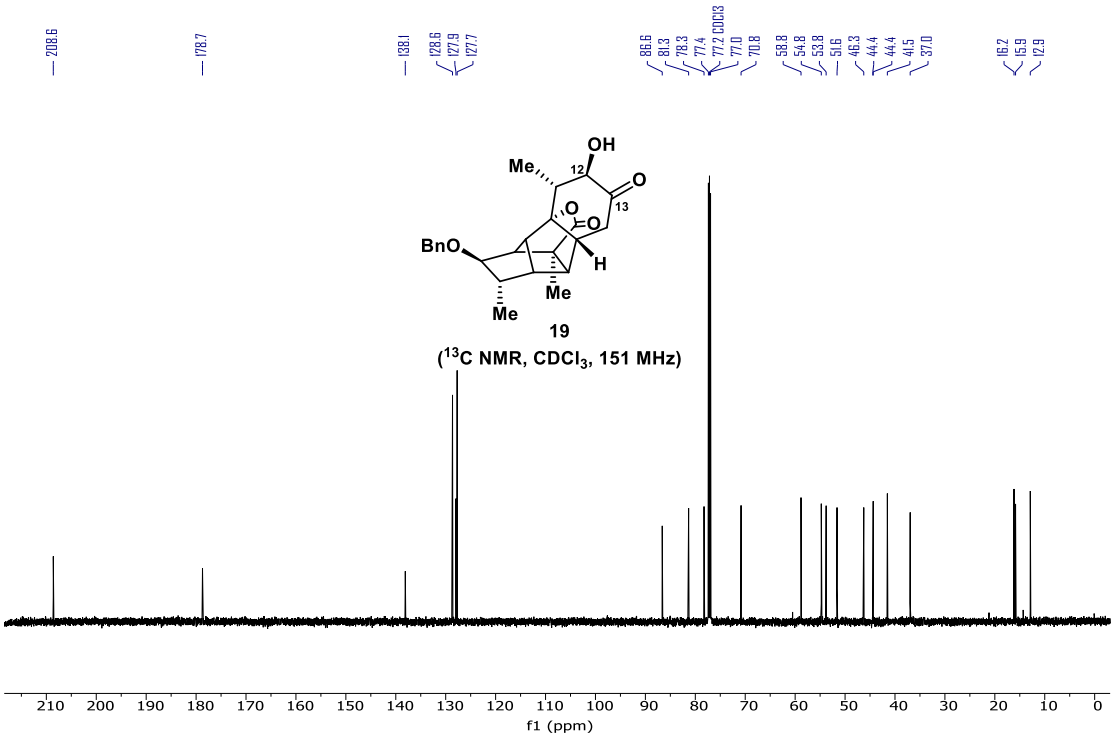
(^{1}H NMR, $CDCl_3$, 400 MHz)

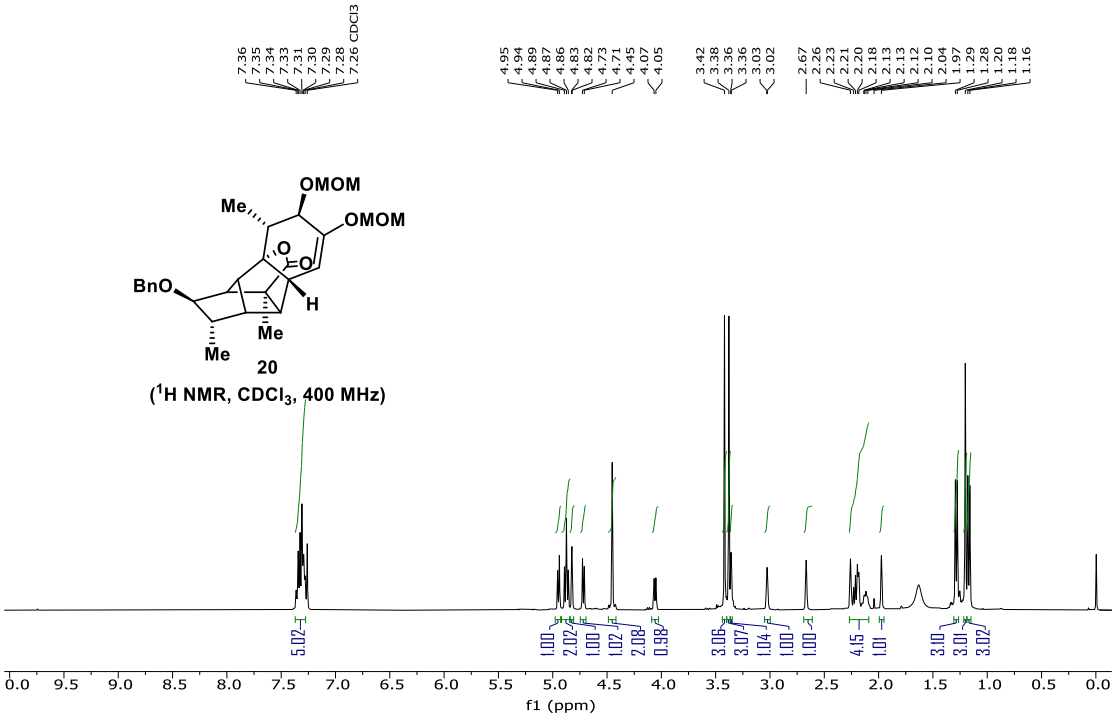


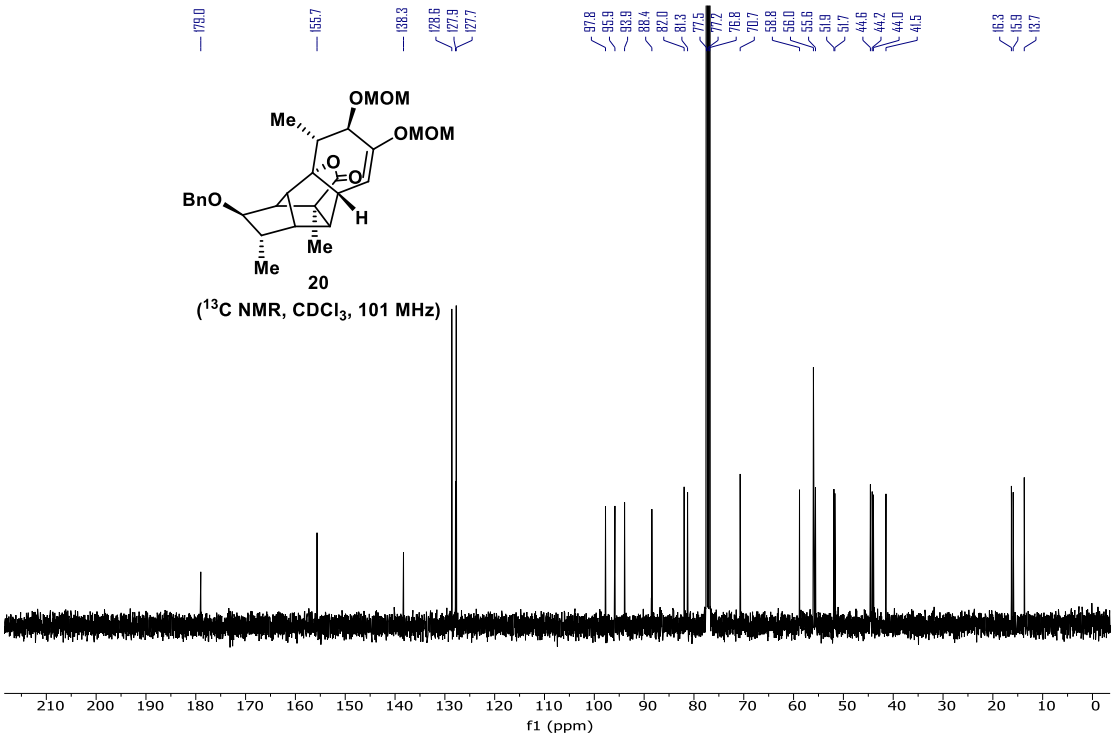
2'

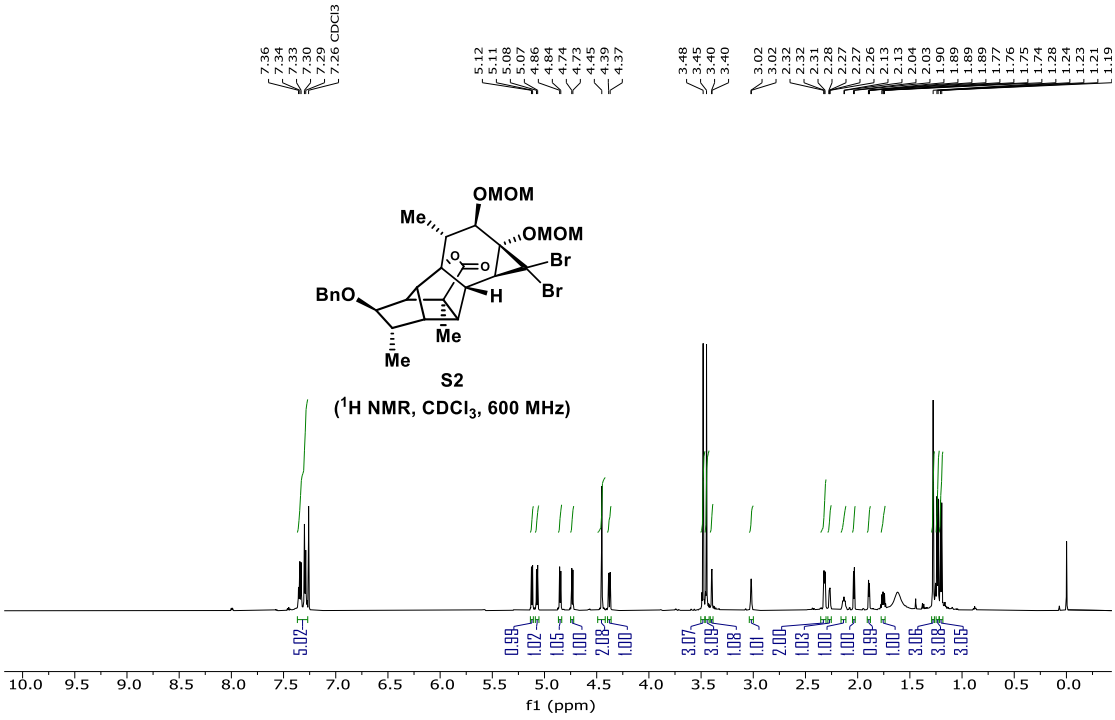
(^{13}C NMR, $CDCl_3$, 101 MHz)

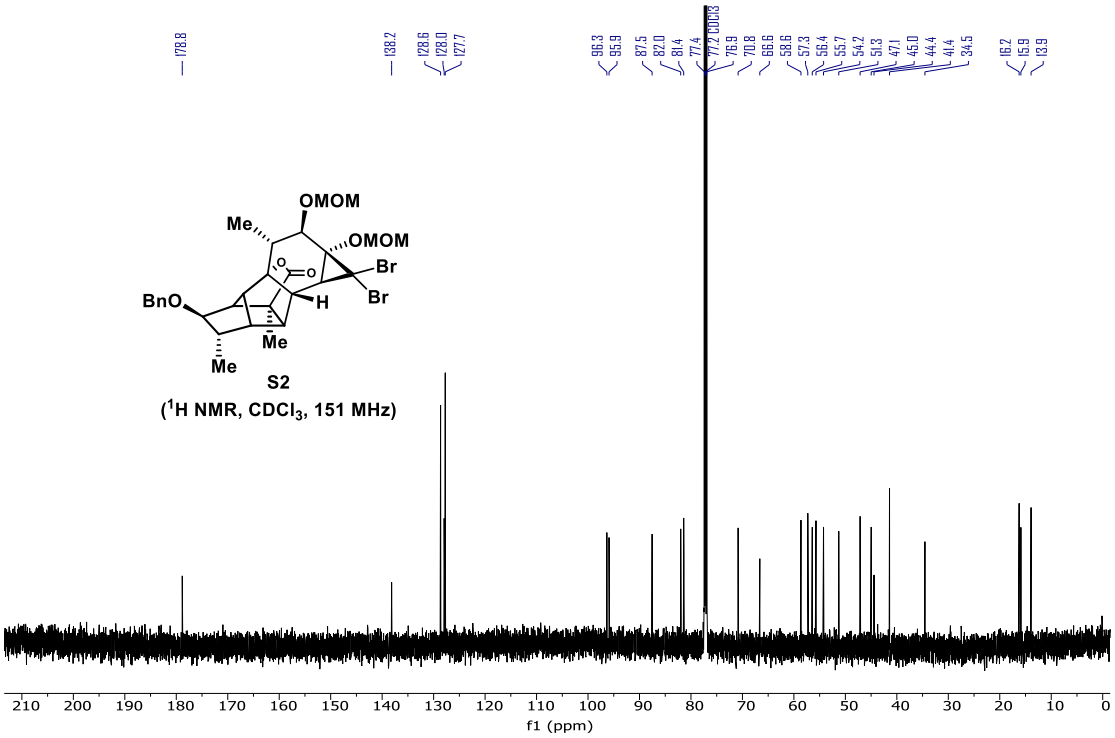

OH
Me
12
O
13
O
O
BnO
H
Me
Me
19
(1H NMR, CDCl3, 600 MHz)
f1 (ppm)

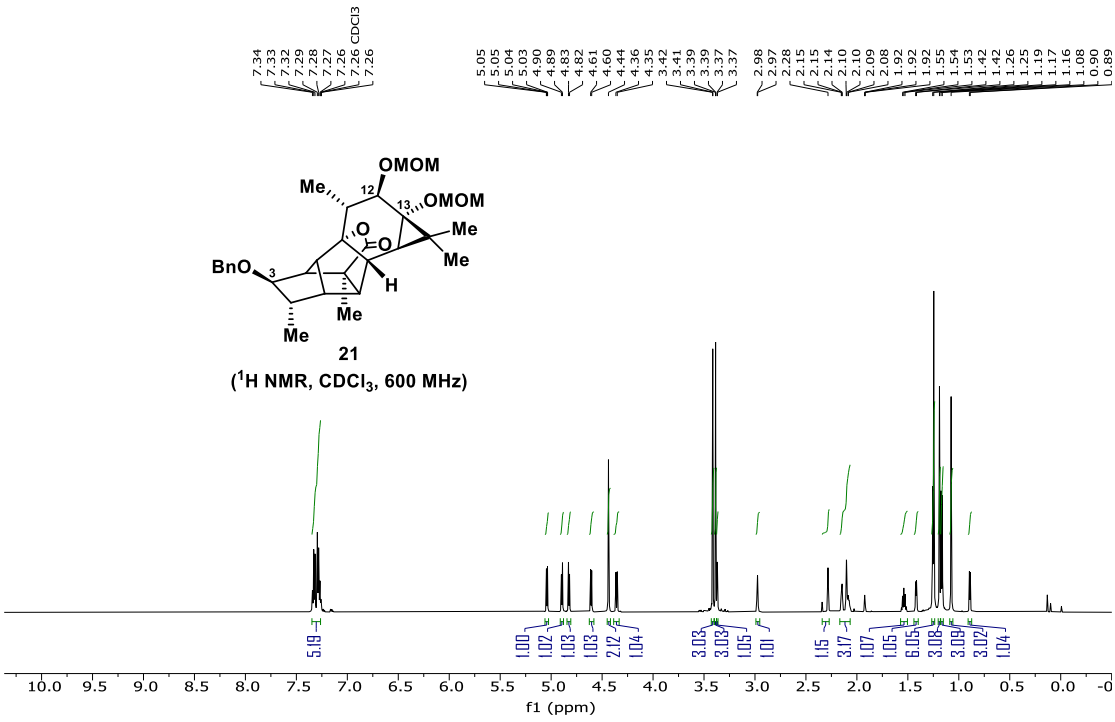

OH
Me
12
O
13
O
O
BnO
H
Me
Me
19
(13C NMR, CDCl3, 151 MHz)
f1 (ppm)

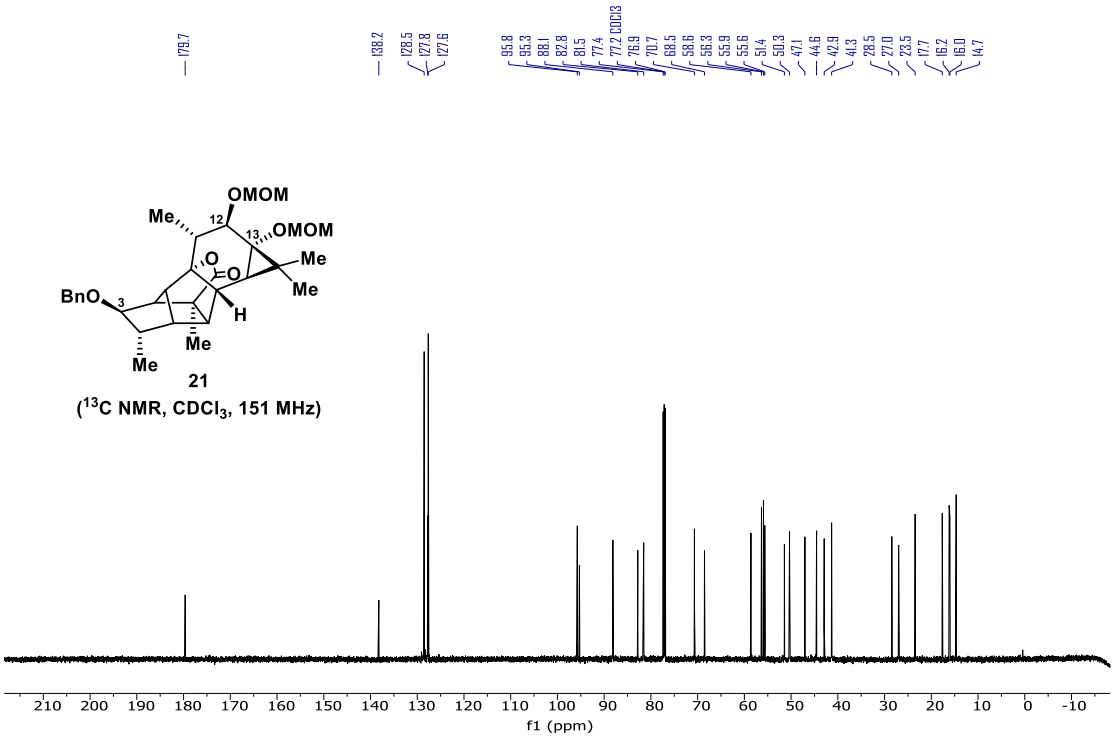

OMOM
Me
OMOM
O
O
BnO
H
Me
Me
20
(1H NMR, CDCl3, 400 MHz)
f1 (ppm)

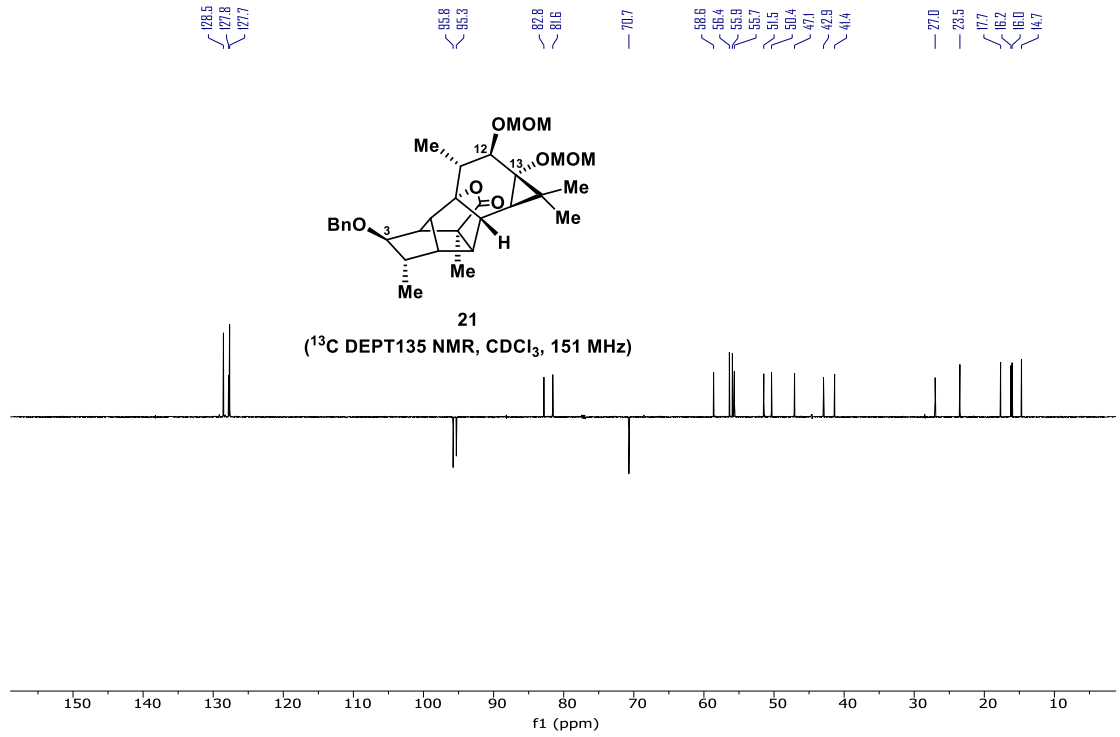

OMOM
Me
OMOM
O
O
BnO
H
Me
Me
20
(13C NMR, CDCl3, 101 MHz)
f1 (ppm)


OMOM
Me
OMOM
Br
Br
BnO
H
Me
Me
S2
(1H NMR, CDCl3, 600 MHz)
f1 (ppm)


OMOM
Me
OMOM
Br
Br
BnO
H
Me
Me
S2
(1H NMR, CDCl3, 151 MHz)
f1 (ppm)

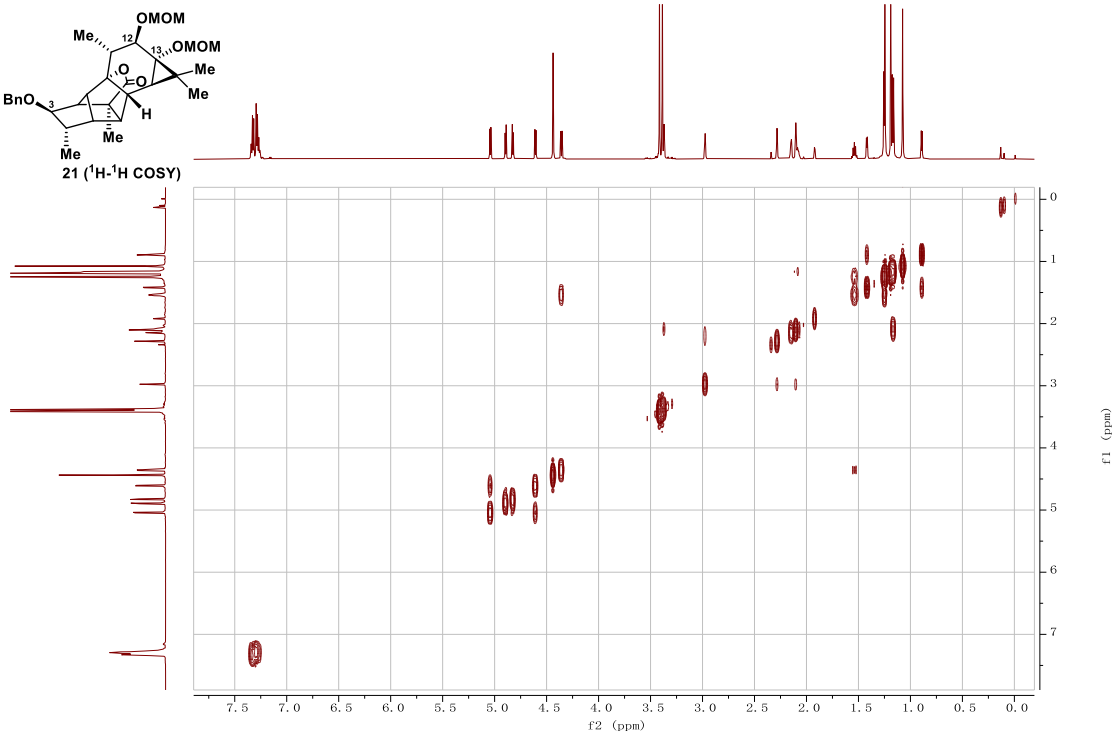

OMOM
Me
12
13
OMOM
Me
Me
O
O
BnO
3
H
Me
Me
21
(1H NMR, CDCl3, 600 MHz)
f1 (ppm)


OMOM
Me
12
13
OMOM
Me
Me
O
O
BnO
3
H
Me
Me
21
(13C NMR, CDCl3, 151 MHz)
f1 (ppm)

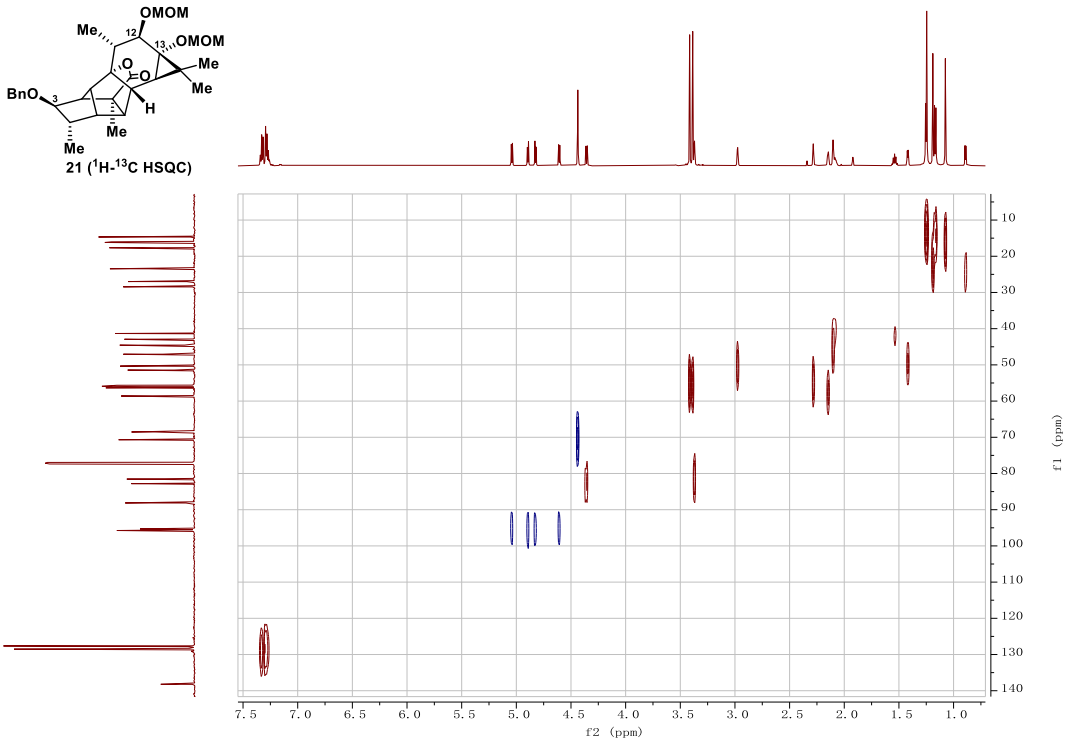


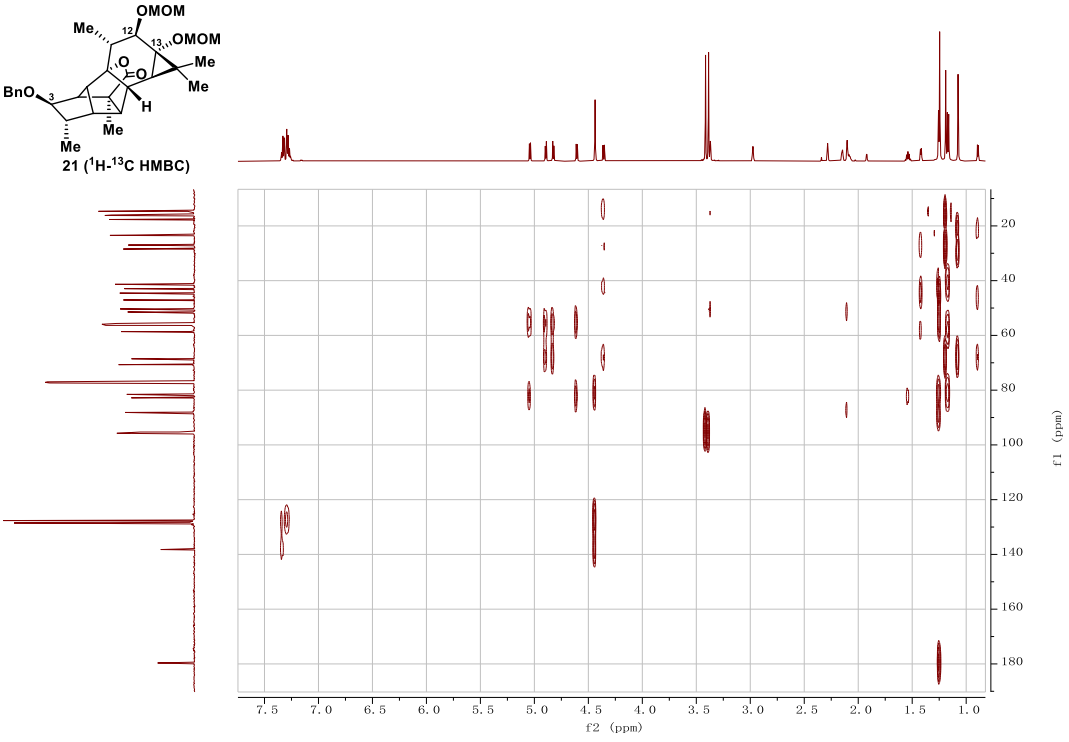
21

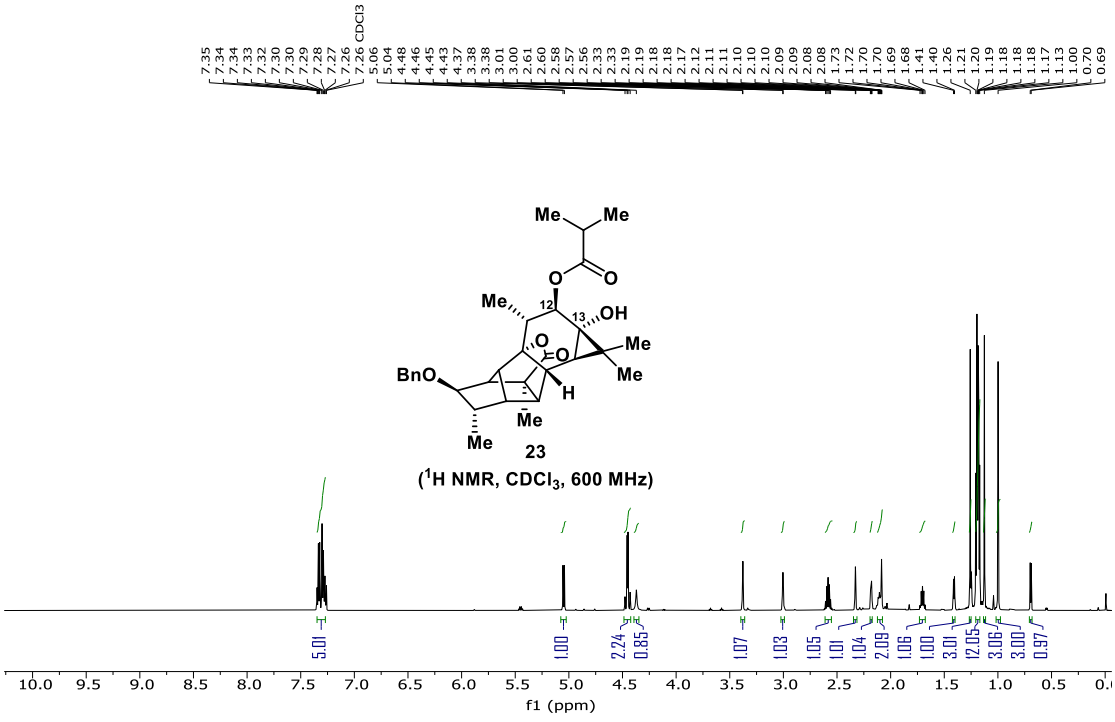
(^{13}C DEPT135 NMR, $CDCl_3$, 151 MHz)

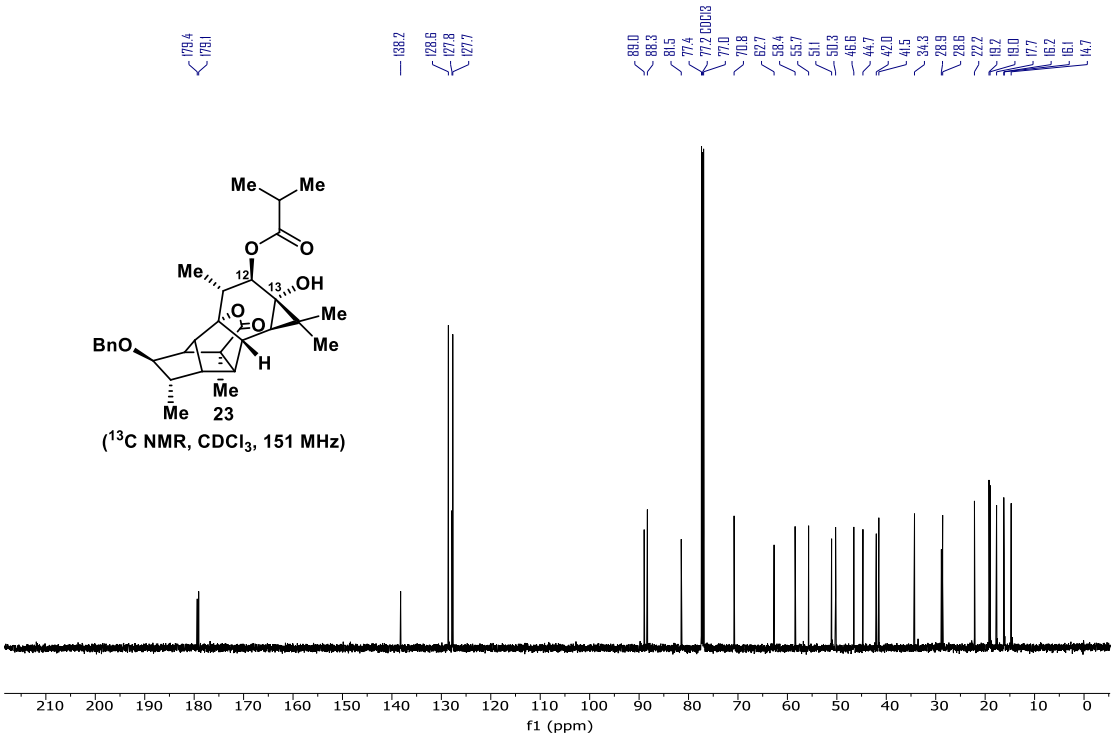


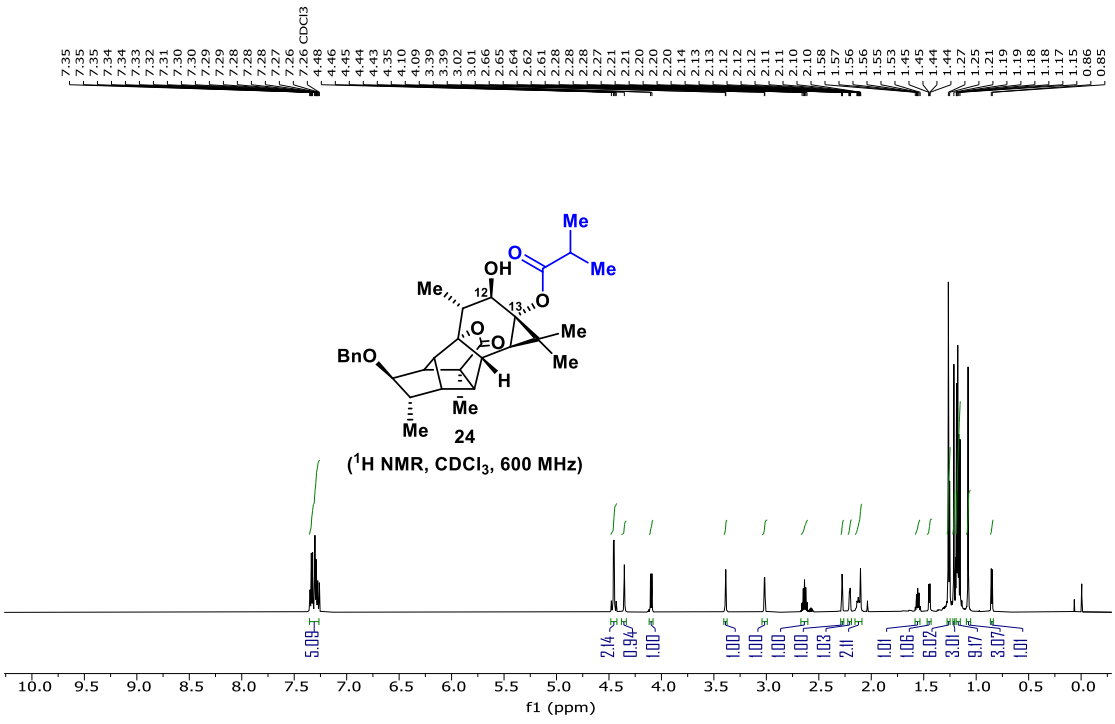
21 (^{1}H-^{1}H COSY)

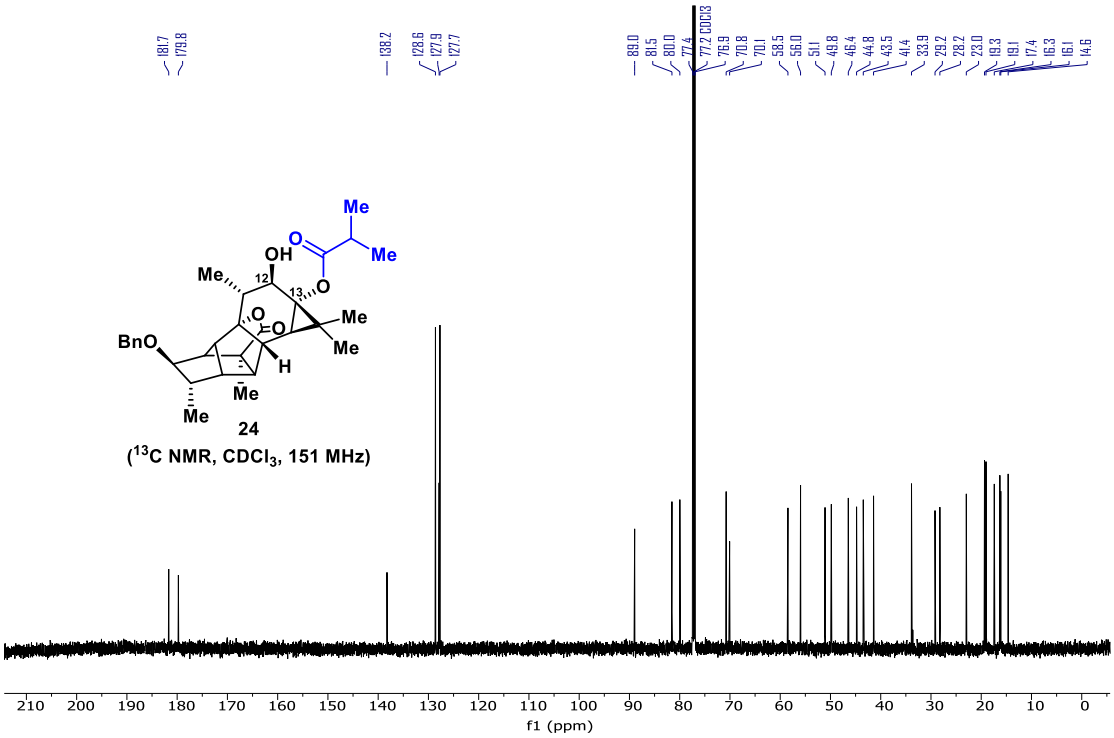

OMOM
Me
12
13
OMOM
O
O
Me
Me
BnO
3
H
Me
Me
21 (1H-13C HSQC)
f2 (ppm)
f1 (ppm)

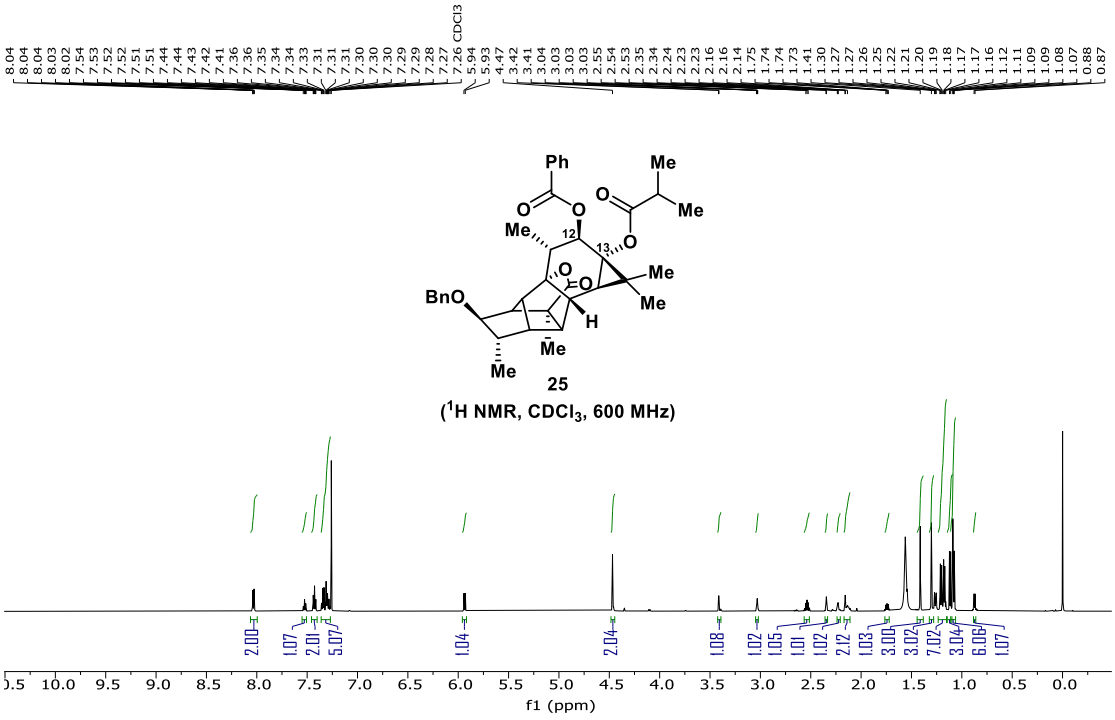

OMOM
Me
12
13
OMOM
O
O
Me
Me
BnO
3
H
Me
Me
21 (1H-13C HMBC)
f2 (ppm)
f1 (ppm)

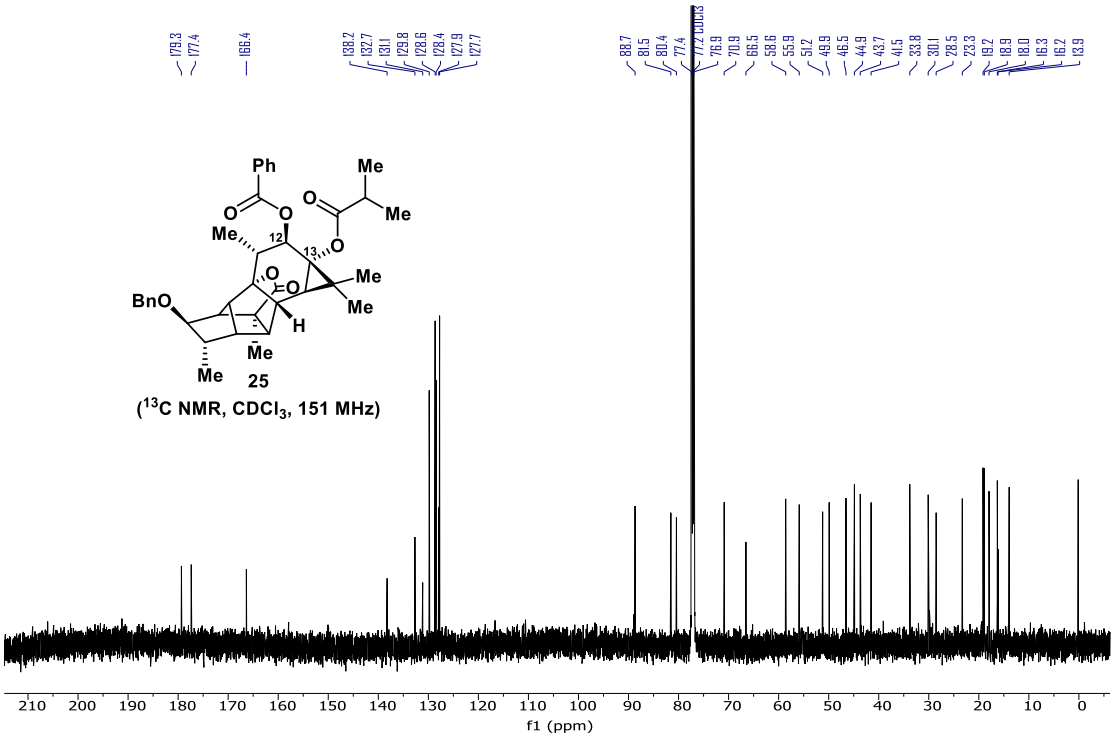

7.35 7.34 7.34 7.33 7.32 7.30 7.30 7.29 7.28 7.27 7.26 7.26 CDCl3
5.06 5.04 4.48 4.46 4.45 4.43 4.37 3.38 3.38 3.01 3.00 2.61 2.60 2.58 2.57 2.56 2.33 2.33 2.19 2.19 2.18 2.18 2.17 2.12 2.11 2.11 2.10 2.10 2.10 2.09 2.09 2.08 2.08 1.73 1.72 1.70 1.70 1.69 1.68 1.41 1.40 1.26 1.21 1.20 1.19 1.18 1.18 1.18 1.17 1.13 1.00 0.70 0.69
Me Me
O
O
Me
12
13 OH
O
O
Me
Me
BnO
H
Me
Me
23
(1H NMR, CDCl3, 600 MHz)
5.01 1.00 2.24 0.85 1.07 1.03 1.05 1.01 1.04 2.09 1.06 1.00 3.01 12.05 3.06 3.00 0.97
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

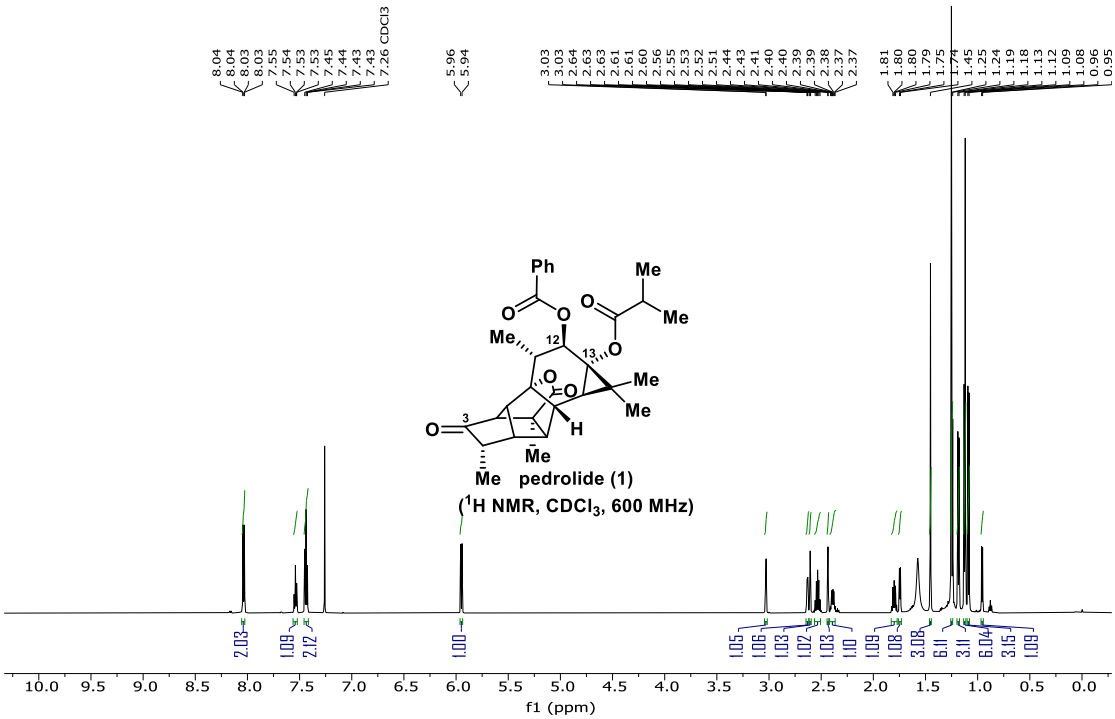

179.4 179.1 138.2 128.6 127.8 127.7 89.0 88.3 81.5 77.4 77.2 CDCl3 77.0 70.8 62.7 58.4 55.7 51.1 50.3 46.6 44.7 42.0 41.5 34.3 28.9 28.6 22.2 19.2 19.0 17.7 16.2 16.1 14.7
Me Me
O
O
Me
12
13 OH
O
O
Me
Me
BnO
H
Me
Me
23
(13C NMR, CDCl3, 151 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

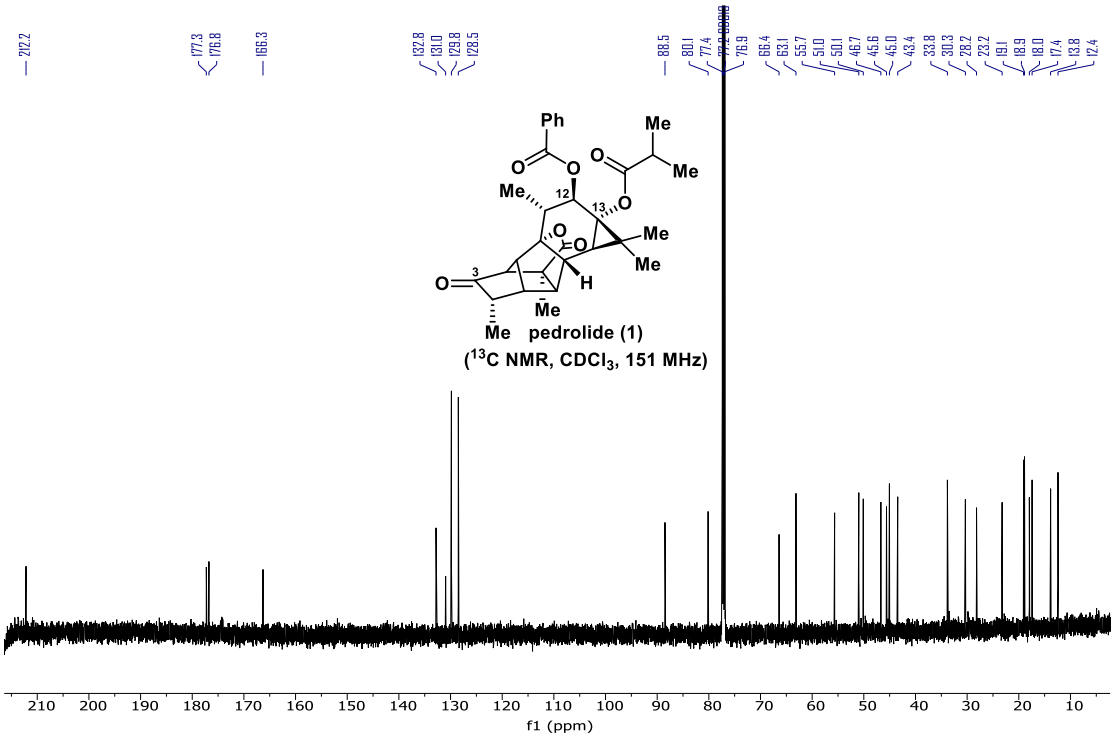

24
(^{1}H NMR, CDCl$_3$, 600 MHz)
f1 (ppm)

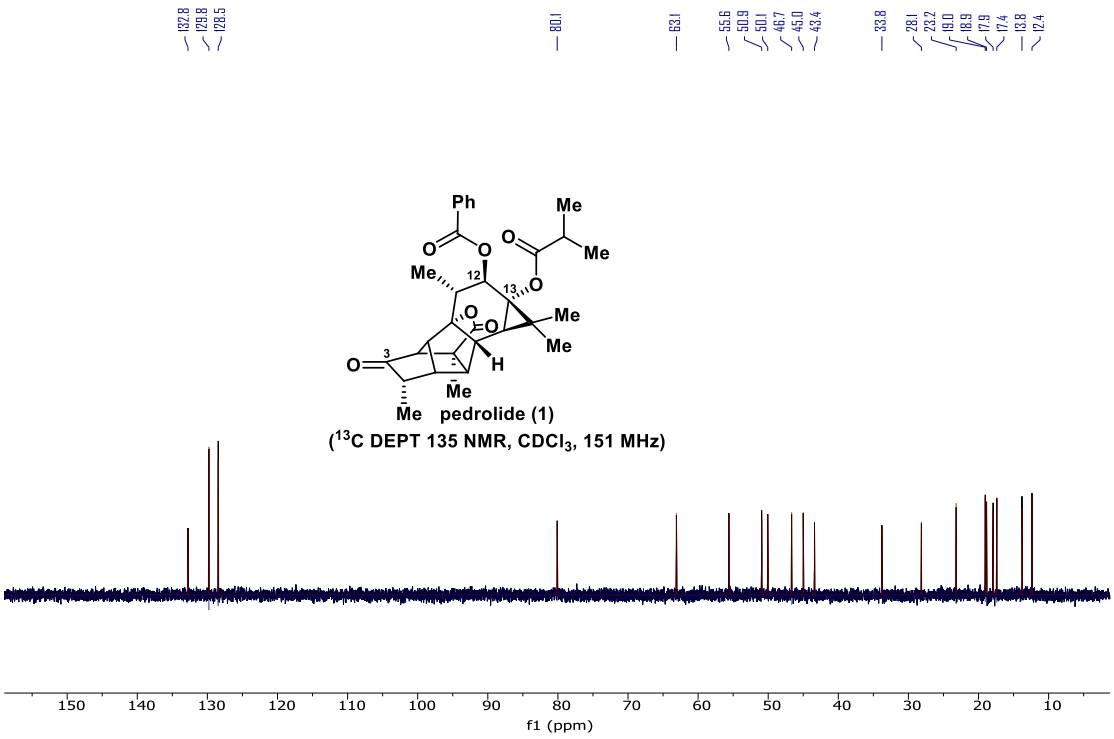

24
(^{13}C NMR, CDCl$_3$, 151 MHz)
f1 (ppm)

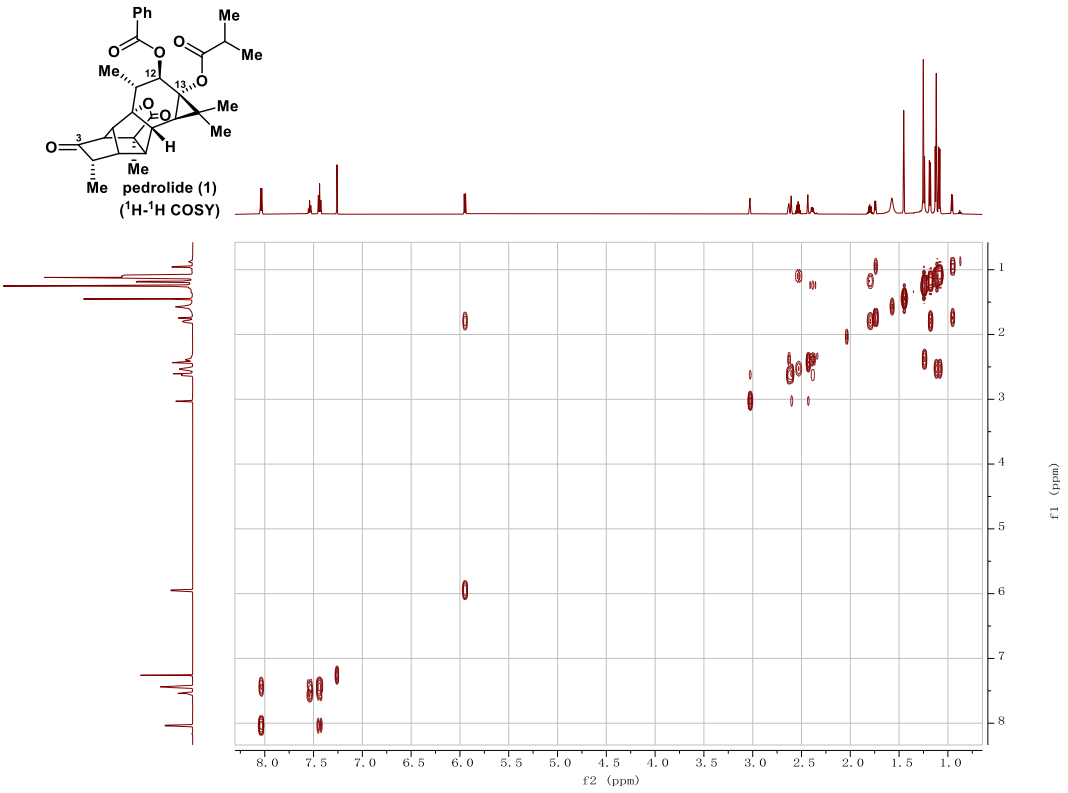

Ph
Me
O
O
O
O
Me
Me
12
13
O
Me
O
O
Me
BnO
H
Me
Me
Me
25
(1H NMR, CDCl3, 600 MHz)
f1 (ppm)

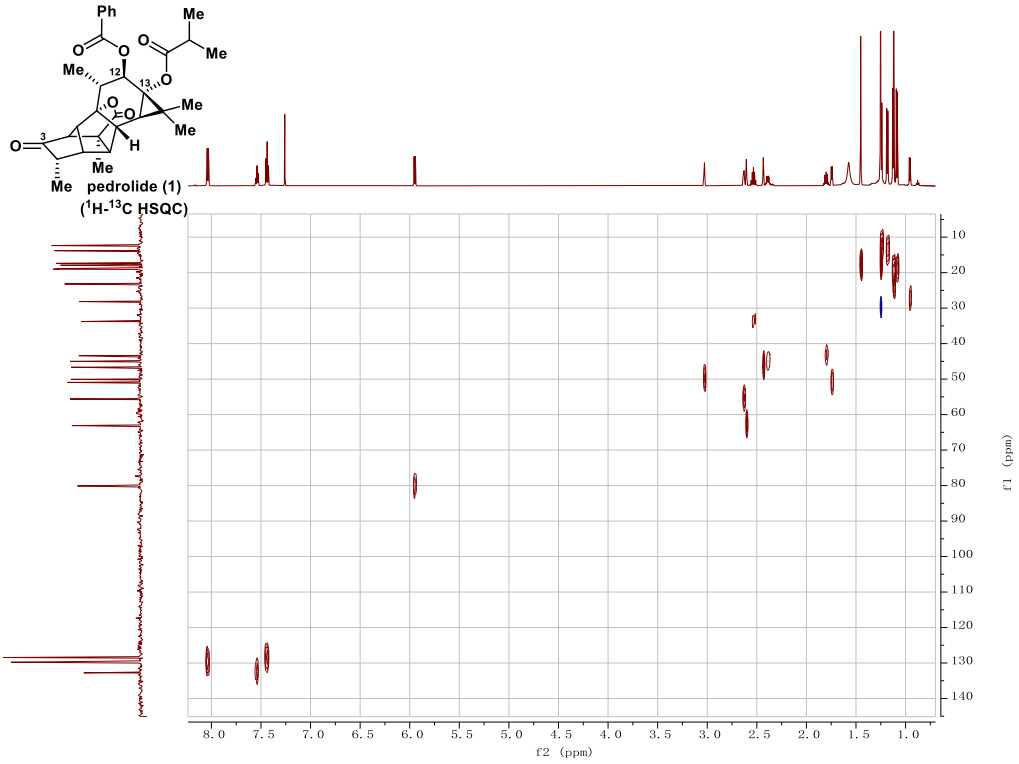

Ph
Me
O
O
O
O
Me
Me
12
13
O
Me
O
O
Me
BnO
H
Me
Me
Me
25
(13C NMR, CDCl3, 151 MHz)
f1 (ppm)

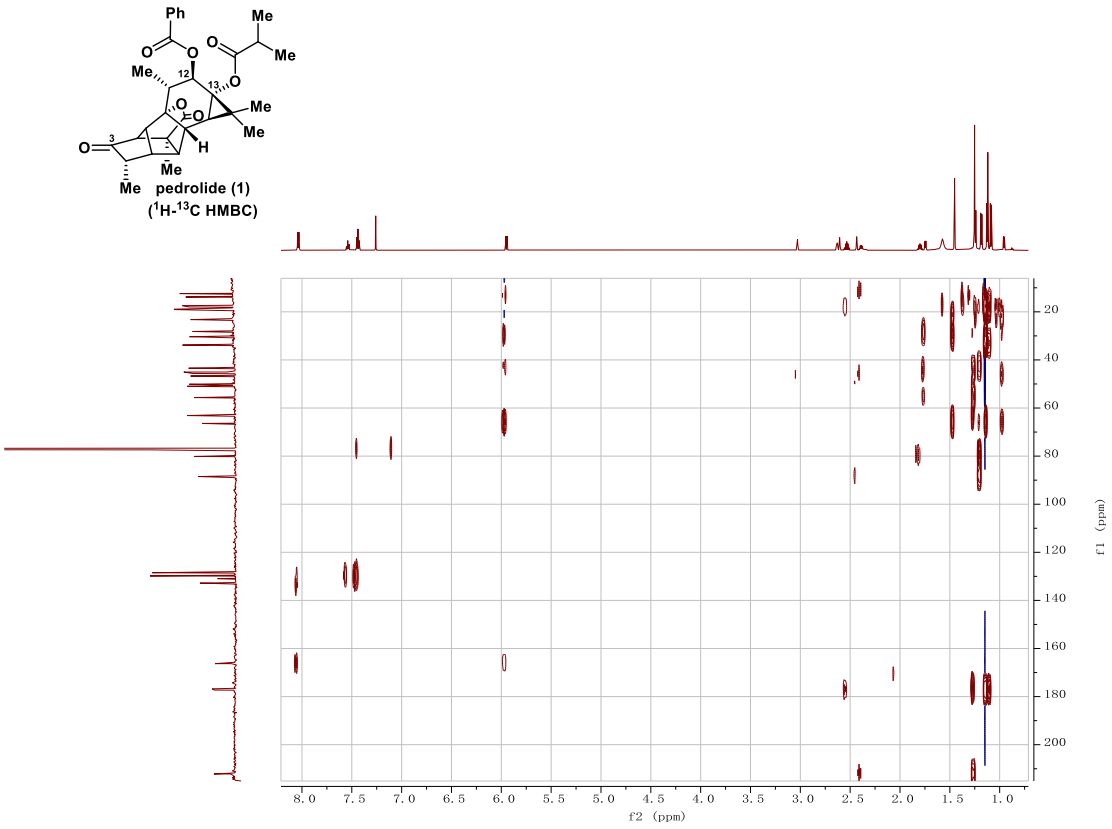

Ph
Me
Me
Me
12
13
Me
Me
Me
3
H
Me
Me
pedrolide (1)
(1H NMR, CDCl3, 600 MHz)
f1 (ppm)


Ph
Me
Me
Me
12
13
Me
Me
Me
3
H
Me
Me
pedrolide (1)
(13C NMR, CDCl3, 151 MHz)
f1 (ppm)


132.8
129.8
128.5
80.1
63.1
55.6
50.9
50.1
46.7
45.0
43.4
33.8
28.1
23.2
19.0
18.9
17.9
17.4
13.8
12.4
Ph
Me
Me
Me
Me
Me
Me
Me
H
Me
Me
pedrolide (1)
(13C DEPT 135 NMR, CDCl3, 151 MHz)
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Ph
Me
Me
Me
Me
Me
Me
Me
H
Me
Me
pedrolide (1)
(1H-1H COSY)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
f1 (ppm)


pedrolide (1)
(1H-13C HSQC)
f2 (ppm)
f1 (ppm)


pedrolide (1)
(1H-13C HMBC)
f2 (ppm)
f1 (ppm)

7. X-Ray Crystal Structures of Compounds 2a, 5 and 13

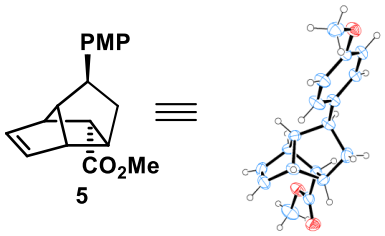


Table S10. Crystal data and structure refinement for **5**.

CCDC number	2312891
Identification code	cxy5524_0m
Empirical formula	$C_{18}H_{20}O_3$
Formula weight	284.34
Temperature/K	200.0(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	9.4282(6)
b/Å	6.3421(3)
c/Å	13.3149(7)
α/°	90
β/°	109.689(3)
γ/°	90
Volume/Å^3	749.61(7)
Z	2
ρ_{calc}g/cm^3	1.260
μ/mm^{-1}	0.432
F(000)	304.0
Crystal size/mm^3	0.21 × 0.19 × 0.18
Radiation	GaKα (λ = 1.34138)
2Θ range for data collection/°	6.134 to 141.09
Index ranges	-13 ≤ h ≤ 13, -8 ≤ k ≤ 8, -18 ≤ l ≤ 18
Reflections collected	53882
Independent reflections	4273 [R_{int} = 0.1131, R_{sigma} = 0.0468]
Data/restraints/parameters	4273/1/192
Goodness-of-fit on F^2	1.060
Final R indexes [I>=2σ (I)]	R_1 = 0.0383, wR_2 = 0.1050
Final R indexes [all data]	R_1 = 0.0437, wR_2 = 0.1068
Largest diff. peak/hole / e Å^{-3}	0.14/-0.18
Flack parameter	0.09(9)

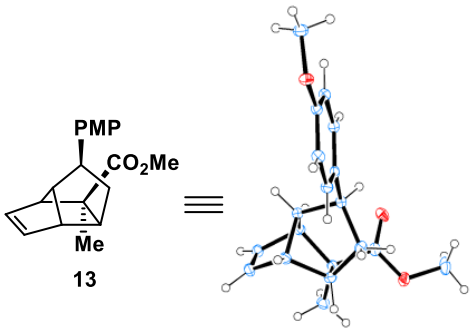
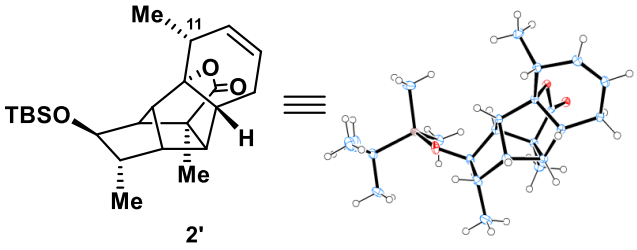


Table S11. Crystal data and structure refinement for **13**.

CCDC number	2312894
Identification code	cxy5522_0m
Empirical formula	$C_{19}H_{22}O_3$
Formula weight	298.36
Temperature/K	100.0(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	6.5200(7)
b/Å	7.9327(7)
c/Å	15.0083(16)
α/°	90
β/°	96.384(6)
γ/°	90
Volume/Å^3	771.43(14)
Z	2
ρ_{calc}g/cm^3	1.284
μ/mm^{-1}	0.435
F(000)	320.0
Crystal size/mm^3	0.25 × 0.18 × 0.14
Radiation	GaKα (λ = 1.34138)
2Θ range for data collection/°	5.154 to 114.308
Index ranges	$-8 \le h \le 8$, $-9 \le k \le 9$, $-18 \le l \le 18$
Reflections collected	26984
Independent reflections	3136 [R_{int} = 0.0496, R_{sigma} = 0.0262]
Data/restraints/parameters	3136/1/202
Goodness-of-fit on F^2	1.056
Final R indexes [I>=2σ (I)]	R_1 = 0.0286, wR_2 = 0.0714
Final R indexes [all data]	R_1 = 0.0293, wR_2 = 0.0721
Largest diff. peak/hole / e Å^{-3}	0.18/-0.19
Flack parameter	0.02(7)



2'

Table S12. Crystal data and structure refinement for **2'**.

CCDC number	2312696
Identification code	cxy5399_0m
Empirical formula	$C_{23}H_{36}O_3Si$
Formula weight	388.61
Temperature/K	100.0(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	7.3823(9)
b/Å	10.3885(13)
c/Å	14.5691(18)
α/°	90
β/°	94.278(3)
γ/°	90
Volume/Å^3	1114.2(2)
Z	2
ρ_{calc}g/cm^3	1.158
μ/mm^{-1}	0.693
F(000)	424.0
Crystal size/mm^3	0.21 × 0.18 × 0.16
Radiation	GaKα (λ = 1.34138)
2Θ range for data collection/°	9.104 to 126.704
Index ranges	-9 ≤ h ≤ 9, -13 ≤ k ≤ 13, -19 ≤ l ≤ 19
Reflections collected	29676
Independent reflections	5464 [R_{int} = 0.0512, R_{sigma} = 0.0379]
Data/restraints/parameters	5464/1/253
Goodness-of-fit on F^2	1.028
Final R indexes [I>=2σ (I)]	R_1 = 0.0498, wR_2 = 0.1276
Final R indexes [all data]	R_1 = 0.0501, wR_2 = 0.1282
Largest diff. peak/hole / e Å^{-3}	0.42/-0.25
Flack parameter	0.00(4)

8. References

1. Fadel, M.; Carreira, E. M. Enantioselective Total Synthesis of (+)-Pedrolide. *J. Am. Chem. Soc.* **2023**, *145*, 8332-8337.

2. Gotoh, H.; Uchimaru, T.; Hayashi, Y. Two Reaction Mechanisms via Iminium Ion Intermediates: The Different Reactivities of Diphenylprolinol Silyl Ether and Trifluoromethyl-Substituted Diarylprolinol Silyl Ether. *Chem. Eur. J.* **2015**, *21*, 12337-12346.

3. Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. Diastereoselective Allylation and Crotylation Reactions of Aldehydes with Potassium Allyl- and Crotyltrifluoroborates under Lewis Acid Catalysis. *Synthesis* **2000**, *2000*, 990-998.

4. Maimone, T. J.; Shi, J.; Ashida, S.; Baran, P. S. Total Synthesis of Vinigrol. *J. Am. Chem. Soc.* **2009**, *131*, 17066-17067.