Supporting Information Appendix

Unified Strategy to Prostaglandins: Chemoenzymatic Total Synthesis of Cloprostenol, Bimatoprost, $PGF_{2\alpha}$, Fluprostenol, and Travoprost Guided by Biocatalytic Retrosynthesis

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Chemical General

MeCN was freshly distilled from CaH_2 under N_2. THF was freshly distilled from Na under N_2 using benzophenone as the indicator. Unless otherwise specified, all reagents and solvents were purchased from commercial sources and used as received. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ using tetramethyl silane (TMS) as internal standards. Coupling constant (*J*) values are given in Hz. Multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. Melting points were measured on MP450 full-automatic melting-point apparatus. Products were purified by flash column chromatography on silica gel purchased from Qingdao Haiyang Chemical Co., Ltd. Optical rotations were measured by a Rudolph AUTOPOL I Automatic Polarimeter. EI-MS were recorded on an Agilent 6890N/5975 spectrometer and ESI-MS were recorded on a Waters Micromass Quattro Micro spectrometer. HRMS(ESI) were recorded on a Bruker micrOTOF spectrometer. HPLC analysis were performed with SFC (Agilent 1260 Infinity II) using Daicel Chiralpak IA column (25 cm × 4.6 mm × 5 μm), Chiralpak IF-3 column (25 cm × 4.6 mm × 5 μm), Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm) and Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm).

Molecular Biology

Reagents

Chemically competent cells of *E. coli* DH5α, *E. coli* BL21 (DE3), and *E. coli* Rosetta-gami 2 (DE3) were purchased from Shanghai Weidi Biotechnology (China). Synthetic genes (pET28a-$CHMO_{Rhodo1}$, pET28a-$CHMO_{Arthro}$, pET28a-$CHMO_{Brevi1}$, pET28a-BVMO-MO14, pET28a-*Ch*KRED20, pET28a-BYueD) were purchased from Genewiz (China) (Table S1). The rest of the enzymes in Table S1 were prepared as we previously described.[1-3] All other reagents were purchased from Sangon Biotech (China) unless otherwise specified. LB medium contained yeast extract (5 g/L), tryptone (10 g/L), NaCl (10 g/L). Antibiotics were used at the following concentration: kanamycin: 50 μg/mL.

Enzymology

Reagents

Nickel(II)-nitrilotriacetic acid (Ni-NTA) agarose was purchased from Sangon. Amicon ultracentrifugal filters were purchased from EMB Millipore. PD-10 desalting columns were purchased from GE Healthcare. Isopropylthio-β-D-galactoside (IPTG) was obtained from Sangon. Lysis buffer consisted of 50 mM NaPi, 300 mM NaCl, 10 mM imidazole, 10% glycerol, pH 7.5. Wash buffer consisted of 50 mM NaPi, 300 mM NaCl, 20 mM imidazole, 10% glycerol, pH 7.5. Elution buffer consisted of 50 mM NaPi, 300 mM NaCl, 250 mM imidazole, 10% glycerol, pH 7.5. Storage buffer consisted of 50 mM NaPi, 300 mM NaCl, 10% glycerol, pH 7.5.

Expression and purification of His_6-tagged recombinant proteins

An approximately 12 h culture of *E. coli* BL21 (DE3) cells or *E. coli* Rosetta-gami 2 (DE3) (for BVMO-MO14) freshly transformed with the appropriate plasmid and grown in LB medium supplemented with kanamycin (50 μg/mL) was diluted 1 : 100 into 0.5 L of the same medium

in a 2 L flask. The culture was shaken at 37 ℃ until the optical density at 600 nm reached 0.6-0.8, then the flask was placed in an ice/water bath for ca. 30 min before the addition of isopropylthio-β-D-galactoside (IPTG) to a final concentration of 100 μM or 1 mM (for BVMO-MO14). The culture was shaken for an additional 16-18 h at 18 ℃ or 16 ℃ (for BVMO-MO14).

All the following purification steps were carried out at 4 ℃. The cells (1.5-2 g wet mass from 0.5 L culture) were collected by centrifugation, and then resuspended in 20 mL of lysis buffer. The cells were lysed by sonication on ice and debris was removed by centrifugation at 13500 rpm for 30 min at 4 ℃. The supernatant was loaded onto a column containing 2-3 mL of Ni-NTA resin previously equilibrated with lysis buffer. After equilibration of the resin with the lysate in an orbital shaker for ca. 30 min, the flow-through was discarded and the resin was washed with 2 × 20 mL of wash buffer. Resin-bound protein was eluted with elution buffer. Fractions of 1 mL were collected and the absorbance at 280 nm was measured by a NanoDrop One spectrophotometer. Fractions with strong absorbance at 280 nm were pooled and concentrated in an Amicon Ultra centrifugal filter unit with 10 kDa molecular weight cut off (MWCO) to a final volume of 2.5 mL, which was used for enzymatic reaction derectly without further purification. The protein concentrations were measured by a NanoDrop One spectrophotometer with calculated extinction coefficient and molecular weight.

Table S1. The details of genes used in this study.

Name	Accession No.	Source	aa
$CHMO_{Rhodo1}$	AAN37494.1	*Rhodococcus sp.* Phi1	541
$CHMO_{Arthro}$	AAN37479.1	*Arthrobacter sp.* BP2	591
$CHMO_{Brevi1}$	AAG01289.1	*Brevibacterium sp.* HCU	553
BVMO-MO14	WP_011596069.1	*Rhodococcus jostii*	547
TdADH	XP_003678559.1	*Torulaspora delbrueckii*	342
YDR368w	NP_010656	*Saccharomyces cerevisiae*	312
CgCR	XP_447302.1	*Candida glabrata*	310
YNL331c	NP_014068.1	*Saccharomyces cerevisiae*	376
YOL151w	NP_014490.1	*Saccharomyces cerevisiae*	342
YDL124w	NP_010159.1	*Saccharomyces cerevisiae*	312
RasADH	EU485985	*Ralstonia sp.* DSMZ 6428	250
KmCR2	XP_022675166.1	*Kluyveromyces marxianus CBS4857*	341
LtCR	XP_002554048.1	*Lachancea thermotolerans*	281
LbADH	CAD66648.1	*Lactobacillus brevis*	252
SyADH	EU427523.1	*Sphingobium yanoikuyae*	263
KRED-F42	WP_023468191.1	*Exiguobacterium sp.* MH3	249
CaADH	WP_010890687.1	*Clostridium acetobutylicum*	251
*Ch*KRED20	AHC30841.1	*Chryseobacterium sp.* CA49	244
BYueD	WP_134982026.1	*Bacillus subtilis*	243

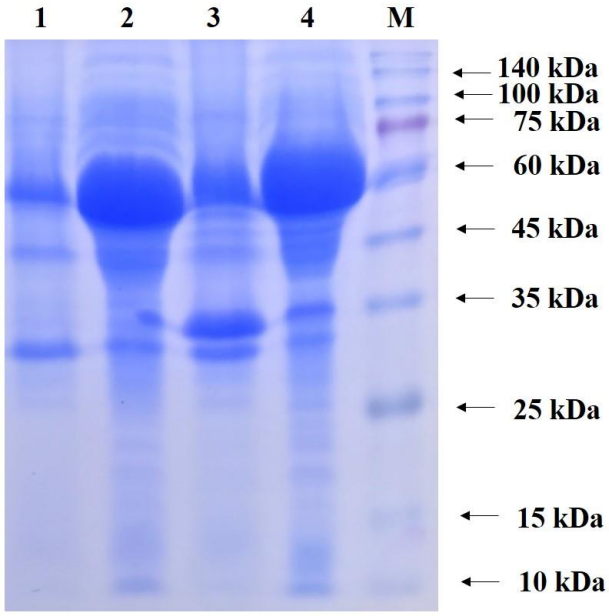


Figure S1. SDS-PAGE analysis of $CHMO_{Brevi1}$ and $CHMO_{Rhodo1}$. Coomassie staining. M: RealBand 3-color Regular Range Protein Marker **(**Sangon Biotech, China). Lane 1: insoluble cell fraction of $CHMO_{Brevi1}$; Lane 2: soluble cell fraction of $CHMO_{Brevi1}$; Lane 3: insoluble cell fraction of $CHMO_{Rhodo1}$; Lane 4: soluble cell fraction of $CHMO_{Rhodo1}$.

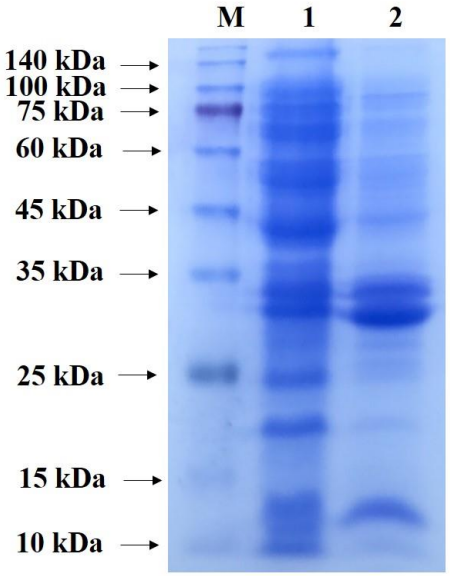


Figure S2. SDS-PAGE analysis of BVMO-MO14. Coomassie staining. M: RealBand 3-color Regular Range Protein Marker **(**Sangon Biotech, China). Lane 1: soluble cell fraction of BVMO-MO14; Lane 2: insoluble cell fraction of BVMO-MO14.

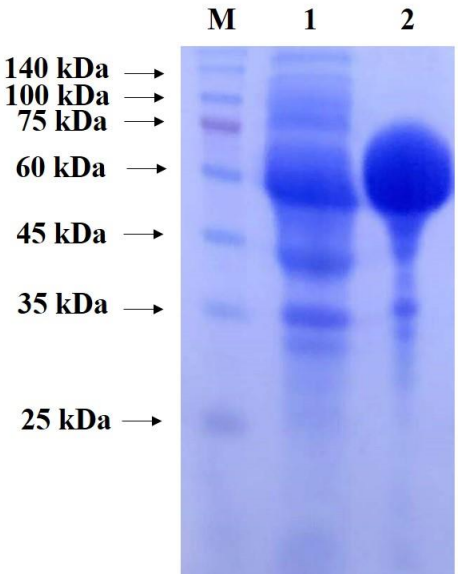


Figure S3. SDS-PAGE analysis of $CHMO_{Arthro}$. Coomassie staining. M: RealBand 3-color Regular Range Protein Marker **(**Sangon Biotech, China). Lane 1: soluble cell fraction of $CHMO_{Arthro}$; Lane 2: insoluble cell fraction of $CHMO_{Arthro}$.

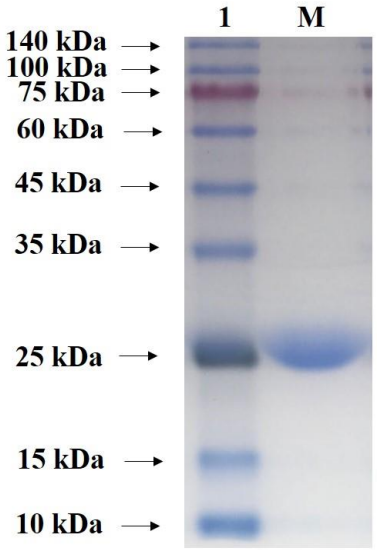
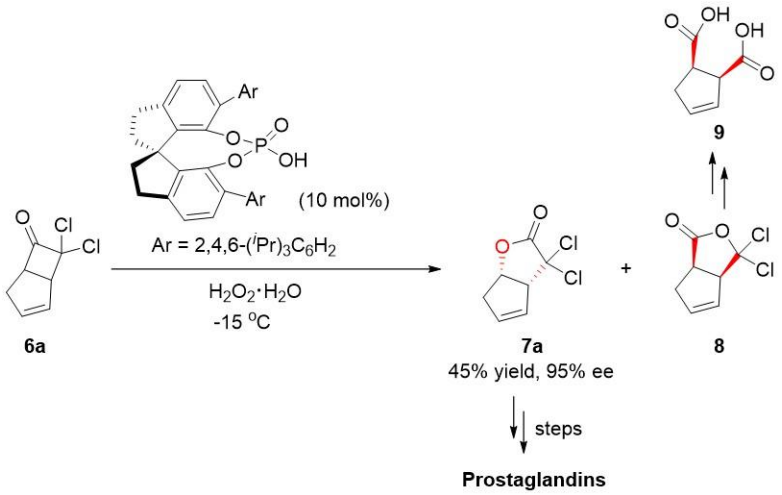
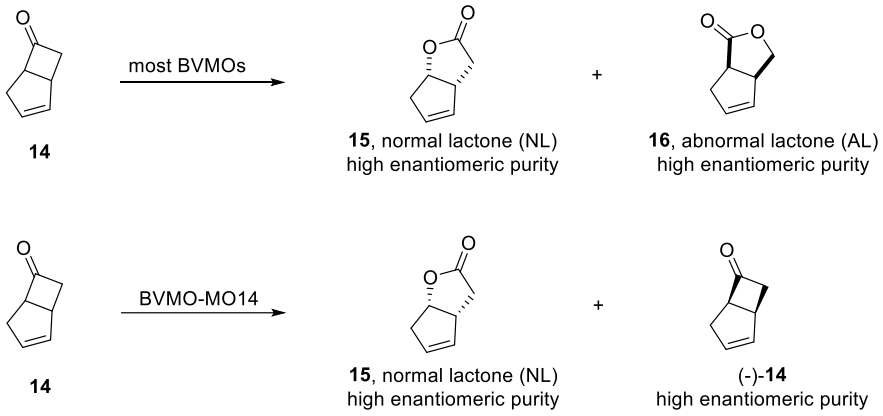


Figure S4. SDS-PAGE analysis of His_6-*Ch*KRED20 after IMAC purification. Coomassie staining. M: RealBand 3-color Regular Range Protein Marker **(**Sangon Biotech, China). Lane 1: His_6-*Ch*KRED20.

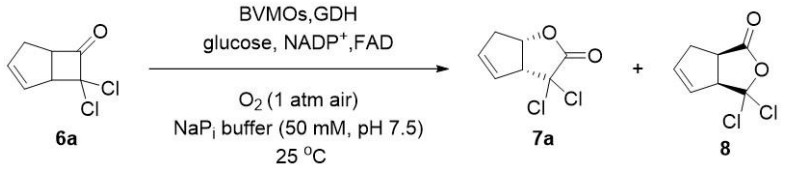


Scheme S1. New synthetic route to prostaglandins recently developed by our group, featuring a chiral spiro-phosphoric acid-catalyzed B-V oxidation.



Scheme S2. BVMO-catalyzed oxidation of bicyclo[3.2.0]hept-2-en-6-one (14).

Table S2. Screening BVMOs for the stereoselective oxidation of bicyclic ketone 6a[a]



Entry	Enzyme	**6a** remained (%)[b]	Yield of **7a** (%)[b]	Ee of **7a** (%)[c]
1	$CHMO_{Arthro}$	11	5	N.D.[d]
2	$CHMO_{Brevi1}$	31	2	N.D.
3	BVMO-MO14	43	0	N.D.
4	$CHMO_{Rhodo1}$	0	25	99

[a] Reaction conditions (1 mL): **6a** (10 mM), glucose (60 mM), $NADP^+$ (0.2 mM), FAD (0.05 mM), 0.89 mL of 20% (w/v) cell-free extract (CFE) of $CHMO_{Rhodo1}$ in NaP_i buffer (50 mM, pH 7.5), 0.016 mL of 15% (w/v) CFE of glucose dehydrogenase (GDH) in NaP_i buffer (50 mM, pH 7.0). Reaction mixtures were incubated at 25 ℃ with 200 rpm shaking for 90 min. [b] Determined by GC analysis using undecane as the internal standard. [c] Determined by SFC analysis. [d] Not Determined (N.D.).

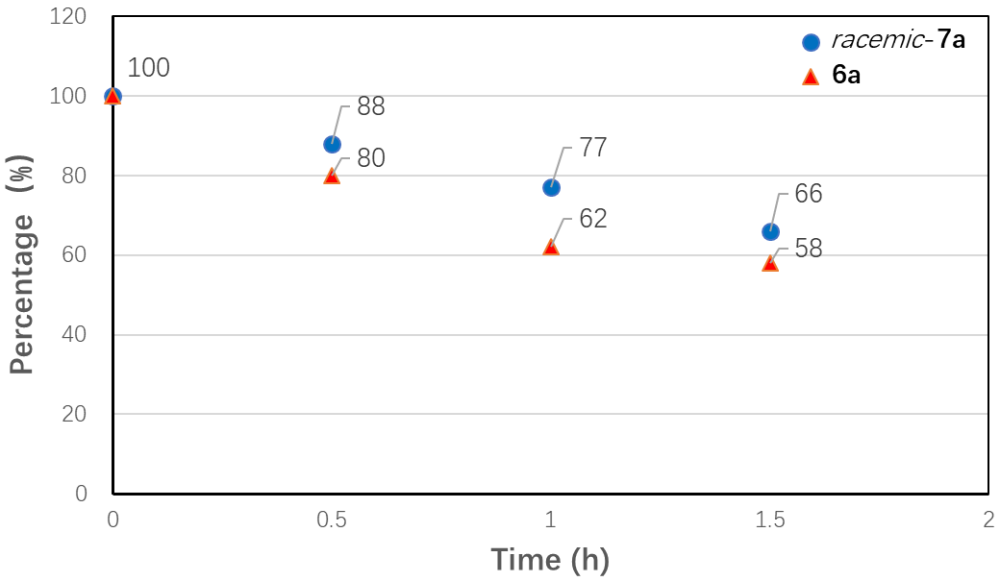


Figure S5: Investigation of the stability of ketone 6a and lactone *racemic*-7a in the absence of enzyme. Reaction conditions (0.2 mL): **6a** or **7a** (10 mM), 2 µL DMSO (1%, v/v) in NaP_i buffer (50 mM, pH 7.5). Reaction mixtures were incubated at 25 °C with 200 rpm shaking. The amount of the remaining **6a** or *racemic*-**7a** was determined by GC analysis using undecane as the internal standard.

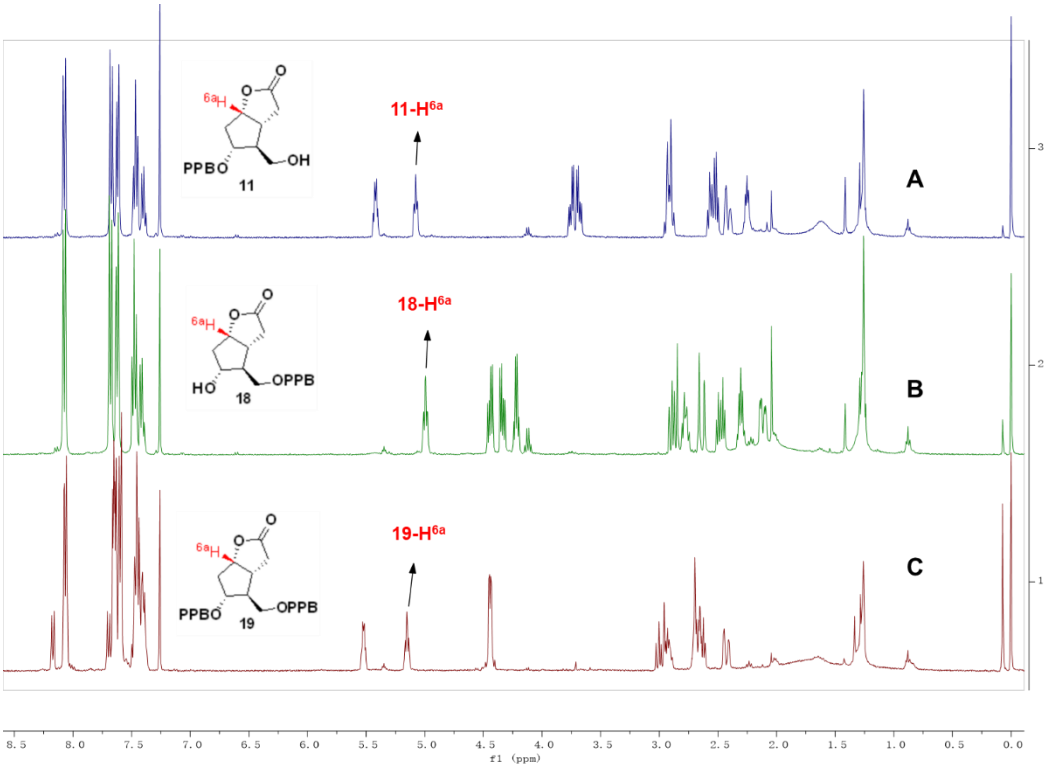


Figure S6: ^{1}H NMR spectra analysis of the products from *p*-phenylbenzoylation of diol 10. Panel A: ^{1}H NMR spectrum of purified **11**; Panel B: ^{1}H NMR spectrum of purified **18**; Panel C: ^{1}H NMR spectrum of purified **19**.

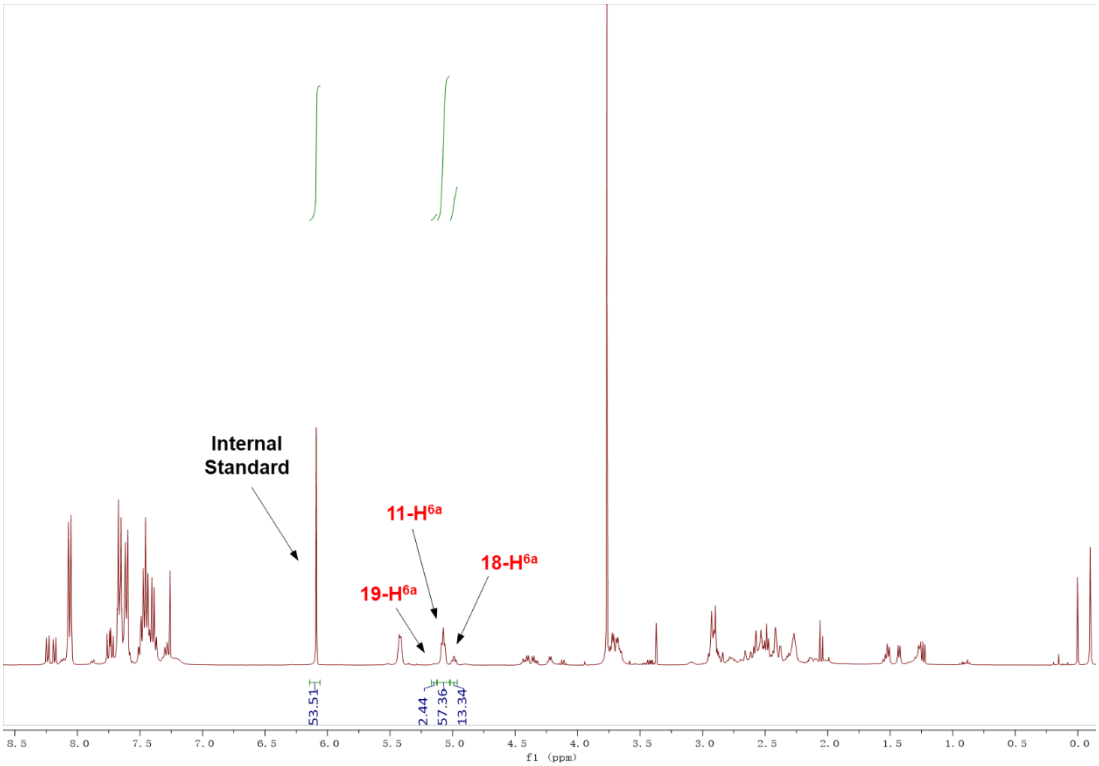
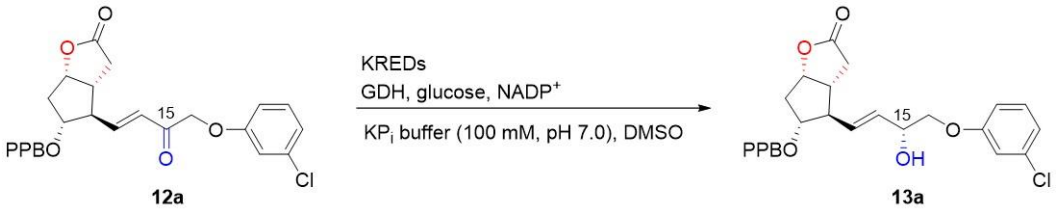


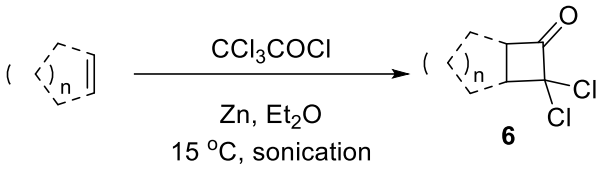
Figure S7. ^{1}H NMR spectrum of the reaction mixture of "Entry 7, Table 2" in the main text. 1, 3, 5 - trimethoxybenzene was used as the internal standard.

Table S3. Screening KREDs for the stereoselective reduction of 12a[a]



Entry	Enzyme	Conv. (%)[b]	dr (C-15, α : β)[b]
1	TdADH	0	N.A.[c]
2	CgCR	0	N.A.
3	YOL151w	4	>99 : 1
4	LtCR	0	N.A.
5	LbADH	0	N.A.
6	KmCR2	28	44 : 56
7	CaADH	0	N.A.
8	*Ch*KRED20	43	97.8 : 2.2
9	YNL331c	32	87 : 13
10	BYueD	0	N.A.
11	YDR368w	0	N.A.
12	YDL124w	0	N.A.
13	SyADH	23	>99 : 1
14	RasADH	0	N.A.
15	KRED-F42	0	N.A.

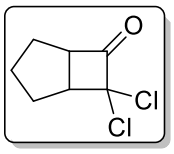
[a] Reaction conditions (0.5 mL): **12a** (10 mM), glucose (20 mM), $NADP^+$ (0.2 mM), KRED (1 mg/mL), 0.1 mL of 15% (w/v) cell-free extract (CFE) of GDH, and DMSO (v/v, 3%) in KP_i buffer (100 mM, pH 7.0). Reaction mixtures were incubated at 30 ℃ with 200 rpm shaking for 17 h. [b] Determined by SFC analysis. [c] Not Applicable (N.A.).



Scheme S3. General procedure A for the synthesis of bicyclic ketones 6.[4]

This is a modified literature procedure.[4] To a mixture of zinc (2 equiv.), cycloalkene (1 equiv.) in anhydrous ether (0.4 M) placed in a sonication bath maintained at 15-20 ℃ was added over a 90 min period a solution of trichloroacetyl chloride (1.44 equiv.) in anhydrous ether (1.15 M). Sonication of the reaction mixture at 15 ℃ continued for another 6.5 h. The mixture was quenched with wet ether and filtered through a sintered glass funnel. The zinc was rinsed with wet ether, and the total filtrate was washed with water (2 x 20 mL), aq. $NaHCO_3$ (5 x 20 mL), and brine (20 mL), dried over Na_2SO_4, filtered, concentrated and purified by silica gel column chromatography (PE) to give the bicyclic ketones **6**.

7,7-Dichlorobicyclo[3.2.0]heptan-6-one (6b)



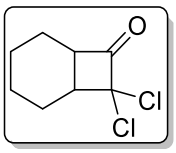
Cyclopentene (3.4 g, 50 mmol) was followed by general procedure A to give the target product **6b** in 79% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (t, *J* = 7.8 Hz, 1H), 3.38 (t, *J* = 8.2 Hz, 1H), 2.38-2.23 (m, 1H), 2.20 (dd, *J* = 12.5, 6.1 Hz, 1H), 1.92-1.75 (m, 2H), 1.68-1.58 (m, 1H), 1.58-1.47 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 88.7, 62.3, 52.6, 30.6, 30.2, 25.9.

HRMS(ESI): Calcd for $C_7H_8Cl_2NaO$ $[M+Na]^+$ 200.9844, found 200.9841.

8,8-Dichlorobicyclo[4.2.0]octan-7-one (6c)

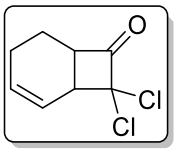


Cyclohexene (4.1 g, 50 mmol) was followed by general procedure A to give the target product **6c** in 76% yield. Spectral data was consistent with literature precedents.[4]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04-3.84 (m, 1H), 3.04-2.89 (m, 1H), 2.22-2.02 (m, 2H), 1.71-1.53 (m, 3H), 1.41-1.28 (m, 1H), 1.23-1.10 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.0, 87.9, 52.8, 43.3, 25.8, 21.7, 21.4, 20.8.

8,8-Dichlorobicyclo[4.2.0]oct-2-en-7-one (6d)

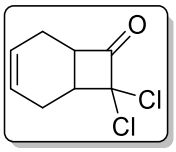


Cyclohexa-1,3-diene (1.0 g, 12.5 mmol) was followed by general procedure A to give the target product **6d** in 79% yield. Spectral data was consistent with literature precedents.[5]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18-6.03 (m, 1H), 5.97-5.79 (m, 1H), 4.26-4.02 (m, 1H), 3.52-3.36 (m, 1H), 2.20-1.92 (m, 3H), 1.71-1.60 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.9, 132.5, 123.1, 86.7, 53.4, 44.3, 20.9, 18.8.

8,8-Dichlorobicyclo[4.2. 0]oct-3-en-7-one (6e)

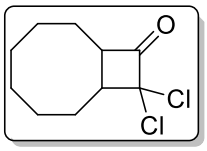


Cyclohexa-1,4-diene (1.0 g, 12.5 mmol) was followed by general procedure A to give the target product **6e** in 39% yield. Spectral data was consistent with literature precedents.[6]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95-5.70 (m, 2H), 4.03 (ddd, *J* = 10.8, 7.1, 2.4 Hz, 1H), 3.32 (ddd, *J* = 10.5, 8.0, 2.2 Hz, 1H), 2.66-2.41 (m, 2H), 2.41-2.27 (m, 1H), 2.16-2.07 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6, 127.4, 126.5, 88.6, 53.9, 45.3, 23.2, 21.4.

10,10-Dichlorobicyclo[6.2.0]decan-9-one (6f)

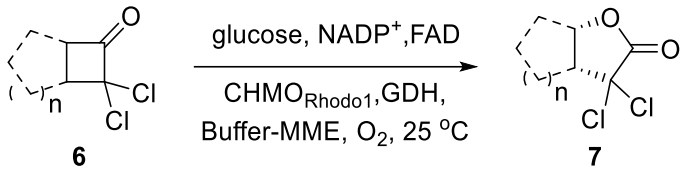


Cyclooctene (3.3 g, 30 mmol) was followed by general procedure A to give the target product **6f** in 68% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (td, *J* = 12.1, 2.2 Hz, 1H), 2.91 (td, *J* = 12.6, 11.0, 2.0 Hz, 1H), 2.08-1.90 (m, 2H), 1.84-1.68 (m, 2H), 1.67-1.19 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 88.8, 59.3, 51.0, 29.0, 28.7, 25.7, 25.3, 24.8, 23.3.

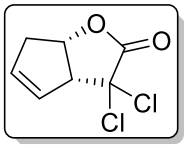
HRMS(ESI): Calcd for $C_{10}H_{14}Cl_2NaO$ $[M+Na]^+$ 243.0314, found 243.0317.



Scheme S4. General procedure B for the synthesis of lactone 7.

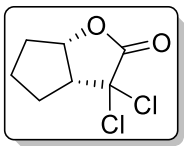
To a slowly stirred solution of $NADP^+$ (0.2 mM, 0.01 mmol), FAD (0.05 mM, 0.0025 mmol), glucose (60 mM, 3 mmol) in water (4.25 mL), 39.45 mL 20% (w/v) CFE of CHMO-Rhodo1 in NaP_i buffer (50 mM, pH 7.5) and 0.8 mL 15% (w/v) CFE of GDH in NaP_i buffer (100 mM, pH 7.0) in 150 mL conical flask was added 5 mL 2-Methoxyethanol (MME), then ketone **6** (1.0 M in DMSO, 0.5 mL, 0.5 mmol) was added to the mixture. The resulting mixture was stirred at 800 rpm under air for 1.5 h. 50 mL Et_2O was added and stirred for 5 min. This mixture was centrifuged for 10 min at 18000 rpm at 4 ℃. The aqueous layer was extracted by Et_2O for another two times. The combined Et_2O layer was then washed with brine and dried over anhydrous Na_2SO_4, filtered and evaporated to give the crude product, which was purified by flash chromatography (hexane : EtOAc = 9 : 1) to give **7**. The ee was determined by SFC analysis.

(3a*R*,6a*S*)-3,3-Dichloro-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (7a)



6a was followed by general procedure B to give the target product in 38% yield with 99% ee.
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10-5.87 (m, 1H), 5.87-5.65 (m, 1H), 5.24 (t, *J* = 4.5 Hz, 1H), 4.22-3.91 (m, 1H), 2.96-2.70 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 133.4, 126.9, 81.1, 79.9, 63.5, 39.4.
$[\alpha]_D^{25}$ = -48.83 (c = 0.18, $CHCl_3$)
[lit.[7]: $[\alpha]_D^{25}$ = +47.97 (c = 0.60, $CHCl_3$, (3a*S*,6a*R*), ee: 99%); $[\alpha]_D^{25}$ = -46.16 (c = 0.60, $CHCl_3$, (3a*R*,6a*S*), ee: 95%)
Chiral SFC (Chiralcel IF-3 column), CO_2 : MeOH = 97/3, Flow rate: 3 mL/min, UV detection at 210 nm, T = 30 ℃, BPR Pressure = 150 bar, BPR Temperature: 60 ℃, retention time: 3.649 min (major), 3.404 min (minor).

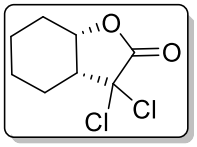
(3a*R*,6a*S*)-3,3-Dichlorohexahydro-2*H*-cyclopenta[*b*]furan-2-one (7b)



6b was followed by general procedure B to give the target product in 30% yield with 99% ee.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (td, *J* = 5.0, 1.4 Hz, 1H), 3.46-3.22 (m, 1H), 2.19-2.08 (m, 1H), 2.08-1.93 (m, 2H), 1.90-1.68 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 84.9, 82.0, 57.7, 32.3, 29.0, 23.9.

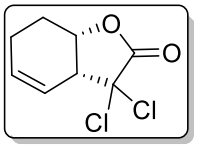
$[\alpha]_D^{25}$ = -58.11 (c = 0.55, $CHCl_3$) [lit.[7]: $[\alpha]_D^{25}$ = +46.12 (c = 0.52, $CHCl_3$, (3a*S*,6a*R*), ee: 90%)]. Chiral SFC (Chiralcel IA column), CO_2 : MeOH = 98/2, Flow rate: 3.0 mL/min, UV detection at 220 nm, T = 30 ℃, BPR Pressure = 150 bar, BPR Temperature: 60 ℃, retention time: 3.615 min (major), 3.249 min (minor).

(3a*R*,7a*S*)-3,3-Dichlorohexahydrobenzofuran-2(3*H*)-one (7c)



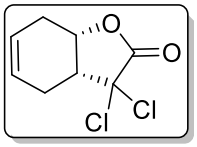
6c was followed by general procedure B to give the target product in 22% yield with 91% ee.
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (d, *J* = 3.4 Hz, 1H), 2.89-2.65 (m, 1H), 2.33 (d, *J* = 15.1 Hz, 1H), 2.08-1.99 (m, 1H), 1.82 (d, *J* = 10.3 Hz, 1H), 1.70-1.57 (m, 2H), 1.38-1.07 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 83.9, 76.7, 50.7, 27.4, 25.5, 23.1, 19.1.
$[\alpha]_D^{25}$ = -13.38 (c = 0.22, $CHCl_3$) [lit.[7]: $[\alpha]_D^{25}$ = +17.52 (c = 0.35, $CHCl_3$, (3a*S*,7a*R*), ee: 99%)]. Chiral SFC (Chiralcel IF-3 column), CO_2 : MeOH = 93/7, Flow rate: 2 mL/min, UV detection at 210 nm, T = 30 ℃, BPR Pressure = 150 bar, BPR Temperature: 60 ℃, retention time: 4.770 min (major), 4.579 min (minor).

(3a*R*,7a*S*)-3,3-Dichloro-3a,6,7,7a-tetrahydrobenzofuran-2(3*H*)-one (7d)



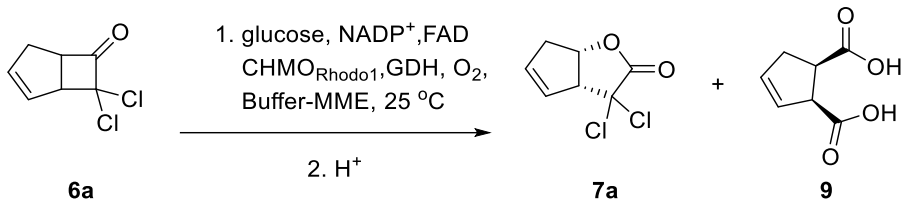
6d was followed by general procedure B to give the target product in 34% yield with 99% ee.
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23-6.00 (m, 1H), 5.70 (d, *J* = 10.0 Hz, 1H), 5.08 (s, 1H), 3.60-3.37 (m, 1H), 2.40-2.25 (m, 1H), 2.25-1.97 (m, 2H), 1.90-1.71 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 132.5, 120.0, 81.6, 76.2, 50.2, 24.2, 19.0.
$[\alpha]_D^{25}$ = -20.13 (c = 0.41, $CHCl_3$) [lit.[7]: $[\alpha]_D^{25}$ = +17.61 (c = 0.42, $CHCl_3$, (3a*S*,7a*R*), ee: 93%)]. Chiral SFC (Chiralcel IA column), CO_2 : MeOH = 90/10, Flow rate: 2 mL/min, UV detection at 210 nm, T =30 ℃, BPR Pressure = 150 bar, BPR Temperature: 60 ℃, retention time: 3.728 min (major), 3.511 min (minor).

(3a*R*,7a*S*)-3,3-Dichloro-3a,4,7,7a-tetrahydrobenzofuran-2(3*H*)-one (7e)



6e was followed by general procedure B to give the target product in 30% yield with 99% ee.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82-5.75 (m, 1H), 5.74-5.61 (m, 1H), 5.11-4.92 (m, 1H), 3.10-2.94 (m, 1H), 2.73-2.59 (m, 1H), 2.59-2.43 (m, 2H), 2.18-2.06 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 123.9, 122.8, 83.0, 75.1, 48.0, 27.0, 23.3.
$[\alpha]_D^{25}$ = -21.38 (c = 0.42, $CHCl_3$)
HRMS (ESI): Calcd for $C_8H_8Cl_2NaO_2$ $[M+Na]^+$ 228.9794, found 228.9788.

Chiral SFC (Chiralcel IA column), CO_2 : MeOH = 97/3, Flow rate: 3 mL/min, UV detection at 210 nm, T =30 ℃, BPR Pressure = 150 bar, BPR Temperature: 60 ℃, retention time: 4.040 min (major), 3.471 min (minor).



6a **7a** **9**

Scheme S5. Synthesis of dicarboxylic acid 9.

To a slowly stirred solution of $NADP^+$ (0.2 mM, 0.01 mmol), FAD (0.05 mM, 0.0025 mmol), glucose (60 mM, 3 mmol) in water (4.25 mL), 39.45 mL 20% (w/v) CFE of CHMO-Rhodo1 in NaP_i buffer (50 mM, pH 7.5) and 0.8 mL 15% (w/v) CFE of GDH in NaP_i buffer (100 mM, pH 7.0) in 150 mL conical flask was added 5 mL MME, then ketone **6a** (1.0 M in DMSO, 0.5 mL, 0.5 mmol) was added to the mixture. The resulting mixture was stirred at 800 rpm under air for 1.5 h. EtOAc (50 mL) was added and stirred for 5 min. This mixture was centrifuged for 10 min at 18000 rpm at 4 ℃. The aqueous layer was acidified by 1 N HCl to pH = 4, and then extracted by EtOAc for another two times. The combined organic layer was then washed with brine and dried with anhydrous Na_2SO_4, filtered and evaporated to give the crude mixture, which was purified by flash chromatography (hexane : EtOAc = 9 : 1) to give **7a** in 38% yield, then eluted by CH_2Cl_2 : MeOH : AcOH = 95 : 5 : 1 to give the dicarboxylic acid **9** in 35% yield.

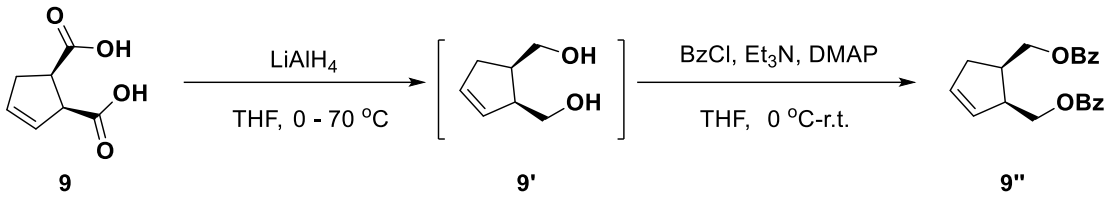
(1*R*,2*S*)-Cyclopent-3-ene-1,2-dicarboxylic acid (9)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 2H), 6.11-5.90 (m, 1H), 5.90-5.61 (m, 1H), 3.84 (d, *J* = 7.2 Hz, 1H), 3.43 (dd, *J* = 18.3, 10.1 Hz, 1H), 2.95-2.83 (m, 1H), 2.68-2.58 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.8, 179.3, 134.0, 127.4, 53.0, 46.0, 34.7.

$[\alpha]_D^{25}$ = +160.96 (c = 0.30, MeOH)

HRMS (ESI): Calcd for $C_7H_7O_4$ $[M-H]^-$ 155.0346, found 155.0350.



9 9' 9''

Scheme S6. Derivatization of dicarboxylic acid 9.

To a stirred suspension of lithium aluminum hydride (40 mg, 1.04 mmol) in dry THF (0.6 mL) was added dropwise a solution of dicarboxylic acid **9** (20 mg, 0.13 mmol) in THF (0.5 mL) at 0 ℃ under N_2 and the reaction mixture was vigorously stirred at 70 ℃ for 3 h. The reaction mixture was cooled to 0 ℃, diluted with EtOAc (3 mL), water (100 μL) was then carefully added. The mixture was stirred for another 20 min, and the resulting suspension was filtered through a pad of Celite, and the amorphous solid was washed several times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude diol product **9'**, which was used in the next step without further purification.

To a stirred solution of diol **9'** in THF (1 mL) was added Et_3N (40 uL, 0.29 mmol) under an ice-bath, then benzoyl chloride (33 μL, 0.29 mmol) was added to the mixture, followed by the addition of 4-dimethylaminopyridine (1.6 mg, 0.013 mmol). The reaction was stirred at room temperature overnight, then water (2 mL) was added, and the aqueous was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated, and then purified by flash chromatography (Hexane : EtOAc = 9 : 1) to give target product **9''** as a colorless oil in 43% yield over 2 steps, and with 82% ee.

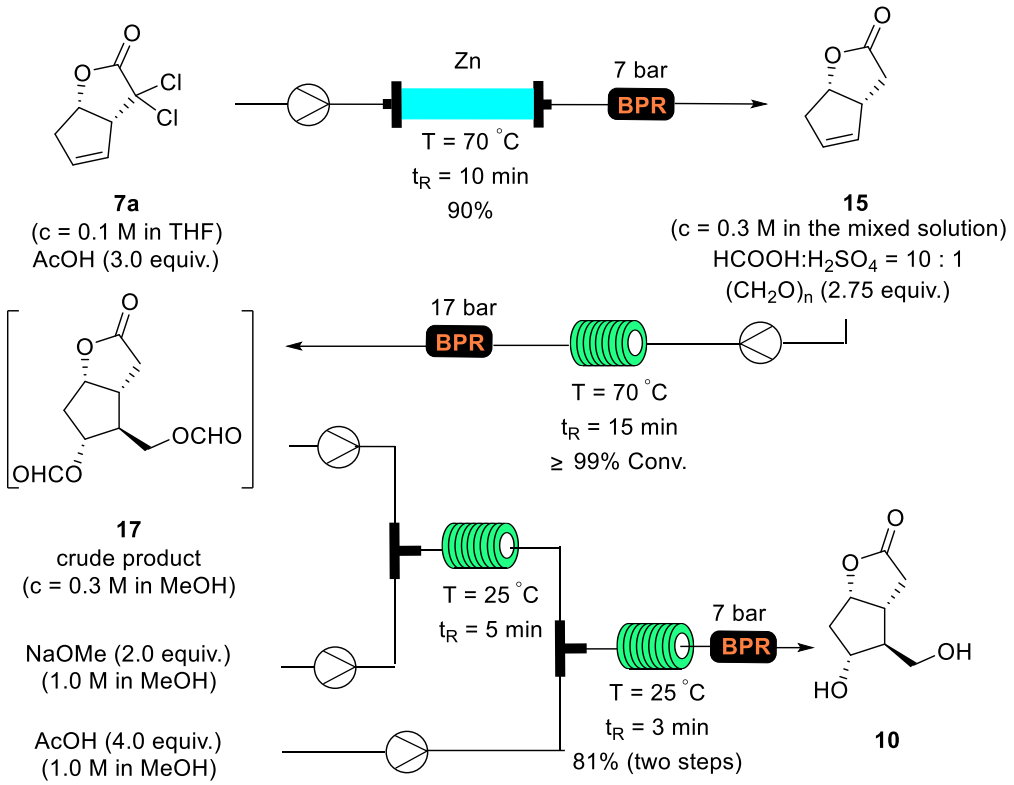
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-7.94 (m, 4H), 7.59-7.50 (m, 2H), 7.46-7.35 (m, 4H), 5.90 (dd, *J* = 5.7, 2.4 Hz, 1H), 5.78 (dd, *J* = 5.7, 2.4 Hz, 1H), 4.54 (d, *J* = 7.4 Hz, 2H), 4.48 (dd, *J* = 11.3, 6.4 Hz, 1H), 4.37 (dd, *J* = 11.3, 5.4 Hz, 1H), 3.36- 3.19 (m, 1H), 2.92 (h, *J* = 7.9 Hz, 1H), 2.57 (dd, *J* = 16.3, 8.4 Hz, 1H), 2.34 (ddd, *J* = 16.4, 8.1, 2.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 166.6, 133.1, 132.1, 131.2, 130.3, 130.2, 129.7, 129.7, 128.5, 65.5, 64.3, 46.0, 39.5, 35.5.

$[\alpha]_D^{25}$ = + 80.93 (c = 0.38, $CHCl_3$) [lit.[7]: $[\alpha]_D^{25}$ = -83.53 (c = 1.01, $CHCl_3$, (1*S*, 2*R*), ee: 91%)]

HRMS: Calcd for $C_{21}H_{20}NaO_4$ $[M+Na]^+$ 359.1254, found 359.1253.

Chiral SFC (Chiralcel IF-3 column), CO_2 : MeOH = 95/5, Flow rate: 2 mL/min, UV detection at 214 nm, T =40 ℃, BPR Pressure = 140 bar, BPR Temperature: 60 ℃, retention time: 15.964 min (major), 15.477 min (minor).



Scheme S7. Synthesis of diol 10 in continuous flow.

The first flow system adopted a packed bed column filled with 8.9 g zinc power with an internal diameter of 1 cm and a length of 15 cm. **7a** (58 mg, 0.3 mmol) in a solution of THF (3 mL) containing AcOH (54 mg, 0.9 mmol) was pumped into the packed bed (flow rate: 0.12 mL/min) at 70 ℃ and 7 bar back-pressure with 10 min residence time. The reaction mixture was collected in a 25 mL output round-bottom flask. The cooled reaction mixture was concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography (PE : EtOAc = 4: 1) to give **15** as a white solid in 90% yield.

(3aR,6aS)-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-2-one (15)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 – 5.70 (m, 1H), 5.66 – 5.47 (m, 1H), 5.24 – 5.03 (m, 1H), 3.58 – 3.36 (m, 1H), 2.84 – 2.66 (m, 3H), 2.44 (d, *J* = 18.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 131.4, 129.9, 83.2, 45.7, 39.7, 33.4.

m.p. = 42.1-42.9 ℃

$[\alpha]_D^{25}$ = -101.83 (c = 0.32, MeOH) (lit.[8]: $[\alpha]_D^{25}$ = -103 (c = 0.8, MeOH), (3a*R*,6a*S*), ee: >98%))

The next flow system consisted of a 0.5 mL piece of PTFE tube with an internal diameter of 0.8 mm (1/16” outer diameter). The $(HCHO)_n$ (149 mg, 1.65 mmol) was stirred in 10 : 1 99% HCOOH /con. H_2SO_4 (2 mL) at room temperature for 4 h to give a clear mixture. Then **15** (75 mg, 0.6 mmol) was dissolved in the above mixture and pumped into the PTFE reactor coil (flow rate: 33.3 μL/min) at 70 ℃ and 17 bar back-pressure with 15 min residence time to afford the crude **17** as major product (a few mono-ester product combined). The reaction mixture was collected in a 25 mL output round-bottom flask. The cooled reaction mixture was neutralized by NaOAc (1.5 g), and then concentrated under reduced pressure to remove the acid. Later on, the residual acid was removed by azeotropy with toluene. After that, EtOAc (15 mL) was added

to the residue and the mixture filtered through celite to remove the inorganic salt, which was washed with EtOAc (3 x 10 mL). The filtrate was concentrated under reduced pressure to give the crude product, which was used directly in the next step without further purification.

The last flow system consisted of two 0.5 mL piece of PTFE tube with an internal diameter of 0.8 mm (1/16" outer diameter). The crude **17** (0.6 mmol) in anhydrous MeOH (2 mL) (flow rate: 62.5 μL/min) combined with NaOMe (1.0 M in MeOH, flow rate: 37.5 μL/min) was pumped into the first 0.5 mL PTFE reactor coil (residence time: 5 min) via a *T*-junction. Then AcOH (1.0 M in MeOH, 75 μL/min) was pumped into the system though the second 0.5 mL PTFE reactor coil (residence time: 3 min) via another *T*-junction to quench the reaction and re-lactonize of some hydrolysate. Both reactions took place at room temperature and 7 bar back-pressure. The reaction mixture was collected in a 25 mL output round-bottom flask. The cooled reaction mixture was concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography (PE : EtOAc = 1 : 3 then EtOAc : MeOH = 9 : 1) to give **10** in 81% yield over two steps as a white solid.

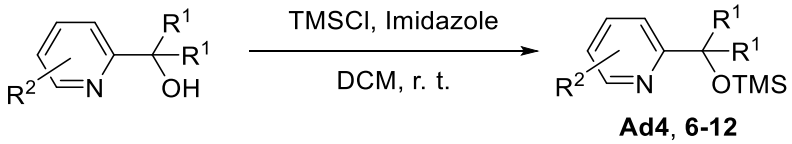
(3*aR*, 4*S*, 5*R*, 6*aS*)-5-Hydroxy-4-(hydroxymethyl)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (10)

^{1}H NMR (400 MHz, Methanol-d_4) δ 4.99 (td, *J* = 7.0, 2.2 Hz, 1H), 4.08 (q, *J* = 5.3 Hz, 1H), 3.57 (dd, *J* = 11.2, 5.9 Hz, 1H), 3.48 (dd, *J* = 11.1, 6.5 Hz, 1H), 2.89 (dd, *J* = 18.1, 10.4 Hz, 1H), 2.79-2.71 (m, 1H), 2.52 (dd, *J* = 18.1 Hz, 1H), 2.31 (dt, *J* = 14.5, 6.3 Hz, 1H), 1.94 (dd, *J* = 12.5, 5.6 Hz, 2H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 180.3, 86.2, 74.9, 63.1, 57.6, 41.3, 41.2, 36.8.

m.p. = 109.5-110.3 ℃

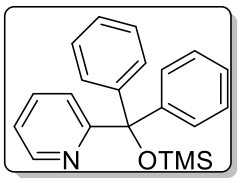
$[\alpha]_D^{25}$ = -43.20 (c = 0.27, MeOH) (lit.[9]: $[\alpha]_D^{20}$ = -43.2 (c = 1.43, MeOH))



Scheme S8. General procedure C for the synthesis of Additive (Ad4, 6-12).

To a solution of pyridine-alkoxide compounds[10-14] in DCM was added imidazole (2.0 eq.), then added dropwise TMSCl (1.5 eq.) at room temperature. After full conversion of starting material, the reaction was quenched by water. The aqueous layer was extracted by DCM (2 x 10 mL), and the combined organic layer was washed with water (2 x 10 mL), and brine (10 mL), dried over Na_2SO_4, filtered and evaporated to give the crude product, which was purified by flash chromatography to give **Additive (Ad4, 6-12)**.

2-(Diphenyl((trimethylsilyl)oxy)methyl)pyridine (Ad4)



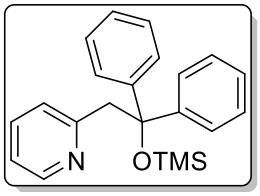
Yield: 0.7 g (70%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61-8.51 (m, 1H), 7.76-7.69 (m, 1H), 7.67-7.60 (m, 1H), 7.43-7.36 (m, 4H), 7.31-7.20 (m, 6H), 7.13-7.07 (m, 1H), -0.12 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 148.5, 146.4, 136.3, 129.0, 127.64 127.2, 121.6, 121.6, 85.0, 2.0.

HRMS (ESI): Calcd for $C_{21}H_{24}NOSi$ $[M+H]^+$ 334.1622, found 334.1631.

2-(2,2-Diphenyl-2-((trimethylsilyl)oxy)ethyl)pyridine (Ad6)



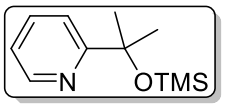
Yield: 0.98 g (94%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38-8.29 (m, 1H), 7.35-7.28 (m, 5H), 7.27-7.16 (m, 6H), 7.02-6.92 (m, 1H), 6.78-6.67 (m, 1H), 3.90 (s, 2H), -0.08 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 148.4, 147.1, 134.9, 127.8, 127.6, 126.9, 124.9, 121.1, 81.0, 50.0, 2.0.

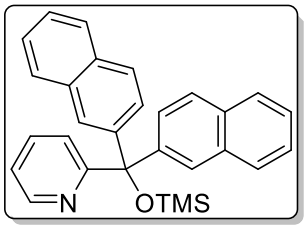
HRMS (ESI): Calcd for $C_{22}H_{28}NOSi$ $[M+H]^+$ 348.1778, found 348.1778.

2-(2-((Trimethylsilyl)oxy)propan-2-yl)pyridine (Ad7)



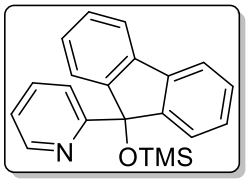
Yield: 0.62 g (85%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81-8.32 (m, 1H), 7.74-7.60 (m, 2H), 7.14-7.08 (m, 1H), 1.62 (s, 6H), 0.14 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 148.2, 136.5, 121.4, 119.4, 77.1, 31.2, 2.5.
HRMS (ESI): Calcd for $C_{11}H_{20}NOSi$ $[M+H]^+$ 210.1309, found 210.1307.

2-(Di(naphthalen-2-yl)((trimethylsilyl)oxy)methyl)pyridine (Ad8)



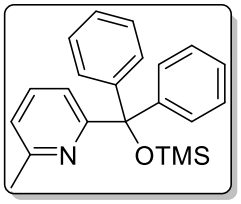
Yield: 0.74 g (85%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67-8.54 (m, 1H), 7.92 (d, 2H), 7.85-7.73 (m, 7H), 7.71-7.64 (m, 1H), 7.60-7.53 (m, 2H), 7.51-7.40 (m, 4H), 7.21-7.09 (m, 1H), -0.08 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 148.5, 143.8, 136.4, 132.9, 132.7, 128.6, 127.7, 127.6, 127.6, 127.3, 126.2, 126.0, 122.0, 121.8, 85.3, 2.2.
HRMS (ESI): Calcd for $C_{29}H_{28}NOSi$ $[M+H]^+$ 434.1935, found 434.1935.

2-(9-((Trimethylsilyl)oxy)-9*H*-fluoren-9-yl)pyridine (Ad9)



Yield: 1.06 g (92%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45-8.23 (m, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.78-7.71 (m, 1H), 7.68 (d, *J* = 7.6 Hz, 2H), 7.40-7.31 (m, 2H), 7.24-7.15 (m, 4H), 7.11-7.03 (m, 1H), -0.27 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 150.1, 149.3, 140.7, 136.6, 129.0, 127.9, 125.3, 121.9, 120.4, 120.2, 86.3, 1.4.
HRMS (ESI): Calcd for $C_{21}H_{22}NOSi$ $[M+H]^+$ 332.1465, found 332.1465.

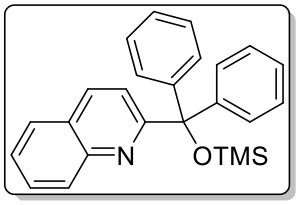
2-(Diphenyl((trimethylsilyl)oxy)methyl)-6-methylpyridine (Ad10)



Yield: 0.67 g (96%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, 1H), 7.38-7.32 (m, 4H), 7.29-7.20 (m, 7H), 6.95 (d, *J* = 7.6 Hz, 1H), 2.47 (s, 3H), -0.10 (s, 9H).

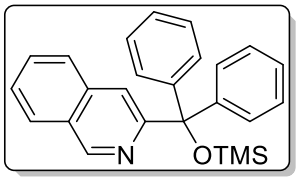
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 157.1, 147.3, 136.1, 129.0, 127.5, 127.0, 121.2, 119.0, 85.0, 24.5, 2.3.
HRMS (ESI): Calcd for $C_{22}H_{26}NOSi$ $[M+H]^+$ 348.1778, found 348.1779.

2-(Diphenyl((trimethylsilyl)oxy)methyl)quinoline (Ad11)

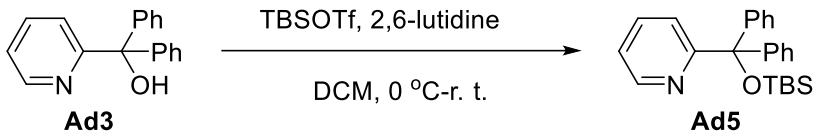


Yield: 265 mg (86%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.04 (m, 2H), 7.84-7.79 (m, 1H), 7.73-7.66 (m, 2H), 7.57-7.51 (m, 1H), 7.51-7.44 (m, 4H), 7.33-7.26 (m, 6H), -0.01 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 147.1, 146.9, 135.8, 129.7, 129.3, 129.1, 127.6, 127.5, 127.2, 126.9, 126.4, 120.5, 85.5, 2.3.
HRMS (ESI): Calcd for $C_{25}H_{26}NOSi$ $[M+H]^+$ 384.1778, found 384.1774.

3-(Diphenyl((trimethylsilyl)oxy)methyl)isoquinoline (Ad12)



Yield: 157 mg (83%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.05 (s, 1H), 7.95-7.86 (m, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.69-7.63 (m, 1H), 7.57-7.51 (m, 1H), 7.49-7.44 (m, 4H), 7.33-7.22 (m, 6H), -0.08 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 151.3, 146.3, 136.1, 130.2, 129.0, 127.5, 127.3, 127.2, 127.1, 127.1, 127.0, 117.5, 84.8, 1.9.
HRMS (ESI): Calcd for $C_{25}H_{26}NOSi$ $[M+H]^+$ 384.1778, found 384.1779.



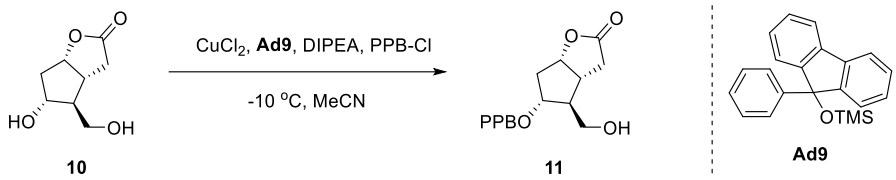
Scheme S9. Synthesis of Additive (Ad5).

To a solution of diphenyl(pyridin-2-yl)methanol[10] (**Ad3**, 134 mg, 0.5 mmol) in DCM (2 mL) was added 2,6-lutidine (107 mg, 1 mmol), then added dropwise TBSOTf (198 mg, 0.75 mmol) at 0℃. After full conversion of starting material, the reaction was quenched by saturated aq. NH_4Cl, and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layer was washed with H_2O, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (PE: EtOAc = 19 : 1 to 9 : 1) gave **Ad5** in 171 mg (91%) yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.6 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.69-7.59 (m, 1H), 7.45-7.38 (m, 4H), 7.37-7.18 (m, 6H), 7.13-7.06 (m, 1H), 1.04 (s, 9H), -0.41 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 148.4, 146.4, 136.2, 129.2, 127.6, 127.2, 121.9, 121.6, 84.9, 26.7, 19.3, -3.1.

HRMS (ESI): Calcd for $C_{24}H_{30}NOSi$ $[M+H]^+$ 376.2091, found 376.2100.



Scheme S10. Synthesis of 11.

A mixture of **Ad9** (33 mg, 0.1 mmol) and $CuCl_2$ (13 mg, 0.1 mmol) in MeCN (5 mL) was stirred at room temperature for 30 min, then diol **10** (172 mg, 1 mmol) in MeCN (5 mL) was added dropwise at -10 ℃ and stirred for another 30 min at this temperature. *N*,*N*-Diisopropylethylamine (DIPEA) (155 mg, 1.2 mmol) in MeCN (1 mL) added dropwise to the mixture, followed by the addition of *p*-phenylbenzoyl chloride (PPB-Cl) (217 mg, 1 mmol) in DCM (5 mL) dropwise at this temperature. After 60 h, the mixture was quenched by saturated aq. NH_4Cl, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with aq. $NaHCO_3$, H_2O, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. ^{1}H NMR analysis of the crude products indicated the regioisomeric ratio was 9.3 : 1. Purification by silica gel column chromatography (PE: EtOAc = 2 : 1 to 2 : 3) gave **11** in 73% yield as a white solid.

(3a*R*,4*S*,5*R*,6a*S*)-4-(hydroxymethyl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl [1,1'-biphenyl]-4-carboxylate (11)

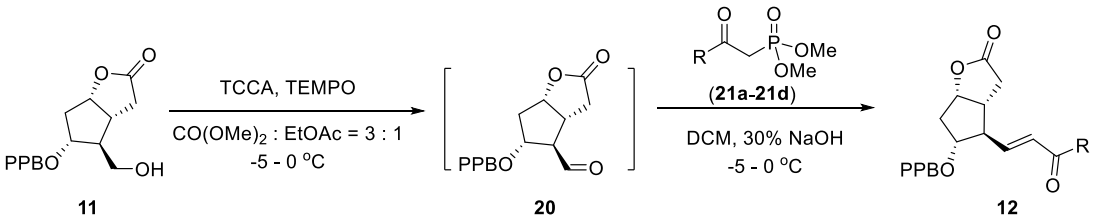
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.50-7.43 (m, 2H), 7.43-7.34 (m, 1H), 5.42 (q, *J* = 4.9 Hz, 1H), 5.08 (t, *J* = 6.0 Hz, 1H), 3.79-3.61 (m, 2H), 3.05-2.80 (m, 2H), 2.53 (ddd, *J* = 21.4, 14.3, 6.6 Hz, 2H), 2.40 (m, 2H), 2.31-2.21 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 166.6, 146.2, 139.9, 130.3, 129.1, 128.4, 128.2, 127.4, 127.3, 84.4, 77.2, 62.0, 54.8, 40.1, 38.3, 35.9.

m.p.: 130-131 ℃

$[\alpha]_D^{25}$ = -86.48 (c = 1.00, $CHCl_3$) [lit[15]: $[\alpha]_D^{25}$ = -87.3 (c = 1.00, $CHCl_3$)]

HRMS (ESI): Calcd for $C_{21}H_{20}NaO_4$ $[M+Na]^+$ 375.1203, found 375.1196



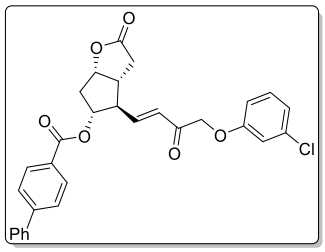
Scheme S11. General procedure D for the synthesis of enones 12.

Alcohol **11** (1.0 equiv.) was slowly added in three portions in intervals of 15 min. to a solution of 2,2,6,6-tetramethylpiperidinooxy (TEMPO, 0.05 equiv.) and trichloroisocyanuric acid (TCCA, 1.0 equiv.) in $CO(OMe)_2$: EtOAc = 3 : 1 (0.25 M) at -5 - 0 ℃. After addition, the reaction was stirred for 0.5 h at this temperature, then quenched by 10% aq. $Na_2S_2O_3$ and saturated aq. $NaHCO_3$. The mixture was filtered through celite to remove the solid, which was

washed with EtOAc (3 x 20 mL). The combined organic phase was washed with aq. $NaHCO_3$, H_2O, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure at temperature below 25 ℃ to give the crude product **20**, which was directly used in the next step without further purification.

Dimethyl phosphonate analogs **21a-21d** [16-19] (1.5 equiv.) in DCM (3 M) was slowly added to 30% aq. NaOH (1.5 equiv.) at -5 - 0 ℃. A solution of **20** in DCM (0.3 M) was added dropwise to this mixture. After addition, the reaction mixture was stirred for 1 h at this temperature. Then H_2O (5 mL) was added to quench this reaction. The aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (PE : EtOAc = 2 : 1) gave enones **12.**

(3a*R*,4*R*,5*R*,6a*S*)-4-((*E*)-4-(3-chlorophenoxy)-3-oxobut-1-en-1-yl)-2-oxohexahydro-2*H*-cyclo-penta[*b*]furan-5-yl [1,1'-biphenyl]-4-carboxylate (12a)



11 (246 mg, 0.7 mmol) was followed by general procedure C to give target product **12a** as a white solid in 71% yield over two steps.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.18 (t, *J* = 8.1 Hz, 1H), 7.00-6.81 (m, 3H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.58 (d, *J* = 15.8 Hz, 1H), 5.35 (q, *J* = 5.7 Hz, 1H), 5.11 (t, *J* = 6.2 Hz, 1H), 4.67 (s, 2H), 3.01-2.85 (m, 3H), 2.70-2.57 (m, 1H), 2.56-2.45 (m, 1H), 2.42-2.25 (m, 1H).

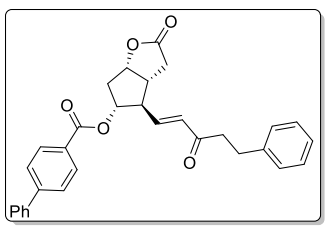
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.7, 175.9, 165.8, 158.4, 146.4, 145.7, 139.9, 135.3, 130.6, 130.4, 129.1, 128.4, 127.9, 127.4, 127.4, 126.6, 122.2, 115.3, 113.0, 83.3, 78.5, 72.4, 54.4, 42.8, 38.0, 35.0.

m.p.: 170.6-171.6 ℃

$[\alpha]_D^{25}$ = -116.25 (c = 1.00, $CHCl_3$)

HRMS (ESI): Calcd for $C_{30}H_{25}ClNaO_6$ $[M+Na]^+$ 539.1232, found 539.1220

(3a*R*,4*R*,5*R*,6a*S*)-2-Oxo-4-((*E*)-3-oxo-5-phenylpent-1-en-1-yl)hexahydro-2*H*-cyclopenta[*b*] furan-5-yl [1,1'-biphenyl]-4-carboxylate (12b)



11 (528 mg, 1.5 mmol) was followed by general procedure C to give target product **12b** as a white solid in 75% yield over two steps.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 7.3 Hz, 2H), 7.53-7.43 (m, 2H), 7.43-7.36 (m, 1H), 7.30-7.24 (m, 2H), 7.23-7.13 (m, 3H), 6.66 (dd, *J* = 15.9, 7.7 Hz, 1H), 6.22 (d, *J* = 16.1 Hz, 1H), 5.31 (q, *J* = 5.1, 4.6 Hz, 1H), 5.16-5.03 (m, 1H), 2.99-2.82 (m, 7H), 2.68-2.56 (m, 1H), 2.56-2.44 (m, 1H), 2.38-2.23 (m, 1H).

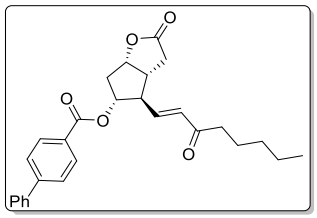
^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7, 175.9, 165.8, 146.4, 143.1, 141.0, 139.9, 131.5, 130.3, 129.1, 128.6, 128.5, 128.4, 128.0, 127.4, 127.3, 126.3, 83.3, 78.6, 54.2, 42.7, 42.6, 38.0, 35.1, 30.1.

m.p.: 121.7-122.7 ℃

$[\alpha]_D^{20}$ = -112.82 (c = 0.39, CH_3CN) [lit.[18]: $[\alpha]_D^{25}$ = -116 (c = 1.26, CH_3CN)]

HRMS (ESI): Calcd for $C_{31}H_{28}NaO_5$ $[M+Na]^+$ 503.1829, found 503.1826

(3a*R*,4*R*,5*R*,6a*S*)-2-oxo-4-((*E*)-3-oxooct-1-en-1-yl)hexahydro-2*H*-cyclopenta[*b*]furan-5-yl [1,1'-biphenyl]-4-carboxylate (12c)



11 (106 mg, 0.3 mmol) was followed by general procedure C to give target product **12c** as a white solid in 73% yield over two steps.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 6.70 (dd, *J* = 15.9, 7.0 Hz, 1H), 6.25 (d, *J* = 15.8 Hz, 1H), 5.34 (q, *J* = 5.3 Hz, 1H), 5.11 (t, *J* = 5.6 Hz, 1H), 2.97-2.84 (m, 3H), 2.70-2.57 (m, 1H), 2.58-2.47 (m, 3H), 2.32 (dd, *J* = 16.0, 4.8 Hz, 1H), 1.65-1.52 (m, 2H), 1.33-1.22 (m, 4H), 0.87 (t, *J* = 6.7 Hz, 3H).

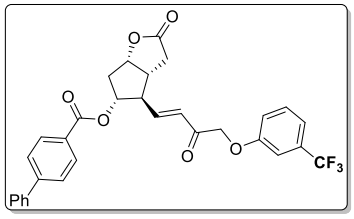
^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 176.0, 165.9, 146.4, 142.6, 139.9, 131.5, 130.3, 129.1, 128.4, 128.0, 127.4, 127.4, 83.4, 78.7, 54.2, 42.7, 41.3, 38.0, 35.1, 31.5, 23.8, 22.6, 14.0.

m.p.: 61.1-66.1 ℃

$[\alpha]_D^{25}$ = -136.64 (c = 0.29, $CHCl_3$) [lit.[15]: $[\alpha]_D^{25}$ = -146 (c = 0.2, $CHCl_3$)]

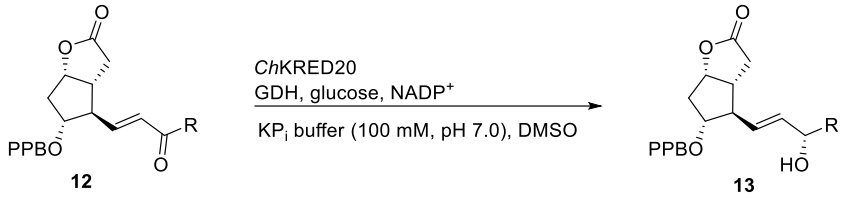
HRMS (ESI): Calcd for $C_{28}H_{30}NaO_5$ $[M+Na]^+$ 469.1985, found 469.1961

(3a*R*,4*R*,5*R*,6a*S*)-2-oxo-4-((*E*)-3-oxo-4-(3-(trifluoromethyl)phenoxy)but-1-en-1-yl) hexahydro-2*H*-cyclopenta[*b*]furan-5-yl [1,1'-biphenyl]-4-carboxylate (12d)



11 (300 mg, 0.85 mmol) was followed by general procedure C to give target product **12d** as a white solid in 74% yield over two steps.

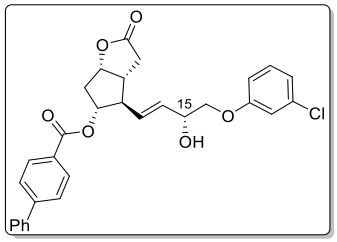
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.66-7.58 (m, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.45-7.35 (m, 2H), 7.28 (s, 1H), 7.15 (t, *J* = 2.1 Hz, 1H), 7.06 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.97 (dd, *J* = 15.7, 8.0 Hz, 1H), 6.62 (dd, *J* = 15.6, 1.1 Hz, 1H), 5.39 (q, *J* = 5.6 Hz, 1H), 5.14 (t, *J* = 5.4 Hz, 1H), 4.76 (s, 2H), 3.08-2.97 (m, 1H), 2.97-2.85 (m, 2H), 2.72 -2.59 (m, 1H), 2.59-2.47 (m, 1H), 2.42-2.31 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 175.9, 165.8, 157.8, 146.4, 145.8, 139.8, 132.2 (q, *J* = 32.6 Hz), 130.4, 130.3, 129.1, 128.4, 127.9, 127.4, 127.3, 126.5, 123.8 (q, *J* = 273.7 Hz), 118.7 (q, *J* = 3.7 Hz), 118.1, 111.7 (q, *J* = 3.7 Hz), 83.3, 78.5, 72.3, 54.4, 42.8, 38.0, 35.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ -61.3.
m.p.: 111.8-113.7℃
$[\alpha]_D^{25}$ = -112.87 (c = 0.67, $CHCl_3$)
HRMS (ESI): Calcd for $C_{31}H_{25}F_3NaO_6$ $[M+Na]^+$ 573.1495, found 573.1502



Scheme S12. General procedure E for the synthesis of allylic alcohols 13.

To a solution of **12** (0.2 mmol) in DMSO (4 mL) was added KP_i buffer (pH = 7.0, 100 mM, 26.8 mL), $NADP^+$ (0.008 mmol in water (210 μL)), glucose (0.4 mmol in water (270 μL)), purified enzyme of *Ch*KRED20 (40 mg, 1 mg/mL) and 8 mL 15% (w/v) CFE of GDH in NaP_i buffer (50 mM, pH 7.0). The mixture was stirred at 30 ℃ (water bath) with 700 rpm for 33 h. EtOAc (40 mL) was added and stirred for 5 min. The mixture was centrifuged for 10 min at 18000 rpm. The aqueous layer was extracted by EtOAc for another two times. The combined EtOAc layer was washed with brine and dried with anhydrous Na_2SO_4, filtered and evaporated to give the crude product, which was purified by flash chromatography (hexane : EtOAc =2 : 1 to 1 : 1) to give **13**. The dr was determined by SFC analysis of the crude product.

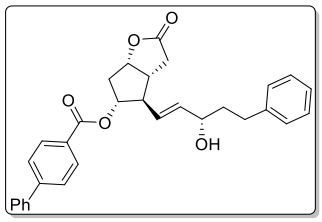
(3a*R*,4*R*,5*R*,6a*S*)-4-((*R, E*)-4-(3-chlorophenoxy)-3-hydroxybut-1-en-1-yl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl [1,1'-biphenyl]-4-carboxylate (13a)



12a (103 mg, 0.2 mmol) was followed by general procedure D to give target product **13a** in 91% yield with 98 : 2 dr. The configuration of the newly generated stereogenic center (C-15, prostaglandin numbering) was assigned to α by comparing to that of **13a** prepared using (-)-DIP-Cl-mediated reduction.[16]

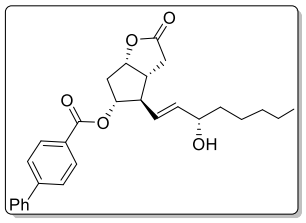
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 7.0 Hz, 2H), 7.54-7.42 (m, 2H), 7.43-7.35 (m, 1H), 7.20-7.08 (m, 1H), 6.93 (d, *J* = 8.3 Hz, 2H), 6.73 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.84 (dd, *J* = 15.6, 7.0 Hz, 1H), 5.74 (dd, *J* = 15.6, 5.0 Hz, 1H), 5.31 (q, *J* = 5.6 Hz, 1H), 5.15-4.94 (m, 1H), 4.64-4.42 (m, 1H), 3.93 (dd, *J* = 9.4, 3.6 Hz, 1H), 3.88-3.76 (m, 1H), 2.95-2.75 (m, 3H), 2.68-2.58 (m, 1H), 2.54 (d, *J* = 16.0 Hz, 1H), 2.44 (d, *J* = 4.0 Hz, 1H), 2.28 (dd, *J* = 15.3, 4.1 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 165.9, 159.0, 146.1, 139.9, 135.0, 131.0, 130.9, 130.3, 130.2, 129.0, 128.3, 128.2, 127.3, 127.2, 121.6, 115.0, 113.1, 83.3, 79.0, 71.8, 70.1, 54.3, 42.7, 37.6, 35.0.
m.p.: 107.6-109.5 ℃
$[\alpha]_D^{25}$ = -108.57 (c = 0.43, $CHCl_3$)
HRMS(ESI): Calcd for $C_{30}H_{27}ClNaO_6$ $[M+Na]^+$ 541.1388, found 541.1378
Chiral SFC (Chiralcel IF-3 column), CO_2 : MeOH = 75/25, Flow rate: 3 mL/min, UV detection at 275 nm, T =30 ℃, BPR Pressure = 140 bar, BPR Temperature: 60 ℃, retention time: 18.834 min (major), 22.498 min (minor).

(3a*R*,4*R*,5*R*,6a*S*)-4-((*S, E*)-3-hydroxy-5-phenylpent-1-en-1-yl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl [1,1'-biphenyl]-4-carboxylate (13b)



12b (96 mg, 0.2 mmol) was followed by general procedure D to give target product **13b** in 80% yield with 99 : 1 dr. The configuration of the newly generated stereogenic center (C-15, prostaglandin numbering) was assigned to α by comparing to that of **13b** prepared using (-)-DIP-Cl-mediated reduction.[20]
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.51-7.43 (m, 2H), 7.43-7.36 (m, 1H), 7.28-7.23 (m, 2H), 7.22-7.09 (m, 3H), 5.70 (dd, *J* = 15.5, 5.6 Hz, 1H), 5.61 (dd, *J* = 15.5, 6.8 Hz, 1H), 5.27 (q, *J* = 5.7 Hz, 1H), 5.13-4.94 (m, 1H), 4.14 (q, *J* = 6.1 Hz, 1H), 2.90-2.73 (m, 3H), 2.73-2.56 (m, 3H), 2.51 (d, *J* = 17.5 Hz, 1H), 2.26 (ddd, *J* = 15.4, 5.3, 1.9 Hz, 1H), 1.87-1.79 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 166.0, 146.1, 141.6, 139.9, 136.1, 130.2, 129.0, 128.7, 128.5, 128.4, 128.3, 128.2, 127.3, 127.2, 126.0, 83.3, 79.1, 71.4, 54.1, 42.7, 38.7, 37.6, 34.9, 31.6.
m.p.:129.6-131.4 ℃
$[\alpha]_D^{25}$ = -93.82 (c = 0.28, $CHCl_3$) [lit.[21]: $[\alpha]_D^{20}$ = -101.59 (c = 0.69, MeCN)]
HRMS (ESI): Calcd for $C_{31}H_{30}NaO_5$ $[M+Na]^+$ 505.1985, found 505.1969.
Chiral SFC (Chiralcel IF-3 column), CO_2 : MeOH = 75/25, Flow rate: 3 mL/min, UV detection at 275 nm, T =30 ℃, BPR Pressure = 130 bar, BPR Temperature: 60 ℃, retention time: 14.928 min (major), 12.468 min (minor).

(3a*R*,4*R*,5*R*,6a*S*)-4-((*S*,*E*)-3-hydroxyoct-1-en-1-yl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl [1,1'-biphenyl]-4-carboxylate (13c)



12c (96 mg, 0.2 mmol) was followed by general procedure D to give target product **13c** in 90% yield with 99 : 1 dr. The configuration of the newly generated stereogenic center (C-15, prostaglandin numbering) was assigned to α by comparing to that of **13c** prepared using (*R*)-CBS-mediated reduction.[22]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.66-7.58 (m, 2H), 7.53-7.45 (m, 2H), 7.45-7.37 (m, 1H), 5.69 (dd, *J* = 15.5, 5.5 Hz, 1H), 5.62 (dd, *J* = 15.5, 6.8 Hz, 1H), 5.30 (q, *J* = 5.7 Hz, 1H), 5.18-5.00 (m, 1H), 4.12 (q, *J* = 6.1 Hz, 1H), 2.97-2.73 (m, 3H), 2.70-2.59 (m, 1H), 2.55 (d, *J* = 16.6 Hz, 1H), 2.28 (ddd, *J* = 15.4, 5.2, 1.9 Hz, 1H), 1.75 (s, 1H), 1.59-1.41 (m, 2H), 1.38-1.23 (m, 6H), 0.87 (t, 3H).

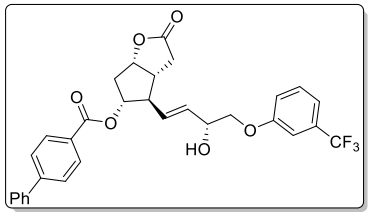
^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 166.0, 146.1, 139.9, 136.4, 130.2, 129.0, 128.4, 128.3, 128.2, 127.3, 127.2, 83.4, 79.1, 72.2, 54.1, 42.7, 37.6, 37.2, 34.9, 31.7, 25.0, 22.6, 14.0.

$[\alpha]_D^{25}$ = -98.05 (c = 0.37, $CHCl_3$)

HRMS (ESI): Calcd for $C_{28}H_{32}NaO_5$ $[M+Na]^+$ 471.2142, found 471.2124.

Chiral SFC (Chiralcel IF-3 column), CO_2 : MeOH = 75/25, Flow rate: 3 mL/min, UV detection at 275 nm, T =30 ℃, BPR Pressure = 130 bar, BPR Temperature: 60 ℃, retention time: 9.336 min (major), 8.148 min (minor).

(3a*R*,4*R*,5*R*,6a*S*)-4-((*R*, *E*)-3-hydroxy-4-(3-(trifluoromethyl)phenoxy)but-1-en-1-yl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl [1,1'-biphenyl]-4-carboxylate(13d)



12d (110 mg, 0.2 mmol) was followed by general procedure D. The crude product **13d** with 87 : 13 dr. The epimers were separated by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1) to give **13d** in 80% yield with 98 : 2 dr. The configuration of the newly generated stereogenic center (C-15, prostaglandin numbering) was assigned to α by comparing to that of **13d** prepared using (*R*)-CBS-mediated reduction.[23]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 7.1 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.43-7.32 (m, 2H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.11 (s, 1H), 7.01 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.86 (dd, *J* = 15.7, 7.2 Hz, 1H), 5.76 (dd, *J* = 15.6, 5.1 Hz, 1H), 5.32 (q, *J* = 5.6 Hz, 1H), 5.19-4.99 (m, 1H), 4.66-4.44 (m, 1H), 3.99 (dd, *J* = 9.3, 3.5 Hz, 1H),

3.87 (dd, *J* = 9.3, 7.3 Hz, 1H), 2.96-2.77 (m, 3H), 2.67-2.49 (m, 2H), 2.44 (d, *J* = 4.0 Hz, 1H), 2.30 (ddd, *J* = 15.4, 5.0, 2.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 166.1, 158.5, 146.2, 139.9, 132.0 (q, *J* = 32.3 Hz), 131.2, 130.8, 130.3, 130.2, 129.1, 128.4, 128.2, 127.4, 127.3, 123.9 (q, *J* = 272.7 Hz), 118.2, 118.2 (q, *J* = 4.0 Hz), 111.4 (q, *J* = 4.0 Hz), 83.5, 79.1, 71.9, 70.2, 54.4, 42.8, 37.7, 35.1.

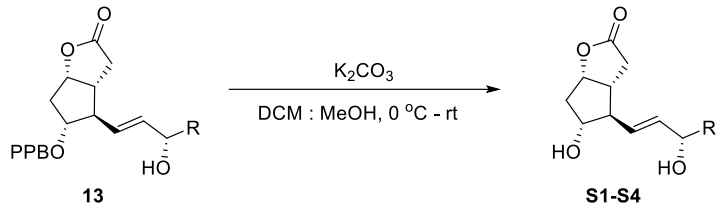
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7.

m.p.: 43.0-45.0 ℃

$[\alpha]_D^{25}$ = -93.44 (c = 0.52, MeCN) [lit.[23]: $[\alpha]_D^{25}$ = -93.8 (c = 1.0, MeCN)]

HRMS(ESI): Calcd for $C_{31}H_{27}F_3NaO_6$ $[M+Na]^+$ 575.1652, found 575.1647.

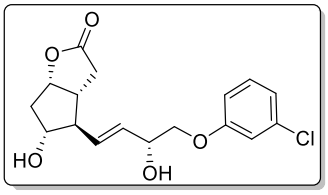
Chiral SFC (Chiralcel IF-3 column), CO_2 : MeOH = 80/20, Flow rate: 1 mL/min, UV detection at 275 nm, T =30 ℃, BPR Pressure = 130 bar, BPR Temperature: 60 ℃, retention time: 40.557 min (major), 44.608 min (minor).



Scheme S13. General procedure F for the synthesis of S1-S4.

This is a modified literature procedure.[24] To an ice-cooled mixture of K_2CO_3 (0.1 mmol, 1.0 equiv.) in MeOH (1 mL) was added dropwise a solution of **13** (0.1 mmol, 1.0 equiv.) in DCM (1 mL). After addition, the mixture was then stirred at room temperature for 2 h. AcOH (0.2 mmol, 2.0 equiv.) was added to the ice-cooled mixture slowly, then the resulting mixture was stirred at room temperature for another 10 min. This colorless solution was evaporated to give the crude product, which was purified by flash chromatography (pure DCM then pure EtOAc) to give the target product **S1-S4**

(3a*R*,4*R*,5*R*,6a*S*)-4-((*R*,*E*)-4-(3-chlorophenoxy)-3-hydroxybut-1-en-1-yl)-5-hydroxyhexahydro -2*H*-cyclopenta[*b*]furan-2-one (S1)

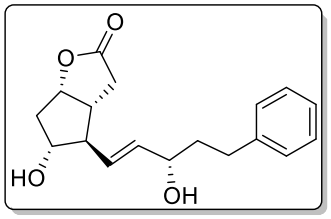


13a (52 mg, 0.1 mmol) was followed by general procedure E to give target product **S1** in 72% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.15 (m, 1H), 6.98-6.92 (m, 1H), 6.92-6.87 (m, 1H), 6.84-6.75 (m, 1H), 5.66 (dd, *J* = 4.9, 2.0 Hz, 2H), 4.89 (td, *J* = 7.0, 3.1 Hz, 1H), 4.56-4.40 (m, 1H), 4.03-3.91 (m, 2H), 3.87 (dd, *J* = 9.5, 7.3 Hz, 1H), 3.49 (s, 1H), 3.39 (s, 1H), 2.71 (dd, *J* = 18.1, 9.6 Hz, 1H), 2.62-2.54 (m, 1H), 2.54-2.45 (m, 1H), 2.41 (dd, *J* = 18.1, 1.8 Hz, 1H), 2.35-2.26 (m, 1H), 1.93 (ddd, *J* = 14.8, 7.8, 3.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 159.2, 135.0, 133.0, 131.3, 130.5, 121.6, 115.2, 113.2, 82.65, 76.4, 71.8, 70.7, 56.4, 42.5, 39.8, 34.3.

(3a*R*,4*R*,5*R*,6a*S*)-5-hydroxy-4-((*S*,*E*)-3-hydroxy-5-phenylpent-1-en-1-yl)hexahydro-2*H*-cyclo-penta[*b*]furan-2-one (S2)

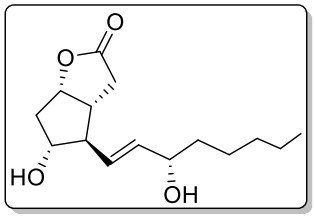


13b (48 mg, 0.1 mmol) was followed by general procedure E to give target product **S2** in 79% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 7.22-7.10 (m, 3H), 5.60 (dd, *J* = 15.3, 7.4 Hz, 1H), 5.41 (dd, *J* = 15.3, 8.6 Hz, 1H), 4.86 (td, *J* = 7.0, 3.2 Hz, 1H), 4.05 (q, *J* = 6.8 Hz, 1H), 3.99-3.81 (m, 2H), 3.27 (s, 1H), 2.78-2.59 (m, 3H), 2.56-2.42 (m, 2H), 2.38 (dd, *J* = 18.1, 1.7 Hz, 1H), 2.22 (q, *J* = 8.6 Hz, 1H), 1.95-1.73 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 141.7, 136.6, 130.7, 128.5, 128.5, 126.1, 82.6, 76.4, 72.2, 56.2, 42.4, 39.8, 38.7, 34.1, 31.8.

(3a*R*,4*R*,5*R*,6a*S*)-5-Hydroxy-4-((*S*,*E*)-3-hydroxyoct-1-en-1-yl)hexahydro-2*H*-cyclopenta[*b*] furan-2-one (S3)

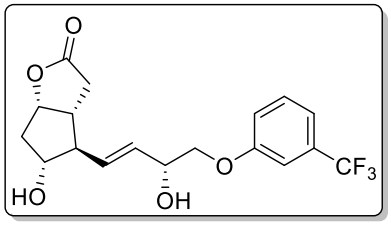


13c (45 mg, 0.1 mmol) was followed by general procedure E to give target product **S3** in 78% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (dd, *J* = 15.3, 7.4 Hz, 1H), 5.41 (dd, *J* = 15.3, 8.5 Hz, 1H), 4.88 (td, *J* = 7.1, 3.2 Hz, 1H), 4.01 (q, *J* = 6.8 Hz, 1H), 3.90 (q, *J* = 7.8 Hz, 1H), 3.75 (s, 1H), 2.94 (s, 1H), 2.70 (dd, *J* = 18.1, 9.5 Hz, 1H), 2.62-2.46 (m, 2H), 2.39 (dd, *J* = 18.1, 1.7 Hz, 1H), 2.22 (q, *J* = 8.7 Hz, 1H), 1.90 (ddd, *J* = 14.7, 8.1, 3.3 Hz, 1H), 1.63-1.49 (m, 1H), 1.49-1.39 (m, 1H), 1.36- 1.20 (m, 6H), 0.87 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 137.0, 130.5, 82.6, 76.4, 73.0, 56.3, 42.5, 39.7, 37.2, 34.1, 31.8, 25.3, 22.7, 14.2.

(3a*R*,4*R*,5*R*,6a*S*)-5-Hydroxy-4-((*R*, *E*)-3-hydroxy-4-(3-(trifluoromethyl)phenoxy)but-1-en-1-yl)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (S4)

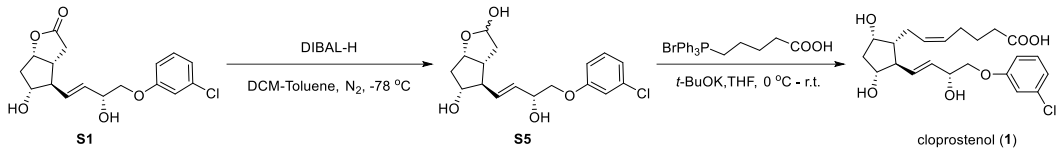


13d (55.2 mg, 0.1 mmol) was followed by general procedure E to give target product **S4** in 75% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.12 (s, 1H), 7.07 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.77-5.59 (m, 2H), 4.89 (td, *J* = 7.0, 3.1 Hz, 1H), 4.60-4.40 (m, 1H), 4.08-3.82 (m, 3H), 3.50 (s, 2H), 2.72 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.59 (q, *J* = 9.3, 8.6 Hz, 1H), 2.51 (dt, *J* = 14.3, 7.0 Hz, 1H), 2.41 (dd, *J* = 18.1, 1.7 Hz, 1H), 2.31 (q, *J* = 7.9 Hz, 1H), 1.93 (ddd, *J* = 14.8, 7.9, 3.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 158.6 133.2, 132.0 (q, *J* = 32.4 Hz), 131.3, 130.3, 124.0 (q, *J* = 273.7 Hz), 118.1, 118.1 (q, *J* = 3.9 Hz), 111.5 (q, *J* = 4.0 Hz), 82.6, 76.4, 71.8, 70.8, 56.4, 42.4, 39.7, 34.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6.



Scheme S14. Synthesis of cloprostenol (1).

Diisobutylaluminium hydride (DIBAL-H) (1.5 M in toluene, 0.21 mL, 0.32 mmol) was slowly added to a solution of **S1** (27.4 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) at -78 ℃. After the mixture was stirred for 2 h at this temperature, the reaction was quenched with MeOH (0.5 mL) at -78 ℃. The mixture was warmed to room temperature and saturated aq. NH_4Cl solution (0.3 mL) was added. The mixture was stirred for 15 min and the white solid was filtrated through a pad of celite. The solid was washed with CH_2Cl_2 (2 x 5 mL) and the filtrate was washed with saturated aq. NH_4Cl solution and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product lactol **S5** as colorless oil, which was directly used in next step without further purification.

(4-Carboxybutyl)(triphenyl)phosphonium bromide (213 mg, 0.48 mmol) was added to a flame-dried three-necked flask under N_2, and anhydrous THF (3 mL) added. The resulting suspension was cooled to 0 ℃. *t*-BuOK (108 mg, 0.96 mmol, in 1mL anhydrous THF) was added via syringe and the resulting orange mixture was stirred at 0 ℃ for 40 min. A solution of the above crude lactol **S5** in anhydrous THF (1.5 mL) was added dropwise via syringe. After completing addition, the mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with H_2O (3 mL) and washed with Et_2O (2 x 10 mL) to remove triphenylphosphine oxide. The aqueous phase was acidified with 1 M HCl to pH 1-2 and extracted with CH_2Cl_2 (5 x 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude material. This crude product was soaked with EtOAc : hexane (8 mL, 1 : 1) and stayed in a sonic bath for 10 min., then stayed overnight. The solids filtered and washed with EtOAc (4 x 5 mL). The filtrate was concentrated under vacuum and purified by column chromatography on silica, eluting with EtOAc : hexane : HOAc (60 : 35 : 5) then DCM : MeOH (90: 10) to give cloprostenol (**1**) (20.9 mg, 61% yield over two steps) as a clear, colorless oil.

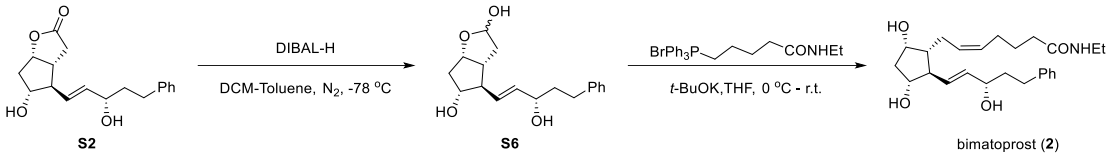
(*Z*)-7-((1*R*,2*R*,3*R*,5*S*)-2-((*R*, *E*)-4-(3-Chlorophenoxy)-3-hydroxybut-1-en-1-yl)-3,5-dihydroxy-cyclopentyl)hept-5-enoic acid (Cloprostenol, 1)

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.26 (t, J = 8.1 Hz, 1H), 7.05-6.83 (m, 3H), 5.83-5.63 (m, 2H), 5.60-5.47 (m, 1H), 5.41-5.27 (m, 1H), 4.56-4.41 (m, 1H), 4.17-4.08 (m, 1H), 4.03-3.82 (m, 3H), 2.46-2.30 (m, 2H), 2.30-2.24 (m, 2H), 2.24-1.99 (m, 4H), 1.68-1.58 (m, 3H), 1.56-1.47 (m, 1H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 176.3, 159.8, 134.5, 134.5, 130.8, 130.2, 129.1, 128.8, 120.5, 114.7, 112.8, 76.3, 72.0, 70.8, 70.5, 54.7, 49.3, 42.9, 33.0, 26.2, 24.8, 24.6.

$[\alpha]_D^{25}$ = +21.00 (c = 0.38, $CHCl_3$) [lit.[11]: $[\alpha]_D^{20}$ = 26.0 (c = 1.5, $CHCl_3$), lit.[25]: $[\alpha]_D^{25}$ = +20.85 (c = 2.00, $CHCl_3$)]

HRMS (ESI): Calcd for $C_{22}H_{29}NaO_6$ $[M+Na]^+$ 447.1545, found 447.1527.



Scheme S15. Synthesis of bimatoprost (2).

To a solution of **S2** (24 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) was added DIBAL-H (1.5 M in toluene, 0.21 mL, 0.32 mmol) at -78 ℃. After 2 h at -78 ℃, MeOH (0.5 mL) was added. The mixture was warmed to room temperature and saturated aq. NH_4Cl solution (0. 5 mL) was added. The mixture was stirred for 15 min and the white solid was filtrated through celite, the solid was washed with CH_2Cl_2 (2 x 5 mL) and the filtrate was washed with saturated aq. NH_4Cl solution and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product lactol **S6** as colorless oil, which was directly used in next step without further purification.

5-(Bromotriphenyl-l5-phosphanyl)-*N*-ethylpentanamide (226 mg, 0.48 mmol) was added to a flame-dried three-necked flask under N_2, and anhydrous THF (3 mL) added. The resulting suspension was cooled to 0 ℃. *t*-BuOK (108 g, 0.96 mmol, in 1 mL anhydrous THF) was added via syringe and the resulting orange mixture stirred at 0 ℃ for 40 min. A solution of the above crude lactol **S6** in anhydrous THF (2 mL) was added dropwise via syringe. After completing addition, the mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with saturated aq. NH_4Cl (3 mL) and extracted with EtOAc (5 x 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude material. This crude product was soaked with EtOAc (10 mL) and stayed in a sonic bath for five minutes. The solids filtered and washed with EtOAc (4 x 5 mL). The filtrate was concentrated under vacuum and purified by column chromatography on silica, eluting with DCM : MeOH (97 : 3) then EtOAc: MeOH (95 : 5) to give bimatoprost (**2**) (19.1 mg, 57% yield over two steps) as a colorless oil.

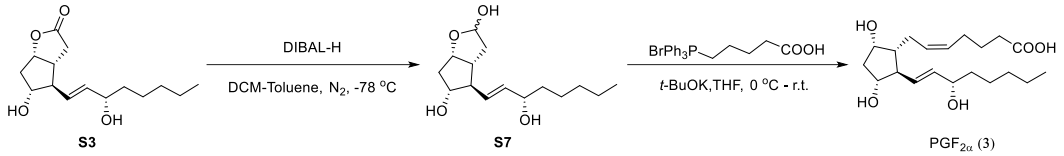
(*Z*)-7-((1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-((*S*,*E*)-3-hydroxy-5-phenylpent-1-en-1-yl)cyclopentyl)-*N*-ethylhept-5-enamide (Bimatoprost, 2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.24 (m, 2H), 7.22-7.08 (m, 3H), 5.76 (s, 1H), 5.59 (dd, *J* = 15.3, 7.1 Hz, 1H), 5.54-5.29 (m, 3H), 4.18-4.03 (m, 2H), 3.92 (s, 1H), 3.23 (m, *J* = 7.1 Hz, 4H), 2.67 (q, *J* = 8.2 Hz, 2H), 2.45-2.23 (m, 3H), 2.23-1.98 (m, 7H), 1.93-1.84 (m, 1H), 1.82-1.75 (m, 1H), 1.70-1.59 (m, 2H), 1.51-1.41 (m, 1H), 1.10 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 142.1, 135.2, 133.3, 129.9, 129.3, 128.6, 128.5, 125.9, 78.0, 72.6, 72.4, 55.7, 50.5, 43.1, 38.9, 36.0, 34.5, 32.0, 26.8, 25.8, 25.5, 14.9.

$[\alpha]_D^{25}$ =+32.38 (c = 0.21, CH_2Cl_2) [lit[26]: $[\alpha]_D^{22}$ = + 32.50 (c = 1.00, MeOH), lit[27]: $[\alpha]_D^{22}$ = +32.70 (c = 0.33, CH_2Cl_2)]

HRMS (ESI): Calcd for $C_{25}H_{37}NNaO_4$ $[M+Na]^+$ 438.2615, found 438.2619.



Scheme S16. Synthesis of $PGF_{2\alpha}$ (3).

DIBAL-H (1.5 M in toluene, 0.27 mL, 0.34 mmol) was slowly added to a solution of **S3** (22.8 mg, 0.085 mmol) in CH_2Cl_2 (2.1 mL) at -78 ℃. After the mixture was stirred for 2 h at this temperature, the reaction was quenched with MeOH (0.5 mL) at -78 ℃. The mixture was warmed to room temperature and saturated aq. NH_4Cl solution (0.3 mL) was added. The mixture was stirred for 15 min and the white solid was filtrated through a pad of celite. the solid washed with CH_2Cl_2 (2 x 5 mL) and the filtrate was washed with saturated aq. NH_4Cl solution and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give colorless oil as crude product lactol **S7**, which was directly used in next step without further purification.

(4-Carboxybutyl) (triphenyl)phosphonium bromide (226 mg, 0.51 mmol) was added to a flame-dried three-necked flask under N_2, and anhydrous THF (3 mL) was added. The resulting suspension was cooled to 0 ℃. *t*-BuOK (115 mg, 1.02 mmol, in 1mL anhydrous THF) was added via syringe and the resulting orange mixture stirred at 0 ℃ for 40 min. A solution of the above crude lactol **S7** in anhydrous THF (1.5 mL) was added dropwise via syringe. After completing addition, the mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with H_2O (3 mL) and washed with Et_2O (10 mL × 2) to remove triphenylphosphine oxide. The aqueous phase was acidified with 1 M HCl to pH 1-2 and extracted with CH_2Cl_2 (5 x 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude material. This crude product was soaked with EtOAc : hexane (8 mL, 1 : 1) and stayed in a sonic bath for 10 min., then stayed overnight. The solid was filtered and washed with EtOAc (4 x 5 mL). The filtrate was concentrated under vacuum and purified by column chromatography on silica, eluting with EtOAc : hexane : HOAc (60 : 35 : 5) then DCM : MeOH : AcOH (90: 10 : 0.1) to give $PGF_{2\alpha}$ (**3**) (24.5 mg, 81% yield over two steps) as a clear, colorless oil.

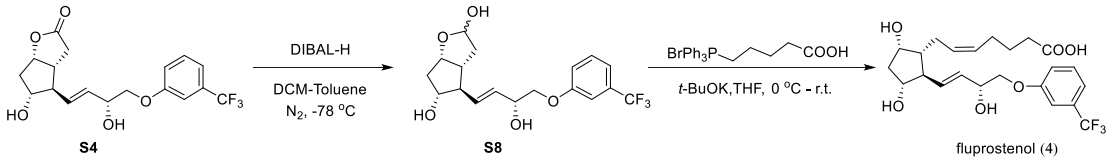
(*Z*)-7-((1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-((*S, E*)-3-hydroxyoct-1-en-1-yl)cyclopentyl)hept-5-enoic acid ($PGF_{2\alpha}$, 3)

^{1}H NMR (500 MHz, ca. 20:1 $CDCl_3$:CD_3OD) δ 5.50 (dd, *J* = 15.2, 7.1 Hz, 1H), 5.46-5.36 (m, 2H), 5.25-5.36 (m, 1H), 4.15-4.06 (m, 1H), 4.01 (q, *J* = 6.6 Hz, 1H), 3.91-3.80 (m, 1H), 3.79-3.45 (m, 3H), 2.38-2.14 (m, 5H), 2.12-1.97 (m, 3H), 1.74-1.58 (m, 3H), 1.58-1.49 (m, 1H), 1.49-1.37 (m, 2H), 1.33-1.19 (m, 6H), 0.84 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (126 MHz, ca. 20:1 $CDCl_3$:CD_3OD) δ 177.0, 135.2, 132.8, 129.7, 129.2, 77.4, 73.1, 72.2, 55.3, 50.1, 42.6, 37.0, 33.4, 31.8, 26.5, 25.3, 24.7, 22.7, 14.1.

$[\alpha]_D^{25}$ = +23.46 (c = 0.23, THF) [lit.[28]: $[\alpha]_D^{22}$ = + 23.50 (*c* = 1.0, THF)]

HRMS (ESI): Calcd for $C_{20}H_{34}NaO_5$ $[M+Na]^+$ 377.2298, found 377.2304.



Scheme S17. Synthesis of fluprostenol (4).

DIBAL-H (1.5 M in toluene, 0.2 mL, 0.3 mmol) was slowly added to a solution of **S4** (28 mg, 0.075 mmol) in CH_2Cl_2 (2 mL) at -78 ℃. After the mixture was stirred for 2 h at this temperature, the reaction was quenched with MeOH (0.5 mL) at -78 ℃. The mixture was warmed to room temperature and saturated aq. NH_4Cl solution (0.3 mL) was added. The mixture was stirred for 15 min and the white solid was filtrated through a pad of celite. the solid washed with CH_2Cl_2 (2 x 5 mL) and the filtrate was washed with saturated aq. NH_4Cl solution and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give colorless oil as crude product lactol **S8**, which was directly used in next step without further purification.

(4-Carboxybutyl) (triphenyl)phosphonium bromide (200 mg, 0.45 mmol) was added to a flame-dried three-necked flask under N_2, and anhydrous THF (2.5 mL) was added. The resulting suspension was cooled to 0 ℃. *t*-BuOK (101 mg, 0.9 mmol, in 1mL anhydrous THF) was added via syringe and the resulting orange mixture stirred at 0 ℃ for 40 min. A solution of the above crude lactol **S8** in anhydrous THF (2 mL) was added dropwise via syringe. After completing addition, the mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with H_2O (3 mL) and washed with Et_2O (10 mL × 2) to remove triphenylphosphine oxide. The aqueous phase was acidified with 1 M HCl to pH 1-2 and extracted with CH_2Cl_2 (5 x 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude material. This crude product was soaked with EtOAc : hexane (8 mL, 1 : 1) and stayed in a sonic bath for 10 min., then stayed overnight. The solid was filtered and washed with EtOAc (4 x 5 mL). The filtrate was concentrated under vacuum and purified by column chromatography on silica, eluting with EtOAc : hexane : HOAc (60 : 35 : 5) then CH_2Cl_2 : MeOH : AcOH (90: 10 : 0.1) to give fluprostenol (**4**) (23.4 mg, 68% yield over two steps) as a clear, colorless oil.

(*Z*)-7-((1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-((*R*, *E*)-3-hydroxy-4-(3-(trifluoromethyl)phenoxy) but-1-en-1-yl)cyclopentyl)hept-5-enoic acid (fluprostenol, 4)

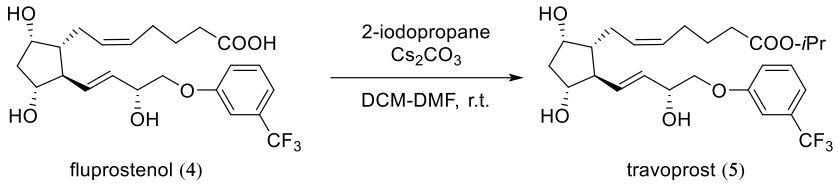
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.13 (s, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 5.75-5.62 (m, 2H), 5.48-5.38 (m, 1H), 5.37-5.28 (m, 1H), 5.09 (s, 3H), 4.55 (q, *J* = 5.6, 4.8 Hz, 1H), 4.20-4.10 (m, 1H), 4.05-3.87 (m, 3H), 2.45-2.33 (m, 1H), 2.34-2.16 (m, 4H), 2.13-2.00 (m, 3H), 1.75 (d, *J* = 15.2 Hz, 1H), 1.69-1.57 (m, 2H), 1.54-1.41 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 158.7, 135.5, 131.9 (q, *J* = 32.3 Hz), 130.2, 129.9, 129.8, 129.1, 124.0 (q, *J* = 273.7 Hz), 118.2, 117.9 (q, *J* = 4.1 Hz), 111.6 (q, *J* = 3.9 Hz), 77.6, 72.6, 71.8, 71.1, 55.6, 50.3, 42.8, 33.0, 26.3, 25.3, 24.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6.

$[\alpha]_D^{25}$ = +23.82 (c = 0.34, $CHCl_3$) [lit.[29]: $[\alpha]_D^{20}$ = + 21.1 (*c* = 1.0, $CHCl_3$)]

HRMS (ESI): Calcd for $C_{23}H_{29}F_3NaO_6$ $[M+Na]^+$ 481.1808, found 481.1807.



Scheme S18. Synthesis of travoprost (5).

To a solution of fluprostenol (**4**) (12 mg, 0.026 mmol) in CH_2Cl_2 (0.15 mL) and DMF (0.15 mL) was added Cs_2CO_3 (13 mg, 0.039 mmol) and 2-iodopropane (8.8 mg, 0.052 mmol). The reaction mixture was stirred at room temperature for 36 h, then diluted with 10 mL CH_2Cl_2, acidulated by 2-3 drops of 3% citric acid aqueous, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude material, which was purified by column chromatography on silica, eluting with EtOAc : hexane (2:1 to 3:1) to give travoprost (**5**) (8.1 mg, 68% yield) as a clear, colorless oil.

Isopropyl (*Z*)-7-((1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-((*R*, *E*)-3-hydroxy-4-(3-(trifluoromethyl)phenoxy)but-1-en-1-yl)cyclopentyl)hept-5-enoate (travoprost, 5)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.14 (s, 1H), 7.09 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.81-5.57 (m, 2H), 5.46-5.32 (m, 2H), 5.06-4.91 (m, 1H), 4.62-4.48 (m, 1H), 4.26-4.14 (m, 1H), 4.04-3.91 (m, 3H), 3.01 (s, 2H), 2.62-2.34 (m, 2H), 2.31-2.15 (m, 4H), 2.13-1.99 (m, 3H), 1.82-1.76 (m, 1H), 1.70-1.62 (m, 2H), 1.58-1.50 (m, 1H), 1.21 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 158.8, 135.4, 132.0 (q, *J* = 32.3 Hz), 130.2, 130.0, 129.6, 129.1, 124.0 (q, *J* = 273.7 Hz), 118.2, 118.0 (q, *J* = 4.1 Hz), 111.6 (q, *J* = 4.0 Hz), 78.1, 73.0, 72.1, 70.9, 67.9, 56.1, 50.5, 43.0, 34.1, 26.7, 25.7, 25.0, 22.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7.

$[\alpha]_D^{20}$ = +15.43 (c = 0.16, CH_2Cl_2) [lit.[29]: $[\alpha]_D^{20}$ = + 16.3 (*c* = 1.0, CH_2Cl_2)]

HRMS (ESI): Calcd for $C_{26}H_{35}F_3NaO_6$ $[M+Na]^+$ 523.2278, found 523.2297.

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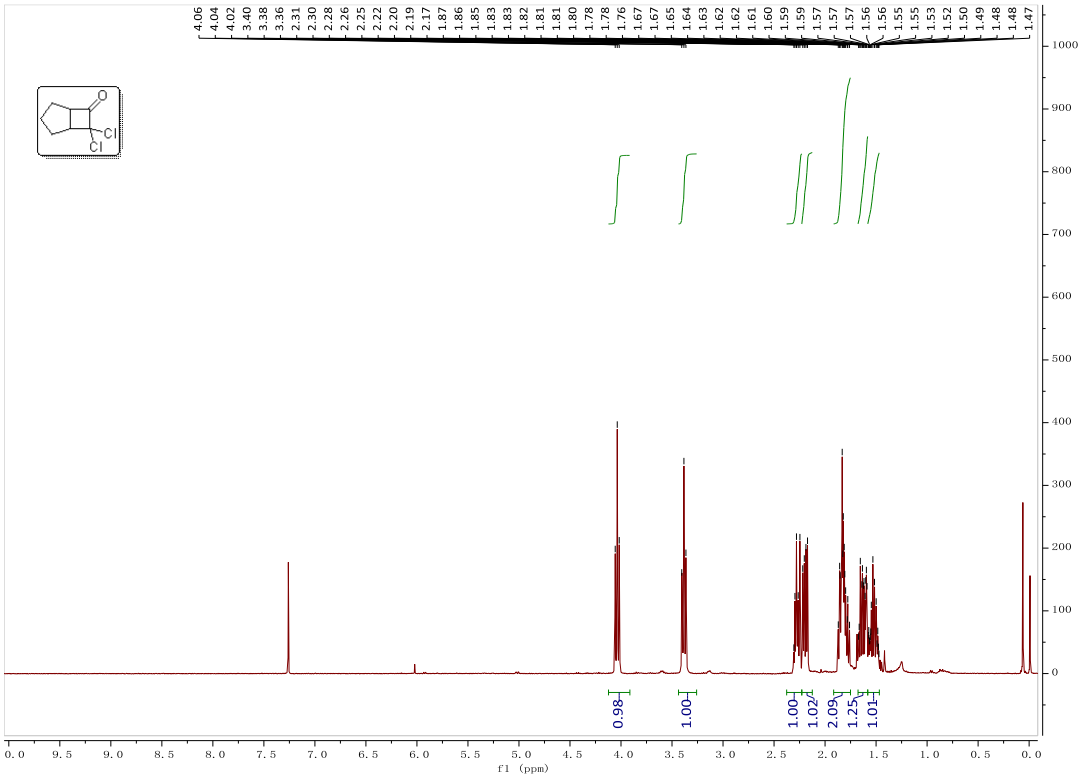
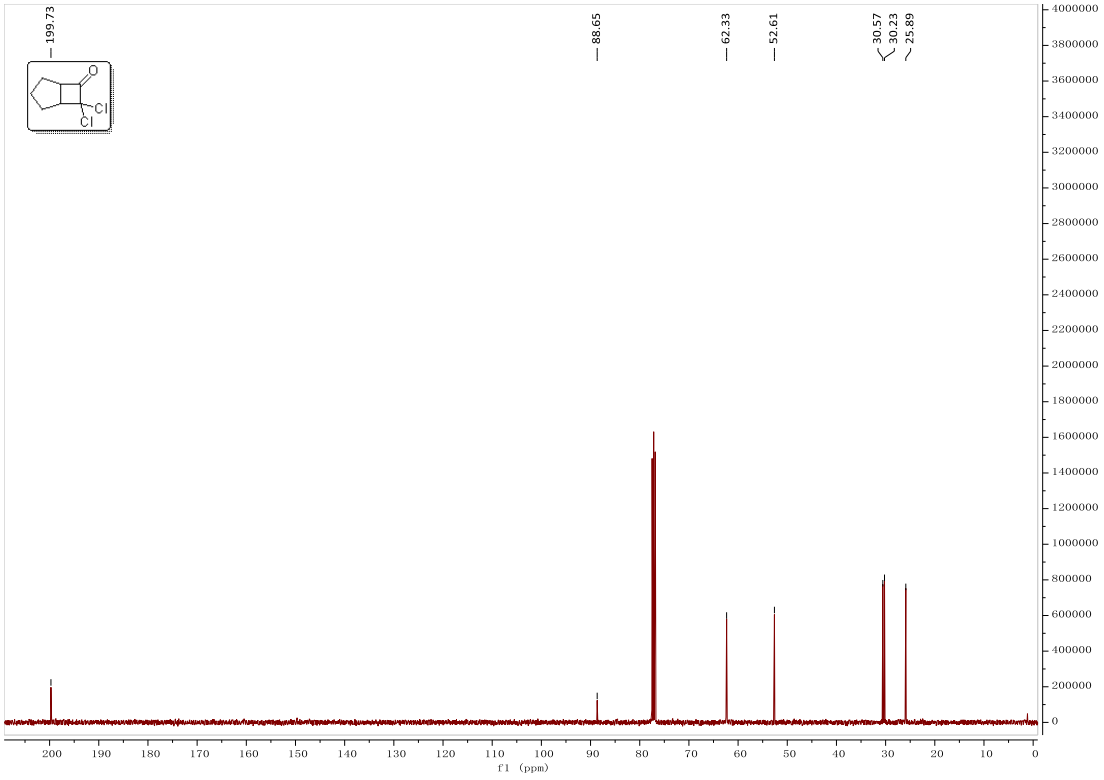
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of 6b



The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of 6b



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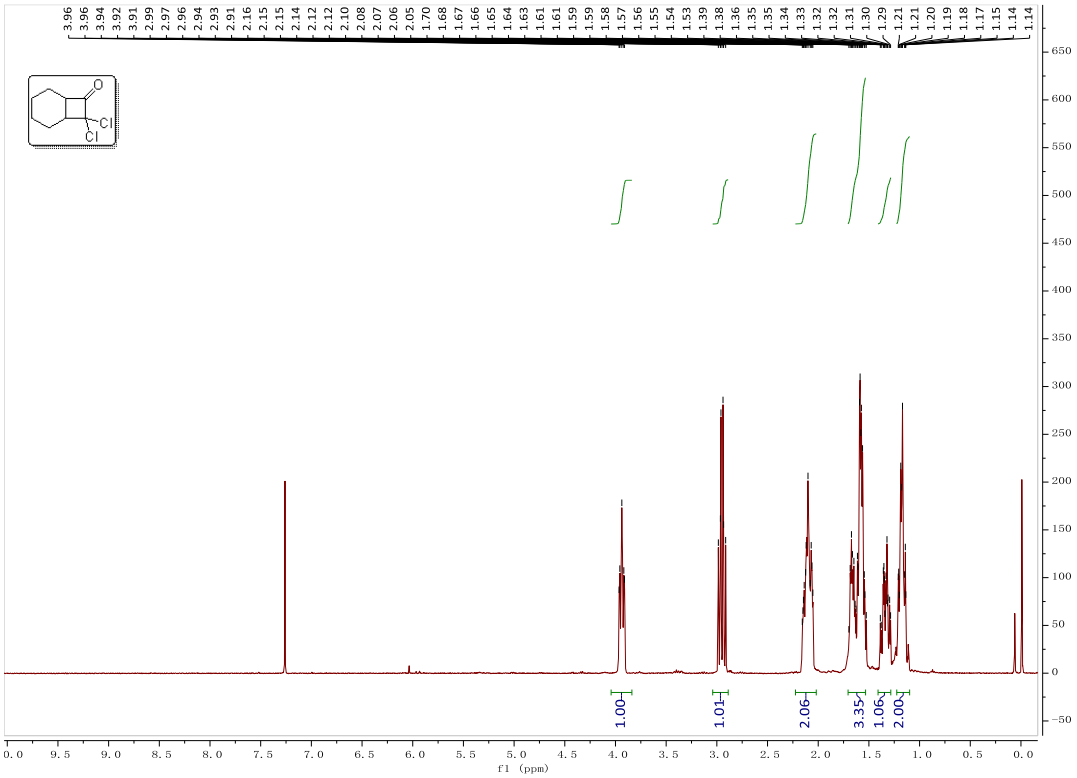

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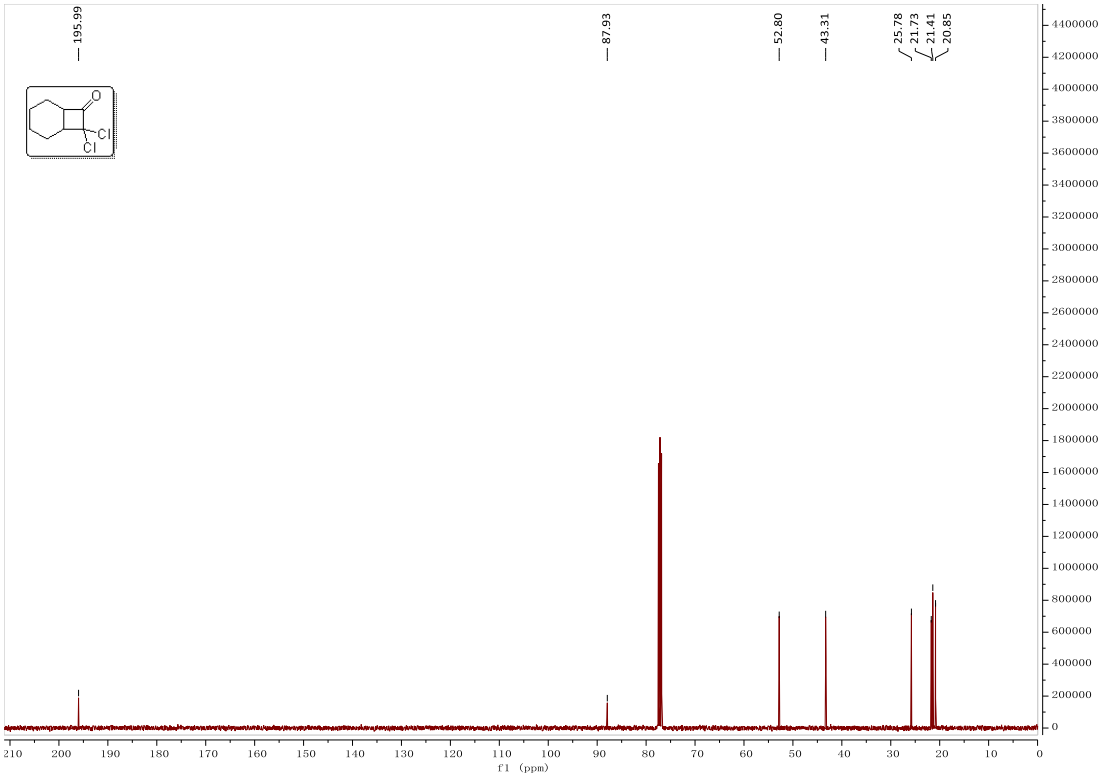

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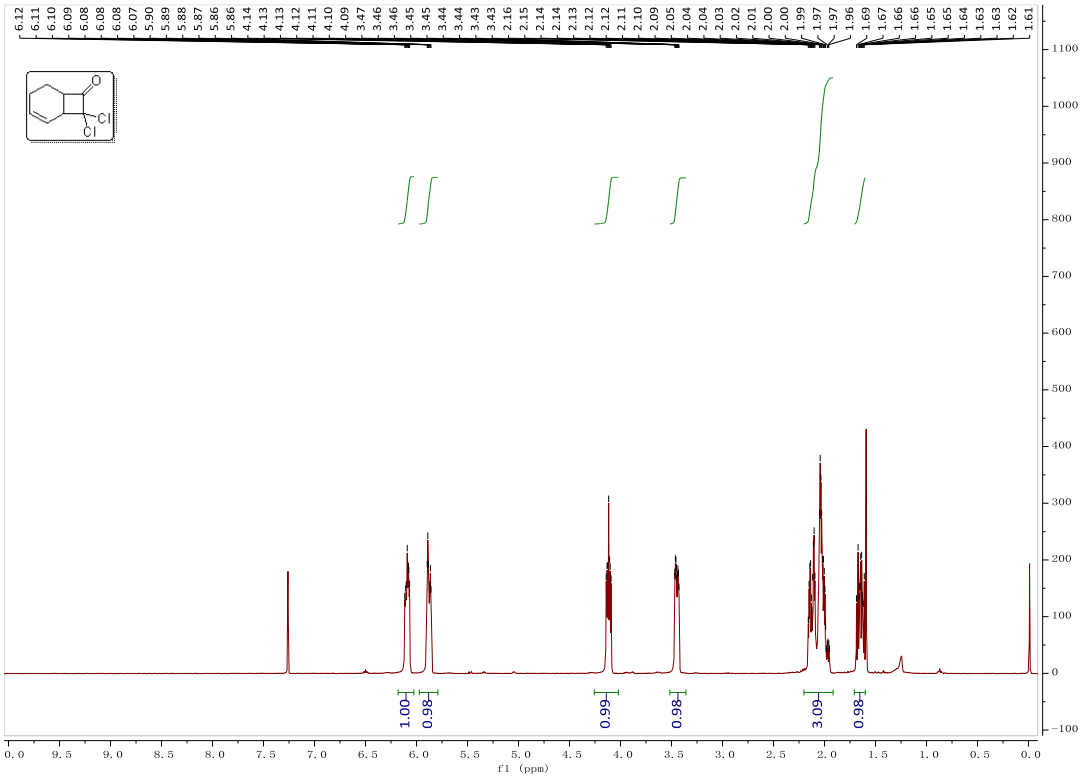

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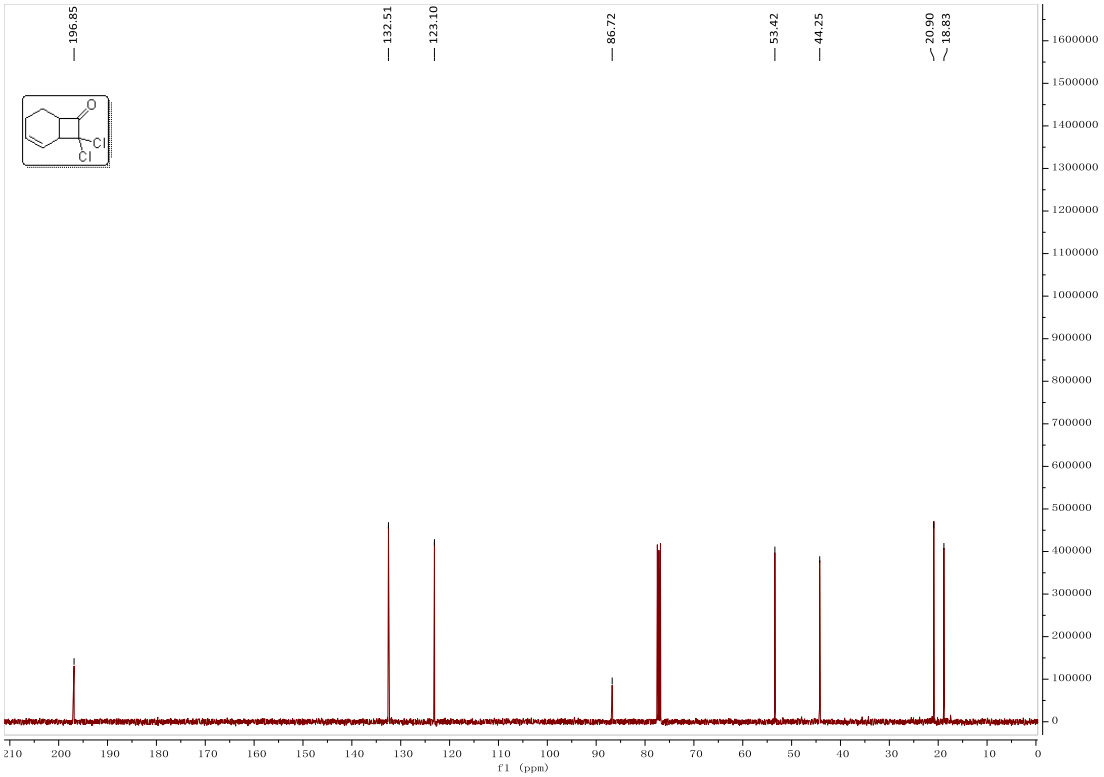

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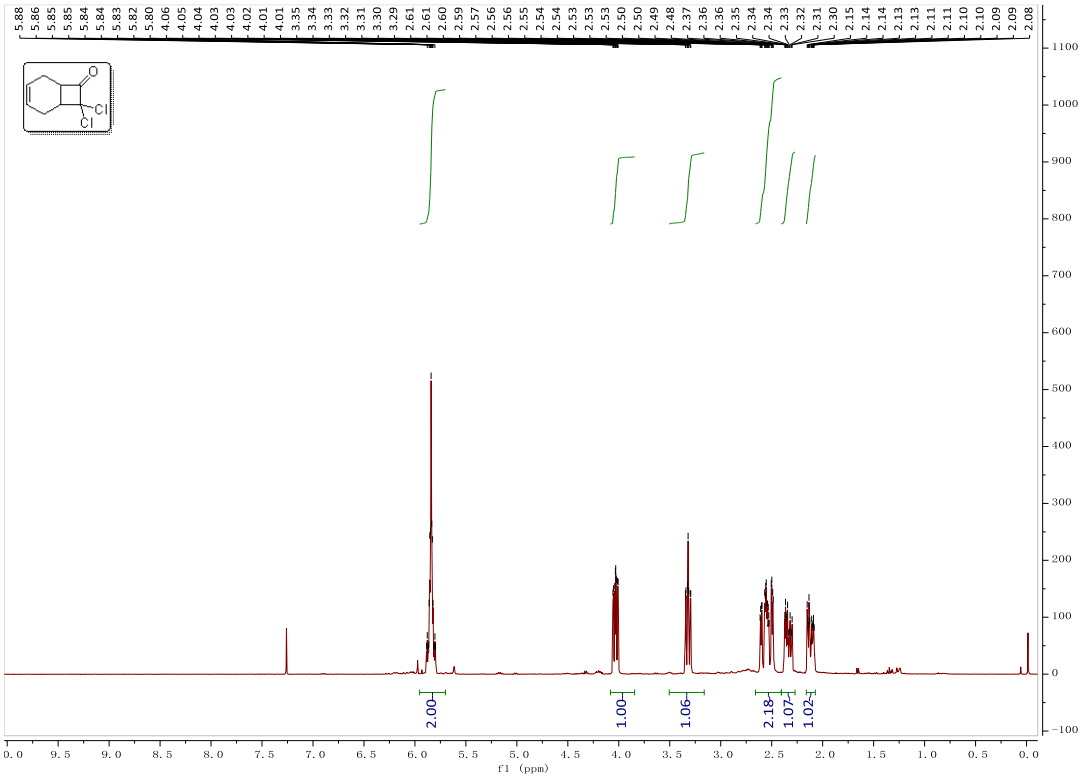

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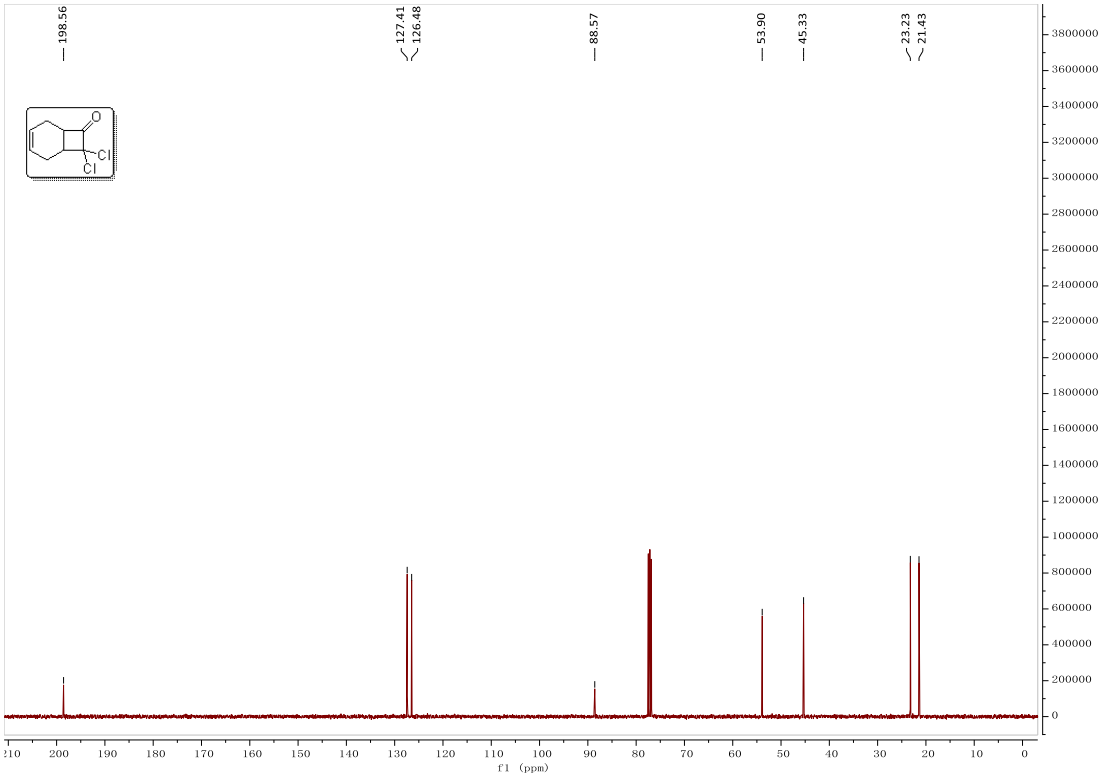

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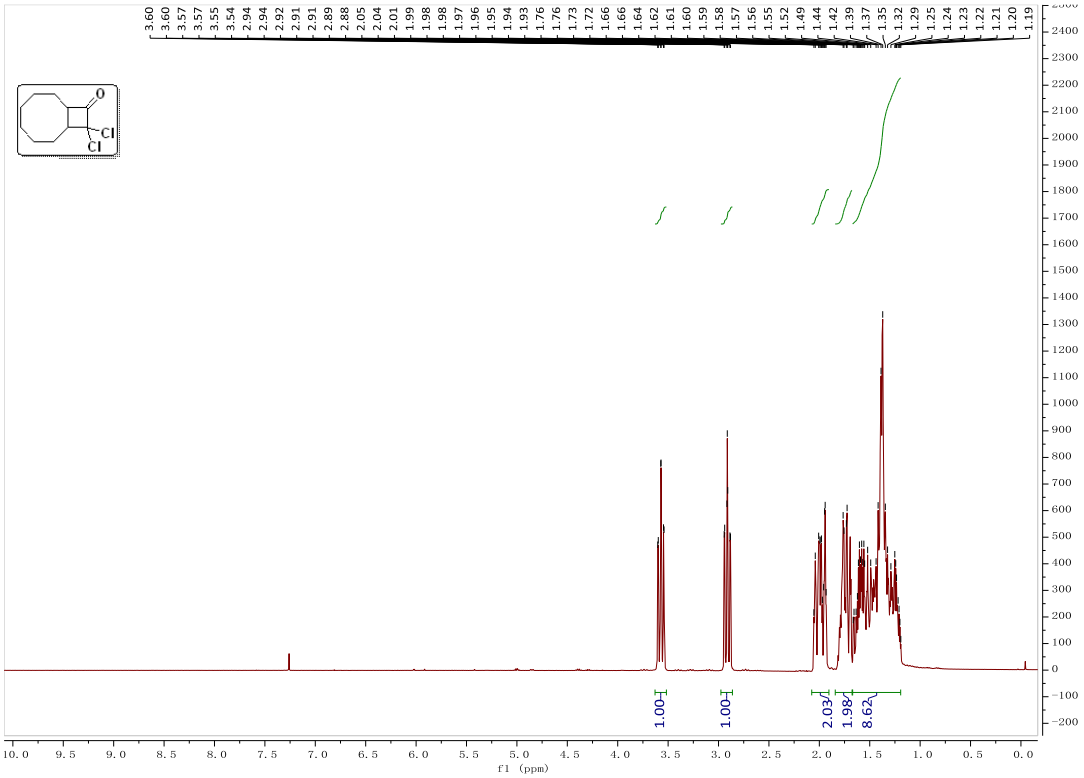

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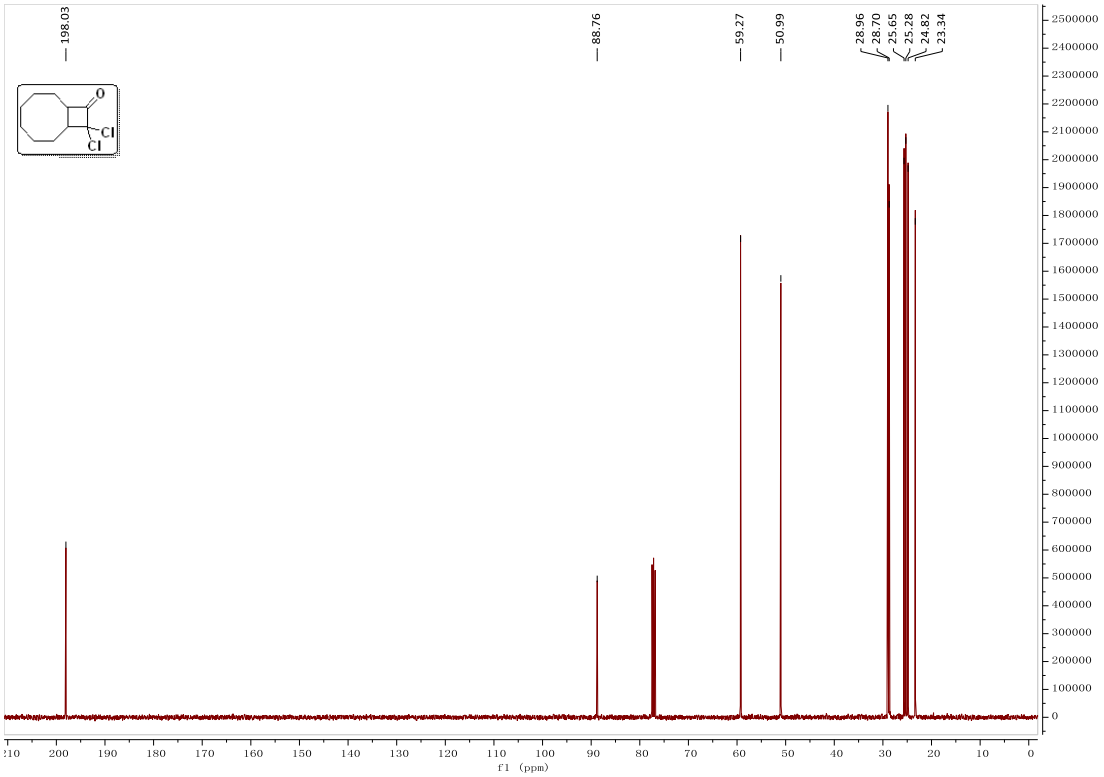

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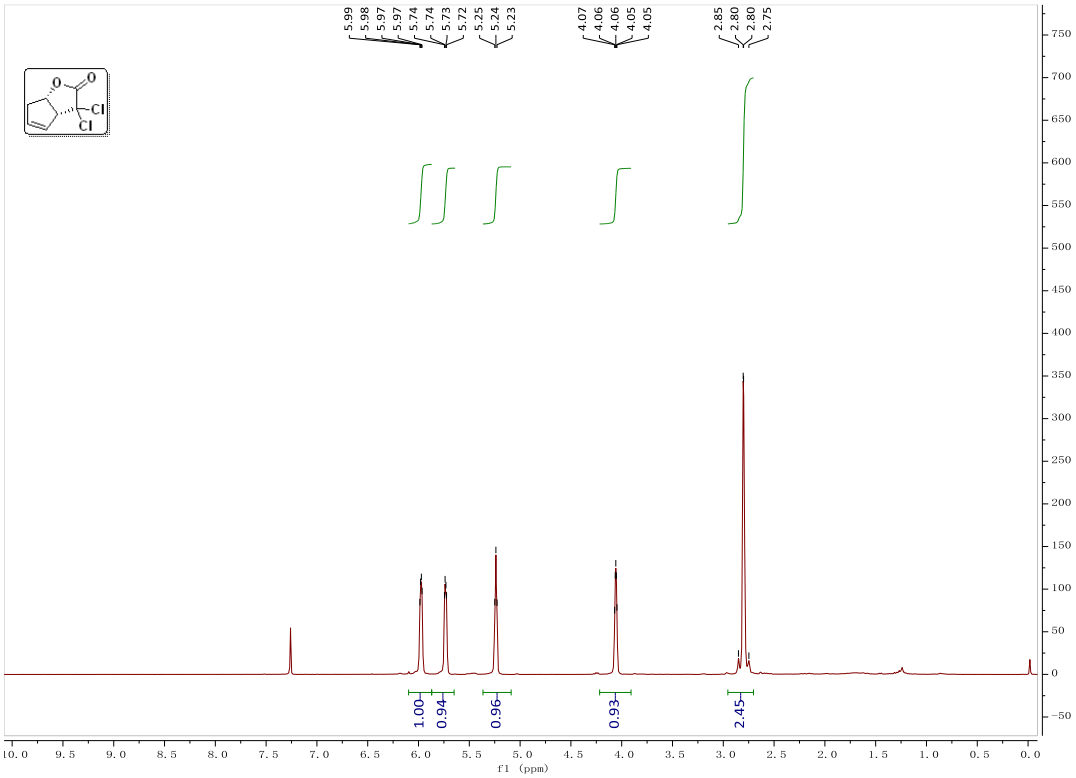

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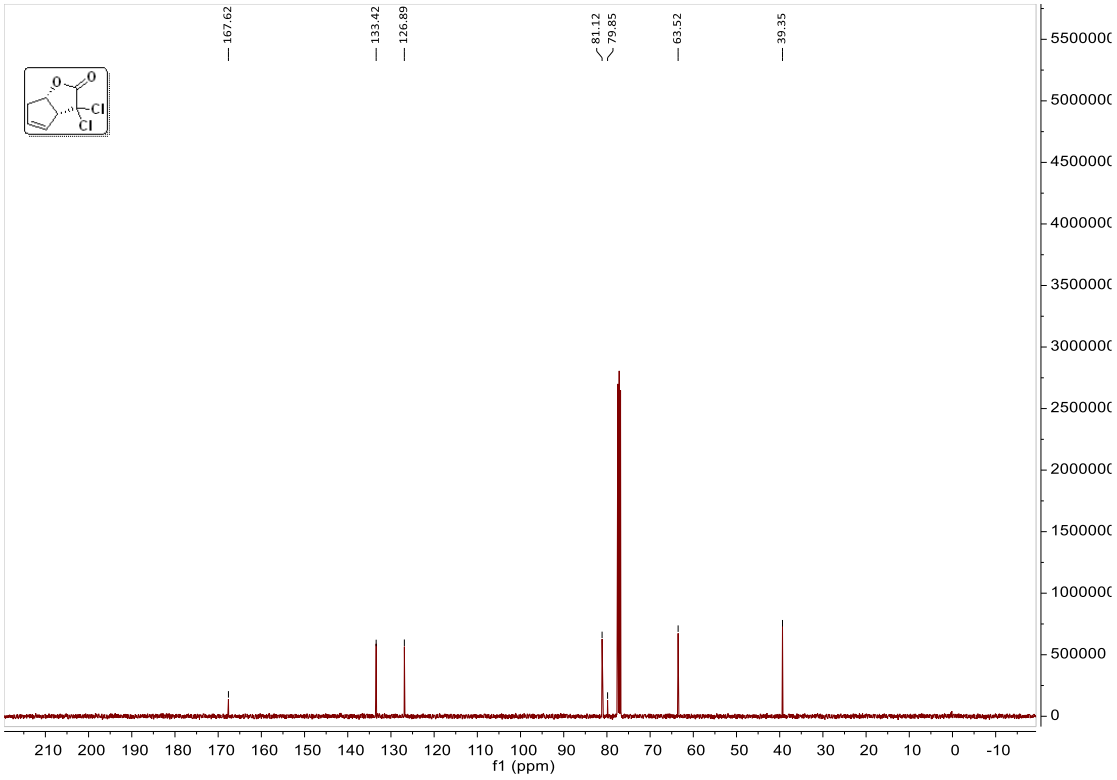

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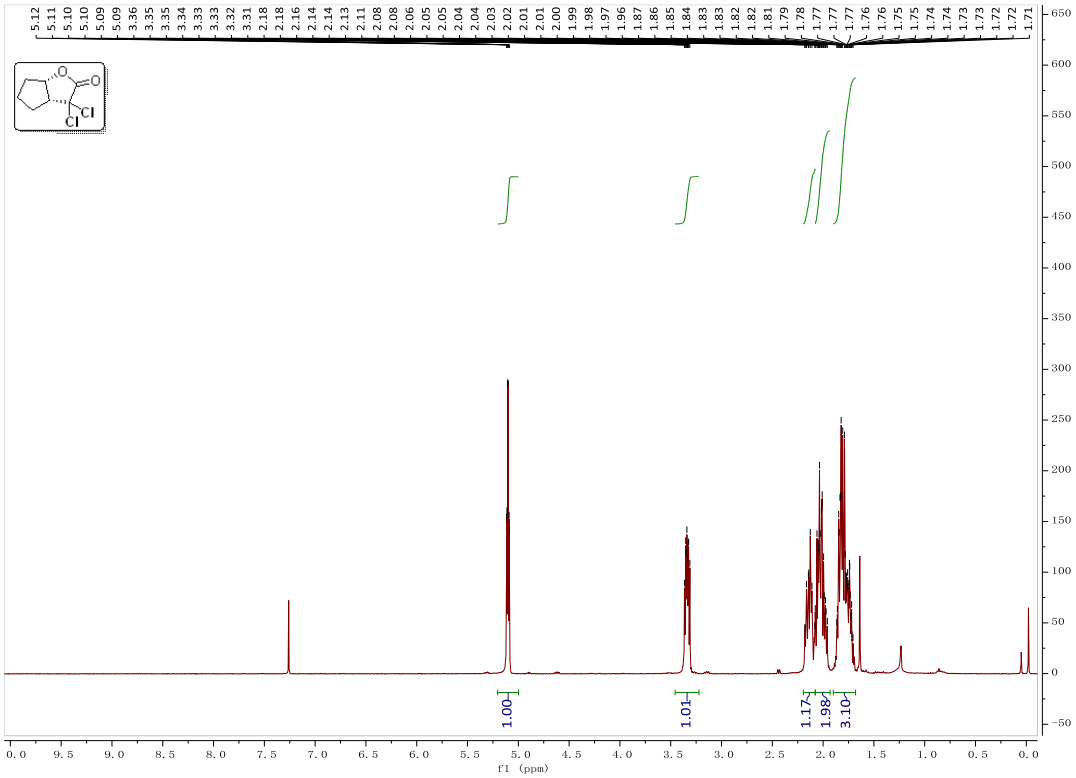

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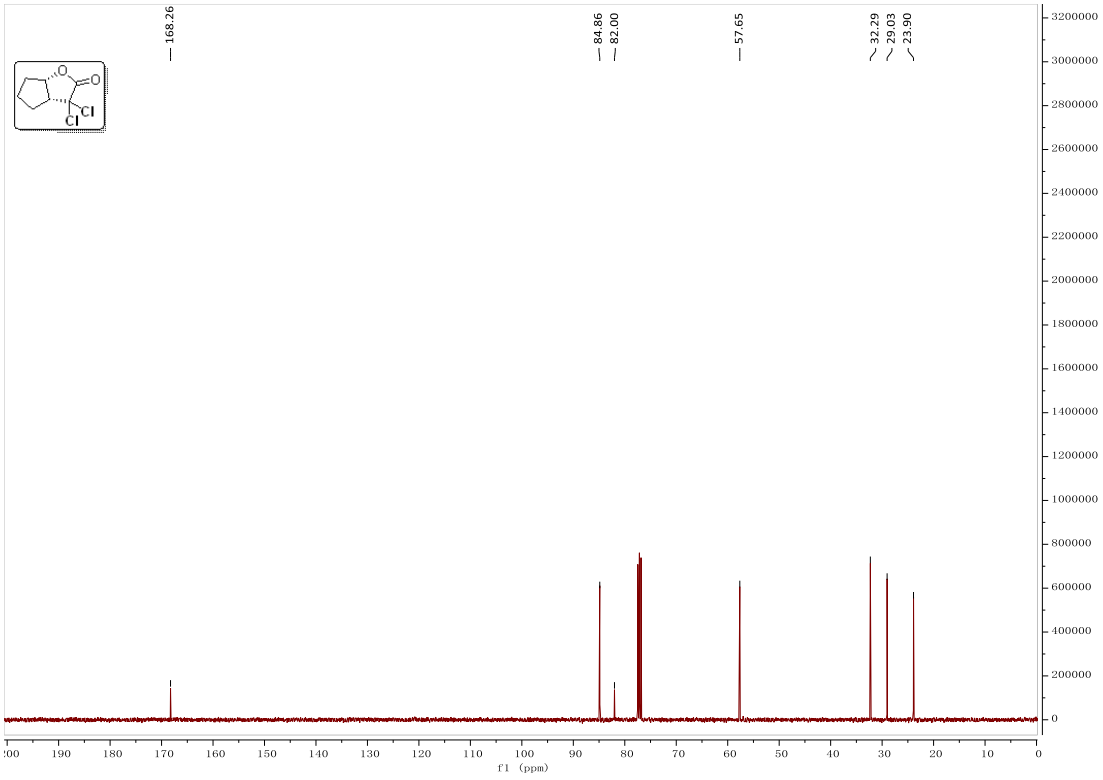

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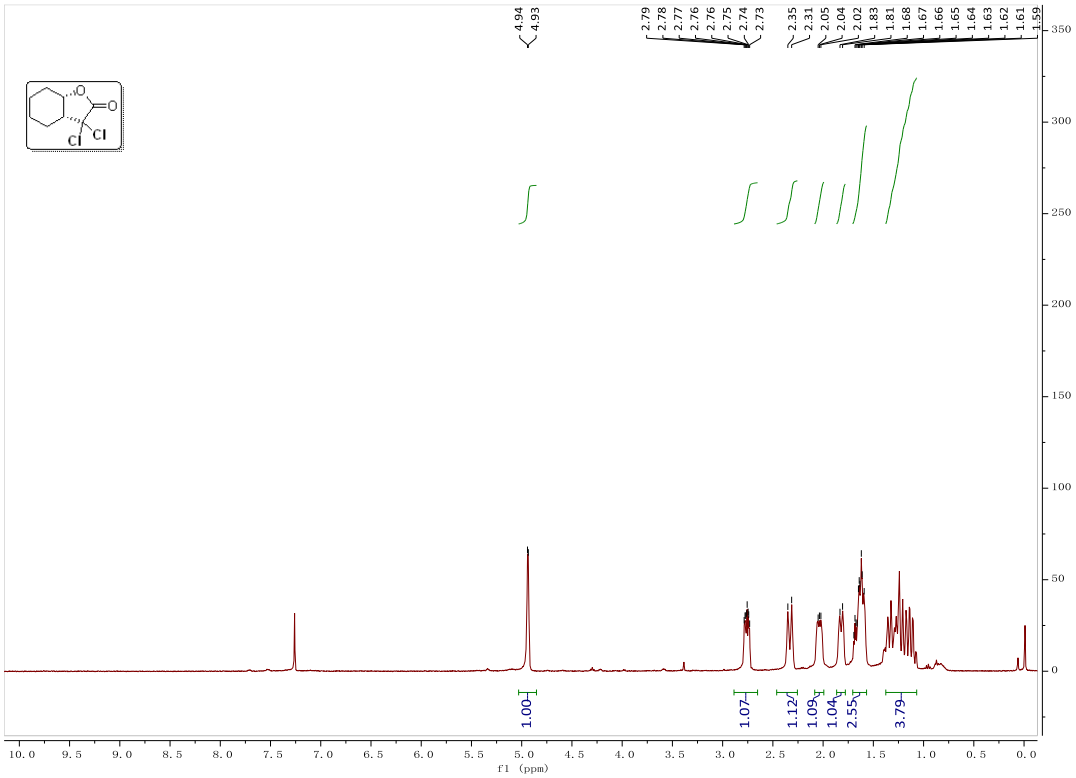

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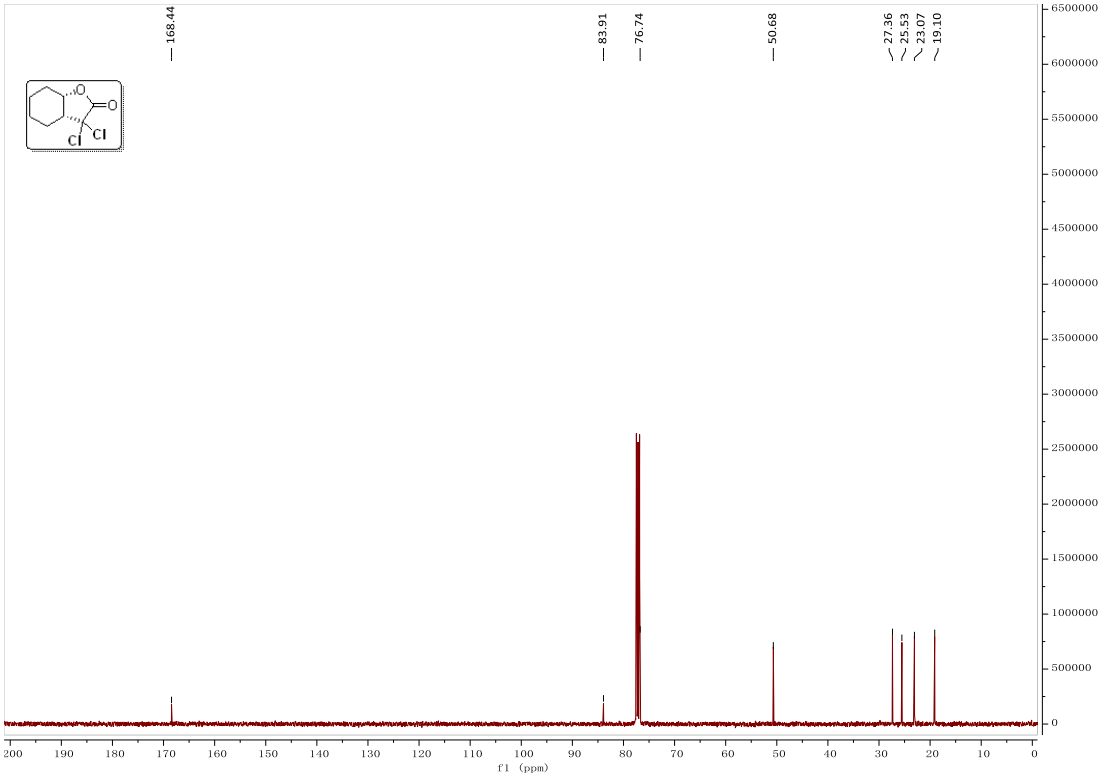

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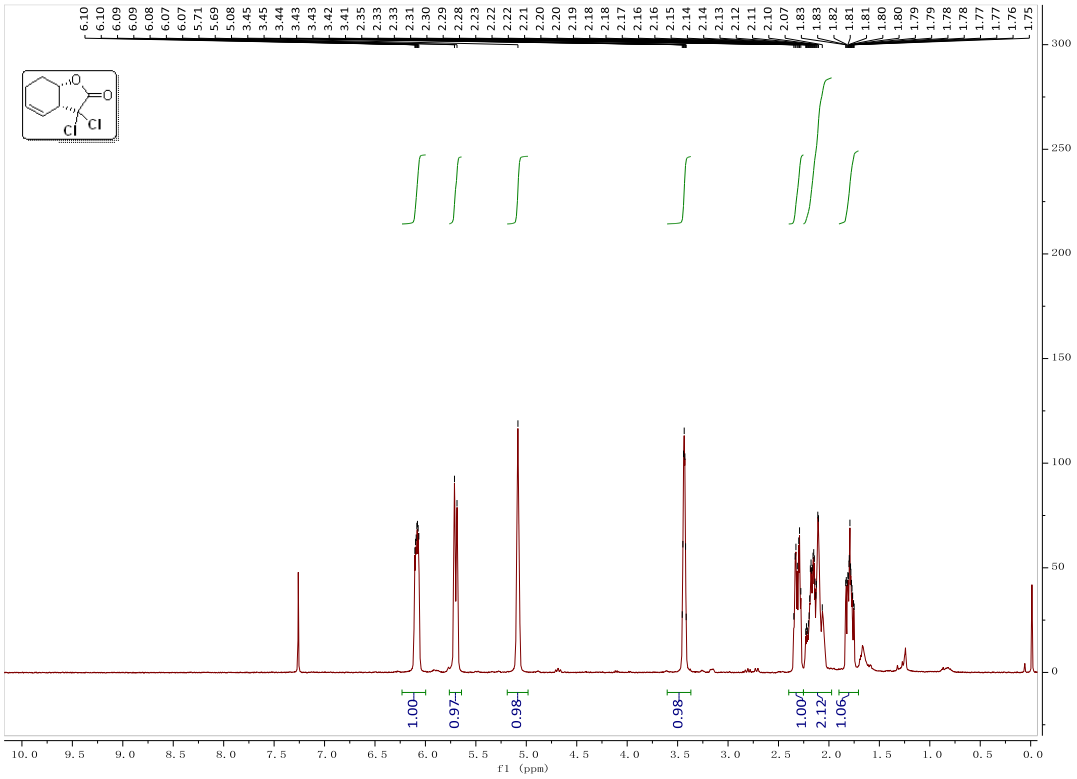

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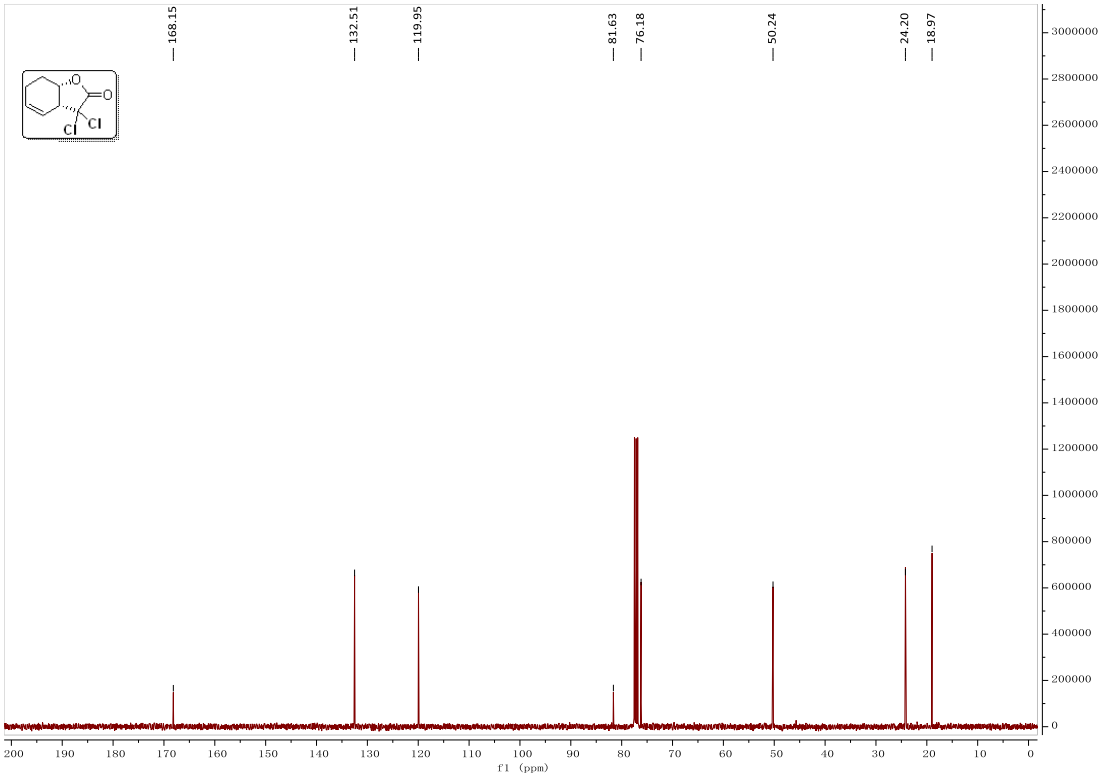

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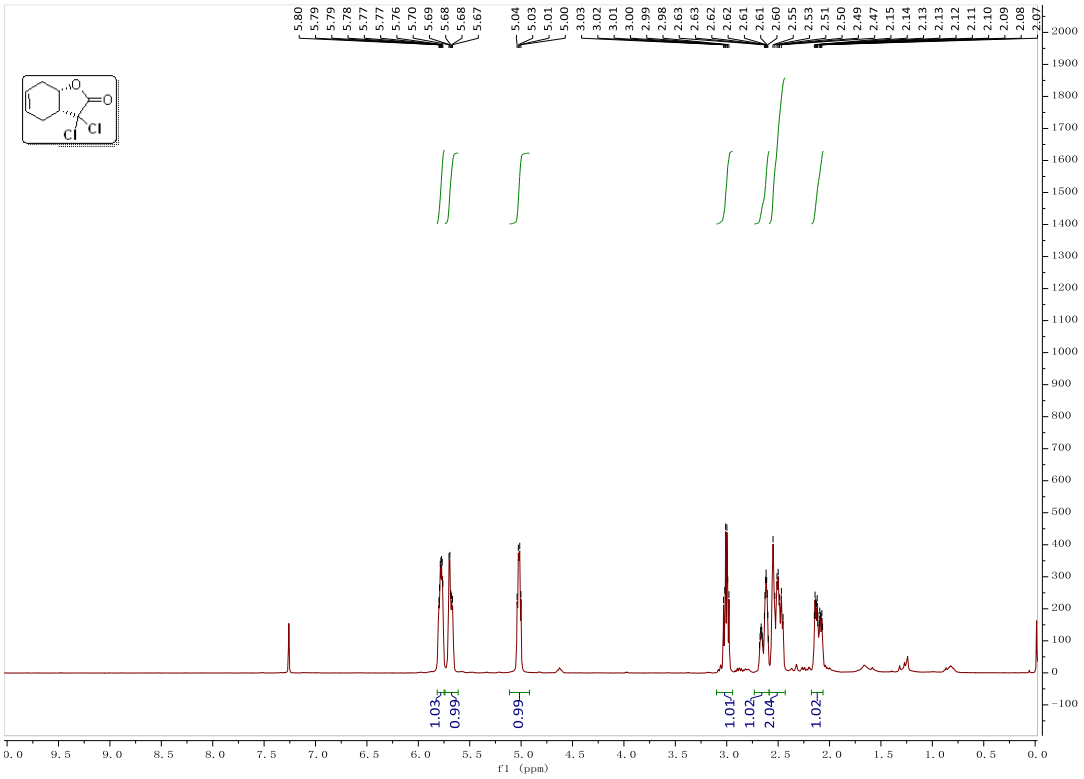
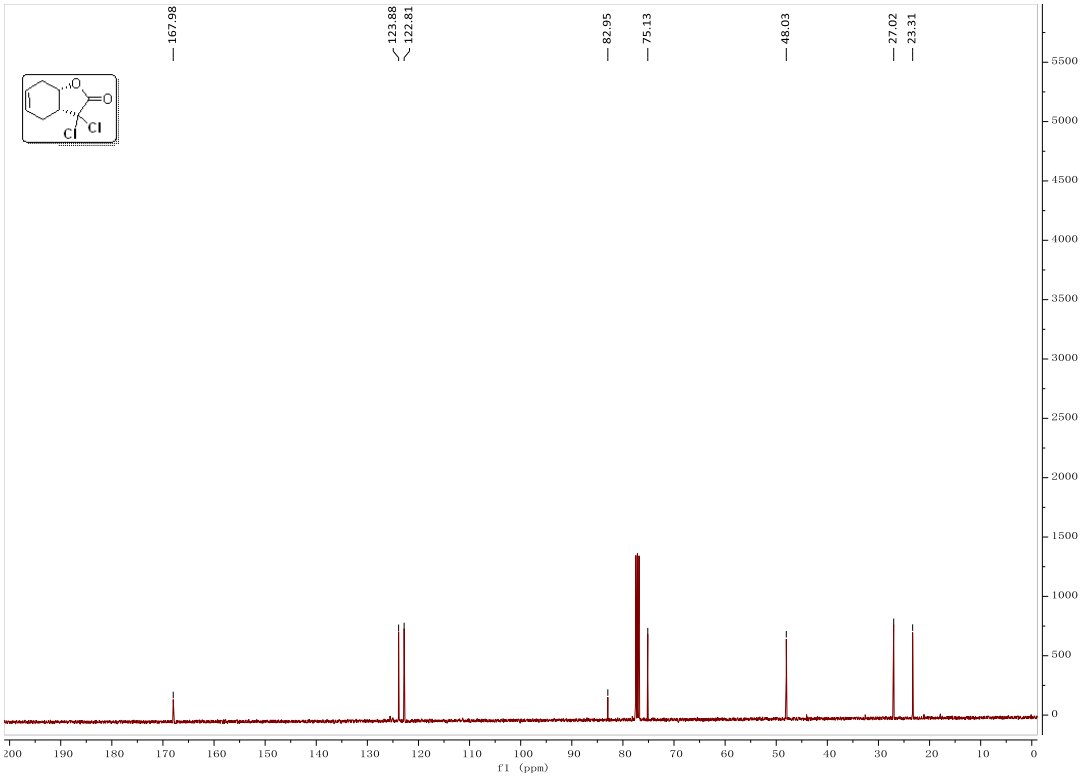
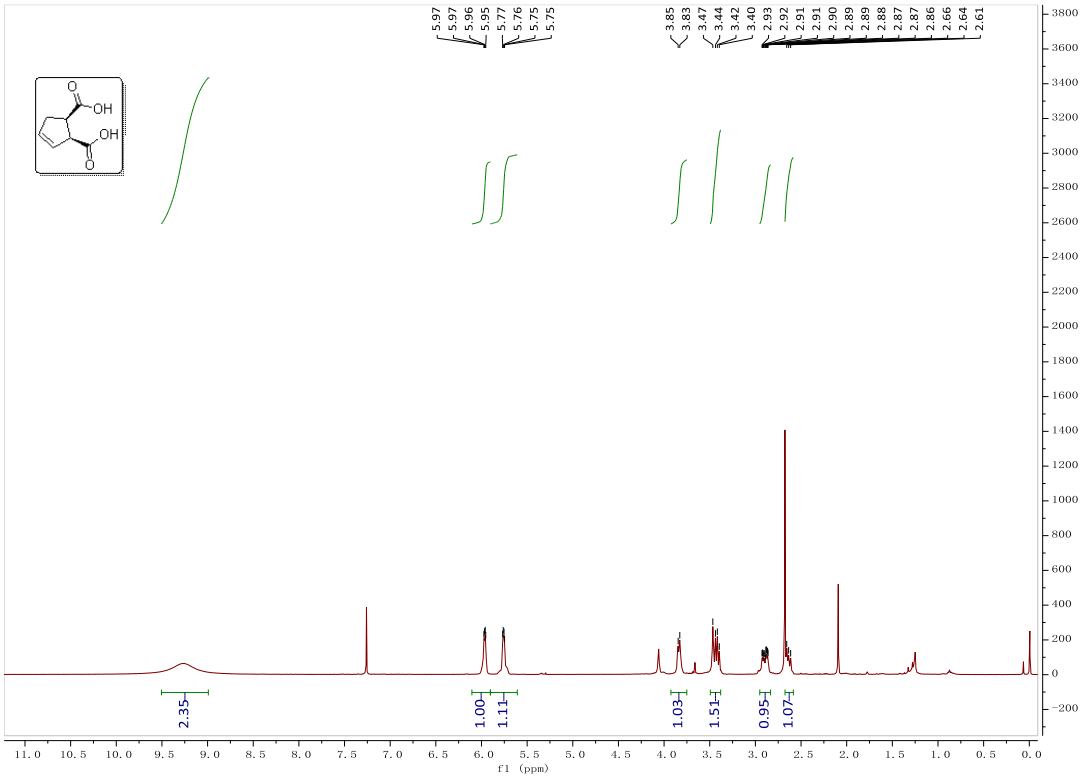


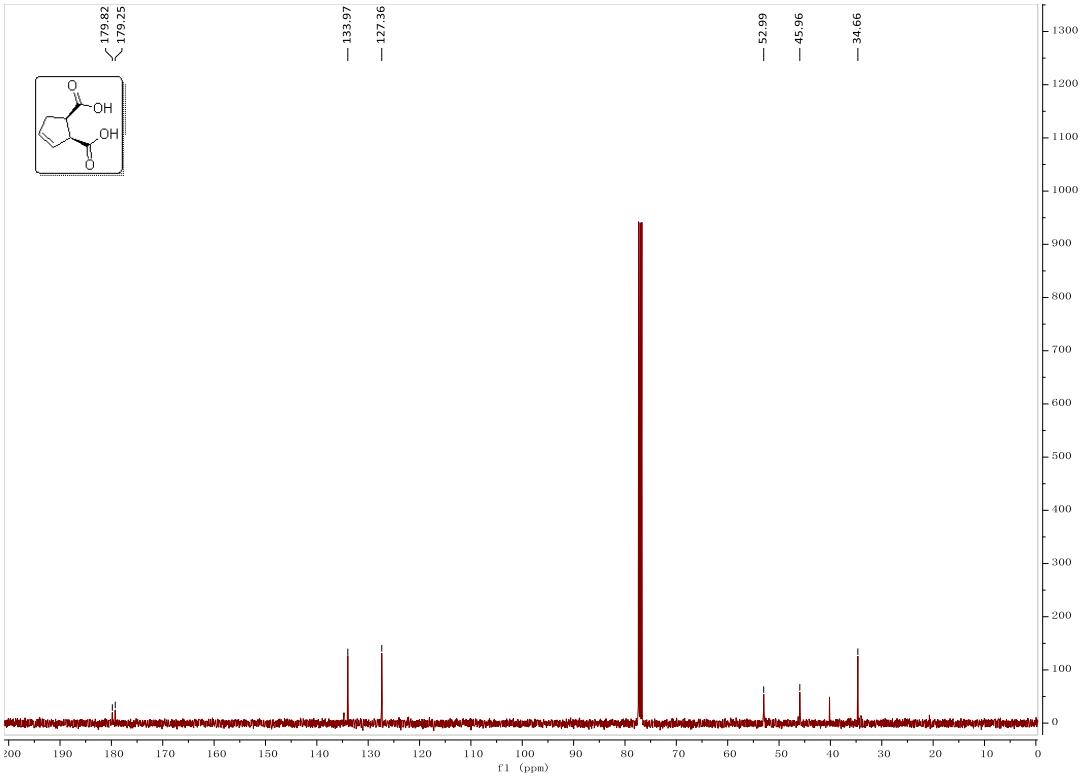
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of 7e



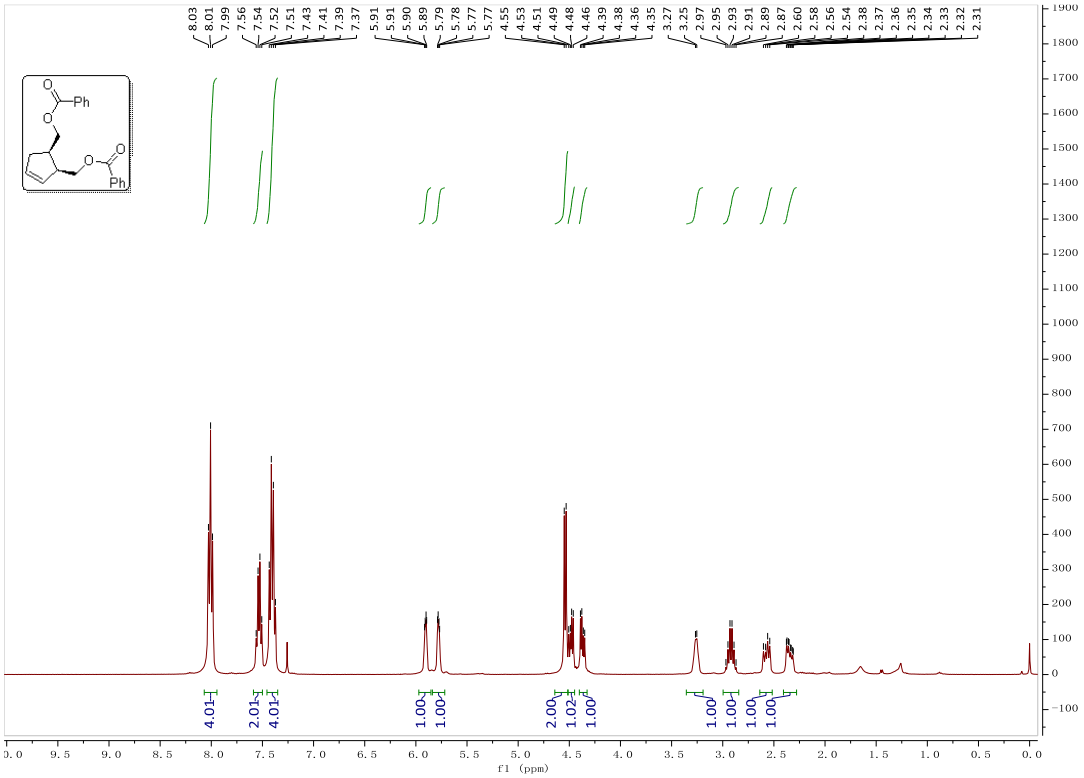
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of 9



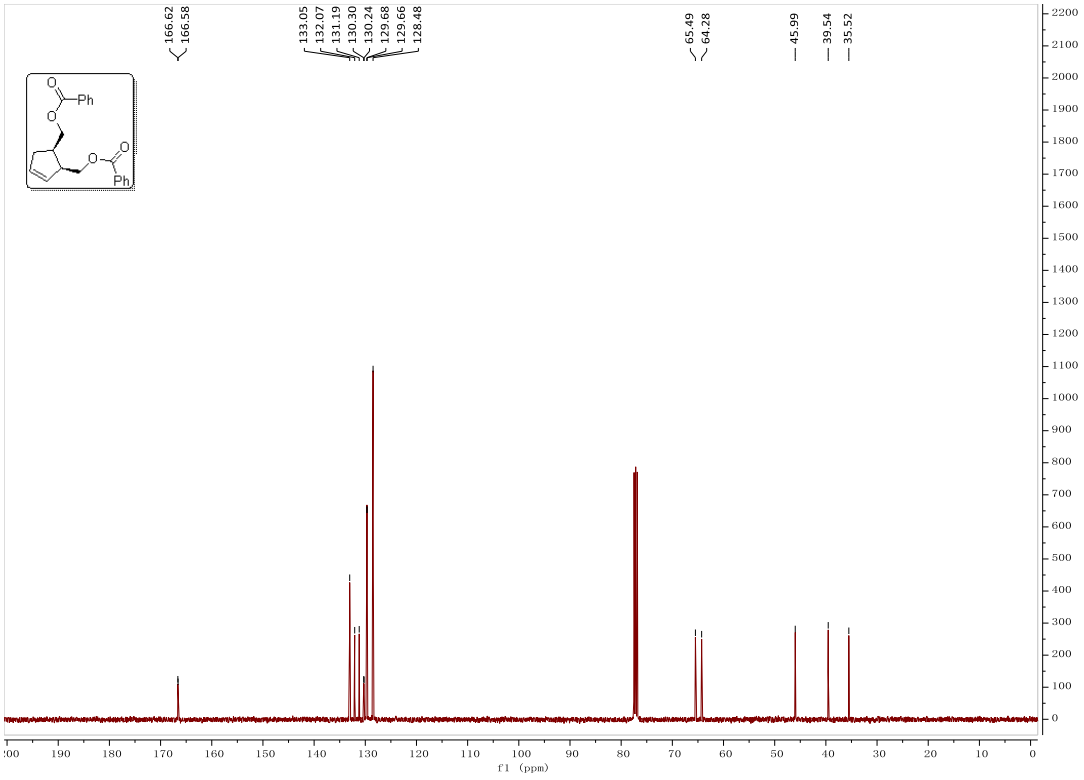
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of 9



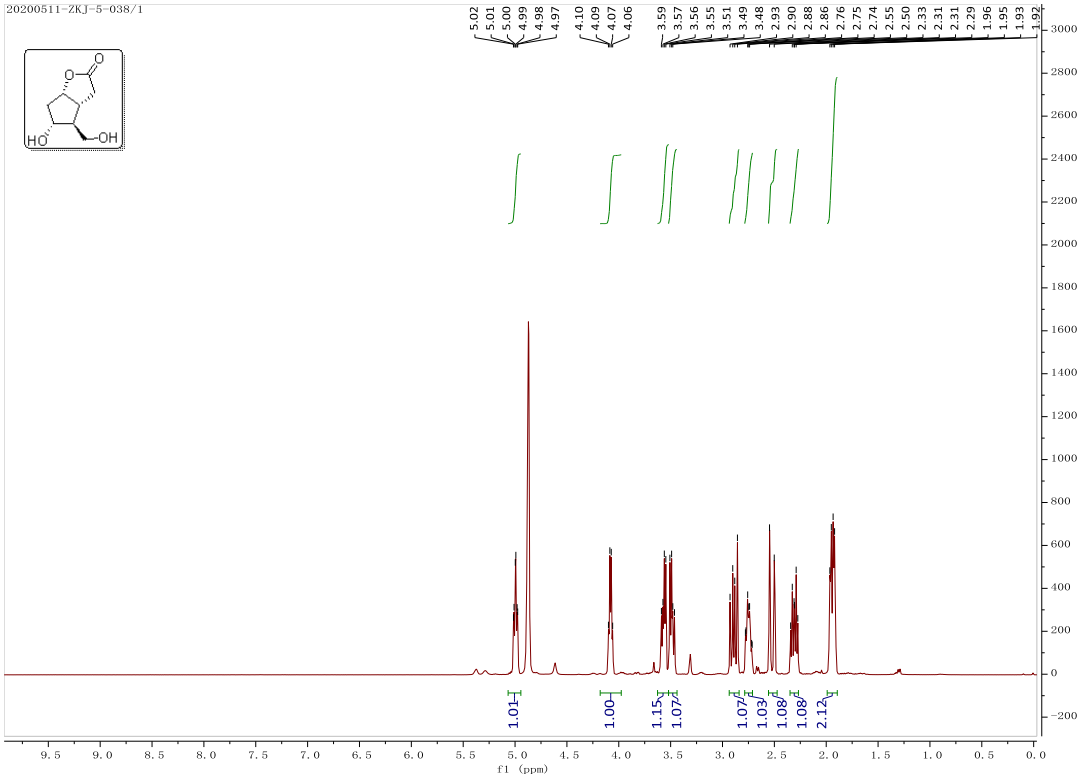
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectra of 9”



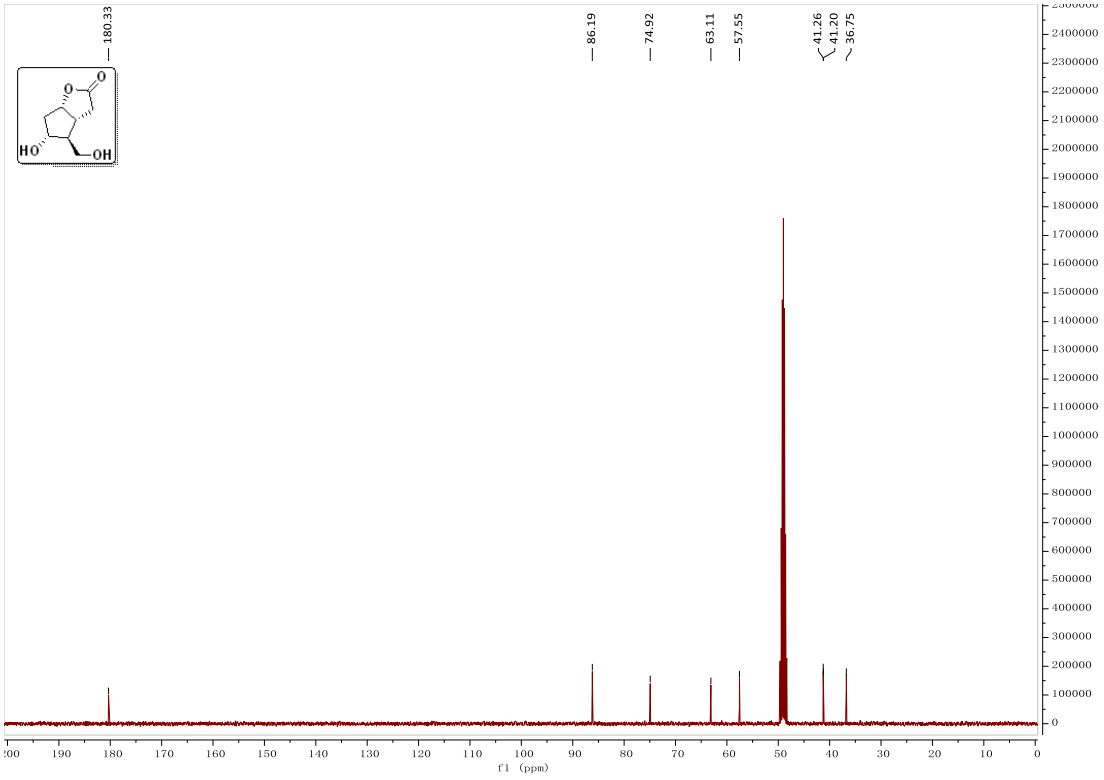
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectra of 9”



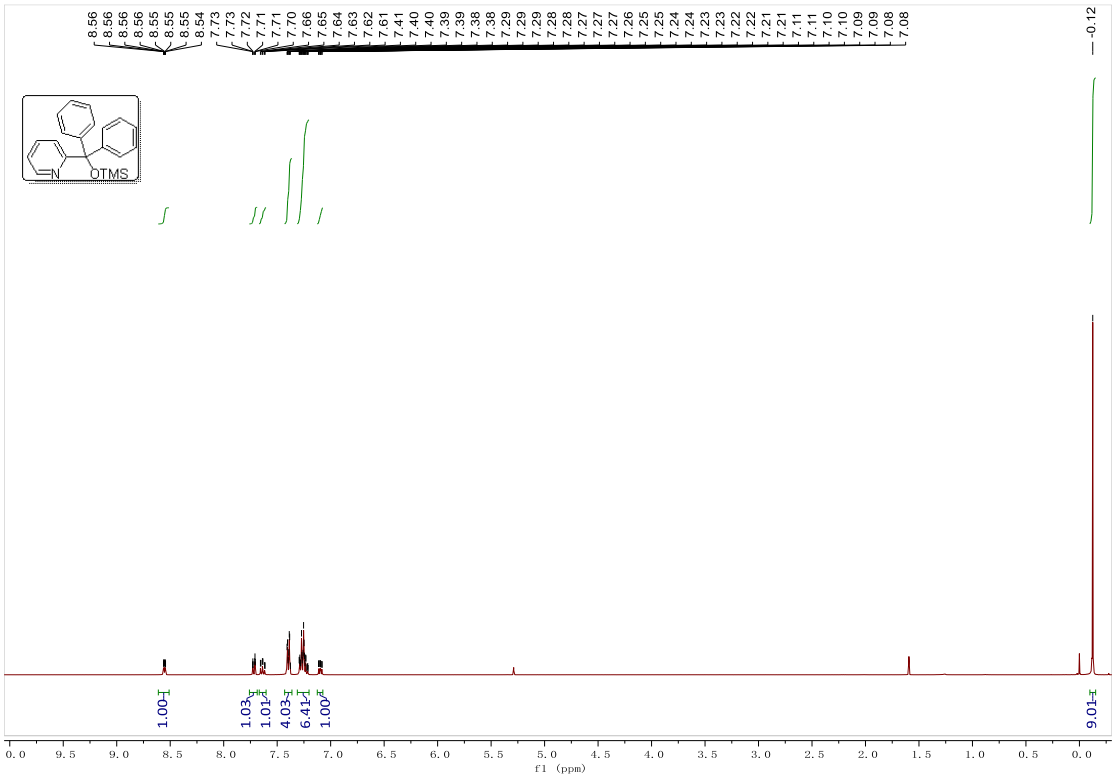
The ^{1}H NMR (400 MHz, Methanol-d_4) Spectrum of 10



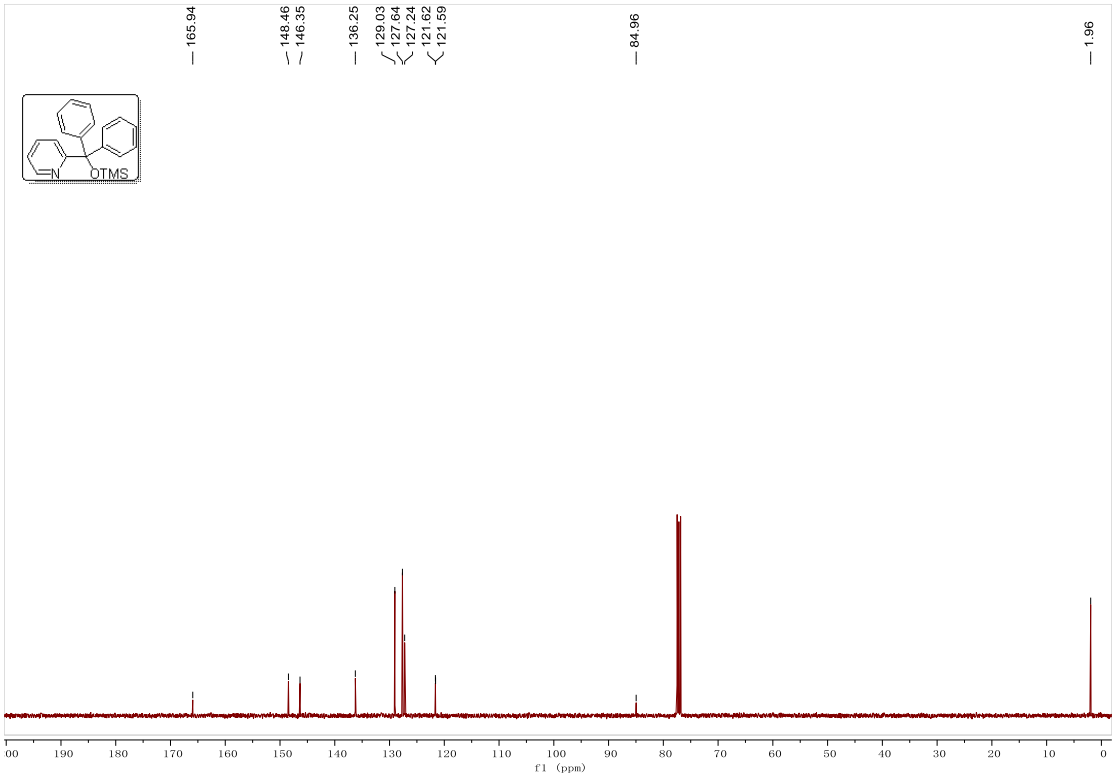
The ^{13}C NMR (101 MHz, Methanol-d_4) Spectrum of 10



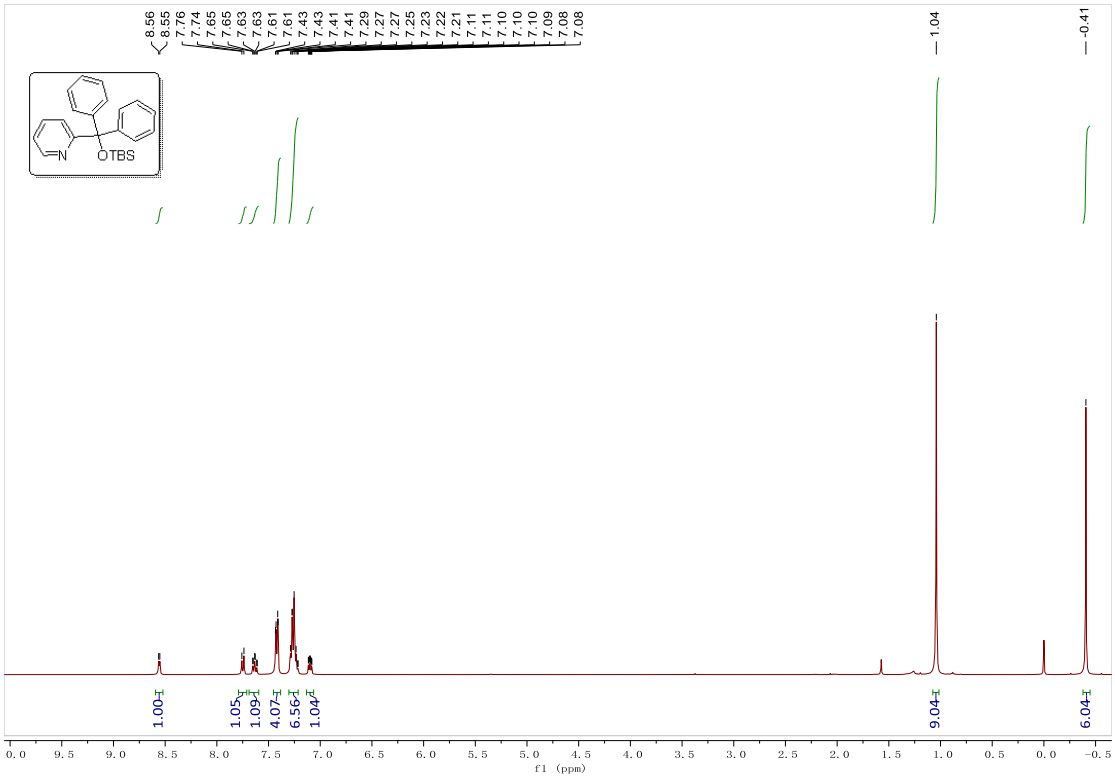
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Ad4



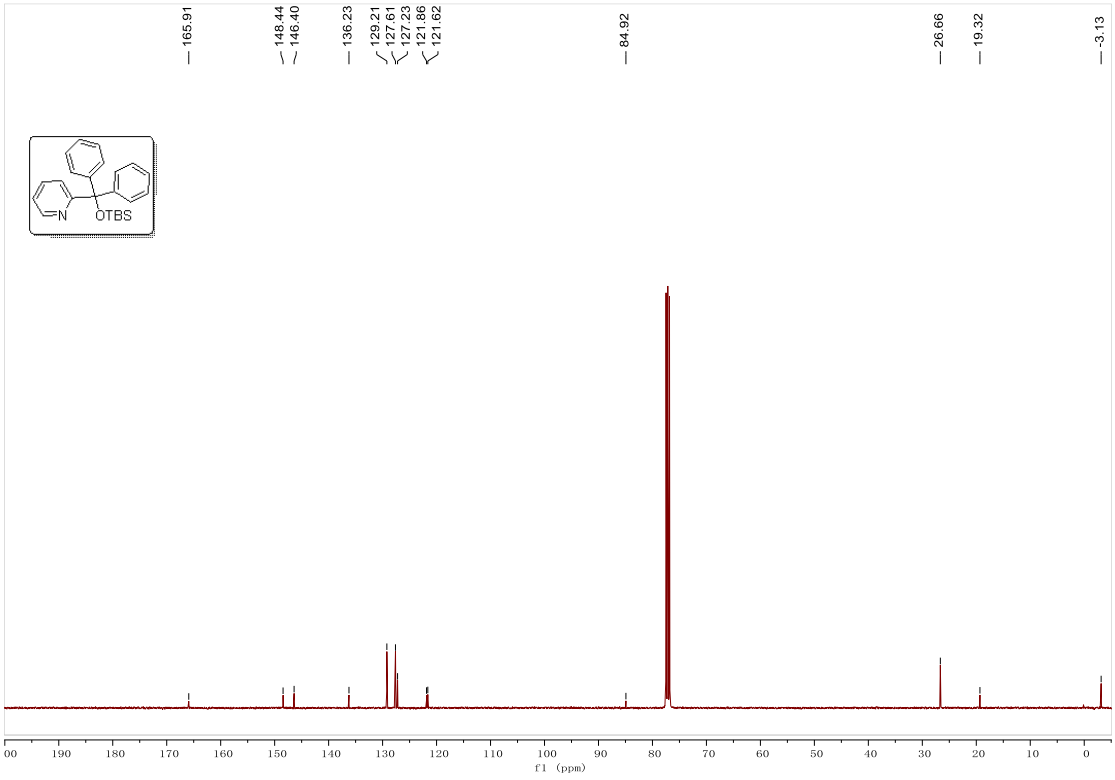
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of Ad4



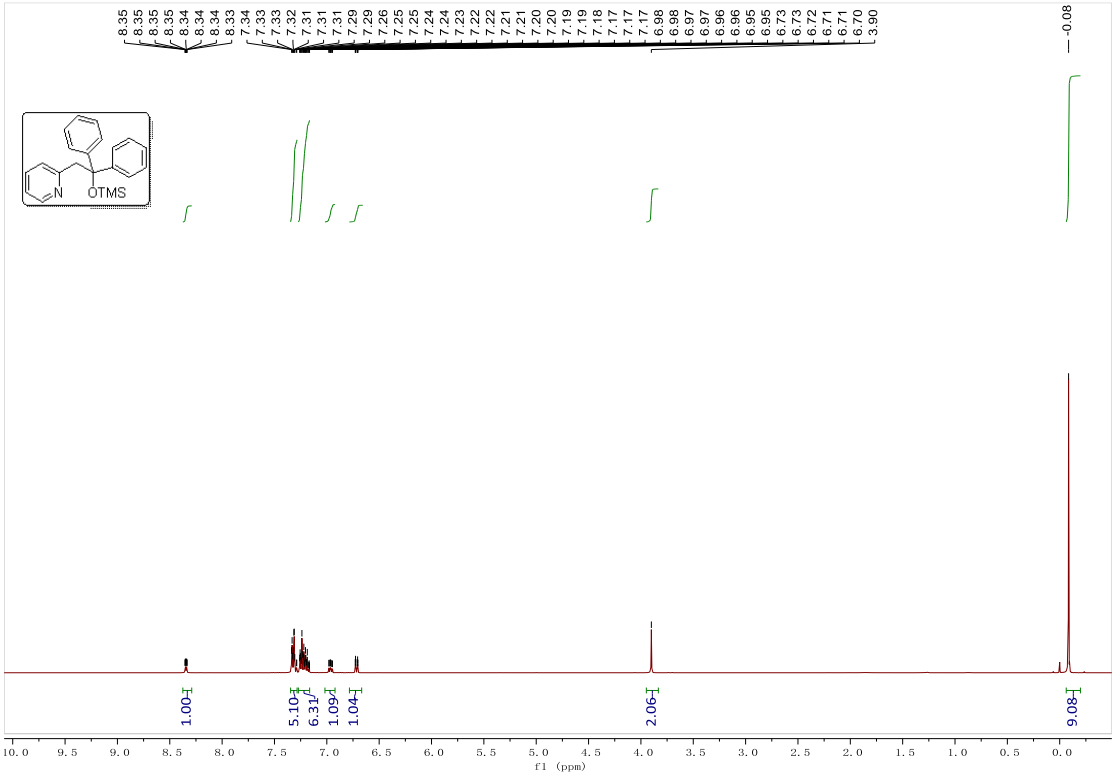
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Ad5



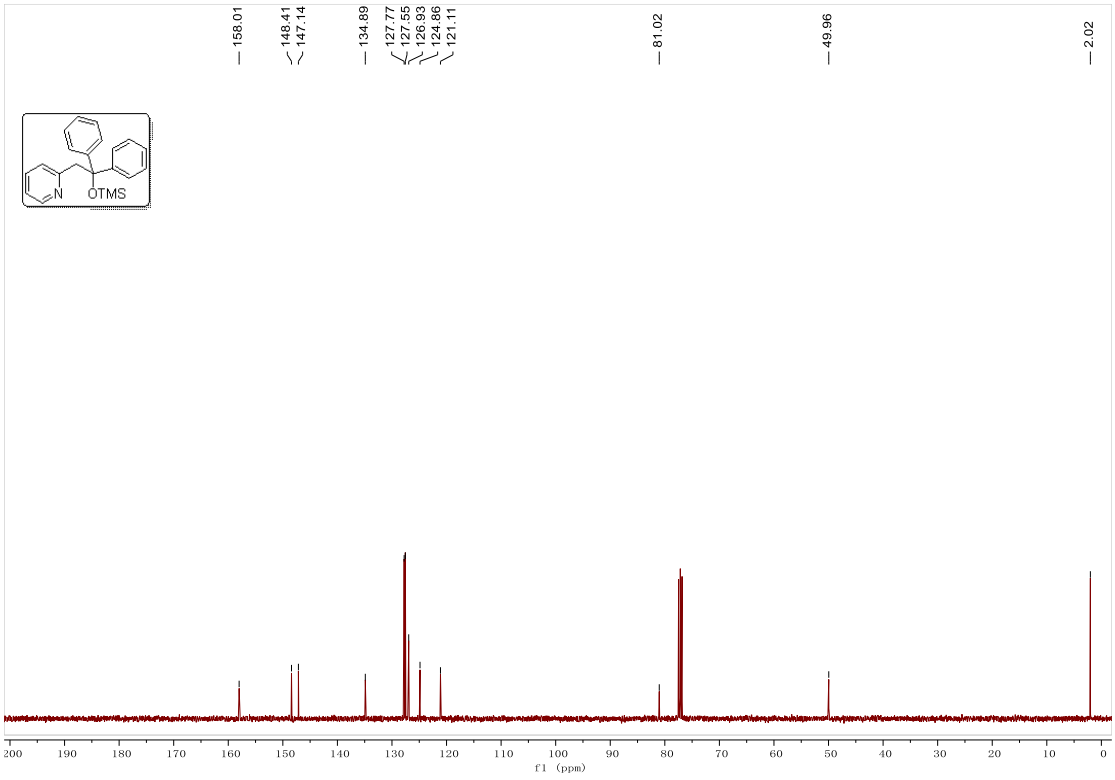
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of Ad5



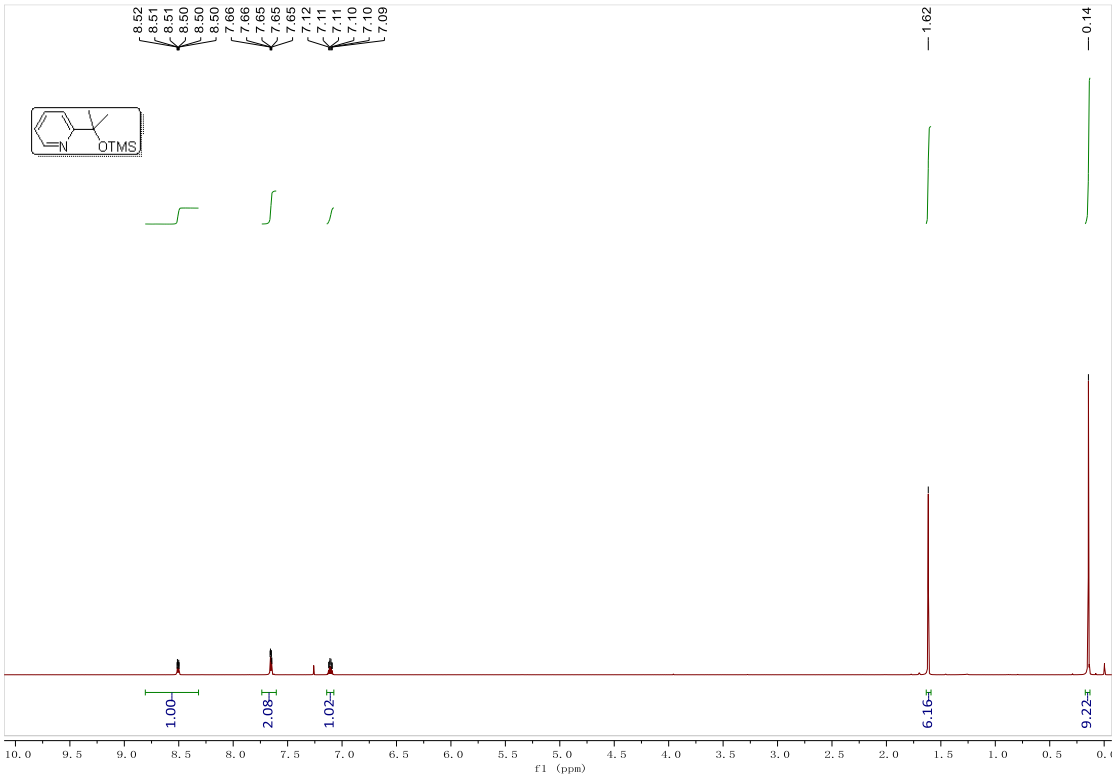
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Ad6



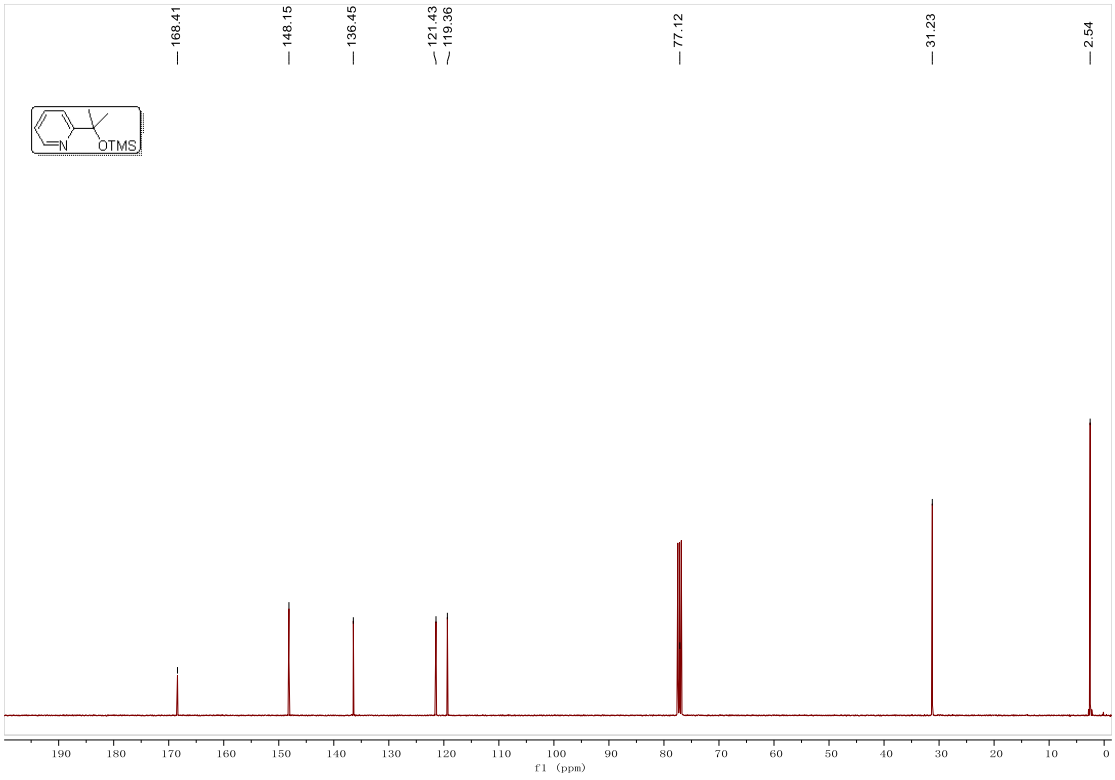
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of Ad6



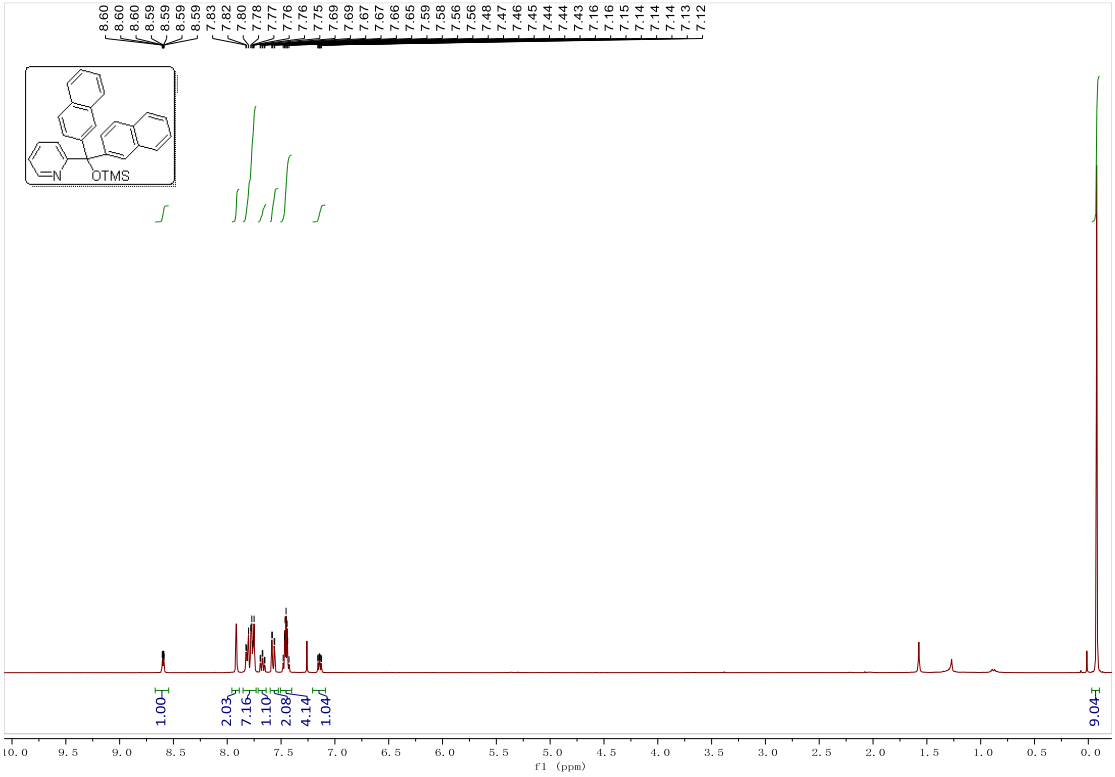
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Ad7



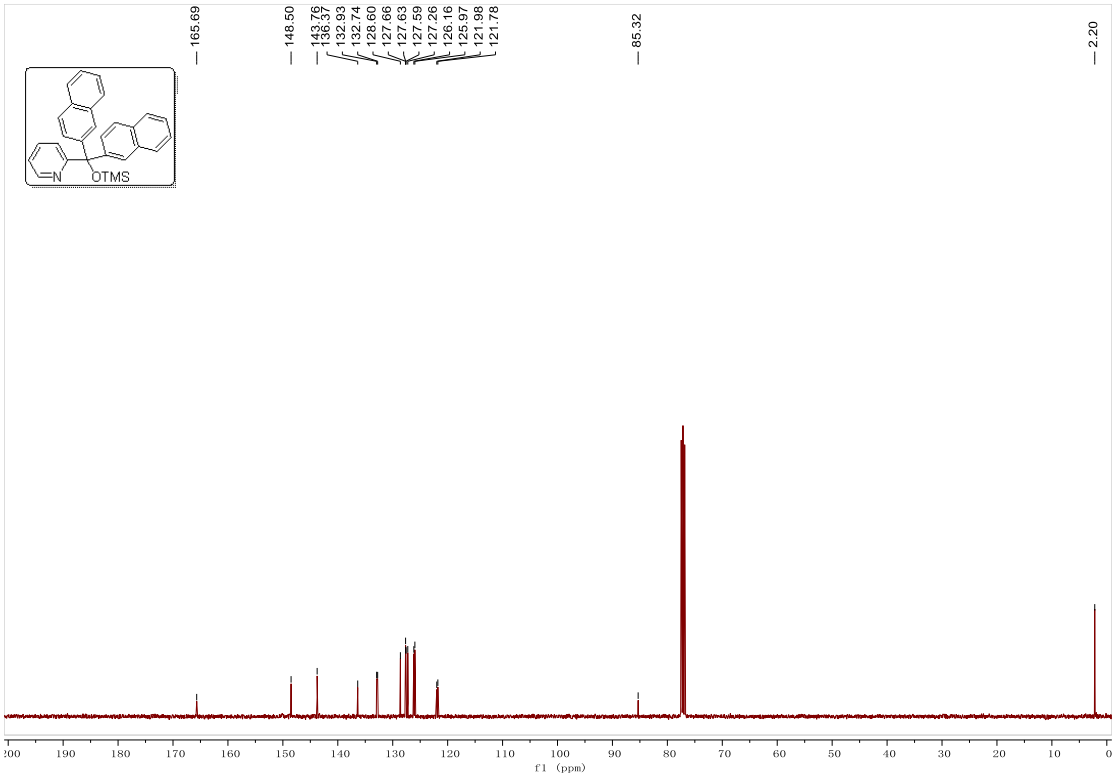
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of Ad7



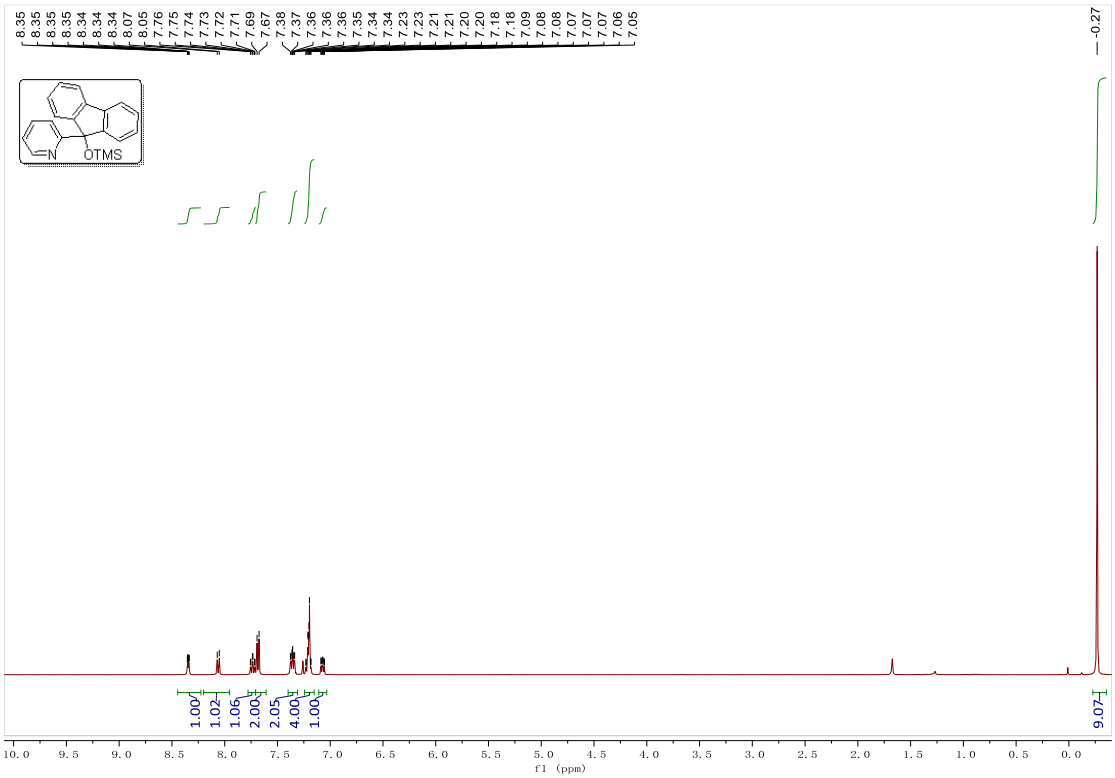
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Ad8



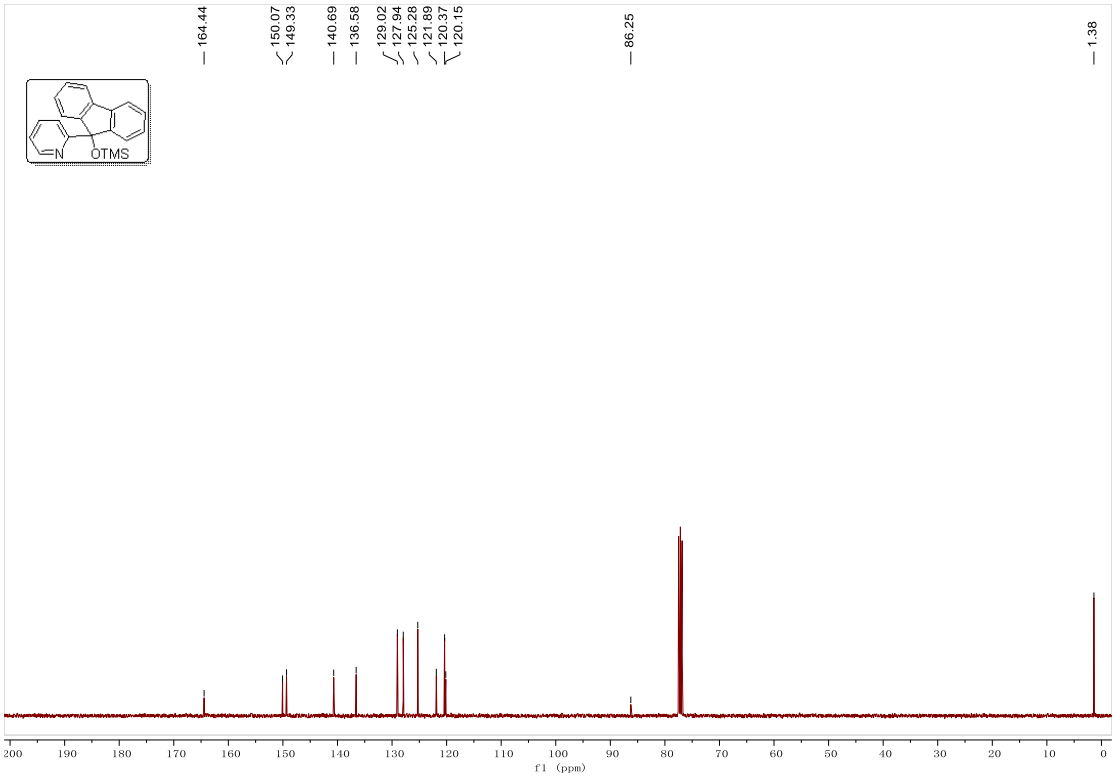
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of Ad8



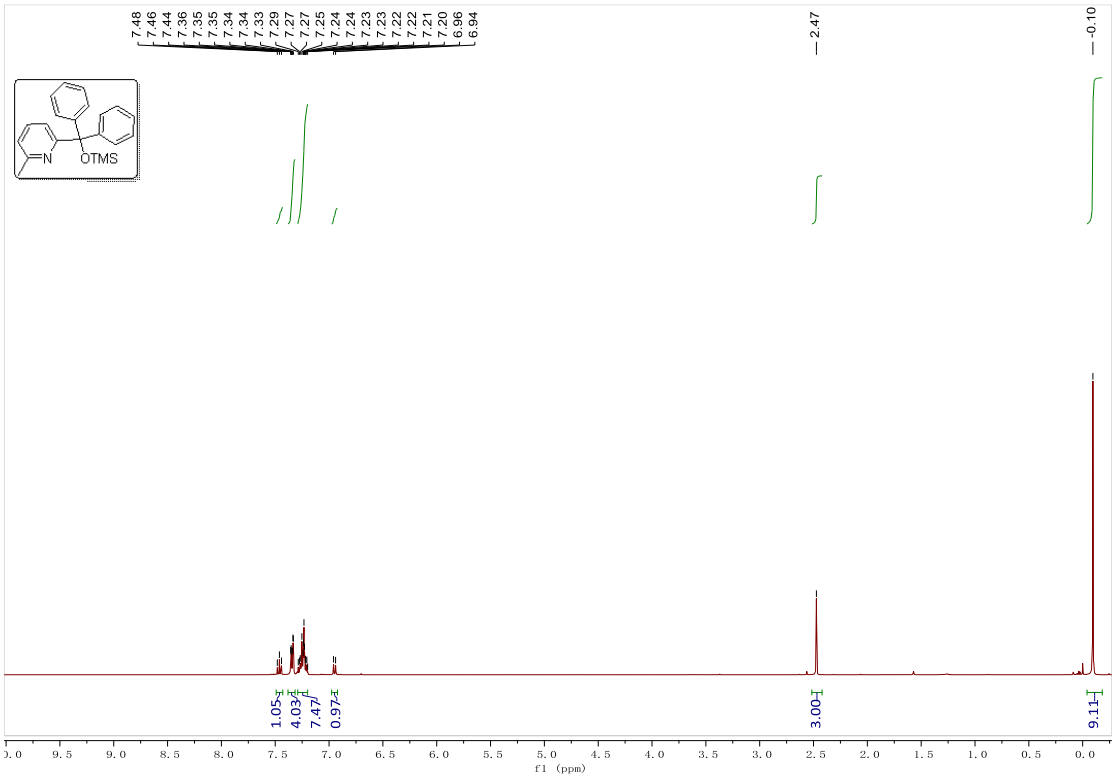
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Ad9



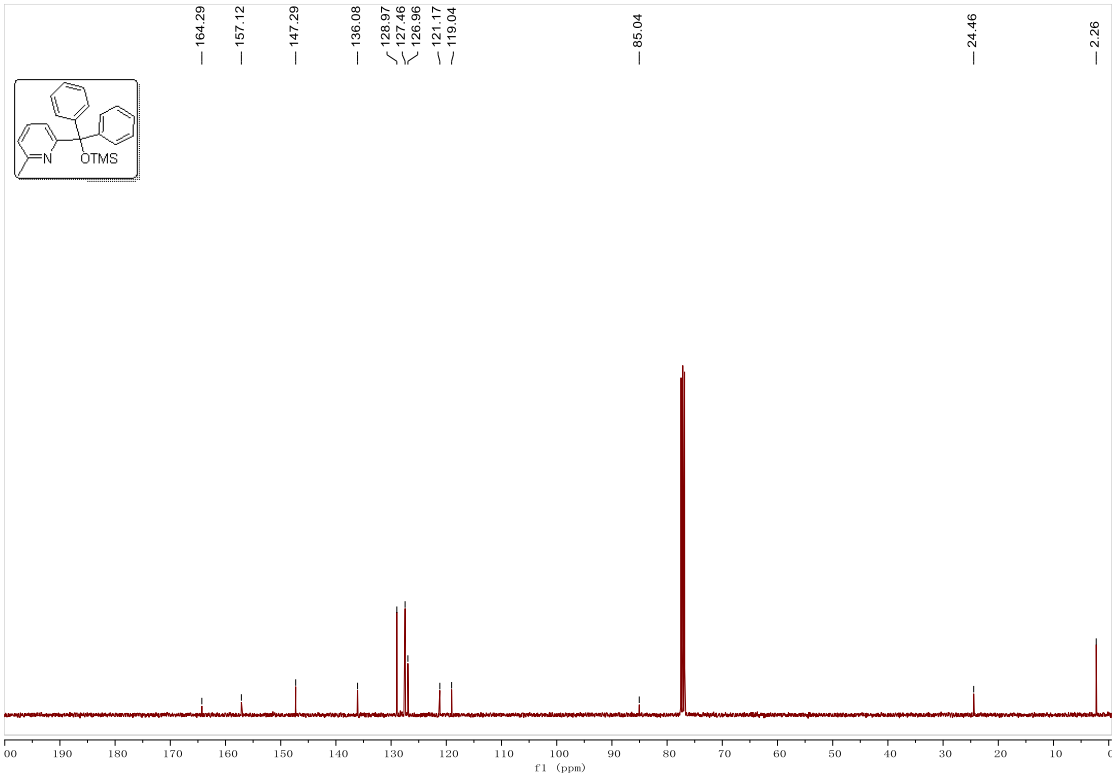
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of Ad9



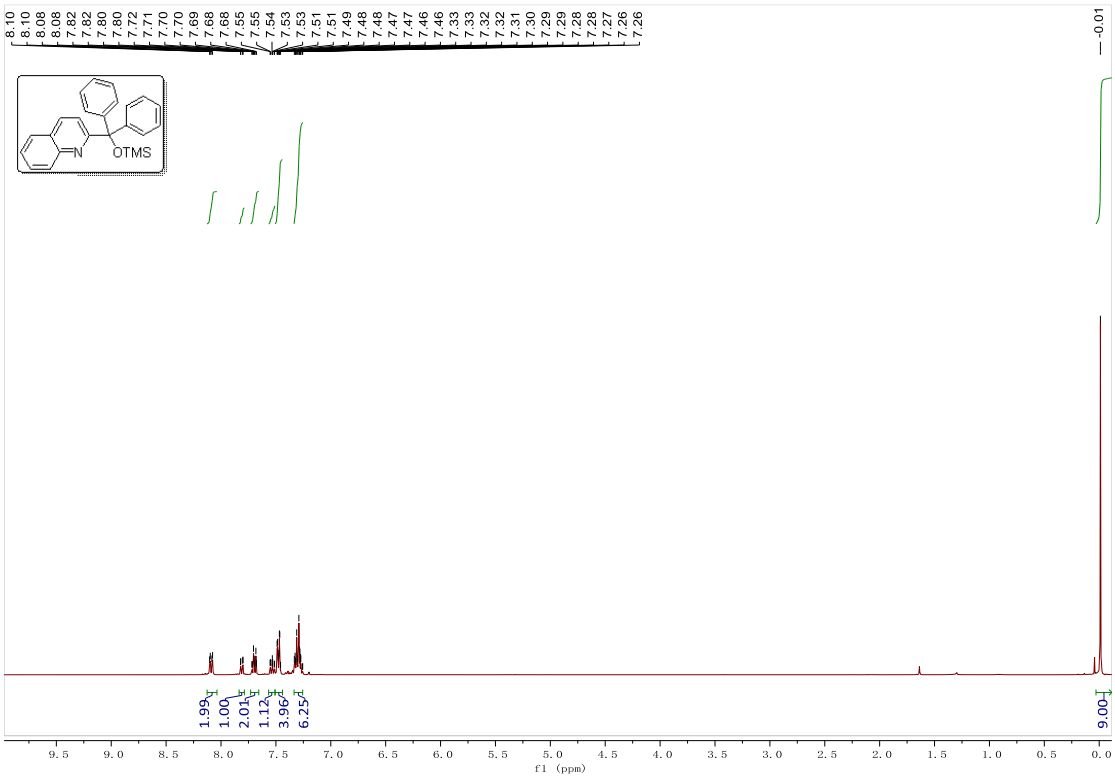
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Ad10



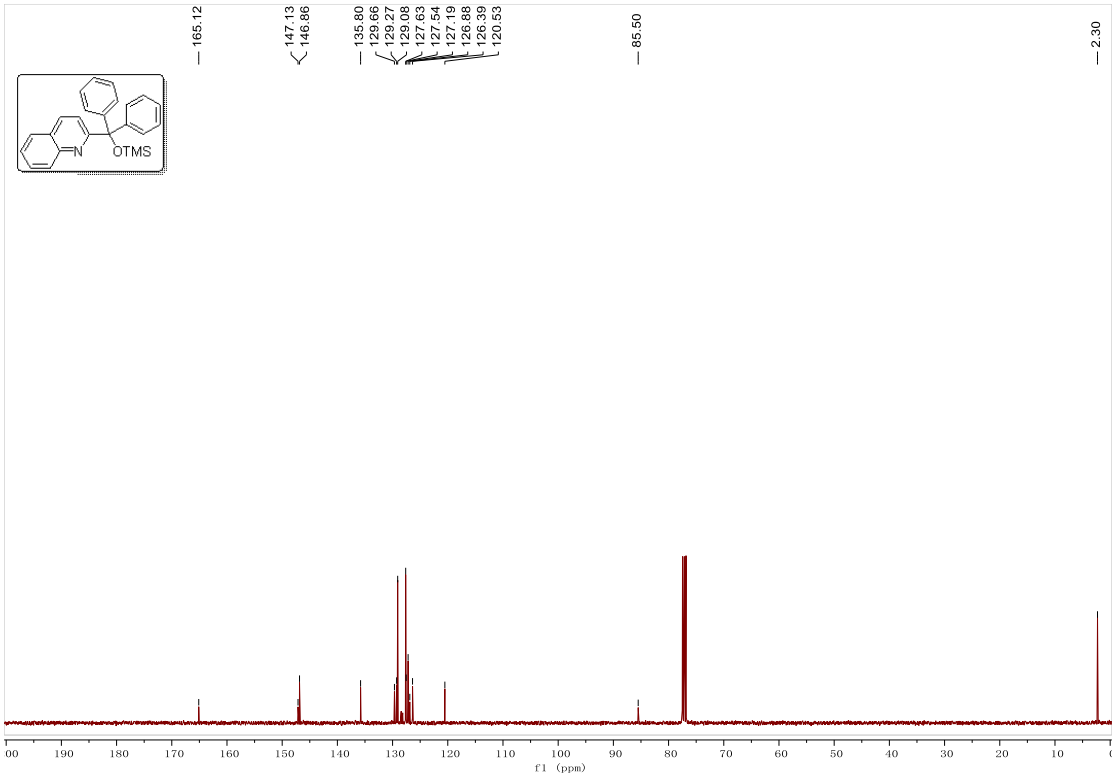
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of Ad10



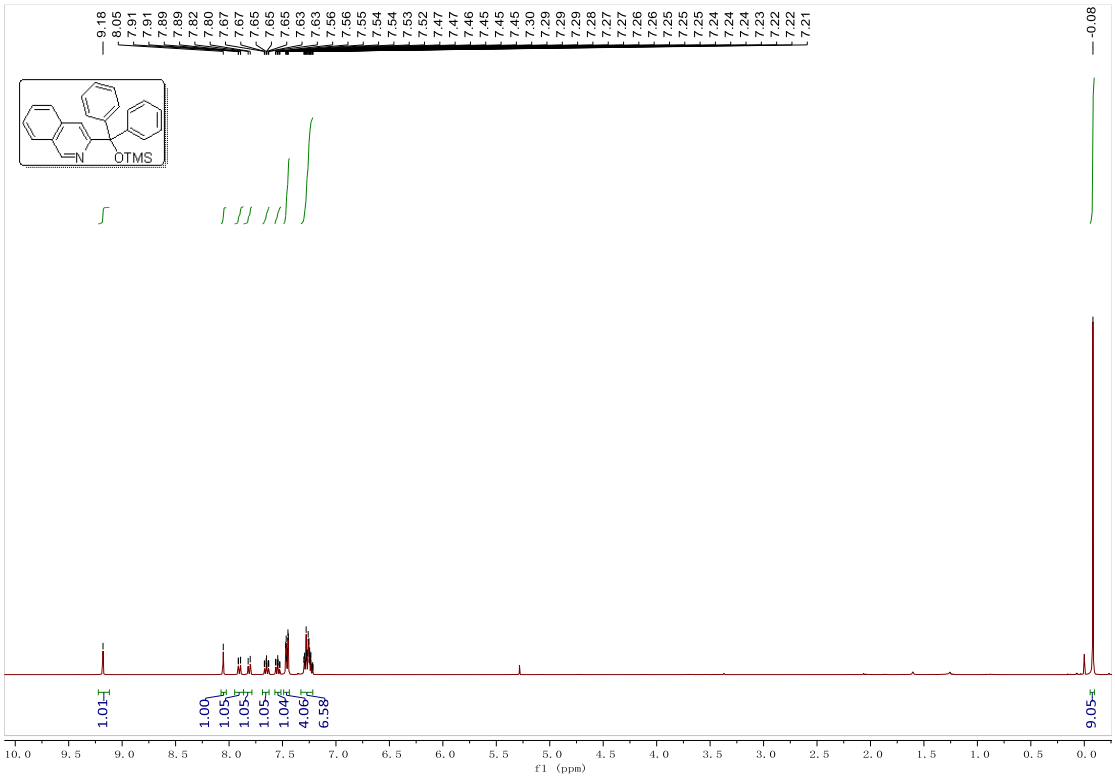
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Ad11



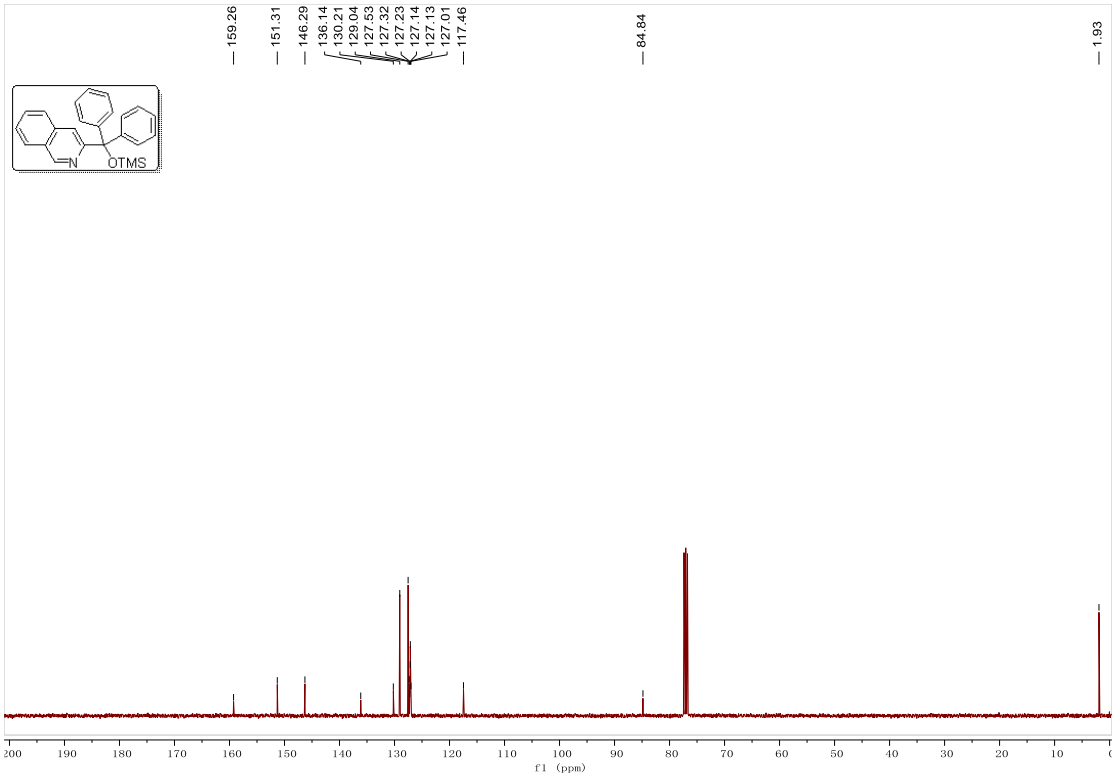
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of Ad11



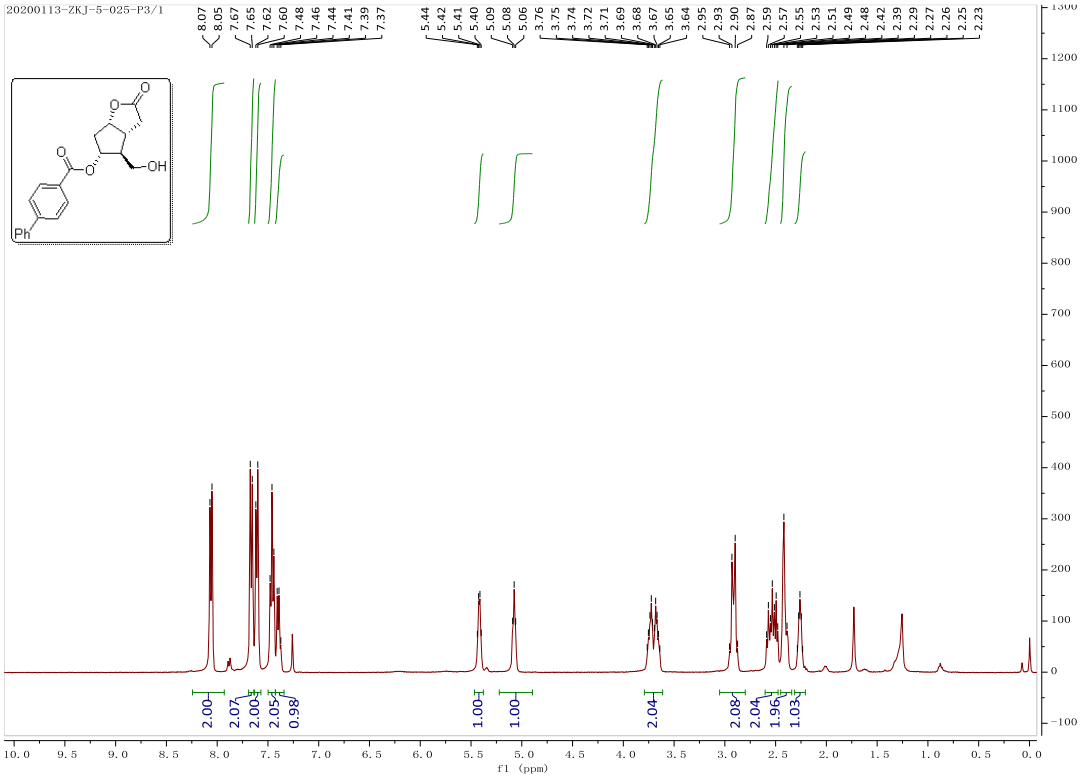
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Ad12



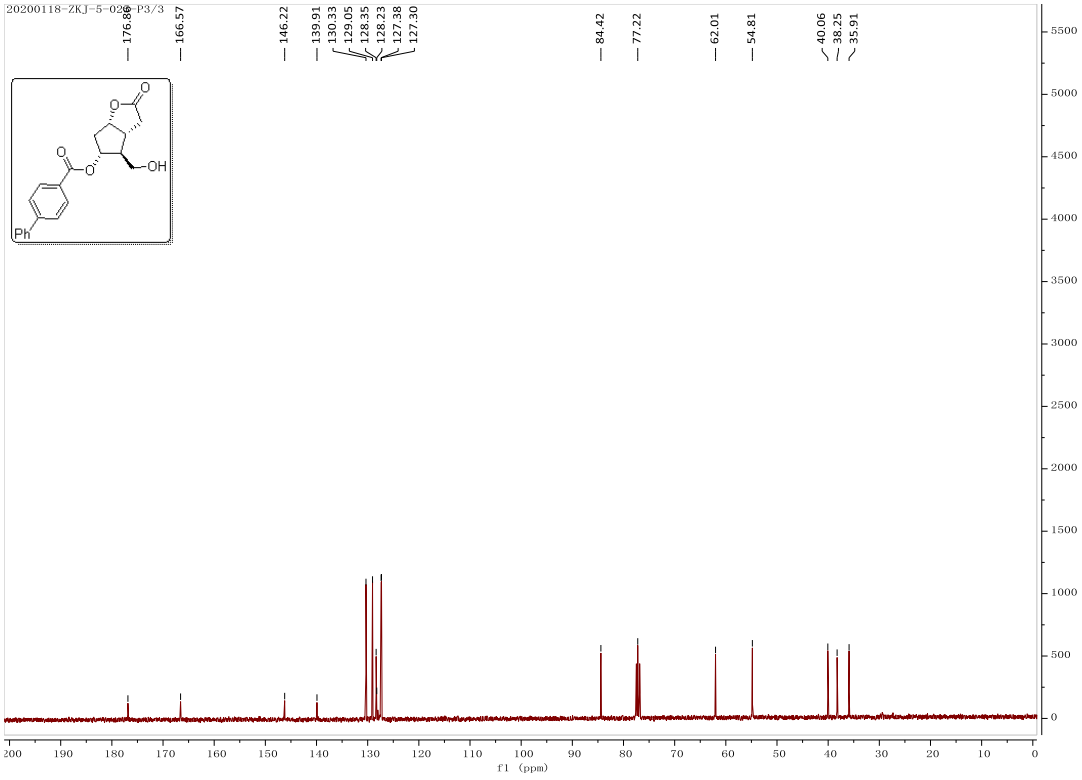
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of Ad12



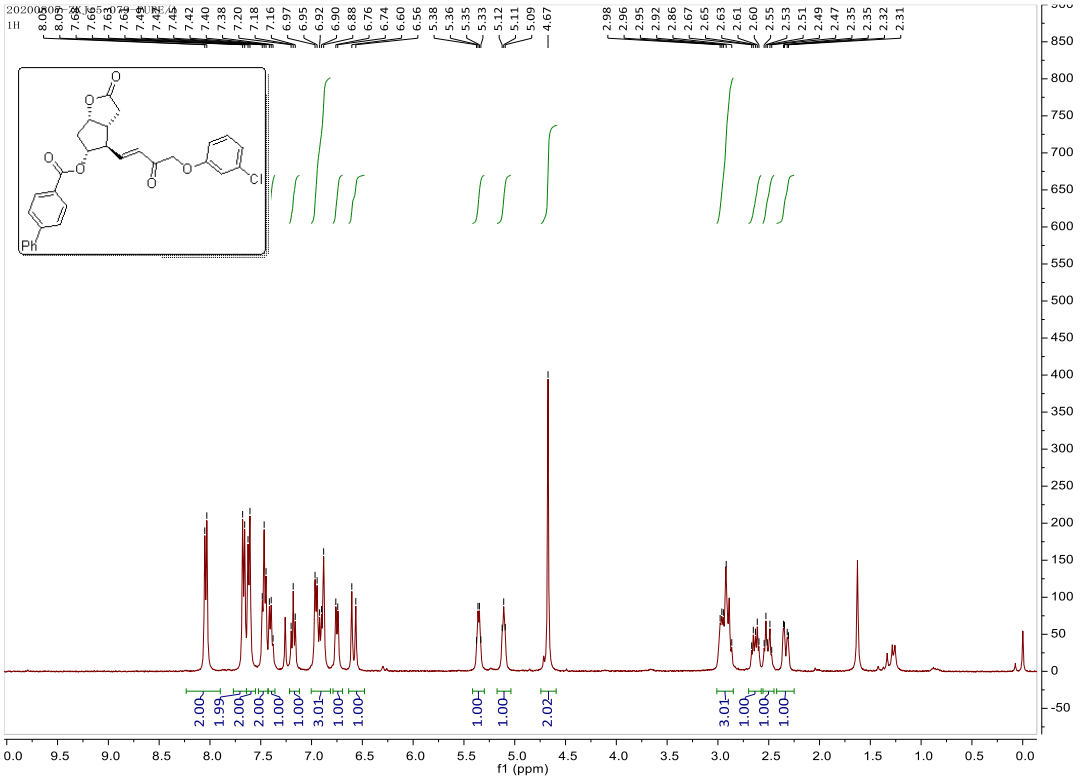
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of 11



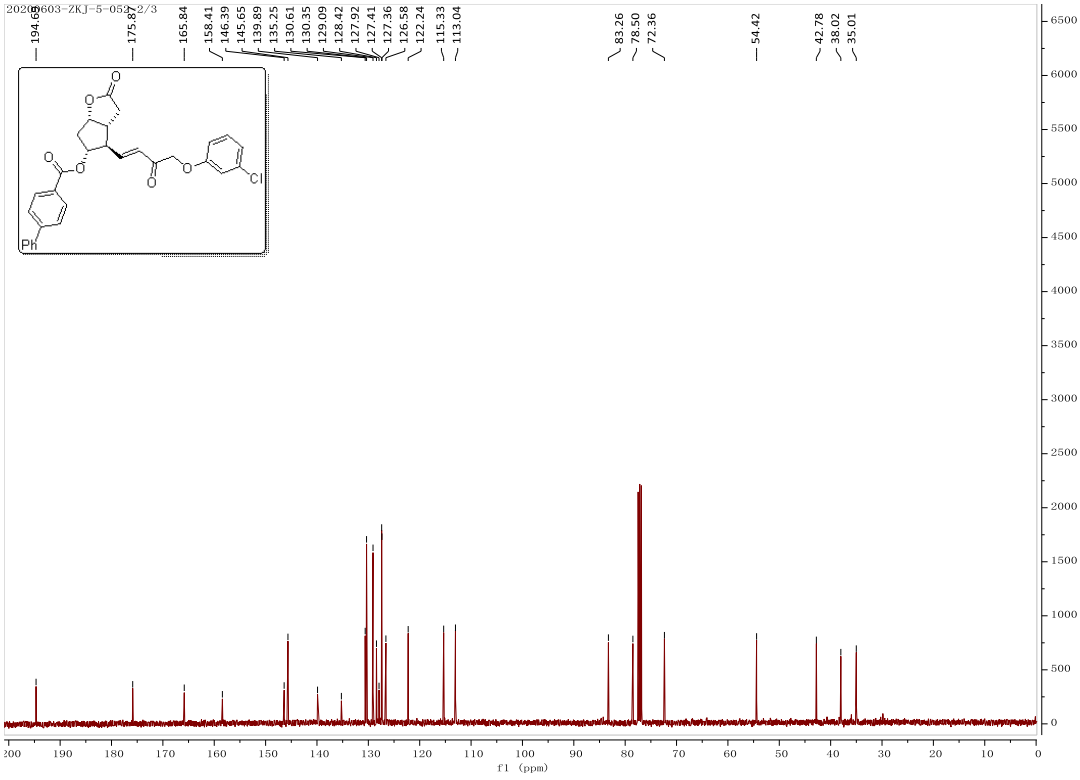
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of 11



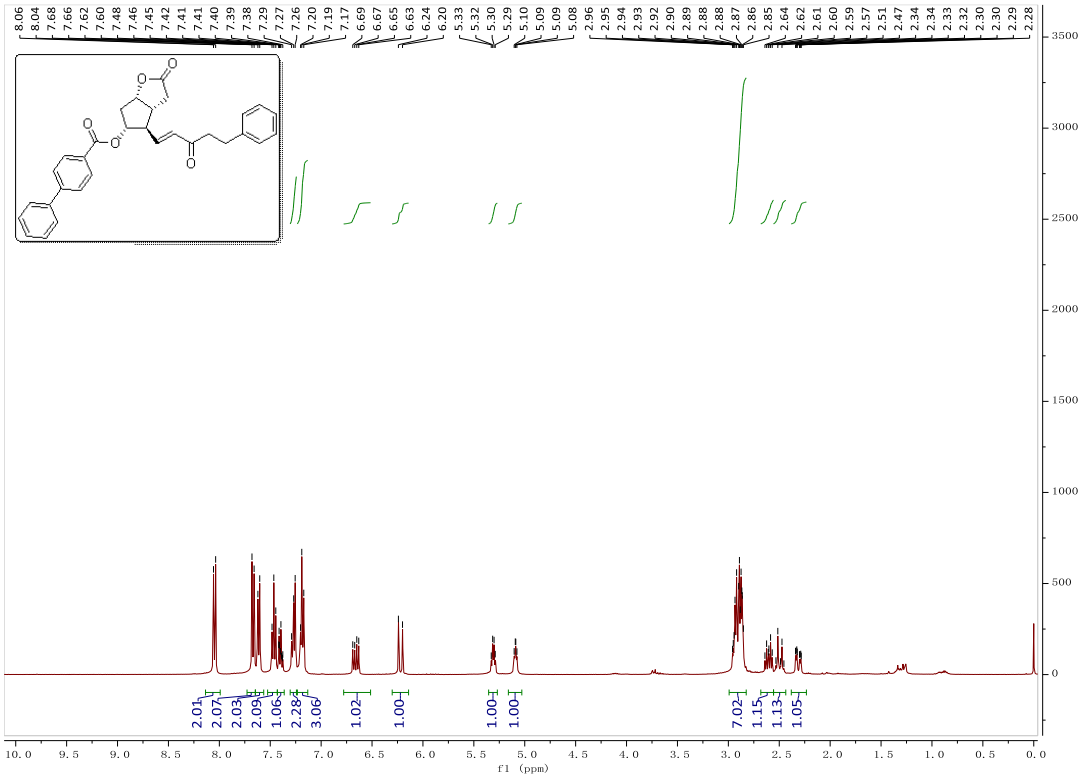
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of 12a



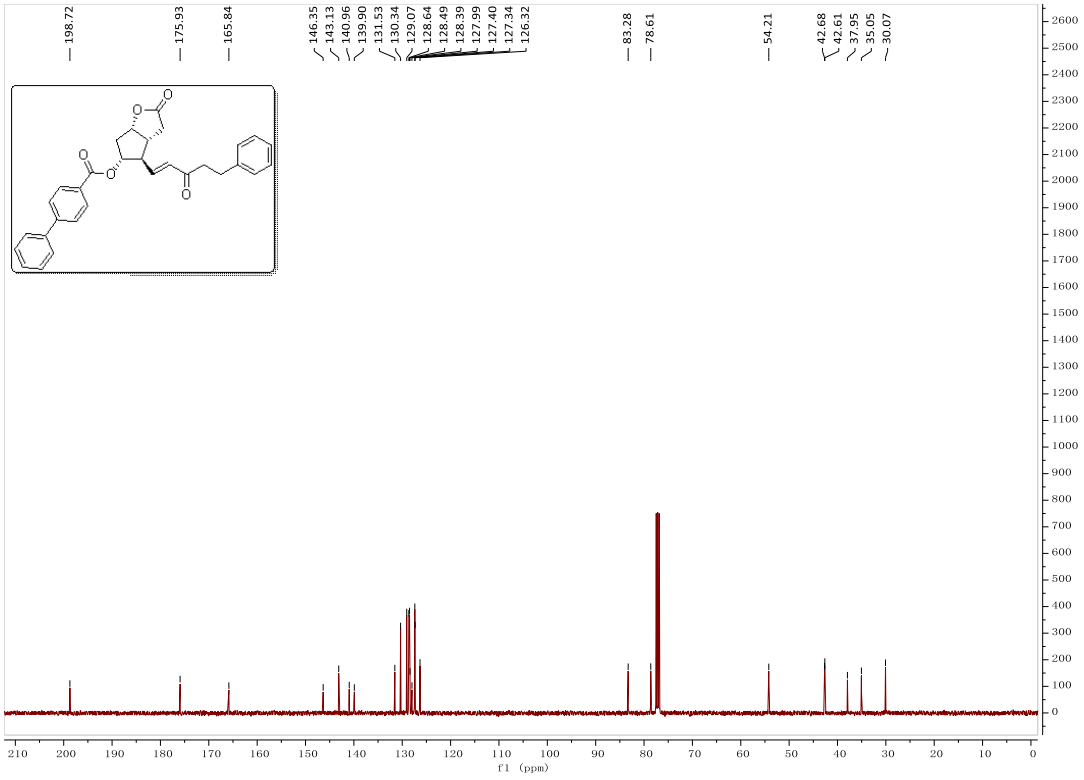
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of 12a



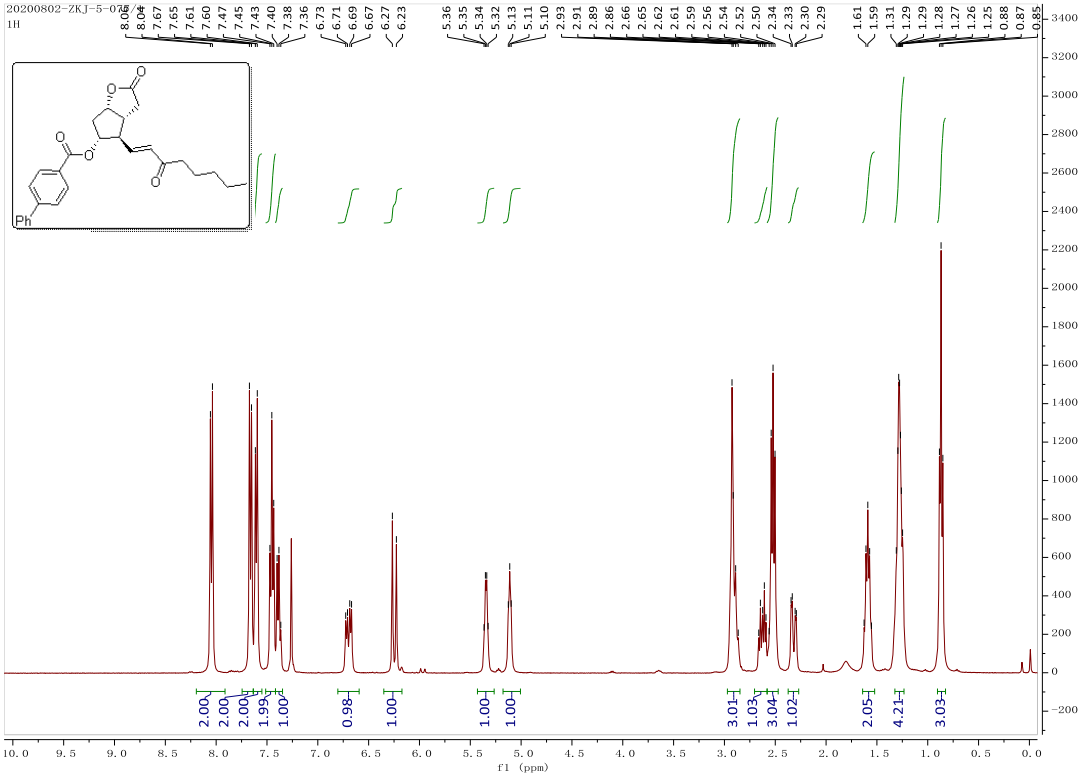
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of 12b



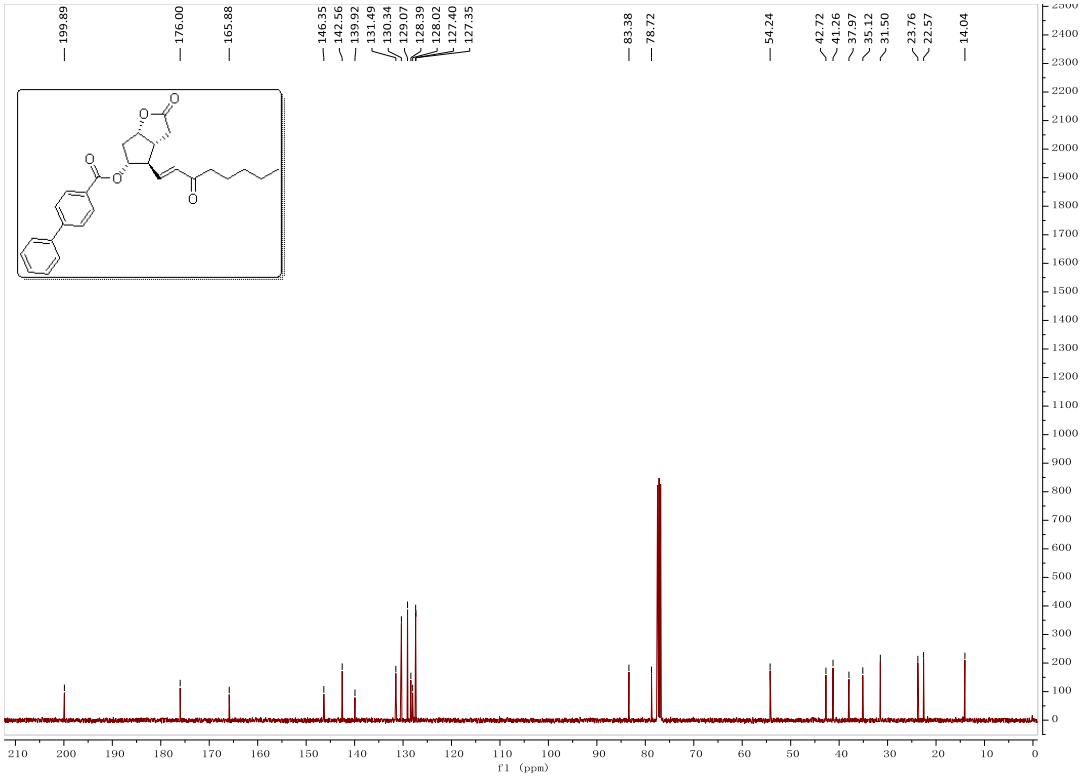
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of 12b



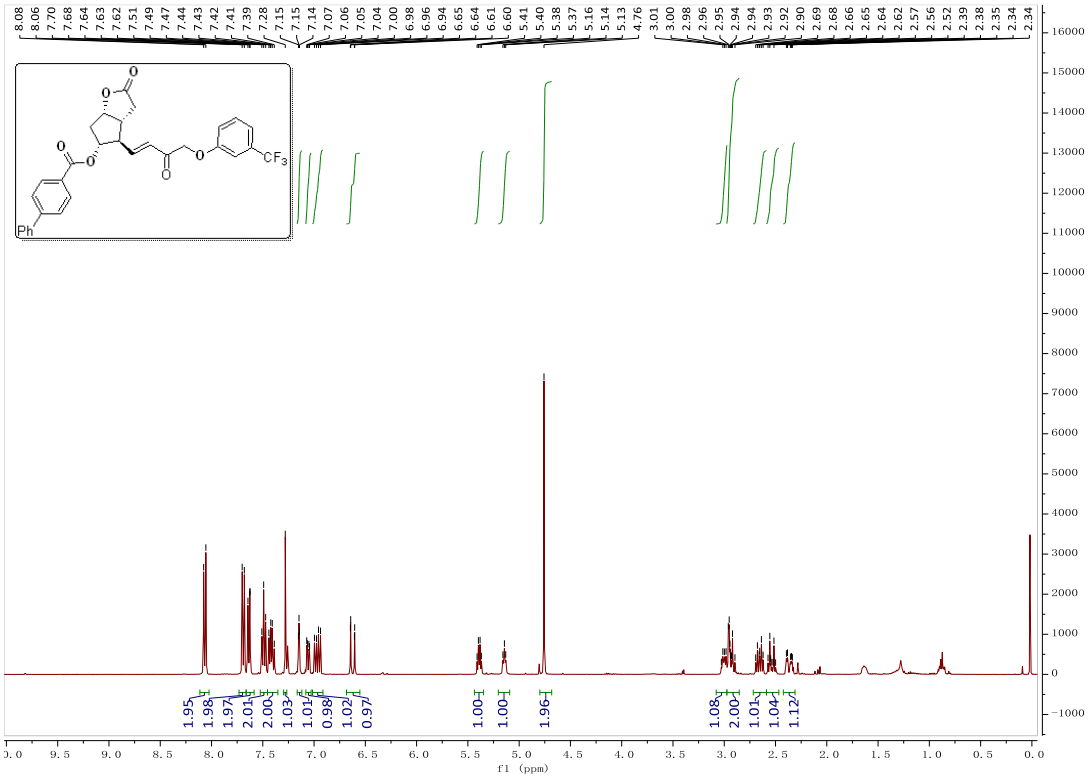
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of 12c



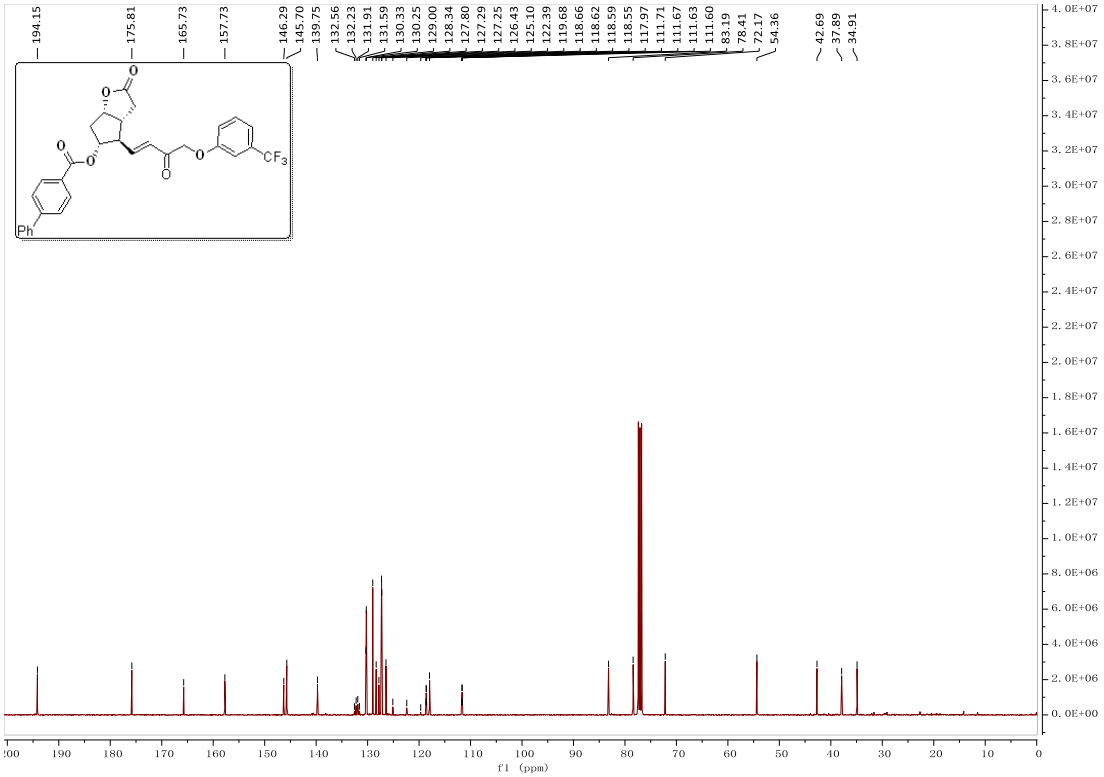
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of 12c



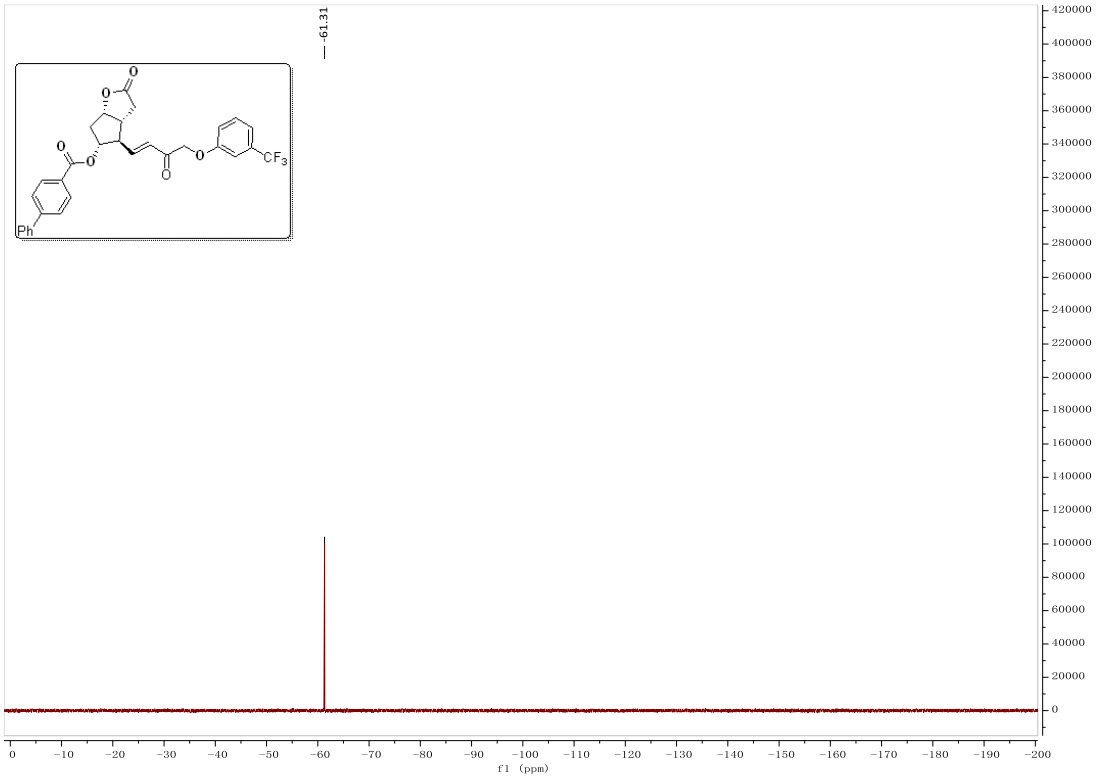
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of 12d



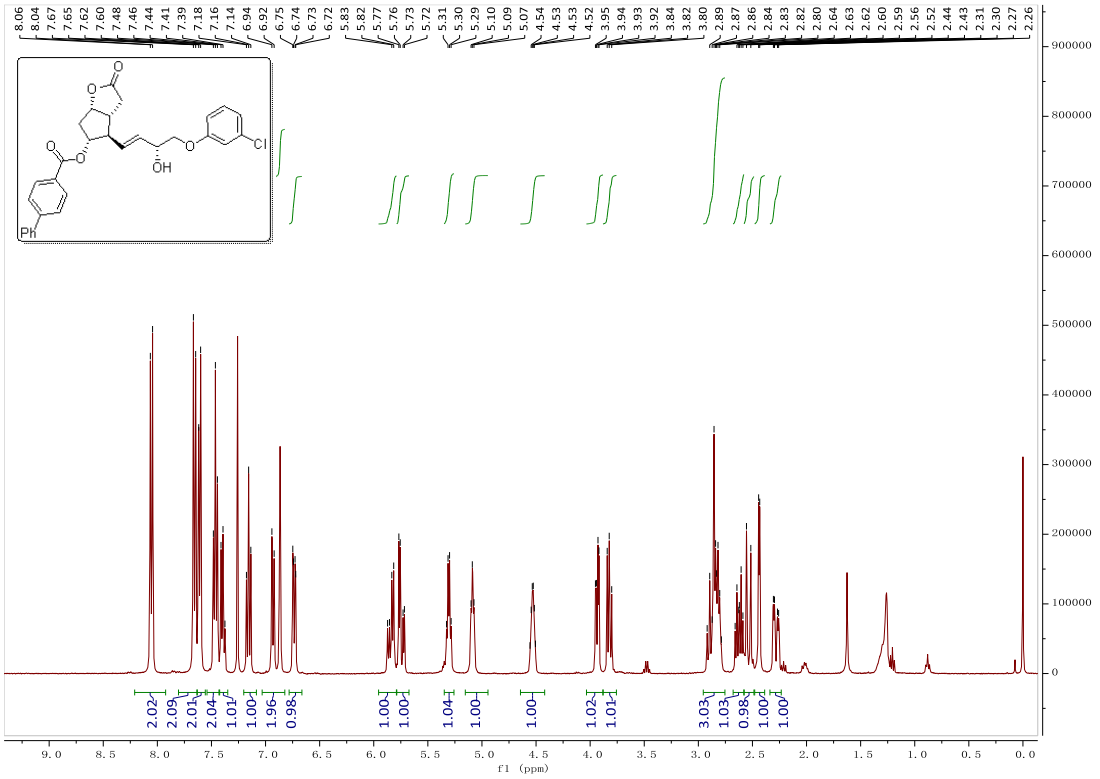
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of 12d



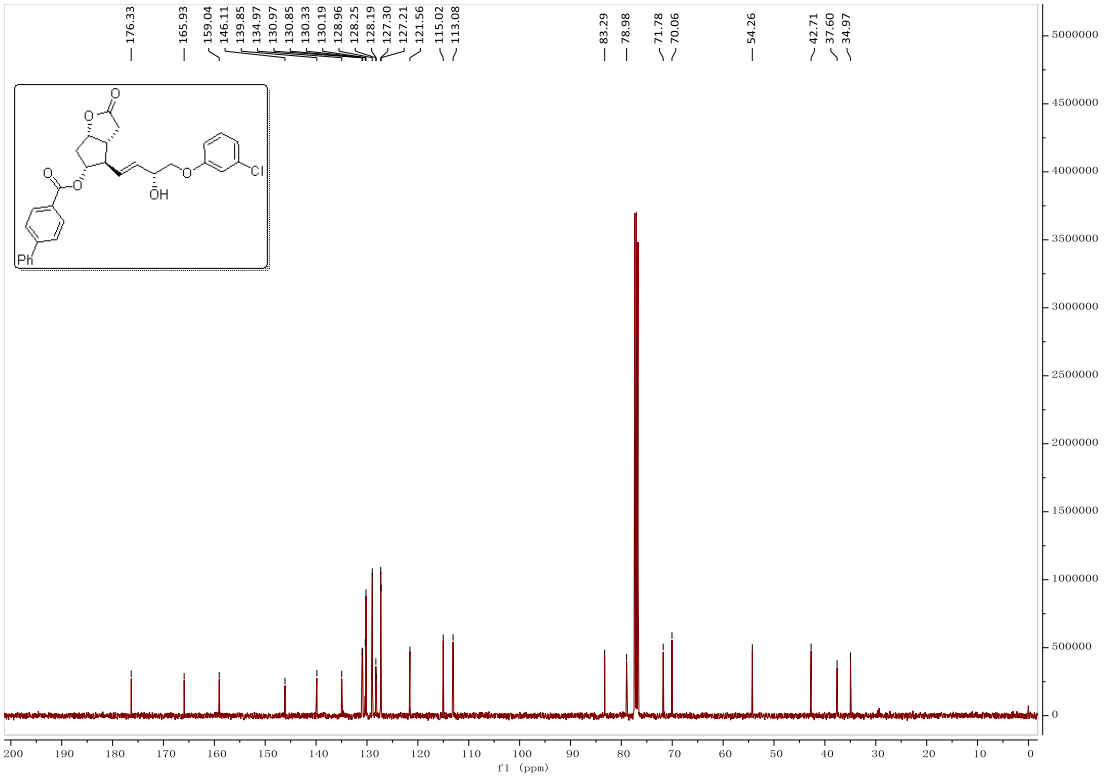
The ^{19}F NMR (376 MHz, $CDCl_3$) Spectrum of 12d



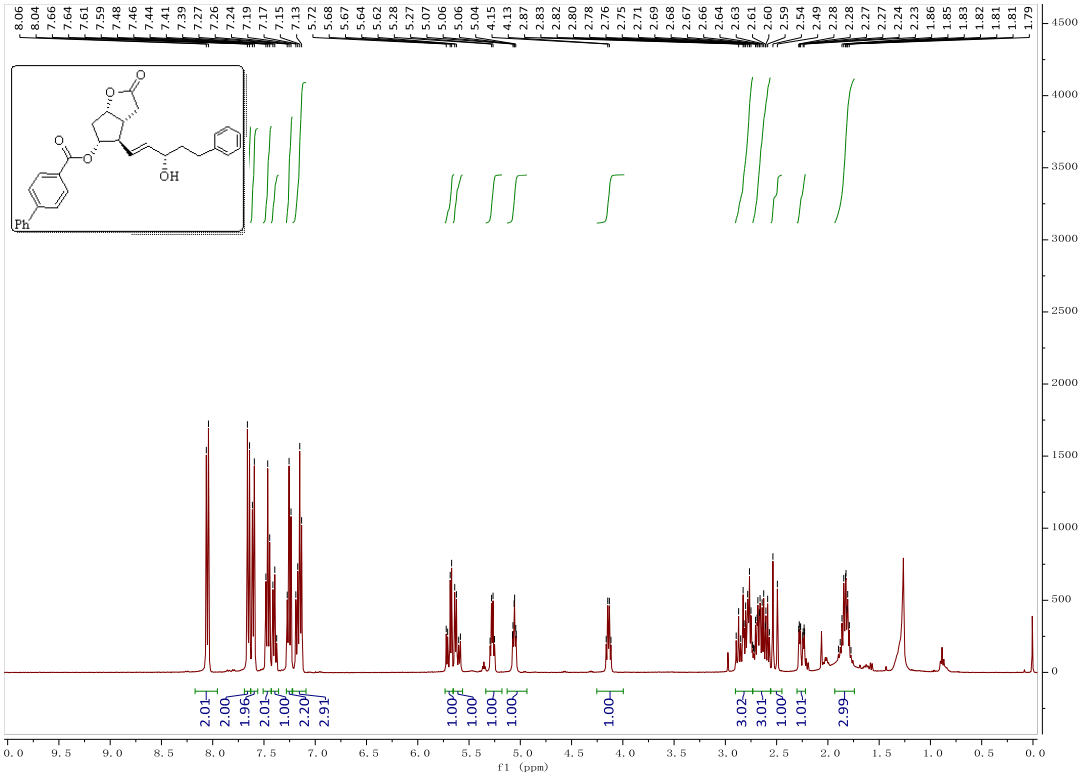
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of 13a



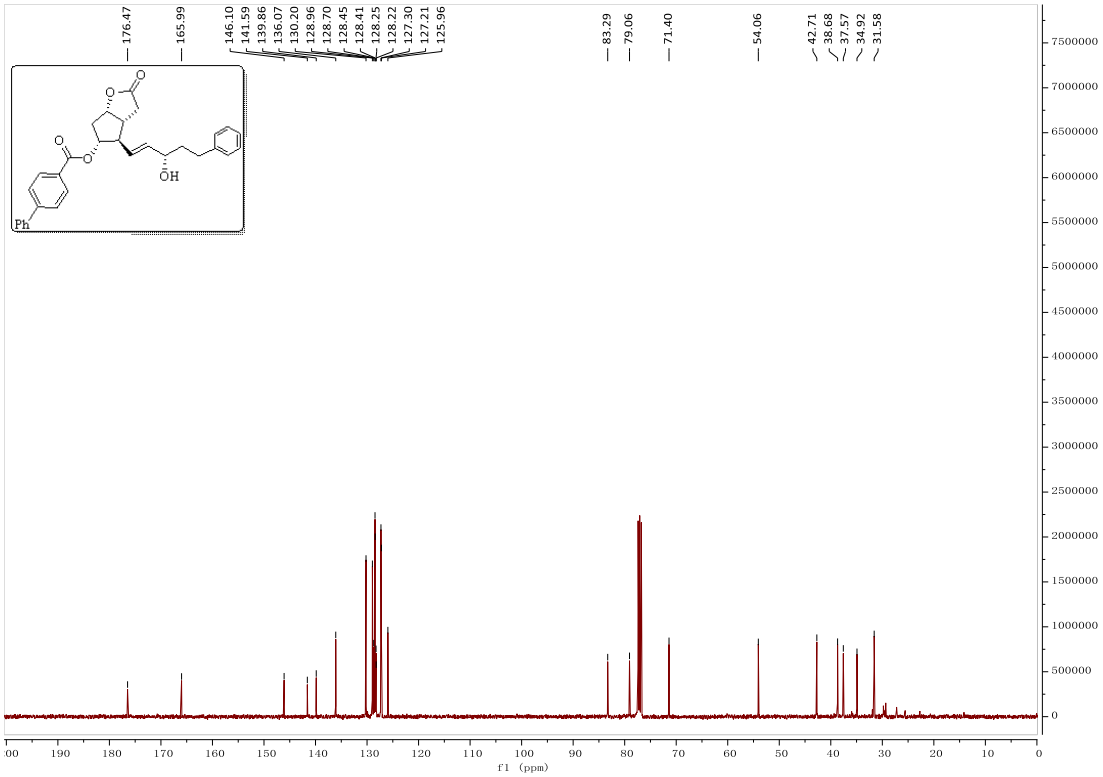
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of 13a



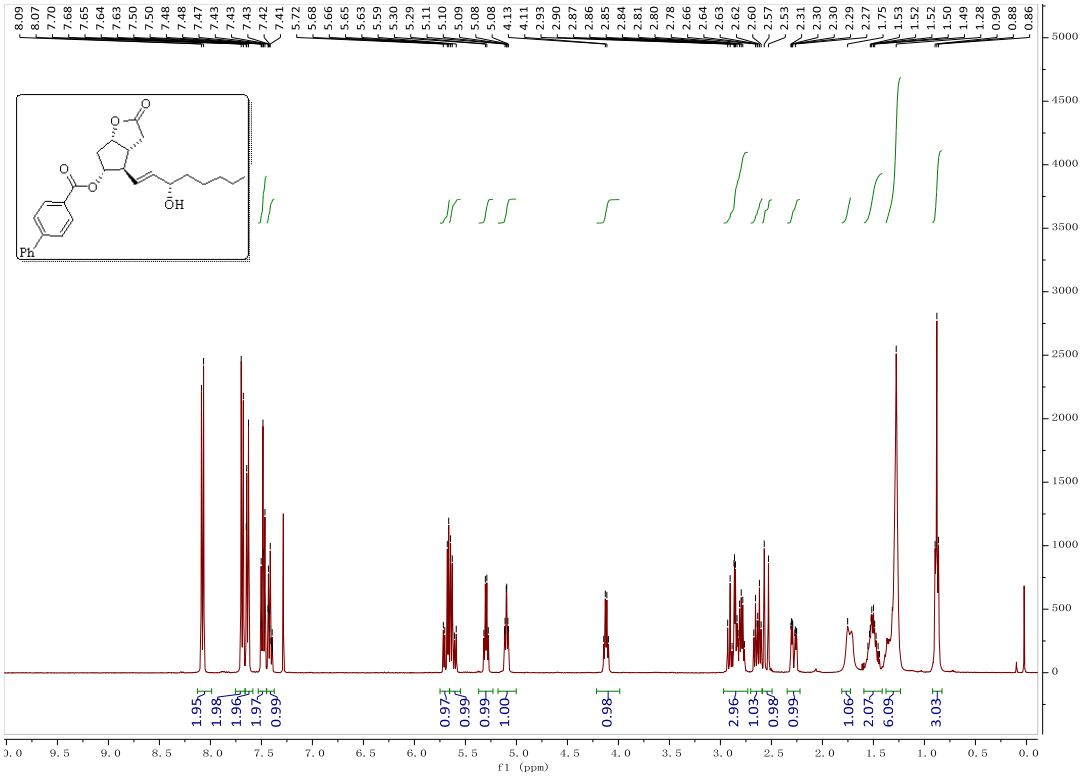
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of 13b



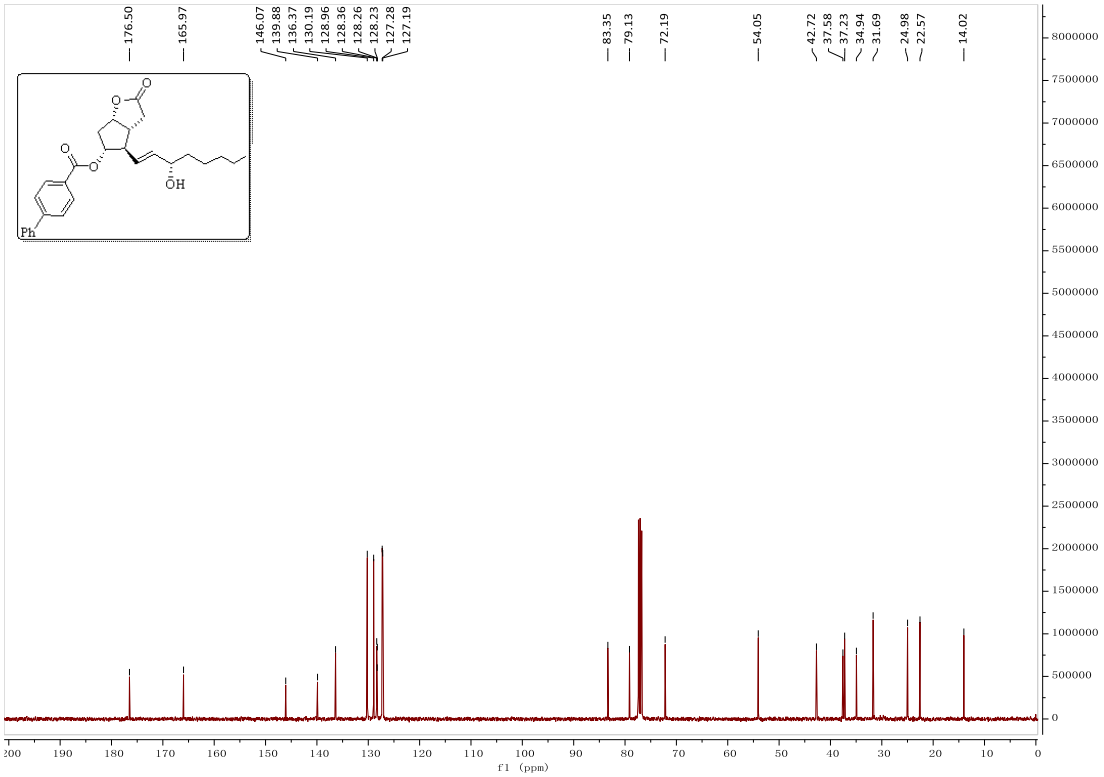
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of 13b



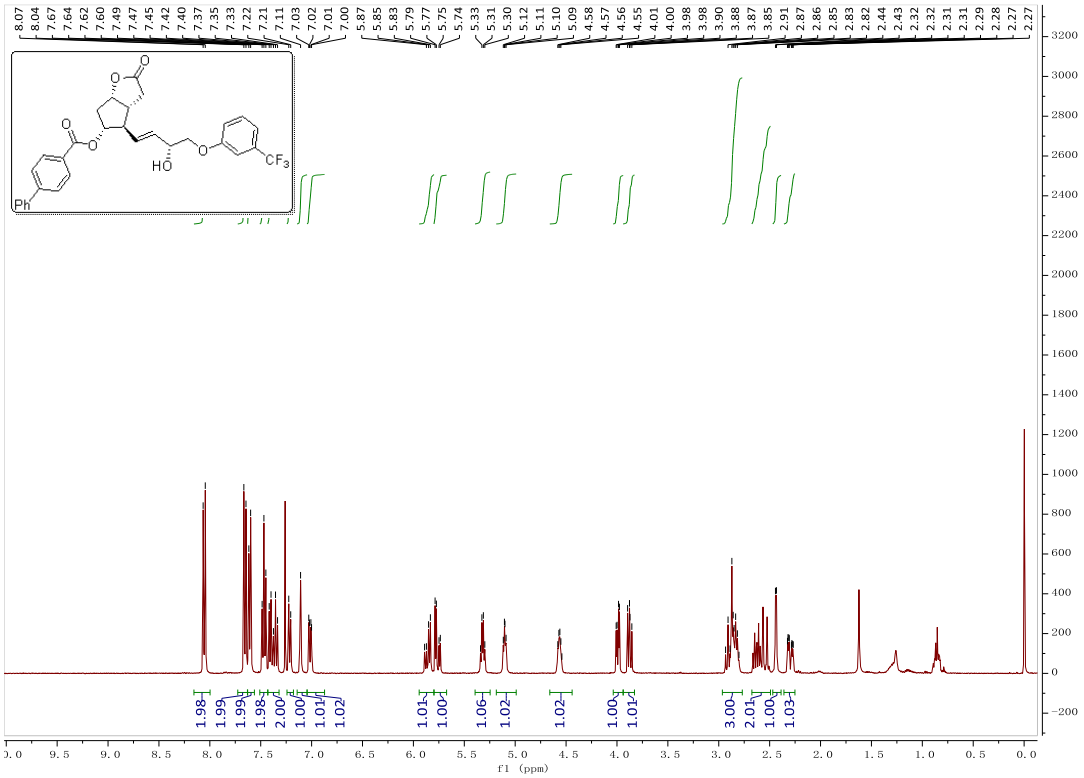
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of 13c



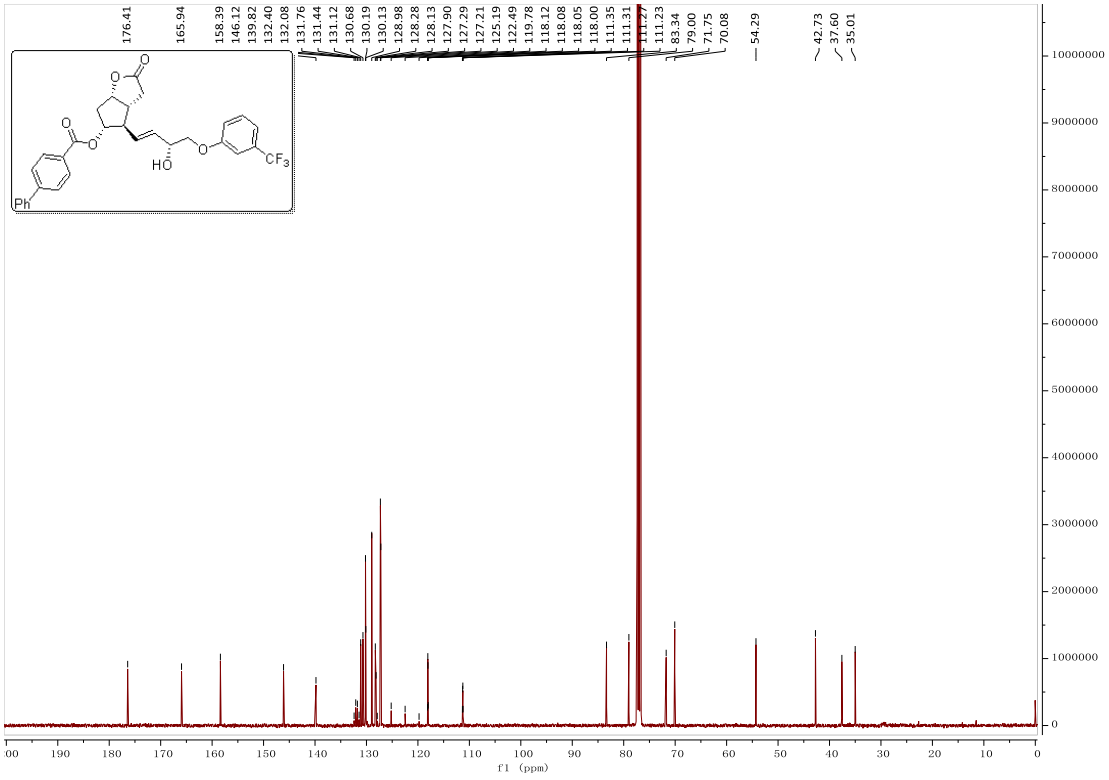
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of 13c



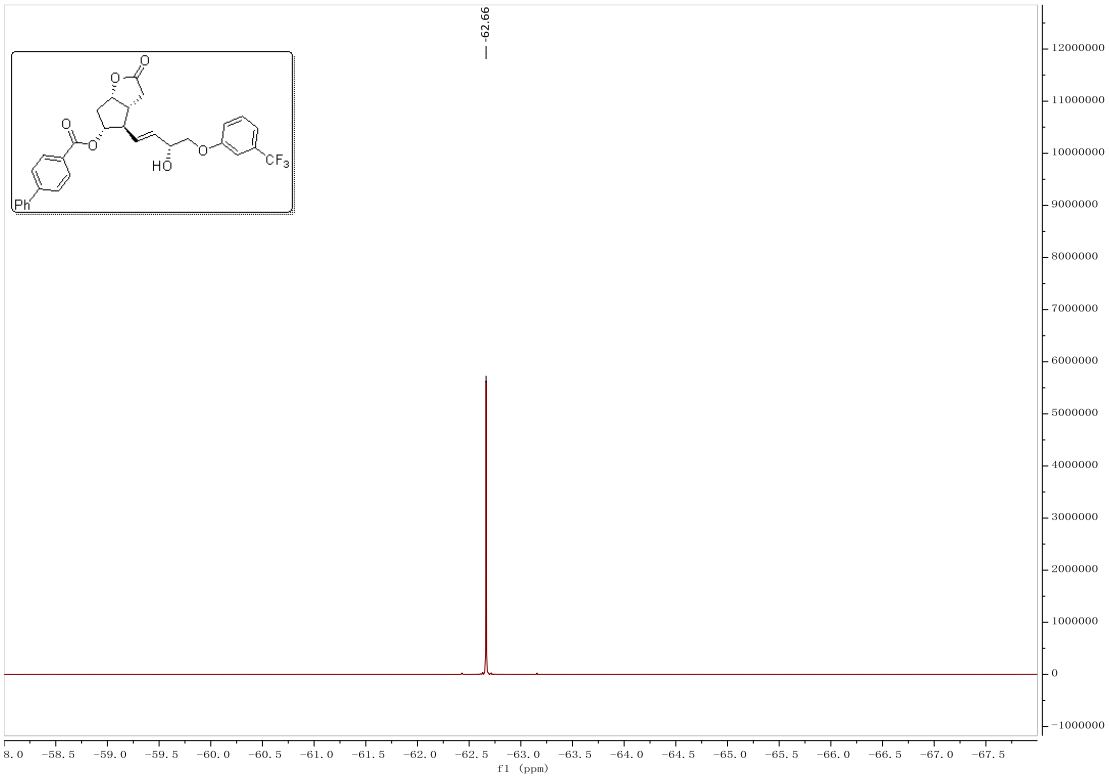
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of 13d



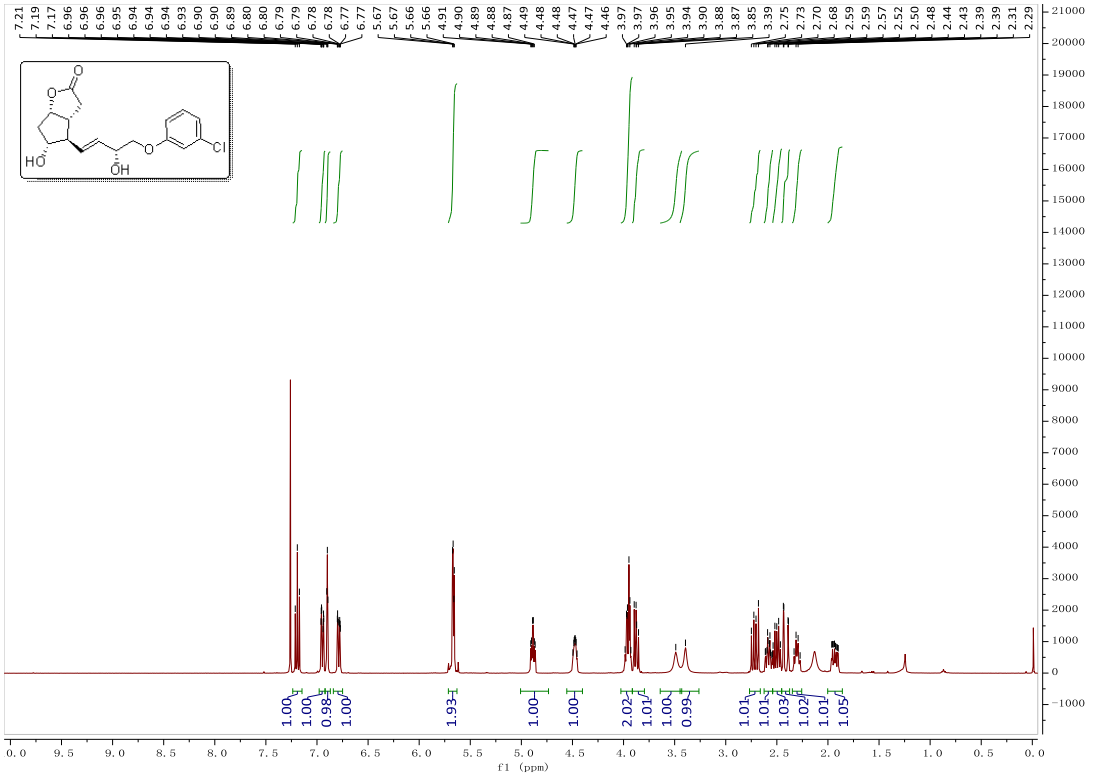
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of 13d



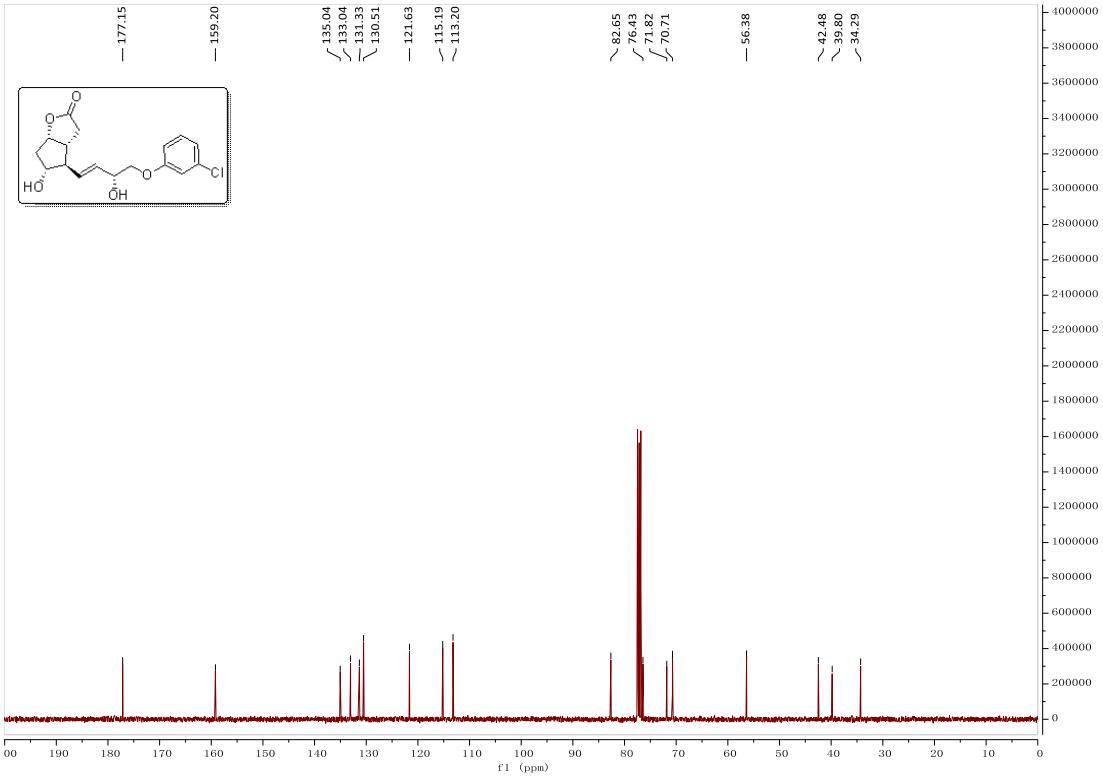
The ^{19}F NMR (376 MHz, $CDCl_3$) Spectrum of 13d



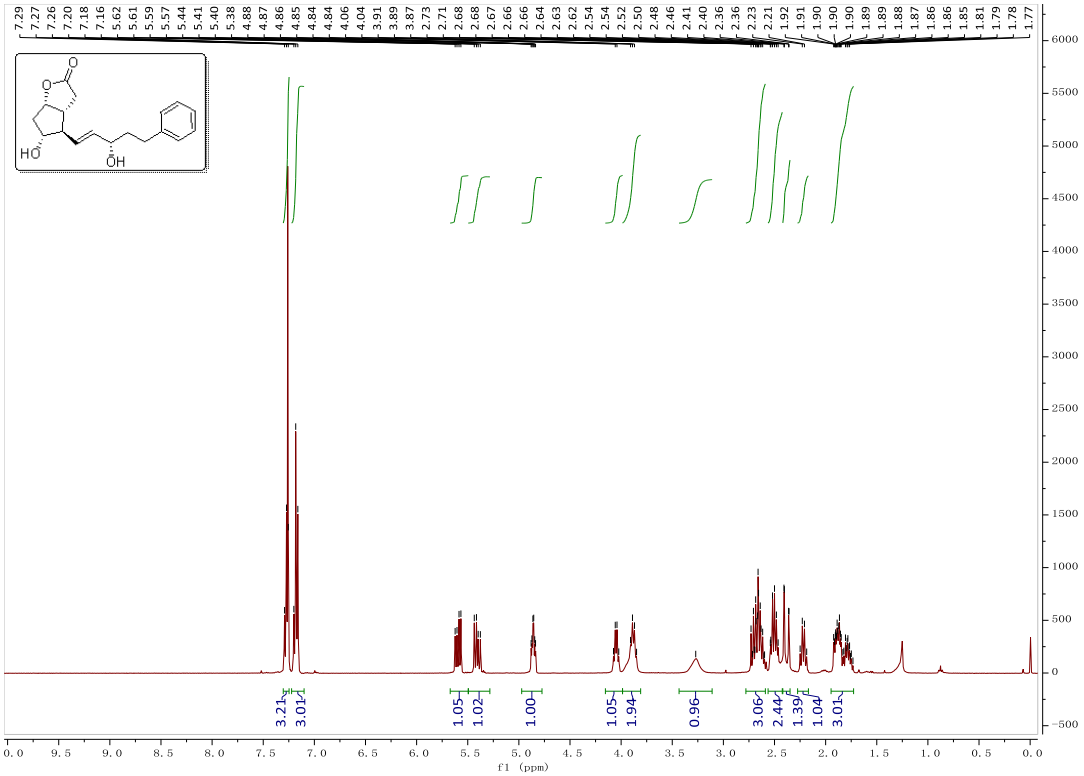
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of S1



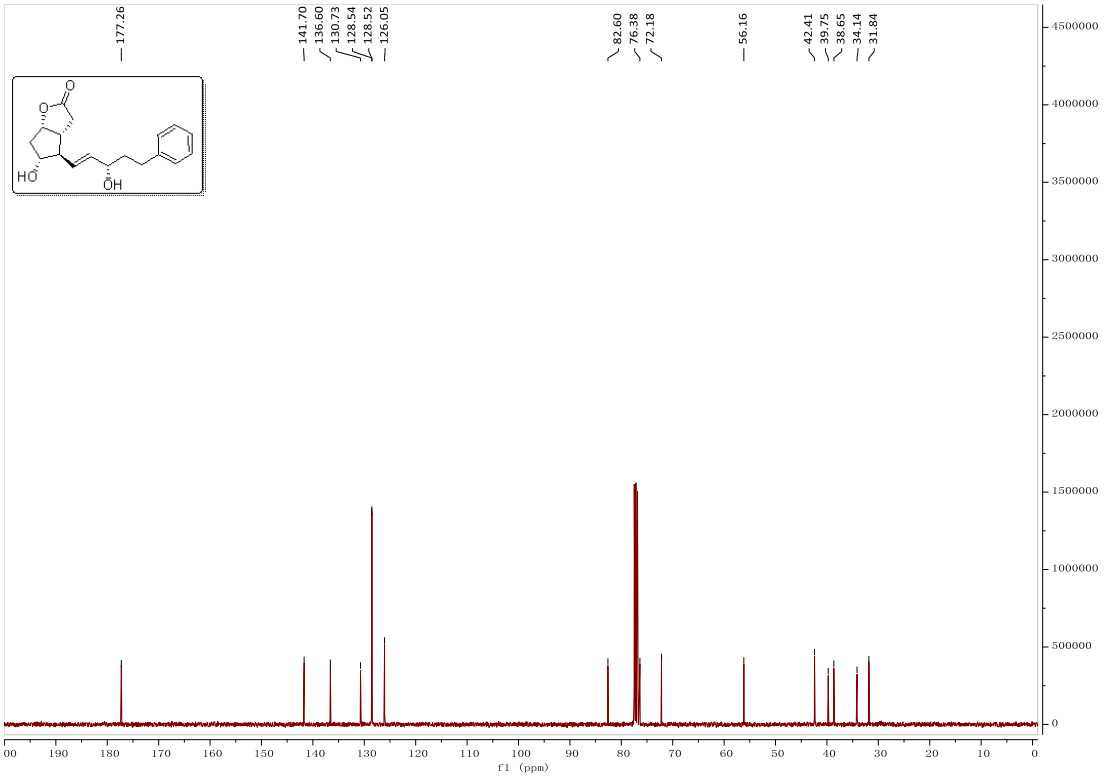
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of S1



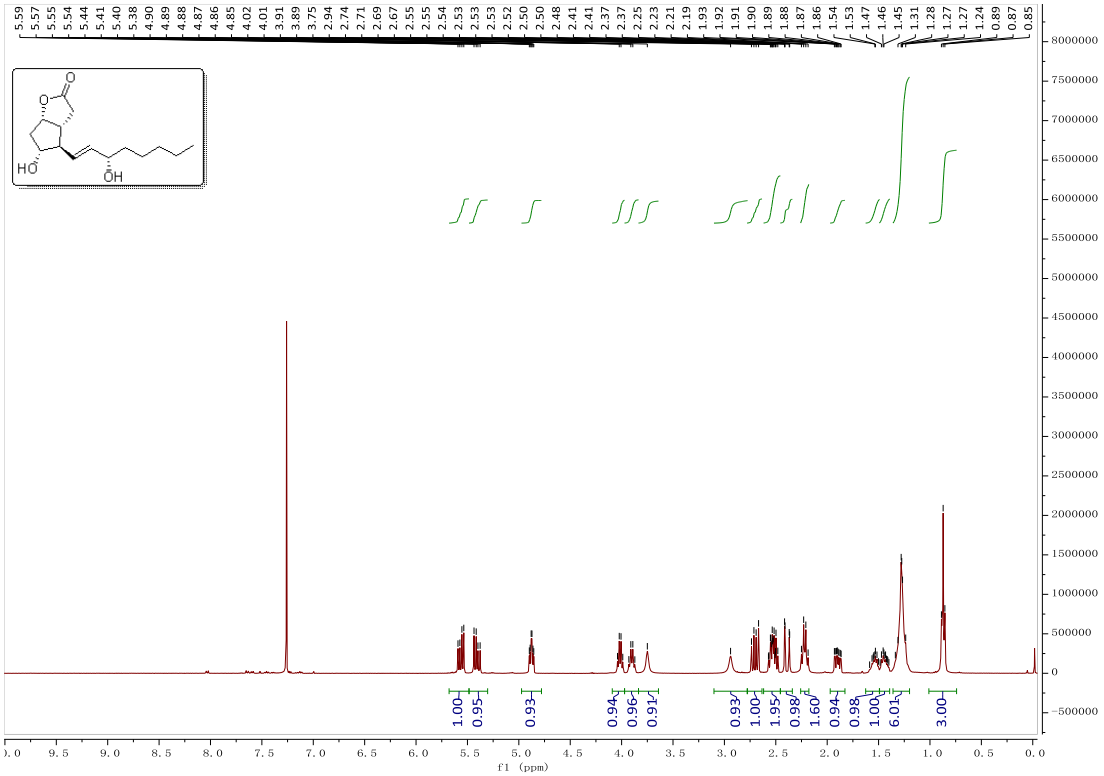
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of S2



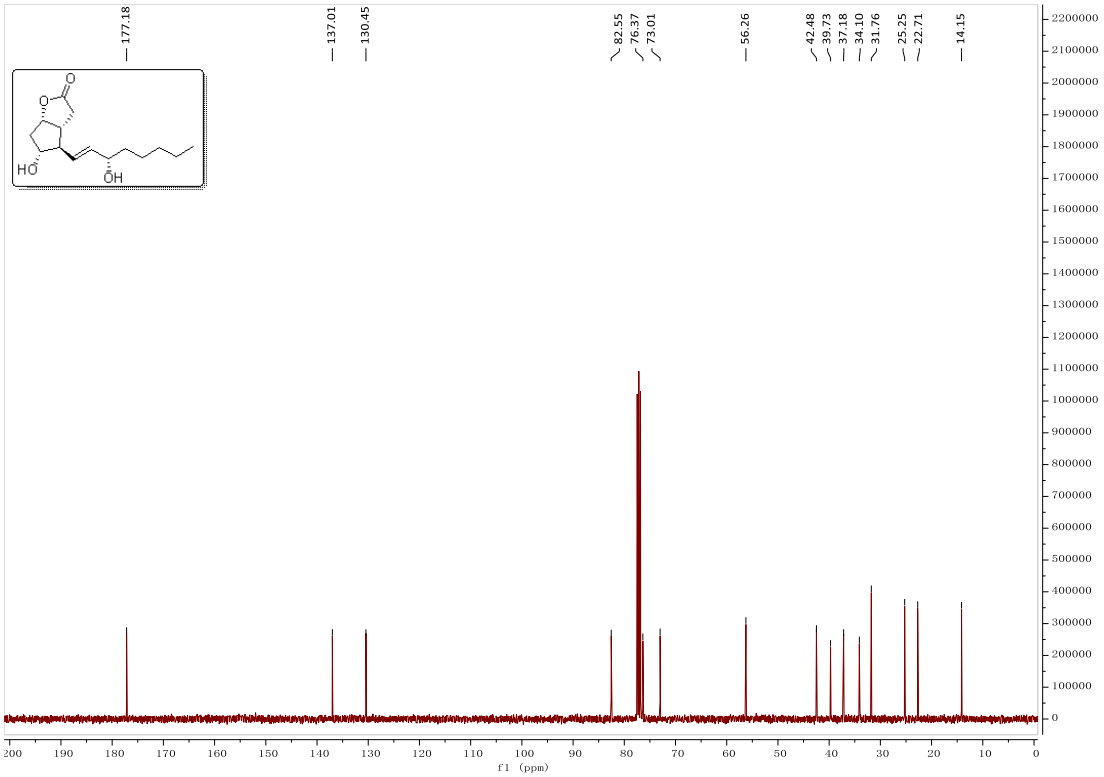
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of S2



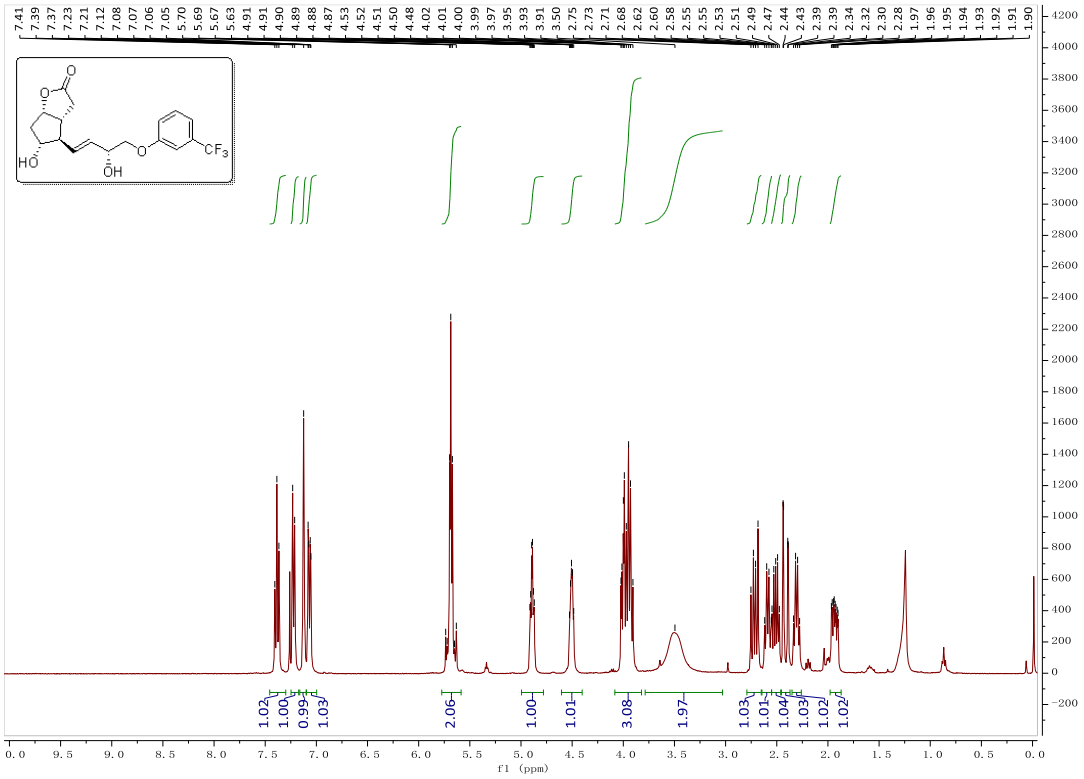
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of S3



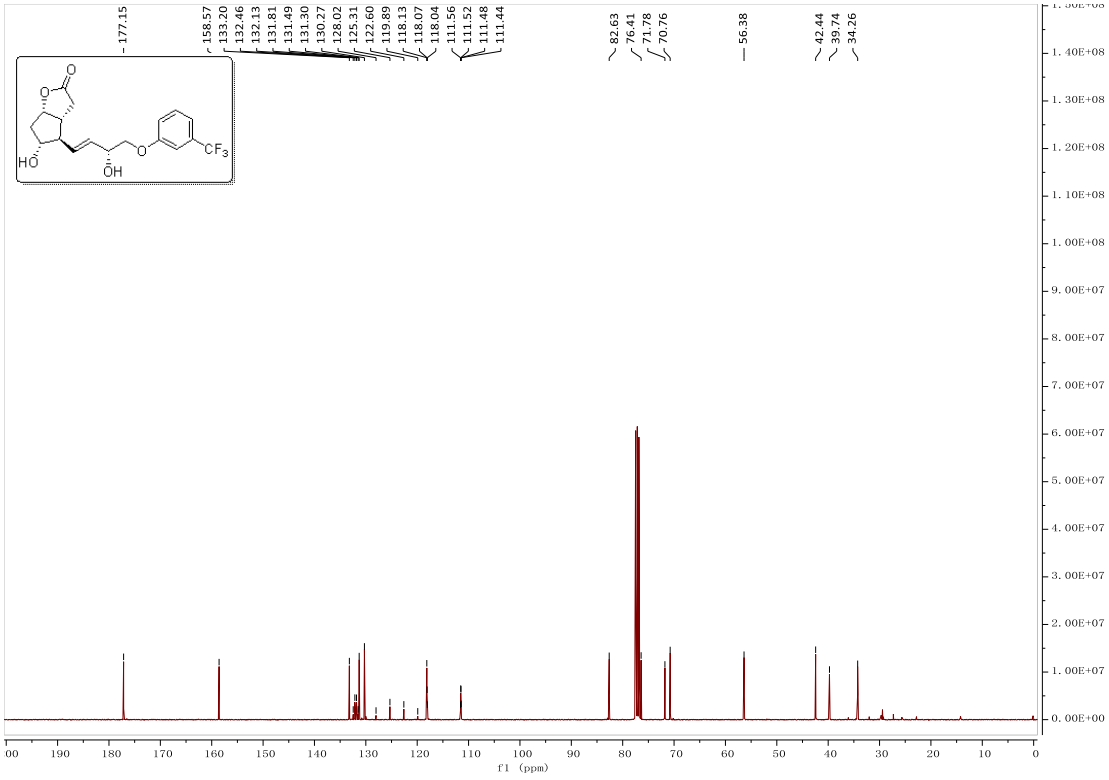
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of S3



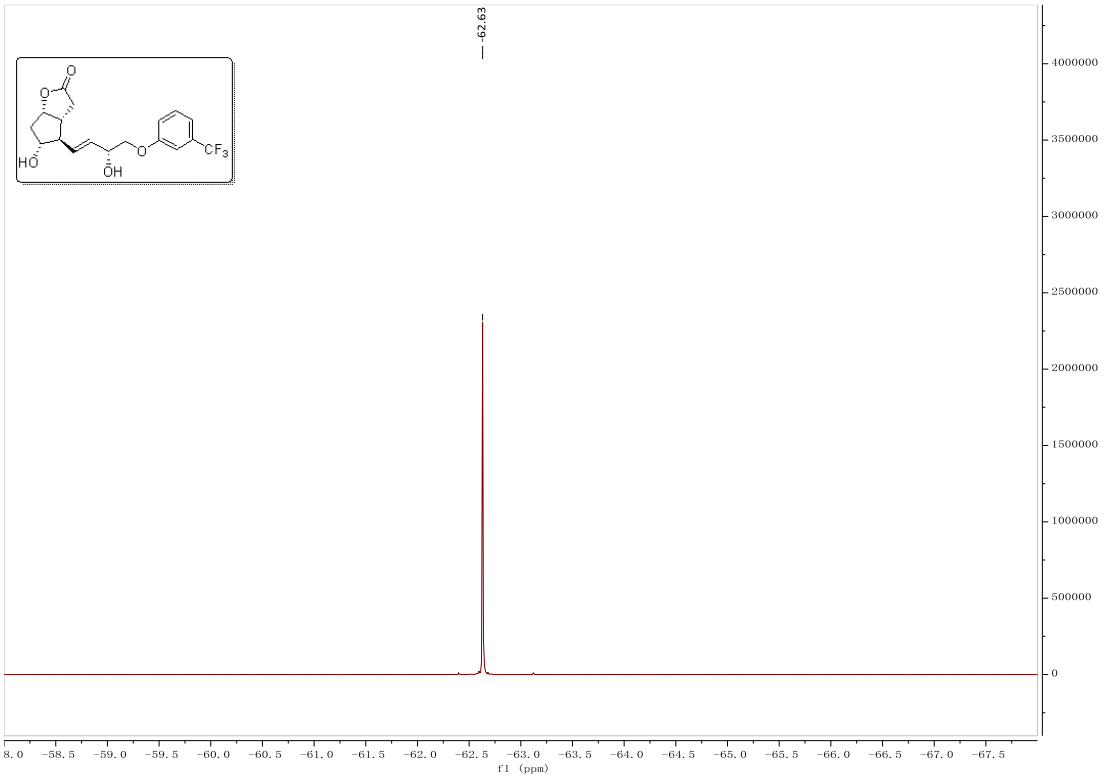
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of S4



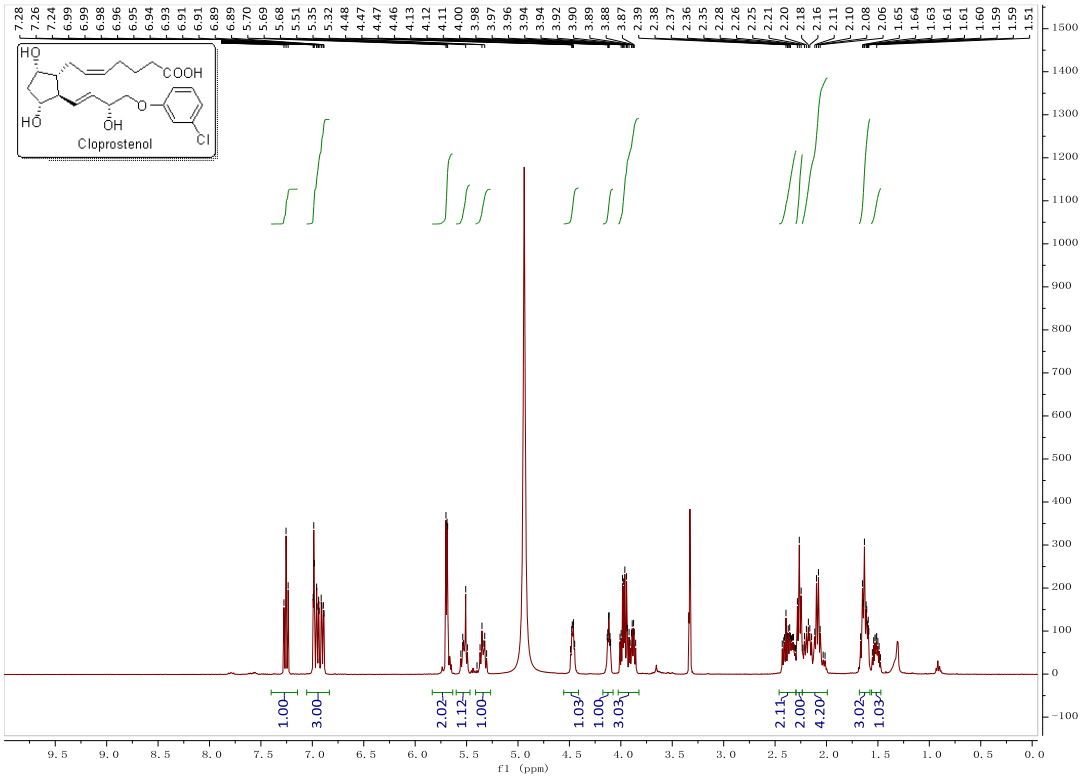
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of S4



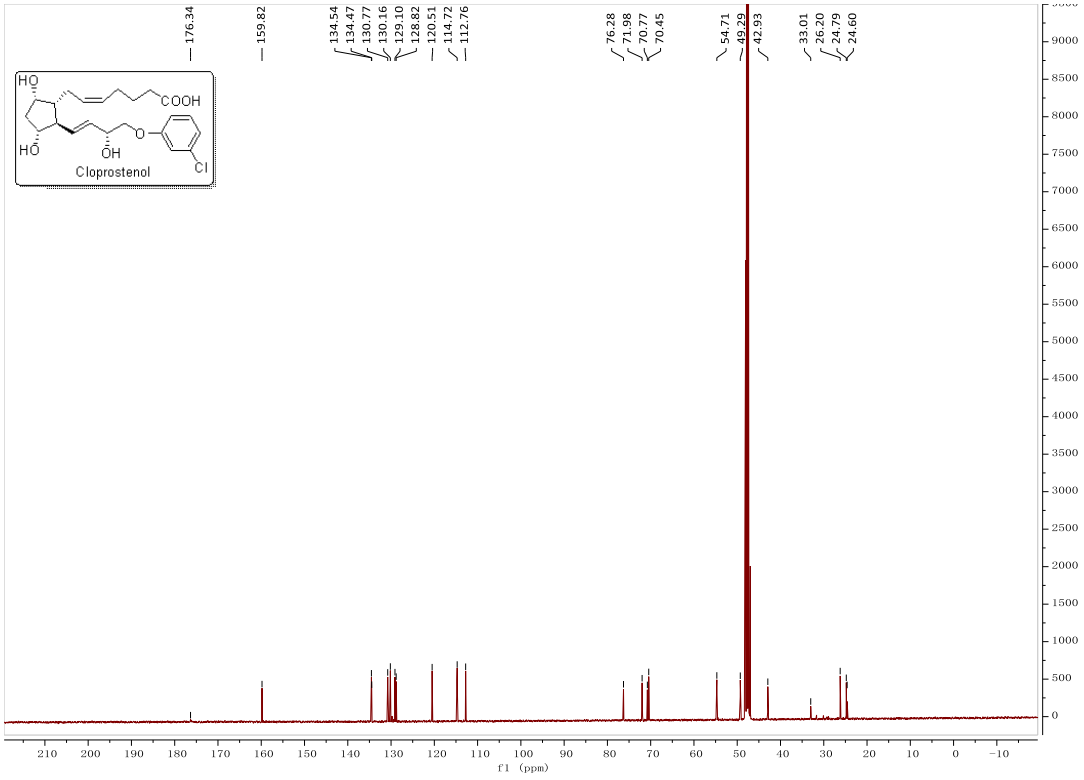
The ^{19}F NMR (376 MHz, $CDCl_3$) Spectrum of S4



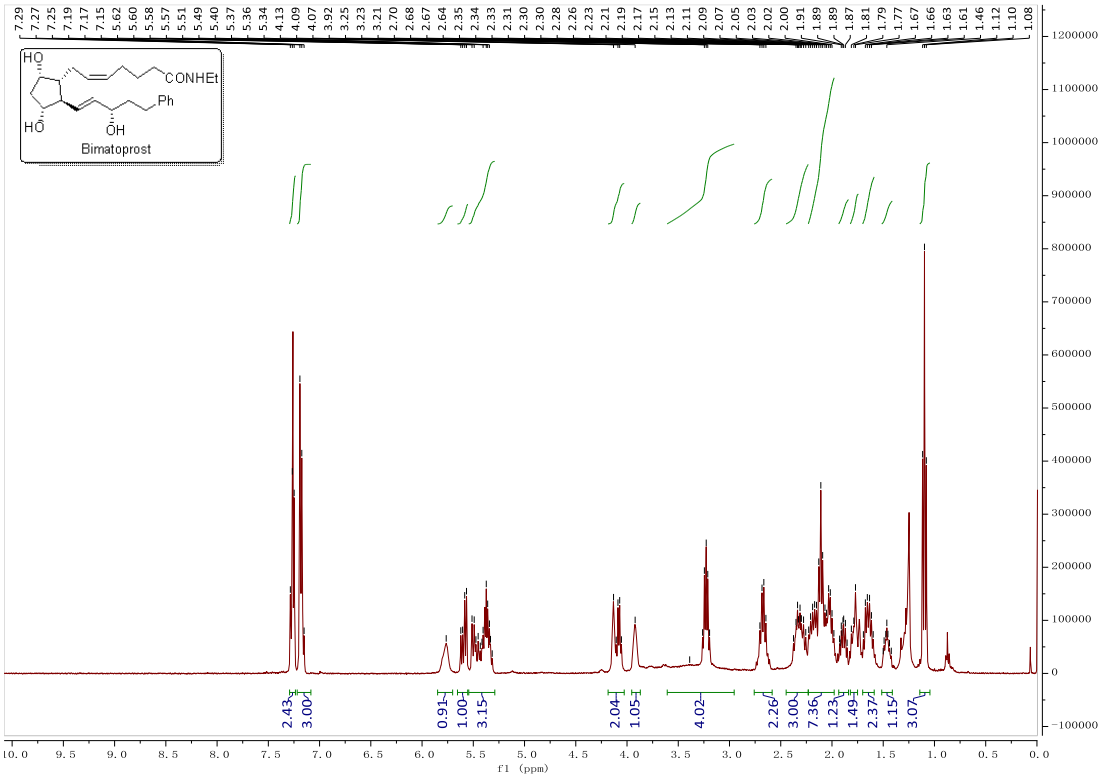
The ^{1}H NMR (400 MHz, Methanol-d_4) Spectrum of 1 (Cloprostenol)



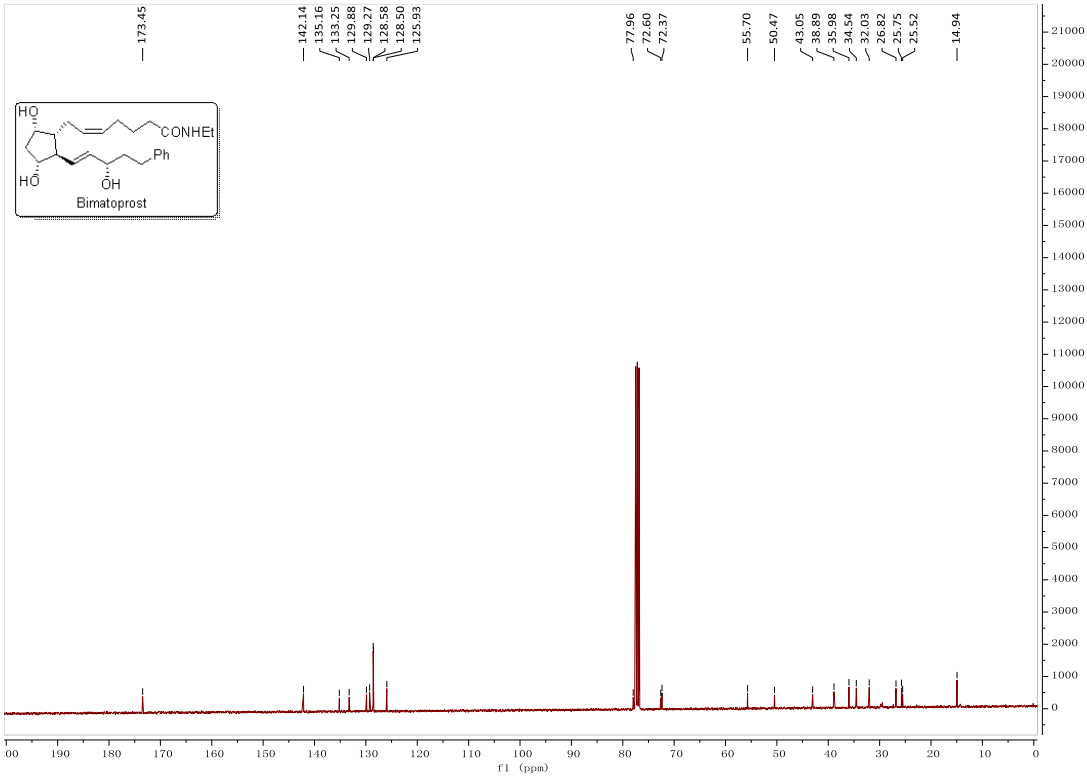
The ^{13}C NMR (101 MHz, Methanol-d_4) Spectrum of 1 (Cloprostenol)



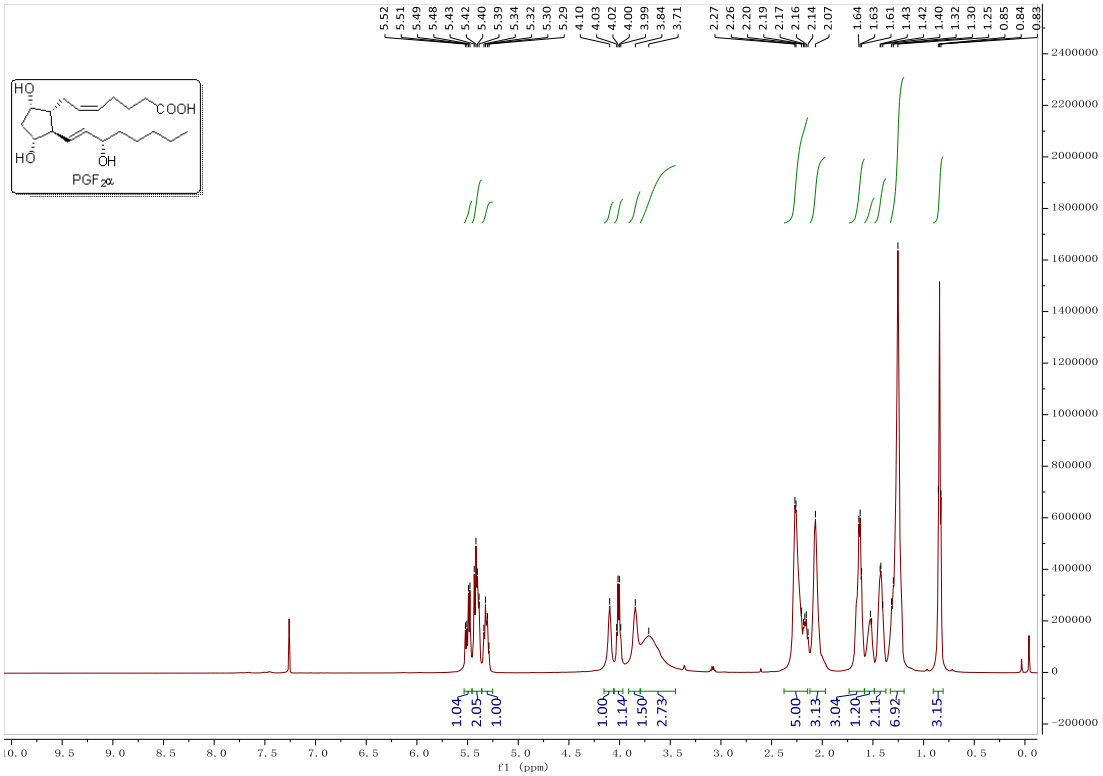
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of 2 (Bimatoprost)



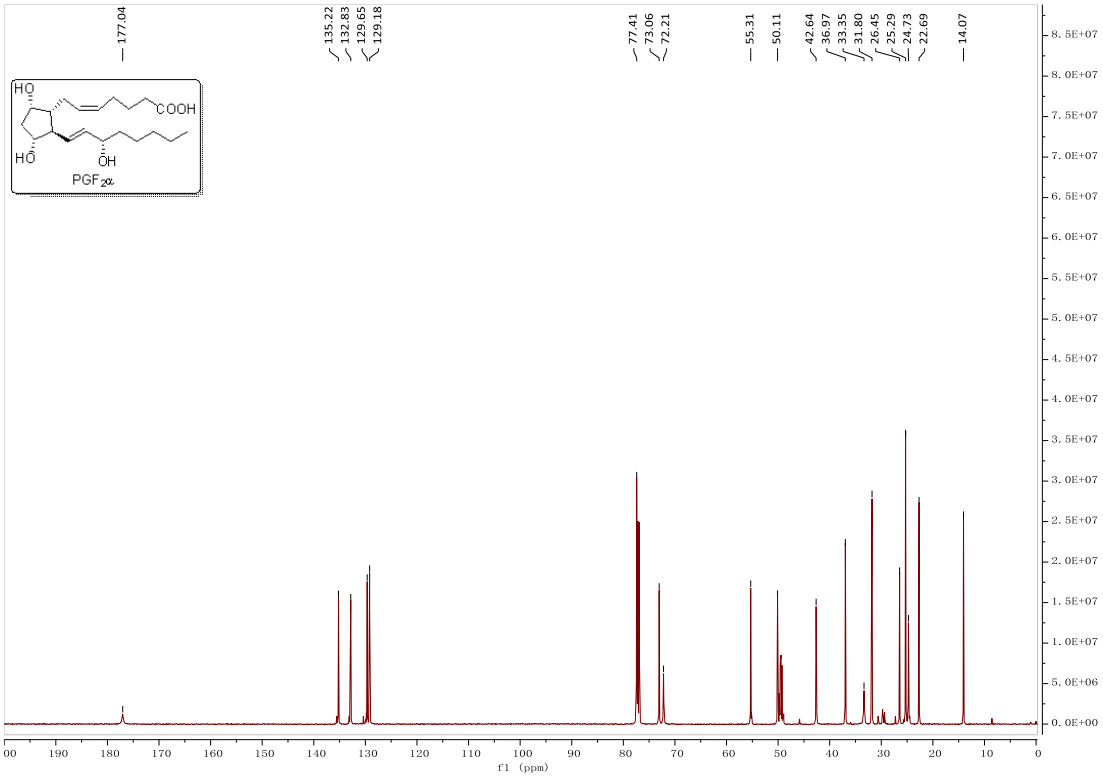
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of 2 (Bimatoprost)



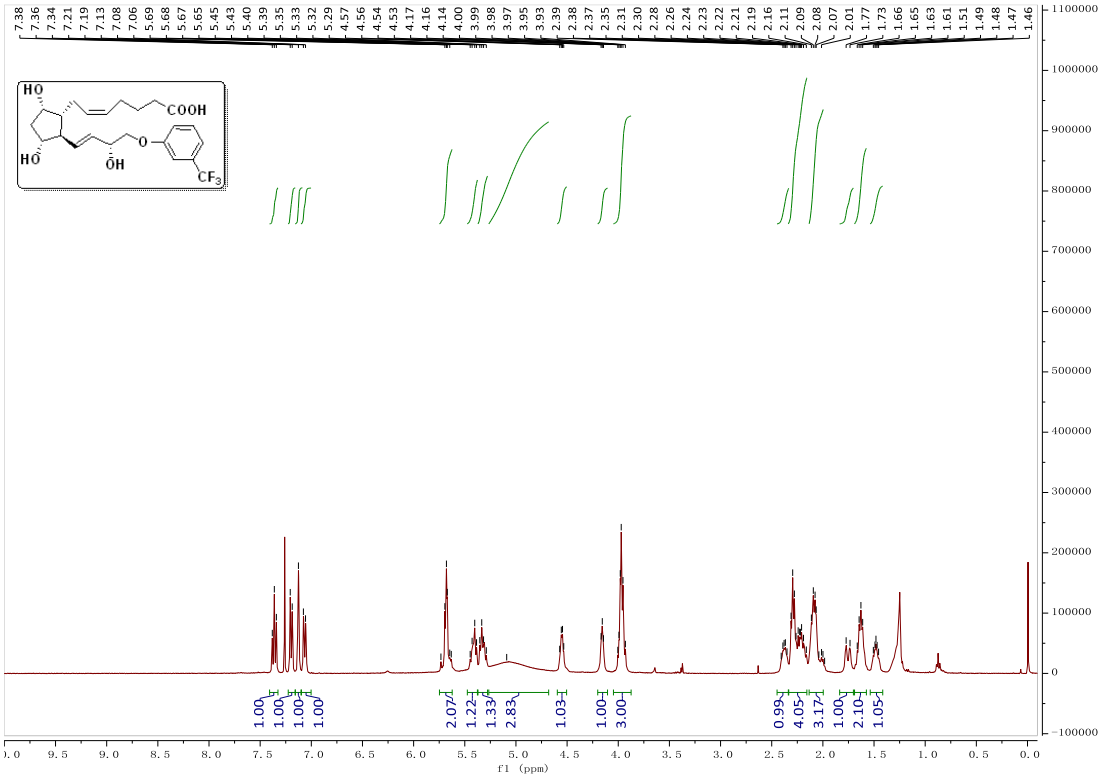
The ^{1}H NMR (500 MHz, ca. 20:1 $CDCl_3$:CD_3OD) Spectrum of 3 ($PGF_{2\alpha}$)



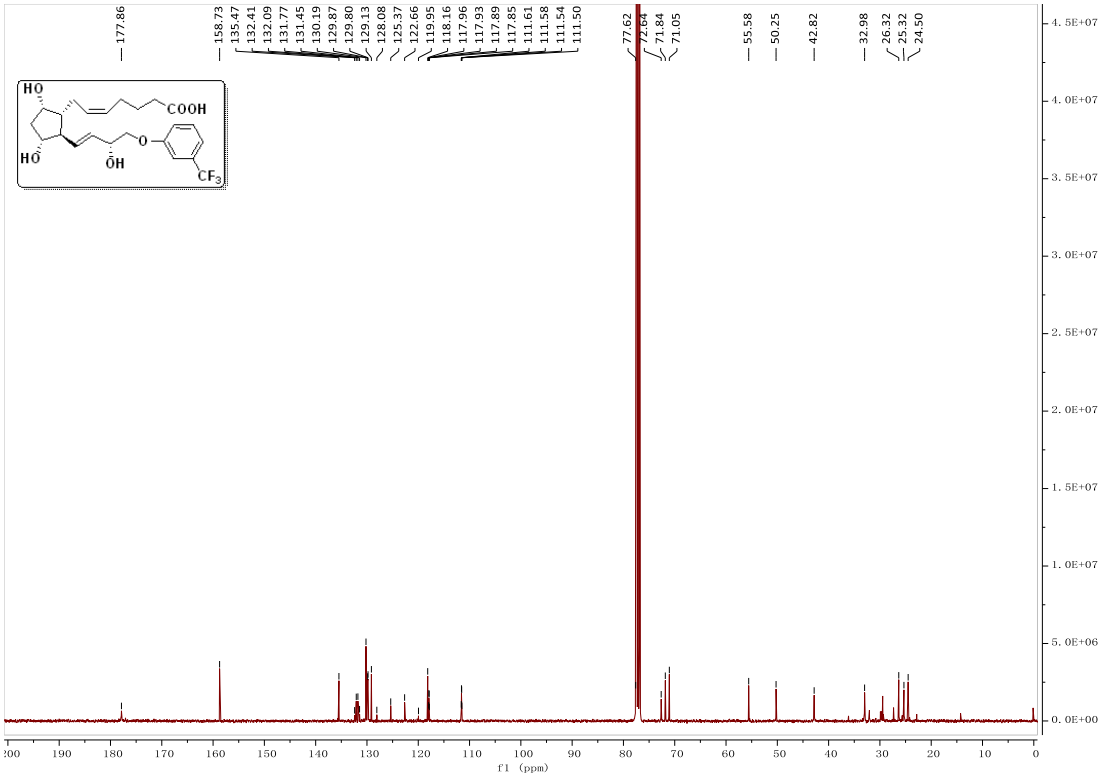
The ^{13}C NMR (126 MHz, ca. 20:1 $CDCl_3$:CD_3OD) Spectrum of 3 ($PGF_{2\alpha}$)



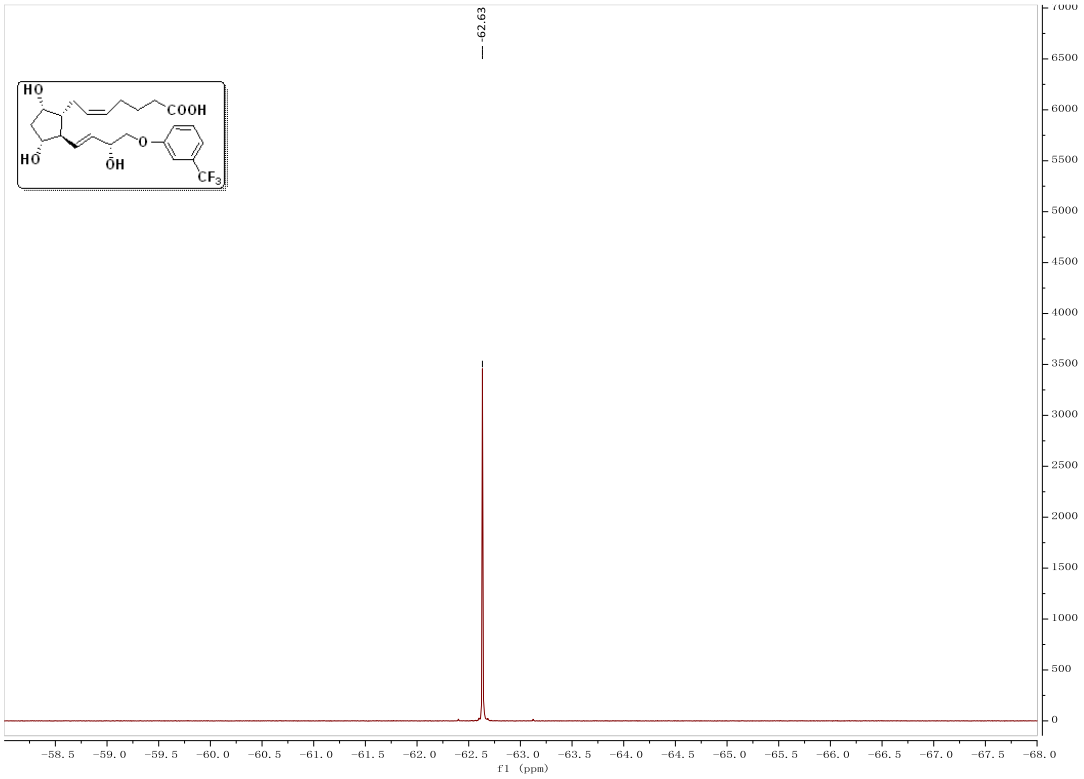
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of 4 (fluprostenol)



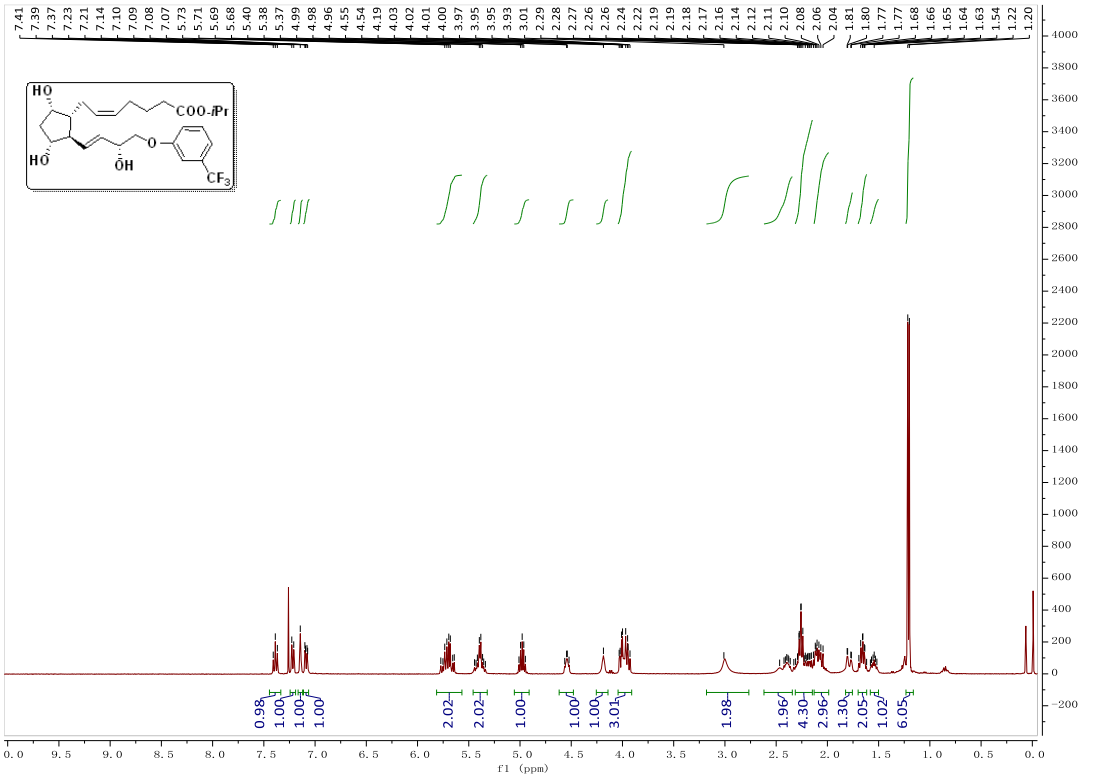
The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of 4 (fluprostenol)



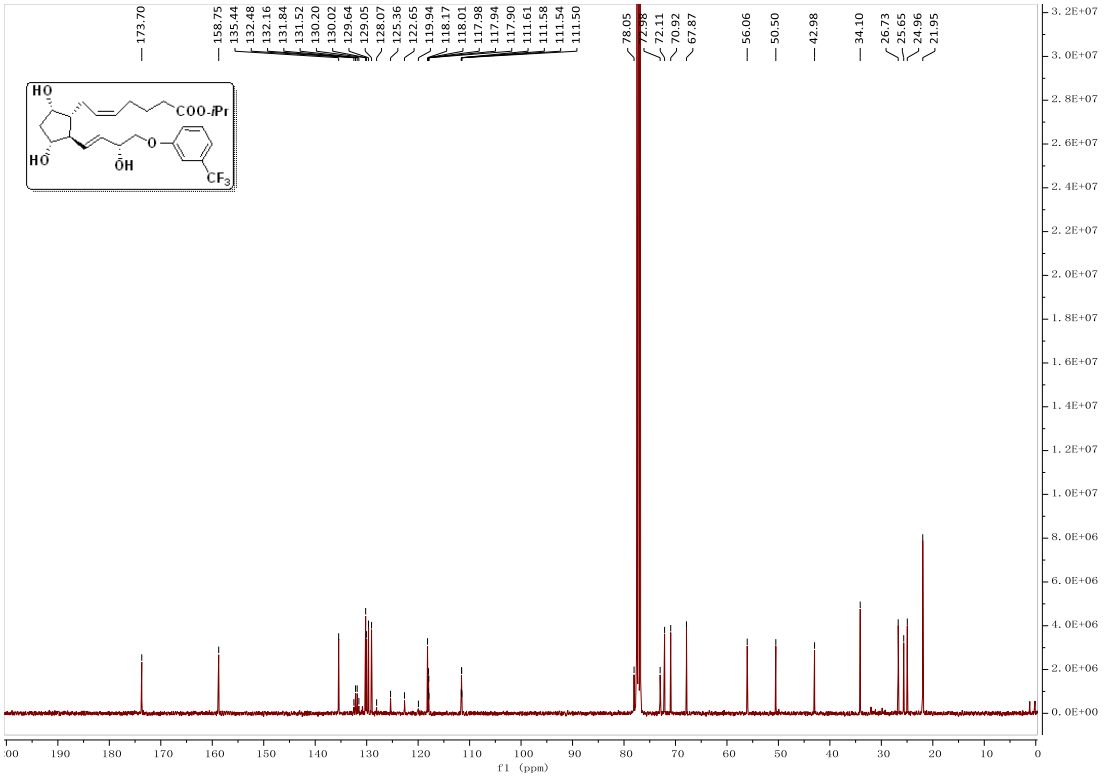
The ^{19}F NMR (376 MHz, $CDCl_3$) Spectrum of 4 (fluprostenol)



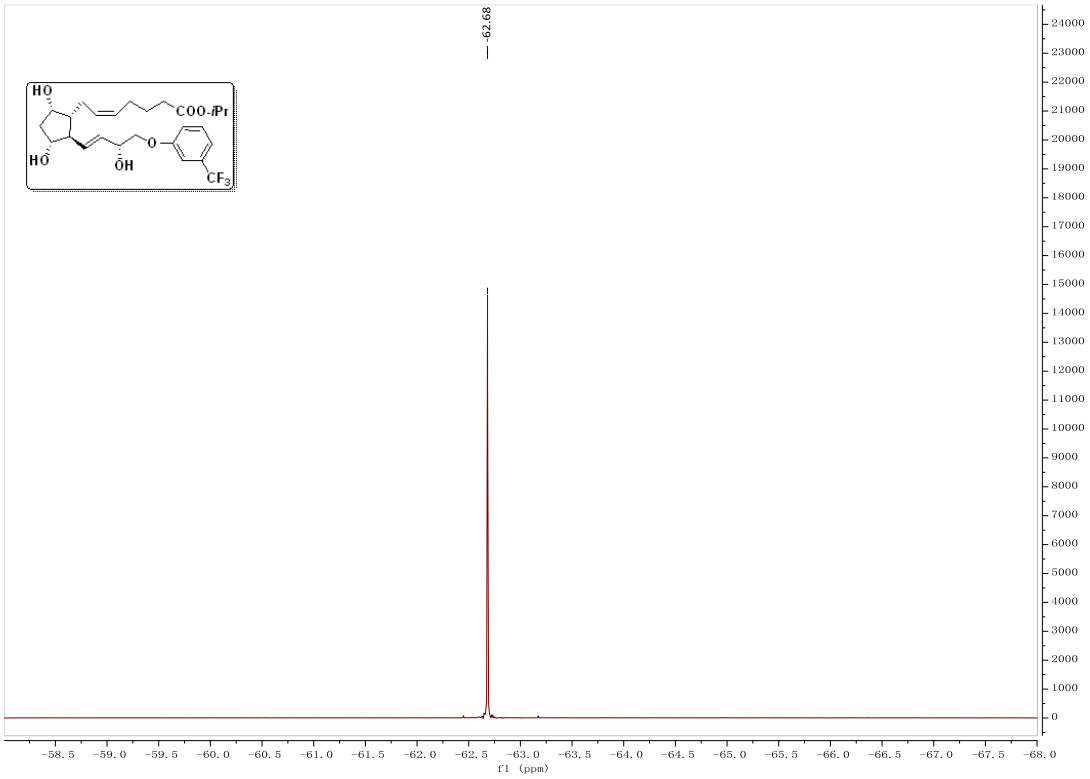
The ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of 5 (travoprost)



The ^{13}C NMR (101 MHz, $CDCl_3$) Spectrum of 5 (travoprost)

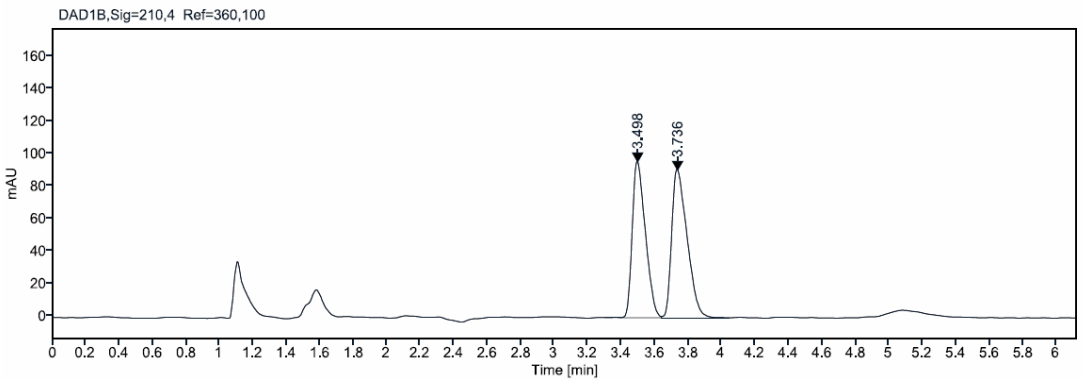


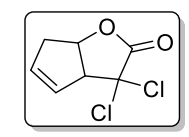
The ^{19}F NMR (376 MHz, $CDCl_3$) Spectrum of 5 (travoprost)



(3a*S*, 6a*R*)-3, 3-Dichloro-3, 3a, 6, 6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (7a)

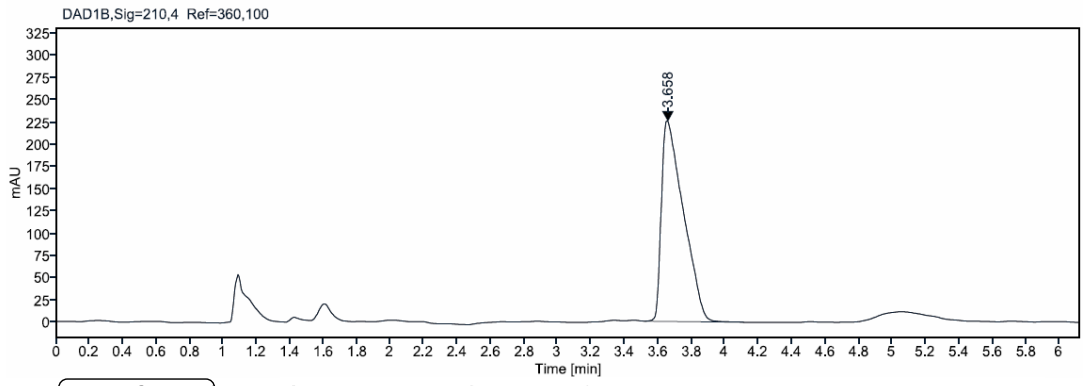
Chiral SFC (Chiralcel IF-3 column), CO_2 : MeOH = 97/3, Flow rate:3 mL/min, UV detection at 210 nm, T = 30 °C, BPR Pressure = 150 bar, BPR Temperature: 60 °C, retention time: 3.649 min (major),3.404 min (minor).

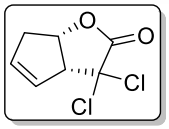




Signal: DAD1B,Sig=210,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
3.498	BV	0.34	523.43	95.35	47.29
3.736	VB	0.40	583.43	90.29	52.71
		Sum	1106.86		



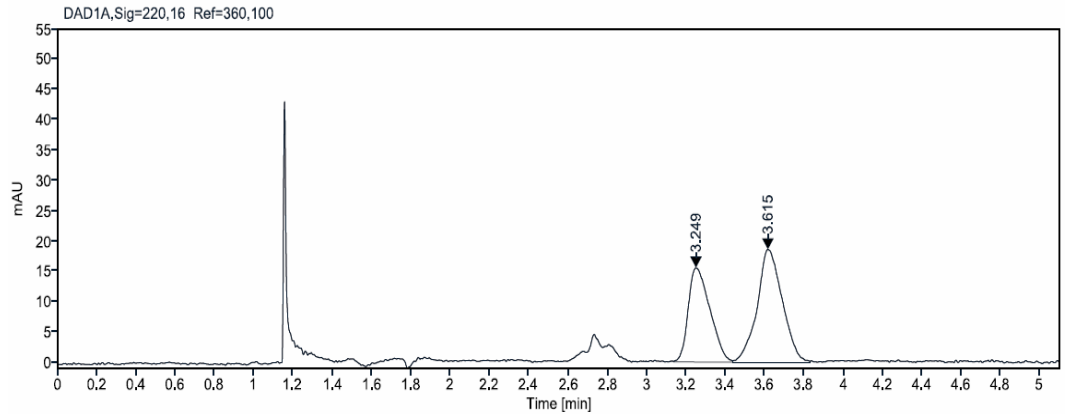


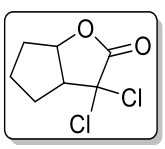
Signal: DAD1B,Sig=210,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
3.658	BBA	0.59	2056.89	224.61	100.00
		Sum	2056.89		

(3a*R*, 6a*S*)-3, 3-Dichlorohexahydro-2*H*-cyclopenta[*b*]furan-2-one (7b)

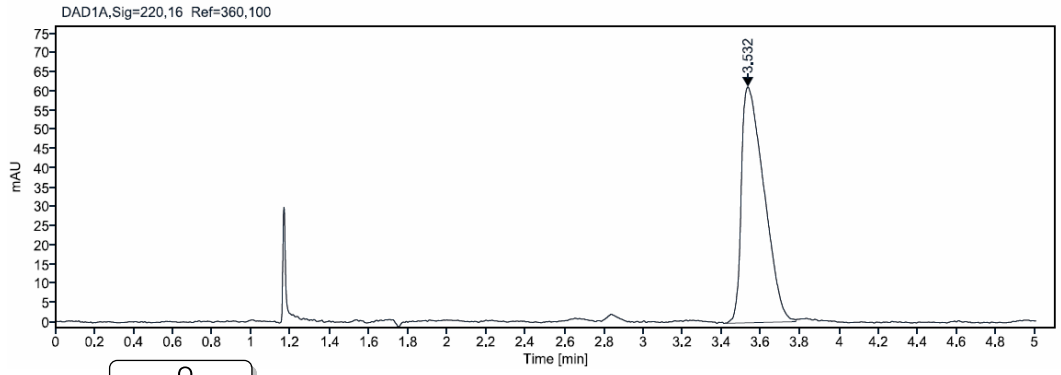
Chiral SFC (Chiralcel IA column), CO_2 : MeOH = 98/2, Flow rate: 3.0 mL/min, UV detection at 220 nm, T = 30 °C, Background pressure = 150 bar, retention time: 3.615 min (major), 3.249 min (minor).

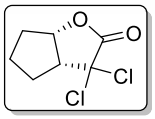




Signal: DAD1A,Sig=220,16 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
3.249	VV	0.30	118.97	15.54	41.88
3.615	VV	0.39	165.13	18.54	58.12
		Sum	284.11		



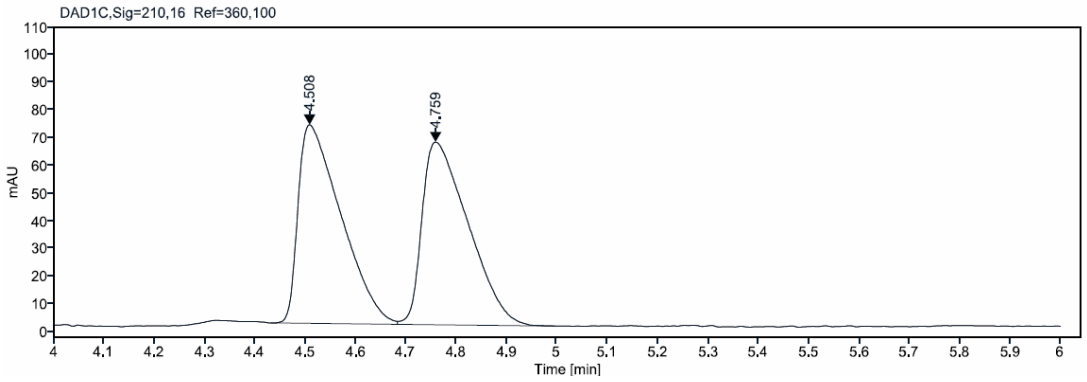


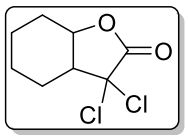
Signal: DAD1A,Sig=220,16 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
3.532	VV	0.35	490.98	61.23	100.00
		Sum	490.98		

(3a*R*, 7a*S*)-3,3-Dichlorohexahydrobenzofuran-2(3*H*)-one (7c)

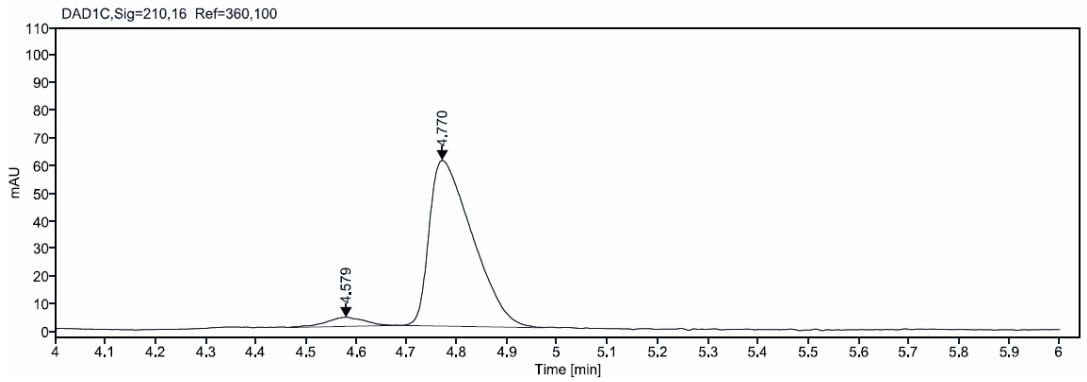
Chiral SFC (Chiralcel IF-3 column), CO_2 : MeOH = 93/7, Flow rate: 2 mL/min, UV detection at 210 nm, T = 30 °C, BPR Pressure = 150 bar, BPR Temperature: 60 °C, retention time: 4.770 min (major), 4.579 min (minor).

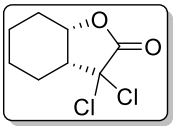




Signal: DAD1C,Sig=210,16 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
4.508	BV	0.25	423.40	71.60	50.24
4.759	VBA	0.31	419.43	65.88	49.76
		Sum	842.83		



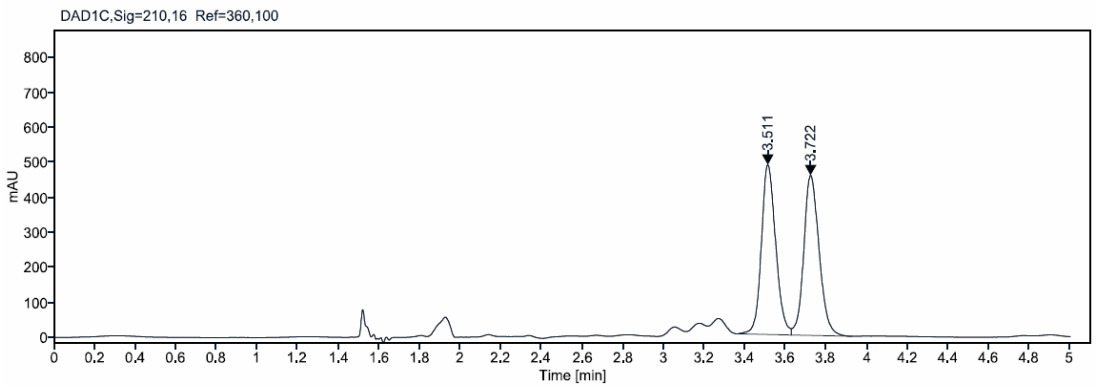


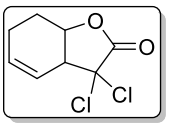
Signal: DAD1C,Sig=210,16 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
4.579	BM m	0.07	17.51	3.25	4.67
4.770	MV m	0.09	357.18	59.92	95.33
		Sum	374.69		

(3a*R*, 7a*S*)-3, 3-Dichloro-3a, 6, 7, 7a-tetrahydrobenzofuran-2(3*H*)-one (7d)

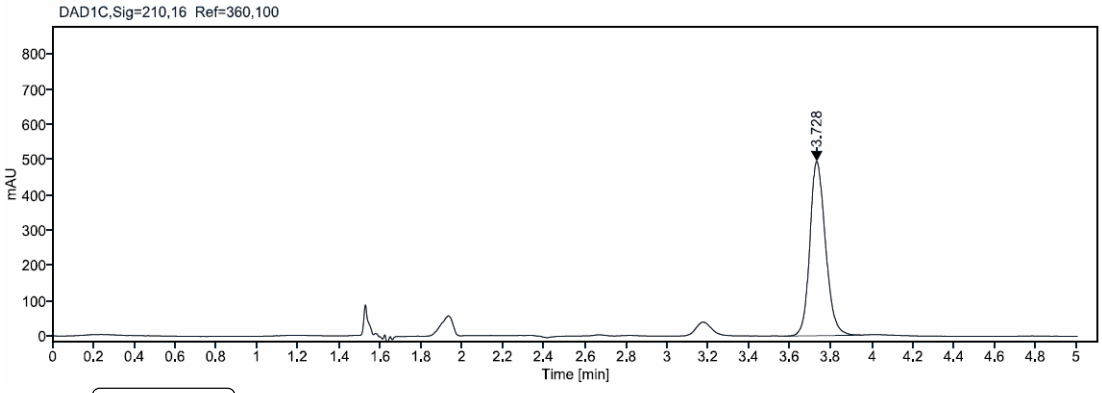
Chiral SFC (Chiralcel IA column), CO_2 : MeOH = 90/10, Flow rate: 2 mL/min, UV detection at 210 nm, T =30 ºC, BPR Pressure = 150 bar, BPR Temperature: 60 ºC, retention time: 3.728 min (major), 3.511 min (minor).

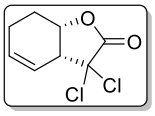




Signal: DAD1C,Sig=210,16 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
3.511	BV	0.27	2384.20	485.28	49.76
3.722	VB	0.30	2406.89	457.98	50.24
		Sum	4791.10		



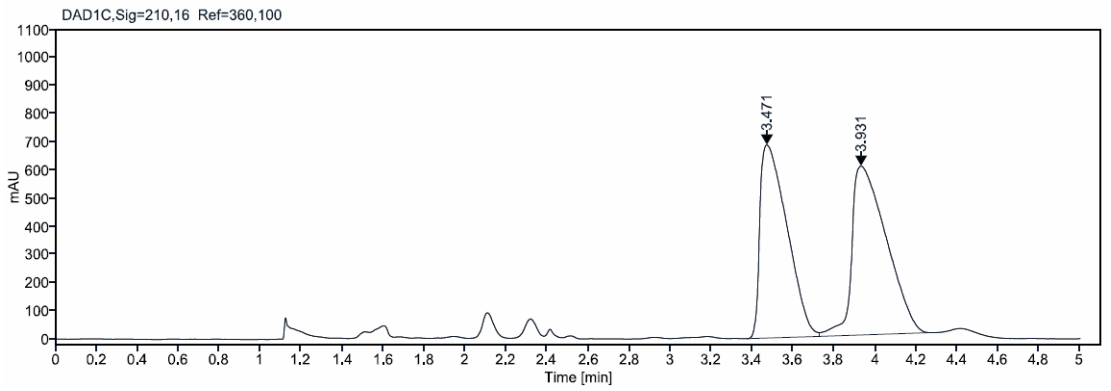


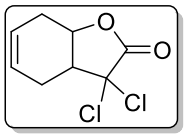
Signal: DAD1C,Sig=210,16 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
3.728	BB	0.38	2630.64	495.05	100.00
		Sum	2630.64		

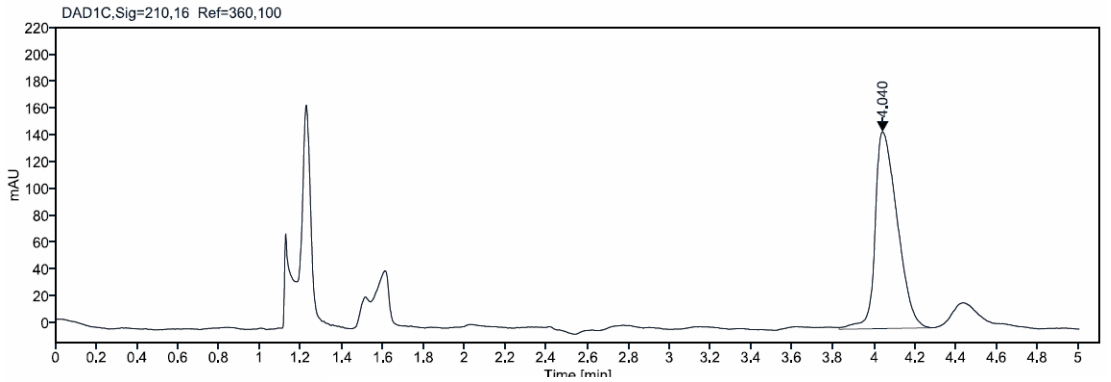
(3a*R*,7a*S*)-3,3-Dichloro-3a,4,7,7a-tetrahydrobenzofuran-2(3*H*)-one (7e)

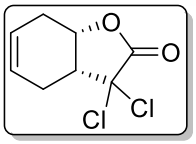
Chiral SFC (Chiralcel IA column), CO_2 : MeOH = 97/3, Flow rate: 3 mL/min, UV detection at 210 nm, T =30 ºC, BPR Pressure = 150 bar, BPR Temperature: 60 ºC, retention time: 4.040 min (major), 3.471 min (minor).





Signal:	DAD1C,Sig=210,16 Ref=360,100				
RT [min]	Type	Width [min]	Area	Height	Area%
3.471	BV	0.35	6288.15	685.47	47.18
3.931	VB	0.54	7038.84	599.43	52.82
		Sum	13326.99		

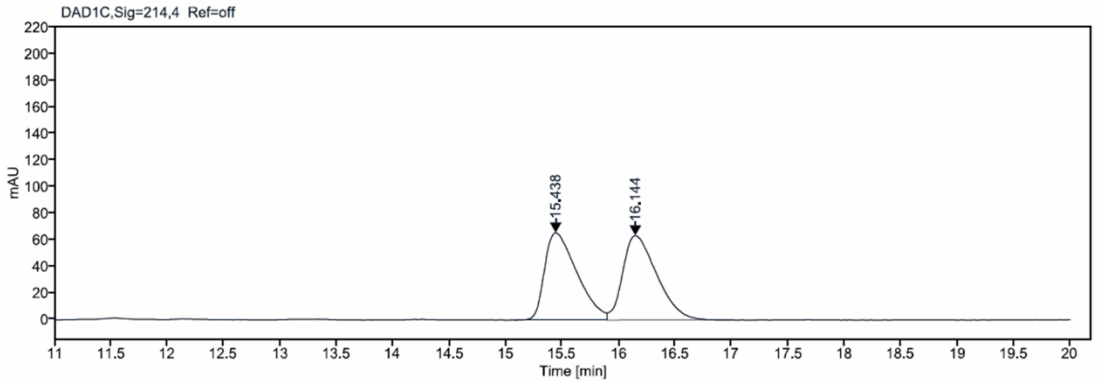


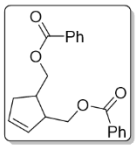


Signal:	DAD1C,Sig=210,16 Ref=360,100				
RT [min]	Type	Width [min]	Area	Height	Area%
4.040	VB	0.45	1105.47	146.66	100.00
		Sum	1105.47		

((1*R*,2*S*)-cyclopent-3-ene-1,2-diyl)bis(methylene) dibenzoate (9'')

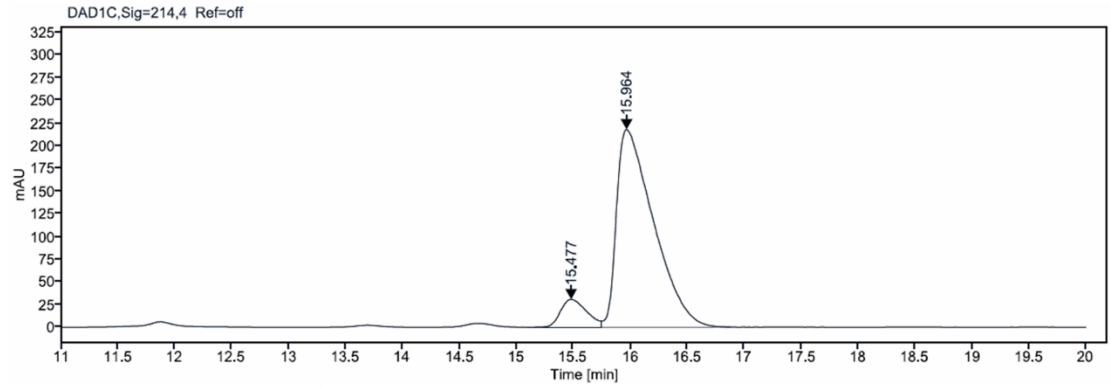
Chiral HPLC (Chiralcel IF-3 column), CO_2 : MeOH = 95/5, Flow rate: 2 mL/min, UV detection at 214 nm, T =40 °C, BPR Pressure = 140 bar, BPR Temperature: 60 °C, retention time: 15.964 min (major), 15.477 min (minor).

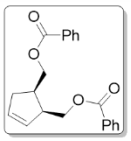




Signal: DAD1C,Sig=214,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%
15.438	VV	0.81	1305.89	65.68	49.50
16.144	VBA	1.11	1332.18	63.48	50.50
		Sum	2638.07		



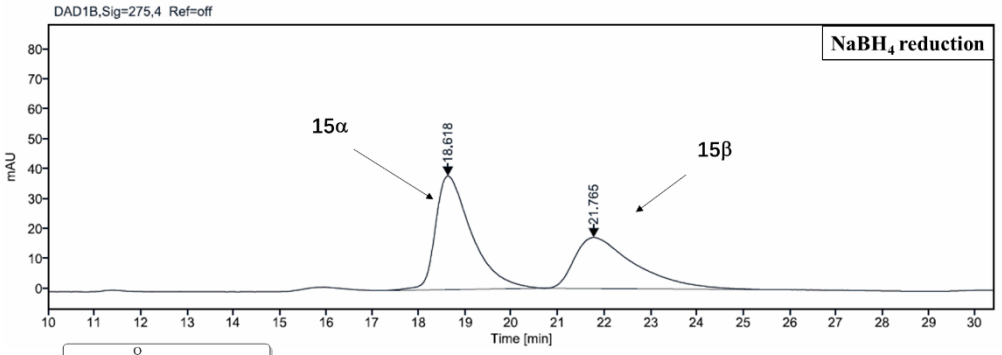


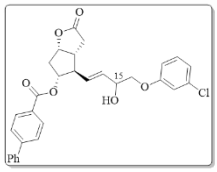
Signal: DAD1C,Sig=214,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%
15.477	BV	0.65	492.60	30.72	9.08
15.964	VB	1.13	4929.58	217.91	90.92
		Sum	5422.19		

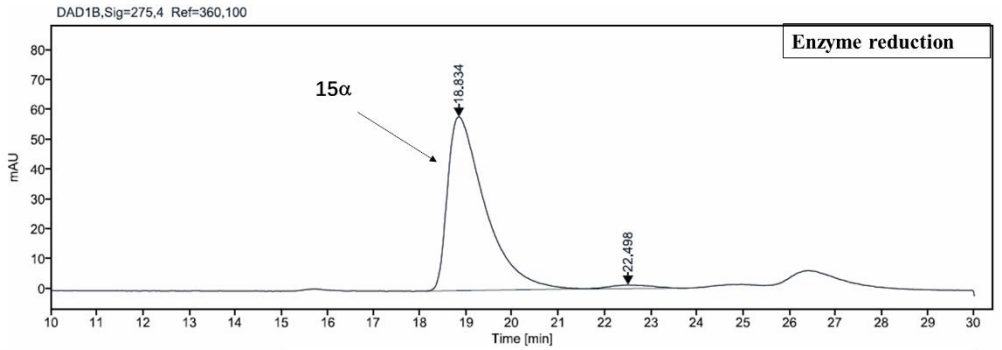
(3a*R*,4*R*,5*R*,6a*S*)-4-((*R*,*E*)-4-(3-Chlorophenoxy)-3-hydroxybut-1-en-1-yl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl [1,1'-biphenyl]-4-carboxylate (13a)

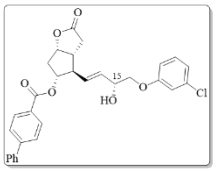
Chiral SFC (Chiralcel IF-3 column), CO_2 : MeOH = 75/25, Flow rate: 3 mL/min, UV detection at 275 nm, T =30 ºC, BPR Pressure = 140 bar, BPR Temperature: 60 ºC, retention time: 18.834 min (major), 22.498 min (minor).



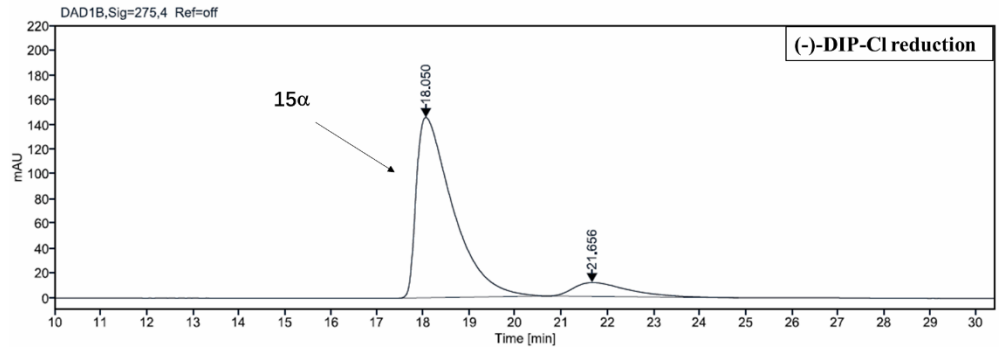


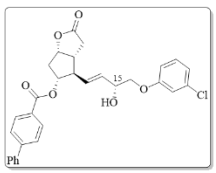
Signal:	DAD1B,Sig=275,4 Ref=off				
RT [min]	Type	Width [min]	Area	Height	Area%
18.618	BB	3.40	2052.55	37.96	57.15
21.765	BB	4.85	1538.96	17.03	42.85
		Sum	3591.52		





Signal:	DAD1B,Sig=275,4 Ref=360,100				
RT [min]	Type	Width [min]	Area	Height	Area%
18.834	BB	3.37	3279.29	58.15	97.85
22.498	MM m	0.73	72.03	1.19	2.15
		Sum	3351.32		

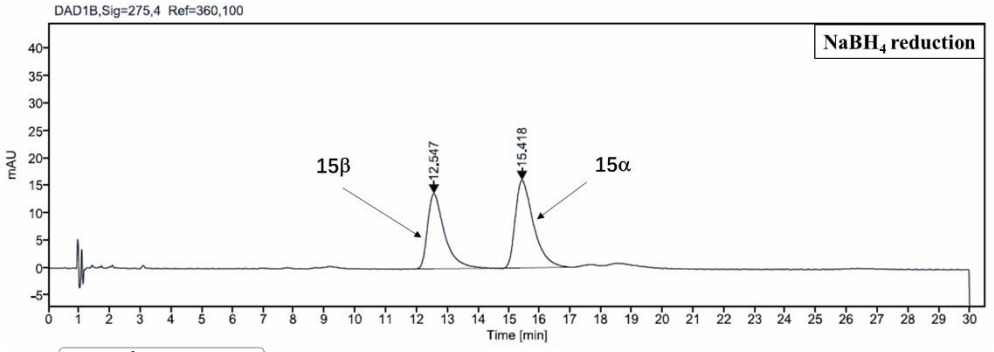


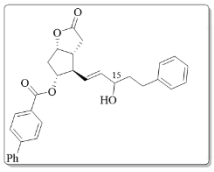


Signal:	DAD1B,Sig=275,4 Ref=off				
RT [min]	Type	Width [min]	Area	Height	Area%
18.050	BB	3.28	8055.07	145.92	89.65
21.656	BB	4.17	929.77	11.26	10.35
		Sum	8984.84		

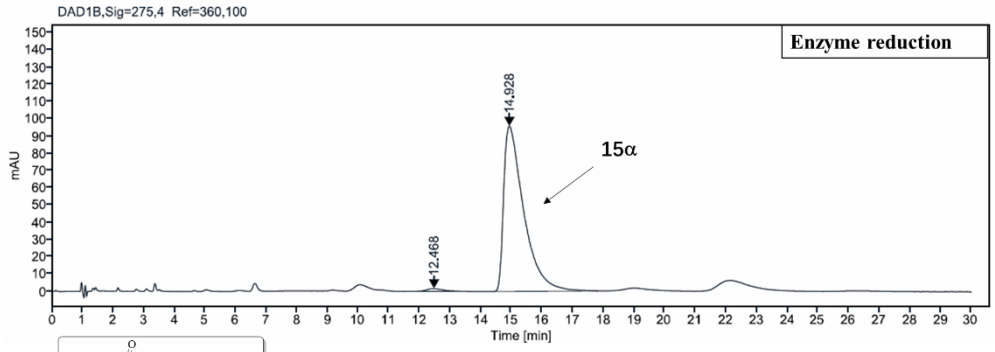
(3a*R*,4*R*,5*R*,6a*S*)-4-((*S*,*E*)-3-Hydroxy-5-phenylpent-1-en-1-yl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl [1,1'-biphenyl]-4-carboxylate (13b)

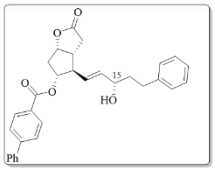
Chiral SFC (Chiralcel IF-3 column), CO_2 : MeOH = 75/25, Flow rate: 3 mL/min, UV detection at 275 nm, T =30 ºC, BPR Pressure = 130 bar, BPR Temperature: 60 ºC, retention time: 14.928 min (major), 12.468 min (minor).



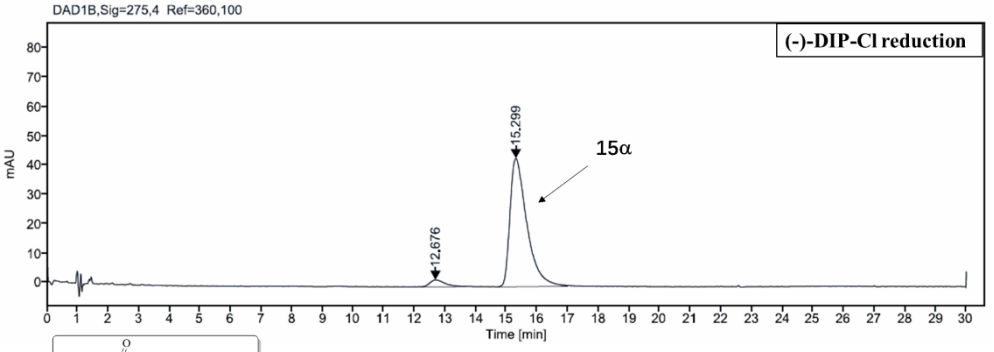


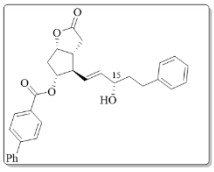
Signal:	DAD1B,Sig=275,4 Ref=360,100				
RT [min]	Type	Width [min]	Area	Height	Area%
12.547	MM m	0.55	528.27	13.68	44.52
15.418	MM m	0.60	658.27	15.98	55.48
		Sum	1186.54		





Signal:	DAD1B,Sig=275,4 Ref=360,100				
RT [min]	Type	Width [min]	Area	Height	Area%
12.468	BB	1.32	56.53	1.60	1.28
14.928	BB	3.41	4353.52	95.89	98.72
		Sum	4410.05		

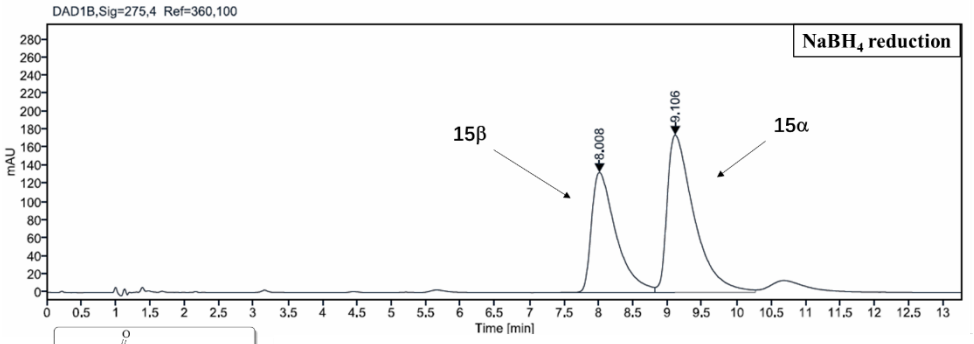


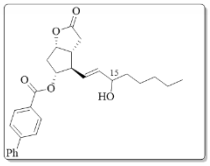


Signal:	DAD1B,Sig=275,4 Ref=360,100				
RT [min]	Type	Width [min]	Area	Height	Area%
12.676	BV	1.45	82.45	2.35	4.70
15.299	VV	2.27	1670.93	43.75	95.30
		Sum	1753.38		

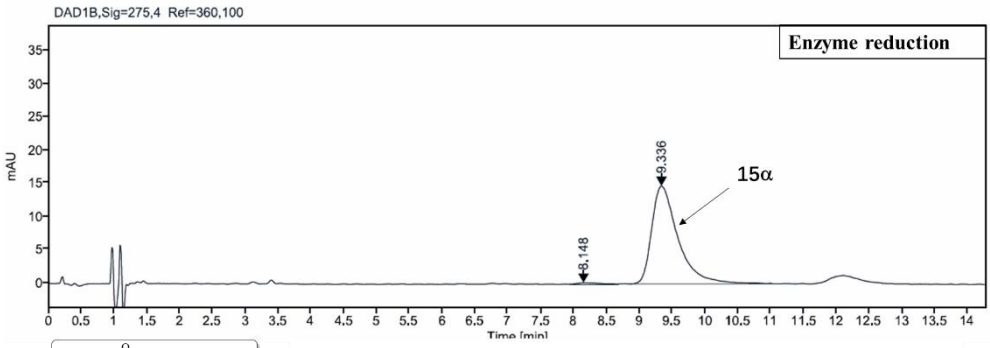
(3a*R*,4*R*,5*R*,6a*S*)-4-((*S*,*E*)-3-hydroxyoct-1-en-1-yl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl [1,1'-biphenyl]-4-carboxylate (13c)

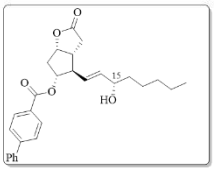
Chiral SFC (Chiralcel IF-3 column), CO_2 : MeOH = 75/25, Flow rate: 3 mL/min, UV detection at 275 nm, T =30 ºC, BPR Pressure = 130 bar, BPR Temperature: 60 ºC, retention time: 9.336 min (major), 8.148 min (minor).



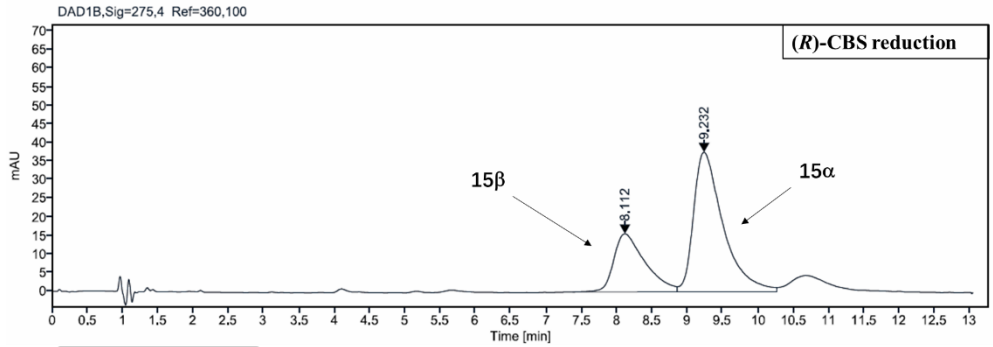


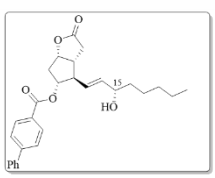
Signal:	DAD1B,Sig=275,4 Ref=360,100				
RT [min]	Type	Width [min]	Area	Height	Area%
8.008	BV	1.57	3285.52	132.97	41.00
9.106	VV	1.46	4728.56	174.37	59.00
		Sum	8014.09		





Signal:	DAD1B,Sig=275,4 Ref=360,100				
RT [min]	Type	Width [min]	Area	Height	Area%
8.148	MM m	0.27	4.82	0.22	1.16
9.336	BM m	0.42	412.63	14.75	98.84
		Sum	417.46		

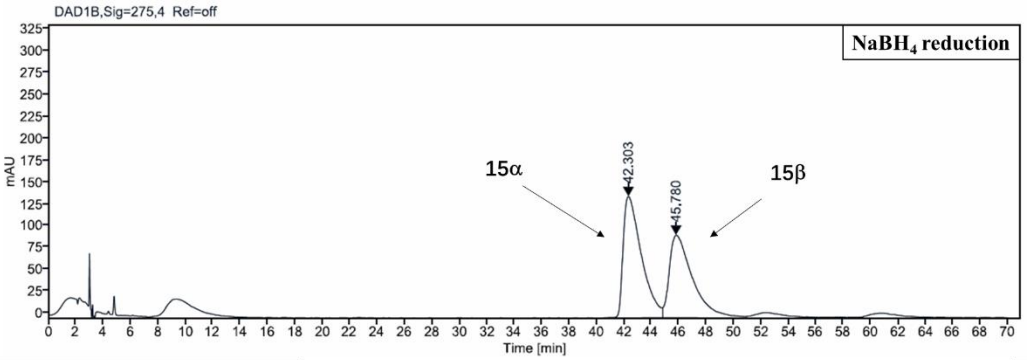


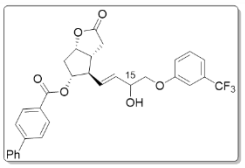


Signal:	DAD1B,Sig=275,4 Ref=360,100				
RT [min]	Type	Width [min]	Area	Height	Area%
8.112	BV	1.48	485.83	15.68	30.68
9.232	VV	1.41	1097.70	37.62	69.32
		Sum	1583.53		

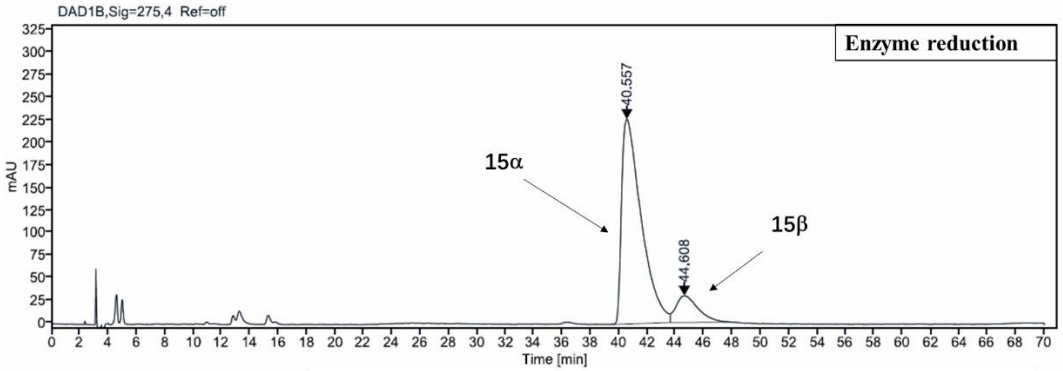
(3a*R*,4*R*,5*R*,6a*S*)-4-((*R*, *E*)-3-hydroxy-4-(3-(trifluoromethyl)phenoxy)but-1-en-1-yl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl [1,1'-biphenyl]-4-carboxylate(13d)

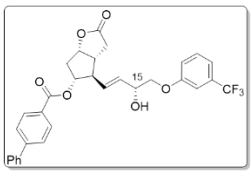
Chiral SFC (Chiralcel IF-3 column), CO_2 : MeOH = 80/20, Flow rate: 1 mL/min, UV detection at 275 nm, T =30 ℃, BPR Pressure = 130 bar, BPR Temperature: 60 ℃, retention time: 40.557 min (major), 44.608 min (minor).



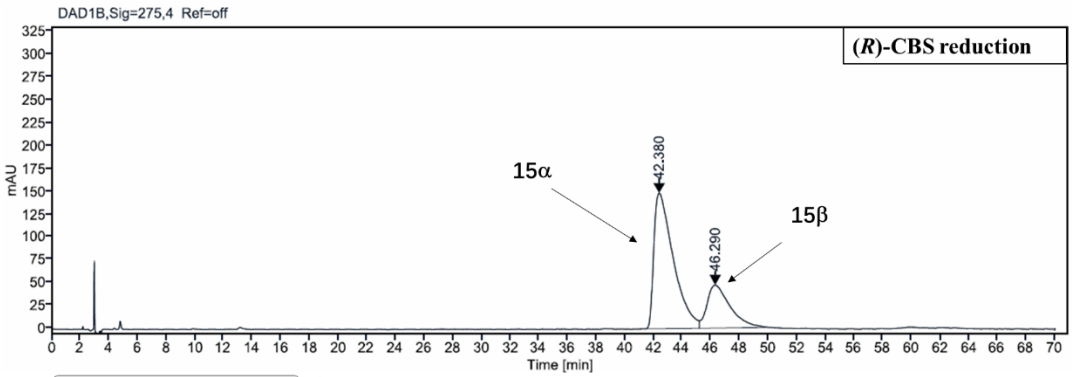


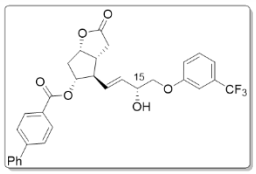
Signal:	DAD1B,Sig=275,4 Ref=off				
RT [min]	Type	Width [min]	Area	Height	Area%
42.303	BM m	1.10	12744.33	138.77	53.68
45.780	MM m	1.37	10996.85	94.31	46.32
		Sum	23741.19		





Signal:	DAD1B,Sig=275,4 Ref=off				
RT [min]	Type	Width [min]	Area	Height	Area%
40.557	BM m	1.17	21848.80	227.25	87.08
44.608	MM m	1.29	3240.52	29.52	12.92
		Sum	25089.32		





Signal:	DAD1B,Sig=275,4 Ref=off				
RT [min]	Type	Width [min]	Area	Height	Area%
42.380	BV	3.79	14048.22	148.81	72.66
46.290	VV	4.61	5285.34	47.24	27.34
		Sum	19333.56		

Crystallographic information

The crystal data of compound **7a** has been deposited in CCDC with number 1975866.

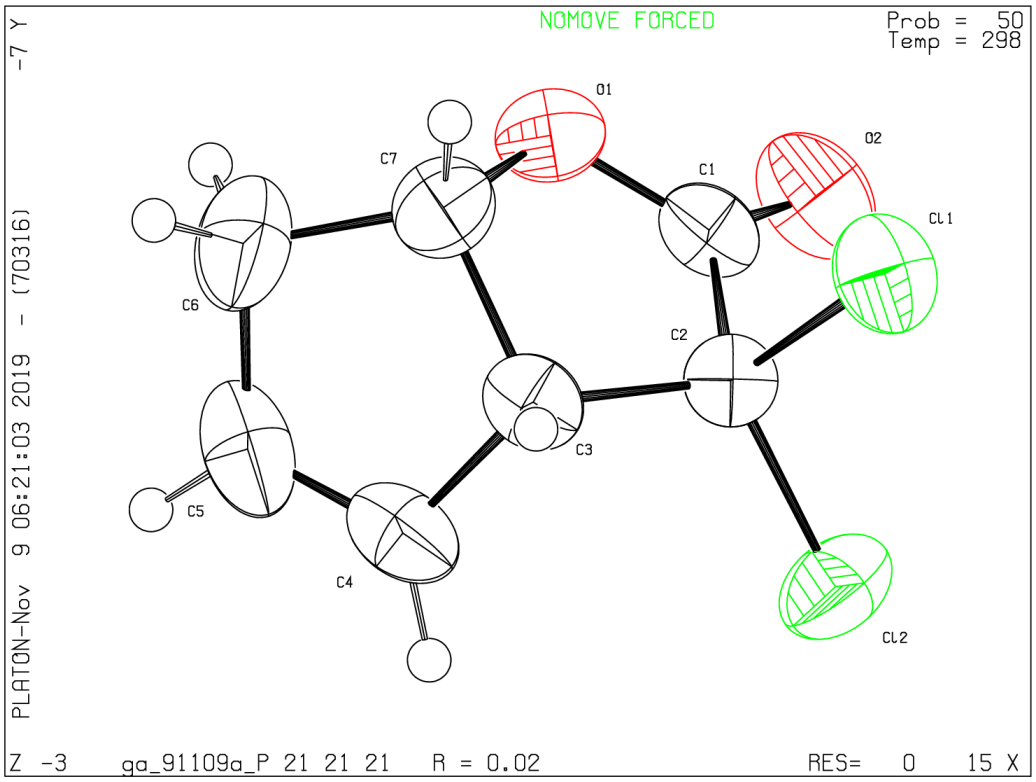


Table 1. Crystal data and structure refinement for CCDC 1975866.

Identification code	CCDC 1975866	
Empirical formula	$C_7H_6Cl_2O_2$	
Formula weight	193.02	
Temperature	298(2) K	
Wavelength	1.34138 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.6662(15) Å	α= 90 °.
	b = 9.925(2) Å	β= 90 °.
	c = 10.643(2) Å	γ = 90 °.
Volume	809.8(3) $Å^3$	
Z	4	
Density (calculated)	1.583 Mg/m^3	
Absorption coefficient	4.502 mm^{-1}	
F(000)	392	
Crystal size	0.280 x 0.130 x 0.120 mm^3	
Theta range for data collection	5.302 to 58.961 °.	
Index ranges	-9<=h<=9, -12<=k<=12, -13<=l<=13	
Reflections collected	14618	
Independent reflections	1748 [R(int) = 0.0604]	
Completeness to theta = 53.594 °	98.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.752 and 0.485	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1748 / 0 / 101	
Goodness-of-fit on F^2	1.058	
Final R indices [I>2sigma(I)]	R1 = 0.0238, wR2 = 0.0594	
R indices (all data)	R1 = 0.0304, wR2 = 0.0605	
Absolute structure parameter	0.037(8)	
Extinction coefficient	0.014(3)	
Largest diff. peak and hole	0.181 and -0.154 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for CCDC 1975866. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	9061(1)	5026(1)	5773(1)	59(1)
Cl(2)	8762(1)	3382(1)	3525(1)	64(1)
O(1)	6398(2)	6702(2)	3896(2)	58(1)
O(2)	8974(3)	6419(2)	2981(2)	69(1)
C(3)	5889(3)	4511(2)	4723(2)	45(1)
C(1)	7840(3)	6017(2)	3650(2)	46(1)
C(2)	7797(3)	4693(2)	4383(2)	42(1)
C(4)	4753(4)	3874(3)	3746(2)	58(1)
C(5)	3435(4)	4640(3)	3428(3)	71(1)
C(6)	3429(4)	5956(4)	4124(3)	77(1)
C(7)	5206(4)	5973(3)	4733(2)	56(1)

Table 3. Bond lengths [Å] and angles [ ] for CCDC 1975866.

Cl(1)-C(2)	1.799(2)
Cl(2)-C(2)	1.753(2)
O(1)-C(1)	1.324(3)
O(1)-C(7)	1.467(3)
O(2)-C(1)	1.192(3)
C(3)-C(4)	1.497(3)
C(3)-C(2)	1.517(3)
C(3)-C(7)	1.543(3)
C(3)-H(3)	0.9800
C(1)-C(2)	1.529(3)
C(4)-C(5)	1.309(4)
C(4)-H(4)	0.9300
C(5)-C(6)	1.502(5)
C(5)-H(5)	0.9300
C(6)-C(7)	1.509(4)
C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700
C(7)-H(7)	0.9800
C(1)-O(1)-C(7)	112.79(17)
C(4)-C(3)-C(2)	116.46(18)
C(4)-C(3)-C(7)	101.8(2)
C(2)-C(3)-C(7)	102.51(18)
C(4)-C(3)-H(3)	111.7
C(2)-C(3)-H(3)	111.7
C(7)-C(3)-H(3)	111.7
O(2)-C(1)-O(1)	123.7(2)
O(2)-C(1)-C(2)	127.4(2)
O(1)-C(1)-C(2)	108.80(18)
C(3)-C(2)-C(1)	104.18(18)
C(3)-C(2)-Cl(2)	116.26(16)
C(1)-C(2)-Cl(2)	111.28(14)
C(3)-C(2)-Cl(1)	110.18(13)
C(1)-C(2)-Cl(1)	104.48(15)
Cl(2)-C(2)-Cl(1)	109.72(12)
C(5)-C(4)-C(3)	112.6(2)

C(5)-C(4)-H(4)	123.7
C(3)-C(4)-H(4)	123.7
C(4)-C(5)-C(6)	112.3(3)
C(4)-C(5)-H(5)	123.8
C(6)-C(5)-H(5)	123.8
C(5)-C(6)-C(7)	102.6(2)
C(5)-C(6)-H(6A)	111.2
C(7)-C(6)-H(6A)	111.2
C(5)-C(6)-H(6B)	111.2
C(7)-C(6)-H(6B)	111.2
H(6A)-C(6)-H(6B)	109.2
O(1)-C(7)-C(6)	107.9(2)
O(1)-C(7)-C(3)	104.38(18)
C(6)-C(7)-C(3)	107.0(2)
O(1)-C(7)-H(7)	112.4
C(6)-C(7)-H(7)	112.4
C(3)-C(7)-H(7)	112.4

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for CCDC 1975866. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	59(1)	78(1)	40(1)	2(1)	-9(1)	-4(1)
Cl(2)	71(1)	62(1)	59(1)	-10(1)	0(1)	21(1)
O(1)	65(1)	42(1)	66(1)	3(1)	0(1)	2(1)
O(2)	70(1)	80(1)	56(1)	16(1)	8(1)	-26(1)
C(3)	51(1)	49(1)	36(1)	3(1)	6(1)	-9(1)
C(1)	52(1)	47(1)	39(1)	4(1)	-4(1)	-11(1)
C(2)	47(1)	45(1)	34(1)	2(1)	1(1)	0(1)
C(4)	62(2)	59(1)	52(1)	-7(1)	6(1)	-21(1)
C(5)	45(2)	106(2)	61(2)	-4(2)	-1(1)	-14(2)
C(6)	50(2)	98(2)	84(2)	-4(2)	7(1)	15(2)
C(7)	55(2)	60(1)	52(1)	-11(1)	8(1)	3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for CCDC 1975866.

	x	y	z	U(eq)
H(3)	5750	4076	5544	54
H(4)	4961	3027	3403	69
H(5)	2597	4396	2838	85
H(6A)	2508	5981	4748	93
H(6B)	3287	6710	3553	93
H(7)	5178	6358	5581	67

Table 6. Torsion angles [°] for CCDC 1975866.

C(7)-O(1)-C(1)-O(2)	179.3(2)
C(7)-O(1)-C(1)-C(2)	-2.3(2)
C(4)-C(3)-C(2)-C(1)	84.2(2)
C(7)-C(3)-C(2)-C(1)	-26.0(2)
C(4)-C(3)-C(2)-Cl(2)	-38.7(2)
C(7)-C(3)-C(2)-Cl(2)	-148.80(15)
C(4)-C(3)-C(2)-Cl(1)	-164.26(17)
C(7)-C(3)-C(2)-Cl(1)	85.59(17)
O(2)-C(1)-C(2)-C(3)	-163.0(2)
O(1)-C(1)-C(2)-C(3)	18.6(2)
O(2)-C(1)-C(2)-Cl(2)	-37.0(3)
O(1)-C(1)-C(2)-Cl(2)	144.66(16)
O(2)-C(1)-C(2)-Cl(1)	81.4(2)
O(1)-C(1)-C(2)-Cl(1)	-97.01(18)
C(2)-C(3)-C(4)-C(5)	-122.3(2)
C(7)-C(3)-C(4)-C(5)	-11.8(3)
C(3)-C(4)-C(5)-C(6)	0.4(3)
C(4)-C(5)-C(6)-C(7)	11.4(3)
C(1)-O(1)-C(7)-C(6)	-128.3(2)
C(1)-O(1)-C(7)-C(3)	-14.7(3)
C(5)-C(6)-C(7)-O(1)	93.7(3)
C(5)-C(6)-C(7)-C(3)	-18.1(3)
C(4)-C(3)-C(7)-O(1)	-95.9(2)
C(2)-C(3)-C(7)-O(1)	24.9(2)
C(4)-C(3)-C(7)-C(6)	18.3(3)
C(2)-C(3)-C(7)-C(6)	139.1(2)

Symmetry transformations used to generate equivalent atoms: