Concise Asymmetric Synthesis of (–)-Bilobalide

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Supplementary Information

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1. General Methods

All reactions were carried out under positive pressure of nitrogen/argon unless otherwise noted. Glassware was oven-dried at 120 °C for a minimum of 12 hours, or flame-dried with a propane torch under high vacuum. Anhydrous dichloromethane (DCM) was distilled from calcium hydride (5% w/v) under positive pressure of nitrogen. Anhydrous tetrahydrofuran (THF) was distilled over sodium/benzophenone ketyl under positive pressure of nitrogen. Anhydrous toluene was was obtained by passing the previously degassed solvent through an activated alumina column. Authentic (–)-bilobalide was purchased from Selleck Chemicals LLC MS. Other commercially available solvents or reagents were used without further purification unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) using precoated silica gel plates from EMD Chemicals (TLC Silica gel 60 F_{254}, 250 µm thickness). Flash column chromatography was performed over Silica gel 60 (particle size 0.04-0.063 mm) from EMD Chemicals and activated neutral alumina (Brockmann I, 150 mesh) from Sigma-Aldrich.

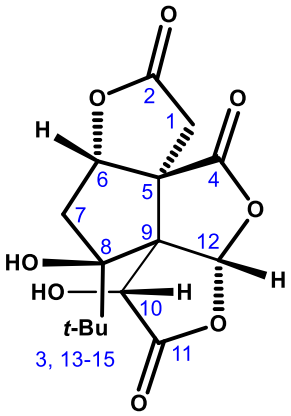
NMR spectra were recorded on Varian-400, Bruker DPX-400, DRX-500, and DRX-600 (cryoprobe) spectrometers using residual solvent peaks as an internal standard ($CDCl_3$ @ 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. HRMS were aquired using a Waters Xero G-2-XS Tof. Optical rotations were measured on an MC-100 Modular Circular Polarimeter from Anton Parr. Enantiomeric excess of chiral samples was determined using a Waters UPC2 SFC with a Daicel IC Column (3mm, 4.6x250 mm). Some crude samples were separated and analyzed using heart-cutting 2D LC-SFC in which the LC dimension consisted of a Waters I-Class LC with a Waters BEH C18 column (1.7 mm, 2.1x100 mm) and the SFC dimension consisted of the Waters UPC2 SFC with a Daicel IC Column (3mm, 4.6x250 mm).

The following reagents were prepared according to their corresponding literature procedure:

1.) (+)-Indabox……..……..(3aR,3a'R,8aS,8a'S)-2,2'-(propane-2,2-diyl)bis(3a,8a-dihydro-8H-indeno[1,2-d]oxazole)[34]
2.) Mn(dpm)$_3$……..……..…Tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III)[35]
3.) Ph(O*i*-Pr)SiH_2……..……..…Isopropoxy(phenyl)silane[24]
4.) *X^{c}PA*……..……**(**11b*R*)-2,6-Di-9-phenanthrenyl-4-hydroxy-dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-oxide[36]
5.) IBX……..……..……2-Iodoxybenzoic acid[37]
6.) TMS-EBX……..……..…….....1-[(trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one[28]

Abbreviations:

THF = Tetrahydrofuran
acac = Acetylacetonate
dpm = 2,2,6,6-tetramethyl-3,5-heptanedionato
BnOAc = Benzyl acetate
LDA = Lithium diisopropylamide
AIBN = Azobisisobutyronitrile
IBX = 2-iodoxybenzoic acid
TMS-EBX = 1-[(Trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one
TBAF = tetrabutylammonium fluoride
LHMDS = Lithium bis(trimethylsilyl)amide
NaHMDS = Sodium bis(trimethylsilyl)amide
KHMDS = Potassium bis(trimethylsilyl)amide
DMAP = 4-(Dimethylamino)pyridine
*m*CPBA = *meta*-Chloroperoxybenzoic acid
NBS = N-Bromosuccinimide



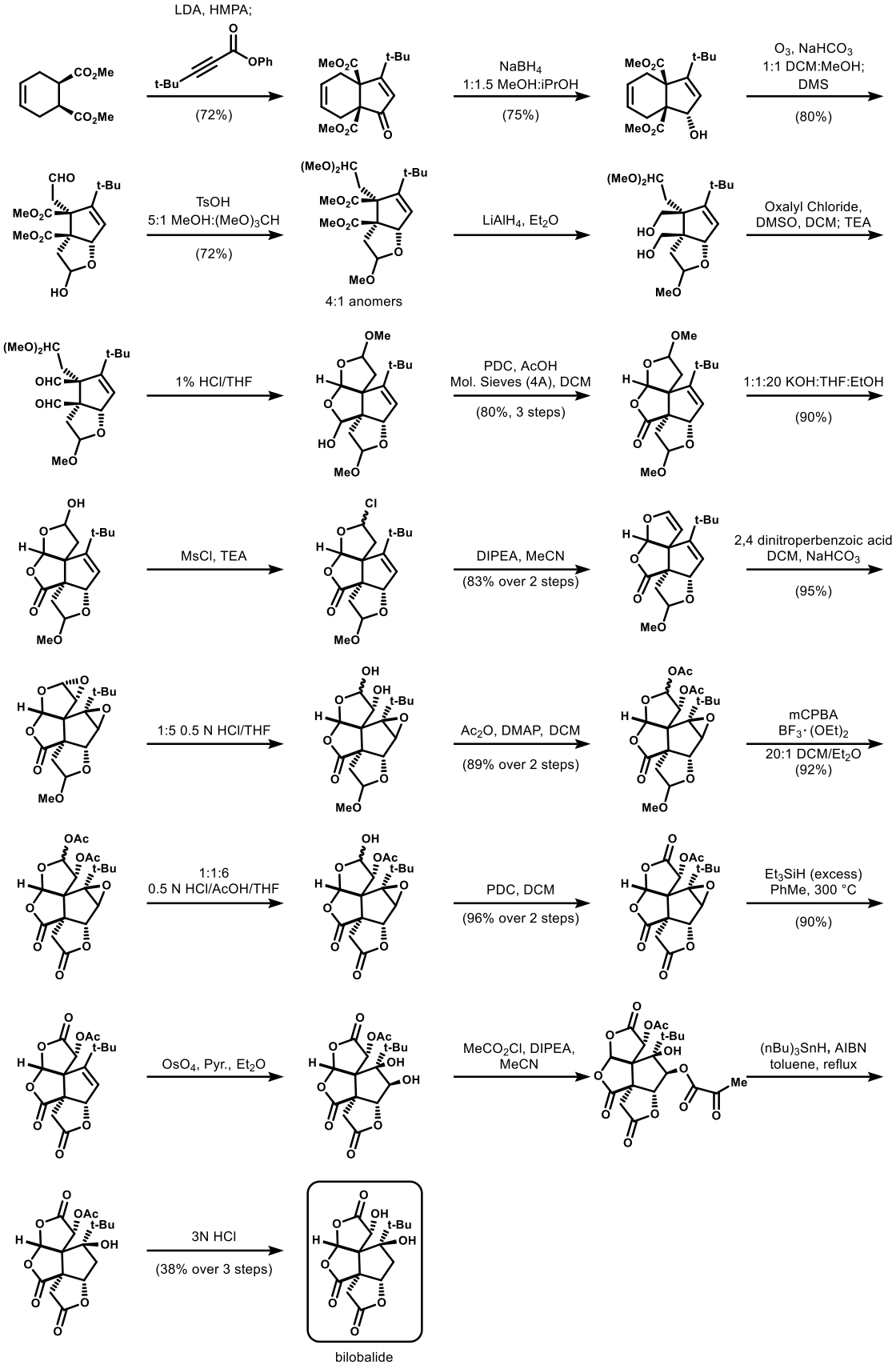
(–)-bilobalide

Scheme S1: Carbon Numbering

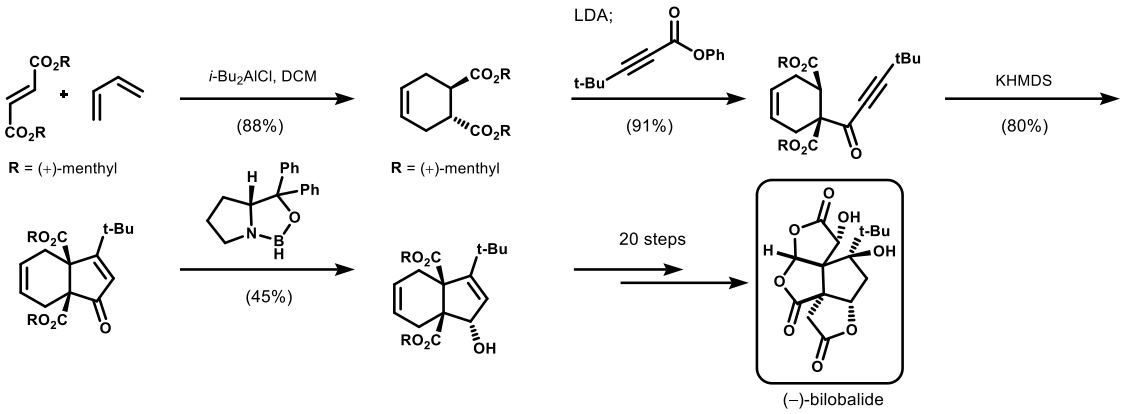
Numbering System: The carbon numbering system as outlined by Nakanishi[3] is utilized throughout the Supplementary Information as well as in the text of the paper.

2. Syntheses of Bilobalide

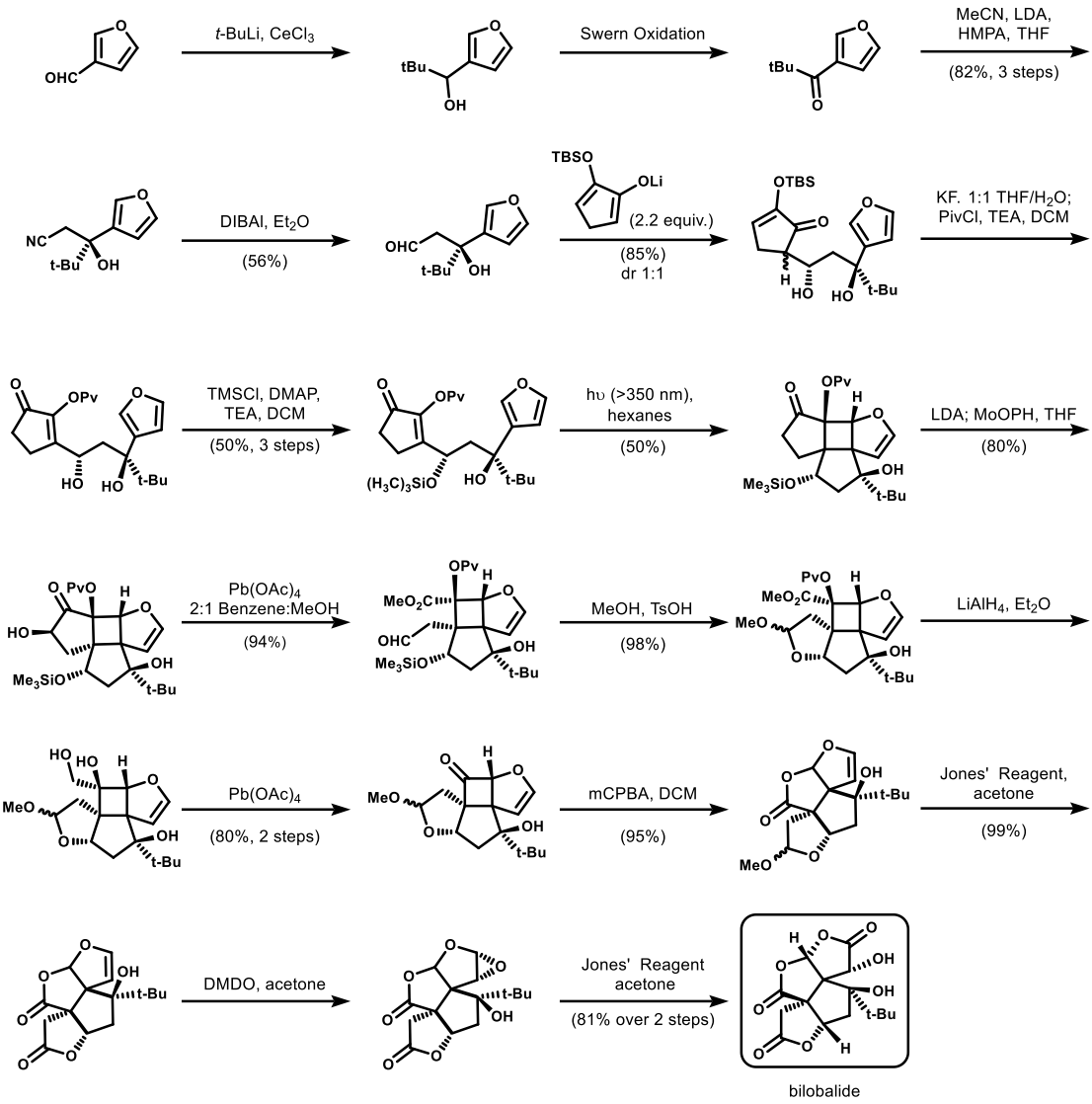
Scheme S2: Corey's synthesis of (±)-bilobalide[6]



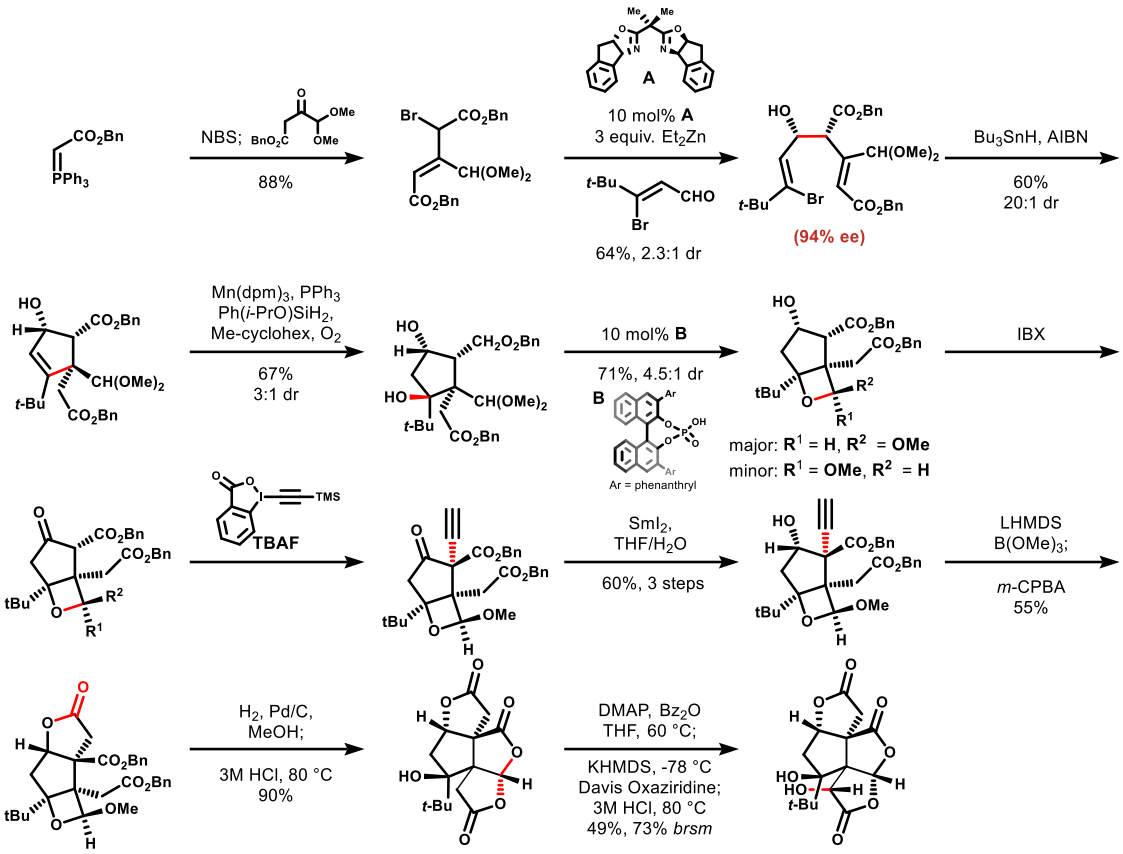
Scheme S3: Corey's synthesis of (–)-bilobalide[7]



Scheme S4: Crimmins' synthesis of (±)-bilobalide[8]

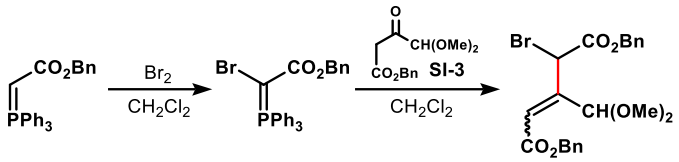


Scheme S5: This synthesis of (–)-bilobalide



3. Experimental Procedures and Characterizations

(±)-6a: Wittig Olefination (two-step) procedure

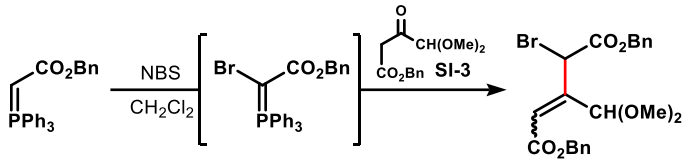


SI-1 SI-2 (±)-6a

To a flame-dried 2-liter round bottom equipped with a magnetic stirbar was added **SI-1** (164 g, 400 mmol, 1.0 equiv) followed by the addition of 800 mL of anhydrous DCM. The solution was cooled to 0 °C, then a solution of Br_2 (20.6 mL, 400 mmol, 1.0 equiv) in 50 mL of anhydrous DCM was added and the reaction was allowed to warm to room temperature and stir for 5 hours. The reaction was then transferred to a 1-liter separatory funnel and washed sequentially with H_2O, *sat.* $NaHCO_3$ 2 times, and then dried with Na_2SO_4 and concentrated *in vacuo*. The crude material was recrystallized from hot DCM/Et_2O/Hex (1:2:10) to afford bromo ylide **SI-2** as a yellow solid (152 g, 76.3% yield). *Note: The product is a strong lachcrymtor and should be weighed out in a well-ventilated fume hood*.

To a flame-dried 250 mL round bottom flask equipped with a magnetic stirbar was added **SI-2** (54.73 g, 111.8 mmol, 1.1 equiv) followed by **SI-3** (25.65 g, 101.1 mmol, 1.0 equiv). Anhydrous DCM was added until both of the reagents were completely dissolved (approx. 70 mL) and then the reaction was allowed to stir overnight. The reaction was concentrated *in vacuo*. Purification by silica gel flash column chromatography (hexanes/EtOAc = 9:1) afforded **(±)-6a** as a colorless oil (37.0 g, 79.4 mmol, 78.5%) and as a mixture of E/Z isomers.

(±)-6a: Wittig Olefination (one-step) procedure



SI-1 SI-2 (±)-6a

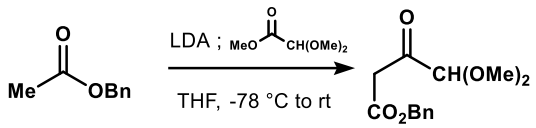
To a flame-dried, 25 mL round bottom flask with a magnetic stirbar were added ylide **SI-1** (225.8 mg, 0.55 mmol, 1.1 equiv) and 1.0 mL of DCM (0.5 M). NBS (107 mg, 0.6 mmol, 1.2 equiv) was added and the reaction was stirred for 12 hours followed by addition of diketone **SI-3** (126.1 mg equiv, 0.5 mmol) as a solution in DCM. Once the diketone was consumed (monitored by TLC, approx. 12 hours), the reaction was concentrated *in vacuo*. Purification by silica gel flash column chromatography (hexanes/EtOAc = 9:1) afforded **(±)-6a** as a colorless oil 204 mg, 0.44 mmol, 88%) and a mixture of E/Z isomers.

Characterization data for major isomer:

R_f	0.60 (hexanes/EtOAc = 5:1, $KMnO_4$)
^{1}H NMR	(600 MHz, $CDCl_3$)
	δ 7.39-7.31 (m, 10H), 6.62 (s, 1H), 5.91 (d, 1H, *J* = 0.6 Hz), 5.28 (d, 1H, *J* = 0.6 Hz), 5.22-5.15 (m, 4H), 3.39 (s, 3H), 3.22 (s, 3H).
^{13}C NMR	(151 MHz, $CDCl_3$)
	δ 167.9, 165.2, 148.7, 125.5, 125.3, 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 126.0, 100.0, 68.0, 66.9, 55.7, 55.5, 41.6.
HRMS (ESI)	Calcd. for $C_{22}H_{23}BrO_6Na$ 485.0576 ($M+Na^+$) found 485.0572.

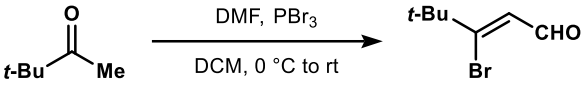
Note: Both **SI-1** and **SI-3** are commercially available however **SI-3** can be prepared according to the procedure shown below.

Claisen Reaction for Formation of SI-3



To a flame-dried, 1L round bottom flask with a magnetic stirbar were added diisopropylamine (30.8 mL, 220 mmol, 1.15 equiv) and 400 mL of THF. This solution was cooled to -78 °C followed by addition of *n*-BuLi (2.6 M in hexanes, 81.0 mL, 210 mmol, 1.1 equiv) and the solution was warmed to 0 °C and stirred for 1 hr to ensure formation of LDA. After cooling again to -78 °C, BnOAc (27.2 mL, 190.4 mmol, 1.0 equiv) was added and the reaction was stirred for 30 minutes. Finally, methyl dimethoxyacetate (24.4 mL, 200 mmol, 1.05 equiv) was added and the reaction was slowly warmed to room temperature over 1.5 hours before being quenched with saturated NH_4Cl (aq.). The aqueous phase was then extracted 3 times with EtOAc, and the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide **SI-3** as a light orange oil. **SI-3** was then used directly without purification.

6b: α,β-unsaturated aldehyde



pinacolone 6b

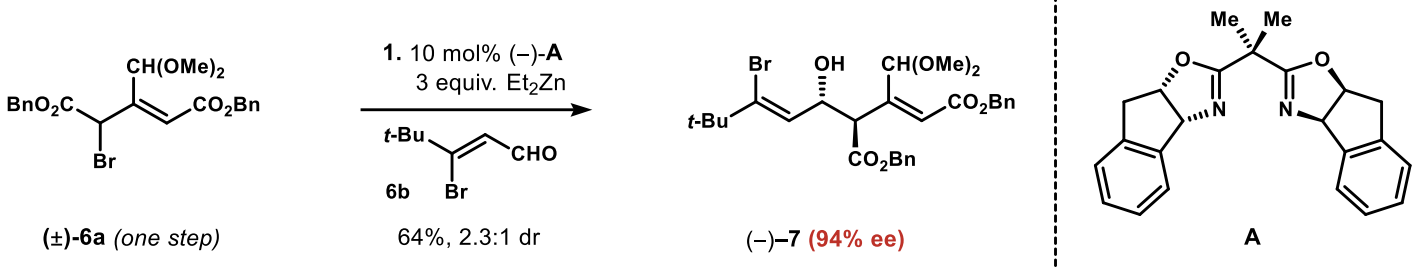
A flame-dried 500 mL flask was equipped with a magnetic stir bar, charged with 120 mL of anhydrous DCM, and then cooled to 0 °C. DMF (37.1 mL, 480 mmol, 4 equiv.) was added to the flask followed by the slow addition of PBr_3 (27.8 mL, 240 mmol, 2 equiv.). The mixture was stirred for 30 minutes followed by the addition of pinacolone (17.6 mL, 120 mmol, 1 equiv). The reaction was then allowed to warm to room temperature and then stirred overnight (12hrs). To quench the reaction, the mixture is poured into a 2L beaker filled with 800 mL of ice (*Caution: If the reaction mixture is not poured slowly, a large exotherm will occur*). The solution is then brought to pH 7 by the addition of KOH pellets and then extracted 3 times with DCM, dried with Na_2SO_4, and concentrated *in vacuo* to afford **6b** as a yellow oil which is used without purification (16.08 g, 84.2 mmol, 70.2%).

Note: If DMF remains after concentration, dissolve the oil in Et_2O and extract 3 times with H_2O, dry with $MgSO_4$, and concentrate *in vacuo* to affod pure **6b**.

Note: This product is volatile and should not be left under vacuum for prolonged periods of time.

R_f	0.45 (hexanes/EtOAc = 20:1, $KMnO_4$)
^{1}H NMR	(600 MHz, $CDCl_3$)
	δ 9.94 (d, J = 6.3 Hz, 1H), 6.34 (d, J = 6.3 Hz, 1H), 1.28 (s, 9H).
^{13}C NMR	(151 MHz, $CDCl_3$)
	δ 195.28, 162.20, 125.49, 41.34, 29.19.
HRMS (ESI)	Calcd. for $C_7H_{12}BrO$ 191.0072. ($M+H^+$) found 191.0069.

(–)-7: Reformatsky (asymmetric)



(±)-6a *(one step)* 64%, 2.3:1 dr (–)–7 (94% ee) A

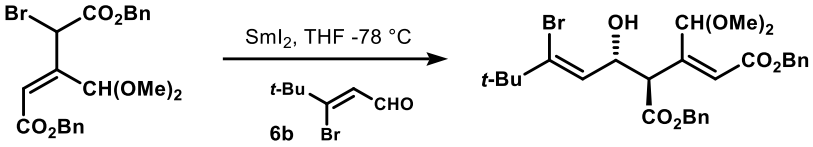
Note: The results of the catalytic asymmetric Reformatsky reaction vary depending on reaction scale. On small scale (1 mmol or less) the *ee* is consistently 94%, the dr is 2.3:1, and the yield of the combination of diastereomers is 64%. On large scale, if the rate of addition or temperature is not carefully controlled, the *ee* can erode to as low as 85% with a concommitant loss of stereoselectivity (2.0:1.0 *dr*).

To a flame dried reaction flask containing a magnetic stirbar were added α-bromo ester **6a** (36 g, 77.8 mmol, 1.0 equiv), aldehyde **6b**[38] (16.9 g, 88.5 mmol, 1.14 equiv), and bisoxazoline ligand **A** (2.79 g, 7.8 mmol, 10 mol%), followed by 972 mL of THF (0.08M). The solution was cooled to -78 °C in a dry ice/acetone bath and diethyl zinc (1 M in hexanes, 233.3 mL, 233.3 mmol, 3.0 equiv) was added dropwise *via* additional funnel. Upon completion of the addition, the mixture was stirred at -78 °C for 4 hrs (time necessary for full consumption of starting material at 10 mol% ligand). The reaction was then carefully quenched at -78 °C with a 3M methanolic HCl solution (6 equiv) and warmed to room temperature. The mixture was then diluted with EtOAc and sat. aq. NH_4Cl and the aqueous layer extracted 3 times with EtOAc. The combined organic layers were then washed with a 10% $CuSO_4$ solution to remove ligand, followed by a 2M HCl wash to remove any residual zinc or copper salts. Finally, the organic layer was washed with saturated $NaHCO_3$ (aq.), brine, and then dried over Na_2SO_4 before being filtered and concentrated *in vacuo*. The crude reaction mixture (2.3:1 *dr*, 92% *ee*) was used in the subsequent reaction. The yield of the mixture of diastereomers was calculated to be 64% from an internal standard (1,3,5-trimethoxybenzene) added to the crude NMR; the yield of the desired *anti*-diastereomer was calculated to be 44% and the yield of the *syn*-diastereomer was calculated to be 20%.

Diastereomers were inseparable *via* silica gel chromatography and were ultimately separated by preparative HPLC for characterization purposes. However, for material throughput purposes, they were carried into the subsequent reaction together, after which they were easily separable by column chromatography or recrystallization.

Note: A major byproduct of the reaction is the proto-debrominated starting material.

(±)-7: Reformatsky (racemic)



(±)-6a *(one step)* (±)–7

A solution of **6a** (23.8 g, 51.3 mmol, 1.0 equiv.) in 25 mL of THF was added to a flame-dried 2-liter round bottom flask equipped with a magnetic stirbar and backfilled with argon. The solution was treated with SmI_2 (0.1 M THF sol. 1-liter, 100 mmol, 1.95 equiv) via a cannula at – 78 ˚C. After addition of the SmI_2 solution, **6b** (11.8 g, 61.6 mmol, 1.2 equiv) was added slowly at – 78 ˚C and stirred for 10 min at –78 ˚C. The reaction was quenched with AcOH (3.52 mL, 61.6 mmol, 1.2 equiv) at – 78 ˚C, followed by the addition of *sat.* NH_4Cl *aq.* (150 ml) and subsequent warming to room temperature. Saturated $Na_2S_2O_3$ (*aq.)* (150 mL) was added and the solution was stirred for 10 minutes before the mixture was concentrated *in vacuo* until aprroximately 200 mL of THF remained. The resulting mixture was diluted with 800 mL of EtOAc and the organic layer was washed with 1 M HCl, *sat.* $Na_2S_2O_3$ *aq.* and H_2O (2 times), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was semi-purified by flash column chromatography (hexanes/EtOAc = 5:1) to provide a semi-pure **7**.

Note: We found that the addition of *sat.* $Na_2S_2O_3$ *aq.* was crucial after the Reformatsky reaction was quenched to reduce any iodine that is generated *in situ*. The solution turns from a dark brown color to a light yellow color after addition of *sat.* $Na_2S_2O_3$ *aq.* Concentration of the crude mixture after work-up without the addition of *sat.* $Na_2S_2O_3$ *aq.* lead to complete decomposition of the product on scales larger than 25 mmol.

***Anti*-(–)-7**

R_f 0.40 (hexanes/EtOAc = 4:1, anisaldehyde)

^{1}H NMR (600 MHz, $CDCl_3$)
δ 7.51 – 7.29 (m, 10H), 6.43 (d, *J* = 0.7 Hz, 1H), 5.99 (d, *J* = 0.8 Hz, 1H), 5.83 (d, *J* = 8.1 Hz, 1H), 5.31 – 5.05 (m, 4H), 4.95 (td, *J* = 7.8, 3.8 Hz, 1H), 3.89 (d, *J* = 7.5 Hz, 1H), 3.47 (s, 3H), 3.29 (s, 3H), 3.04 (d, *J* = 4.5 Hz, 1H), 1.15 (s, 10H).

^{13}C NMR (151 MHz, $CDCl_3$)
δ 170.43, 165.17, 148.92, 144.19, 135.66, 135.63, 128.73, 128.62, 128.52, 128.38, 128.36, 128.29, 125.28, 123.06, 99.99, 73.42, 67.00, 66.60, 56.25, 55.33, 50.63, 39.91, 29.47.

HRMS (ESI) Calcd. for $C_{29}H_{35}BrO_7Na$ 597.1464 ($M+Na^+$) found 597.1456.

***Syn*-(–)-7**

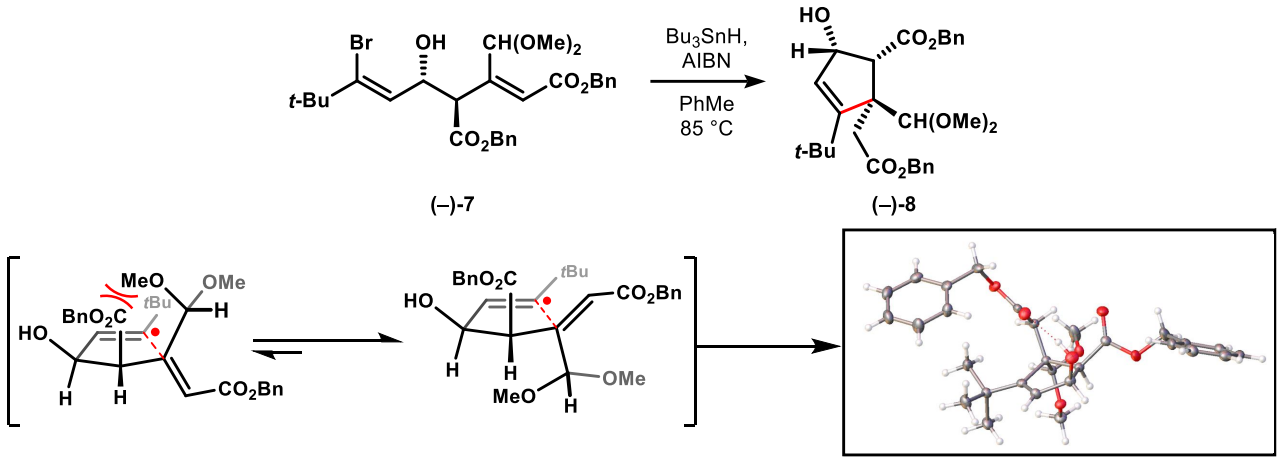
R_f 0.40 (hexanes/EtOAc = 4:1, anisaldehyde)

^{1}H NMR (600 MHz, $CDCl_3$)
δ 7.39 – 7.27 (m, 10H), 6.21 (s, 1H), 5.89 (s, 1H), 5.76 (d, *J* = 8.0 Hz, 1H), 5.24 – 5.09 (m, 4H), 4.94 – 4.86 (m, 1H), 3.86 (d, *J* = 6.5 Hz, 1H), 3.41 (s, 3H), 3.23 (s, 3H), 2.94 (d, *J* = 6.7 Hz, 1H), 1.10 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$)
δ 172.18, 165.16, 148.66, 143.37, 135.77, 135.68, 128.71, 128.64, 128.46, 128.41, 128.39, 126.09, 122.68, 100.12, 73.39, 67.10, 66.48, 55.87, 55.10, 49.95, 39.81, 29.39.

HRMS (ESI) Calcd. for $C_{29}H_{35}BrO_7Na$ 597.1464 ($M+Na^+$) found 597.1456.

(–)-8: Giese Reaction



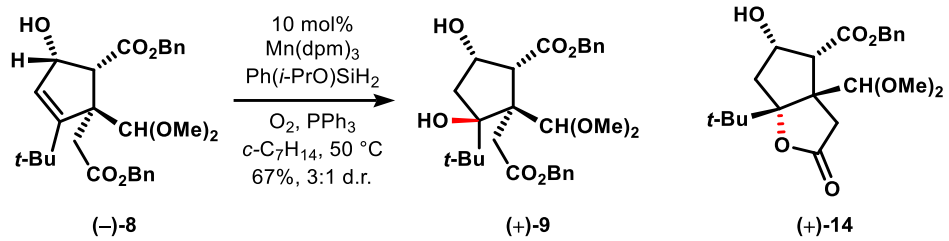
Scheme S6: Diastereoselectivity model for the Giese reaction

A 1-liter oven dried 3-neck flask was equipped with a reflux condenser, a 250 mL oven-dried addition funnel, a magnetic stirbar, and a septum. The flask was then charged with crude **(–)-7** followed by 390 mL of anhydrous toluene. The mixture was then heated to 85 °C and then a solution of Bu_3SnH (31.5 mL, 116.7 mmol, 1.5 equiv) and AIBN (1.3g, 7.8 mmol, 0.1 equiv) in toluene (100 mL) was slowly added dropwise via the addition funnel over 1 hour. Once the solution had finished adding to the reaction, the addition funnel was rinsed with one portion of toluene (10 ml) and then stirred for an additional 30 min at 85 ˚C. Once TLC had indicated that the SM was consumed, the mixture was removed from the oil bath and allowed to cool to room temperature. The resulting mixture was concentrated *in vacuo* in a **well-ventilated** fume hood. The Bu_3SnH and its byproducts were removed by passing the material through a plug of 10% KF impregnated silica (hexanes/EtOAc = 8:1 → 1:1). After concentrating the filtered material *in vacuo*, the yield of the desired cyclopentene diastereomer was calculated to be 60% *via* addition of an internal standard (1,3,5-trimethoxybenzene) to the crude NMR. Recrystallization of the crude mixture from hot Et_2O/pentane (1:4) provided (–)-**8** as a white crystalline solid in excellent *ee* (8.050 g, 16.23 mmol, 2 steps, 21 %, >99% *ee*).

Note: When we performed this two-step sequence using the racemic procedure, we obtained an isolated yield of 12.3 g of **8** after the radical conjugate addition (54% yield over 2 steps after column chromatography). However, **8** can be purified without chromatography *via* recrystallization from hot Et_2O/pentanes 1:4 to afford a white powder in 39% yield over 2 steps. Recovery and concentration of the mother liquor shows a complex mixture of **8** and uncharacterized byproducts from which **8** could not be recovered.

R_f	0.45 (hexanes/EtOAc = 3:1, anisaldehyde)
^{1}H NMR	(600 MHz, $CDCl_3$)
	δ 7.39-7.33 (m, 10H), 5.85 (d, 1H, *J* = 2.4 Hz), 5.21 (d, 1H, *J* = 12.6 Hz), 5.15 (d, 1H, *J* = 12.0 Hz), 5.11 (d, 1H, *J* = 12.6 Hz), 5.04 (d, 1H, *J* = 12.0 Hz), 4.78 (ddd, 1H, *J* = 2.4, 7.8, 12.0 Hz), 4.57 (d, 1H, *J* = 12.0 Hz), 4.29 (s, 1H), 3.73 (d, 1H, *J* = 7.8 Hz), 3.54 (d, 1H, *J* = 18.0 Hz), 3.51 (s, 3H), 3.36 (s, 3H), 2.78 (d, 1H, *J* = 18.0 Hz), 1.09 (s, 9H).
^{13}C NMR	(151 MHz, $CDCl_3$)
	δ 173.4, 171.6, 154.6, 136.8, 135.8, 130.4, 128.8, 128.6, 128.5, 128.4, 127.9, 127.8, 110.8, 74.5, 66.7, 65.7, 60.8, 60.8, 56.2, 51.5, 37.0, 34.3, 32.0, 29.9, 28.4.
HRMS (ESI)	Calcd. for $C_{29}H_{36}O_7Na$ 519.2359 ($M+Na^+$) found 519.2357.
$[\alpha]_D^{20}$	–4.1 (*c* = 1.0, $CHCl_3$)

(+)-9: Mukaiyama Hydration



(–)-8 (+)-9 (+)-14

A one liter oven-dried round bottom flask equipped with a magnetic stir bar was charged with **8** (8.050g, 16.2 mmol, 1.0 equiv). To the flask was then added 320 mL of methyl-cyclohexane, $Mn(dpm)_3$ (980 mg, 1.62 mmol, 0.1 equiv), triphenylphosphine (6.34 g, 24.3 mmol, 1.5 equiv), and the solution was placed under an O_2 atmosphere (balloon). The reaction was heated to 50 °C followed by the dropwise addition of monoisopropoxy(phenyl)silane (8.9 mL, 48.3 mmol, 3 equiv). The mixture was then stirred under an oxygen atmosphere for 1.5 hrs. After completion, the reaction was cooled to 0 °C and quenched with a freshly prepared 10% (aq.) solution of KF (150 mL), extracted 3 times with EtOAc and dried over $Na_2S_2O_4$. The crude mixture was filtered through a celite plug and eluted with EtOAc to remove any remaining Mn salts and then concentrated under reduced pressure. The crude product was purified *via* flash column chromatography (Et_2O/Hexanes 2:3) to provide **9** as a colorless oil (5.58 g, 10.9 mmol, 67 %) (*d.r.* = 3:1).

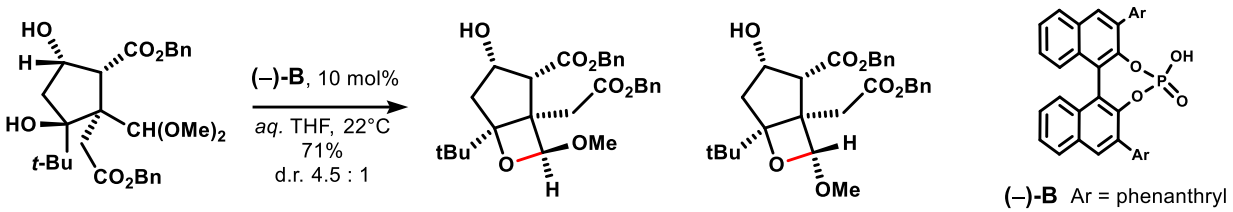
(+)-9

R_f	0.55 (hexanes/EtOAc = 3:1, anisaldehyde)
^{1}H NMR	(600 MHz, $CDCl_3$)
	δ 7.48-7.30 (m, 10H), 5.44 (s, 1H), 5.19 (d, 1H, *J* = 12.0 Hz), 5.08 (d, 2H, *J* = 12.0 Hz), 5.03 (d, 1H, *J* = 12.0 Hz), 4.99 (br d, 1H, *J* = 1.8 Hz), 4.75 (br s, 1H), 4.56-4.53 (m, 1H), 3.72 (d, 1H, *J* = 6.0 Hz), 3.39 (s, 3H), 3.28 (s, 3H), 3.17 (d, 2H, *J* = 6.0 Hz), 2.14 (dd, 1H, *J* = 7.8, 14.4 Hz), 1.99 (dt, 1H, *J* = 3.0, 14.4 Hz), 1.05 (s, 9H).
^{13}C NMR	(151 MHz, $CDCl_3$)
	δ 175.0, 172.3, 136.1, 135.5, 129.4, 128.7, 128.7, 128.6, 128.4, 128.3, 127.8, 127.1, 109.6, 90.6, 68.8, 67.5, 66.1, 65.5, 60.0, 58.4, 58.3, 49.7, 44.3, 39.4, 36.5, 28.4.
HRMS (ESI)	Calcd. for $C_{29}H_{38}O_8Na$ 537.2464 ($M+Na^+$) found 537.2469.
$[\alpha]_D^{20}$	+11.9 (*c* = 1.0, $CHCl_3$)

(+)-14

R_f	0.05 (hexanes/EtOAc = 3:1, anisaldehyde)
^{1}H NMR	(600 MHz, $CDCl_3$)
	δ 7.43 – 7.29 (m, 5H), 5.21 (d, *J* = 12.3 Hz, 1H), 5.14 (d, *J* = 12.3 Hz, 1H), 4.56 – 4.42 (m, 2H), 3.65 (d, *J* = 5.9 Hz, 1H), 3.47 (s, 3H), 3.37 (s, 3H), 3.26 (d, *J* = 18.3 Hz, 1H), 2.73 – 2.61 (m, 2H), 2.31 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.22 (dd, *J* = 14.9, 2.2 Hz, 1H), 1.07 (s, 9H).
^{13}C NMR	(151 MHz, $CDCl_3$)
	δ 174.88, 171.54, 135.82, 128.70, 128.50, 128.45, 108.07, 102.99, 71.63, 66.72, 62.14, 59.51, 56.13, 53.16, 42.17, 38.66, 37.12, 27.37.
HRMS (ESI)	Calcd. for $C_{22}H_{30}O_7Na$ 429.1889 ($M+Na^+$) found 429.1883.
$[\alpha]_D^{20}$	+1.6 (*c* = 1.0, $CHCl_3$)

(+)-10 and (+)-11: Oxetane-acetal Formation



(±)-9, 50 °C (±)-10, 1.7 : (±)-11, 1

(+)-9, 50 °C (+)-10, 2.7 : (+)-11, 1

(–)-B Ar = phenanthryl

To a 14.7 mL solution of THF/H_2O (2:1) in a 50 mL round bottom flask equipped with a magnetic stirbar was added **9** (5.34 g, 10.4 mmol, 1.0 equiv.) and **(–)-B**[36] (730 mg, 1.04 mmol, 0.1 equiv.) and the reaction was stirred for 12 hours at room temperature. The reaction was monitored by TLC and upon completion was diluted with EtOAc and the layers were separated. The aqueous phase was extracted 3 times with EtOAc and then the combined organic layers were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Hexanes/EtOAc 2:1) to provide **10** as a colorless viscous oil (3.55 g, 7.4 mmol, 71% yield).

Re-isolation of the chiral phosphoric acid (XcPA):

After the endo product **10** had finished eluting off the column, the eluent was increased to (Hexanes/EtOAc 1:1) in order to isolate **11** as a colorless viscous oil. The column was subsequently flushed with two column volumes of DCM and then 1:19 MeOH/DCM was used to elute the XcPA **B** as a pale yellow solid. The XcPA should be dissolved in DCM and washed with 6M HCl prior to use.

endo (+)-10

R_f 0.25 (hexanes/EtOAc = 2:1, anisaldehyde)

^{1}H NMR (600 MHz, $CDCl_3$)
δ 7.38-7.27 (m, 10H), 5.18 (d, 1H, *J* = 12.6 Hz), 5.09 (s, 1H), 5.06-5.03 (m, 1H), 5.02 (d, 1H, *J* = 12.0 Hz), 4.91 (d, 1H, *J* = 12.6 Hz), 4.86 (d, 1H, *J* = 12.0 Hz), 3.68 (d, 1H, *J* = 7.8 Hz), 3.35 (s, 3H), 3.14 (d, 1H, *J* = 15.0 Hz), 2.92 (d, 1H, *J* = 15.0 Hz), 2.23 (dd, 1H, *J* = 10.8, 13.2 Hz), 2.11 (dt, 1H, *J* = 6.6, 13.2 Hz), 1.04 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$)
δ 172.26, 170.24, 135.77, 135.60, 128.68, 128.66, 128.63, 128.50, 128.48, 128.35, 105.22, 95.40, 72.03, 66.72, 66.44, 56.54, 55.34, 52.76, 41.65, 36.89, 36.22, 26.58.

HRMS (ESI) Calcd. for $C_{28}H_{35}O_7$ 483.2383 ($M+H^+$) found 483.2389.

$[\alpha]_D^{20}$ +42.5 (*c* = 1.0, $CHCl_3$)

exo (+)-11

R_f 0.30 (hexanes/EtOAc = 2:1, anisaldehyde)

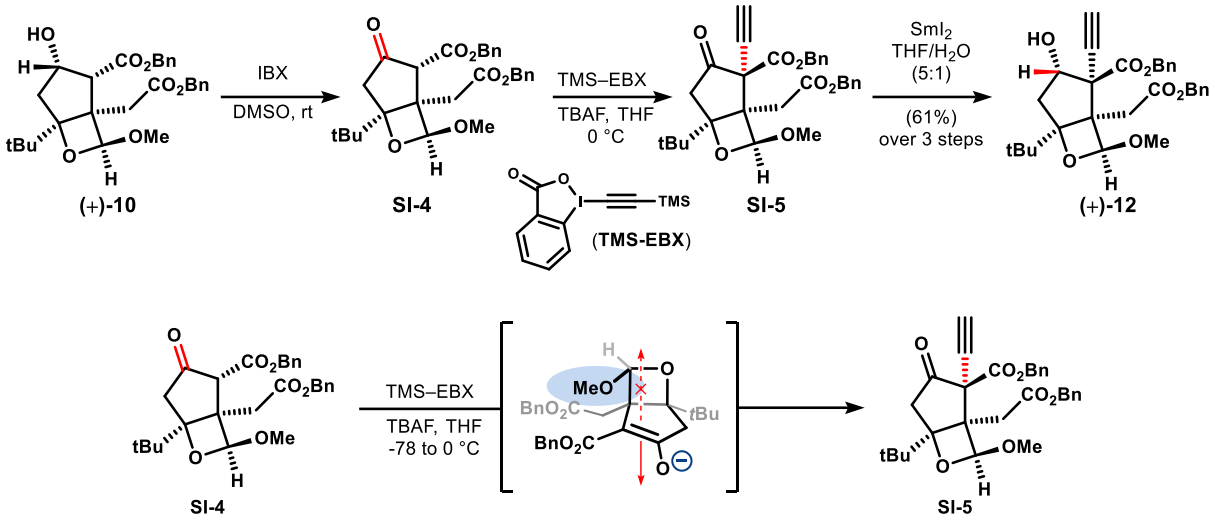
^{1}H NMR (600 MHz, $CDCl_3$)
δ 7.34-7.25 (m, 10H), 5.10 (d, 1H, *J* = 12.6 Hz), 5.01 (d, 1H, *J* = 12.6 Hz), 4.99 (d, 1H, *J* = 12.6 Hz), 4.89 (d, 1H, *J* = 12.6 Hz), 4.81 (s, 1H), 4.81-4.77 (m, 1H), 3.78 (d, 1H, *J* = 7.8 Hz), 3.47 (d, 1H, *J* = 17.4 Hz), 3.30 (s, 3H), 2.59 (d, 1H, *J* = 17.4 Hz), 2.33 (dd, 1H, *J* = 10.8, 13.2 Hz), 2.14 (dd, 1H, *J* = 6.6, 13.2 Hz), 1.00 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$)
δ 171.74, 170.85, 136.02, 135.64, 128.67, 128.63, 128.51, 128.47, 128.32, 128.27, 105.11, 97.90, 71.77, 66.55, 66.27, 56.24, 55.45, 54.92, 41.19, 36.17, 32.50, 26.73, 1.16.

HRMS (ESI) for $C_{28}H_{35}O_7$ 483.2383 ($M+H^+$) found 483.2379.

$[\alpha]_D^{20}$ +3.9 (*c* = 1.0, $CHCl_3$)

(+)-12: Three -Step Alkynylation Sequence



Scheme S7: Diastereoselectivity model for the alkynylation

IBX oxidation

A solution of **10** (172 mg, 0.36 mmol, 1.0 equiv) and freshly prepared IBX (301 mg, 1.074 mmol, 3 equiv) in 3.0 mL of DMSO was stirred for 2.5 h at 22 ˚C in a 10 mL round bottom equipped with a magnetic stirbar. The solution was then cooled to 0 °C followed by the slow addition of *sat.* $Na_2S_2O_3$ *aq.* (3.0 mL) and EtOAc (15.0 mL). The organic layer was subsequently washed with H_2O 4 times and then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give crude **SI-4**.

TMS-EBX alkynylation

A flame-dried 25 mL round bottom flask equipped with a magnetic stirbar was charged with TMS-EBX (370 mg, 1.074 mmol, equiv) followed by a solution of crude **SI-4** in 7.16 mL of THF. The solution was cooled to –78 ˚C followed by addition of TBAF (1.0 M in THF, 1.07 mL, 1.074 mmol, 3 equiv), and then the solution was warmed slowly to –20 °C over 1hr. *Note: The reaction precipitates a brown solid which can cause the reaction to stop stirring, so a mechanical stirring apparatus is recommended.* Once the solution had reached –20 °C the reaction was monitored by TLC and once SM was consumed the reaction was quenched with *sat.* NH_4Cl *aq.* and warmed to room temperature. The layers were separated, and the aqueous phase was extracted 3 times with EtOAc. The organic layers were combined, and then washed with *sat.* $NaHCO_3$ *aq.* (1x) and H_2O (2x), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give afford **SI-5**. The crude mixture was dissolved in Et_2O and then filtered through a fritted funnel to remove insoluble salts that affect the next reaction.

Note: Filtration of the crude material through a silica, florisil, or celite plug led to decomposition of **SI-5** via elimination of the oxetane acetal. The insoluble salts <u>*do not*</u> have to be removed; <u>*however*</u>, if they are not, a large excess of SmI_2 must be used in the subsequent reaction.

Note: This alkynylated intermediate is highly unstable and cannot be purified. The ketone should be immediately reduced using the procedure that follows to provide a stable secondary alcohol that can be purified.

SmI_2-mediated ketone reduction

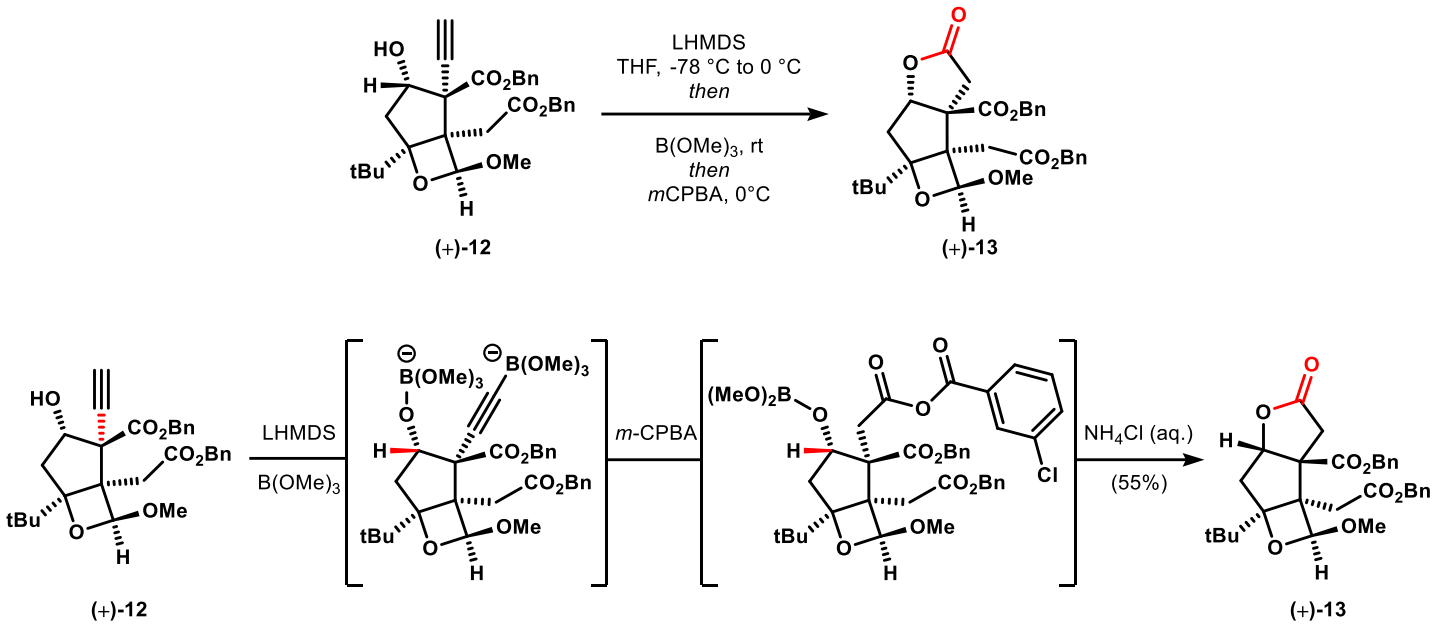
A solution of crude **SI-5** in 1.0 mL of THF and 1.0 mL of degassed H_2O were added to a 100 mL round bottom flask under an argon atmosphere. The solution was then cooled to 0 ˚C, treated with SmI_2 (0.1 M in THF, 30 mL, 3.0 mmol, 8.4 equiv), and stirred for 30 mins at 0 ˚C. EtOAc (120 mL) was then added and the reaction was transferred to a separatory funnel. The organic layer was washed sequentially with 1 M HCl and H_2O, followed by $Na_2S_2O_3$ and H_2O again, before being dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes/EtOAc = 5:1 → 4:1) to provide **12** as a colorless oil (111 mg, 0.22 mmol, 3 steps, 61%).

Note: When this three-step sequence was performed on a scale of 5.16 mmol, the alkynylation reaction did not go to completion do to the formation of an unstirrable slurry as the reaction warmed from -78 °C to -20 °C. As a consequence of this, only 1.0g of pure **12** was isolated after flash column chromatography (1.0g, 1.96 mmol, 3 steps, 38%).

Note: On larger scales (e.g. greater than 1 mmol), the pure material is contaminated with benzyl alcohol, likely from ester hydrolysis. The benzyl alcohol can be azeotroped away from the pure product by concentrating the oil with a 2:1 mixture of H_2O:MeCN at least 3 times.

R_f	0.40 (hexanes/acetone = 3:1, anisaldehyde or CAM)
^{1}H NMR	(600 MHz, $CDCl_3$)
	δ 7.36-7.28 (m, 10H), 5.71 (s, 1H), 5.30 (d, 1H, *J* = 12.6 Hz), 5.27 (ddd, 1H, *J* = 4.2, 6.0, 10.8 Hz), 5.07 (d, 1H, *J* = 12.0 Hz), 5.01 (d, 1H, *J* = 12.6 Hz), 4.84 (d, 1H, *J* = 12.0 Hz), 3.48 (d, 1H, *J* = 15.6 Hz), 3.30 (d, 1H, *J* = 15.6 Hz), 3.19 (s, 3H), 2.81 (d, 1H, *J* = 4.2 Hz), 2.58 (s, 1H), 2.09 (dd, 1H, *J* = 6.0, 13.2 Hz), 2.02 (dd, 1H, *J* = 10.8, 13.2 Hz), 1.04 (s, 9H).
^{13}C NMR	(151 MHz, $CDCl_3$)
	δ 170.55, 169.47, 136.03, 135.64, 128.71, 128.60, 128.52, 128.42, 128.30, 128.22, 102.93, 93.07, 78.75, 78.00, 72.69, 67.13, 66.49, 59.03, 58.80, 56.68, 38.65, 36.29, 35.69, 26.26.
HRMS (ESI)	Calcd. for $C_{30}H_{35}O_7$ 507.2383 ($M+H^+$) found 507.2393.
$[\alpha]_D^{20}$	+26.9 (*c* = 1.0, $CHCl_3$)

(+)-13: Alkyne Oxidation

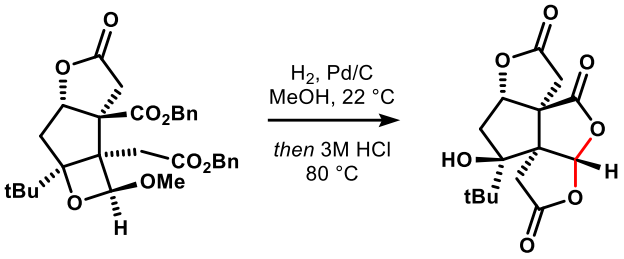


Scheme S8: A possible reaction mechanism for alkyne oxidation.

A solution of **12** (100.0 mg, 0.2 mmol, 1.0 equiv) in 2.0 mL of THF was added to a flame dried reaction vial equipped with a magnetic stir bar. The solution was cooled to –78 ˚C followed by addition of LHMDS (1.0M in THF, 600 µL, 0.6 mmol, 3 equiv), and the solution was stirred for 1 hr at 0 ˚C. $B(OMe)_3$ (111 µL, 1.0 mmol, 5 equiv) was added and the resulting solution was warmed to room temperature and stirred for 1.5 hrs. The solution was cooled to 0 °C and then *m*-CPBA (100%, 172 mg, 1.0 mmol, 5 equiv) was added portionwise (*Note: The reaction exotherms violently if mCPBA is added in a single portion),* and the reaction was stirred for 30 min. The reaction was quenched with *sat.* NH_4Cl *aq.* and extracted 3 times with EtOAc. The organic layer was then washed 1 time with *sat.* $Na_2S_2O_3$ *aq.*, 1 time with *sat.* $NaHCO_3$ *aq.*, 1 time with 3 M HCl, and then dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes/EtOAc = 5:1 → 4:1) to provide **13** as a colorless oil (57 mg, 0.11 mmol, 55 %)

R_f	0.60 (hexanes/EtOAc = 2:1, CAM)
^{1}H NMR	(600 MHz, $CDCl_3$)
	δ 7.37-7.30 (m, 10H), 5.68 (t, 1H, *J* = 7.8 Hz), 5.56 (s, 1H), 5.24 (d, 1H, *J* = 12.0 Hz), 5.15 (d, 1H, *J* = 12.0 Hz), 5.06 (d, 1H, *J* = 12.0 Hz), 5.00 (d, 1H, *J* = 12.0 Hz), 3.35 (d, 1H, *J* = 14.4 Hz), 3.10 (s, 3H), 2.69 (d, 1H, *J* = 17.4 Hz), 2.63 (d, 1H, *J* = 14.4 Hz), 2.62 (d, 1H, *J* = 17.4 Hz), 2.51 (dd, 1H, *J* = 7.8, 15.0 Hz), 1.83 (dd, 1H, *J* = 7.8, 15.0 Hz), 1.04 (s, 9H).
^{13}C NMR	(151 MHz, $CDCl_3$)
	δ 173.39, 171.58, 169.83, 141.03, 135.58, 128.79, 128.68, 128.67, 128.65, 128.48, 128.41, 128.31, 127.73, 127.08, 103.21, 95.99, 83.21, 67.18, 66.99, 65.44, 60.26, 58.69, 56.56, 40.29, 36.98, 36.57, 36.29, 26.06
HRMS (ESI)	Calcd. for $C_{30}H_{35}O_8$ 523.2332 ($M+H^+$) found 523.2332.
$[\alpha]_D^{20}$	+45.7 (*c* = 1.0, $CHCl_3$)

(–)-5: Global Deprotection to 10-Des-hydroxybilobalide



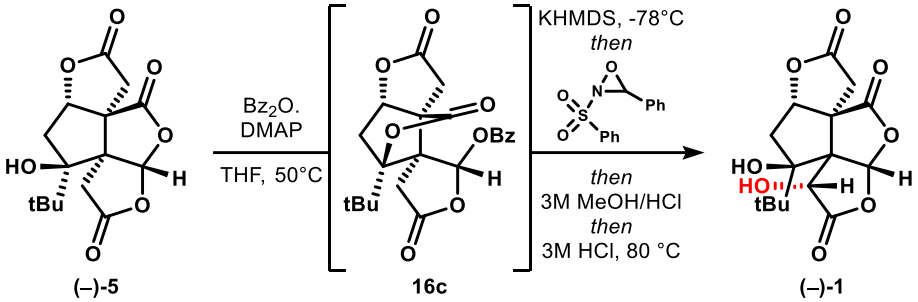
(+)-13 (–)-5

A reaction vial equipped with a magnetic stir bar was charged with a solution of **13** (50.0 mg, 0.0957 mmol) in 1.1 mL of MeOH and Pd/C (10%, 6.0 mg). The vial was evacuated under vacuum, backfilled with H_2, and then stirred under a H_2 atmosphere for 2h at 22 ˚C. After the starting material had been completely consumed, the flask was placed under vacuum to remove the H_2 atmosphere and backfilled with N_2. This process was repeated three times to ensure all the H_2 had been removed. 2.0 mL of 3M HCl was then added to the mixture and the reaction was heated to 80 ˚C overnight open to air. The resulting mixture was filtered off through a Celite pad and washed with MeOH. The filtrate was concentrated *in vacuo* and azeotroped two times with toluene to provide **5** as a light brown solid (26.5 mg, 0.0861 mmol, 90% yield).

Note: Compound **5** does not stain under any traditional staining methods. In order to develop TLC's with **5** the compound must be run up the plate in Hexanes/Acetone (3:2) followed by direct heating of the TLC plate on a hot plate at 350 °C for 10 minutes, after which a brown spot will appear on the plate, which indicates **5** (This new band is also UV active and stains with $KMnO_4$, or anisaldehyde). This method is used to locate **5** when running a preparative TLC plate. A thin portion of the plate is cut off with a TLC cutter and then heated as mentioned above to locate **5**. The R_f is marked and then the appropriate band is cut from the remainder of the undeveloped preparative TLC plate. Due to the unique solubility profile of **5**, column chromatography was unsuccessful to purify the product. However, on larger scales triturating the crude mixture 3 times with Et_2O afforded the pure product. The Et_2O was then concentrated *in vacuo* and **5** was then purified from the mixture *via* pTLC.

R_f	0.50 (hexanes/acetone = 3:2, UV detection after heating over 15 min. on TLC plate)
^{1}H NMR	(600 MHz, acetone-*d*6) δ 6.50 (s, 1H), 5.05 (dd, 1H, *J* = 7.2, 8.4 Hz), 4.63 (br s, 1H), 3.58 (d, 1H, *J* = 18.6 Hz), 3.21 (d, 1H, *J* = 18.6 Hz), 2.99 (d, 1H, *J* = 19.2 Hz), 2.78 (d, 1H, *J* = 19.2 Hz), 2.75 (dd, 1H, *J* = 7.2, 13.2 Hz), 2.22 (dd, 1H, *J* = 8.4, 13.2 Hz), 1.19 (s, 9H).
^{13}C NMR	(151 MHz, acetone-*d*6) δ 179.2, 173.7, 171.7, 104.8, 87.6, 85.3, 63.3, 58.7, 43.0, 38.3, 35.1, 34.8., 27.13
HRMS (ESI)	Calcd. for $C_{15}H_{19}O_7$ 311.1131 ($M+H^+$) found 311.1135.
$[\alpha]_D^{20}$	–50.0 (*c* =0.7, $CHCl_3$)

(–)-1: *alpha*-hydroxylation to Bilobalide



To a flame dried reaction vial containing a magnetic stirbar was transferred *des*-hydroxybilobalide **5** (3 mg, 0.00967 mmol). To remove any trace water, the starting material was azeotroped with toluene at least three times by heating to 80 °C under a strong positive pressure of dry N_2 until all solvent was evaporated and only a white solid remained in the flask. The reaction was then placed back under high vacuum. DMAP (1.8 mg, 0.0145 mmol, 1.5 equiv) and benzoic anhydride (3.3 mg, 0.0145 mmol, 1.5 equiv) were added, and the vial was evacuated and backfilled three times with dry argon gas followed by addition of 0.38 mL of THF. The reaction was then heated to 60 °C until the starting material was fully consumed, resulting in the formation of a new spot representing the benzoyl-iso-deshydroxy-bilobalide (intermediate **16c)**. The same staining procedure for **5** had to be applied for **1** as well, since both **16c** and **1** do not stain under any traditional methods. At this point, the reaction was cooled to room temperature, and then to -78 °C followed by the addition of a KHMDS solution (0.1 ml, 0.029mmol, 3 equiv). After stirring for 1 hour at -78 °C, Davis reagent was added dropwise from a stock solution in THF (7.6 mg/50 µL THF, 0.029 mmol, 3 equiv) and the resulting mixture was stirred for additional 2 hours (the conversion was lower after 1 hour, but did not increase after 2 hours) at -78 °C. At this point, the reaction was quenched with 3.0M methanolic HCl (33 µL, 0.0967 mmol, 10 equiv) and warmed to room temperature. Aqueous 3M HCl (0.3 mL) was then added and the reaction was heated to 85 °C for 24 hours to deprotect and isomerize all material in the *iso*-bilobalide form, back to the bilobalide scaffold. The reaction was then concentrated and the yield of **1** (49%, 0.00474 mmol, 73% *brsm*) was obtained *via* NMR with dibromomethane as an internal standard made as a stock solution in acetone-d_6 in a 1 mL volumetric flask.

Note: Formation of *neo*-bilobalide (**15**) often arises as a regiochemical byproduct of this reaction when enough care is not taken to effectively purify all reagents and remove any trace of water from the reaction. This is likely due to hydrolysis of the benzoate and re-formation of *des*-OH-bilobalide from which *neo*-bilobalide is known to form under these reaction conditions from our own experiments. Further study of this process and of the intracacies of this reaction are underway.

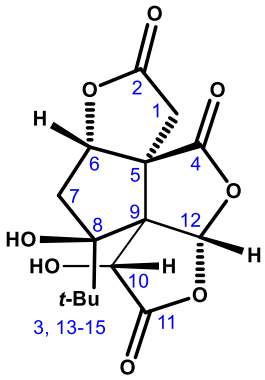
***Notes on the oxidation of des-hydroxy-bilobalide to bilobalide*:** Both the regioselectivity and yield of this reaction were sensitive to reagent quality, as well as thorough exclusion of water from the reaction. DMAP was recrystallized from hot toluene and then cooling to -20 °C overnight. Bz_2O was purified by dissolving the commercial material in Et_2O and then washing 3 times with $NaHCO_3$. The organic layer was then dried with $MgSO_4$ and concentrated to afford a solid white powder free of any detectable benzoic acid. The reaction never exceeded 50% conversion by crude NMR, and yields and selectivities were best on small scale. ***Notes on the purification of bilobalide from the reaction*:** Due to the high solubility of **1** in water, the crude reactions were directly concentrated and then semi-purified by pTLC (3:1 DCM/Acetone) to remove some of the oxaziridine byproducts. The semi-pure material was then purified by preparative HPLC, followed by 3 additional purifications *via* pTLC to afford pure bilobalide (0.7 mg, 0.00215 mmol, 22.2% isolated yield). The low isolated yield is attributed to material loss from iterative purifications. Mass-directed preparative HPLC conditions: Waters Autopurification LC with a Waters BEH C13 Column (5 mm, 19x160 mm) using a 0.1% aqueous formic acid:acetonitrile gradient (30 mL/min, main segment of gradient at 10-25% acetonitrile over 8 minutes) at ambient temperature. Fractionation was triggered by a Waters QDa single quadrupole mass spec (ESI+).

R_f	0.50 (DCM/acetone = 4:1, UV detection after heating over 15 min. on TLC plate)
^{1}H NMR	(600 MHz, acetone-*d*6)
	δ 6.39 (d, *J* = 4.2 Hz, 1H), 6.37 (s, 1H), 5.40 (d, *J* = 4.1 Hz, 1H), 5.00 (t, *J* = 7.0 Hz, 1H), 4.63 (s, 1H), 3.03 (d, *J* = 18.1 Hz, 1H), 2.81 (d, *J* = 18.2 Hz, 3H), 2.75 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.33 (dd, *J* = 13.7, 6.9 Hz, 1H), 1.22 (s, 9H).
^{13}C NMR	(151 MHz, acetone-*d*6)
	δ 178.43, 173.77, 173.58, 100.61, 87.59, 83.93, 69.89, 66.58, 59.18, 43.34, 38.37, 37.01, 27.19.
HRMS (ESI)	Calcd. for $C_{15}H_{19}O_8$ 327.1080 ($M+H^+$) found 327.1069.
Synthetic $[\alpha]_D^{20}$	–49.0 (*c* =0.10, acetone)
Authentic $[\alpha]_D^{20}$	–50.7 (*c* =0.14, acetone)

Table S1: Comparison of ^{1}H and ^{13}C NMR data for Authentic vs. Synthetic (–)-bilobalide

Comparison of ^{1}H NMR data for Authentic vs. Synthetic (–)-bilobalide

Carbon Number	(–)-bilobalide, Authentic	(–)-bilobalide, Synthetic
1a	2.81 (d, *J* = 18.0 hz, 1H)	2.81 (d, *J* = 18.2 hz, 1H)
1b	3.03 (d, *J* = 18.1 hz, 1H)	3.03 (d, *J* = 18.1 hz, 1H)
6	5.00 (t, *J* = 7.0 hz, 1H)	5.00 (t, *J* = 7.0 hz, 1H)
7a	2.33 (dd, *J* = 13.6, 6.9 hz, 1H)	2.33 (dd, *J* = 13.7, 6.9 hz, 1H)
7b	2.75 (dd, *J* = 13.6, 7.1 hz, 1H)	2.75 (dd, *J* = 13.6, 7.2 hz, 1H)
8-OH	4.60 (s, 1H)	4.63 (s, 1H)
10	5.41 (d, *J* = 4.3 hz, 1H)	5.40 (d, *J* = 4.1 hz, 1H)
10-OH	6.35 (d, *J* = 4.3 hz, 1H)	6.39 (d, *J* = 4.2 hz, 1H)
12	6.37 (s, 1H)	6.37 (s, 1H)
13-15	1.22 (s, 9H)	1.22 (s, 9H)

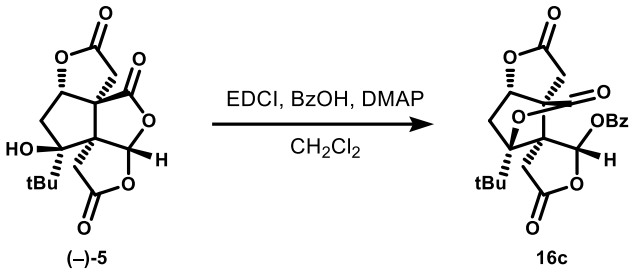


(–)-bilobalide

Comparison of ^{13}C NMR data for Authentic vs. Synthetic (–)-bilobalide

Carbon Number	(–)-bilobalide, Authentic	(–)-bilobalide, Synthetic
1	37.04	37.01
2	173.59	173.58
3	38.40	38.37
4	178.44	178.43
5	59.21	59.18
6	83.95	83.94
7	43.38	43.34
8	87.63	87.59
9	66.60	66.58
10	69.92	69.89
11	173.78	173.77
12	100.63	100.61
13-15	27.21	27.19

16c: Benzoylation of 5



To a flame dried reaction vial containing a magnetic stirbar was added *des*hydroxybilobalide **5** (3 mg, 0.0097 mmol, 1.0 equiv)**,** EDCI (4.51 mg, 0.029 mmol, 3.0 equiv), benzoic acid (3.54 mg, 0.029 mmol, 3.0 equiv), and DMAP (3 mg, 0.00967 mmol), followed by addition of DCM (0.1M) at room temperature. The reaction was stirred at room temperature until the starting material was consumed, after which the reaction was concentrated and loaded directly onto a preparative TLC plate for purification (40% acetone/hexanes) to afford **16c** as a white solid and in quantitative conversion.

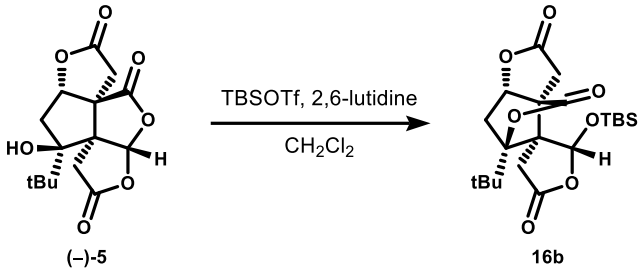
Similar to the procedure shown on S18 for the hydroxylation of (–)-5, 16c can be isolated and subsequently hydroxylated using KHMDS and Davis oxaziridine to provide the same ratio of bilobalide to *neo*-bilobalide (91:9), as shown in Figure 3 of the manuscript.

R_f 0.50 (hexanes:acetone = 2:1, UV detection after heating over 15 min. on TLC plate)

^{1}H NMR (600 MHz, acetone-*d*6)
δ 8.18 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.80 – 7.70 (m, 1H), 7.65 – 7.58 (m, 2H), 4.76 (dd, *J* = 7.9, 3.9 Hz, 1H), 3.35 (d, *J* = 18.1 Hz, 1H), 3.31 (d, *J* = 18.1 Hz, 1H), 3.21 (d, *J* = 18.8 Hz, 1H), 3.07 (d, *J* = 18.8 Hz, 1H), 2.89 (dd, *J* = 15.2, 3.9 Hz, 1H), 2.83 (dd, *J* = 15.1, 7.8 Hz, 1H), 1.24 (s, 9H).

^{13}C NMR (151 MHz, acetone-*d*6)
13C NMR (151 MHz, Acetone) δ 174.61, 173.71, 170.22, 165.24, 135.54, 131.09, 130.07, 129.10, 101.58, 95.31, 79.86, 63.37, 62.04, 36.10, 35.13, 31.40, 30.69, 26.79.

16b: TBS protection of 5

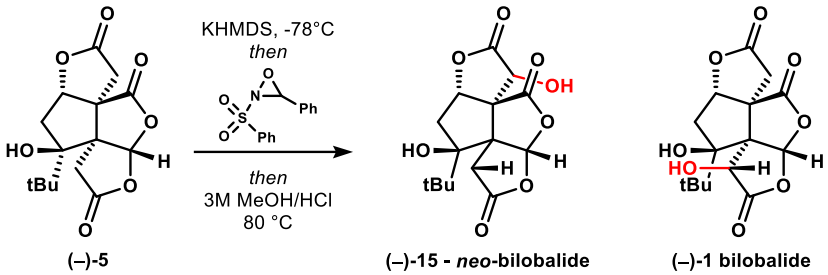


To a flame dried reaction vial containing a magnetic stirbar was added *des*hydroxybilobalide **5** (3 mg, 0.0097 mmol, 1.0 equiv) and DCM (0.1M). 2,6-lutidine (2.25 *μL*, 0.019 mmol, 2.0 equiv) and TBSOTf (4.37 *μL*, 0.019 mmol, 2.0 equiv) were then added at room temperature and the reaction was stirred until starting material was fully consumed, after which the reaction was concentrated and loaded directly onto a preparative TLC plate for purification (40% acetone/hexanes) to afford **16b** as a colorless oil and in quantitative conversion.

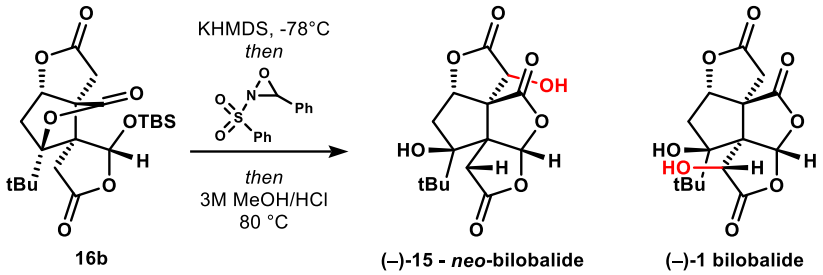
R_f 0.50 (hexanes:acetone = 2:1, UV detection after heating over 15 min. on TLC plate)

^{1}H NMR (600 MHz, acetone-*d*6)
δ 6.11 (s, 1H), 4.68 (dd, *J* = 7.9, 3.8 Hz, 1H), 3.28 (d, *J* = 18.2 Hz, 1H), 3.07 (d, *J* = 18.2 Hz, 1H), 2.84 (d, *J* = 18.6 Hz, 1H), 2.78 (dd, *J* = 15.2, 3.8 Hz, 1H), 2.76 (d, *J* = 18.2 Hz, 1H), 2.72 (dd, *J* = 15.1, 8.0 Hz, 1H), 1.14 (s, 9H), 0.93 (s, 9H), 0.19 (d, *J* = 1.5 Hz, 6H).

15: alpha-hydroxylation to *neo*-bilobalide



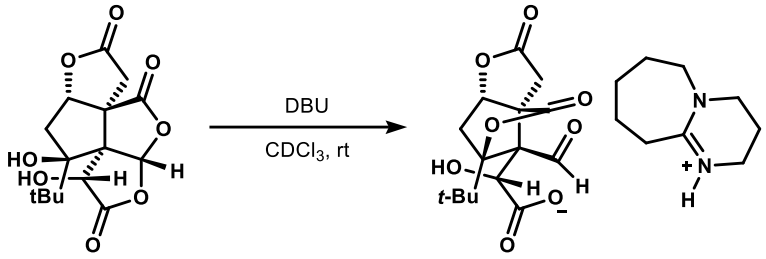
To a flame dried reaction vial containing a magnetic stirbar was transferred *des*hydroxybilobalide **5** (3 mg, 0.0097 mmol). To remove any trace water, the starting material was azeotroped with toluene at least three times by heating to 80 °C under a strong positive pressure of dry N_2 until all solvent was evaporated and only a white solid remained in the flask. The reaction vial was placed under an argon atmosphere and then THF (300 µL) was added. The reaction was cooled to -78 °C followed by the addition of a KHMDS solution (0.19M in THF, 0.1 ml, 0.019mmol, 2 equiv). After stirring for 1 hour at -78 °C, Davis reagent was added dropwise from a stock solution in THF (7.6 mg/50 µL THF, 0.019 mmol, 2 equiv) and the resulting mixture was stirred for additional 2 hours at -78 °C. At this point, the reaction was quenched with 3.0M methanolic HCl (33 µL, 0.0967 mmol, 10 equiv) and warmed to room temperature. Aqueous 3M HCl (0.3 mL) was then added and the reaction was heated to 85 °C for 24 hours to deprotect and isomerize all material in the *iso*-bilobalide form, back to the bilobalide scaffold. The reaction was then concentrated, and the crude NMR showed the ratio of **15** to **1** to be 100:1.



To a flame dried reaction vial containing a magnetic stirbar was transferred *des*hydroxybilobalide **5** (4.1 mg, 0.00967 mmol). To remove any trace water, the starting material was azeotroped with toluene at least three times by heating to 80 °C under a strong positive pressure of dry N_2 until all solvent was evaporated and only a white solid remained in the flask. The reaction vial was placed under an argon atmosphere and then THF (300 µL) was added. The reaction was cooled to -78 °C followed by the addition of a KHMDS solution (0.15M in THF, 0.1 ml, 0.015 mmol, 1.5 equiv). After stirring for 1 hour at -78 °C, Davis reagent was added dropwise from a stock solution in THF (3.8 mg/50 µL THF, 0.015 mmol, 1.5 equiv) and the resulting mixture was stirred for additional 2 hours at -78 °C. At this point, the reaction was quenched with 3.0M methanolic HCl (33 µL, 0.0967 mmol, 10 equiv) and warmed to room temperature. Aqueous 3M HCl (0.3 mL) was then added and the reaction was heated to 85 °C for 24 hours to deprotect and isomerize all material in the *iso*-bilobalide form, back to the bilobalide scaffold. The reaction was then concentrated, and the crude NMR showed the ratio of **15** to **1** to be 94:6.

R_f	0.50 (DCM:acetone = 7:3, UV detection after heating over 15 min. on TLC plate)
^{1}H NMR	(600 MHz, acetone-*d*6)
	δ 6.50 (s, 1H), 5.92 (d, *J* = 6.1 Hz, 1H), 5.01 – 4.92 (m, 2H), 4.67 (s, 1H), 3.58 (d, *J* = 18.6 Hz, 1H), 3.27 (d, *J* = 18.5 Hz, 1H), 2.65 (dd, *J* = 13.0, 6.4 Hz, 1H), 2.23 (dd, *J* = 12.9, 9.9 Hz, 1H), 1.17 (s, 9H).
^{13}C NMR	(151 MHz, acetone-*d*6)
	δ 175.19, 174.69, 171.64, 104.71, 88.21, 82.70, 69.55, 63.15, 62.81, 41.51, 38.25, 34.77, 27.01.
HRMS (ESI)	Calcd. for $C_{15}H_{19}O_8$ 327.1080 ($M+H^+$) found 327.1068.

SI-6: Skeleton rearrangement to form *iso*-bilobalide



(–)–**1** **SI-6**

To an oven-dried NMR-tube was added **(–)-1** (2.0mg, 0.0061 mmol) followed by $CDCl_3$ (500µL) and was subsequently capped with an NMR tube septum. DBU (0.84µL, 0.0061 mmol) was added as a stock solution in 100µL of $CDCl_3$ to the NMR tube and the spectrum was taken within 5 minutes of preparing the sample. The product observed in non-isolable, and decomposes back to starting material immediately upon acidification. Structure assignment was determined by homology to the known *iso*-bilobalide scaffold as well as 2D NMR (see pages S45-S49). All attemps to recrystallize the product resulted in the isolation of an amorphous solid.

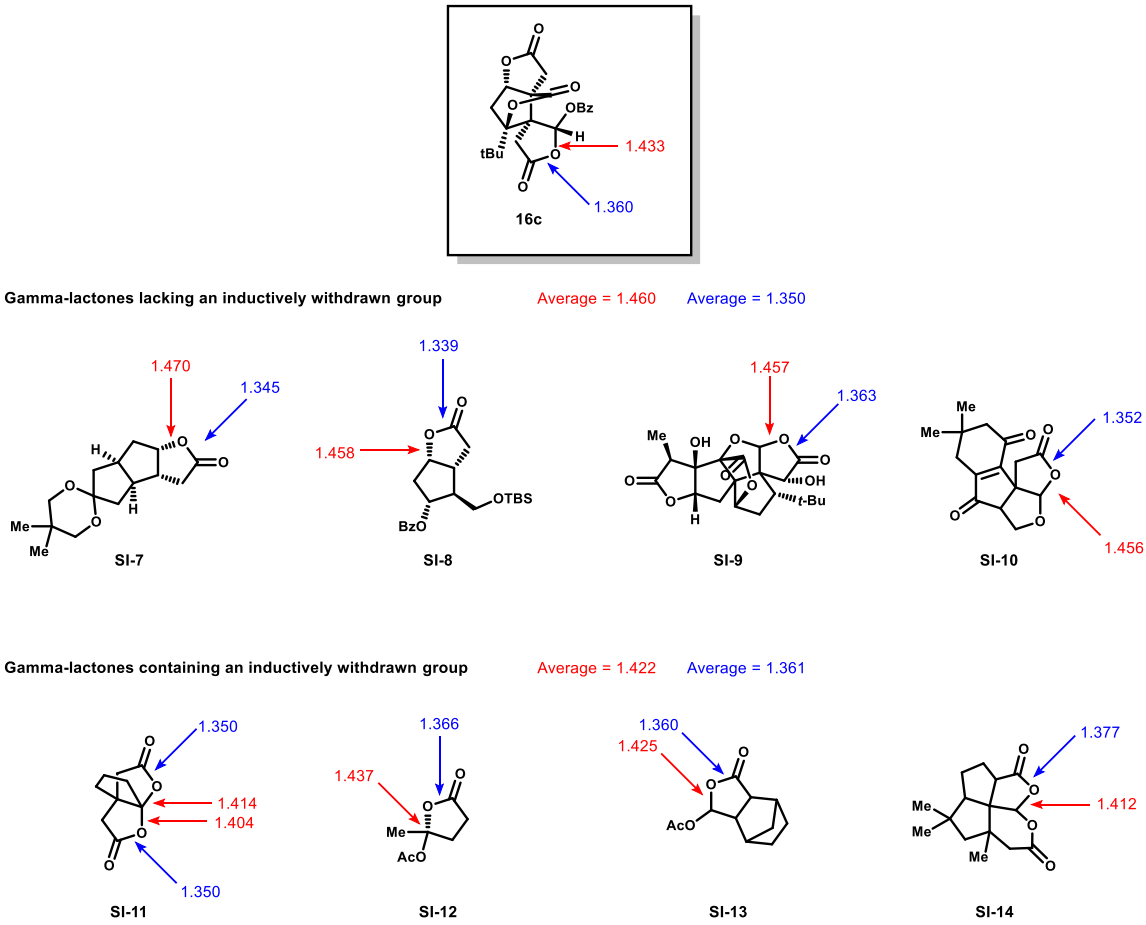
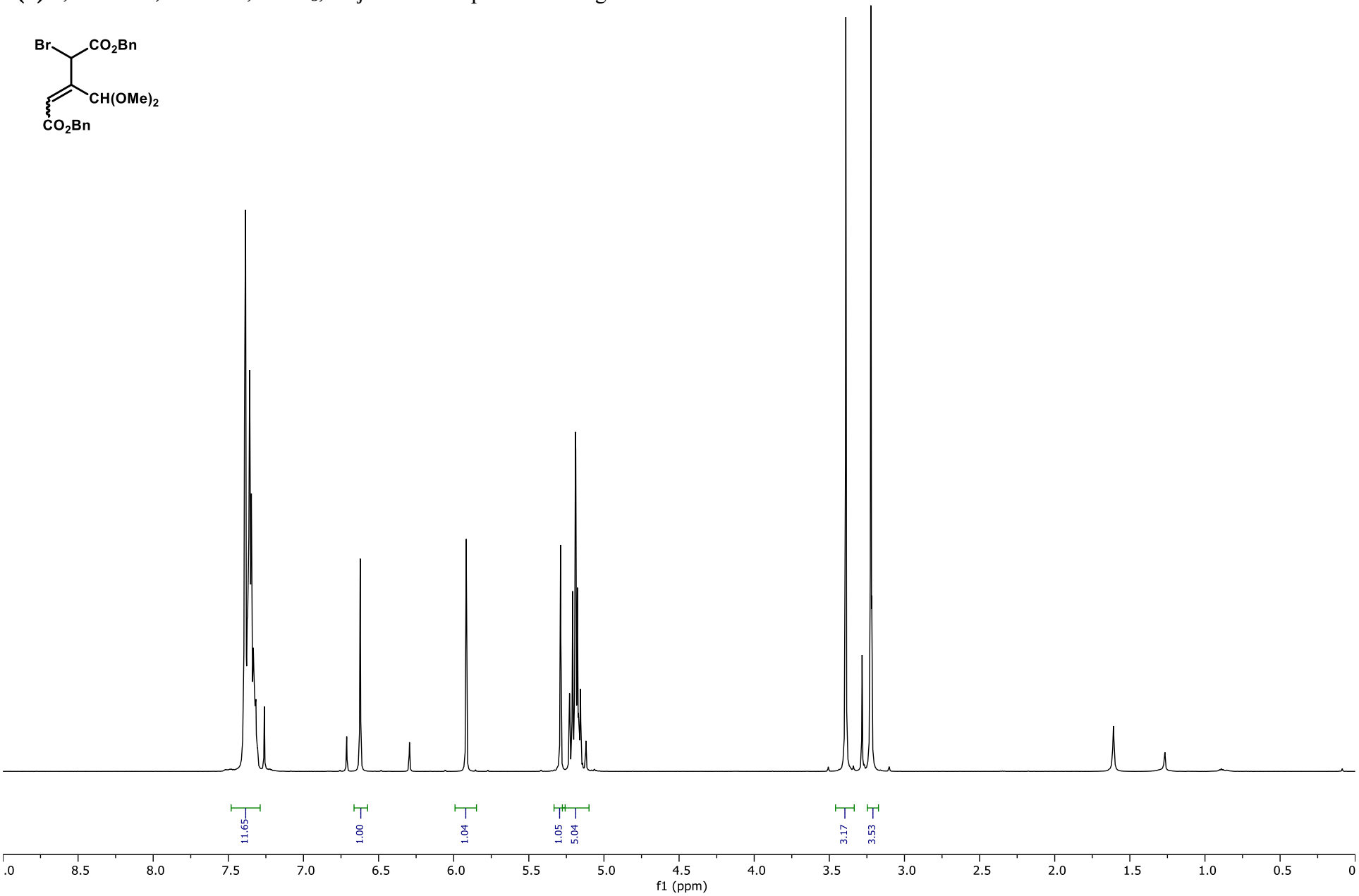


Table S2: Bond lengths of a representative example of gamma-lactones lacking an inductively withdrawn group vs those containing an inductively withdrawn group.

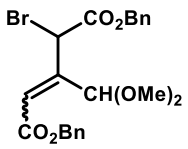
The .cif files for compounds **SI-7**[39], **SI-8**[40], **SI-9**[41], **SI-10**[42], **SI-11**[43], **SI-12**[44], **SI-13**[45], **SI-14**[46], were obtained from the Crystallography Open Database which can be accessed at http://www.crystallography.net/cod/

4. NMR Spectra

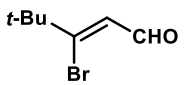
(±)-6, ^{1}H NMR, 600MHz, $CDCl_3$, major isomer's peaks are integrated



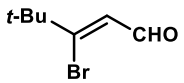
(±)-6, ^{13}C NMR, 151MHz, $CDCl_3$



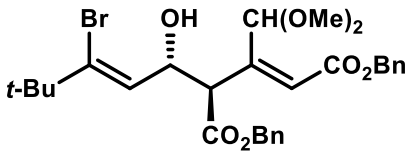
6b, ^{1}H NMR, 600MHz, $CDCl_3$



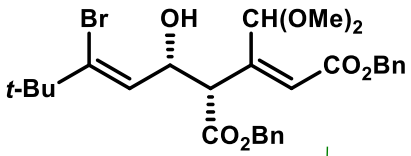
6b, ^{13}C NMR, 151MHz, $CDCl_3$



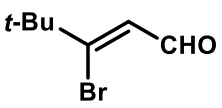
(–)-7 crude, ^{1}H NMR, 600MHz, $CDCl_3$



anti - **7**

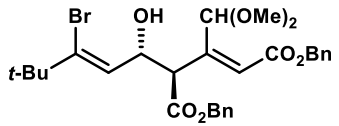


syn - **7**



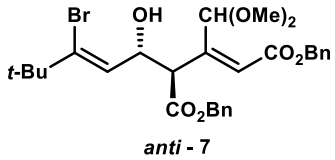
6b

(–)-7 *anti*-diastereomer, ^{1}H NMR, 600MHz, $CDCl_3$



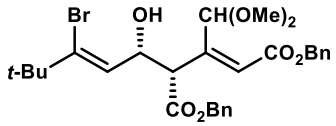
anti - 7

(–)-7 *anti*-diastereomer, ^{13}C NMR, 151MHz, $CDCl_3$



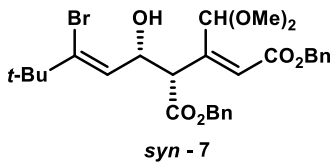
***anti* - 7**

(–)-7 *syn*-diastereomer, ^{1}H NMR, 600MHz, $CDCl_3$



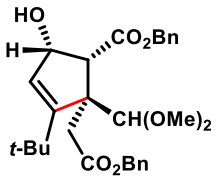
syn - 7

(–)-7 *syn*-diastereomer**,** ^{13}C NMR, 151MHz, $CDCl_3$

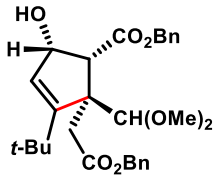


***syn* - 7**

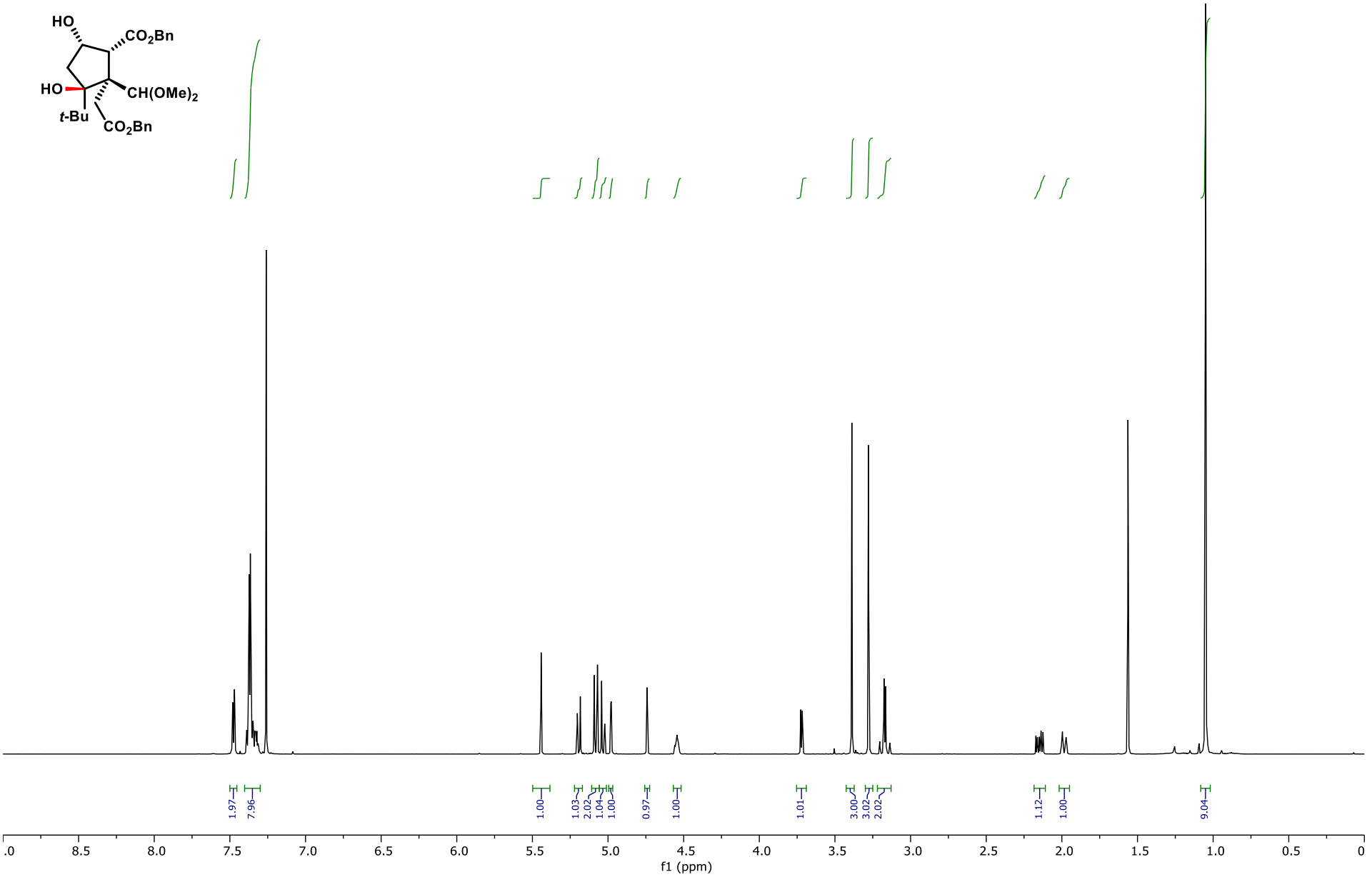
(–)-8, ^{1}H NMR, 600MHz, $CDCl_3$



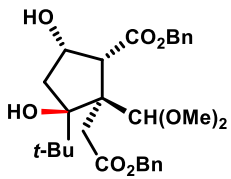
(–)-8, ^{13}C NMR, 151MHz, $CDCl_3$



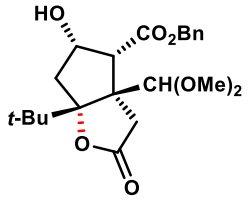
(+)-9, ^{1}H NMR, 600MHz, $CDCl_3$



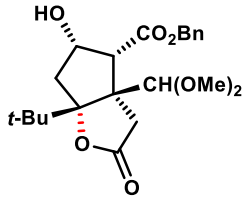
(+)-9, ^{13}C NMR, 151MHz, $CDCl_3$



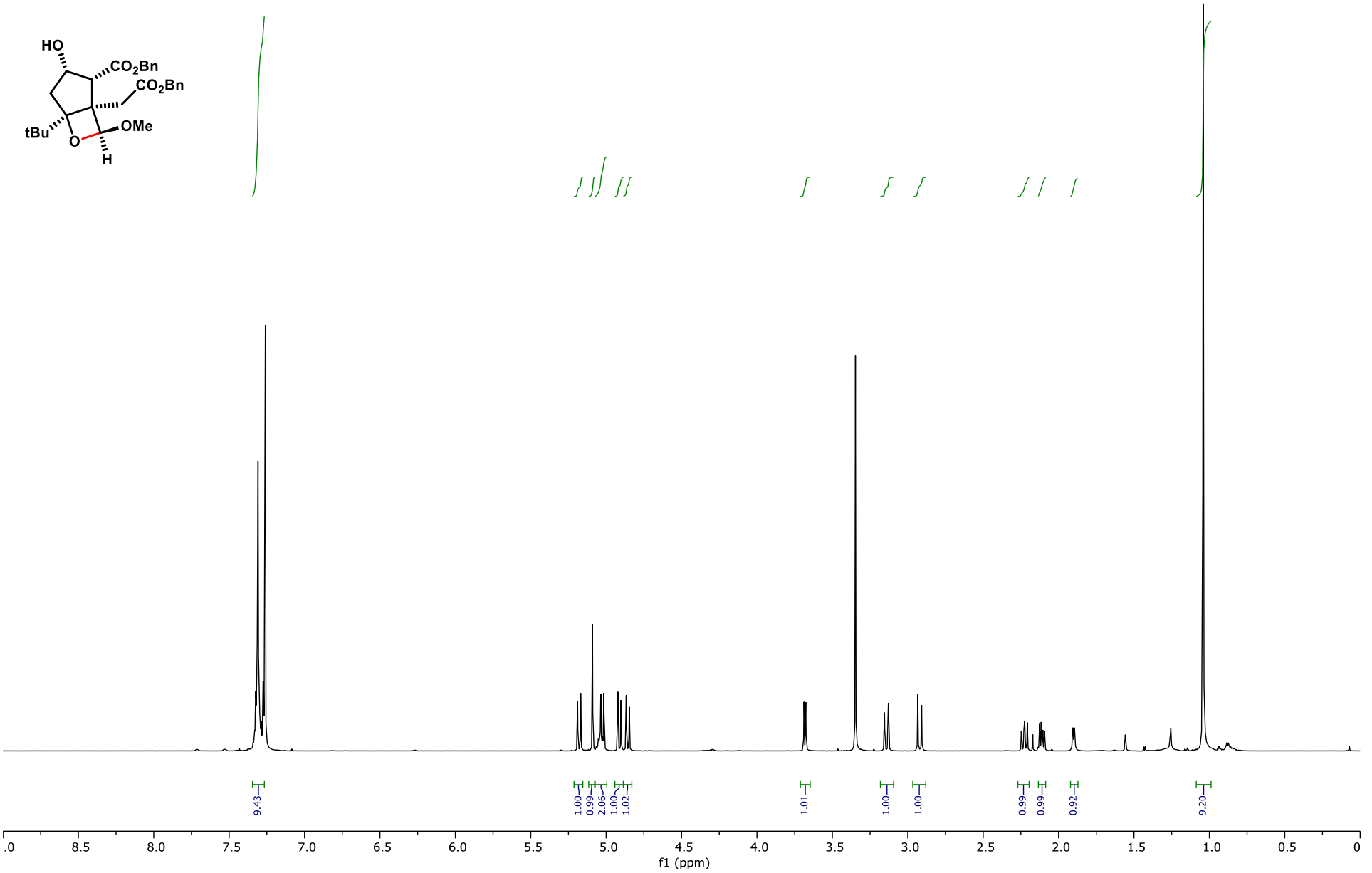
(+)-14, ^{1}H NMR, 600MHz, $CDCl_3$



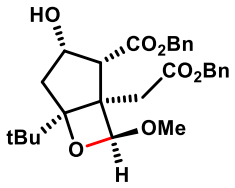
(+)-14, ^{13}C NMR, 151MHz, $CDCl_3$



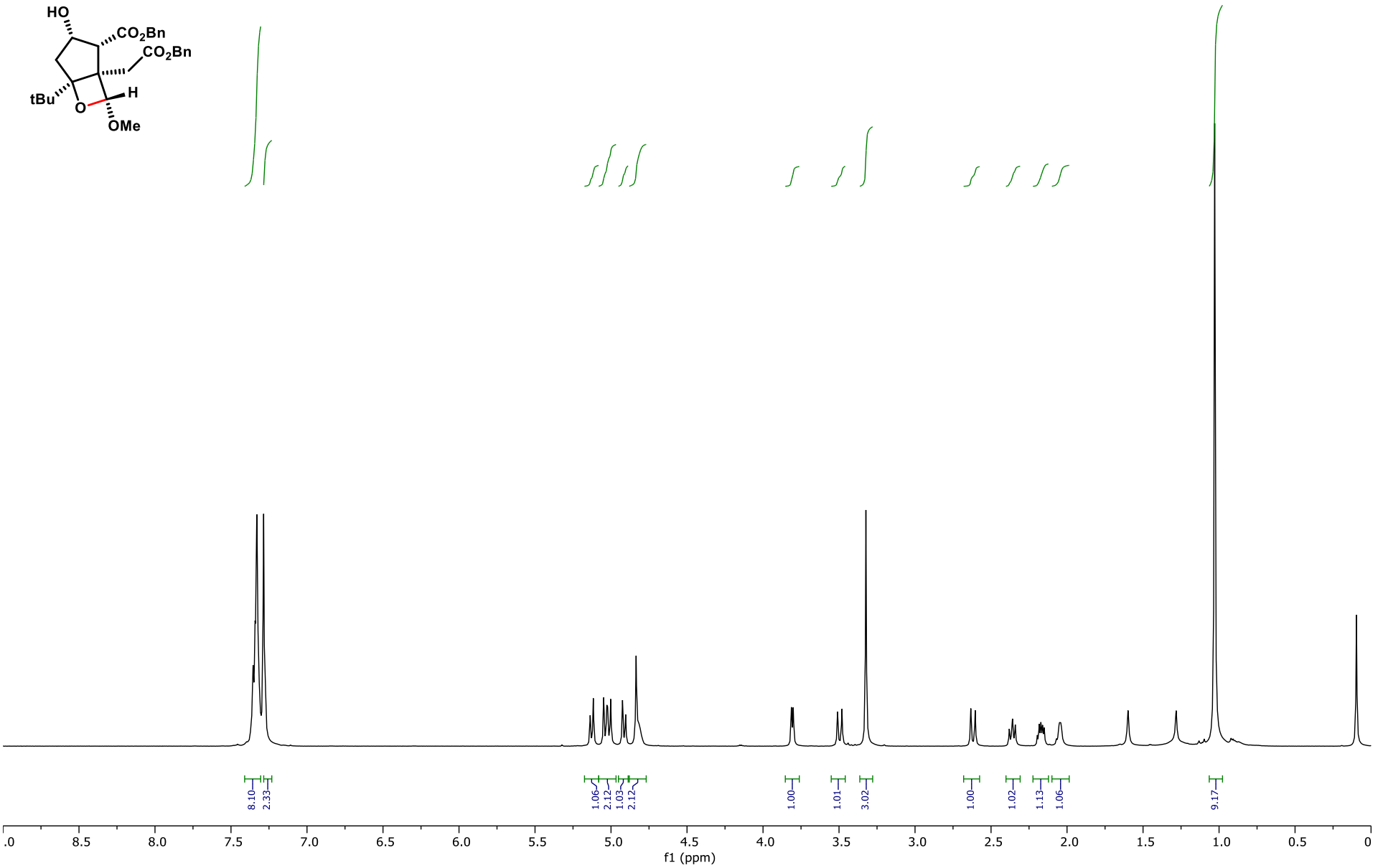
(+)-10, ^{1}H NMR, 600MHz, $CDCl_3$



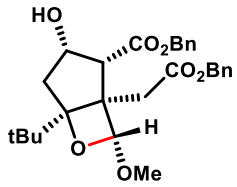
(+)-10, ^{13}C NMR, 151MHz, $CDCl_3$



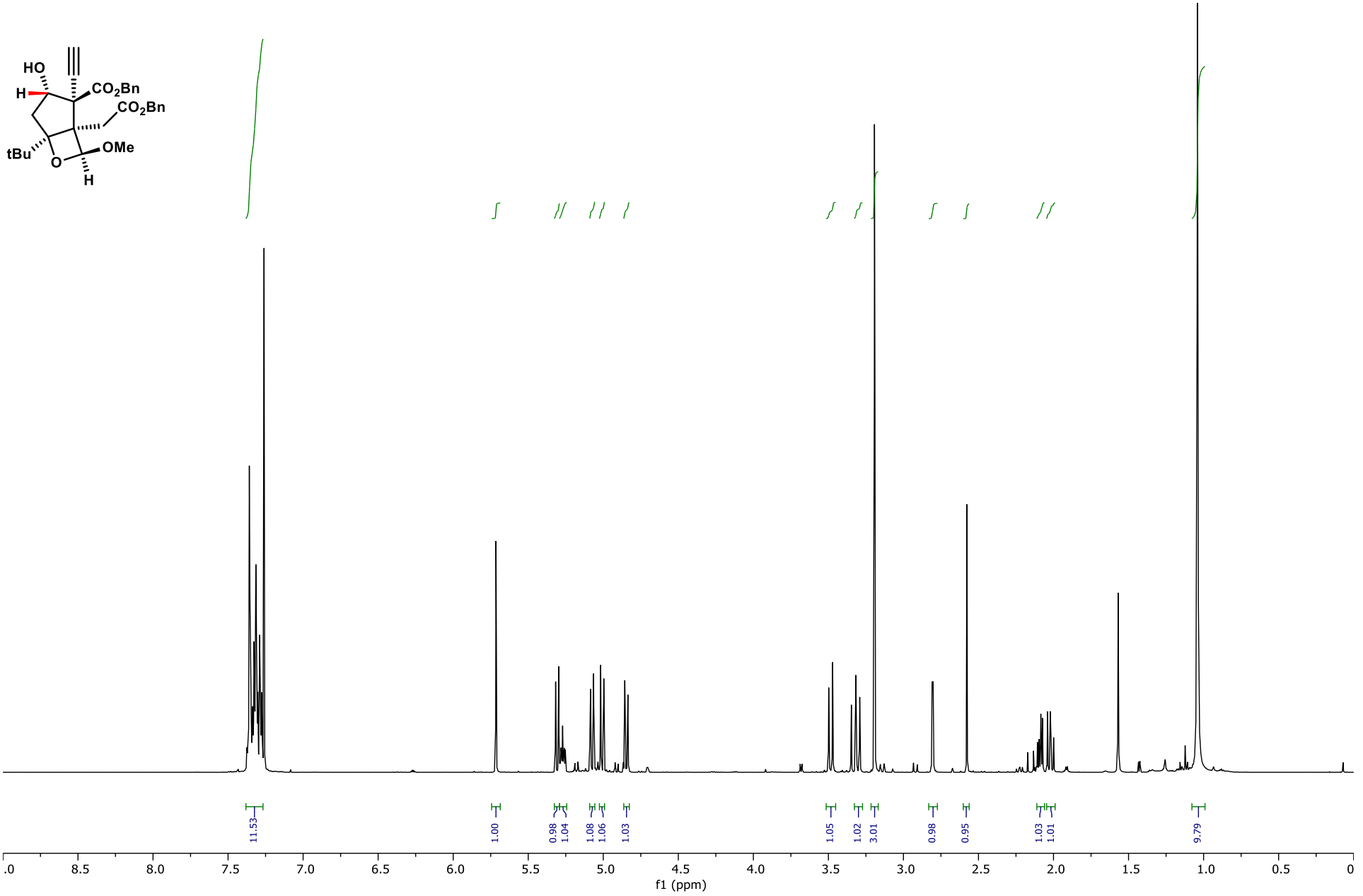
(+)-11, ^{1}H NMR, 600MHz, $CDCl_3$



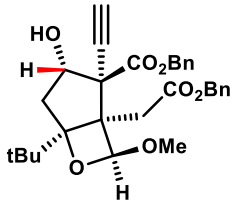
(+)-11, ^{13}C NMR, 151MHz, $CDCl_3$



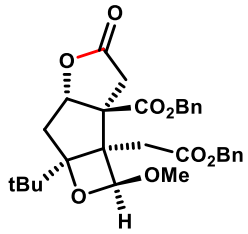
(+)-12, ^{1}H NMR, 600MHz, $CDCl_3$



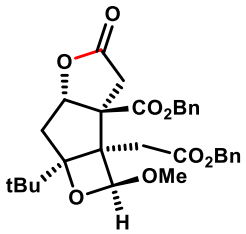
(+)-12, ^{13}C NMR, 151MHz, $CDCl_3$



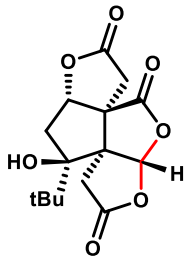
(+)-13, ^{1}H NMR, 600MHz, $CDCl_3$



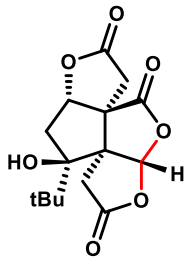
(+)-13, ^{13}C NMR, 151MHz, $CDCl_3$



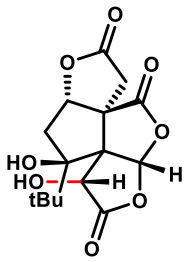
(–)-5, ^{1}H NMR, 600MHz, acetone-d_6



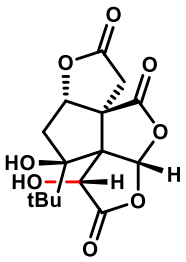
(–)-5, ^{13}C NMR, 151MHz, acetone-d_6



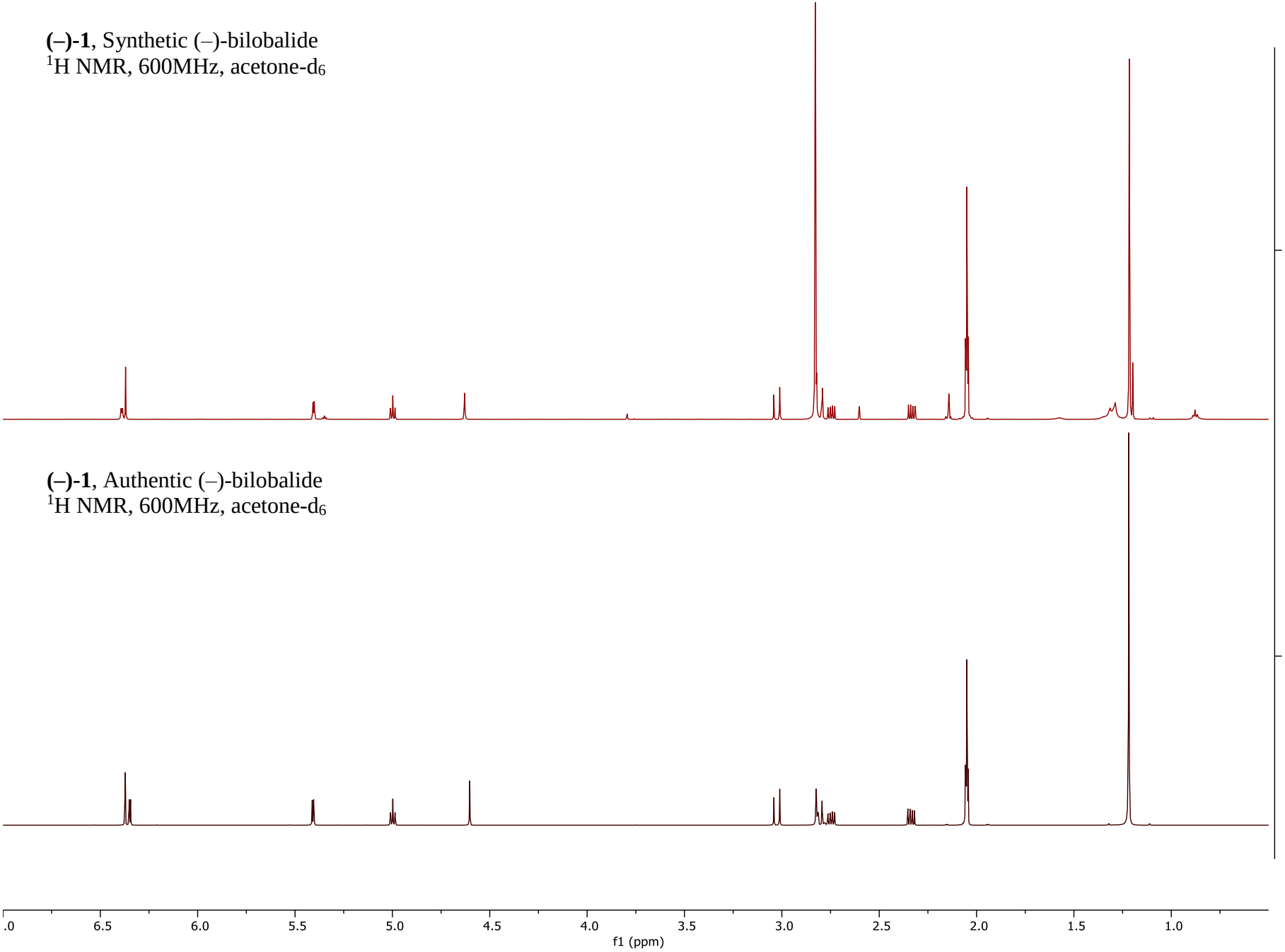
(–)-1, ^{1}H NMR, 600MHz, acetone-d_6



(–)-1, ^{13}C NMR, 151MHz, acetone-d_6

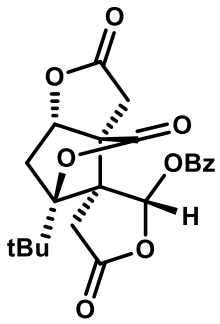


(–)-1, Synthetic (–)-bilobalide
^{1}H NMR, 600MHz, acetone-d_6

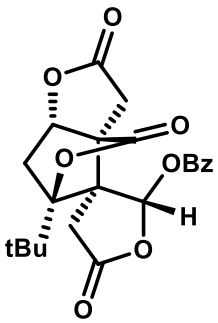


(–)-1, Authentic (–)-bilobalide
^{1}H NMR, 600MHz, acetone-d_6

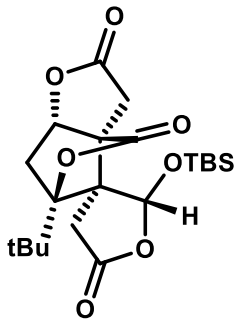
16c, ^{1}H NMR, 600MHz, acetone-d_6



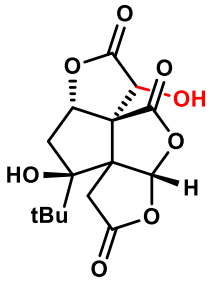
16c, ^{13}C NMR, 151MHz, acetone-d_6



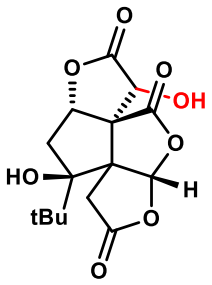
16b, ^{1}H NMR, 600MHz, acetone-d$_6$



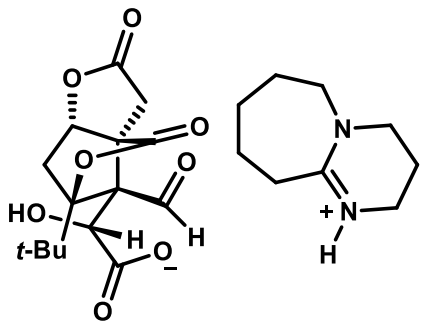
15, ^{1}H NMR, 600MHz, acetone-d_6



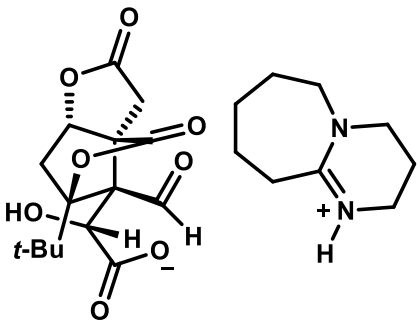
15, ^{1}H NMR, 600MHz, acetone-d_6



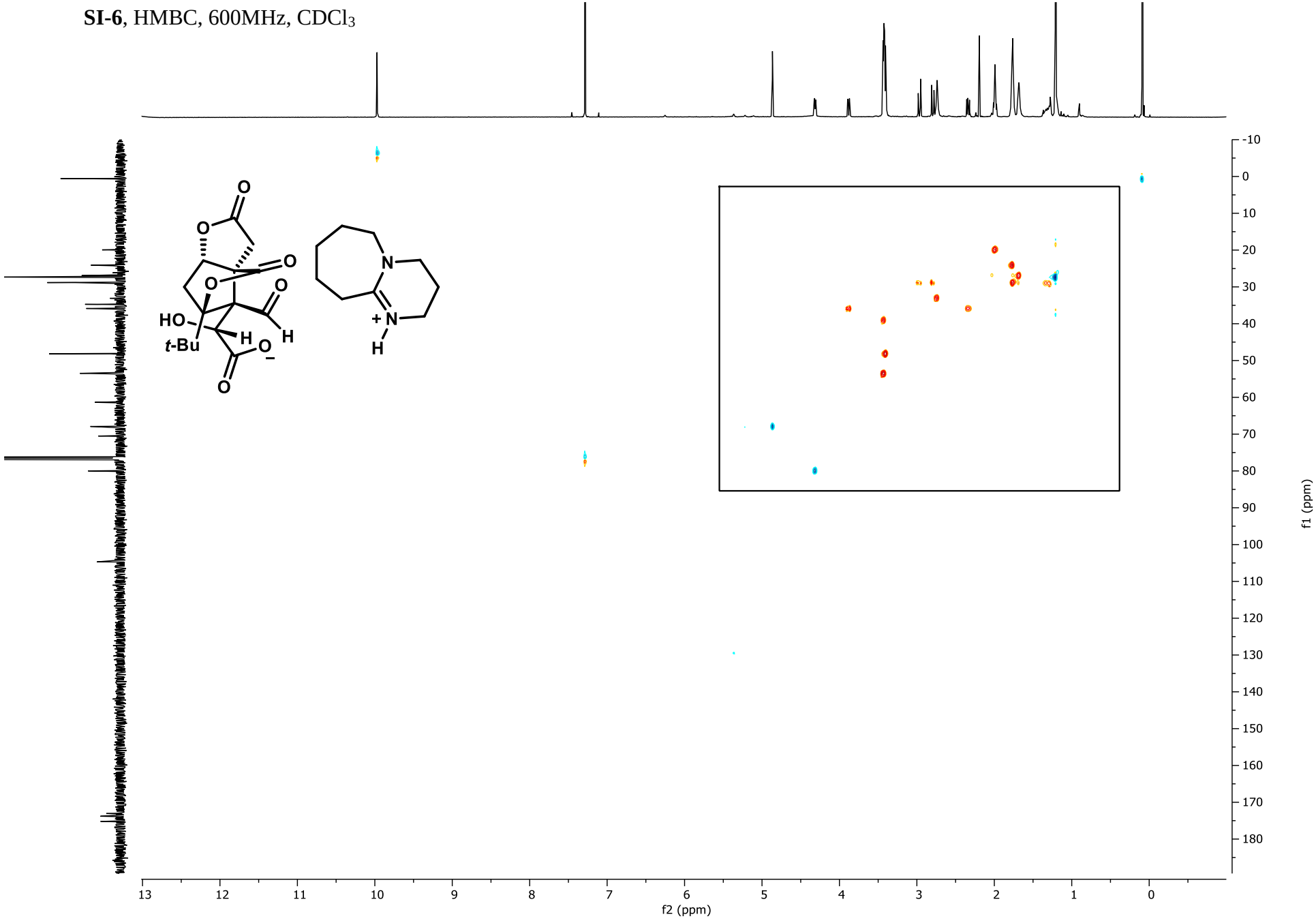
SI-6, ^{1}H NMR, 600MHz, $CDCl_3$



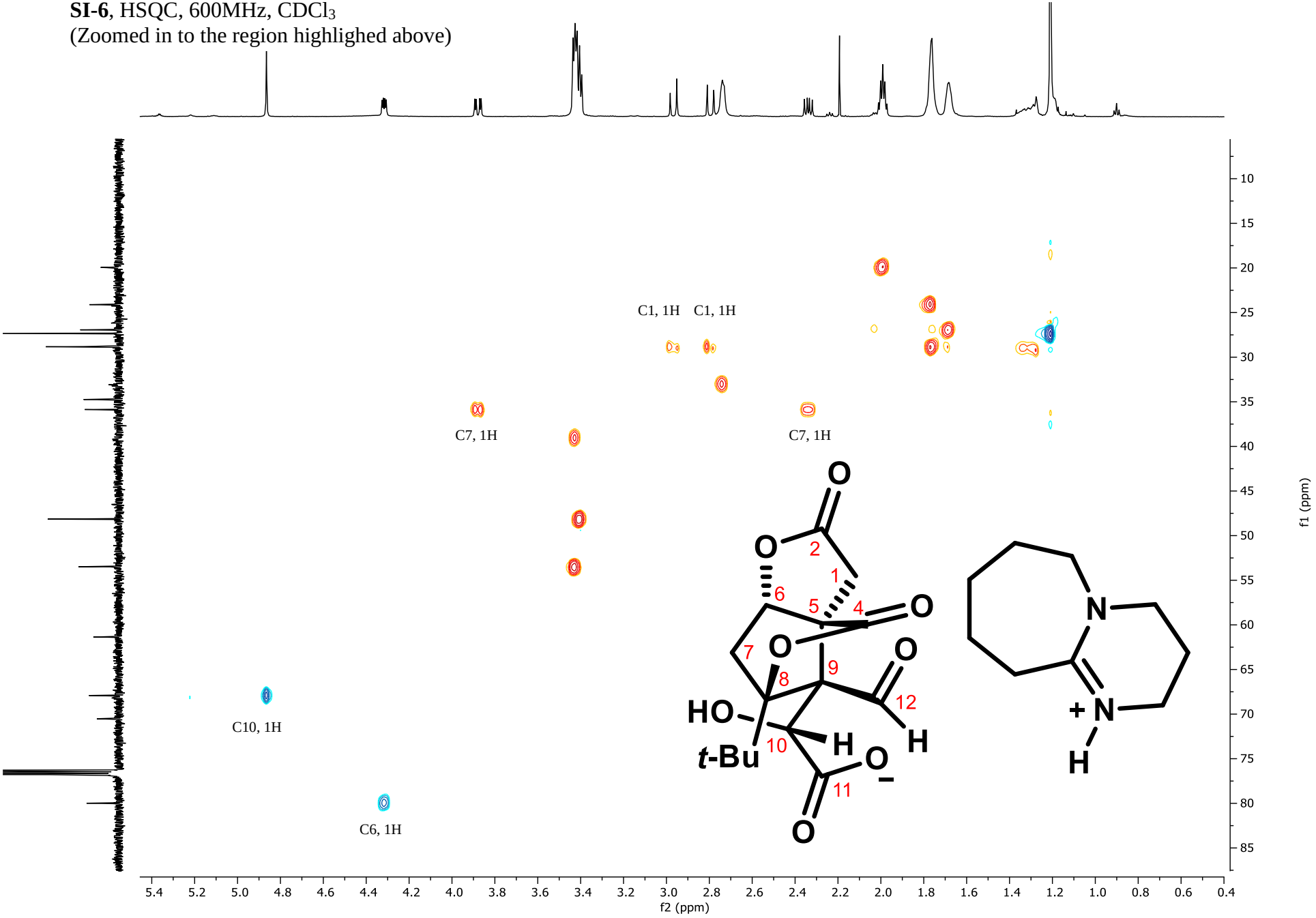
SI-6, ^{13}C NMR, 151MHz, $CDCl_3$



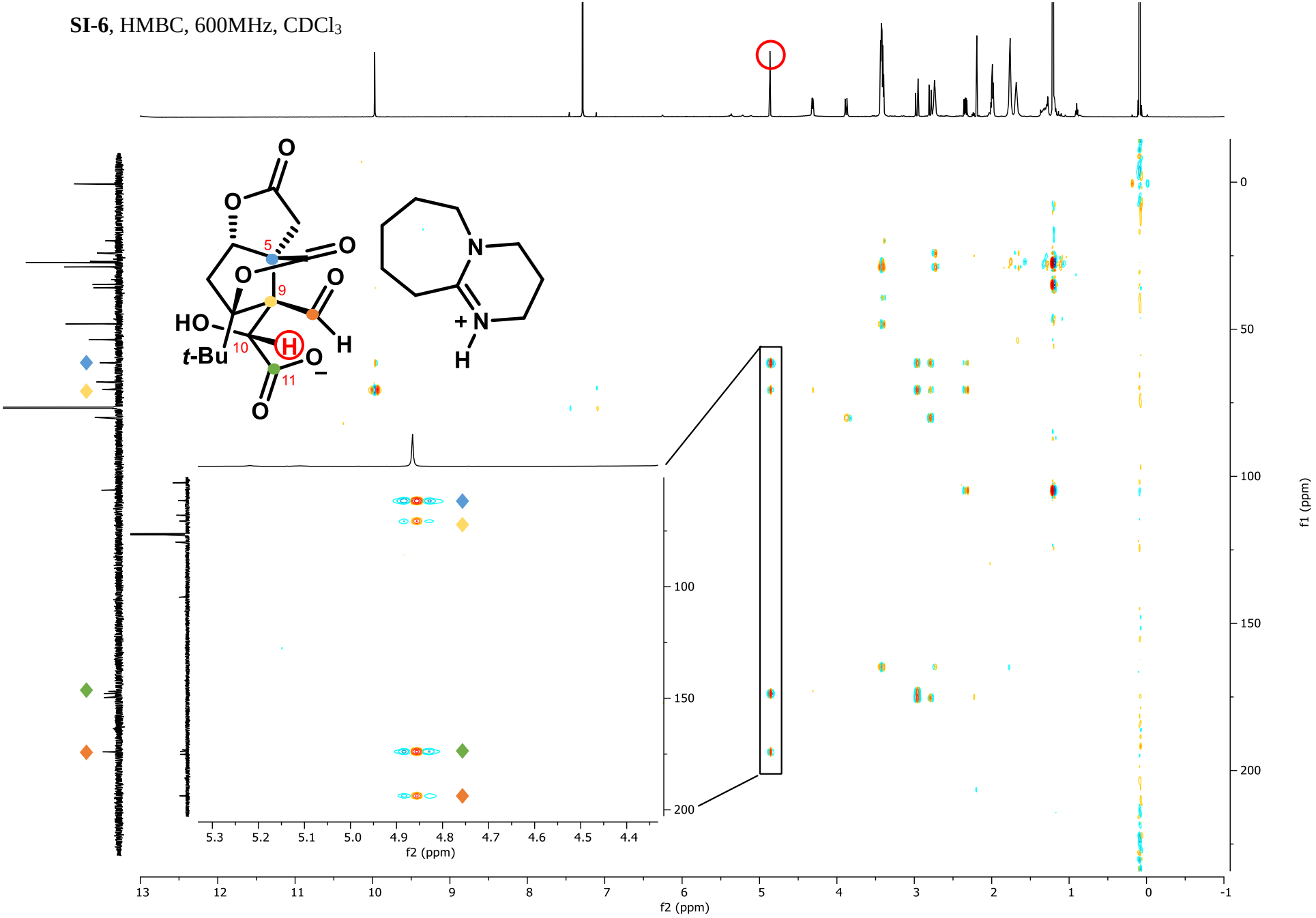
SI-6, HMBC, 600MHz, $CDCl_3$



SI-6, HSQC, 600MHz, $CDCl_3$
(Zoomed in to the region highlighed above)



SI-6, HMBC, 600MHz, $CDCl_3$



5. X-Ray Data for bilobalide intermediates

(–)-8 Giese Reaction

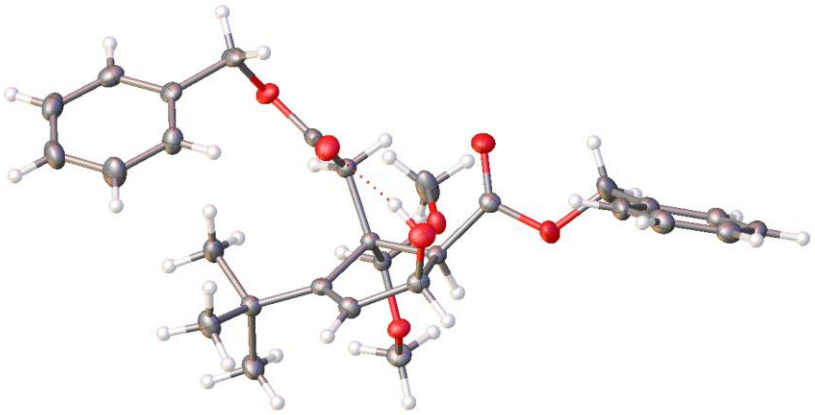


Table S3. Crystal data and structure refinement for Shenvi164.

Report date	2019-02-22	
Identification code	shenvi164	
Empirical formula	C29 H36 O7	
Molecular formula	C29 H36 O7	
Formula weight	496.58	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 10.5436(2) Å	α= 90°.
	b = 11.0100(2) Å	β= 109.0470(10)°.
	c = 11.7398(2) Å	γ = 90°.
Volume	1288.20(4) $Å^3$	
Z	2	
Density (calculated)	1.280 Mg/m^3	
Absorption coefficient	0.739 mm^{-1}	
F(000)	532	
Crystal size	0.215 x 0.125 x 0.1 mm^3	
Crystal color, habit	colorless block	
Theta range for data collection	3.983 to 71.019°.	
Index ranges	-10<=h<=12, -13<=k<=13, -14<=l<=13	
Reflections collected	11031	
Independent reflections	4674 [R(int) = 0.0197]	
Completeness to theta = 67.500°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7534 and 0.6507	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4674 / 1 / 331	
Goodness-of-fit on F^2	1.026	
Final R indices [I>2sigma(I)]	R1 = 0.0245, wR2 = 0.0633	
R indices (all data)	R1 = 0.0248, wR2 = 0.0635	
Absolute structure parameter	-0.01(3)	
Largest diff. peak and hole	0.259 and -0.159 $e.Å^{-3}$	

(±)-12 Fully Substituted Cyclopentane

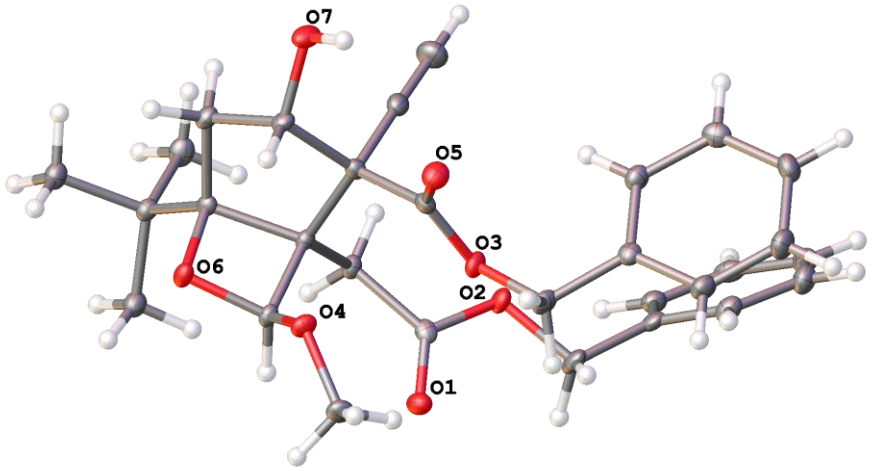


Table S4. Crystal data and structure refinement for shenvi158_0m_a.

Identification code	RMD 1006-P	
Empirical formula	C30 H34 O7	
Formula weight	506.57	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c [racemic]	
Unit cell dimensions	a = 8.7120(4) Å	α= 90°.
	b = 22.5701(10) Å	β= 100.619(3)°.
	c = 13.2257(6) Å	γ = 90°.
Volume	2556.0(2) $Å^3$	
Z	4	
Density (calculated)	1.316 Mg/m^3	
Absorption coefficient	0.093 mm^{-1}	
F(000)	1080	
Crystal size	0.33 x 0.32 x 0.30 mm^3	
Theta range for data collection	2.749 to 27.132°.	
Index ranges	-11<=h<=11, -28<=k<=28, -15<=l<=16	
Reflections collected	17895	
Independent reflections	5638 [R(int) = 0.0588]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7455 and 0.6948	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5638 / 0 / 339	
Goodness-of-fit on F^2	1.010	
Final R indices [I>2sigma(I)]	R1 = 0.0480, wR2 = 0.0917	
R indices (all data)	R1 = 0.0873, wR2 = 0.1068	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.332 and -0.261 e.$Å^{-3}$	

(–)-5 Des-Hydroxy-Bilobalide

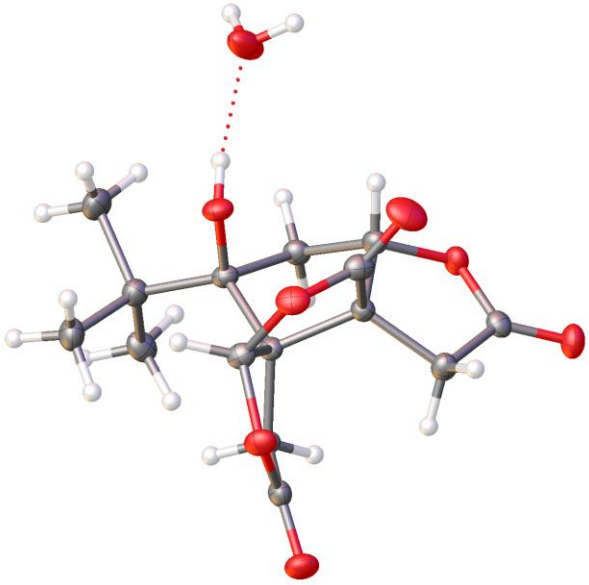


Table S5. Crystal data and structure refinement for Shenvi163.

Report date	2019-02-22	
Identification code	shenvi163	
Empirical formula	C15 H20 O8	
Molecular formula	C15 H18 O7, H2 O	
Formula weight	328.31	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 6.4622(2) Å	α= 90°.
	b = 14.0095(4) Å	β= 109.8840(10)°.
	c = 8.7984(2) Å	γ = 90°.
Volume	749.05(4) $Å^3$	
Z	2	
Density (calculated)	1.456 Mg/m^3	
Absorption coefficient	1.013 mm^{-1}	
F(000)	348	
Crystal size	0.2 x 0.16 x 0.04 mm^3	
Crystal color, habit	colorless plate	
Theta range for data collection	5.346 to 68.369°.	
Index ranges	-7<=h<=7, -16<=k<=16, -10<=l<=10	
Reflections collected	7420	
Independent reflections	2652 [R(int) = 0.0214]	
Completeness to theta = 67.500°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7531 and 0.6695	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2652 / 1 / 215	
Goodness-of-fit on F^2	1.051	
Final R indices [I>2sigma(I)]	R1 = 0.0244, wR2 = 0.0620	
R indices (all data)	R1 = 0.0249, wR2 = 0.0623	
Absolute structure parameter	0.04(5)	
Largest diff. peak and hole	0.182 and -0.152 e.$Å^{-3}$	

(±)-16c benzoyl-iso-deshydroxy-bilobalide

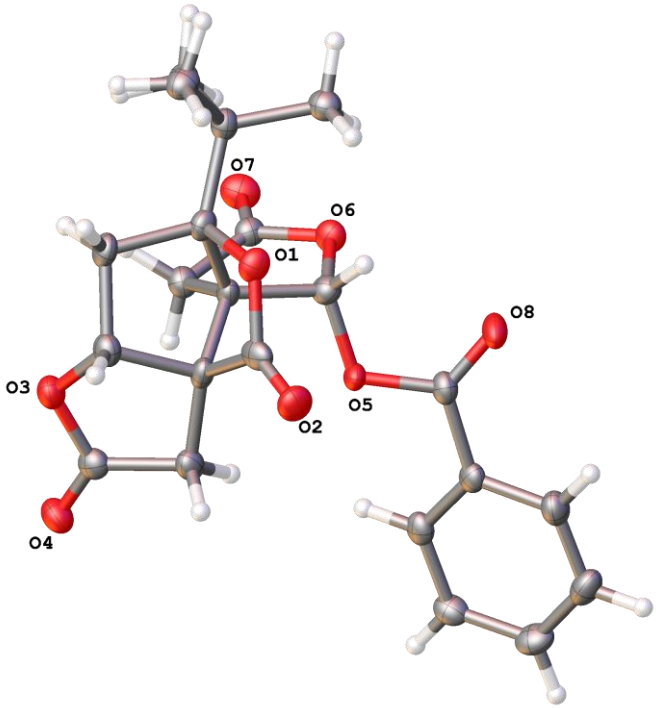


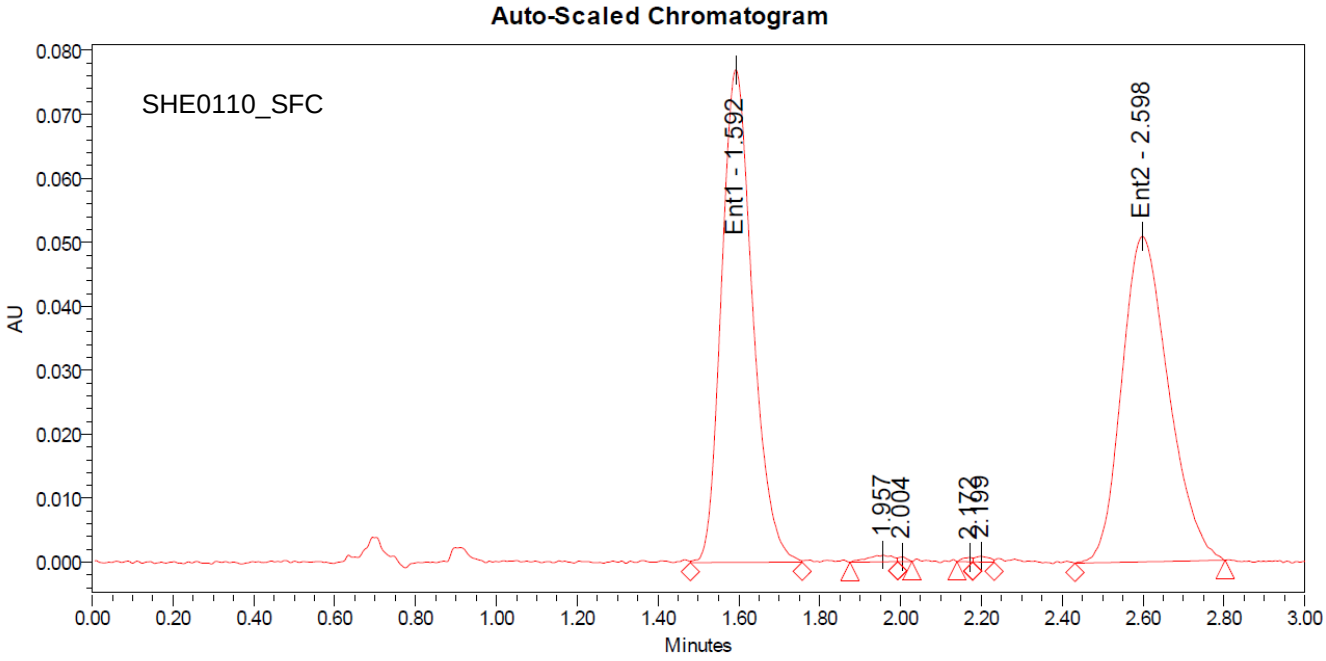
Table S6. Crystal data and structure refinement for shenvi135.

Identification code	MB-02-229	
Empirical formula	C22 H22 O8	
Formula weight	414.39	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 14.6104(16) Å	α= 90°.
	b = 15.3669(16) Å	β= 105.350(3)°.
	c = 8.9641(9) Å	γ = 90°.
Volume	1940.8(4) $Å^3$	
Z	4	
Density (calculated)	1.418 Mg/m^3	
Absorption coefficient	0.109 mm^{-1}	
F(000)	872	
Crystal size	0.28 x 0.26 x 0.04 mm^3	
Theta range for data collection	1.445 to 25.373°.	
Index ranges	-14<=h<=17, -17<=k<=12, -10<=l<=10	
Reflections collected	6293	
Independent reflections	3473 [R(int) = 0.0385]	
Completeness to theta = 25.242°	98.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.2589 and 0.2076	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3473 / 0 / 274	
Goodness-of-fit on F^2	1.007	
Final R indices [I>2sigma(I)]	R1 = 0.0542, wR2 = 0.1189	
R indices (all data)	R1 = 0.1041, wR2 = 0.1338	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.301 and -0.250 $e.Å^{-3}$	

Chiral SFC Traces for (–)-7

2D LC-SFC Conditions (heart-cutting method): LC Dimension: 0.1% aqueous formic acid:acetonitrile gradient (0.6 mL/min, 15-99% acetonitrile over 2.1 minutes) at 55 °C. The heart cut was performed at 2.18 minutes using a 6-port 2-position valve equipped with a 10 mL transfer loop; SFC Dimension: isocratic conditions (4 mL/min, 15% MeOH / CO_2, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (214 nm).

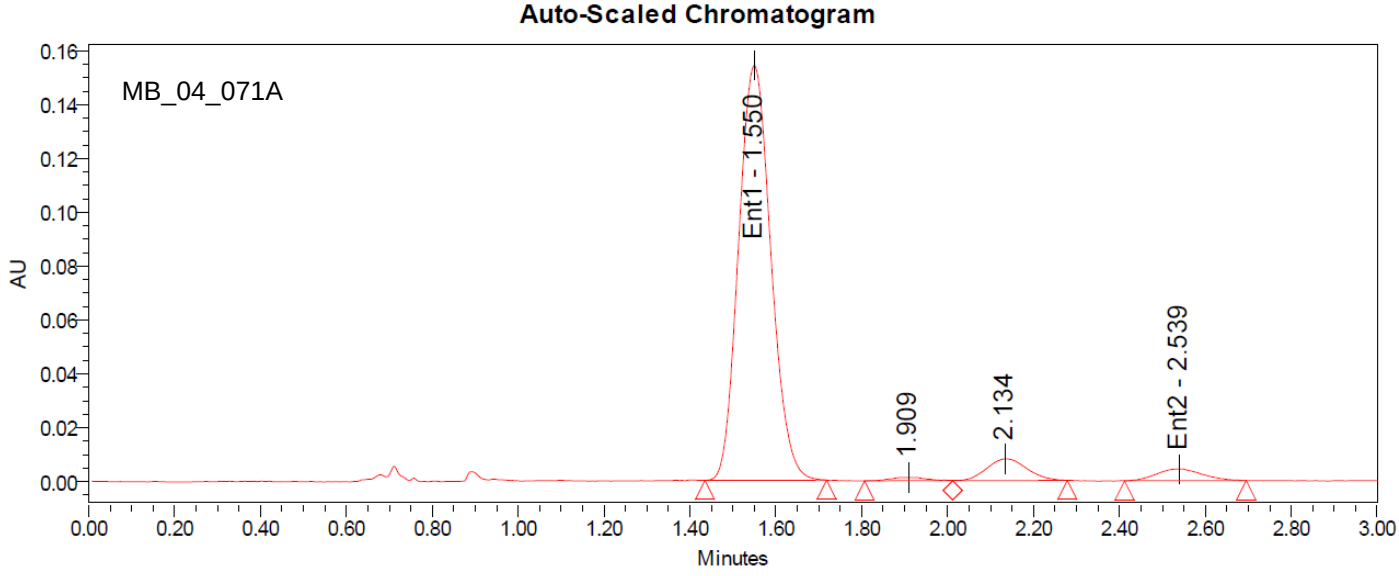
Chromatogram of (±)- **7**



Area Summarized by Name

	SampleName	ent1	ent2	ee	Ent1	Ent2
1	SHE0110_SFC	50.22	49.78	0.43	412275	408731

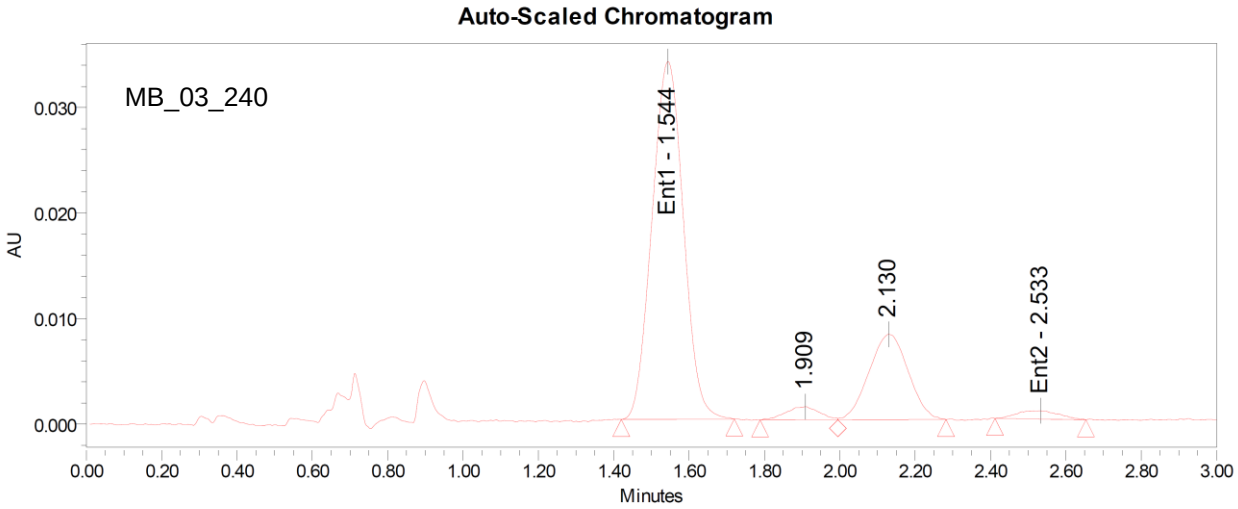
Chromatogram of enantioenriched (–)-**7** following large-scale asymmetric Reformatsky reaction



Area Summarized by Name

	SampleName	ent1	ent2	ee	Ent1	Ent2
1	MB-04-071A	96.17	3.83	92.35	806814	32094

Chromatogram of enantioenriched (–)-**7** following small-scale asymmetric Reformatsky reaction

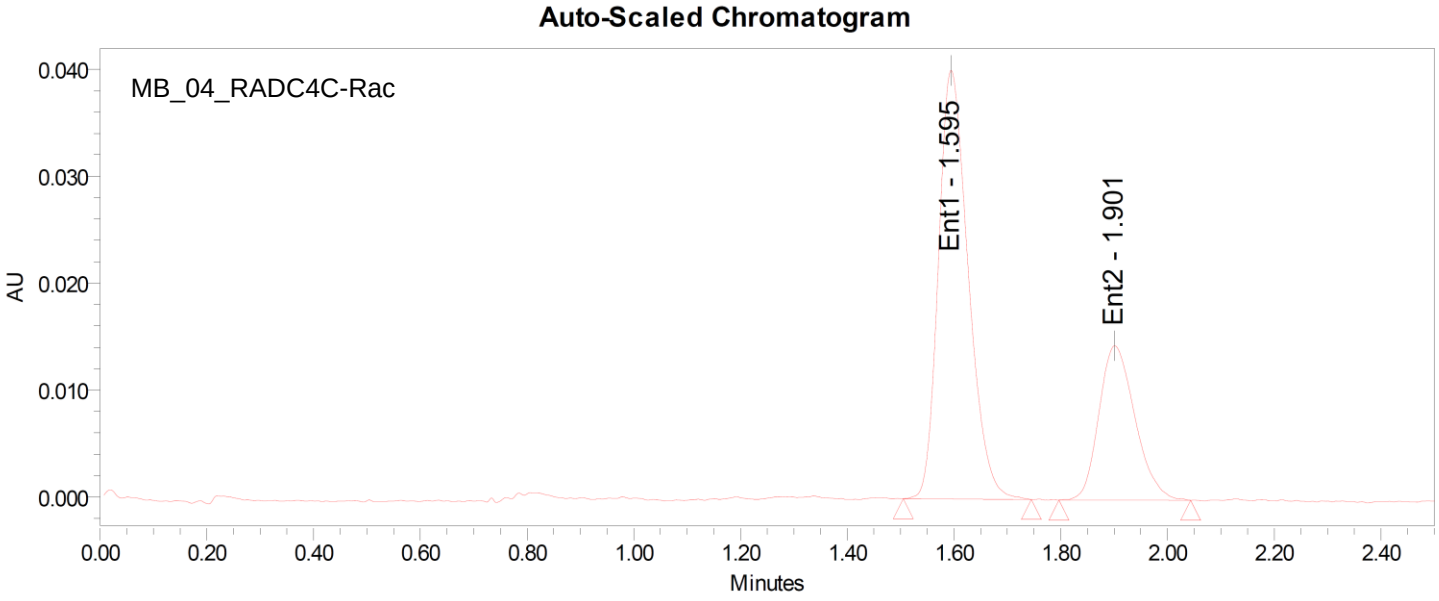


SampleName	ent1	ent2	ee	Ent1	Ent2
MB-03-240	96.98	3.02	93.96	196326	6117

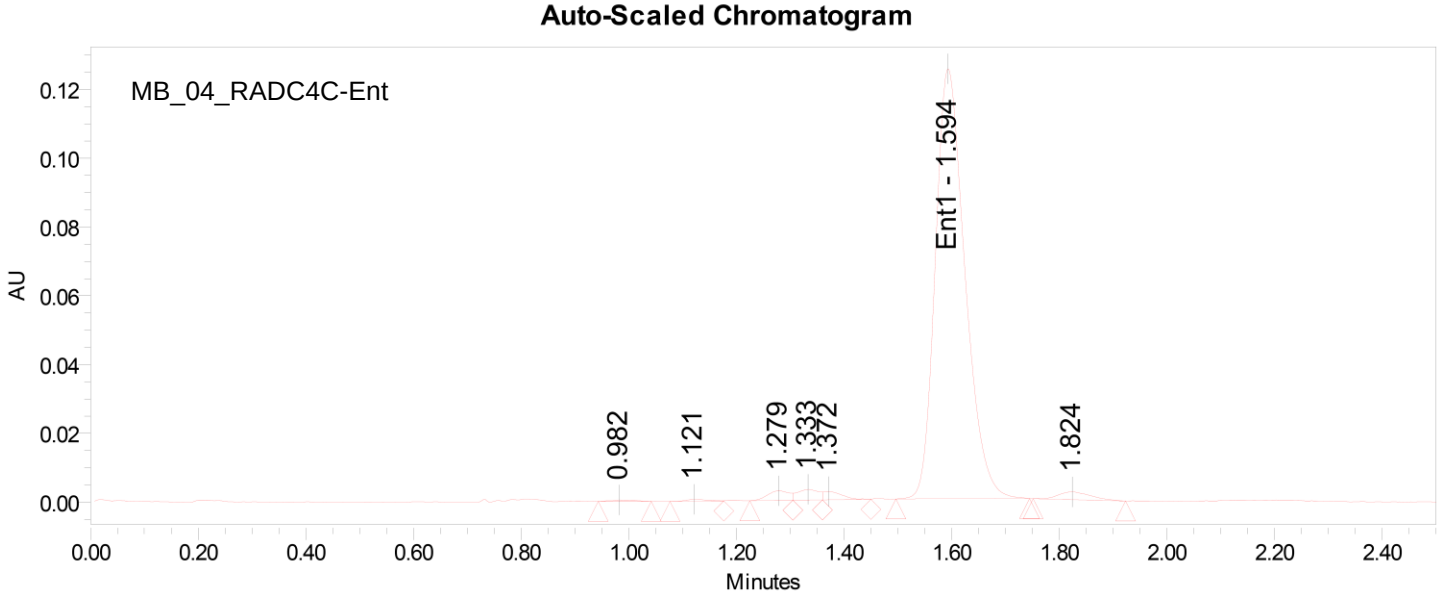
Chiral SFC Traces for (–)-8

Chiral SFC conditions: Isocratic conditions (4 mL/min, 25% MeOH / CO_2, 1600 psi backpressure) at 30 °C. The enantiomers were detected by UV light (214 nm).

Chromatogram of (±)-**8**



Chromatogram of enantipure **(–)**-8



Area Summarized by Name

	SampleName	ent1	ent2	ee	Ent1	Ent2
1	MB_04_RADC4C-Rac	69.69	30.31	39.37	155747	67753
2	MB_04_RADC4C-Ent	100.00		100.00	478869	

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