Supporting Information

Remodeling Natural Products: Chemistry and Serine Hydrolase Activity of a Rocaglate-Derived β-Lactone

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I. GENERAL INFORMATION

A. Instrumentation and methods

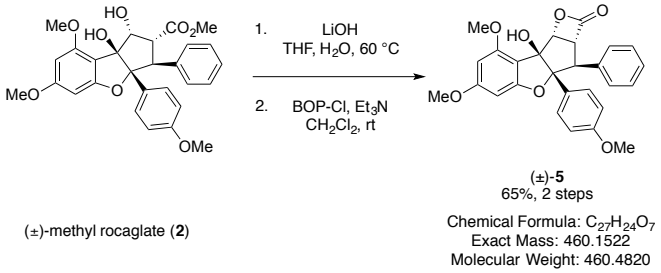
^{1}H NMR spectra were recorded at 300, 400, or 500 MHz at ambient temperature with $CDCl_3$, CD_3OD, DMSO-d_6 or benzene-d_6 (Cambridge Isotope Laboratories, Inc.) as solvents. Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (br = broad, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants in Hz. ^{13}C NMR spectra were recorded at 75.0,

100.0, or 125 MHz at ambient temperature with the same solvents unless otherwise stated. Chemical shifts are reported in parts per million relative to the deuterated solvents. All ^{13}C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. High-resolution mass spectra were obtained in the Boston University Chemical Instrumentation Center using a Waters Q-TOF API-US mass spectrometer. Melting points were recorded on a Mel-Temp apparatus (Laboratory Devices). Analytical LC-MS was performed on a Waters Acquity UPLC (Ultra Performance Liquid Chromatography (Waters MassLynx Version 4.1) with a Binary solvent manager, SQ mass spectrometer, Water 2996 PDA (PhotoDiode Array) detector, and ELSD (Evaporative Light Scattering Detector). An Acquity UPLC BEH C_{18} 1.7 μm column was used for analytical UPLC-MS. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and specific rotations are given $[\alpha]_D^{20}$ (concentration in grams/100 mL solvent). Chiral HPLC analysis of enantioenriched compounds was performed using a Waters 1525 Binary HPLC Pump with a Waters 2487 diode array detector. Preparative HPLC was performed on a Gilson PLC2020 using a Waters SunFire™ Prep C18 OBD™ 5μm 19X50 mm column.

Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200-400 mesh silica gel (Scientific Absorbents, Inc.). Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. HPLC grade tetrahydrofuran, methylene chloride, diethyl ether, toluene, acetonitrile, and benzene were purchased from Fisher and VWR and were purified and dried by passing through a PURE SOLV® solvent purification system (Innovative Technology, Inc.). Other ACS grade solvents for chromatography were purchased from Clean Harbors.

Photochemistry experiments were performed using a Rayonet RPR-100 photochemical reactor equipped with RPR-3500 irradiation lamps (UVA 315-400 nm). Other photochemical reactions were performed in enclosed box using a Hanovia 450 W medium pressure mercury lamp housed in a quartz immersion well, cooled with a Thermo Neslab-ULT 80 system circulator. Pyrex test tubes (16 x 100 mm) were mounted on a support approximately 5.0 cm from the immersion well lamp. All other reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

II. EXPERIMENTAL PROCEDURES AND COMPOUND CHARACTERIZATION



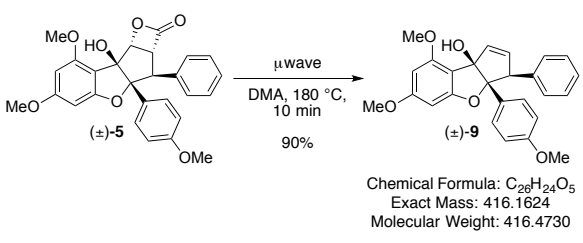
(±)-methyl rocaglate (**2**)

(±)-**5**
65%, 2 steps
Chemical Formula: $C_{27}H_{24}O_7$
Exact Mass: 460.1522
Molecular Weight: 460.4820

A. Preparation and characterization of β-lactones and derivatives

(±)-(2a*R*,3*S*,3a*R*,8b*S*,8c*R*)-8b-Hydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-3-phenyl-3,3a,8b,8c-tetrahydrooxeto[2',3':3,4]cyclopenta[1,2-

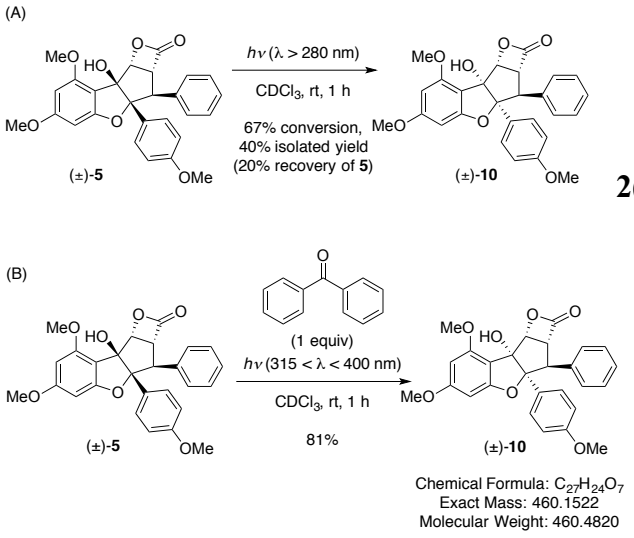
***b*]benzofuran-2(2a*H*)-one 4**: To a 50 mL flask charged with a stir bar was added methyl rocaglate (**2**)[S1] (82 mg, 0.16 mmol, 1.0 equiv) and THF (6.0 mL). To the stirring solution was added a solution of LiOH (20.0 mg, 0.83 mmol, 5.0 equiv) in water (4.0 mL). The resulting yellow solution was then heated at 60 °C for 5 h. The reaction was then cooled to rt, and diethyl ether (5 mL) and hydrochloric acid (1 N) were added. Hydrochloric acid (1 N) was added until the water layer reached a pH of ~ 2 (3 mL). The organic phase was then separated and the aqueous layer was then further extracted with diethyl ether (3 X 10 mL). The combined organic layers were washed with brine, dried over soldium sulfate, filtered and concentrated *in vacuo* to afford rocagloic acid (not depicted) as a yellow foam (79 mg, quantitative). The crude product was used in the next step without further purification. A dry 10 mL flask was charged with rocagloic acid (79 mg, 0.16 mmol, 1.0 equiv) from the previous step, a stir bar, and dichloromethane under argon. The resulting solution was then cooled to 0 °C. Triethylamine (69 µL, 0.50 mmol, 3.0 equiv) and *bis*(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl, 55 mg, 0.22 mmol, 1.3 equiv) were subsequently added. The reaction mixture was warmed to rt and stirred for 1 h. Water (4 mL) and CH_2Cl_2 (4 mL) were added and the organic phase was separated. The aqueous layer was then further extracted with CH_2Cl_2 (3 X 10 mL). The combined organic layers were washed with dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a yellow foam. Please note that without the aqueous workup (*i.e.* directly loading the concentrated reaction mixture on silica) we observed a significantly diminished yield of **5** after chromatography. The crude yellow solid was purified by column chromatography (elutes at 35:65 EtOAc/hexanes) to afford β-lactone **5** as a white solid (49 mg, 0.11 mmol, 65%). The product was crystallized *via* slow evaporation from toluene. R_f = 0.48 (1:1 EtOAc/hexanes); **m.p.** 184-185 ºC; **IR** νmax (film): 3438, 2939, 2839, 1830, 1600, 1514, 1454, 1252, 1218, 1182, 1147, 1128, 1037, 819, 735 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15-7.14 (ovrlp m, 3H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.98-6.95 (m, 2H), 6.64 (d, *J* = 8.8 Hz, 2H), 6.24 (d, *J* = 2.0 Hz, 1H), 6.09 (d, *J* = 2.0 Hz, 1H), 5.41 (d, *J* = 5.0 Hz, 1H), 4.55 (dd, *J* = 5.6, 5.0 Hz, 1H), 4.10 (d, *J* = 5.6 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.70 (s, 3H), 2.64 (s, 1H); **^{13}C NMR** (100 MHz, CD_3Cl) δ 169.3, 164.2, 160.0, 159.0, 157.7, 137.1, 128.8 (2C), 128.7 (2C), 128.2 (2C), 127.3, 126.6, 112.9 (2C), 108.1, 106.8, 93.1, 89.8, 89.7, 83.0, 60.3, 55.8, 55.7, 55.2, 54.8; **HR-MS**: *m/z* Calcd for $[C_{27}H_{24}O_7+H]^+$ 461.1600, found 461.1597 (-0.65 ppm).



(±)-(3*S*,3a*R*,8b*R*)-6,8-Dimethoxy-3a-(4-methoxyphenyl)-3-phenyl-3,3a-dihydro-8b*H*-cyclopenta[*b*]benzofuran-8b-ol 9: To a microwave vial was added β-lactone **5** (11 mg, 0.024 mmol, 1 equiv), a stir bar, and *N,N*-dimethylacetamide (0.5 mL). The mixture was then heated at 180 °C for 10 min. Water was then added (2 mL) and the mixture was extracted with EtOAc (3 X 5 mL). The combined organic

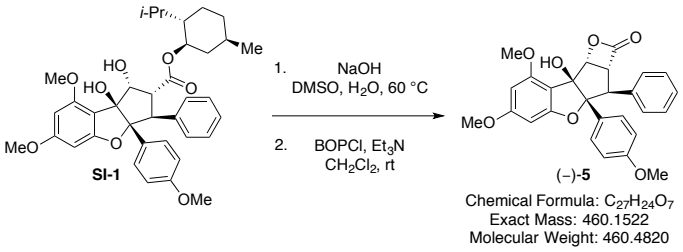
[S1] Synthesis of methyl rocaglate (**2**): Roche, S. P.; Cencic, R.; Pelletier J.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2010**, *49*, 6533−6538.

extracts were then washed with a 1:4 mixture of brine/water (3 X 5 mL), washed with brine, and dried over sodium sulfate. The extracts were then filtered and concentrated *in vacuo* to afford a yellow foam. The crude solid was then purified by column chromatography (3:7 EtOAc/hexanes) to afford a white solid (9 mg, 0.022 mmol, 90%). R_f = 0.16 (25:75 EtOAc/hexanes); **m.p.** 130−133 ºC; **IR** νmax (film): 3463, 2956, 1614, 1600, 1514, 1499, 1453, 1247, 1219, 1201, 1147, 1111, 1031, 814 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.8 Hz, 2H), 7.12−7.01 (ovrlp m, 5H), 6.60 (d, *J* = 8.8 Hz, 2H), 6.55 (dd, *J* = 6.2, 2.6 Hz, 1H), 6.30 (dd, *J* = 6.2, 2.0 Hz, 1H), 6.28 (d, *J* = 2.0 Hz, 1H), 6.09 (d, *J* = 2.0 Hz, 1H), 4.37 (dd, *J* = 2.6, 2.0 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.67 (s, 3H), 1.90 (s, 1H); **^{13}C NMR** (125 MHz, CD_3Cl) δ 163.5, 160.3, 158.6, 157.3, 139.2, 135.5 133.8, 128.6 (2C), 128.1 (2C), 127.9 (2C), 127.6, 126.5, 112.6 (2C), 109.7, 106.8, 92.5, 92.1, 89.1, 62.0, 55.8, 55.7, 55.1; **HR-MS**: *m/z* Calcd for $[C_{26}H_{24}O_5+Na]^+$ 439.1521, found 439.1516 (-1.1 ppm).

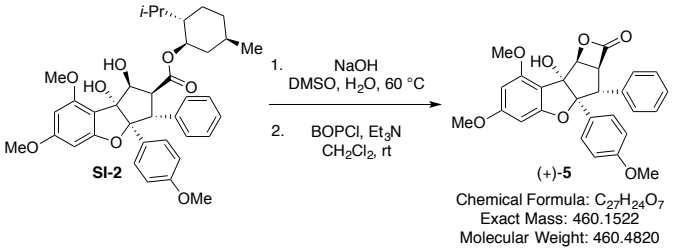


(±)-(2a*R*,3*S*,3a*S*,8b*R*,8c*R*)-8b-Hydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-3-phenyl-3,3a,8b,8c-tetrahydrooxeto[2',3':3,4]cyclopenta[1,2-*b*]benzofuran-2(2a*H*)-one 10: Procedure (A): To an NMR tube was added a solution of **5** (10 mg, 0.022 mmol, 1 equiv) in $CDCl_3$ (1.0 mL). The solution was then degassed with argon for 2 min and sealed. The sample was then irradiated using the Hanovia lamp set up (*vide supra*) at rt for 1 h and the reaction was monitored using ^{1}H NMR. Please note that an NMR tube was used not only for reaction monitoring, but also for a higher conversion due to the better surface area/volume ratio than that of a test tube. The reaction mixture was concentrated and purified *via* preparative TLC (3:7 EtOAc/hexanes, two migrations) to afford β-lactone **10** as a white solid (4 mg, 0.0087 mmol, 40%). β-Lactone **5** was recovered (2 mg, 0.0043 mmol, 20%). Procedure (B):To a test tube was added β-lactone **5** (11 mg, 0.024 mmol), benzophenone (4 mg, 0.024 mmol, 1 equiv) and $CDCl_3$ (1.0 mL). After degassing for 2 min with N_2, the solution was then irradiated in the Rayonet photoreactor for 2.5 h (cooling fan was turned on). The crude mixture was concentrated and purified by preparative TLC (3:7 EtOAc/hexanes, two migrations) to afford β-lactone **10** as a white solid (9 mg, 0.020 mmol, 81%). Compound **10** was crystallized by vapor diffusion using benzene/hexanes. R_f = 0.52 (1:1 EtOAc/hexanes); **m.p.** 125 ºC; **IR** νmax (film): 3466, 2939, 2839, 1827, 1597, 1514, 1201, 1150 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.8 Hz, 2H), 7.12 (br t, *J* = 7.0 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.73 (br dd, *J* = 7.0, 7.0 Hz, 2H), 6.03 (d, *J* = 2.0 Hz, 1H), 5.72 (d, *J* = 4.6 Hz, 1H), 5.40 (d, *J* = 2.0 Hz, 1H), 4.49 (br d, *J* = 2.0 Hz, 1H), 4.34 (dd, *J* = 4.6, 2.0 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.61 (s, 3H), 2.19 (s, 1H); **^{13}C NMR** (100 MHz, CD_3Cl) δ 169.8, 164.7, 162.0, 159.9, 157.9, 137.9,

129.3, 128.6 (2C), 128.3 (2C), 127.7 (2C), 127.0, 114.0 (2C), 104.7, 102.1, 92.7, 88.2, 88.0 (2C), 77.5, 59.3, 55.7, 55.4, 53.2; **HR-MS**: *m/z* Calcd for $[C_{27}H_{24}O_7\text{-}H_2O]^+$ 443.1495, found 443.1490 (-1.1 ppm).



(−)-(2a*R*,3*S*,3a*R*,8b*S*,8c*R*)-8b-Hydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-3-phenyl-3,3a,8b,8c-tetrahydrooxeto[2',3':3,4]cyclopenta[1,2-*b*]benzofuran-2(2a*H*)-one 5: Menthyl ester **SI-1** was prepared from (±)-methyl rocaglate (**2**) using previously reported methods.[S2] A round bottom flask was charged with menthyl ester **SI-1** (12.0 mg, 0.0194 mmol, 1.0 equiv), DMSO (0.7 mL), and a stir bar under argon. A 2.8 N aqueous solution of NaOH (60 µL, 0.168 mmol, 8.7 equiv) was then added at rt. The resulting mixture was heated at 60 °C for 3 h. The reaction was cooled to room temperature, acidified to pH ~ 1 using 1N HCl, and extracted with ethyl ether (3 x 10 mL). The combined organic extracts were washed with 1N HCl (4 x 5 mL). The organic phase was dried with sodium sulfate and concentrated. (−)-Rocagloic acid (not shown) was purified by column chromatography ($MeOH/CH_2Cl_2$ 2.5:97.5, then flushed with EtOAc/MeOH 9:1) to provide a white solid (5.0 mg, 0.0104 mmol, 54%). (−)-β-Lactone **5** was prepared from (−)-rocagloic acid using the same procedure to prepare (±)-**5** from (±)-rocagloic acid. Enantiopurity was determined using analytical chiral HPLC (> 97% ee). $[\alpha]_D^{26} = -218.2°$ (*c* = 0.1, $CHCl_3$); other spectroscopic data for compound (−)-**5** were found to be identical to its racemate (see above).

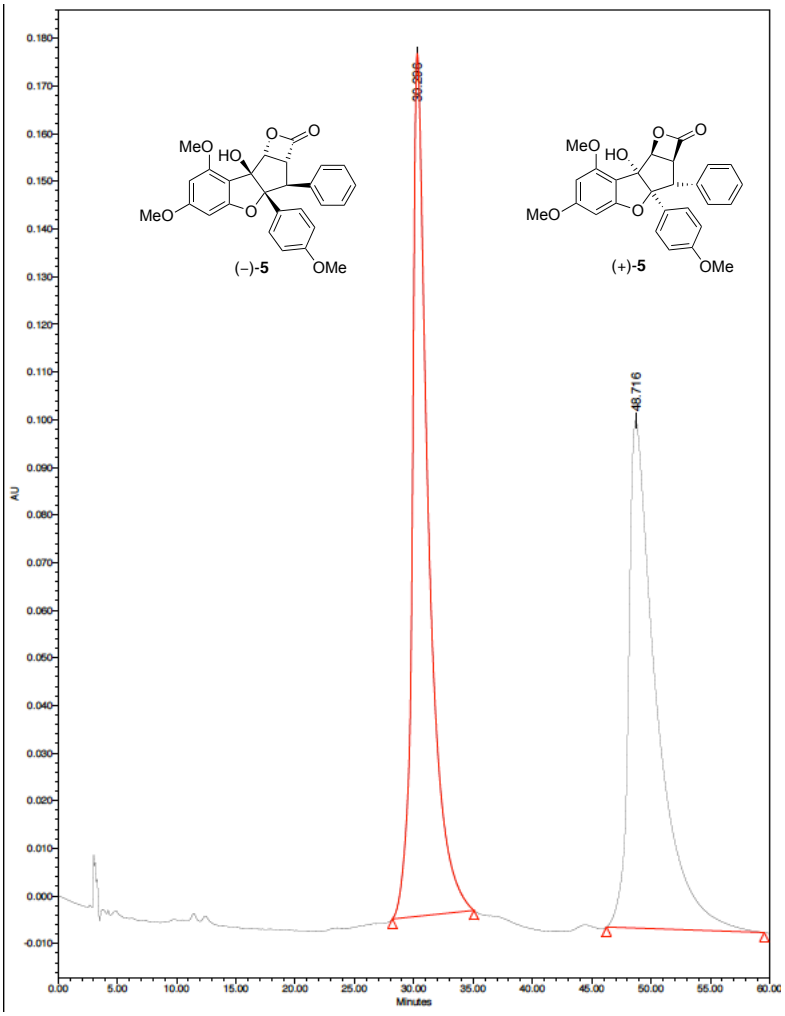


(+)-(2a*R*,3*S*,3a*R*,8b*S*,8c*R*)-8b-Hydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-3-phenyl-3,3a,8b,8c-tetrahydrooxeto[2',3':3,4]cyclopenta[1,2-*b*]benzofuran-2(2a*H*)-one 5: Menthyl ester **SI-2** was prepared from (±)-methyl rocaglate (**2**) using previously reported methods.[S2] A round bottom flask was charged with menthyl ester **SI-2** (33.0 mg, 0.0535 mmol, 1.0 equiv), DMSO (2.0 mL), and a stir bar under argon. A 2.8 N aqueous solution of NaOH (152 µL, 0.426 mmol, 8.0 equiv) was then added at rt. The resulting mixture was heated at 60 °C for 3 h. The reaction was cooled to room temperature, acidified to pH ~ 1 using 1N HCl, and extracted with ethyl ether (3 x 10 mL). The combined organic extracts were washed with 1N HCl (4 x 5 mL). The organic phase was dried with sodium sulfate and concentrated. (+)-Rocagloic acid (not shown) was purified by column chromatography ($MeOH/CH_2Cl_2$ 2.5:97.5, then flushed with EtOAc/MeOH 9:1) to provide a white solid (14.0 mg, 0.0293 mmol, 55%). (+)-β-Lactone **5** was prepared from (+)-rocagloic acid

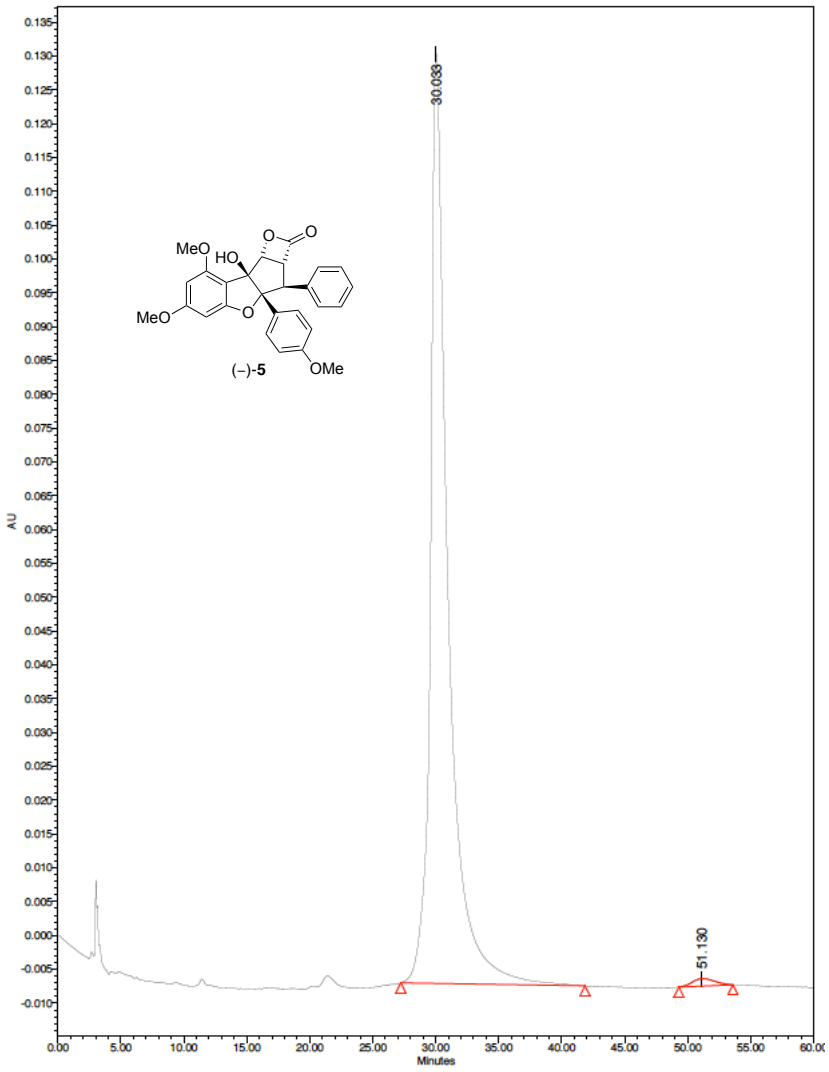
[S2] Rodrigo, C. M.; Cencic, R.; Roche, S. P.; Pelletier, J.; Porco Jr., J. A. *J. Med. Chem.* **2011**, *55*, 558−562.

using the same procedure to prepare (±)-**5** from (±)-rocagloic acid. Enantiopurity was determined using analytical chiral HPLC (>97% ee). $[\alpha]_D^{26}$ = +218.2° (*c* = 0.1, $CHCl_3$); other spectroscopic data of compound (+)-**5** are identical to its racemate (see above).

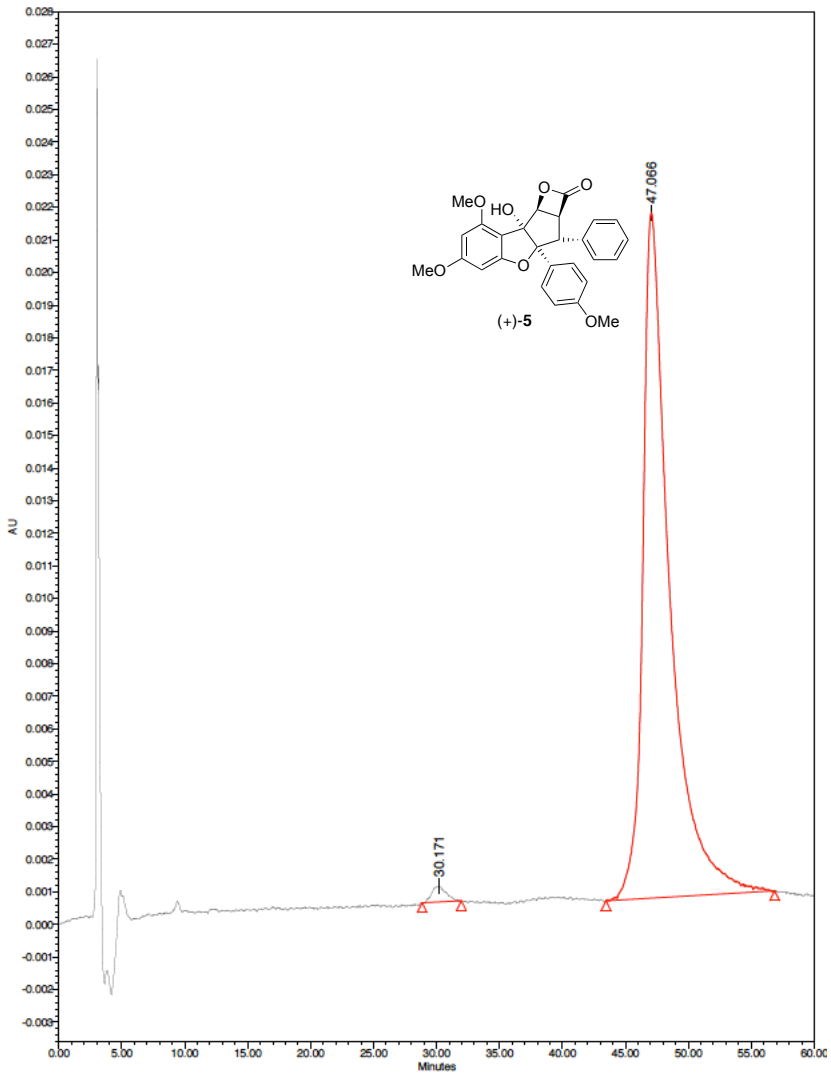
Analysis of (−)-5 and (+)-5: Chiral HPLC analysis of (±)-**5**: Regis Pirkle covalent (*R*,*R*) WHELK-O 1 column was used, with an isocratic mobile phase of isopropanol/hexanes (20:80) with a flow rate of 1.0 mL/min for 60 min.



	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		30.296	17351230	49.95	181096	bb			Unknown	
2		48.716	17383307	50.05	106587	bb			Unknown	



	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		30.033	13188846	98.77	137335	Bb			Unknown	
2		51.130	164004	1.23	1191	bb			Unknown	



	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		30.171	38377	1.21	476	bb			Unknown	
2		47.066	3134829	98.79	21024	bb			Unknown	

B. X-ray Crystallographic Data

X-ray crystallographic data for (±)-5

Crystals of compound (±)-**5** suitable for X-ray analysis were obtained by slow evaporation from toluene. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC # 943262). Copies of the data can be obtained free of charge through application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)- 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

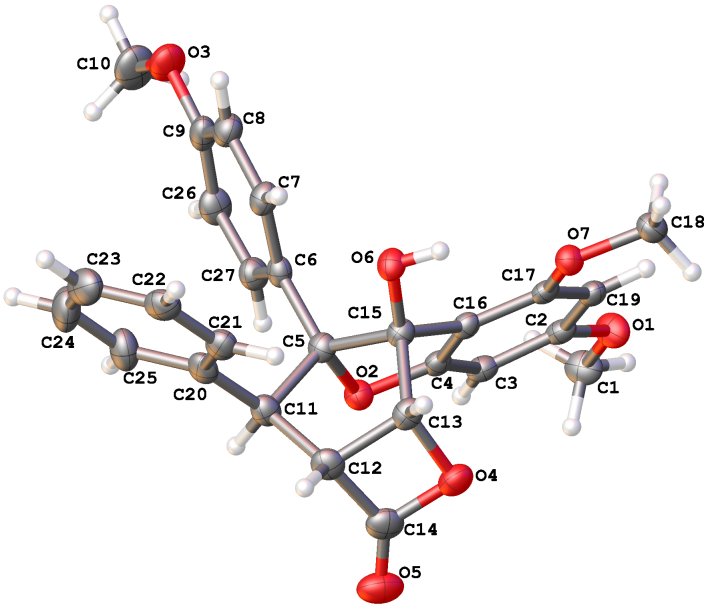


Table SI-1. Crystal data and structure refinement for β-lactone **5**.

Identification code **5**

Crystal data

$C_{27}H_{24}O_7$	V = 2225.7 (2) Å^3
M_r = 460.46	Z = 4
Monoclinic, $P2_1/n$	Cu $K\alpha$ radiation, λ = 1.54178 Å
a = 13.0969 (8) Å	μ = 0.82 mm^{-1}
b = 10.2768 (7) Å	T = 100 K
c = 17.7108 (11) Å	0.3 × 0.1 × 0.03 mm
β = 110.980 (3)°	

Data collection

Bruker Proteum-R diffractometer	3761 independent reflections

Absorption correction: multi-scan *SADABS* (Sheldrick, 1997)	3242 reflections with $I > 2\sigma(I)$
$T_{min} = 0.691$, $T_{max} = 0.753$	$R_{int} = 0.052$
23432 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.048$	0 restraints
$wR(F^2) = 0.123$	H atoms treated by a mixture of independent and constrained refinement
$S = 1.14$	$\Delta\rangle_{max} = 0.31$ e Å^{-3}
3761 reflections	$\Delta\rangle_{min} = -0.22$ e Å^{-3}
313 parameters	

Data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT* (Bruker, 2006); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: OLEX2 (Dolmanov, *et al.* 2009); software used to prepare material for publication: PublCIF v.1.9.5_c (IUCr).

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\text{sigma}(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

CheckCIF Alert and Discussion:

PLAT029_ALERT_3_B _diffrn_measured_fraction_theta_full Low ·····. 0.954 Discussion: The diffraction pattern included many reflections with somewhat distorted shapes, resulting in a larger-than normal number of data being rejected during scaling. Though the missing data caused the overall measured fraction to be somewhat low, the structural model is unambiguous and meets the purposes of this crystallographic study.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}	
O1	0.43058 (12)	0.84898 (15)	0.96350 (10)	0.0314 (4)	

O2	0.14243 (11)	0.52518 (14)	0.87848 (8)	0.0238 (3)	
O3	0.23477 (14)	0.26063 (19)	1.21647 (9)	0.0406 (4)	
O4	0.17904 (13)	0.48504 (16)	0.72192 (9)	0.0325 (4)	
O5	0.00529 (15)	0.56643 (19)	0.67774 (10)	0.0435 (5)	
O6	0.30868 (13)	0.24304 (14)	0.88130 (9)	0.0252 (3)	
H6	0.370 (2)	0.248 (3)	0.8742 (16)	0.038*	
O7	0.48210 (11)	0.42245 (14)	0.87630 (8)	0.0237 (3)	
C1	0.36111 (19)	0.9449 (2)	0.97883 (14)	0.0330 (5)	
H1A	0.2993	0.9627	0.9288	0.050*	
H1B	0.4027	1.0251	0.9981	0.050*	
H1C	0.3338	0.9124	1.0201	0.050*	
C2	0.38618 (17)	0.7300 (2)	0.93617 (12)	0.0238 (5)	
C3	0.27690 (17)	0.6999 (2)	0.92154 (12)	0.0233 (5)	
H3	0.2271	0.7612	0.9291	0.028*	
C4	0.24630 (16)	0.5742 (2)	0.89514 (11)	0.0213 (4)	
C5	0.15559 (17)	0.3824 (2)	0.88577 (12)	0.0229 (5)	
C6	0.17561 (16)	0.3474 (2)	0.97355 (12)	0.0225 (5)	
C7	0.22874 (18)	0.2338 (2)	1.01083 (13)	0.0267 (5)	
H7	0.2518	0.1726	0.9801	0.032*	
C8	0.24849 (18)	0.2087 (2)	1.09164 (14)	0.0308 (5)	
H8	0.2873	0.1325	1.1162	0.037*	
C9	0.21173 (18)	0.2947 (2)	1.13715 (13)	0.0310 (5)	
C10	0.1889 (2)	0.3419 (3)	1.26197 (16)	0.0514 (8)	
H10A	0.2180	0.4303	1.2647	0.077*	
H10B	0.2081	0.3070	1.3168	0.077*	
H10C	0.1091	0.3439	1.2355	0.077*	
C11	0.05132 (17)	0.3250 (2)	0.82092 (12)	0.0263 (5)	
H11	-0.0136	0.3773	0.8197	0.032*	
C12	0.07092 (18)	0.3452 (2)	0.74117 (13)	0.0282 (5)	
H12	0.0336	0.2794	0.6987	0.034*	
C13	0.19450 (18)	0.3547 (2)	0.76042 (13)	0.0261 (5)	
H13	0.2245	0.2874	0.7332	0.031*	
C14	0.06962 (19)	0.4825 (3)	0.70820 (13)	0.0327 (5)	
C15	0.25227 (16)	0.3605 (2)	0.85373 (12)	0.0219 (4)	
C16	0.31497 (16)	0.4834 (2)	0.88265 (11)	0.0207 (4)	
C17	0.42213 (16)	0.5170 (2)	0.89473 (11)	0.0212 (4)	
C18	0.59190 (17)	0.4541 (2)	0.88465 (13)	0.0286 (5)	
H18A	0.5913	0.5261	0.8482	0.043*	
H18B	0.6267	0.3779	0.8708	0.043*	

H18C	0.6329	0.4799	0.9406	0.043*	
C19	0.45886 (17)	0.6408 (2)	0.92346 (12)	0.0228 (5)	
H19	0.5329	0.6645	0.9344	0.027*	
C20	0.03269 (17)	0.1840 (2)	0.83627 (13)	0.0279 (5)	
C21	0.08037 (18)	0.0824 (2)	0.80873 (13)	0.0288 (5)	
H21	0.1255	0.1012	0.7784	0.035*	
C22	0.06290 (19)	-0.0460 (2)	0.82499 (14)	0.0340 (6)	
H22	0.0952	-0.1143	0.8051	0.041*	
C23	-0.0011 (2)	-0.0749 (3)	0.86973 (15)	0.0422 (6)	
H23	-0.0126	-0.1628	0.8811	0.051*	
C24	-0.0484 (2)	0.0249 (3)	0.89801 (17)	0.0469 (7)	
H24	-0.0923	0.0055	0.9291	0.056*	
C25	-0.03207 (19)	0.1530 (3)	0.88127 (15)	0.0379 (6)	
H25	-0.0655	0.2208	0.9007	0.046*	
C26	0.15567 (19)	0.4055 (3)	1.10066 (14)	0.0328 (5)	
H26	0.1287	0.4639	1.1307	0.039*	
C27	0.13885 (17)	0.4315 (2)	1.01994 (13)	0.0281 (5)	
H27	0.1013	0.5086	0.9959	0.034*	

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0327 (8)	0.0185 (8)	0.0394 (9)	-0.0036 (6)	0.0084 (7)	-0.0046 (7)
O2	0.0245 (7)	0.0212 (8)	0.0260 (7)	-0.0005 (6)	0.0094 (6)	-0.0022 (6)
O3	0.0452 (10)	0.0550 (12)	0.0237 (8)	-0.0082 (9)	0.0148 (7)	-0.0001 (8)
O4	0.0401 (9)	0.0329 (10)	0.0243 (8)	-0.0022 (7)	0.0111 (7)	0.0031 (7)
O5	0.0505 (11)	0.0479 (12)	0.0278 (9)	0.0131 (9)	0.0088 (8)	0.0041 (8)
O6	0.0279 (8)	0.0191 (8)	0.0313 (8)	-0.0004 (6)	0.0139 (6)	-0.0009 (6)
O7	0.0243 (7)	0.0229 (8)	0.0251 (7)	-0.0002 (6)	0.0105 (6)	-0.0016 (6)
C1	0.0378 (13)	0.0205 (13)	0.0364 (13)	-0.0009 (10)	0.0080 (10)	-0.0057 (10)
C2	0.0319 (11)	0.0191 (12)	0.0167 (10)	-0.0029 (9)	0.0042 (8)	0.0019 (8)
C3	0.0291 (11)	0.0201 (11)	0.0198 (10)	0.0029 (9)	0.0078 (8)	0.0014 (8)
C4	0.0251 (10)	0.0231 (12)	0.0153 (9)	-0.0018 (8)	0.0069 (8)	0.0015 (8)
C5	0.0252 (11)	0.0192 (11)	0.0242 (10)	-0.0026 (8)	0.0089 (9)	-0.0025 (8)
C6	0.0218 (10)	0.0232 (12)	0.0236 (10)	-0.0062 (8)	0.0094 (8)	-0.0050 (9)
C7	0.0317 (11)	0.0239 (12)	0.0275 (11)	-0.0042 (9)	0.0143 (9)	-0.0020 (9)
C8	0.0326 (12)	0.0298 (13)	0.0306 (12)	-0.0053 (10)	0.0123 (10)	0.0017 (10)
C9	0.0290 (11)	0.0412 (15)	0.0240 (11)	-0.0125 (10)	0.0109 (9)	-0.0028 (10)
C10	0.0589 (17)	0.074 (2)	0.0285 (13)	-0.0092 (15)	0.0241 (13)	-0.0062 (13)

C11	0.0246 (11)	0.0308 (13)	0.0232 (11)	-0.0025 (9)	0.0081 (9)	-0.0052 (9)
C12	0.0306 (11)	0.0310 (13)	0.0205 (10)	-0.0030 (10)	0.0061 (9)	-0.0066 (9)
C13	0.0341 (12)	0.0225 (12)	0.0232 (11)	-0.0031 (9)	0.0120 (9)	-0.0030 (9)
C14	0.0378 (13)	0.0392 (15)	0.0192 (10)	0.0020 (11)	0.0080 (9)	-0.0025 (10)
C15	0.0252 (10)	0.0194 (11)	0.0218 (10)	-0.0011 (8)	0.0093 (8)	-0.0015 (8)
C16	0.0257 (10)	0.0192 (11)	0.0172 (9)	-0.0021 (8)	0.0075 (8)	-0.0002 (8)
C17	0.0261 (10)	0.0220 (11)	0.0151 (9)	0.0002 (8)	0.0068 (8)	0.0038 (8)
C18	0.0240 (11)	0.0330 (14)	0.0276 (11)	0.0002 (9)	0.0077 (9)	0.0008 (10)
C19	0.0241 (10)	0.0238 (12)	0.0184 (10)	-0.0029 (9)	0.0050 (8)	0.0032 (8)
C20	0.0231 (10)	0.0329 (13)	0.0230 (10)	-0.0085 (9)	0.0026 (8)	-0.0061 (9)
C21	0.0281 (11)	0.0314 (13)	0.0229 (11)	-0.0065 (10)	0.0043 (9)	-0.0030 (9)
C22	0.0329 (12)	0.0337 (14)	0.0274 (11)	-0.0050 (10)	0.0011 (10)	-0.0029 (10)
C23	0.0407 (14)	0.0363 (15)	0.0412 (14)	-0.0155 (12)	0.0047 (11)	0.0005 (12)
C24	0.0423 (15)	0.0547 (19)	0.0490 (16)	-0.0194 (13)	0.0228 (13)	-0.0019 (13)
C25	0.0329 (12)	0.0427 (16)	0.0418 (14)	-0.0130 (11)	0.0179 (11)	-0.0092 (11)
C26	0.0335 (12)	0.0402 (15)	0.0290 (12)	-0.0037 (10)	0.0165 (10)	-0.0089 (10)
C27	0.0265 (11)	0.0316 (13)	0.0283 (11)	-0.0016 (9)	0.0122 (9)	-0.0025 (9)

Geometric parameters (Å, º)

O1—C2	1.366 (3)	C10—H10B	0.9800
O1—C1	1.431 (3)	C10—H10C	0.9800
O2—C4	1.380 (2)	C11—C20	1.510 (3)
O2—C5	1.478 (3)	C11—C12	1.537 (3)
O3—C9	1.372 (3)	C11—H11	1.0000
O3—C10	1.433 (3)	C12—C14	1.524 (3)
O4—C14	1.365 (3)	C12—C13	1.533 (3)
O4—C13	1.484 (3)	C12—H12	1.0000
O5—C14	1.191 (3)	C13—C15	1.553 (3)
O6—C15	1.408 (3)	C13—H13	1.0000
O6—H6	0.86 (3)	C15—C16	1.494 (3)
O7—C17	1.361 (2)	C16—C17	1.385 (3)
O7—C18	1.429 (3)	C17—C19	1.391 (3)
C1—H1A	0.9800	C18—H18A	0.9800
C1—H1B	0.9800	C18—H18B	0.9800
C1—H1C	0.9800	C18—H18C	0.9800
C2—C3	1.395 (3)	C19—H19	0.9500
C2—C19	1.397 (3)	C20—C21	1.391 (3)
C3—C4	1.383 (3)	C20—C25	1.393 (3)

C3—H3	0.9500	C21—C22	1.386 (3)
C4—C16	1.368 (3)	C21—H21	0.9500
C5—C6	1.524 (3)	C22—C23	1.376 (4)
C5—C11	1.552 (3)	C22—H22	0.9500
C5—C15	1.578 (3)	C23—C24	1.382 (4)
C6—C27	1.392 (3)	C23—H23	0.9500
C6—C7	1.397 (3)	C24—C25	1.383 (4)
C7—C8	1.385 (3)	C24—H24	0.9500
C7—H7	0.9500	C25—H25	0.9500
C8—C9	1.393 (3)	C26—C27	1.392 (3)
C8—H8	0.9500	C26—H26	0.9500
C9—C26	1.384 (4)	C27—H27	0.9500
C10—H10A	0.9800		
C2—O1—C1	117.67 (17)	C11—C12—H12	113.7
C4—O2—C5	105.59 (15)	O4—C13—C12	89.74 (16)
C9—O3—C10	116.4 (2)	O4—C13—C15	112.87 (17)
C14—O4—C13	91.51 (16)	C12—C13—C15	108.21 (16)
C15—O6—H6	107.7 (18)	O4—C13—H13	114.5
C17—O7—C18	117.30 (17)	C12—C13—H13	114.5
O1—C1—H1A	109.5	C15—C13—H13	114.5
O1—C1—H1B	109.5	O5—C14—O4	126.4 (2)
H1A—C1—H1B	109.5	O5—C14—C12	138.8 (2)
O1—C1—H1C	109.5	O4—C14—C12	94.73 (18)
H1A—C1—H1C	109.5	O6—C15—C16	116.77 (17)
H1B—C1—H1C	109.5	O6—C15—C13	109.35 (17)
O1—C2—C3	122.89 (19)	C16—C15—C13	113.32 (17)
O1—C2—C19	114.61 (19)	O6—C15—C5	112.74 (17)
C3—C2—C19	122.5 (2)	C16—C15—C5	99.75 (16)
C4—C3—C2	115.09 (19)	C13—C15—C5	103.90 (16)
C4—C3—H3	122.5	C4—C16—C17	119.58 (19)
C2—C3—H3	122.5	C4—C16—C15	108.65 (18)
C16—C4—O2	111.81 (18)	C17—C16—C15	131.73 (19)
C16—C4—C3	124.32 (19)	O7—C17—C16	115.14 (18)
O2—C4—C3	123.87 (18)	O7—C17—C19	125.97 (18)
O2—C5—C6	107.19 (16)	C16—C17—C19	118.89 (19)
O2—C5—C11	105.58 (17)	O7—C18—H18A	109.5
C6—C5—C11	116.72 (17)	O7—C18—H18B	109.5
O2—C5—C15	101.17 (15)	H18A—C18—H18B	109.5

C6—C5—C15	117.77 (17)	O7—C18—H18C	109.5
C11—C5—C15	106.64 (16)	H18A—C18—H18C	109.5
C27—C6—C7	117.3 (2)	H18B—C18—H18C	109.5
C27—C6—C5	119.09 (19)	C17—C19—C2	119.54 (19)
C7—C6—C5	123.62 (19)	C17—C19—H19	120.2
C8—C7—C6	121.4 (2)	C2—C19—H19	120.2
C8—C7—H7	119.3	C21—C20—C25	118.1 (2)
C6—C7—H7	119.3	C21—C20—C11	122.4 (2)
C7—C8—C9	120.3 (2)	C25—C20—C11	119.5 (2)
C7—C8—H8	119.9	C22—C21—C20	120.9 (2)
C9—C8—H8	119.9	C22—C21—H21	119.6
O3—C9—C26	125.0 (2)	C20—C21—H21	119.6
O3—C9—C8	115.8 (2)	C23—C22—C21	120.3 (2)
C26—C9—C8	119.2 (2)	C23—C22—H22	119.8
O3—C10—H10A	109.5	C21—C22—H22	119.8
O3—C10—H10B	109.5	C22—C23—C24	119.5 (3)
H10A—C10—H10B	109.5	C22—C23—H23	120.2
O3—C10—H10C	109.5	C24—C23—H23	120.2
H10A—C10—H10C	109.5	C23—C24—C25	120.3 (2)
H10B—C10—H10C	109.5	C23—C24—H24	119.8
C20—C11—C12	112.71 (18)	C25—C24—H24	119.8
C20—C11—C5	112.80 (18)	C24—C25—C20	120.8 (2)
C12—C11—C5	103.67 (17)	C24—C25—H25	119.6
C20—C11—H11	109.2	C20—C25—H25	119.6
C12—C11—H11	109.2	C9—C26—C27	120.0 (2)
C5—C11—H11	109.2	C9—C26—H26	120.0
C14—C12—C13	83.84 (17)	C27—C26—H26	120.0
C14—C12—C11	119.63 (19)	C6—C27—C26	121.8 (2)
C13—C12—C11	108.33 (17)	C6—C27—H27	119.1
C14—C12—H12	113.7	C26—C27—H27	119.1
C13—C12—H12	113.7		
C1—O1—C2—C3	1.1 (3)	C12—C13—C15—C16	-118.3 (2)
C1—O1—C2—C19	-179.25 (18)	O4—C13—C15—C5	86.7 (2)
O1—C2—C3—C4	-179.11 (18)	C12—C13—C15—C5	-11.0 (2)
C19—C2—C3—C4	1.3 (3)	O2—C5—C15—O6	157.65 (15)
C5—O2—C4—C16	22.6 (2)	C6—C5—C15—O6	41.3 (2)
C5—O2—C4—C3	-157.22 (19)	C11—C5—C15—O6	-92.2 (2)

C2—C3—C4—C16	-0.7 (3)	O2—C5—C15—C16	33.08 (18)
C2—C3—C4—O2	179.09 (17)	C6—C5—C15—C16	-83.3 (2)
C4—O2—C5—C6	89.51 (17)	C11—C5—C15—C16	143.25 (17)
C4—O2—C5—C11	-145.39 (15)	O2—C5—C15—C13	-84.07 (17)
C4—O2—C5—C15	-34.41 (18)	C6—C5—C15—C13	159.55 (18)
O2—C5—C6—C27	24.0 (2)	C11—C5—C15—C13	26.1 (2)
C11—C5—C6—C27	-94.1 (2)	O2—C4—C16—C17	178.56 (17)
C15—C5—C6—C27	137.1 (2)	C3—C4—C16—C17	-1.6 (3)
O2—C5—C6—C7	-156.51 (18)	O2—C4—C16—C15	0.7 (2)
C11—C5—C6—C7	85.4 (2)	C3—C4—C16—C15	-179.53 (18)
C15—C5—C6—C7	-43.4 (3)	O6—C15—C16—C4	-143.30 (17)
C27—C6—C7—C8	-2.9 (3)	C13—C15—C16—C4	88.3 (2)
C5—C6—C7—C8	177.6 (2)	C5—C15—C16—C4	-21.6 (2)
C6—C7—C8—C9	2.5 (3)	O6—C15—C16—C17	39.2 (3)
C10—O3—C9—C26	5.3 (3)	C13—C15—C16—C17	-89.3 (3)
C10—O3—C9—C8	-174.5 (2)	C5—C15—C16—C17	160.9 (2)
C7—C8—C9—O3	179.6 (2)	C18—O7—C17—C16	177.57 (17)
C7—C8—C9—C26	-0.2 (3)	C18—O7—C17—C19	-2.1 (3)
O2—C5—C11—C20	-161.72 (16)	C4—C16—C17—O7	-176.40 (17)
C6—C5—C11—C20	-42.8 (3)	C15—C16—C17—O7	0.9 (3)
C15—C5—C11—C20	91.2 (2)	C4—C16—C17—C19	3.3 (3)
O2—C5—C11—C12	76.06 (19)	C15—C16—C17—C19	-179.37 (19)
C6—C5—C11—C12	-165.00 (18)	O7—C17—C19—C2	176.99 (18)
C15—C5—C11—C12	-31.0 (2)	C16—C17—C19—C2	-2.7 (3)
C20—C11—C12—C14	168.44 (19)	O1—C2—C19—C17	-179.25 (17)
C5—C11—C12—C14	-69.3 (2)	C3—C2—C19—C17	0.4 (3)
C20—C11—C12—C13	-98.2 (2)	C12—C11—C20—C21	30.6 (3)
C5—C11—C12—C13	24.1 (2)	C5—C11—C20—C21	-86.4 (2)
C14—O4—C13—C12	3.29 (16)	C12—C11—C20—C25	-151.1 (2)
C14—O4—C13—C15	-106.42 (18)	C5—C11—C20—C25	91.9 (2)
C14—C12—C13—O4	-2.96 (14)	C25—C20—C21—C22	0.6 (3)
C11—C12—C13—O4	-122.18 (18)	C11—C20—C21—C22	179.0 (2)
C14—C12—C13—C15	111.09 (18)	C20—C21—C22—C23	-0.8 (3)
C11—C12—C13—	-8.1 (2)	C21—C22—C23—	0.4 (4)

C15		C24	
C13—O4—C14—O5	178.6 (2)	C22—C23—C24—C25	0.3 (4)
C13—O4—C14—C12	-3.32 (16)	C23—C24—C25—C20	-0.5 (4)
C13—C12—C14—O5	-179.1 (3)	C21—C20—C25—C24	0.0 (3)
C11—C12—C14—O5	-71.5 (4)	C11—C20—C25—C24	-178.4 (2)
C13—C12—C14—O4	3.23 (15)	O3—C9—C26—C27	178.7 (2)
C11—C12—C14—O4	110.8 (2)	C8—C9—C26—C27	-1.5 (3)
O4—C13—C15—O6	-152.74 (16)	C7—C6—C27—C26	1.1 (3)
C12—C13—C15—O6	109.59 (19)	C5—C6—C27—C26	-179.3 (2)
O4—C13—C15—C16	-20.6 (2)	C9—C26—C27—C6	1.0 (3)

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X-ray crystallographic data for (±)-10

Crystals of compound (±)-**10** suitable for X-ray analysis were obtained by vapor diffusion from benzene/hexanes. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC # 943263). Copies of the data can be obtained free of charge through application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)- 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

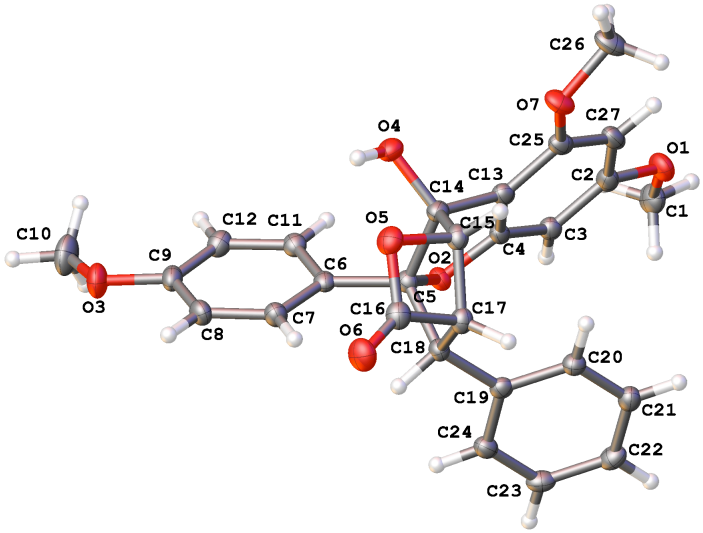

Table SI-2. Crystal data and structure refinement for β-lactone **10**.

Identification code **10**

Crystal data

$C_{27}H_{24}O_7$	$F(000) = 968$
$M_r = 460.46$	$D_x = 1.378$ Mg m^{-3}
Monoclinic, $P2_1/c$	Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å
Hall symbol: -P 2ybc	Cell parameters from 9922 reflections
$a = 9.8122$ (2) Å	$\theta = 4.5–66.5°$
$b = 22.2466$ (5) Å	$\mu = 0.82$ mm^{-1}
$c = 10.2293$ (2) Å	$T = 100$ K
$\beta = 96.410$ (1)°	Fragment, colorless
$V = 2218.98$ (8) Å^3	0.13 × 0.12 × 0.05 mm
$Z = 4$	

Data collection

Bruker Proteum-R diffractometer	3856 independent reflections
Radiation source: rotating anode	3657 reflections with $I > 2\sigma(I)$
multilayer	$R_{int} = 0.043$
ω & ϕ scans	$\theta_{max} = 66.5°$, $\theta_{min} = 4.5°$
Absorption correction: multi-scan *SADABS* (Sheldrick, 1997)	$h = -11 \rightarrow 11$
$T_{min} = 0.717$, $T_{max} = 0.753$	$k = -26 \rightarrow 26$
82996 measured reflections	$l = -12 \rightarrow 12$

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.035$	Hydrogen site location: inferred from neighbouring sites
$wR(F^2) = 0.090$	H atoms treated by a mixture of independent and constrained refinement
$S = 1.05$	$w = 1/[\sigma^2(F_o^2) + (0.0397P)^2 + 1.2596P]$ where $P = (F_o^2 + 2F_c^2)/3$
3856 reflections	$(\Delta/\sigma)_{max} = 0.001$
313 parameters	$\Delta\rangle_{max} = 0.31$ e Å^{-3}
0 restraints	$\Delta\rangle_{min} = -0.19$ e Å^{-3}

Data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT* (Bruker, 2006); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: OLEX2 (Dolmanov, *et al.* 2009); software used to prepare material for publication: *publCIF* v.1.9.5_c (IUCr).

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\text{sigma}(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	-0.27620 (10)	0.76182 (5)	0.57089 (11)	0.0291 (2)
O2	0.11927 (9)	0.63543 (4)	0.54357 (9)	0.0185 (2)
O3	0.69823 (11)	0.54323 (5)	0.78244 (11)	0.0337 (3)
O4	0.34782 (10)	0.74124 (4)	0.51269 (10)	0.0239 (2)
H4	0.426 (2)	0.7327 (8)	0.4868 (18)	0.036*
O5	0.42013 (10)	0.69939 (5)	0.27409 (10)	0.0264 (2)
O6	0.46134 (11)	0.61648 (5)	0.15070 (11)	0.0327 (3)
O7	0.11270 (11)	0.82930 (4)	0.37440 (10)	0.0270 (2)
C1	-0.33431 (15)	0.72076 (7)	0.65666 (16)	0.0306 (3)
H1A	-0.3548	0.6826	0.6107	0.046*
H1B	-0.4190	0.7378	0.6834	0.046*
H1C	-0.2689	0.7137	0.7348	0.046*
C2	-0.15005 (14)	0.74767 (6)	0.53580 (14)	0.0228 (3)
C3	-0.08570 (14)	0.69292 (6)	0.56362 (13)	0.0200 (3)
H3	-0.1272	0.6617	0.6088	0.024*
C4	0.04296 (13)	0.68651 (6)	0.52130 (12)	0.0180 (3)
C5	0.23444 (13)	0.63931 (6)	0.46545 (13)	0.0177 (3)
C6	0.35819 (13)	0.61362 (6)	0.54968 (13)	0.0184 (3)
C7	0.46666 (14)	0.58547 (6)	0.49665 (14)	0.0224 (3)
H7	0.4639	0.5815	0.4039	0.027*
C8	0.57839 (15)	0.56323 (6)	0.57700 (15)	0.0252 (3)
H8	0.6518	0.5448	0.5388	0.030*
C9	0.58399 (14)	0.56768 (6)	0.71253 (14)	0.0242 (3)
C10	0.69930 (18)	0.53957 (9)	0.92184 (17)	0.0417 (4)
H10A	0.6901	0.5800	0.9579	0.063*
H10B	0.7859	0.5217	0.9603	0.063*
H10C	0.6226	0.5145	0.9430	0.063*
C11	0.36799 (14)	0.61960 (6)	0.68601 (14)	0.0209 (3)
H11	0.2973	0.6401	0.7242	0.025*
C12	0.47819 (14)	0.59642 (6)	0.76791 (14)	0.0239 (3)
H12	0.4812	0.6002	0.8607	0.029*
C13	0.10776 (14)	0.73034 (6)	0.45574 (13)	0.0196 (3)
C14	0.24702 (14)	0.70884 (6)	0.43075 (13)	0.0198 (3)
C15	0.27253 (14)	0.71124 (6)	0.28775 (14)	0.0219 (3)
H15	0.2329	0.7471	0.2383	0.026*
C16	0.38555 (15)	0.64817 (7)	0.20261 (14)	0.0247 (3)
C17	0.23484 (14)	0.65082 (6)	0.22251 (13)	0.0216 (3)
H17	0.1697	0.6528	0.1401	0.026*

C18	0.19398 (14)	0.60678 (6)	0.32908 (13)	0.0190 (3)
H18	0.2517	0.5698	0.3267	0.023*
C19	0.04449 (14)	0.58796 (6)	0.30718 (12)	0.0187 (3)
C20	-0.05966 (14)	0.62704 (6)	0.25680 (13)	0.0205 (3)
H20	-0.0369	0.6667	0.2322	0.025*
C21	-0.19596 (15)	0.60896 (6)	0.24212 (14)	0.0234 (3)
H21	-0.2656	0.6361	0.2073	0.028*
C22	-0.23058 (15)	0.55124 (6)	0.27841 (14)	0.0241 (3)
H22	-0.3237	0.5387	0.2686	0.029*
C23	-0.12823 (15)	0.51215 (6)	0.32902 (14)	0.0242 (3)
H23	-0.1515	0.4728	0.3551	0.029*
C24	0.00822 (14)	0.53005 (6)	0.34198 (13)	0.0216 (3)
H24	0.0776	0.5025	0.3750	0.026*
C25	0.04133 (15)	0.78576 (6)	0.43163 (13)	0.0216 (3)
C26	0.05541 (18)	0.88866 (6)	0.36907 (16)	0.0331 (4)
H26A	-0.0296	0.8890	0.3089	0.050*
H26B	0.1211	0.9169	0.3375	0.050*
H26C	0.0356	0.9007	0.4572	0.050*
C27	-0.08828 (15)	0.79374 (6)	0.46977 (14)	0.0241 (3)
H27	-0.1356	0.8305	0.4512	0.029*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0233 (5)	0.0274 (5)	0.0374 (6)	0.0083 (4)	0.0062 (4)	-0.0026 (4)
O2	0.0177 (5)	0.0166 (4)	0.0219 (5)	0.0024 (4)	0.0045 (4)	0.0024 (4)
O3	0.0249 (6)	0.0413 (6)	0.0330 (6)	0.0088 (5)	-0.0056 (5)	0.0062 (5)
O4	0.0225 (5)	0.0218 (5)	0.0267 (5)	-0.0044 (4)	0.0002 (4)	-0.0013 (4)
O5	0.0202 (5)	0.0299 (5)	0.0295 (5)	-0.0036 (4)	0.0048 (4)	0.0022 (4)
O6	0.0249 (5)	0.0389 (6)	0.0359 (6)	0.0057 (5)	0.0098 (5)	-0.0003 (5)
O7	0.0366 (6)	0.0157 (5)	0.0293 (5)	0.0022 (4)	0.0067 (4)	0.0042 (4)
C1	0.0201 (7)	0.0346 (8)	0.0379 (8)	0.0035 (6)	0.0062 (6)	-0.0024 (7)
C2	0.0205 (7)	0.0249 (7)	0.0226 (7)	0.0046 (6)	0.0001 (5)	-0.0060 (6)
C3	0.0201 (7)	0.0204 (7)	0.0194 (6)	0.0009 (5)	0.0018 (5)	-0.0011 (5)
C4	0.0202 (7)	0.0160 (6)	0.0168 (6)	0.0028 (5)	-0.0018 (5)	-0.0014 (5)
C5	0.0157 (6)	0.0179 (7)	0.0200 (7)	0.0004 (5)	0.0036 (5)	0.0005 (5)
C6	0.0168 (7)	0.0145 (6)	0.0236 (7)	-0.0017 (5)	0.0008 (5)	0.0017 (5)
C7	0.0220 (7)	0.0221 (7)	0.0228 (7)	0.0028 (5)	0.0010 (6)	-0.0007 (5)
C8	0.0199 (7)	0.0233 (7)	0.0321 (8)	0.0048 (6)	0.0014 (6)	-0.0021 (6)

C9	0.0193 (7)	0.0212 (7)	0.0305 (8)	-0.0002 (5)	-0.0045 (6)	0.0048 (6)
C10	0.0318 (9)	0.0569 (11)	0.0337 (9)	0.0039 (8)	-0.0078 (7)	0.0151 (8)
C11	0.0185 (7)	0.0198 (7)	0.0245 (7)	-0.0015 (5)	0.0031 (5)	0.0013 (5)
C12	0.0219 (7)	0.0268 (7)	0.0225 (7)	-0.0031 (6)	0.0000 (6)	0.0030 (6)
C13	0.0219 (7)	0.0185 (7)	0.0182 (6)	0.0008 (5)	0.0005 (5)	-0.0016 (5)
C14	0.0207 (7)	0.0163 (6)	0.0220 (7)	-0.0011 (5)	0.0000 (5)	0.0013 (5)
C15	0.0173 (7)	0.0229 (7)	0.0256 (7)	-0.0001 (5)	0.0030 (5)	0.0038 (6)
C16	0.0227 (7)	0.0272 (7)	0.0246 (7)	0.0001 (6)	0.0042 (6)	0.0046 (6)
C17	0.0189 (7)	0.0255 (7)	0.0204 (7)	0.0014 (5)	0.0025 (5)	0.0008 (5)
C18	0.0175 (7)	0.0177 (6)	0.0216 (7)	0.0018 (5)	0.0009 (5)	0.0005 (5)
C19	0.0200 (7)	0.0193 (7)	0.0167 (6)	-0.0007 (5)	0.0022 (5)	-0.0027 (5)
C20	0.0211 (7)	0.0184 (6)	0.0219 (7)	-0.0009 (5)	0.0015 (5)	0.0002 (5)
C21	0.0207 (7)	0.0248 (7)	0.0242 (7)	0.0021 (6)	0.0002 (6)	-0.0018 (6)
C22	0.0196 (7)	0.0280 (7)	0.0251 (7)	-0.0055 (6)	0.0043 (6)	-0.0047 (6)
C23	0.0290 (8)	0.0193 (7)	0.0246 (7)	-0.0062 (6)	0.0051 (6)	-0.0023 (5)
C24	0.0243 (7)	0.0182 (7)	0.0220 (7)	0.0015 (5)	0.0014 (6)	-0.0009 (5)
C25	0.0286 (7)	0.0176 (7)	0.0179 (6)	0.0005 (6)	-0.0006 (5)	-0.0003 (5)
C26	0.0489 (10)	0.0173 (7)	0.0335 (8)	0.0054 (7)	0.0064 (7)	0.0040 (6)
C27	0.0296 (8)	0.0185 (7)	0.0231 (7)	0.0072 (6)	-0.0016 (6)	-0.0019 (5)

Geometric parameters (Å, º)

O1—C2	1.3635 (17)	C10—H10B	0.9800
O1—C1	1.4285 (19)	C10—H10C	0.9800
O2—C4	1.3660 (16)	C11—C12	1.391 (2)
O2—C5	1.4576 (15)	C11—H11	0.9500
O3—C9	1.3729 (17)	C12—H12	0.9500
O3—C10	1.427 (2)	C13—C25	1.4037 (19)
O4—C14	1.4197 (16)	C13—C14	1.4963 (19)
O4—H4	0.86 (2)	C14—C15	1.5124 (19)
O5—C16	1.3758 (18)	C15—C17	1.5277 (19)
O5—C15	1.4939 (16)	C15—H15	1.0000
O6—C16	1.1917 (18)	C16—C17	1.5162 (19)
O7—C25	1.3649 (17)	C17—C18	1.5513 (18)
O7—C26	1.4337 (17)	C17—H17	1.0000
C1—H1A	0.9800	C18—C19	1.5178 (18)
C1—H1B	0.9800	C18—H18	1.0000
C1—H1C	0.9800	C19—C24	1.3934 (19)
C2—C3	1.387 (2)	C19—C20	1.3959 (19)

C2—C27	1.402 (2)	C20—C21	1.389 (2)
C3—C4	1.3870 (19)	C20—H20	0.9500
C3—H3	0.9500	C21—C22	1.389 (2)
C4—C13	1.3783 (19)	C21—H21	0.9500
C5—C6	1.5198 (18)	C22—C23	1.385 (2)
C5—C18	1.5822 (18)	C22—H22	0.9500
C5—C14	1.5948 (18)	C23—C24	1.389 (2)
C6—C11	1.394 (2)	C23—H23	0.9500
C6—C7	1.3957 (19)	C24—H24	0.9500
C7—C8	1.386 (2)	C25—C27	1.383 (2)
C7—H7	0.9500	C26—H26A	0.9800
C8—C9	1.385 (2)	C26—H26B	0.9800
C8—H8	0.9500	C26—H26C	0.9800
C9—C12	1.392 (2)	C27—H27	0.9500
C10—H10A	0.9800		
C2—O1—C1	116.77 (11)	C13—C14—C15	114.00 (11)
C4—O2—C5	107.66 (9)	O4—C14—C5	115.29 (11)
C9—O3—C10	117.23 (12)	C13—C14—C5	100.20 (10)
C14—O4—H4	107.1 (12)	C15—C14—C5	105.96 (10)
C16—O5—C15	90.68 (10)	O5—C15—C14	110.55 (11)
C25—O7—C26	116.88 (11)	O5—C15—C17	89.64 (10)
O1—C1—H1A	109.5	C14—C15—C17	109.46 (11)
O1—C1—H1B	109.5	O5—C15—H15	114.8
H1A—C1—H1B	109.5	C14—C15—H15	114.8
O1—C1—H1C	109.5	C17—C15—H15	114.8
H1A—C1—H1C	109.5	O6—C16—O5	126.70 (13)
H1B—C1—H1C	109.5	O6—C16—C17	138.54 (14)
O1—C2—C3	123.68 (13)	O5—C16—C17	94.75 (11)
O1—C2—C27	114.34 (12)	C16—C17—C15	84.30 (10)
C3—C2—C27	121.97 (13)	C16—C17—C18	113.72 (11)
C2—C3—C4	115.83 (13)	C15—C17—C18	108.52 (11)
C2—C3—H3	122.1	C16—C17—H17	115.4
C4—C3—H3	122.1	C15—C17—H17	115.4
O2—C4—C13	113.30 (11)	C18—C17—H17	115.4
O2—C4—C3	122.31 (12)	C19—C18—C17	113.07 (11)
C13—C4—C3	124.38 (12)	C19—C18—C5	113.55 (10)
O2—C5—C6	106.63 (10)	C17—C18—C5	105.76 (10)
O2—C5—C18	108.83 (10)	C19—C18—H18	108.1

C6—C5—C18	115.71 (10)	C17—C18—H18	108.1
O2—C5—C14	105.27 (10)	C5—C18—H18	108.1
C6—C5—C14	114.46 (11)	C24—C19—C20	118.22 (12)
C18—C5—C14	105.39 (10)	C24—C19—C18	119.19 (12)
C11—C6—C7	117.47 (12)	C20—C19—C18	122.56 (12)
C11—C6—C5	119.53 (12)	C21—C20—C19	121.06 (13)
C7—C6—C5	122.96 (12)	C21—C20—H20	119.5
C8—C7—C6	121.11 (13)	C19—C20—H20	119.5
C8—C7—H7	119.4	C20—C21—C22	120.01 (13)
C6—C7—H7	119.4	C20—C21—H21	120.0
C9—C8—C7	120.56 (13)	C22—C21—H21	120.0
C9—C8—H8	119.7	C23—C22—C21	119.46 (13)
C7—C8—H8	119.7	C23—C22—H22	120.3
O3—C9—C8	115.59 (13)	C21—C22—H22	120.3
O3—C9—C12	124.93 (13)	C22—C23—C24	120.45 (13)
C8—C9—C12	119.48 (13)	C22—C23—H23	119.8
O3—C10—H10A	109.5	C24—C23—H23	119.8
O3—C10—H10B	109.5	C23—C24—C19	120.78 (13)
H10A—C10—H10B	109.5	C23—C24—H24	119.6
O3—C10—H10C	109.5	C19—C24—H24	119.6
H10A—C10—H10C	109.5	O7—C25—C27	124.20 (12)
H10B—C10—H10C	109.5	O7—C25—C13	116.63 (12)
C12—C11—C6	121.97 (13)	C27—C25—C13	119.14 (13)
C12—C11—H11	119.0	O7—C26—H26A	109.5
C6—C11—H11	119.0	O7—C26—H26B	109.5
C11—C12—C9	119.34 (13)	H26A—C26—H26B	109.5
C11—C12—H12	120.3	O7—C26—H26C	109.5
C9—C12—H12	120.3	H26A—C26—H26C	109.5
C4—C13—C25	118.45 (13)	H26B—C26—H26C	109.5
C4—C13—C14	109.67 (11)	C25—C27—C2	120.19 (13)
C25—C13—C14	131.74 (12)	C25—C27—H27	119.9
O4—C14—C13	109.04 (11)	C2—C27—H27	119.9
O4—C14—C15	111.93 (11)		
C1—O1—C2—C3	9.1 (2)	C16—O5—C15—C17	6.15 (10)
C1—O1—C2—C27	-170.10 (12)	O4—C14—C15—O5	45.85 (14)
O1—C2—C3—C4	-179.54 (12)	C13—C14—C15—O5	170.19 (11)
C27—C2—C3—C4	-0.4 (2)	C5—C14—C15—O5	-80.60 (13)
C5—O2—C4—C13	-11.81 (14)	O4—C14—C15—C17	143.05 (11)

C5—O2—C4—C3	169.29 (12)	C13—C14—C15—C17	-92.61 (13)
C2—C3—C4—O2	178.97 (12)	C5—C14—C15—C17	16.60 (14)
C2—C3—C4—C13	0.2 (2)	C15—O5—C16—O6	175.10 (15)
C4—O2—C5—C6	140.94 (10)	C15—O5—C16—C17	-6.22 (10)
C4—O2—C5—C18	-93.60 (11)	O6—C16—C17—C15	-175.49 (19)
C4—O2—C5—C14	18.97 (13)	O5—C16—C17—C15	6.11 (10)
O2—C5—C6—C11	-31.22 (15)	O6—C16—C17—C18	76.8 (2)
C18—C5—C6—C11	-152.39 (12)	O5—C16—C17—C18	-101.64 (12)
C14—C5—C6—C11	84.75 (15)	O5—C15—C17—C16	-5.61 (9)
O2—C5—C6—C7	150.88 (12)	C14—C15—C17—C16	-117.34 (12)
C18—C5—C6—C7	29.71 (18)	O5—C15—C17—C18	107.52 (11)
C14—C5—C6—C7	-93.15 (15)	C14—C15—C17—C18	-4.20 (15)
C11—C6—C7—C8	1.3 (2)	C16—C17—C18—C19	-153.34 (12)
C5—C6—C7—C8	179.28 (12)	C15—C17—C18—C19	114.78 (12)
C6—C7—C8—C9	0.9 (2)	C16—C17—C18—C5	81.81 (13)
C10—O3—C9—C8	-171.71 (14)	C15—C17—C18—C5	-10.07 (14)
C10—O3—C9—C12	9.2 (2)	O2—C5—C18—C19	7.66 (14)
C7—C8—C9—O3	178.91 (13)	C6—C5—C18—C19	127.63 (12)
C7—C8—C9—C12	-2.0 (2)	C14—C5—C18—C19	-104.83 (12)
C7—C6—C11—C12	-2.7 (2)	O2—C5—C18—C17	132.21 (10)
C5—C6—C11—C12	179.32 (12)	C6—C5—C18—C17	-107.81 (12)
C6—C11—C12—C9	1.7 (2)	C14—C5—C18—C17	19.72 (13)
O3—C9—C12—C11	179.70 (13)	C17—C18—C19—C24	145.99 (12)
C8—C9—C12—C11	0.7 (2)	C5—C18—C19—C24	-93.50 (14)
O2—C4—C13—C25	-177.66 (11)	C17—C18—C19—C20	-35.94 (17)
C3—C4—C13—C25	1.2 (2)	C5—C18—C19—C20	84.57 (15)
O2—C4—C13—C14	-1.34 (15)	C24—C19—C20—C21	0.3 (2)
C3—C4—C13—C14	177.53 (12)	C18—C19—C20—C21	-177.82 (12)
C4—C13—C14—O4	-109.08 (12)	C19—C20—C21—C22	0.3 (2)
C25—C13—C14—O4	66.59 (18)	C20—C21—C22—C23	0.0 (2)
C4—C13—C14—C15	125.05 (12)	C21—C22—C23—C24	-0.8 (2)

C25—C13—C14—C15	-59.29 (19)	C22—C23—C24—C19	1.4 (2)
C4—C13—C14—C5	12.34 (14)	C20—C19—C24—C23	-1.14 (19)
C25—C13—C14—C5	-171.99 (14)	C18—C19—C24—C23	177.01 (12)
O2—C5—C14—O4	98.28 (12)	C26—O7—C25—C27	7.9 (2)
C6—C5—C14—O4	-18.48 (16)	C26—O7—C25—C13	-170.10 (13)
C18—C5—C14—O4	-146.75 (11)	C4—C13—C25—O7	175.74 (12)
O2—C5—C14—C13	-18.57 (12)	C14—C13—C25—O7	0.4 (2)
C6—C5—C14—C13	-135.32 (11)	C4—C13—C25—C27	-2.41 (19)
C18—C5—C14—C13	96.40 (11)	C14—C13—C25—C27	-177.77 (14)
O2—C5—C14—C15	-137.35 (10)	O7—C25—C27—C2	-175.76 (13)
C6—C5—C14—C15	105.90 (12)	C13—C25—C27—C2	2.2 (2)
C18—C5—C14—C15	-22.38 (13)	O1—C2—C27—C25	178.38 (12)
C16—O5—C15—C14	116.86 (12)	C3—C2—C27—C25	-0.8 (2)

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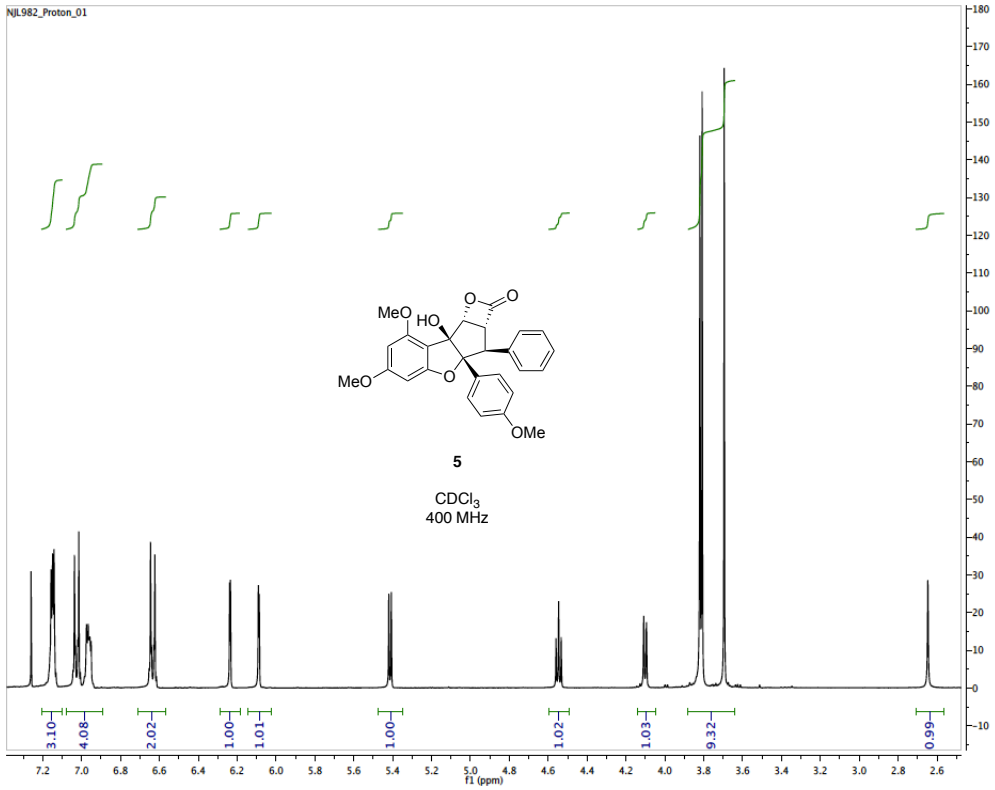
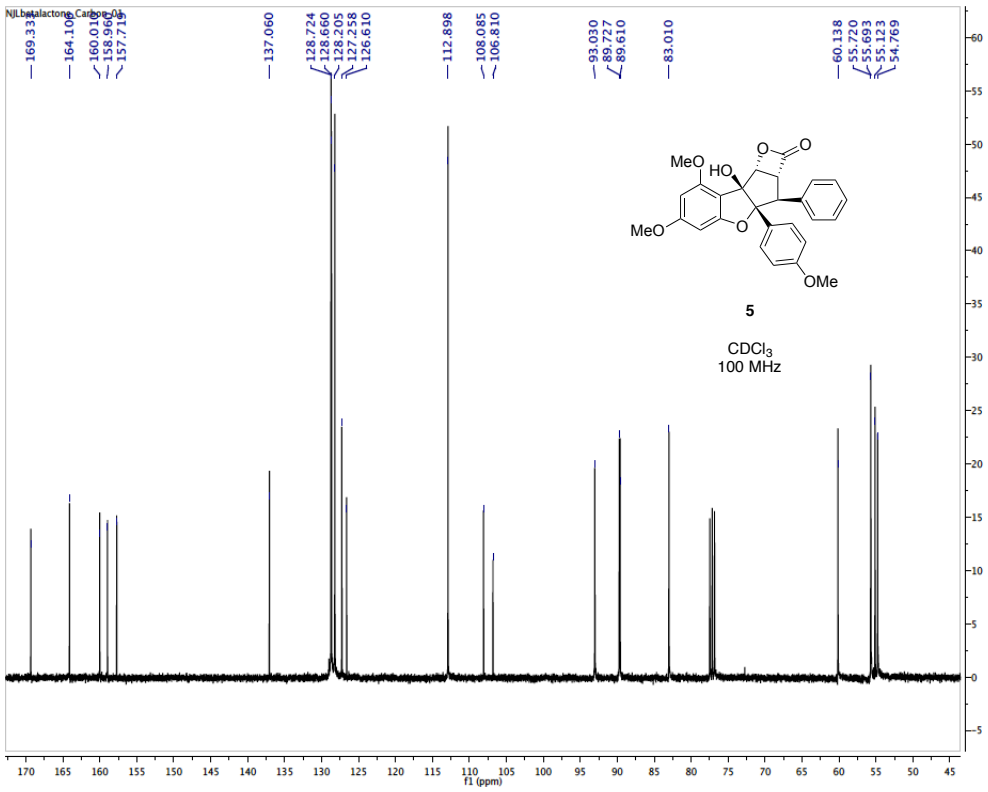
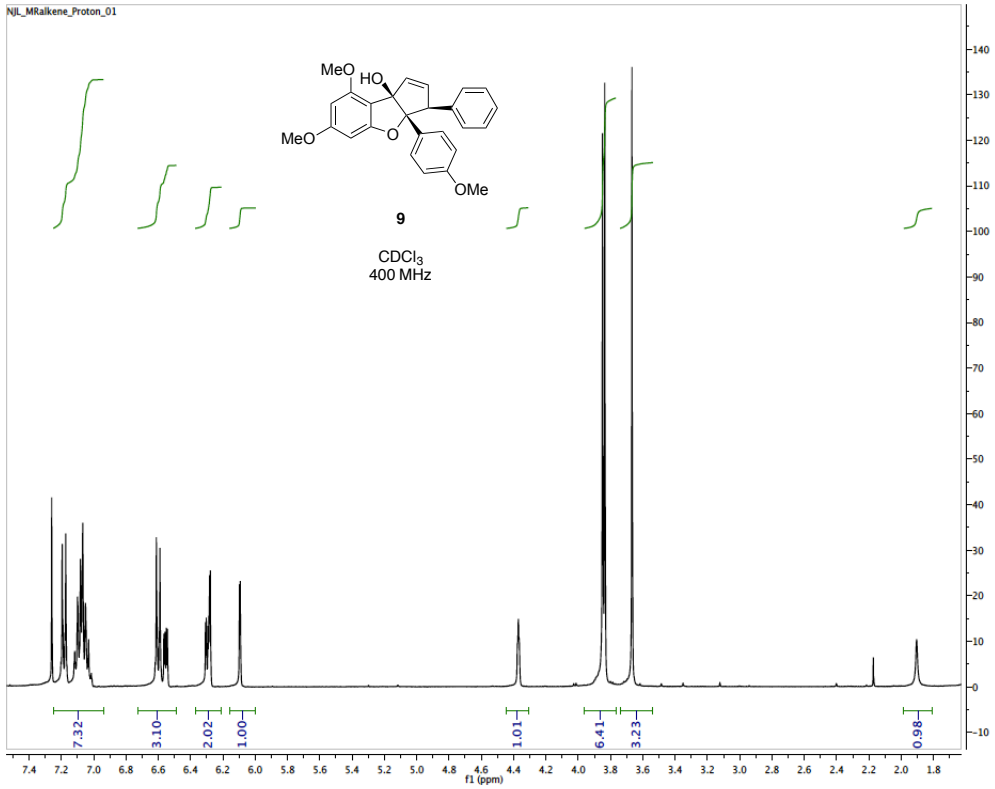
Dolmanov, O. V., *et al.* (2009). OLEX2: A complete structure solution, refinement and analysis program. J. Appl. Cryst. 42, 339-341 (2009).

C. Selected Spectra



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O
OMe
9
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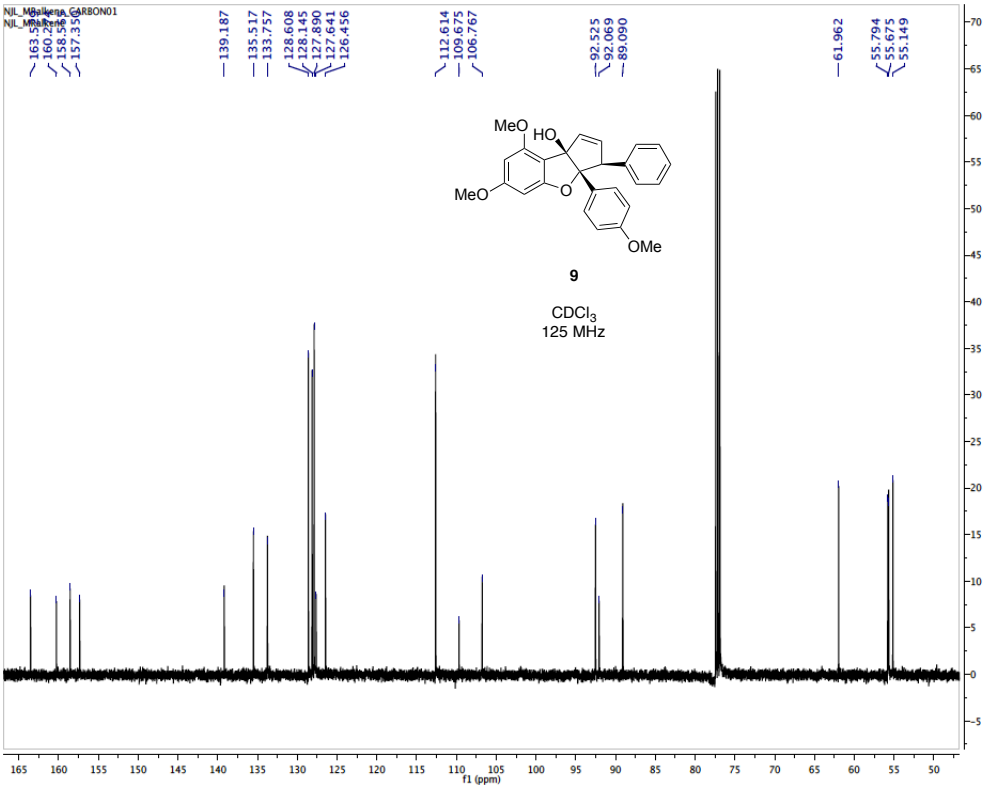
1.01
6.41
3.23
0.98
f1 (ppm)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126.456
112.614
109.675
106.767
92.525
92.069
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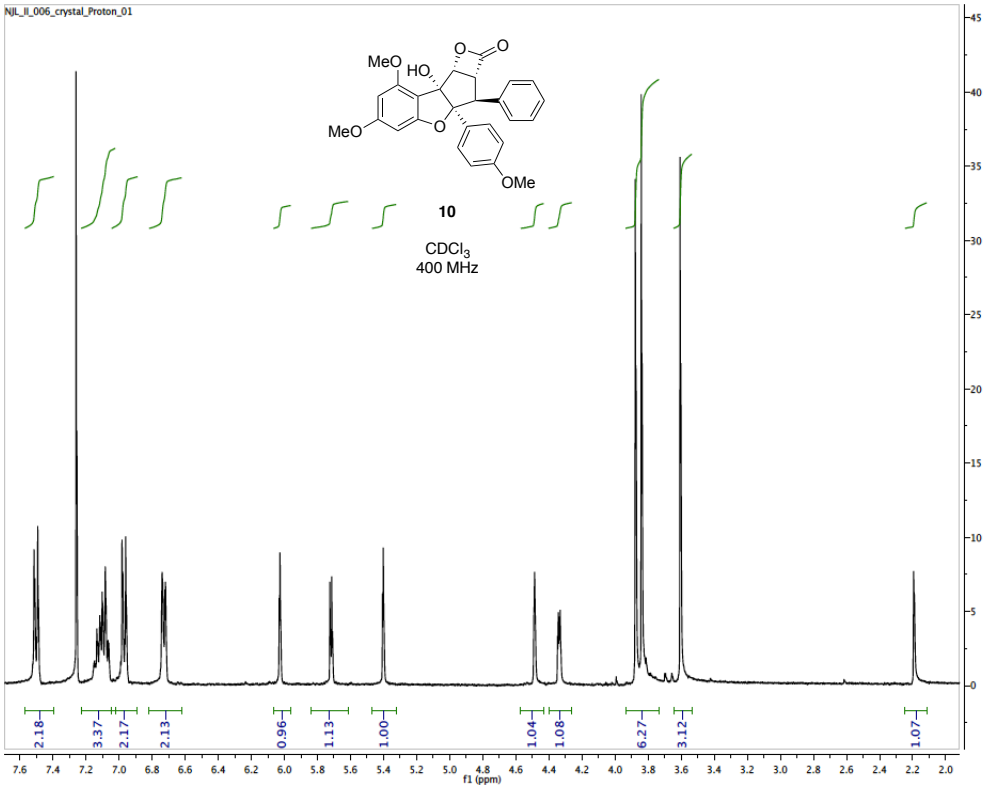
MeO
O
OMe
9
CDCl3
125 MHz
f1 (ppm)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MeO
OMe
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400 MHz
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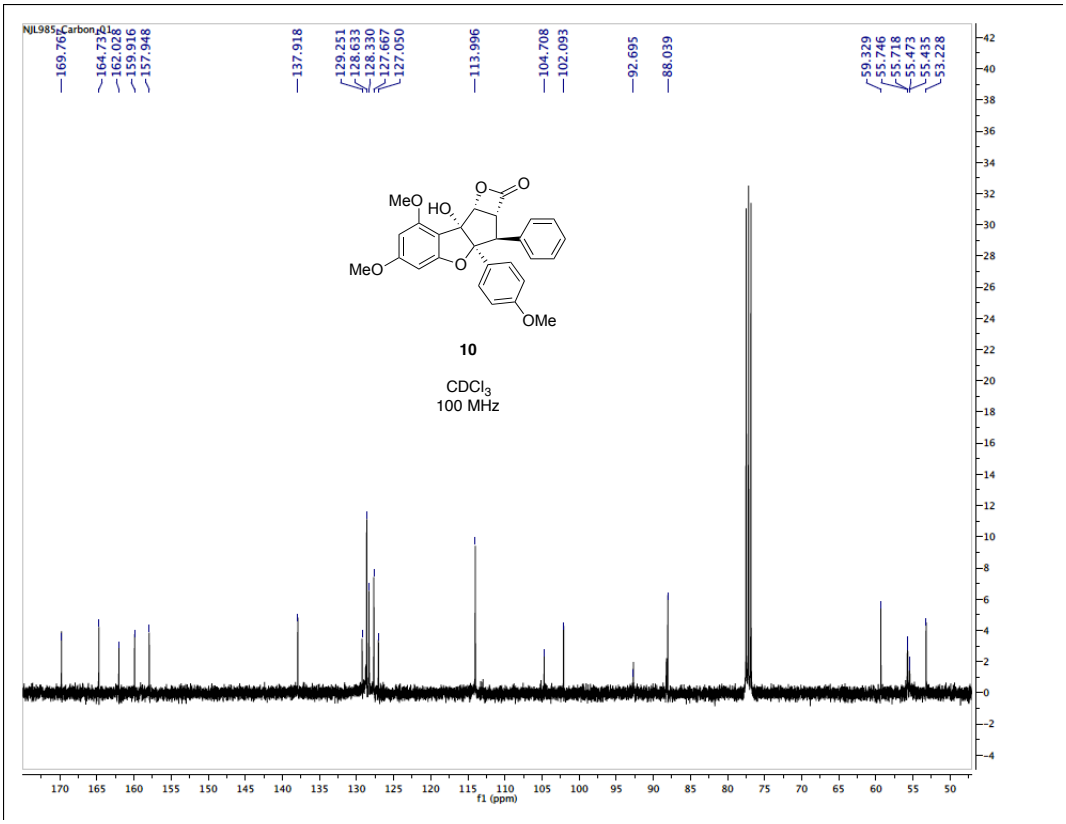
1.00
1.04
1.08
6.27
3.12
1.07
f1 (ppm)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113.996
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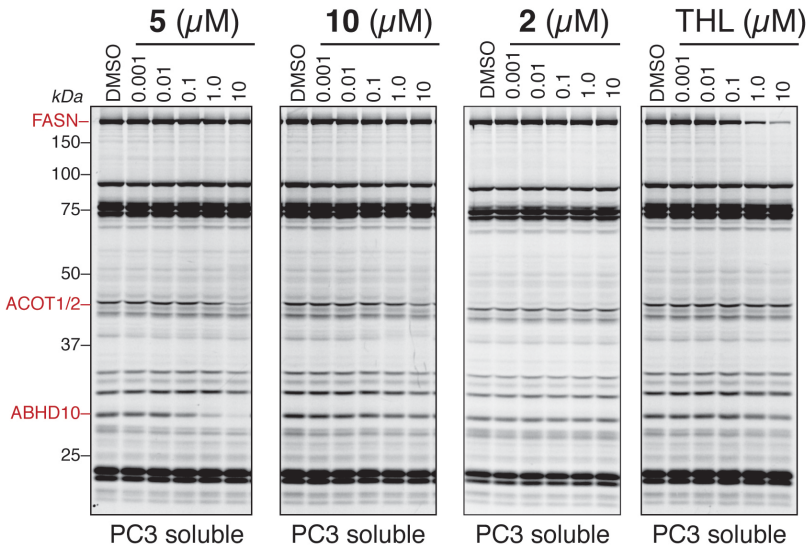
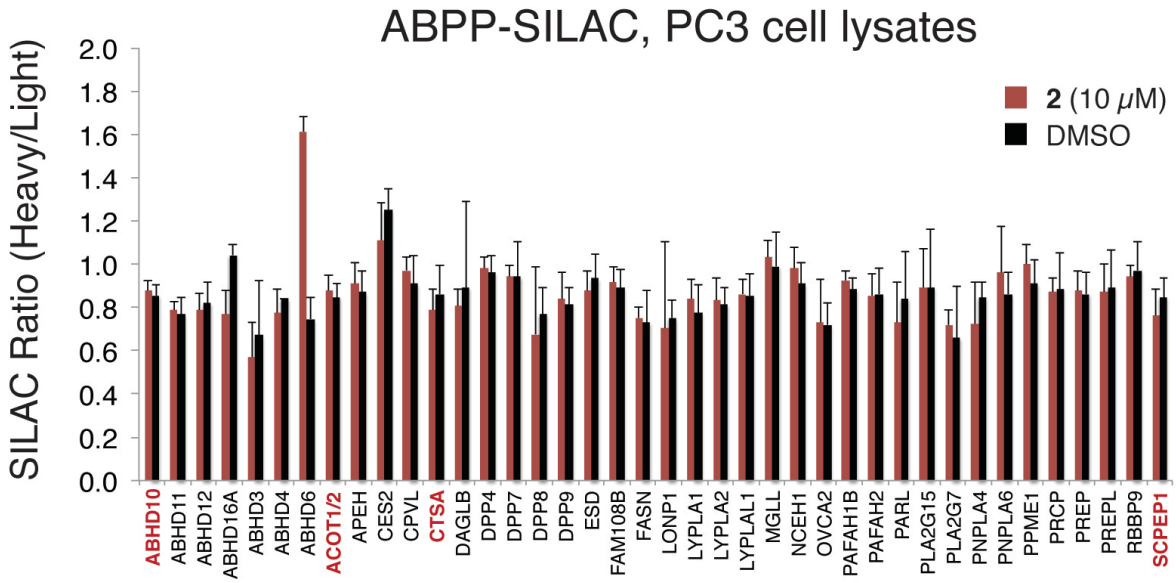
102.093
92.695
88.039
59.329
55.746
55.718
55.473
55.435
53.228
MeO
HO
MeO
OMe
10
CDCl3
100 MHz
f1 (ppm)

III. ACTIVITY-BASED PROTEIN PROFILING



Supplementary Figure 1. *In vitro* gel-based competitive ABPP of β-lactone (±)-**5**, (±)-**10**, (±)-**2** and tetrahydrolipstatin (THL). The soluble fraction of PC3 cell lysates were treated with DMSO or compound (0.001–10 μM) for 30 min followed by FP-Rh (30 min). Gel profiles show distinct targets for each inhibitor. Notably, ACOT1/2 and ABHD10, two primary targets of **5**, are not significantly inhibited by **10** (the di-*epi* isomer of **5)**, (±)-**2** or THL.



Supplementary Figure 2. ABPP-SILAC analysis of (±)-**2** (10 μM) and DMSO (heavy amino acid-labeled proteome) versus DMSO (light amino acid-labeled proteome) in PC3 cell proteomes for all quantifiable serine hydrolases. Data are presented as the mean ± standard deviations of heavy/light ratios for multiple unique peptides from each enzyme. The primary targets of (±)-**5** are shown in red.

Cell and Tissue Proteome Preparation. Tissue proteomes from mouse organs were homogenized in DPBS (Corning Cellgro) using the NextAdvance BBX24B Bullet Blender and the appropriate tissue-specific protocol (http://www.nextadvance.com/api/index.cfm/products.info/c/421/Bullet-Blender#/Protocols). Immediately after homogenization, samples were centrifuged at 3,000 g for 4 minutes at 4 ºC to remove beads and insoluble debris. Cell proteomes were prepared from PC3 cells grown in RPMI-1640 media (Caisson Labs) with 10% FBS (Omega Scientific, Inc.). Cells were harvested with a cell scraper and washed 2x with DPBS then lysed using probe sonication with the Branson Sonifier 250. Membrane and soluble cell and tissue fractions were prepared by ultracentrifugation (100,000 g, 45 min). Membrane pellets were resuspended in DPBS by probe sonication. The DC Protein Assay from Bio-Rad was then used to measure proteome concentrations and proteomes were diluted in DPBS to 1.0 mg/mL total protein concentration for ABPP experiments.

***In Vitro* Competitive Activity-Based Protein Profiling.** Cell and tissue proteomes (50 µL, 1 mg/mL) were treated with inhibitors (1 µL in DMSO) or DMSO (1 µL) and incubated for 30 minutes at 37 °C. FP-Rh[S3] (1 µL, 50 µM in DMSO) was then added to each proteome and incubated for another 30 minutes at room temperature. Samples were then quenched with 4X SDS Loading Buffer (17 µL) and proteins were resolved by SDS-PAGE (10% Acrylamide Gels made in-house). Serine hydrolase activity was determined after fluorescent gel imaging on a Hitachi FMBio II by quantifying the fluorescence intensity of target gel bands using ImageJ 1.45s.

***In Situ* Cell Labeling.** PC3 cells were grown in 6 cm dishes in RPMI-1640 media (10% FBS). When cells reached confluency, the media was removed and replaced with serum-free RPMI-1640 (3 mL) containing either DMSO (0.2%) or inhibitor (1-10,000 nM, 0.2% DMSO). The cells were incubated for 2 hours at 37 °C before the media was removed and the cells were washed (DPBS, 2 x 3 mL), harvested, and lysed with a probe sonicator. The soluble fraction was obtained by ultracentrifugation (100,000 g, 45 min). A portion of each sample (50 µL, 1 mg/mL) was then treated with FP-Rhodamine and analyzed by SDS-PAGE as described above.

***In Vitro* Competitive SILAC-ABPP.** SILAC-ABPP experiments and analysis were performed as described before.[S4-S7] Briefly, cell pellets from 'heavy' and 'light' labeled cells were lysed in DPBS using probe

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[S4] Adibekian, A.; Martin, B. R.; Wang, C.; Hsu, K. –L.; Bachovchin, D. A.; Niessen, S.; Hoover, H.; Cravatt, B. F. *Nat. Chem.*

sonication, and protein concentration was determined using the DC Assay. Heavy and light protein samples (500 μL, 2 mg/mL) were incubated separately at 37 °C for 30 minutes with inhibitor (1 μL in DMSO) or DMSO (1 μL), respectively. The samples were then incubated with FP-Biotin[S3] (500 μM, 1 μL) for 60 minutes at room temperature and then quenched by combining them into a methanol:chloroform mixture (4:1, 2.5 mL). The FP-labeled proteins were enriched, trypsin-digested and the tryptic peptides resolved by two-dimensional liquid chromatography using strong cation exchange and C18 resins and analyzed by tandem MS using an Agilent 1100-series quaternary pump and Thermo Scientific LTQ Orbitrap ion trap mass spectrometer. MS2 data were searched using the ProLuCID algorithm (http://fields.scripps.edu/downloads.php) against a UniProt human protein sequence database concatenated with a reverse decoy database for false positive assessment. Heavy and light peptides identified from the ProLuCID search were quantified by in-house software described previously.[S7]

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