

Supporting Information

Biomimetic Kinetic Resolution: Highly Enantio- and Diastereoselective Transfer Hydrogenation of Aglain Ketones to Access Flavagline Natural Products

Steven D. Stone,[‡] Neil J. Lajkiewicz,[‡] Luke Whitesell,[‡] Ahmed Hilmy,[‡] and John A. Porco, Jr.*[‡]

[‡]*Department of Chemistry and Center for Molecular Discovery (BU-CMD), Boston University, Boston, Massachusetts 02215, United States*

[‡]*Whitehead Institute for Biomedical Research (WIBR), Cambridge, Massachusetts 02142, United States*

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I. GENERAL INFORMATION

A. Instrumentation and methods

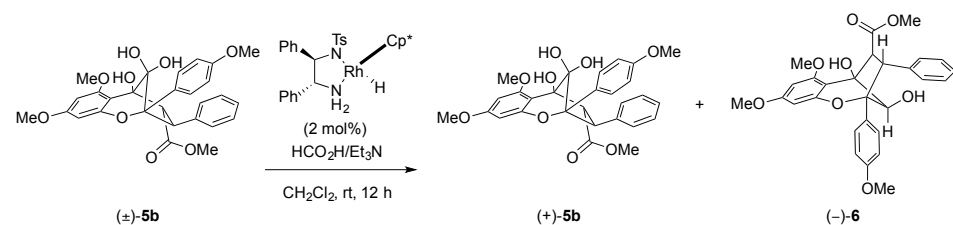
¹H NMR spectra were recorded at 400 or 500 MHz at ambient temperature with CDCl₃ (Cambridge Isotope Laboratories, Inc.) as solvent. Data for ¹H NMR are reported as follows: chemical shift, integration, multiplicity (brs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling

constants in Hz. ^{13}C NMR spectra were recorded at 100.0 or 125 MHz at ambient temperature with the same solvents unless otherwise stated. ^{19}F NMR spectra were recorded at 376 or 470 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 $[\alpha]_{\text{D}}^{20}$ (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 SunFireTM Prep C18 OBDTM 5 μm 19X50 mm column.

Analytical thin layer chromatography was performed using 0.25mm 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 ($\lambda = 315\text{-}400\text{ nm}$). Microwave experiments were performed using a CEM Discover microwave. All other reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

II. EXPERIMENTAL PROCEDURES AND COMPOUND CHARACTERIZATION

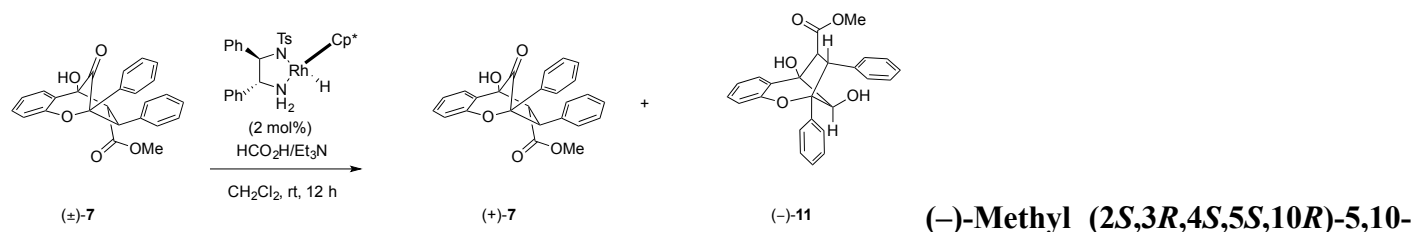


General procedure A:

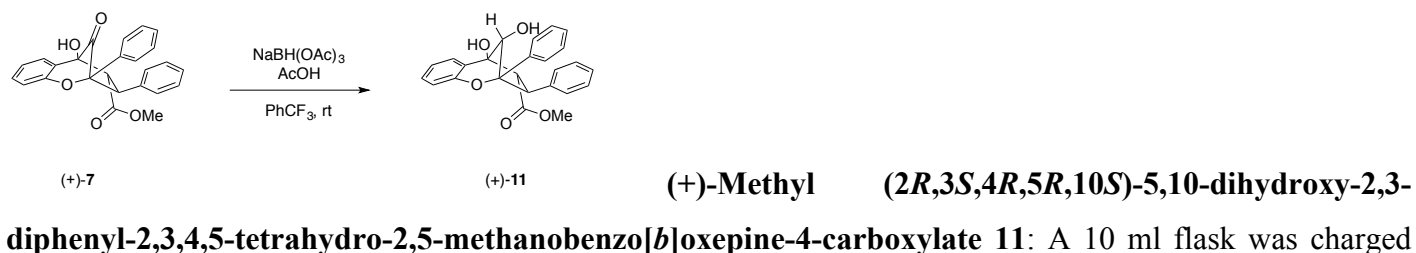
(-)-Methyl (2*S*,3*R*,4*S*,5*S*,10*R*)-5,10-dihydroxy-6,8-dimethoxy-2-(4-methoxyphenyl)-3-phenyl-2,3,4,5-

tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate 6: A dry flask was charged with a stir bar, ($\pm$)-**5b** (107 mg, 0.218 mmol, 1 equiv) and CH₂Cl₂ (5 mL). In a separate flask, [RhCl₂(Cp*)]₂ (1.1 mg, 0.00218 mmol, 1 mol%), (*R,R*)-*N*-Tosyl diphenylethylenediamine (1.6 mg, 0.00436 mmol, 2 mol%), formic acid (0.008 mL, 0.059 mmol, 1.0 equiv), triethylamine (0.03 mL, 0.059 mmol, 1.0 equiv), and CH₂Cl₂ (2 mL) were combined and stirred for 30 min. At this time, the entire contents of the separate flask were added to the reaction mixture, and the reaction was allowed to stir at room temp for 12 h. After this time, a saturated sodium bicarbonate solution was added (5 mL), and the reaction was diluted and extracted with CH₂Cl₂ (3 x 10 mL), then dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified *via* SiO₂ gel column chromatography (2:3 EtOAc/hexanes) to afford (–)-**6** in 45% yield (46 mg, 0.0946 mmol) as a white solid. Aglain (+)-**5b** (6:4 EtOAc/hexanes) was also isolated in 42% yield (53 mg, 0.108 mmol) as a white solid. The enantiopurity of (–)-**6** was determined using analytical chiral HPLC (96% ee) and the ee of (+)-**5b** (single enantiomer) was determined by synthesizing (–)-methyl rocaglate from (+)-**4b** (see below). Spectroscopic data are identical to those previously reported.^{S1} Enantiopurity was determined using analytical chiral HPLC.

Note: for reactions with other catalytic systems, identical conditions were utilized as those outlined above, with 2 mol% of the other metal-ligand systems employed.



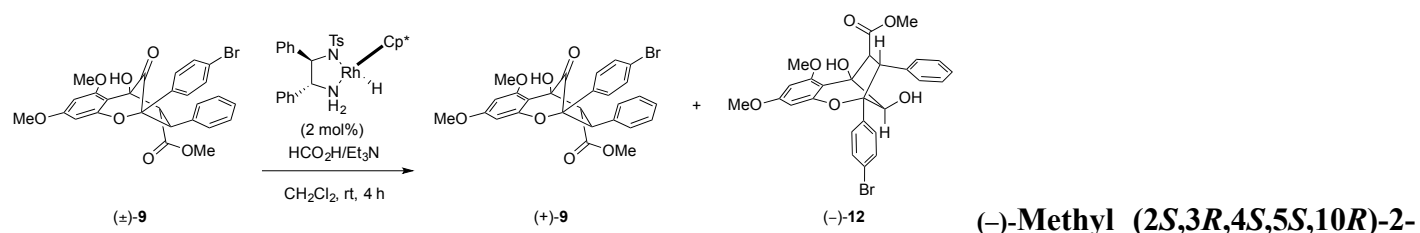
dihydroxy-2,3-diphenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate 11: See general procedure A. Cycloadduct **7** was prepared using previously reported methods.^{S2} The yield of the reduced product (–)-**11** was 16% (32 mg, 0.080 mmol) as a white solid; the yield of the reisolated starting material was 22% (43 mg, 0.108 mmol). Spectroscopic data for compound (–)-**11** were found to be identical to those previously reported.^{S1} Enantiopurity of (–)-**11** was determined using analytical HPLC (78% ee).



^{S1} Lajkiewicz, N. J.; Roche, S. P.; Gerard, B.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2012**, *134*, 13108-13113.

^{S2} Gerard, B.; Sangji, S.; O'Leary, D. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 7754-7755.

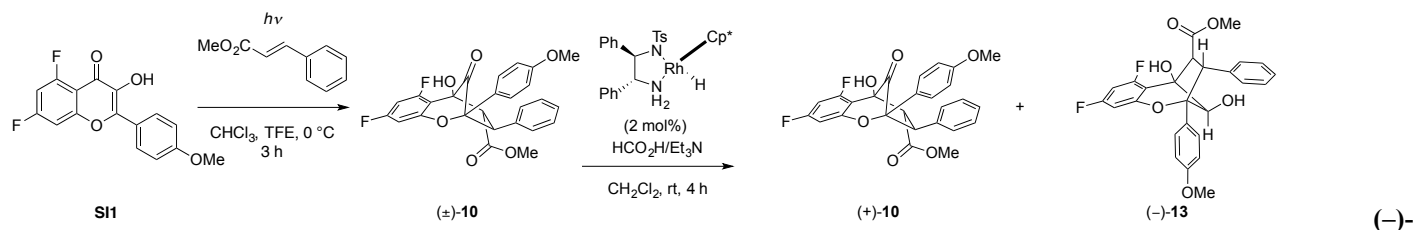
with desmethoxyaglain (+)-**7** (20 mg, 0.050 mmol) and trifluorotoluene (1.25 mL). The solution was heated to 60°C for 4 h, then cooled to 0 °C. Acetic acid (29 µl, 0.500 mmol) and sodium triacetoxyborohydride (64 mg, 0.300 mmol) were then added. The solution was warmed to room temperature and stirred for 12 h. The solution was diluted with ethyl acetate (10 mL) and saturated aqueous ammonium chloride was added (10 mL) and the solution was stirred for an additional 30 min. The solution was then extracted with ethyl acetate (3 X 10 mL) and washed with brine (10 mL), dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was separated using SiO₂ column chromatography (20% EtOAc:hexanes), and the reduced product was isolated (8 mg, 0.020 mmol, 22%) as a white solid. The spectroscopic data for compound (+)-**11** are identical to those previously reported.^{S1} Enantiopurity was determined using analytical chiral HPLC analysis (19% ee)



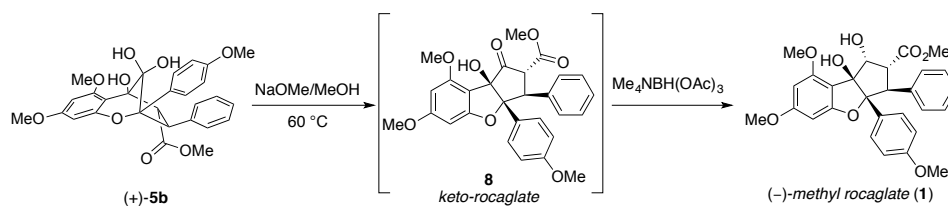
(4-Bromophenyl)-5,10-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,4,5-tetrahydro-2,5-

methanobenzo[b]oxepine-4-carboxylate **12:** See general procedure A. Aglain **9** was prepared using methods previously reported.^{S3} The yield of the reduced product **12** was 41% (64 mg, 0.130 mmol); the yield of the reisolated starting material **9** was 43% (67 mg, 0.140 mmol). The crude material was purified using SiO₂ chromatography (60% EtOAc:hexanes, *R_f* = 0.4); **m.p.** 122-125°C; **IR** *v*_{max} (film): 3028, 3009, 1736, 1620, 1590, 1494, 1458, 1215, 1202, 1149, 1126, 1093, 1007, 824, 757; **¹H NMR** (400 MHz, CDCl₃) δ 7.42 (d, *J* = 8.0 Hz, 2H), 7.25 (m, 4H), 7.07 (m, 3H), 6.10 (m, 2H), 5.71 (s, 1H), 4.77 (s, 1H), 4.37 (d, *J* = 9.6 Hz, 1H), 3.86 (d, *J* = 9.6 Hz), 3.85 (s, 3H), 3.75 (s, 3H), 3.62 (s, 1H), 3.60 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 172.2, 161.4, 157.9, 153.4, 140.8, 136.8, 130.7, 130.6, 130.2, 130.1, 128.2, 126.6, 121.9, 80.6, 80.5, 79.2, 64.7, 56.9, 56.0, 55.4, 51.8; **HR/MS**: *m/z* Calcd for [C₂₇H₂₅BrO₇+H]⁺ 541.0862, found 541.0880 (+3.3 ppm); enantiopurity was determined using analytical chiral HPLC (>99% ee);); [α]_D²⁶ = -83.017° (*c* = 0.2, CHCl₃). Enantiopurity of (+)-**9** was determined after conversion to its methyl rocaglate analog (see general procedure B below) (-)-**14** (88% ee).

^{S3} Thuaud, F.; Ribeiro, N.; Gaiddon, C.; Cresteil, T.; Désaubry, L. *J. Med. Chem.* **2011**, *54*, 411-415.



Methyl (2*S*,3*R*,4*S*,5*S*,10*R*)-6,8-difluoro-5,10-dihydroxy-2-(4-methoxyphenyl)-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate 13: 3-HF **SI1** was prepared according to a previously reported procedure.^{S4} To a Pyrex tube was added 3-HF **SI1** (115 mg, 0.394 mmol, 1 equiv), methyl cinnamate (320 mg, 1.97 mmol, 5 equiv), chloroform (9.2 mL), and 2,2,2-trifluoroethanol (4 mL). The resulting mixture was first sonicated, then sparged with argon while sonicating for 10 min. The tube was then sealed and chilled to 0 °C. The resulting solution was irradiated using a Rayonet RPR-100 photochemical reactor for 3 h at 0 °C. The reaction mixture was then concentrated and purified *via* column chromatography to provide (±)-**10** as a yellow oil (80 mg, 0.172 mmol, 44%). For reduction procedure, see general procedure A. The yield of the reduced product was 13% (9 mg, 0.0192 mmol) as a white solid; the yield of the reisolated starting material was 31% (22 mg, 0.047 mmol) as a clear oil. The crude material was purified using SiO₂ chromatography. *R_f* = 0.3 (30% EtOAc:hexanes); **m.p.** decomposed; **IR** *v*_{max} (film): 2926, 2850, 1742, 1624, 1600, 1518, 1491, 1441, 1255, 1178, 1124, 1047, 1009 831.5, 758; **¹H NMR** (500 MHz, CDCl₃) δ 7.39 (d, *J* = 6.5 Hz, 2H), 7.05 (m, 3H), 6.68 (d, *J* = 6.5 Hz, 2H), 6.39 (m, 2H), 4.83 (s, 1H), 4.34 (d, *J* = 9.0 Hz, 1H), 4.19 (br s, 1H), 3.83 (d, *J* = 9.0 Hz), 3.71 (s, 3H), 3.68 (s, 3H), 3.43 (s, 1H); **¹³C NMR** (125 MHz, CDCl₃) δ 171.6, 159.0, 140.8, 130.2, 130.1, 128.9, 128.1, 126.5, 113.0, 100.6 (d, *J* = 3.6 Hz), 97.0 (dd, *J*₁ = *J*₂ = 1.5 Hz), 90.2, 85.6, 79.5, 64.5, 56.2, 55.1, 52.3, 49.7; **¹⁹F NMR** (376 MHz, CDCl₃) -108.7 (dd, *J*₁ = 8.7, *J*₂ = 17.3 Hz), -117.6 (m); **HR/MS**: *m/z* Calcd for [C₂₆H₂₂F₂O₆+Na]⁺ 491.1282, found 491.1270 (-2.4 ppm); Enantiopurity of **13** was determined using analytical chiral HPLC (74% ee); [α]_D²⁶ = -27.785° (*c* = 0.1, CHCl₃).

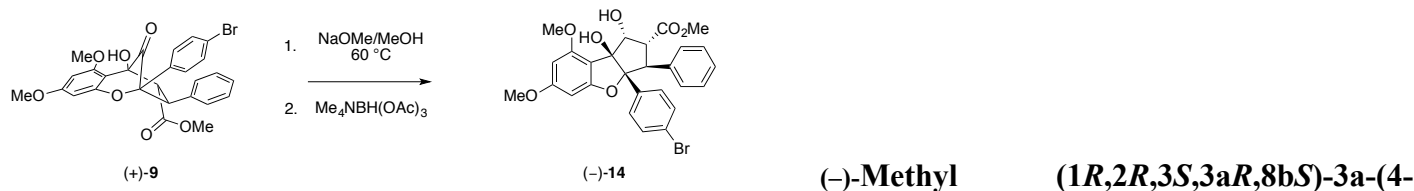


General Procedure B: (-)-

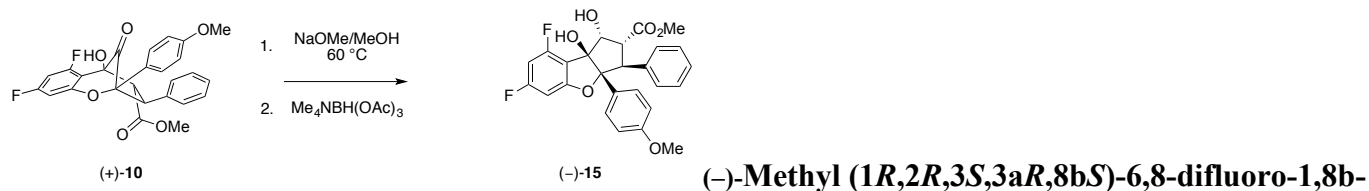
Methyl rocaglate 1: To a flame dried round bottom flask was added (+)-**5b** (5 mg, 0.0102 mmol) in methanol (0.4 mL). To the solution was added a freshly prepared solution of sodium methoxide in methanol (0.090 mL, 0.3 M, 0.0255 mmol) and the solution was heated at 60 °C and stirred for 30 min. The solution

^{S4} Britton, R. G.; Horner-Glister, E.; Pomenya, O. A.; Smith, E. E.; Denton, R.; Jenkins, P. R.; Steward, W. P.; Brown, K.; Gescher, A.; Sale, S. *Eur. J. Med. Chem.* **2012**, *54*, 952-958.

was cooled to rt and was concentrated *in vacuo*. Upon redilution in ethyl acetate (10 mL), the reaction was quenched with saturated aqueous ammonium chloride (5 mL) followed by 1 N HCl (0.5 mL). The aqueous layer was extracted with ethyl acetate (3 X 10 mL) and the combined organic fractions were dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was taken to the next step without further purification. The crude mixture was diluted in MeCN (1 mL) and to this solution was added acetic acid (10 μ L, 0.102 mmol) and tetramethylammonium triacetoxymethylborohydride (16.1 mg, 0.0612 mmol). The solution was stirred overnight at room temperature. The solution was then quenched with saturated aqueous ammonium chloride for 30 min. The mixture was extracted with ethyl acetate (3 X 10 mL) and the combined organic fractions were dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified using SiO₂ column chromatography (1:1 EtOAc:hexanes) to afford a white solid (4 mg, 0.008 mmol, 80%). The spectroscopic data was identical to those previously reported.^{S2} Enantiopurity of (–)-**1** (and therefore of (+)-**5b**) was determined using analytical chiral HPLC (>99% ee).



(–)-Methyl (1*R*,2*R*,3*S*,3*aR*,8*bS*)-3*a*-(4-bromophenyl)-1,8*b*-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,3*a*,8*b*-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate **14:** See general procedure B. Enantiopurity was determined using analytical chiral HPLC (88% ee). $[\alpha]_D^{26} = -75.37^\circ$ ($c = 0.1$, CHCl₃); other spectroscopic data are identical to those previously reported.^{S3}

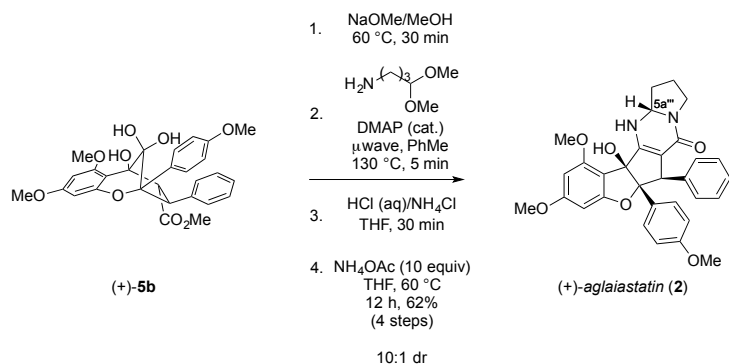


(–)-Methyl (1*R*,2*R*,3*S*,3*aR*,8*bS*)-6,8-difluoro-1,8*b*-dihydroxy-3*a*-(4-methoxyphenyl)-3-phenyl-2,3,3*a*,8*b*-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate **15:** See general procedure B. $R_f = 0.3$ (2:8 EtOAc:hexanes); **m.p.** decomposed; **IR** ν_{max} (film): 3000, 1738, 1631, 1616, 1515, 1495, 1443, 1300, 1254, 1217, 1175, 1118, 1089, 1036, 998, 829, 758; **¹H NMR** (500 MHz, CDCl₃) δ 7.10-7.05 (m, 5H), 7.00 (d, $J = 7.8$ Hz, 2H), 6.65 (d, $J = 7.8$ Hz, 2H), 6.60 (d, $J = 9.3$ Hz, 1H), 6.45 (dd, $J_1 = J_2 = 9.3$ Hz, 1H), 4.91 (d, $J = 5.5$ Hz, 1H), 4.49 (d, $J = 14.0$ Hz, 1H), 3.99 (dd, J_1

^{S2} Gerard, B.; Sangji, S.; O'Leary, D. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 7754-7755.

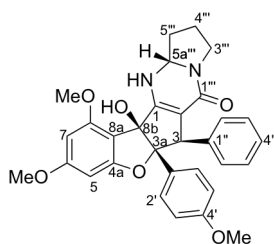
^{S3} Thuaud, F.; Ribeiro, N.; Gaidon, C.; Cresteil, T.; Désaubry, L. *J. Med. Chem.* **2011**, *54*, 411-415.

= 5.5 Hz, $J_2 = 14.0$ Hz, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 2.96 (brs, 1H), 1.90 (brs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.6, 159.0, 136.2, 128.7, 127.9, 127.6, 126.8, 125.5, 113.0, 97.3, 95.5, 93.3, 78.5, 56.0, 55.1, 52.4, 50.6 ; ^{19}F NMR (470 MHz, CDCl_3) -106.2 (dd, $J_1 = 8.9$, $J_2 = 14.1$ Hz), -113.7 (dd, $J_1 = J_2 = 8.9$ Hz); HR/MS: m/z Calcd for $[\text{C}_{26}\text{H}_{22}\text{F}_2\text{O}_6 + \text{Na}]^+$ 491.1282, found 491.1281 (-0.20 ppm); Enantiopurity was determined using analytical chiral HPLC (41% ee); $[\alpha]_{\text{D}}^{26} = -73.480^\circ$ ($c = 0.1$, CHCl_3).



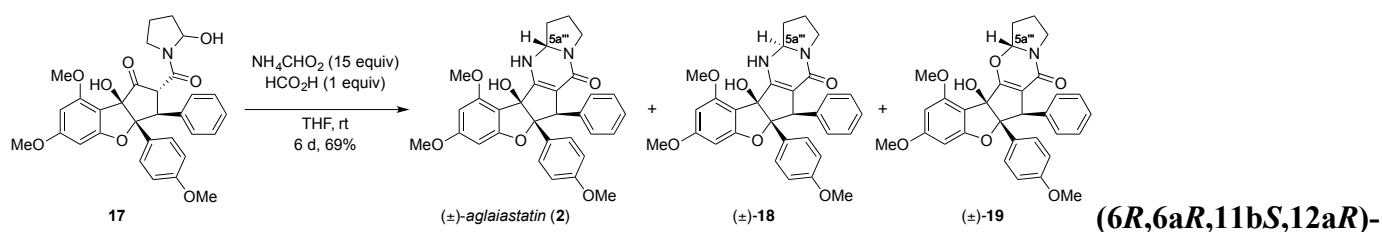
(+)-Aglaiastatin (2): To a flame-dried round bottom flask was added hydrate (+)-5b (46 mg, 0.0946 mmol, 1 equiv) in methanol (3 mL) at rt under an argon atmosphere. To this solution was added sodium methoxide, 0.3 M (0.10 mL, 0.296 mmol, 3 equiv) and the reaction mixture was stirred for 30 min at 60 °C. The reaction was cooled to rt, then concentrated *in vacuo*. The reaction was then diluted with ethyl acetate (20 mL) then quenched with concentrated ammonium chloride (20 mL) followed by 1 N HCl (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude material (keto-rocaglate **8**) was taken forward without further purification. The crude mixture (**8**) was diluted in toluene (2 mL) and was heated to 110 °C. 4,4-dimethoxybutanamine (12 mg, 0.0946 mmol, 1.0 equiv) and 4-dimethylaminopyridine (3 mg, 0.0236 mmol, 0.25 equiv) were added and the reaction was heated using microwave conditions (300 W) at 130 °C for 5 min. The crude reaction mixture was concentrated *in vacuo* then used in the next reaction without further purification. The crude material (**16**) was diluted in THF (1 mL) and cooled to 0 °C. At 0 °C a saturated ammonium chloride solution/1 N HCl aqueous solution (1 mL) was added dropwise. A precipitate formed immediately. After addition, the reaction was brought to rt and was stirred for 30 min. The reaction mixture was then extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were washed with brine, dried over sodium sulfate, then concentrated *in vacuo*. The crude material was taken without purification to the next step. The crude hemiaminal (**17**) was diluted in THF (3 mL) in a dry flask under argon. Ammonium acetate, dried with a vacuum dessicator for 4 h (78 mg, 0.946 mmol, 10 equiv) was added along with a stir bar under argon and the solution was heated and stirred at 60 °C for 12 h. The reaction was cooled to rt, then diluted with ethyl acetate (10 mL) and water (5 mL). The organic phase was separated, and the aqueous layer

was then extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. ¹H NMR analysis revealed a 10:1 mixture of diastereomers. The crude material was purified *via* SiO₂ gel column chromatography (4:6 → 1:0 EtOAc/hexanes, bright blue spot under short wave UV) to afford (+)-aglaiastatin (**2**) in 62% (31 mg, 0.0589 mmol). Aglaiastatin (**2**) was found to be unstable to air (readily oxidizes to aglaroxin C (**3**)) *R_f* = 0.2 (8:2 EtOAc/hexanes); [α]_D²⁷ = + 86.1° (*c* = 0.2, CHCl₃); **m.p.** 157 °C; **IR** *v*_{max} (film): 2953, 2924, 2854, 1621, 1514, 1464, 1428, 1251, 1204, 1149, 1114 cm⁻¹; **¹H NMR** (500 MHz, CDCl₃) δ 7.13 (d, *J* = 9.0 Hz, 2H), 7.10 (d, *J* = 7.5 Hz, 2H), 7.03 (dd, *J*₁ = *J*₂ = 7.5 Hz, 2H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.59 (d, *J* = 9.0 Hz, 2H), 6.28 (d, *J* = 2.0 Hz, 1H), 6.08 (d, *J* = 2.0 Hz, 1H), 5.24 (s, 1H), 5.23 (m, 1H), 4.60 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.66 (s, 3H), 3.62 (m, 2H), 3.50 (m, 2H), 2.46 (m, 2H), 2.01 (m, 4H), 1.88 (s, 1H); **¹³C NMR** (125 MHz, CDCl₃) δ 163.9, 162.3, 161.1, 158.4, 157.5, 138.8, 128.5, 128.2, 127.4, 127.3, 125.9, 112.4, 107.2, 105.1, 92.8, 89.4, 88.1, 70.2, 57.3, 55.7, 55.5, 55.0, 44.0, 33.3, 22.8; **HR-MS**: *m/z* Calcd for [C₃₁H₃₀N₂O₆+H]⁺ 527.2182, found 527.2159 (-4.4 ppm).

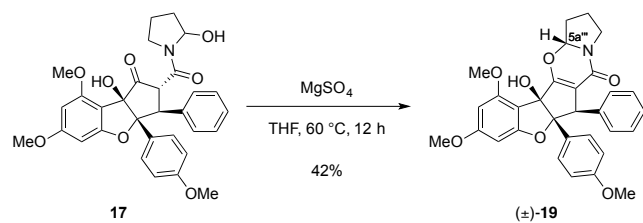
Table SI-1 Comparison of ^1H and ^{13}C spectra for natural and synthetic aglaiastatin (**2**)

Position	Natural ^{S5}	Synthetic	Natural ^{S5}	Synthetic
	δ_{H} (ppm)	δ_{H} (ppm)	δ_{C} (ppm)	δ_{C} (ppm)
1			157.2	157.5
2			106.5	106.3
3	4.60 (1H, s)	4.60 (1H, s)	57.3	57.4
3a			105.1	105.2
4a			161.1	161.2
5	6.28 (1H, d, $J=2.0$)	6.28 (1H, d, $J=2.0$)	89.4	89.5
6			164	164.0
7	6.08 (1H, d, $J=2.0$)	6.08 (1H, d, $J=2.0$)	92.8	92.9
8			157.5	157.6
8a			107.2	107.3
8b			88.2	88.3
6-OCH ₃	3.83 (3H, s)	3.83 (3H, s)	55.5 ^b	55.6
8-OCH ₃	3.83 (3H, s)	3.84 (3H, s)	55.8 ^b	55.9
8b-OH	1.97 (1H, br s)	1.88 (1H, br s)		
1'			127.2	127.47
2',6'	7.13 (2H, d, $J=9.0$)	7.13 (2H, d, $J=9.0$)	128.3	128.4
3',5'	6.58 (2H, d, $J=9.0$)	6.59 (2H, d, $J=9.0$)	112.5	112.5
4'			158.5	158.5
4'-OCH ₃	3.66 (3H, s)	3.66 (3H, s)	55	55.1
1''			138.8	139.0
2'',6''	7.10 (2H, d, $J=7.4$)	7.10 (2H, d, $J=7.5$)	128.5	128.6
3'',5''	7.03 (2H, dd, $J=7.4, 7.4$)	7.03 (2H, dd, $J=7.5, 7.5$)	127.4	127.49
4''	6.95 (1H, dd, $J=7.4, 7.4$)	6.96 (1H, dd, $J=7.5, 7.5$)	126	126.0
1'''			162.3	162.5
3'''	3.48 (1H, m)	3.50 (1H, m)	44	44.1
	3.62 (1H, m)	3.62 (1H, m)		
4'''	1.94–2.06 (2H, m)	2.01 (2H, m)	22.8	22.9
5'''	1.97–2.06 (1H, m)	2.01 (1H, m)	32.5	32.5
	2.47 (1H, m)	2.46 (1H, m)		
5a'''	5.23 (1H, m)	5.23 (1H, m)	70.3	70.3
6'''-NH	5.24 (1H, s)	5.24 (1H, s)		

^{S5} Ohse, T.; Ohba, S.; Yamamoto, T.; Koyano, T.; Umezawa, K. *J. Nat. Prod.* **1996**, *59*, 650-652.

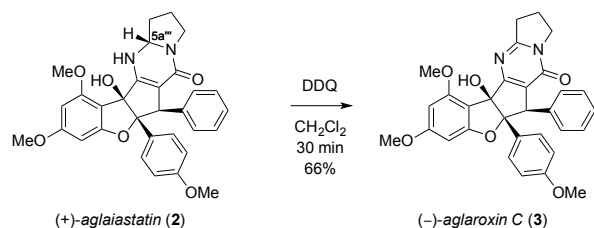


11b-Hydroxy-9,11-dimethoxy-6a-(4-methoxyphenyl)-6-phenyl-1,2,3,6,6a,11b,12,12a-octahydro-5H-benzofuro[2',3':4,5]cyclopenta[1,2-d]pyrrolo[1,2-a]pyrimidin-5-one 18: Hemiaminal **17** was prepared from aglain (±)-**5b** (40 mg, 0.0825 mmol, 1 equiv) following the first three steps outlined for (+)-*aglaiastatin* (**2**) (*vide supra*). The crude hemiaminal **17** was diluted with THF (2 mL) in a dry flask under argon. Ammonium formate (dried with a vacuum dessicator for 4 h, 76 mg, 1.21 mmol, 15 equiv) was added along with a stir bar under argon. To the resulting mixture was added formic acid (0.005 mL, 0.08 mmol, 1 equiv) and the mixture was stirred at rt for 6 d. The reaction was cooled to 0 °C, then quenched with a saturated sodium bicarbonate solution. The mixture was diluted with ethyl acetate (10 mL) and water (5 mL). The organic phase was separated and the aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. ¹H NMR analysis revealed a 1.2:1:1.2 ratio of products **2:18:19**. The crude material was purified *via* SiO₂ gel column chromatography (4:6 → 1:0 EtOAc/hexanes) to afford (±)-*aglaiastatin* (**2**) in 23% (10 mg, 0.0190 mmol), (±)-**18** 18% (8 mg, 0.0152 mmol), and (±)-**19** 28% (12 mg, 0.0228 mmol) yields as amorphous white solids. *Epi-aglaiastatin* **18**: *R_f* = 0.16 (2:1 EtOAc:hexanes); **IR** *v*_{max} (film): 3395, 2954, 1621, 1513, 1454, 1427, 1250, 1148, 1113 cm⁻¹; **¹H NMR** (500 MHz, CDCl₃) δ 7.05 (d, *J* = 9.0 Hz, 2H), 7.03-6.99 (ovrlp m, 3H), 6.95 (br d, *J* = 8.0 Hz, 2H), 6.55 (d, *J* = 9.0 Hz, 2H), 6.27 (d, *J* = 2.0 Hz, 1H), 6.07 (d, *J* = 2.0 Hz), 5.26 (s, 1H), 5.06 (dd, *J* = 8.0, 5.0 Hz, 1H), 4.48 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.66 (s, 3H), 3.63 (ddd, *J* = 11.5, 7.5, 7.5 Hz, 1H), 3.40 (ddd, *J* = 11.5, 9.0, 4.0 Hz, 1H), 2.30-2.04 (m, 4H); **¹³C NMR** (125 MHz, CDCl₃) δ 163.9, 162.9, 161.3, 158.6, 157.7, 157.2, 138.3, 129.7 (2C), 128.9 (2C), 127.3 (2C), 127.0, 126.4, 112.3 (2C), 107.3, 106.2, 104.0, 92.8, 89.6, 89.4, 72.5, 58.9, 55.90, 55.86, 55.2, 43.0, 33.0, 21.7; **HR-MS**: *m/z* Calcd for [C₃₁H₃₀N₂O₆+H]⁺ 527.2182, found 527.2169 (-2.5 ppm).



(6*R*,6*aR*,11*bS*,12*aR*)-11*b*-hydroxy-9,11-dimethoxy-6*a*-(4-methoxyphenyl)-6-phenyl-1,2,3,6*a*,11*b*,12*a*-hexahydrobenzofuro[3',2':3,4]cyclopenta[1,2-

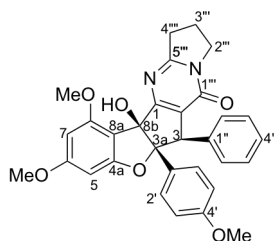
e]pyrrolo[2,1-*b*][1,3]oxazin-5(6*H*)-one **41**: Hemiaminal **17** was prepared from aglain ($\pm$)-**5b** (18 mg, 0.0367 mmol, 1 equiv) following the first three steps outlined for (+)-aglaiastatin (**1**) (*vide supra*). The crude hemiaminal **17** was diluted with THF (2 mL) in a dry flask under argon. Magnesium sulfate (48 mg, 0.399 mmol, 11 equiv) was added along with a stir bar under argon. The mixture was stirred at $60\text{ }^\circ\text{C}$ for 12 h. The reaction was cooled to rt, then filtered, and concentrated *in vacuo*. The crude material was purified *via* SiO_2 gel column chromatography (4:6 $\rightarrow$ 7:3 EtOAc/hexanes) to afford ($\pm$)-**19** (8 mg, 0.0152 mmol) in 42% yield as an amorphous white solid. Oxazinone **19** was recrystallized from EtOAc with slow diffusion of hexanes. R_f = 0.59 (EtOAc); **m.p.** 192-195 $^\circ\text{C}$; **IR** ν_{max} (film): 3509, 2955, 1658, 1623, 1514, 1501, 1456, 1441, 1351, 1251, 1149, 1114, 1043 cm^{-1} ; **^1H NMR** (500 MHz, CDCl_3) δ 7.11-6.99 (ovrlp m, 7H), 6.57 (br d, J = 9.0 Hz, 2H), 6.25 (d, J = 2.0 Hz, 1H), 6.06 (d, J = 2.0 Hz, 1H), 5.84 (ddd, J = 5.5, 4.0, 1.0 Hz, 1H), 4.59 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.72 (ddd, J = 12.5 Hz, 10.5 Hz, 6.5 Hz, 1H), 3.66 (s, 3H), 3.42 (ddd, J = 12.5, 10.5, 6.5 Hz, 1H), 2.55 (s, 1H), 2.48 (ddd, J = 13.0, 7.0, 7.0 Hz, 1H), 2.44-2.37 (m, 1H), 2.04 (ddd, J = 13.5, 7.0, 7.0 Hz, 1H), 1.96 (ddd, J = 13.0, 7.0 Hz, 7.0 Hz); **^{13}C NMR** (125 MHz, CDCl_3) δ 167.1, 164.0, 161.3, 160.8, 158.6, 158.1, 137.8, 128.68 (2C), 128.66 (2C), 127.8 (2C), 126.9, 126.6, 112.53, 112.45 (2C), 106.3, 103.7, 92.8, 91.8, 89.1, 88.0, 55.8, 55.7, 55.6, 55.1, 44.7, 31.8, 22.4; **HR-MS**: m/z Calcd for $[\text{C}_{31}\text{H}_{30}\text{NO}_7 + \text{H}]^+$ 528.2022, found 528.2006 (-3.0 ppm).



(-)-Aglaroxin C (3): To a dry 10 mL flask was added (+)-

aglaiastatin (**2**) (7 mg, 0.0133 mmol, 1 equiv), a stir bar, and CH_2Cl_2 (0.5 mL) under argon. DDQ (3.3 mg, 0.0146 mmol, 1.1 equiv) was added in one portion under argon and the reaction was stirred for 30 min at rt. The reaction mixture was filtered with cotton and was purified using preparative TLC (9:1 EtOAc/hexanes).

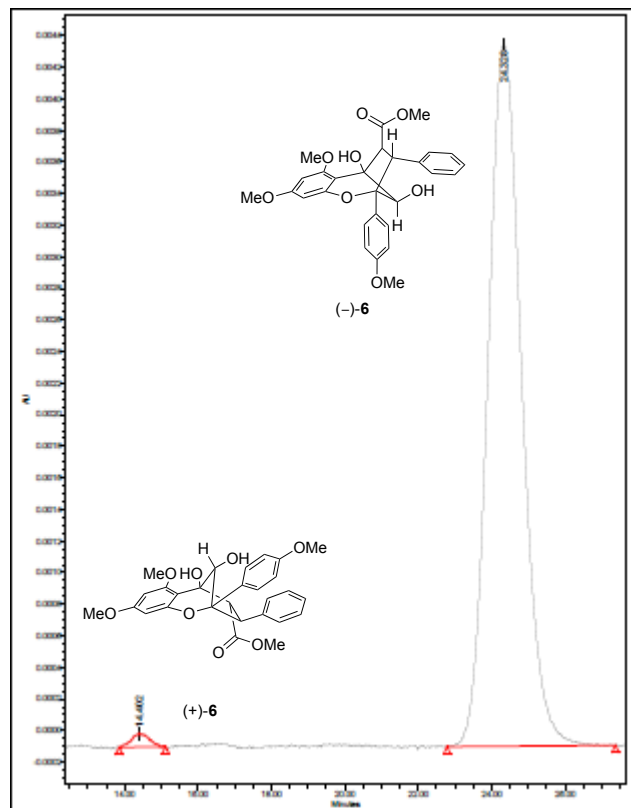
Aglaroxin C (**3**) was isolated as an amorphous yellow solid in 66% yield (4.6 mg, 0.00877 mmol). $R_f = 0.08$ (EtOAc); $[\alpha]_D^{27} = -49.2^\circ$ ($c = 0.1$, CHCl_3) **IR** ν_{max} (film): 3802, 3326, 2973, 2927, 2854, 1677, 1616, 1579, 1261, 1149 cm^{-1} ; **^1H NMR** (500 MHz, CDCl_3) δ 7.08 (d, $J = 9.0$ Hz, 2H), 7.06 (ovrlp m, 3H), 6.89 (m, 2H), 6.56 (d, $J = 9.0$ Hz, 2H), 6.20 (d, $J = 2.0$ Hz, 1H), 6.05 (d, $J = 2.0$ Hz, 1H), 4.69 (s, 1H), 4.12 (ovrlp m, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 3.66 (s, 3H), 3.31 (s, 1H), 3.22 (m, 2H), 2.30 (m, 2H); **^{13}C NMR** (125 MHz, CDCl_3) δ 166.9, 166.2, 163.6, 161.0, 159.2, 158.7, 158.2, 137.1, 129.4 (2C), 129.1 (2C), 127.9 (2C), 127.2, 126.9, 121.8, 112.4 (2C), 107.4, 103.7, 92.8, 90.5, 89.2, 57.1, 55.81, 55.75, 55.2, 46.9, 33.0, 19.7; **HR-MS**: m/z Calcd for $[\text{C}_{31}\text{H}_{28}\text{N}_2\text{O}_6 + \text{Na}]^+$ 547.1845, found 547.1860 (+2.7 ppm).

Table SI-2 Comparison of ^1H and ^{13}C spectra for natural and synthetic aglaroxin C (**3**)

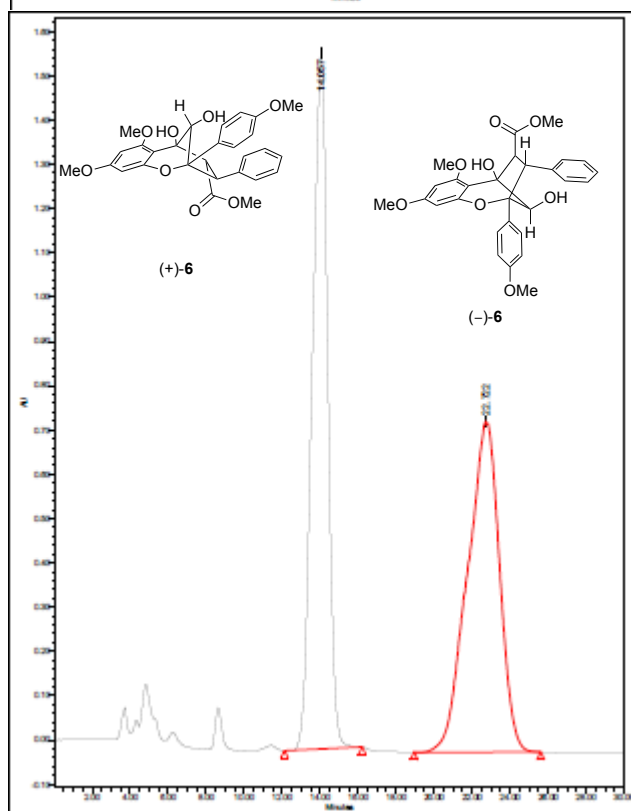
Position	Natural ^{S6}	Synthetic	Natural ^{S6}	Synthetic
	δ_{H} (ppm)	δ_{H} (ppm)	δ_{C} (ppm)	δ_{C} (ppm)
1			159.0	159.2
2			90.3	90.5
3	4.69 (1H, s)	4.69 (1H, s)	56.9	57.1
3a			103.6	103.7
4a			160.8	161.0
5	6.19 (1H, d, $J=2.0$)	6.20 (1H, d, $J=2.0$)	92.6	92.8
6			163.4	163.6
7	6.04 (1H, d, $J=2.0$)	6.05 (1H, d, $J=2.0$)	89.0	89.2
8			158.0	158.2
8a			107.2	107.4
8b			121.4	121.8
6-OCH ₃	3.78 (3H, s)	3.79 (3H, s)	55.5	55.75
8-OCH ₃	3.83 (3H, s)	3.84 (3H, s)	55.6	55.81
8b-OH	3.35 (1H, s)	3.31 (1H, s)		
1'			127.0	127.2
2',6'	7.08 (2H, d, $J=9.0$)	7.08 (2H, d, $J=9.0$)	128.9	129.1
3',5'	6.55 (2H, d, $J=9.0$)	6.56 (2H, d, $J=9.0$)	112.2	112.4
4'			158.6	158.7
4'-OCH ₃	3.65 (3H, s)	3.66 (3H, s)	54.9	55.2
1''			136.9	137.1
2'',6''	7.06 (2H, m)	7.06 (2H, m)	129.2	129.4
3'',5''	6.89 (2H, m)	6.89 (2H, m)	127.6	127.9
4''	7.06 (1H, m)	7.06 (1H, m)	126.7	126.9
1'''			166.7	166.9
2'''	4.09 (2H, m)	4.12 (2H, m)	46.7	46.9
3'''	2.25 (2H, m)	2.30 (2H, m)	19.4	19.7
4'''	3.20 (2H, m)	3.22 (2H, m)	32.7	33.0
5'''			166.0	166.2

^{S6} Kokpol, U.; Venaskulchai, B.; Simpson, J.; Weavers, R. T. *J. Chem. Soc., Chem. Commun.* **1994**, 773-774.

Chiral HPLC Analysis of (-)-6 and (+)-6: A Chiralpak AD column was used, with an isocratic mobile phase of isopropanol:hexanes (1:4) with a flow rate of 1.0 mL/min for 30 min.

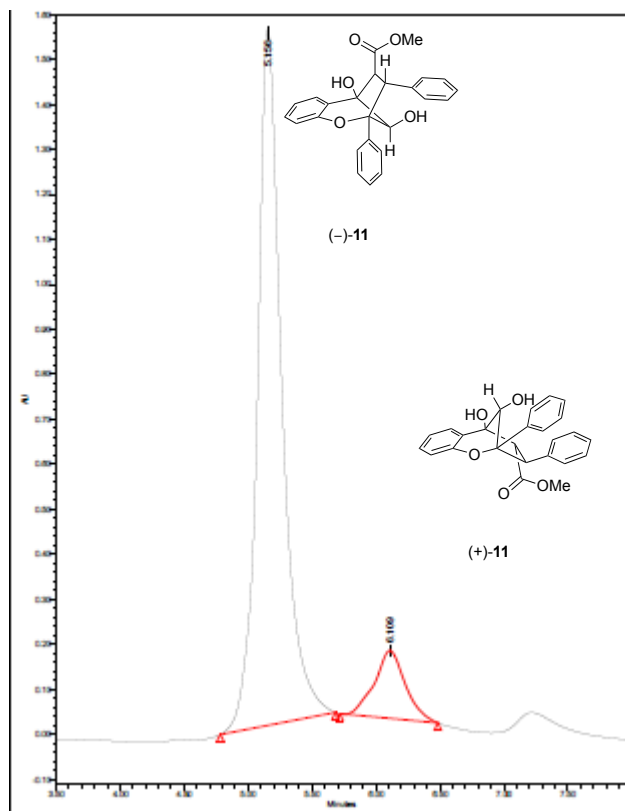


	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type
1		14.402	2896	1.02	85	bb
2		24.328	282336	98.98	4448	bb

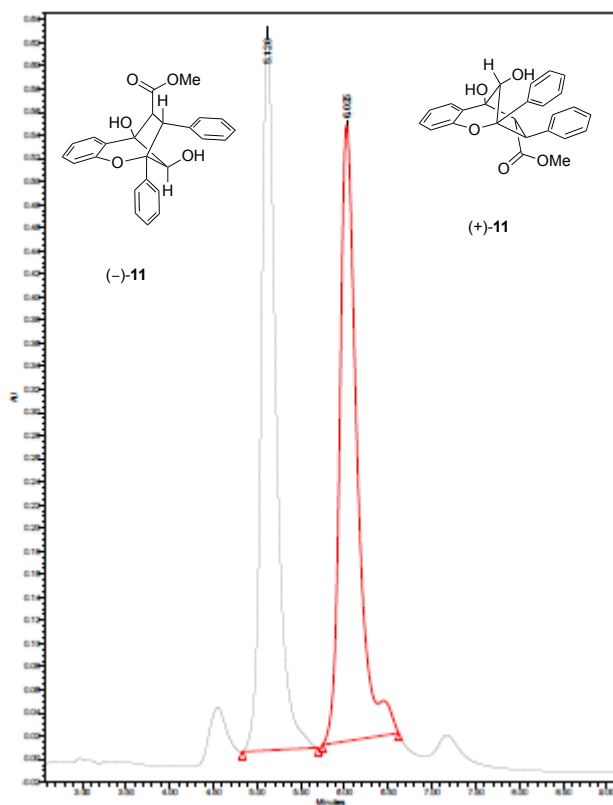


	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type
1		14.057	87442829	50.05	1570207	bb
2		22.722	87259888	49.95	745483	bb

Chiral HPLC Analysis of (-)-11 and (+)-11: A Chiralpak AD column was used, with an isocratic mobile phase of isopropanol:hexanes (1:4) with a flow rate of 1.0 mL/min for 15 min.

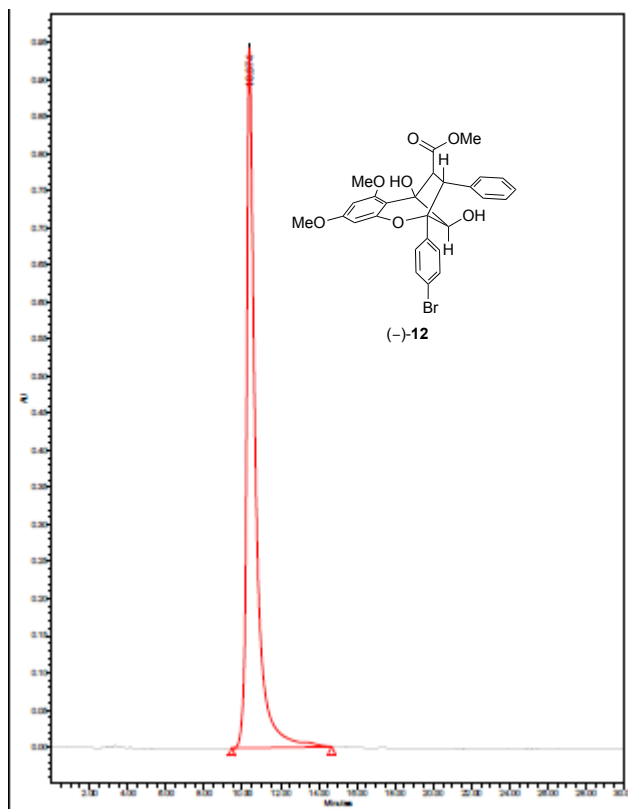


	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type
1		5.156	20491876	88.97	1549553	bb
2		6.109	2541090	11.03	150956	bb

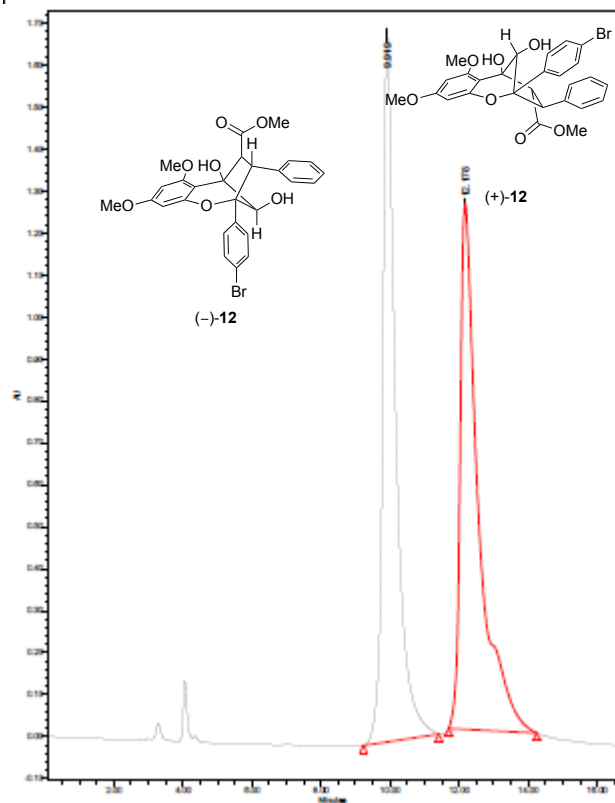


	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type
1		5.120	7440719	50.24	624965	bb
2		6.025	7369310	49.76	535755	bb

Chiral HPLC Analysis of (-)-12 and (+)-12: A Chiralpak AD column was used, with an isocratic mobile phase of isopropanol:hexanes (1:4) with a flow rate of 1.0 mL/min for 30 min.

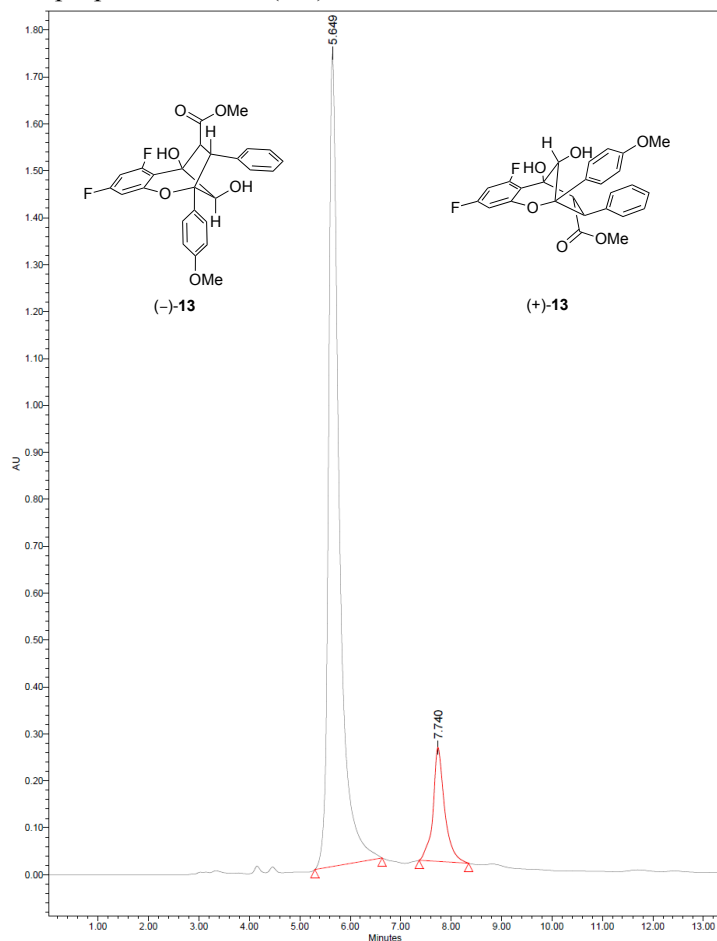


	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type
1		10.374	30740819	100.00	944421	bb

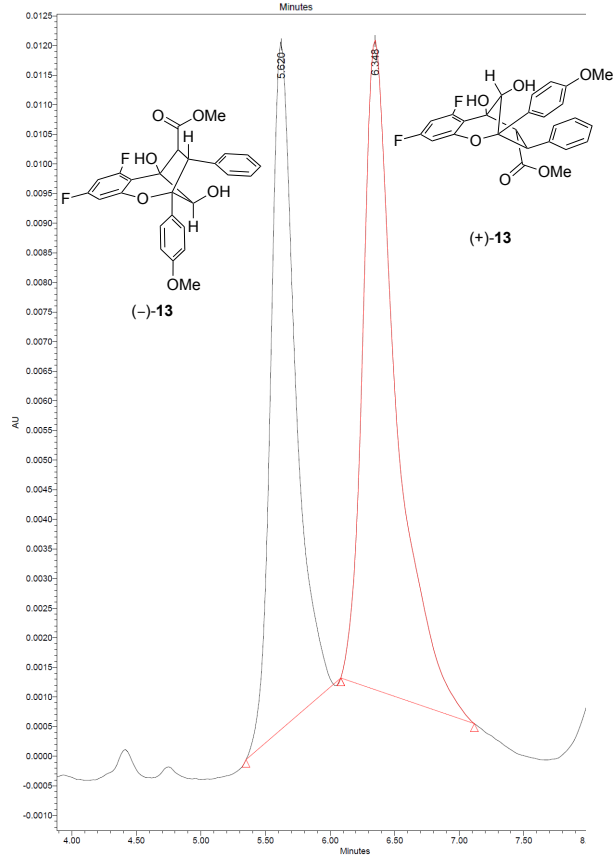


	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type
1		9.919	44760248	49.24	1683933	bb
2		12.178	46140663	50.76	1250871	bb

Chiral HPLC Analysis of (-)-13 and (+)-13: A Chiralpak AD column was used, with an isocratic mobile phase of isopropanol:hexanes (1:4) with a flow rate of 1.0 mL/min for 15 min.

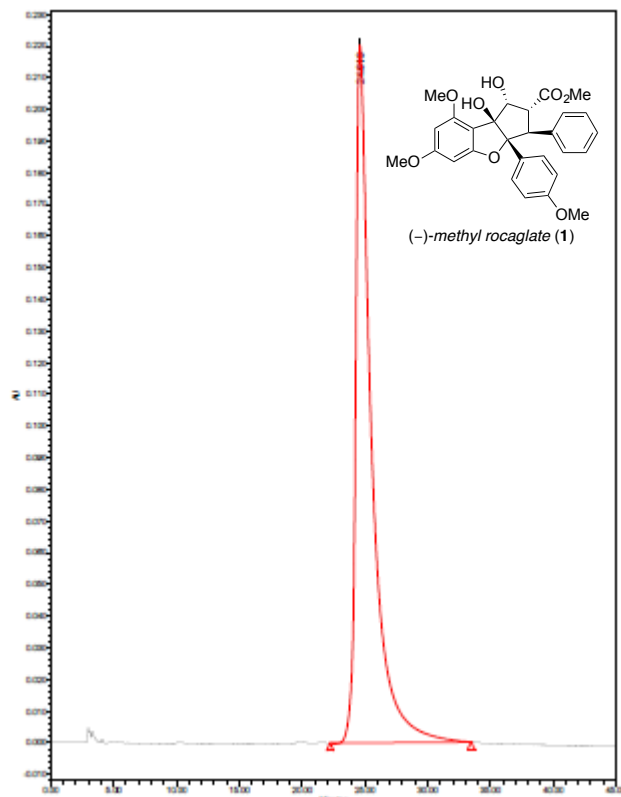


	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type
1		5.649	25604631	86.81	1734568	bb
2		7.740	3889766	13.19	243517	bb

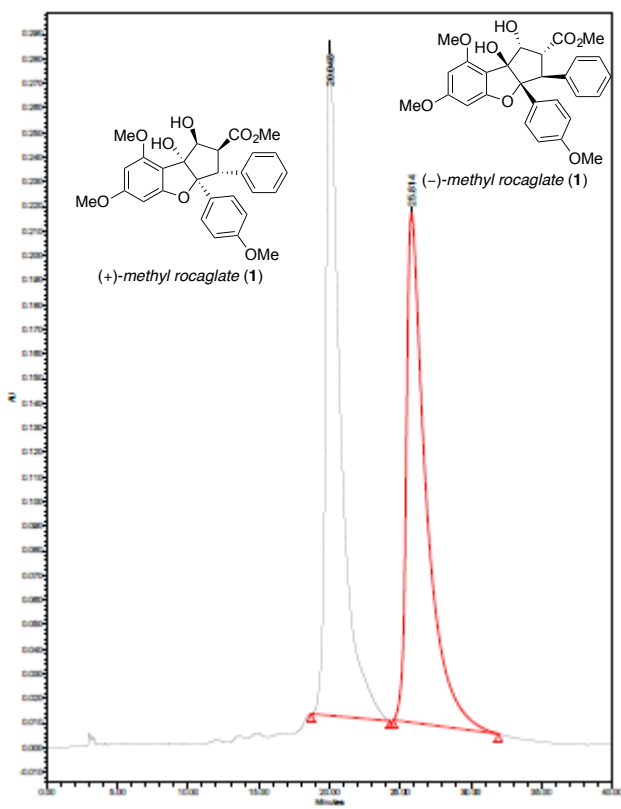


	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type
1		5.620	156080	43.66	11615	bb
2		6.348	201422	56.34	10968	bb

Chiral HPLC Analysis of (-)-1 and (+)-1: A Regis Pirkle covalent (*R,R*) WHELK-O 1 column was used, with an isocratic mobile phase of isopropanol:hexanes (1:4) with a flow rate of 1.0 mL/min for 60 min.

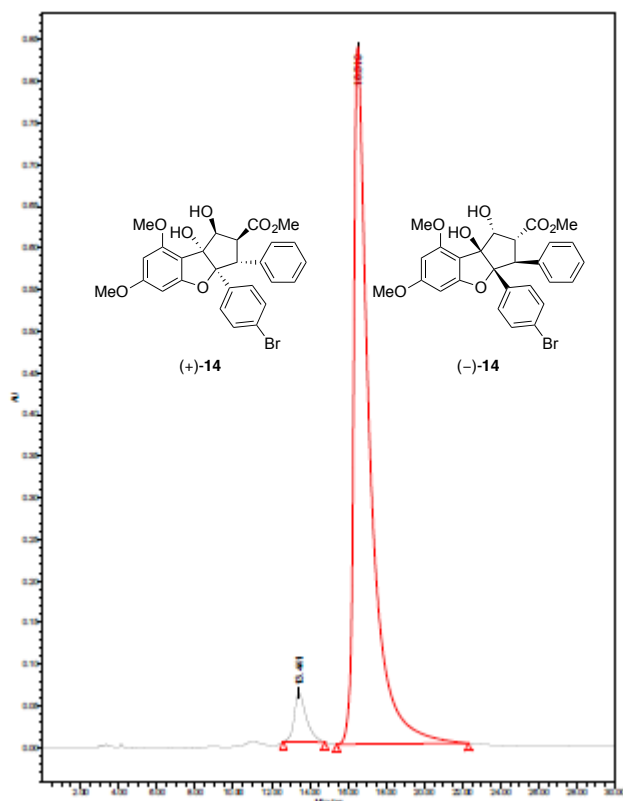


	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type
1		24.619	19579203	100.00	220251	bb

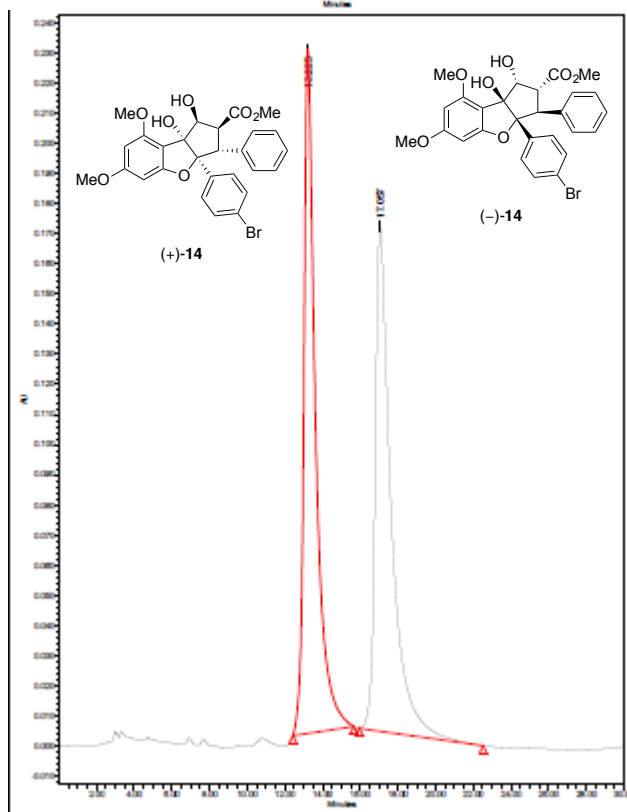


	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type
1		20.048	20129680	50.01	271443	bb
2		25.814	20124230	49.99	206837	bb

Chiral HPLC Analysis of (-)-14 and (+)-14: A Regis Pirkle covalent (*R,R*) WHELK-O 1 column was used, with an isocratic mobile phase of isopropanol:hexanes (1:4) with a flow rate of 1.0 mL/min for 45 min.

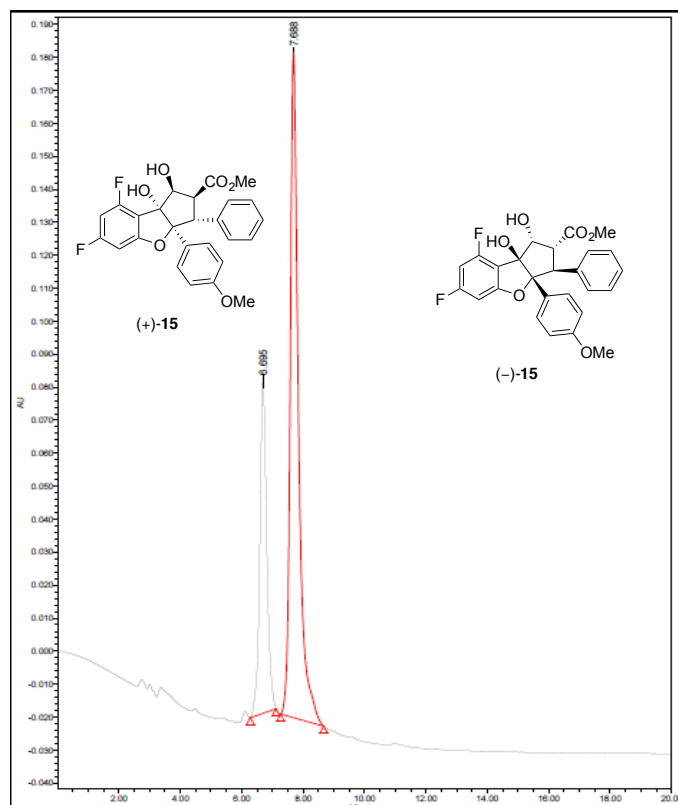


	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type
1		13.441	2611099	5.05	58691	bb
2		16.519	49134425	94.95	836632	bb

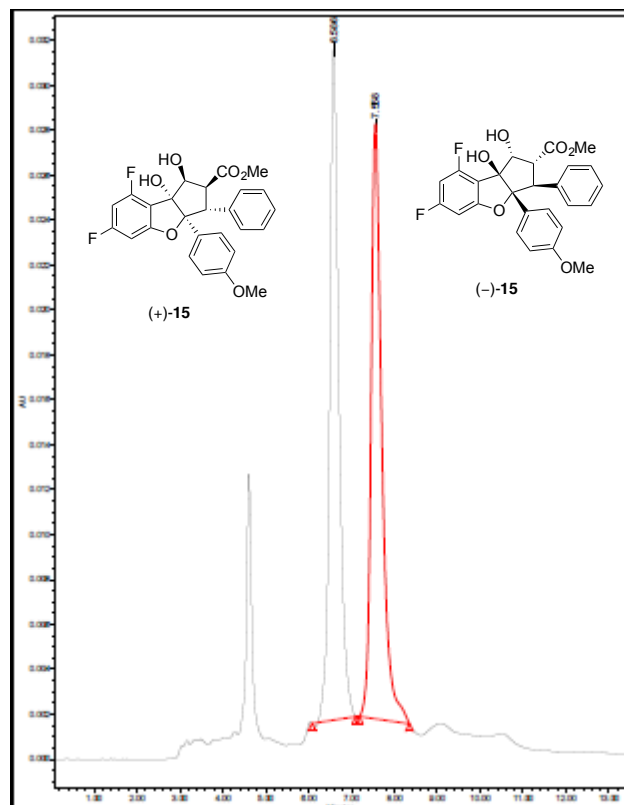


	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type
1		13.225	9832936	49.89	227351	bb
2		17.057	9875025	50.11	167916	bb

Chiral HPLC Analysis of (-)-15 and (+)-15: A Regis Pirkle covalent (*R,R*) WHELK-O 1 column was used, with an isocratic mobile phase of isopropanol:hexanes (1:4) with a flow rate of 1.0 mL/min for 30 min.



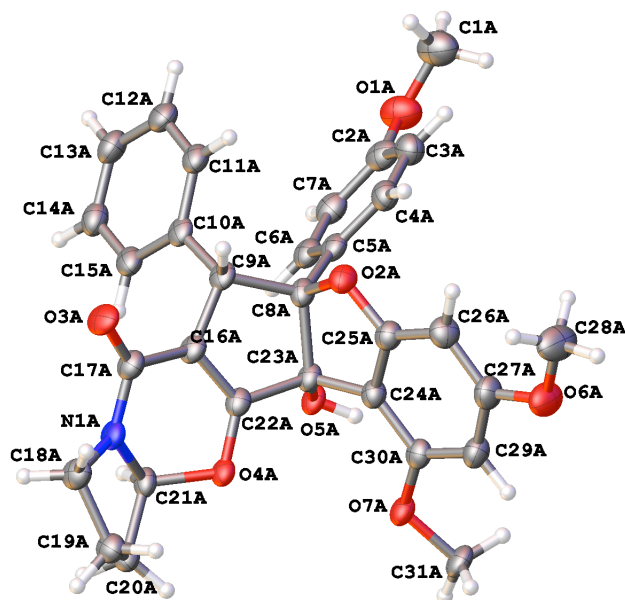
	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type
1		6.695	1589326	29.54	100792	bb
2		7.688	3790519	70.46	201936	bb



	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)
1		6.586	449925	49.46	29922
2		7.558	459775	50.54	26542

X-ray Crystal Structure of Oxazinone 19

Crystals of compound ($\pm$)-**19** suitable for X-ray analysis were obtained by vapor diffusion from EtOAc/hexanes. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1028723). 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).



Identification code **19**

Refinement

Crystal data, data collection and structure refinement details are summarized in Table 1.

Results and discussion

Computing details

Program(s) used to solve structure: XT (Sheldrick, 2008); program(s) used to refine structure: XL (Sheldrick, 2008); molecular graphics: Olex2 (Dolomanov *et al.*, 2009); software used to prepare material for publication: Olex2 (Dolomanov *et al.*, 2009).

References

Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K. & Puschmann, H. (2009). *J. Appl. Cryst.* **42**, 339–341.

Sheldrick, G. M. (2008). *Acta Cryst. A* **64**, 112–122.

Table SI-3. Crystal data and structure refinement for oxazinone **19**.

Crystal data

$C_{31}H_{29}NO_7$	$V = 5024.1 (4) \text{ \AA}^3$
$M_r = 527.55$	$Z = 8$
Triclinic, $P\bar{1}$	$F(000) = 2224$
$a = 16.4623 (7) \text{ \AA}$	$D_x = 1.395 \text{ Mg m}^{-3}$
$b = 16.6870 (7) \text{ \AA}$	Cu $K\alpha$ radiation, $\lambda = 1.54178 \text{ \AA}$
$c = 21.9358 (10) \text{ \AA}$	$\mu = 0.81 \text{ mm}^{-1}$
$\alpha = 72.571 (3)^\circ$	$T = 100 \text{ K}$
$\beta = 74.463 (2)^\circ$	Prism, colorless
$\gamma = 62.139 (2)^\circ$	$0.17 \times 0.09 \times 0.07 \text{ mm}$

Data collection

Absorption correction: multi-scan <i>SADABS</i> (Sheldrick, 1997)	$\theta_{\max} = 66.8^\circ$, $\theta_{\min} = 3.1^\circ$
$T_{\min} = 0.665$, $T_{\max} = 0.753$	$h = -18 \rightarrow 19$
17631 measured reflections	$k = -18 \rightarrow 19$
17631 independent reflections	$l = 0 \rightarrow 26$
15808 reflections with $I > 2\sigma(I)$	

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.055$	H-atom parameters constrained
$wR(F^2) = 0.154$	$w = 1/[\sigma^2(F_o^2) + (0.067P)^2 + 2.886P]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.03$	$(\Delta/\sigma)_{\max} = 0.001$
17631 reflections	$\Delta_{\max} = 0.56 \text{ e \AA}^{-3}$
1432 parameters	$\Delta_{\min} = -0.38 \text{ e \AA}^{-3}$
1392 restraints	

Special details

<i>Geometry.</i> 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.
<i>Refinement.</i> Refined as a 2-component twin.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\text{\AA}^2$)

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$	Occ. (<1)
O5B	0.30430 (10)	0.65161 (10)	0.92696 (7)	0.0279 (3)	
H5B	0.3296	0.6759	0.9397	0.042*	
O4B	0.13564 (10)	0.64900 (10)	1.01547 (7)	0.0263 (3)	
O4C	0.14391 (11)	0.64588 (11)	0.51652 (7)	0.0303 (3)	
O5A	0.78779 (10)	0.65898 (11)	0.95595 (7)	0.0277 (3)	
H5A	0.8327	0.6711	0.9343	0.042*	
O4A	0.70705 (10)	0.57801 (10)	0.89879 (7)	0.0266 (3)	
O7B	0.22828 (11)	0.77819 (11)	1.02839 (7)	0.0309 (3)	
O2C	0.32761 (10)	0.66842 (11)	0.32699 (7)	0.0321 (3)	
O3B	-0.04113 (10)	0.66348 (12)	0.91134 (7)	0.0320 (3)	
O2B	0.13865 (10)	0.84045 (11)	0.82912 (7)	0.0294 (3)	
O7C	0.27871 (11)	0.72180 (12)	0.53158 (8)	0.0354 (4)	
O7A	0.86846 (10)	0.66356 (11)	0.81284 (7)	0.0295 (3)	
O5C	0.15065 (11)	0.81588 (11)	0.43020 (8)	0.0317 (3)	
H5C	0.1805	0.8370	0.4414	0.048*	
O00D	0.15821 (11)	0.29929 (11)	0.46433 (8)	0.0324 (3)	
H00D	0.1692	0.3459	0.4457	0.049*	
O2A	0.58680 (10)	0.86717 (11)	0.90515 (7)	0.0302 (3)	
O00F	0.08866 (11)	0.21168 (11)	0.40466 (8)	0.0336 (4)	
O6B	0.05047 (12)	1.09445 (11)	0.92440 (8)	0.0359 (4)	
O3A	0.43146 (11)	0.67726 (13)	0.96602 (9)	0.0387 (4)	
O3C	0.16713 (13)	0.46989 (12)	0.41489 (8)	0.0381 (4)	
O6C	0.59310 (11)	0.56501 (13)	0.42586 (8)	0.0416 (4)	
O00K	0.14803 (12)	0.38938 (12)	0.32102 (8)	0.0369 (4)	
N1B	0.02179 (12)	0.60528 (13)	1.00497 (9)	0.0268 (4)	
O1C	0.09357 (12)	1.06719 (12)	0.17123 (9)	0.0403 (4)	
O1A	0.71592 (14)	0.91966 (15)	1.13264 (10)	0.0521 (5)	
O00O	0.37893 (12)	0.12002 (13)	0.41397 (9)	0.0449 (4)	
N1C	0.10598 (14)	0.52922 (14)	0.50644 (9)	0.0321 (4)	
N1A	0.56553 (12)	0.55752 (13)	0.93383 (9)	0.0289 (4)	
O6A	0.72086 (13)	0.96290 (13)	0.68649 (8)	0.0451 (4)	
O00S	0.21359 (14)	-0.06548 (12)	0.46349 (10)	0.0475 (5)	
O1B	0.51109 (13)	0.67316 (15)	0.64372 (9)	0.0492 (5)	
O00U	0.43715 (16)	0.21242 (16)	0.65269 (12)	0.0612 (6)	
C24B	0.18221 (14)	0.81272 (15)	0.92743 (10)	0.0269 (4)	
C22B	0.14818 (14)	0.67364 (15)	0.95004 (10)	0.0251 (4)	
C30B	0.18399 (15)	0.84395 (16)	0.97907 (11)	0.0283 (4)	

O00Y	0.44669 (13)	0.27942 (15)	0.19687 (9)	0.0494 (5)	
C24C	0.30847 (16)	0.69099 (16)	0.42913 (11)	0.0302 (5)	
C22A	0.66365 (14)	0.65074 (15)	0.92804 (10)	0.0265 (4)	
C16B	0.10384 (14)	0.66330 (15)	0.91190 (10)	0.0262 (4)	
C16C	0.15658 (15)	0.61788 (16)	0.41350 (11)	0.0304 (5)	
C9B	0.13241 (14)	0.69493 (16)	0.84117 (10)	0.0276 (4)	
H9B	0.0755	0.7453	0.8233	0.033*	
N014	0.08346 (15)	0.06501 (14)	0.43673 (10)	0.0392 (5)	
C30C	0.34289 (17)	0.68586 (17)	0.48221 (11)	0.0328 (5)	
C25B	0.13717 (15)	0.87825 (16)	0.87692 (10)	0.0284 (5)	
C22C	0.16618 (15)	0.66135 (15)	0.45157 (10)	0.0280 (5)	
C27B	0.09555 (15)	1.00121 (16)	0.92740 (11)	0.0308 (5)	
C17B	0.02275 (14)	0.64238 (15)	0.94078 (10)	0.0264 (4)	
C19B	-0.03906 (16)	0.61274 (17)	1.11263 (11)	0.0324 (5)	
H19E	-0.0697	0.5840	1.1522	0.039*	
H19F	-0.0601	0.6786	1.1133	0.039*	
C10B	0.17358 (14)	0.62062 (16)	0.80166 (11)	0.0281 (5)	
C23C	0.21044 (15)	0.72743 (15)	0.41732 (11)	0.0289 (5)	
C29B	0.14131 (16)	0.93841 (16)	0.97899 (11)	0.0316 (5)	
H29B	0.1433	0.9600	1.0138	0.038*	
C17C	0.14157 (16)	0.53333 (16)	0.44313 (11)	0.0311 (5)	
C25C	0.37034 (16)	0.65649 (16)	0.37674 (11)	0.0309 (5)	
C15B	0.18268 (16)	0.64710 (18)	0.73422 (11)	0.0326 (5)	
H15B	0.1607	0.7110	0.7145	0.039*	
C26B	0.09297 (15)	0.97243 (16)	0.87483 (11)	0.0308 (5)	
H26B	0.0625	1.0152	0.8395	0.037*	
C8C	0.22699 (15)	0.71836 (16)	0.34353 (11)	0.0293 (5)	
C21B	0.10210 (15)	0.57704 (15)	1.03512 (11)	0.0278 (4)	
H21B	0.1526	0.5181	1.0233	0.033*	
C23B	0.21437 (14)	0.71681 (15)	0.91552 (10)	0.0254 (4)	
C15A	0.55823 (15)	0.65111 (17)	1.10328 (12)	0.0326 (5)	
H15A	0.5896	0.5985	1.0838	0.039*	
C23A	0.70966 (14)	0.71243 (15)	0.92381 (10)	0.0264 (4)	
C18B	-0.05953 (15)	0.60315 (17)	1.05210 (11)	0.0309 (5)	
H18E	-0.0642	0.5440	1.0588	0.037*	
H18F	-0.1177	0.6552	1.0385	0.037*	
C21A	0.66567 (15)	0.51188 (15)	0.92935 (11)	0.0283 (5)	
H21A	0.6835	0.4801	0.9734	0.034*	
C9A	0.54733 (14)	0.75712 (16)	0.99146 (11)	0.0286 (5)	
H9A	0.4885	0.8055	0.9751	0.034*	

C25A	0.65193 (16)	0.85471 (16)	0.85074 (11)	0.0304 (5)	
C10A	0.52808 (14)	0.73966 (16)	1.06456 (11)	0.0291 (5)	
C7A	0.72005 (16)	0.79947 (18)	1.09631 (12)	0.0357 (5)	
H7A	0.7511	0.7576	1.1316	0.043*	
C5A	0.65530 (15)	0.82691 (16)	1.00129 (11)	0.0291 (5)	
C20B	0.06692 (15)	0.56107 (16)	1.10703 (11)	0.0305 (5)	
H20E	0.0915	0.5861	1.1299	0.037*	
H20F	0.0859	0.4942	1.1256	0.037*	
C24A	0.72506 (15)	0.76863 (15)	0.85715 (11)	0.0274 (4)	
C26C	0.46563 (16)	0.61317 (17)	0.37517 (11)	0.0341 (5)	
H26C	0.5066	0.5881	0.3392	0.041*	
C5C	0.19377 (16)	0.81069 (16)	0.29679 (11)	0.0298 (5)	
C5B	0.28375 (15)	0.72081 (16)	0.79160 (11)	0.0290 (5)	
C20C	0.06354 (18)	0.56893 (18)	0.60744 (11)	0.0369 (5)	
H20G	-0.0025	0.5827	0.6251	0.044*	
H20H	0.0863	0.5956	0.6304	0.044*	
C20A	0.69544 (16)	0.44134 (16)	0.88884 (12)	0.0320 (5)	
H20I	0.7049	0.3796	0.9165	0.038*	
H20J	0.7539	0.4366	0.8592	0.038*	
C16A	0.57809 (15)	0.67472 (16)	0.96302 (11)	0.0290 (5)	
C10C	0.11127 (16)	0.68652 (16)	0.30067 (11)	0.0314 (5)	
C30A	0.79765 (15)	0.74941 (16)	0.80540 (11)	0.0294 (5)	
C14B	0.22324 (17)	0.58166 (18)	0.69578 (12)	0.0371 (5)	
H14B	0.2297	0.6009	0.6501	0.044*	
C29C	0.43879 (17)	0.64517 (17)	0.48194 (12)	0.0355 (5)	
H29C	0.4631	0.6427	0.5175	0.043*	
C6A	0.69999 (15)	0.76673 (17)	1.05430 (11)	0.0319 (5)	
H6A	0.7166	0.7023	1.0613	0.038*	
C4A	0.63226 (16)	0.92013 (17)	0.99220 (12)	0.0337 (5)	
H4A	0.6026	0.9617	0.9563	0.040*	
C6C	0.09970 (16)	0.87313 (16)	0.30274 (11)	0.0314 (5)	
H6C	0.0566	0.8574	0.3368	0.038*	
C2A	0.69507 (16)	0.89382 (19)	1.08730 (12)	0.0381 (5)	
C17A	0.51740 (15)	0.63629 (17)	0.95674 (11)	0.0310 (5)	
C30D	0.23712 (18)	0.32789 (18)	0.31438 (12)	0.0363 (5)	
C9C	0.18593 (16)	0.64950 (16)	0.34308 (11)	0.0303 (5)	
H9C	0.2389	0.5946	0.3273	0.036*	
C11B	0.20418 (15)	0.52683 (17)	0.82928 (11)	0.0324 (5)	
H11B	0.1982	0.5073	0.8750	0.039*	
C21C	0.07501 (16)	0.60745 (17)	0.53560 (11)	0.0320 (5)	

H21C	0.0140	0.6560	0.5227	0.038*	
C3A	0.65160 (18)	0.95465 (19)	1.03465 (13)	0.0398 (6)	
H3A	0.6352	1.0190	1.0277	0.048*	
C27C	0.49855 (16)	0.60824 (17)	0.42917 (12)	0.0357 (5)	
C6D	0.27523 (18)	0.21189 (17)	0.56535 (12)	0.0365 (5)	
H6D	0.2113	0.2257	0.5699	0.044*	
C4B	0.35565 (15)	0.63268 (17)	0.79428 (11)	0.0320 (5)	
H4B	0.3517	0.5844	0.8296	0.038*	
C8B	0.19709 (15)	0.74107 (15)	0.84193 (10)	0.0270 (4)	
C28B	0.05276 (18)	1.12923 (17)	0.97568 (12)	0.0371 (5)	
H28D	0.0163	1.1965	0.9681	0.056*	
H28E	0.1172	1.1146	0.9773	0.056*	
H28F	0.0263	1.1005	1.0168	0.056*	
C3B	0.43349 (16)	0.61315 (18)	0.74658 (12)	0.0355 (5)	
H3B	0.4821	0.5524	0.7496	0.043*	
C7C	0.06887 (16)	0.95684 (16)	0.26007 (11)	0.0325 (5)	
H7C	0.0048	0.9979	0.2646	0.039*	
C28C	0.63071 (18)	0.5518 (2)	0.48145 (13)	0.0432 (6)	
H28G	0.6980	0.5142	0.4747	0.065*	
H28H	0.6017	0.5201	0.5194	0.065*	
H28I	0.6183	0.6121	0.4884	0.065*	
C8D	0.30369 (17)	0.14694 (18)	0.46745 (12)	0.0390 (6)	
C18C	0.1115 (2)	0.44464 (18)	0.55444 (12)	0.0397 (6)	
H18G	0.1660	0.3894	0.5416	0.048*	
H18H	0.0543	0.4353	0.5612	0.048*	
C8A	0.62596 (15)	0.79154 (15)	0.95856 (11)	0.0278 (5)	
C11A	0.48187 (15)	0.81549 (17)	1.09440 (11)	0.0327 (5)	
H11A	0.4591	0.8763	1.0687	0.039*	
C29A	0.79332 (17)	0.81767 (17)	0.74971 (11)	0.0335 (5)	
H29A	0.8432	0.8058	0.7147	0.040*	
C14C	-0.04688 (19)	0.73866 (19)	0.28515 (13)	0.0421 (6)	
H14C	-0.1098	0.7507	0.3031	0.051*	
C19A	0.61537 (16)	0.47750 (17)	0.85079 (12)	0.0339 (5)	
H19I	0.6219	0.5230	0.8110	0.041*	
H19J	0.6126	0.4262	0.8389	0.041*	
C19C	0.12179 (19)	0.46497 (18)	0.61455 (12)	0.0390 (5)	
H19G	0.0976	0.4306	0.6544	0.047*	
H19H	0.1876	0.4486	0.6154	0.047*	
C3C	0.22366 (17)	0.92121 (18)	0.20315 (12)	0.0376 (5)	
H3C	0.2666	0.9371	0.1690	0.045*	

C31B	0.2506 (2)	0.80941 (18)	1.07310 (13)	0.0442 (6)	
H31D	0.2828	0.8489	1.0493	0.066*	
H31E	0.2909	0.7559	1.1015	0.066*	
H31F	0.1933	0.8449	1.0992	0.066*	
C18A	0.52956 (16)	0.52302 (18)	0.89760 (12)	0.0353 (5)	
H18I	0.4793	0.5743	0.8743	0.042*	
H18J	0.5061	0.4776	0.9264	0.042*	
C7D	0.30639 (19)	0.22668 (18)	0.61205 (13)	0.0411 (6)	
H7D	0.2639	0.2511	0.6478	0.049*	
C2D	0.4000 (2)	0.20570 (19)	0.60628 (14)	0.0461 (6)	
C12B	0.24361 (17)	0.46112 (18)	0.79054 (13)	0.0384 (5)	
H12B	0.2632	0.3972	0.8100	0.046*	
C29D	0.30161 (18)	0.33356 (18)	0.25873 (12)	0.0381 (5)	
H29D	0.2835	0.3845	0.2235	0.046*	
C22D	0.16481 (16)	0.17140 (17)	0.43468 (11)	0.0336 (5)	
C12C	0.0704 (2)	0.73521 (18)	0.19293 (12)	0.0410 (6)	
H12C	0.0884	0.7456	0.1474	0.049*	
C11C	0.13612 (18)	0.70084 (17)	0.23363 (12)	0.0362 (5)	
H11C	0.1993	0.6868	0.2154	0.043*	
C31A	0.95455 (16)	0.65361 (18)	0.77052 (11)	0.0343 (5)	
H31J	0.9470	0.6600	0.7262	0.051*	
H31K	1.0033	0.5924	0.7845	0.051*	
H31L	0.9720	0.7016	0.7719	0.051*	
C15C	0.01883 (17)	0.70536 (17)	0.32596 (12)	0.0365 (5)	
H15C	0.0002	0.6954	0.3715	0.044*	
C27A	0.71671 (18)	0.90321 (17)	0.74465 (11)	0.0363 (5)	
C31C	0.31045 (19)	0.7390 (2)	0.57884 (13)	0.0444 (6)	
H31G	0.3459	0.7760	0.5572	0.067*	
H31H	0.3503	0.6800	0.6035	0.067*	
H31I	0.2569	0.7729	0.6082	0.067*	
C20D	-0.04518 (18)	0.19115 (19)	0.39516 (13)	0.0415 (6)	
H20A	-0.1039	0.1938	0.4237	0.050*	0.703 (8)
H20B	-0.0569	0.2527	0.3665	0.050*	0.703 (8)
H20C	-0.1036	0.2406	0.4112	0.050*	0.297 (8)
H20D	-0.0257	0.2143	0.3491	0.050*	0.297 (8)
C21D	0.02978 (17)	0.16299 (17)	0.43463 (12)	0.0361 (5)	
H21D	0.0012	0.1744	0.4793	0.043*	
C13A	0.49878 (17)	0.71545 (19)	1.19867 (12)	0.0391 (5)	
H13A	0.4892	0.7073	1.2444	0.047*	
C5D	0.33533 (17)	0.17734 (18)	0.51200 (12)	0.0390 (5)	

C14A	0.54279 (17)	0.63920 (18)	1.17006 (12)	0.0378 (5)	
H14A	0.5625	0.5786	1.1962	0.045*	
C26A	0.64367 (17)	0.92420 (17)	0.79530 (11)	0.0349 (5)	
H26A	0.5912	0.9825	0.7923	0.042*	
C2B	0.43941 (17)	0.68329 (19)	0.69459 (12)	0.0378 (5)	
C2C	0.13110 (17)	0.98177 (17)	0.21017 (12)	0.0338 (5)	
C12A	0.46870 (16)	0.80368 (18)	1.16055 (12)	0.0369 (5)	
H12A	0.4389	0.8562	1.1801	0.044*	
C24D	0.26687 (17)	0.25272 (18)	0.36631 (12)	0.0371 (5)	
C17D	0.16742 (19)	0.01942 (17)	0.45761 (12)	0.0397 (6)	
C10D	0.26190 (18)	0.03983 (17)	0.57199 (13)	0.0387 (5)	
C15D	0.17208 (19)	0.06372 (18)	0.60629 (13)	0.0412 (6)	
H15D	0.1212	0.0850	0.5841	0.049*	
C16D	0.19950 (18)	0.08357 (17)	0.46652 (12)	0.0386 (5)	
C6B	0.29095 (18)	0.78983 (18)	0.73908 (11)	0.0360 (5)	
H6B	0.2423	0.8506	0.7358	0.043*	
C4C	0.25410 (16)	0.83606 (17)	0.24658 (12)	0.0352 (5)	
H4C	0.3180	0.7945	0.2414	0.042*	
C7B	0.36860 (19)	0.77106 (19)	0.69115 (12)	0.0407 (6)	
H7B	0.3727	0.8193	0.6558	0.049*	
C23D	0.21740 (16)	0.22601 (17)	0.43259 (11)	0.0346 (5)	
C25D	0.35765 (18)	0.18897 (19)	0.36007 (12)	0.0409 (6)	
C13B	0.25435 (17)	0.4885 (2)	0.72378 (13)	0.0416 (6)	
H13B	0.2829	0.4435	0.6974	0.050*	
C12D	0.31978 (19)	-0.00048 (18)	0.67246 (13)	0.0431 (6)	
H12D	0.3705	-0.0223	0.6949	0.052*	
C13C	-0.02154 (19)	0.75427 (18)	0.21913 (13)	0.0426 (6)	
H13C	-0.0670	0.7781	0.1916	0.051*	
C27D	0.39088 (19)	0.2660 (2)	0.25485 (12)	0.0418 (6)	
C9D	0.28047 (18)	0.06005 (18)	0.49837 (12)	0.0400 (6)	
H9D	0.3341	0.0045	0.4840	0.048*	
C13D	0.2299 (2)	0.02586 (19)	0.70571 (13)	0.0451 (6)	
H13D	0.2187	0.0228	0.7510	0.054*	
C14D	0.1566 (2)	0.05664 (19)	0.67252 (14)	0.0444 (6)	
H14D	0.0951	0.0730	0.6954	0.053*	
C31D	0.1256 (2)	0.47649 (19)	0.27590 (13)	0.0433 (6)	
H31A	0.1319	0.4670	0.2326	0.065*	
H31B	0.1680	0.5028	0.2755	0.065*	
H31C	0.0615	0.5192	0.2888	0.065*	
C4D	0.42779 (19)	0.1637 (2)	0.50480 (14)	0.0474 (6)	

H4D	0.4697	0.1447	0.4672	0.057*	
C1C	0.15620 (19)	1.09610 (19)	0.12185 (13)	0.0424 (6)	
H1CA	0.1853	1.0545	0.0912	0.064*	
H1CB	0.2043	1.0943	0.1413	0.064*	
H1CC	0.1221	1.1594	0.0991	0.064*	
C11D	0.33536 (19)	0.00505 (18)	0.60648 (13)	0.0415 (6)	
H11D	0.3973	-0.0152	0.5842	0.050*	
C26D	0.42214 (18)	0.1914 (2)	0.30492 (13)	0.0437 (6)	
H26D	0.4840	0.1446	0.3017	0.052*	
C3D	0.4588 (2)	0.1776 (2)	0.55194 (16)	0.0527 (7)	
H3D	0.5219	0.1674	0.5464	0.063*	
C18D	0.0473 (2)	0.0287 (2)	0.40200 (17)	0.0550 (8)	
H18A	0.0068	-0.0001	0.4319	0.066*	0.703 (8)
H18B	0.0982	-0.0170	0.3775	0.066*	0.703 (8)
H18C	0.0507	-0.0335	0.4250	0.066*	0.297 (8)
H18D	0.0808	0.0258	0.3573	0.066*	0.297 (8)
C1A	0.6712 (2)	1.0153 (2)	1.13357 (17)	0.0562 (8)	
H1AA	0.6947	1.0495	1.0940	0.084*	
H1AB	0.6838	1.0253	1.1712	0.084*	
H1AC	0.6040	1.0373	1.1362	0.084*	
C1B	0.5919 (2)	0.5901 (2)	0.64986 (15)	0.0515 (7)	
H1BA	0.6413	0.5956	0.6145	0.077*	
H1BB	0.5790	0.5392	0.6480	0.077*	
H1BC	0.6119	0.5774	0.6913	0.077*	
C28D	0.5332 (2)	0.2057 (2)	0.18639 (14)	0.0515 (7)	
H28A	0.5621	0.2181	0.1414	0.077*	
H28B	0.5250	0.1486	0.1950	0.077*	
H28C	0.5733	0.1986	0.2154	0.077*	
C28A	0.6407 (2)	1.0484 (2)	0.67552 (14)	0.0549 (8)	
H28J	0.6505	1.0826	0.6314	0.082*	
H28K	0.6303	1.0855	0.7064	0.082*	
H28L	0.5863	1.0359	0.6813	0.082*	
C1D	0.3812 (3)	0.2201 (3)	0.71478 (19)	0.0741 (11)	
H1DA	0.3271	0.2802	0.7116	0.111*	
H1DB	0.4179	0.2150	0.7454	0.111*	
H1DC	0.3601	0.1704	0.7299	0.111*	
C19D	-0.0089 (3)	0.1182 (3)	0.3562 (2)	0.0447 (12)	0.703 (8)
H19A	0.0316	0.1317	0.3159	0.054*	0.703 (8)
H19B	-0.0604	0.1131	0.3449	0.054*	0.703 (8)
C19E	-0.0589 (6)	0.1057 (6)	0.4028 (4)	0.042 (3)	0.297 (8)

H19C	-0.0861	0.1092	0.3664	0.051*	0.297 (8)
H19D	-0.0984	0.0940	0.4441	0.051*	0.297 (8)

Document origin: *publCIF* [Westrip, S. P. (2010). *J. Apply. Cryst.*, **43**, 920-925].

Ground State Conformers for *N*-Acyliminiums

The following calculations were done using Spartan '10 (Wavefunction, Inc. Irvine, CA):

Rotamer **20a** with Acetate Counterion

A conformer distribution for *N*-acyliminium **20a** with an acetate counterion was searched (MMFF level of theory) and the single point energies of the lowest energy structures were computed using B3LYP/6-31G* level of theory. The lowest energy conformer was then subjected to an equilibrium geometry calculation at the B3LYP/6-31G* level to provide the ground state of **20a** shown:

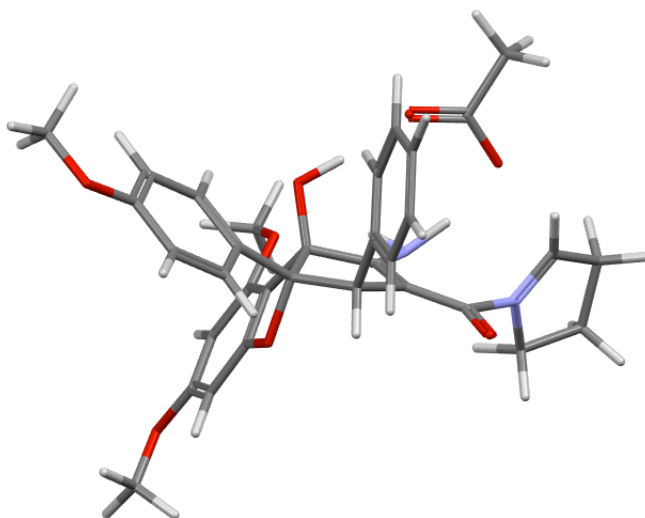


Table SI-3 Cartesian Coordinates for the Ground State of Rotamer **20a** with Acetate Counterion

Atom	X (Å)	Y (Å)	Z (Å)
C(1)	-3.0827	-3.3004	-0.4968
H(2)	-3.582	-4.1125	-1.0093
C(3)	-3.5312	-2.9674	0.8033
C(4)	-2.946	-1.9323	1.5484
H(5)	-3.2773	-1.6635	2.5422
C(6)	-1.907	-1.2376	0.9354
C(7)	-1.4607	-1.5282	-0.3468
C(8)	-2.0326	-2.5848	-1.0576
O(9)	-1.4636	-2.8328	-2.2932
O(10)	-4.5563	-3.731	1.2458
C(11)	-2.1051	-3.786	-3.1507
H(12)	-2.0617	-4.7914	-2.7181
H(13)	-1.5503	-3.7646	-4.0895
H(14)	-3.1477	-3.5041	-3.3287
C(15)	-5.1076	-3.4662	2.534
H(16)	-4.3587	-3.6059	3.3227
H(17)	-5.9121	-4.1907	2.6634
H(18)	-5.5163	-2.4503	2.5885
O(19)	-1.2139	-0.2225	1.5116

C(20)	-0.3064	-0.6237	-0.6664
C(21)	-0.4491	0.4931	0.4475
C(22)	1.7118	-0.5839	0.6388
C(23)	1.0294	-1.2953	-0.3171
C(24)	0.9746	0.6903	1.0562
H(25)	0.8665	0.7312	2.1438
C(26)	-1.2359	1.7515	0.1451
C(27)	-2.836	4.0612	-0.163
C(28)	-1.2823	2.7474	1.1411
C(29)	-2.0249	1.9361	-0.9929
C(30)	-2.8151	3.0774	-1.156
C(31)	-2.0608	3.8819	0.995
H(32)	-0.7073	2.6273	2.0542
H(33)	-2.0229	1.197	-1.7816
H(34)	-3.4049	3.1815	-2.0593
H(35)	-2.0908	4.647	1.7642
C(36)	1.7683	1.9112	0.5995
C(37)	3.3466	4.0987	-0.194
C(38)	1.9595	2.1965	-0.7625
C(39)	2.3834	2.7311	1.5524
C(40)	3.1675	3.8183	1.1602
C(41)	2.7372	3.2862	-1.1539
H(42)	1.4723	1.5874	-1.5203
H(43)	2.25	2.5162	2.6099
H(44)	3.6345	4.4454	1.9146
H(45)	2.8588	3.5086	-2.2108
H(46)	3.9498	4.9485	-0.5007
O(47)	-3.5598	5.2084	-0.218
C(48)	-4.3702	5.445	-1.3625
H(49)	-4.8505	6.4094	-1.192
H(50)	-5.1391	4.6702	-1.4754
H(51)	-3.7663	5.4955	-2.2774
C(52)	2.9879	-0.8471	1.2271
O(53)	3.4406	-0.5195	2.2958
C(54)	5.0665	-2.4417	0.8728
C(55)	6.1244	-2.5037	-0.2546
C(56)	5.4374	-1.8544	-1.4888
H(57)	4.6032	-3.4074	1.0996
H(58)	7.0122	-1.9328	0.0267
H(59)	6.4395	-3.5292	-0.4538
H(60)	5.1293	-2.5801	-2.256
H(61)	6.0557	-1.1131	-2.0078
N(62)	1.3477	-2.4419	-0.9722
H(63)	1.9913	-3.1006	-0.5565

O(64)	-0.2255	-0.1583	-2.0059
H(65)	-0.6891	-0.81	-2.561
H(66)	0.6028	-2.8691	-1.5171
H(67)	5.4176	-2.0023	1.8075
C(68)	4.2224	-1.2182	-0.9115
H(69)	3.5472	-0.5279	-1.4111
N(70)	4.0138	-1.5475	0.3159

Rotamer 20b with Acetate Counterion

A conformer distribution for *N*-acyliminium **20b** with an acetate counterion was searched (MMFF level of theory) and single point energies of the lowest energy structures were computed using B3LYP/6-31G* level of theory. The lowest energy conformer was then subjected to an equilibrium geometry calculation at the B3LYP/6-31G* level to provide the ground state of **20b** shown:

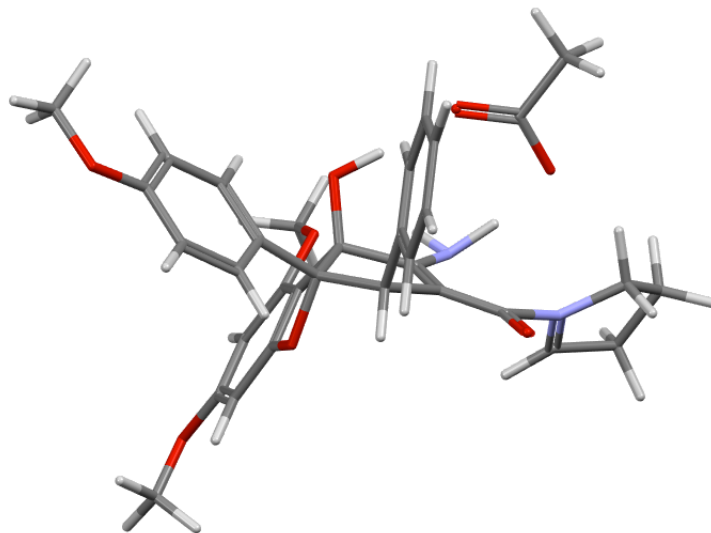


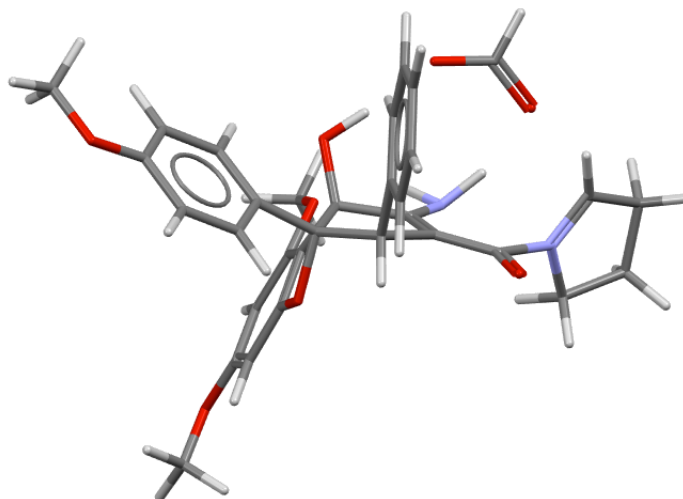
Table SI-4 Cartesian Coordinates for the Ground State of Rotamer **20b** with Acetate Counterion

Atom	X (Å)	Y (Å)	Z (Å)
C(1)	1.1028	4.1147	0.5616
H(2)	1.4875	5.0035	1.0448
C(3)	0.7528	4.2088	-0.8055
C(4)	0.2256	3.1185	-1.5132
H(5)	-0.0663	3.1771	-2.553
C(6)	0.0554	1.9354	-0.797
C(7)	0.3866	1.8157	0.5478
C(8)	0.9273	2.9094	1.2336
O(9)	1.2333	2.6866	2.5555
O(10)	0.9682	5.4284	-1.351
C(11)	1.681	3.7978	3.3399
H(12)	2.6272	4.1929	2.9538
H(13)	1.8279	3.4102	4.3486
H(14)	0.9282	4.593	3.3557
C(15)	0.5993	5.6509	-2.71
H(16)	1.1648	4.9992	-3.3873
H(17)	0.8475	6.6925	-2.9153
H(18)	-0.4752	5.4931	-2.8596
O(19)	-0.4344	0.7888	-1.3264
C(20)	0.1277	0.3977	0.9795
C(21)	-0.766	-0.1581	-0.2115
C(22)	1.3374	-1.3231	-0.187

C(23)	1.4198	-0.4123	0.8436
C(24)	-0.1135	-1.506	-0.6452
H(25)	-0.1542	-1.5605	-1.7368
C(26)	-2.2683	-0.126	-0.0557
C(27)	-5.0896	0.0666	-0.0032
C(28)	-2.9207	0.7698	0.8103
C(29)	-3.0681	-0.9008	-0.9047
C(30)	-4.4593	-0.8183	-0.887
C(31)	-4.3037	0.8638	0.8425
H(32)	-2.3482	1.4013	1.4769
H(33)	-2.6088	-1.5925	-1.6021
H(34)	-5.0349	-1.4435	-1.5592
H(35)	-4.803	1.5496	1.5194
C(36)	-0.706	-2.7951	-0.0805
C(37)	-1.713	-5.2309	0.897
C(38)	-1.0028	-2.9473	1.2818
C(39)	-0.9138	-3.8804	-0.9405
C(40)	-1.4137	-5.0907	-0.4579
C(41)	-1.5075	-4.1548	1.7634
H(42)	-0.862	-2.1202	1.9719
H(43)	-0.6744	-3.7803	-1.9964
H(44)	-1.568	-5.9208	-1.1415
H(45)	-1.7446	-4.2534	2.8193
H(46)	-2.1057	-6.1702	1.2761
O(47)	-6.4318	0.2272	0.1119
C(48)	-7.2859	-0.5588	-0.7111
H(49)	-8.3032	-0.2705	-0.4429
H(50)	-7.1491	-1.6306	-0.5207
H(51)	-7.118	-0.3522	-1.7756
C(52)	2.3511	-2.114	-0.7958
O(53)	2.2692	-3.0759	-1.5219
C(54)	4.9348	-2.586	-0.6524
C(55)	6.1752	-1.679	-0.5124
C(56)	5.6694	-0.2632	-0.8953
H(57)	4.8738	-3.1276	-1.5995
H(58)	6.5346	-1.6824	0.5201
H(59)	6.995	-2.0133	-1.1502
H(60)	5.9179	0.0252	-1.9278
H(61)	6.0473	0.5424	-0.2561
N(62)	2.4306	-0.1225	1.698
H(63)	2.1906	0.5008	2.4628
O(64)	-0.3779	0.2201	2.2885
H(65)	-0.3941	1.0847	2.7304
H(66)	3.1165	-0.829	1.9243

H(67)	4.803	-3.3055	0.1584
C(68)	4.1892	-0.3963	-0.7944
H(69)	3.4591	0.4036	-0.8817
N(70)	3.8028	-1.6133	-0.6301

Rotamer SI2a with Formate Counterion



SI2a

A conformer distribution of *N*-acyliminium **SI2a** with a formate counterion (the counterpart to **20a**) was searched (MMFF level of theory) and single point energies of the lowest energy structures were computed using B3LYP/6-31G* level of theory. The lowest energy conformer was then subjected to an equilibrium geometry calculation at the B3LYP/6-31G* level to provide the ground state of **SI2a** shown. Rotamer **SI2a** was 1.0 kcal/mol lower in energy than rotamer **SI2b** (page S40).

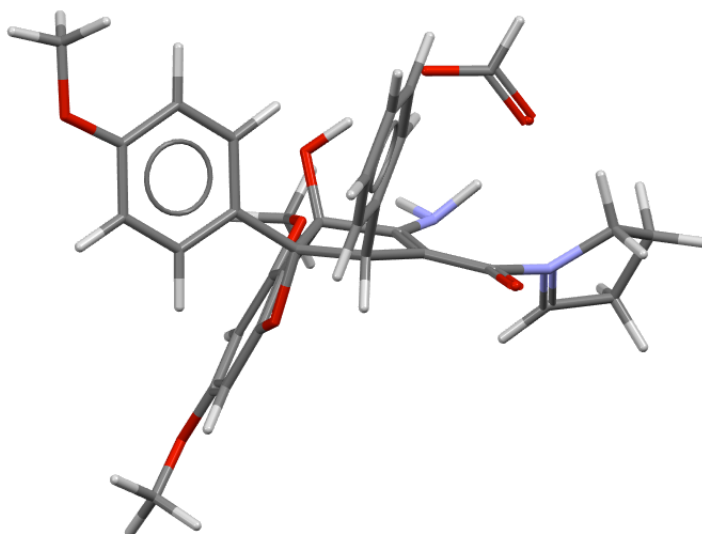
Table SI-5 Cartesian Coordinates for the Ground State of Rotamer **SI2a** with Formate Counterion

Atom	X (Å)	Y (Å)	Z (Å)
C(1)	-1.298	4.309	0.434
H(2)	-1.31	5.262	0.945
C(3)	-1.889	4.243	-0.842
C(4)	-1.904	3.059	-1.587
H(5)	-2.348	2.98	-2.571
C(6)	-1.316	1.946	-0.987
C(7)	-0.749	1.965	0.279
C(8)	-0.706	3.171	0.988
O(9)	-0.044	3.16	2.185
O(10)	-2.428	5.42	-1.276
C(11)	-0.067	4.338	2.979
H(12)	0.43	5.176	2.473
H(13)	0.474	4.091	3.894
H(14)	-1.095	4.626	3.23
C(15)	-3.048	5.442	-2.553
H(16)	-2.337	5.191	-3.35
H(17)	-3.405	6.464	-2.694

H(18)	-3.899	4.75	-2.598
O(19)	-1.224	0.734	-1.595
C(20)	-0.172	0.594	0.559
C(21)	-0.862	-0.282	-0.572
C(22)	1.545	-0.388	-0.81
C(23)	1.309	0.532	0.195
C(24)	0.279	-1.127	-1.229
H(25)	0.148	-1.057	-2.314
C(26)	-2.153	-1.02	-0.261
C(27)	-4.636	-2.321	0.091
C(28)	-2.792	-1.68	-1.329
C(29)	-2.795	-1.02	0.979
C(30)	-4.024	-1.665	1.161
C(31)	-4.008	-2.322	-1.164
H(32)	-2.33	-1.678	-2.312
H(33)	-2.334	-0.524	1.823
H(34)	-4.484	-1.644	2.142
H(35)	-4.495	-2.831	-1.99
C(36)	0.327	-2.609	-0.869
C(37)	0.446	-5.357	-0.276
C(38)	0.495	-3.047	0.452
C(39)	0.234	-3.567	-1.885
C(40)	0.291	-4.931	-1.595
C(41)	0.548	-4.409	0.745
H(42)	0.588	-2.331	1.262
H(43)	0.125	-3.24	-2.917
H(44)	0.218	-5.658	-2.4
H(45)	0.671	-4.728	1.777
H(46)	0.489	-6.418	-0.044
O(47)	-5.831	-2.981	0.159
C(48)	-6.494	-3.027	1.411
H(49)	-7.406	-3.604	1.247
H(50)	-6.759	-2.022	1.766
H(51)	-5.882	-3.526	2.175
C(52)	2.76	-0.693	-1.478
O(53)	2.952	-1.415	-2.437
C(54)	4.403	1.359	-1.347
C(55)	5.805	1.537	-0.711
C(56)	6.034	0.263	0.151
H(57)	3.656	2.055	-0.957
H(58)	6.571	1.627	-1.485
H(59)	5.842	2.441	-0.1

H(60)	6.044	0.449	1.229
H(61)	6.954	-0.277	-0.101
N(62)	2.167	1.305	0.899
H(63)	1.693	1.868	1.603
O(64)	-0.318	0.175	1.894
H(65)	0.517	-0.248	2.224
H(66)	2.987	0.796	1.312
H(67)	4.401	1.398	-2.44
C(68)	4.839	-0.578	-0.141
H(69)	4.671	-1.59	0.202
N(70)	4.004	-0.007	-0.936
C(71)	3.2	-1.013	2.895
H(72)	3.728	-1.705	3.589
O(73)	3.971	-0.286	2.177
O(74)	1.955	-1.037	2.919

Rotamer SI2b with Formate Counterion



SI2b

A conformer distribution of *N*-acyliminium **SI2b** with a formate counterion (the counterpart to **20b**) was searched (MMFF level of theory) and single point energies of the lowest energy structures were computed using B3LYP/6-31G* level of theory. The lowest energy conformer was then subjected to an equilibrium geometry calculation at the B3LYP/6-31G* level to provide the ground state of **20b** pictured above. Rotamer **20b**/formate was 1.0 kcal/mol higher in energy than rotamer **20a**/formate.

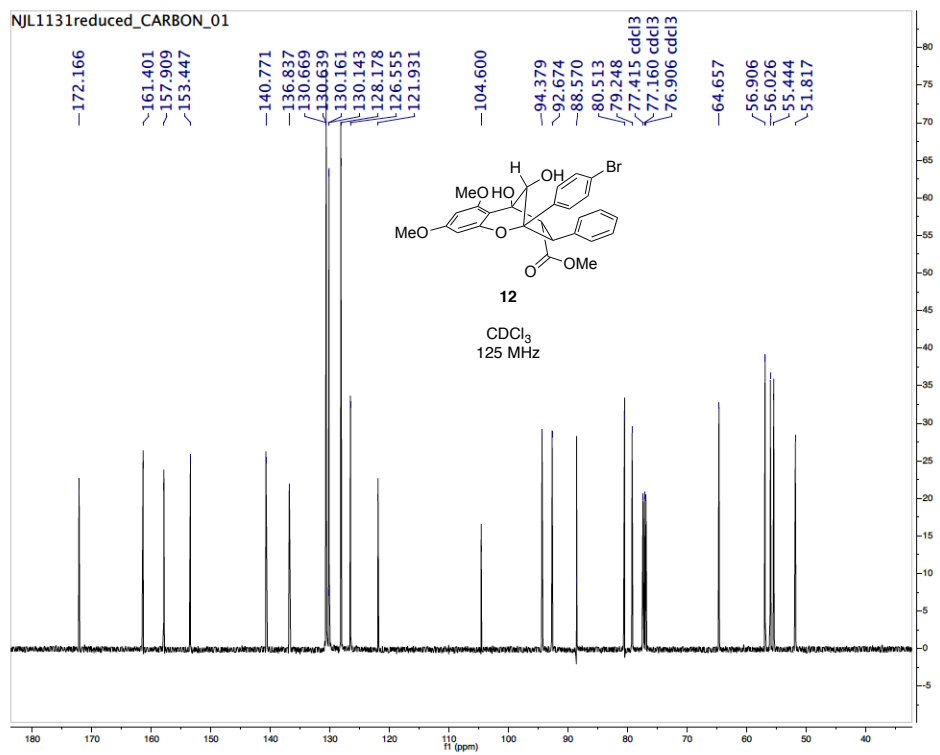
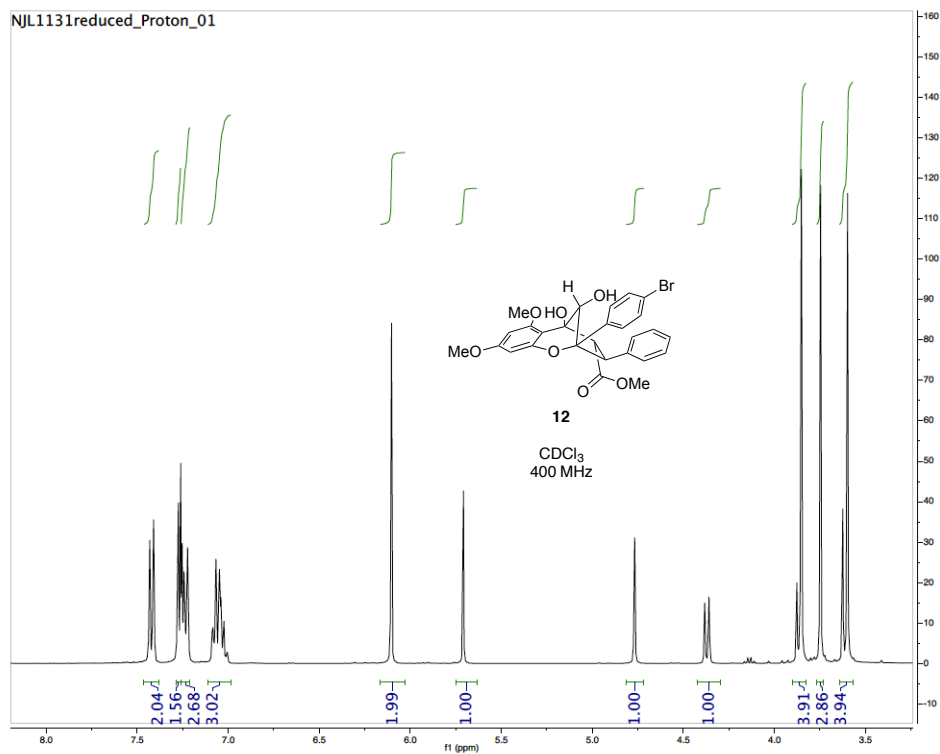
Table SI-6 Cartesian Coordinates for the Ground State of Rotamer **SI2b** with Formate Counterion

Atom	X (Å)	Y (Å)	Z (Å)
C(1)	-1.236	4.457	0.156
H(2)	-1.239	5.434	0.621
C(3)	-1.781	4.346	-1.137
C(4)	-1.806	3.126	-1.822
H(5)	-2.216	3.012	-2.817
C(6)	-1.279	2.029	-1.143
C(7)	-0.754	2.093	0.137
C(8)	-0.703	3.331	0.789
O(9)	-0.097	3.361	2.014
O(10)	-2.266	5.515	-1.649
C(11)	-0.14	4.571	2.759
H(12)	0.401	5.379	2.249
H(13)	0.347	4.351	3.711
H(14)	-1.174	4.886	2.942
C(15)	-2.858	5.487	-2.938
H(16)	-2.138	5.175	-3.706
H(17)	-3.18	6.511	-3.141
H(18)	-3.728	4.819	-2.967

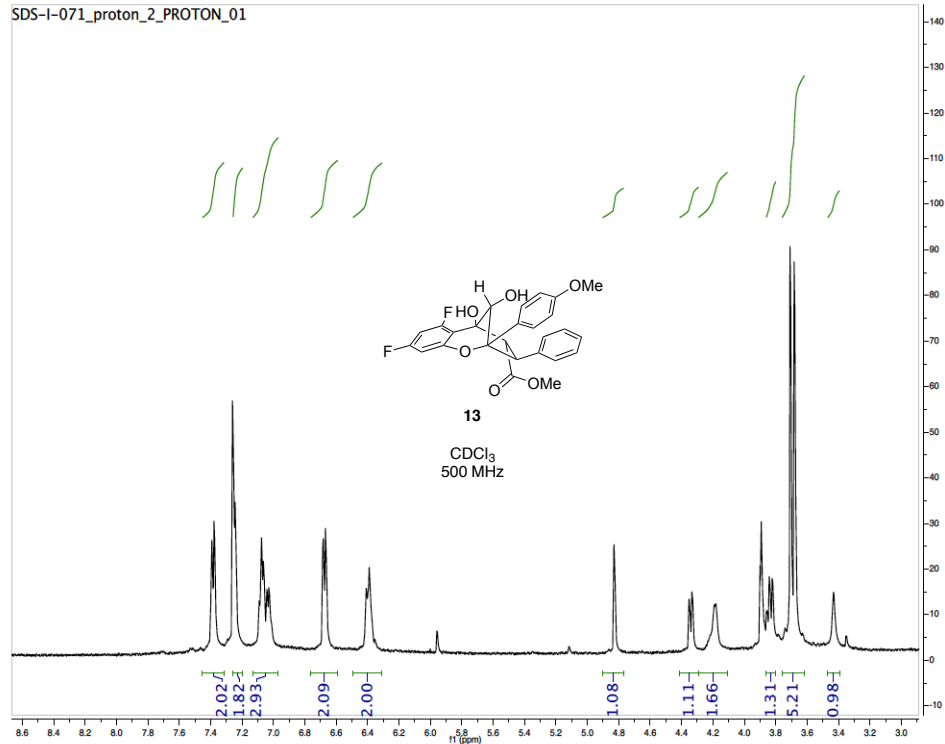
O(19)	-1.216	0.782	-1.685
C(20)	-0.244	0.72	0.518
C(21)	-0.894	-0.187	-0.625
C(22)	1.532	-0.348	-0.713
C(23)	1.255	0.603	0.26
C(24)	0.277	-1.058	-1.213
H(25)	0.199	-0.958	-2.301
C(26)	-2.177	-0.917	-0.259
C(27)	-4.561	-2.31	0.343
C(28)	-3.296	-0.844	-1.104
C(29)	-2.28	-1.712	0.889
C(30)	-3.456	-2.399	1.196
C(31)	-4.471	-1.525	-0.812
H(32)	-3.244	-0.241	-2.003
H(33)	-1.444	-1.797	1.568
H(34)	-3.491	-2.997	2.099
H(35)	-5.333	-1.463	-1.469
C(36)	0.242	-2.552	-0.912
C(37)	0.132	-5.325	-0.443
C(38)	0.721	-3.091	0.29
C(39)	-0.292	-3.422	-1.87
C(40)	-0.35	-4.797	-1.642
C(41)	0.665	-4.467	0.519
H(42)	1.131	-2.442	1.059
H(43)	-0.667	-3.016	-2.807
H(44)	-0.766	-5.453	-2.402
H(45)	1.039	-4.866	1.459
H(46)	0.093	-6.397	-0.263
O(47)	-5.756	-2.943	0.547
C(48)	-5.892	-3.751	1.704
H(49)	-6.903	-4.161	1.667
H(50)	-5.773	-3.164	2.624
H(51)	-5.166	-4.575	1.71
C(52)	2.782	-0.742	-1.258
O(53)	3.042	-1.599	-2.079
C(54)	5.195	-0.727	-0.263
C(55)	6.095	0.401	0.277
C(56)	5.549	1.696	-0.38
H(57)	5.606	-1.29	-1.106
H(58)	5.958	0.451	1.359
H(59)	7.151	0.233	0.054
H(60)	6.133	2.028	-1.25
H(61)	5.487	2.55	0.303
N(62)	2.087	1.358	1.011

H(63)	1.577	1.926	1.686
O(64)	-0.51	0.383	1.852
H(65)	0.251	-0.133	2.223
H(66)	2.859	0.801	1.481
H(67)	4.86	-1.404	0.522
C(68)	4.191	1.281	-0.839
H(69)	3.411	1.931	-1.22
N(70)	4.008	0.015	-0.762
C(71)	2.911	-1.046	2.946
H(72)	3.382	-1.788	3.631
O(73)	3.733	-0.309	2.31
O(74)	1.661	-1.045	2.895

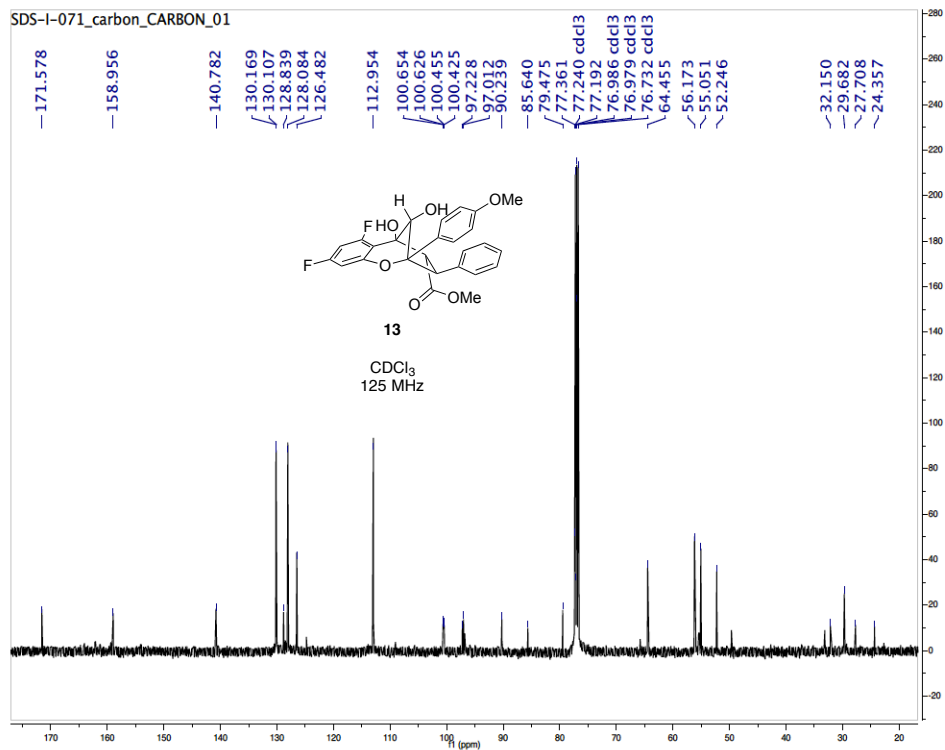
Select NMR Spectra

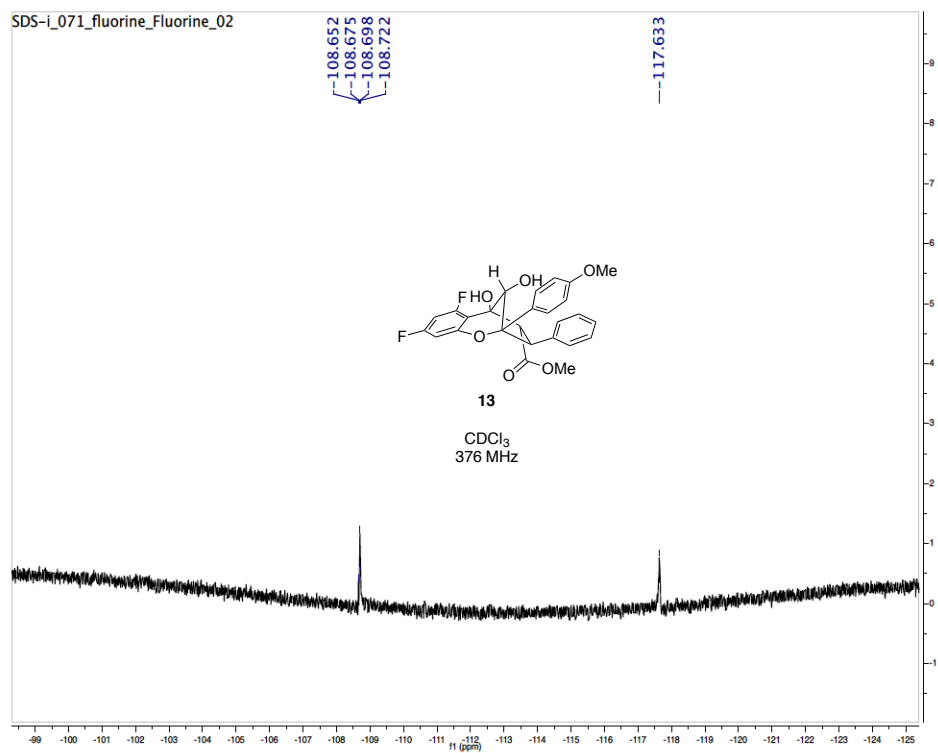


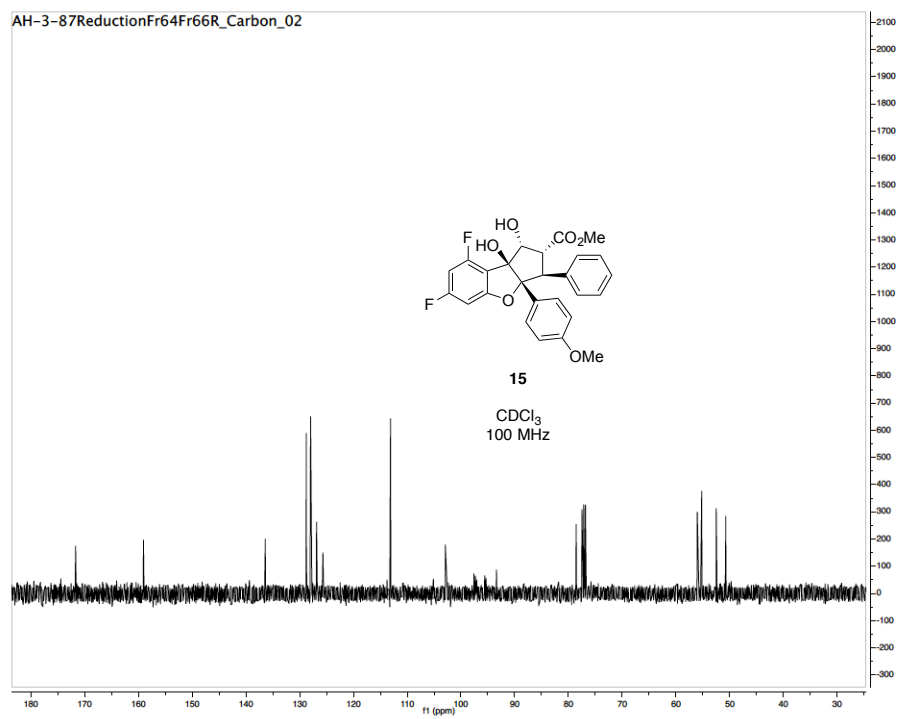
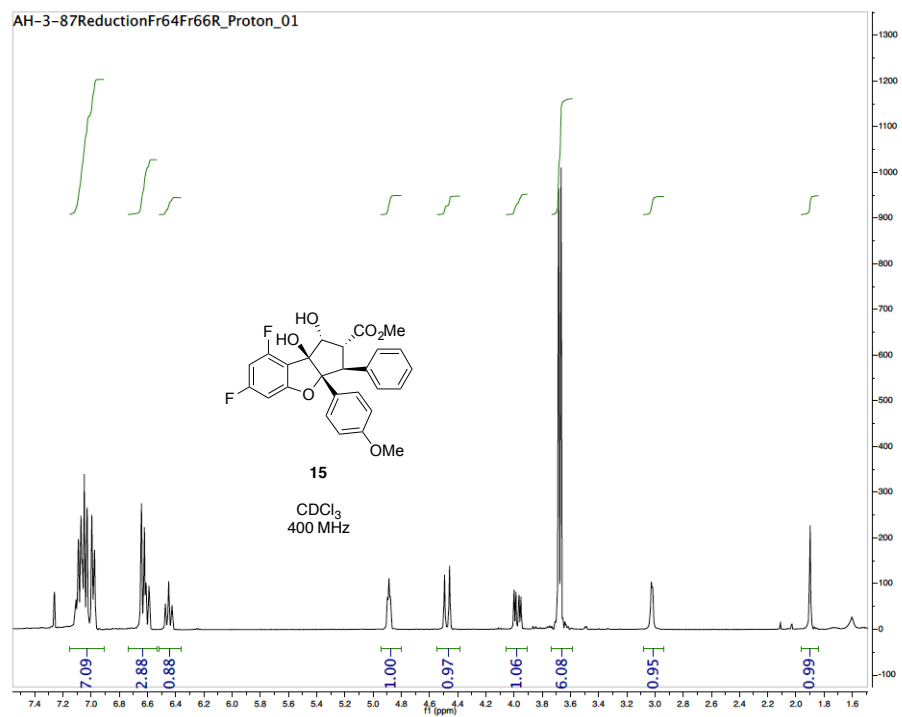
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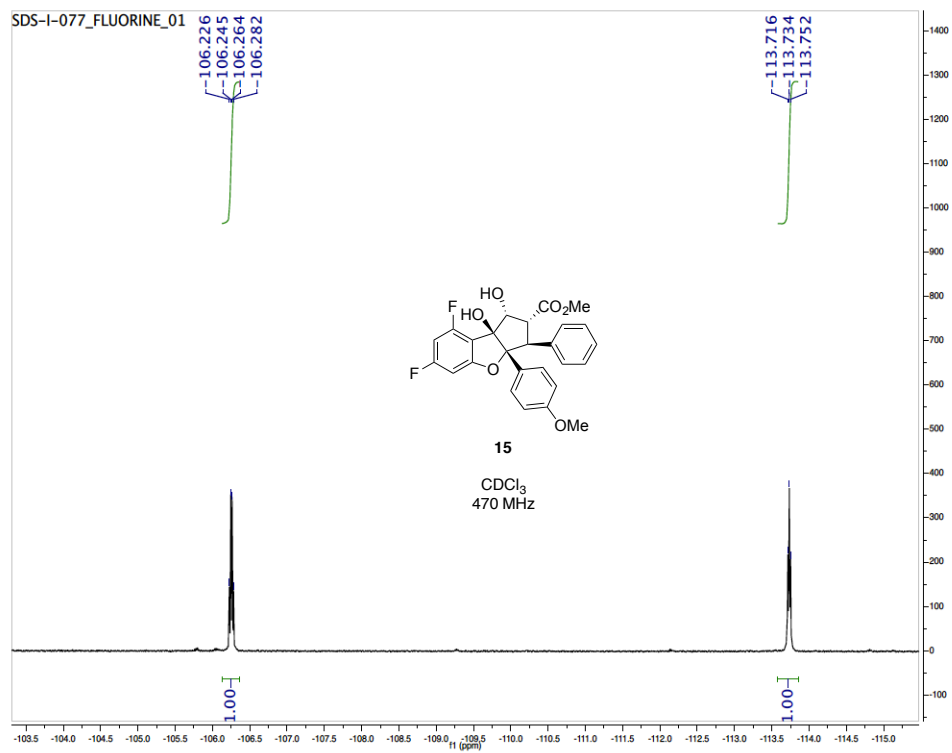


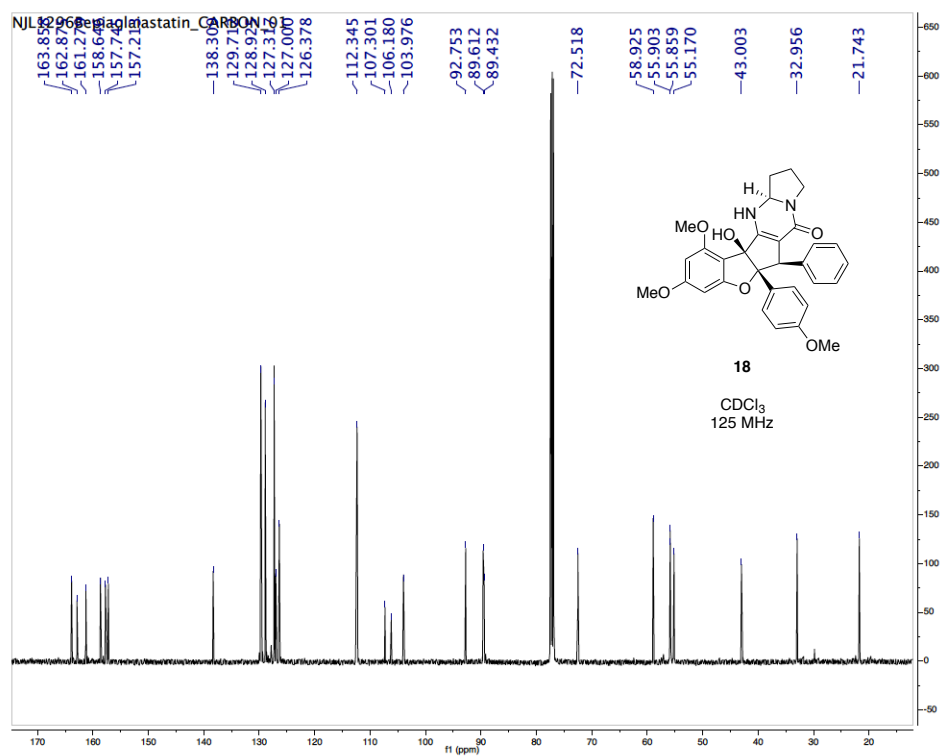
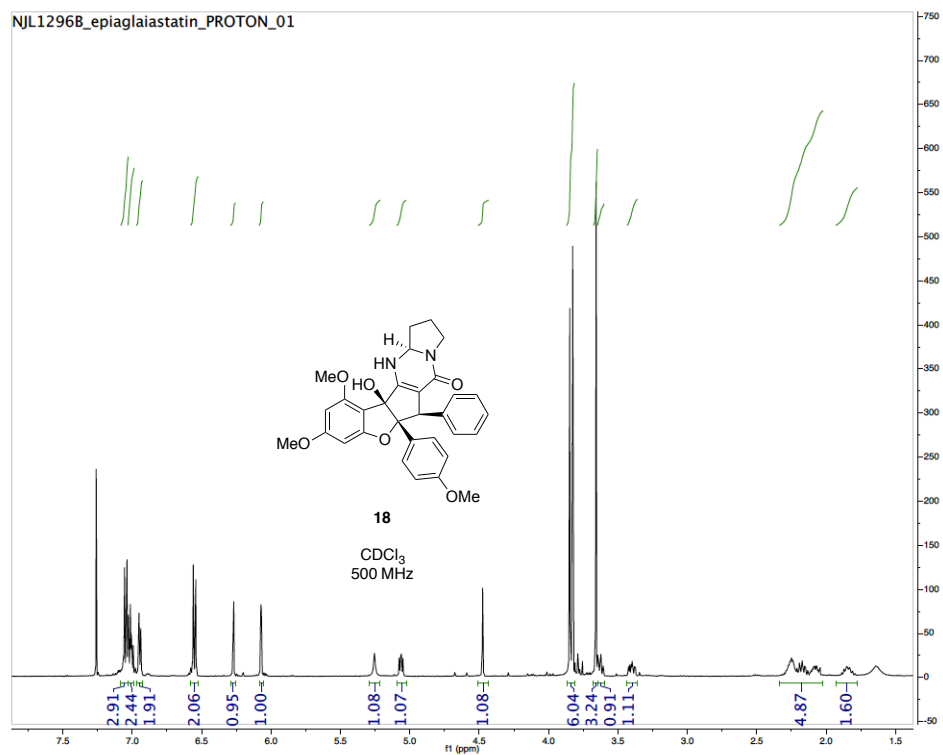
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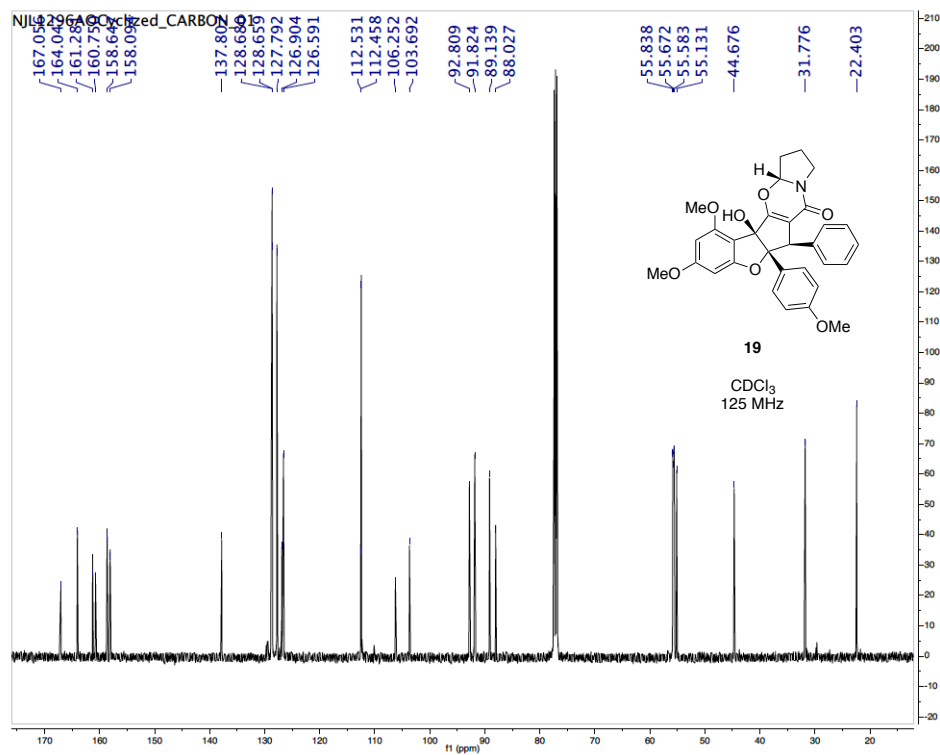
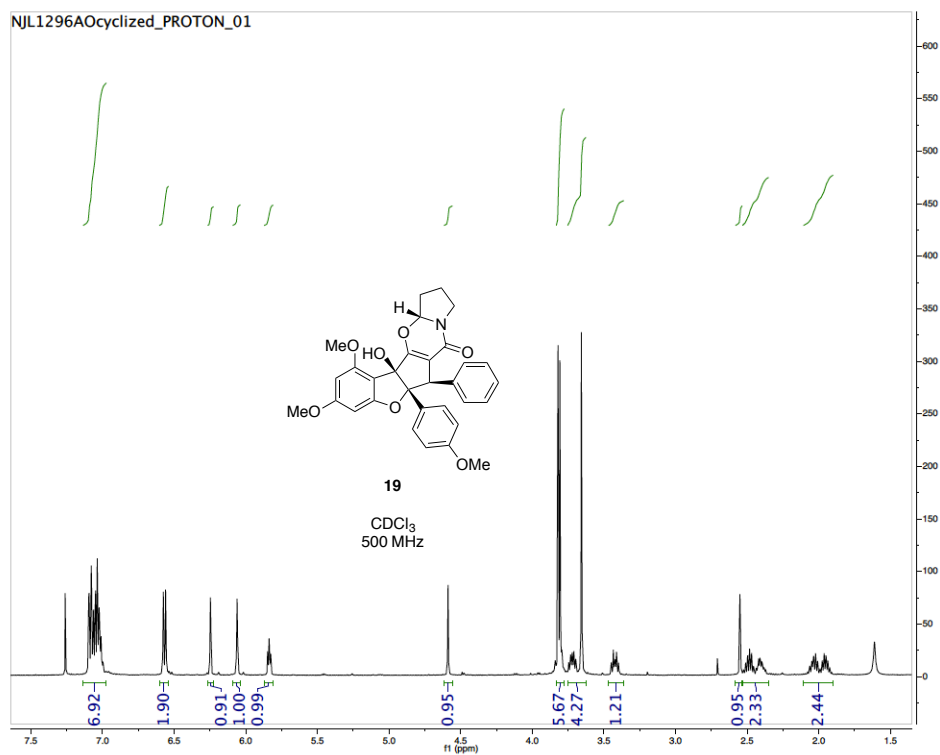




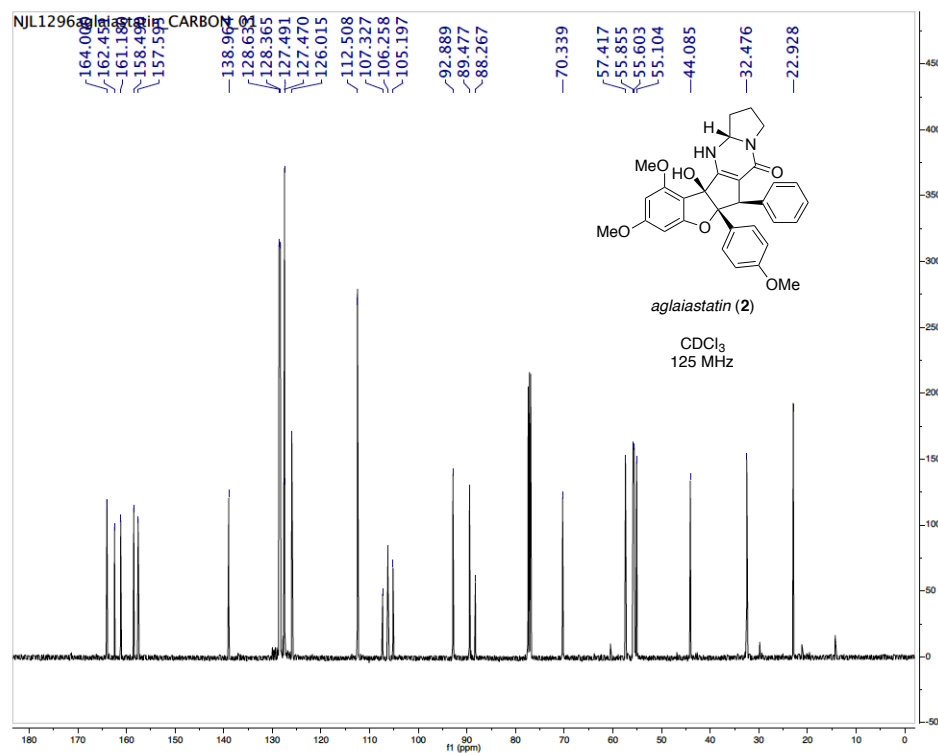
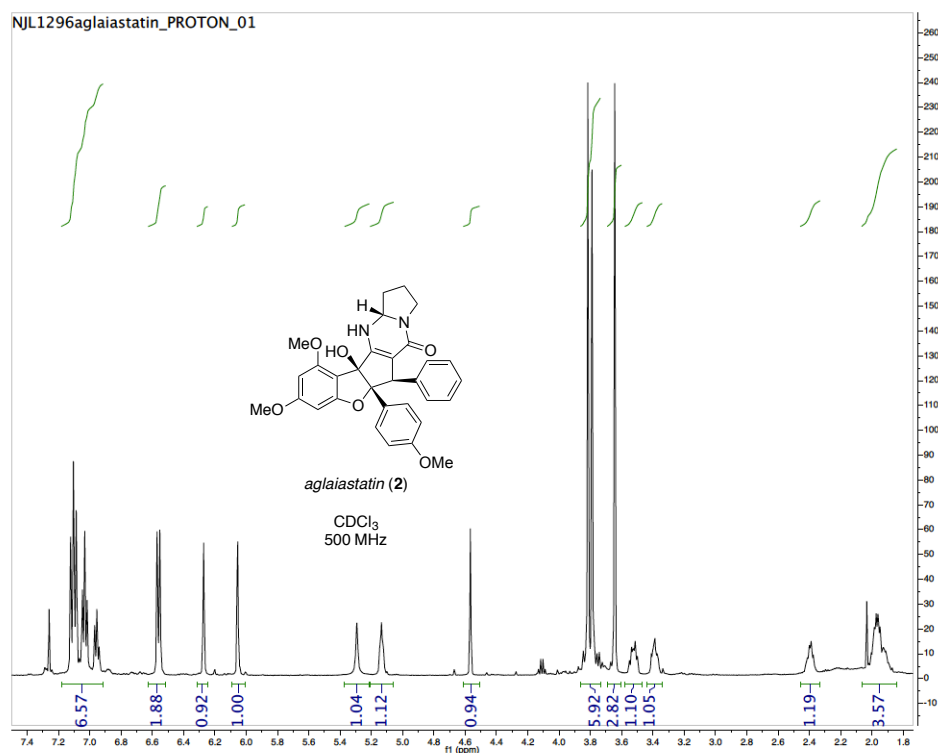


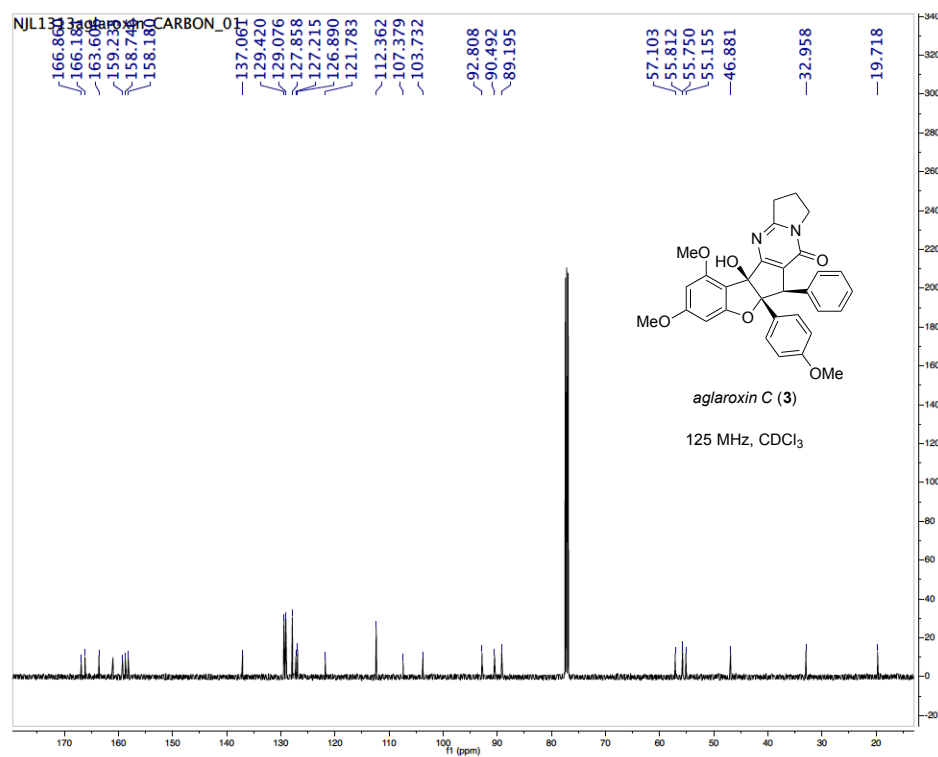
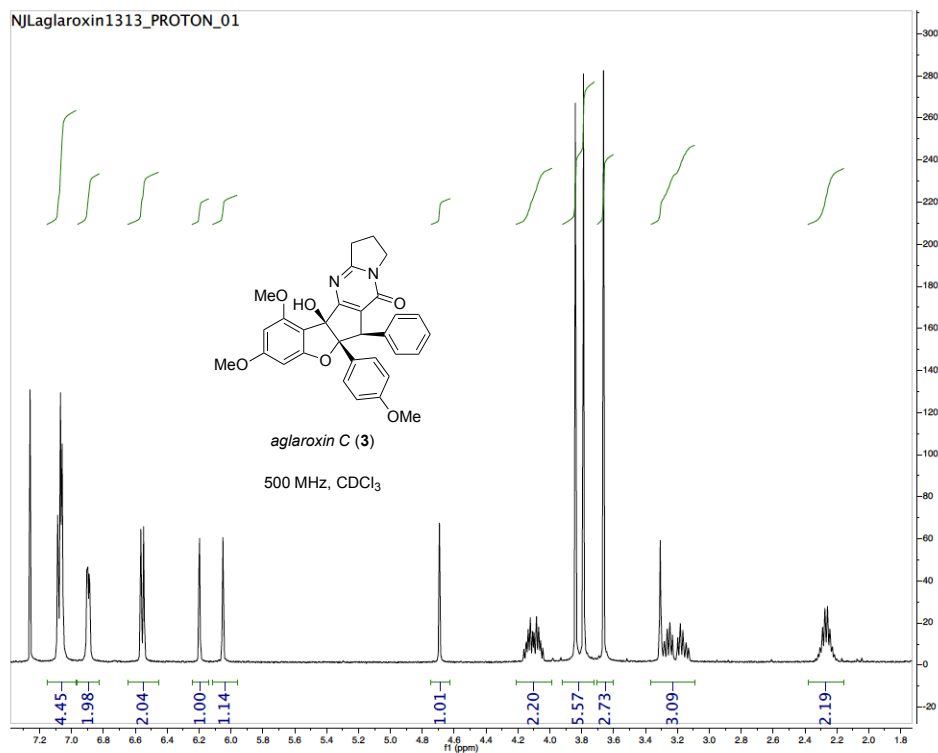


NJL1296AOcyclized_PROTON_01



NJL1296aglaiaastatin_PROTON_01



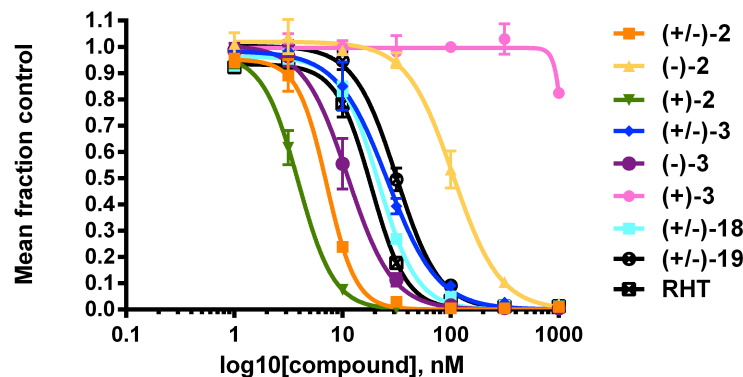


Biological Assays

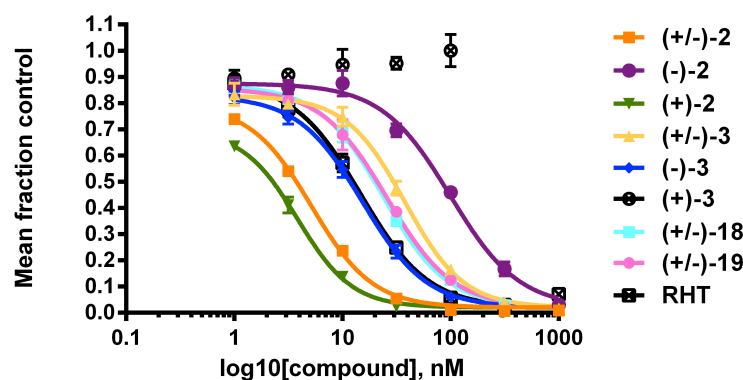
Cytotoxicity Assays. Human 293T cancer cells ((American Type Culture Collection) were grown under 5% CO₂ in DMEM supplemented with 10% FBS. Surveillance testing for *Mycoplasma* contamination was performed on a monthly basis and was consistently negative. Compounds were formulated in DMSO and maintained at –80°C in the dark prior to testing. Cells were seeded into 384-well plates (1,000 cells/40 µl/well) and were allowed to adhere overnight. Serial dilutions of compounds or DMSO vehicle control (not exceeding 0.1%) were added to quadruplicate wells using an HP D300 digital dispenser (Hewlett Packard) and plates incubated for an additional 3 days prior to assay of relative viable cell number by reduction of the dye resazurin (Alamar Blue®) as previously described. Statistical analysis of raw data to define IC₅₀ values was performed by variable slope four parameter curve fitting using GraphPad Prism 6 software.

Reporter Assays. Luciferase reporter cell lines were generated by infecting 293T cells with either a lentiviral vector expressing firefly luciferase from a strong constitutive CMV promoter (“constitutive reporter”) or a previously reported lentiviral vector encoding a fusion protein consisting of enhanced GFP fused to firefly luciferase under control of *HSP70B*’ promoter elements (“heat-shock reporter”, Santagata et al, ACS Chemical Biology, 2011). To evaluate concentration-dependent inhibition of reporter activity, cells were seeded in white 384-well plates (20,000 cells/40 µl/well). The following day, serial compound dilutions were added to quadruplicate wells and plates subjected to heat-shock at 42°C for 90 min. After overnight incubation at 37°C, measurement of relative luciferase activity was achieved using Steady-Glo luciferase assay reagent (Promega) per manufacturer’s recommendations and an Envision plate luminometer (Perkin-Elmer). Statistical analysis of raw data to define IC₅₀ (heat-shock reporter) and EC₅₀ (constitutive reporter) values was performed by variable slope four parameter curve fitting using GraphPad Prism 6 software.

(a) Cytotoxicity



(b) Heat-shock reporter



(c) Constitutive reporter inhibition

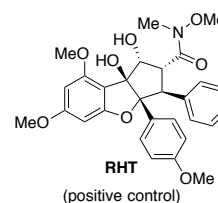
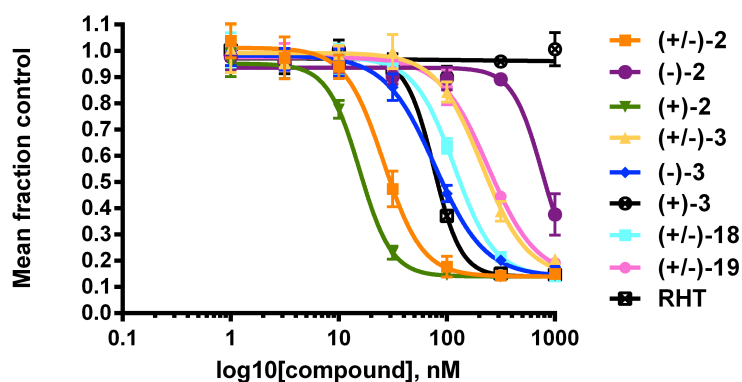


Figure Legend

Concentration-dependent biological activity of aglaiastatins: (a) **Cytotoxicity:** Inhibition of cell proliferation and survival. After addition of the indicated compounds in 384-well format, cells were cultured for 3 days. Relative viable cell number was determined by reduction of the dye resazurin (Alamar Blue®) using a microplate fluorometer (Tecan). (b) **Heat-shock reporter** and (c) **Constitutive reporter inhibition:** After addition of the indicated compounds in 384-well format, reporter cells were subjected to moderate heat-shock, cultured overnight and luciferase activity measured on a microplate luminometer. All data are plotted as the mean ratio of treated to control with each determinations performed in quadruplicate. Error bars: SD