Identification of gp120 Residue His105 as a Novel Target for HIV-1 Neutralization by Small-Molecule CD4-Mimics

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Supporting Information

Summary of Crystallographic Data

Table S1—*Summary of Crystallographic Data*

Diffraction Data Statistics

Dataset	CJF-II-204 (**14**)	CJF-III-049-S (**16**)	CJF-III-049-R (**17**)
Beamline	APS 24-ID-C	APS 24-ID-E	APS 24-ID-E
(Å)	0.9792	0.9792	0.9792
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimension (Å)	72.19 121.05 195.62	71.81 120.66 195.25	71.58 120.75 195.28
Z_a[a]	4	4	4
Bragg spacings (Å)[b]	48.90-2.80 (2.91-2.80)	48.81-2.75 (2.85-2.75)	48.82-2.70 (2.79-2.70)
Total reflections	279481	295051	314373
Unique reflections	43050	44923	47367
Completeness (%)	99.4	99.8	99.9
$CC_{1/2}$ (%)[c]	99.9 (45.7)	99.5 (80.2)	99.8 (77.6)
$\langle I/\sigma(I)\rangle$ [d]	12.5 (2.5)	10.5(2.1)	11.6(1.8)
Rmerge[e]	0.176 (1.53)	0.159 (0.999)	0.113 (1.279)
Rmeas[f]	0.210 (1.801)	0.188 (1.188)	0.155(1.516)
Rwork[g]	0.230	0.244	0.235
Rfree[h]	0.299	0.284	0.279
RMS bond deviation (Å)	0.019	0.005	0.003
RMS angle deviation (°)	1.28	1.01	0.96
Average B factor (Å^2)	61.2	65.4	71.6
Ramachandran analysis favored/allowed (%)	94.1 / 0.8	93.7 / 1.5	92.2 / 1.7
PDB code			

a Z_a stands for number of subunits per asymmetric unit.

b Values in the outermost shell are given in parentheses.

c $CC_{1/2}$ is the correlation coefficient of integrated intensities between randomly split two half data sets

d $\langle I/\sigma(I)\rangle = \langle\langle Ii\rangle\rangle / \langle\sigma(\langle Ii\rangle)\rangle$

e $R_{merge} = (\Sigma |Ii - \langle Ii \rangle|) / \Sigma |Ii|$, where Ii is the integrated intensity of a given reflection.

f R_{meas} is the redundancy-independent merging R factor (50).

g $R_{work} = (\Sigma | |Fo| - |Fc| |) / \Sigma|Fo|$, where Fo and Fc denote observed and calculated structure factors, respectively.

h R_{free} was calculated using 5% of data excluded from refinement.

Experimental Methods

Cell lines

293T human embryonic kidney (HEK) cells, COS-1 African green monkey kidney fibroblasts, HOS human osteosarcoma cells, and Cf2Th canine thymocytes (American Type Culture Collection) will be used at 37°C and 5% CO_2 in DMEM with 10% fetal bovine serum (FBS; Sigma) and 100 ug/ml of penicillin-streptomycin (Mediatech, Inc.). Cf2Th cells stably expressing human CD4-CCR5, CCR5, or CD4-CXCR4 will be grown in medium supplemented with 200 ug/ml hygromycin (Roche Diagnostics) and 400 ug/ml G418 (Invitrogen).

Measurement of Compound toxicity

The effect of a 48-h incubation with each compound on the viability of Cf2Th-CD4/CCR5 cells will be evaluated using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay.[1] Approximately 1.5 x 10^4 cells will be plated in each well of a 96-well plate. The DMSO control or various concentrations of compounds will be added to duplicate wells. Additional control wells will be prepared without cells. The plates will be incubated for 48 h at 37°C in 5% CO_2, after which, 1/5 volume of the assay solution (Abcam) will be added to each well. The plates will be incubated for an additional 3 h at 37°C and 5% CO_2. The absorbances at 570 nm and 605 nm will be measured. R represents the ratio of the absorbance at 570nm to that at 605nm. The cell viability will be calculated by $(R_{sample} - R_{no\ cells})/ (R_{DMSO} - R_{no\ cells})$ x 100.

Recombinant viruses expressing luciferase

293T HEK cells will be cotransfected with plasmids expressing the pCMVΔP1Δenv HIV-1 Gag-Pol packaging construct, the HIV-1 Envs or control envelope glycoproteins from amphotropic murine leukemia virus (AMLV), human T-lymphotropic virus-1 (HTLV-1), simian immunodeficiency virus (SIV_{mac239}), and human immunodeficiency virus-2 ($HIV\text{-}2_{UC1}$), and the firefly luciferase-expressing vector at a DNA ratio of 1:1:3 ug using the Effectene transfection reagent (Qiagen).[2] The plasmids expressing the HIV-1 Envs and Rev protein will be based on pSVIIIenv.[2] Cotransfection produced recombinant luciferase-expressing viruses capable of a single round of infection. The virus-containing supernatants will be harvested between 36 and 40 h after transfection, cleared of debris by low-speed centrifugation, aliquoted, and frozen at -80°C until further use. The reverse transcriptase (RT) levels of all viruses will be measured as previously described.[3]

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[1] Madani, N.; Princiotto, A. M.; Schön, A.; LaLonde, J.; Feng, Y.; Freire, E.; Park, J.; Courter, J. R.; Jones, D. M.; Robinson, J.; Liao, H. X.; Moody, M. A.; Permar, S.; Haynes, B.; Smith, A. B., 3rd; Wyatt, R.; Sodroski, J., CD4-mimetic small molecules sensitize human immunodeficiency virus to vaccine-elicited antibodies. *J Virol* **2014,** *88* (12), 6542-55.

[2] van Meerloo, J.; Kaspers, G. J.; Cloos, J., Cell sensitivity assays: the MTT assay. *Methods in molecular biology (Clifton, N.J.)* **2011,** *731*, 237-45.

[3] Rho, H. M.; Poiesz, B.; Ruscetti, F. W.; Gallo, R. C., Characterization of the reverse transcriptase from a new retrovirus (HTLV) produced by a human cutaneous T-cell lymphoma cell line. *Virology* **1981,** *112* (1), 355-60.

Infection by single-round luciferase viruses

Cf2Th-CD4/CCR5, Cf2Th-CCR5, or Cf2Th-CD4/CXCR4 target cells will be seeded at a density of 6 x 10^3 cells/well in 96-well luminometer-compatible tissue culture plates (PerkinElmer) 24 h before infection. On the day of infection, increasing concentrations of different compounds will be incubated with recombinant viruses at 37°C for 30 min. In the case of washout assays, increasing concentrations of compound will be incubated with recombinant viruses at 37°C for 30 min; the virus will be pelleted by centrifugation at 21,000 x *g* for 15 to 30 min at room temperature, the supernatant will be discarded, and the virus pellet will be washed once with medium before resuspension in medium. In the case of sensitization assays, a constant concentration of compound will be incubated with virus at 37°C for 30 min; then, increasing concentrations of antibody were added to the virus-compound mixture and incubated at 37°C for an additional 30 min. In all the above-described cases, the mixtures are then added to the target cells. At this point, in assays involving Cf2Th-CCR5 target cells or recombinant viruses with poor entry (x10^5 relative light units [RLU]/20ul), the virus-compound mixtures are spinoculated onto target cells by centrifugation at 1,800 rpm for 30 min at 21°C.[4] In all cases, the virus-compound-target cell mixtures will be diluted 1:4 in medium and incubated for 48 to 72 h at 37°C; after this time, the medium is removed from each well and the cells are lysed by the addition of 30 ul of passive lysis buffer (Promega) and three freeze-thaw cycles. An EG&G Berthold LB 96V microplate luminometer is used to measure the luciferase activity of each well after the addition of 100 ul of luciferin buffer (15 mM $MgSO_4$, 15 mM KPO_4 [pH 7.8], 1 mM ATP, and 1 mM dithiothreitol) and 50 ul of 1 mM firefly D-luciferin free acid, 99% (Prolume).

[4] O'Doherty, U.; Swiggard, W. J.; Malim, M. H., Human immunodeficiency virus type 1 spinoculation enhances infection through virus binding. *J Virol* **2000,** *74* (21), 10074-80.

Modeling

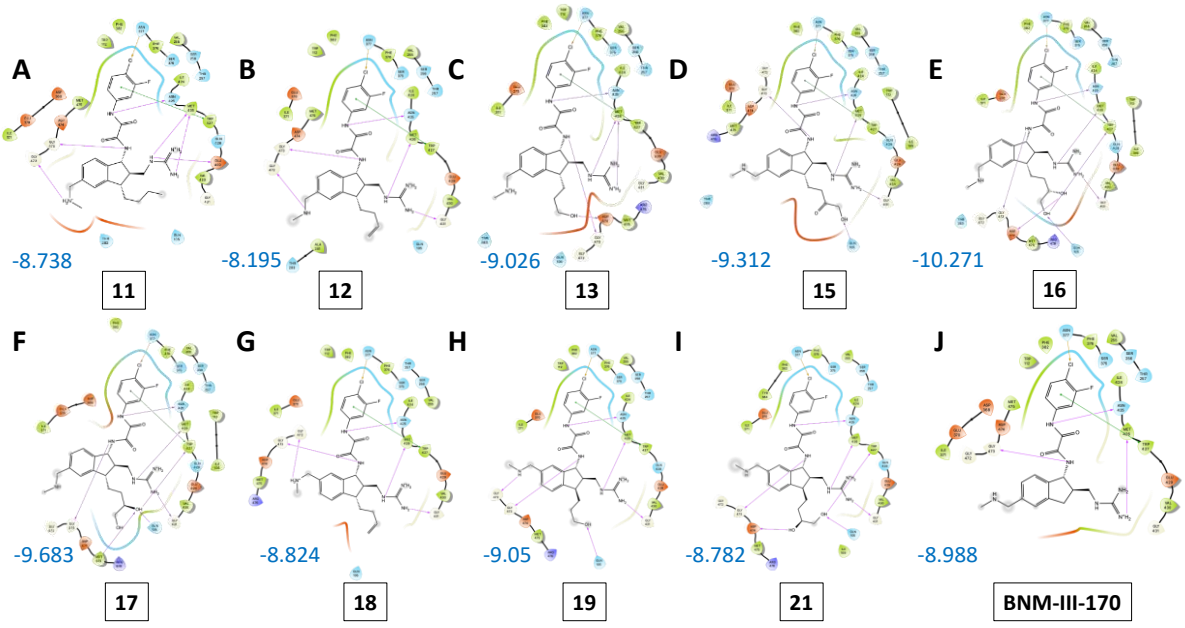

Figure S1 2D representation of ligand interaction for **11-13**, **15-19**, **21**, and BNM-III-170 (A-J) docked in JR-FL Phe43 pocket. The values of GlideScore are shown in blue (kcal/mol). The gp120 residues are colored as follows: green, nonpolar; blue, polar; indigo, basic; red, acidic.

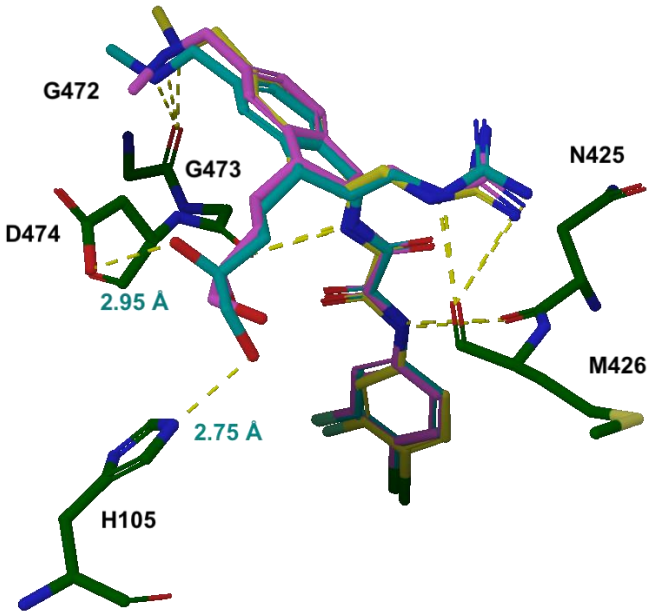

Figure S2 Superimposition of the crystal structure of BNM-III-170 (yellow) and the docking pose of **16** (cyan - *R*) and **17** (purple - *S*) in C1086 Phe43 pocket of gp120 core monomer.

The target structures were taken from core monomer JR-FL gp120 (PDB ID: 2B4C)[5] and C1086 gp120 (PDB ID: 5F4P)[6] prepared using Protein Preparation Wizard at default settings and energy-minimized using GPU-accelerated Desmond software (Schrödinger Inc., 2020) [7-11]. The pretreated gp120 core monomer was used as receptor for the subsequent docking calculation of **11-13**, **15-19**, **21**, and BNM-III-170. Docking performed using Glide[12-14] with the standard precision (SP) scoring function and the number of output poses was increased to 50[15]. The oxalamide torsional angle was restrained to 180° to keep the carbonyl groups in dipole-minimizing trans conformation.

Protein Purification and X-ray Crystallography

A plasmid of gp120 Clade C1086 was donated by Lei Chen from Peter Kwong's laboratory (National Institute of Health). 600ug plasmid was transfected into 1L HEK293 GnTI$^-$ suspension cells and expressed into the supernatant. The supernatant was dripped through the 17b-conjugated Protein A column and was washed with 100 ml 1x PBS. The gp120 bound to the conjugated 17b resin was eluted with IgG elution buffer (Pierce). The gp120 was deglycosylated overnight in a 37℃ water bath with endoglycosidase H and purified with a Con-A column and a Superdex 200 column (GE Healthcare). The purified deglycosylated gp120 was concentrated to 10 mg/ml.

Crystallization of unliganded gp120 Clade C1086 was performed at 290 K using the hanging drop vapor diffusion method. The crystals grew in drops consisting of 1 µL of protein and 1 µL of reservoir solution against 300 µL of reservoir solution 23% (w/v) PEG 1500, 0.1 M CaCl2, 0.1 M imidazole pH 6.5. For each experiment, the compound of interest was dissolved in 100% DMSO. Single crystals were picked from the mother liquor and soaked in 2µL of a stabilization buffer that contained 26% PEG 1500 (w/v), 0.1 M CaCl2, 0.1 M imidazole pH 6.5, 2.5 mM Tris-HCl pH 7.5, 350 mM NaCl, 0.02% NaN3, 5% (v/v) DMSO and 200 M of the compound. The clade C1086 gp120 crystals were soaked for 30 min in the stabilization buffer, and then

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[5] Huang, C.-c.; Tang, M.; Zhang, M.-Y.; Majeed, S.; Montabana, E.; Stanfield, R. L.; Dimitrov, D. S.; Korber, B.; Sodroski, J.; Wilson, I. A.; Wyatt, R.; Kwong, P. D., Structure of a V3-Containing HIV-1 gp120 Core. *Science* **2005,** *310* (5750), 1025.

[6] Melillo, B.; Liang, S.; Park, J.; Schön, A.; Courter, J. R.; LaLonde, J. M.; Wendler, D. J.; Princiotto, A. M.; Seaman, M. S.; Freire, E.; Sodroski, J.; Madani, N.; Hendrickson, W. A.; Smith, A. B., Small-Molecule CD4-Mimics: Structure-Based Optimization of HIV-1 Entry Inhibition. *ACS Medicinal Chemistry Letters* **2016,** *7* (3), 330-334.

[7] *Maestro*, version 12.6; Schrödinger, LLC, New York, NY, 2020.

[8] *Epike*, version 5.4; Schrödinger, LLC, New York, NY, 2020.

[9] *Prime*; Schrödinger, LLC, New York, NY, 2020.

[10] *Desmond*; version 6.4; Schrödinger, LLC, New York, NY, 2020.

[11] Bowers, Kevin J., et al., Scalable algorithms for molecular dynamics simulations on on commodity clusters. ACM/IEEE CS 2006 Conf. 2006, 43-43.

[12] *Glide*, version 8.9; Schrödinger, LLC, New York, NY, 2020.

[13] Halgren, Thomas A., et al., Glide: a new approach for rapid, accurate docking and scoring. 2. Enrichment factors in database screening. J. Med. Chem. 47.7 (2004): 1750-1759.

[14] Friesner, Richard A., et al., Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. J. Med. Chem. 47.7 (2004): 1739-1749.

[15] Zou, Shitao, et al., Long-acting BMS-378806 analogues stabilize the state-1 conformation of the human immunodeficiency virus type 1 envelope glycoproteins. J. Virol. 94.10 (2020): e00148-20.

transferred for 5 seconds into cryo-protectant, composed from the stabilization buffer but with 30% ethylene glycol.

Diffraction data for were collected at the NE-CAT beamlines of the Advanced Photon Source at Argonne National Laboratory. Crystals of clade C1086 with CJF-II-204 (**14**) used the 24ID-C beamline while those for CJF-III-049-S (**16**) and CJF-III-049-R (**17**) used 24ID-E. Although previous crystals of complexes of CD4 mimetic compounds with C1086 gp120 were in a $C222_1$ lattice, these crystals proved to be in space group $P2_12_12_1$ with four copies in the asymmetric unit. The crystal structures were solved by the molecular replacement module in PHENIX using unliganded clade C1086 (PDB ID: 3TGR).

Table S2 -- Complete hydrogen bond distances between compounds and gp120 Clade C1086

Compoound		gp120 Clade C1086		Distances (Å)
Name	Atom	Residue	Atom	
16	Butanediol primary OH (chain A)	H105	N_ε	2.99
	Butanediol primary OH (chain B)	H105	N_ε	3.00
	Butanediol primary OH (chain C)	H105	N_ε	3.00
	Butanediol primary OH (chain D)	H105	N_ε	3.01
	Average	**H105**	**N_ε**	**3.00**
16	Butanediol secondary OH (chain A)	D474	O_1	3.12
	Butanediol secondary OH (chain B)	D474	O_1	2.98
	Butanediol secondary OH (chain C)	D474	O_1	3.05
	Butanediol secondary OH (chain D)	D474	O_1	3.02
	Average	**D474**	**O_1**	**3.04**
17	Butanediol primary OH (chain A)	H105	N_ε	3.20
	Butanediol primary OH (chain B)	H105	N_ε	3.13
	Butanediol primary OH (chain C)	H105	N_ε	3.15
	Butanediol primary OH (chain D)	H105	N_ε	3.05
	Average	**H105**	**N_ε**	**3.13**
17	Butanediol secondary OH (chain A)	D474	O_1	2.85
	Butanediol secondary OH (chain B)	D474	O_1	2.85
	Butanediol secondary OH (chain C)	D474	O_1	3.02
	Butanediol secondary OH (chain D)	D474	O_1	2.92
	Average	**D474**	**O_1**	**2.91**
14 S diastereom	Butanediol primary OH (chain A)	H105	N_ε	2.94
	Butanediol primary OH (chain B)	H105	N_ε	2.94
	Butanediol primary OH (chain C)	H105	N_ε	2.88
	Butanediol primary OH (chain D)	H105	N_ε	2.94

er (Q=0.7)	**Average**	**H105**	**N_ε**	**2.93**
14 R diastereomer (Q=0.3)	Butanediol primary OH (chain A)	H105	N_ε	2.99
	Butanediol primary OH (chain B)	H105	N_ε	3.01
	Butanediol primary OH (chain C)	H105	N_ε	2.93
	Butanediol primary OH (chain D)	H105	N_ε	2.98
	Average	**H105**	**N_ε**	**2.98**
14 S diastereomer (Q=0.7)	Butanediol secondary OH (chain A)	D474	O_1	2.96
	Butanediol secondary OH (chain B)	D474	O_1	2.93
	Butanediol secondary OH (chain C)	D474	O_1	2.87
	Butanediol secondary OH (chain D)	D474	O_1	2.77
	Average	**D474**	**O_1**	**2.88**
14 R diastereomer (Q=0.3)	Butanediol secondary OH (chain A)	D474	O_1	3.06
	Butanediol secondary OH (chain B)	D474	O_1	3.14
	Butanediol secondary OH (chain C)	D474	O_1	3.00
	Butanediol secondary OH (chain D)	D474	O_1	2.99
	Average	**D474**	**O_1**	**3.05**

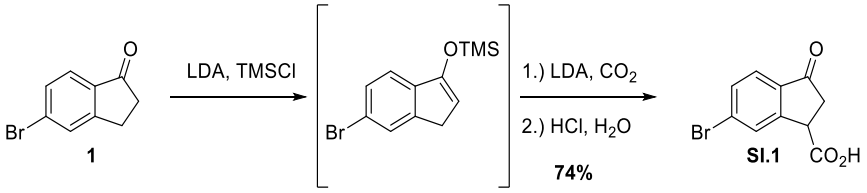
Small Molecule Synthesis

General Information

All reactions were conducted in oven-dried glassware under an inert atmosphere of nitrogen or argon, unless otherwise stated. All solvents were reagent or high-performance liquid chromatography (HPLC) grade. Anhydrous CH_2Cl_2 and THF were obtained from the Pure SolveTM PS-400 system under an argon atmosphere. All reagents were purchased from commercially available sources and used as received. Reactions were magnetically stirred under a nitrogen atmosphere, unless otherwise noted and reactions were monitored by Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F-254 plates (40-55 micron, 230-400 mesh) and visualized by UV light or staining with p-anisaldehyde (acetic acid, sulfuric acid, and methanol) and heating. Reactions were cooled with a Neslab CC 100 Immersion Cooler equipped with a Neslab Cryotrol temperature probe where noted. Yields refer to chromatographically and spectroscopically pure compounds. Optical rotations were measured on a JASCO P-2000 polarimeter. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker Avance III 500-MHz spectrometer, a Bruker DRX500 500-MHz spectrometer, a Bruker NEO600 600-MHz spectrometer, or a Bruker NEO400 400-MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to chloroform (δ 7.26) methanol (δ 3.31), or acetone (δ 2.05) for ^{1}H NMR, and chloroform (δ 77.2) methanol (δ 49.0), or acetone (δ 29.8) for ^{13}C NMR. Infrared spectra were recorded using a JASCO 480-Plus FT-IR spectrometer. High resolution mass spectra (HRMS) were recorded at the University of Pennsylvania Mass Spectroscopy Service Center on either a VG Micromass 70/70H or VG ZAB-E spectrometer. Analytical HPLC was performed with a Waters HPLC-MS system, consisting of a 515 pump and Sunfire C18 reverse phase column (20 µL injection volume, 5 µm packing material, 4.5 × 50 mm column dimensions) with detection accomplished by a Micromass ZQ mass spectrometer and 2996 PDA detector. Preparative scale HPLC was

performed with a Gilson 333/334 preparative pump system equipped with a 5 mL injection loop, Sunfire C18 OBD column (5 µm packing material, 19 x 100 mm column dimensions) or a Chiralpak® AD-H column (5 µm packing material, 21 x 250 mm column dimensions) equipped with a UV-Vis dual wavelength (210 and 254 nm) detector and 215 liquid handling module. Solvent systems were comprised of H_2O containing 0.1% v/v trifluoroacetic acid, and acetonitrile containing 0.1% v/v trifluoroacetic acid or HPLC grade isopropanol and hexanes. SFC analyses were performed with a JASCO system equipped with a PU-280-CO_2 plus CO_2 Delivery System, a CO-2060 plus Intelligent Column Thermostat/Selector, an HC-2068-01 Heater Controller, a BP-2080 plus Automatic Back Pressure Regulator, an MD-2018 plus Photodiode Array Detector (200-648 nm), and PU-2080 plus Intelligent HPLC Pumps. Lyophilization was performed in a Labconco FreeZone 12 Plus lyophilizer (0.148 mbar). The purity of new compounds was judged by NMR and LCMS (>95%).

Synthesis of 3,5-Substituted Common Intermediate

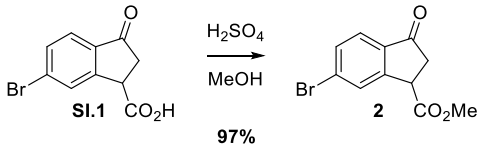


5-Bromo-3-oxo-2,3-dihydro-1H-indene-1-carboxylic acid (SI.1) To a flame dried 1 L round-bottomed flask with stirring bar, 5-bromoindanone (**1,** 10.0 g, 1.0 equiv.) was added and capped with a septum. THF (160 mL, 0.3 M) was then added at room temperature and the resulting solution was cooled to -78 °C in a dry ice/acetone bath. Some precipitate formed upon cooling. A freshly prepared solution of LDA[a] (49.75 mL, 1.0 M, 1.05 equiv.) was then added to the stirring reaction mixture over 15 minutes. The reaction was then homogenous and was stirred for 30 minutes. Freshly distilled TMSCl (6.61 mL, 1.1 equiv.) was then added via syringe to the reaction mixture over 15 minutes. Upon completion of this addition, the reaction was stirred for an additional 30 minutes. A second portion of LDA (56.9 mL, 1.0 M, 1.2 equiv.) was then added over 15 minutes. The reaction was then stirred for an additional 30 minutes. At this time, a balloon was used to bubble CO_2 into the solution at -78 °C for 30 minutes followed by warming to room temperature for 1 hour. The balloon was then removed along with the septum, and 3M HCl in water was added until pH paper indicated an acidic solution. The aqueous layer was extracted with EtOAc (3 x 200 mL). The organic layers were then combined, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to a yellow solid. The solid was then triturated with 300 mL of a 1:1 mixture of CH_2Cl_2:hexanes and filtered to obtain a yellow crystalline solid (**SI.1**). The solvent of the filtrate was then concentrated *in vacuo* and resubjected to the same trituration conditions as described above to obtain a second crop of **SI.1** (9.06 g, 74% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.73 – 7.55 (m, 2H), 4.33 (dd, *J* = 8.3, 3.6 Hz, 1H), 3.16 (dd, *J* = 19.2, 3.6 Hz, 1H), 2.92 (dd, *J* = 19.2, 8.2 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 202.51, 176.16, 151.86, 135.38, 132.96, 130.71, 130.26, 125.40, 43.22, 39.32; **IR** (thin film, KBr) ν_{max} 3127, 2911, 1715, 1591, 1408, 1313, 1206, 1152, 1045, 803 cm^{-1} ; **HRMS** (ESI) *m/z* 295.9913 [calcd for $C_{12}H_{11}BrNO_3$ $(M+H+CH_3CN)^+$ 295.9922].

[a] *Method for LDA preparation:* In a flame dried 500 mL 2-neck flask equipped with a 100 mL addition funnel and stir bar, diisopropylamine (freshly distilled over CaH_2, 15.34 mL, 1.0 equiv.) was dissolved in anhydrous THF (50.66 mL) and cooled to -78 °C in a dry ice/acetone bath. *n*-

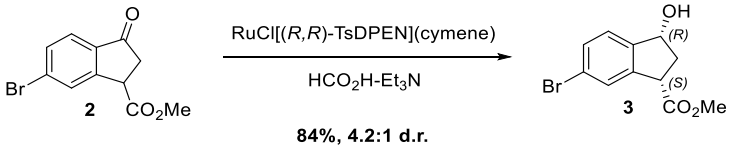
BuLi (44 mL, 2.5 M in hexanes, 1.0 equiv.) was then added dropwise over 15 minutes via addition funnel. The resulting clear yellow solution (V_t = 110 mL, 1.0 M) was allowed to warm to room temperature and stirred for 30 minutes. The solution was then used directly in the reaction as described above.



Methyl 5-bromo-3-oxo-2,3-dihydro-1H-indene-1-carboxylate (2) In a 500 mL round bottom flask with stir bar, **SI.1** (9.06 g, 1.0 equiv.) was dissolved in methanol (72 mL, 0.5 M). To this solution was added 12 drops of concentrated H_2SO_4. The flask was equipped with a reflux condenser and heated to 60 °C in an oil bath. The reaction was allowed to stir for 16 hours, or until TLC (50% EtOAc/hexanes) indicated complete consumption of starting material. The reaction was removed from heat and allowed to cool to room temperature. A saturated aq. solution of $NaHCO_3$ was then added until pH paper indicated it was basic. The aqueous layer was then extracted with EtOAc (3 x 150 mL). The organic layers were then combined, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Crude **2** was used in the next reaction without further purification (9.27 g, 97% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.67 – 7.52 (m, 2H), 4.28 (dd, *J* = 8.2, 3.6 Hz, 1H), 3.81 (s, 3H), 3.15 (dd, *J* = 19.1, 3.7 Hz, 1H), 2.88 (dd, *J* = 19.1, 8.2 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 202.76, 171.74, 152.63, 135.42, 132.69, 130.49, 130.10, 125.29, 53.12, 43.46, 39.61; **IR** (thin film, KBr) ν_{max} 2938, 1716, 1592, 1434, 1159, 1040, 820 cm^{-1} ; **HRMS** (EI) *m/z* 267.9713 [calcd for $C_{11}H_9{}^{79}BrO_3$ $(M)^+$ 267.9735], *m/z* 269.9714 [calcd for $C_{11}H_9{}^{81}BrO_3$ $(M)^+$ 269.9715].

Note: Isotope overlap of $(M\text{-}2H)^+$ with $(M(^{79}Br))^+$ skews $(M(^{79}Br))^+$ isotope measurement, therefore $(M(^{81}Br))^+$ is also supplied for further evidence.

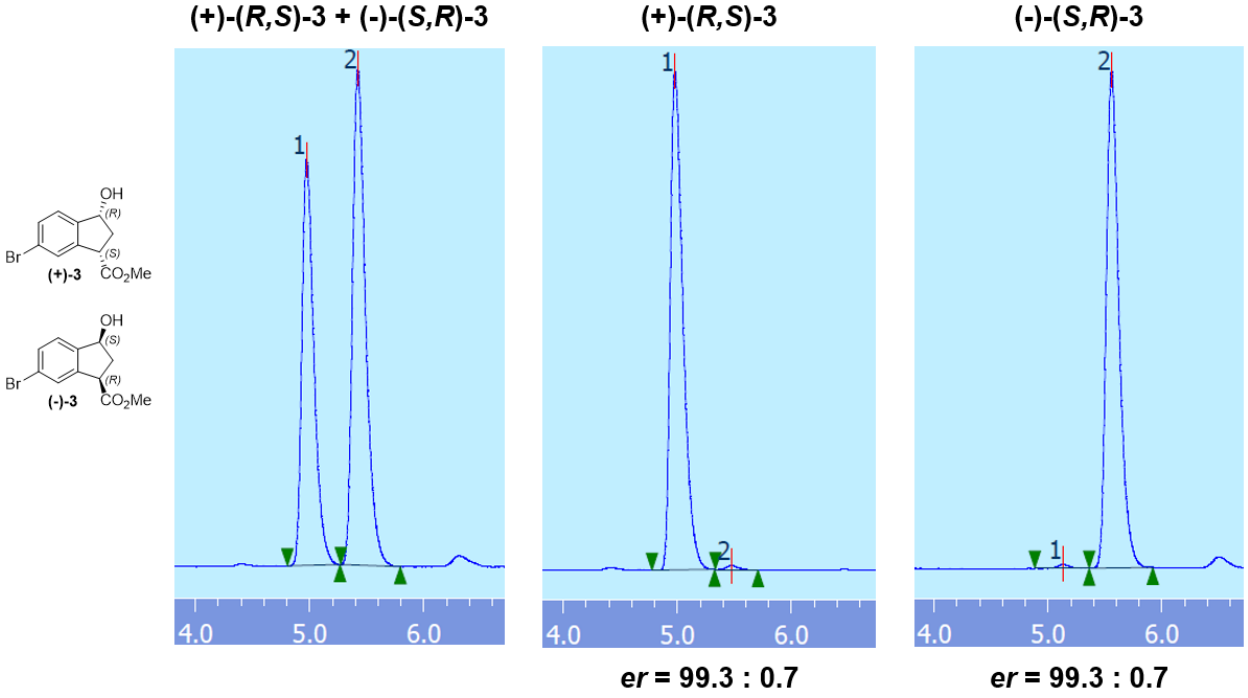


Methyl (1S,3R)-5-bromo-3-hydroxy-2,3-dihydro-1H-indene-1-carboxylate (3) In a 250 mL 2-neck round bottom flask with stir bar, **2** (9.27 g, 1.0 equiv.) was added and capped with septa. To the flask was then added freshly distilled and sparged (30 minutes with N_2 balloon) DCE (36 mL, 1.0 M) and 5:2 HCO_2H:NEt_3 azeotrope (18 mL, 0.5 mL/g starting material). Under a positive pressure of N_2, RuCl[(*R*,*R*)-TsDPEN](*p*-cymene) (480 mg, 2 mol %) was then added in one portion to the reaction flask. The reaction was then stirred for 16 hours, at which time an aliquot was taken and showed consumption of starting material by NMR analysis. The reaction was quenched with water (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to a black oil. The diastereomers were separated by flash column chromatography (100% CH_2Cl_2). TLC (100% CH_2Cl_2) was monitored to determined when fractions began to contain the undesired diastereomer. Fractions containing the desired diastereomer were then concentrated *in vacuo* and dissolved in Et_2O (300 mL). The solvent was allowed to evaporate, forming crystals of **3** that

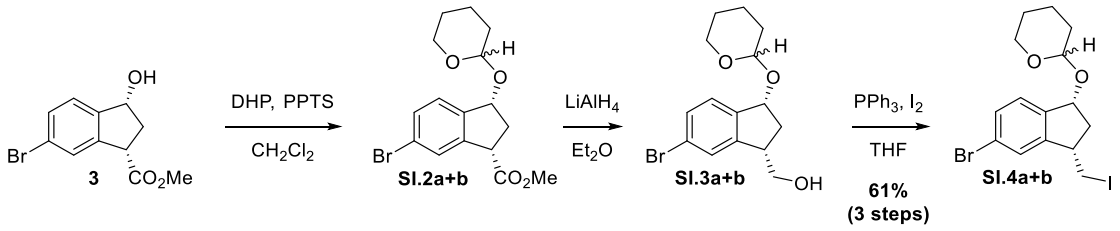
were filtered and collected. NMR confirmed the d.r. to be >20:1 (7.8 g, 84% yield of both diastereomers. Isolated 4.31 g of desired diastereomer).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 1.9 Hz, 1H), 7.45 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 5.09 (s, 1H), 4.00 (dd, *J* = 8.1, 3.0 Hz, 1H), 3.78 (s, 3H), 3.13 (s, 1H), 2.59 (ddd, *J* = 14.6, 8.0, 6.8 Hz, 1H), 2.32 (dt, *J* = 14.2, 2.8 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 175.35, 144.59, 142.63, 132.03, 128.23, 127.12, 122.93, 74.78, 53.10, 48.39, 38.84. **IR** (thin film, KBr) ν_{max} 3309, 2946, 1739, 1602, 1434, 1169, 1061, 819 cm^{-1}; **HRMS** (EI) *m/z* 269.9879 [calcd for $C_{11}H_{11}BrO_3$ $(M)^+$ 269.9892]; **$[\alpha]_D^{23}$** +46.2 (*c* 1.17, CH_2Cl_2).

Enantiomeric excess determined by SFC (see below):



Method: column: Chiralpak® IA; eluent: 5% MeOH in supercritical CO_2; flow rate: 4 mL/min; pressure: 12 MPa. Retention times: **(+)-(*R*,*S*)-3**: 5.0 min, **(–)-(*S*,*R*)-3**: 5.4 min.



Methyl (1S,3R)-5-bromo-3-((tetrahydro-2H-pyran-2-yl)oxy)-2,3-dihydro-1H-indene-1-carboxylate (SI.2a+b) In a 250 mL round-bottomed flask with stir bar, **3** (4.32 g, 1.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (48.2 mL, 0.33 M). To the stirring mixture, PPTS (200 mg, 5 mol %) was added in one portion at room temperature. Then, 3,4-dihydro-2H-pyran (DHP) (2.90 mL, 2.0 equiv.) was added in one portion. The reaction was allowed to stir overnight at room temperature. TLC (30% EtOAc/hexanes) indicated complete consumption of starting material after 16 hours. The reaction was quenched with aq. saturated $NaHCO_3$ (50 mL) and the

aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to an oil. The product was purified by flash column chromatography (10% to 20% EtOAc in hexanes) to give the product **SI.2a+b** as a clear oil. **SI.2a+b** was an inseparable 1:1 diastereomeric mixture.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 6.3, 1H), 7.44 – 7.40 (m, 1H), 7.35 (d, *J* = 8.1 Hz, 0.5H), 7.22 (d, *J* = 8.1 Hz, 0.5H), 5.22 (t, *J* = 6.7 Hz, 0.5H), 5.02 (t, *J* = 6.9 Hz, 0.5H), 4.91 (t, *J* = 3.6 Hz, 0.5H), 4.85 (t, *J* = 3.6 Hz, 0.5H), 4.02 – 3.88 (m, 2H), 3.78 (s, 3H), 3.61 – 3.56 (m, 1H), 2.79 (dt, *J* = 13.2, 7.5 Hz, 0.5H), 2.71 (dt, *J* = 13.2, 7.5 Hz, 0.5H), 2.49 (ddd, *J* = 13.2, 8.3, 6.8 Hz, 0.5H), 2.39 (ddd, *J* = 13.1, 8.0, 6.4 Hz, 0.5H), 1.89 – 1.73 (m, 2H), 1.70 – 1.52 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.84, 172.70, 142.62, 142.56, 141.78, 141.72, 131.28, 131.05, 128.50, 128.35, 126.80, 126.33, 122.48, 122.47, 99.67, 97.00, 79.70, 76.74, 62.75, 62.58, 52.53, 52.46, 47.17, 47.12, 38.20, 35.51, 31.04, 30.92, 25.65, 19.60, 19.46; **IR** (thin film, KBr) ν_{max} 2946, 1741, 1595, 1470, 1435, 1404, 1339, 1261, 1200, 1132, 1066, 1034, 989, 904, 815 cm^{-1}; **HRMS** (EI) *m/z* 268.9821 [calcd for $C_{11}H_{10}BrO_3$ (M-THP)$^+$ 268.9813]; **$[\alpha]_D^{23}$** +258.1 (*c* 0.875, CH_2Cl_2).

((1S,3R)-5-Bromo-3-((tetrahydro-2H-pyran-2-yl)oxy)-2,3-dihydro-1H-inden-1-yl)methanol (SI.3a+b) In a 250 mL 2-neck flask with stir bar, **SI.2a+b** (1.0 equiv.) from the previous step was added and dissolved in anhydrous Et_2O (79 mL, 0.2 M). The solution was cooled to 0 °C in an ice/water bath. Under a positive pressure of N_2, LAH powder (721 mg, 1.2 equiv.) was added to the reaction flask. The reaction was stirred at 0 °C for 3 hours, at which time TLC (30% EtOAc in hexanes) indicated complete consumption of starting material. The reaction was quenched with the Fieser & Fieser workup[16] (721 µL H_2O, 721 µL 20% NaOH (w/v), followed by 2.16 mL H_2O). The reaction was then warmed to room temperature and $MgSO_4$ was added. The mixture was allowed to stir for 15 minutes. After this time, the solid was filtered and washed thoroughly with Et_2O (300 mL). The filtrate was then concentrated *in vacuo* to a clear oil which was purified by flash column chromatography (25% to 35% EtOAc/hexanes) to give the product **SI.3a+b** as a clear oil. **SI.3a+b** was an inseparable 1:1 diastereomeric mixture.

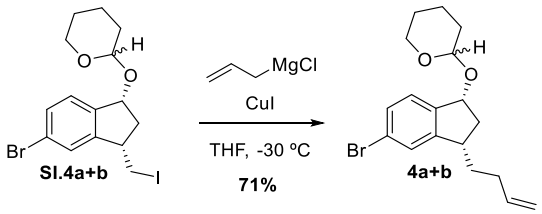
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 13.2, 1H), 7.41 – 7.33 (m, 1.5H), 7.23 (d, *J* = 8.0 Hz, 0.5H), 5.17 (dd, *J* = 6.7, 3.8 Hz, 0.5H), 5.08 (dd, *J* = 6.6, 2.9 Hz, 0.5H), 4.89 (dd, *J* = 3.4, 3.0 Hz, 0.5H), 4.82 (dd, *J* = 3.4, 3.4 Hz, 0.5H), 3.97 – 3.83 (m, 3H), 3.62 – 3.55 (m, 1H), 3.33 – 3.28 (m, 1H), 2.64 – 2.52 (m, 1H), 2.08 – 1.50 (m, 9H); **IR** (thin film, KBr) ν_{max} 3433, 2952, 1645, 1474, 1340, 1138, 1018 cm^{-1}; **HRMS** (EI) *m/z* 240.9868 [calcd for $C_{10}H_{10}BrO_2$ (M-THP)$^+$ 240.9864]; **$[\alpha]_D^{23}$** +243.2 (*c* 0.8, CH_2Cl_2).

2-(((1R,3S)-5-Bromo-3-(iodomethyl)-2,3-dihydro-1H-inden-1-yl)oxy)tetrahydro-2H-pyran (SI.4a+b) In a 250 mL round-bottomed flask with stir bar, **SI.3a+b** (1.0 equiv.) from the previous step was dissolved in THF (78 mL, 0.2 M). To the stirring solution was added PPh_3 (5.30 g, 1.3 equiv.) and imidazole (1.38 g, 1.3 equiv.) at room temperature. The reaction was then cooled to 0 °C in an ice/water bath. A solution of iodine (5.13 g, 1.3 equiv.) in THF (20 mL, 1.0 M) was then added dropwise to the stirring reaction mixture via syringe over 15 minutes. The reaction was then warmed to room temperature and allowed to stir for 2 hours. At this time, TLC (30% EtOAc/hexanes) indicated complete consumption of starting material. A saturated aq. solution of $Na_2S_2O_3$ (80 mL) was then added and the aqueous layer was extracted with Et_2O (3 x 100 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to an oil. The product was purified by flash column chromatography (10% EtOAc/hexanes) to give the product

[16] Fieser, L. F.; Fieser, M. **Reagents for Organic Synthesis**, 1967, 581-595.

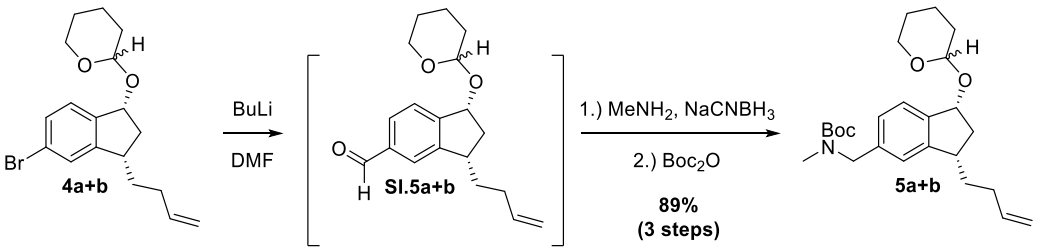
SI.4a+b as a clear oil (4.16 g, 61% over 3 steps). **SI.4a+b** was an inseparable 1:1 diastereomeric mixture.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2H), 7.34 (d, *J* = 8.7 Hz, 0.5H), 7.21 (d, *J* = 8.0 Hz, 0.5H), 5.15 (dd, *J* = 6.0, 6.0 Hz, 0.5H), 5.00 (dd, *J* = 6.0, 6.0 Hz, 0.5H), 4.87 – 4.84 (m, 1H), 3.99 – 3.93 (m, 1H), 3.62 – 3.54 (m, 2H), 3.38 – 3.31 (m, 1H), 2.75 – 2.65 (m, 1H), 2.06 – 2.00 (m, 0.5H), 1.90 – 1.70 (m, 2.5H), 1.68 – 1.49 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.58, 146.23, 142.97, 142.75, 131.13, 130.84, 127.75, 127.39, 127.31, 126.98, 122.54, 122.47, 98.78, 97.32, 78.47, 77.40, 76.71, 62.74, 45.51, 45.22, 42.47, 40.63, 31.16, 31.00, 25.64, 19.65, 19.60, 10.94, 10.92; **IR** (thin film, KBr) ν_{max} 2934, 2858, 1595, 1469, 1338, 1259, 1125, 1034, 986, 869, 815 cm^{-1} ; **$[\alpha]_D^{23}$** +80.7 (*c* 1.99, CH_2Cl_2).



2-(((1R,3S)-5-Bromo-3-(but-3-en-1-yl)-2,3-dihydro-1H-inden-1-yl)oxy)tetrahydro-2H-pyran (4a+b) In a 250 mL round-bottomed with stir bar, **SI.4a+b** (4.16 g, 1.0 equiv.) and CuI (0.906 g, 0.4 equiv.) were added and the flask was capped with a septum. To the flask was added anhydrous THF (50 mL, 0.2 M) and the heterogeneous mixture was cooled to -30 °C in a xylenes/dry ice bath. Once equilibrated to -30 °C, allylmagnesium chloride in THF (9.51 mL, 2.0 equiv., 2.0 M) was added dropwise over 10 minutes via syringe. The mixture was allowed to stir at -30 °C for 30 minutes, followed by warming to room temperature. After an additional hour of stirring, TLC (10% EtOAc/hexanes) indicated complete consumption of starting material. The reaction was cooled to 0 °C and quenched with brine (50 mL) and 33% w/v aqueous NH_4OH (50 mL). The aqueous layer was extracted with Et_2O (3 x 100 mL) and the organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to an oil. The product was purified by flash column chromatography (5% EtOAc/hexanes) to give the product **4a+b** as a clear oil. (2.36 g, 71% yield). **4a+b** was an inseparable 1:1 diastereomeric mixture.

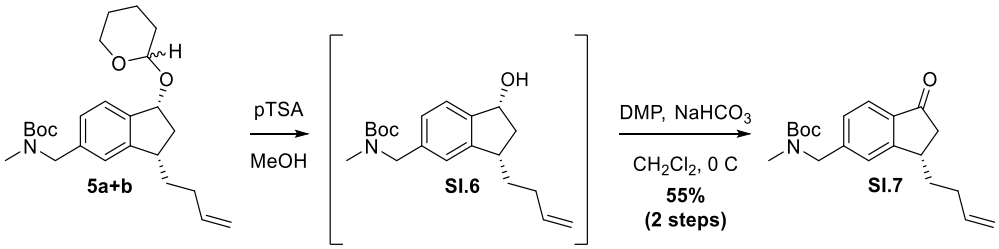
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 2.5H), 7.19 (d, *J* = 7.9 Hz, 0.5H), 5.86 (dddd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H), 5.18 (dd, *J* = 6.8, 6.8 Hz, 0.5H), 5.09 – 5.05 (m, 1H), 5.02 – 4.98 (m, 1.5H), 4.90 (t, *J* = 3.6 Hz, 0.5H), 4.85 (t, *J* = 3.6 Hz, 0.5H), 4.03 – 3.94 (m, 1H), 3.61 – 3.56 (m, 1H), 3.03 – 2.95 (m, 1H), 2.68 (ddt, *J* = 12.5, 9.5, 7.1 Hz, 1H), 2.26 – 2.10 (m, 2H), 2.06 – 1.96 (m, 1H), 1.91 – 1.74 (m, 2.5H), 1.69 – 1.52 (m, 5.5H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 149.06, 148.85, 142.72, 142.69, 138.51, 138.42, 130.07, 129.84, 127.19, 126.92, 126.49, 126.09, 122.21, 122.13, 115.12, 115.06, 99.75, 96.98, 80.14, 62.90, 62.66, 41.63, 41.47, 41.46, 39.36, 34.63, 34.61, 31.84, 31.77, 31.18, 31.10, 25.67, 25.64, 19.83, 19.64; **IR** (thin film, KBr) ν_{max} 3073, 2925, 1639, 1597, 1470, 1338, 1200, 1133, 1063, 1035, 993, 910, 869, 813 cm^{-1}; **HRMS** (EI) *m/z* 350.0883 [calcd for $C_{18}H_{23}BrO_2$ $(M)^+$ 350.0881]; **$[\alpha]_D^{23}$** +40.1 (*c* 1.25, CH_2Cl_2).



Tert-butyl (((1R,3S)-3-(but-3-en-1-yl)-1-((tetrahydro-2H-pyran-2-yl)oxy)-2,3-dihydro-1H-inden-5-yl)methyl)(methyl)carbamate (5a+b) In an oven-dried 100 mL round-bottomed flask with stir bar, **4a+b** (2.36 g, 1.0 equiv.) was added and the flask was capped with a septum. To the flask was added anhydrous THF (22.5 mL, 0.3 M) and the solution was cooled to -78 °C in an acetone/dry ice bath. Once equilibrated, *n*-butyllithium in hexanes (2.95 mL, 1.1 equiv., 2.5 M) was added dropwise via syringe over 10 minutes. The reaction was allowed to stir for 15 minutes before addition of DMF (620 µL, 1.2 equiv.). The reaction was allowed to stir for 15 minutes and was warmed to room temperature. The reaction was allowed to stir for an additional 30 minutes at room temperature when TLC (10% EtOAc/hexanes) indicated complete consumption of starting material. The reaction was quenched with brine (50 mL) and the aqueous layer was extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give crude **SI.5a+b** as a clear oil. This material was used in the next step without further purification.

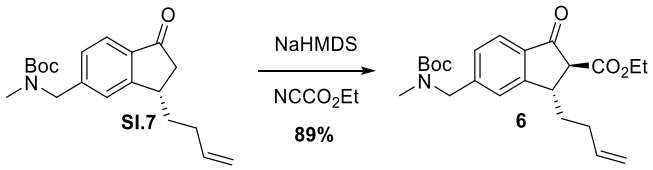
To a solution of crude **SI.5a+b** in MeOH/CH_2Cl_2 (5:1 ratio, 7.89 mL, 0.85 M) was added 40 wt% aqueous $MeNH_2$ (1.97 mL, 3.4 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 hour, followed by the addition of $NaBH_4$ (0.66 g, 2.6 equiv) in one portion. The resulting suspension was continued to stir at 0 ºC for 2 hours, or until TLC (10% EtOAc/hexanes) indicated complete consumption of starting material. The reaction mixture was then treated with an aqueous saturated solution of $NaHCO_3$ (20 mL). The resulting mixture was allowed to warm to room temperature and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give an oil. This was dissolved in CH_2Cl_2 (6.71 mL) and this solution was cooled to 0 °C, to which a solution of Boc_2O (1.70 mL, 1.05 equiv) in CH_2Cl_2 (3.2 mL, 2.3 M) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 hour. The solvent was then concentrated *in vacuo* to give crude **5a+b** as an oil, which was purified by flash column chromatography (10% EtOAc/hexanes) to give the product **5a+b** as a clear oil (2.49 g, 89% over 3 steps). **5a+b** was an inseparable 1:1 diastereomeric mixture.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.7 Hz, 0.5H), 7.28 (d, *J* = 8.2 Hz, 0.5H), 7.19 – 6.98 (m, 2H), 5.86 (dddd, *J* = 16.9, 11.3, 6.4, 6.4 Hz, 1H), 5.27 – 5.23 (m, 0.5H), 5.07 – 5.04 (m, 1.5H), 5.00 – 4.93 (m, 1.5H), 4.88 – 4.86 (m, 0.5H), 4.41 (s, 2H), 4.05 (ddd, *J* = 11.7, 8.5, 3.5 Hz, 0.5H), 3.98 (ddd, *J* = 11.2, 7.4, 3.4 Hz, 0.5H), 3.62 – 3.56 (m, 1H), 3.07 – 2.94 (m, 1H), 2.82 – 2.66 (m, 4H), 2.26 – 2.11 (m, 2H), 2.08 – 1.99 (m, 1H), 1.94 – 1.48 (m, 17H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.13, 148.25, 148.10, 147.22, 147.02, 142.83, 142.79, 142.68, 138.80, 138.71, 138.25, 138.21, 138.19, 124.92, 124.66, 124.60, 124.32, 114.93, 114.88, 99.86, 99.80, 96.73, 96.65, 80.69, 80.53, 79.79, 77.40, 62.91, 62.75, 62.52, 62.48, 52.83, 44.26, 43.32, 42.13, 41.65, 41.56, 41.51, 39.43, 36.68, 36.57, 34.87, 34.85, 34.01, 33.97, 32.00, 31.94, 31.24, 31.20, 31.18, 28.66, 25.77, 25.72, 20.40, 19.91, 19.81, 19.62, 19.60; **IR** (thin film, KBr) ν_{max} 3074, 2929, 2863, 1698, 1453, 1391, 1136, 1034, 992, 913, 870, 816 cm^{-1}; **HRMS** (ESI) *m/z* 438.2614 [calcd for $C_{25}H_{37}NO_4Na$ $(M+Na)^+$ 438.2620] ; **$[\alpha]_D^{23}$** +19.5 (*c* 2.86, CH_2Cl_2).



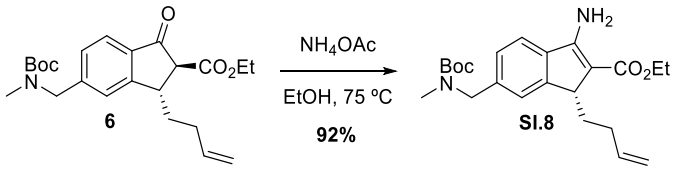
Tert-butyl (S)-((3-(but-3-en-1-yl)-1-oxo-2,3-dihydro-1H-inden-5-yl)methyl)(methyl) carbamate (SI.7) To a solution of **5a+b** (2.49 g, 1.0 equiv.) in MeOH (100 mL, 0.06 M) was added *p*TSA (251 mg, 0.22 equiv) at room temperature. The resulting solution was stirred at room temperature for 1 hour, at which time TLC (20% EtOAc/hexanes) indicated complete consumption of starting material. The reaction mixture was then treated with a saturated aq. solution of $NaHCO_3$ (50 mL) and extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give crude **SI.6** as an oil. This residue was taken up in anhydrous CH_2Cl_2 (60 mL, 0.1 M) and solid $NaHCO_3$ (2.02 g, 4.0 equiv) was added at room temperature. The resulting suspension was cooled to at 0 °C in an ice/water bath and DMP (3.82 g, 1.5 equiv) was then added in one portion. The reaction was then warmed to room temperature and was allowed to stir for 1 hour, at which time TLC (20% EtOAc/hexanes) indicated complete consumption of starting material. The reaction mixture was then treated with a saturated aq. solution of $Na_2S_2O_3$ (60 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 60 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give an oil, which was purified by flash column chromatography (15% EtOAc/hexanes) to give **SI.7** (1.09 g, 55% yield, 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.9 Hz, 1H), 7.33 (s, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 5.83 (dddd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H), 5.07 – 5.00 (m, 2H), 4.50 (s, 2H), 3.39 – 3.34 (m, 1H), 2.90 – 2.82 (m, 4H), 2.37 (dd, *J* = 18.9, 3.3 Hz, 1H), 2.19 – 2.14 (m, 2H), 2.04 – 1.98 (m, 1H), 1.70 – 1.31 (m, 10H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 205.78, 159.46, 145.92, 137.84, 136.22, 123.98, 115.57, 80.22, 43.37, 37.76, 35.47, 34.54, 31.94, 28.59; **IR** (thin film, KBr) ν_{max} 3080, 2981, 2927, 1713, 1608, 1394, 1237, 1145, 1046, 877 cm^{-1} ; **HRMS** (ESI) *m/z* 330.2064 [calcd for $C_{20}H_{28}NO_3$ $(M+H)^+$ 330.2069] ; **$[\alpha]_D^{23}$** +20.6 (*c* 0.85, CH_2Cl_2).



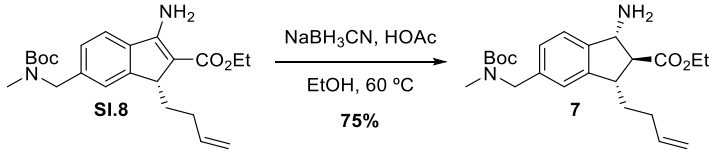
Ethyl (2S,3S)-3-(but-3-en-1-yl)-5-(((tert-butoxycarbonyl)(methyl)amino)methyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (6) In an oven dried 100 mL round-bottomed flask with stir bar, **SI.7** (1.09 g, 1.0 equiv.) was dissolved in anhydrous THF (33.1 mL, 0.1 M). This solution was then cooled to -78 °C in a dry ice/acetone bath. A solution of NaHMDS in THF (6.62 mL, 1.0 M, 2.1 equiv.) was then added dropwise to the stirring solution. After 30 minutes, Mander's reagent (0.425 mL, 1.3 equiv.) was added dropwise. The reaction was allowed to stir for an additional hour. The flask was warmed to room temperature and was quenched with brine (50 mL). The aqueous layer was then extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give an oil. The oil was then purified by flash column chromatography (15% EtOAc/hexanes) to give **6** as a yellow oil (1.18 g, 89% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.34 (s, 1H), 7.25 (s, 1H), 5.82 (dddd, *J* = 16.9, 10.3, 6.5, 6.5 Hz, 1H), 5.07 – 5.00 (m, 2H), 4.50 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.79 – 3.72 (m, 1H), 3.37 (d, *J* = 4.0 Hz, 1H), 2.86 – 2.78 (s, 3H), 2.21 – 2.07 (m, 3H), 1.71 – 1.59 (m, 1H), 1.48 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.65, 169.43, 159.44, 158.04, 147.03, 137.39, 134.51, 127.13, 124.88, 123.96, 123.58, 115.91, 80.28, 61.83, 60.58, 53.04, 52.36, 42.58, 34.68, 31.72, 29.85, 28.61, 28.56, 14.35; **IR** (thin film, KBr) ν_{max} 3073, 2976, 2929, 2850, 1696, 1608, 1566, 1466, 1401, 1146, 1016, 914, 877 cm^{-1}; **HRMS** (ESI) *m/z* 402.2278 [calcd for $C_{23}H_{32}NO_5$ $(M+H)^+$ 402.2280]; **$[\alpha]_D^{23}$** -49.8 (*c* 1.11, CH_2Cl_2).



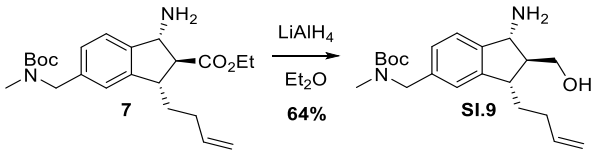
Ethyl (R)-3-amino-1-(but-3-en-1-yl)-6-(((tert-butoxycarbonyl)(methyl)amino)methyl)-1H-ind-ene-2-carboxylate (SI.8) In a 100 mL round-bottomed flask with stir bar, **6** (1.18 g, 1.0 equiv.) and ammonium acetate (2.27 g, 10 equiv.) were dissolved in ethanol (7.35 mL, 0.4 M) at room temperature. The flask was fitted with a reflux condenser and heated to 75 °C in an oil bath. After 16 hours, TLC indicated complete consumption of starting material (20% EtOAc/hexanes). The reaction was then cooled to room temperature and quenched with aq. sat. $NaHCO_3$ (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give a brown oil, which was purified by flash column chromatography (15% EtOAc/hexanes) to give **SI.8** as a yellow oil (1.08 g, 92% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.21 (s, 1H), 6.00 (br s, 2H), 5.69 (dddd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H), 4.88 – 4.82 (m, 2H), 4.49 (s, 2H), 4.32 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.22 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.82 (dd, *J* = 5.0, 4.4 Hz, 1H), 2.83 (s, 3H), 2.17 – 2.07 (m, 2H), 1.86 – 1.78 (m, 1H), 1.58 – 1.43 (m, 10H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.98, 156.26, 149.37, 139.48, 139.22, 136.97, 126.38, 125.79, 122.82, 118.96, 114.16, 101.76, 79.99, 59.10, 53.04, 52.30, 45.37, 34.29, 30.59, 28.81, 28.63, 14.89; **IR** (thin film, KBr) ν_{max} 3451, 3341, 2976, 2915, 1664, 1536, 1391, 1265, 1139 cm^{-1}; **HRMS** (ESI) *m/z* 401.2427 [calcd for $C_{23}H_{33}N_2O_4$ $(M+H)^+$ 401.2440]; **$[\alpha]_D^{23}$** -15.3 (*c* 1.26, CH_2Cl_2).



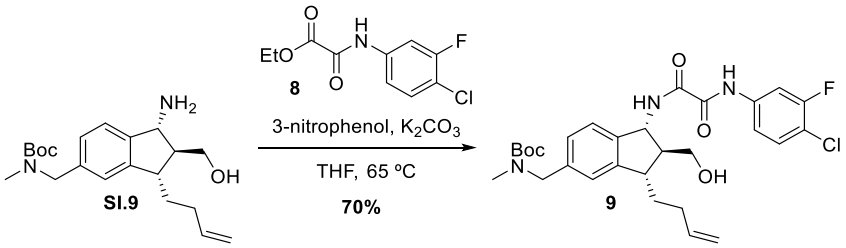
Ethyl (1R,2S,3S)-1-amino-3-(but-3-en-1-yl)-5-(((tert-butoxycarbonyl)(methyl)amino)methyl-)-2,3-dihydro-1H-indene-2-carboxylate (7) In a 100 mL round-bottomed flask with stir bar, **SI.8**, (1.08 g, 1.0 equiv.), $NaBH_3CN$ (1.02 g, 6 equiv.), and AcOH (1.23 mL, 8 equiv.) were dissolved in ethanol (9.0 mL, 0.3 M) at room temperature. The flask was sealed with a septum and fitted with a reflux condenser. The reaction was heated to 60 °C in an oil bath and allowed to stir overnight. After 16 hours, TLC indicated complete consumption of starting material (50% EtOAc/hexanes) with the product staining well in $KMnO_4$. The reaction was then cooled to room temperature and quenched with 1M NaOH (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give an oil, which was purified by flash column chromatography (50% to 100% EtOAc/hexanes) to give **7** as a yellow oil (0.808 g, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.7 Hz, 1H), 7.13 – 7.03 (m, 2H), 5.84 (dddd, *J* = 16.8, 10.2, 6.3, 6.3 Hz, 1H), 5.08 – 5.02 (m, 1H), 5.00 – 4.97 (m, 1H), 4.48 (d, *J* = 8.4 Hz, 1H), 4.41 (s, 2H), 4.29 – 4.21 (m, 2H), 3.47 – 3.41 (m, 1H), 2.81 (s, 3H), 2.57 (dd, *J* = 8.9, 8.9 Hz, 1H), 2.19 – 2.04 (m, 3H), 1.91 (s, 2H), 1.75 – 1.67 (m, 1H), 1.47 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.59, 145.44, 144.43, 143.54, 138.29, 126.64, 123.60, 115.07, 79.90, 63.30, 61.03, 60.65, 52.78, 45.09, 34.06, 33.43, 31.41, 30.95, 28.64, 14.51; **IR** (thin film, KBr) ν_{max} 3366, 3074, 2976, 2921, 2402, 2350, 2251, 1695, 1462, 1392, 1234, 1147, 1032, 874 cm^{-1}; **HRMS** (ESI) *m/z* 403.2608 [calcd for $C_{23}H_{35}N_2O_4$ $(M+H)^+$ 403.2597]; **$[\alpha]_D^{23}$** -2.1 (*c* 1.51, CH_2Cl_2).



Tert-butyl (((1R,2S,3S)-1-amino-3-(but-3-en-1-yl)-2-(hydroxymethyl)-2,3-dihydro-1H-inden-5-yl)methyl)(methyl)carbamate (SI.9) In a 100 mL round-bottomed flask with stir bar, **7** (808 mg, 1.0 equiv.) was added and dissolved in anhydrous Et_2O (9.6 mL, 0.2 M). The solution was then cooled to 0 °C in an ice/water bath. LAH powder (146 mg, 1.2 equiv.) was added to the reaction flask. The reaction was stirred at 0 °C for 2 hours, at which time TLC (10% MeOH/CH_2Cl_2) indicated complete consumption of starting material. The reaction was quenched with the Fieser & Fieser[16] workup (150 µL H_2O, 150 µL 20% NaOH (w/v), followed by 450 µL H_2O). The reaction was then warmed to room temperature and $MgSO_4$ was added. The mixture was allowed to stir for 30 minutes. After this time, the solid was filtered and washed thoroughly with Et_2O. The filtrate was then concentrated *in vacuo* to an oil, which was purified by flash column chromatography (10% MeOH/CH_2Cl_2) to give **SI.9** as a yellow oil (441 mg, 64%).

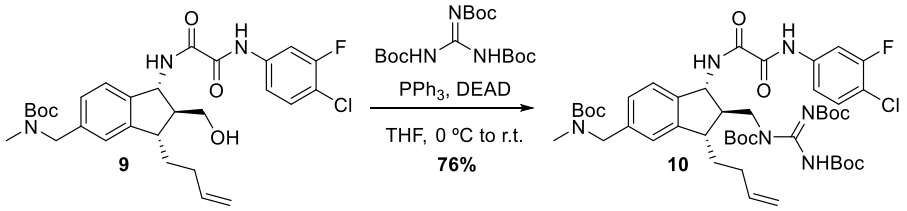
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.7 Hz, 1H), 7.10 – 7.05 (m, 2H) 5.83 (dddd, *J* = 16.8, 10.2, 6.5, 6.5 Hz, 1H), 5.06 – 5.02 (m, 1H), 4.98 – 4.96 (m, 1H), 4.40 (s, 2H), 4.15 (d, *J* = 8.4 Hz, 1H), 4.06 (dd, *J* = 10.4, 4.3 Hz, 1H), 3.86 (dd, *J* = 9.8, 9.8 Hz, 1H), 2.88 – 2.73 (m, 7H), 2.19 – 2.12 (m, 2H), 2.08 – 2.01(m, 1H), 1.95 – 1.88 (m, 1H), 1.81 – 1.73 (m, 1H), 1.47 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.30, 155.91, 145.49, 145.20, 138.50, 137.88, 126.65, 126.29, 123.13, 122.77, 115.08, 79.85, 66.19, 61.23, 57.61, 52.78, 52.10, 43.14, 34.01, 32.51, 31.24, 28.63; **IR** (thin film, KBr) ν_{max} 3353, 3074, 2975, 2925, 2361, 1694, 1482, 1453, 1393, 1366, 1302, 1246, 1172, 1148, 909, 874, 932, 818 cm^{-1}; **HRMS** (ESI) *m/z* 361.2500 [calcd for $C_{21}H_{33}N_2O_3$ $(M+H)^+$ 361.2491]; **$[\alpha]_D^{23}$** +3.6 (*c* 0.75, CH_2Cl_2).



Tert-butyl (((1R,2S,3S)-3-(but-3-en-1-yl)-1-(2-((4-chloro-3-fluorophenyl)amino)-2-oxoacetamido)-2-(hydroxymethyl)-2,3-dihydro-1H-inden-5-yl)methyl)(methyl)carbamate (9) In a 25 mL round-bottomed flask equipped with a reflux condenser and stir bar, a mixture of **SI.9** (441 mg, 1.0 equiv.), **8** (340 mg, 1.15 equiv.), 3-nitrophenol (33.6 mg, 0.2 equiv.), and K_2CO_3 (33.3 mg, 0.2 equiv.) in THF (1.505 mL, 0.8 M) was stirred at 65 ºC for 16 h. The resulting suspension was allowed to cool to room temperature and then treated with 10 wt% K_2CO_3 (5 mL). The resulting mixture was further stirred at room temperature for 1 hr, and then diluted with EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give an oil, which was purified by flash column chromatography (50% to 100% EtOAc/hexanes) to give **9** as a colorless amorphous solid (472 mg, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.71 (dd, *J* = 10.6, 2.4 Hz, 1H), 7.37 (t, *J* = 8.3 Hz, 1H), 7.28 (dd, *J* = 2.6, 1.0 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.14 – 7.12 (m, 2H), 5.83 (dddd, *J* = 16.8, 10.1, 6.5, 6.5 Hz, 1H), 5.20 (dd, *J* = 8.5, 6.0 Hz, 1H), 5.07 – 4.98

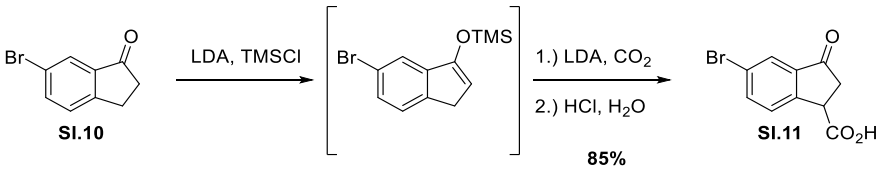
(m, 2H), 4.43 (s, 2H), 3.86 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.73 (dd, *J* = 11.4, 8.3 Hz, 1H), 2.92 (q, *J* = 6.8 Hz, 1H), 2.82 (s, 3H), 2.58 – 2.38 (s, 1H), 2.31 – 2.10 (m, 3H), 1.97 – 1.89 (m, 1H), 1.81 – 1.72 (m, 1H), 1.48 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 160.18, 158.18 (d, J_{CF} = 248.5 Hz), 157.24, 146.44, 139.67, 138.72, 138.08, 136.33 (d, J_{CF} = 9.8 Hz), 131.04, 124.43, 117.51 (d, J_{CF} = 18.4 Hz), 116.26 (d, J_{CF} = 3.7 Hz), 115.43, 108.72 (d, J_{CF} = 26.2 Hz), 80.01, 68.67, 64.21, 58.18, 57.67, 44.60, 34.19, 31.18, 28.63, 27.97, 22.36; **IR** (thin film, KBr) ν_{max} 3353, 3287, 3075, 2975, 2926, 1671, 1594, 1514, 1454, 1427, 1394, 1366, 1304, 1243, 1150, 1066, 973 cm^{-1}; **HRMS** (ESI) *m/z* 560.2335 [calcd for $C_{29}H_{36}ClFN_3O_5$ $(M+H)^+$ 560.2328]; **$[\alpha]_D^{23}$** -10.0 (*c* 1.75, CH_2Cl_2).



Compound 10 In a 100 mL round-bottomed flask with stir bar, a mixture of **9** (472 mg, 1.0 equiv.), PPh_3 (354 mg, 1.6 equiv.), and N,N′,N″-tri-Boc-guanidine (1.06 g, 3.5 equiv.) in anhydrous THF (21.1 mL, 0.04 M) was stirred at room temperature until a well-dispersed suspension had formed. This mixture was cooled at 0 ºC and treated with diethyl azodicarboxylate (198 µL, 1.5 equiv.) dropwise at such a rate that each drop was only added after the color change resulting from the previous drop had dissipated. After the addition was completed, the reaction was allowed to warm to room temperature and stir for 18 hr. TLC (30% EtOAc/hexanes) indicated complete consumption of starting material at this time. The reaction was then quenched with brine (25 mL) and the aqueous layer was extracted with EtOAc (3 x 25 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give a white solid which was purified by flash column chromatography (20% EtOAc/hexanes) to give a mixture of **10** and N,N′,N″-tri-Boc-guanidine. The residue was treated with Et_2O (5 mL) and the insoluble material was removed via vacuum filtration. The filtrate was concentrated *in vacuo* to give **10** as an off-white amorphous solid (576 mg, 76%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.32 (s, 1H), 9.29 (s, 1H), 7.81 (s, 1H), 7.71 (dd, *J* = 10.6, 2.4 Hz, 1H), 7.36 (t, *J* = 8.3 Hz, 1H), 7.21 – 7.17 (m, 2H), 7.11 – 7.05 (m, 2H), 5.83 (dddd, *J* = 16.8, 10.2, 6.5, 6.5 Hz, 1H), 5.25 (dd, *J* = 8.3, 5.6 Hz, 1H), 5.10 – 5.06 (m, 1H), 5.01 – 4.98 (m, 1H) 4.42 (s, 2H), 4.08 – 4.01 (m, 2H), 2.90 – 2.76 (m, 4H), 2.62 – 2.57 (m, 1H), 2.26 – 2.16 (m, 2H), 1.91 – 1.77 (m, 2H), 1.47 (s, 36H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 159.18, 158.25 (d, J_{CF} = 248.5 Hz), 157.66, 153.62, 146.13, 139.76, 139.02, 138.34, 136.61 (d, J_{CF} = 9.7 Hz), 130.98, 124.85, 117.09 (d, J_{CF} = 18.4 Hz), 115.93 (d, J_{CF} = 3.2 Hz), 115.38, 108.41 (d, J_{CF} = 26.2 Hz), 83.90, 58.42, 51.74, 49.88, 46.39, 34.09, 31.28, 28.65, 28.52, 28.41, 28.25, 28.18, 28.17; **IR** (thin film, KBr) ν_{max} 3276, 3075, 2977, 2931, 1758, 1683, 1607, 1508, 1455, 1427, 1394, 1368, 1247, 1140, 1060, 872, 854 cm^{-1}; **HRMS** (ESI) *m/z* 901.4263 [calcd for $C_{45}H_{63}ClFN_6O_{10}$ $(M+H)^+$ 901.4278]; **$[\alpha]_D^{23}$** +210.2 (*c* 1.06, CH_2Cl_2).

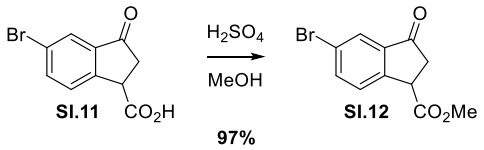
Synthesis of 3,6-Substituted Common Intermediate



6-Bromo-3-oxo-2,3-dihydro-1H-indene-1-carboxylic acid (SI.11) To a flame dried 1 L round-bottomed flask with stirring bar, 6-bromoindanone (**SI.10,** 10.0 g, 1.0 equiv.) was added and capped with a septum. THF (160 mL, 0.3 M) was then added at room temperature and the resulting solution was cooled to -78 °C in a dry ice/acetone bath. Some precipitate formed upon cooling. A freshly prepared solution of LDA[a] (49.75 mL, 1.0 M, 1.05 equiv.) was then added to the stirring reaction mixture over 15 minutes. The reaction was then homogenous and was stirred for 30 minutes. Freshly distilled TMSCl (6.61 mL, 1.1 equiv.) was then added via syringe to the reaction mixture over 15 minutes. Upon completion of this addition, the reaction was stirred for an additional 30 minutes. A second portion of LDA (56.9 mL, 1.0 M, 1.2 equiv.) was then added over 15 minutes. The reaction was then stirred for an additional 30 minutes. At this time, a balloon was used to bubble CO_2 into the solution at -78 °C for 30 minutes followed by warming to room temperature for 1 hour. The balloon was then removed along with the septum, and 3M HCl in water was added until pH paper indicated an acidic solution. The aqueous layer was extracted with EtOAc (3 x 200 mL). The organic layers were then combined, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to a yellow solid. The solid was then triturated with 300 mL of a 1:1 mixture of CH_2Cl_2:hexanes and filtered to obtain a yellow crystalline solid (**SI.11**). The solvent of the filtrate was then concentrated *in vacuo* and resubjected to the same trituration conditions as described above to obtain a second crop of **SI.11** (10.3 g, 85% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 2.0 Hz, 1H), 7.76 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 4.28 (dd, *J* = 8.2, 3.5 Hz, 1H), 3.17 (dd, *J* = 19.3, 3.5 Hz, 1H), 2.93 (dd, *J* = 19.2, 8.1 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 202.21, 176.44, 148.91, 138.31, 138.13, 128.47, 127.26, 123.84, 43.22, 39.57; **IR** (thin film, KBr) ν_{max} 3127, 2911, 1715, 1591, 1408, 1313, 1206, 1152, 1045, 803 cm^{-1} ; **HRMS** (EI) *m/z* 253.9584 [calcd for $C_{10}H_7BrO_3$ $(M)^+$ 253.9579].

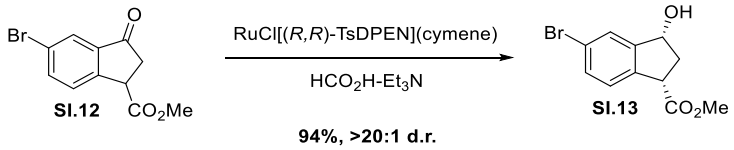
[a] *Method for LDA preparation:* In a flame dried 500 mL 2-neck flask equipped with a 100 mL addition funnel and stir bar, diisopropylamine (freshly distilled over CaH_2, 15.34 mL, 1.0 equiv.) was dissolved in anhydrous THF (50.66 mL) and cooled to -78 °C in a dry ice/acetone bath. *n*-BuLi (44 mL, 2.5 M in hexanes, 1.0 equiv.) was then added dropwise over 15 minutes via addition funnel. The resulting clear yellow solution (V_t = 110 mL, 1.0 M) was allowed to warm to room temperature and stirred for 30 minutes. The solution was then used directly in the reaction as described above.



Methyl 6-bromo-3-oxo-2,3-dihydro-1H-indene-1-carboxylate (SI.12) In a 500 mL round bottom flask with stir bar, **SI.11** (10.3 g, 1.0 equiv.) was dissolved in methanol (80 mL, 0.5 M). To this solution was added 15 drops of concentrated H_2SO_4. The flask was equipped with a reflux condenser and heated to 60 °C in an oil bath. The reaction was allowed to stir for 16 hours, or until TLC (50% EtOAc/hexanes) indicated complete consumption of starting material.

The reaction was removed from heat and allowed to cool to room temperature. A saturated aq. solution of $NaHCO_3$ was then added until pH paper indicated it was basic. The aqueous layer was then extracted with EtOAc (3 x 200 mL). The organic layers were then combined, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Crude **SI.12** was used in the next reaction without further purification (10.4 g, 97% yield).

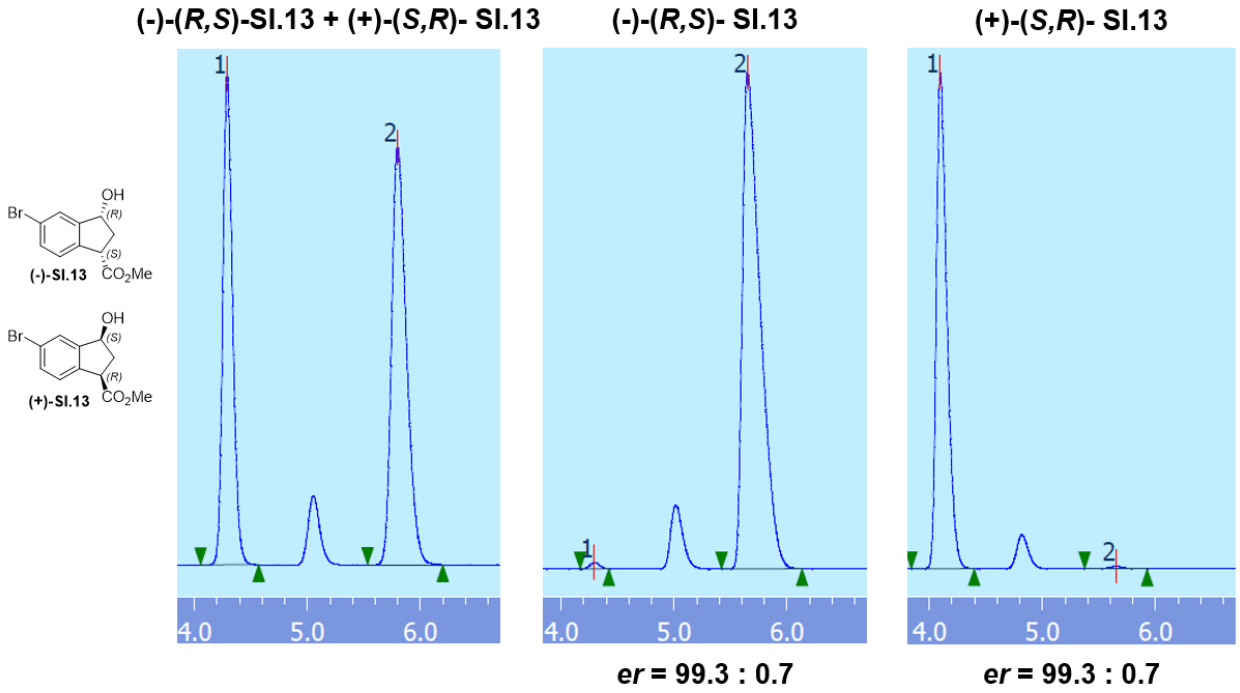
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 1.9 Hz, 1H), 7.73 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 4.24 (dd, *J* = 8.1, 3.5 Hz, 1H), 3.78 (s, 3H), 3.16 (dd, *J* = 19.2, 3.6 Hz, 1H), 2.91 (dd, *J* = 19.2, 8.1 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 202.56, 171.80, 149.70, 138.31, 137.94, 128.35, 127.09, 123.48, 53.02, 43.44, 39.83; **IR** (thin film, KBr) ν_{max} 3001, 2951, 2929, 1725, 1714, 1594, 1574, 1434, 1339, 1194, 1171, 1160, 1056, 986 cm^{-1} ; **HRMS** (EI) *m/z* 267.9724 [calcd for $C_{11}H_9BrO_3$ $(M)^+$ 267.9735].



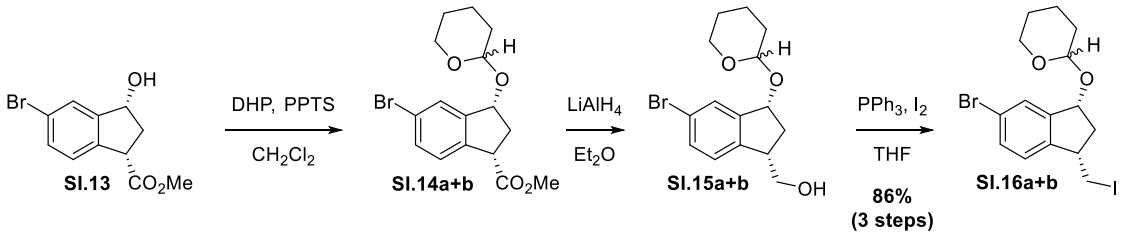
Methyl (1S,3R)-6-bromo-3-hydroxy-2,3-dihydro-1H-indene-1-carboxylate (SI.13) In a 250 mL 2-neck round bottom flask with stir bar, **SI.12** (10.4 g, 1.0 equiv.) was added and capped with septa. To the flask was then added freshly distilled and sparged (30 minutes with N_2 balloon) DCE (40 mL, 1.0 M) and 5:2 HCO_2H:NEt_3 azeotrope (21 mL, 0.5 mL/g starting material). Under a positive pressure of N_2, RuCl[(*R*,*R*)-TsDPEN](*p*-cymene) (490 mg, 2 mol %) was then added in one portion to the reaction flask. The reaction was then stirred for 16 hours, at which time an aliquot was taken and showed consumption of starting material by NMR analysis. The reaction was quenched with water (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 150 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to a black oil. This was dissolved in Et_2O (400 mL) and the solvent was allowed to evaporate, forming crystals of **SI.13** that were filtered and collected. NMR confirmed the d.r. to be >20:1 (10.4 g, 94% yield of both diastereomers).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 1.6 Hz, 1H), 7.42 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 5.11 (dd, *J* = 6.8, 2.5 Hz, 1H), 3.96 (dd, *J* = 8.0, 3.1 Hz, 1H), 3.76 (s, 3H), 2.60 (ddd, *J* = 14.7, 8.0, 6.9 Hz, 1H), 2.32 (dt, *J* = 14.1, 2.9 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 175.23, 147.58, 139.19, 132.00, 128.72, 126.41, 122.45, 74.81, 52.83, 47.92, 38.69; **IR** (thin film, KBr) ν_{max} 3281, 2951, 1745, 1468, 1336, 1265, 1210, 1173, 1066, 961, 852 cm^{-1} ; **HRMS** (EI) *m/z* 269.9881 [calcd for $C_{11}H_{11}BrO_3$ $(M)^+$ 269.9892]; **$[\alpha]_D^{23}$** -51.6 (*c* 0.47, CH_2Cl_2).

Enantiomeric excess determined by SFC (see below):



Method: column: Chiralpak® IA; eluent: 7% MeOH in supercritical CO_2; flow rate: 4 mL/min; pressure: 12 MPa. Retention times: **(–)-(*R,S*)-SI.13**: 4.3 min, **(+)-(*S,R*)-SI.13**: 5.8 min.



Methyl (1S,3R)-6-bromo-3-((tetrahydro-2H-pyran-2-yl)oxy)-2,3-dihydro-1H-indene-1-carboxylate (SI.14a+b) In a 250 mL round-bottomed flask with stir bar, **SI.13** (6.62 g, 1.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (74 mL, 0.33 M). To the stirring mixture, PPTS (307 mg, 5 mol %) was added in one portion at room temperature. Then, 3,4-dihydro-2H-pyran (DHP) (4.46 mL, 2.0 equiv.) was added in one portion. The reaction was allowed to stir overnight at room temperature. TLC (30% EtOAc/hexanes) indicated complete consumption of starting material after 16 hours. The reaction was quenched with aq. saturated $NaHCO_3$ (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to an oil. The product was purified by flash column chromatography (10% to 20% EtOAc in hexanes) to give the product **SI.14a+b** as a clear oil. **SI.14a+b** was an inseparable 1:1 diastereomeric mixture.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (s, 0.5H), 7.48 (s, 0.5H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 5.26 (t, *J* = 6.8 Hz, 0.5H), 5.05 (t, *J* = 7.1 Hz, 0.5H), 4.92 (t, *J* = 3.3 Hz, 0.5H), 4.86 (t, *J* = 3.5 Hz, 0.5H), 4.02 – 3.94 (m, 1H), 3.89 – 3.83 (m, 1H), 3.76 (s, 3H), 3.61 – 3.56 (m, 1H), 2.81 (dt, *J* = 13.3, 7.5 Hz, 0.5H), 2.73 (dt, *J* = 13.1, 7.5 Hz, 0.5H), 2.50 – 2.45 (m, 0.5H), 2.40 – 2.35 (m, 0.5H), 1.94 – 1.49 (m, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 172.99, 172.85, 145.93, 145.81, 138.57, 138.43, 131.68, 131.64, 128.42, 127.98, 126.84, 126.72, 122.09, 121.88, 99.92, 96.90, 79.94, 76.73, 62.72, 62.60, 52.45, 52.39, 46.90, 46.87, 38.40, 35.67, 30.99, 30.90, 29.87,

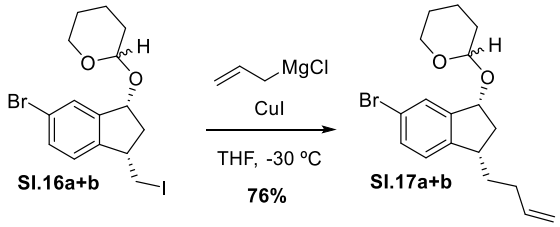
25.63, 19.55, 19.44; **IR** (thin film, KBr) ν_{max} 2936, 1737, 1640, 1471, 1200, 1034 cm^{-1} ; **HRMS** (EI) *m/z* 354.0475 [calcd for $C_{16}H_{19}BrO_4$ $(M)^+$ 354.0467]; **$[\alpha]_D^{23}$** -7.2 (*c* 1.85, CH_2Cl_2).

((1S,3R)-6-Bromo-3-((tetrahydro-2H-pyran-2-yl)oxy)-2,3-dihydro-1H-inden-1-yl)methanol (SI.15a+b) In a 500 mL 2-neck flask with stir bar, **SI.14a+b** (1.0 equiv.) from the previous step was added and dissolved in anhydrous Et_2O (122 mL, 0.2 M). The solution was cooled to 0 °C in an ice/water bath. Under a positive pressure of N_2, LAH powder (1.11 g, 1.2 equiv.) was added to the reaction flask. The reaction was stirred at 0 °C for 3 hours, at which time TLC (30% EtOAc in hexanes) indicated complete consumption of starting material. The reaction was quenched with the Fieser & Fieser workup[16] (1.11 mL H_2O, 1.11 mL 20% NaOH (w/v), followed by 3.33 mL H_2O). The reaction was then warmed to room temperature and $MgSO_4$ was added. The mixture was allowed to stir for 15 minutes. After this time, the solid was filtered and washed thoroughly with Et_2O (400 mL). The filtrate was then concentrated *in vacuo* to a clear oil which was purified by flash column chromatography (25% to 35% EtOAc/hexanes) to give the product **SI.15a+b** as a clear oil. **SI.15a+b** was an inseparable 1:1 diastereomeric mixture.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 0.5H), 7.49 (s, 0.5H), 7.46 – 7.39 (m, 1H), 7.22 (dd, *J* = 12.9, 8.1 Hz, 1H), 5.21 (dd, *J* = 6.6, 4.1 Hz, 0.5H), 5.09 (dd, *J* = 6.6, 3.2 Hz, 0.5H), 4.91 – 4.83 (m, 1H), 3.98 – 3.82 (m, 2H), 3.63 – 3.58 (m, 1H), 3.29 – 3.24 (m, 1H), 2.65 – 2.54 (m, 1H), 2.08 – 2.01 (m, 0.5H), 1.96 – 1.47 (m, 7.5H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 146.10, 145.38, 143.59, 142.96, 132.11, 131.92, 128.93, 128.66, 128.37, 126.46, 125.99, 125.92, 121.37, 121.03, 97.79, 97.11, 78.47, 77.71, 74.37, 66.07, 66.00, 65.49, 62.88, 62.43, 45.40, 45.05, 44.95, 39.43, 37.98, 36.10, 31.01, 30.80, 25.60, 25.57, 19.60, 19.32 **IR** (thin film, KBr) ν_{max} 3433, 2952, 1645, 1474, 1340, 1138, 1018 cm^{-1} ; **HRMS** (EI) *m/z* 326.0498 [calcd for $C_{15}H_{19}BrO_3$ $(M)^+$ 326.0518].

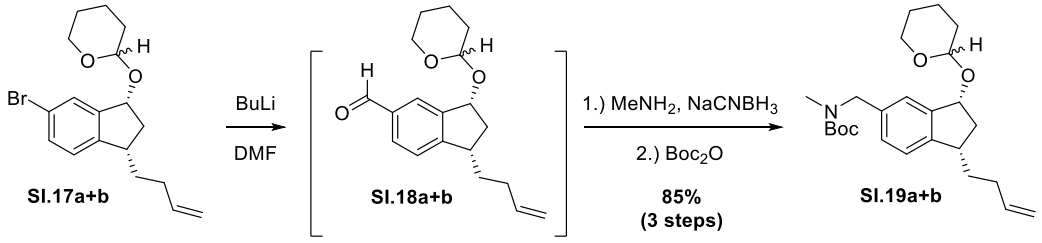
2-(((1R,3S)-6-Bromo-3-(iodomethyl)-2,3-dihydro-1H-inden-1-yl)oxy)tetrahydro-2H-pyran (SI.16a+b) In a 500 mL round-bottomed flask with stir bar, **SI.15a+b** (1.0 equiv.) from the previous step was dissolved in THF (122 mL, 0.2 M). To the stirring solution was added PPh_3 (8.33 g, 1.3 equiv.) and imidazole (2.16 g, 1.3 equiv.) at room temperature. The reaction was then cooled to 0 °C in an ice/water bath. A solution of iodine (8.06 g, 1.3 equiv.) in THF (32 mL, 1.0 M) was then added dropwise to the stirring reaction mixture via syringe over 15 minutes. The reaction was then warmed to room temperature and allowed to stir for 2 hours. At this time, TLC (30% EtOAc/hexanes) indicated complete consumption of starting material. A saturated aq. solution of $Na_2S_2O_3$ (125 mL) was then added and the aqueous layer was extracted with Et_2O (3 x 150 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to an oil. The product was purified by flash column chromatography (10% EtOAc/hexanes) to give the product **SI.16a+b** as a clear oil (9.18 g, 86% over 3 steps). **SI.16a+b** was an inseparable 1:1 diastereomeric mixture.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 0.5H), 7.46 (s, 0.5H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 22.5, 8.1 Hz, 1H), 5.19 (t, *J* = 6.2 Hz, 0.5H), 5.02 (t, *J* = 6.2 Hz, 0.5H), 4.90 – 4.84 (m, 1H), 4.00 – 3.93 (m, 1H), 3.62 – 3.55 (m, 2H), 3.36 – 3.25 (m, 1H), 2.72 (tt, *J* = 13.3, 6.8 Hz, 1H), 2.03 – 1.98 (m, 0.5H), 1.88 – 1.74 (m, 3.5H), 1.67 – 1.53 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 146.26, 146.17, 143.11, 142.88, 131.65, 131.63, 128.93, 128.53, 125.90, 125.52, 121.79, 121.54, 99.16, 97.20, 78.78, 76.61, 62.75, 44.95, 44.74, 42.67, 40.71, 31.11, 30.97, 25.63, 19.62, 19.59, 11.14, 11.11; **LRMS** (ESI) *m/z* 459.1 [calcd for $C_{15}H_{18}BrIO_2Na$ $(M+Na)^+$ 458.9]. **IR** (thin film, KBr) ν_{max} 2939, 2849, 1594, 1470, 1410, 1338, 1258, 1200, 1167, 1124, 1076, 1034, 989, 909, 869, 815 cm^{-1}.



2-(((1R,3S)-6-Bromo-3-(but-3-en-1-yl)-2,3-dihydro-1H-inden-1-yl)oxy)tetrahydro-2H-pyran (SI.17a+b) In a 500 mL round-bottomed with stir bar, **SI.16a+b** (9.18 g, 1.0 equiv.) and CuI (2.0 g, 0.5 equiv.) were added and the flask was capped with a septum. To the flask was added anhydrous THF (105 mL, 0.2 M) and the heterogeneous mixture was cooled to -30 °C in a xylenes/dry ice bath. Once equilibrated to -30 °C, allylmagnesium chloride in THF (21.0 mL, 2.0 equiv., 2.0 M) was added dropwise over 10 minutes via syringe. The mixture was allowed to stir at -30 °C for 30 minutes, followed by warming to room temperature. After an additional hour of stirring, TLC (10% EtOAc/hexanes) indicated complete consumption of starting material. The reaction was cooled to 0 °C and quenched with brine (75 mL) and 33% w/v aqueous NH_4OH (75 mL). The aqueous layer was extracted with Et_2O (3 x 150 mL) and the organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to an oil. The product was purified by flash column chromatography (5% EtOAc/hexanes) to give the product **SI.17a+b** as a clear oil (5.62 g, 76% yield). **SI.17a+b** was an inseparable 1:1 diastereomeric mixture.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 0.5H), 7.44 (s, 0.5H), 7.37 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.15 – 7.04 (m, 1H), 5.86 (dddd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H), 5.22 (dd, *J* = 6.9, 6.9 Hz, 0.5H), 5.10 – 4.96 (m, 2.5H), 4.90 (t, *J* = 3.6 Hz, 0.5H), 4.85 (t, *J* = 3.6 Hz, 0.5H), 4.05 – 3.93 (m, 1H), 3.62 – 3.56 (m, 1H), 2.99 – 2.90 (m, 1H), 2.73 – 2.66 (m, 1H), 2.25 – 2.09 (m, 2H), 2.07 – 1.98 (m, 1H), 1.95 – 1.50 (m, 8H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 146.14, 146.08, 145.47, 145.38, 138.60, 138.51, 131.17, 128.03, 127.65, 125.42, 125.19, 120.71, 120.49, 115.09, 115.04, 100.05, 96.85, 80.42, 77.34, 62.93, 62.63, 41.70, 41.22, 41.11, 39.47, 34.58, 34.55, 31.85, 31.80, 31.14, 31.10, 25.67, 25.65, 19.83, 19.60; **LRMS** (ESI) *m/z* 351.3 [calcd for $C_{18}H_{24}BrO_2$ $(M+H)^+$ 351.1]. **IR** (thin film, KBr) ν_{max} 3073, 2925, 1639, 1597, 1470, 1338, 1200, 1133, 1063, 1035, 993, 910, 869, 813 cm^{-1}.

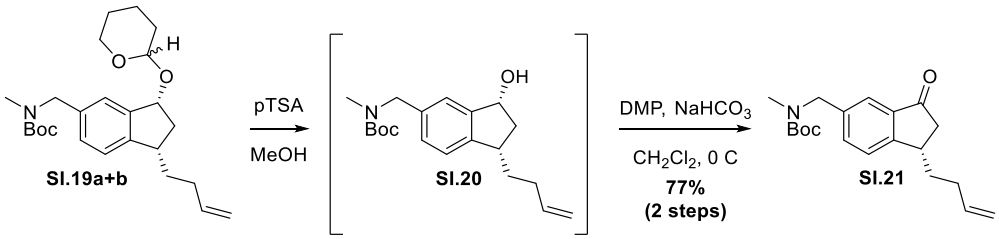


Tert-butyl (((1R,3S)-3-(but-3-en-1-yl)-1-((tetrahydro-2H-pyran-2-yl)oxy)-2,3-dihydro-1H-inden-5-yl)methyl)(methyl)carbamate (SI.19a+b) In an oven-dried 250 mL round-bottomed flask with stir bar, **SI.17a+b** (5.62 g, 1.0 equiv.) was added and the flask was capped with a septum. To the flask was added anhydrous THF (53.3 mL, 0.3 M) and the solution was cooled to -78 °C in an acetone/dry ice bath. Once equilibrated, *n*-butyllithium in hexanes (7.04 mL, 1.1 equiv., 2.5 M) was added dropwise via syringe over 10 minutes. The reaction was allowed to stir for 15 minutes before addition of DMF (1.48 mL, 1.2 equiv.). The reaction was allowed to stir for 15 minutes and was warmed to room temperature. The reaction was allowed to stir for an additional 30 minutes at room temperature when TLC (10% EtOAc/hexanes) indicated complete consumption of starting material. The reaction was quenched with brine (75 mL) and the aqueous layer was extracted with EtOAc (3 x 75 mL). The organic layers were combined, dried

over Na_2SO_4, and concentrated *in vacuo* to give crude **SI.18a+b** as a clear oil. This material was used in the next step without further purification.

To a solution of crude **SI.18a+b** in MeOH/CH_2Cl_2 (5:1 ratio, 20 mL, 0.85 M) was added 40 wt% aqueous $MeNH_2$ (4.71 mL, 3.4 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 hour, followed by the addition of $NaBH_4$ (1.57 g, 2.6 equiv) in one portion. The resulting suspension was continued to stir at 0 ºC for 2 hours, or until TLC (10% EtOAc/hexanes) indicated complete consumption of starting material. The reaction mixture was then treated with an aqueous saturated solution of $NaHCO_3$ (50 mL). The resulting mixture was allowed to warm to room temperature and extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give an oil. This was dissolved in CH_2Cl_2 (16 mL) and this solution was cooled to 0 °C, to which a solution of Boc_2O (4.04 mL, 1.05 equiv) in CH_2Cl_2 (7.65 mL, 2.3 M) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 hour. The solvent was then concentrated *in vacuo* to give crude **SI.19a+b** as an oil, which was purified by flash column chromatography (10% EtOAc/hexanes) to give the product **SI.19a+b** as a clear oil (5.65 g, 85% over 3 steps). **SI.19a+b** was an inseparable 1:1 diastereomeric mixture.

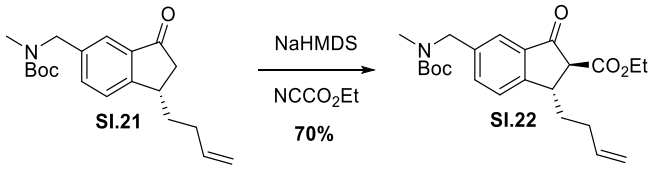
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 0.5H), 7.21 – 7.06 (m, 2.5H), 5.87 (dddd, *J* = 16.9, 11.3, 6.4, 6.4 Hz, 1H), 5.24 (t, *J* = 6.8 Hz, 0.5H), 5.10 – 4.96 (m, 2.5H), 4.93 (t, *J* = 3.5 Hz, 0.5H), 4.88 (t, *J* = 3.5 Hz, 0.5H), 4.41 (s, 2H), 4.07 – 4.02 (m, 0.5H), 4.00 – 3.96 (m, 0.5H), 3.61 – 3.55 (m, 1H), 3.05 – 2.94 (m, 1H), 2.83 – 2.67 (m, 4H), 2.27 – 2.11 (m, 2H), 2.10 – 1.99 (m, 1H), 1.93 – 1.46 (m, 17H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 145.67, 138.81, 138.72, 136.96, 136.76, 123.83, 123.65, 114.88, 114.82, 100.03, 96.57, 62.91, 62.43, 52.69, 41.34, 41.25, 39.46, 34.80, 33.98, 31.96, 31.91, 31.15, 28.62, 25.71, 25.66, 19.89, 19.52; **IR** (thin film, KBr) ν_{max} 3075, 2927, 2868, 1697, 1481, 1453, 1391, 1365, 1319, 1239, 1200, 1174, 1136, 1077, 1062, 1034, 998, 970, 906 cm^{-1}; **HRMS** (ESI) *m/z* 438.2643 [calcd for $C_{25}H_{37}NO_4Na$ $(M+Na)^+$ 438.2620]; **$[\alpha]_D^{23}$** -7.9 (*c* 1.02, CH_2Cl_2).



Tert-butyl (S)-((3-(but-3-en-1-yl)-1-oxo-2,3-dihydro-1H-inden-6-yl)methyl)(methyl) carbamate (SI.21) In a 500 mL round-bottomed flask with stir bar, *p*TSA (569.1 mg, 0.22 equiv) was added to a solution of **SI.19a+b** (5.65 g, 1.0 equiv.) in MeOH (227 mL, 0.06 M) at room temperature. The resulting solution was stirred at room temperature for 1 hour, at which time TLC (20% EtOAc/hexanes) indicated complete consumption of starting material. The reaction mixture was then treated with a saturated aq. solution of $NaHCO_3$ (100 mL) and extracted with EtOAc (3 x 100 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give crude **SI.20** as an oil. This residue was taken up in anhydrous CH_2Cl_2 (123 mL, 0.1 M) and solid $NaHCO_3$ (4.14 g, 4.0 equiv) was added at room temperature in a 500 mL round-bottomed flask. The resulting suspension was cooled to at 0 °C in an ice/water bath and DMP (7.84 g, 1.5 equiv) was then added in one portion. The reaction was then warmed to room temperature and was allowed to stir for 1 hour, at which time TLC (20% EtOAc/hexanes) indicated complete consumption of starting material. The reaction mixture was then treated with a saturated aq. solution of $Na_2S_2O_3$ (100 mL). The resulting mixture was extracted with CH_2Cl_2

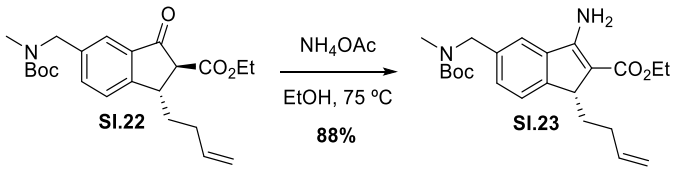
(3 x 100 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give an oil, which was purified by flash column chromatography (15% EtOAc/hexanes) to give **SI.21** as a clear oil (3.47 g, 77% yield, 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.43 (m, 3H), 5.84 (dddd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H), 5.07 – 5.00 (m, 2H), 4.46 (s, 2H), 3.39 – 3.34 (m, 1H), 2.90 – 2.78 (m, 4H), 2.38 (dd, *J* = 19.0, 3.0 Hz, 1H), 2.21 – 2.12 (m, 2H), 2.05 – 1.98 (m, 1H), 1.58 (td, *J* = 14.6, 8.8 Hz, 1H), 1.48 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 205.96, 157.87, 156.13, 138.07, 137.73, 137.09, 134.42, 133.85, 125.85, 122.18, 115.38, 79.90, 52.30, 51.54, 43.31, 37.46, 35.31, 34.08, 31.78, 28.46; **IR** (thin film, KBr) ν_{max} 3075, 2975, 2926, 2360, 1714, 1697, 1640, 1617, 1579, 1486, 1453, 1391, 1365, 1286, 1239, 1146, 1112, 1044, 980, 916 cm^{-1} ; **HRMS** (ESI) *m/z* 352.1876 [calcd for $C_{20}H_{27}NO_3Na$ $(M+Na)^+$ 352.1889] ; **$[\alpha]_D^{23}$** +9.3 (*c* 1.14, CH_2Cl_2).



Ethyl (2S,3S)-3-(but-3-en-1-yl)-6-(((tert-butoxycarbonyl)(methyl)amino)methyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (SI.22) In an oven dried 250 mL round-bottomed flask with stir bar, **SI.21** (3.47 g, 1.0 equiv.) was dissolved in anhydrous THF (101 mL, 0.1 M). This solution was then cooled to -78 °C in a dry ice/acetone bath. A solution of NaHMDS in THF (21.0 mL, 1.0 M, 2.1 equiv.) was then added dropwise to the stirring solution. After 30 minutes, Mander's reagent (1.32 mL, 1.3 equiv.) was added dropwise. The reaction was allowed to stir for an additional hour. The flask was warmed to room temperature and was quenched with brine (100 mL). The aqueous layer was then extracted with EtOAc (3 x 100 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give an oil. The oil was then purified by flash column chromatography (15% EtOAc/hexanes) to give **SI.22** as a yellow oil (2.94 g, 70% yield).

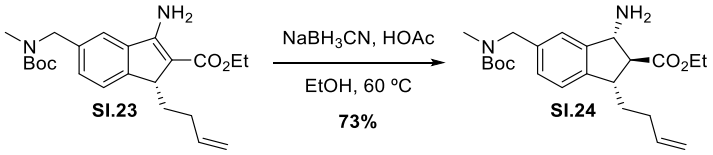
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 – 7.47 (m, 3H), 5.83 (dddd, *J* = 16.9, 10.2, 6.5, 6.5 Hz, 1H), 5.07 – 5.00 (m, 2H), 4.46 (s, 2H), 4.24 (q, *J* = 7.1, 2H), 3.78 – 3.72 (m, 1H), 3.38 (d, *J* = 3.9 Hz, 1H), 2.86 – 2.78 (m, 3H), 2.24 – 2.04 (m, 3H), 1.70 – 1.60 (m, 1H), 1.48 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.11, 169.40, 156.63, 146.82, 138.82, 137.45, 135.59, 125.85, 123.16, 115.90, 114.54, 80.15, 61.86, 60.68, 60.23, 43.61, 42.48, 37.63, 34.69, 34.30, 31.74, 29.86, 28.86, 28.64, 28.61, 14.65, 14.37; **IR** (thin film, KBr) ν_{max} 3076, 2977, 2929, 2360, 1741, 1713, 1481, 1392, 1366, 1248, 1148, 1022, 877 cm^{-1} ; **HRMS** (ESI) *m/z* 424.2108 [calcd for $C_{23}H_{31}NO_5Na$ $(M+Na)^+$ 424.2100]; **$[\alpha]_D^{23}$** -37.4 (*c* 1.37, CH_2Cl_2).



Ethyl (R)-3-amino-1-(but-3-en-1-yl)-6-(((tert-butoxycarbonyl)(methyl)amino)methyl)-1H-ind-ene-2-carboxylate (SI.23) In a 100 mL round-bottomed flask with stir bar, **SI.22** (2.91 g, 1.0 equiv.) and ammonium acetate (5.58 g, 10 equiv.) were dissolved in ethanol (18.1 mL, 0.4 M) at room temperature. The flask was fitted with a reflux condenser and heated to 75 °C in an oil bath. After 16 hours, TLC indicated complete consumption of starting material (20%

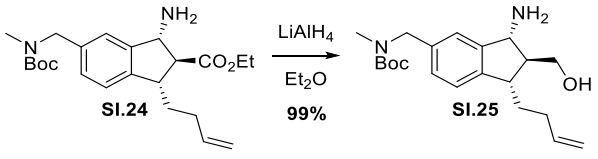
EtOAc/hexanes). The reaction was then cooled to room temperature and quenched with aq. sat. $NaHCO_3$ (40 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give a brown oil, which was purified by flash column chromatography (15% EtOAc/hexanes) to give **SI.23** as a yellow oil (2.56 g, 88% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.7 Hz, 1H), 7.28 – 7.16 (m, 2H), 5.98 (brs, 2H), 5.70 (dddd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H), 4.90 – 4.82 (m, 2H), 4.48 (s, 2H), 4.38 – 4.28 (m, 1H), 4.25 – 4.19 (m, 1H), 3.82 (dd, *J* = 4.7, 4.7 Hz, 1H), 2.83 (s, 3H), 2.19 – 2.08 (m, 2H), 1.86 – 1.79 (m, 1H), 1.61 – 1.43 (m, 10H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.93, 156.26, 147.94, 139.48, 139.22, 136.97, 126.38, 125.79, 122.82, 118.96, 114.16, 101.76, 79.99, 59.10, 53.04, 52.30, 45.37, 34.29, 30.59, 28.81, 28.63, 14.89; **IR** (thin film, KBr) ν_{max} 3441, 3337, 3073, 2976, 2929, 2360, 1663, 1628, 1540, 1453, 1392, 1366, 1259, 1146, 1093, 909 cm^{-1} ; **HRMS** (ESI) *m/z* 401.2427 [calcd for $C_{23}H_{33}N_2O_4$ $(M+H)^+$ 401.2440]; **$[\alpha]_D^{23}$** -44.5 (*c* 0.83, CH_2Cl_2).



Ethyl (1R,2S,3S)-1-amino-3-(but-3-en-1-yl)-6-(((tert-butoxycarbonyl)(methyl)amino)methyl-)-2,3-dihydro-1H-indene-2-carboxylate (SI.24) In a 100 mL round-bottomed flask with stir bar, **SI.23**, (2.56 g, 1.0 equiv.), $NaBH_3CN$ (2.01 g, 6 equiv.), and AcOH (2.92 mL, 8 equiv.) were dissolved in ethanol (21.3 mL, 0.3 M) at room temperature. The flask was sealed with a septum and fitted with a reflux condenser. The reaction was heated to 60 °C in an oil bath and allowed to stir overnight. After 16 hours, TLC indicated complete consumption of starting material (50% EtOAc/hexanes) with the product staining well in $KMnO_4$. The reaction was then cooled to room temperature and quenched with 1M NaOH (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give an oil, which was purified by flash column chromatography (50% to 100% EtOAc/hexanes) to give **SI.24** as a yellow oil (1.88 g, 73% yield).

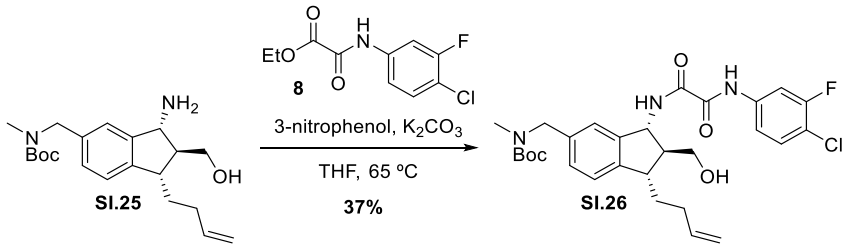
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.08 (m, 3H), 5.85 (dddd, *J* = 16.8, 10.3, 6.4, 6.4 Hz, 1H), 5.06 – 5.02 (m, 1H), 5.00 – 4.97 (m, 1H), 4.48 (d, *J* = 8.5 Hz, 1H), 4.41 (s, 2H), 4.28 – 4.21 (m, 2H), 3.46 – 3.41 (m, 1H), 2.81 (s, 3H), 2.58 (dd, *J* = 8.9, 8.9 Hz, 1H), 2.18 – 2.03 (m, 3H), 1.91 (s, 2H), 1.77 – 1.66 (m, 1H), 1.48 (s, 9H), 1.32 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.61, 155.98, 144.91, 143.04, 138.43, 137.56, 127.70, 127.23, 124.21, 123.59, 122.60, 115.03, 79.89, 63.46, 61.00, 60.76, 57.90, 52.72, 52.01, 44.97, 44.29, 34.11, 33.87, 33.48, 31.49, 31.00, 28.66, 14.52; **IR** (thin film, KBr) ν_{max} 3381, 3074, 2976, 2928, 2360, 1727, 1694, 1482, 1453, 1392, 1366, 1238, 1173, 1031, 911, 877 cm^{-1} ; **HRMS** (ESI) *m/z* 403.2595 [calcd for $C_{23}H_{35}N_2O_4$ $(M+H)^+$ 403.2597]; **$[\alpha]_D^{23}$** -9.5 (*c* 1.11, CH_2Cl_2).



Tert-butyl (((1R,2S,3S)-1-amino-3-(but-3-en-1-yl)-2-(hydroxymethyl)-2,3-dihydro-1H-inden-6-yl)methyl)(methyl)carbamate (SI.25) In a 200 mL round-bottomed flask with stir bar, **SI.24** (1.88 g, 1.0 equiv.) was added and dissolved in anhydrous Et_2O (23.4 mL, 0.2 M). The solution

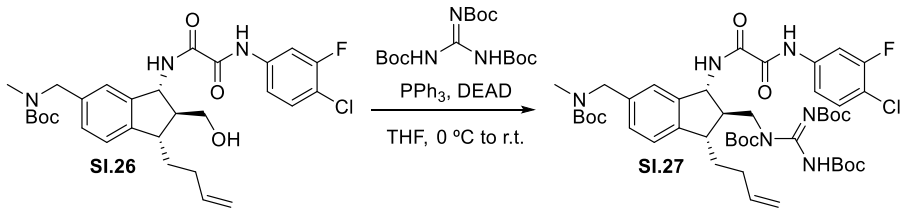
was then cooled to 0 °C in an ice/water bath. LAH powder (213 mg, 1.2 equiv.) was added to the reaction flask. The reaction was stirred at 0 °C for 2 hours, at which time TLC (10% MeOH/CH_2Cl_2) indicated complete consumption of starting material. The reaction was quenched with the Fieser & Fieser workup[16] (213 µL H_2O, 213 µL 20% NaOH (w/v), followed by 640 µL H_2O). The reaction was then warmed to room temperature and $MgSO_4$ was added. The mixture was allowed to stir for 30 minutes. After this time, the solid was filtered and washed thoroughly with Et_2O (100 mL). The filtrate was then concentrated *in vacuo* to an oil, which was purified by flash column chromatography (10% MeOH/CH_2Cl_2) to give **SI.25** as a yellow oil (1.68 g, 99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (brs, 1H), 7.20 – 7.06 (m, 2H), 5.82 (dddd, *J* = 16.8, 10.2, 6.5, 6.5 Hz, 1H), 5.06 – 5.02 (m, 1H), 5.00 – 4.96 (m, 1H), 4.42 – 4.17 (br m, 6H), 4.18 (d, *J* = 8.4 Hz, 1H), 4.07 (dd, *J* = 6.5, 4.0 Hz, 1H), 3.79 – 3.75 (m, 1H), 2.77 (s, 3H), 2.31 – 2.24 (m, 1H), 2.21 – 2.12 (m, 2H), 1.92 (dq, *J* = 13.8, 7.6, 7.1 Hz, 1H), 1.82 – 1.74 (m, 1H), 1.45 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.35, 144.45, 143.43, 138.44, 137.42, 127.98, 124.72, 124.13, 122.34, 115.38, 115.17, 80.00, 65.38, 60.57, 55.92, 52.66, 52.02, 43.40, 34.21, 32.87, 31.31, 29.88, 28.66, 14.30; **IR** (thin film, KBr) ν_{max} 3353, 3074, 2975, 2925, 2361, 1694, 1482, 1453, 1393, 1366, 1302, 1246, 1148, 909, 874, 832 cm^{-1} ; **HRMS** (ESI) *m/z* 361.2496 [calcd for $C_{21}H_{33}N_2O_3$ $(M+H)^+$ 361.2491]; **$[\alpha]_D^{23}$** -22.9 (*c* 0.93, CH_2Cl_2).



Tert-butyl (((1R,2S,3S)-3-(but-3-en-1-yl)-1-(2-((4-chloro-3-fluorophenyl)amino)-2-oxoacetamido)-2-(hydroxymethyl)-2,3-dihydro-1H-inden-6-yl)methyl)(methyl)carbamate (SI.26) In a 100 mL round-bottomed flask equipped with a reflux condenser and stir bar, a mixture of **SI.25** (1.68 g, 1.0 equiv.), **8** (1.32 g, 1.15 equiv.), 3-nitrophenol (130 mg, 0.2 equiv.), and K_2CO_3 (130 mg, 0.2 equiv.) in THF (10 mL, 0.8 M) was stirred at 65 ºC for 16 h. The resulting suspension was allowed to cool to room temperature and then treated with 10 wt% K_2CO_3 (20 mL). The resulting mixture was further stirred at room temperature for 1 hr, and then diluted with EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give an oil, which was purified by flash column chromatography (50% to 100% EtOAc/hexanes) to give **SI.26** as a colorless amorphous solid (974 mg, 37% yield).

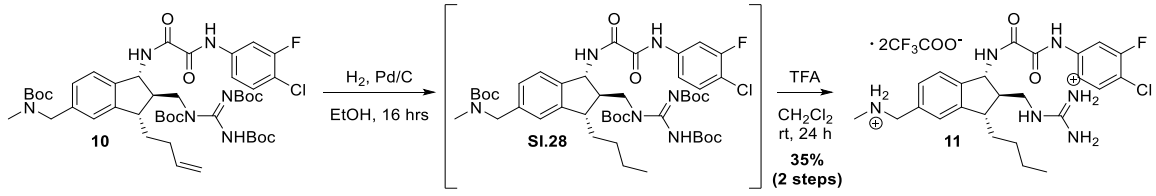
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.94 (brs, 1H), 7.71 (dd, *J* = 10.5, 2.3 Hz, 1H), 7.38 (t, *J* = 8.3 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.23 – 7.19 (m, 2H), 7.10 (s, 1H), 5.84 (dddd, *J* = 16.8, 10.2, 6.5, 6.5 Hz, 1H), 5.21 (dd, *J* = 7.2, 7.2 Hz, 1H), 5.07 – 4.99 (m, 2H), 4.41 (s, 2H), 3.86 (dd, *J* = 11.3, 3.4 Hz, 1H), 3.74 (dd, *J* = 9.6, 9.6 Hz, 1H), 2.97 – 2.80 (m, 4H), 2.27 – 2.14 (m, 3H), 1.97 – 1.90 (m, 1H), 1.81 – 1.74 (m, 1H), 1.47 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 160.20, 158.25 (d, J_{CF} = 248.5 Hz), 157.18, 144.97, 140.12, 138.16, 138.14, 136.31 (d, J_{CF} = 9.7 Hz), 131.06, 128.79, 128.30, 124.73, 123.51, 123.04, 117.52 (d, J_{CF} = 18.4 Hz), 116.23 (d, J_{CF} = 3.5 Hz), 115.40, 108.70 (d, J_{CF} = 26.2 Hz), 80.08, 64.16, 58.26, 57.70, 52.57, 51.94, 44.39, 34.17, 31.20, 29.88, 28.63; **IR** (thin film, KBr) ν_{max} 3353, 3287, 3075, 2975, 2926, 2248, 1671, 1594, 1514, 1427, 1366, 1304, 1243, 1150, 1066, 973 cm^{-1} ; **HRMS** (ESI) *m/z* 582.2143 [calcd for $C_{29}H_{35}ClFN_3O_5Na$ $(M+Na)^+$ 582.2147]; **$[\alpha]_D^{23}$** -52.8 (*c* 0.88, CH_2Cl_2).



Compound SI.27 In a 200 mL round-bottomed flask with stir bar, a mixture of **SI.26** (974 mg, 1.0 equiv.), PPh_3 (730 mg, 1.6 equiv.), and N,N′,N″-tri-Boc-guanidine (2.19 g, 3.5 equiv.) in anhydrous THF (44 mL, 0.04 M) was stirred at room temperature until a well-dispersed suspension had formed. This mixture was cooled at 0 ºC and treated with diethyl azodicarboxylate (410 µL, 1.5 equiv.) dropwise at such a rate that each drop was only added after the color change resulting from the previous drop had dissipated. After the addition was completed, the reaction was allowed to warm to room temperature and stir for 18 hr. TLC (30% EtOAc/hexanes) indicated complete consumption of starting material at this time. The reaction was then quenched with brine (50 mL) and the aqueous layer was extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give a white solid which was purified by flash column chromatography (20% EtOAc/hexanes) to give a mixture of **SI.27** and N,N′,N″-tri-Boc-guanidine. The residue was treated with Et_2O (10 mL) and the insoluble material was removed via vacuum filtration. The filtrate was concentrated *in vacuo* to give **SI.27** as an off-white amorphous solid (1.22 g, 78%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.31 (s, 1H), 9.28 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.71 (dd, *J* = 10.6, 2.3 Hz, 1H), 7.37 (t, *J* = 8.3 Hz, 1H), 7.23 – 7.11 (m, 2H), 7.06 (s, 1H), 5.84 (dddd, *J* = 16.9, 10.1, 6.5, 6.5 Hz, 1H), 5.26 (dd, *J* = 8.3, 5.6 Hz, 1H), 5.10 – 5.06 (m, 1H), 5.01 – 4.98 (m, 1H), 4.42 (s, 2H), 4.08 – 4.01 (m, 2H), 2.91 – 2.87 (m, 1H), 2.77 (s, 3H), 2.62 – 2.57 (m, 1H), 2.26 – 2.18 (m, 2H), 1.91 – 1.77 (m, 2H), 1.48 (s, 36H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.19, 158.25 (d, J_{CF} = 248.5 Hz), 157.63, 153.59, 149.96, 144.67, 138.43, 137.73, 136.62 (d, J_{CF} = 9.7 Hz), 130.99, 124.54, 117.09 (d, J_{CF} = 18.4 Hz), 115.92 (d, J_{CF} = 3.2 Hz), 115.31, 108.41 (d, J_{CF} = 26.2 Hz), 83.87, 82.75, 80.82, 79.90, 58.58, 51.83, 49.88, 46.15, 34.05, 31.27, 28.61, 28.25, 28.20, 28.18, 28.00; **IR** (thin film, KBr) ν_{max} 3286, 3074, 2978, 2932, 1759, 1685, 1608, 1509, 1455, 1393, 1368, 1246, 1142, 1064, 973, 875 cm^{-1} ; **HRMS** (ESI) *m/z* 923.4092 [calcd for $C_{45}H_{62}ClFN_6O_{10}Na$ $(M+Na)^+$ 923.4098]; **$[\alpha]_D^{22}$** +171.2 (*c* 1.31, CH_2Cl_2).

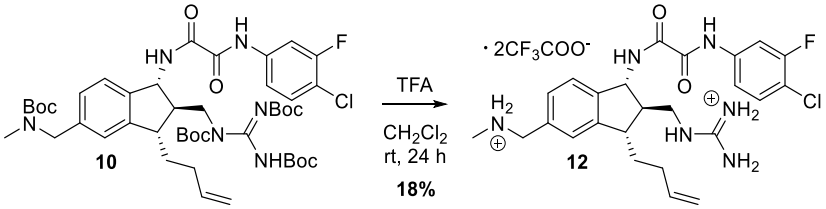
<u>Synthesis of 3,5-Substituted Compounds Submitted for Biological Evaluation</u>



Compound 11 Pd/C (10%, 5 mg) was added in one portion to a stirred solution of **10** (20 mg, 1.0 equiv.) in EtOH (300 µL, 0.1 M) at rt under argon. The flask was flushed three times with a balloon of hydrogen and the resultant black suspension was stirred under a balloon of hydrogen for 12 h. The suspension was filtered through a short plug of Celite® and the plug was washed with CH_2Cl_2 (10 mL). The filtrate was concentrated *in vacuo* . The crude residue was taken up in CH_2Cl_2 (222 µL, 0.1 M) and cooled to 0 °C in an ice-water bath. TFA (86 µL, 50 equiv.) was added and the mixture was allowed to warm to rt. The reaction was allowed to stir for 18 hours. The solution was then concentrated *in vacuo* and the resulting crude residue taken up in 1:1

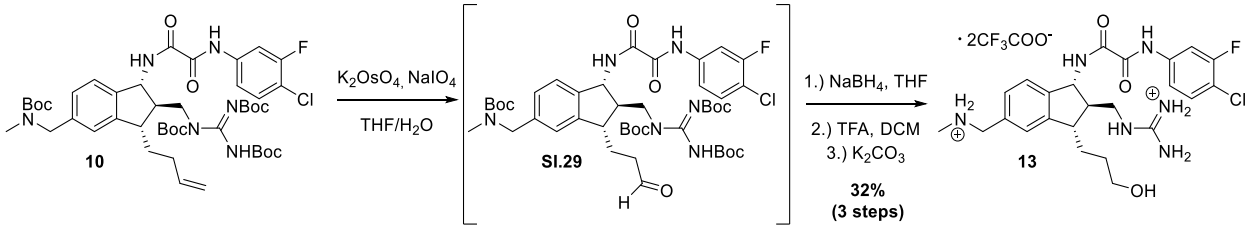
CH_3CN:H_2O. The clear solution was purified by HPLC (2 injections of 1000 µL each). Eluant: 25:75 to 75:25 acetonitrile/water (12-minute gradient). Flow rate: 15 mL/min. Product retention time: 7.8 – 8.2 min. Product fractions were combined, and acetonitrile was removed *in vacuo*. The resulting aqueous solution was deep-frozen (–78 ºC bath) and lyophilized (0.148 mbar) to give the bis-trifluoroacetate salt **11** as a white powder (5.6 mg, 35%).

^{1}H NMR (500 MHz, CD_3OD) δ 7.87 (d, *J* = 11.6 Hz, 1H), 7.53 – 7.43 (m, 2H), 7.40 – 7.33 (m, 2H), 5.25 (d, *J* = 7.3 Hz, 1H), 4.21 (s, 2H), 3.60 – 3.46 (m, 2H), 3.05 – 3.02 (m, 1H), 2.72 (s, 3H), 2.56 – 2.44 (m, 1H), 1.96 – 1.81 (m, 2H), 1.54 – 1.38 (m, 4H), 0.97 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (150 MHz, CD_3OD) δ 162.92 (q, J_{CF} = 35.5 Hz, TFA), 161.90, 159.62, 159.15 (d, J_{CF} = 245.5 Hz) 158.94, 147.82, 143.54, 139.04 (d, J_{CF} = 9.9 Hz), 133.03, 131.76, 130.07, 126.75, 126.14, 118.06 (d, J_{CF} = 3.5 Hz), 117.26 (d, J_{CF} = 17.9 Hz), 109.75 (d, J_{CF} = 26.3 Hz), 58.35, 53.49, 53.32, 47.02, 44.29, 34.63, 33.06, 30.12, 24.17, 14.37; **HRMS** (ESI) *m/z* 503.2330 [calcd for $C_{25}H_{33}ClFN_6O_2$ $(M+H)^+$ 503.2338].



Compound 12 Compound **10** (20 mg, 1.0 equiv.) was taken up in CH_2Cl_2 (222 µL, 0.1 M) and cooled to 0 °C in an ice-water bath. TFA (85.5 µL, 50 equiv.) was added and the mixture was allowed to warm to rt. Reaction was allowed to stir for 18 hours. The solution was then concentrated *in vacuo* and the resulting crude residue taken up in 1:1 CH_3CN:H_2O. The clear solution was purified by HPLC (2 injections of 1000 µL each). Eluant: 25:75 to 75:25 acetonitrile/water (12-minute gradient). Flow rate: 15 mL/min. Product retention time: 7.8-8.1 min. Product fractions were combined, and acetonitrile was removed *in vacuo*. The resulting aqueous solution was deep-frozen (–78 ºC bath) and lyophilized (0.148 mbar) to give the bis-trifluoroacetate salt **12** as a white powder (2.9 mg, 18%).

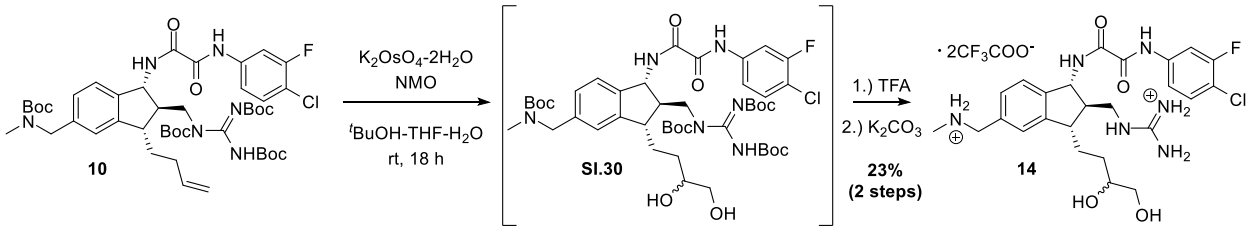
^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (dd, *J* = 11.4, 2.3 Hz, 1H), 7.51 (dd, *J* = 9.1, 2.1 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.40 – 7.33 (m, 2H), 5.91 (dddd, *J* = 16.9, 10.2, 6.5, 6.5 Hz, 1H), 5.24 (d, *J* = 7.0 Hz, 1H), 5.13 – 5.07 (m, 1H), 5.03 – 4.99 (m, 1H), 4.21 (s, 2H), 3.57 – 3.46 (m, 2H), 3.07 (q, *J* = 6.3 Hz, 1H), 2.72 (s, 3H), 2.52 (p, *J* = 7.1 Hz, 1H), 2.33 – 2.16 (m, 2H), 2.10 – 1.85 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD) δ 162.92 (q, J_{CF} = 35.5 Hz, TFA), 161.87, 159.61, 159.15 (d, J_{CF} = 245.5 Hz),158.95, 147.60, 143.50, 139.41, 139.04 (d, J_{CF} = 9.9 Hz), 133.11, 131.74, 130.19, 126.79, 126.22, 118.06 (d, J_{CF} = 3.5 Hz), 117.26 (d, J_{CF} = 17.9 Hz), 115.56, 109.75 (d, J_{CF} = 26.3 Hz), 58.38, 53.45, 53.21, 46.58, 44.30, 34.33, 33.04, 32.01. **HRMS** (ESI) *m/z* 501.2185 [calcd for $C_{25}H_{31}ClFN_6O_2$ $(M+H)^+$ 501.2181].



Compound 13 Open to air at rt, $K_2OsO_4 \cdot 2H_2O$ (0.25 mg, 2 mol%) was added in one portion to a stirred solution of **10** (31mg, 1.0 equiv.) in a 4:1 THF:H_2O mixture (172 µL, 0.2 M). To this

mixture was added $NaIO_4$ (22 mg, 3.0 equiv.) in one portion. Reaction was stirred for 4 hours, at which time TLC (30% EA/hexanes) indicated consumption of starting material. Aqueous saturated $NaHCO_3$ (0.5 mL) was added and the aqueous layer was extracted with Et_2O (3 x 0.5 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was then taken up in EtOH (350 µL, 0.1 M) and cooled to 0 °C in an ice-water bath. To this solution, $NaBH_4$ (3 mg, 2 equiv.) was added in one portion. The reaction was allowed to stir for 30 mins, at which time H_2O (300 µL) was added. The aqueous layer was extracted with EtOAc (3 x 0.5 mL) and the organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was taken up in CH_2Cl_2 (1 mL, 0.04 M) and cooled to 0 °C in an ice-water bath. TFA (146.3 µL, 50 equiv.) was added and the mixture was allowed to warm to rt. The reaction was allowed to stir for 18 hours. To this solution was added solid K_2CO_3 (150 mg) and the solution was allowed to stir for 3 additional hours. The solid residue was then filtered and washed with MeOH (1 mL). The filtered solution was then concentrated *in vacuo* and the resulting crude residue taken up in 1:1 CH_3CN:H_2O. The clear solution was purified by HPLC (2 injections of 1000 µL each). Eluant: 25:75 to 75:25 acetonitrile/water (12-minute gradient). Flow rate: 15 mL/min. Product retention time: 5.8-6.3 min. Product fractions were combined, and acetonitrile was removed *in vacuo*. The resulting aqueous solution was deep-frozen (–78 ºC bath) and lyophilized (0.148 mbar) to give the bis-trifluoroacetate salt **13** as a white powder (8 mg, 32%).

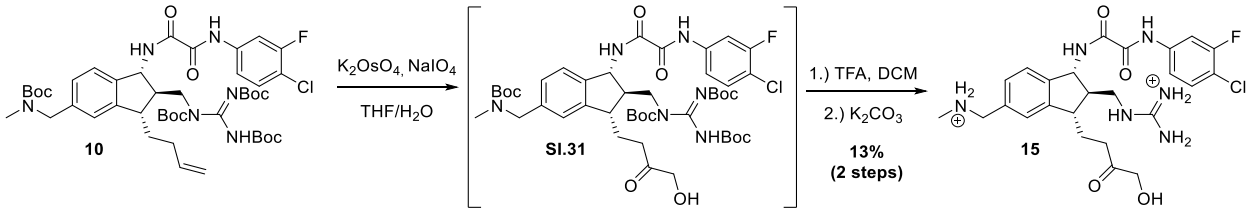
^{1}H NMR (500 MHz, CD_3OD) δ 7.88 (dd, *J* = 11.3, 2.3 Hz, 1H), 7.52 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.48 – 7.45 (m, 2H), 7.39 – 7.34 (m, 2H), 5.27 (d, *J* = 7.5 Hz, 1H), 4.21 (s, 2H), 3.65 (t, *J* = 6.2 Hz, 2H), 3.58 (dd, *J* = 14.0, 5.3 Hz, 1H), 3.51 (dd, *J* = 14.0, 7.2 Hz, 1H), 3.08 (q, *J* = 6.1 Hz, 1H), 2.72 (s, 3H), 2.55 – 2.50 (m, 1H), 2.01 – 1.91 (m, 2H), 1.76 – 1.68 (m, 1H), 1.66 – 1.56 (m, 1H); **^{13}C NMR** (150 MHz, CD_3OD) δ 162.89 (q, J_{CF} = 35.5 Hz, TFA), 161.91, 159.61, 159.15 (d, J_{CF} = 245.8 Hz), 158.93, 147.42, 143.67, 139.04 (d, J_{CF} = 9.9 Hz), 133.01, 131.77, 130.14, 126.73, 126.11, 118.06 (d, J_{CF} = 3.5 Hz), 117.31 (d, J_{CF} = 19 Hz), 109.75 (d, J_{CF} = 26.3 Hz), 62.85, 58.33, 53.48, 53.06, 49.57, 46.69, 44.16, 33.05, 30.55, 30.20; **HRMS** (ESI) *m/z* 505.2118 [calcd for $C_{24}H_{31}ClFN_6O_3$ $(M+H)^+$ 505.2130].



Compound 14 Open to air at rt, $K_2OsO_4 \cdot 2H_2O$ (5.5 mg, 7 mol%) was added in one portion to a stirred solution of **18** (192.1 mg, 1.0 equiv.) in a 5:5:1 THF:^{t}BuOH:H_2O mixture (7.1 mL, 0.03 M). To this mixture was added 4-methylmorpholine N-oxide (32.5 mg, 1.3 equiv.) in one portion. Reaction was stirred for 20 hours, at which time TLC (30% EA/hexanes) indicated consumption of starting material. Aqueous saturated $Na_2S_2O_3$ (10 mL) was added and the aqueous layer was extracted with Et_2O (3 x 5 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was taken up in CH_2Cl_2 (1.2 mL, 0.1 M) and cooled to 0 °C in an ice-water bath. TFA (272.5 µL, 50 equiv.) was added and the mixture was allowed to warm to rt. The reaction was allowed to stir for 18 hours. To this solution was added solid K_2CO_3 (300 mg) and the solution was allowed to stir for 3 additional hours. The solid residue was then filtered and washed with MeOH (3 mL). The filtered solution was then concentrated *in vacuo* and the resulting crude residue taken up in 1:1 CH_3CN:H_2O. The clear solution was

purified by HPLC (3 injections of 1000 µL each). Eluant: 25:75 to 75:25 acetonitrile/water (12-minute gradient). Flow rate: 15 mL/min. Product retention time: 7.5 - 8.0 min. Product fractions were combined, and acetonitrile was removed *in vacuo*. The resulting aqueous solution was deep-frozen (–78 ºC bath) and lyophilized (0.148 mbar) to give the bis-trifluoroacetate salt **14** as a white powder (38.2 mg, 23%).

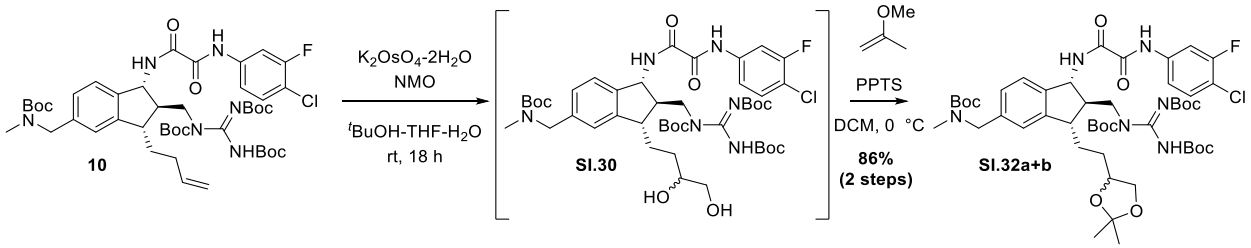
^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (dd, *J* = 11.4, 2.3 Hz, 1H), 7.51 (dd, *J* = 9.1, 2.1 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.39 – 7.32 (m, 2H), 5.26 (d, *J* = 7.4 Hz, 1H), 4.21 (s, 2H), 3.68 – 3.62 (m, 1H), 3.61 – 3.47 (m, 4H), 3.09 (q, *J* = 5.8 Hz, 1H), 2.71 (s, 3H), 2.58 – 2.46 (m, 1H), 2.16 – 2.06 (m, 1H), 1.98 – 1.85 (m, 1H), 1.75 – 1.58 (m, 1H), 1.57 – 1.47 (m, 0.5H), 1.44 – 1.35 (m, 0.5H); **^{13}C NMR** (150 MHz, CD_3OD) δ 162.83 (q, J_{CF} = 35 Hz, TFA), 161.90, 161.89, 159.61, 159.15 (d, J_{CF} = 245.5 Hz) 158.93, 158.92, 147.35, 147.30, 143.68, 143.66, 139.04 (d, J_{CF} = 9.9 Hz), 132.99, 131.75, 130.15, 130.13, 126.77, 126.74, 126.06, 118.06 (d, J_{CF} = 3.5 Hz), 117.26 (d, J_{CF} = 18 Hz), 109.75 (d, J_{CF} = 27 Hz), 73.27, 73.16, 67.21, 67.19, 58.34, 53.48, 53.47, 52.90, 52.87, 49.57, 46.81, 44.16, 33.05, 33.03, 30.81, 30.77, 30.00, 29.85; **IR** (thin film, KBr) ν_{max} 3286, 2978, 2932, 1671, 1558, 1540, 1508, 1456, 1428, 1201, 1133 cm^{-1}; **HRMS** (ESI) *m/z* 535.2234 [calcd for $C_{25}H_{33}ClFN_6O_4$ $(M+H)^+$ 535.2236]; **[α]$_D^{24}$** +21.2 (*c* 0.12, CH_3OH).



Compound 15 Open to air at rt, $K_2OsO_4 \cdot 2H_2O$ (0.22 mg, 7 mol%) was added in one portion to a stirred solution of **10** (27mg, 1.0 equiv.) in a 4:1 THF:H_2O mixture (500 µL, 0.06 M). To this mixture was added $NaIO_4$ (20 mg, 3.0 equiv.) in one portion. Reaction was stirred for 4 hours, at which time TLC (30% EA/hexanes) indicated consumption of starting material. Aqueous saturated $NaHCO_3$ (1 mL) was added and the aqueous layer was extracted with Et_2O (3 x 1 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was taken up in CH_2Cl_2 (1 mL, 0.03 M) and cooled to 0 °C in an ice-water bath. TFA (146.3 µL, 50 equiv.) was added and the mixture was allowed to warm to rt. The reaction was allowed to stir for 18 hours. To this solution was added solid K_2CO_3 (150 mg) and the solution was allowed to stir for 3 additional hours. The solid residue was then filtered and washed with MeOH (1 mL). The filtered solution was then concentrated *in vacuo* and the resulting crude residue taken up in 1:1 CH_3CN:H_2O. The clear solution was purified by HPLC (2 injections of 1000 µL each). Eluant: 25:75 to 75:25 acetonitrile/water (12-minute gradient). Flow rate: 15 mL/min. Product retention time: 6.3-6.8 min. Product fractions were combined, and acetonitrile was removed *in vacuo*. The resulting aqueous solution was deep-frozen (–78 ºC bath) and lyophilized (0.148 mbar) to give the bis-trifluoroacetate salt **15** as a white powder (3 mg, 13%).

^{1}H NMR (500 MHz, CD_3OD) δ 7.87 (dd, *J* = 11.3, 2.2 Hz, 1H), 7.51 (dd, *J* = 9.1, 2.0 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.40 – 7.32 (m, 2H), 5.25 (d, *J* = 7.6 Hz, 1H), 4.24 – 4.15 (m, 4H), 3.59 (dd, *J* = 14.1, 5.3 Hz, 1H), 3.51 (dd, *J* = 14.0, 7.5 Hz, 1H), 3.10 (q, *J* = 5.5 Hz, 1H), 2.72 (s, 3H), 2.61 (t, *J* = 7.3 Hz, 2H), 2.50 – 2.44 (m, 1H), 2.22 – 2.18 (m, 2H); **^{13}C NMR** (150 MHz, CD_3OD) δ 212.60, 162.83 (q, J_{CF} = 35 Hz, TFA), 161.87, 159.59, 159.15 (d, J_{CF} = 245.5 Hz), 158.90, 146.60, 143.90, 139.02 (d, J_{CF} = 9.9 Hz), 133.11, 131.77, 130.33, 126.69, 126.15, 118.05 (d, J_{CF} = 3.5 Hz), 117.31 (d, J_{CF} = 17 Hz), 109.75 (d, J_{CF} = 28 Hz), 68.73, 58.31, 53.45, 52.58, 49.57,

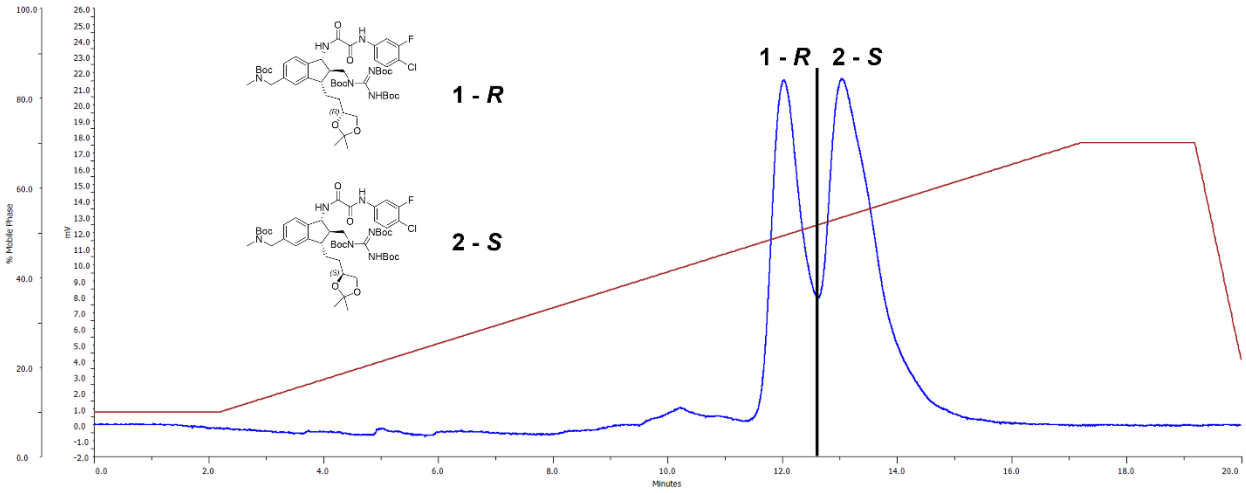
46.29, 44.10, 35.54, 33.09, 26.73; **HRMS** (ESI) *m/z* 533.2073 [calcd for $C_{25}H_{31}ClFN_6O_4$ $(M+H)^+$ 533.2079].



Compound SI.32a+b Open to air at rt, $K_2OsO_4 \cdot 2H_2O$ (3 mg, 7 mol%) was added in one portion to a stirred solution of **10** (100 mg, 1.0 equiv.) in a 5:5:1 THF:^{t}BuOH:H_2O mixture (1.1 mL, 0.1 M). To this mixture was added 4-methylmorpholine N-oxide (17 mg, 1.3 equiv.) in one portion. Reaction was stirred for 20 hours, at which time TLC (30% EA/hexanes) indicated consumption of starting material. Aqueous saturated $Na_2S_2O_3$ (2 mL) was added and the aqueous layer was extracted with Et_2O (3 x 2 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude **SI.30** and PPTS (2.8 mg, 0.1 equiv.) were dissolved in anhydrous CH_2Cl_2 (1 mL) and cooled to 0 °C in an ice-water bath. To this mixture was added 2-methoxypropene (22 µL, 2.0 equiv.) in one portion. Reaction was warned to rt and stirred for 1 hour, at which time TLC (50% EA/hexanes) indicated consumption of starting material. Aqueous saturated $NaHCO_3$ (1 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (25% – 30% EtOAc/hexanes) to give **SI.32a+b** (93 mg, 86%) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.80 (s, 1H), 7.71 (d, *J* = 10.6 Hz, 1H), 7.37 (t, *J* = 8.3 Hz, 1H), 7.19 (dd, *J* = 19.7, 8.2 Hz, 2H), 7.09 (s, 2H), 5.23 (dd, *J* = 7.0, 7.0 Hz, 1H), 4.41 (s, 2H), 4.10 – 4.02 (m, 4H), 3.53 – 3.48 (m, 2H), 2.94 (q, *J* = 5.8 Hz, 1H), 2.80 (s, 3H), 2.63 – 2.56 (m, 1H), 2.02 – 1.89 (m, 1H), 1.84 – 1.56 (m, 3H), 1.47 (s, 36H), 1.40 (s, 1.5H), 1.39 (s, 1.5H), 1.34 (s, 3H). **LRMS** (ESI) *m/z* 975.9 [calcd for $C_{48}H_{69}ClFN_6O_{12}$ $(M+H)^+$ 975.5].

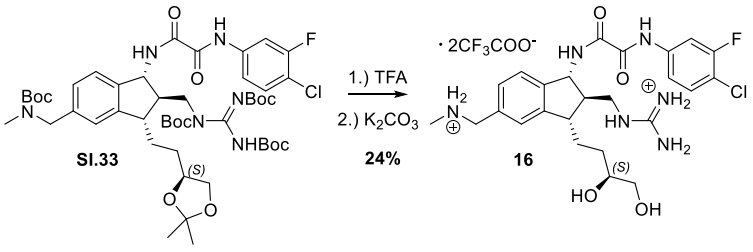
The resulting diastereomeric mixture was taken up in 3 mL 5% isopropanol in hexanes. The clear solution was purified by normal phase chiral HPLC (3 injections of 1000 µL each). Eluant: 10:90 to 70:30 isopropanol/hexanes (15-minute gradient). Flow rate: 15 mL/min. Product retention times: Peak 1 11.5-12.3 min. Peak 2 12.8-14.5 min. Peak 1 and Peak 2 product fractions were combined separately, and isopropanol/hexanes was removed *in vacuo*. See below for chromatogram of the separation.



Method: column: Chiralpak® AD-H (21 x 250 mm, 5 µm); eluent: 10% isopropanol in hexanes to 70% isopropanol in hexanes; gradient time: 15 mins; flow rate: 15 mL/min; pressure: 900 psi. Retention times: (*R*) Diastereomer (**SI.34**) = 11.9 min, (*S*) Diastereomer (**SI.33**) = 13.2 min.

Peak 1 (SI.34): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.81 (s, 1H), 7.71 (dd, *J* = 10.6, 2.3 Hz, 1H), 7.37 (t, *J* = 8.3 Hz, 1H), 7.19 (dd, *J* = 19.0, 7.4 Hz, 2H), 7.08 (s, 2H), 5.23 (dd, *J* = 7.0, 7.0 Hz, 1H), 4.41 (s, 2H), 4.11 – 4.02 (m, 4H), 3.52 (dd, *J* = 7.5 Hz, 1H), 2.94 (q, *J* = 5.8 Hz, 1H), 2.80 (s, 3H), 2.63 – 2.56 (m, 1H), 1.96 – 1.88 (m, 1H), 1.84 – 1.58 (m, 3H), 1.47 (s, 36H), 1.39 (s, 3H), 1.34 (s, 3H).

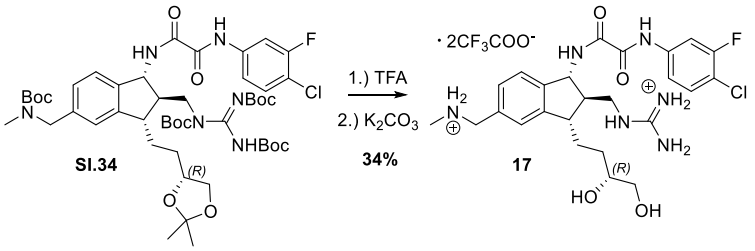
Peak 2 (SI.33): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.80 (s, 1H), 7.71 (dd, *J* = 10.6, 2.3 Hz, 1H), 7.37 (t, *J* = 8.3 Hz, 1H), 7.19 (dd, *J* = 19.7, 8.2 Hz, 2H), 7.09 (s, 2H), 5.23 (dd, *J* = 7.0, 7.0 Hz, 1H), 4.41 (s, 2H), 4.10 – 4.02 (m, 4H), 3.51 (dd, *J* = 7.5 Hz, 1H), 2.92 (q, *J* = 5.8 Hz, 1H), 2.80 (s, 3H), 2.63 – 2.56 (m, 1H), 2.02 – 1.89 (m, 1H), 1.84 – 1.56 (m, 3H), 1.47 (s, 36H), 1.40 (s, 3H), 1.34 (s, 3H).



Peak 2 - Compound 16 The crude residue (16 mg, 1.0 equiv.) was taken up in CH_2Cl_2 (200 µL, 0.1 M) and cooled to 0 °C in an ice-water bath. TFA (38 µL, 50 equiv.) was added and the mixture was allowed to warm to rt. The reaction was allowed to stir for 18 hours. To this solution was added solid K_2CO_3 (40 mg) and the solution was allowed to stir for 3 additional hours. The solid residue was then filtered and washed with MeOH (300 µL). The filtered solution was then concentrated *in vacuo* and the resulting crude residue taken up in 1:1 CH_3CN:H_2O. The clear solution was purified by HPLC (1 injection of 1000 µL). Eluant: 25:75 to 75:25 acetonitrile/water (12-minute gradient). Flow rate: 15 mL/min. Product retention time: 7.5 - 8.0

min. Product fractions were combined, and acetonitrile was removed *in vacuo*. The resulting aqueous solution was deep-frozen (–78 ºC bath) and lyophilized (0.148 mbar) to give the bis-trifluoroacetate salt **16** as a white powder (3 mg, 24%).

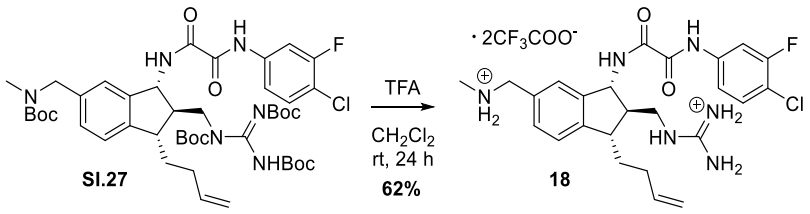
^{1}H NMR (500 MHz, CD_3OD) δ 7.88 (dd, *J* = 11.3, 2.2 Hz, 1H), 7.51 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.40 – 7.30 (m, 2H), 5.26 (d, *J* = 7.5 Hz, 1H), 4.20 (s, 2H), 3.68 – 3.63 (m, 1H), 3.58 (dd, *J* = 13.9, 5.1 Hz, 1H), 3.54 – 3.44 (m, 3H), 3.09 (q, *J* = 5.8 Hz, 1H), 2.71 (s, 3H), 2.55 – 2.50 (m, 1H), 2.14 – 2.07 (m, 1H), 1.96 – 1.89 (m, 1H), 1.65 – 1.60 (m, 1H), 1.56 – 1.48 (m, 1H); **^{13}C NMR** (125 MHz, CD_3OD) δ 162.83 (q, J_{CF} = 35.5 Hz, TFA), 161.87, 159.60, 159.07 (d, J_{CF} = 245 Hz), 158.89, 147.33, 143.66, 139.04 (d, J_{CF} = 9.9 Hz), 132.99, 131.75, 130.14, 126.75, 126.04, 118.06 (d, J_{CF} = 3.5 Hz), 117.25 (d, J_{CF} = 19 Hz), 109.75 (d, J_{CF} = 26.3 Hz), 73.26, 67.18, 58.32, 53.45, 52.84, 49.63, 46.78, 44.13, 33.02, 30.78, 29.95; **HRMS** (ESI) *m/z* 535.2233 [calcd for $C_{25}H_{33}ClFN_6O_4$ $(M+H)^+$ 535.2236].



Peak 1 - Compound 17 The crude residue (18 mg, 1.0 equiv.) was taken up in CH_2Cl_2 (200 µL, 0.1 M) and cooled to 0 °C in an ice-water bath. TFA (44 µL, 50 equiv.) was added and the mixture was allowed to warm to rt. The reaction was allowed to stir for 18 hours. To this solution was added solid K_2CO_3 (50 mg) and the solution was allowed to stir for 3 additional hours. The solid residue was then filtered and washed with MeOH (300 µL). The filtered solution was then concentrated *in vacuo* and the resulting crude residue taken up in 1:1 CH_3CN:H_2O. The clear solution was purified by HPLC (1 injection of 1000 µL). Eluant: 25:75 to 75:25 acetonitrile/water (12-minute gradient). Flow rate: 15 mL/min. Product retention time: 7.5 - 8.0 min. Product fractions were combined, and acetonitrile was removed *in vacuo*. The resulting aqueous solution was deep-frozen (–78 ºC bath) and lyophilized (0.148 mbar) to give the bis-trifluoroacetate salt **17** as a white powder (5 mg, 34%).

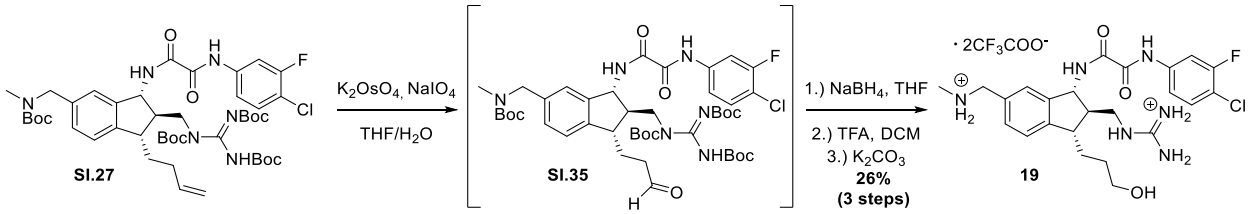
^{1}H NMR (500 MHz, CD_3OD) δ 7.88 (dd, *J* = 11.3, 2.1 Hz, 1H), 7.51 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.39 – 7.32 (m, 2H), 5.26 (d, *J* = 7.6 Hz, 1H), 4.21 (s, 2H), 3.68 – 3.63 (m, 1H), 3.57 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.52 – 3.49 (m, 3H), 3.10 (q, *J* = 5.5 Hz, 1H), 2.72 (s, 3H), 2.55 – 2.49 (m, 1H), 2.15 – 2.07 (m, 1H), 1.96 – 1.89 (m, 1H), 1.75 – 1.68 (m, 1H), 1.43 – 1.35 (m, 1H); **^{13}C NMR** (125 MHz, CD_3OD) δ 162.82 (q, J_{CF} = 35.5 Hz, TFA), 161.90, 159.60, 159.15 (d, J_{CF} = 245.8 Hz), 158.90, 147.27, 143.67, 139.04 (d, J_{CF} = 9.9 Hz), 132.99, 131.76, 130.16, 126.77, 126.05, 118.06 (d, J_{CF} = 3.5 Hz), 117.31 (d, J_{CF} = 19 Hz), 109.73 (d, J_{CF} = 26.3 Hz), 73.15, 67.20, 58.31, 53.47, 52.87, 46.77, 44.12, 33.05, 30.73, 29.79; **HRMS** (ESI) *m/z* 535.2222 [calcd for $C_{25}H_{33}ClFN_6O_4$ $(M+H)^+$ 535.2236].

Synthesis of 3,6-Substituted Compounds Submitted for Biological Evaluation



Compound 18 A solution of **SI.27** (25 mg, 1.0 equiv.) in CH_2Cl_2 (277 µL, 0.1 M) was cooled to 0 °C in an ice-water bath. TFA (107 µL, 50 equiv.) was added and the mixture was allowed to warm to rt. Reaction was allowed to stir for 18 hours. The solution was then concentrated *in vacuo* and the resulting crude residue taken up in 1:1 CH_3CN:H_2O. The clear solution was purified by HPLC (2 injections of 1000 µL each). Eluant: 25:75 to 75:25 acetonitrile/water (12-minute gradient). Flow rate: 15 mL/min. Product retention time: 7.8-8.0 min. Product fractions were combined, and acetonitrile was removed *in vacuo*. The resulting aqueous solution was deep-frozen (–78 ºC bath) and lyophilized (0.148 mbar) to give the bis-trifluoroacetate salt **18** as a white powder (12.5 mg, 62%).

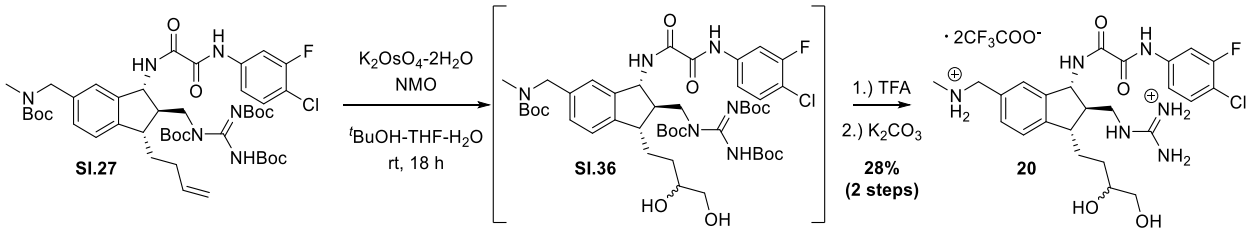
^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (dd, *J* = 11.4, 2.2 Hz, 1H), 7.52 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.49 – 7.40 (m, 3H), 7.37 (s, 1H), 5.90 (dddd, *J* = 16.9, 10.2, 6.5, 6.5 Hz, 1H), 5.26 (d, *J* = 7.1 Hz, 1H), 5.11 – 5.06 (m, 1H), 5.02 – 4.99 (m, 1H), 4.18 (s, 2H), 3.56 (dd, *J* = 13.9, 5.4 Hz, 1H), 3.49 (dd, *J* = 14.0, 7.1 Hz, 1H), 3.07 (q, *J* = 6.1 Hz, 1H), 2.70 (s, 3H), 2.53 (p, *J* = 7.2 Hz, 1H), 2.31 – 2.14 (m, 2H), 2.04 – 1.89 (m, 2H); **^{13}C NMR** (150 MHz, CD_3OD) δ 162.92 (q, J_{CF} = 35.5 Hz, TFA), 161.83, 159.60, 159.06 (d, J_{CF} = 245.8 Hz), 158.96, 148.02, 143.10, 139.40, 139.04 (d, J_{CF} = 9.9 Hz) 131.85, 131.75, 131.45, 126.80, 126.12, 119.24, 118.06 (d, J_{CF} = 3.5 Hz), 117.31 (d, J_{CF} = 19 Hz), 115.54, 109.70 (d, J_{CF} = 26.3 Hz), 58.39, 53.30, 53.15, 49.57, 46.50, 44.27, 34.20, 32.98, 31.97; **HRMS** (ESI) *m/z* 501.2167 [calcd for $C_{25}H_{31}ClFN_6O_2$ $(M+H)^+$ 501.2181].



Compound 19 Open to air at rt, $K_2OsO_4 \cdot 2H_2O$ (1 mg, 7 mol %) was added in one portion to a stirred solution of **SI.27** (100 mg, 1.0 equiv.) in a 4:1 THF:H_2O mixture (560 µL, 0.2 M). To this mixture was added $NaIO_4$ (71 mg, 3.0 equiv.) in one portion. Reaction was stirred for 4 hours, at which time TLC (30% EA/hexanes) indicated consumption of starting material. Aqueous saturated $NaHCO_3$ (1 mL) was added and the aqueous layer was extracted with Et_2O (3 x 1 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was then taken up in EtOH (1.11 mL, 0.1 M) and cooled to 0 °C in an ice-water bath. To this solution, $NaBH_4$ (10 mg, 2.0 equiv.) was added in one portion. The reaction was allowed to stir for 30 mins, at which time H_2O (2 mL) was added. The aqueous layer was extracted with EtOAc (3 x 2 mL) and the organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was taken up in CH_2Cl_2 (1.1 mL, 0.1 M) and cooled to 0 °C in an ice-water bath. TFA (342.1 µL, 40 equiv.) was added and the mixture was allowed to warm to rt. The reaction was allowed to stir for 18 hours. To this solution was added solid K_2CO_3 (400 mg) and the solution was allowed to stir for 3 additional hours. The solid residue was then filtered and washed with MeOH (1 mL). The filtered solution was then concentrated *in vacuo* and the resulting crude residue taken up in 1:1 CH_3CN:H_2O. The clear solution was

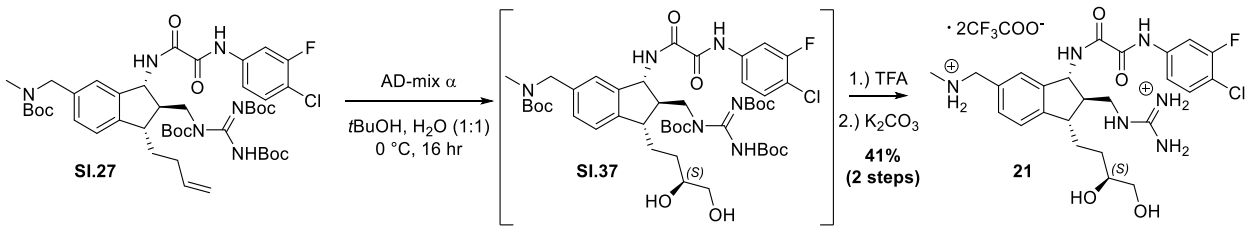
purified by HPLC (2 injections of 1000 µL each). Eluant: 25:75 to 75:25 acetonitrile/water (12-minute gradient). Flow rate: 15 mL/min. Product retention time: 5.8-6.3 min. Product fractions were combined, and acetonitrile was removed *in vacuo*. The resulting aqueous solution was deep-frozen (–78 ºC bath) and lyophilized (0.148 mbar) to give the bis-trifluoroacetate salt **19** as a white powder (21.2 mg, 26%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.00 (dd, *J* = 11.6, 2.4 Hz, 1H), 7.75 – 7.72 (m, 1H), 7.54 – 7.46 (m, 3H), 7.35 (d, *J* = 7.8 Hz, 1H), 5.29 (d, *J* = 7.9 Hz, 1H), 4.31 (s, 2H), 3.72 – 3.57 (m, 4H), 3.18 (q, *J* = 5.7 Hz, 1H), 2.77 (s, 3H), 2.70 – 2.63 (m, 1H), 1.96 – 1.88 (m, 2H), 1.75 – 1.54 (m, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2CO$) δ 159.19, 147.51, 142.78, 139.02 (d, J_{CF} = 9.9 Hz) 131.64, 131.50, 131.10, 126.49, 125.37, 117.87 (d, J_{CF} = 2.9 Hz), 116.19(d, J_{CF} = 17.5 Hz), 109.26 (d, J_{CF} = 26.0 Hz)109.40, 62.42, 57.92, 52.95, 52.71, 45.57, 43.35, 32.75, 30.59, 30.53; **HRMS** (ESI) *m/z* 505.2145 [calcd for $C_{24}H_{31}ClFN_6O_3$ $(M+H)^+$ 505.2130].



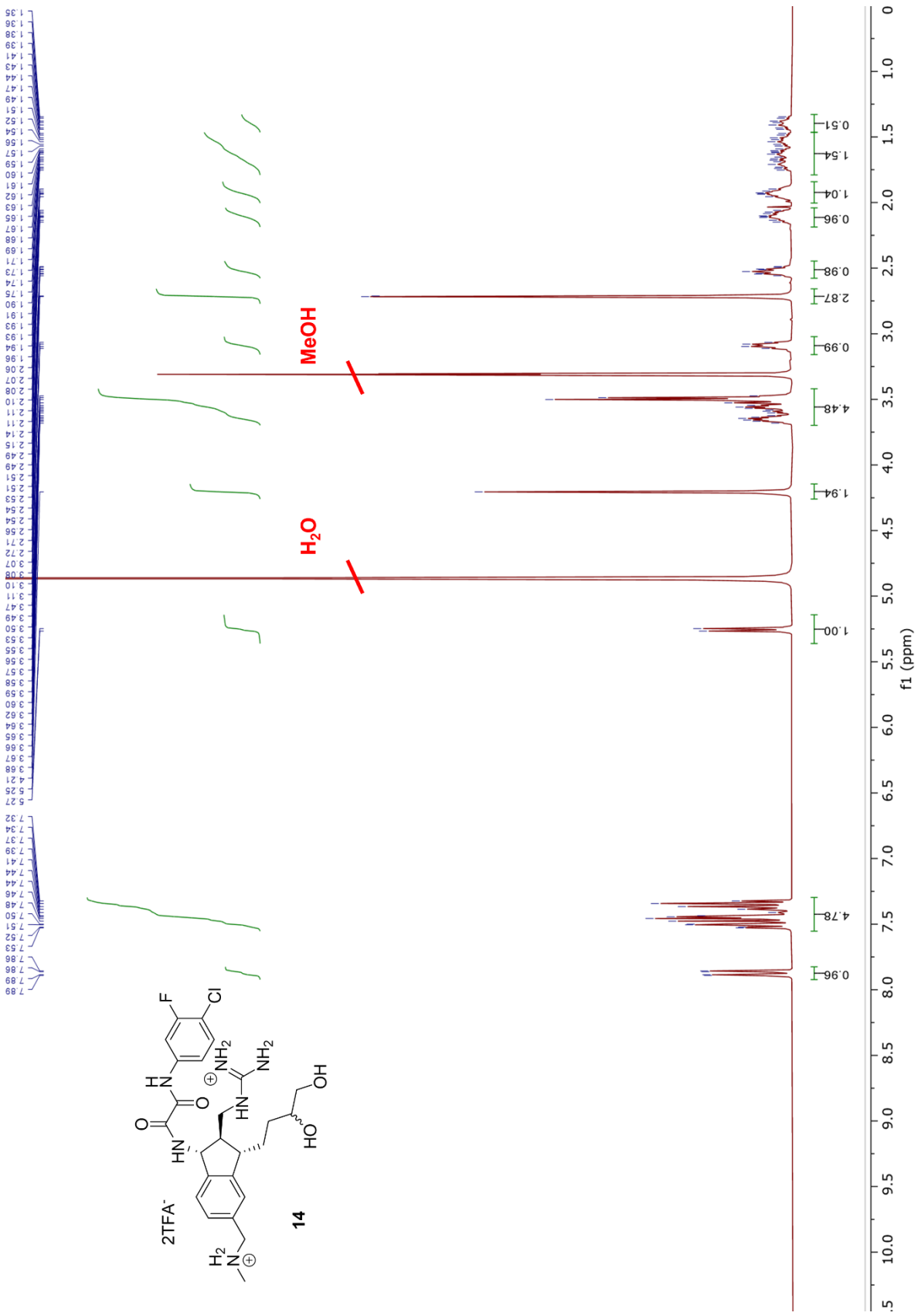
Compound 20 Open to air at rt, $K_2OsO_4 \cdot 2H_2O$ (1 mg, 7 mol%) was added in one portion to a stirred solution of **SI.27** (24.1 mg, 1.0 equiv.) in a 5:5:1 THF:^{t}BuOH:H_2O mixture (900 µL, 0.03 M). To this mixture was added 4-methylmorpholine N-oxide (4 mg, 1.3 equiv.) in one portion. Reaction was stirred for 20 hours, at which time TLC (30% EA/hexanes) indicated consumption of starting material. Aqueous saturated $Na_2S_2O_3$ (1 mL) was added and the aqueous layer was extracted with Et_2O (3 x 1 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was taken up in CH_2Cl_2 (270 µL, 0.1 M) and cooled to 0 °C in an ice-water bath. TFA (86 µL, 50 equiv.) was added and the mixture was allowed to warm to rt. The reaction was allowed to stir for 18 hours. To this solution was added solid K_2CO_3 (100 mg) and the solution was allowed to stir for 3 additional hours. The solid residue was then filtered and washed with MeOH (1 mL). The filtered solution was then concentrated *in vacuo* and the resulting crude residue taken up in 1:1 CH_3CN:H_2O. The clear solution was purified by HPLC (2 injections of 1000 µL each). Eluant: 25:75 to 75:25 acetonitrile/water (12-minute gradient). Flow rate: 15 mL/min. Product retention time: 7.5 – 8 min. Product fractions were combined, and acetonitrile was removed *in vacuo*. The resulting aqueous solution was deep-frozen (–78 ºC bath) and lyophilized (0.148 mbar) to give the bis-trifluoroacetate salt **20** as a white powder (5.8 mg, 28%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (dd, *J* = 11.4, 2.2 Hz, 1H), 7.52 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.48 – 7.41 (m, 3H), 7.36 (s, 1H), 5.27 (d, *J* = 7.4 Hz, 1H), 4.17 (s, 2H), 3.67 – 3.61 (m, 1H), 3.60 – 3.46 (m, 4H), 3.08 (p, *J* = 6.0 Hz, 1H), 2.69 (s, 3H), 2.57 – 2.49 (m, 1H), 2.15 – 2.01 (m, 1H), 1.96 – 1.87 (m, 1H), 1.75 – 1.57 (m, 1H), 1.55 – 1.39 (m, 1H); **^{13}C NMR** (150 MHz, CD_3OD) δ 162.82 (q, J_{CF} = 35.5 Hz, TFA), 161.84, 159.60, 159.12 (d, J_{CF} = 245.8 Hz), 158.94, 158.34, 147.91, 147.83, 143.24, 143.16, 139.04 (d, J_{CF} = 9.9 Hz), 131.80, 131.77, 131.40, 131.39, 126.67, 126.65, 126.21, 126.12, 118.06 (d, J_{CF} = 3.5 Hz), 117.31 (d, J_{CF} = 19 Hz), 109.75 (d, J_{CF} = 26.3 Hz), 73.32, 73.19, 67.26, 67.18, 58.37, 53.32, 53.07, 52.88, 46.86, 46.81, 44.24, 44.20, 32.98, 31.12, 30.89, 30.23, 30.07; **HRMS** (ESI) *m/z* 535.2231 [calcd for $C_{25}H_{33}ClFN_6O_4$ $(M+H)^+$ 535.2236].



Compound 21 Open to air at rt, AD-mix α (93 mg, 1.4g/mmol substrate) was dissolved in a 1:1 ^{t}BuOH:H_2O mixture (670 µL, 0.1 M) and was cooled to 0 ºC using an isopropanol bath cooled with a temperature controlled cryostat. To this cooled solution was added **SI.27** (50 mg, 1.0 equiv.). Reaction was stirred for 18 hours, at which time TLC (30% EA/hexanes) indicated consumption of starting material. Aqueous saturated $Na_2S_2O_3$ (1 mL) was added and the aqueous layer was extracted with EtOAc (3 x 1 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was taken up in CH_2Cl_2 (670 µL, 0.1 M) and cooled to 0 °C in an ice-water bath. TFA (206 µL, 40 equiv.) was added and the mixture was allowed to warm to rt. The reaction was allowed to stir for 18 hours. To this solution was added solid K_2CO_3 (250 mg) and the solution was allowed to stir for 3 additional hours. The solid residue was then filtered and washed with MeOH (2 mL). The filtered solution was then concentrated *in vacuo* and the resulting crude residue taken up in 1:1 CH_3CN:H_2O. The clear solution was purified by HPLC (3 injections of 1000 µL each). Eluant: 25:75 to 75:25 acetonitrile/water (12-minute gradient). Flow rate: 15 mL/min. Product retention time: 7.5 – 8 min. Product fractions were combined, and acetonitrile was removed *in vacuo*. The resulting aqueous solution was deep-frozen (–78 ºC bath) and lyophilized (0.148 mbar) to give the bis-trifluoroacetate salt **21** as a white powder (21 mg, 41%). *>20:1 diastereoselectivity observed by ^{1}H NMR post-deprotection.

^{1}H NMR (400 MHz, CD_3OD) δ 7.88 (dd, *J* = 11.4, 2.2 Hz, 1H), 7.52 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.48 – 7.42 (m, 3H), 7.36 (s, 1H), 5.27 (d, *J* = 7.5 Hz, 1H), 4.17 (s, 2H), 3.67 – 3.55 (m, 2H), 3.53 – 3.46 (m, 3H), 3.09 (q, *J* = 5.7 Hz, 1H), 2.69 (s, 3H), 2.57 – 2.50 (m, 1H), 2.15 – 2.03 (m, 1H), 1.96 – 1.87 (m, 1H), 1.66 – 1.57 (m, 1H), 1.55 – 1.46 (m, 1H); **^{13}C NMR** (150 MHz, CD_3OD) δ 162.85 (q, J_{CF} = 35.5 Hz, TFA), 161.84, 159.60, 159.25 (d, J_{CF} = 245.5f Hz), 158.93, 147.83, 143.21, 139.04 (d, J_{CF} = 9.9 Hz), 131.80, 131.76, 131.39, 126.66, 126.12, 118.00 (d, J_{CF} = 3.5 Hz), 117.31 (d, J_{CF} = 19 Hz), 109.75 (d, J_{CF} = 26.3 Hz), 73.33, 67.26, 58.37, 53.31, 52.88, 46.81, 44.20, 32.98, 30.91, 30.10; **HRMS** (ESI) *m/z* 535.2238 [calcd for $C_{25}H_{33}ClFN_6O_4$ $(M+H)^+$ 535.2236].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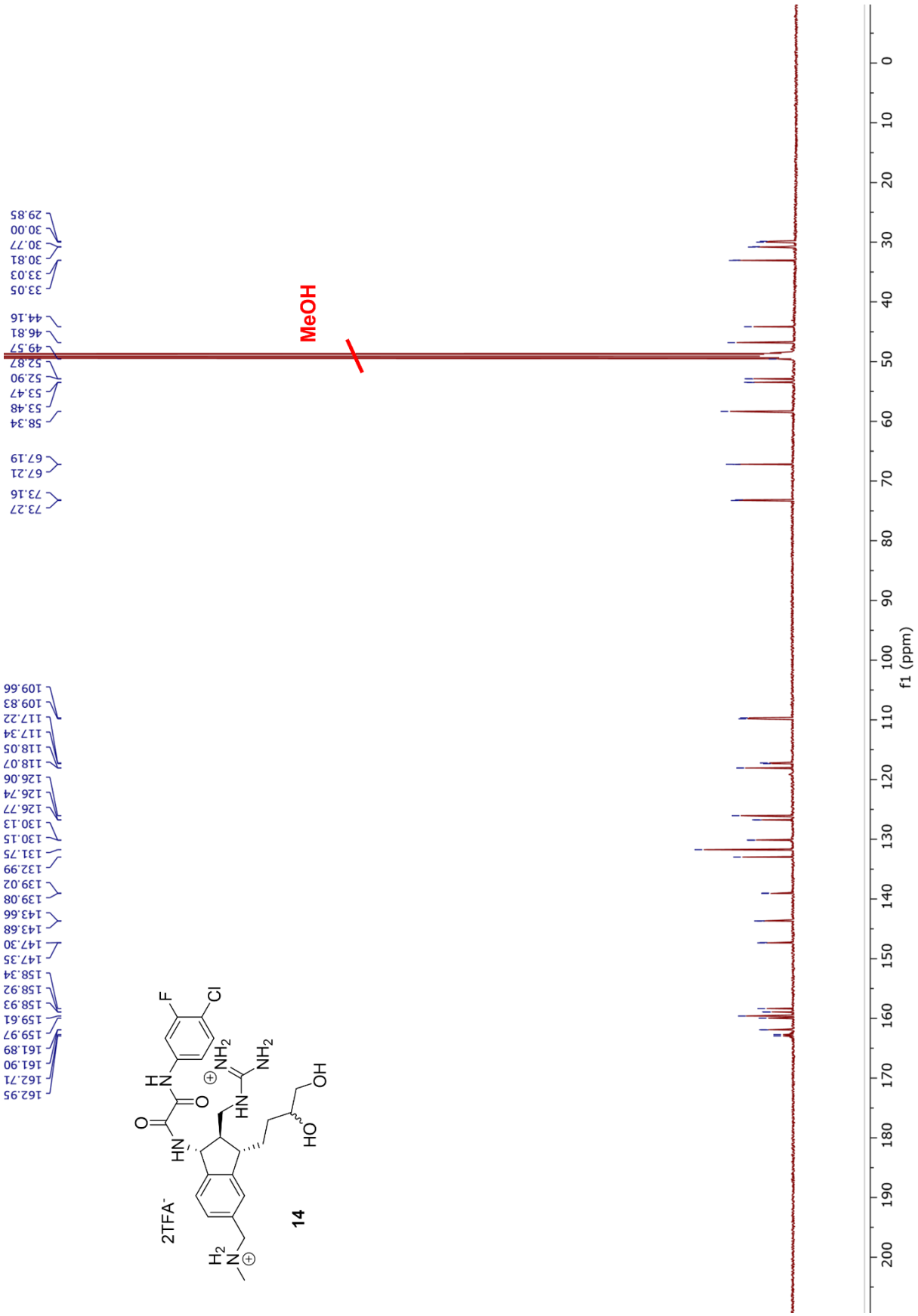
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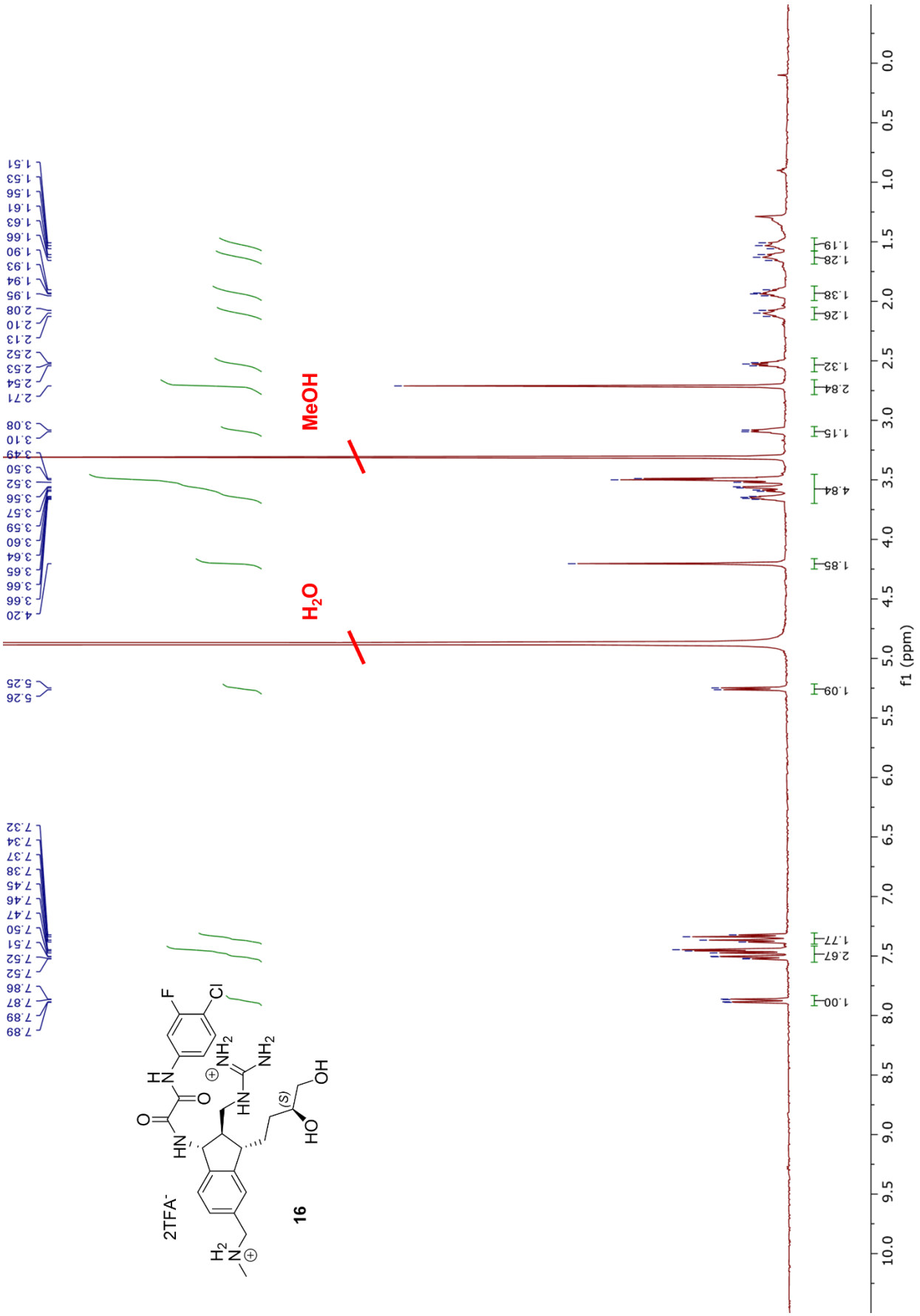
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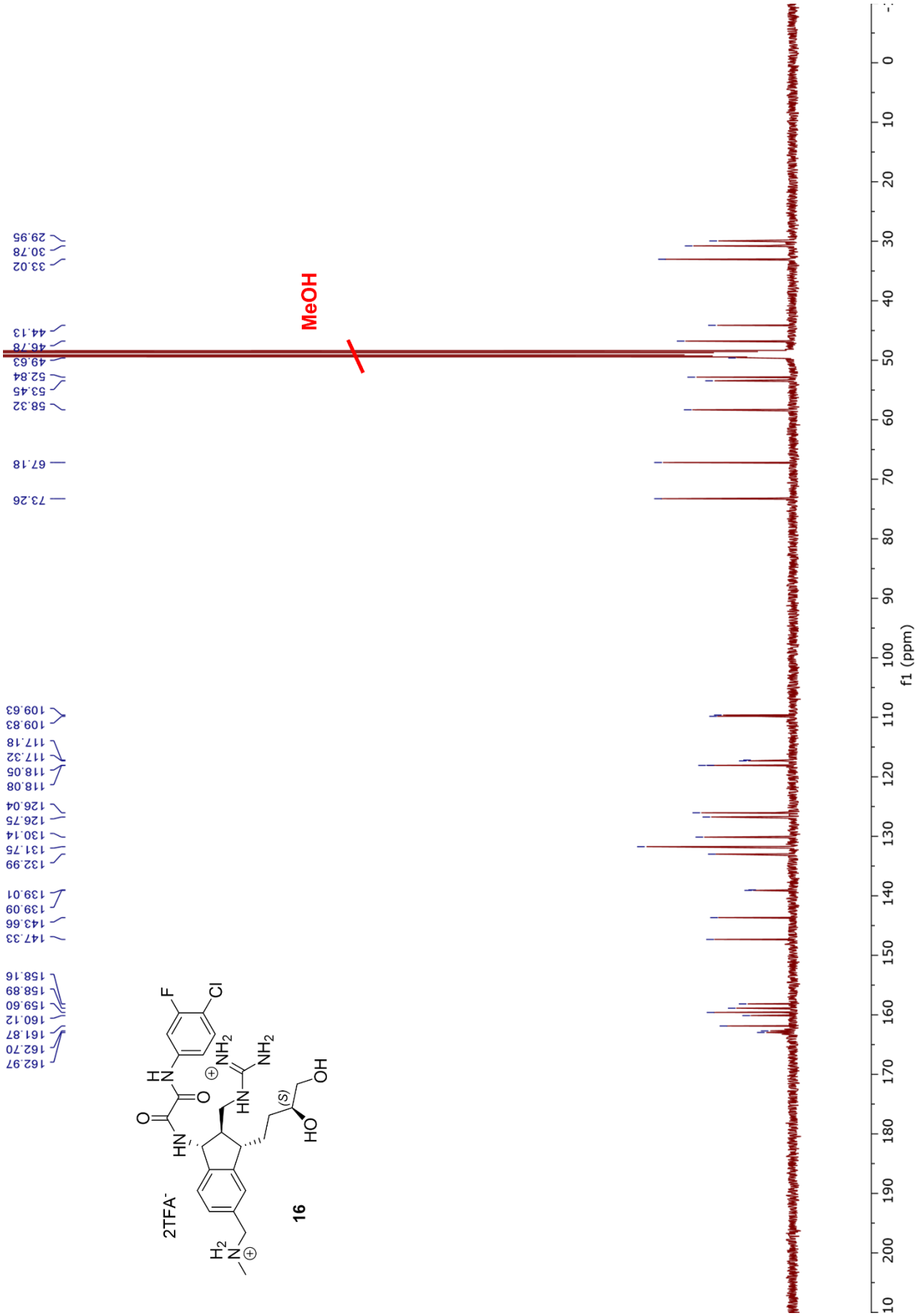
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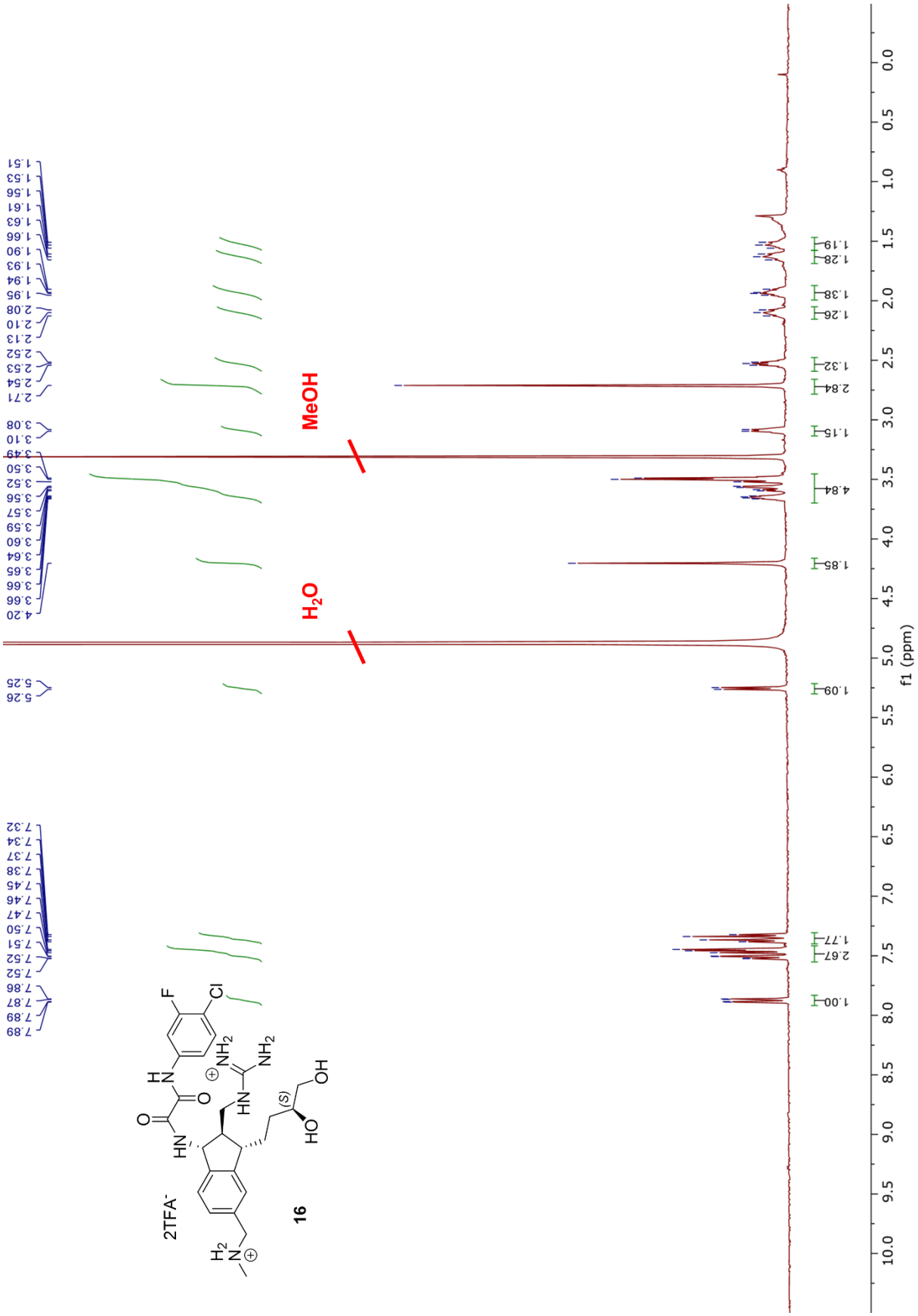
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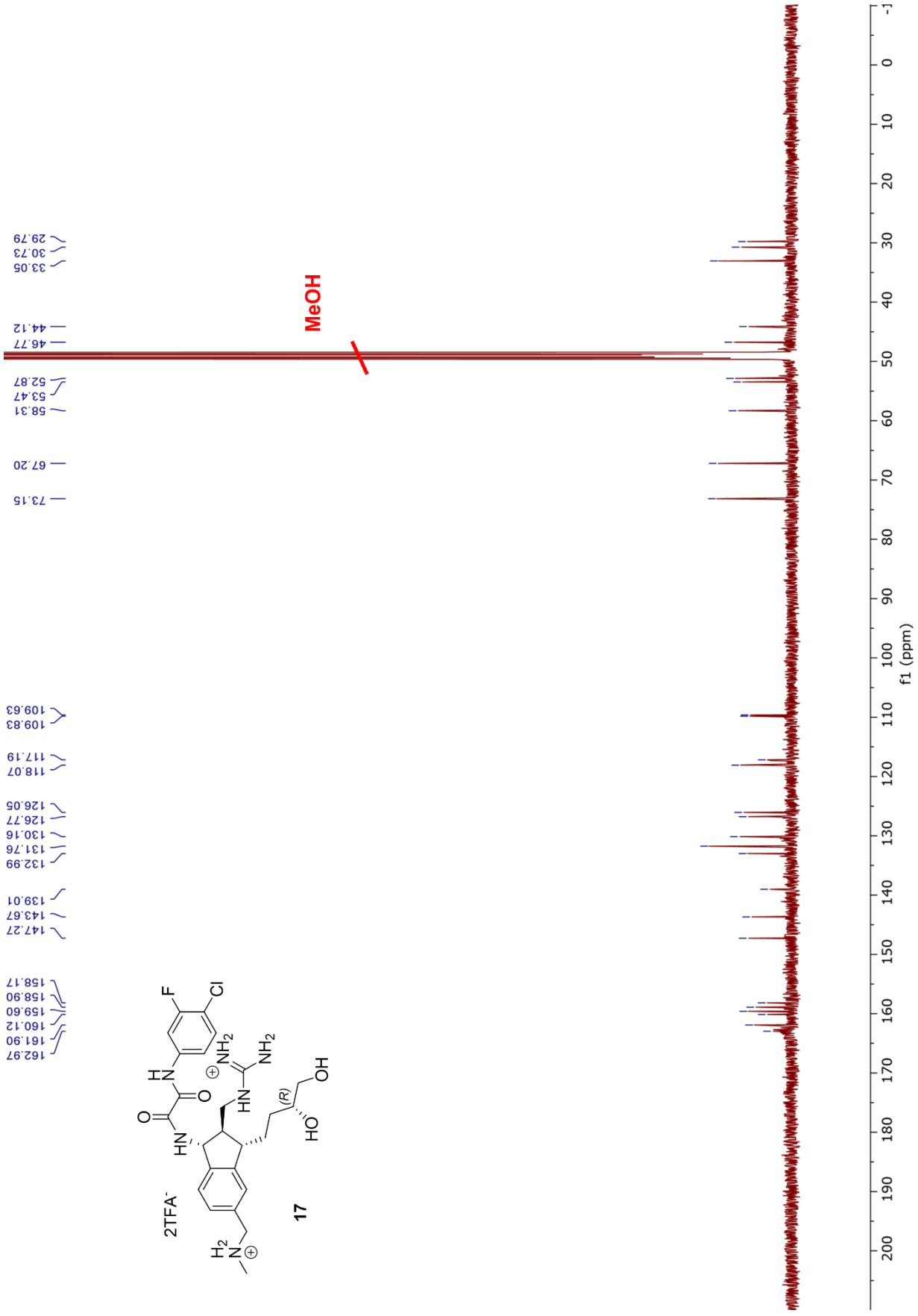
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147.27
158.17
158.90
159.60
160.12
161.90
162.97
f1 (ppm)
2TFA-
17