SUPPORTING INFORMATION

Lead change of a HIF-2α antagonist guided by multiparameter optimization and structure based drug design

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Table of Content

Table S1. Statistics for X-ray data collection and structure refinement

Data Collection	Compound Number	Compound Number	Compound Number	Compound Number
PDB ID	6X2H	6D0B	6X21	6X28
Space Group	C121	C121	C121	C121
Unit Cell a, b, c, (Å), β	73.045, 84.443, 41.473, 106.73	73.841, 83.254, 41.474, 106.94	73.793, 83.504, 41.373, 106.78	73.189, 83.787, 41.408, 106.42
Wavelength (Å)	0.9719	0.97915	0.9715	0.9715
Resolution (Å)[1]	1.96	1.6	1.54	1.92
R_{sym} (%)[2]	8.5	7.1	5.8	9.8
$\langle I/\sigma I \rangle$[3]	22.9	27	11.2	14.3
Completeness (%)[4]	99.7	99.6	98.2	99.8
Redundancy	3.5	3.6	3.5	3.5
Refinement				
Resolution (Å)	29.04 to 2	26.93 to1.6	26.97 to 1.54	28.82 to 1.92
R-Factor (%)[5]	20.31	20.03	20.6	22.68
R_{free} (%)[6]	25.83	23.49	23.27	28.67
Protein atoms	1797	1797	1760	1771
Water Molecules	42	149	88	28
Unique Reflections	15467	29943	33105	17355
R.m.s.d.[7]				
Bonds	0.019	0.023	0.025	0.019
Angles	2.268	2.315	2.398	2.049
Clash Score	10	11	7	10
Ligand Statistics				
RSCC	0.94	0.939	0.972	0.934
RSR	0.109	0.11	0.103	0.13

[1]Statistics for highest resolution of bin of reflections in parentheses.

[2]$R_{sym} = \Sigma_h \Sigma_j | I_{hj} - \langle I_h | / = \Sigma_h \Sigma_j I_{hj}$, where I_{hj} is the intensity of observation j of reflection h and $\langle I_h \rangle$ is the mean intensity for multiply recorded reflections.

[3]Intensity signal to noise ratio.

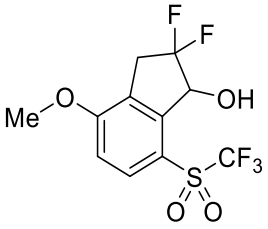
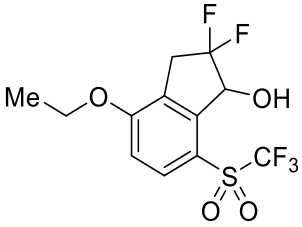
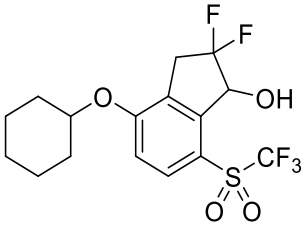
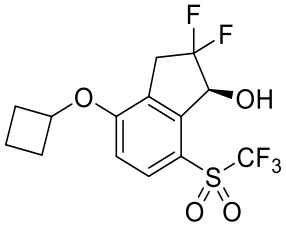
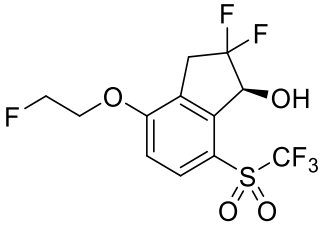
[4]Completeness of the unique diffraction data.

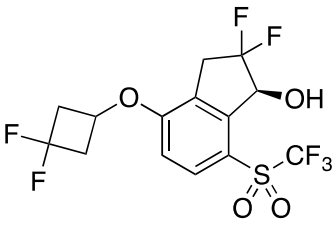
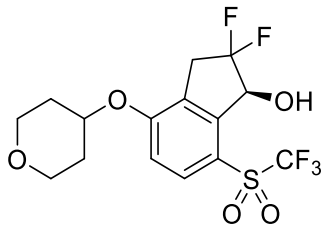
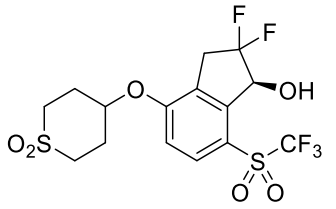
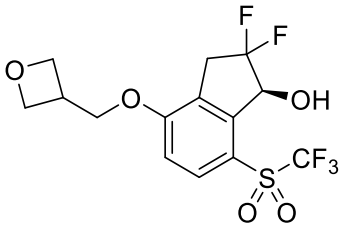
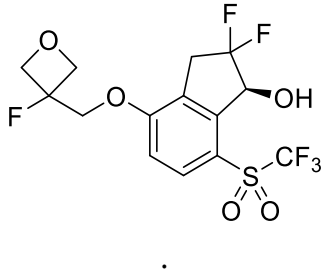
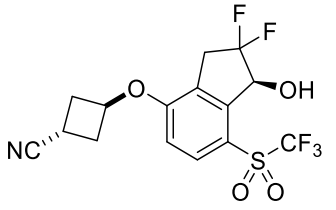
[5]R-factor = $\Sigma_h ||F_o| - |F_c|| / \Sigma_h |F_o|$, where F_o and F_c are the observed and calculated structure factor amplitudes for reflection h.

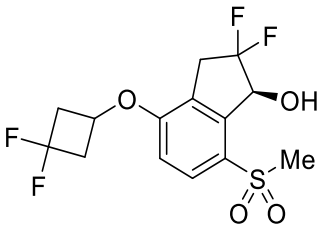
[6]R_{free} is calculated against a 5% random sampling of the reflections that were removed before structure refinement.

[7]Root mean square deviation of bond lengths and bond angles.

Table S2. Tabulated LCMS data for the library examples **1**-**5** and **7**-**13** were prepared in a similar fashion to **6** (see end note 8, data below).

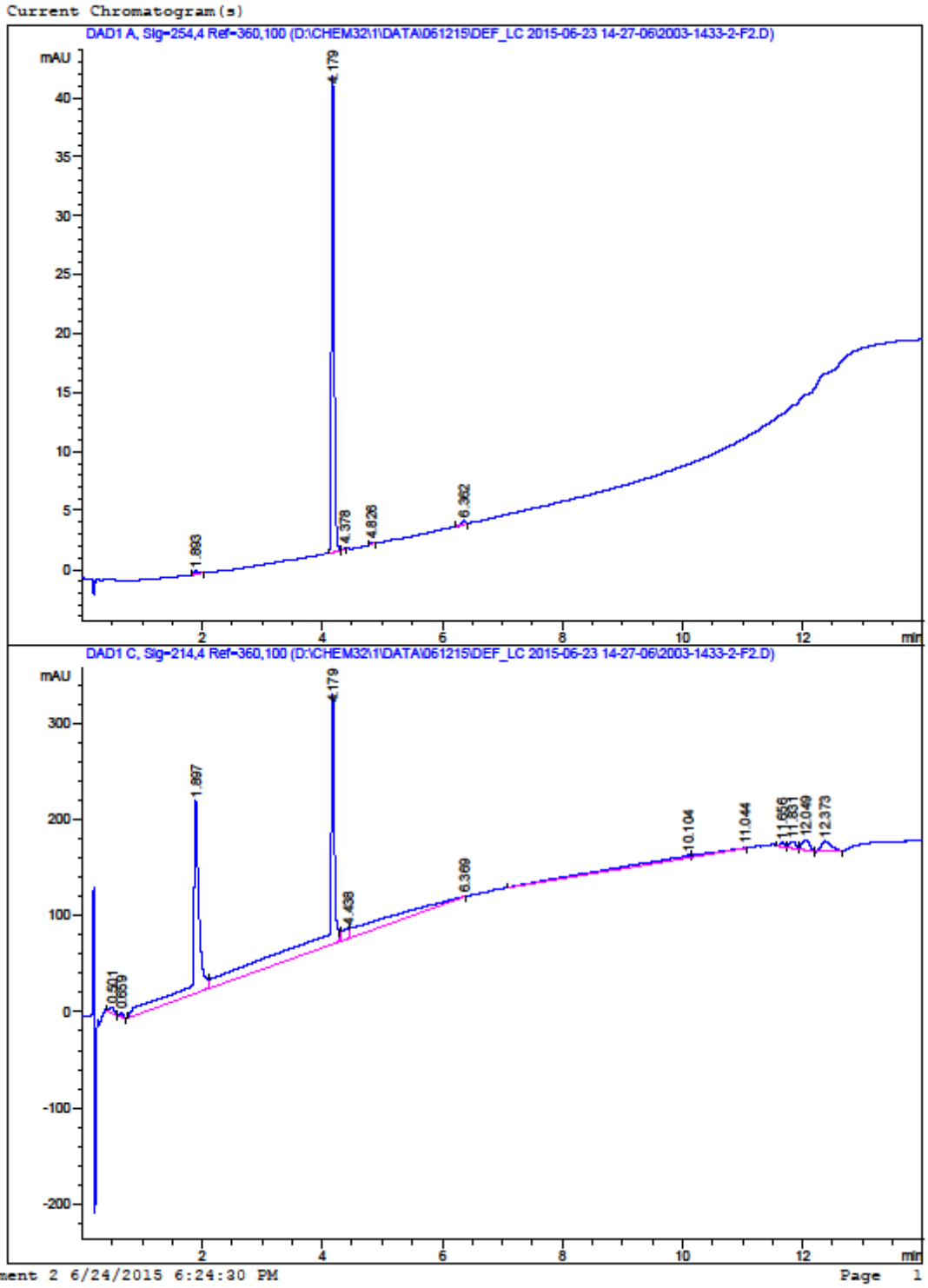
Example	Structure	IUPAC Name	Exact Mass $[M+H]^+$, $[M+NH_4]^+$, $[M-H]^-$, or $[M+HCO_2^-]$
1		2,2-difluoro-4-methoxy-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-1-ol	LCMS ESI (-) m/z 331 (M-H)
2		4-ethoxy-2,2-difluoro-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-1-ol	LCMS ESI (-) m/z 345 (M-H)
3		4-(cyclohexyloxy)-2,2-difluoro-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-1-ol	LCMS ESI (-) m/z 399 (M-H)
4		(S)-4-cyclobutoxy-2,2-difluoro-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-1-ol	LCMS ESI (-) m/z 371 (M-H)
5		(S)-2,2-difluoro-4-(2-fluoroethoxy)-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-1-ol	LCMS ESI (-) m/z: 363 (M-H)

7		(S)-4-(3,3-difluorocyclobutoxy)-2,2-difluoro-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-1-ol	LCMS ESI (-) m/z: 407 (M-H)
8		(S)-2,2-difluoro-4-((tetrahydro-2H-pyran-4-yl)oxy)-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-1-ol	LCMS ESI (+) m/z: 420 (M+NH_4)
9		(S)-4-((2,2-difluoro-1-hydroxy-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-4-yl)oxy)tetrahydro-2H-thiopyran 1,1-dioxide	LCMS ESI (-) m/z: 495 (M+HCO_2^-)
10		(S)-2,2-difluoro-4-(oxetan-3-ylmethoxy)-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-1-ol	LCMS ESI (-) m/z: 387 (M-H)
11		(S)-2,2-difluoro-4-((3-fluorooxetan-3-yl)methoxy)-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-1-ol	LCMS ESI (-) m/z 405 (M-H)
12		(trans)-3-(((S)-2,2-difluoro-1-hydroxy-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-4-yl)oxy)cyclobutane-1-carbonitrile	LCMS ESI (+) m/z: 415 (M+NH_4)

13		(S)-4-(3,3-difluorocyclobutoxy)-2,2-difluoro-7-(methylsulfonyl)-2,3-dihydro-1H-inden-1-ol	LCMS ESI (+) m/z: 355 (M+H)

HPLC Trace of Example 24 run from $CDCl_3$ NMR sample (1.897 min signal at 214 nm is $CDCl_3$)

Print of window 38: Current Chromatogram(s)



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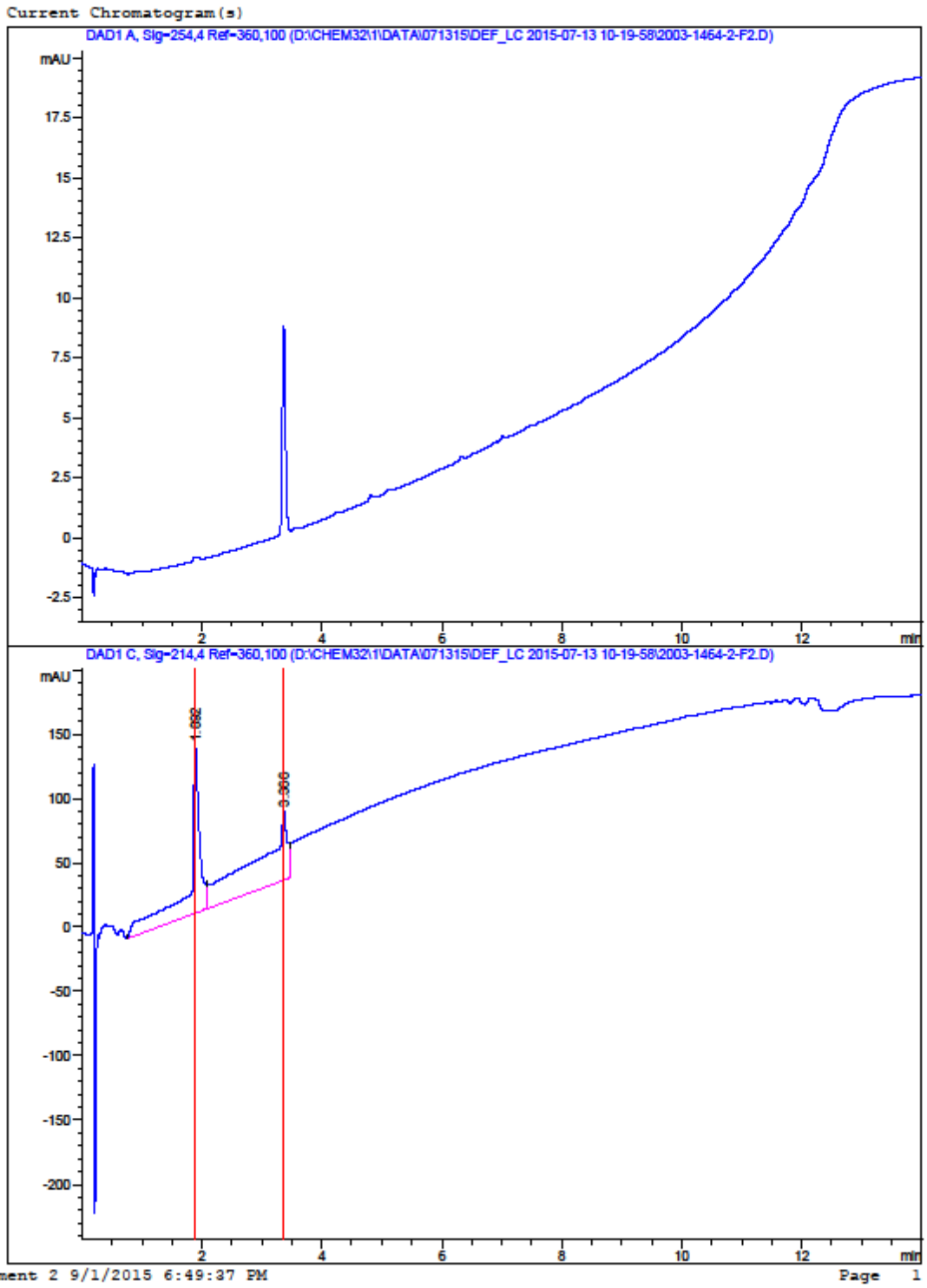
HPLC Trace of Example 27 run from $CDCl_3$ NMR sample (1.892 min signal at 214 nm is $CDCl_3$, due to low UV absorbance full NMR of 27 is included)

Print of window 38: Current Chromatogram(s)



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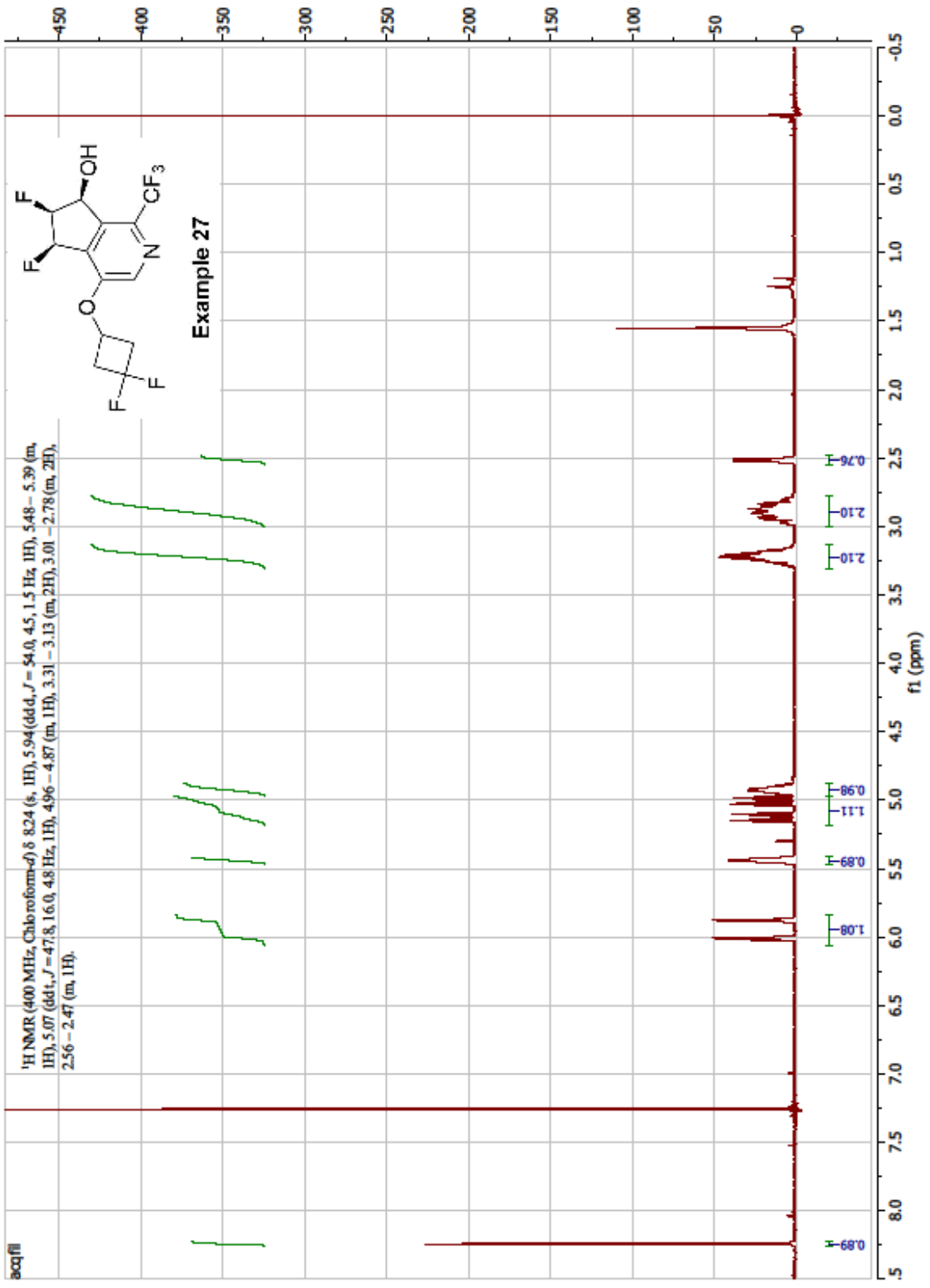
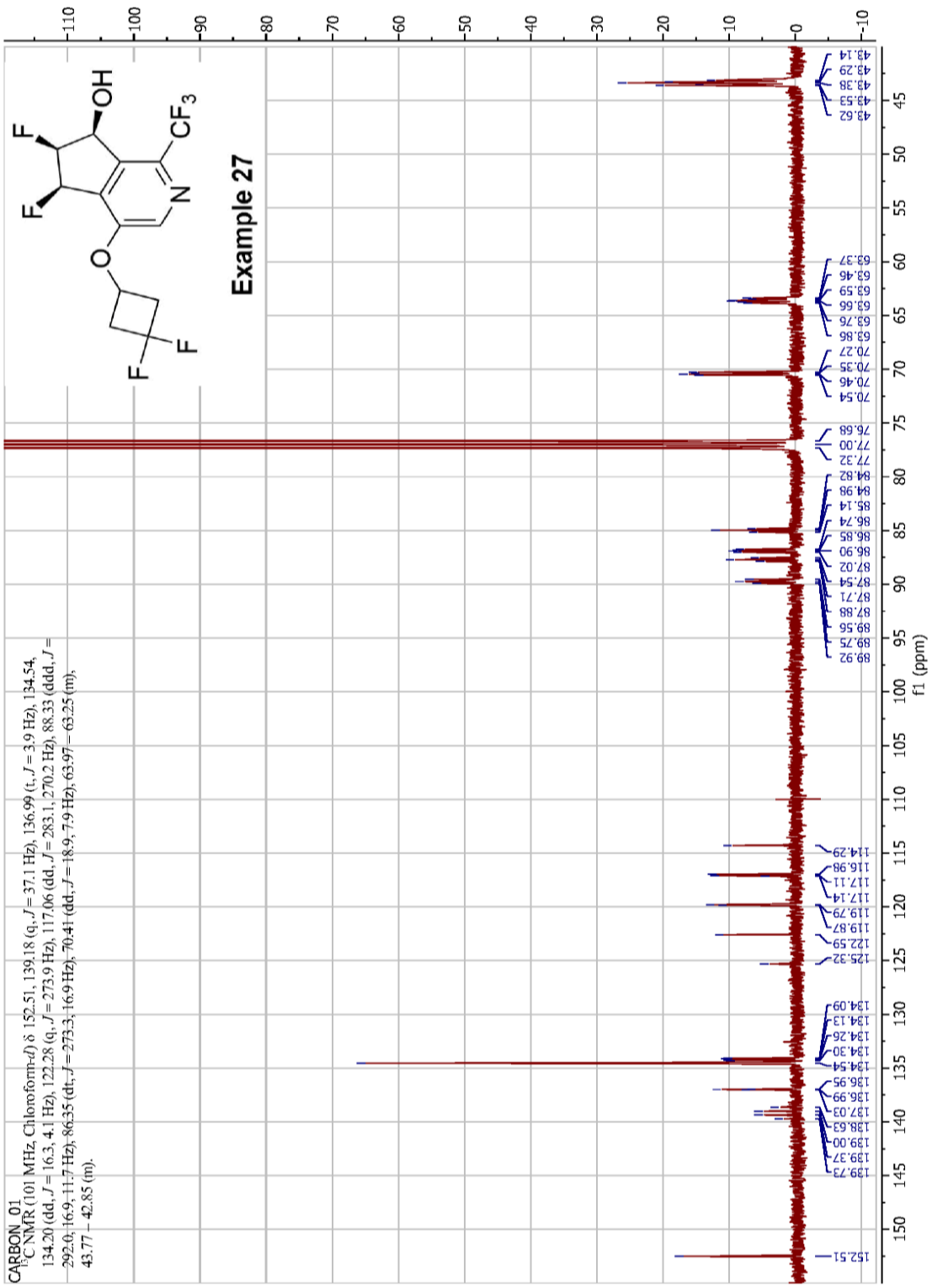
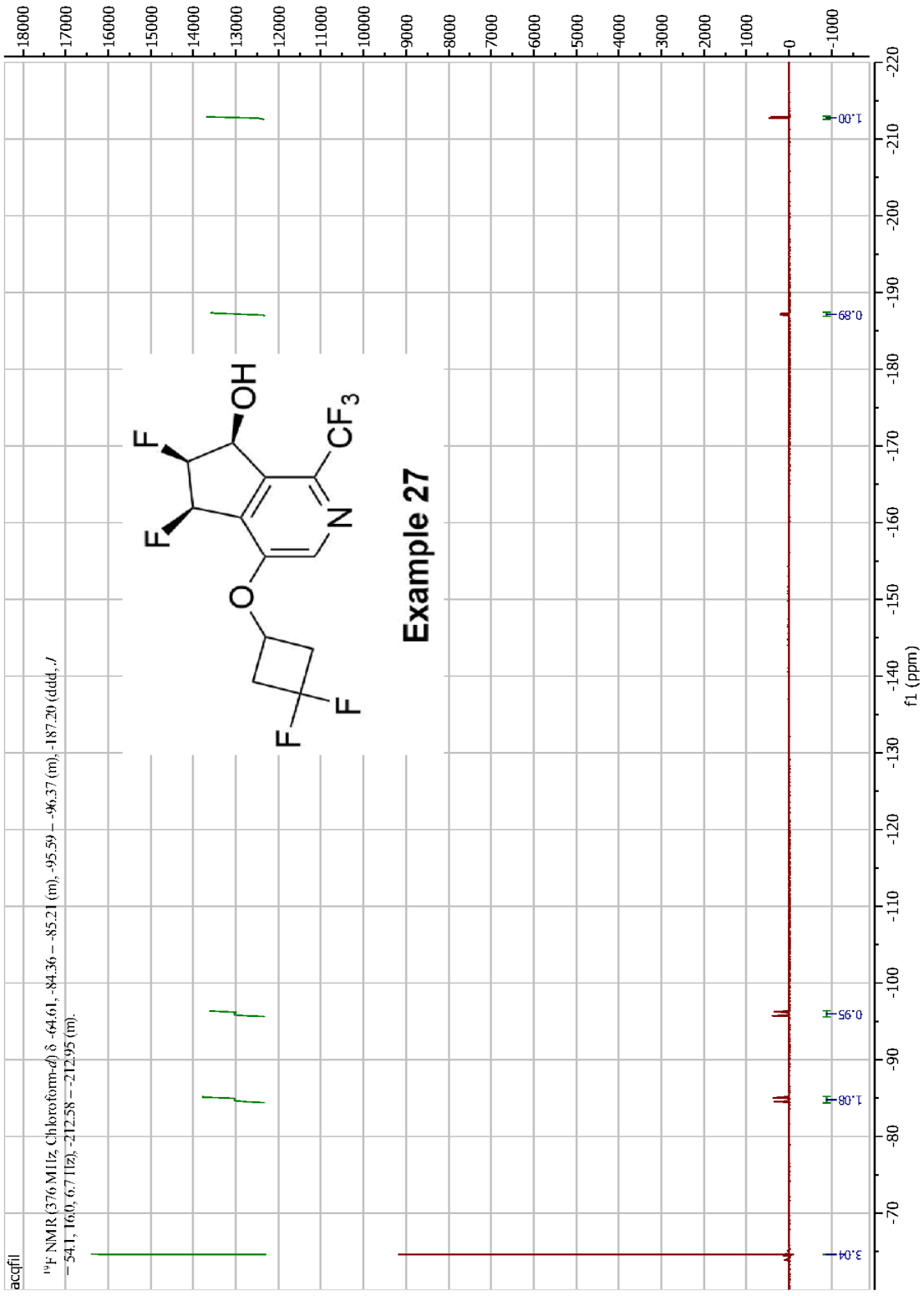
^{1}H NMR spectrum for example 27



^{13}C NMR spectrum for example 27



^{19}F NMR spectrum for example 27



Computational methods:

The complex coordinates of **7**, **12**, **13**, **14** were taken from co-crystal structures of HIF-2α. The residues Tyr281 was truncated to only keep the side chain and the Cα atom. All quantum mechanical (QM) calculations were performed with Gaussian 09[1] software package. The complex of 12 was optimized with the restraints on the Tyr281 atoms as well as heavy atoms of the inhibitors, at B3LYP[2,3]/6-31+G(d,p) level of theory. Single point calculations were performed on the optimized structures at MP2[4]/6-311++g(d,p) level of theory. Electro-potential surfaces (EPS) were generated with NBO calculation at M062x[5]/def2tzvpp level of theory and visualized with PyMoL[6] software package.

Atomic coordinates

12_complex

C	-5.07919	-3.57010	-0.17971
C	-4.77764	-2.36489	-0.77978
C	-3.63114	-1.66622	-0.47224
C	-2.73711	-2.16838	0.43355
O	-1.56886	-1.49471	0.72850
C	-3.00224	-3.37630	1.04543
C	-4.18479	-4.06366	0.72776
O	0.43999	-2.91464	0.92059
N	-4.70988	6.00309	-1.42779
C	-3.92964	5.26587	-0.98187
C	-2.97794	4.29871	-0.44425
C	-3.58282	3.05160	0.16570
C	-2.16767	3.48914	-1.44258
C	-2.46672	2.29985	-0.56644
O	-1.43837	2.11959	0.38551
C	-0.34792	1.35096	-0.02712
C	-0.18605	0.85134	-1.31598
C	0.90399	0.03922	-1.67999
C	0.55994	1.07656	0.90804
C	0.52935	1.58281	2.33369
C	1.97618	1.31021	2.76359
F	2.12997	0.96966	4.07996
F	2.75703	2.42922	2.55844
C	1.66104	0.29017	0.58672
C	2.44659	0.18960	1.83049
O	2.09370	-1.04204	2.40530
C	1.85278	-0.27775	-0.70861
S	3.07250	-1.32171	-1.10885
O	2.77200	-2.23561	-2.13893
O	3.52937	-1.86545	0.10024
C	4.30684	-0.25413	-1.78593
F	4.66390	0.69697	-0.89741
F	5.39734	-0.96300	-2.10811
F	3.85097	0.36280	-2.89304

H	-5.46402	-1.94762	-1.51462
H	-3.41206	-0.72655	-0.96975
H	-0.82581	-2.13277	0.84034
H	-2.30630	-3.78357	1.77222
H	-4.38109	-5.01307	1.22244
H	0.85631	-3.42335	0.21354
H	1.15092	-2.44965	1.40310
H	-2.32914	4.82027	0.26736
H	-4.57437	2.81823	-0.22782
H	-3.58097	2.96286	1.25238
H	-1.11768	3.75894	-1.56853
H	-2.64734	3.43075	-2.42404
H	-2.72506	1.34397	-1.03006
H	-0.91554	1.07158	-2.08499
H	0.97373	-0.35912	-2.68532
H	-0.17164	1.00293	2.94253
H	0.27221	2.64092	2.41378
H	3.53211	0.25463	1.68153
H	2.61029	-1.20203	3.20764
C	-6.33230	-4.38188	-0.55697
H	-6.11632	-5.07939	-1.37531
H	-6.68908	-4.96861	0.29484
H	-7.14670	-3.72808	-0.88452

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C	5.16139	-0.78104	0.39296
C	4.97889	-0.33220	-1.04177
C	3.95674	-1.70417	0.31972
C	3.58038	-0.94699	-0.92789
O	2.71595	0.12465	-0.61047
C	1.35356	-0.17858	-0.56502
C	0.83184	-1.45979	-0.71759
C	-0.55156	-1.71750	-0.71385
C	0.53122	0.85454	-0.39052
C	0.96095	2.28935	-0.17522
C	-0.33763	2.89655	0.37018
F	-0.47177	4.21148	0.05997
F	-0.41569	2.82178	1.70834
C	-0.84298	0.64202	-0.36494
C	-1.44100	1.97375	-0.15726
O	-1.82216	2.42293	-1.43198
C	-1.42891	-0.64542	-0.55530
S	-3.06916	-0.97064	-0.57493
O	-3.42026	-2.04685	-1.44668
O	-3.64508	0.29235	-0.99713
C	-3.49225	-1.37410	0.99235
F	-3.05980	-0.39055	1.71664

F	-4.81184	-1.39684	1.19587
F	-2.88678	-2.48866	1.36936
H	5.60039	-0.89049	-1.71032
H	4.93446	0.73420	-1.11734
H	3.26829	-1.51224	1.11602
H	4.24745	-2.70895	0.09435
H	3.12730	-1.48770	-1.73241
H	1.50801	-2.27962	-0.84241
H	-0.92217	-2.71451	-0.83015
H	1.17004	2.72971	-1.12773
H	1.69974	2.31205	0.59845
H	-2.26648	1.95534	0.52328
H	-2.61864	1.96365	-1.70818
F	6.35454	-1.34174	0.68364
F	5.19874	0.13850	1.38065

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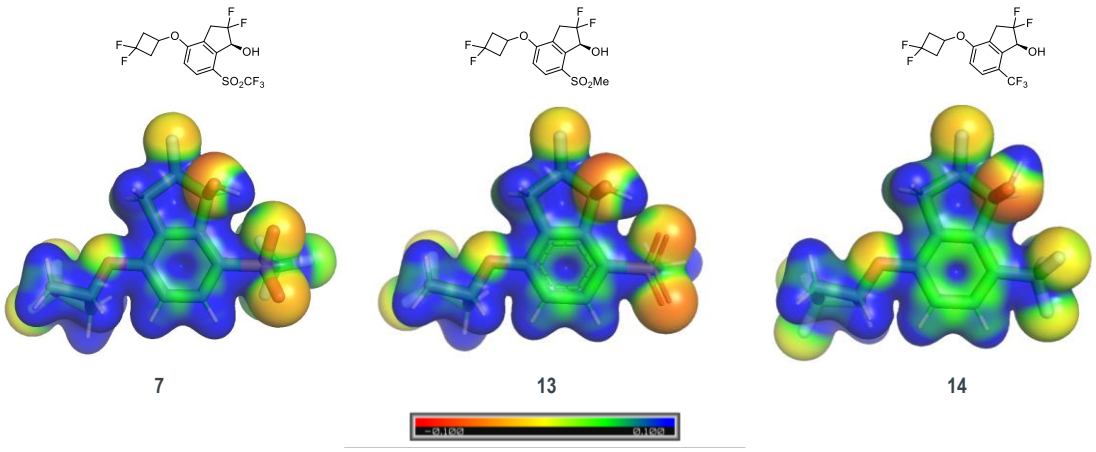
C	4.79676	-0.41727	0.27209
C	4.45423	-0.21144	-1.18857
C	3.69723	-1.45154	0.44539
C	3.14392	-0.93242	-0.85687
O	2.19617	0.08755	-0.61640
C	0.88251	-0.33391	-0.40013
C	0.49231	-1.66731	-0.31788
C	-0.85041	-2.05234	-0.14726
C	-0.03063	0.63044	-0.29892
C	0.25670	2.11570	-0.33272
C	-1.05300	2.67202	0.23969
F	-1.35286	3.90556	-0.24168
F	-1.01683	2.79460	1.57611
C	-1.36740	0.29406	-0.11411
C	-2.08797	1.57863	-0.04406
O	-2.61480	1.79018	-1.32845
C	-1.82353	-1.05734	-0.06217
S	-3.41530	-1.53686	0.11925
O	-3.71529	-2.76172	-0.55246
O	-4.15615	-0.41363	-0.42350
C	-3.66738	-1.73571	1.76091
H	5.07796	-0.80302	-1.82567
H	4.28869	0.82188	-1.41161
H	3.05692	-1.20731	1.26713
H	4.07645	-2.44652	0.33996
H	2.69014	-1.63000	-1.52945
H	1.24138	-2.42824	-0.38698
H	-1.11880	-3.08622	-0.08419
H	0.34115	2.42395	-1.35388
H	1.04733	2.32627	0.35682

H	-2.85040	1.58525	0.70664
H	-3.37609	1.22031	-1.45992
F	6.06282	-0.81071	0.52665
F	4.81195	0.64115	1.10994
H	-3.06052	-2.52918	2.14434
H	-4.70036	-1.82978	2.02356
H	-3.35439	-0.81164	2.20026

14

C	0.61264	-0.01572	-0.45361
C	0.40109	-1.39330	-0.48700
H	1.22826	-2.05767	-0.68898
C	-0.41844	0.80570	-0.17806
C	-0.38116	2.31711	-0.07619
H	-0.33381	2.79266	-1.05586
H	0.44936	2.66595	0.53755
C	-1.74038	2.53969	0.60960
H	-1.60319	2.58482	1.68996
F	-2.29644	3.75503	0.28691
C	-1.67056	0.27909	0.00860
C	-1.87634	-1.09833	-0.04961
C	-2.64174	1.35832	0.28429
H	-3.36165	1.12373	1.06840
O	-3.36554	1.64353	-0.93190
H	-4.01950	2.31662	-0.72949
C	-3.21794	-1.75450	0.18140
F	-3.18629	-3.03791	-0.08274
F	-4.20220	-1.21859	-0.50337
F	-3.47642	-1.65138	1.44604
O	1.83732	0.52898	-0.62339
C	2.94943	-0.32937	-0.73090
H	2.62696	-1.07592	-1.45667
C	3.45263	-0.76693	0.64743
H	3.43925	-1.84411	0.81354
H	2.97107	-0.26398	1.48608
C	4.22101	0.49053	-0.94561
H	4.08980	1.56670	-0.83283
H	4.73990	0.28388	-1.88164
C	4.81213	-0.20327	0.26949
F	5.69358	-1.13758	0.01435
F	5.34485	0.57058	1.16151
C	-0.82407	-1.90108	-0.26981
H	-0.96401	-2.96189	-0.27225

Electrostatic potential (ESP) surface:



Visualization of calculated ESP of **7**, **13** and **14**, **14** has smallest positive surface area in the aromatic center (blue).

General synthesis of 1-13 as illustrated by (*S*)-4-(2,2-difluoroethoxy)-2,2-difluoro-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1*H*-inden-1-ol (6). *Step A: Preparation of 4-fluoro-7-((trifluoromethyl)sulfonyl)-2,3-dihydrospiro[indene-1,2'-[1,3]dioxolane] (**30**).* Trimethylsily trifluoromethanesulfonate (10.6 g, 47.8 mmol) was added dropwise to a solution of 4-fluoro-7-(trifluoromethylsulfonyl)indan-1-one (**29**)[7] (27.0 g, 95.7 mmol) and trimethyl(2-trimethylsiilyloxyethoxy)silane (23.7 g, 114.8 mmol) in dichloromethane (500 mL) at -78 °C. The reaction mixture was allowed to warm to ambient temperature and stirred at ambient temperature for 2 hours. The reaction was then quenched with excess triethyl amine. The volatiles were removed under reduced pressure. The residue was taken up in ethyl acetate (500 mL) and organics were washed with water, brine dried (sodium sulfate), filtered and concentrated under reduced pressure. The residue obtained was purified by flash chromatography on silica gel 4:1 hexane/ethyl acetate to give 4-fluoro-7-((trifluoromethyl)sulfonyl)-2,3-dihydrospiro[indene-1,2'-[1,3]dioxolane] (25.0 g, 80%) as solid.

Step B[8]: Preparation of 4-((4-methoxybenzyl)oxy)-7-((trifluoromethyl)sulfonyl)-2,3-dihydrospiro[indene-1,2'-[1,3]dioxolane]. A solution of 4'-fluoro-7'-(trifluoromethylsulfonyl)spiro[1,3-dioxolane-2,1'-indane] (**30**) (1.0 g, 3.07 mmol) and 4-methoxybenzyl alcohol (760 µL, 6.13 mmol) in acetonitrile (9.3 mL) at 25 °C was treated with potassium hydroxide (516 mg, 9.2 mmol) and stirred at 25 °C for 1.5 h. The reaction mixture was poured into 150 mL of water and extracted with 3 x 40 mL EtOAc. The combined organics were rinsed with 20 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 10-25% EtOAc/hexane to afford 4-((4-methoxybenzyl)oxy)-7-((trifluoromethyl)sulfonyl)-2,3-dihydrospiro[indene-1,2'-[1,3]dioxolane] as a solid (1.08 g, 79%). LCMS ESI (+) $[M+H]^+$ m/z 445.

*Step C: Preparation of 4-((4-methoxybenzyl)oxy)-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-1-one (**31**).* In a glass pressure vessel, a solution of 4'-[(4-methoxyphenyl)methoxy]-7'-(trifluoromethylsulfonyl)spiro[1,3-dioxolane-2,1'-indane] (1.08 g, 2.43 mmol) in a mixture acetone (20 mL) and water (20 mL) was treated with pyridinium p-toluenesulfonate (122.1 mg, 0.49 mmol), sealed and stirred at 80 °C overnight. Volatiles were removed by concentration under reduced pressure. The residue was poured into 40 mL of saturated aqueous $NaHCO_3$ and extracted with 3 x 50 mL EtOAc. The combined organics were rinsed with 30 mL of brine, dried with $MgSO_4$,

filtered, and concentrated to dryness. The product was used without further purificaction. LCMS ESI (+) $[M+H]^+$ m/z 401.

Step D: Preparation of 2,2-difluoro-4-((4-methoxybenzyl)oxy)-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-1-one. 2,2-dimethylpropanoic acid (50 mg, 0.46 mmol) was added to a flask containing a suspension of 4-[(4-methoxyphenyl)methoxy]-7-(trifluoromethylsulfonyl)indan-1-one (**31**) (922 mg, 2.3 mmol) and 3-methoxypropan-1-amine (0.35 mL, 3.45 mmol) in a mixture of toluene (14 mL) and cyclohexane (14 mL). This was refluxed with a Dean-Stark trap attached at 104 ^oC. After 2.5 h, the reaction mixture was cooled and volatiles removed by concentration under reduced pressure. The residue was dissolved in acetonitrile (24 mL) and treated sequentially with sodium sulfate (850 mg, 6.0 mmol) and and 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate (2.13g, 6.0 mmol). The resulting suspension stirred at 60 ^oC for 2 h. After cooling to room temperature, the reaction mixture was treated with concentrated hydrochloric acid (600 uL, 7.2 mmol) and water (10 mL). The resulting mixture stirred for 20 min. Volatiles were removed by concentration under reduced pressure. The reaction mixture was poured into 20 mL of water and extracted with 3 x 30 mL EtOAc. The combined organics were rinsed with 20 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 5-40% EtOAc/hexane to afford 2,2-difluoro-4-((4-methoxybenzyl)oxy)-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1*H*-inden-1-one as a solid (520 mg, 50%). LCMS ESI (+) $[M+H]^+$ m/z 437.

*Step E: Preparation of (S)-2,2-difluoro-4-((4-methoxybenzyl)oxy)-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-1-ol (**32**).* A solution of 2,2-difluoro-4-[(4-methoxyphenyl)methoxy]-7-(trifluoromethylsulfonyl)indan-1-one (520 mg, 1.19 mmol) in dichloromethane (11.9 mL) was cooled to 0 ^oC and sparged with nitrogen for 5 minutes. During this time, formic acid (130 µL, 3.58 mmol) and triethylamine (330 uL, 2.38 mmol) were sequentially added. Once the sparging was complete, RuCl(p-cymene)[(*R*,*R*)-Ts-DPEN] (22.8 mg, 0.036 mmol) was added under a continuous stream of nitrogen. The reaction vessel was sealed and put into the refrigerator to react overnight. Once complete, the reaction mixture was poured into 30 mL of saturated aqueous $NaHCO_3$ and extracted with 3 x 30 mL CH_2Cl_2. The combined organics were

rinsed with 20 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 10-40% EtOAc/hexane to afford (*S*)-2,2-difluoro-4-((4-methoxybenzyl)oxy)-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1*H*-inden-1-ol as a solid (370 mg, 71%). LCMS ESI (+) $[M+NH_4]^+$ m/z 456.

Step F: Preparation of (S)-tert-butyl((2,2-difluoro-4-((4-methoxybenzyl)oxy)-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-1-yl)oxy)dimethylsilane. A solution of (*S*)-2,2-difluoro-4-[(4-methoxyphenyl)methoxy]-7-(trifluoromethylsulfonyl)indan-1-ol (**32**) (370 mg, 0.84 mmol) and 2,6-lutidine (780 μL, 7.76 mmol) in dichloromethane (8.4 mL) at -78 °C was treated with tert-butyldimethylsilyl trifluoromethanesulfonate (980 μL, 4.22 mmol) and allowed to warm to room temperature over 2 h. The reaction mixture was poured into 30 mL of saturated aqueous $NaHCO_3$ and extracted with 3 x 20 mL CH_2Cl_2. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 5-20% EtOAc/hexane to afford (*S*)-*tert*-butyl((2,2-difluoro-4-((4-methoxybenzyl)oxy)-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1*H*-inden-1-yl)oxy)dimethylsilane (460 mg, quant). LCMS ESI (-) $[M-H]^-$ m/z 551.

*Step G: Preparation of (S)-1-((tert-butyldimethylsilyl)oxy)-2,2-difluoro-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-4-ol (**33**).* A solution of tert-butyl-[(1S)-2,2-difluoro-4-[(4-methoxyphenyl)methoxy]-7-(trifluoromethylsulfonyl)indan-1-yl]oxy-dimethyl-silane (460 mg, 0.83 mmol) in dichloromethane (3.0 mL) at 25 °C was treated with trifluoroacetic acid (3.0 mL) and stirred at 25 °C. After 1 h, volatiles were removed by concentration under reduced pressure. To the resulting residue was added 6 mL of toluene and the organic volatiles were once again removed by concentration under reduced pressure. This process was repeated twice. Purification was achieved by chromatography on reverse phase by injection of a DMF solution of the product residue. 40-100% CH_3CN/Water was used as eluent. (*S*)-1-((*tert*-butyldimethylsilyl)oxy)-2,2-difluoro-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1*H*-inden-4-ol was isolated a thick orange oil (236 mg, 89%). LCMS ESI (-) $[M-H]^-$ m/z 431.

*Step H: Preparation of (S)-4-(2,2-difluoroethoxy)-2,2-difluoro-7-((trifluoromethyl)sulfonyl)-2,3-dihydro-1H-inden-1-ol (**6**).* A solution of (1S)-1-[tert-butyl(dimethyl)silyl]oxy-2,2-difluoro-7-(trifluoromethylsulfonyl)indan-4-ol (**33**) (20.2

mg, 0.047 mmol), triphenylphosphine (25.7 mg, 0.093 mmol), and 2,2-difluoroethanol (11.8 μL, 0.19 mmol) in tetrahydrofuran (0.5 mL) at 25 °C was treated with diisopropyl azodicarboxylate (18.3 μL, 0.093 mmol). After stirring overnight, to the reaction mixture was added sequentially acetic acid (8.0 μL, 0.14 mmol) and tetrabutylammonium fluoride (1.0 M in THF, 7.0 μL, 0.07 mmol). The resulting mixture was heated to 60 °C for 2 h. The reaction mixture was poured into 30 mL of water containing 1 mL of saturated aqueous $NaHCO_3$ and extracted with 3 x 20 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 1-10% EtOAc/CH_2Cl_2 to afford **6** as a clear solid (7.1 mg, 40%). Retention time HPLC (14 min) = 4.95 min; LCMS ESI (-) $[M-H]^-$ m/z 381; ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.7 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 6.15 (tt, J = 54.5, 3.9 Hz, 1H), 5.38 (dd, J = 13.5, 3.8 Hz, 1H), 4.44-4.29 (m, 2H), 3.58 – 3.36 (m, 2H), 3.16 (d, J = 3.8 Hz, 1H).

The remaining examples **1-5** and **7-13** were prepared in a similar fashion to **6** by substituting 2,2-difluoroethanol with the appropriate alcohol for the Mitsunobu reaction in Step H. Tabulated LCMS data for this library can be found in the supporting information.

General synthesis of 14 as illustrated by (*S*)-4-(2,2-difluoroethoxy)-2,2-difluoro-7-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-ol. *Step A: Preparation of 4-(2,2-difluoroethoxy)-2,3-dihydro-1H-inden-1-one.* Diisopropyl azodicarboxylate (0.80 mL, 4.05 mmol) was added dropwise to an ice-cold solution of 4-hydroxyindan-1-one (**34**) (500 mg, 0.37 mmol), triphenylphosphine (974 mg, 3.71 mmol), and 2,2-difluoroethanol (0.26 mL, 4.05 mmol) in tetrahydrofuran (20 mL). The mixture was allowed to stir overnight at 50 °C. The reaction mixture was evaporated and the residue was partitioned between EtOAc and water. The EtOAc was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on a Biotage 100 g SNAP column with a 20% to 80% EtOAc:hexane gradient to afford 4-(2,2-difluoroethoxy)-2,3-dihydro-1*H*-inden-1-one (610 mg, 2.87 mmol, 85% yield) as a pale yellow crystalline solid.

Step B: Preparation of 4-(2,2-difluoroethoxy)-7-iodo-2,3-dihydro-1H-inden-1-one. 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (1020 mg, 2.87 mmol) was added to an ice-cold solution of iodine (802 mg, 3.16 mmol) in acetonitrile (30 mL). This was stirred at 0 °C for a few minutes, then 4-(2,2-difluoroethoxy)-2,3-dihydro-1*H*-inden-1-

one (610 mg, 2.87 mmol) was added. The resulting mixture was stirred at ambient temperature for 4 h. The reaction mixture was evaporated partitioned between EtOAc and dilute aqueous sodium thiosulfate. The EtOAc was washed with aqueous sodium thiosulfate, brine, dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on a Biotage 25 g SNAP column with a 5% to 50% EtOAc:hexane gradient to afford 4-(2,2-difluoroethoxy)-7-iodo-2,3-dihydro-1*H*-inden-1-one (660 mg, 1.95 mmol, 67.9 % yield).

Step C: Preparation of 4-(2,2-difluoroethoxy)-2,2-difluoro-7-iodo-2,3-dihydro-1H-inden-1-one. Pivalic acid (100 mg, 0.98 mmol) was added to a mixture of 4-(2,2-difluoroethoxy)-7-iodo-2,3-dihydro-1*H*-inden-1-one (660 mg, 1.95 mmol) and 3-methoxypropylamine (1.00 mL, 9.76 mmol) in cyclohexane (10 mL) and toluene (50 mL). The mixture was refluxed with a Dean-Stark trap attached for a total of 9 h, then stirred at ambient temperature overnight. The reaction mixture was evaporated and the intermediate imine was dissolved in acetonitrile (20 mL) and treated sequentially with sodium sulfate (275 mg, 1.94 mmol) and 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (1493 mg, 4.03 mmol). The mixture was heated at 70 ^{o}C. After 1 h, the cooled reaction mixture was treated with 1M HCl (5.65 mL, 5.65 mmol) and stirred at room temperature for 10 minutes. The reaction mixture was evaporated and the residue was partitioned between EtOAc and water. The EtOAc was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on a Biotage 50 g SNAP column with a 5% to 60% EtOAc:hexane followed by a reverse phase separation on a Biotage 25+ column with a 20% to 80% acetonitrile:water gradient to afford 4-(2,2-difluoroethoxy)-2,2-difluoro-7-iodo-2,3-dihydro-1*H*-inden-1-one (190 mg, 0.51 mmol, 32% yield over 2 steps).

Step D: Preparation of 4-(2,2-difluoroethoxy)-2,2-difluoro-7-(trifluoromethyl)-2,3-dihydro-1H-inden-1-one. Methyl 2,2-difluoro-2-fluorosulfonyl-acetate (0.10 mL, 0.80mmol) was added to a vial containing 4-(2,2-difluoroethoxy)-2,2-difluoro-7-iodo-2,3-dihydro-1*H*-inden-1-one (60.0 mg, 0.160 mmol) and copper(I) iodide (61.1 mg, 0.320 mmol) in DMF (2 mL). The sealed vial was heated at 100 ^{o}C. After 2 h, the vial was carefully vented, and the reaction mixture was partitioned between EtOAc and water. The EtOAc was washed with 2 portions of brine, dried over $MgSO_4$, filtered, and evaporated to afford 4-(2,2-difluoroethoxy)-2,2-difluoro-7-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-one (50 mg, 0.158 mmol, 99 % yield). *m/z* (ES-API-pos) $[M+H]^+$ 317.

Step F: Preparation of (S)-4-(2,2-difluoroethoxy)-2,2-difluoro-7-(trifluoromethyl)-2,3-dihydro-1H-inden-1-ol. To an ice cold solution of 4-(2,2-difluoroethoxy)-2,2-difluoro-7-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-one (50 mg, 0.158 mmol) in dichloromethane (10 mL)

sparged with nitrogen, was added, formic acid (0.02 mL, 0.630mmol) and triethylamine (0.06 mL, 0.40 mmol). After more nitrogen sparging, RuCl(p-cymene)[(R,R)-Ts-DPEN] (3.02 mg, 0.0048mmol) was added, the flask was sealed with a septum, and placed in a 4 ^{o}C refrigerator overnight. The reaction mixture was evaporated and the residue was chromatographed on a Biotage 10 g Ultra SNAP column with a 10% to 80% EtOAc:hexane to afford (*S*)-4-(2,2-difluoroethoxy)-2,2-difluoro-7-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-ol (39.9 mg, 0.125 mmol, 79% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 1H), 6.89 (d, 1H), 6.11 (tt, 1H), 5.25-5.20 (m, 1H), 4.33-4.20 (m, 2H), 3.50-3.30 (m, 2H), 2.62-2.59 (m, 1H); m/z (ES-API-neg) [M+HCO_2^-] 363.

(*S*)-4-(3,3-difluorocyclobutoxy)-2,2-difluoro-7-(trifluoromethyl)-2,3-dihydro-1H-inden-1-ol (14). The procedure for the synthesis of (*S*)-4-(2,2-difluoroethoxy)-2,2-difluoro-7-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-ol, in the **General synthesis of 14**, was followed. 3,3-difluorocyclobutanol was used in place of 2,2-difluoroethanol in Step A. Characterization data for **14**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 8.5 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 5.24 (dd, *J* = 11.8, 5.0 Hz, 1H), 4.79 – 4.65 (m, 1H), 3.51 – 3.27 (m, 2H), 3.22 – 3.07 (m, 2H), 2.78 (tdd, *J* = 14.8, 13.0, 5.3 Hz, 2H), 2.46 (dd, *J* = 4.9, 2.0 Hz, 1H); LCMS ESI (-) m/z 389 (M+HCO_2^-).

(*R*)-4-(3,5-Difluorophenoxy)-7-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-ol (18). *Step A: 4-Fluoro-7-(trifluoromethyl)indan-1-one.* A solution of 7-bromo-4-fluoro-indan-1-one (**36**) (1.00 g, 4.37 mmol) in DMF (15 mL) in a microwave vial was treated with copper(I) iodide (1.66 g, 8.73 mmol) and methyl 2,2-difluoro-2-fluorosulfonyl-acetate (2.78 mL, 21.8 mmol). The vial was sealed and heated in a heating bath at 100 ^{o}C overnight. CAUTION: Pressure buildup from released CO_2 is likely. Additional aliquots of methyl 2,2-difluoro-2-sulfonylacetate and CuI were added, the vial was resealed, and heating continued for another 24 hours. The reaction mixture was diluted with water and EtOAc, filtered through celite, and the layers separated. The EtOAc was washed with water, brine, dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on a Biotage 50 g SNAP column with a 10% to 60% dichloromethane:hexane gradient to give 4-fluoro-7-(trifluoromethyl)indan-1-one (209 mg, 0.96 mmol, 22% yield) as a tan solid.

Step B: (1R)-4-fluoro-7-(trifluoromethyl)indan-1-ol. To a solution of 4-fluoro-7-(trifluoromethyl)indan-1-one (209 mg, 0.96 mmol) in dichloromethane (7 mL) was added formic acid (0.05 mL, 1.2 mmol) and triethylamine (0.15 mL, 1.05 mmol). The reaction mixture was sparged with nitrogen and RuCl(p-cymene)[(*R*,*R*)-Ts-DPEN] (12.2 mg, 0.02 mmol) was added in one portion. The reaction mixture was stirred at room temperature overnight under nitrogen. The

solvent was evaporated and the residue was chromatographed on a Biotage 25 g SNAP column with a 5% to 30% EtOAc:hexane gradient to give (1*R*)-4-fluoro-7-(trifluoromethyl)indan-1-ol (169 mg, 0.77 mmol, 80% yield) as a tan solid. Mosher ester analysis (^{1}H NMR ($CDCl_3$)) of the methoxy signal integrations indicated a 90 % enantiomeric excess.

*Step C: (R)-4-(3,5-Difluorophenoxy)-7-(trifluoromethyl)-2,3-dihydro-1H-inden-1-ol **(18)**.* 3,5-Difluorophenol (13 mg, 0.10 mmol) was added to a mixture of (1*R*)-4-fluoro-7-(trifluoromethyl)indan-1-ol (21 mg, 0.10 mmol) and cesium carbonate (46.6 mg, 0.14 mmol) in DMF (0.5 mL) in a vial. The vial was sealed and heated at 135 ^{o}C for 24 hours. The reaction mixture was partitioned between EtOAc and 0.3 M aqueous NaOH. The EtOAc was washed with dilute aqueous NaOH, water, brine, dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on a Biotage 10 g SNAP column with a 5% to 40% EtOAc:hexane gradient to give an impure product. This was rechromatographed on a Biotage 10 g SNAP column with a 5% to 30% EtOAc:hexane gradient followed by re-chromatographing on a Biotage 12M RP column with a 20% to 90% acetonitrile:water gradient to give (*R*)-4-(3,5-difluorophenoxy)-7-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-ol (**18**) (2.4 mg, 0.007 mmol, 8% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ δ 7.55 – 7.48 (m, 1H), 7.00 – 6.93 (m, 1H), 6.58 (tt, J = 8.9, 2.3 Hz, 1H), 6.53 – 6.45 (m, 2H), 5.53 (s, 1H), 3.06 (dt, J = 16.3, 7.9 Hz, 1H), 2.80 (ddd, J = 16.7, 8.7, 2.6 Hz, 1H), 2.41 – 2.30 (m, 1H), 2.27 – 2.16 (m, 1H), 2.04 (s, 1H). *m/z* (ES-API-neg) [M-H] = 329.0.

3-fluoro-5-(((6*R*,7*S*)-6-fluoro-7-hydroxy-1-(methylsulfonyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-4-yl)oxy)benzonitrile (20). *Step A: Preparation of 5-bromo-2-(methylthio)nicotinic acid.* A solution of 5-bromo-2-fluoro-pyridine-3-carboxylic acid (**37**) (3.50 g, 15.91 mmol) in DMF (62 mL) at 0 ^{o}C was treated with potassium carbonate (2.42 g, 17.5 mmol) and vigorously stirred at 0 ^{o}C for 7 minutes. During this time, nitrogen was sparged through the solution. Then sodium thiomethoxide (1.23 g, 16.7 mmol) was added in one portion to the reaction vessel under continuous nitrogen stream. The reaction vessel was sealed and the ice bath removed. The solution turned from a tan color to faint yellow. The reaction mixture was left to stir overnight. The reaction mixture was poured onto 10% citirc acid solution inducing precipitation of a white solid. The solid was filtered and rinsed exhausitvely with water. Finally, the white solid was dried overnight under high vacuum in the presence of solid NaOH and used without further purification (3.63 g, 92%). LCMS ESI (+) (M+H) m/z 248 / 250.

Step B: Preparation of 5-bromo-4-formyl-2-(methylthio)nicotinic acid. A solution of 2,2,6,6-tetramethyl-piperidine (3.26 mL, 19.35 mmol) in tetrahydrofuran (40.3 mL) at -50 C

was treated with n-butyllithium (~2.5M in hexanes, 7.09 mL, 17.73 mmol) and stirred for 5 min. Then 5-bromo-2-methylsulfanyl-pyridine-3-carboxylic acid (2.00 g, 8.06 mmol) was added via cannula over 30 min as a solution in 60 mL of THF. The resulting mixture stirred for 30 min at -50 C. The reaction mixture was quenched by the addition of *N,N*-dimethylformamide (0.94 mL, 12.09 mmol). 15 minutes following addition of the DMF, the reaction mixture was quenched by the addition of 40 mL of 10% citiric acid solution (aqueous) and the reaction warmed to room temperature. After stirring for 30 min, excess THF removed by concentration under reduced pressure. The leftover mixture was poured into 120 mL of 3% citric acid (aqueous) and extracted with 3 x 50 mL EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated to dryness. 2.41 g of an orange solid was isolated and used without further purification. The material was contaminated with about 22% citric acid based on proton integration of the unpurified NMR spectra. LCMS ESI (+) (M+H) m/z 276 / 278.

*Step C: Preparation of methyl (E)-5-bromo-4-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-(methylthio)nicotinate (**38**).* A solution of 7-bromo-1-hydroxy-4-methylsulfanyl-1H-furo[3,4-c]pyridin-3-one (2.21 g, 8.00 mmol), lithium chloride (anhydrous, 339.1 mg, 8.00 mmol) and ethyl 2-diethoxyphosphorylacetate (1.60 mL, 8.00 mmol) in acetonitrile (80 mL) at 25 C was treated with 1;8-Diazabicyclo[5.4.0]undec-7-ene (2.87 mL, 19.20 mmol) and stirred at 25 C for 2 h. Initially, the solution is heterogenous with the pyridine being insoluble. Upon addition of the DBU, the solution becomes homogenous and darkens in color. After 1 h, the reaction appears to be mostly complete with formation of a precipitate. Volatiles were removed by concentration under reduced pressure. The product residue was solubilized with 25 mL of DMF and treated with dimethyl sulfate (1.89 mL, 20.00 mmol). After 2 h, the reaction mixture was poured into 300 mL of water and extracted with 4 x 40 mL Et_2O. The combined organics were rinsed with 20 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 5-20% EtOAc/hexane to afford methyl (*E*)-5-bromo-4-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-(methylthio)nicotinate as a white solid (1.90 g, 66%). LCMS ESI (+) (M+H) m/z 360 / 362.

Step D: Preparation of methyl 5-bromo-4-(3-ethoxy-3-oxopropyl)-2-(methylthio)nicotinate. A solution of methyl 5-bromo-4-[(E)-3-ethoxy-3-oxo-prop-1-enyl]-2-methylsulfanyl-pyridine-3-carboxylate (**38**) (1.87 g, 5.19 mmol) and cobalt(II) chloride hexahydrate (123.5 mg, 0.52 mmol) in methanol (20.8 mL) at 0 ^oC was sparged with nitrogen for 3 min and treated with sodium borohydride (98.2 mg, 2.60 mmol) under

continuous nitrogen stream. The vessel was sealed and the contents stirred at 0 ^{o}C for 10 min. LCMS at this time indicated partial consumption of the olefin. An additional portion of sodium borohydride (98.2 mg, 2.60 mmol) was added to drive the reaction to completion. The reaction mixture was quenched by the addition of 30 mL of saturated aqueous NH_4Cl. Volatiles were removed by concentration under reduced pressure. The reaction mixture was poured into 30 mL of water and extracted with 3 x 40 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 5-15% EtOAc/hexane to afford the desired product as a solid (1.08 g, 57%). LCMS ESI (+) (M+H) m/z 362 / 364.

Step E: Preparation of ethyl 4-bromo-1-(methylthio)-5,6-dihydro-7H-cyclopenta[c]pyridin-7-one. A solution of methyl 5-bromo-4-(3-ethoxy-3-oxo-propyl)-2-methylsulfanyl-pyridine-3-carboxylate (1.08 g, 2.98 mmol) in tetrahydrofuran (29.8 mL) at -78 ^{o}C was treated with lithium bis(trimethylsilyl)amide (~1.0 M in THF, 7.16 mL, 7.16 mmol) by dropwise addition over 30 minutes. Once the addition was complete, LCMS indicated a small amount of starting material remained so an additional 1 mL of lithium bis(trimethylsilyl)amide solution was added and the reaction allowed to stir for a further 15 minutes. The reaction mixture was quenched by the addition of 30 mL of saturated aqueous NH_4Cl. THF was removed by concentration under reduced pressure. The reaction mixture diluted with 60 mL of EtOAc and an additional 30 mL of water. A thick precipitate formed that could be eliminated by the addition of 10% citric acid solution. The reaction mixture was extracted with 3 x 30 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The intermediate product was transferred into a microwave tube using 9.1 mL of DMSO. The resulting mixtre was diluted with 900 uL of water. The vessel was sealed and heated to 150 ^{o}C by microwave irradiation for 40 min. The reaction mixture was diluted with 120 mL of water to induce precipitation of the product and vigorously stirred for 30 min. The precipitate was collected, dried overnight under high vacuum in the presence of solid NaOH, and used without further purification. Beige solid (705 mg, 92%). LCMS ESI (+) (M+H) m/z 258 / 260.

*Step F: Preparation of 4-bromo-1-(methylsulfonyl)-5,6-dihydro-7H-cyclopenta[c]pyridin-7-one (**39**).* A solution of 4-bromo-1-methylsulfanyl-5,6-dihydrocyclopenta[c]pyridin-7-one (364.5 mg, 1.41 mmol) in methanol (11.3 mL) at 0 ^{o}C was treated with a solution of oxone® (1.91 g, 3.11 mmol) in water (11.3 mL) . The reaction was left to stir for 24 h. Volatiles were removed by concentration under reduced pressure. The reaction mixture was poured into 40 mL of water and extracted with 3 x 20 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The off white solid was used without further purification. LCMS ESI (+) (M+H) m/z 290 / 292.

Step G: Preparation of 4-bromo-1-(methylsulfonyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolane]. Trimethylsilyl trifluoromethanesulfonate (331 uL, 1.83 mmol) was added to a solution of 4-bromo-1-methylsulfonyl-5,6-dihydrocyclopenta[c]pyridin-7-one (**39**) (354 mg, 1.22 mmol) and trimethyl(2-trimethylsilyloxyethoxy)silane (1.20 mL, 4.88 mmol) in dichloromethane (14 mL) cooled in an ice bath. The ice bath was removed. After 3 h, an additional portion of trimethyl(2-trimethylsilyloxyethoxy)silane (1.20 mL, 4.88 mmol) was added. The reaction was left to stir for 24 h and was quenched by the addition of triethylamine (1.02 mL, 7.32 mmol). The reaction mixture stirred for 10 min following the quench. Volatiles were removed and the residue suspended into 30 mL of saturated aqueous $NaHCO_3$ and extracted with 3 x 20 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with MgSO4, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 15-50% EtOAc/hexane to afford 4-bromo-1-(methylsulfonyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolane] as a white solid (74.5 mg, 18%). LCMS ESI (+) (M+H) m/z 334 / 336. The bulk of the product was isolated as the enol ether (295 mg, 59%).

*Step H: Preparation of 1-(methylsulfonyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolan]-4-ol (**40**).* A solution of 4'-bromo-1'-methylsulfonyl-spiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine] (74.5 mg, 0.22 mmol) and 2-(di-t-butylphosphino)-3,6-dimethoxy-2',4',6'-tri-i-propyl-1,1'-biphenyl (5.4 mg, 0.011 mmol) in 1,4-dioxane (1.5mL) was sparged with nitrogen for 3 mins. The reaction mixture was then treated sequentially with freshly ground

potassium hydroxide (37.5 mg, 0.67 mmol), water (80.3 uL, 4.46 mmol) and [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium; ditert-butyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (9.5 mg, 0.011 mmol) under continuous nitrogen stream. The vessel was sealed and heated to 80 ^{o}C for 1 h and 30 min. The reaction mixture was quenched by the addition of acetic acid (51.0 uL, 0.89 mmol). The reaction mixture was poured into 75 mL of water and extracted with 4 x 20 mL EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated to dryness. The product was used without further purification (77.9mg). LCMS ESI (+) (M+H) m/z 272.

Step I: Preparation of 3-fluoro-5-((1-(methylsulfonyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)benzonitrile. A suspension of potassium carbonate (30.6 mg, 0.22 mmol) in acetonitrile (1.5 mL) at 25 ^{o}C was treated with 1'-methylsulfonylspiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine]-4'-ol (**40**) (40.0 mg, 0.15 mmol) and stirred at 25 ^{o}C for 10 min. The resulting mixture was treated with (3-cyano-5-fluoro-phenyl)-(4-methoxyphenyl)iodonium; 4-methylbenzenesulfonate (116.2 mg, 0.22 mmol) and heated to 50 ^{o}C for 3 h. Volatiles were removed by concentration under reduced pressure. The reaction mixture was poured into 20 mL of water and extracted with 3 x 15 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 20-50% EtOAc/hexane to afford (3-fluoro-5-((1-(methylsulfonyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)benzonitrile as a solid (25.1 mg, 44%). LCMS ESI (+) (M+H) m/z 391.

*Step J: Preparation of 3-fluoro-5-((1-(methylsulfonyl)-7-oxo-6,7-dihydro-5H-cyclopenta[c]pyridin-4-yl)oxy)benzonitrile (**41**).* A solution of 4'-(3,3-difluorocyclobutoxy)-6'-fluoro-1'-methylsulfonyl-spiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine] (25.1 mg, 0.064 mmol) in dichloromethane (3.0 mL) at 0 ^{o}C was treated with perchloric acid (70% in water, 330 uL) and stirred at 0 ^{o}C for 2 h and then at room temperature for 30 min. The reaction mixture was carefully quenched with 5 mL of saturated $NaHCO_3$/10 mL of water and extracted with 3 x 15 mL CH_2Cl_2. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and

concentrated to dryness. The product was used without further purification. LCMS ESI (+) (M+H) m/z 347.

Step K: Preparation of 3-((7-((tert-butyldimethylsilyl)oxy)-1-(methylsulfonyl)-5H-cyclopenta[c]pyridin-4-yl)oxy)-5-fluorobenzonitrile. A solution of triethylamine (71.4 uL, 0.51 mmol) and 3-fluoro-5-[[7-oxo-1-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyridin-4-yl]oxy]benzonitrile (**41**) (22.2 mg, 0.064 mmol) in dichloromethane (3.0 mL) at 0 °C was treated with tert-butyldimethylsilyl trifluoromethanesulfonate (58.2 uL, 0.38 mmol). The ice bath was removed and the reaction mixture stirred for 2 h. The reaction mixture was poured into 30 mL of saturated $NaHCO_3$ and extracted with 3 x 20 mL CH_2Cl_2. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The product was used without further purification. LCMS ESI (+) (M+H) m/z 461.

Step L: Preparation of 3-fluoro-5-((6-fluoro-1-(methylsulfonyl)-7-oxo-6,7-dihydro-5H-cyclopenta[c]pyridin-4-yl)oxy)benzonitrile. A solution of 3-[[7-[tert-butyl(dimethyl)silyl]oxy-1-(trifluoromethyl)-5H-cyclopenta[c]pyridin-4-yl]oxy]-5-fluoro-benzonitrile (29.5 mg, 0.064 mmol) in acetonitrile (2.6 mL) at 25 °C was treated with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate) (24.9 mg, 0.070 mmol) and stirred at 25 °C for 1 h. Volatiles were removed by concentration under reduced pressure. The reaction mixture was poured into 30 mL of water and extracted with 3 x 10 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 10-25% EtOAc/hexane to afford 3-fluoro-5-((6-fluoro-1-(methylsulfonyl)-7-oxo-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-4-yl)oxy)benzonitrile as a thin film (11.1 mg, 48%). LCMS ESI (+) (M+H) m/z 365.

*Step M: Preparation of 3-fluoro-5-(((6R,7S)-6-fluoro-7-hydroxy-1-(methylsulfonyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-4-yl)oxy)benzonitrile (**20**).* A solution of 6-fluoro-4-[(5-fluoro-3-pyridyl)oxy]-1-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyridin-7-one (11.1 mg, 0.031 mmol) in dichloromethane (2.0 mL) was cooled to 0 °C and sparged with nitrogen for 5 min. During this time formic acid (3.4 uL, 0.091 mmol) and triethylamine (8.4 uL, 0.061 mmol) were sequentially added. Once the sparging was complete, RuCl(p-cymene)[(*R*,*R*)-Ts-DPEN] (0.4 mg, 0.0006 mmol)

was added under a continuous stream of nitrogen. The reaction vessel was sealed and put into the refrigerator to react overnight. Volatiles were removed by concentration under reduced pressure. The residue was purified by chromatography on silica using 20-60% EtOAc/hexane to afford 3-fluoro-5-(((6*R*,7*S*)-6-fluoro-7-hydroxy-1-(methylsulfonyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-4-yl)oxy)benzonitrile (**20**) as a white solid (7.0 mg, 63%). Retention time HPLC (14 min) = 3.16 min; LCMS ESI (+) (M+H) m/z 367; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 0.5 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.15 – 7.13 (m, 1H), 7.03 (dt, J = 9.0, 2.3 Hz, 1H), 5.69 (dt, J = 14.5, 4.2 Hz, 1H), 5.54 – 5.36 (m, 1H), 4.24 (d, J = 4.1 Hz, 1H), 3.36 – 3.24 (m, 1H), 3.34 (s, 3H), 3.09 (ddd, J = 26.3, 18.0, 5.2 Hz, 1H).

3-fluoro-5-(((6*R*,7*S*)-6-fluoro-7-hydroxy-1-(trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-4-yl)oxy)benzonitrile (21). *Step A: Preparation of 4-bromo-1-(trifluoromethyl)-5,6-dihydro-7H-cyclopenta[c]pyridin-7-one (**43**).* A suspension of 4-bromo-5,6-dihydrocyclopenta[c]pyridin-7-one (**42**) (1.0 g, 4.72 mmol) and bis(((trifluoromethyl)sulfinyl)oxy)zinc (4.69 g, 14.15 mmol) in a mixture of dichloromethane (30 mL) and water (15 mL) at 0 ^oC was treated with tert-butyl hydroperoxide (~70% in water, 2.58 mL, 18.86 mmol, added via pipette using a plastic tip) and stirred overnight while warming to room temperature. Additional portions of bis(((trifluoromethyl)sulfinyl)oxy)zinc (2.35 g, 7.07 mmol) and tert-butyl hydroperoxide (2.58mL, 18.86mmol) were added sequentially to drive the reaction to completion. After stirring for an additional day, the reaction vessel was placed into a water bath and carefully quenched by the addition of saturated $NaHCO_3$. Once effervescence ceased, the reaction mixture filtered through a pad of celite to remove solids. The pad of celite was rinsed with additional dichloromethane. The filtrate was separated and the aqueous portion extracted further with 2 x 20 mL CH_2Cl_2. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 30-90% CH_2Cl_2/hexane to afford 4-bromo-1-(trifluoromethyl)-5,6-dihydro-7*H*-cyclopenta[*c*]pyridin-7-one (**43**) as an off-white solid (390 mg, 30%). The desired regioisomer elutes first. LCMS ESI (+) (M+H) m/z 280 / 282.

*Step B: Preparation of 4-bromo-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolane] and 4-bromo-1-(trifluoromethyl)-7-(2-((trimethylsilyl)oxy)ethoxy)-5H-cyclopenta[c]pyridine (**57**).* Trimethylsilyl trifluoromethanesulfonate (75.9 uL, 0.42 mmol) was added to a solution of 4-bromo-1-

(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyridin-7-one (389 mg, 1.39 mmol) and trimethyl(2-trimethylsilyloxyethoxy)silane (1.37 mL, 5.56 mmol) in dichloromethane (13.6 mL) cooled in an ice bath. The mixture was allowed to slowly warm to ambient temperature. After 5 h, an additional 1.3 mL of trimethyl(2-trimethylsilyloxyethoxy)silane and 76 uL of trimethylsilyl trifluoromethanesulfonate were added. After another 16 h, the reaction mixture was treated with triethylamine (770 uL, 5.56 mmol), stirred for 10 min, and then concentrated. The residue was treated with 20 mL EtOAc and 20 mL of water and the layers separated. The aqueous portion was extracted further with 2 x 20 mL of EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated. Purification was achieved by chromatography on silica using 5-20% EtOAc/hexane to afford 4-bromo-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolane] as a white solid (262 mg, 58%) and 4-bromo-1-(trifluoromethyl)-7-(2-((trimethylsilyl)oxy)ethoxy)-5*H*-cyclopenta[*c*]pyridine (**57**) as a white solid (170 mg, 31%).

*Step C: Preparation of 1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolan]-4-ol (**44**).* A solution of 4'-bromo-1'-(trifluoromethyl)spiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine] (226.4 mg, 0.70 mmol) and 2-(di-t-butylphosphino)-3,6-dimethoxy-2',4',6'-tri-i-propyl-1,1'-biphenyl (8.5 mg, 0.017 mmol) in 1,4-dioxane (7.0 mL) was sparged with nitrogen for 3 mins. The reaction mixture was then treated sequentially with freshly ground potassium hydroxide (117.6 mg, 2.10 mmol), water (252 uL, 13.97 mmol) and [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium; ditert-butyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (14.9 mg, 0.017 mmol) under continuous nitrogen stream. The vessel was sealed and heated to 80 ^{o}C for 1 h and 30 min. The reaction mixture was quenched by the addition of acetic acid (160 uL, 2.79 mmol). The reaction mixture was poured into 75 mL of water and extracted with 4 x 20 mL EtOAc. The combined organics were dried with MgSO4, filtered, and concentrated to dryness. The brown solid was used without further purification. LCMS ESI (-) (M-H) m/z 260.

*Step D: Preparation of 3-fluoro-5-((1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)benzonitrile (**45**).* A suspension of potassium tert-butoxide (28.4 mg, 0.25 mmol) in tetrahydrofuran (1.5 mL) at 0 ^{o}C was treated with 1'-(trifluoromethyl)spiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine]-4'-ol (**44**) (60.0 mg, 0.23 mmol) and stirred at 0 ^{o}C for 15 min. The resulting mixture was treated with (3-cyano-5-fluoro-phenyl)-(4-methoxyphenyl)iodonium; 4-methylbenzenesulfonate[9] (144.8 mg, 0.28 mmol) and heated to 40 ^{o}C. The reaction mixture was filtered through a plastic filter cup using EtOAc to

rinse. Volatiles were removed by concentration under reduced pressure. Purification was achieved by chromatography on silica using 10-40% EtOAc/hexanes to afford a solid (42 mg, 48%). LCMS ESI (+) (M+H) m/z 381.

*Step E: Preparation of 3-fluoro-5-((7-oxo-1-(trifluoromethyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-4-yl)oxy)benzonitrile (**46**).* A solution of 3-fluoro-5-[1'-(trifluoromethyl)spiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine]-4'-yl]oxy-benzonitrile (**45**) (42.0 mg, 0.11 mmol) in dichloromethane (2.0 mL) at 0 ^{o}C was treated with perchloric acid (70% in water, 240 uL) and stirred at 0 ^{o}C for 30 min. The reaction mixture was carefully quenched by the addition of 15 mL of saturated $NaHCO_3$ and extracted with 3 x 15 mL CH_2Cl_2. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The solid residue was used immediately in the next step without further purification. LCMS ESI (+) (M+H) m/z 337.

Step F: Preparation of 3-((7-((tert-butyldimethylsilyl)oxy)-1-(trifluoromethyl)-5H-cyclopenta[c]pyridin-4-yl)oxy)-5-fluorobenzonitrile. A solution of triethylamine (122 uL, 0.88 mmol) and 3-fluoro-5-[[7-oxo-1-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyridin-4-yl]oxy]benzonitrile (37.0 mg, 0.11 mmol) in dichloromethane (2.2 mL) at 0 ^{o}C was treated with tert-butyldimethylsilyl triflate (152 ul, 0.66 mmol). The ice bath was removed and the reaction mixture left to stir for 2 h. The reaction mixture was poured into 30 mL of saturated $NaHCO_3$ and extracted with 3 x 20 mL CH_2Cl_2. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The product was used without further purification. LCMS ESI (+) (M+H) m/z 451.

Step G: Preparation of 3-fluoro-5-((6-fluoro-7-oxo-1-(trifluoromethyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-4-yl)oxy)benzonitrile. A solution of 3-[[7-[tert-butyl(dimethyl)silyl]oxy-1-(trifluoromethyl)-5H-cyclopenta[c]pyridin-4-yl]oxy]-5-fluoro-benzonitrile (49.56mg, 0.1100mmol) in acetonitrile (2.2 mL) at 25 ^{o}C was treated with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate) (42.9 mg, 0.12 mmol) and stirred at 25 ^{o}C for 1 h. Volatiles were removed by concentration under reduced pressure The reaction mixture was poured into 30 mL of water and extracted with 3 x 10 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 10-25% EtOAc/hexane to afford a thin film (37.8 mg, 97%). LCMS ESI (+) (M+H) m/z 355.

*Step H: Preparation of 3-fluoro-5-(((6R,7S)-6-fluoro-7-hydroxy-1-(trifluoromethyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-4-yl)oxy)benzonitrile (**21**).* A solution of 3-fluoro-5-[[6-fluoro-7-oxo-1-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyridin-4-yl]oxy]benzonitrile

(15.3 mg, 0.043 mmol) in dichloromethane (1.5 mL) was cooled to 0 °C and sparged with nitrogen for 5 min. During this time formic acid (4.9 uL, 0.13 mmol) and triethylamine (12.0 uL, 0.086 mmol) were sequentially added. Once the sparging was complete, RuCl(p-cymene)[(*R*,*R*)-Ts-DPEN] (0.5 mg, 0.00086 mmol) was added under a continuous stream of nitrogen. The reaction vessel was sealed and placed into the refrigerator to react overnight. Volatiles were removed by concentration under reduced pressure. The residue was purified by chromatography on silica using 10-30% EtOAc/hexane to afford 3-fluoro-5-(((6*R*,7*S*)-6-fluoro-7-hydroxy-1-(trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-4-yl)oxy)benzonitrile (**21**) as a clear solid (11.8 mg, 77%). Retention time HPLC (14 min) = 4.19 min; LCMS ESI (+) (M+H) m/z 357; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.22 (ddd, J = 7.5, 2.2, 1.3 Hz, 1H), 7.12 – 7.06 (m, 1H), 6.99 (dt, J = 9.1, 2.3 Hz, 1H), 5.55 – 5.46 (m, 1H), 5.46 – 5.27 (m, 1H), 3.26 (ddd, J = 20.2, 17.9, 3.6 Hz, 1H), 3.11 (ddd, J = 23.3, 17.9, 5.6 Hz, 1H), 2.67 (dd, J = 7.6, 4.8 Hz, 1H).

3-fluoro-5-(((cis)-6-fluoro-5-hydroxy-4-(trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-1-yl)oxy)benzonitrile (22). *Step A: Preparation of ethyl (E)-3-(2-fluoro-4-iodopyridin-3-yl)acrylate.* A solution of 2-fluoro-4-iodo-3-pyridinecarboxyaldehyde (1.00 g, 3.98 mmol), lithium chloride (168.9 mg, 3.98 mmol) and ethyl 2-diethoxyphosphorylacetate (800 uL, 3.98 mmol) in acetonitrile (20 mL) at 25 °C was treated with 1;8-Diazabicyclo[5.4.0]undec-7-ene (630 uL, 4.18 mmol) and stirred at 25 °C for 2 h. Volatiles were removed by concentration under reduced pressure. The reaction mixture was poured into 30 mL of water and extracted with 3 x 20 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 100% CH_2Cl_2 to afford ethyl (*E*)-3-(2-fluoro-4-iodopyridin-3-yl)acrylate as white solid (1.1 g, 86%). LCMS ESI (+) (M+H) m/z 322.

Step B: Preparation of ethyl (E)-3-(4-cyano-2-fluoropyridin-3-yl)acrylate. A solution of ethyl (E)-3-(2-fluoro-4-iodo-3-pyridyl)prop-2-enoate (900 mg, 2.80 mmol) and zinc cyanide (987.3 mg, 8.41 mmol) in N,N-dimethylacetamide (10 mL) was sparged with nitrogen for 3 mins. The reaction mixture was then treated sequentially with 1,1′-Ferrocenediyl-bis(diphenylphosphine) (61.3 mg, 0.11 mmol) and tris(dibenzylideneacetone)dipalladium(0) (51.3 mg, 0.056 mmol) under continuous nitrogen stream. The vessel was sealed and heated to 110 °C for 30 min. The reaction mixture was poured into 100 mL of water and extracted with 3 x 25 mL TBME. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica

using 5-25% EtOAc/hexanes to afford ethyl (*E*)-3-(4-cyano-2-fluoropyridin-3-yl)acrylate as a solid (594 mg, 97%). LCMS ESI (+) (M+H) m/z 221.

*Step C: Preparation of ethyl 3-(4-cyano-2-fluoropyridin-3-yl)propanoate (**48**).* A suspension of ethyl (E)-3-(4-cyano-2-fluoro-3-pyridyl)prop-2-enoate (560 mg, 2.54 mmol) and palladium on carbon (10 wt. %, 67.7 mg, 0.064 mmol) in methanol (25.4 mL) at 25 ^{o}C was sparged with nitrogen for 3 min. Then the solution was sparged with hydrogen for 1 min and left under a hydrogen balloon for 3 h. The reaction mixture was carefully sparged with nitrogen for 3 minutes and then filtered through a pad of celite using MeOH as a rinse. The filtrate was concentrated and purification was achieved by chromatography on silica using 5-25% EtOAc/hexanes to afford ethyl 3-(4-cyano-2-fluoropyridin-3-yl)propanoate (391 mg, 68%). LCMS ESI (+) (M+H) m/z 223.

*Step D: Preparation of 1-hydroxy-6,7-dihydro-5H-cyclopenta[c]pyridin-5-one (**49**).* A solution of ethyl 3-(4-cyano-2-fluoro-3-pyridyl)propanoate (**48**) (383. 8mg, 1.73 mmol) in tetrahydrofuran (10 mL) at -78 ^{o}C was treated with lithium bis(trimethylsilyl)amide (1.0 M in THF, 2.25mL, 2.25mmol) by slow dropwise addition over 5 min. The reaction mixture stirred for 20 min at this temperature. Reaction progress was monitored by TLC. Putative product and starting material have the same mass. Product more polar and different color under UV light. The reaction mixture was quenched by the addition of 5 mL of saturated NH_4Cl. Organic volatiles were removed by concentration under reduced pressure. The reaction mixture was extracted with 3 x 20 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The intermediate product was used without further purification. The intermediate vinylogous carbamate was suspended in 6.6 mL of dioxane and treated with 1.3 mL of water and 2.0 mL of conc. H_2SO_4. The resulting mixture was heated to 120 ^{o}C by microwave irradiation for 45 min. Volatiles were removed by concentration under reduced pressure. The reaction mixture was poured into 30 mL of water and extracted with 5 x 15 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 2-8% MeOH/CH_2Cl_2 to afford 1-hydroxy-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-5-one as a beige solid (167 mg, 65%). LCMS ESI (+) (M+H) m/z 150.

*Step E: Preparation of 5-(2-((trimethylsilyl)oxy)ethoxy)-7H-cyclopenta[c]pyridin-1-ol (**50**).* Trimethylsilyl trifluoromethanesulfonate (263 uL, 1.46 mmol) was added to a solution of 1-hydroxy-6,7-dihydrocyclopenta[c]pyridin-5-one (**49**) (167 mg, 1.12 mmol) and trimethyl(2-trimethylsilyloxyethoxy)silane (1.10 mL, 4.48 mmol) in dichloromethane (11.2 mL) cooled in an ice bath. The ice bath was removed and the reaction stirred at ambient temperature overnight. The

next day, an additional portion of trimethylsilyl trifluoromethanesulfonate (263 uL, 1.46 mmol) was added. After 4 h, the reaction mixture was treated with triethylamine (624 uL, 4.48 mmol), stirred 10min, then evaporated. The residue was treated with 20 mL of 30% IPA/$CHCl_3$ and 20 mL water and the layers separated. The aqueous layer was further extracted with 3 x 10 mL of 30% IPA/$CHCl_3$. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated. Purification was achieved by chromatography on silica using 2-10% MeOH/CH_2Cl_2 to afford a clear solid (105 mg) that was a ~1:1 mixture of 5-(2-((trimethylsilyl)oxy)ethoxy)-7*H*-cyclopenta[*c*]pyridin-1-ol (**50**) and the ketalized product, 6,7-dihydrospiro[cyclopenta[*c*]pyridine-5,2'-[1,3]dioxolan]-1-ol. LCMS ESI (+) (M+H) m/z 194 (ketal).

*Step F: Preparation of 6-fluoro-6,7-dihydrospiro[cyclopenta[c]pyridine-5,2'-[1,3]dioxolan]-1-ol (**51**).* A solution of 5-(2-trimethylsilyloxyethoxy)-7H-cyclopenta[c]pyridin-1-ol (**50**) (~1:1 with the ketal, 105 mg) and sodium sulfate (281 mg, 1.98 mmol) in acetonitrile (7.9 mL) was stirred for 10 min and then treated with Selectfluor® (154 mg, 0.44 mmol) and stirred at 25 ^oC for 1 h. LCMS indicates formation of the fluoro ketal and the fluoro ketone from the enol ether. Volatiles were removed by concentration under reduced pressure. The reaction mixture was poured into 30 mL of water and extracted with 3 x 15 mL 30% IPA/$CHCl_3$. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 2-10% MeOH/CH_2Cl_2 to afford the desired product as a mixture with the ketal impurity from the start and the fluoro ketone impurity from the reaction. LCMS ESI (+) (M+H) m/z 212 (Also observed are 168 for the fluoro ketone and 194 for the ketal).

Step G: Preparation of 3-fluoro-5-((6-fluoro-4-iodo-6,7-dihydrospiro[cyclopenta[c]pyridine-5,2'-[1,3]dioxolan]-1-yl)oxy)benzonitrile. A solution of spiro[1,3-dioxolane-2,5'-6,7-dihydrocyclopenta[c]pyridine]-1'-ol (**51**) (141.9 mg, containing ketal and fluoro ketone impurities) in acetonitrile (7.3 mL) was treated with *N*-iodosuccinimide (181.8 mg, 0.81 mmol) and heated to 80 ^oC over 1 h. Volatiles were removed by concentration under reduced pressure and kept under high vacuum to remove any iodine that had formed during the reaction. The residue was redissolved in acetonitrile (7.3 mL) and treated with potassium carbonate (304.5 mg, 2.2 mmol) and (3-cyano-5-fluoro-phenyl)-(4-methoxyphenyl)iodonium; 4-methylbenzenesulfonate[55] (578.8 mg, 1.10 mmol). The reaction was heated to 80 ^oC for 1 h. The reaction mixture was cooled and recharged with potassium carbonate (100 mg, ~1 equiv) and diaryliodonium salt (385 mg, ~1 equiv). The reaction mixture was heated to 80 ^oC for another hour. Volatiles were removed by concentration under reduced pressure. The reaction mixture

was poured into 30 mL of water and extracted with 3 x 20 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 5-25% EtOAc/hexanes. The isolated product is a mixture of the ketal and fluoroketal derivatives in a ~3:2 ratio. LCMS ESI (+) (M+H) m/z 320 (ketal) and 338 (desired product).

*Step H: Preparation of 3-fluoro-5-((6-fluoro-4-iodo-5-oxo-6,7-dihydro-5H-cyclopenta[c]pyridin-1-yl)oxy)benzonitrile (**52**).* A solution of 3-fluoro-5-((6-fluoro-4-iodo-6,7-dihydrospiro[cyclopenta[*c*]pyridine-5,2'-[1,3]dioxolan]-1-yl)oxy)benzonitrile (22.2 mg, 0.050 mmol) (also contains the ketal impurity) in dichloromethane (1.0 mL) at 0 ^oC was treated with 70% aqueous perchloric acid (200 uL) and stirred at 25 ^oC for 2 h. The reaction mixture was cooled to 0 ^oC, carefully quenched with a mixture of 5 mL of saturated $NaHCO_3$ / 10 mL of water and extracted with 3 x 15 mL CH_2Cl_2. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 60-100% CH_2Cl_2/hexanes to afford the fluoroketone (6.0 mg) and ketone (7.5 mg) derivatives as thin films. LCMS ESI (+) (M+H) m/z 395 (ketone) and 413 (desired product).

Step I: Preparation of 3-fluoro-5-((6-fluoro-5-oxo-4-(trifluoromethyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-1-yl)oxy)benzonitrile. A solution of 3-fluoro-5-[(6-fluoro-4-iodo-5-oxo-6,7-dihydrocyclopenta[c]pyridin-1-yl)oxy]benzonitrile (**52**) (6.0 mg, 0.015 mmol) and copper (2.8 mg, 0.044 mmol) in DMF (0.5 mL) was sparged with nitrogen for 3 mins. The reaction mixture was then treated with sulfonium, diphenyl(trifluoromethyl)-, 1,1,1-trifluoromethanesulfonate (1:1) (11.8 mg, 0.030 mmol) under continuous nitrogen stream. The vessel was sealed and heated to 60 ^oC for 6 h. The reaction mixture was poured into 20 mL of water and extracted with 3 x 15 mL TBME. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 5-25% EtOAc/hexanes to afford 3-fluoro-5-((6-fluoro-5-oxo-4-(trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-1-yl)oxy)benzonitrile as a thin film (4.3 mg, 83%). LCMS ESI (+) (M+H) m/z 355.

*Step J: Preparation of 3-fluoro-5-(((cis)-6-fluoro-5-hydroxy-4-(trifluoromethyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-1-yl)oxy)benzonitrile (**22**).* A solution of 3-fluoro-5-[[6-fluoro-5-oxo-4-(trifluoromethyl)-6,7-dihydrocyclopenta[c]pyridin-1-yl]oxy]benzonitrile (4.3mg, 0.012 mmol) in methanol (1.0 mL) at 0 ^oC was treated with sodium borohydride (0.5 mg, 0.012 mmol) and stirred at 0 ^oC for 15 min. The reaction was then quenched by the addition of 1 mL of saturated NH_4Cl. Volatiles were removed by concentration under reduced pressure. The

reaction mixture was poured into 20 mL of water and extracted with 3 x 10 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 15-40% EtOAc/hexanes to afford 3-fluoro-5-(((cis)-6-fluoro-5-hydroxy-4-(trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-1-yl)oxy)benzonitrile (**22**) as a thin film (3.6 mg, 83%). Retention time HPLC (14 min) = 5.66 min; LCMS ESI (+) (M+H) m/z 357; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 – 8.33 (m, 1H), 7.36 – 7.31 (m, 1H), 7.28 (ddd, J = 7.6, 2.4, 1.3 Hz, 1H), 7.23 (dt, J = 9.1, 2.3 Hz, 1H), 5.53 – 5.35 (m, 2H), 3.40 (ddd, J = 21.8, 17.6, 1.6 Hz, 1H), 3.22 (ddd, J = 29.5, 17.7, 4.9 Hz, 1H), 2.75 – 2.67 (m, 1H).

3-fluoro-5-((7-hydroxy-1-(trifluoromethyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-4-yl)oxy)benzonitrile (23). *Step A: Preparation of 3-fluoro-5-((7-hydroxy-1-(trifluoromethyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-4-yl)oxy)benzonitrile (**23**).* A solution of 3-fluoro-5-[[7-oxo-1-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyridin-4-yl]oxy]benzonitrile (**46**) (6.9 mg, 0.021 mmol) in methanol (2 mL) at 0 ^oC was treated with sodium borohydide (0.78 mg, 0.021 mmol) and stirred at 0 ^oC for 30 min. The reaction mixture was quenched by the addition of 0.25 mL of saturated aqueous NH_4Cl. Volatiles were removed by concentration under reduced pressure. The reaction mixture was poured into 20 mL of water and extracted with 3 x 20 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 10-30% EtOAc/hexanes (**23**) (6.1 mg, 88%). LCMS ESI (+) (M+H) m/z 339; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.21 (ddd, J = 7.4, 2.2, 1.2 Hz, 1H), 7.07 (dt, J = 2.2, 1.1 Hz, 1H), 6.96 (dt, J = 9.2, 2.3 Hz, 1H), 5.67 – 5.60 (m, 1H), 3.07 (dt, J = 17.6, 8.2 Hz, 1H), 2.81 (ddd, J = 17.7, 8.8, 2.9 Hz, 1H), 2.49 – 2.35 (m, 1H), 2.33 – 2.20 (m, 2H).

3-(((5*R*,6*S*,7*S*)-5,6-difluoro-7-hydroxy-1-(trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-4-yl)oxy)-5-fluorobenzonitrile (24). *Step A: Preparation of 3-((5-bromo-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)-5-fluorobenzonitrile.* A suspension of 3-fluoro-5-[1'-(trifluoromethyl)spiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine]-4'-yl]oxy-benzonitrile (**45**) (1520 mg, 4.00 mmol), 2,2'-azobisisobutyronitrile (65.6 mg, 0.40 mmol), magnesium oxide (483.2 mg, 12.00 mmol) and *N*-bromosuccinimide (924.8 mg, 5.20 mmol) in 1,2-dichloroethane (40.0 mL) was sparged with nitrogen for 3 mins. The vessel was sealed and heated to 80 ^oC for 3 h. Initial LCMS after 1 h

indicates product formation, however starting material remains. Additional 2,2'-azobisisobutyronitrile (65.6 mg, 0.40 mmol) and *N*-bromosuccinimide (924.8 mg, 5.20 mmol) was added to help drive the reaction to completion. Heating was continued for an additional 1.5 h. The reaction mixture was left at room temperature overnight. MgO was removed by filtration through celite and rinsing of the filter cake with CH_2Cl_2. The filtrate was treated with 30 mL of saturated aqueous $NaHCO_3$, stirred for 10 min, and extracted with 3 x 30 mL CH_2Cl_2. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 5-25% EtOAc/hexanes to afford 3-((5-bromo-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)-5-fluorobenzonitrile as a yellow foam (931 mg, 51%). LCMS ESI (+) (M+H) m/z 459 / 461.

*Step B: Preparation of 3-fluoro-5-((5-hydroxy-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)benzonitrile (**53**):* A solution of 3-[5'-bromo-1'-(trifluoromethyl)spiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine]-4'-yl]oxy-5-fluoro-benzonitrile (931 mg, 2.03 mmol) in a mixture of 1,2-dimethoxyethane (15.0 mL) and water (5.0 mL) at 25 ^oC was treated with silver(I) carbonate (1.12 g, 4.05 mmol) and stirred at 85 ^oC for 8 h. An additional portion of silver(I) carbonate (1.12 g, 4.05 mmol) was added and the reaction mixture left to heat at 85 ^oC overnight. The reaction mixture was diluted with EtOAc and filtered through celite. The filtrate was washed with water and brine, dried and concentrated. Purification was achieved by chromatography on silica using 20-55% EtOAc/hexanes to afford 3-fluoro-5-((5-hydroxy-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)benzonitrile as a yellow solid (295 mg, 37%). LCMS ESI (+) (M+H) m/z 397.

Step C: Preparation of 3-fluoro-5-((5-oxo-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)benzonitrile. A solution of 3-fluoro-5-[5'-hydroxy-1'-(trifluoromethyl)spiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine]-4'-yl]oxy-benzonitrile (295.6 mg, 0.75 mmol) in dichloromethane (15.0 mL) at 25 ^oC was treated with Dess-Martin periodinane (395.5 mg, 0.93 mmol). After 1 h, an additional 20 mg of Martin's reagent was added to drive the reaction to completion. After stirring for another 30 min, the reaction was quenched by the addition of 6 mL of saturated $Na_2S_2O_3$ solution and 6 mL of saturated $NaHCO_3$ solution. The resulting biphase stirred for 10 min. The reaction mixture was poured into 10 mL of water and extracted with 3 x 20 mL CH_2Cl_2. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The product, 3-fluoro-5-((5-oxo-1-(trifluoromethyl)-5,6-

dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)benzonitrile (264 mg), was used without further purification. LCMS ESI (+) (M+H) m/z 395.

*Step D: Preparation of 3-fluoro-5-((6-fluoro-5-oxo-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)benzonitrile (**54**).* A solution of 3-fluoro-5-[5'-oxo-1'-(trifluoromethyl)spiro[1,3-dioxolane-2,7'-6H-cyclopenta[c]pyridine]-4'-yl]oxy-benzonitrile (293.7 mg, 0.75 mmol) and triethylamine (520 uL, 3.73 mmol) in dichloromethane (15.0 mL) at 0 ^{o}C was treated with tert-butyldimethylsilyl trifluoromethane (690 uL, 2.98 mmol) and stirred at 0 ^{o}C for 30 min. The reaction mixture slowly turns dark red following TBSOTf addition. The reaction mixture was left to stir for 5 h slowly warming to room temperature (LCMS of the enol ether can be observed: ESI (+) (M+H) m/z 509). The reaction mixture was poured into 15 mL of saturated $NaHCO_3$, stirred for 10 min, and extracted with 3 x 15 mL CH_2Cl_2. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The crude residue was dissolved in 4 mL of acetonitrile and treated with Selectfluor® (263.9 mg, 0.75 mmol). The reaction stirred for 3 h at room temperature. Volatiles were removed by concentration under reduced pressure. The reaction mixture was poured into 30 mL of water and extracted with 3 x 15 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 5-30% EtOAc/hexanes to afford 3-fluoro-5-((6-fluoro-5-oxo-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)benzonitrile as a white solid (206 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.32-7.28 (m, 1H), 7.21-7.18 (m, 1H), 7.13-7.08 (m, 1H), 5.20 (d, 1H), 4.51-4.31 (m, 4H).

*Step E: Preparation of 3-fluoro-5-(((5R,6R)-6-fluoro-5-hydroxy-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)benzonitrile (**55**).* A solution of 3-fluoro-5-[6'-fluoro-5'-oxo-1'-(trifluoromethyl)spiro[1,3-dioxolane-2,7'-6H-cyclopenta[c]pyridine]-4'-yl]oxy-benzonitrile (**54**) (206.mg, 0.50 mmol) in dichloromethane (10.0 mL) was cooled to 0 ^{o}C and sparged with nitrogen for 5 min. During this time, formic acid (57 uL, 1.50 mmol) and triethylamine (104 uL, 0.75 mmol) were sequentially added. Once sparging was complete, RuCl(p-cymene)[(*S*,*S*)-Ts-DPEN] (6.4 mg, 0.010 mmol) was added under a continuous stream of nitrogen. The reaction vessel was sealed and put into the refrigerator to react overnight. Volatiles were removed by concentration under reduced pressure. Purification was achieved by chromatography on silica using 20-45% EtOAc/hexanes to afford 3-fluoro-5-(((5*R*,6*R*)-6-fluoro-5-hydroxy-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-

[1,3]dioxolan]-4-yl)oxy)benzonitrile as a clear solid (200 mg, 97%). LCMS ESI (+) (M+H) m/z 415.

Step F: Preparation of (5S,6R)-4-(3-cyano-5-fluorophenoxy)-6-fluoro-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolan]-5-yl 4-nitrobenzoate. A solution of 3-fluoro-5-[(5'R,6'R)-6'-fluoro-5'-hydroxy-1'-(trifluoromethyl)spiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine]-4'-yl]oxy-benzonitrile (**55**) (200 mg, 0.48 mmol), polymer supported triphenylphosphine (~2.06 mmol/g, 938.0 mg, 1.93 mmol), and 4-nitrobenzoic acid (322.72mg, 1.93mmol) in tetrahydrofuran (9.7 mL) at 25 ^{o}C was treated with diisopropyl azodicarboxylate (371 uL, 1.88 mmol) and stirred for 2 h. LCMS indicates product formation. The reaction mixture was filtered and the filter cake rinsed with EtOAc. The filtrate was concentrated and purified by chromatography on silica using 10-35% EtOAc/hexanes to afford (5*S*,6*R*)-4-(3-cyano-5-fluorophenoxy)-6-fluoro-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolan]-5-yl 4-nitrobenzoate as a white solid (221 mg, 81%). LCMS ESI (+) (M+H) m/z 564.

*Step G: Preparation of 3-fluoro-5-(((5S,6R)-6-fluoro-5-hydroxy-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)benzonitrile (**56**).* A solution of [(5'S,6'R)-4'-(3-cyano-5-fluoro-phenoxy)-6'-fluoro-1'-(trifluoromethyl)spiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine]-5'-yl] 4-nitrobenzoate (238 mg, 0.42 mmol) in tetrahydrofuran (8.0 mL) at 25 ^{o}C was treated with a solution of freshly prepared solution of lithium hydroxide hydrate (19.5 mg, 0.46 mmol) in water (2.4 mL) and stirred at 25 ^{o}C for 30 min. An additional portion of lithium hydroxide hydrate (10.0 mg, 0.24 mmol) in water (1.2 mL) was added and the reaction mixture stirred for 30 minutes. 2.0 mL of saturated NH_4Cl was added to the reaction mixture and volatiles were removed under reduced pressure. The reaction mixture was poured into 10 mL of saturated $NaHCO_3$ and extracted with 3 x 15 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 5-10% EtOAc/dichloromethane to afford 3-fluoro-5-(((5*S*,6*R*)-6-fluoro-5-hydroxy-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)benzonitrile as a white solid (137 mg, 78%). LCMS ESI (+) (M+H) m/z 415.

Step H: Preparation of 3-(((5R,6S)-5,6-difluoro-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)-5-fluorobenzonitrile: A solution of 3-fluoro-5-[(5'S,6'R)-6'-fluoro-5'-hydroxy-1'-(trifluoromethyl)spiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine]-4'-yl]oxy-benzonitrile (**56**) (137 mg, 0.33 mmol) in dichloromethane (6.6 mL) at 25 ^{o}C was treated with diethylaminosulfur trifluoride (87.4 uL, 0.66

mmol). The reaction mixture was allowed to stir for 30 minutes. The reaction mixture was quenched by the careful addition of 2 mL of aqueous saturated $NaHCO_3$. The resulting mixture vigorously stirred for 30 min. The reaction mixture was poured into 20 mL of water and extracted with 3 x 10 mL CH_2Cl_2. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 10-30% EtOAc/hexanes to afford 3-(((5*R*,6*S*)-5,6-difluoro-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolan]-4-yl)oxy)-5-fluorobenzonitrile as a white solid (92.7 mg, 67%). LCMS ESI (+) (M+H) m/z 417.

*Step I: Preparation of 3-(((5R,6S,7S)-5,6-difluoro-7-hydroxy-1-(trifluoromethyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-4-yl)oxy)-5-fluorobenzonitrile (**24**).* A solution of 3-[(5'R,6'S)-5',6'-difluoro-1'-(trifluoromethyl)spiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine]-4'-yl]oxy-5-fluoro-benzonitrile (92.7 mg, 0.22 mmol) in dichloromethane (5.0 mL) at 0 ^oC was treated with 70% aqueous perchloric acid (1.0 mL) and stirred at 44 ^oC for 3 h. The reaction mixture was cooled to 0 ^oC, carefully quenched with a mixture of 10 mL of saturated $NaHCO_3$ / 10 mL of water and extracted with 3 x 15 mL CH_2Cl_2. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The intermediate ketone product was used immediately without further purification by dissolving in 4 mL of MeOH, cooling to 0 ^oC, and treating with sodium borohydride (8.4 mg, 0.22 mmol). The reaction stirred for 15 min and was then quenched by the addition of 1 mL of saturated NH_4Cl. Volatiles were removed by concentration under reduced pressure. The reaction mixture was poured into 20 mL of water and extracted with 3 x 10 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 10-45% EtOAc/hexanes to afford 3-(((5*R*,6*S*,7*S*)-5,6-difluoro-7-hydroxy-1-(trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-4-yl)oxy)-5-fluorobenzonitrile (**24**) as a white solid (60.2 mg, 72%). Retention time HPLC (14 min) = 4.18 min; LCMS ESI (+) (M+H) m/z 375; ^1H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.28 (ddd, J = 7.6, 2.3, 1.2 Hz, 1H), 7.21 – 7.17 (m, 1H), 7.09 (dt, J = 8.9, 2.4 Hz, 1H), 5.92 (dd, J = 52.8, 4.4 Hz, 1H), 5.55 – 5.44 (m, 1H), 5.19 (ddt, J = 48.8, 13.3, 4.6 Hz, 1H), 2.69 (ddd, J = 7.2, 3.0, 0.7 Hz, 1H).

(*R*)-4-(3,3-difluorocyclobutoxy)-1-(trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-ol (25) and (6*R*,7*S*)-4-(3,3-difluorocyclobutoxy)-6-fluoro-1-(trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-ol (26). *Step A: Preparation of 4-bromo-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolane] (**44**) and 4-bromo-1-(trifluoromethyl)-7-(2-((trimethylsilyl)oxy)ethoxy)-5H-cyclopenta[c]pyridine (**57**).*

Trimethylsilyl trifluoromethanesulfonate (75.9 uL, 0.42 mmol) was added to a solution of 4-bromo-1-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyridin-7-one (**43**) (389 mg, 1.39 mmol) and trimethyl(2-trimethylsilyloxyethoxy)silane (1.37 mL, 5.56 mmol) in dichloromethane (13.6 mL) cooled in an ice bath. The mixture was allowed to slowly warm to ambient temperature. After 5 h, an additional 1.3 mL of trimethyl(2-trimethylsilyloxyethoxy)silane and 76 uL of trimethylsilyl trifluoromethanesulfonate were added. After another 16 h, the reaction mixture was treated with triethylamine (770 uL, 5.56 mmol), stirred for 10min, and then concentrated. The residue was treated with 20 mL EtOAc and 20 mL of water and the layers separated. The aqueous portion was extracted further with 2 x 20 mL of EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated. Purification was achieved by chromatography on silica using 5-20% EtOAc/hexane to afford 4-bromo-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolane] as a white solid (262 mg, 58%) and 4-bromo-1-(trifluoromethyl)-7-(2-((trimethylsilyl)oxy)ethoxy)-5*H*-cyclopenta[*c*]pyridine (**57**) as a white solid (170 mg, 31%). Data for 4-bromo-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolane]: LCMS ESI (+) (M+H) m/z 324 / 326. Data for 4-bromo-1-(trifluoromethyl)-7-(2-((trimethylsilyl)oxy)ethoxy)-5*H*-cyclopenta[*c*]pyridine (**57**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, 1H), 5.59 (t, 1H), 4.10 (t, 2H), 3.96 (t, 2H), 3.36 (d, 2H), 0.15 (s, 9H).

Step B: Preparation of 4-bromo-6-fluoro-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolane] and 4-bromo-6-fluoro-1-(trifluoromethyl)-5,6-dihydro-7H-cyclopenta[c]pyridin-7-one. A solution of 2-[[4-bromo-1-(trifluoromethyl)-5H-cyclopenta[c]pyridin-7-yl]oxy]ethoxy-trimethyl-silane (146.6 mg, 0.37 mmol) and sodium sulfate (262.7 mg, 1.85 mmol) in acetonitrile (3.7 mL) was stirred for 10 min and then treated with selectfluor® (145.2 mg, 0.41 mmol) and stirred at 25 ^{o}C for 1 h. Volatiles were removed by concentration under reduced pressure. The reaction mixture was poured into 30 mL of water and extracted with 3 x 15 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 5-20% EtOAc/hexane to afford 4-bromo-6-fluoro-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolane] as a white solid (96.2 mg, 76%) and 4-bromo-6-fluoro-1-(trifluoromethyl)-5,6-dihydro-7*H*-cyclopenta[*c*]pyridin-7-one as a thin film (6.7 mg, 7%). Data for 4-bromo-6-fluoro-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolane]: LCMS ESI (+) (M+H) m/z 342 / 344. Data for 4-bromo-6-fluoro-1-(trifluoromethyl)-5,6-dihydro-7*H*-cyclopenta[*c*]pyridin-7-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (s, 1H), 5.35 (ddd, 1H), 3.69 (dt, 1H), 3.26 (ddd, 1H).

*Step C: Preparation of 1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolan]-4-ol (**44**) and 6-fluoro-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolan]-4-ol (**58**).* A solution of 4'-bromo-6'-fluoro-1'-(trifluoromethyl)spiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine] (96.2mg, 0.2800mmol) and 2-(di-t-butylphosphino)-3,6-dimethoxy-2',4',6'-tri-i-propyl-1,1'-biphenyl (3.4 mg, 0.007 mmol) in 1,4-dioxane (5.0 mL) was sparged with nitrogen for 3 mins. The reaction mixture was then treated sequentially with potassium hydroxide (47.3 mg, 0.84 mmol), water (101 uL, 5.62 mmol) and [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium; di-t-butyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (6.0 mg, 0.007 mmol) under continuous nitrogen stream. The vessel was sealed and heated to 80 C for 1 h and 30 min. The reaction mixture was quenched by the addition of acetic acid (64.3 uL, 1.13 mmol). The reaction mixture was poured into 75 mL of water and extracted with 4 x 20 mL EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated to dryness. The product was used without further purification (87 mg). During the reaction, some of the hydrodefluorinated product formed as an inseparable impurity (2:1 product to hydrodefluorination). Data for 1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolan]-4-ol (**44**): LCMS ESI (+) (M+H) m/z 262. Data for 6-fluoro-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolan]-4-ol (**58**): LCMS ESI (+) (M+H) m/z 280.

Step D: Preparation of 4-(3,3-difluorocyclobutoxy)-6-fluoro-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolane] and 4-(3,3-difluorocyclobutoxy)-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolane]. A solution of impure 6'-fluoro-1'-(trifluoromethyl)spiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine]-4'-ol (44.0 mg, 0.16 mmol), polymer supported triphenylphosphine (~2.06 mmol/g, 306.2 mg, 0.63 mmol), and 3,3-difluoro-cyclobutanol (68.1 mg, 0.63 mmol) in tetrahydrofuran (3.2 mL) was treated with diisopropyl azodicarboxylate (120 uL, 0.61 mmol) and stirred at 60 ^{o}C for 2 h. The reaction mixture was filtered and the filter cake rinsed with 20 mL EtOAc. The filtrate was concentrated and purified by chromatography on silica using 10-30% EtOAc/hexane to afford a clear solid (39.0 mg, 67%) that was a 2:1 mixture of the fluorinated and hydrodefluorinated products. Data for 4-(3,3-difluorocyclobutoxy)-6-fluoro-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[c]pyridine-7,2'-[1,3]dioxolane] LCMS ESI (+) (M+H) m/z 370. Data for 4-(3,3-difluorocyclobutoxy)-1-(trifluoromethyl)-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-[1,3]dioxolane]: LCMS ESI (+) (M+H) m/z 352.

Step E: Preparation of 4-(3,3-difluorocyclobutoxy)-6-fluoro-1-(trifluoromethyl)-5,6-dihydro-7H-cyclopenta[c]pyridin-7-one and 4-(3,3-difluorocyclobutoxy)-1-(trifluoromethyl)-5,6-

dihydro-7H-cyclopenta[c]pyridin-7-one. A solution of impure 4'-(3,3-difluorocyclobutoxy)-6'-fluoro-1'-(trifluoromethyl)spiro[1,3-dioxolane-2,7'-5,6-dihydrocyclopenta[c]pyridine] (39.0 mg, 0.106 mmol) in dichloromethane (2.0 mL) at 0 ^{o}C was treated with perchloric acid (70% in water, 200 uL) and stirred at 0 ^{o}C for 3 h. The reaction mixture was quenched by the addition of 5 mL of saturated aqueous $NaHCO_3$. The resulting mixture was extracted with 3 x 15 mL CH_2Cl_2. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The product was used without further purification as a 2:1 mixture of fluorinated and hydrodefluorinated ketones. Data for 4-(3,3-difluorocyclobutoxy)-6-fluoro-1-(trifluoromethyl)-5,6-dihydro-7*H*-cyclopenta[*c*]pyridin-7-one: LCMS ESI (+) (M+H) m/z 326. Data for 4-(3,3-difluorocyclobutoxy)-1-(trifluoromethyl)-5,6-dihydro-7*H*-cyclopenta[*c*]pyridin-7-one: LCMS ESI (+) (M+H) m/z 308.

*Step G: Preparation of (R)-4-(3,3-difluorocyclobutoxy)-1-(trifluoromethyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-7-ol (**25**) and (6R,7S)-4-(3,3-difluorocyclobutoxy)-6-fluoro-1-(trifluoromethyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-7-ol (**26**).* A solution of impure 4-(3,3-difluorocyclobutoxy)-6-fluoro-1-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyridin-7-one (33.8 mg, 0.10 mmol) in dichloromethane (4.0 mL) was cooled to 0 ^{o}C and sparged with nitrogen for 5 min. During this time formic acid (11.8 uL, 0.31 mmol) and triethylamine (28.8 uL, 0.21 mmol) were sequentially added. Once sparging was complete, RuCl(p-cymene)[(*R*,*R*)-Ts-DPEN] (1.3 mg, 0.002 mmol) was added under a continuous stream of nitrogen. The reaction vessel was sealed and placed into the refrigerator to react overnight. Volatiles were removed by concentration under reduced pressure. The residue was purified by chromatography on silica using 4-18% EtOAc/CH_2Cl_2 to afford (6*R*,7*S*)-4-(3,3-difluorocyclobutoxy)-6-fluoro-1-(trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-ol (**26**) as a clear solid (5.4 mg, 16%) and (*R*)-4-(3,3-difluorocyclobutoxy)-1-(trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-ol (**25**) as a clear solid (7.4 mg, 23%). Data for (6*R*,7*S*)-4-(3,3-difluorocyclobutoxy)-6-fluoro-1-(trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-ol (**26**): Retention time HPLC (14 min) = 3.59 min; LCMS ESI (+) (M+H) m/z 328; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 5.48 – 5.24 (m, 2H), 4.91 – 4.78 (m, 1H), 3.37 – 3.07 (m, 4H), 2.92 – 2.72 (m, 2H), 2.60 (dd, J = 7.3, 4.8 Hz, 1H). Data for (*R*)-4-(3,3-difluorocyclobutoxy)-1-(trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-7-ol (**25**): Retention time HPLC (14 min) = 3.95 min; LCMS ESI (+) (M+H) m/z 310; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 5.61 – 5.53 (m, 1H), 4.90 – 4.77 (m, 1H), 3.26 – 3.05 (m, 3H), 2.95 – 2.72 (m, 3H), 2.39 (dtd, J = 15.0, 8.5, 6.7 Hz, 1H), 2.30 – 2.19 (m, 1H), 2.13 – 2.08 (m, 1H).

(6*R*,7*S*)-4-(3,3-difluorocyclobutoxy)-1-(difluoromethyl)-6-fluoro-6,7-dihydro-5H-cyclopenta[*c*]pyridin-7-ol (28). *Step A: Preparation of 4-bromo-1-(difluoromethyl)-5,6-dihydro-7H-cyclopenta[c]pyridin-7-one (**60**).* A suspension of bis(difluoromethylsulfonyl)zinc (8.6 g, 29.1 mmol) and 4-bromo-5,6-dihydrocyclopenta[*c*]pyridin-7-one (2.0 g, 9.43 mmol) in a mixture of dichloromethane (50 mL) and water (25 mL) at 0 ^{o}C was treated with tert-butyl hydroperoxide (~70% in water, 10 mL, 72 mmol, added via pipette using a plastic tip) and stirred for 2 d, the reaction vessel was placed into a water bath and carefully quenched by the addition of saturated $NaHCO_3$ and Na_2SO_3. Once effervescence ceased, the reaction mixture filtered through a pad of celite to remove solids. The pad of celite was rinsed with additional dichloromethane. The filtrate was separated and the aqueous portion extracted further with 2 x 20 mL CH_2Cl_2. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 50% CH_2Cl_2/hexane to afford 4-bromo-1-(difluoromethyl)-5,6-dihydro-7H-cyclopenta[*c*]pyridin-7-one (**60**) (1.1 g, 44.5%) as an off-white solid. LCMS ESI (+) (M+H) m/z 262/264; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (s, 1H), 7.48 (t, J = 53.8 Hz, 1H), 3.22 – 3.14 (m, 2H), 2.87 – 2.79 (m, 2H).

Step B: Preparation of 4-bromo-1-(difluoromethyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-7-ol. To a solution of 4-bromo-1-(difluoromethyl)-5,6-dihydrocyclopenta[*c*]pyridin-7-one (**60**) (830 mg, 3.17 mmol) in methanol (5 mL) was added $NaBH_4$ (0.19 g, 5 mmol) at 0 ^{o}C. The mixture was stirred at rt for 1 h. After the reaction, it was poured into water and stirred for another 0.5 h. The product was extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, concentrated to dryness to give pure product 4-bromo-1-(difluoromethyl)-6,7-dihydro-5H-cyclopenta[*c*]pyridin-7-ol (800 mg, 95.6%).

*Step C: Preparation of 4-bromo-1-(difluoromethyl)-7-((tetrahydro-2H-pyran-2-yl)oxy)-6,7-dihydro-5H-cyclopenta[c]pyridine (**61**).* To a solution of 3,4-dihydro-2*H*-pyran (382.3 mg, 4.54 mmol) and 4-bromo-1-(difluoromethyl)-6,7-dihydro-5H-cyclopenta[*c*]pyridin-7-ol (800 mg, 3.03 mmol) in dichloromethane (5 mL) was added 4-methylbenzenesulfonic acid (52.2 mg, 0.30 mmol) at 0 ^{o}C. The mixture was stirred at rt for 40 min. After the reaction, aqueous sodium bicarbonate solution was added, and stirred for 10 min. The product was extracted with DCM, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product 4-bromo-1-(difluoromethyl)-7-((tetrahydro-2H-pyran-2-yl)oxy)-6,7-dihydro-5H-cyclopenta[*c*]pyridine (**61**) (1000 mg, 94.8% yield) which was used directly for the next step.

Step D: Preparation of 4-(3,3-difluorocyclobutoxy)-1-(difluoromethyl)-7-((tetrahydro-2H-pyran-2-yl)oxy)-6,7-dihydro-5H-cyclopenta[c]pyridine: A solution of 4-bromo-1-(difluoromethyl)-7-tetrahydropyran-2-yloxy-6,7-dihydro-5H-cyclopenta[*c*]pyridine (**61**) (250 mg, 0.72 mmol), 3,3-difluoro-cyclobutanol (155.2 mg, 1.44 mmol), cesium carbonate (280.7 mg, 0.86 mmol), *t*BuBrettPhos (10.0 mg, 0.02 mmol) and *t*BuBrettPhos-Pd-G3 (12.0 mg, 0.014 mmol) in toluene (2.2 mL) under nitrogen atmosphere in a sealed tube was stirred at 105 ^{o}C overnight. After the reaction, the mixture was poured into water, and the product was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, concentrated and purified by prep-TLC to give pure product 4-(3,3-difluorocyclobutoxy)-1-(difluoromethyl)-7-((tetrahydro-2H-pyran-2-yl)oxy)-6,7-dihydro-5H-cyclopenta[*c*]pyridine (25 mg, 9.2%).

Step E: Preparation of 4-(3,3-difluorocyclobutoxy)-1-(difluoromethyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-7-ol. To a solution of 4-(3,3-difluorocyclobutoxy)-1-(difluoromethyl)-7-tetrahydropyran-2-yloxy-6,7-dihydro-5H-cyclopenta[c]pyridine (25.mg, 0.07mmol) in tetrahydrofuran (2 mL) was added HCl (aq, 3M, 5 mL). The mixture was stirred at rt for 2h. After the reaction, $NaHCO_3$ (aq) was added to quench the reaction. The product was extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered and concentrated to give crude product 4-(3,3-difluorocyclobutoxy)-1-(difluoromethyl)-6,7-dihydro-5H-cyclopenta[*c*]pyridin-7-ol (25 mg) which was used directly in the next step.

*Step F: Preparation of 4-(3,3-difluorocyclobutoxy)-1-(difluoromethyl)-5,6-dihydro-7H-cyclopenta[c]pyridin-7-one (**62**).* To a solution of unpurified 4-(3,3-difluorocyclobutoxy)-1-(difluoromethyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-7-ol (25 mg, 0.09 mmol) in dichloromethane (5 mL) was added Dess-Martin reagent (84 mg, 0.20 mmol) at 0 ^{o}C . The resulting mixture was stirred at rt for 3 h. $NaHCO_3$ (aq) was added to quench the reaction, the product was extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified by prep-TLC to give pure product 4-(3,3-difluorocyclobutoxy)-1-(difluoromethyl)-5,6-dihydro-7H-cyclopenta[*c*]pyridin-7-one (**62**) (13 mg, 52.3%) as a white solid. LCMS ESI (+) (M+H) m/z 290.

Step G: Preparation of 4-(3,3-difluorocyclobutoxy)-1-(difluoromethyl)-6-fluoro-5,6-dihydro-7H-cyclopenta[c]pyridin-7-one. Steps F and G of **Example 21** were followed. Purification was achieved by chromatography on silica using 10% EtOAc/hexane to afford 4-(3,3-difluorocyclobutoxy)-1-(difluoromethyl)-6-fluoro-5,6-dihydro-7H-cyclopenta[*c*]pyridin-7-one (10 mg, 82% yield) as a white solid.

*Step H: Preparation of (6R,7S)-4-(3,3-difluorocyclobutoxy)-1-(difluoromethyl)-6-fluoro-6,7-dihydro-5H-cyclopenta[c]pyridin-7-ol (**28**).* A solution of the 4-(3,3-

difluorocyclobutoxy)-1-(difluoromethyl)-6-fluoro-5,6-dihydrocyclopenta[*c*]pyridin-7-one (10 mg, 0.033 mmol) in dichloromethane (3 mL) was cooled to 0 °C and sparged with nitrogen for 5 min. formic acid (4.9 μL, 0.13 mmol) and triethylamine (13.6 μL, 0.098 mmol) were sequentially added. Then [(*R*,*R*)-Ts-DPEN]RuCl(*p*-cymene) (3.8 mg, 0.010 mmol) was added under a continuous stream of nitrogen. The reaction vessel was sealed and put into the refrigerator to react overnight. Volatiles were removed by concentration under reduced pressure. The residue was purified by prep-TLC to give (6*R*,7*S*)-4-(3,3-difluorocyclobutoxy)-1-(difluoromethyl)-6-fluoro-6,7-dihydro-5H-cyclopenta[*c*]pyridin-7-ol (**28**) (4.0 mg, 39.7%). Data for (6*R*,7*S*)-4-(3,3-difluorocyclobutoxy)-1-(difluoromethyl)-6-fluoro-6,7-dihydro-5H-cyclopenta[*c*]pyridin-7-ol (**28**): LCMS ESI (+) (M+H) m/z 310; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 6.93 (t, J = 54.8 Hz, 1H), 5.50 – 5.27 (m, 2H), 4.88 – 4.76 (m, 1H), 3.30 (ddd, J = 21.6, 18.2, 2.5 Hz, 1H), 3.24 – 3.01 (m, 3H), 2.90 – 2.74 (m, 2H), 2.71 (dd, J = 8.3, 4.5 Hz, 1H).

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[7] Previously described as intermediate **31g** in: Wehn, P. M.; Rizzi, J. P.; Dixon, D. D.; Grina, J. A.; Schlachter, S. T.; Wang, B.; Xu, R.; Yang, H.; Du, X.; Han, G.; Wang, K.; Cao, Z.; Cheng, T.; Czerwinski, R. M.; Goggin, B. S.; Huang, H.; Halfmann, M. M.; Maddie, M. A.; Morton, E. L.; Olive, S. R.; Tan, H.; Xie, S.; Wong, T.; Josey, J. A.; Wallace, E. M. Design and activity of specific hypoxia-inducible factor-2α (HIF-2α) inhibitors for the treatment of clear cell renal cell carcinoma: Discovery of clinical candidate (S)-3-((2,2-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile (PT2385). *J. Med. Chem.* **2018**, *61*, 9691– 9721, DOI: 10.1021/acs.jmedchem.8b01196

[8] For examples 1-3, the R-group was installed as the appropriate alcohol in Step B. Thus, methanol was used in place of PMB-OH for the S_{NAr} reaction for example 1. The other steps were followed until step E,

where the sequence ended and $NaBH_4$ in MeOH was used for racemic reduction of the ketone. $NaBH_4$ reduction in MeOH was previously described in reference for end note 7.

[9] Prepared by the following method: A solution of 3-fluoro-5-iodo-benzonitrile (4.79g, 19.38mmol) and ANISOLE (2.11mL, 19.38mmol) in a mixture of dichloromethane (77 mL) and trifluoroethanol (77 mL) at room temperature was treated sequentially with 3-chloroperbenzoic acid (4.78 g, 19.38 mmol) and p-toluenesulfonic acid monohydrate (3.69 g, 19.38 mmol). The reaction mixture was left to stir overnight. Initial LCMS indicates formation of the diaryliodonium. The reaction mixture was concentrated to dryness and then the residue suspended in 24 mL of Et_2O and stirred for 10 min. A precipitate formed which was collected, rinsed with more Et_2O, dried under high vac in the presence of solid NaOH, and used without further purification (7.11 g of product, 69% yield).