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Design of Development Candidate eFT226, a First in Class Inhibitor of Eukaryotic Initiation Factor 4A RNA Helicase

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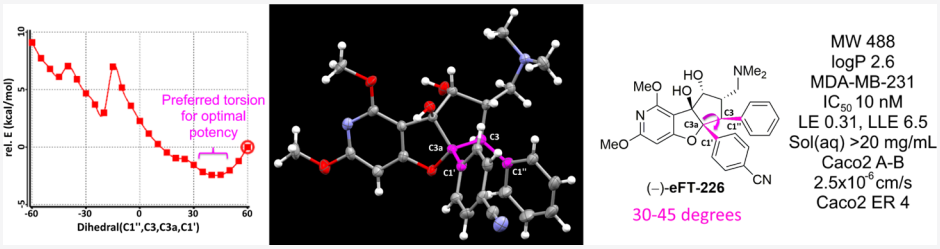

ABSTRACT: Dysregulation of protein translation is a key driver for the pathogenesis of many cancers. Eukaryotic initiation factor 4A (eIF4A), an ATP-dependent DEAD-box RNA helicase, is a critical component of the eIF4F complex, which regulates cap-dependent protein synthesis. The flavagline class of natural products (*i.e.*, rocaglamide A) has been shown to inhibit protein synthesis by stabilizing a translation−incompetent complex for select messenger RNAs (mRNAs) with eIF4A. Despite showing promising anticancer phenotypes, the development of flavagline derivatives as therapeutic agents has been hampered because of poor drug-like properties as well as synthetic complexity. A focused effort was undertaken utilizing a ligand-based design strategy to identify a chemotype with optimized physicochemical properties. Also, detailed mechanistic studies were undertaken to further elucidate mRNA sequence selectivity, key regulated target genes, and the associated antitumor phenotype. This work led to the design of **eFT226** (Zotatifin), a compound with excellent physicochemical properties and significant antitumor activity that supports clinical development.

INTRODUCTION

The dysregulation of messenger RNA (mRNA) translation is a common feature in malignancies, demonstrated by an upregulation of oncoproteins, growth factors, and signal transduction proteins associated with proliferation, survival, and metastasis.[1−4] The expression of oncogenic drivers is held under tight translational control and is regulated by the eukaryotic translation initiation factor 4F (eIF4F) complex.[5,6] The eIF4F complex consists of the 5′-mRNA cap binding protein eIF4E, a large scaffolding protein eIF4G and the DEAD box RNA helicase eukaryotic initiation factor 4A (eIF4A). eIF4A functions in an ATP-dependent manner to unwind an mRNA secondary structure to enable ribosome scanning and translation initiation.[6] The eIF4F subunits are frequently overexpressed in various malignancies; therefore, targeting the components of the eIF4F complex to renormalize dysregulated translation is an emerging strategy in anticancer drug discovery.[2,7−11] Our efforts focused on the identification of inhibitors of eIF4A-mediated translation.

Activation of eIF4F has a direct role in tumorigenesis due to increased synthesis of oncogenes with highly structured 5′-UTRs that are dependent on enhanced eIF4A RNA helicase activity for translation.[1−6,12] Several natural product classes have been reported to inhibit eIF4A-mediated translation and exhibit antiproliferative and antitumor phenotypes both *in vitro* and *in vivo*.[13−20] The flavaglines, exemplified by silvestrol (**1**) and rocaglamide A (**2**), have been shown to bind and stabilize a translation incompetent RNA/eIF4A complex. Recent studies demonstrate that the formation of a ternary complex between eIF4A, mRNA, and rocaglamide A is specific for polypurine motifs in the 5′-UTR of select mRNAs resulting in a small molecule sequence-selective translational repressor.[21,22] Hippuristanol (**3**), an oxygenated steroid, has been shown to bind an allosteric site in the C-terminal domain of eIF4A and stabilizes a conformation that is incompatible with RNA

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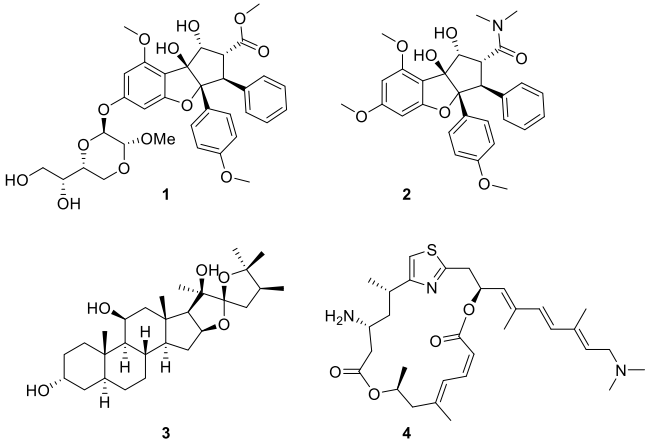
binding.[23] Pateamine A (**4**) has been reported to irreversibly bind eIF4A, resulting in the stabilization of an RNA/eIF4A complex discordant with translation.[24] Numerous drug discovery efforts have been invested in the flavaglines, however, to date, none of these programs have led to the advancement of a development candidate into human clinical studies. Major challenges include overcoming poor drug-like properties such as metabolic instability and poor solubility, as well as developing a robust synthetic methodology to produce the drug substance on a scale necessary to support clinical development. Thus, one of our main tactics in exploiting the flavagline class of molecules was to focus on improving physicochemical properties. The optimization of properties such as log *P* and aqueous solubility were important to support controlled intravenous delivery of an optimal therapeutic dose. Herein we report on our design efforts that led to the identification of **eFT226**, the first eIF4A inhibitor to enter human clinical studies.



OPTIMIZATION OF THE FLAVAGLINE-BASED NATURAL PRODUCTS TO YIELD EFT226

From the known flavagline-based derivatives, we focused our initial attention on rocaglamide A (**2**) which has published literature supporting its mechanism for inhibiting eIF4A-mediated translation.[13,25,26] During the design and development of **eFT226**, an X-ray crystal structure of a rocaglamide derivative/mRNA/eIF4A1 complex had not been published. Utilizing reported eIF4A1 mutational data (mutations conferring resistance to flavagline derivatives),[25] a small molecule crystal structure of a flavagline from the Cambridge Structural Database (CSD), and an X-ray structure of related isoform eIF4A3 bound to polyuracil RNA (2HYI),[27] a molecular model was devised to analyze the potential binding complex formed between RNA, rocaglamide A, and eIF4A1 (Figure 1). In this model, the phenyl A and D rings of rocaglamide A are positioned to promote pi-stacking with the RNA bases at the RNA/eIF4A1 interface (see Table 1 for compound ring assignment). The phenyl D and E rings are proposed to bind into two adjacent hydrophobic pockets on eIF4A1 which contain amino acid residues that have been shown through mutational studies to be critical for small molecule binding. A predicted hydrogen bond between an N−H side chain of Gln 195 and rocaglamide A's carbonyl oxygen of the dimethyl amide group provides additional protein ligand stabilization. This model allowed us to make key inferences to aid in design, namely: (1) a key contributor to the binding interaction could

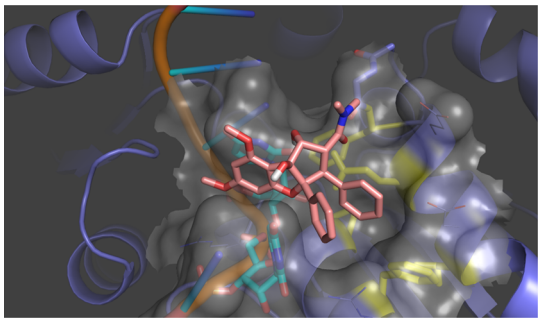


Figure 1. Modeled binding mode of rocaglamide A (pink) to a complex formed by poly-U RNA (light blue) and eIF4A3 (dark blue). Residues of eIF4A shown to confer resistance to rocaglamide analogues are highlighted in (yellow), PDB ID 2HYI.

be pi-stacking between the mRNA bases, the benzofuran and one of the phenyl rings of the natural product; (2) the phenyl ring distal to the mRNA binds in a pocket of quite limited size and thus might accommodate limited substitution; (3) the potential importance of the hydrogen bond between Gln 195 and the small molecule; and (4) that silvestrol's dioxane ring likely binds in an open site on the opposite side of the RNA from the rocaglamide core and thus may not be an efficient binding element. Although this model was useful, it was considered low resolution, prompting the development of additional computational methodologies for assessing compound designs.

We were intrigued at the outset of the program by the unique three-dimensional structure of the flavagline core, a result of five contiguous stereocenters in the molecule on a five-membered-ring. Unlike six-membered-rings, the conformations of five-membered rings are much less predictable because they undergo pseudorotation. Understanding the preferred conformation of this system and how this is related to the observed phenotypes and potency SAR for this class of molecules was deemed critical for the optimization process that could offer a ligand-based modeling methodology for evaluating potential compounds. *Ab initio*, density functional theory (DFT) calculations performed on rocaglamide A predicted the low energy conformation to have an intramolecular hydrogen bond between the secondary hydroxyl and the methoxy group at the 8-position. Importantly, the preferred low energy torsional angle between the phenyl D and E rings was found to be approximately 40° (Figure 2). We hypothesized that this preferred torsion might be a prerequisite for potent binding to the protein−RNA complex and might be utilized to prioritize potential targets. DFT calculations that drove the aryl−aryl torsional angle between ±60° at 5° increments of a flavagline molecule produced an energy profile, an example of which is shown in Figure 2 for rocaglamide A. It was discovered that cores that embodied a 40-degree aryl−aryl torsion as a preferred low-energy conformation tended to display highest potency while cores without a low energy 40° torsion generally did not produce potent molecules. This model was used prospectively to filter out molecular designs lacking the desired energy profile.

Recently, an X-ray crystal structure (2 Å resolution) of the ternary complex formed between eIF4A1, rocaglamide A, and a polypurine RNA sequence was disclosed (Figure 3).[22] Interestingly, the binding mode of rocaglamide A in the crystal structure is quite analogous to our proposed model and confirms the 40° aryl−aryl torsion hypothesis. The X-ray

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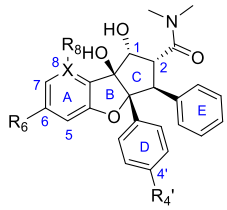
Table 1. SAR Data for Flavagline Derivatives 2−23



compound	X	R_8	R_6	$R_{4'}$	cell IC_{50} nM	clog *P*	LE	LLE
2 (-)	C	OMe	OMe	OMe	20 ± 9	3.72	0.29	4.0
5 (*rac*)	N		OMe	OMe	990	3.05	0.25	3.3
6 (*rac*)	C	H	OMe	OMe	198 ± 51	3.73	0.28	3.3
7 (-)	N		OMe	CN	159 ± 84	2.56	0.27	4.2
8 (-)	N		Cl	CN	87 ± 26	2.92	0.29	4.1
9 (-)	N		CN	CN	385 ± 147	1.73	0.25	4.7
10 (*rac*)	C	H	Cl	OMe	52 ± 15	4.49	0.31	3.1
11 (*rac*)	C	H	Cl	CN	19 ± 3	4.01	0.33	4.0
12 (*rac*)	C	H	OMe	CN	68 ± 18	3.24	0.29	4.2
13 (*rac*)	C	H	CN	OMe	38 ± 1	3.40	0.30	4.3
14 (*rac*)	C	H	CN	CN	26 ± 2	2.91	0.31	5.0
15 (-)	N		Cl	OMe	283 ± 142	3.40	0.27	3.1
16 (-)	N		CN	OMe	601 ± 266	2.22	0.25	4.0
17 (-)	N		Cl	Me	143 ± 24	3.98	0.29	2.9
18 (-)	N		Cl	Cl	160 ± 46	4.19	0.26	2.6
19 (-)	N		Cl	F	>1000	3.62		
20 (-)	N		Cl	CF_2H	241 ± 58	3.67	0.26	2.9
21 (-)	N		Cl	CF_3	320 ± 68	4.36	0.25	0.21
22 (-)	N		Cl	OCF_3	603 ± 167	4.51	0.23	1.7
23 (-)	N		Cl	SO_2Me	>1000	1.84		

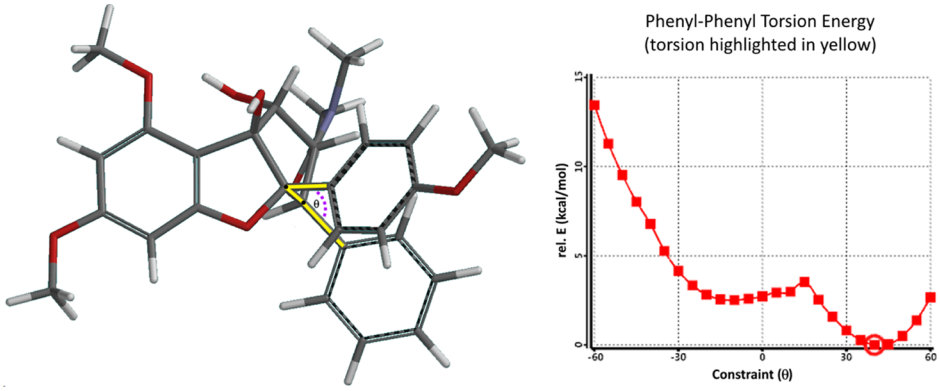


Figure 2. Conformational analysis of rocaglamide A.

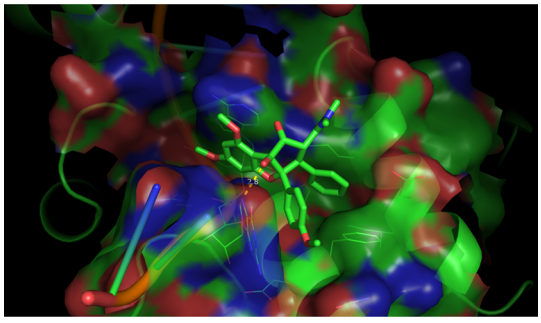


Figure 3. X-ray structure of a ternary complex formed between rocaglamide A, eIF4A1, and a polypurine RNA sequence showing the hydrogen bond from the tertiary hydroxyl group to the purine N7, PDB ID 5ZC9.[22]

structure discloses an additional hydrogen bonding interaction between the rocaglamide tertiary hydroxyl and N7 of an adjacent RNA guanine base. This interaction is hypothesized to impart sequence selectivity for the stabilization of purine sequences to eIF4A1.

Initial efforts focused on optimization of the phenyl A ring of rocaglamide A to promote pi-stacking with the RNA base and impart sequence selectivity. We reasoned that the pi-stacking interaction with RNA could potentially accommodate a heterocycle in place of the phenyl A ring, a strategy that would lower the lipophilicity of the core. Replacement of the phenyl A ring in the rocaglamide system with a heterocycle is unprecedented in the literature. We focused on utilizing pyridine as a replacement as this would be a minimal structural change and one that could greatly reduce the log *P*(−0.67) of the scaffold. Incorporation of the pyridine nitrogen at the 8-

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position of the core was explored first because the nitrogen at this position could potentially mimic the methoxy group's hydrogen bond acceptor properties and eliminating one of the methoxy groups would further reduce the lipophilicity of the system. As stated earlier, conformational analysis of rocaglamide A indicated that the methoxy oxygen at the 8-position forms a 7-membered intramolecular hydrogen bond with the secondary hydroxyl at the 1-position, reinforcing the bioactive conformation of the natural product core. Replacement with a pyridine would enable a six-membered intramolecular hydrogen bonding arrangement. Pyridine **5** (Table 1) was synthesized and was found to be 25-fold less potent than rocaglamide A in the MDA-MB-231 breast cancer cell proliferation assay. It should also be noted that for racemates, the potencies are assumed to be 50% as potent as the active enantiomer (the opposite enantiomers are completely inactive; data not shown). To fully evaluate this structural change, the des-8-methoxy derivative of rocaglamide A was also prepared (**6**) and was found to be 5-fold more potent than **5**. Interestingly, lipophilic ligand efficiency (LLE) analysis showed that the loss in potency for the pyridine system is entirely driven by a reduction in clog *P* (**5** and **6** are iso-LLE). To further reduce the lipophilicity and potentially improve potency [as well as ligand efficiency (LE) and LLE], the 4′-methoxy group was replaced with a nitrile, a modification previously reported in the literature to improve the potency of the rocaglamide system.[14] Nitrile analogue **7** was found to have threefold improved potency versus **5**, an increase similar to that reported for this modification in related chemotypes. Modeling of compound **7** in the binding pocket suggested that the nitrile group fits into a narrow groove formed by the RNA and eIF4A and is positioned to potentially interact with the side chain of Asn 167 (Figure 4). We were encouraged at this point because

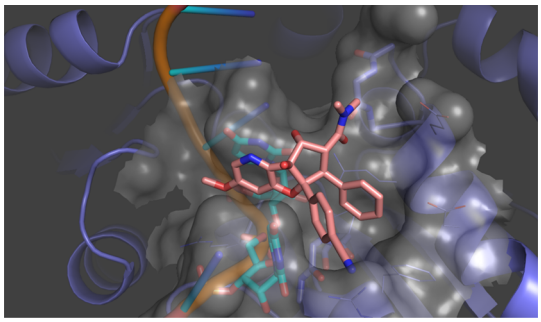

Figure 4. Modeling of compound **7** in the binding pocket formed from eIF4A in complex with poly-U RNA, PDB ID 2HYI.

compound **7** has similar LE and LLE values as rocaglamide A, however with a significant overall reduction in clog *P* (−1.2 logs). A review of the literature suggested that replacement of the 6-position methoxy of the rocaglamide core with either a chloro or nitrile group could also improve potency.[14] Chloro analogue **8** showed slightly improved potency versus **7** while maintaining LLE, whereas the nitrile analogue **9** exhibited modestly reduced potency, however, with an improved LLE. An X-ray structure was obtained for compound **8** and confirmed the intramolecular hydrogen bond between the secondary hydroxyl and the pyridine nitrogen (Figure 5). The structure also showed a torsional angle of 40° between the D and E phenyl rings, consistent with earlier conformational analyses conducted with rocaglamide A.

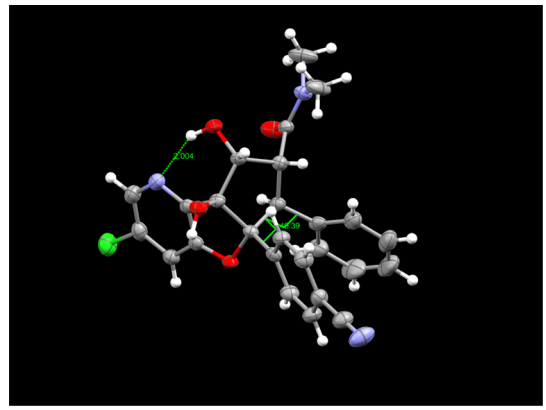

Figure 5. X-ray structure for compound **8** highlighting the intramolecular hydrogen bond between the secondary hydroxyl and the pyridine nitrogen and the 40° Ar−Ar torsion.

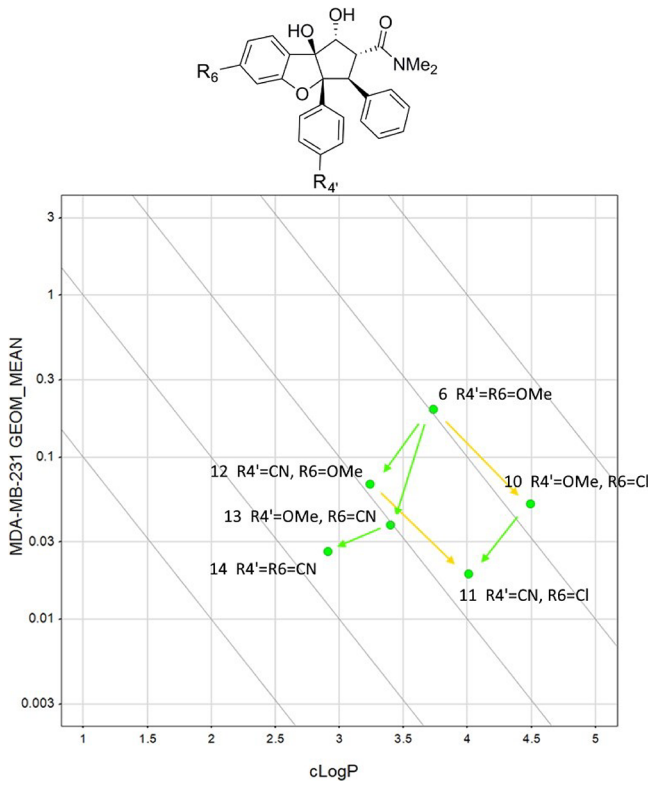

Figure 6. LLE plot for ring A phenyl series. Iso-LLE changes between compounds are shown with yellow arrows while changes resulting in LLE improvement are shown in green.

The decreased potency with nitrile **9** was the first indication of divergence of potency SAR between the pyridine and phenyl A-ring systems. Comparison of phenyl analogues **6**, **10**−**14** with an LLE analysis (Figure 6) indicated that the increase in potency with 6-chloro substitution is driven by a lipophilicity increase, whereas both 4′-nitrile and 6-nitrile substitutions lead to potency increases *via* enthalpic contributions. Interestingly, the analogous plot with pyridines **5**, **7**−**9**, and **15**−**16** (Figure 7) indicated that the potency increase with 4′-nitrile substitution is enthalpically driven, but both the increase in potency with 6-chloro substitution and the decrease in potency with 6-nitrile substitution follow iso-LLE shifts, indicative of lipophilic-driven potency changes. It should be noted that the permeability properties of the 6-nitrile analogues were similar to

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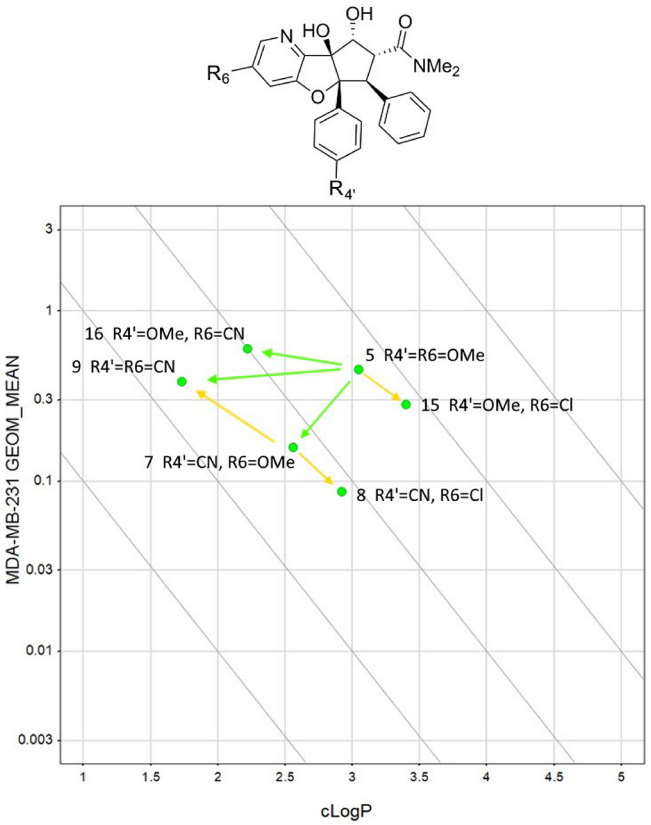


Figure 7. LLE plot for ring A pyridine series. Iso-LLE changes between compounds are shown with yellow arrows while changes resulting in LLE improvement are shown in green.

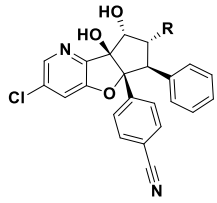
the 6-methoxy analogues; thus, variations in cell permeability were ruled out as possible explanations for the observed potency SAR (data not shown). One explanation for the SAR differences between the pyridine and phenyl systems could be subtle differential effects of ring substitution on the pi stacking interactions with RNA in the ternary complex.

Utilizing chloro analogue **8** the 4′-position was further interrogated (analogues **17**−**23** in Table 1), focusing on functional groups previously unexplored in the literature at this position of the molecule. Ultimately, all changes at this position resulted in a loss of potency versus the nitrile substituent.

Modifications to the dimethyl amide functionality at the 2-position of compound **8** were also explored (Table 2). Complete removal of the amide side chain (**24**) resulted in a significant reduction in potency. Interestingly, the secondary (**25**) and primary amide (**26**) derivatives had slightly improved or equal potency, respectively. However, in both cases the permeability was reduced (CACO AB = 0.5×10^{-6} cm/s) versus tertiary amide **8** (CACO AB = 1.8×10^{-6} cm/s). Several amide isosteres were also tested (**27**−**30**), as well as the amino and alcohol analogues **31** and **32**, respectively, and all were found to be less potent than the parent system.

At this point, further exploration of the pyridine A ring was conducted to improve potency while continuing to optimize the physicochemical properties of the scaffold. Analogues **33**−**36** were synthesized to probe the optimal pyridine regioisomers of this system (Table 3). The 7-position pyridyl isomers, having either cyano substitution at the 6-position (**33**) or methoxy substitution at the 8-position (**34**), demonstrated modest potency. Interestingly, the 6-position pyridyl isomer (**35**),

Table 2. Modifications to the 2-Position of the Flavagline Core



compound	R	cell IC_{50} nM
24 (*rac*)	H	670 ± 12
25 (-)	CONHMe	32 ± 4
26 (-)	$CONH_2$	90 ± 24
27 (*rac*)	2-oxazole	236 ± 63
28 (*rac*)	$SO_2N(Me)_2$	304 ± 73
29 (*rac*)	SO_2NHMe	2037 ± 978
30 (-)	SO_2Me	3018 ± 110
31 (-)	$CH_2N(Me)_2$	239 ± 123
32 (*rac*)	CH_2OH	1465 ± 1657

utilizing the methoxy substitution at the 8-position, was found to be 2−3-fold more potent than **8** (equal LE and improved LLE *vs* **8**) and within 2-fold of the potency of rocaglamide A. This was a striking result given previous reports of the importance of 6-position substitution (phenyl A ring chemotype) for potency.[14] Also intriguing, the 5-pyridyl isomer (**36**) is inactive, further demonstrating that subtle electronic differences in the A-ring can have a dramatic impact on potency. Modeling of **36** in the RNA/eIF4A binding site indicated that the lone pair of electrons of the 5-pyridine would be in close proximity to the polar RNA backbone, a situation that would be highly disfavored for binding (Figure 8).

Based on the improved potency and LLE relative to **8**, compound **35** was selected for further optimization. Analysis of the DMPK properties of **35** (Table 4) revealed poor CACO permeability and aqueous solubility; however, a good rat PK profile was observed following intravenous dosing. The poor aqueous solubility was a concern as this could potentially create formulation challenges for clinical studies utilizing IV infusions. Therefore, a strategy was sought that could greatly improve the aqueous solubility of the scaffold as well as improve permeability properties. Replacement of the dimethyl amide group at the 2-position with a solubilizing basic amine side chain was revisited in the context of analogue **35**. Previously, replacement with the dimethylamino-methylene side chain in the 8-pyridyl series resulted in a 2−3-fold loss of potency (**31** *vs* **7**). The analogous analogue was prepared in the 6-pyridyl series (**37**) and was found to be within 2-fold of the potency of dimethyl amide **35** (Table 4). The basic amine side chain greatly improved the aqueous solubility of the scaffold (>20 mg/mL for **37** *vs* 0.22 mg/mL for **35**) while maintaining the overall LE. The LLE of **37**, however, was slightly reduced versus **35**. Compound **37** showed no inhibition in a hERG functional patch-clamp assay, a liability often associated with basic molecules. However, incorporation of the basic amine did further increase Pgp-mediated efflux and resulted in higher rat IV clearance (Table 4). Given the solubility advantages of the amine side chain, an extensive effort was conducted to optimize this group to maintain the attractive solubility, potency, and hERG off-target profiles and mitigate issues with efflux and IV clearance. A focused library (compounds **38**−**52**) was generated in which the sterics, lipophilicity, and pK_a properties

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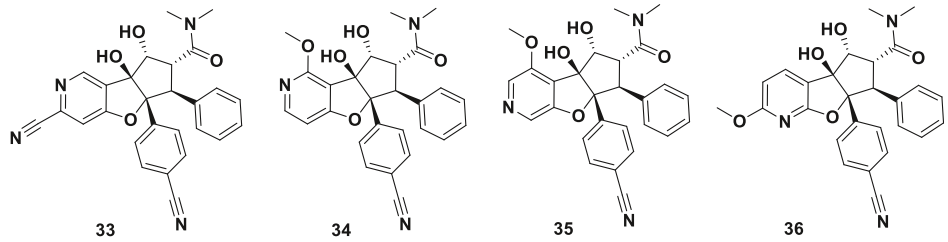
Table 3. Profiles of Pyridine Analogues 33−36



compound	cell IC_{50} nM	clog *P*	LE	LLE
33 (-)	308 ± 84	1.93	0.26	4.6
34 (*rac*)	314 ± 19	2.96	0.27	3.8
35 (-)	33 ± 9	2.56	0.29	4.9
36 (*rac*)	>1000	2.96		

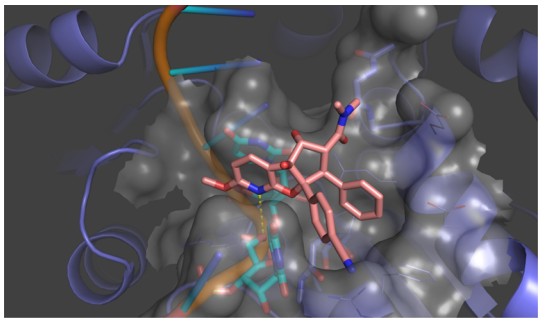
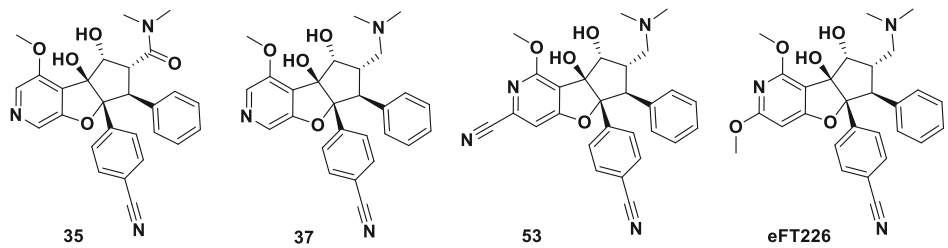


Figure 8. Binding model for compound **36**. The 3.9 Å contact between the pyridine nitrogen of **36** and one of the phosphate ether oxygens of the RNA backbone is shown, PDB ID 2HYI.

of the amine side chain of **37** were modulated (Table 5). Analogues with similar basicity as **37** (*i.e.*, **40**, **41**, **49**, **50**, **52**), regardless of sterics and lipophilicity of the amine, were found to have poor permeability properties. Reducing the pK_a of the amine (*i.e.*, analogues **42**−**46**, **51**) in general reduced efflux, but also reduced antiproliferative potency. Analysis of hERG SAR indicated a strong correlation to lipophilicity (preferred range clog *P* < 2.5) but not to pK_a (comparing analogues **41** and **42**). Ultimately, the library was unsuccessful in identifying amine-containing candidates in the 6-pyridyl series with the desired potency, hERG, and permeability properties.

At this stage it was decided to analyze the 2-position amino side chain in the context of the 7-pyridyl system (represented by analogues **33** and **34**), with the expectation that this system might have improved permeability due to increased shielding of the pyridine nitrogen. It was also reasoned that a potency increase was possible by combining substitutions at the 8 and 6-positions of the A-ring (mimicking the original substitution pattern of rocaglamide A). Thus, compound **53** was prepared and found to be 3−4 fold more potent versus **37** (equal LE and improved LLE; Table 4) and maintained excellent aqueous solubility. Compound **53** also showed an improved CACO profile, however, the efflux ratio was still deemed to be too high (efflux was viewed as a risk for potential MDR-based resistance mechanisms). Analogue **53** was evaluated in rat IV PK and found to have reduced clearance versus **37** (Table 4). To mitigate the efflux liability of this system, the PSA was reduced by replacing the 6-position nitrile with a methoxy group. This modification ultimately led to the discovery of **eFT226**, an analogue with similar potency as compound **53**, however with improved LE, LLE, CACO permeability, and reduced efflux (Table 4). It is interesting to note that despite significant optimization efforts at the 8 and 6-positions, ultimately **eFT226** retained the A-ring bis-methoxy substitution pattern found in rocaglamide A. As stated previously, two prioritized goals for the program were to identify a development candidate with reduced lipophilicity and increased aqueous solubility versus the rocaglamide natural products. The experimentally measured log *P* and log *D* 7.4 values for **eFT226** are 2.6 and 1.5, respectively, thus demonstrating a high level of lipophilic optimization (**eFT226** LLE = 6.5). The thermodynamic aqueous solubility of **eFT226**, driven in large part by the basic dimethylamino side chain (pK_a = 8.6), is > 20 mg/mL (as

Table 4. Potency, Solubility, CACO Permeability and *in Vivo* Rat PK (1 mg/kg) Properties for 35, 37, 53, and eFT226



compound	cell IC_{50} nM	LE	LLE	solubility mg/mL	CACO AB 1×10^{-6} cm/s	CACO ER	hERG IC_{50} μM	Cl mL/min/kg	Vdss L/kg	$T_{1/2}$ h	AUC h μg/mL
35 (-)	33 ± 9	0.29	4.9	0.22	0.65	5		18	1.1	2.0	0.95
37 (-)	54 ± 4	0.29	4.6	>20	0.21	22	>10	39	5.2	2.9	0.44
53 (-)	15 ± 3	0.29	5.3	>20	1.0	11	>10	26	10.3	11.0	0.73
eFT226 (-)	10.6 ± 0.9	0.31	6.5	>20	2.5	4	>10	48	13.0	4.4	0.39

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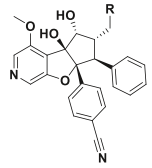
Table 5. SAR Studies for 2-Position Amine Analogues



Compound	R	CACO AB 10^{-6} cm/s	CACO ER	RLM, HLM	hERG %INH @ 10 μM	Cell IC $_{50}$ nM	clogP
37 (+)		0.2	23	72, 75	11	54 ± 4	2.6
38 (rac)		0.3	3.9	90,98	<10	482 ± 68	2.1
39 (rac)		0.11	4.0	104, 106	11	211 ± 39	1.8
40 (-)		0.3	35	76, 73	40	62 ± 8	3.7
41 (-)		0.6	17	56, 81	18	50 ± 1	3.2
42 (-)		4.8	1.7	42, 45	30	158 ± 29	2.6
43 (-)		1.5	5.3	52, 40	< 10	121 ± 53	2.0
44 (-)		2.6	3.2	<1, 1	11	250 ± 26	3.2
45 (+)		7.1	1.3	<1, <1	-	196 ± 33	3.4
46 (-)		1.9	5.7	-	< 10	208 ± 32	3.3
47 (-)		0.1	41	74, 81	-	124 ± 8	1.8
48 (-)		-	-	92, 99	< 10	301 ± 78	3.3
49 (-)		0.1	57	77, 61	16	140 ± 37	3.9
50 (-)		0.5	35	68, 62	-	143 ± 96	3.5
51 (-)		1.9	5.3	51, 51	-	101 ± 15	2.3
52 (rac)		0.1	27	77, 75	11	143 ± 14	2.4

HCl salt), representing a significant improvement versus rocaglamide A. Both of these properties greatly enhance the drug-ability of **eFT226** facilitating intravenous delivery.

CHARACTERIZATION OF CLINICAL CANDIDATE EFT226

Sequence recognition motifs within the 5′-UTR of select target genes have been shown to drive sensitivity to rocaglate inhibition of eIF4A1.[21,22,28] The sequence specificity of **eFT226** for polypurine (AGAGAG), G-quadruplex like (GGCGGC), or control 5′-UTR recognition motifs was tested using surface plasmon resonance. Direct binding studies showed that eIF4A1 alone bound weakly (3−8 μM) to RNA and only in the presence of ATP. Addition of **eFT226** induced the formation of an RNA sequence-dependent ternary complex between eIF4A1 and polypurine (AGAGAG) RNA motifs in a nucleotide (ATP, ADP) independent manner. **eFT226** increased the binding affinity (K_D) of eIF4A1 to an AGAGAG polypurine RNA oligonucleotide by >100-fold in the presence of ATP (K_D 21−69 nM) due to a change in binding kinetic rates resulting in a slow off rate and prolonged residence time for eIF4A1 bound to the polypurine RNA motif (Figure 9), a

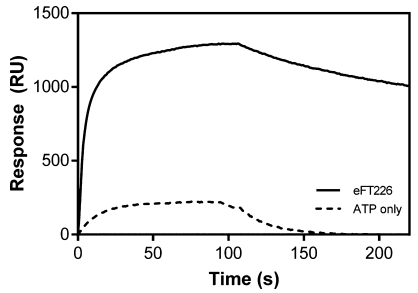


Figure 9. eFT226 enhances formation of eIF4A1/RNA complex. Sensograms of eIF4A1 binding to rAGA surface in the presence (solid) or absence (dashed) of **eFT226**. The sensograms were fitted using a global fitting function to determine the equilibrium dissociation constant and binding kinetics. Running buffer contained 14.4 mM Hepes pH 7.4, 108 mM NaCl, 1 mM $MgCl_2$, 0.36 mM TCEP, 1 mM ATP, and 1% dimethyl sulfoxide (DMSO). Data were collected at 25 °C.

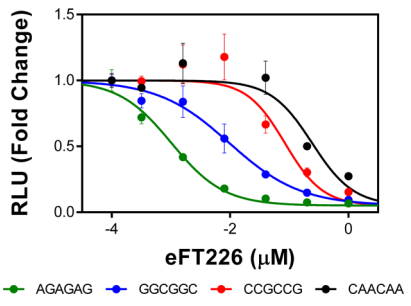


Figure 10. eFT226 inhibition of reporter gene expression is dependent upon the 5′ UTR sequence. Relative luciferase expressed by luciferase reporter mRNAs containing 5′-UTRs encoding unique 6-mer sequence motifs. The luciferase reporter gene constructs were transiently transfected into the MDA-MB-231 cell line and treated with increasing concentrations of **eFT226** for 4 h in triplicate. Data were fitted to a four-parameter dose response curve. AGAGAG (green); GGCGGC (blue); CCGCCG (red) and CAACAA (black).

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mechanism of inhibition similar to that reported for Rocaglamide A (Table 6).[21] **eFT226** did not induce a stable ternary complex with RNA oligonucleotides containing GGCGGC, CCGCCG, or CAACAA sequence motifs (Table 6), nor was binding observed for eIF4A1 to DNA oligo sequences (Supporting Information), demonstrating the selectivity of the **eFT226** induced ternary complex.

Table 6. Binding Characteristics of eFT226-Induced Ternary Complex Formation with Different RNA Sequences

RNA sequence	K_D (μM) with **eFT226**	K_D (μM) without **eFT226**	K_D (μM) with Roc A
AGAGAG + ATP	0.021 (±0.001)	8.0 (±0.9)	0.156 (±0.007)
GGCGGC + ATP	3.19 (±0.03)	8.0 (±0.3)	NA
CCGCCG + ATP	9.6 (±0.4)	3.27 (±0.06)	NA
CAACAA + ATP	2.43 (±0.01)	3.78 (±0.05)	NA

RNA sequence	half-life $t_{1/2}$, s
AGAGAG + ATP + **eFT226**	79
AGAGAG + AMP-PNP + **eFT226**	2311

The binding kinetics for the formation of the ternary complex with eIF4A1−**eFT226**−AGAGAG RNA was evaluated when ATP was replaced with AMP-PNP, a nonhydrolysable analogue of ATP. After formation of the ternary complex, the SPR surfaces were washed with buffer containing only ATP or AMP-PNP to evaluate the ternary complex dissociation. The dissociation rate of eIF4A1 from the polypurine RNA was ∼30-fold slower when using the nonhydrolysable ATP analogue, suggesting that ATP hydrolysis results in a conformational change that destabilizes the eIF4A1−**eFT226**−polypurine RNA complex (Table 6). Collectively, these results demonstrate that **eFT226** is a potent and reversible inhibitor of eIF4A through the formation of a stable ternary complex with select polypurine RNA motifs.

To determine whether the sequences that facilitate the formation of the ternary complex enable selective inhibition of protein synthesis with **eFT226** treatment, MDA-MB-231 cells were transiently transfected with a luciferase reporter system containing specific tandem sequence motif repeats in the 5′-UTR (see Table 7). Treatment with **eFT226** inhibited translation of each reporter construct in a dose-dependent manner (Figure 10). However, **eFT226** was 16-145-fold more effective at inhibiting luciferase reporter gene expression for the GGCGGC and AGAGAG constructs, respectively, versus a CAACAA sequence element (Table 7). These data are consistent with the order of binding affinity observed *in vitro* and the antiproliferative potency of **eFT226** in the MDA-MB-231 tumor cell line. In addition, eFT226 was not effective at inhibiting translation for the reporter construct containing a complementary CCGCCG motif.

Table 7. Sequence Specificity of eFT226 Translational Regulation in a Cell-Based Assay

5′-UTR sequence motif	**eFT226** IC_{50} (nM)	Roc A IC_{50} (nM)	hippuristanol IC_{50} (nM)	CHX IC_{50} (nM)
AGAGAG	1.5 ± 0.4	4.7	426	226 ± 55
GGCGGC	13.8 ± 2.0	47	369	101 ± 10
CCGCCG	92 ± 18	135	210	87 ± 6
CAACAA	218 ± 55	231	204	142 ± 12

Additional translational inhibitors were evaluated in the luciferase reporter assay (Table 7). Rocaglamide A demonstrated 5′-UTR sequence dependent inhibition of luciferase reporter gene expression similar to **eFT226**, consistant with interacting at the same binding site. Hippuristanol, an initiation inhibitor which binds at the C-terminus of eIF4A and blocks RNA binding, inhibited luciferase reporter gene expression with an IC_{50} of 200−400 nM; however, inhibition was independent of the sequence motif in the 5′-UTR (Table 7). Inhibition by cycloheximide (CHX), an elongation inhibitor, also showed no dependence on 5′-UTR sequence. These findings are consistent with **eFT226** inhibition converting eIF4A into a sequence-selective translational repressor.

The selectivity of **eFT226** for eIF4A was shown by introducing a mutation into the putative drug binding site of the eIF4A1 gene in the **eFT226** sensitive HAP1 cell line. Based on literature and molecular modeling of the putative drug binding site, a mutation was introduced in eIF4A1 converting phenylalanine 163 to leucine (F163L).[25,29] Treatment of tumor cell lines with **eFT226** (see Figure 11) downregulates the expression of several key oncogenic proteins, including c-MYC, MCL-1, and Cyclin D1. To examine if this effect of **eFT226** is altered in eIF4A1 F163L cells, HAP1 wt and eIF4A1 F163L cells were treated for 24 h with either DMSO or increasing concentrations of **eFT226** followed by Western blot analysis. A dose-dependent decrease in the protein levels of **eFT226** target genes such as c-MYC, MCL-1, and Cyclin D1 was observed in the parental HAP1 cells; however, the protein levels remained unchanged in the **eFT226** treated HAP1 eIF4A1 F163L mutant clone (Figure 11). These results indicate that mutation of eIF4A1 suppresses the ability of **eFT226** to diminish steady-state protein levels, supporting that eIF4A is the cellular target of this compound.

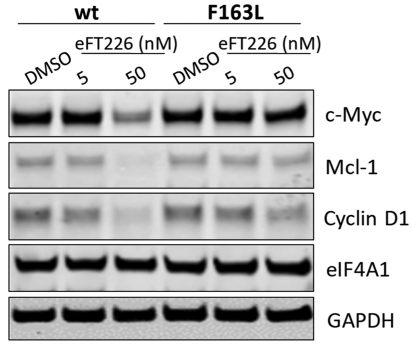

Figure 11. Downregulation of eIF4A target genes by **eFT226** is rescued with eIF4A1 F163L knock-in mutation. Protein levels of eIF4A sensitive genes after treatment with **eFT226** for 24 h in HAP1 wt or eIF4A1 F163L mutant cells.

To investigate if **eFT226**-dependent growth inhibition is affected by the F163L eIF4A1 mutation, proliferation assays were conducted with parental HAP1 and eIF4A1 F163L mutant HAP1 cells. 72 h treatment with **eFT226** yielded striking differences in proliferation between the parental and eIF4A1 F163L HAP1 cells, as shown in a representative experiment in Figure 12. The eIF4A1 F163L clone was ∼60-fold less sensitive to the antiproliferative effects of **eFT226** (average CI_{50} = 371 *vs* 6.3 nM in parental HAP1 cells). Importantly, treating with hippuristanol, a structurally distinct eIF4A inhibitor, led to equivalent growth arrest in parental and

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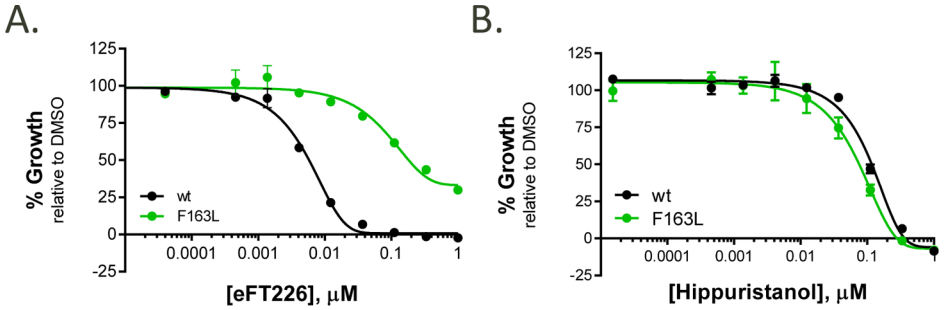

Figure 12. eIF4A1 mutation (F163L) rescues **eFT226** activity linking antitumor phenotype to eIF4A1 inhibition. (A) Potent inhibition of cell growth was observed with 72 h **eFT226** treatment of HAP1 wild-type cells. The HAP1 eIF4A1 F163L mutant cells were resistant to **eFT226** treatment. (B) eIF4A1 F163L mutation demonstrated resistance only to **eFT226**. Mutation at this binding site did not rescue the antiproliferative effect of hippuristanol.

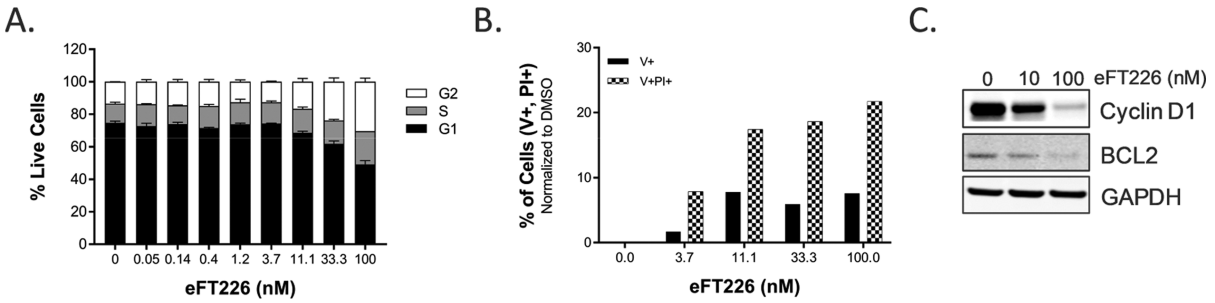

Figure 13. eFT226 modulates key drivers of tumorigenesis in a dose-dependent manner. (A) Cell cycle progression was assessed by DNA staining using DRAQ5 and monitoring fluorescence by flow cytometry. Tumor cells treated with increasing concentrations of **eFT226** for 24 h resulted in G2 arrest. (B) Incubation of MDA-MB-231 tumor cells with increasing concentrations of **eFT226** for 24 h were analyzed by annexin (V+) and PI flow cytometry. A dose-dependent increase in cells undergoing apoptosis and cell death (V+ PI+) was observed with **eFT226** treatment. (C) Treatment of MDA-MB-231 cancer cells with **eFT226** downregulates the protein levels of **eFT226**-sensitive target genes (Cyclin D1 and BCL2) as analyzed by Western blot.

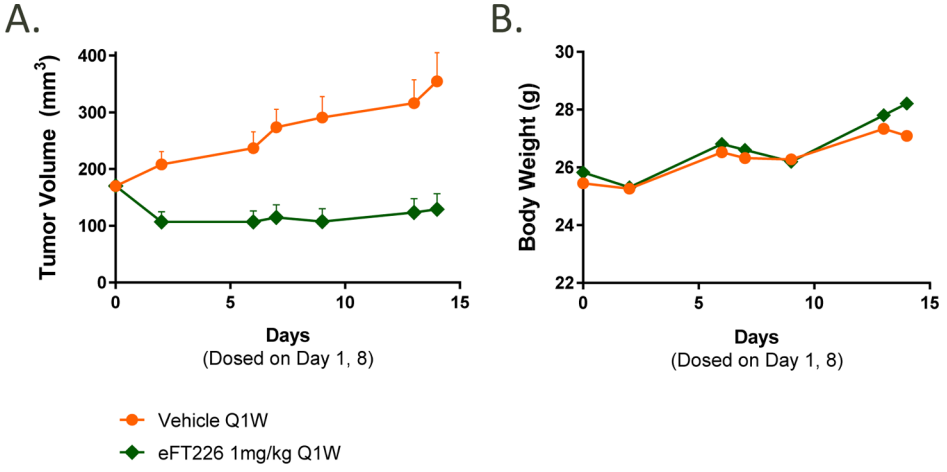

Figure 14. eFT226 efficacy in orthotopic MDA-MB-231 TNBC model. (A) Athymic nude mice (10 mice/group) implanted in the mammary fat pad with MDA-MB-231 cells were treated once weekly (Q1W) with either vehicle or **eFT226** by IV for 14 days to assess effect on tumor growth. Treatment with **eFT226** results in tumor regression during the treatment duration. (B) Effect of vehicle or drug treatment on body weight change over the course of treatment in tumor bearing mice.

eIF4A1 F163L HAP1 cells, consistent with unique binding sites for these different class of compounds targeting eIF4A1. These data indicate that **eFT226** mediates growth repression through eIF4A1. Although both eIF4A1 and eIF4A2 have been reported to cycle through the eIF4F complex *in vitro*, the ability of an eIF4A1 selective mutation to rescue **eFT226**'s cellular phenotype supports eIF4A1 as the anticancer target. The mutational studies reported here also suggest that eIF4A1 is the target of **eFT226**; however, because eIF4A2 is expressed at a much lower level than eIF4A1 in this cell line, we cannot rule out the role of eIF4A2.

eFT226 was also evaluated in a CEREP panel of 114 *in vitro* radioligand binding and enzyme assays covering a diverse range of off-target enzymes, receptors, ion channels, and transporters at a concentration of 10 μM. Significant activity, defined as exceeding 50% binding or inhibition, was detected for only one target (54% inhibition of Ca^{2+} channel; L, diltiazem site), indicating that **eFT226** is a very selective ligand for eIF4A.

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The antiproliferative activity and mechanism of action were further evaluated in the MDA-MB-231 breast cancer cell line. The concentration for 50% inhibition of MDA-MB-231 cell proliferation (CI_{50}) with **eFT226** treatment was determined to be 10.6 ± 0.9 nM (Table 4). Cell cycle analysis showed a dose-dependent increase in the G2/M population, indicating cell cycle arrest in response to **eFT226** treatment (Figure 13A). A dose-dependent increase in the percentage of apoptotic and dead cells measured by annexin V and PI (propidium iodide) staining was also seen with **eFT226** treatment (Figure 13B).

Exposure of MDA-MB-231 cells to **eFT226** for 24 h confirmed that eIF4A-dependent oncoproteins were rapidly downregulated at the protein level relative to control. Potent downregulation of Cyclin D1 and BCL2 was observed whereas the protein level of housekeeping genes (*i.e.*, GAPDH) were unchanged (Figure 13C). Modulation of these target genes is consistent with the observed block in cell cycle progression and induction of apoptosis.

The antitumor efficacy of **eFT226** was assessed in the MDA-MB-231 orthotopic xenograft model treated once weekly for 2 weeks with drug or vehicle control administered IV. Treatment with 1 mg/kg of **eFT226** Q1W led to 122% tumor growth inhibition or regression throughout the duration of the study (Figure 14A). **eFT226** was well tolerated as seen by a lack of body weight loss (Figure 14B). **eFT226** demonstrated good cross-species IV PK and low plasma protein binding (Table 8). The aqueous solubility of **eFT226** is excellent (>20 mg/mL), allowing for simple formulations to be utilized for intravenous delivery.

Table 8. Nonclinical eFT226 Plasma Protein Binding and Pharmacokinetic Parameters after a Single Intravenous Bolus Dose

species	$T_{1/2}$ (h)	CL (mL/min/kg)	V_{ss} (L/kg)	plasma protein binding % bound
mouse	10.9	15.8	12.1	74.8
rat	4.39	48.3	13	73.4
dog	NR[a]	<12.4[a]	17.8[a]	81.2
monkey	14.9	11.7	12.2	63.5
human	NA	NA	NA	66.8

[a] $T_{1/2}$ not reported (NR) due to insufficient terminal phase characterization. In lieu of V_{ss} estimate, V_d (dose/C_0) was calculated and reported in this table. CL estimated from AUC_{0-t}.

CONCLUSIONS

Targeting dysregulated translation is a growing strategy in oncology-based drug discovery. The expression of many key oncoproteins is translationally controlled by eIF4A and the eIF4F complex. The flavagline natural product class, represented by rocaglamide A, is known to inhibit translation through the stabilization of a ternary complex between the natural product, eIF4A, and select mRNA sequences. Herein we describe the optimization of rocaglamide A, focusing on improving the drug-like properties of this system, to yield the development candidate **eFT226** (Zotatifin). **eFT226** is a potent, highly selective inhibitor of eIF4A-mediated translation with excellent physicochemical properties. Similar to rocaglamide A, specificity for polypurine RNA sequences was demonstrated. **eFT226** revealed good cross-species IV PK and was shown to be highly efficacious and well tolerated in a triple negative breast cancer orthotopic xenograft model with once weekly dosing, supportive of its advancement into human clinical studies.

SYNTHETIC CHEMISTRY

Several synthetic approaches toward flavagline natural products, such as silvestrol (**1**), and rocaglamide A (**2**), as well as analogues thereof, have been published in recent years.[14−19,30,31] Out of these, the [3 + 2]-photocycloaddition approach disclosed by Porco and co-workers is arguably the most efficient one, as it provides rapid access to the flavaglines' sterically congested cyclopenta[*b*]benzofuran core.[19,32−36] Three steps consisting of a [3 + 2]-photocycloaddition of substituted flavonoles with methyl cinnamates, followed by base-induced ketol rearrangement and directed reduction, constitute the key sequence of this biomimetic strategy (Scheme 1).

The conciseness and efficiency of Porco's approach prompted us to investigate its utility in the synthesis of the novel rocaglamide-inspired eIF4A inhibitors discussed in this paper (Schemes 2−24).[37] A salient feature of the work described herein is the successful application of this strategy to the synthesis of analogues featuring heterocyclic A-rings (*cf.* **5**, **7**−**9**, **15**−**53**, **eFT226**; see **1** and **2** in Scheme 1 for labeling of the rings and numbering).

Analogues Containing Carbocyclic A-Rings. The general synthesis of 8-unsubstituted, A-carbocyclic rocaglamide analogues **6** and **10**−**14**, featuring electron withdrawing as well as electron donating substituents in the 6- and 4′-positions of the rocaglamide scaffold, is shown in Scheme 2.

While the overall synthetic strategy shown in Scheme 2 was applied to the synthesis of all A-ring carbocyclic targets, it is noteworthy that the exact timing of the incorporation of the desired 6- and 4′-substituents depended on the target and was largely dictated by synthetic feasibility as well as availability of the required starting materials. More specifically, and as shown in Schemes 3 and 4, the synthesis of compounds *rac*-**6** and *rac*-**10** relied on an early installation of the desired 6- and 4′-substituents. Thus, the synthesis of *rac*-**6** commenced with the regioselective O-methylation of resacetophenone (92% yield), followed by aldol condensation (90% yield) (Scheme 3a). The so-obtained chalcone was then treated with hydrogen peroxide under basic conditions, which induced an oxidative Algar−Flynn−Oyamada (AFO) cyclization[38−40] to give **69** in a modest but sufficient yield of 20%.

At this point, flavonol **69** was subjected to a [3 + 2]-cycloaddition with methyl cinnamate (**55**) under photochemical conditions. In general, it proved favorable to simply remove the excess methyl cinnamate chromatographically upon completion of the reaction and move the otherwise unpurified crude product through the sequence of base induced ketol-rearrangement and directed ketone reduction to ultimately give compound **70**, which was obtained in 36% yield over three steps. Saponification of the ester in **70** (84% yield) followed by amide coupling (33% yield) completed the synthesis of *rac*-**6**. The synthesis of *rac*-**10** followed a closely related synthetic strategy as detailed in Scheme 3b, starting from appropriately substituted acetophenone **71** with the 6-Cl substituent in place. It is noteworthy that in this case, the yields of both the AFO cyclization to give **72** (63%) and the key photocycloaddition/ketol-rearrangement/directed reduction sequence (**72** → **73**, 52% over three steps) were significantly improved compared to the sequence leading to *rac*-**6**, an observation that might point at the impact of the electronic nature of the chalcone and the

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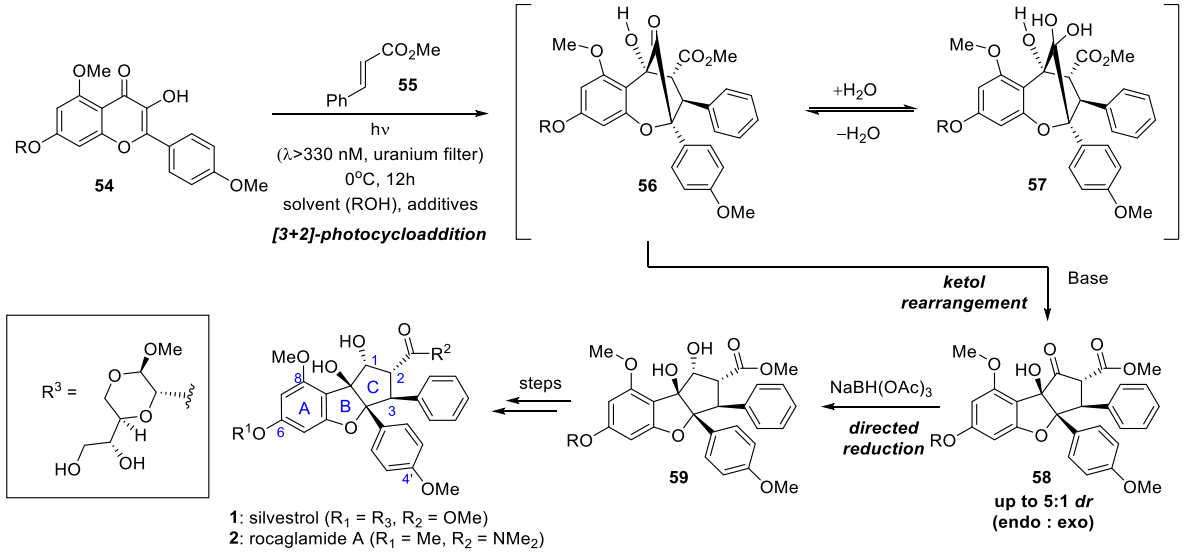
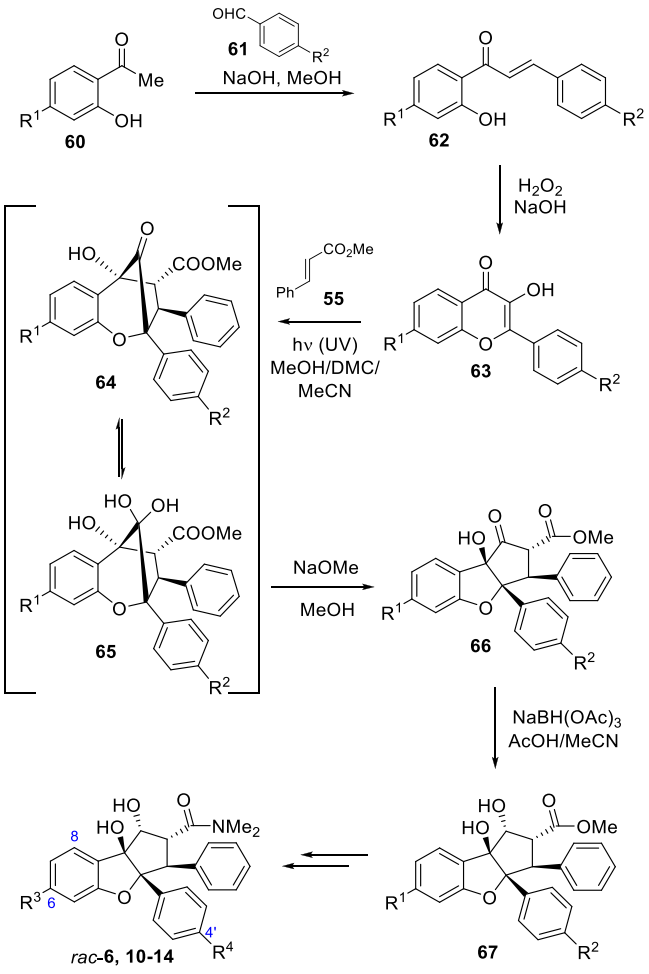
Scheme 1. Key Steps in Porco's Synthetic Approach toward Silvestrol (1) and Rocaglamide a (2) Using a Biomimetic Photocycloaddition Strategy



Scheme 2. General Synthetic Route toward Carbocyclic A-Ring Analogues 6 and 10−14



flavonol system on the efficiency of the AFO reaction and photocycloaddition, respectively.

The synthesis of analogues *rac*-**11**−*rac*-**13** relied on a late stage introduction of substituents at the 4′- and 6-positions but otherwise followed the same strategy as discussed for compounds *rac*-**6** and *rac*-**10** (Scheme 4). Compound *rac*-**11** was obtained in an eight-step sequence, starting with the aldol condensation of methyl ketone **71** and *para*-bromobenzaldehyde (quantitative), followed by AFO cyclization (47% yield) (Scheme 4a). The subsequent conversion of flavonol **74** to intermediate **75** was achieved *via* the previously established photocycloaddition/ketol-rearrangement/directed reduction sequence, which proceeded in an overall yield of 31%. Ester hydrolysis (93%), EDC/HOBt-mediated amide coupling (85%), and palladium-catalyzed 4′-cyanation (14%) afforded analogue *rac*-**11**.

Analogues *rac*-**12** and *rac*-**13** were successfully synthesized starting from monobenzylated resacetophenone **76** (Scheme 4b). In the case of *rac*-**12**, compound **76** was successfully transformed into flavonol **77** (18% overall), which was converted into **78** in three steps utilizing the established phtotochemical protocol (29% overall). As detailed in Scheme 4b, compound **78** was then subjected to straightforward ester hydrolysis, amide coupling, hydrogenolytic debenzylation, O-methylation to install the 6-methoxy group, and finally palladium-catalyzed cyanation to install the 4′-CN moiety and provide *rac*-**12**. Compound *rac*-**13** was synthesized in analogous 10 steps, starting from **76**, as described in detail in Scheme 4b. In this case, aldol condensation with *para*-methoxybenzaldehyde followed by AFO reaction gave **79** (47% overall), photocycloaddition/ketol-rearrangement/directed reduction gave **80** (63% overall), and ester hydrolysis, amide coupling, debenzylation, triflation, and palladium-catalyzed cyanation afforded compound *rac*-**13**.

Finally, analogue *rac*-**14** could be synthesized starting from a key intermediate in the synthesis of *rac*-**12**, that is, **78** (Scheme 5). Thus, the 4′-CN group could be successfully introduced *via* Pd-catalyzed cyanation of **78** (81%). In a three-step sequence involving hydrogenolytic debenzylation, triflation, and Pd-catalyzed cyanation, the 6-benzyloxy group was then replaced with the 6-CN group in 36% overall yield. Ester saponification (69%) followed by amide coupling (41%) completed the synthesis of *rac*-**14**.

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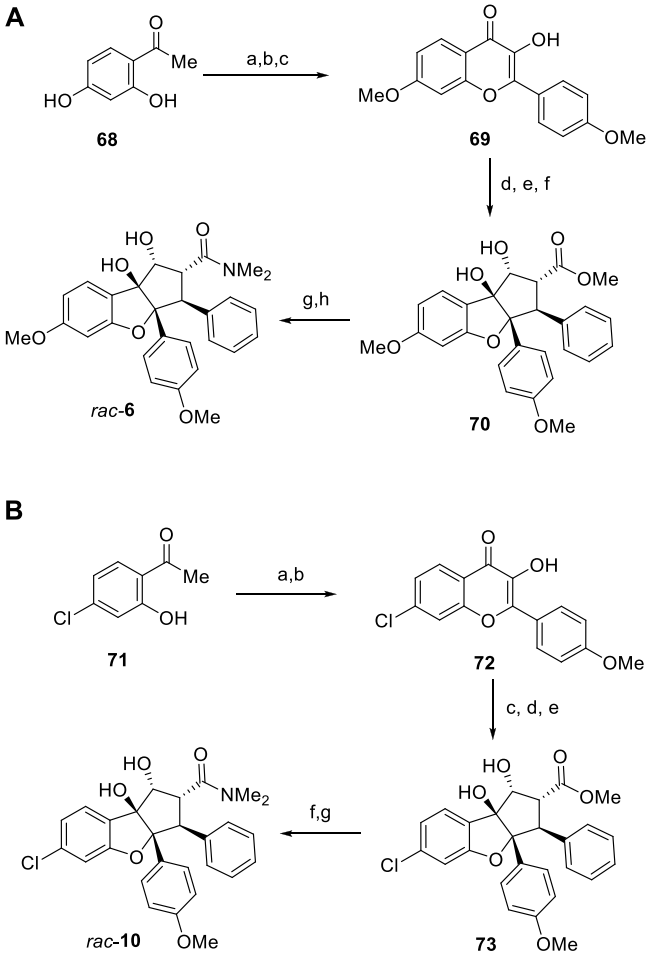
Scheme 3. (A) Synthesis of *rac*-6; (a) MeI, Acetone, rt (92%); (b) *p*-MeO-benzaldehyde, NaOH, MeOH, 90%; (c) NaOH, H_2O_2, Ethanol, 20%; (d) Methyl Cinnamate (55), 400 W UV, DCM, MeOH, MeCN; (e) NaOMe, MeOH, 100 °C; (f) $NaBH(OAc)_3$, AcOH, MeCN, 36% over Three Steps; (g) LiOH, MeOH, Water, 84%; (h) $HNMe_2$−HCl, EDC, HOBt, DIPEA, DCM, 33%; (B) Synthesis of *rac*-10. (a) *p*-MeO-benzaldehyde, NaOH, MeOH, 89%; (b) NaOH, H_2O_2, Ethanol, Water, 63%; (c) Methyl Cinnamate (55), 400 W UV, DCM, MeOH, MeCN; (d) NaOMe, MeOH, 80 °C; (e) $NaBH(OAc)_3$, AcOH, MeCN, 52% over Three Steps; (f) LiOH, MeOH, Water, 86%; (g) $HNMe_2$−HCl, EDC, HOBt, DIPEA, DCM, 90%



Synthesis of 8-Aza Analogues Featuring Different Substituents in the 6- and 4′-Positions. Focusing on the expansion of the photochemical synthetic strategy to include systems featuring heterocyclic A-rings, we envisioned the general strategy outlined in Scheme 6 for the synthesis of 8-aza analogues.

As evident from this general approach, the initial development of a concise synthetic route toward functionalized 2-acetyl-3-hydroxypyridine analogues (*cf.* **83**, Scheme 6) was essential. In this context, the synthesis of analogues *rac*-**5** and (−)-**7** required 2-acetyl-3-hydroxy-5-methoxypyridine (**90**), which could be obtained in four straightforward steps starting from commercially available 2-cyano-3,5-difluoropyridine (**86**), as detailed in Scheme 7a. This intermediate was successfully utilized in the synthesis of analogues *rac*-**5** and (−)-**7** (Scheme 7b). Thus, aldol condensation of **90** with *para*-methoxybenzaldehyde followed by AFO cyclization gave **91** in 23% yield over two steps. The crucial photocycloaddition/ketol rearrangement/directed reduction sequence then diastereoselectively transformed **91** into ester **92** (24% yield over three steps), which in turn was then converted into final target *rac*-**5** *via* ester saponification and amide coupling. Importantly, the successful synthesis of *rac*-**5** using the photochemical strategy validated this approach for the synthesis of flavaglines featuring heterocyclic A-rings.

Compound (−)-**7** was obtained in a similar fashion, which suggested that differently substituted azaflavonols could be successfully used as photocycloaddition partners. Thus, the synthesis of (−)-**7** commenced with the aldol condensation of **90** with *para*-bromobenzaldehyde. AFO reaction then afforded azaflavonol **93** and was followed by photochemical, stepwise conversion of the latter intermediate into **94**. Although this sequence proceeded in only low yields (7% over five steps), it enabled the preparation of enough material for the completion of this target, which was accomplished in a three-step sequence followed by chiral HPLC separation as outlined in Scheme 7b.

The synthesis of 8-aza 6-Cl analogues **8**, **15**, and **17**−**23** featuring electron-donating as well as electron-withdrawing substituents in the 4′-position started from 2-acetyl-3-hydroxy-5-chloropyridine (**98**), which could be readily prepared in three steps from 2-cyano-3-nitro-5-chloro pyridine (**95**) (Scheme 8a).

With key pyridine **98** in hand, the previously established strategy featuring a photocycloaddition-ketol rearrangement sequence was envisioned for the construction of the sterically congested cyclopenta[4,5]furo[3,2-*b*]pyridine cores of 8-aza 6-Cl analogues **8**, **15**, and **17**−**23** (Schemes 8b,c).

With respect to compounds **15** and **17**−**23**, an early-stage introduction of the desired 4′-substituent *via* aldol condensation of **98** with an appropriately substituted benzaldehyde **61** proved synthetically most favorable (Scheme 8b). All but one required benzaldehyde (*cf.* **61**) were commercially available, the exception being the somewhat unstable *para*-difluoromethyl benzaldehyde, which was freshly prepared from 1-bromo-4-(difluoromethyl)benzene *via* bromo-lithium exchange followed by quenching with DMF (see the Experimental Section for details).

While all of these analogues (**15** and **17**−**23**) were successfully obtained using the strategy outlined in Scheme 8, it is noteworthy that the exact yields for each of the following steps (in particular the AFO reaction: 14−78%, and the photocycloaddition/ketol rearrangement/directed reduction sequence: 7−26%) appeared to depend on the nature of the 4′ substituents, although no clear trend with respect to the effect of electron-donating or electron-withdrawing character of those substituents on the yields became evident (see Experimental Section for details). The two final steps (ester saponification, amide coupling; see steps f-g, Scheme 8b) generally proceeded in a rather uneventful fashion and afforded the desired targets as a racemic mixture of both enantiomers, which could easily be separated by chiral HPLC (steps h, Scheme 8b).

Compound (−)-**8** was synthesized in a similar fashion, but in this case the synthesis relied on a late stage introduction of the 4'-cyano substituent (Scheme 8c). Initially, aldol condensation of **98** with *para*-bromobenzaldehyde followed by oxidative AFO cyclization led to azaflavonol **102** in 19% overall yield. Photocycloaddtion, ketol rearrangement, and diastereoselective ketone reduction led to key intermediate **103** in good yields

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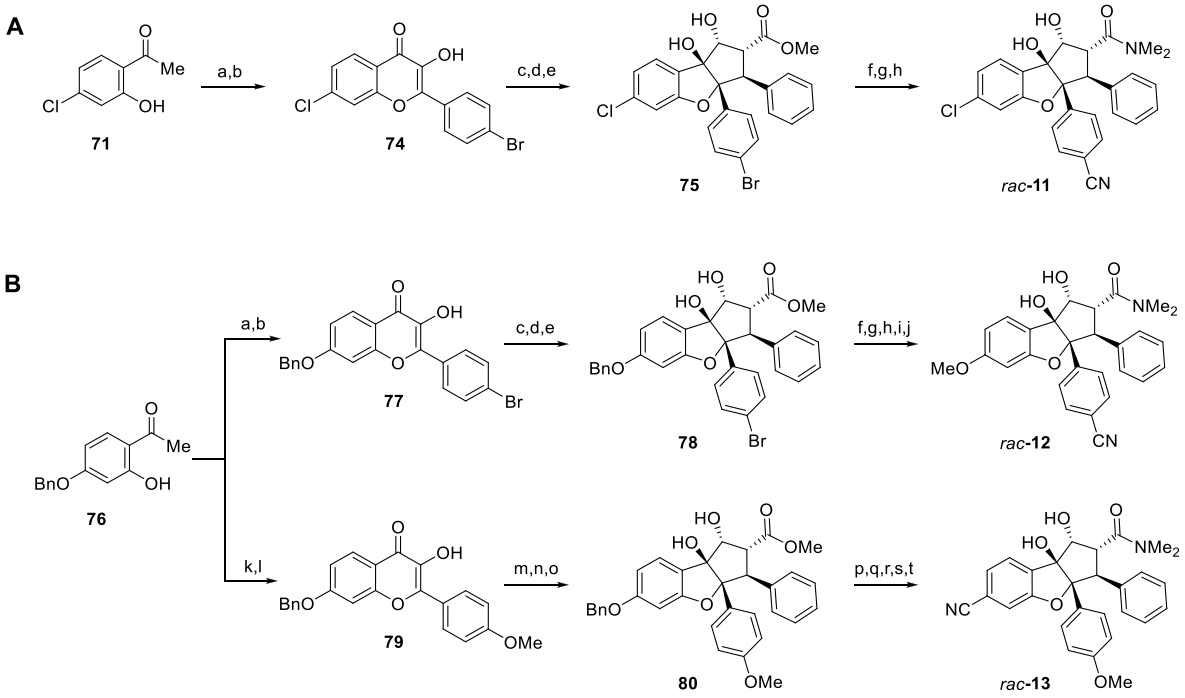
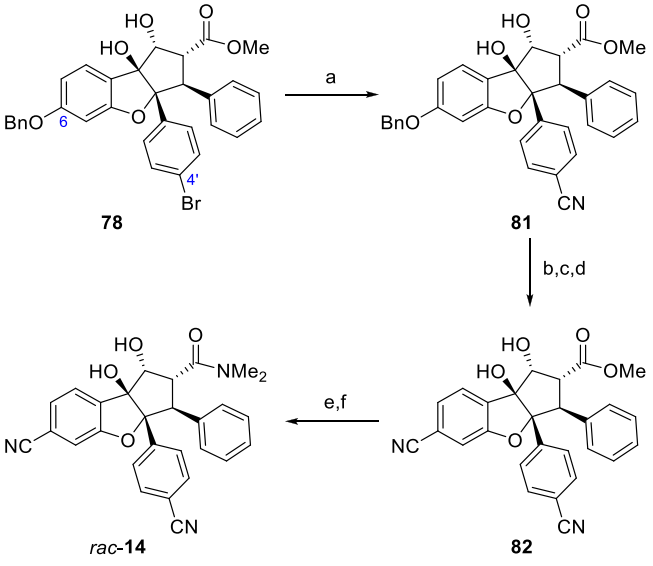
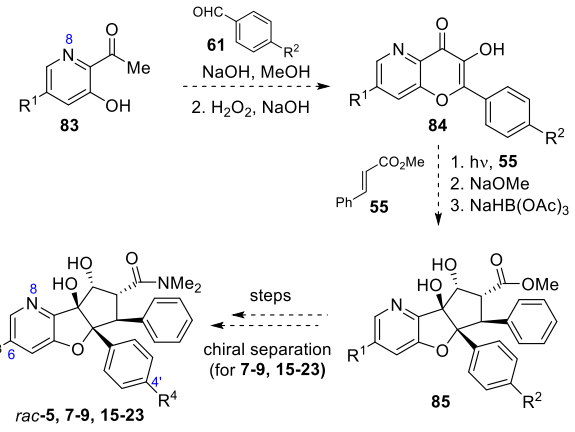
Scheme 4. (A) Synthesis of *rac*-11; (a) *p*-Br-benzaldehyde, NaOH, MeOH, 90 °C, Quant.; (b) NaOH, H_2O_2, Ethanol, 47%; (c) Methyl Cinnamate (55), 400 W UV, DCM, MeOH, MeCN; (d) NaOMe, MeOH, 90 °C; (e) $NaBH(OAc)_3$, AcOH, MeCN, 31% over Three Steps; (f) LiOH, MeOH, Water, 93%; (g) $HNMe_2$−HCl, EDC-HCl, HOBt, DIPEA, DCM, 85%; (h) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 120 °C, 14%; (B) Synthesis of *rac*-12 and *rac*-13; (a) *p*-MeO-benzaldehyde, NaOH, MeOH, Reflux, 40%; (b) NaOH, H_2O_2, Ethanol, 46%; (c) Methyl Cinnamate (55), 400 W UV, DCM, MeOH, MeCN; (d) NaOMe, MeOH, 90 °C; (e) $NaBH(OAc)_3$, AcOH, MeCN, 29% over Three Steps; (f) LiOH, THF, Water, 71%; (g) $HNMe_2$−HCl, EDC, HOBt, DIPEA, DCM, 69%; (h) $Pd(OH)_2$, Ethyl Acetate, rt; (i) MeI, K_2CO_3, Acetone, rt, 77% over Two Steps; (j) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 120 °C, 45%; (k) *p*-MeO-benzaldehyde, NaOH, MeOH, Reflux, 81%; (l) NaOH, H_2O_2, Ethanol, 58%; (m) Methyl Cinnamate (55), 400 W UV, DCM, MeOH, MeCN; (n) NaOMe, MeOH, 80 °C; (o) $NaBH(OAc)_3$, AcOH, MeCN, 63% over Three Steps; (p) LiOH, MeOH, Water; (q) $HNMe_2$−HCl, EDC, HOBt, DIPEA, DCM, 95% over Two Steps; (r) H_2, $Pd(OH)_2$, EtOAc; (s) Tf_2O, DCM, 56%; (t) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 110 °C, 25%



Scheme 5. Synthesis of *rac*-14; (a) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 100 °C, 81%; (b) H_2, $Pd(OH)_2$, EtOAc, 81%; (c) Tf_2O, DIPEA, DCM, THF, 51%; (d) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 120 °C, 86%; (e) LiOH, MeOH, Water, 69%; (f) $HNMe_2$−HCl, EDC, HOBt, DIPEA, DCM, 41%



Scheme 6. Envisioned Synthetic Route toward 8-Aza Analogues *rac*-5 and Enantiopure 7−9 and 15−23



(55%). Ester hydrolysis to give acid **104** and subsequent amide coupling (86% overall) was then followed by high-yielding Pd-catalyzed 4′-cyanation (83%) to provide access to analogue **8** in racemic form. The racemate was then resolved using chiral HPLC to give enantiopure analogue (−)-**8**.

Compounds (−)-**9** and (−)-**16** were synthesized as detailed in Scheme 9. Key pyridine **109** was synthesized in four steps from commercially available 2-cyano-3,5-dichloropyridine

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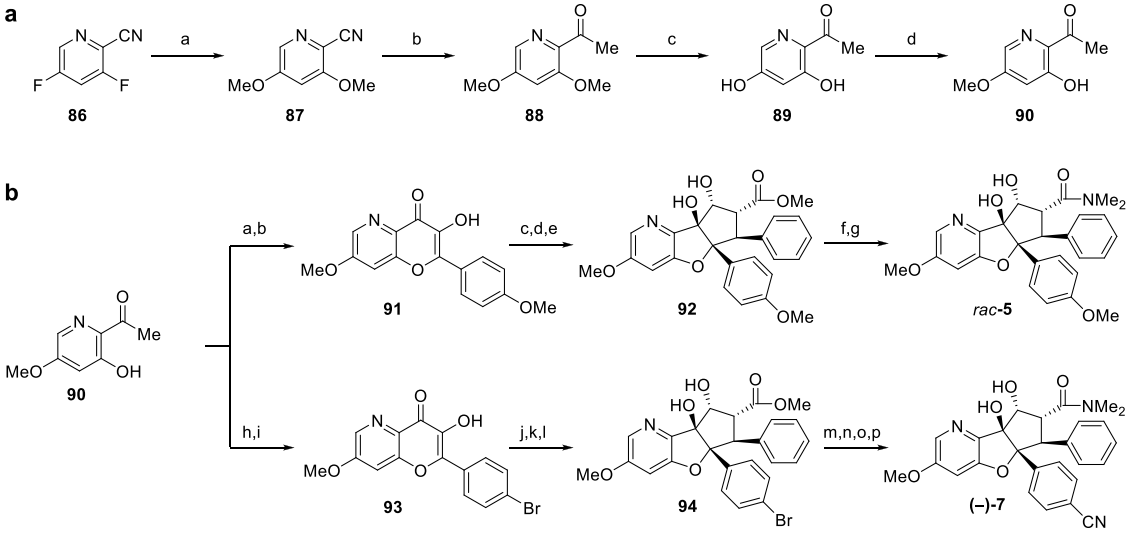
Scheme 7. (A) Synthesis of Key Intermediate 90; (a) NaOMe, MeOH, Reflux (85%); (b) MeMgCl, THF, −20 °C to rt, 65%; (c) HBr, AcOH, 150 °C, 35%; (d) MeI, K_2CO_3, Acetone 0 °C to rt; (B) Synthesis of analogues *rac*-5 and (−)-7; (a) *para*-Methoxybenzaldehyde, NaOH, MeOH, Reflux; (b) H_2O_2, aq NaOH, EtOH, 0 °C to rt, 23% over Two Steps; (c) Methyl Cinnamate (55), MeCN, MeOH, DCM, rt, *hν*; (d) NaOMe, MeOH, 80 °C; (e) $NaHB(OAc)_3$, AcOH, MeCN, rt, 24% over Three Steps; (f) LiOH, MeOH, H_2O, rt, 77%; (g) EDC, HOBt, DIPEA, Me_2NH−HCl, DCM, 0 °C to rt, 8%; (h) 4-Bromobenzaldehyde, NaOH, MeOH, Reflux; (i) H_2O_2, aq NaOH, EtOH, 0 °C to rt; (j) Methyl Cinnamate, MeCN, MeOH, DCM, rt, *hν*; (k) NaOMe, MeOH, 80 °C; (l) $NaHB(OAc)_3$, AcOH, MeCN, rt, 7% over Five Steps; (m) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 140 °C; (n) LiOH, MeOH, H_2O, rt; (o) EDC, HOBt, DIPEA, Me_2NH−HCl, DCM, 0 °C to rt, 15% over Three Steps; (p) Chiral HPLC Separation



(**105**) (Scheme 9a) *via* S_NAr replacement of both chlorides with benzylalcohol (step a), followed by Grignard-addition to the nitrile to install the methyl ketone moiety (step b), hydrogenolytic removal of both benzyl groups (step c, 89%), and regioselective monobenzylation of the 5-OH group over the 3-OH group, taking advantage of the fact that the latter is engaged in a hydrogen bond with the methyl ketone in the 2-position (step d, 94%).

At this point, enantiopure (−)-**9** and (−)-**16** could be obtained utilizing the same strategy that had successfully been applied to other 8-aza analogues (Scheme 9b), beginning with aldol condensation of **109** with a suitable benzaldehyde and subsequent AFO reaction. Thus, **110** was prepared from **109** in two steps (steps a,b; 28% overall) and further transformed into **111** (steps c−e, 38% overall). A series of functional group manipulations as well as chiral HPLC separation then completed the synthesis of (−)-**9**. Analogously, azaflavonol **112** was could be prepared from **109** (steps m,n) and subsequently converted into **113** in three steps (steps o−q). Again, the functional group manipulations including debenzylation (step r; 7% over six steps), triflation of the resulting C6 phenol, and subsequent cyanation followed by stepwise conversion of the C2 ester to the corresponding dimethyl amide (steps s−v; 19% over four steps) afforded *rac*-**16**, which was subjected to chiral HPLC separation to provide enantiopure (−)-**16**.

Modification of the 2-Position in 8-Aza Analogues. Acid **104**, which had been previously prepared in the context of the synthesis of analogue (−)-**8** (Scheme 8c, step f), proved to be a valuable intermediate in the synthesis of 2-unsubstituted and various 2-substituted 8-aza analogues. Thus, 2-unsubstituted analogue *rac*-**24** was synthesized from **104** *via* Barton-decarboxylation (Scheme 10, steps a,b), followed by Pd-catalyzed cyanation (step c).

2-(dimethylamino)methyl-substituted analogue (−)-**31** could be conveniently prepared from acid **104** *via* EDC-mediated amide coupling (76% yield) and amide reduction with borane−DMS complex (61% yield) to give amine **117**, followed by Pd-catalyzed cyanation (46%) and chiral HPLC separation (Scheme 11). 2-Oxazole-substituted analogue *rac*-**27** was prepared from acid **104** in four steps, starting with the coupling of **104** with amine primary **118** to give amide **119** in 64% yield (step e, Scheme 11). Hydrolysis of the acetal with aqueous hydrochloric acid (step f) followed by cyclodehydration (step g; 21%, two steps) and Pd-catalyzed cyanation (step h; 23%) gave *rac*-**27**.

The synthesis of *rac*-**32**, (−)-**25**, and (−)-**26** is shown in Scheme 12. Reduction of ester **103** with LAH, followed by cyanation gave access to triol *rac*-**32** (Scheme 12). Introduction of the 4′-cyano group (step c; 78%) followed by ester saponification (step d; 78%) led to acid **120**. High-yielding EDC/HOBt-mediated amide coupling using the HCl salts of ammonia and methylamine, followed by chiral HPLC separation, provided (−)-**26** and (−)-**25**, respectively.

It was discovered that *α,β*-unsaturated *β*-aryl sulfonamides were suitable alkene components for the photocycloaddition with azaflavonols, as detailed in Scheme 13. Thus, photocycloaddition of previously synthesized azaflavonol **102** with *α,β*-unsaturated sulfonamides **121** and **123**, followed by base-induced ketol rearrangement and directed reduction, gave **122** in 2% overall yield and **124** in 9% overall yield, respectively. Although the observed yields for this sequence are substantially lower than the yield observed for the analogous sequence of **102** with methyl cinnamate (**55**) (*cf.* Scheme 8c, steps c−e, 56% overall yield), the approach still allowed for the preparation of enough material of **122** and **124** to complete the synthesis of *rac*-**28** and *rac*-**29**, respectively. Thus, **122** was successfully transformed into *rac*-**28** *via* Pd-catalyzed 4′-cyanation in low

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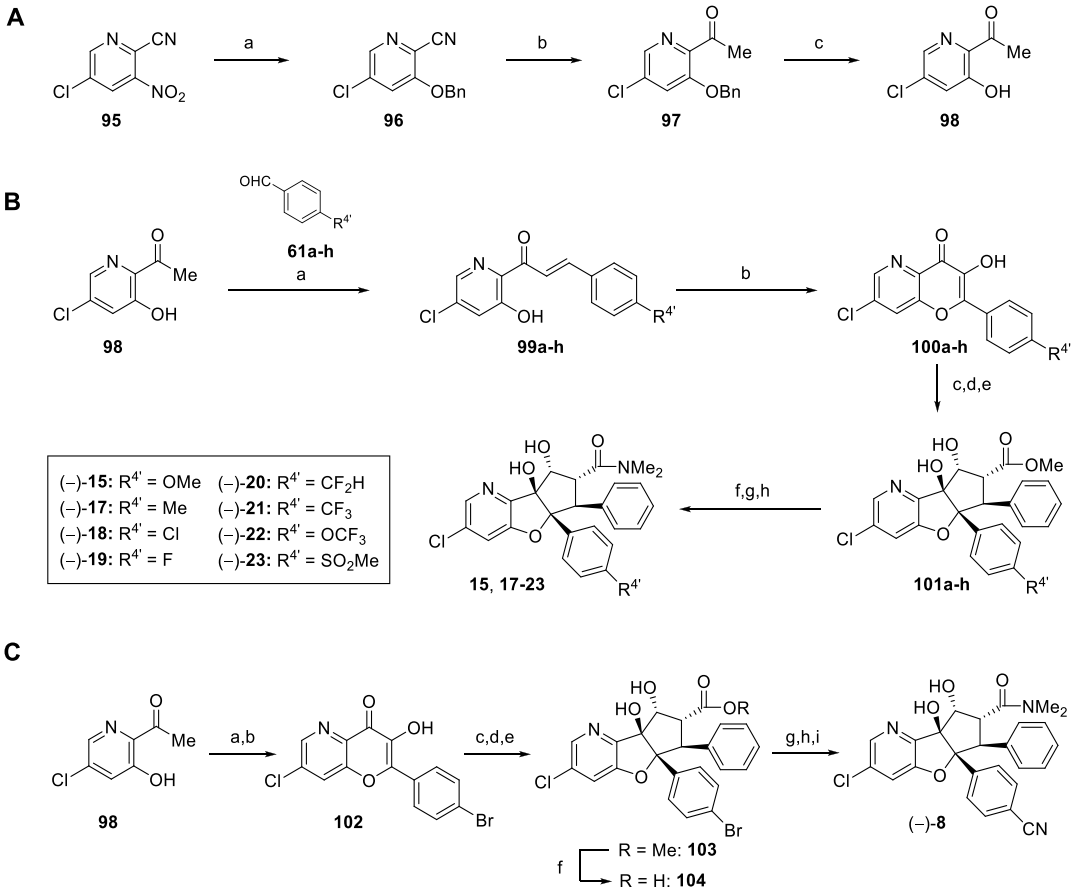
Scheme 8. (A) Synthesis of Key Intermediate 98; (a) BnOH, NaH, THF, rt, 84%; (b) MeMgBr, THF, −30 °C to rt, 64%; (c) H_2, $Pd(OH)_2$, EtOAc, 65%; (B) Synthesis of Analogues 15 and 17−23. (a) NaOH, 4-Substituted Benzaldehyde 61, MeOH, Δ; (b) H_2O_2, NaOH, EtOH/DCM, rt; (c) Methyl Cinnamate, MeCN, MeOH, DCM, *hν*; (d) NaOMe, MeOH, Δ; (e) $NaHB(OAc)_3$, AcOH, MeCN, rt; (f) LiOH, THF/Water, rt; (g) EDC, HOBt, DIPEA, Me_2NH−HCl, DCM; (h) Chiral HPLC Separation; (c) Synthesis of analogue 8. (a) *para*-Bromobenzaldehyde, NaOH, MeOH, Reflux, 61%; (b) H_2O_2, aq NaOH, EtOH, DCM, rt, 31%; (c) Methyl Cinnamate (55), MeCN, MeOH, DCM, rt, *hν*; (d) NaOMe, MeOH, 70 °C; (e) $NaHB(OAc)_3$, AcOH, MeCN, rt, 55% over Three Steps; (f) LiOH, MeOH, H_2O, rt, Quant.; (h) EDC, HOBt, DIPEA, DCM, 0 °C, Then Me_2NH−HCl, rt, 86%; (i) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 140 °C, 83%; (j) Chiral HPLC Separation



yields (7%). **124** was subjected to high yielding acidic N-debenzylation (92%, followed by Pd-catalyzed cyanation, which again—as in the case of *rac*-**28**—proceeded in rather low yields of 8% to give *rac*-**29**.

In the case of analogue (−)-**30**, a different approach for the installation of the methyl sulfone moiety was identified (Scheme 14). Krapcho-decarboxylation with the 1-ketone in place gave **126** (Scheme 14) in 33% yield. Copper(II)bromide-mediated sulfonylation with sodium methanesulfinate[41] followed by directed reduction with sodium triacetoxyborohydride provided methyl sulfone **127** in 4% overall yield. 4′-Cyanation (72%) followed by chiral separation completed the synthesis of (−)-**30**.

Synthesis 5-, 6-, and 7-Aza analogues. The synthesis of other 5-, 6-, and 7-aza analogues was achieved utilizing the same photochemical strategy that had successfully been used for the synthesis of 8-aza analogues discussed above (Scheme 6), highlighting the generality of this approach in the synthesis of rocaglamide analogues featuring A-ring pyridines. The synthesis of *rac*-**35** is shown in Scheme 15. The required acetyl pyridine **131** was synthesized in three steps from commercially available acid **128** *via* Weinreb amide formation, Grignard addition to obtain the methyl ketone, and *O*-demethylation (steps a−c). Aldol condensation and AFO reaction then led to azaflavonol **132**. Using the established photochemistry/ketol rearrangement/directed reduction protocol, **132** was transformed into **133** in three steps (steps f−h, 28% overall). Ester hydrolysis followed by amide coupling proceeded as expected to give **134**. The subsequent 4′,6-dicyanation (step k) occurred in 36% yield using conditions closely related to those utilized in the synthesis of (−)-**8** and was followed by chiral HPLC separation to provide (−)-**33**.

Along the same lines, 7-aza analogue *rac*-**34** was synthesized as detailed in Scheme 16. In this case, the required pyridine **139** was obtained in three steps from 2-methoxy-4-aminopyridine **135** *via* electrophilic bromination (step a, 92%), Pd-catalyzed coupling with enol ether stannane **137**, which was followed by acidic hydrolysis of the resulting enolether to the desired methyl ketone (step b, 49%) and conversion of the amino group into a hydroxy group *via* the transient diazonium salt (step c, 37%). From this point on, a familiar sequence (steps d−k) was pursued to complete the synthesis of *rac*-**34** (see Scheme 16 for details). It is noteworthy that the three-step conversion of **140** to **141** proceeded in unusually low yields (*ca.* 1% overall). While suboptimal electronic match between azaflavonol **140** and methyl cinnamate (**55**) in the photo-

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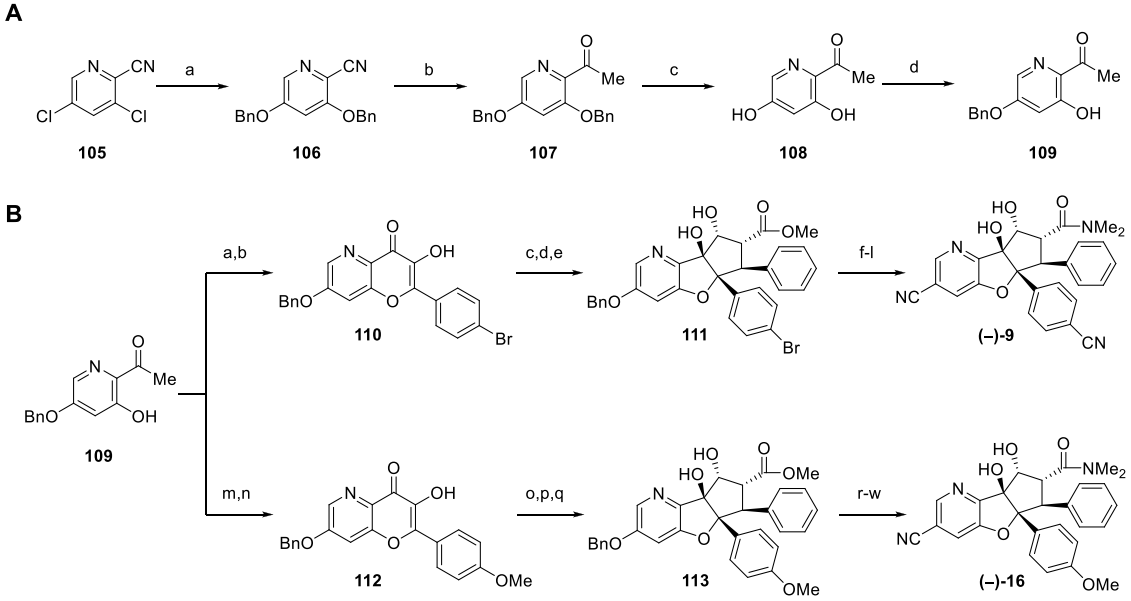
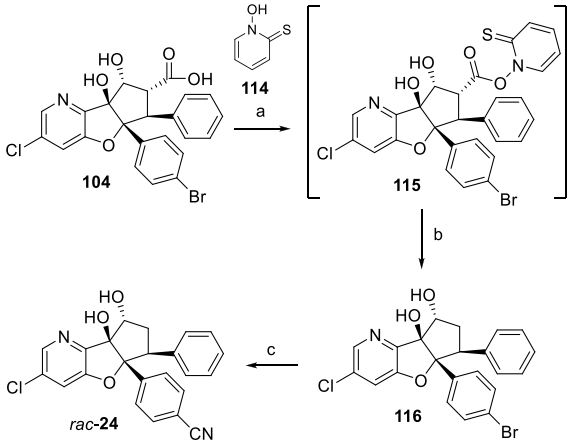
Scheme 9. (A) Synthesis of Key Intermediate 109; (a) BnOH, NaH, THF, 0 °C to rt; (b) MeMgBr, THF, −30 °C to rt; (c) H_2, $Pd(OH)_2$, EtOAc, rt, 89%; (d) K_2CO_3, BnBr, Acetone, 94%; (B) Synthesis of Analogues (−)-9 and (−)-16; (a) 4-Bromobenzaldehyde, NaOH, MeOH, 85 °C, 59%; (b) H_2O_2, NaOH, EtOH/DCM, rt, 53%; (c) Methyl Cinnamate (55), MeCN, MeOH, DCM, rt, *hν*; (d) NaOMe, MeOH, 70 °C; (e) $NaHB(OAc)_3$, AcOH, MeCN, rt, 38% over Three Steps; (f) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 125 °C (97%); (g) H_2, $Pd(OH)_2$, EtOAc, rt, 97%; (h) Tf_2O, DIPEA, DCM, −78 °C to 0 °C, 77%; (i) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 125 °C; (j) LiOH, THF/Water, 37% over Two Steps; (k) TEA, Me_2NH−HCl, T3P, DCM/EtOAc, rt, 31%; (l) Chiral HPLC Separation; (m) NaOH, 4-Methoxybenzaldehyde, MeOH, Reflux; (n) H_2O_2, NaOH, EtOH/DCM, rt; (o) Methyl Cinnamate (55), MeCN, MeOH, DCM, *hν*; (p) NaOMe, MeOH, 70 °C; (q) $NaHB(OAc)_3$, AcOH, MeCN, rt; (r) H_2, $Pd(OH)_2$, EtOAc, 7% over Six Steps; (s) Tf_2O, DIPEA, DCM, −78 °C to rt; (t) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 85 °C; (u) LiOH, THF/Water, rt; (v) EDC, HOBt, DIPEA, Me_2NH−HCl, DCM, 0 °C to rt, 19% over Four Steps; (w) Chiral HPLC Separation



Scheme 10. Synthesis of *rac*-24; (a) 114, DCC, DCM, rt; (b) AIBN, Bu_3SnH, C_6H_6, 80 °C, 10% over Two Steps; (c) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 140 °C, 16%



cycloaddition step might contribute to this outcome, this observation is difficult to rationalize at this point, given the moderate to good yields for this sequence observed in other cases described herein. The remaining three steps proceeded as expected to give *rac*-**34**.

The synthesis of 6-aza analogue (−)-**35** is shown in Scheme 17. 3,5-Dichloro-4-cyanopyridine was subjected to a selective S_NAr reaction with sodium *para*-methoxybenzylate at 0 °C, leading to intermediate **143** (76%). Displacement of the second chloride under S_NAr with sodium methoxide occurred under more forcing conditions (80 °C) to give **144**, which was then reacted with methylmagnesium bromide to afford, upon treatement with aqueous HCl, key pyridine **145**. The established two step procedure (aldol condensation, AFO reaction) transformed **145** into azaflavonol **146**. The latter was successfully transformed into aza-rocaglate intermediate **147** using the well-established three step procedure featuring the photocycloaddition with methyl cinnamate (**55**) as a key step, which proceeded with an acceptable overall yield of 35% over three steps. Functional group modifications followed by chiral separation ultimately afforded analogue (−)-**35**.

The synthesis of analogue *rac*-**36** required the preparation of key pyridone **153** (Scheme 18). This was achieved in a five-step sequence starting from 2,6-dichloronicotinic acid (**150**), involving regioselective S_NAr reaction with methanol in the presence of potassium *t*-butoxide (step a), followed by Weinreb amide formation (step b) and Grignard addition (step c) to provide methyl ketone **152**, S_NAr with deprotonated PMB-alcohol (step d), and acidic PMB deprotection (step e). Transformation of **153** into **154** *via* aldol condensation and AFO reaction proceeded as expected; however, the three-step conversion of **154** to **155** was associated with very low yields of only 3%, again suggesting an inefficient photocycloaddition, potentially as a result of suboptimal electronic match of both cycloaddition partners. The remaining steps (k−m) proceeded as expected to provide 5-aza analogue *rac*-**36**.

Synthesis of 6-Aza Analogues Featuring Basic Amines in the 2-Position. The majority of analogues featuring basic amine substituents in the 2-position, that is, enantiopure **37**, **40**−**44**, **46**−**48**, **50**, and **51**, as well as racemic **38** and **39**, could

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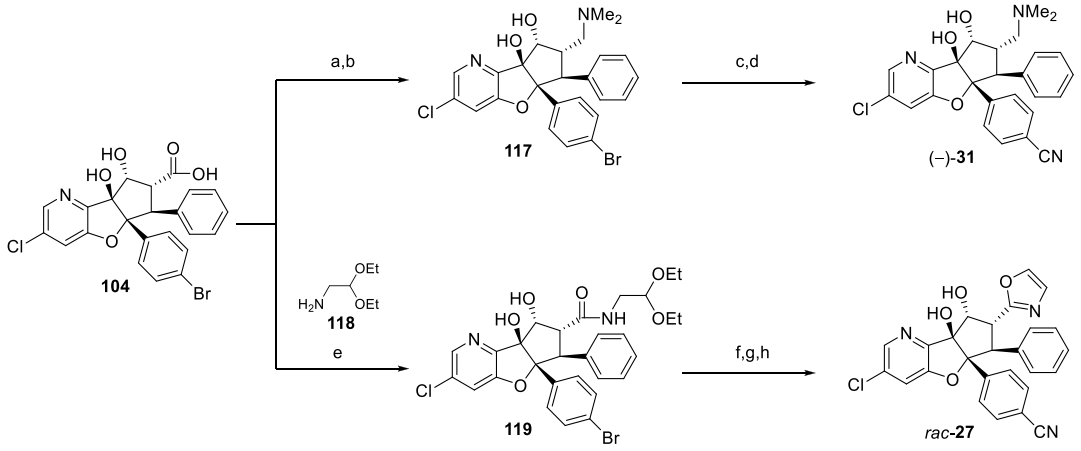
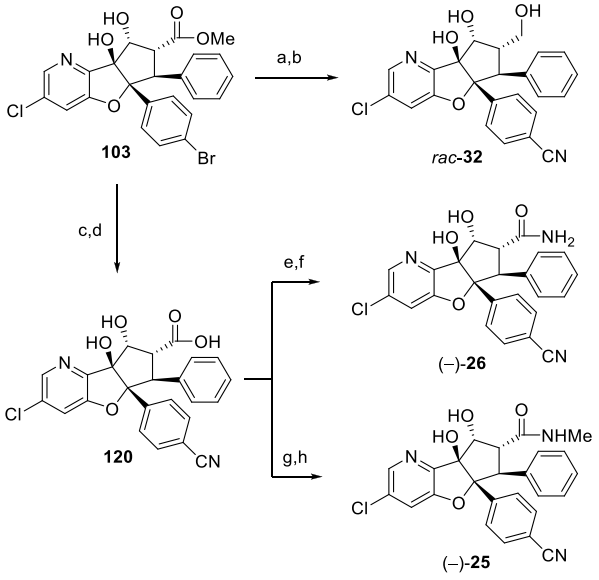
Scheme 11. Synthesis of *rac*-27, (−)-31, and *rac*-32; (a) $NHMe_2$−HCl, EDC, HOBt, DIPEA, DCM, 0 °C to rt, 76%; (b) BH_3-DMS, THF, 0 °C to rt, Then MeOH, 0 °C to Reflux, 61%; (c) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 130 °C, 46%; (d) Chiral HPLC Separation; (e) EDC, HOBt, DIPEA, 0 °C, Then 118, 0 °C to 35 °C, 64%; (f) HCl(aq), THF, rt; (g) PPh_3, I_2, TEA, DCM, rt, 21% over Two Steps; (h) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 150 °C, 23%



Scheme 12. Synthesis of *rac*-32, (−)-25, and (−)-26; (a) LAH, THF, 0 °C to rt, 49%; (b) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, Water, MW, 100 °C, 71%; (c) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 125 °C, 78%; (d) LiOH, MeOH, Water, rt, 78%; (e) EDC, HOBt, DIPEA, DCM, 0 °C, Then NH_4Cl, rt, 78%; (f) Chiral HPLC Separation; (g) EDC, HOBt, DIPEA, DCM, 0 °C, Then $MeNH_2$−HCl, rt, 90%; (h) Chiral HPLC Separation



be prepared in a straightforward way starting from key carboxylic acid **148** (Scheme 19), which had been prepared in the context of the synthesis of (−)-**35** (Scheme 17). Thus, in each of these cases, amide coupling of **148** with an appropriate amine gave access to amide **157**. Borane reduction then transformed the amide into the corresponding amine **158**, which was subjected to 4′-cyanation and, for **37**, **40**−**44**, **46**−**48**, **50**, and **51**, chiral separation to provide the desired final compound (for details, see the Experimental Section).

The remaining 6-aza analogues of the focused amine library, that is, (+)-**45**, (−)-**49**, and *rac*-**52**, were synthesized as shown in Schemes 20−22. The synthesis of (+)-**45** utilized **158b**, an intermediate in the synthesis of *rac*-**38** (Scheme 20). This compound was first trifluoroacetylated. Subsequent amide reduction then gave **160**, which was subjected to Pd-catalyzed cyanation (24% yield over three steps) to give *rac*-**45**. Chiral separation then provided analogue (+)-**45**.

Amine analogue (−)-**49** was prepared from *rac*-**48** (Scheme 21). *In situ* TBS protection of the secondary alcohol followed by reductive amination with concomitant desilylation (step a, 55%) was followed by chiral HPLC separation to obtain enantiopure (−)-**49**. It is noteworthy that the initial TBS protection was crucial for the success of the sequence, as in the absence of a protective group the secondary alcohol at C1 reacts with the iminium generated *in situ* in the reductive amination step to form a cyclic aminal.

The final route toward analogue *rac*-**52** is shown in Scheme 22. Homologation of acid **148** was achieved in a four-step sequence, involving borane reduction (step a), mesylation of the resulting primary alcohol (step b), displacement of the mesylate with cyanide (step c), and basic nitrile hydrolysis (step d) to give **163** in 41% overall yield. Initial attempts to achieve an amide coupling with **163** only led to formation of lactone **164** (92%), which could then be transformed into amide **165** in a separate step in 47% yield. Amide reduction to give **166** (71%) and subsequent Pd-catalyzed cyanation (19%) completed the synthesis of *rac*-**52**.

Synthesis of (−)-53 and eFT226. 6,8-disubstituted 7-aza analogues (−)-**53** and **eFT226** were synthesized using closely related routes (Schemes 23 and 24). The synthesis of the key azaflavonol intermediates **174** and **175** is shown in Scheme 23 and commenced with the regioselective transformation of 2,4,6-trichloropyridine (**167**) into **168** *via* S_NAr with sodium benzylate at 0 °C (72% yield). A second S_NAr reaction at elevated temperatures was used to install the methoxy group and afforded **169** in 56% yield. Regioselective, directed lithiation followed by quenching with acetaldehyde led to secondary alcohol **170** (65%), which was oxidized to ketone (**171**, 75%). Hydrogenolytic debenzylation was carried out in ethyl acetate to avoid reductive dechlorination and provided hydroxypyridine **172** in 88% yield. Aldol condensation with *para*-bromobenzaldehyde followed by AFO cyclization gave **174**, a critical intermediate in the synthesis of (−)-**53** (see below), in 19% overall yield. It was found that modification of the 6-position and installation of the methoxy group that is

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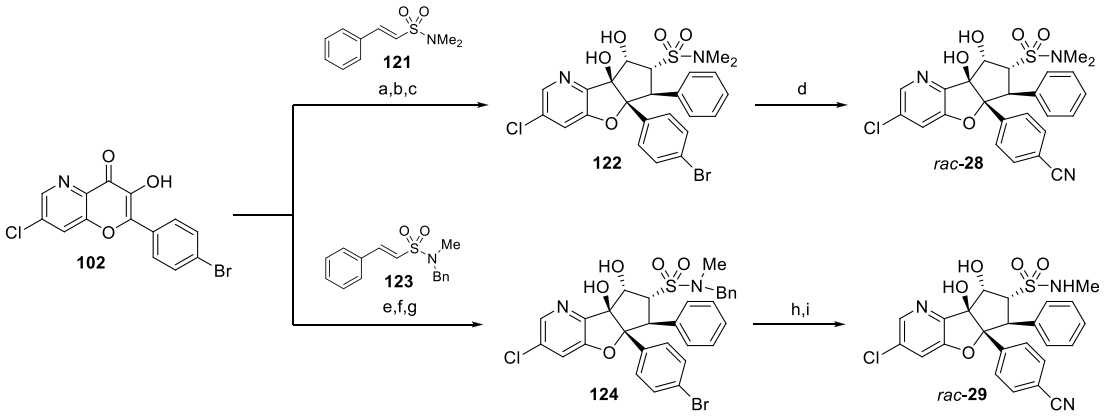
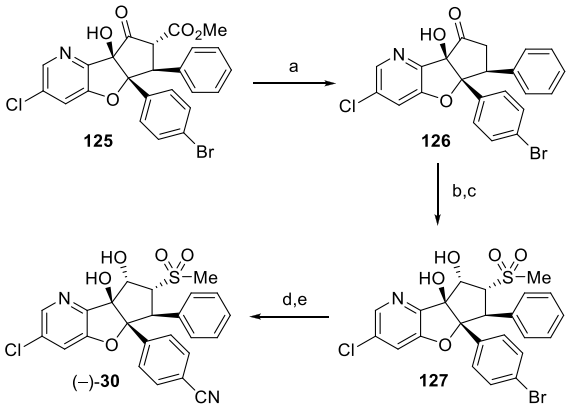
Scheme 13. Synthesis of *rac*-28 and *rac*-29. (a) 121, DCM, MeOH, MeCN, rt, *hν*; (b) NaOMe, MeOH, 80 °C; (c) $NaHB(OAc)_3$, AcOH, MeCN, rt, 2% over Three Steps; (d) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 140 °C, 7%; (e) 123, DCM, MeOH, MeCN, rt, *hν*; (f) NaOMe, MeOH, 80 °C; (g) $NaHB(OAc)_3$, AcOH, MeCN, rt, 9% over Three Steps; (h) TFA, Triflic acid, DCM, 92%; (i) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 125 °C, 8%



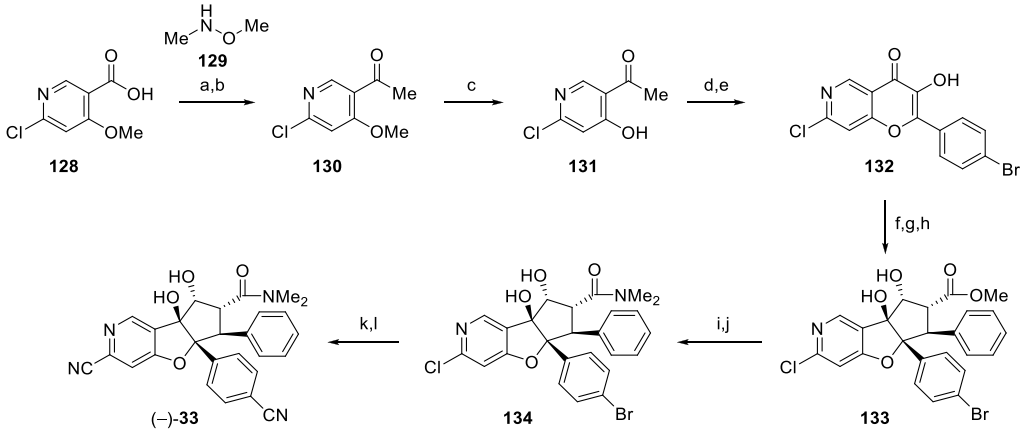
Scheme 14. Synthesis of (−)-30; (a) LiCl, DMSO, 150 °C, 33%; (b) Sodium Methanesulfinate, $CuBr_2$, DBU, DMSO, rt; (c) $NaHB(OAc)_3$, AcOH, MeCN, rt, 4% over Two Steps; (d) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMSO, 150 °C, 72%; (e) Chiral HPLC Separation



present in **eFT226** was synthetically most feasible at this stage of the synthesis, while its installation later on proved challenging. Thus, treatment of **174** with sodium methoxide in MeOH/DMF at 80 °C yielded azaflavonol **175**, a key intermediate in the synthesis of **eFT226**.

Both key azaflavonols **174** and **175** were utilized in the synthesis of (−)-**53** and (−)-**eFT226**, respectively, as outlined in Scheme 24. Thus, the established three step sequence of photocycloaddition/ketol rearrangement/directed reduction transformed **174** into **176** in 27% yield. Ester hydrolysis, amide coupling and amide reduction (75% overall) gave **177**. Pd-catalyzed 4′,6-dicyanation (63%) and chiral HPLC separation completed the synthesis of (−)-**53**. **eFT226** was synthesized using the same strategy. In the three-step sequence converting **175** to **178** best results were obtained when chloroform/2,2,2-trifluoroethanol (TFE) was used as the solvent system in the photocycloaddition step,[19] in which case the overall yield over three steps was 40%. Installation of the dimethylaminomethyl sidechain *via* ester hydrolysis/amide coupling/amide reduction (**178** → **179**) was achieved in 76% yield over three steps. Pd-catalyzed 4′-cyanation led to racemic

Scheme 15. Synthesis of (−)-33; (a) EDC, HOBt, DIPEA, 129-HCl, DCM, 0 °C to rt, 63%; (b) MeMgBr, THF, 0 °C to rt, 88%; (c) AcOH, HCl (aq), 100 °C, 68%; (d) 4-Bromobenzaldehyde, NaOH, MeOH, DCM, 90 °C, 97%; (e) H_2O_2, aq NaOH, MeOH, rt, 30%; (f) Methyl Cinnamate (55), MeCN, MeOH, DCM, rt, *hν*; (g) NaOMe, MeOH, 90 °C; (h) $NaHB(OAc)_3$, AcOH, MeCN, rt, 28% over Three Steps; (i) LiOH, THF, H_2O, rt, 91%; (j) EDC, HOBt, DIPEA, Me_2NH−HCl, DCM, 0 to 40 °C, 71%; (k) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 150 °C, 36%; (l) Chiral HPLC Separation



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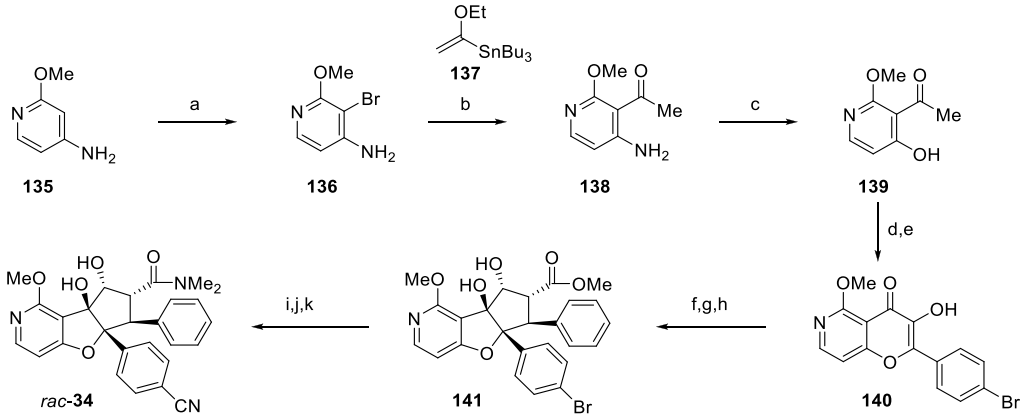
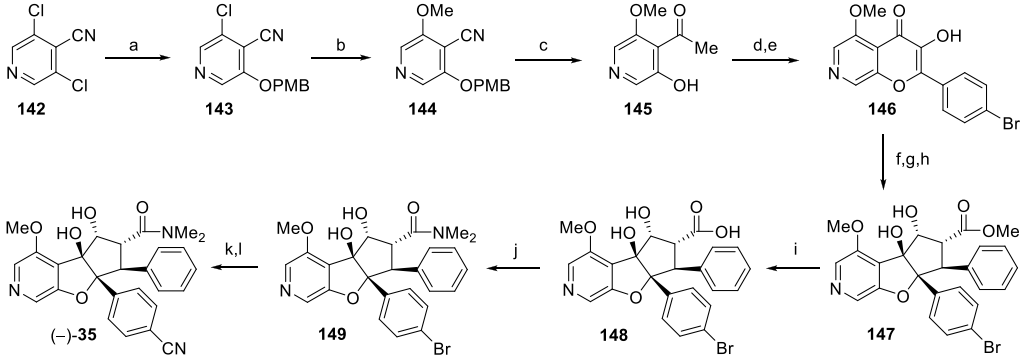
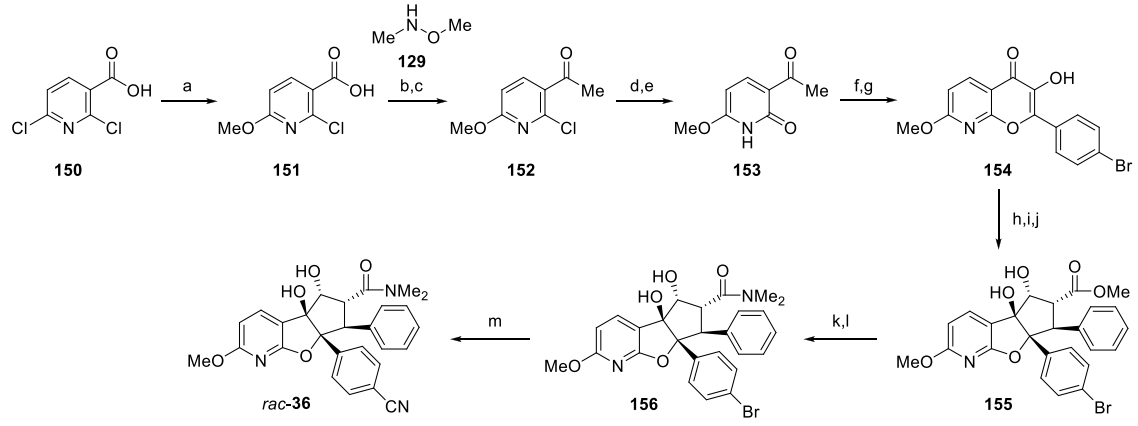
Scheme 16. Synthesis of *rac*-34; (a) NBS, DCM, 0 °C, 92%; (b) 137, cat. $PdCl_2(PPh_3)_2$, Toluene, 100 °C, Then HCl (aq) 49%; (c) $NaNO_2$, H_2SO_4, Dioxane, Water, 0 to 50 °C, 37%; (d) 4-Bromobenzaldehyde, NaOH, MeOH, Reflux, 68%; (e) H_2O_2, aq NaOH, EtOH, 0 °C to rt, 32%; (f) Methyl Cinnamate (55), MeCN, MeOH, DCM, rt, *hν*; (g) NaOMe, MeOH, 80 °C; (h) $NaHB(OAc)_3$, AcOH, MeCN, rt, 1% over Three Steps; (i) LiOH, THF, H_2O, rt, 67%; (j) EDC, HOBt, DIPEA, Me_2NH–HCl, DCM, 0 °C to rt, Quant.; (k) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 140 °C, 19%



Scheme 17. Synthesis of (−)-35; (a) PMBOH, NaH, THF, 0 °C to rt, 76%; (b) NaOMe, MeOH, 80 °C, 46%; (c) MeMgBr, THF, 0 °C to rt; Then HCl(aq), rt, 52%; (d) *para*-bromobenzaldehyde, NaOH, MeOH, Reflux, 80%; (e) H_2O_2, aq NaOH, EtOH, DCM, 0 °C to rt, 29%; (f) Methyl Cinnamate (55), MeCN, MeOH, DCM, rt, hn; (g) NaOMe, MeOH, 80 °C; (h) $NaHB(OAc)_3$, AcOH, MeCN, rt, 35% over Three Steps; (i) LiOH, MeOH, H_2O, rt, 79%: (j) $NHMe_2$–HCl, EDC, HOBt, DIPEA, DCM, 0 °C to rt, 65%; (k) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 140 °C; 50%; (l) Chiral HPLC Separation



Scheme 18. Synthesis of *rac*-36. (a) *t*-BuOK, MeOH, 80 °C; (b) EDC, HOBt, DIPEA, 129-HCl, DCM, 0 °C to rt, 75% over Two Steps; (c) MeMgBr, Et_2O, THF, 0 °C to rt; (d) PMB-OH, NaH, THF, 0 °C to rt, 47% over Two Steps; (e) TFA, DCM, 0 °C to rt; (f) 4-Bromobenzaldehyde, NaOH, MeOH, 80 °C; (g) H_2O_2, aq NaOH, EtOH, DCM, rt, 40% over Three Steps; (h) Methyl Cinnamate (55), MeCN, MeOH, DCM, rt, *hν*; (i) NaOMe, MeOH, 80 °C; (j) $NaHB(OAc)_3$, AcOH, MeCN, rt, 3% over Three Steps; (k) LiOH, MeOH, H_2O, rt, 93%; (l) EDC, HOBt, DIPEA, Me_2NH–HCl, DCM, 0 °C to rt, 38%; (m) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 140 °C, 22%



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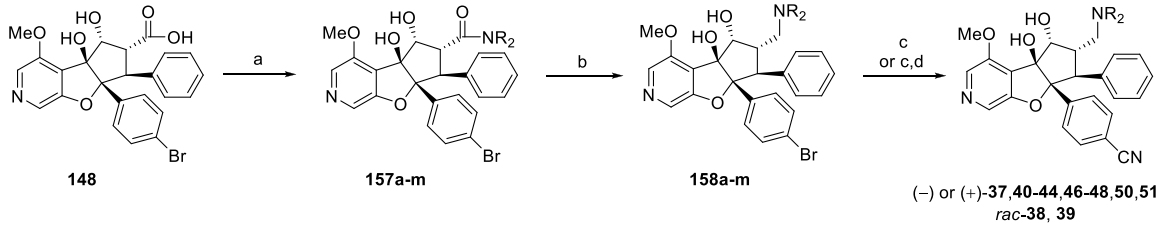
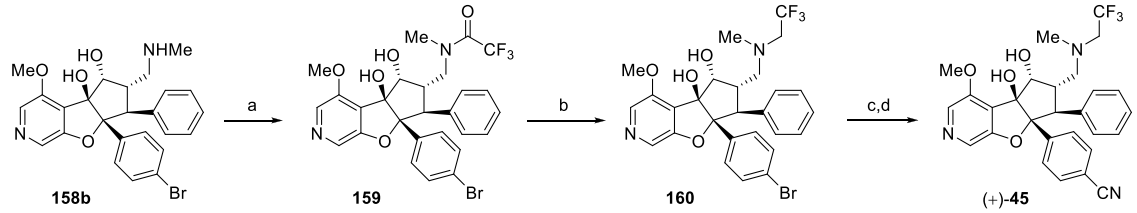
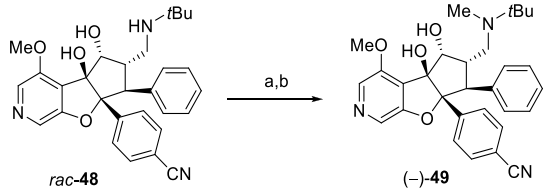
Scheme 19. General Synthesis of 6-Aza-2-amine analogues Enantiopure 37, 40−44, 46−48, 50, 51, and Racemic 38, 39; (a) R_2NH, EDC, HOBT, DCM, or R_2NH, HATU, DIPEA, DMF; (b) BH_3-DMS, THF, Δ, Then MeOH, Δ; (c) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, Δ; (d) Chiral HPLC Separation (for 37, 40−44, 46−48, 50, and 51)



Scheme 20. Synthesis of (+)-45. (a) TFAA, TEA, DCM, 0 °C to rt; (b) BH_3-DMS, THF, 60 °C, Then MeOH, Δ; (c) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, MW, 140 °C, 24% over Three Steps; (d) Chiral HPLC Separation



Scheme 21. Synthesis of (−)-49. (a) TBSOTf, 2,6-Lutidine, DCM, 0°C-rt; Then $(H_2CO)_n$, NaOAc, $NaBH(OAc)_3$, rt, 55%; (b) Chiral HPLC Separation



eFT226 in 73% yield, which was then subjected to chiral HPLC separation to afford enantiopure (−)-**eFT226**. A crystal structure analysis of (−)-**eFT226** single crystals was successfully obtained and confirmed the structural assignment (Figure 15).

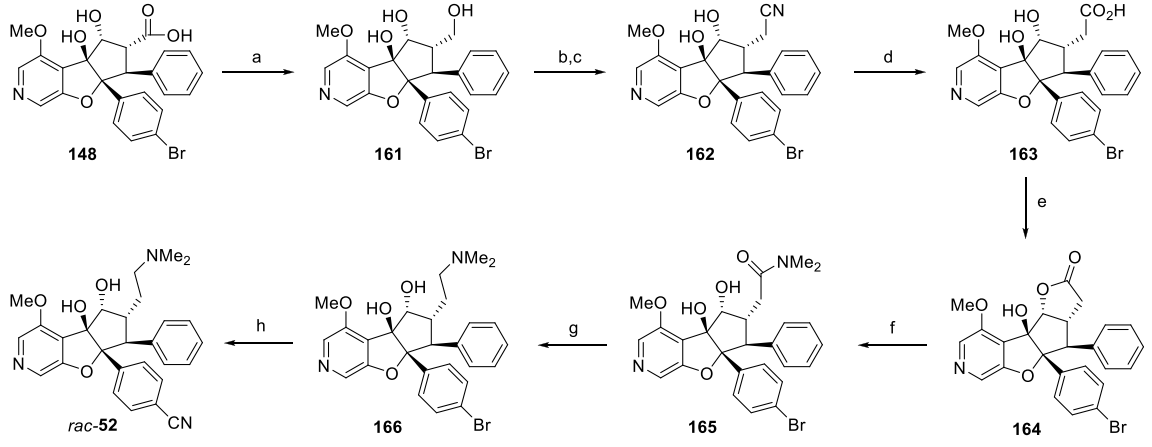
EXPERIMENTAL SECTION

Reagents. Hippuristanol and Rocaglamide A were synthesized and QCed at Julilant Life Sciences (Uttar Pradesh, India). Cycloheximide was purchased from Sigma-Aldrich (St. Louis, MO).

Liver Microsome Stability. Incubations were conducted at 1 μM test article (TA), 0.5 mg/mL liver microsomal protein in 100 mM phosphate buffer (PB; pH 7.4), 2 mM NADPH at 37 °C with a final organic concentration of 0.1% DMSO, and 0.9% acetonitrile (MeCN). Liver microsomes used in these experiments were obtained from BioIVT (Hicksville, NY).

Each TA stock solution (10 mM DMSO) was diluted to 1 mM with DMSO and then diluted an additional 10-fold with MeCN to 100 μM. Stock microsomes (20 mg/mL) are thawed and diluted into PB to 0.633 mg/mL. A solution of NADPH was made in PB at 8.33 mg/mL. The diluted microsomes were added to a 96-well plate (98.75 μL) designated as master plate. The 100 μM TA (1.25 μL) was spiked into the master plate and, following a 10 min preincubation period, reactions were initiated by transferring equal aliquots from the master plate (40 μL) to two clean plates. To one of these plates (T0 control plate), 100 μL of MeCN containing an internal standard (IS) was

Scheme 22. Synthesis of *rac*-52; (a) BH_3-DMS, THF, 0 °C to rt, Then MeOH, 70 °C, 93%; (b) MsCl, Pyridine, 0 °C to rt, 80%; (c) KCN, DMSO, 80 °C, 58%; (d) 10% NaOH (aq), THF, 125 °C, 94%; (e) Me_2NH−HCl, EDC-HCl, HOBT, DIPEA, DCM, 0 °C to rt, 92%; (f) Me_2NH, THF, T3P, EtOAc, 80 °C, 47%; (g) BH_3-DMS, THF, 0 °C to rt, Then MeOH, 0 °C to 70 °C, 71%; (h) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, 140 °C, 19%



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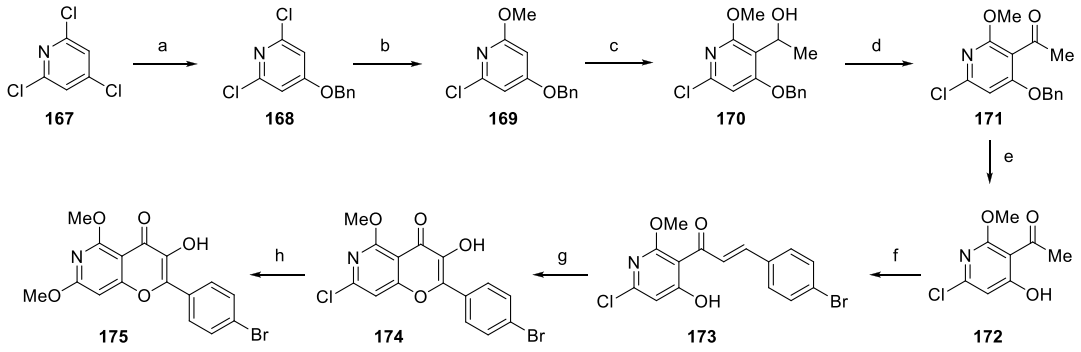
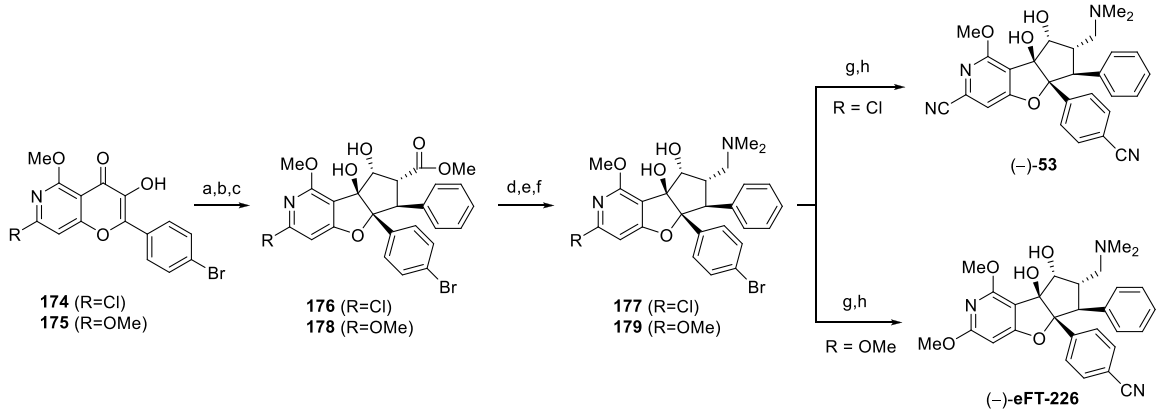
Scheme 23. Synthesis of Azaflavonols 174 and 175; (a) BnOH, NaH, DMF, 0 °C, 72%; (b) NaOMe, MeOH, Toluene, 70 °C, 56%; (c) *n*-BuLi, THF, −75 °C, Then Acetaldehyde, 65%; (d) DMP, DCM, 75%; (e) H_2, Cat. Pd/C, EtOAc, 88%; (f) *para*-Bromobenzaldehyde, NaOMe, MeOH, DMF, Quant.; (g) NaOH (aq), H_2O_2 (aq), EtOH, DCM, Water, 19%; (h) NaOMe, MeOH, DMF, 80 °C, 98%



Scheme 24. Completion of the Synthesis of (−)-53 and (−)-eFT226; (a) Methyl Cinnamate (55), MeCN, MeOH, DCM (R = Cl) or Methyl Cinnamate (55), $CHCl_3$, TFE (R = OMe), 0 °C, *hν*; (b) NaOMe, MeOH, 60 °C; (c) $NaHB(OAc)_3$, AcOH, MeCN, rt, 27% (R = Cl), 40% (R = OMe) (Yield over Three Steps); (d) LiOH, MeOH, Water, 50 °C (R = Cl), 90%, or LiOH(aq), MeOH, THF, rt (R = OMe), 93%; (e) HATU, DIPEA, Me_2NH, THF, DMF, rt, 95% (R = Cl), 92% (R = OMe); (f) BH_3-DMS, THF, 40 °C, Then MeOH, 65−70 °C, 88% (R = Cl), 89% (R = OMe); (g) Zn, $Zn(CN)_2$, Pd_2dba_3, dppf, DMF, Water, MW, 120 °C, 63% (R = Cl), 73% (R = OMe); (h) Chiral HPLC Separation



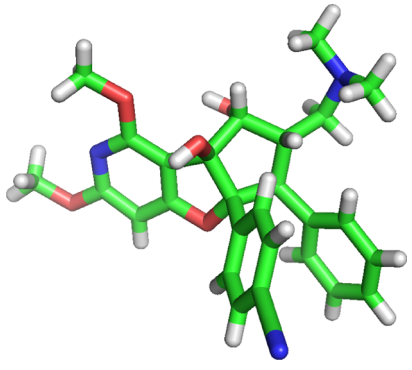


Figure 15. X-ray structure of (−)-**eFT226**.

added. To the other plate (T30 reaction plate), NADPH solution (10 μL) was added to initiate the reaction. To the T0 control plate, NADPH solution was added (10 μL) and the plate was vortexed at 1000 rpm for 5 min to precipitate protein. After the 30 min incubation period, the T30 plate was taken from the incubator, and 100 μL MeCN with IS was added. Subseqeuntly the plate was vortexed at 1000 rpm for 5 min to quench reactions. Precipitated proteins were removed by centrifugation, and supernatants were transferred to new 96-well polypropylene plates. Plates were capped with pierceable septa and subjected to bioanalysis by LC/MS/MS. The MS model used was an AB SCIEX TripleTOF 5600+ operated in electrospray ionization TOF MS (+) mode. All experiments were run in duplicate, and the mean percent remaining at 30 min was determined as follows.

$$\%\ \text{remaining at 30 min} = \frac{\text{mean at 30 min(analyte peak area/IS peak area)}}{\text{mean at 0 min(analyte peak area/IS peak area)}}$$

Caco-2 Permeability and Efflux Studies. CACOReady 96-well kits were purchased from ADMECell (Alameda, CA). Two weeks after seeding, ADMECell ships the kits in a proprietary semi-solid medium. The media was changed after arrival, and all assays were performed on day 21 post-seeding. A 10 mM stock solution of each TA was prepared and stored at −20 °C until needed for experimentation. A working buffer was prepared in Hanks' balanced salt solution (HBSS) with 10 mM HEPES and 15 mM glucose at pH 7.4. An acceptor buffer was prepared from the working buffer with an addition of 1% bovine serum albumin. The dosing buffer was prepared from the working buffer with the addition of TA resulting in a final concentration of 5 μM TA and 1% DMSO. Prior to the start of the assay cell junction, integrity was assessed by transepithelial electrical resistance (TEER). For use in the assay, wells required a TEER measurement of at least 500 $\Omega \cdot cm^2$. Apical and basolateral sides of the cell monolayers were washed once with HBSS. Apical-to-basolateral (A-to-B) experiments were dosed with 65 μL of dosing buffer (75 μL final volume) on the apical side of the cell monolayer and 250 μL of acceptor buffer on the basolateral

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Table 9. 5′-UTR Sequence Motifs

CAACAA	5′-AAGCTTGAA$(CAACAA)_{13}$CACCCCATGG-3′
AGAGAG	5′-AAGCTTGAA$(\mathbf{AGAGAG}CAACAA)_6\mathbf{AGAGAG}$CACCCCATGG-3′
CCGCCG	5′-AAGCTTGAA$(\mathbf{CCGCCG}CAACAA)_6\mathbf{CCGCCG}$CACCCCATGG-3′
GGCGGC	5′-AAGCTTGAA$(\mathbf{GGCGGC}CAACAA)_6\mathbf{GGCGGC}$CACCCCATGG-3′

side of the cell monolayer. Basolateral-to-apical (B-to-A) experiments were dosed with 250 μL of dosing buffer on the basolateral side of the cell monolayer and 65 μL of acceptor buffer (75 μL final volume) on the apical side of the cell monolayer. Cell monolayers were incubated at 37 °C with 5% CO_2 in a humidified incubator for 2 h. After the assay, cell junction integrity was again tested for damage with a Lucifer yellow permeability assay. In order for cells to be of considered viable, Lucifer yellow paracellular flux needed to be less than 0.3%. Post assay, concentrations of TA from acceptor and donor compartments were determined by LC/MS/MS using standard calibrators ranging in concentration from 0.001 to 5 μM. The MS model used was a Sciex API 4000 operated in electrospray ionization MRM-(+) mode. Calculations of P_{app} and efflux were performed according to the following formulas

$$P_{app} = \frac{dQ}{dt} \times \frac{1}{A \times C_0}; \quad \text{efflux} = \frac{P_{app,BA}}{P_{app,AB}}$$

where dQ/d*t*: the amount of TA in the acceptor (nmol) over the duration of the assay (seconds). A: area of transwell (cm^2). C_0: concentration of TA in the donor well at the start of the assay (μM). $P_{app,BA}$: apparent permeability of TA in the B-to-A direction. $P_{app,AB}$: apparent permeability of the TA in the A-to-B direction.

Assignment of specific P-gp efflux was accomplished for some compounds (*e.g.*, **eFT226**) by conducting additional bi-direction permeability assays which included a P-gp inhibitor (valspodar, 5 μM) in the dosing buffer. These experiments consistently attenuated efflux.

***In Vivo* Pharmacokinetics.** Jugular vein-catheterized Sprague dawley rats of both genders were administered a single IV bolus dose of each TA *via* the saphenous vein, at a nominal level of 1 mg/kg (free base) in a suitable formulation. Following dosing, blood was collected from all animals *via* jugular vein into microtubes containing K_2EDTA at 0.083, 0.25, 0.50, 1, 2, 4, 8, and 24 h post-dose. Blood samples were initially stored on ice and subsequently centrifuged to separate plasma. Plasma samples were kept on ice prior to storage in a −80 °C freezer until time of processing for bioanalysis. Plasma bioanalysis was performed on all time points using bioanalytical methods that included using protein precipitation followed by liquid chromatography−mass spectrometry (LC/MS) analysis. The MS model used was an AB SCIEX TripleTOF 5600+ operated in electrospray ionization TOF MS (+) mode. The analyte quantified was the respective free base form of each TA. Bioanalytical time versus concentration data were imported into Phoenix 64 WinNonlin software and PK parameters calculated using noncompartemental analysis.

Thermodynamic Solubility. Dry powders of each TA were weighed into 1 dram vials. Deionized water was added to each vial to reach the desired nominal free base concentration of 20 mg/mL. Compounds isolated as the HCl salt (*i.e.*, **37**, **53**, **eFT226**) incorporated a salt correction factor of ∼1.08 mg TA per mg of free base during the weighing process. Teflon-coated StirStix were added to each dram vial and then capped. Samples were placed on a plate heater (Watlow, St. Louis, MO) with the temperature set to 37C and covered with a Styrofoam cover. Samples were heated and stirred on a magnetized paddles stirrer (V&P Scientific, San Diego, CA) for 18 h. Post incubation, samples were filtered in an AcroPrep Advance 1 mL 0.2 μm Supor filter plate (Pall Corporations, Ann Arbor, MI). The filtrate (60 μL) was added to 20 μL of DMSO and analyzed by HPLC-UV (Agilent 1100 series, Santa Clara, CA) with appropriate standard(s) to determine soluble concentration in each experiment. TAs solutions determined to be above the standard(s) concentration were further diluted using a 3:1 deionized water/DMSO solution to below the highest standard concentration.

pK_a/log *P*. Ionization constants (pK_a's) and octanol water partition coefficients (log *P*, log *D* 7.4) were determined at Pion, Inc (Billerica, MA). A PULSE instrument (Pion Inc.) was used to measure pH of the solutions. The instrument was equipped with three precision dispensers (capable of adding a minimum volume of 0.042 μL and a high-impedance (1015 Ω) pH circuit. The double junction combination pH electrode was standardized using the Avdeef−Bucher four−parameter equation. The standard aqueous method based on potentiometric titration routinely determines pK_a values from 3 to 11. The cosolvent method is narrower by about 1 pH unit, specifically due to electrode calibration in the presence of organic solvents. Furthermore, if precipitation of the compound occurred during pH-metric titrations, that may affect the results increasing the error limits on the pK_a determination. In these cases, the pK_a value cannot be reliably determined. The aqueous pK_a values were extrapolated from the pK_a values in cosolvents as a reciprocal function of the dielectric constant (ε) of each of the co-solvent mixture using Yasuda−Shedlovsky extrapolation procedure. The extrapolation plots are used to calculate the aqueous pK_a from the pK_a (p_sK_a) measured in cosolvent. However, if p_sK_a values are outside of the pH region specified for the method, the aqueous pK_a cannot be determined. log *P*/log *D* values are calculated based on the difference between accurately determined aqueous pK_a values and pKa determined in the presence of 1-octanol (p_oK_a). In cases when the p_oK_a or/and pK_a values cannot be reliably determined, the log *P*/log *D* results are reported as "Not Available" (N/A). The pK_a experiments for the compound have been performed using the potentiometric and the UV-metric methods. The log *P*/log *D* experiments were performed using the potentiometric method.

Biacore Binding Studies. RNA 18-mer oligonucleotides were custom synthesized from GE Healthcare Dharmacon Inc (Chicago, IL) and biotinylated on the 3′ end and contained the following repeat sequences:

(AGAGAG): 5′-A.G.A.G.A.G.A.G.A.G.A.G.A.G.A.G.A.G-Bi-3′;

(GGCGGC): 5′G.G.C.G.G.C.G.G.C.G.G.C.G.G.C.G.G.C−Bi-3′;

(CCGCCG): 5′C.C.G.C.C.G.C.C.G.C.C.G.C.C.G.C.C.G-Bi-3′; and

(CAACAA): 5′-C.A.A.C.A.A.C.A.A.C.C.A.C.C.A.C.C.A-Bi-3′

Full length recombinant eIF4A1 protein was prepared at Beryllium Discovery (Bainbridge Island, WA) and was kept at −80 °C until use in the following storage buffer: 20 mM Tris pH 7.5, 200 mM NaCl, 1% glycerol, and 1 mM TCEP. Biacore studies were conducted at Biosensor Tools (Salt Lake City, UT) on a ProteOn XPR36 protein interaction array system BioRad (Hercules, CA) using NLC sensor chips functionalized with streptavidin for capturing biotinylated biomolecules. Running buffer contained 14.4 mM Hepes pH 7.4, 108 mM NaCl, 1 mM $MgCl_2$, 0.36 mM TCEP, 1 mM ATP, and 1% DMSO. Data were collected at 25 °C. The formation of the ternary complex was tested with eIF4A1 and **eFT226** in the presence or absence of nucleotides (ATP and AMP-PNP). Once the complex was formed on the RNA surface, dissociation of eIF4A1 was determined by washing the surface for 110 s in the presence of compound and ATP, followed by a wash without compound (ATP only). Response data for the full concentration series were fit globally to a 1:1 interaction model using the data processing and analysis software Scrubber, BioLogic Software (Canberra, Australia).

Cell-Based Reporter Assay. Seven tandem repeats of various sequence motifs (see Table 9) were cloned into the 5′-UTR of the luciferase reporter vector pGL3 (Promega Corp., Madison, WI) at Genewiz (San Diego). DNA templates were PCR amplified using Phusion High-fidelity PCR Master Mix (New England Biolabs, Ipswich, MA) from the reporter vector using the forward and reverse primers described in Table 10 that incorporates the T7 promoter

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Table 10. Reporter Construct Forward and Reverse qPCR Primers.

forward (CAACAA)	5′-GGGCACTAATACGACTCACTATAGGAAGCTTGAA$(CAA)_{26}$CACC-3′
forward (AGAGAG)	5′-GGGCACTAATACGACTCACTATAGGAAGCTTGAA(**AGAGAG**CAACAA)$_6$**AGAGAG**CACC-3′
forward (CCGCCG)	5′-GGGCACTAATACGACTCACTATAGGAAGCTTGAA(**CCGCCG**CAACAA)$_6$**CCGCCG**CACC-3′
forward (GGCGGC)	5′-GGGCACTAATACGACTCACTATAGGAAGCTTGAA(**GGCGGC**CAACAA)$_6$**GGCGGC**CACC-3′
reverse (Firefly)	5′-TTACACGGCGATCTTTCCGCCCTT-3′

sequence for subsequent RNA transcription. Reactions were purified using the Qiagen PCR clean up kit and eluted in 50 μL water. RNA was transcribed from the DNA templates using the mMESSAGE mMACHINE T7 Ultra kit (Ambion ThermoFisher, Waltham, MA). RNA was purified with the RNA Mega Clear Kit and eluted with 30 μL elution buffer (Ambion ThermoFisher, Waltham, MA). Using the manufacturer's instructions, RNA was transiently transfected in bulk into exponentially growing MDA-MB-231 cancer cells using the TransIT mRNA transfection kit (Mirus Bio, Madison, WI), and the transfected cells were then seeded into 96-well plates. The transfected cells were treated with various concentrations of translation inhibitors (**eFT226**, RocA, hippuristanol, and cycloheximide) or control (DMSO) for 4 h at 37 °C. Cells were rinsed with 100 μL of PBS and lysed using 50 μL of 1x passive lysis buffer (Promega Corp., Madison, WI). After shaking for 20 min at room temperature, 100 μL of luciferase assay reagent (Promega Corp., Madison, WI) was added, and luminescence was quantitated using a Victor (PerkinElmer) plate reader. The data were fitted using GraphPad Prism (GraphPad Software, La Jolla, CA) and a four-parameter dose response equation.

Generation of HAP1 eIF4A1 F163L Cell Line. The pSpCas9 BB-2A-Puro (PX459) v2.0 vector containing the Cas9 nuclease and a sgRNA targeting the sequence surrounding F163 in human eIF4A1 (5′-CATATCAAACACACG GCCAG-3′) was purchased from Genescript (Piscataway, NJ). The ssODN donor template (5′GCCTGTATCGGGGGCACCAACGTGCGTGCTGAGGTG-CAGAAACTGCAGAT GGAAGCTCCCCACATCATCGTGGG-TACACCTGGCCGTGTGCTCGATATGCTTAACCGGAGA-TACCTGTGTGAGTAATTCGGTTCTCCAATCCCCTGGGT-CACTTTGCTCTTGTGCACG-3′; PAM mutation is italicized, F163L mutation underlined and novel TaqαI restriction site is in bold) was purchased from Integrated DNA Technologies (Coralville, IA). The vector and ssODN were cotransfected into exponentially-growing HAP1 cells (Horizon Discovery, Cambridge, UK) using X-tremeGENE 9 (Roche; Basel, Switzerland), and 2 days later, a single cell suspension was transferred into 96-well plates at approximately 1 cell/well. After 2 weeks, following gDNA extraction each clone was assayed for the presence of the TaqαI restriction site by PCR amplification and subsequent restriction enzyme digest of the region of interest in human eIF4A1 (Herculase DNA polymerase from Agilent Technologies; Santa Clara, CA and TaqαI from New England Biolabs; Ipswich, MA). The undigested PCR product from potential positive clones was ligated into the TOPO-Blunt vector (ThermoFisher, Waltham, MA) and subjected to Sanger sequencing to verify correct nucleotide changes.

Cell Culture, Antibodies, and Immunoblotting. MDA-MB-231 (ATCC, Manassas, VA) and HAP1 cells were maintained in DMEM supplemented with 10% FBS and 1× penicillin/streptomycin. The GAPDH antibody was purchased from Santa Cruz Biotechnology (Dallas, TX). The c-MYC antibody was purchased from Abcam (Cambridge, UK). The Cyclin D1 antibody was purchased from Cell Marque (Rocklin, CA). Antibodies against MCL-1, BCL2, and eIF4A1 were purchased from Cell Signaling Technology (Danvers, MA). Secondary antibodies (Goat anti-rabbit IRDye-680, Goat anti-mouse IRDye-800, Donkey anti-rabbit IRDye-800CW, and Donkey anti-mouse IRDye-680RD) for Odyssey infrared imaging were purchased from LI-COR (Lincoln, NE).

For immunoblotting, exponentially growing cells were seeded into 6-well plates at 0.5 million cells/mL and cultured overnight followed by treatment with the indicated concentrations of **eFT226** or DMSO for 24 h. Cells were pelleted by centrifugation, washed once with ice-cold PBS and lysed in 1× cell lysis buffer from Cell Signaling Technology (Danvers, MA) supplemented with a final concentration of 1 mM PMSF. Protein concentrations in cell lysates were quantitated by BCA protein assay from Thermofisher Scientific (Waltham, MA) and equal amounts of total protein were resolved by SDS-PAGE, immunoblotted with the indicated antibodies and visualized by LI-COR Odyssey imager.

Cell Proliferation Assay. Exponentially growing cells were seeded at 2000−5000 cells per well in 96-well flat bottom white polystyrene plates (Thermo Fisher) and cultured overnight. The following day, compound was added in a 3-fold dilution series along with a DMSO control. The final DMSO concentration was 0.1%. Cells were incubated for 72 h at 37 °C in a CO_2 incubator. Baseline viability of untreated cells was measured on the day of treatment and proliferation was measured after 72 h of treatment using CellTiter-Glo reagent from Promega (Madison, WI) according to manufactures instructions. Dose−response curves were plotted using Prism 6 software, and CI_{50} values were calculated using a 4 parameter, variable slope nonlinear regression model. Calculation of % inhibition: % inhibition = 1 − (((cells + inhibitor) − baseline)/((cells + DMSO) − baseline))) × 100.

Analysis of Cell Cycle. Exponentially growing cells were seeded in 96-well plates and cultured overnight. Cells were then treated with **eFT226** or DMSO for 24 h. Cells were washed once with PBS, dissociated from plates by adding Trypsin−EDTA (0.25%) from Thermofisher Scientific (Waltham, MA), and incubated at 37 °C for 3 min. Trypsin is neutralized with culture medium containing 20% FBS, and the cell suspension is transferred to a round bottom 96-well plate. Cells are left to rest at room temperature for 15 min before washing with PBS. Cells are stained with LIVE/DEAD Fixable Dead Cell Stain kit from Thermo Fisher Scientific (Waltham, MA) and formalin fixed. Cell cycle was assessed by DNA staining using DRAQ5 from Thermo Fisher Scientific (Waltham, MA). Fluoresence of the cells was analyzed by flow cytometry using Attune NxT flow cytometer from Thermofisher Scientific (Waltham, MA).

Analysis of Apoptosis and Cell Death. For analysis of apoptosis by Annexin V staining, exponentially growing cells were seeded at 10,000 cells per well in a 96-well tissue culture treated plates and cultured overnight. Cells were then treated with **eFT226** or DMSO for 24 h. Apoptosis and cell death are measured using BD Annexin V FITC Apoptosis Detection Kit from BD Biosciences (San Jose, CA) according to the manufacturer's instructions. Briefly, cells were washed once with PBS, dissociated from plates by adding Trypsin−EDTA (0.25%) from Thermofisher Scientific (Waltham, MA), and incubated at 37 °C for 3 min. Trypsin is neutralized with culture medium containing 20% FBS, and the cell suspension is transferred to a round bottom 96-well plate. Cells are left to rest at room temperature for 15 min before washing once with PBS and resuspended in 1× annexin V binding buffer containing annexin V and PI. Cells were incubated at room temperature for 15 min followed by dilution in 1× annexin V binding buffer. Fluorescence of the cells was analyzed by flow cytometry using Attune NxT flow cytometer Thermo Fisher Scientific (Waltham, MA).

***In Vivo* Efficacy Studies.** All animal studies were carried out in accordance with the guidelines established by the Institutional Animal Care and Use Committee at Explora BioLabs (San Diego, CA). For MDA-MB-231 xenografts, athymic nude ((NCr) nu/nu fisol, Simonsen) were implanted orthotopically in the mammary fat pad with 5×10^6 cells in 0.1 mL of unsupplemented DMEM and an equal volume (1:1) ratio of Matrigel (BD Biosciences) for tumor development. When the mean tumor sizes reached approximately 170 mm^3 (MDA-MB-231), the mice were randomized and size-

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matched into vehicle and treatment groups. The tumor size was measured in length and width with a caliper twice a week. The tumor volume was calculated by the formula $L \times W \times W/2$ according to NCI standards. Body weights were collected prior to study start, and twice a week during the study. **eFT226** was formulated in 5% dextrose in water (D5W), heated and/or vortexed to make a clear solution.

Computation. *Rocaglamide A binding model.* The protein employed for the model was the PDB ID 2HYI structure of eIF4E3 from the pdb database because this was the only eIF4A structure at the time that had an RNA strand bound.[27] The initial conformation of rocaglamide A was obtained using a rocaglamide analogue structure from the Cambridge Structural Database (CSD), FROJM03. The structure of rocaglamide A was constructed in 3D from this starting model using the editing tools available in Benchware 3D and minimized in the gas phase using the MMFF. The resulting 3D model was placed by hand into the 2HYI protein structure with a Connelly surface representation displayed to reveal potential binding pockets of the protein in the region supported by the mutational data.[25] Only one pose was deemed reasonable for further study, and it was minimized in the presence of the protein using the MMFF and Benchware. Subsequent models of compounds 7 and 36 were generated from the rocaglamide A model by editing the structure with the 3D tools of Benchware and minimizing in the gas phase using the MMFF; no re-optimization to the protein was performed.

Torsional modeling. All torsional studies were performed using Spartan '14 version 1.1.8 from Wavefunction, Inc. For each derivative of interest, the structure was constructed in 3D using the editing tools in Spartan and the equilibrium geometry calculated using DFT and either EDF2 or B3LYP at the 6-31G* level of theory. The torsional energy surface was then generated by driving the C1′−C3a−C3−C1″ from 60° to −30 or −60 in 5° increments using the energy profile function. Plots were generated with the torsional angle value on the *x*-axis and the relative energy on the *y*-axis using the smooth function to draw a line.

Chemistry. All reagents and solvents were used as purchased from commercial sources unless otherwise noted. Microwave reactions were performed with a Biotage Initiator focused beam microwave reactor. Reactions were monitored, and analytical purities were assessed on the following instruments: Waters Acquity UPLC with SQD mass equipped with Acquity UPLC BEH C-18 (2.1 × 100 mm, 1.7 μm) and Acquity UPLC HSS T3 (2.1 × 100 mm, 1.8 μm) columns (LCMS); Shimadzu LC-10AD liquid chromatograph system equipped with a Shimadzu SCL-10A System controller and SPD-10A UV/Vis detector, a PerkinElmer Series 200 Autosampler and a Phenomenex Gemini NX-C18 column (3 μm, 30 × 4.6 mm) (LCMS). Analytical chiral separations and determinations of enantiomeric excesses were performed using a Waters Alliance 2695 Separations Module with Waters 2998 Photo Diode Array Detector (HPLC) or a Waters Acquity UPCC with a Waters Photo Diode Array detector (UPCC/analytical SFC) equipped with Diacel Chiralpak IA (4.6 × 250 mm, 5 μm), Diacel Chiralpak IC (4.6 × 250 mm, 5 μm), or Diacel Chiralpak IG (4.6 × 250 mm, 5 μm) columns. Final compounds for biological evaluation were obtained in ≥95% purity as determined by LCMS.

Flash column chromatography was performed with a Teledyne ISCO CombiFlash Rf200+ system or a Yamazen Smart Flash EPLC W-Prep 2XY system using normal-phase silica columns (230−400 mesh). HPLC purification was performed using a Waters automated purification system with Waters 2767 sample controller, 2545 binary gradient pump, and 2998 Photo Diode Array Detector/2489 UV Detector; or a Gilson automated purification system equipped with a Gilson 215 liquid handler and 333 and 334 pumps using Phenomenex Gemini NX-C18 columns (10 μm, 250 × 30 mm or 10 μm, 250 × 50 mm). SFC purification was performed on a Waters SFC 200q system with waters 2489 UV/vis detector. Chiral SFC separations were performed using Diacel Chiralpak IA (21 × 250 mm, 5 μm), Diacel Chiralpak IC (30 × 250 mm, 5 μm), and Diacel Chiralpak IG (21 × 250 mm, 5 μm) columns.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz Avance III HD Nanobay with a BBFO probe, Bruker 400 MHz Avance II with a Dual 13C probe, Agilent MR400 spectrometer, Bruker DRX 500, and Bruker AV-500 spectrometer. Coupling constants (J) are reported in hertz (Hz). Chemical shifts (δ) of NMR spectra are reported in parts per million (ppm) and are calibrated using residual undeuterated solvent for ^{1}H NMR [^{1}H = 7.26 ($CHCl_3$), 2.50 (D_5H-DMSO) ppm] and ^{13}C deuterated solvent for ^{13}C NMR [39.52 (DMSO-d_6) ppm] as an internal reference at 298 K.[42] The following abbreviations were used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad.

High-resolution mass spectrometry (HRMS) was performed using a Triple TOF 5600+ mass spectrometer (hybrid quadrupole time-of-flight platform; AB Sciex) connected to a 1290 UHPLC system (Agilent). The mass spectrometer was operated in electrospray positive ionization mode (ESI+). Acquisition was a full scan from m/z 100 to 1000 with a pulser frequency of 18.092 kHz and accumulation time of 250 ms.

Optical rotations were measured using an Optical activity ltd polarimeter (model: polAAr 3002).

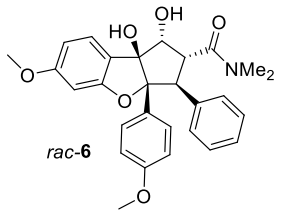
Single-crystal X-ray diffraction studies were carried out on a Bruker D8 Platinum^{135} CCD diffractometer equipped with Cu Kα radiation (λ = 1.5478).

Photocycloadditions were carried out using the following equipment: Medium Pressure Mercury Vapor Lamp (Vendor: SAIC, INDIA; model: MVL4; Power Supply model: MVL41, wattage: 400 W, diameter: 22 mm); Amit Scientific UV reactor (250 mL/500 mL/1000 mL/5 L/10 L).

*Synthesis of rac-(1R,2R,3S,3aR,8bS)-1,8b-Dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxamide (rac-**6**). 1-(2-Hydroxy-4-methoxyphenyl)ethan-1-one (**S1**).* To a solution of 1-(2,4-dihydroxyphenyl)ethan-1-one (**68**) (50.0 g, 329 mmol) in acetone (500 mL), potassium carbonate (136.0 g, 984.0 mmol) was added at room temperature. The reaction mixture was stirred for 15 min at room temperature, and then methyl iodide (20 mL, 46 g 0.32 mol) was added. The reaction mixture was stirred at room temperature for 16 h, after which acetone was removed under reduced pressure, and the solid obtained was washed with ice cold water 3 times and dried under high vacuum, affording 1-(2-hydroxy-4-methoxyphenyl)ethan-1-one (**68**) as a white solid. Yield: 50.0 g (0.301 mol, 92%). MS (ESI) m/z: 165.07 $[M-1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.80 (d, J = 8.8 Hz, 1H), 6.49−6.44 (m, 2H), 3.79 (s, 3H), 2.55 (s, 3H).

*(E)-1-(2-Hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**S2**).* To a solution of 1-(2-hydroxy-4-methoxyphenyl)-ethan-1-one (**S1**) (50.0 g, 301 mmol) in methanol (250 mL), sodium hydroxide (36.0 g, 900 mmol) was added followed by 4-methoxybenzaldehyde (55.0 g, 404 mmol). The reaction was then heated to reflux for 1 h. Afterward, the reaction mix was cooled and the solid was obtained by filtration, washed with water, and dried under high vacuum to afford (*E*)-1-(2-hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**S2**) as a yellow solid. Yield: 77.0 g (271 mmol, 90%). MS (ESI) m/z: 285.2 $[M+1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.22 (d, J = 8.5 Hz, 1H), 7.91−7.76 (m, 4H), 7.01 (d, J = 7.9 Hz, 2H), 6.52−6.47 (m, 2H), 3.82 (s, 6H).

*3-Hydroxy-7-methoxy-2-(4-methoxyphenyl)-4H-chromen-4-One (**69**).* To a solution of (*E*)-1-(2-hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**S2**) (77.0 g, 271 mmol) in ethanol (500 mL) at room temperature, sodium hydroxide (32.0 g, 800 mmol, 10% aq solution) was added, followed by hydrogen peroxide (19 mL, 810 mmol). The reaction mixture was stirred for 2 h at room temperature (reaction is exothermic), after which the reaction mixture was cooled and neutralized to pH ≈ 7 by the addition of 5 N hydrochloric acid. The precipitate was collected by filtration and dried



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under vacuum to afford 3-hydroxy-7-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (**69**) as a pale yellow solid. Yield: 16.0 g (53.6 mmol, 20%). MS (ESI) *m*/*z*: 299.10 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 9.31 (br s, 1H), 8.18 (d, *J* = 7.9 Hz, 2H), 7.97 (d, *J* = 8.5, 1H), 7.25 (s, 1H), 7.10 (d, *J* = 8.1, 2H), 7.02 (d, *J* = 8.1, 1H), 3.90 (s, 3H), 3.84 (s, 3H).

*rac-Methyl (3S,4S,5R)-5-Hydroxy-8-methoxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[b]-oxepine-4-carboxylate (**S3**).* A solution of 3-hydroxy-7-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (16.0 g, 53.6 mmol) and methyl cinnamate (86.9 g, 536 mmol) in dichloromethane (200 mL), acetonitrile (100 mL) and methanol (100 mL) was placed in a UV reactor flask. The reaction mixture was irradiated under 400 watts UV light for 15 h. After completion, the solvent was removed under reduced pressure, and the residue was purified over a plug of silica gel by eluting the compound with 5% methanol in dichloromethane. The desired fractions were concentrated under reduced pressure to afford methyl *rac*-(3*S*,4*S*,5*R*)-5-hydroxy-8-methoxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (**S3**) as a brown solid. Yield: 18.0 g, crude.

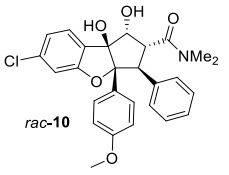
*rac-Methyl (2R,3S,3aR,8bR)-8b-Hydroxy-6-methoxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta-[b]benzofuran-2-carboxylate (**S4**).* The crude *rac*-methyl 8a-hydroxy-5-methoxy-2a-(4-methoxyphenyl)-8-oxo-2-phenyl-2,2a,8,8a-tetrahydro-1*H*-cyclobuta[*b*]chromene-1-carboxylate (**S3**) (18.0 g) was suspended in methanol (250 mL), treated with 25% sodium methoxide in methanol (90 mL. 85 g solution; 21 g, 0.39 mol NaOMe), and heated to 100 °C for 2 h. The solvent was then removed under reduced pressure. The crude product was then diluted with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over sodium sulphate, and concentrated under reduced pressure to afford *rac*-methyl (2*R*,3*S*,3a*R*,8b*R*)-8b-hydroxy-6-methoxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**S4**) as a brown solid. Yield: 18.0 g, crude.

*rac-Methyl (1R,2R,3S,3aR,8bS)-1,8b-Dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta-[b]benzofuran-2-carboxylate (**70**).* A solution of crude *rac*-methyl (2*R*,3*S*,3a*R*,8b*R*)-8b-hydroxy-6-methoxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (18.0 g) in acetonitrile (360 mL) was cooled to 0 °C, and acetic acid (22.35 mL, 390.8 mmol) and sodium triacetoxyborohydride (49.77 g, 234.8 mmol) were added at 0 °C. The mixture was stirred for 12 h at room temperature. Afterward, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated and dried over sodium sulphate, filtered, and concentrated to give the crude product. The crude product was then purified by silica gel column chromatography eluting with 2−3% in methanol in dichloromethane. The desired fractions were concentrated to afford *rac*-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**70**) as a white solid. Yield: 8.0 g (19 mmol, 36% over three steps). MS (ESI) *m*/*z*: 461.01 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.30 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 9.4 Hz, 1H), 7.05−7.00 (m, 5H), 6.82 (d, *J* = 7.0 Hz, 2H), 6.64−6.62 (m, 3H), 6.52−6.47 (m, 1H), 5.73 (t, *J* = 8.4 Hz, 1H), 5.28 (s, 1H), 4.75 (t, *J* = 12.5 Hz, 1H), 4.05−4.00 (m, 1H), 3.89−3.83 (m, 1H), 3.77 (s, 3H), 3.74 (s, 1H), 3.67 (s, 3H), 3.46 (s, 3H).

*rac-(1R,2R,3S,3aR,8bS)-1,8b-dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]-benzofuran-2-carboxylic Acid (**S5**).* To a solution of *rac*-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**70**) (8.0 g, 19 mmol) in methanol/water (3:1, 200 mL), lithium hydroxide (9.97 g, 416 mmol) was added. The reaction was stirred for 16 h at room temperature. The reaction mixture was then cooled to 0 °C and acidified to pH ≈ 3 with 1 N hydrochloric acid. The precipitate was collected by filtration and dried under high vacuum to afford (1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (**S5**) as an off-white solid. Yield: 7.0 g (16 mmol, 84%). MS (ESI) *m*/*z*: 449.02 $[M + 1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.05 (br s, 1H), 7.29 (d, *J* = 8.36 Hz, 1H), 7.06−7.00 (m, 5H), 6.88 (d, *J* = 7.3 Hz, 2H), 6.63−6.55 (m, 3H), 6.51−6.44 (m, 1H), 5.64−5.58 (m, 1H), 5.28−5.20 (m, 1H), 4.73 (d, *J* = 7.1 Hz, 1H), 4.01 (d, *J* = 7.1 Hz, 1H), 3.77−3.73 (m, 4H), 3.62 (s, 3H).

*rac-(1R,2R,3S,3aR,8bS)-1,8b-Dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxamide (rac-**6**).* To a solution of *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (**S5**) (7.0 g, 14 mmol) in dichloromethane (140 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (8.9 g, 47 mmol), hydroxybenzotriazole (6.3 g, 47 mmol), and Hünig's base (16.8 mL, 12.5 g, 96.4 mmol) were added at 0 °C. The reaction mixture was stirred for 5 min. Dimethylamine·HCl (6.34 g, 77.8 mmol) was then added at the same temperature and the reaction was stirred for 16 h at room temperature. After completion, the reaction mass was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to give the crude product which was purified by silica gel column chromatography eluting with 70−90% EtOAc in hexanes to afford *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-dihydroxy-6-methoxy-3a-(4-methoxyphenyl)-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide (*rac*-**6**) as an off-white solid. Yield: 2.2 g (4.6 mmol, 33%). MS (ESI) *m*/*z*: 476.01 $[M + 1]^+$; HRMS (ESI): calcd, 476.2068 $[M + H]^+$; found, 476.2069; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.38 (d, *J* = 8.3 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 2H), 7.03−6.95 (m, 3H), 6.78 (d, *J* = 6.7 Hz, 2H), 6.67−6.64 (m, 3H), 6.51−6.48 (m, 1H), 5.44 (d, *J* = 4 Hz, 1H), 5.12 (s, 1H), 4.88 (t, *J* = 8.3 Hz, 1H), 4.12 (d, *J* = 13.2 Hz, 1H), 3.94 (dd, *J* = 8.6, 13.1 Hz, 1H), 3.78 (s, 3H), 3.64 (s, 3 H), 3.17 (s, 3H), 2.71 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.61, 161.18, 159.02, 157.55, 139.04, 129.04, 128.73, 128.18, 127.70, 127.24, 125.69, 122.69, 112.14, 106.90, 100.71, 95.96, 90.94, 77.52, 55.34, 54.80, 54.34, 46.92, 36.38, 35.07.

Synthesis of rac-(1R,2R,3S,3aR,8bS)-6-Chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-



rac-**10**

*1H-cyclopenta[b]benzofuran-2-carboxamide (rac-**10**). (E)-1-(4-Chloro-2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**S6**).* To a solution of 1-(4-chloro-2-hydroxyphenyl)ethan-1-one (**71**) (10.0 g, 58.6 mmol) in methanol (60 mL), sodium hydroxide (7.0 g, 180 mmol) and 4-methoxybenzaldehyde (7.9 g, 58 mmol) were successively added. The reaction mixture was heated to reflux for 30 min, then cooled. The resulting solid was collected by filtration, washed with water, and dried under high vacuum to afford (*E*)-1-(4-chloro-2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**S6**) as a yellow solid. Yield: 15.0 g (52.1 mmol, 89%). MS (ESI) *m*/*z*: 287.06 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.10−7.93 (m, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.76−7.68 (m, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.87 (br s, 2H), 3.82 (s, 3H).

*7-Chloro-3-hydroxy-2-(4-methoxyphenyl)-4H-chromen-4-One (**72**).* To a solution of (*E*)-1-(4-chloro-2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**S6**) (15.0 g, 52.1 mmol) in ethanol (100 mL) and water (60 mL) at room temperature, sodium hydroxide (8.3 g, 0.21 mol, 10% aq solution) was added, followed by hydrogen peroxide (14.6 g, 129 mmol, 30% aq solution) at room temperature. The reaction mixture was stirred for 1 h at room temperature (exothermic) and then cooled and neutralized to pH ≈ 7 by addition of 6 N hydrochloric acid. The resulting precipitate was collected by filtration and dried under vacuum to afford 7-chloro-3-hydroxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (**72**) as a pale yellow solid. Yield:

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10.0 g (33.0 mmol, 63%). MS (ESI) m/z: 302.42 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 9.61 (s, 1H), 8.21 (d, J = 8.7 Hz, 2H), 8.09 (d, J = 8.5 Hz, 1H), 7.98 (s, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.7 Hz, 2H), 3.85 (s, 3H).

*rac-methyl (3S,4S,5R)-8-Chloro-5-hydroxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[b]oxepine-4-carboxylate (**S7**).* A solution of 7-chloro-3-hydroxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (**72**) (10.0 g, 33.0 mmol) and methyl cinnamate (53.6 g, 330 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated under 400 W UV light for 24 h in a UV reactor flask. The solvent was then removed under reduced pressure, and the residue was purified by eluting through a plug of silica gel with ethyl acetate. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl 5-chloro-8a-hydroxy-2a-(4-methoxyphenyl)-8-oxo-2-phenyl-2,2a,8,8a-tetrahydro-1*H*-cyclobuta[*b*]chromene-1-carboxylate (**S7**) as a brown solid. Yield: 15.0 g, crude.

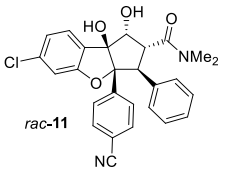
*rac-Methyl (2R,3S,3aR,8bR)-6-Chloro-8b-hydroxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]-benzofuran-2-carboxylate (**S8**).* The crude *rac*-methyl (3*S*,4*S*,5*R*)-8-chloro-5-hydroxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (**S7**) (15.0 g) was suspended in methanol (150 mL), treated with 25% sodium methoxide in methanol (50 mL solution; 12 g NaOMe, 0.22 mol), and then heated at 70 °C for 2 h. Afterward, the solvent was removed under reduced pressure and the remaining crude product was treated with saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford methyl (2*R*,3*S*,3a*R*,8b*R*)-6-chloro-8b-hydroxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**S8**) as a brown solid. Yield: 14.0 g, crude.

*rac-Methyl (1R,2R,3S,3aR,8bS)-6-Chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]-benzofuran-2-carboxylate (**73**).* The crude *rac*-methyl (2*R*,3*S*,3a*R*,8b*R*)-6-chloro-8b-hydroxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**S8**) (14.0 g) was added to a solution of sodium triacetoxyborohydride (38.0 g, 179 mmol) in acetonitrile (300 mL) and acetic acid (18.0 mL). This mixture was stirred for 4 h at room temperature. After completion, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product, which was purified by silica gel (100−200 mesh) column chromatography eluting with 50% ethyl acetate in hexanes. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzofuran-2-carboxylate (**73**) as a white solid. Yield: 8.0 g (17.1 mmol, 52% over three steps). MS (ESI) m/z: 465.31 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.38 (d, J = 8.0 Hz, 1H), 7.14 (s, 1H), 7.05−6.98 (m, 6H), 6.84 (d, J = 7.16 Hz, 2H), 6.63 (d, J = 8.4 Hz, 2H), 5.85 (d, J = 5.6 Hz, 1H), 5.57 (s, 1H), 4.74 (t, J = 6.3 Hz, 1H), 4.07 (d, J = 13.9 Hz, 1H), 3.90 (dd, J = 13.7 Hz, 7.0 Hz, 1H), 3.62 (s, 3H), 3.52 (s, 3H).

*rac-(1R,2R,3S,3aR,8bS)-6-Chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]-benzofuran-2-carboxylic Acid (**S9**).* To a solution of *rac*-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**S8**) (3.0 g, 6.4 mmol) in methanol/water (3:1, 120 mL), lithium hydroxide (3.70 g, 154 mmol) was added. The reaction mixture was stirred for 4 h at room temperature and then cooled to 0 °C and acidified with 5 N hydrochloric acid to pH ≈ 3. The resulting precipitate was collected by filtration and dried under high vacuum to afford *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzofuran-2-carboxylic acid (**S9**) as an off-white solid. Yield: 2.5 g (5.5 mmol, 86%). MS (ESI) m/z: 450.99 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.28 (d, J = 7.9 Hz, 1H), 7.11 (d, J = 7.2 Hz, 2H), 7.05 (s, 1H), 7.0 (t, J = 7.3 Hz, 2H), 6.96−6.90 (m, 4H), 6.57 (d, J = 8.7 Hz, 2H), 5.29 (s, 1H), 4.36 (d, J = 5.4 Hz, 1H), 4.10 (d, J = 13.5 Hz, 1H), 3.59 (s, 3H).

*rac-(1R,2R,3S,3aR,8bS)-6-Chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxamide (rac-**10**).* To a solution of (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (**S9**) (2.5 g, 5.5 mmol) in dichloromethane (55 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (3.1 g, 16 mmol), hydroxybenzotriazole (2.2 g, 16 mmol), and Hünig's base (5.6 mL, 32 mmol) were added. The mixture was stirred for 5 min at 0 °C, after which dimethylamine hydrochloride (2.25 g, 27.6 mmol) was added at same temperature. Then, the reaction mixture was stirred for 8 h at room temperature, after which it was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, which was purified by silica gel column chromatography eluting with 70−90% ethyl acetate in hexanes to afford *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-chloro-1,8b-dihydroxy-3a-(4-methoxyphenyl)-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide (*rac*-**10**) as a white solid. Yield: 2.4 g (5.0 mmol, 90%). MS (ESI) m/z: 480.10 $[M + 1]^+$; UPLC: 98.93%; HRMS (ESI): calcd, 480.1572 $[M + H]^+$; found, 480.1590; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.46 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 10.0 Hz, 1H), 7.16 (d, 1.4, 2H), 7.08−6.97 (m, 4H), 6.79 (d, J = 7.0 Hz, 2H), 6.67 (d, J = 8.7 Hz, 2H), 5.60 (d, J = 6.1 Hz, 1H), 5.42 (s, 1H), 4.89 (t, J = 6.5 Hz, 1H), 4.14 (d, J = 13.2 Hz, 1H), 3.98 (dd, J = 8.2 Hz, 13.1 Hz, 1H), 3.64 (s, 3H), 3.18 (s, 3H), 2.71 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.40, 158.68, 157.67, 138.71, 133.67, 129.85, 129.79, 128.69, 127.73, 127.65, 127.30, 125.79, 120.30, 112.20, 110.67, 101.05, 90.83, 77.42, 54.81, 54.49, 46.95, 36.40, 35.09.

*Synthesis of rac-(1R,2R,3S,3aR,8bS)-6-Chloro-3a-(4-cyanophenyl)-1,8b-dihydroxy-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxamide (rac-**11**). (E)-3-(4-Bromophenyl)-1-(4-chloro-2-hydroxyphenyl)prop-2-en-1-one (**S10**).* To a solution of 1-(4-chloro-2-hydroxyphenyl)ethan-1-one (**71**) (5.0 g, 29 mmol) in methanol (10 mL), sodium hydroxide (3.5 g, 88 mmol) was added, followed by 4-bromobenzaldehyde (5.4 g, 30 mmol). The reaction mixture was heated to reflux at 90 °C for 2 h. Then, the mixture was cooled and the solid was collected by filtration, washed with water, and dried under high vacuum to afford (*E*)-3-(4-bromophenyl)-1-(4-chloro-2-hydroxyphenyl)prop-2-en-1-one (**S10**) as a yellow solid. Yield: 10.0 g (29.6 mmol, quant.). MS (ESI) m/z: 337.12 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.56 (d, J = 16.1 Hz, 1H), 7.66−7.47 (m, 5H), 7.17 (d, J = 9.9 Hz, 1H), 6.22 (d, J = 12.7 Hz, 1H), 5.91 (d, J = 7.4 Hz, 1H).



rac-**11**

*2-(4-Bromophenyl)-7-chloro-3-hydroxy-4H-chromen-4-one (**74**).* To a solution of (*E*)-3-(4-bromophenyl)-1-(4-chloro-2-hydroxyphenyl)prop-2-en-1-one (**S10**) (10.0 g, 29.6 mmol) in ethanol (10 mL) at room-temperature, sodium hydroxide (3.5 g, 88 mmol, 10% aq solution) and subsequently hydrogen peroxide (30% aq solution, 2.0 mL, 2.22 g, 0.66 g H_2O_2, 19.6 mmol) were added. The reaction mixture was stirred for 2 h at room temperature (reaction is exothermic). Then, it was cooled and neutralized to pH ≈ 7 by addition of 6 N hydrochloric acid. The resulting precipitate was collected by filtration and dried under vacuum to afford 2-(4-bromophenyl)-7-chloro-3-hydroxy-4*H*-chromen-4-one (**74**) as a pale yellow solid. Yield: 5.0 g (14 mmol, 47%). MS (ESI) m/z: 351.09 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.18 (d, J = 8.6 Hz, 2H),

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8.10 (d, J = 8.6 Hz, 1H), 7.99 (s, 1H), 7.78 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.5 Hz, 1H).

*rac-Methyl (3S,4S,5R)-2-(4-Bromophenyl)-8-Chloro-5-hydroxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[b]oxepine-4-carboxylate (**S11**).* A solution of 2-(4-bromophenyl)-7-chloro-3-hydroxy-4*H*-chromen-4-one (**74**) (5.0 g, 14 mmol) and methyl cinnamate (**55**) (23.0 g, 142 mmol) in dichloromethane (100 mL), acetonitrile (60 mL), and methanol (60 mL) was irradiated under 400 W UV light for 48 h in a UV reactor flask. Then, the solvent was removed under reduced pressure, and the residue was purified over a plug of silica gel eluting with 5% methanol in dichloromethane. The desired fractions were concentrated under reduced pressure to afford methyl (3*S*,4*S*,5*R*)-2-(4-bromophenyl)-8-chloro-5-hydroxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (**S11**) as a brown solid. Yield: 3.5 g, crude.

*rac-Methyl (3S, 3aR, 8bR)-3a-(4-Bromophenyl)-6-Chloro-8b-hydroxy-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]-benzofuran-2-carboxylate (**S12**).* The crude *rac*-methyl (3*S*,4*S*,5*R*)-2-(4-bromophenyl)-8-chloro-5-hydroxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (**S11**) (3.5 g) was suspended in methanol (20 mL), treated with 25% sodium methoxide in methanol (8.0 mL, 7.6 g solution; 1.9 g NaOMe, 35 mmol), and heated at 90 °C for 3 h. Then, the solvent was removed under reduced pressure. The crude product was treated with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure to afford *rac*-methyl (3*S*,3a*R*,8b*R*)-3a-(4-bromophenyl)-6-chloro-8b-hydroxy-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**S11**) as a brown solid. Yield: 3.0 g, crude.

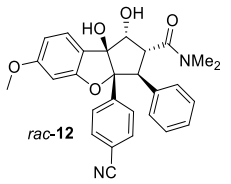
*rac-Methyl (1R,2R,3S,3aR,8bS)-3a-(4-Bromophenyl)-6-Chloro-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]-benzofuran-2-carboxylate (**75**).* A solution of crude *rac*-methyl (3*S*,3a*R*,8b*R*)-3a-(4-bromophenyl)-6-chloro-8b-hydroxy-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**S12**) (3.0 g) in acetonitrile (50 mL) was cooled to 0 °C, and acetic acid (3.3 mL, 3.5 g, 58 mmol) and sodium triacetoxyborohydride (7.4 g, 35 mmol) were added. The resulting mixture was stirred for 6 h at room temperature. Then, the mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated and dried over sodium sulfate, filtered, and concentrated to give the crude product which was purified by silica gel column chromatography eluting with 2−3% in methanol in dichloromethane. The desired fractions were concentrated to afford *rac*-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-6-chloro-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzofuran-2-carboxylate (**75**) as a yellow solid. Yield: 2.2 g (4.3 mmol, 31% over three steps). MS (ESI) m/z: 517.12 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.35 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.16 (s, 1H), 7.07−7.00 (m, 6H), 6.90 (d, J = 7.2 Hz, 2H), 5.93 (d, J = 5.6 Hz, 1H), 5.84 (d, J = 5.8 Hz, 1H), 4.72 (t, J = 6.1 Hz, 1H), 4.19 (d, J = 13.0, 1H), 4.09−4.00 (m, 2H), 3.54 (s, 3H).

*rac-(1R,2R,3S,3aR,8bS)-3a-(4-Bromophenyl)-6-Chloro-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]-benzofuran-2-carboxylic Acid (**S13**).* To a solution of *rac*-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-6-chloro-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**75**) (2.2 g, 4.3 mmol) in methanol/water (3:1, 10.3 mL), lithium hydroxide (2.04 g, 85.4 mmol) was added. The reaction mixture was stirred for 16 h at room temperature, then cooled to 0 °C and acidified with 1 N hydrochloric acid to pH ≈ 3. The resulting precipitate was collected by filtration and dried under high vacuum to afford *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-6-chloro-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (**S13**) as an off-white solid. Yield: 2.0 g (4.0 mmol, 93%). MS (ESI) m/z: 503.02 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.18 (s, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 10.2 Hz, 2H), 7.23 (s, 1H), 7.15−6.99 (m, 6H), 6.91 (d, J = 7.2 Hz, 2H), 5.76 (t, J = 5.8 Hz, 1H), 5.68 (d, J = 11.6 Hz, 1H), 4.68 (t, J = 5.9 Hz, 1H), 4.18−4.02 (m, 1H), 3.93−3.79 (m, 1H).

*rac-(1R,2R,3S,3aR,8bS)-3a-(4-Bromophenyl)-6-chloro-1,8b-dihydroxy-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxamide (**S14**).* To a solution of *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-6-chloro-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (**S13**) (2.0 g, 4.0 mmol) in dichloromethane (50 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.15 g, 6.00 mmol), hydroxybenzotriazole (0.9 g, 7 mmol) and Hünig's base (1.5 g, 12 mmol) were added at 0 °C. The reaction mixture was stirred for 5 min at this temperature. Dimethylamine hydrochloride (3.25 g, 39.9 mmol) was then added at same temperature. The mixture was stirred for 16 h at room temperature. It was next diluted with dichloromethane and washed with cold water. The organic layer was separated and dried over sodium sulfate, filtered and concentrated to give the crude product, which was purified by silica gel column chromatography eluting with 70−90% ethyl acetate in hexane to afford (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-6-chloro-1,8b-dihydroxy-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzofuran-2-carboxamide (**S14**) as yellow solid. Yield: 1.8 g (3.4 mmol, 85%). MS (ESI) m/z: 528.15 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.44 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 1.6 Hz, 1H), 7.12 (d, J = 8.6 Hz, 2H), 7.05−6.99 (m, 4H), 6.84 (d, J = 7.1 Hz, 2H), 5.61 (d, J = 6.0 Hz, 1H), 5.57 (s, 1H), 4.87 (t, J = 7.3 Hz, 1H), 4.23 (d, J = 13.1 Hz, 1H), 4.08−4.02 (m, 1H), 3.20 (s, 3H), 2.71 (s, 3H).

*rac-(1R,2R,3S,3aR,8bS)-6-Chloro-3a-(4-cyanophenyl)-1,8b-dihydroxy-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxamide (rac-**11**).* To a solution of (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-6-chloro-1,8b-dihydroxy-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzofuran-2-carboxamide (**S14**) (1.0 g, 1.9 mmol) in *N*,*N*-dimethylformamide (10 mL), zinc cyanide (0.33 g, 2.8 mmol) was added. The mixture was purged with argon for 5 min, after which tetrakis(triphenylphosphine)palladium(0) (0.43 g, 0.37 mmol) was added. The mixture was purged with argon for an additional 5 min and then stirred for 2 h at 120 °C. Afterward, the reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was washed with water and the organic layer was concentrated under reduced pressure. The crude product was purified by preparative HPLC to afford *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-chloro-3a-(4-cyanophenyl)-1,8b-dihydroxy-*N*,*N*-dimethyl-3-phenyl 2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide (*rac*-**11**) as an off-white solid. Yield: 0.13 g (0.27 mmol, 14%). MS (ESI) m/z: 475.17 $[M + 1]^+$; UPLC 97.95%; HRMS (ESI): calcd, 475.1419 $[M + H]^+$; found, 475.1431; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.56 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 1.6 Hz, 1H), 7.07−6.96 (m, 4H), 6.84 (d, J = 7.2 Hz, 2H), 5.68 (s, 1H), 5.63 (d, J = 6.0 Hz, 1H), 4.88 (t, J = 6.8 Hz, 1H), 4.30 (d, J = 13.2 Hz, 1H), 4.14 (dd, J = 13.1, 7.8 Hz, 1H), 3.22 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.16, 158.48, 141.84, 138.10, 134.20, 133.88, 130.58, 129.33, 129.10, 128.56, 127.56, 127.52, 126.06, 120.74, 110.72, 109.17, 101.10, 91.67, 77.54, 55.09, 47.19, 36.46, 35.15.

*Synthesis of rac-(1R,2R,3S,3aR,8bS)-3a-(4-Cyanophenyl)-1,8b-dihydroxy-6-methoxy-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxamide (rac-**12**).* To a solution of 1-(4-(benzyloxy)-2-hydroxyphenyl)ethan-1-one (**76**) (50.0 g, 206 mmol) in methanol (300 mL), sodium hydroxide (24.79 g, 619.8 mmol) was added followed by 4-bromobenzaldehyde (38.29 g, 207.0 mmol). The reaction mixture was refluxed for 1 h. Then, it was cooled, and the solid was obtained by



rac-**12**

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filtration, washed with water, and dried under high vacuum to afford (*E*)-1-(4-(benzyloxy)-2-hydroxyphenyl)-3-(4-bromophenyl)prop-2-en-1-one (**S15**) as a yellow solid. Yield: 34.0 g (83.1 mmol, 40%). ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.22 (d, J = 15.3 Hz, 1H), 8.10 (d, J = 9.4 Hz, 1H), 7.79 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.2 Hz, 3H), 7.45−7.34 (m, 6H), 6.42 (s, 2H), 5.15 (s, 2H).

*7-(Benzyloxy)-2-(4-bromophenyl)-3-hydroxy-4H-chromen-4-one (**77**).* To a solution of (*E*)-1-(4-(benzyloxy)-2-hydroxyphenyl)-3-(4-bromophenyl)prop-2-en-1-one (**S15**) (34.00 g, 83.07 mmol) in ethanol (500 mL), sodium hydroxide (11.32 g, 283.0 mmol, 10% aq solution) and hydrogen peroxide (6.6 mL, 0.28 mol) were subsequently added at room temperature. The reaction mixture was stirred for 2 h at room temperature (reaction is exothermic!). Afterward, the reaction mixture was cooled and neutralized to pH ≈ 7 by addition of 5 N hydrochloric acid. The solid precipitate was collected by filtration and dried under vacuum to afford 7-(benzyloxy)-2-(4-bromophenyl)-3-hydroxy-4*H*-chromen-4-one (**77**) as a pale yellow solid. Yield: 16.0 g (37.8 mmol, 46%). MS (ESI) m/z: 422 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 9.75 (s, 1H), 8.16 (d, J = 8.2 Hz, 2H), 8.01 (d, J = 8.7 Hz, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.51−7.36 (m, 6H), 7.11 (d, J = 8.3 Hz, 1H), 5.27 (s, 2H).

*rac-(3R,4S,5S)-8-(Benzyloxy)-2-(4-bromophenyl)-5-hydroxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[b]oxepin-4-yl Acetate (**S16**).* A solution of 2-(4-bromophenyl)-7-chloro-3-hydroxy-4*H*-pyrano[3,2-*c*]pyridin-4-one (**77**) (7.00 g, 16.5 mmol) and methyl cinnamate (**S5**) (26.8 g, 165 mmol) in dichloromethane (100 mL), acetonitrile (50 mL), and methanol (50 mL) was irradiated in a UV reactor flask for 24 h under 400 W UV light. The solvent was then removed under reduced pressure and the remaining solid was purified over a plug of silica gel by eluting the compound with ethyl acetate. The desired fractions were concentrated under reduced pressure to afford *rac*-(3*R*,4*S*,5*S*)-8-(benzyloxy)-2-(4-bromophenyl)-5-hydroxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepin-4-yl acetate (**S16**). Yield: 8.8 g, crude.

*rac-Methyl (2R,3S,3aR,8bR)-6-(benzyloxy)-3a-(4-bromophenyl)-8b-hydroxy-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta-[b]benzofuran-2-carboxylate (**S17**).* The crude *rac*-(3*R*,4*S*,5*S*)-8-(benzyloxy)-2-(4-bromophenyl)-5-hydroxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepin-4-yl acetate (**S16**) (8.8 g) was suspended in methanol (50 mL), treated with sodium methoxide (25% in methanol, 8.8 mL, 8.3 g solution; 2.1 g, 38 mmol, NaOMe), and heated to 90 °C for 3 h. Next, the solvent was removed under reduced pressure. The crude product was treated with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give *rac*-methyl (2*R*,3*S*,3a*R*,8b*R*)-6-(benzyloxy)-3a-(4-bromophenyl)-8b-hydroxy-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**S17**) as brown oil. Yield: 8.9 g, crude.

*rac-Methyl (1R,2R,3S,3aR,8bS)-6-(benzyloxy)-3a-(4-bromophenyl)-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta-[b]benzofuran-2-carboxylate (**78**).* To a solution of sodium triacetoxyborohydride (18.41 g, 86.86 mmol) and crude *rac*-methyl (2*R*,3*S*,3a*R*,8b*R*)-6-(benzyloxy)-3a-(4-bromophenyl)-8b-hydroxy-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**S17**) (8.30 g) in acetonitrile (100 mL) at 0 °C, acetic acid (8.64 mL, 9.06 g, 150 mmol) was added. The resulting mixture was stirred for 4 h at room temperature and then partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the crude product which was purified by silica gel column chromatography by eluting with 30% ethyl acetate in hexanes. The desired fractions were concentrated to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylate (**78**) as an off-white solid. Yield: 2.6 g (4.4 mmol, 29% over three steps). MS (ESI) m/z: 585 $[M - 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.47 (d, J = 7.3 Hz, 2H), 7.41 (t, J = 7.2 Hz, 2H), 7.35−7.23 (m, 4H), 7.07−6.99 (m, 5H), 6.88 (d, J = 7.2 Hz, 2H), 6.73 (s, 1H), 6.61 (d, J = 2.0 Hz, 1H), 5.75 (t, J = 3.7 Hz, 1H), 5.46 (s, 1H), 5.21 (s, 2H), 4.71 (t, J = 6.4 Hz, 1H), 4.14 (d, J = 13.9 Hz, 1H), 4.05−3.96 (m, 1H), 3.52 (s, 3H).

*rac-(1R,2R,3S,3aR,8bS)-6-(Benzyloxy)-3a-(4-bromophenyl)-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]-benzofuran-2-carboxylic Acid (**S18**).* To a solution of *rac*-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-3a-(4-bromophenyl)-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**78**) (2.6 g, 4.4 mmol) in tetrahydrofuran and water (3:1, 80 mL), lithium hydroxide (2.5 g, 104 mmol) was added. The reaction mixture was stirred for 16 h at room temperature, then cooled to 0 °C and acidified with 1 M hydrochloric acid to pH ≈ 3. The precipitate was collected by filtration and dried under vacuum to afford *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-3a-(4-bromophenyl)-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (**S18**) as an off-white solid. Yield: 1.79 g (3.12 mmol, 71%); MS (ESI) m/z: 571.27 $[M - 1]^-$.

*rac-(1R,2R,3S,3aR,8bS)-6-(Benzyloxy)-3a-(4-bromophenyl)-1,8b-dihydroxy-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxamide (**S19**).* To a solution of *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-3a-(4-bromophenyl)-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (**S18**) (1.79 g, 3.12 mmol) in dichloromethane (25 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.797 g, 9.374 mmol), 1-hydroxybenzotriazole (1.29 g, 9.55 mmol), and *N*,*N*-diisopropylethylamine (3.19 mL, 18.3 mmol) were added at 0 °C. The mixture was stirred for 5 min. Dimethylamine hydrochloride (1.29 g, 15.8 mmol) was then added at the same temperature, and the reaction was stirred for 16 h at room temperature. Then, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated and dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, which was recrystallized from ethanol to afford *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-3a-(4-bromophenyl)-1,8b-dihydroxy-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzofuran-2-carboxamide (**11**) as a white solid. Yield: 1.29 g (2.14 mmol, 69%.) MS (ESI) m/z: 600.02 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.47 (d, J = 7.2 Hz, 2H), 7.42 (t, J = 7.1 Hz, 2H), 7.36−7.26 (m, 4H), 7.13 (d, J = 8.5 Hz, 2H), 7.03−6.96 (m, 3H), 6.82 (d, J = 7.2 Hz, 2H), 6.75 (d, J = 2.0 Hz, 1H), 6.59 (dd, J = 2.0 Hz, 8.3 Hz, 1H), 5.47 (d, J = 5.9 Hz, 1H), 5.29 (s, 1H), 5.14 (s, 2H), 4.87 (t, J = 7.16 Hz, 1H). 4.21 (d, J = 13.1 Hz, 1H), 4.05−3.99 (m, 1H), 3.20 (s, 3H), 2.67 (s, 3H).

*rac-(1R,2R,3S,3aR,8bS)-3a-(4-Bromophenyl)-1,6,8b-trihydroxy-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]-benzofuran-2-carboxamide (**S20**).* A flask containing ethyl acetate (40 mL) was charged with *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-3a-(4-bromophenyl)-1,8b-dihydroxy-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide (**S19**) (1.08 g, 1.80 mmol). Palladium hydroxide (0.246 g, 1.75 mmol, 50% wet) was added at room temperature under nitrogen. The reaction was flushed with hydrogen gas twice and stirred at room temperature for 6 h under hydrogen pressure. The reaction mixture was then passed through Celite, and the filtrate was concentrated under reduced pressure to afford (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-1,6,8b-trihydroxy-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide (**12**) as a brown oil. Yield: 1.0 g (crude), MS (ESI) m/z: 509.98 $[M + 1]^+$.

*rac-(1R,2R,3S,3aR,8bS)-3a-(4-Bromophenyl)-1,6,8b-trihydroxy-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]-benzofuran-2-carboxamide (**S21**).* To a solution of *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-1,6,8b-trihydroxy-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide (**S20**) (0.8 g, 2 mmol) in acetone (30 mL), methyl iodide (0.300 g, 2.11 mmol), and potassium carbonate (0.552 g, 3.99 mmol) were added. The mixture was stirred for 16 h at room temperature, then diluted with dichloromethane, and washed with cold water. The organic layer was separated and dried over anhydrous sodium sulphate, filtered, and concentrated to give crude *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-1,6,8b-trihydroxy-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide (**S21**) as an off-white solid. Yield: 0.800 g (1.53 mmol, 77%); ^{1}H NMR (400 MHz,

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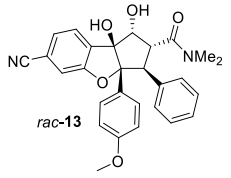
DMSO-d_6): δ/ppm 7.35 (d, J = 8.3 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4, 2H), 7.05−6.96 (m, 3H), 6.83 (d, J = 7.1 Hz, 2H), 6.67 (d, J = 1.8 Hz, 1H), 6.53−6.50 (dd, J = 2.1 Hz, 8.3 Hz, 1H), 5.47 (d, J = 6.0 Hz, 1H), 5.29 (s, 1H), 4.86 (t, J = 6.9 Hz, 1H), 4.20 (d, J = 13.3, 1H), 4.04−3.83 (m, 1H), 3.78 (s, 3H), 3.24 (s, 3H), 2.72 (s, 3H).

*rac-(1R,2R,3S,3aR,8bS)-3a-(4-Cyanophenyl)-1,8b-dihydroxy-6-methoxy-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxamide (rac-**12**).* To a solution of *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-bromophenyl)-1,8b-dihydroxy-6-methoxy-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzofuran-2-carboxamide (**S21**) (0.20 g, 0.38 mmol) in *N*,*N*-dimethylformamide (2 mL), zinc cyanide (0.134 g, 1.14 mmol) was added. The mixture was degassed with argon for 5 min. Tetrakis-(triphenylphosphine)palladium(0) (0.044 g, 0.038 mmol) was added to the reaction mixture which was then degassed for another 5 min and then heated at 120 °C for 1 h. Afterward, the reaction was cooled to room temperature and filtered through Celite. The filtrate was concentrated and treated with ice-cold water. The resulting crude precipitate was collected by filtration and purified by column chromatography in 100−200 silica mesh by eluting with 20−70% ethyl acetate in hexanes. Then, the desired fractions were concentrated under vacuum to afford (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-cyanophenyl)-1,8b-dihydroxy-6-methoxy-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide (*rac*-**12**) as an off-white solid. Yield: 0.08 g (0.17 mmol, 45%). HRMS (ESI): calcd, 471.1914 $[M + H]^+$; found, 471.1929; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.55 (d, J = 8.3 Hz, 2H), 7.36 (dd, J = 8.3 Hz, 14.7 Hz, 3H), 7.04−6.95 (m, 3H), 6.83 (d, J = 7.2 Hz, 2H), 6.69 (d, J = 2 Hz, 1H), 6.52 (dd, J = 2.2 Hz, 8.4 Hz,1H), 5.49 (d, J = 5.9 Hz, 1H), 5.39 (s, 1H), 4.88 (t, J = 6.4 Hz, 1H), 4.27 (d, J = 13.2 Hz, 1H), 4.08 (dd, J = 8.0, 13.2 Hz, 1H), 3.78 (s, 3H), 3.21 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.37, 161.33, 158.84, 142.40, 138.41, 130.53, 128.64, 128.62, 127.52, 127.47, 125.97, 121.89, 118.91, 108.98, 107.31, 100.80, 95.98, 91.75, 77.62, 55.39, 54.93, 47.10, 36.44, 35.13.

*Synthesis of rac-(1R,2R,3S,3aR,8bS)-6-Cyano-1,8b-dihydroxy-3a-(4-methoxyphenyl)-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxamide (rac-**13**).*



rac-**13**

*(E)-1-(4-(Benzyloxy)-2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**S22**).* To a solution of 1-(4-(benzyloxy)-2-hydroxyphenyl)ethan-1-one (**76**) (25.0 g, 103 mmol) in methanol (117 mL), sodium hydroxide (12.4 g, 310 mmol) and *p*-methoxybenzaldehyde (14.0 g, 103 mmol) were added successively. The reaction mixture was refluxed for 30 min and then cooled. The precipitated solid was collected by filtration, washed with water, and dried under high vacuum to afford (*E*)-1-(4-(benzyloxy)-2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**S22**) as a yellow solid. Yield: 30.0 g (83.2 mmol, 81%). MS (ESI) m/z: 361 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.1 (br s, 1H), 7.97 (d, J = 14.4 Hz, 1H), 7.85 (d, J = 7.0 Hz, 2H), 7.75 (d, J = 15.1 Hz, 1H), 7.47−7.34 (m, 6H), 7.02 (d, J = 7.5 Hz, 2H), 6.50 (s, 2H), 5.18 (s, 2H), 3.82 (s, 3H).

*7-(Benzyloxy)-3-hydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one (**79**).* To a solution of (*E*)-1-(4-(benzyloxy)-2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**S22**) (30.0 g, 83.2 mmol) in ethyl acetate (100 mL) at room temperature, sodium hydroxide (6.6 g, 170 mmol, 10% aq solution) and hydrogen peroxide (14 g, 0.41 mol, 30% aq solution) were added. The reaction mixture was stirred for 2 h at room temperature (reaction is exothermic). The reaction mixture was then cooled and neutralized to pH ≈ 7 by addition of 6 N hydrochloric acid. The resulting precipitate was collected by filtration and dried under vacuum to afford 7-(benzyloxy)-3-hydroxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (**79**) as a pale yellow solid. Yield: 18.0 g (48.1 mmol, 58%); MS (ESI) m/z: 375.27 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.18 (d, J = 7.8 Hz, 2H), 8.00 (d, J = 5.9 Hz, 1H), 7.51−7.49 (m, 1H), 7.42−3.88 (m, 6H), 7.17−7.12 (m, 2H), 5.27 (s, 2H), 3.85 (s, 3H).

*rac-Methyl (3S,4S,5R)-8-(Benzyloxy)-5-hydroxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo-[b]oxepine-4-carboxylate (**S23**).* A solution of 7-(benzyloxy)-3-hydroxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (**79**) (9.0 g, 24 mmol) and methyl cinnamate (**55**) (39.0 g, 240 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated with 400 W UV light in a UV reactor flask for 15 h. Then, the solvent was removed under reduced pressure, and the residue was purified by eluting through a plug of silica gel with ethyl acetate. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (3*S*,4*S*,5*R*)-8-(benzyloxy)-5-hydroxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (**S23**). Yield: 15.0 g, crude.

*rac-Methyl (2R,3S,3aR,8bR)-6-(Benzyloxy)-8b-hydroxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta-[b]benzofuran-2-carboxylate (**S24**).* The crude *rac*-methyl (3*S*,4*S*,5*R*)-8-(benzyloxy)-5-hydroxy-2-(4-methoxyphenyl)-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanobenzo[*b*]oxepine-4-carboxylate (**S23**) (12.8 g) was suspended in methanol (100 mL), treated with 25% sodium methoxide in methanol (20 mL solution, 4.7 g NaOMe, 87 mmol), and heated at 70 °C for 1 h. The solvent was then removed under reduced pressure, and the crude product was treated with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford methyl (2*R*,3*S*,3a*R*,8b*R*)-6-(benzyloxy)-8b-hydroxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**S24**). Yield: 10.0 g, crude.

*rac-Methyl (1R,2R,3S,3aR,8bS)-6-(Benzyloxy)-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta-[b]benzofuran-2-carboxylate (**80**).* The crude *rac*-methyl (2*R*,3*S*,3a*R*,8b*R*)-6-(benzyloxy)-8b-hydroxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**S24**) (10.0 g) was added to a solution of sodium triacetoxyborohydride (23.6 g, 111 mmol) in acetonitrile (200 mL) and acetic acid (11 mL, 190 mmol). The resulting mixture was stirred for 4 h at room temperature. Then, it was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure to obtain the crude product which was purified by silica gel column chromatography eluting with 60% ethyl acetate in hexanes. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**80**) as a pale yellow solid. Yield: 7.0 g (13.0 mmol, 63% over three steps). MS (ESI) m/z: 539.33 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.47 (d, J = 7.0 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.35 (d, J = 7.0 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.05−7.01 (m, 4H), 6.82 (d, J = 7.2 Hz, 2H), 6.72 (s, 1H), 6.63 (d, J = 8.6 Hz, 2H), 6.58 (d, J = 8.2 Hz, 1H), 5.73 (d, J = 5.8, 1H), 5.29 (s, 1H), 5.13 (s, 2H), 4.75 (t, J = 6.6 Hz, 1H), 4.02 (s, 1H), 3.86 (dd, J = 7.2 Hz, 13.9 Hz, 1H), 3.62 (s, 3H), 3.51 (s, 3H).

*rac-(1R,2R,3S,3aR,8bS)-6-(Benzyloxy)-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]-benzofuran-2-carboxylic Acid (**S25**).* To a solution of methyl *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**80**) (4.0 g, 7.4 mmol) in methanol/water (3:1, 120 mL), lithium hydroxide (4.2 g, 180 mmol) was added. The reaction mixture was stirred for 3 h at room temperature, then cooled to 0 °C and acidified with 5 N hydrochloric acid to pH ≈ 3. The resulting precipitate was collected by filtration and dried under high vacuum to afford *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzofuran-2-carboxylic acid (**S25**) as an off-white solid. Yield: 6.0 g (crude). MS (ESI) m/z: 523.1 $[M - 1]^-$;^{1}H NMR (400 MHz,

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DMSO-d_6): δ/ppm 7.47 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.7 Hz, 2H), 7.34 (d, J = 7.2 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.06−6.96 (m, 7H), 6.65 (s, 1H), 6.58 (d, J = 8.8 Hz 2H), 6.53 (d, J = 9.5 Hz, 1H), 5.11 (s, 2H), 5.03 (s, 1H), 4.45 (d, J = 4.92 Hz, 1H), 4.02 (d, J = 13.2 Hz, 1H), 3.60 (s, 3H), 3.51−3.42 (m, 1H).

*rac-(1R,2R,3S,3aR,8bS)-6-(Benzyloxy)-1,8b-dihydroxy-3a-(4-methoxyphenyl)-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxamide (**S26**).* To a solution of *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (4.0 g, 7.6 mmol) in dichloromethane (40 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.38 g, 22.8 mmol), hydroxybenzotriazole (3.09 g, 20.2 mmol), and DIPEA (8.0 mL, 45.9 mmol) were added at 0 °C. This mixture was stirred for 5 min at 0 °C. Then, dimethylamine hydrochloride (3.09 g, 38.16 mmol) was added, and the mixture was stirred for 8 h at room temperature. Afterward, the mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated and dried over sodium sulfate, filtered, and concentrated to give the crude product which was purified by silica gel column chromatography eluting with 70−90% ethyl acetate in hexane to afford *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-1,8b-dihydroxy-3a-(4-methoxyphenyl)-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide (**S26**) as a white solid. Yield: 4 g (7.2 mmol, 95% over two steps). MS (ESI) m/z: 552.25 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.48 (d, J = 7.3 Hz, 2H), 7.43−7.29 (m, 4H), 7.07 (d, J = 8.4 Hz, 2H), 7.03−6.97 (m, 3H), 6.78 (d, J = 6.9 Hz, 2H), 6.73 (s, 1H), 6.66 (d, J = 8.3 Hz, 2H), 6.57 (d, J = 8.0 Hz, 1H), 5.45 (d, J = 5.9 Hz, 1H), 5.13 (s, 3H), 4.89 (t, J = 6.4 Hz, 1H), 4.13 (d, J = 13 Hz, 1H), 3.94 (dd, J = 3.9 Hz, 12.3 Hz, 1H), 3.64 (s, 3H), 3.17 (s, 3H), 2.71 (s, 3H).

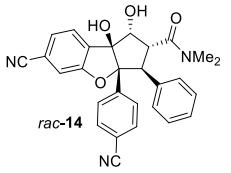
*rac-(1R,2R,3S,3aR,8bS)-1,6,8b-trihydroxy-3a-(4-methoxyphenyl)-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxamide (**S27**).* To a solution of (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-1,8b-dihydroxy-3a-(4-methoxyphenyl)-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide (**S26**) (2.0 g, 3.6 mmol) in ethyl acetate (100 mL), palladium hydroxide (0.66 g, 4.7 mmol) was added. The reaction mixture was stirred under a hydrogen atmosphere for 2 h at room temperature and then filtered through Celite and concentrated under vacuum to afford *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,6,8b-trihydroxy-3a-(4-methoxyphenyl)-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide (**S27**) as an off-white solid. Yield: 1.5 g, crude. MS (ESI) m/z: 460.4 $[M - 1]^-$.

*rac-(1R,2R,3S,3aR,8bS)-2-(dimethylcarbamoyl)-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-6-yl Trifluoromethanesulfonate (**S28**).* To a solution of crude *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,6,8b-trihydroxy-3a-(4-methoxyphenyl)-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide (**S27**) (1.4 g) in dichloromethane (100 mL) at 0 °C, DIPEA (1.28 mL, 7.35 mmol) was added. Triflic anhydride (3.34 mmol) diluted in dichloromethane (10 mL) was added dropwise to the reaction mixture while it was stirred at −40 °C for 1 h. Then, the reaction mixture was neutralized with saturated sodium bicarbonate solution and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to afford (1*R*,2*R*,3*S*,3a*R*,8b*S*)-2-(dimethylcarbamoyl)-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-6-yl trifluoromethanesulfonate (**S28**) as an off-white solid. Yield: 1.0 g (1.7 mmol, 56% over two steps). MS (ESI) m/z: 592.0 $[M - 1]^-$.

*rac-(1R,2R,3S,3aR,8bS)-6-Cyano-1,8b-dihydroxy-3a-(4-methoxyphenyl)-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxamide (rac-**13**).* To a solution of *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-2-(dimethylcarbamoyl)-1,8b-dihydroxy-3a-(4-methoxyphenyl)-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzofuran-6-yl trifluoromethanesulfonate (**S28**) (0.50 g, 0.84 mmol) in *N*,*N*-dimethylacetamide (20 mL), zinc cyanide (0.3 g, 3 mmol) was added. The reaction mixture was degassed with argon for 15 min. Tetrakis(triphenylphosphine)palladium(0) (0.09 g, 0.084 mmol) was added to the reaction mixture. The mixture was degassed for an additional 5 min and then heated at 110 °C for 1 h. Next, the reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated and treated with ice-cold water, and the resulting precipitate was collected by filtration. The crude product was purified by silica gel column chromatography eluting with 90% ethyl acetate in hexanes to afford *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-cyano-1,8b-dihydroxy-3a-(4-methoxyphenyl)-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide (*rac*-**13**) as an off-white solid. Yield: 0.10 g (0.21 mmol, 25%), MS (ESI) m/z: 471.17 $[M + 1]^+$; UPLC: 96.39%; HRMS (ESI): calcd, 471.1914 $[M + H]^+$; found, 471.1927; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.63 (d, J = 7.7 Hz, 1H), 7.56 (s, 1H), 7.41 (d, J = 7.3 Hz, 1H), 7.08 (d, J = 8.6 Hz, 2H), 7.04−6.98 (m, 3H), 6.80 (d, J = 7.1 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 5.70 (d, J = 6.0 Hz, 1H), 5.66 (s, 1H), 4.91 (t, J = 7.0 Hz, 1H), 4.15 (d, J = 13.1 Hz, 1H), 4.0 (dd, J = 7.88 Hz, 13.1 Hz, 1H), 3.64 (s, 3H), 3.19 (s, 3H), 2.71 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.24, 157.79, 157.75, 138.51, 136.50, 129.71, 128.69, 127.74, 127.34, 127.31, 125.86, 124.67, 119.01, 113.79, 112.24, 111.75, 100.95, 91.06, 77.52, 54.82, 54.70, 47.05, 36.41, 35.10.

*Synthesis of rac-(1R,2R,3S,3aR,8bS)-6-Cyano-3a-(4-cyanophenyl)-1,8b-dihydroxy-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxamide (rac-**14**). rac-Methyl (1R,2R,3S,3aR,8bS)-6-(Benzyloxy)-3a-(4-cyanophenyl)-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxylate (**81**).* To a solution of *rac*-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-3a-(4-bromophenyl)-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**78**) (1.50 g, 2.55 mmol) in *N*,*N*-dimethylformamide (5.0 mL), zinc cyanide (0.899 g, 7.65 mmol) was added. The reaction mixture was degassed with argon for 5 min. Then, tetrakis-(triphenylphosphine)palladium (0.442 g, 0.382 mmol) was added. The mixture was degassed for an additional 5 min and then incubated at 100 °C for 1 h in a microwave reactor. The mixture was then filtered through Celite and washed with ethyl acetate. The filtrate was concentrated, ice water was added, and the resulting precipitate was collected by filtration and washed with ethanol and pentane to afford methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-3a-(4-cyanophenyl)-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzofuran-2-carboxylate (**81**) as a white solid. Yield: 1.1 g (2.1 mmol, 81%). MS (ESI) m/z: 332.3 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.51 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 7.2 Hz, 2H), 7.41 (t, J = 7.1 Hz, 2H), 7.36−7.30 (m, 3H), 7.25 (d, J = 8.4 Hz, 1H), 7.07−6.98 (m, 3H), 6.89 (d, J = 7.1 Hz, 2H), 6.76 (d, J = 1.9 Hz, 1H), 6.61 (d, J = 8.3 Hz, 1H), 5.73 (s, 1H), 5.57 (s, 1H), 5.13 (s, 2H). 4.71 (t, J = 6.5 Hz, 1H), 3.54 (s, 3H).

*rac-Methyl (1R,2R,3S,3aR,8bS)-3a-(4-Cyanophenyl)-1,6,8b-trihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]-benzofuran-2-carboxylate (**S29**).* A flask containing ethyl acetate (10 mL) was charged with *rac*-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-(benzyloxy)-3a-(4-cyanophenyl)-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**81**) (1.1 g, 2.1 mmol), and palladium hydroxide (50% wet, 0.579 g, 4.12 mmol) was added at room temperature. The reaction mixture was purged with hydrogen twice and stirred under hydrogen pressure for 16 h. Then, the reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure to afford *rac*-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-cyanophenyl)-1,6,8b-trihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**S29**) as a white solid. Yield: 0.76 g (1.7 mmol, 81%). MS (ESI) m/z: 442.00 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 9.52 (s, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.1 Hz, 1H), 7.06−6.99 (m, 3H), 6.87 (d, J = 7.2 Hz, 2H), 6.42 (d, J = 1.7 Hz, 1H), 6.37 (d, J = 8.32 Hz,



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1H), 5.66 (d, J = 5.8 Hz, 1H), 5.46 (s, 1H), 4.68 (t, J = 6.4 Hz, 1H), 4.20 (d, J = 13.4 Hz, 1H), 4.01 (dd, J = 6.3 Hz, 13.2 Hz, 1H), 3.58 (s, 3H).

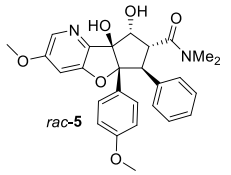
*rac-Methyl (1R,2R,3S,3aR,8bS)-3a-(4-Cyanophenyl)-1,8b-dihydroxy-3-phenyl-6-(((trifluoro-methyl)sulfonyl)oxy)-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxylate (**S30**).* To a solution of *rac*-methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-cyanophenyl)-1,6,8b-trihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzofuran-2-carboxylate (**S19**) (0.76 g, 1.7 mmol) in dichloromethane and tetrahydrofuran (1:1, 10.0 mL) at −78 °C, DIPEA (0.350 mL, 2.00 mmol) and triflic anhydride (0.307 mL, 1.82 mmol) were added successively. The reaction mixture was stirred for 3 h at −78 °C. Then, the reaction was quenched with sodium bicarbonate solution (5.0 mL) and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-cyanophenyl)-1,8b-dihydroxy-3-phenyl-6-(((trifluoromethyl)-sulfonyl)oxy)-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**S30**) as a brown solid. Yield: 0.50 g (0.87 mmol, 51%). MS (ESI) m/z: 574.36 $[M-1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.54−7.48 (m, 3H), 7.33−7.30 (m, 3H), 7.09−6.99 (m, 4H), 6.92 (d, J = 7.4 Hz, 1H), 5.98−5.96 (m, 2H), 5.75 (s, 1H), 4.74 (t, J = 6.0 Hz, 1H), 4.28 (d, J = 13.8 Hz, 1H), 4.13 (dd, J = 6.1, 13.7 Hz, 1H), 3.55 (s, 3H).

*rac-Methyl (1R,2R,3S,3aR,8bS)-6-cyano-3a-(4-cyanophenyl)-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]-benzofuran-2-carboxylate (**82**).* To a solution of methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-3a-(4-cyanophenyl)-1,8b-dihydroxy-3-phenyl-6-(((trifluoromethyl)-sulfonyl)oxy)-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**S30**) (0.50 g, 0.87 mmol) in *N*,*N*-dimethylformamide (5.0 mL), zinc cyanide (0.305 g, 2.60 mmol) was added. The reaction mixture was degassed with argon for 5 min. Tetrakis(triphenylphosphine)palladium (0.442 g, 0.382 mmol) was added and degassing was continued for an additional 5 min. Then, the mixture was irradiated at 120 °C for 1 h in a microwave reactor. The mixture was filtered through Celite, washed with ethyl acetate, and concentrated to give the crude product which was purified by silica gel column chromatography eluting with 30% ethyl acetate in hexanes. The desired fractions were concentrated under reduced pressure to afford methyl (1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-cyano-3a-(4-cyanophenyl)-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]-benzofuran-2-carboxylate (**82**) as a white solid. Yield: 0.34 g (0.75 mmol, 86%), MS (ESI) m/z: 451.03 $[M-1]^-$.

*rac-(1R,2R,3S,3aR,8bS)-6-Cyano-3a-(4-cyanophenyl)-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]-benzofuran-2-carboxylic Acid (**S31**).* To a solution of *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-cyano-3a-(4-cyanophenyl)-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**82**) (0.34 g, 0.75 mmol) in tetrahydrofuran and water (3:1, 10 mL), lithium hydroxide (0.40 g, 17 mmol) was added. The reaction mixture was stirred for 16 h at room temperature, then cooled to 0 °C, and acidified with citric acid solution to pH ≈ 2−3. The resulting precipitate was collected by filtration and dried under vacuum to afford *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-cyano-3a-(4-cyanophenyl)-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (**S31**) as a white solid. Yield: 0.23 g (0.52 mmol, 69%). MS (ESI) m/z: 437.40 $[M-1]^-$. 1H NMR (400 MHz, DMSO-d_6): δ/ppm 12.11 (s, 1H), 7.58 (s, 1H), 7.52−7.48 (s, 3H), 7.44 (d, J = 7.4 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.08−7.04 (m, 2H), 7.00 (d, J = 6.9 Hz, 2H), 6.95 (d, J = 7.2 Hz, 2H), 4.70 (d, J = 5.7 Hz, 1H), 4.28 (d, J = 13.6 Hz, 1H), 4.05−3.98 (m, 2H).

*rac-(1R,2R,3S,3aR,8bS)-6-Cyano-3a-(4-cyanophenyl)-1,8b-dihydroxy-N,N-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta-[b]benzofuran-2-carboxamide (rac-**14**).* To a solution of *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-cyano-3a-(4-cyanophenyl)-1,8b-dihydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (**S31**) (0.23 g, 0.52 mmol) in dichloromethane (10 mL), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (0.105 g, 0.786 mmol), hydroxybenzotriazole (0.106 g, 0.786 mmol), and DIPEA (0.20 g, 1.5 mmol) were added at room temperature. The mixture was stirred for 5 min. Dimethylamine hydrochloride (0.042 g, 0.515 mmol) was then added, and stirring was continued for 16 h at room temperature. Then, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product which was purified by silica gel column chromatography eluting with 60−70% ethyl acetate in hexanes. The desired fractions were concentrated to afford *rac*-(1*R*,2*R*,3*S*,3a*R*,8b*S*)-6-cyano-3a-(4-cyanophenyl)-1,8b-dihydroxy-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide (*rac*-**14**) as a white solid. Yield: 0.10 g (0.21 mmol, 41%). MS (ESI) m/z: 466.16 $[M+1]^+$; HRMS (ESI): calcd, 466.1761 $[M+H]^+$; found, 466.1784; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.61−7.57 (m, 3H), 7.55 (s, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.05−6.97 (m, 3H), 6.85 (d, J = 7.2 Hz, 2H),5.91 (s, 1H), 5.73 (d, J = 6.0 Hz, 1H), 4.90 (t, J = 6.9 Hz, 1H), 4.33 (d, J = 13.1 Hz, 1H), 4.18 (dd, J = 7.4 Hz, 13.2 Hz, 1H), 3.23 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.00, 157.61, 141.50, 137.92, 135.75, 130.61, 129.22, 128.54, 127.58, 127.54, 126.11, 125.10, 118.89, 118.79, 113.84, 111.97, 109.28, 100.98, 91.91, 77.66, 55.30, 47.32, 36.48, 35.17.

*Synthesis of (5aR,6S,7R,8R,8aS)-8,8a-Dihydroxy-3-methoxy-5a-(4-methoxyphenyl)-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide (rac-**5**). 3,5-Dimethoxypicolinonitrile (**87**).* To a solution of 3,5-difluoropicolinonitrile (**86**) (50 g, 360 mmol) in methanol (80 mL), sodium methoxide (25% in methanol, 50 mL, 12 g NaOMe, 0.22 mol) was added. The reaction mixture was refluxed at 100 °C for 12 h. After completion, the solvent was removed under reduced pressure and the crude product was treated with saturated ammonium chloride solution (50 mL). The precipitated solid was collected by filtration, washed with water, and dried under vacuum to afford 3,5-dimethoxypicolinonitrile (**87**) as a white solid. Yield: 42.0 g (256 mmol, 85%). MS (ESI) m/z: 165.23 $[M+1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.37 (d, J = 2.0 Hz, 1H), 8.02 (d, J = 1.9 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H).



*1-(3,5-Dimethoxypyridin-2-yl)ethan-1-one (**88**).* To a solution of 3,5-dimethoxypicolinonitrile (**87**) (42.0 g, 256 mmol) in dry tetrahydrofuran (100 mL) at −20 °C, methyl magnesium chloride (255.8 mL, 767.4 mmol) was added dropwise over a period of 30 min. The reaction mixture was slowly brought to room temperature and stirred for additional 12 h. After completion, the reaction was quenched with 6 M hydrochloric acid, acidified to pH ≈ 3, and extracted with ethyl acetate. The organic layer was washed with 1 M sodium hydroxide solution and water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 1-(3,5-dimethoxypyridin-2-yl)ethan-1-one (**88**) as a yellow oil. Yield: 30.0 g (166 mmol, 65%). MS (ESI) m/z: 181.61 $[M+1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.97 (d, J = 1.6 Hz, 1H), 6.81 (d, J = 1.7 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 2.61 (s, 3H).

*1-(3,5-Dihydroxypyridin-2-yl)ethan-1-one (**89**).* A sealed tube was charged with 1-(3,5-dimethoxypyridin-2-yl)ethan-1-one (**88**) (30.0 g, 166 mmol). Hydrobromic acid (33% in acetic acid, 300 mL) was added, and the reaction mixture was heated at 150 °C for 16 h. Volatiles were then removed under reduced pressure and the crude product was basified to pH ≈ 8 using 10% sodium hydroxide. Ethyl acetate (300 mL) was added. The solution was passed through a Celite bed which was then washed with ethyl acetate (100 mL). The organic layer was separated from the combined filtrate and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 1-(3,5-dihydroxypyridin-2-yl)ethan-1-one (**89**) as a brown oil. Yield: 9.0 g (59 mmol, 35%); MS (ESI) m/z: 152.0 $[M-1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.06 (s, 1H), 11.51 (br

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s, 1H), 7.85 (d, J = 1.96 Hz, 1H), 6.66 (d, J = 1.96 Hz, 1H), 2.59 (s, 3H).

*1-(3-Hydroxy-5-methoxypyridin-2-yl)ethan-1-one (**90**).* To a solution of 1-(3,5-dihydroxypyridin-2-yl)ethan-1-one (**89**) (9.0 g, 59 mmol) in acetone (100 mL) at 0 °C, potassium carbonate (24.3 g, 176 mmol) was added followed by methyl iodide (8.3 g, 58 mmol). The reaction mixture was then stirred at room temperature for 6 h, after which the solvent was distilled off and water (20 mL) was added. The aq phase was extracted with 5% methanol in dichloromethane (100 mL). The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford 1-(3-hydroxy-5-methoxypyridin-2-yl)ethan-1-one (**90**) as an off-white solid. Yield: 8.5 g, crude. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.15 (s, 1H), 7.97 (d, J = 2.2 Hz, 1H), 7.00 (d, J = 2.2 Hz, 1H), 3.89 (s, 3H), 2.62 (s, 3H).

*(E)-1-(3-Hydroxy-5-methoxypyridin-2-yl)-3-(4-methoxyphenyl)-prop-2-en-1-one (**S32**).* To a solution of 1-(3-hydroxy-5-methoxypyridin-2-yl)ethan-1-one (**90**) (8.5 g, 50 mmol) in methanol (50 mL), sodium hydroxide (6.1 g, 150 mmol) was added followed by 4-methoxybenzaldehyde (6.9 g, 50 mmol). The reaction mixture was heated refluxed for 4 h, after which it cooled to room temperature. The solid obtained was collected by filtration, washed with water, and dried under vacuum to afford (*E*)-1-(3-hydroxy-5-methoxypyridin-2-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (**S32**) as a yellow solid. Yield: 9.0 g, crude; MS (ESI) m/z: 286.23 [M + 1]$^+$.

*3-Hydroxy-7-methoxy-2-(4-methoxyphenyl)-4H-pyrano[3,2-b]-pyridin-4-one (**91**).* To a solution of (*E*)-1-(3-hydroxy-5-methoxypyridin-2-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (**90**) (9.0 g, 32 mmol) in methanol (50 mL) at 0 °C, sodium hydroxide (3.78 g, 93.8 mmol) was added followed by hydrogen peroxide (10.7 mL, 94.7 mmol). The reaction mixture was stirred for 6 h at room temperature (reaction is exothermic!). It was then cooled and neutralized to pH ≈ 7 by the addition of 6 M hydrogen chloride. The precipitated solid was filtered and dried under vacuum to afford 3-hydroxy-7-methoxy-2-(4-methoxyphenyl)-4*H*-pyrano[3,2-*b*]pyridin-4-one (**91**) as a yellow solid. Yield: 3.5 g (12 mmol, 23%). MS (ESI) m/z: 300.08 [M + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.42−8.36 (m, 3H), 7.73 (s, 1H), 7.07 (d, J = 7.56 Hz, 2H), 3.97 (s, 3H), 3.83 (s, 3H), 3.65 (br s, 1H).

*rac-Methyl (7S,8S,9R)-9-hydroxy-3-methoxy-6-(4-methoxyphenyl)-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-b]pyridine-8-carboxylate (**S33**).* A solution of 3-hydroxy-7-methoxy-2-(4-methoxyphenyl)-4*H*-pyrano[3,2-*b*]pyridin-4-one (**91**) (3.5 g, 11 mmol) and methyl cinnamate (**55**) (19 g, 120 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was placed in a UV reactor flask. The reaction mixture was irradiated for 15 h under 400 W UV light. Afterward, the solvent was removed under reduced pressure and the residual solid was purified over a plug of silica gel by eluting the compound with ethyl acetate. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (7*S*,8*S*,9*R*)-9-hydroxy-3-methoxy-6-(4-methoxyphenyl)-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**S33**) as a light yellow solid. Yield: 3.0 g, crude.

*rac-Methyl (5aR,6S,7R,8aR)-8a-hydroxy-3-methoxy-5a-(4-methoxyphenyl)-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-carboxylate (**S34**).* The crude compound *rac*-methyl (7*S*,8*S*,9*R*)-9-hydroxy-3-methoxy-6-(4-methoxyphenyl)-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]-pyridine-8-carboxylate (**S33**) was suspended in methanol (30 mL) and treated with 25% sodium methoxide in methanol (30 mL, 28 g, 7.1 g NaOMe, 0.13 mol). The reaction mixture was heated at 80 °C for 2 h, after which the solvent was removed under reduced pressure. The crude product was treated with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-8a-hydroxy-3-methoxy-5a-(4-methoxyphenyl)-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]-furo[3,2-*b*]pyridine-7-carboxylate (**S34**).

*rac-Methyl (5aR,6S,7R,8R,8aS)-8,8a-dihydroxy-3-methoxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-carboxylate (**92**).* To a solution of sodium triacetoxyborohydride (8.27 g, 39.0 mmol) and *rac*-methyl (5a*R*,6*S*,7-*R*,8a*R*)-8a-hydroxy-3-methoxy-5a-(4-methoxyphenyl)-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S34**) (3.0 g, 6.5 mmol) in acetonitrile (50 mL), acetic acid (3.9 g, 65 mmol) was added. The resulting mixture was stirred for 4 h at room temperature after which it was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product which was then purified by silica gel column chromatography eluting with 50% ethyl acetate in hexanes. The desired fractions were concentrated to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-8,8a-dihydroxy-3-methoxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**92**) as an off-white solid. Yield: 1.2 g (2.6 mmol, 24% over three steps). MS (ESI) m/z: 464.29 [M + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.87 (d, J = 2.2 Hz, 1H), 7.15 (d, J = 2.2 Hz, 1H), 7.07−6.99 (m, 5H), 6.92 (d, J = 7.3 Hz, 2H), 6.58 (d, J = 8.8 Hz, 2H), 5.47 (d, J = 5.3 Hz, 1H), 4.66 (t, J = 5.24 Hz, 1H), 4.31 (d, J = 13.8 Hz, 1H), 4.03−3.97 (m, 2H), 3.85 (s, 3H), 3.59 (s, 3H), 3.54 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-8,8a-Dihydroxy-3-methoxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]-furo[3,2-b]pyridine-7-carboxylic Acid (**S35**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-8,8a-dihydroxy-3-methoxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S35**) (1.2 g, 2.6 mmol) in methanol and water (3:1, 20 mL), lithium hydroxide (1.49 g, 62.2 mmol) was added, and the reaction was stirred for 16 h at room temperature. The reaction mixture was then cooled to 0 °C and acidified with 1 M hydrochloric acid to pH ≈ 2−3. The precipitate was collected by filtration and dried under vacuum to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-8,8a-dihydroxy-3-methoxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S35**) as an off-white solid. Yield: 0.9 g (2.0 mmol, 77%); MS (ESI) m/z: 450.28 [M + 1]$^+$.

*rac-(5aR,6S,7R,8R,8aS)-8,8a-Dihydroxy-3-methoxy-5a-(4-methoxyphenyl)-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide (rac-**5**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-8,8a-dihydroxy-3-methoxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]-furo[3,2-*b*]pyridine-7-carboxylic acid (**S35**) (0.9 g, 2.0 mmol) in dichloromethane (30 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (1.15 g, 7.41 mmol), hydroxybenzotriazole (0.8 g, 5.2 mmol), and *N*,*N*-diisopropylethylamine (1.55 g, 12.0 mmol) were added. The mixture was stirred for 5 min. Dimethylamine hydrochloride (0.814 g, 10.0 mmol) was then added at the same temperature, and the mixture was stirred for 12 h at room temperature, after which it was diluted with dichloromethane and washed with cold water. The organic layer was separated and dried over sodium sulphate, filtered, and concentrated to give the crude product which was purified by silica gel column chromatography eluting with 70−90% ethyl acetate in hexanes to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-8,8a-dihydroxy-3-methoxy-5a-(4-methoxyphenyl)-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (*rac*-**5**) as an off-white solid. Yield: 0.077 g (0.16 mmol, 8%). MS (ESI) m/z: 477.22 [M + 1]$^+$; HRMS (ESI): calcd, 477.2020 [M + H]$^+$; found, 477.2021; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.89 (d, J = 2.4 Hz, 1H), 7.20 (d, J = 2.4 Hz, 1H), 7.09−7.00 (m, 4H), 6.94−6.98 (m, 1H), 6.86 (d, J = 7.2 Hz, 2H), 6.64 (d, J = 9.2 Hz, 2H), 5.61 (s, 1H), 5.05 (d, J = 5.2 Hz, 1H), 4.84 (t, J = 6.0 Hz, 1H), 4.31 (d, J = 13.2 Hz, 1H), 4.09 (dd, J = 13.2 Hz, 6.4 Hz, 1H), 3.86 (s, 3H), 3.61 (s, 3H), 3.22 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (101 MHz, DMSO): δ/ppm 168.46, 157.59, 157.04, 153.51, 142.99, 138.77, 130.27, 128.56, 127.96, 127.79, 127.30, 125.68, 112.04, 103.12, 101.80, 89.03, 78.12, 55.93, 55.40, 54.77, 47.87, 36.45, 35.14.

*Synthesis of (5aR,6S,7R,8R,8aS)-5a-(4-Cyanophenyl)-8,8a-dihydroxy-3-methoxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**7**). (E)-3-(4-Bromophenyl)-1-(3-hydroxy-5-methoxypyridin-2-yl)prop-2-en-1-one (**S36**).* To a solution of 1-(3-hydroxy-5-methoxypyridin-2-yl)ethan-1-one (**90**) (8.0 g, 49 mmol) in methanol (120 mL), sodium

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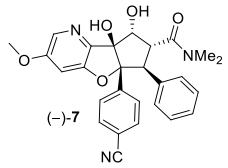

hydroxide (5.74 g, 144 mmol) was added followed by 4-bromobenzaldehyde (8.85 g, 47.8 mmol). The mixture was heated to reflux for 2 h. Then, the reaction mixture was cooled and the resulting solid was collected by filtration, washed with water, and dried under vacuum to afford crude (*E*)-3-(4-bromophenyl)-1-(3-hydroxy-5-methoxypyridin-2-yl)prop-2-en-1-one as a yellow solid. Yield: 14.0 g. UPLC: 89.75%; MS (ESI) *m*/*z*: 334.01 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.44 (d, J = 16.0 Hz, 1H), 7.60−7.58 (m, 4H), 7.40 (d, J = 2 Hz, 1H), 7.22 (d, J = 2.0 Hz, 1H), 6.20 (s, 1H), 3.69 (s, 3H).

*2-(4-Bromophenyl)-3-hydroxy-7-methoxy-4H-pyrano[3,2-b]-pyridin-4-one (**93**).* To a solution of crude (*E*)-3-(4-bromophenyl)-1-(3-hydroxy-5-methoxypyridin-2-yl)prop-2-en-1-one (14.0 g) in ethanol (200 mL) at room temperature, sodium hydroxide (11.73 g, 293.3 mmol) was added followed by hydrogen peroxide (30% aq, 23.25 mL, 7.742 g H_2O_2, 227.6 mmol). This reaction mixture was stirred for 1 h (reaction is exothermic). Then, the mixture was cooled and neutralized to pH ≈ 7 by addition of 6 N hydrochloric acid. The resulting precipitate was collected by filtration and dried under vacuum to afford crude 2-(4-bromophenyl)-3-hydroxy-7-methoxy-4*H*-pyrano[3,2-*b*]-pyridin-4-one as a pale yellow solid. Yield: 12.0 g. UPLC: 72.42%; MS (ESI) *m*/*z*: 348.05 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 9.98 (br s, 1H), 8.48 (s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 7.82−77 (m, 3H), 3.98 (s, 3H).

*rac-Methyl (5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-8,8a-dihydroxy-3-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-carboxylate (**94**).* A solution of crude 2-(4-bromophenyl)-3-hydroxy-7-methoxy-4*H*-pyrano[3,2-*b*]pyridin-4-one (6.0 g) and methyl cinnamate (27.9 g, 172 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated under 400 W UV light for 15 h in a UV reactor flask. After this time, the solvent was removed under reduced pressure, and the residue was purified over a plug of silica gel eluting with ethyl acetate. The desired fractions were concentrated under reduced pressure to afford crude methyl (7*S*,8*S*,9*R*)-6-(4-bromophenyl)-9-hydroxy-3-methoxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino-[3,2-*b*]pyridine-8-carboxylate (**S37**) (3.5 g, crude). This crude compound (**S37**) was suspended in methanol (20 mL) and treated with 25% sodium methoxide in methanol (20 mL, 19 g solution; 4.8 g, 89 mmol NaOMe). This mixture was heated at 70 °C for 1 h. Then, the solvent was removed under reduced pressure, and the crude product was treated with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure to give crude methyl (5a*R*,6*S*,7*R*,8a*R*)-5a-(4-bromophenyl)-8a-hydroxy-3-methoxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S38**). The crude material (**S38**) (3.5 g) was added to a solution of sodium triacetoxyborohydride (9.72 g, 4.58 mmol) in acetonitrile (30 mL) and acetic acid (4.57 mL, 4.79 g, 79.8 mmol), and the resulting mixture was stirred for 4 h at room temperature. After this time, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure to obtain the crude product, which was purified by silica gel column chromatography eluting with 50% ethyl acetate in hexanes. The desired fractions were concentrated to afford methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-8,8a-dihydroxy-3-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**94**) as a pale yellow solid. Yield: 0.80 g (*ca.* 1.6 mmol, 7% over five steps). UPLC: 90.64%; MS (ESI) *m*/*z*: 510.03 $[M + 1]^-$.

*rac-Methyl (5aR,6S,7R,8R,8aS)-5a-(4-Cyanophenyl)-8,8a-dihydroxy-3-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-carboxylate (**S39**).* To a mixture of methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-8,8a-dihydroxy-3-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**94**) (0.80 g, *ca.* 1.6 mmol) in dimethylformamide at room temperature, zinc cyanide (1.123 g, 9.562 mmol) and zinc dust (0.022 g, 0.336 mmol) were added. The mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino) ferrocene (0.041 g, 0.0740 mmol) and tris(dibenzylideneacetone)dipalladium (0.078 g, 0.0852 mmol) were added to the reaction mixture which was then degassed with argon for an additional 5 min and then heated at 140 °C for 2 h. After completion, the reaction was cooled to room temperature and filtered with Celite. The filtrate was concentrated and treated with ice-cold water, the solid precipitate was collected by filtration, and the crude product was triturated with *n*-pentane. The so-obtained solid was collected by filtration and dried under vacuum to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-cyanophenyl)-8,8a-dihydroxy-3-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S39**) as a brown solid. Yield: 0.75 g (crude). UPLC: 61.54%; MS (ESI) *m*/*z*: 459.35 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.89 (d, J = 2.2 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.22−6.53 (m, 6H), 5.99 (s, 1H), 5.60 (d, J = 5.36 Hz 1H), 4.63 (t, J = 5.28 Hz, 1H), 4.49 (d, J = 13.76 Hz, 1H), 4.18 (dd, J = 4.6 Hz, 13.9 Hz, 1H), 3.85 (s, 3H), 3.66 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-5a-(4-Cyanophenyl)-8,8a-dihydroxy-3-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo-[3,2-b]pyridine-7-carboxylic Acid (**S40**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-cyanophenyl)-8,8a-dihydroxy-3-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S39**) (0.75 g, crude) in methanol/water (3:1, 12 mL), lithium hydroxide (monohydrate, 0.411 g, 9.80 mmol) was added. The reaction mixture was stirred for 6 h at room temperature. After this time, the reaction mixture was cooled to 0 °C and acidified with 1 M citric acid to pH ≈ 5. The resulting precipitate was collected by filtration and dried under vacuum to afford (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-cyanophenyl)-8,8a-dihydroxy-3-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S40**) as an off-white solid. Yield: 0.6 g (crude). UPLC: 61.54%; MS (ESI) *m*/*z*: 445.35 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.87 (d, J = 2.2 Hz, 1H), 7.47 (d, J = 7.5 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.06−6.87 (m, 6H), 5.87 (s, 1H), 4.54 (s 1H), 4.48 (d, J = 4.46 Hz,1H), 3.91 (br s, 1H), 3.85 (s, 3H).

*(−)-(5aR,6S,7R,8R,8aS)-3-Cyano-5a-(4-cyanophenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**7**).* To a solution of (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-cyanophenyl)-8,8a-dihydroxy-3-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S40**) (0.6 g, crude) in methylene chloride (30 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.77 g, 4.0 mmol), hydroxybenzotriazole (0.54 g, 4.0 mmol) and *N*,*N*-diisopropylethylamine (1.04 g, 8.05 mmol) were added. This mixture was stirred for 5 min. Then, dimethylamine hydrochloride (0.55 g, 6.8 mmol) was added, and the mixture was stirred for 12 h at room temperature. After this time, the mixture was diluted with methylene chloride and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by reverse-phase prep-HPLC to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-cyanophenyl)-8,8a-dihydroxy-3-methoxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxamide (*rac*-**7**) as a white solid. The enantiomers were separated by chiral preparative HPLC [Chiralpak IB (4.6 × 250) mm]. Yield: 110 mg (0.233 mmol, 15% over 3 steps). Peak 1 (54 mg, (−)-**7**), $[\alpha]_D$ −106° (*c* 0.1, $CHCl_3$), R_t 6.86, ee >99%. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.9 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 2.4 Hz, 1H), 7.05 (s, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 6.90 (d, J = 7.4 Hz, 2H), 5.88 (s, 1H), 5.16 (br s, 1H), 4.77 (br s, 1H), 4.54 (d, J = 13.2 Hz, 1H), 4.25 (dd, J = 13.2, 5.8 Hz, 1H), 3.86 (s, 3H), 3.26 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.22, 157.04, 142.39, 142.03, 138.29, 130.67, 130.31, 128.50, 127.68, 127.49, 125.87, 118.85, 109.59, 109.00, 102.87, 101.62, 90.56, 78.01, 56.06, 55.95, 48.42, 36.54, 35.22; MS (ESI) *m*/*z*: 472.37 $[M + 1]^+$;

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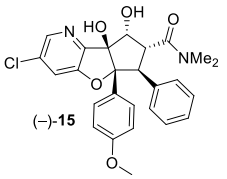
HRMS (ESI): calcd, 472.1867 [M + H]$^+$; found, 472.1866; UPLC: 96.33%. Peak 2 (45 mg, (+)-7), $[\alpha]_D$ +147.1° (*c* 0.1, $CHCl_3$), R_t 12.85, ee >99%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.9 (d, *J* = 2.4 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 2.2 Hz, 1H), 7.05 (s, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 2H), 5.88 (s, 1H), 5.17 (br s, 1H), 4.78 (d, *J* = 5.6 Hz, 1H), 4.55 (d, *J* = 13.2 Hz, 1H), 4.27 (dd, *J* = 13.2, 5.6 Hz 1H), 3.86 (s, 3H), 3.26 (s, 3H), 2.77 (s, 3H); MS (ESI) *m*/*z*: 472.37 [M + 1]$^+$; UPLC: 99.95%.

Synthesis of (−)-(5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-5a-(4-methoxyphenyl)-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-



*6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**15**).* *3-(Benzyloxy)-5-chloropicolinonitrile (**96**).* A flask containing tetrahydrofuran (250 mL) under nitrogen at room temperature was charged with 5-chloro-3-nitropicolinonitrile (**95**) (25.0 g, 136 mmol), and sodium hydride (11.0 g, 458 mmol) was added. The suspension was stirred for 30 min, after which benzyl alcohol (29.5 mL, 30.68 g, 284 mmol) was added, and stirring was continued for another 3 h. Then, the reaction was cooled to 0 °C and quenched with saturated NH_4Cl solution. The mixture was diluted with ethyl acetate (200 mL). The organic layer was separated, washed with water (2 × 50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product. The crude product was treated with pentane (100 mL) to obtain a solid which was collected by filtration and dried under vacuum to afford 3-(benzyloxy)-5-chloropicolinonitrile (**96**) as a brownish solid. Yield: 28.0 g (114 mmol, 84%). MS (ESI) *m*/*z*: 245.09 [M − 1]$^+$; LCMS: 97.31%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.40 (s, 1H), 8.18 (s, 1H), 7.49−7.37 (m, 5H), 5.37 (s, 2H).

*1-(3-(Benzyloxy)-5-chloropyridin-2-yl)ethan-1-one (**97**).* To a solution of 3-(benzyloxy)-5-chloropicolinonitrile (**96**) (28.0 g, 114 mmol) in dry tetrahydrofuran (250 mL) at −30 °C, methyl magnesium chloride (3 M, 114.0 mL, 342.0 mmol) was added dropwise over a period of 30 min. The reaction mixture was slowly brought to room temperature and stirred for 2 h. The reaction was then quenched with 6 N HCl (pH ≈ 3) and stirred for another 2 h. The mixture was extracted with ethyl acetate (200 mL) and the organic layer was separated, washed with 1 N NaOH solution (50 mL) and then water (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford 1-(3-(benzyloxy)-5-chloropyridin-2-yl)ethan-1-one (**97**) as a yellow oil. Yield: 19.0 g, crude. LCMS: 79.76%; MS (ESI) *m*/*z*: 262.10 [M + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.29 (d, *J* = 1.1 Hz, 1H), 7.95 (d, *J* = 1.1 Hz, 1H), 7.49−7.30 (m, 5H), 5.28 (s, 2H), 2.53 (s, 3H).

*1-(5-Chloro-3-hydroxypyridin-2-yl)ethan-1-one (**98**).* A flask containing ethyl acetate (300 mL) was charged with crude 1-(3-(benzyloxy)-5-chloropyridin-2-yl)ethan-1-one (**97**) (19.0 g) and palladium(II) hydroxide (50% wet) (10.0 g, 35.6 mmol) at room temperature. The reaction mixture was purged with hydrogen twice and stirred under hydrogen pressure for 16 h. Next, the reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to afford 1-(5-chloro-3-hydroxypyridin-2-yl)ethan-1-one (**98**) as a brown oil.

Yield: 8.0 g, crude. UPLC: 83.70%; MS (ESI) *m*/*z*: 170.03 [M − 1]$^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 11.70 (br s, 1H), 8.35 (s, 1H), 7.71 (d, *J* = 1.1 Hz, 1H), 2.59 (s, 3H).

*(E)-1-(5-Chloro-3-hydroxypyridin-2-yl)-3-(4-methoxyphenyl)-prop-2-en-1-one (**99a**).* To a solution of crude 1-(5-chloro-3-hydroxypyridin-2-yl)ethan-1-one (**98**) (8.0 g) in methanol (50 mL), sodium hydroxide (5.6 g, 140 mmol) was added followed by 4-methoxybenzaldehyde (**61a**) (6.9 mL, 7.7 g, 57 mmol). The mixture was heated to reflux for 30 min. After this time, the reaction mixture was cooled, and the solid was collected by filtration, washed with water, and then dried under high vacuum to afford (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (**99a**) as a yellow solid. Yield: 10.5 g, crude. UPLC: 84.19%; MS (ESI) *m*/*z*: 290.02 [M + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.14 (d, *J* = 16.0 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 16.1 Hz, 1H), 7.31 (s, 1H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.66 (s, 1H), 3.79 (s, 3H).

*7-Chloro-3-hydroxy-2-(4-methoxyphenyl)-4H-pyrano[3,2-b]-pyridin-4-one (**100a**).* To a solution of crude (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (**99a**) (10.5 g) in ethanol (100 mL) at room temperature, sodium hydroxide (10.0 g, 250 mmol) was added followed by hydrogen peroxide (10.73 mL 30% aq solution, 3.57 g H_2O_2, 105 mmol). The reaction mixture was stirred for 1 h at room temperature (reaction is exothermic!). Then, the mixture was cooled to room temperature and neutralized to pH ≈ 7 by addition of 6 N HCl. The resulting precipitate was collected by filtration and dried under vacuum to afford 7-chloro-3-hydroxy-2-(4-methoxyphenyl)-4*H*-pyrano[3,2-*b*]pyridin-4-one as a brick-red solid. Yield: 6.5 g, crude. UPLC: 71.3%; MS (ESI) *m*/*z*: 304.17 [M + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.04 (s, 1H), 7.46 (s, 1H), 7.13 (d, *J* = 7.3 Hz, 2H), 6.88 (d, *J* = 7.3 Hz, 2H), 5.94 (s, 1H), 3.74 (s, 3H).

*rac-Methyl (5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-carboxylate (**101a**).* A solution of 7-chloro-3-hydroxy-2-(4-methoxyphenyl)-4*H*-pyrano[3,2-*b*]pyridin-4-one (**100a**) (6.5 g, crude) and methyl cinnamate (34.7 g, 214 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated under 400 W UV light for 15 h in a UV reactor flask. Then, the solvent was removed under reduced pressure, and the residue was purified over a plug of silica gel eluting with ethyl acetate. The desired fractions were concentrated under reduced pressure to afford intermediate **S41a** (4.0 g, crude). The crude compound (**S41a**) was suspended in methanol (30 mL) and treated with 25% sodium methoxide in methanol (30 mL, 28 g solution; 7.0 g, 0.13 mol NaOMe). The mixture was heated at 70 °C for 1 h. Then, the solvent was removed under reduced pressure, and the crude product was treated with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-3-chloro-8a-hydroxy-5a-(4-methoxyphenyl)-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S42a**) (2.8 g, crude). Crude compound (**S42a**) (2.8 g) was added to a solution of sodium triacetoxyborohydride (8.9 g, 42 mmol) in acetonitrile (30 mL) and acetic acid (3.6 mL, 60.2 mmol). The resulting mixture was stirred for 4 h at room temperature. Then, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (50 mL) and ethyl acetate (100 mL). The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure to obtain the crude product. This was purified by silica gel column chromatography eluting with 50% ethyl acetate in hexanes. The desired fractions were concentrated to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*b*]pyridine-7-carboxylate (**101a**) as a yellow solid. Yield: 0.70 g. UPLC: 70.6%; MS (ESI) *m*/*z*: 464.29 [M − 1]$^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.18 (d, *J* = 1.9 Hz, 1H), 7.67 (s, 1H), 7.41−7.27 (m, 2H), 7.10−6.91 (m, 6H), 6.57 (d, *J* = 8.8 Hz, 1H), 5.98 (s, 1H), 5.69−5.67 (m, 1H), 4.65−4.63 (m, 1H), 4.43−4.36 (m, 1H), 4.09−4.01 (m, 1H), 3.58 (s, 3H), 3.56 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylic Acid (**S43a**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**101a**) (0.70 g, from previous step; used without further purification) in methanol/water (3:1, 12 mL), lithium hydroxide (0.539 g, 22.5 mmol) was added. The reaction mixture was stirred for 6 h at room temperature, then cooled to 0 °C, and acidified with 1 N HCl to pH ≈ 3. The resulting precipitate was collected by filtration and

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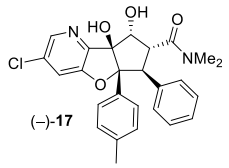
dried under vacuum to afford (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S43a**) as an off-white solid. Yield: 0.40 g. UPLC: 85.43%; MS (ESI) *m*/*z*: 452.11 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.15 (d, J = 1.7 Hz, 1H), 7.63 (d, J = 1.4 Hz, 1H), 7.11−6.87 (m, 7H), 6.56 (d, J = 8.9 Hz, 2H), 5.87 (s, 1H), 4.57 (br s, 1H), 4.39 (d, J = 13.8 Hz, 1H), 3.87−3.83 (m, 1H), 3.51 (s, 3H).

*(−)-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-Chloro-8,8a-dihydroxy-5a-(4-methoxyphenyl)-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**15**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*b*]pyridine-7-carboxylic acid (**S43a**) (0.4 g, from previous step; used without further purification) in methylene chloride (30 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.508 g, 3.27 mmol), hydroxybenzotriazole (0.35 g, 2.3 mmol), and DIPEA (0.9 mL, 0.7 g, 5.17 mmol) were added. The mixture was stirred for 5 min. Dimethylamine hydrochloride (0.357 g, 4.37 mmol) was added to the mixture which was then stirred for 12 h at room temperature. After this time, the mixture was diluted with methylene chloride (25 mL) and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by silica gel column chromatography eluting with 70−90% ethyl acetate in hexanes to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-5a-(4-methoxyphenyl)-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (*rac*-**15**) as a white solid. Yield: 100 mg (0.208 mmol, *ca.* 2% over nine steps). The enantiomers were separated using a Chiralpak IB (4.6 × 250) mm column. Peak 1 (30 mg,(−)-**15**), $[\alpha]_D$ −179.0° (*c* 0.1, $CHCl_3$), ee >99%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.18 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 7.04−7.02 (m, 4H), 6.95 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 7.6 Hz, 2H), 6.61 (d, J = 8.8 Hz, 2H), 5.22 (d, J = 5.6 Hz, 1H), 4.75 (t, J = 5.6 Hz, 1H), 4.48 (d, J = 13.2 Hz, 1H), 4.19 (dd, J = 6.0 Hz, 13.2 Hz 1H), 3.60 (s, 3H), 3.25 (s, 3H), 2.76 (s, 3H); 13C NMR (101 MHz, DMSO-d_6): δ/ppm 168.28, 157.61, 153.37, 150.07, 140.27, 138.66, 130.90, 128.53, 127.87, 127.82, 127.33, 125.65, 117.16, 111.96, 102.20, 90.13, 77.95, 55.93, 54.76, 48.30, 36.54, 35.20; MS (ESI) *m*/*z*: 481.33 $[M + 1]^+$; HRMS (ESI): calcd, 481.1525 $[M + H]^+$; found, 481.1522; UPLC: 99.92%. Peak-2 (50 mg, (+)-**15**), $[\alpha]_D$ +180.0° (*c* 0.1, $CHCl_3$), ee >99%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.18 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 7.04−7.02 (m, 4H), 6.95 (t, J = 7.4 Hz, 1H), 6.89 (d, J = 7.6 Hz, 2H), 6.61 (d, J = 8.8 Hz, 2H), 5.22 (d, J = 5.5 Hz, 1H), 4.75 (t, J = 5.6 Hz, 1H), 4.48 (d, J = 13.6 Hz, 1H), 4.18 (dd, J = 5.6 Hz, 13.6 Hz, 1H), 3.60 (s, 3H), 3.25 (s, 3H), 2.76 (s, 3H); MS (ESI) *m*/*z*: 481.33 $[M + 1]^+$; UPLC: 99.26%.

(−)-(5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a-(p-tolyl)-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo-



(−)-**17**

*[3,2-b]pyridine-7-carboxamide ((−)-**17**).* *(E)-1-(5-Chloro-3-hydroxypyridin-2-yl)-3-(p-tolyl)prop-2-en-1-one (**99b**).* To a solution of 1-(5-chloro-3-hydroxypyridin-2-yl)ethan-1-one (**98**) (6.0 g, 35 mmol) in methanol (30 mL), sodium hydroxide (4.19 g, 105 mmol), and 4-methylbenzaldehyde (**61b**) (4.19 g, 34.9 mmol) were added. The reaction mixture was heated at 85 °C for 2 h. Then, the reaction mixture was cooled, and the resulting precipitate was collected by filtration, washed with water, and dried under vacuum to afford (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(*p*-tolyl)prop-2-en-1-one (**99b**) as a yellow solid. Yield: 5.0 g (18 mmol, 52%). MS (ESI) *m*/*z*: 274.13 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.24 (d, J = 15.9 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 7.6 Hz, 2H), 7.44−7.35 (m, 2H), 7.22 (d, J = 7.2 Hz, 2H), 6.71 (br s, 1H), 2.32 (s, 3H).

*7-Chloro-3-hydroxy-2-(p-tolyl)-4H-pyrano[3,2-b]pyridin-4-one (**100b**).* To a solution of (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(*p*-tolyl)prop-2-en-1-one (**99b**) (5.0 g, 18 mmol) in ethanol/dichloromethane (1:1, 20 mL) at room temperature, sodium hydroxide (6.45 g, 161 mmol) was added followed by 30% hydrogen peroxide (4.8 mL, 1.6 g H_2O_2, 47 mmol). The reaction mixture was stirred for 1 h (reaction is exothermic!). Then, the mixture was cooled and neutralized with 6 M hydrochloric acid. The resulting precipitate was collected by filtration and dried under vacuum to afford 7-chloro-3-hydroxy-2-(*p*-tolyl)-4*H*-pyrano[3,2-*b*]pyridin-4-one (**100b**) as a brown solid. Yield: 1.66 g (5.77 mmol, 32%). MS (ESI) *m*/*z*: 288.14 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.78 (s, 1H), 8.66 (s, 1H), 8.18 (d, J = 7.9 Hz, 2H), 7.47 (d, J = 7.9 Hz, 2H), 2.39 (s, 3H).

*rac-Methyl (6S,7S,8S,9R)-3-Chloro-9-hydroxy-10-oxo-7-phenyl-6-(p-tolyl)-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-b]pyridine-8-carboxylate (**S41b**).* A solution of 7-chloro-3-hydroxy-2-(*p*-tolyl)-4*H*-pyrano[3,2-*b*]pyridin-4-one (**100b**) (1.3 g, 4.5 mmol) and methyl cinnamate (**55**) (6.99 g, 43.1 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated for 15 h under 400 W UV light in a UV reactor flask. After this time, the solvent was removed under reduced pressure, and the residue was purified by Combi-flash (12 g, RediSep column) using ethyl acetate as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (6*S*,7*S*,8*S*,9*R*)-3-chloro-9-hydroxy-10-oxo-7-phenyl-6-(*p*-tolyl)-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**S41b**). Yield: 1.1 g, crude.

*rac-Methyl (5aR,6S,7R,8aR)-3-Chloro-8a-hydroxy-8-oxo-6-phenyl-5a-(p-tolyl)-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**S42b**).* The crude methyl (6*S*,7*S*,8*S*,9*R*)-3-chloro-9-hydroxy-10-oxo-7-phenyl-6-(*p*-tolyl)-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**S41b**) (1.1 g) was suspended in methanol (10 mL), and sodium methoxide (25% in methanol, 10 mL, 9.5 g solution, 2.4 g NaOMe, 44 mmol NaOMe) was added to this suspension. The reaction mixture was heated at 90 °C for 1 h. Then, the solvent was removed under reduced pressure, the reaction was quenched with ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford methyl (5a*R*,6*S*,7*R*,8a*R*)-3-chloro-8a-hydroxy-8-oxo-6-phenyl-5a-(*p*-tolyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S42b**). Yield: 0.9 g; crude.

*rac-Methyl (5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-6-phenyl-5a-(p-tolyl)-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**101b**).* To a solution of crude methyl (5a*R*,6*S*,7*R*,8a*R*)-3-chloro-8a-hydroxy-8-oxo-6-phenyl-5a-(*p*-tolyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S42b**) (0.9 g) in acetonitrile (10 mL), sodium triacetoxyborohydride (2.54 g, 11.9 mmol) and acetic acid (1.1 mL, 1.2 g, 19 mmol) were added. The resulting mixture was stirred for 16 h at room temperature. After this time, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the crude product, which was purified by Combi-flash (4 g, RediSep column) using 70% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-6-phenyl-5a-(*p*-tolyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**101b**) as a light yellow solid. Yield: 0.25 g (0.56 mmol, 12% over three steps). MS (ESI) *m*/*z*: 452.33 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.17 (d, J = 9.6 Hz, 1H), 7.67 (s, 1H), 7.38 (d, J = 6.0 Hz, 2H), 7.28−6.95 (m, 5H), 6.82 (d, J = 8.0 Hz, 2H), 5.98 (s, 1H), 5.68 (s, 1H), 4.64 (s, 1H), 4.43 (d, J = 14.4 Hz, 1H), 4.10−4.05 (m, 1H), 3.56 (s, 3H), 2.09 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-6-phenyl-5a-(p-tolyl)-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylic Acid (**S43b**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-6-phenyl-5a-(*p*-tolyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**101b**)

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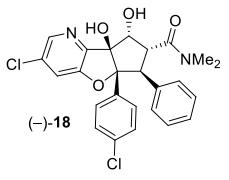
(0.25 g, 0.56 mmol) in tetrahydrofuran and water (3:1, 4.0 mL), lithium hydroxide (0.26 g, 9.6 mmol) was added. The reaction mixture was stirred for 6 h at room temperature. After this time, the reaction mixture was cooled to 0 °C and acidified with 1 M hydrogen chloride to pH ≈ 3. The resulting precipitate was collected by filtration, washed with water, and dried under vacuum to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-6-phenyl-5a-(*p*-tolyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S43b**) as a yellow solid. Yield: 0.13 g (0.29 mmol, 51%). MS (ESI) *m*/*z*: 438.32 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.16 (s, 1H), 8.17 (s, 1H), 7.66 (s, 1H), 7.06−7.03 (m, 2H), 6.98−6.92 (m, 4H), 6.82 (d, *J* = 8.1 Hz, 2H), 5.93 (s, 1H), 4.64 (d, *J* = 4.5 Hz, 1H), 4.41 (d, *J* = 13.7 Hz, 1H), 4.03−3.94 (m, 1H), 2.08 (s, 3H).

*(−)-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-Chloro-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a-(p-tolyl)-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo-[3,2-b]pyridine-7-carboxamide ((−)-**17**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-6-phenyl-5a-(*p*-tolyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S43b**) (0.13 g, 0.30 mmol) in dichloromethane (5.0 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.046 g, 0.240 mmol), 1-hydroxybenzotriazole (anhydrous, 0.067 g, 0.496 mmol), and *N*,*N*-diisopropylethylamine (0.15 mL, 0.11 g, 0.86 mmol) were added. The reaction mixture was stirred for 5 min. Then, dimethylamine hydrochloride (0.032 g, 0.392 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 16 h. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by Combi-flash (4 g, RediSep column) using 70% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated under reduced pressure to afford racemic (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a-(*p*-tolyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (*rac*-**17**) as a white solid. Yield: 0.07 g (0.15 mmol, 50%). MS (ESI) *m*/*z*: 465.32 $[M + 1]^+$. The enantiomers were separated by chiral preparative HPLC [Chiralpak IB (4.6 × 250) mm]. Peak 1 (13 mg, (+)-**17**); $[\alpha]_D$ +212.0° (*c* 0.1, $CHCl_3$); R_t 10.18 min, ee >95%; MS (ESI) *m*/*z*: 465.32 $[M + 1]^+$; UPLC 97.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.18 (d, *J* = 2.0 Hz, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.11−6.94 (m, 5H), 6.90 (d, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 5.88 (s, 1H), 5.23 (t, *J* = 5.5, 1H), 4.77 (t, *J* = 5.6 Hz, 1H), 4.51 (d, *J* = 13.2 Hz, 1H), 4.23−4.18 (dd, *J* = 13.2, 5.6 Hz, 1H), 3.25 (s, 3H), 2.76 (s, 3H), 2.11 (s, 3H). Peak-2 (9 mg, (−)-**17**); $[\alpha]_D$ −191.1° (*c* 0.1, $CHCl_3$); R_t 22.4 min, ee >99%; MS (ESI) *m*/*z*: 465.32 $[M + 1]^+$; HRMS (ESI): calcd, 465.1576 $[M + H]^+$; found, 465.1571; UPLC 99.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.18 (d, *J* = 2.0 Hz, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.03−6.94 (m, 5H), 6.90 (d, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 5.88 (s, 1H), 5.23 (d, *J* = 5.6, 1H), 4.77 (t, *J* = 5.6 Hz, 1H), 4.50 (d, *J* = 13.2 Hz, 1H), 4.23−4.18 (dd, *J* = 13.2, 5.6 Hz, 1H), 3.25 (s, 3H), 2.76 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.29, 153.40, 150.04, 140.28, 138.64, 135.22, 132.88, 130.91, 127.87, 127.33, 127.27, 127.18, 125.65, 117.15, 102.34, 90.26, 77.97, 55.93, 48.37, 36.57, 35.22, 20.54.

*Synthesis of (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-Chloro-5a-(4-chlorophenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-*



*cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**18**).* *(E)-1-(5-Chloro-3-hydroxypyridin-2-yl)-3-(4-chlorophenyl)prop-2-en-1-one (**99c**).* To a solution of 1-(5-chloro-3-hydroxypyridin-2-yl)ethan-1-one (**98**) (4.0 g, 23 mmol) in methanol (20 mL), sodium hydroxide (2.8 g, 70 mmol) was added followed by 4-chlorobenzaldehyde (**61c**) (3.3 g, 23 mmol). The reaction mixture was heated to reflux for 10 min. Then, the reaction mixture was cooled to room temperature and diluted with water (20 mL). The precipitated solid was collected by filtration, washed with water and *n*-pentane, and dried under vacuum to afford (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(4-chlorophenyl)-prop-2-en-1-one (**99c**) as a yellow solid. Yield: 6.1 g (21 mmol, 90%). MS (ESI) *m*/*z*: 292.15 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.30 (d, *J* = 16.0 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 16.0 Hz, 1H), 7.31 (d, *J* = 2.0 Hz, 1H), 6.66 (d, *J* = 2.0 Hz, 1H).

*7-Chloro-2-(4-chlorophenyl)-3-hydroxy-4H-pyrano[3,2-b]-pyridin-4-one (**100c**).* To a solution of (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(4-chlorophenyl)prop-2-en-1-one (**99c**) (7.0 g, 24 mmol) in ethanol (400 mL) and dichloromethane (66 mL) at 0 °C, 10% aq sodium hydroxide (31 mL, 67 g solution, 6.7 g NaOH, 170 mmol) was added followed by 30% aq hydrogen peroxide (37.5 mL, 41.6 g solution, 12.5 g H_2O_2, 367 mmol). The reaction mixture was stirred for 30 min at room temperature (reaction is exothermic!). Then, the mixture was cooled and neutralized to pH ≈ 7 with 6 M hydrochloric acid. The mixture was extracted with ethyl acetate (100 mL). The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The so-obtained solid was triturated with ethanol, filtered, and dried under vacuum to afford 7-chloro-2-(4-chlorophenyl)-3-hydroxy-4*H*-pyrano[3,2-*b*]-pyridin-4-one (**100c**) as a light yellow solid. Yield: 2.81 g (9.12 mmol, 43%). MS (ESI) *m*/*z*: 308.04 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 10.20 (br s, 1H), 8.80 (br s, 1H), 8.62 (br s, 1H), 8.27 (d, *J* = 7.6 Hz, 2H), 7.68−7.62 (m, 2H).

*rac-Methyl (7S,8S,9R)-3-Chloro-6-(4-chlorophenyl)-9-hydroxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-b]-pyridine-8-carboxylate (**S41c**).* A solution of 7-chloro-2-(4-chlorophenyl)-3-hydroxy-4*H*-pyrano[3,2-*b*]pyridin-4-one (**100c**) (2.8 g, 9.1 mmol) and methyl cinnamate (**5**, 14.7 g, 90.3 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated for 8 h under 400 W UV light in a UV reactor flask. After this time, the solvent was removed under reduced pressure, and the residue was purified over a plug of silica gel eluting with ethyl acetate. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (7*S*,8*S*,9*R*)-3-chloro-6-(4-chlorophenyl)-9-hydroxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino-[3,2-*b*]pyridine-8-carboxylate (**S41c**) as a brown solid. Yield: 3.1 g, crude.

*rac-Methyl (5a*R*,6*S*,7*R*,8a*R*)-3-Chloro-5a-(4-chlorophenyl)-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]-furo[3,2-b]pyridine-7-carboxylate (**S42c**).* The crude *rac*-methyl (7*S*,8*S*,9*R*)-3-chloro-6-(4-chlorophenyl)-9-hydroxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**S41c**) (3.1 g) was suspended in methanol (30 mL) and treated with 25% sodium methoxide in methanol (20 mL, 19 g solution, 4.7 g NaOMe, 87 mmol). The reaction mixture was heated at 80 °C for 2 h. After this time, the solvent was removed under reduced pressure. The crude product was treated with aqueous ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-3-chloro-5a-(4-chlorophenyl)-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*b*]pyridine-7-carboxylate (**S42c**). Yield: 2.35 g, crude.

*rac-Methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-Chloro-5a-(4-chlorophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]-furo[3,2-b]pyridine-7-carboxylate (**101c**).* To a solution of sodium triacetoxyborohydride (6.23 g, 29.4 mmol) and *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-3-chloro-5a-(4-chlorophenyl)-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S42c**) (2.3 g) in acetonitrile (60 mL), acetic acid (2.9 mL, 3.0 g, 50 mmol) was added. The resulting mixture was stirred for 18 h at room temperature. Then, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to give the crude product, which was purified by silica gel column chromatography using 60% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated under reduced pressure to afford methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-

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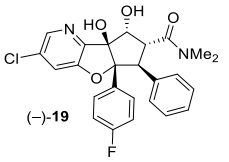
5a-(4-chlorophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**101c**) as a white solid. Yield: 1.1 g (2.3 mmol, 26% over three steps). MS (ESI) *m*/*z*: 472.15 [M + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (s, 1H), 7.69 (s, 1H), 7.36−7.05 (m, 6H), 6.99−6.97 (m, 3H), 6.15 (s, 1H), 5.76 (d, *J* = 5.2 Hz, 1H), 4.63 (t, 5.2 Hz, 1H), 4.52 (d, *J* = 14.0 Hz, 1H), 4.14 (dd, *J* = 5.2 Hz, 13.2 Hz, 1H), 3.57 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-chlorophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylic Acid (**S43c**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-chlorophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**101c**) (1.0 g, 2.1 mmol) in methanol, tetrahydrofuran, and water (3:2:1, 18 mL), lithium hydroxide (0.89 g, 37 mmol) was added. The reaction mixture was stirred for 3 h at room temperature. After this time, the reaction mixture was cooled to 0 °C and acidified with 1 M hydrochloric acid to pH ≈ 2−3. The resulting precipitate was collected by filtration and dried under vacuum to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-chlorophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S43c**) as a white solid. Yield: 0.55 g (1.2 mmol, 57%). MS (ESI) *m*/*z*: 458.14 [M + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.2 (br s, 1H), 8.19 (s, 1H), 7.68 (s, 1H), 7.06−7.00 (m, 9H), 6.08 (s, 1H), 4.60 (s, 1H), 4.48 (d, *J* = 14.0 Hz, 1H), 4.00 (d, *J* = 13.6 Hz, 1H).

*(−)-(5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-chlorophenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**18**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-chlorophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S43c**) (0.3 g, 0.7 mmol) in dichloromethane (8 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (0.30 g, 1.9 mmol), 1-hydroxybenzotriazole (0.29 g, 2.1 mmol), and *N*,*N*-diisopropylethylamine (0.69 mL, 0.51 g, 3.9 mmol) were added. The mixture was stirred for 5 min. Dimethylamine hydrochloride (0.27 g, 3.3 mmol) was then added at the same temperature, and the reaction was stirred for 48 h at room temperature. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to give the crude product which was purified by silica gel column chromatography using 2−3% dichloromethane in methanol as the eluent. The desired fractions were concentrated under reduced pressure to afford racemic (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-chlorophenyl)-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (*rac*-**18**) as a white solid. The enantiomers were separated by chiral preparative HPLC [Chiralpak IB (4.6 × 250) mm]. Peak 1 (64 mg, (+)-**18**), $[\alpha]_D$ +212.3° (*c* 0.1, $CHCl_3$), R_t 9.727 min, ee >99%, ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (d, *J* = 2.0 Hz, 1H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.05 (m, 4H), 6.95 (d, *J* = 7.2 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 2H), 6.04 (s, 1H), 5.28 (d, *J* = 5.7 Hz, 1H), 4.7 (t, *J* = 5.4 Hz, 1H), 4.57 (d, *J* = 13.2 Hz, 1H), 4.25 (dd, *J* = 13.2, 5.2 Hz, 1H), 3.26 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.13, 153.30, 149.66, 140.54, 138.41, 135.17, 131.13, 130.96, 129.29, 127.83, 127.47, 126.43, 125.81, 117.18, 101.94, 90.70, 77.90, 56.15, 48.58, 36.59, 35.25; UPLC: 99.92%. Peak-2 (68 mg, (−)-**18**), $[\alpha]_D$ −209.6° (*c* 0.1, $CHCl_3$), R_t 23.133 min, ee >99%, ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (d, *J* = 2.0 Hz, 1H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.03 (m, 4H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 2H), 6.04 (s, 1H), 5.29 (d, *J* = 5.6 Hz, 1H), 4.73 (t, *J* = 5.4 Hz, 1H), 4.57 (d, *J* = 13.2 Hz, 1H), 4.25 (dd, *J* = 13.2, 5.2 Hz, 1H), 3.26 (s, 3H), 2.77 (s, 3H); HRMS (ESI): calcd, 485.1029 [M + H]$^+$; found, 485.1035; UPLC: 99.83%.

*Synthesis of (5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-fluorophenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**19**). (E)-1-(5-Chloro-3-hydroxypyridin-2-yl)-3-(4-fluorophenyl)prop-2-en-1-one (**99d**).* To a solution of 1-(5-chloro-3-hydroxypyridin-2-yl)ethan-1-one (**98**) (5.0 g, 29 mmol) in methanol (25 mL), sodium hydroxide (3.5 g, 88 mmol) was added followed by 4-fluorobenzaldehyde (**61d**) (4.35 g, 35.0 mmol). The reaction mixture was heated at 80 °C for 1 h.



(−)-**19**

Then, the reaction mixture was cooled and the precipitated solid was collected by filtration, washed with water, and dried under vacuum to afford (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(4-fluorophenyl)-prop-2-en-1-one (**99d**) as a pale yellow solid. Yield: 4.2 g (15 mmol, 52%). MS (ESI) *m*/*z*: 276.16 [M − 1]$^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.23 (d, *J* = 16.0 Hz, 1H), 7.72−7.68 (dd, *J* = 13.6, 5.9 Hz, 2H), 7.43 (d, *J* = 15.8 Hz, 1H), 7.33 (s, 1H), 7.26−7.21 (dd, *J* = 17.6, 8.9 Hz, 2H), 6.69 (s, 1H).

*7-Chloro-2-(4-fluorophenyl)-3-hydroxy-4H-pyrano[3,2-b]-pyridin-4-one (**100d**).* To a solution of (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(4-fluorophenyl)prop-2-en-1-one (**99d**) (3.0 g, 11 mmol) in ethanol and dichloromethane (1:1, 100 mL), sodium hydroxide solution (10% aq, 30.0 mL, 33.3 g solution, 3.33 g NaOH, 83.3 mmol) was added followed by hydrogen peroxide (30% aq, 6.7 mL, 7.4 g solution, 2.2 g H_2O_2, 66 mmol) at room temperature. The reaction mixture was stirred for 1 h (reaction is exothermic). Then, the reaction mixture was poured into ice-cold water, neutralized with 6 M hydrochloric acid, and extracted with dichloromethane (100 mL). The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product, which was triturated with diethyl ether and *n*-pentane to afford 7-(chloro)-2-(4-fluoroophenyl)-3-hydroxy-4*H*-pyrano[3,2-*b*]pyridin-4-one (**100d**) as a yellow solid. Yield: 2.5 g (8.6 mmol, 78%). MS (ESI) *m*/*z*: 290.07 [M − 1]$^-$.

*rac-Methyl (7S,8S,9R)-3-Chloro-6-(4-fluorophenyl)-9-hydroxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-b]-pyridine-8-carboxylate (**S41d**).* A solution of 7-(chloro)-2-(4-fluoroophenyl)-3-hydroxy-4*H*-pyrano[3,2-*b*]pyridin-4-one (**100d**) (2.5 g, 8.6 mmol) and methyl cinnamate (**55**) (13.9 g, 85.7 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated under 400 W UV light for 16 h in a UV reactor flask. After this time, the solvent was removed under reduced pressure, and the residue was purified by Combi-flash (24 g, RediSep column) using ethyl acetate as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (7*S*,8*S*,9*R*)-3-chloro-6-(4-fluorophenyl)-9-hydroxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**S41d**). Yield: 2.5 g, crude.

*rac-Methyl (5aR,6S,7R,8aR)-3-Chloro-5a-(4-fluorophenyl)-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]-furo[3,2-b]pyridine-7-carboxylate (**S42d**).* The crude *rac*-methyl (7*S*,8*S*,9*R*)-3-chloro-6-(4-fluorophenyl)-9-hydroxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**S41d**) (1.3 g) was suspended in methanol (15 mL), treated with sodium methoxide (25% in methanol, 15 mL, 14 g solution, 3.5 g NaOMe, 66 mmol), and heated at 80 °C for 1 h. Then, the solvent was removed under reduced pressure, and the reaction mixture was treated with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure to afford methyl (5a*R*,6*S*,7-*R*,8a*R*)-3-chloro-5a-(4-fluorophenyl)-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S42d**). Yield: 1.4 g, crude.

*rac-Methyl (5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-fluorophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]-furo[3,2-b]pyridine-7-carboxylate (**101d**).* To a solution of sodium triacetoxyborohydride (1.8 g, 8.5 mmol) and crude *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-3-(chloro)-5a-(4-fluorophenyl)-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S42d**) (1.3 g) in acetonitrile (50 mL), acetic acid (1.7 mL, 1.8 g, 30 mmol) was added. The resulting mixture was stirred for 4 h at room temperature. After this time, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over sodium

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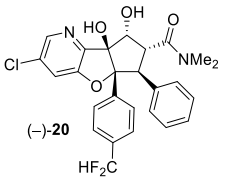
sulfate, and concentrated under reduced pressure to obtain the crude product, which was purified by Combi-flash (4 g, RediSep column) using 50% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-fluorophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**101d**) as a light yellow solid. Yield: 0.32 g (0.71 mmol, 17% over 3 steps). MS (ESI) *m*/*z*: 456.17 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.19 (s, 1H), 7.68 (s, 1H), 7.12−7.04 (m, 4H), 7.00−6.95 (m, 3H), 6.84−6.80 (m, 2H), 6.12 (s, 1H), 5.73 (d, *J* = 5.9 Hz, 1H), 4.63 (d, *J* = 5.4 Hz, 1H), 4.47 (d, *J* = 13.3 Hz, 1H), 4.15−4.10 (dd, *J* = 13.2, 4.4 Hz, 1H), 3.56 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-fluorophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylic Acid (**S43d**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-fluoroophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**101**) (0.30 g, 0.66 mmol) in methanol and water (3:1, 12 mL), lithium hydroxide (0.158 g, 6.60 mmol) was added. The reaction mixture was stirred for 6 h at room temperature. After this time, the reaction mixture was cooled to 0 °C and acidified with 6 M hydrochloric acid to pH ≈ 3. The resulting precipitate was collected by filtration and dried under vacuum to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-fluorophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S43**) as a yellow solid. Yield: 0.25 g (0.57 mmol, 86%). MS (ESI) *m*/*z*: 442.20 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.11 (br s, 1H), 8.19 (s, 1H), 7.67 (s, 1H), 7.10−7.06 (m, 4H), 7.04−6.98 (m, 3H), 6.84−6.80 (dd, *J* = 17.2, 8.64 Hz, 2H), 6.06 (s, 1H), 5.69 (br s, 1H), 4.63 (d, *J* = 4.5 Hz, 1H), 4.43 (d, *J* = 13.9 Hz, 1H), 4.01−3.96 (dd, *J* = 12.8, 3.5 Hz, 1H).

*(5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-fluorophenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**19**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-fluorophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S43d**) (0.25 g, 0.57 mmol) in dichloromethane (10 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.32 g, 1.7 mmol), 1-hydroxybenzotriazole (0.23 g, 1.7 mmol), and *N*,*N*-diisopropylethylamine (0.6 mL, 0.4 g, 3 mmol) were added at 0 °C. The reaction mixture was stirred for 5 min. Then, dimethylamine hydrochloride (0.23 g, 2.8 mmol) was added at the same temperature, and the mixture was stirred for 16 h at 40 °C. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to provide the crude product, which was purified by Combi-flash (12 g, RediSep column) using 5% methanol in dichloromethane as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-(5a*R*,6*S*,7*R*,8-*R*,8a*S*)-3-chloro-5a-(4-fluorophenyl)-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (*rac*-**19**). Yield: 100 mg (0214 mmol, 37%). The enantiomers were separated by chiral preparative HPLC [Chiralpak ID (4.6 × 250) mm]; peak 1 (26 mg, (+)-**19**); $[\alpha]_D$ +182.2° (*c* 0.3, $CHCl_3$); R_t 5.88 min, ee >99%; MS (ESI) *m*/*z*: 469.34 $[M + 1]^+$; UPLC: 99.07%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (d, *J* = 1.9 Hz, 1H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.16−7.13 (m, 2H), 7.02 (t, *J* = 7.2 Hz, 2H), 6.97−6.93 (m, 1H), 6.90−6.87 (m, 4H), 6.01 (s, 1H), 5.28 (d, *J* = 5.6 Hz, 1H), 4.75 (t, *J* = 5.5 Hz, 1H), 4.53 (d, *J* = 13.3 Hz, 1H), 4.22 (dd, *J* = 13.2, 5.4 Hz, 1H), 3.26 (s, 3H), 2.77 (s, 3H). Peak-2 (34 mg, (−)-**19**); $[\alpha]_D$ −201.4° (*c* 0.29, $CHCl_3$); R_t 10.86 min, ee >99%; MS (ESI) *m*/*z*: 469.34 $[M + 1]^+$; HRMS (ESI): calcd, 469.1325 $[M + H]^+$; found, 469.1326; UPLC: 99.78%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (d, *J* = 1.9 Hz, 1H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.16−7.13 (m, 2H), 7.03 (t, *J* = 7.2 Hz, 2H), 6.97−6.82 (m, 4H), 6.01 (s, 1H), 5.28 (d, *J* = 5.6 Hz, 1H), 4.75 (t, *J* = 5.5 Hz, 1H), 4.53 (d, *J* = 13.2 Hz, 1H), 4.22 (dd, *J* = 13.3, 5.4 Hz, 1H), 3.26 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.17, 160.78 (d, *J* = 242 Hz), 153.29, 149.79, 140.48, 138.49, 132.19 (d, *J* = 3.0 Hz), 130.94, 129.41 (d, *J* = 7.7 Hz), 127.83, 127.40, 125.75, 117.19, 113.23 (d, *J* = 21.1 Hz), 101.98, 90.48, 77.92, 56.17, 48.47, 36.57, 35.23.

*Synthesis of (5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-(difluoromethyl)-phenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**20**).*



*4-(Difluoromethyl)benzaldehyde (**61e**).* To a solution of 1-bromo-4-(difluoromethyl)benzene (**S44**) (20.0 g, 96.6 mmol) in dry tetrahydrofuran (200 mL), *n*-butyllithium in hexanes (2.5 M, 38.6 mL, 96.5 mmol) was added dropwise over a period of 30 min at −78 °C. The reaction mixture was stirred for 1 h at −78 °C. Then, *N*,*N*-dimethylformamide (35.3 mL, 33.3 g, 456 mmol) was added at same temperature and the mixture was stirred for 1 h. The reaction mixture was then brought to 0 °C, treated with saturated ammonium chloride solution, and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by Combi-flash (12 g, RediSep column) using 2% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated below 30 °C under reduced pressure to afford unstable 4-(difluoromethyl)-benzaldehyde (**61e**) as a light yellow liquid, which was immediately used in the next step. Yield: 9.0 g (58 mmol, 60%). MS (ESI) *m*/*z*: poor ionization; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 10.29 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 7.9 Hz, 2H), 6.85−6.57 (m, 1H).

*(E)-1-(5-Chloro-3-hydroxypyridin-2-yl)-3-(4-(difluoromethyl)-phenyl)prop-2-en-1-one (**99e**).* To a solution of 1-(5-chloro-3-hydroxypyridin-2-yl)ethan-1-one (**98**) (10.4 g, 60.6 mmol) in methanol (50 mL), sodium hydroxide (7.3 g, 180 mmol) and 4-(difluoromethyl)benzaldehyde (**61e**) (9.5 g, 61 mmol) were added. The reaction mixture was heated at 90 °C for 1 h. Then, it was cooled, and the resulting solid was collected by filtration, washed with water, and dried under vacuum to afford (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(4-(difluoromethyl)phenyl)prop-2-en-1-one (**99e**) as a yellow solid. Yield: 20.0 g, crude. MS (ESI) *m*/*z*: 308.3 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.38 (d, *J* = 16.0 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 16.0 Hz, 1H), 7.38 (s, 1H), 7.28−6.91 (m, 1H), 6.77 (s, 1H).

*7-Chloro-2-(4-(difluoromethyl)phenyl)-3-hydroxy-4H-pyrano-[3,2-b]pyridin-4-one (**100e**).* To a solution of crude (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(4-(difluoromethyl)phenyl)prop-2-en-1-one (**99e**) (20.0 g) in ethanol/dichloromethane (150 mL), 10% aq sodium hydroxide (129 mL, 143 g solution, 14.3 g NaOH, 358 mmol) was added followed by 30% aq hydrogen peroxide (26.5 mL, 29.4 g solution, 8.82 g H_2O_2, 259 mmol) at room temperature. The reaction mixture was stirred for 1 h (reaction is exothermic). Then, the reaction mixture was cooled and neutralized with 6 M hydrochloric acid to pH ≈ 7. The mixture was concentrated in vacuo, and the precipitated solid was filtered and dried under vacuum to afford 7-chloro-2-(4-(difluoromethyl)phenyl)-3-hydroxy-4*H*-pyrano[3,2-*b*]pyridin-4-one (**100e**) as a yellow solid. Yield: 3.0 g (9.3 mmol, 15% over two steps). MS (ESI) *m*/*z*: 322.17 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 10.26 (br s, 1H), 8.81 (s, 1H), 8.64 (s, 1H), 8.36 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.27−6.84 (m, 1H).

*rac-Methyl (6S,7S,8S,9R)-3-Chloro-6-(4-(difluoromethyl)phenyl)-9-hydroxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-b]pyridine-8-carboxylate (**S41e**).* A solution of 7-chloro-2-(4-(difluoromethyl)phenyl)-3-hydroxy-4*H*-pyrano[3,2-*b*]-pyridin-4-one (**100e**) (3.0 g, 9.3 mmol) and methyl cinnamate (**55**) (13.82 g, 85.21 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated for 16 h under 400 W UV light in a UV reactor flask. After this time, the solvent was removed under reduced pressure, and the crude product was purified

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by Combi-flash (12 g, RediSep column) using ethyl acetate as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (6*S*,7*S*,8*S*,9*R*)-3-chloro-6-(4-(difluoromethyl)phenyl)-9-hydroxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**S41e**) as a brown solid. Yield: 3.0 g, crude.

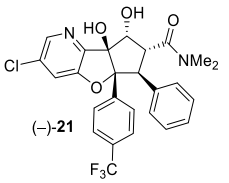
*rac-Methyl (5aR,6S,7R,8aR)-3-Chloro-5a-(4-(difluoromethyl)-phenyl)-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**S42e**).* The crude *rac*-methyl (6*S*,7*S*,8*S*,9*R*)-3-chloro-6-(4-(difluoromethyl)phenyl)-9-hydroxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**S41e**) (3.0 g) was suspended in methanol (30 mL), treated with sodium methoxide (25% in methanol, 25 mL, 24 g solution, 5.9 g NaOMe, 110 mmol NaOMe), and heated at 90 °C for 3 h. After this time, the solvent was removed under reduced pressure. The mixture was treated with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-3-chloro-5a-(4-(difluoromethyl)phenyl)-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S42e**) as a brown solid. Yield: 2.5 g, crude, MS (ESI) *m*/*z*: 486.19 $[M + 1]^+$.

*rac-Methyl (5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-(difluoromethyl)-phenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**101e**).* To a solution of sodium triacetoxyborohydride (5.2 g, 25 mmol) and *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-3-chloro-5a-(4-(difluoromethyl)phenyl)-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*b*]pyridine-7-carboxylate (**S42e**) (2.5 g, crude) in acetonitrile (50 mL), acetic acid (2.4 mL, 2.52 g, 42.0 mmol) was added. The resulting mixture was stirred at room temperature for 4 h. Then, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure to obtain the crude product, which was purified by Combi-flash (12 g, RediSep) using 30% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-(difluoromethyl)phenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]-furo[3,2-*b*]pyridine-7-carboxylate (**101e**) as an off-white solid. Yield: 1.0 g (2.0 mmol, 22% over three steps). MS (ESI) *m*/*z*: 486.29 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (d, J = 1.8 Hz, 1H), 7.70 (d, J = 1.9 Hz, 1H), 7.26−7.22 (m, 4H), 7.06−6.96 (m, 6H), 6.17 (s, 1H), 5.75 (d, J = 5.6 Hz, 1H), 4.65 (t, J = 5.2 Hz, 1H), 4.52 (d, J = 13.8 Hz, 1H), 4.22−4.17 (dd, J = 13.6, 4.2 Hz, 1H), 3.54 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-(difluoromethyl)phenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]-furo[3,2-b]pyridine-7-carboxylic Acid (**S43e**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-(difluoromethyl)phenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]-furo[3,2-*b*]pyridine-7-carboxylate (**101e**) (1.2 g, 2.5 mmol) in methanol and water (3:1, 16 mL), lithium hydroxide (0.55 g, 23.0 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. After this time, the reaction mixture was cooled to 0 °C and acidified with 1 M hydrochloric acid to pH ≈ 3. The resulting precipitate was collected by filtration and dried under vacuum to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-(difluoromethyl)-phenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S43e**) as a yellow solid. Yield: 1.05 g (2.2 mmol, 88%). MS (ESI) *m*/*z*: 472.2 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.14 (s, 1H), 7.64 (s, 1H), 7.20−7.15 (m, 7H), 7.04−7.00 (dd, J = 14.7, 7.5 Hz, 2H), 6.94−6.91 (dd, J = 14.0, 6.7 Hz, 1H), 6.91−6.67 (m, 1H), 5.94 (s, 1H), 4.50 (d, J = 13.9 Hz, 1H), 4.41 (br s, 1H), 3.69 (d, J = 14.7 Hz, 1H).

*(5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-(difluoromethyl)phenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**20**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-(difluoromethyl)-phenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S43e**) (0.6 g, 1.3 mmol) in dichloromethane (50 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.72 g, 3.8 mmol), 1-hydroxybenzotriazole (0.513 g, 3.80 mmol) and *N*,*N*-diisopropylethylamine (1.34 mL, 0.994 g, 7.69 mmol) were added. The reaction mixture was stirred for 5 min. Then, dimethylamine hydrochloride (0.514 g, 6.30 mmol) was added at same temperature and the mixture was stirred for 16 h at 40 °C. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to provide the crude product, which was purified by Combi-flash (4 g, RediSep) using 70% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated under reduced pressure to afford racemic (5a*R*,6*S*,7*R*,8-*R*,8a*S*)-3-chloro-5a-(4-(difluoromethyl)phenyl)-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (*rac*-**20**) as a white solid. Yield: 400 mg (0.799 mmol, 61%). The enantiomers were separated by chiral preparative HPLC [Chiralpak ID (4.6 × 250) mm]. Peak 1 (116 mg, (+)-**20**), $[\alpha]_D$ +218.2° (*c* 0.25, $CHCl_3$), R_t 8.37 min, ee >99%; MS (ESI) *m*/*z*: 501.40 $[M + 1]^+$; UPLC: 99.38%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.28−7.22 (m, 4H), 7.03−6.91 (m, 5H), 6.85 (t, J = 56.0 Hz, 1H), 6.06 (s, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.76 (t, J = 5.6 Hz, 1H), 4.60 (d, J = 13.2 Hz, 1H), 4.30 (dd, J = 13.2, 5.2 Hz, 1H), 3.28 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.15, 153.30, 149.69, 140.55, 139.05 (t, J = 2.1 Hz), 138.35, 131.94 (t, J = 21.9 Hz), 130.97, 127.82, 127.43, 125.78, 123.82 (t, J = 6.1 Hz), 117.23, 114.87 (t, J = 235 Hz), 102.11, 90.76, 77.95, 56.21, 48.58, 36.60, 35.25. Peak-2 (129 mg, (−)-**20**), $[\alpha]_D$ −190° (*c* 0.28, $CHCl_3$), R_t 18.28 min, ee >99%; MS (ESI) *m*/*z*: 501.40 $[M + 1]^+$; HRMS (ESI): calcd, 501.1387 $[M + H]^+$; found, 501.1397; UPLC: 99.29%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.28 (dd, J = 16.8 Hz, 8.4 Hz, 4H), 7.03−6.91 (m, 5H), 6.85 (t, J = 56.0 Hz, 1H), 6.06 (s, 1H), 5.30 (d, J = 5.6 Hz, 1H), 4.76 (t, J = 5.6 Hz, 1H), 4.60 (d, J = 13.2 Hz, 1H), 4.30 (dd, J = 13.2, 5.2 Hz, 1H), 3.28 (s, 3H), 2.79 (s, 3H).

Synthesis of (5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a-(4-(trifluoromethyl)phenyl)-5a,7,8,8a-tetra-



*hydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**21**).* *(E)-1-(5-Chloro-3-hydroxypyridin-2-yl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**99e**).* To a solution of 1-(5-chloro-3-hydroxypyridin-2-yl)ethan-1-one (**98**) (6.0 g, 35 mmol) in methanol (20 mL), sodium hydroxide (4.2 g, 0.11 mol) and 4-(trifluoromethyl)benzaldehyde (**61e**) (6.1 g, 35 mmol) were added. The reaction mixture was heated at 90 °C for 1 h. After this time, the reaction mixture was cooled, and the resulting precipitate was collected by filtration, washed with water, and dried under vacuum to afford (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(4-(trifluoromethyl)phenyl)-prop-2-en-1-one (**99e**) as a yellow solid. Yield: 6.0 g (18 mmol, 51%). MS (ESI) *m*/*z*: 328.26 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.41 (d, J = 16.0 Hz, 1H), 7.86 (d, J = 7.6 Hz, 2H), 7.75 (d, J = 7.9 Hz, 2H), 7.49 (d, J = 16.1 Hz, 1H), 7.36 (s, 1H), 6.73 (s, 1H).

*7-Chloro-3-hydroxy-2-(4-(trifluoromethyl)phenyl)-4H-pyrano-[3,2-b]pyridin-4-one (**100f**).* To a solution of (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**99f**) (6.0 g, 18 mmol) in ethanol and dichloromethane (1:1, 200 mL) at room temperature, 10% aq sodium hydroxide (50.1 mL sln, 5.56 g NaOH, 139 mmol) was added followed by 30% aq hydrogen peroxide (12.5 mL sln, 4.16 g H_2O_2, 122 mmol). The reaction mixture was stirred for 30 min (reaction is exothermic!). After this time, the reaction mixture was cooled and neutralized with 6 M hydrogen chloride to pH ≈ 7. Then, the dichloromethane was removed by distillation, and the precipitated solid was collected by filtration and

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washed with ethanol and *n*-pentane. The so-obtained material was dried under vacuum to afford 7-chloro-3-hydroxy-2-(4-(trifluoromethyl)phenyl)-4*H*-pyrano[3,2-*b*]pyridin-4-one (**100f**) as a light orange solid. Yield: 3.5 g (10 mmol, 56%). MS (ESI) *m*/*z*: 342.06 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.74 (s, 1H), 8.60 (s, 1H), 8.57 (d, *J* = 7.0 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H).

*rac-Methyl (6S,7S,8S,9R)-3-Chloro-9-hydroxy-10-oxo-7-phenyl-6-(4-(trifluoromethyl)-phenyl)-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-b]pyridine-8-carboxylate (**S41f**).* A solution of 7-chloro-3-hydroxy-2-(4-(trifluoromethyl)phenyl)-4*H*-pyrano[3,2-*b*]-pyridin-4-one (**100f**) (3.0 g, 8.8 mmol) and methyl cinnamate (**55**) (14.2 g, 87.6 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated for 24 h under 400 W UV light in a UV reactor flask. After this time, the solvent was removed under reduced pressure, and the residue was purified by Combi-flash (24 g RediSep column) using ethyl acetate as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (6*S*,7*S*,8*S*,9*R*)-3-chloro-9-hydroxy-10-oxo-7-phenyl-6-(4-(trifluoromethyl)-phenyl)-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**S41f**) as a sticky brown solid. Yield: 3.0 g, crude. MS (ESI) *m*/*z*: 504.39 $[M + 1]^+$.

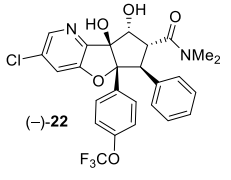
*rac-Methyl (5aR,6S,7R,8aR)-3-Chloro-8a-hydroxy-8-oxo-6-phenyl-5a-(4-(trifluoromethyl)-phenyl)-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**S42f**).* The crude *rac*-methyl (6*S*,7*S*,8*S*,9*R*)-3-chloro-9-hydroxy-10-oxo-7-phenyl-6-(4-(trifluoromethyl)-phenyl)-6,7,8,9-tetrahydro-6,9-methanooxepino-[3,2-*b*]pyridine-8-carboxylate (**S41f**) (3.0 g) was suspended in methanol (30 mL) and treated with 25% sodium methoxide in methanol (30 mL, 28 g solution, 7.1 g NaOMe, 13 mmol). This mixture was heated at 90 °C for 3 h. After this time, the solvent was removed under reduced pressure. The crude product was treated with aqueous ammonium chloride and extracted with ethyl acetate. The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford methyl (5a*R*,6*S*,7-*R*,8a*R*)-3-chloro-8a-hydroxy-8-oxo-6-phenyl-5a-(4-(trifluoromethyl)-phenyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S42f**) as a sticky brown solid. Yield: 2.5 g, crude; MS (ESI) *m*/*z*: 504.10 $[M + 1]^+$.

*rac-Methyl (5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-6-phenyl-5a-(4-(trifluoromethyl)-phenyl)-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**101f**).* To a solution of crude *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-3-chloro-8a-hydroxy-8-oxo-6-phenyl-5a-(4-(trifluoromethyl)phenyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S42f**) (2.5 g) in acetonitrile (250 mL) at 0 °C, sodium triacetoxyborohydride (6.0 g, 28 mmol) and acetic acid (3.0 mL, 3.2 g, 52 mmol) were added. The resulting mixture was stirred for 10 h at room temperature. After this time, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the crude product, which was purified by Combi-flash (12 g RediSep column) using 70% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-6-phenyl-5a-(4-(trifluoromethyl)phenyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**101f**) as an off-white solid. Yield: 1.1 g (2.1 mmol, 25% over three steps). MS (ESI) *m*/*z*: 506.8 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.21 (d, *J* = 1.8 Hz, 1H), 7.72 (d, *J* = 1.8 Hz, 1H), 7.37−7.30 (m, 4H), 7.07−6.97 (m, 5H), 6.23 (s, 1H), 5.80−5.74 (dd, *J* = 16.3, 4.0 Hz, 1H), 4.65 (t, *J* = 5.0 Hz, 1H), 4.55 (d, *J* = 13.7 Hz, 1H), 4.24−4.19 (dd, *J* = 13.8, 4.7 Hz, 1H), 3.58 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-6-phenyl-5a-(4-(trifluoromethyl)phenyl)-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]-furo[3,2-b]pyridine-7-carboxylic Acid (**S43f**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-6-phenyl-5a-(4-(trifluoromethyl)phenyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]-furo[3,2-*b*]pyridine-7-carboxylate (**101f**) (1.1 g, 2.1 mmol) in methanol and water (3:1, 13 mL), lithium hydroxide monohydrate (2.19 g, 52.2 mmol) was added. The reaction mixture was stirred for 3 h at room temperature. After this time, the reaction mixture was cooled to 0 °C and acidified with 6 M hydrogen chloride to pH ≈ 6. The resulting precipitate was collected by filtration and dried under vacuum to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-6-phenyl-5a-(4-(trifluoromethyl)phenyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S43f**) as an off-white solid. Yield: 900 mg (1.83 mmol, 87%). MS (ESI) *m*/*z*: 492.5 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.15 (d, *J* = 1.6 Hz, 1H), 7.65 (d, *J* = 1.6 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 6.8 Hz, 2H), 7.05−7.01 (dd, *J* = 15.2, 7.6 Hz, 2H), 6.94 (d, *J* = 6.8 Hz, 1H), 5.97 (s, 1H), 4.52 (d, *J* = 13.6 Hz, 1H), 4.41 (s, 1H), 3.66 (br s, 1H).

*(5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a-(4-(trifluoromethyl)phenyl)-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**21**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-6-phenyl-5a-(4-(trifluoromethyl)phenyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S43f**) (0.90 g, 1.8 mmol) in dichloromethane (50 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.0 g, 5.2 mmol), 1-hydroxybenzotriazole (0.74 g, 4.8 mmol), and *N*,*N*-diisopropylethylamine (1.9 mL, 1.4 g, 11 mmol) were added. This reaction mixture was stirred for 5 min. Then, dimethylamine hydrochloride (0.74 g, 9.1 mmol) was added at same temperature, and the mixture was stirred for 20 h at room temperature. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product which was purified by Combi-flash (4 g RediSep column) using 5% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a-(4-(trifluoromethyl)phenyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (*rac*-**21**) as an off-white solid. Yield: 0.5 g (0.96 mmol, 54%). The enantiomers were separated by chiral preparative HPLC [Chiralpak ID (4.6 × 250) mm]. Peak 1 (50 mg, (+)-**21**); $[\alpha]_D$ +212.0° (*c* 0.1, $CHCl_3$); R_t 6.26 min, ee >99%; MS (ESI) *m*/*z*: 519.30 $[M + 1]^+$; UPLC 97%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.21 (d, *J* = 2.0 Hz, 1H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.35 (dd, *J* = 13.6 Hz, 8.9 Hz, 4H), 7.04−7.00 (m, 2H), 6.96−6.91 (m, 3H), 6.13 (s, 1H), 5.34 (d, *J* = 5.6 Hz, 1H), 4.77 (t, *J* = 5.4 Hz, 1H), 4.64 (d, *J* = 13.2 Hz, 1H), 4.34 (dd, *J* = 13.2, 5.2 Hz, 1H), 3.28 (s, 3H), 2.78 (s, 3H). Peak-2 (50 mg, (−)-**21**); $[\alpha]_D$ −194.5° (*c* 0.1, $CHCl_3$); R_t 12.49 min, ee >99%; MS (ESI) *m*/*z*: 519.31 $[M + 1]^+$; HRMS (ESI): calcd, 519.1292 $[M + H]^+$; found, 519.1293; UPLC 99%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.21 (d, *J* = 2.0 Hz, 1H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.35 (dd, *J* = 13.6 Hz, 8.9 Hz, 4H), 7.04−7.00 (m, 2H), 6.96−6.91 (m, 3H), 6.13 (s, 1H), 5.34 (d, *J* = 5.6 Hz, 1H), 4.77 (t, *J* = 5.4 Hz, 1H), 4.64 (d, *J* = 13.2 Hz, 1H), 4.34 (dd, *J* = 13.2, 5.2 Hz, 1H), 3.28 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.05, 153.25, 149.51, 140.93, 140.67, 138.20, 131.00, 128.24, 127.78, 127.47, 126.91 (q, *J* = 31.4 Hz), 125.84, 124.23 (q, *J* = 272 Hz), 123.20 (q, *J* = 3.8 Hz), 117.26, 101.94, 90.96, 77.92, 56.31, 48.68, 36.60, 35.26.

*Synthesis of (5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a-(4-(trifluoromethoxy)phenyl)-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**22**).* *(E)-1-(5-Chloro-3-hydroxypyridin-2-yl)-3-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one (**99g**).* To a solution of 1-(5-chloro-3-hydroxypyridin-2-yl)ethan-1-one (**98**) (7.0 g, 41 mmol) and 4-(trifluoromethoxy)benzaldehyde (**61g**) (7.75 g, 40.8 mmol) in methanol (35 mL), sodium hydroxide (4.89 g, 122 mmol) was added. This reaction mixture was heated to reflux for 30 min. Then, the reaction mixture was cooled to room temperature and diluted with



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water (50 mL). The resulting precipitate was collected by filtration, washed with water and then *n*-pentane, and dried under vacuum to afford (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(4-(trifluoromethoxy)-phenyl)prop-2-en-1-one (**99g**) as a yellow solid. Yield: 7.1 g (21 mmol, 50%); MS (ESI) *m*/*z*: 342.18 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.22 (d, J = 16.08 Hz, 1H), 7.92 (d, J = 4.92 Hz, 2H), 7.89 (s, 1H), 7.73 (d, J = 16.24 Hz, 1H), 7.43 (d, J = 7.24 Hz, 2H), 7.31 (s, 1H).

*7-Chloro-3-hydroxy-2-(4-(trifluoromethoxy)phenyl)-4H-pyrano-[3,2-b]pyridin-4-one (**100g**).* To a solution of (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one (**99g**) (5.0 g, 15 mmol) in ethanol (50 mL) at 0 °C, 10% aq sodium hydroxide (36.1 mL, 40.1 g solution, 4.01 g, 100 mmol) was added followed by 30% aq hydrogen peroxide (11.15 mL, 12.38 g solution, 3.713 g H_2O_2, 101.5 mmol). The reaction mixture was stirred for 30 min at room temperature (reaction is exothermic). Then, the mixture was cooled and neutralized by the addition of 6 M hydrochloric acid to pH ≈ 7. The resulting precipitate was collected by filtration, washed with ethanol and then pentane, and dried under vacuum to afford 7-chloro-3-hydroxy-2-(4-(trifluoromethoxy)phenyl)-4*H*-pyrano[3,2-*b*]-pyridin-4-one (**100g**) as a white solid. Yield: 2.8 g (7.8 mmol, 52%). MS (ESI) *m*/*z*: 356.14 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 10.22 (br s, 1H), 8.81 (s, 1H), 8.62 (s, 1H), 8.34 (d, J = 7.4 Hz, 2H), 7.60 (d, J = 6.7 Hz, 2H).

rac-Methyl (7S,8S,9R)-3-Chloro-9-hydroxy-10-oxo-7-phenyl-6-(4-(trifluoromethoxy)-phenyl)-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-b]pyridine-8-carboxylate (S41g). A solution of 7-chloro-3-hydroxy-2-(4-(trifluoromethoxy)phenyl)-4*H*-pyrano[3,2-*b*]pyridin-4-one (**100g**) (2.8 g, 7.8 mmol) and methyl cinnamate (**55**) (12.69 g, 78.24 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated under 400 W UV light in a UV reactor flask for 24 h. After this time, the solvent was removed under reduced pressure, and the residue was purified over a plug of silica gel eluting the compound with 5% methanol in dichloromethane. The desired fractions were concentrated under reduced pressure to afford methyl (7*S*,8*S*,9*R*)-3-chloro-9-hydroxy-10-oxo-7-phenyl-6-(4-(trifluoromethoxy)phenyl)-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**S41g**) as a brown solid. Yield: 3.0 g, crude.

*rac-Methyl (5aR,6S,7R,8aR)-3-Chloro-8a-hydroxy-8-oxo-6-phenyl-5a-(4-(trifluoromethoxy)phenyl)-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**S42g**).* The crude *rac*-methyl (7*S*,8*S*,9*R*)-3-chloro-9-hydroxy-10-oxo-7-phenyl-6-(4-(trifluoromethoxy)phenyl)-6,7,8,9-tetrahydro-6,9-methanooxepino-[3,2-*b*]pyridine-8-carboxylate (**S41g**) (3.0 g) was suspended in methanol (60 mL) and treated with 25% sodium methoxide in methanol (12.4 mL, 11.7 g solution, 2.93 g NaOMe, 54.2 mmol). The reaction was heated at 80 °C for 4 h. After this time, the solvent was removed under reduced pressure. The crude product was diluted with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7-*R*,8a*R*)-3-chloro-8a-hydroxy-8-oxo-6-phenyl-5a-(4-(trifluoromethoxy)phenyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]-furo[3,2-*b*]pyridine-7-carboxylate (**S42g**) as a brown solid. Yield: 3.0 g, crude.

*rac-Methyl (5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-6-phenyl-5a-(4-(trifluoromethoxy)phenyl)-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**101g**).* A solution of *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-3-chloro-8a-hydroxy-8-oxo-6-phenyl-5a-(4-(trifluoromethoxy)phenyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S42g**) (3.0 g) in acetonitrile (60 mL) was cooled to 0 °C. To this solution acetic acid (3.46 g, 57.6 mmol) and sodium triacetoxyborohydride (7.3 g, 34 mmol) were added. The resulting mixture was stirred for 12 h at room temperature. After completion, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by silica gel column chromatography using 2−3% in methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-6-phenyl-5a-(4-(trifluoromethoxy)phenyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**101g**) as a white solid. Yield: 0.6 g (1.2 mmol, 15% over three steps). MS (ESI) *m*/*z*: 522.2 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.21 (d, J = 1.8 Hz, 1H), 7.70 (s, 1H), 7.20 (d, J = 8.7 Hz, 2H), 7.06−6.95 (m, 7H), 6.21 (s, 1H), 5.76 (d, J = 5.7 Hz, 1H), 4.66 (t, J = 5.1 Hz, 1H), 4.49 (d, J = 13.8 Hz, 1H), 4.17−4.13 (dd, J = 13.8, 4.7 Hz, 1H), 3.57 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-6-phenyl-5a-(4-(trifluoromethoxy)-phenyl)-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-carboxylic Acid (**S43g**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-6-phenyl-5a-(4-(trifluoromethoxy)phenyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**101g**) (0.6 g, 1.2 mmol) in a mixture of methanol, tetrahydrofuran. and water (2:1:1, 12 mL) was added lithium hydroxide (anhydrous, 0.27 g, 11 mmol). The reaction mixture was stirred for 6 h at room temperature. Then, it was concentrated, cooled to 0 °C, and acidified with 1 M hydrochloric acid to pH ≈ 2−3. The resulting precipitate was collected by filtration and dried under vacuum to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-6-phenyl-5a-(4-(trifluoromethoxy)phenyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S43g**) as an off-white solid. Yield: 0.45 g (0.89 mmol, 74%). MS (ESI) *m*/*z*: 506.19 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.17 (s, 1H), 7.66 (s, 1H), 7.16 (d, J = 8.6 Hz, 2H), 7.04−6.96 (m, 7H), 6.07 (s, 1H), 4.53 (br s, 1H), 4.46 (d, J = 13.8 Hz, 1H), 3.84−3.81 (m, 1H).

*(5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a-(4-(trifluoromethoxy)phenyl)-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**22**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-6-phenyl-5a-(4-(trifluoromethoxy)phenyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S43g**) (0.3 g, 0.6 mmol) in dichloromethane (10 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (0.275 g, 1.77 mmol), hydroxybenzotriazole (0.271 g, 2.00 mmol) and *N*,*N*-diisopropylethylamine (0.58 mL, 0.43 g, 3.32 mmol) were added. This reaction mixture was stirred for 5 min. Then, dimethylamine hydrochloride (0.241 g, 2.96 mmol) was added at the same temperature, and the mixture was stirred for 16 h at room temperature. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by silica gel column chromatography using 2−3% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford racemic (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a-(4-(trifluoromethoxy)phenyl)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxamide (*rac*-**22**) as an off-white solid. Yield: 0.146 g (0.273 mmol, 45%). The enantiomers were separated by chiral preparative HPLC [Chiralpak IB (4.6 × 250) mm]. Peak 1 (79 mg, (+) -**22**), $[\alpha]_D$ +211° (*c* 0.1, $CHCl_3$), R_t 5.982 min, ee >99%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (d, J = 2.0 Hz, 1H), 7.71 (d, J = 2.0 Hz, 1H), 7.24 (d, J = 8.8 Hz, 2H), 7.04−6.98 (m, 4H), 6.94 (t, J = 7.2 Hz, 1H), 6.89 (d, J = 7.6 Hz, 2H), 6.10 (s, 1H), 5.31 (d, J = 5.6 Hz, 1H), 4.76 (t, J = 5.4 Hz, 1H), 4.55 (d, J = 13.6 Hz, 1H), 4.25 (dd, J = 13.2, 5.2 Hz, 1H), 3.26 (s, 3H), 2.77 (s, 3H); MS (ESI) *m*/*z*: 535.36 $[M + 1]^+$; UPLC: 98.9%. Peak-2 (67 mg, (−)-**22**), $[\alpha]_D$ −217.4° (*c* 0.1, $CHCl_3$), R_t 12.093 min, ee >99%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (d, J = 2.0 Hz, 1H), 7.71 (d, J = 2.0 Hz, 1H), 7.24 (d, J = 8.8 Hz, 2H), 7.04−6.98 (m, 4H), 6.95 (t, J = 6.8 Hz, 1H), 6.89 (d, J = 7.6 Hz, 2H), 6.10 (s, 1H), 5.31 (d, J = 5.6 Hz, 1H), 4.76 (t, J = 5.4 Hz, 1H), 4.55 (d, J = 13.2 Hz, 1H), 4.25 (dd, J = 13.2, 5.2 Hz, 1H), 3.26 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.09, 153.22, 149.66, 146.84, 140.59, 138.32, 135.51, 130.97, 129.33, 127.79, 127.39, 125.76, 118.91, 117.25, 101.85, 90.63, 77.94, 56.31, 48.53, 36.57, 35.24. MS (ESI) *m*/*z*: 535.39 $[M + 1]^+$; HRMS (ESI): calcd, 535.1242 $[M + H]^+$; found, 535.1254; UPLC: 99.57%.

Synthesis of (5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-N,N-dimethyl-5a-(4-(methylsulfonyl)phenyl)-6-phenyl-5a,7,8,8a-tetra-

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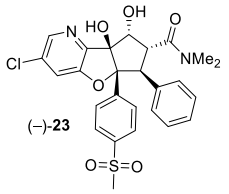

(−)-**23**

*hydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**23**).* *(E)-1-(5-Chloro-3-hydroxypyridin-2-yl)-3-(4-(methylsulfonyl)phenyl)prop-2-en-1-one (**99h**).* To a solution of 1-(5-chloro-3-hydroxypyridin-2-yl)ethan-1-one (**98**) (4.0 g, 23 mmol) in methanol (20 mL), sodium hydroxide (2.8 g, 70 mmol) was added followed by 4-(methylsulfonyl)benzaldehyde (**61h**) (4.3 g, 23 mmol). The reaction mixture was heated to reflux for 30 min. Then, the mixture was cooled to room temperature and diluted with water (20 mL). The resulting precipitate was collected by filtration, washed with water and then *n*-pentane, and dried under vacuum to afford (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(4-(methylsulfonyl)phenyl)prop-2-en-1-one (**99h**) as a yellow solid. Yield: 5.3 g (16 mmol, 70%). MS (ESI) *m*/*z*: 338.15 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.36 (d, J = 14.4 Hz, 1H), 7.97 (s, 4H), 7.76−7.65 (m, 2H), 7.11 (br s, 1H), 3.24 (s, 3H).

*7-Chloro-3-hydroxy-2-(4-(methylsulfonyl)phenyl)-4H-pyrano-[3,2-b]pyridin-4-one (**100h**).* To a solution of (*E*)-1-(5-chloro-3-hydroxypyridin-2-yl)-3-(4-(methylsulfonyl)-phenyl)prop-2-en-1-one (**99h**) (5.3 g, 16 mmol) in ethanol (30 mL) and dichloromethane (6 mL) at 0 °C, 10% aq sodium hydroxide (40 mL, 44 g solution, 4.4 g NaOH, 110 mmol) was added followed by 30% hydrogen peroxide in water (11.3 mL, 12.5 g solution, 3.76 g H_2O_2, 111 mmol). The reaction mixture was stirred for 30 min at room temperature (reaction is exothermic). Then, the reaction mixture was cooled and neutralized to pH ≈ 7 by the addition of 6 M hydrochloric acid. The mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with water and then brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The solid obtained was triturated with *n*-pentane and ethanol, filtered, and dried under vacuum to afford 7-chloro-3-hydroxy-2-(4-(methylsulfonyl)phenyl)-4*H*-pyrano[3,2-*b*]-pyridin-4-one (**100h**) as a light brown solid. Yield: 0.80 g (2.3 mmol, 14%). MS (ESI) *m*/*z*: 352.13 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 10.50 (br s, 1H), 8.82 (s, 1H), 8.66 (s, 1H), 8.45 (d, J = 6.2 Hz, 2H), 8.12 (d, J = 6.7 Hz, 2H).

*rac-Methyl (7S,8S,9R)-3-Chloro-9-hydroxy-6-(4-(methylsulfonyl)-phenyl)-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino-[3,2-b]pyridine-8-carboxylate (**S41h**).* A solution of 7-chloro-3-hydroxy-2-(4-(methylsulfonyl)phenyl)-4*H*-pyrano[3,2-*b*]pyridin-4-one (**100h**) (1.9 g, 5.4 mmol) and methyl cinnamate (**55**) (8.8 g, 54 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated under 400 W UV light in a UV reactor flask for 8 h. After this time, the solvent was removed under reduced pressure, and the residue was purified over a plug of silica gel eluting the compound with ethyl acetate. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (7*S*,8*S*,9*R*)-3-chloro-9-hydroxy-6-(4-(methylsulfonyl)phenyl)-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**S41h**) as a brown solid. Yield: 2.5 g, crude.

*rac-Methyl (5aR,6S,7R,8aR)-3-Chloro-8a-hydroxy-5a-(4-(methylsulfonyl)phenyl)-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**S42h**).* The crude *rac*-methyl (7*S*,8*S*,9*R*)-3-chloro-9-hydroxy-6-(4-(methylsulfonyl)-phenyl)-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**S41h**) (2.5 g) was suspended in methanol (30 mL), treated with 25% sodium methoxide in methanol (15 mL, 14 g solution, 3.5 g NaOMe, 66 mmol), and heated at 80 °C for 2 h. Then, the solvent was removed under reduced pressure. The crude product was diluted with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-3-chloro-8a-hydroxy-5a-(4-(methylsulfonyl)phenyl)-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]-pyridine-7-carboxylate (**S42h**). Yield: 1.6 g, crude.

*rac-Methyl (5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-5a-(4-(methylsulfonyl)phenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**101h**).* To a solution of sodium triacetoxyborohydride (3.96 g, 18.8 mmol), a solution of the crude methyl (5a*R*,6*S*,7*R*,8a*R*)-3-chloro-8a-hydroxy-5a-(4-(methylsulfonyl)phenyl)-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S42h**) (1.6 g) in acetonitrile (30 mL) and acetic acid (1.78 mL, 1.87 g, 31.1 mmol) was added. The resulting mixture was stirred for 12 h at room temperature. After this time, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to give the crude product, which was purified by silica gel column chromatography using 2−3% dichloromethane in methanol as the eluent. The desired fractions were concentrated to afford methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-5a-(4-(methylsulfonyl)phenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**101h**) as a brown solid. Yield: 0.6 g (1.2 mmol, 22% over three steps); MS (ESI) *m*/*z*: 516.1 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.21 (s, 1H), 7.73 (s, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.07−6.96 (m, 5H), 6.28 (s, 1H), 5.79 (d, J = 5.5 Hz, 1H), 4.66 (t, J = 5.1 Hz, 1H), 4.56 (d, J = 13.8 Hz, 1H), 4.26−4.22 (dd, J = 13.8, 4.4 Hz, 1H), 3.58 (s, 3H), 3.02 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-5a-(4-(methylsulfonyl)phenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylic Acid (**S43h**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-5a-(4-(methylsulfonyl)-phenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**101h**) (0.6 g, 1.2 mmol) in a mixture of methanol, tetrahydrofuran, and water (2:1:1, 12 mL), lithium hydroxide (anhydrous, 0.27 g, 11 mmol) was added. The reaction mixture was stirred for 2 h at room temperature. After completion, the reaction mixture was cooled to 0 °C and acidified with 1 M hydrochloric acid to pH ≈ 2−3. The precipitate was filtered and dried under vacuum to afford (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-5a-(4-(methylsulfonyl)phenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S43h**) as an off-white solid. Yield: 0.45 g (0.90 mmol, 75%); MS (ESI) *m*/*z*: 502.04 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.30 (br s,1H), 8.21 (s, 1H), 7.73 (s, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 7.06−6.96 (m, 5H), 6.23 (s, 1H), 5.75 (br s, 1H), 4.65 (br s, 1H), 4.52 (d, J = 13.6 Hz, 1H), 4.11 (m, 1H), 3.01 (s, 3H).

*(5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-N,N-dimethyl-5a-(4-(methylsulfonyl)phenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**23**).* To a solution of (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-5a-(4-(methylsulfonyl)-phenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S43h**) (0.3 g, 0.6 mmol) in dichloromethane (8 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (0.28 g, 1.8 mmol), hydroxybenzotriazole (0.27 g, 2.0 mmol), and *N*,*N*-diisopropylethylamine (0.46 g, 3.6 mmol) were added. The mixture was stirred for 10 min. Then, dimethylamine hydrochloride (0.24 g, 2.9 mmol) was then added at the same temperature, and the reaction mixture was stirred for 32 h at room temperature. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to obtain the crude product. This was purified by silica gel column chromatography using 2−3% dichloromethane in methanol as the eluent. The desired fractions were concentrated under reduced pressure to afford racemic (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-*N*,*N*-dimethyl-5a-(4-(methylsulfonyl)phenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (*rac*-**23**) as an off-white solid. Yield: 0.159 g (0.30 mmol, 50%). The enantiomers were separated by chiral preparative HPLC [Chiralpak IB (4.6 × 250) mm]. Peak 1 (47 mg, (+)-**23**), $[\alpha]_D$ +196.1° (*c* 0.1, $CHCl_3$), R_t 8.089 min, ee >99%, ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.21 (d, J = 2.0 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.04 (t, J = 7.2 Hz,

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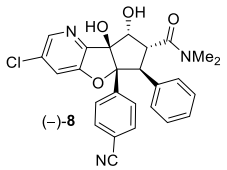
2H), 6.96 (t, J = 9.6 Hz, 3H), 6.16 (br s, 1H), 5.38 (br s, 1H), 4.77 (d, J = 5.2 Hz, 1H), 4.64 (d, J = 13.6 Hz, 1H), 4.35 (dd, J = 13.2, 5.2 Hz, 1H), 3.28 (s, 3H), 3.03 (s, 3H), 2.78 (s, 3H); MS (ESI) m/z: 529.35 $[M + 1]^+$; UPLC: 99.92%. Peak-2 (44 mg, (−)-**23**), $[\alpha]_D$ −173.2° (c 0.1, $CHCl_3$), R_t 16.147 min, ee >99%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.21 (d, J = 2.0 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.04 (t, J = 7.2 Hz, 2H), 6.96 (t, J = 9.6 Hz, 3H), 6.18 (br s, 1H), 5.36 (br s, 1H), 4.77 (d, J = 5.2 Hz, 1H), 4.64 (d, J = 13.2 Hz, 1H), 4.35 (dd, J = 13.2, 5.2 Hz, 1H), 3.28 (s, 3H), 3.03 (s, 3H), 2.98 (s, 3H); 13C NMR (101 MHz, DMSO-d_6): δ/ppm 168.03, 153.18, 149.49, 142.12, 140.71, 138.68, 138.08, 131.00, 128.40, 127.79, 127.51, 125.90, 124.99, 117.31, 101.98, 91.00, 77.91, 56.37, 48.68, 43.53, 36.61, 35.25. MS (ESI) m/z: 529.34 $[M + 1]^+$; HRMS (ESI): calcd, 529.1195 $[M + H]^+$; found, 529.1201; UPLC: 99.83%.

*Synthesis of (5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**8**).* 

*(E)-3-(4-Bromophenyl)-1-(5-chloro-3-hydroxypyridin-2-yl)prop-2-en-1-one (**S44**).* To a solution of l-(5-chloro-3-hydroxypyridin-2-yl)ethan-L-one (**98**) (10.0 g, 58.3 mmol) and sodium hydroxide (7.0 g, 0.18 mol) in methanol (100 mL), 4-bromobenzaldehyde (10.75 g, 58.10 mmol) was added, and the reaction mixture was heated to reflux for 30 min. After completion, the reaction mixture was cooled and the precipitated solid was collected by filtration, washed with water, and dried under high vacuum to afford (*E*)-3-(4-bromophenyl)-1 -(5-chloro-3-hydroxypyridin-2-yl)prop-2-en-1-one (**S44**) as a yellow solid. Yield: 12.0 g (35.4 mmol, 61%); MS (ESI) m/z: 338.95 $[M + 1]^+$. The so-obtained material was directly used in the next step without further purification.

*2-(4-Bromophenyl)-7-chloro-3-hydroxy-4H-pyrano[3,2-b]-pyridin-4-one (**102**).* To a solution of (*E*)-3-(4-bromophenyl)-l-(5-chloro-3-hydroxypyridin-2-yl)prop-2-en-L-one (**S44**) (12.0 g, 35.4 mmol) and sodium hydroxide (10.0 g, 250 mmol) in ethanol (120 mL) and dichloromethane (40 mL), hydrogen peroxide (*ca.* 30% in water, 8.97 mL, 9.96 g solution; 2.99 g, 87.9 mmol) was added at room temperature. The reaction mass was stirred for 1 h at room temperature (reaction is exothermic). Then, the reaction mixture was cooled and neutralized to pH ≈ 7 by addition of 6 M hydrochloric acid. The precipitated solid was collected by filtration and dried under vacuum to afford 2-(4-bromophenyl)-7-chloro-3-hydroxy-4*H*-pyrano-[3,2-*b*]pyridin-4-one (**102**) as a pale yellow solid. Yield: 4.0 g (11 mmol, 31%). MS (ESI) m/z: 352.2 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6[6]): δ/ppm 10.23 (s, 1H), 8.80 (d, J = 2.0 Hz, 1H), 8.61 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H).

*rac-Methyl (7S,8S,9R)-6-(4-Bromophenyl)-3-chloro-9-hydroxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-b]-pyridine-8-carboxylate (**S45**).* A solution of 2-(4-bromophenyl)-7-chloro-3-hydroxy-4*H*-pyrano[3,2-*b*]pyridin-4-one (**102**) (25.0 g, 70.9 mmol) and methyl cinnamate (**55**) (171.2 g, 1.056 mol) in dichloromethane (800 mL), acetonitrile (400 mL), and methanol (400 mL) was irradiated under 400 W UV light for 16 h in a UV reactor flask. Then, the solvent was removed under reduced pressure, and the residue was purified over a plug of silica gel eluting the compound with ethyl acetate. The desired fractions were concentrated under reduced pressure to afford crude (7*S*,8*S*,9*R*)-6-(4-bromophenyl)-3-chloro-9-hydroxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**7**) as a yellow-brown solid. Yield: 30.0 g, crude; MS (ESI) m/z: 514.12 $[M + 1]^+$. Used without further purification.

*rac-Methyl (5aR,6S,7R,8aR)-5a-(4-Bromophenyl)-3-chloro-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]-furo[3,2-b]pyridine-7-carboxylate (**125**).* Crude *rac*-(7*S*,8*S*,9*R*)-6-(4-bromophenyl)-3-chloro-9-hydroxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**S45**) (9.0 g) was suspended in methanol (100 mL) and treated with 25% sodium methoxide in methanol (20.0 mL, 18.9 g solution; 4.73 g, 87.6 mmol NaOMe). The reaction mixture was heated at 80 °C for 3 h. After this time, the solvent was removed under reduced pressure. The crude product was diluted with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*b*]pyridine-7-carboxylate (**125**). Yield: 9.0 g, crude. Used without further purification.

*rac-Methyl (5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]-furo[3,2-b]pyridine-7-carboxylate (**103**).* Acetic acid (9.9 mL, 10 g, 0.17 mol) was added to a solution of sodium triacetoxyborohydride (22.23 g, 104.9 mmol) and crude methyl *rac*-(5a*R*,6*S*,7*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**125**) (9.0 g) in acetonitrile (90 mL) at 0 °C. The resulting mixture was stirred for 4 h at room temperature. Then, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to get the crude product, which was purified by silica gel column chromatography eluting with 1−5% methanol in dichloromethane. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]-pyridine-7-carboxylate (**103**) as an off-white solid. Yield: 6.0 g (11.6 mmol, 55%). MS (ESI) m/z: 516.13 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6[6]): δ/ppm 8.20 (d, J = 2.0 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.22−7.18 (m, 2H), 7.10−6.97 (m, 7H), 6.15 (s, 1H), 5.75 (d, J = 5.8 Hz, 1H), 4.63 (dd, J = 5.8, 4.8 Hz, 1H), 4.51 (d, J = 13.9 Hz, 1H), 4.15 (dd, J = 13.9, 4.8 Hz, 1H), 3.57 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylic Acid (**104**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**103**) (3.3 g, 6.4 mmol) in methanol/water (3:1, 11 mL) was added lithium hydroxide (3.68 g, 154 mmol). The reaction mixture was stirred for 3 h at room temperature. Then, it was cooled to 0 °C and acidified with 5 M hydrogen chloride to pH ≈ 3. The resulting precipitate was collected by filtration and dried under high vacuum to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**104**) as an off-white solid that was used without further purification. Yield: 3.2 g (6.4 mmol, quantitative). MS (ESI) m/z: 502.02 $[M + 1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.13 (s, 1H), 7.61 (d, 1H), 7.21−7.16 (m, 4H), 7.04 (t, J = 7.4 Hz, 2H), 6.95 (d, J = 8.3 Hz, 3H), 5.8 (s, 1H), 4.47 (d, J = 14.0 Hz, 1H), 4.35 (s, 1H), 3.57 (d, J = 13.2 Hz, 1H), 3.40−3.33 (m, 1H).

*rac-(5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-carboxamide (**S46**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**104**) (3.2 g, 6.4 mmol) in dichloromethane (30 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (3.6 g, 19 mmol), hydroxybenzotriazole (2.8 g, 21 mmol), and DIPEA (7.3 mL, 5.4 g, 42 mmol) were added. This mixture was stirred for 5 min at this temperature, then dimethylamine hydrochloride (2.8 g, 34 mmol) was added and the mixture was stirred for 12 h at room temperature. The reaction mixture was then diluted with dichloromethane and washed with cold water. The organic layer was separated and dried over sodium sulfate, filtered, and concentrated to give the crude product, which was purified by silica gel column chromatog-

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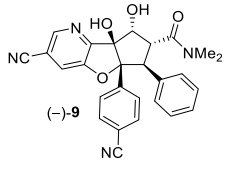
raphy eluting with 70−90% ethyl acetate in hexanes to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*b*]pyridine-7-carboxamide (**S46**) as a white solid. Yield: 2.9 g (5.5 mmol, 86%). MS (ESI) *m*/*z*: 529.05 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.19 (s, 1H), 7.69 (s, 1H), 7.21 (d, J = 8.4 Hz, 2H), 7.06−7.01 (m, 4H), 6.97 (d, J = 6.6 Hz 1H), 6.92 (d, J = 7.1 Hz, 2H), 6.04 (s, 1H), 5.75 (s, 1H), 5.29 (d, J = 5.6 Hz, 1H), 4.72 (d, J = 4.8 Hz, 1H), 4.57 (d, J = 13.3 Hz, 1H), 4.25 (dd, J = 5.2 Hz, 12.9 Hz, 1H), 3.26 (s, 3H), 2.77 (s, 3H).

*(5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**8**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*b*]pyridine-7-carboxamide (**S46**) (1.5 g, 2.8 mmol) in *N*,*N*-dimethylformamide (25 mL), zinc cyanide (6.0 g, 51 mmol) and zinc (0.022 g, 0.034 mmol) were added. The mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (0.041 g, 0.074 mmol) and tris(dibenzylideneacetone)-dipalladium (0.078 g, 0.085 mmol) were added. The mixture was degassed for another 5 min and then heated at 140 °C for 1 h. The mixture was then cooled to room temperature and passed through Celite. The filtrate was concentrated and treated with ice-cold water. The precipitated crude product was purified by reverse-phase prep HPLC. The desired fractions were concentrated under vacuum to afford *rac*-(5a*R*,6*S*,7*R*,8-*R*,8a*S*)-3-chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (*rac*-**8**) as an off-white solid. Yield: 1.1 g (2.3 mmol, 83%). The enantiomers were separated by chiral preparative HPLC [Chiralpak IB (4.6 × 250) mm]. Peak 1 (40 mg, (−)-**8**), $[\alpha]_D$ −180.5° (*c* 0.1, $CHCl_3$), R_t 7.95 min, ee >99%; MS (ESI) *m*/*z*: 476.35 $[M + 1]^+$; HRMS (ESI): calcd, 476.1372 $[M + H]^+$; found, 476.1365; UPLC: 98.31%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.21 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 7.03 (t, J = 7.2 Hz, 2H), 6.97−6.91 (m, 3H), 6.15 (s, 1H), 5.34 (d, J = 5.6 Hz, 1H), 4.73 (t, J = 5.2 Hz, 1H), 4.66 (d, J = 13.2 Hz, 1H), 4.34 (dd, J = 13.2, 5.2 Hz, 1H), 3.28 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.00, 153.22, 149.39, 142.06, 140.72, 138.12, 131.00, 130.27, 128.48, 127.76, 127.52, 125.89, 118.80, 117.25, 109.10, 101.94, 91.20, 77.88, 56.39, 48.78, 36.60, 35.26. Peak 2 (41 mg, (+)-**8**), $[\alpha]_D$ +180° (*c* 0.1, $CHCl_3$), R_t 15.19 min, ee >98.5%; MS (ESI) *m*/*z*: 476.35 $[M + 1]^+$; UPLC: 98.76%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.21 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H), 7.03 (t, J = 7.2 Hz, 2H), 6.97−6.91 (m, 3H), 6.15 (s, 1H), 5.34 (d, J = 5.8 Hz, 1H), 4.73 (t, J = 5.4 Hz, 1H), 4.66 (d, J = 13.2 Hz, 1H), 4.34 (dd, J = 13.2, 5.4 Hz, 1H), 3.28 (s, 3H), 2.78 (s, 3H).

Synthesis of (5aR,6S,7R,8R,8aS)-3-Cyano-5a-(4-cyanophenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-



*cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**9**).* *3,5-Bis(benzyloxy)picolinonitrile (**106**).* A flask containing THF (500 mL) was charged with 3, 5-dichloropicolinonitrile (**105**) (65.0 g, 377.2 mmol) under nitrogen, and sodium hydride (27.2 g, 1.13 mol) was added at 0 °C. The suspension was stirred at room temperature for 30 min, benzyl alcohol (81.37 mL, 84.62 g, 782.5 mmol) was added, and stirring was continued for another 3 h. Then, the reaction was quenched with saturated ammonium chloride solution at 0 °C. The mixture was extracted with ethyl acetate (1000 mL). The organic layer was separated, washed with water (2 × 200 mL) and brine (100 mL), dried over sodium sulfate, concentrated, and triturated with pentane. The precipitate was collected by filtration and dried under vacuum to afford 3,5-bis(benzyloxy)picolinonitrile (**106**) as an off-white solid. Yield: 130.0 g, crude. MS (ESI) *m*/*z*: 317.21 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.12 (s, 1H), 7.55 (s, 1H), 7.48−7.30 (m, 10H), 5.35 (s, 2H), 5.30 (s, 2H).

*1-(3,5-Bis(benzyloxy)pyridin-2-yl)ethan-1-one (**107**).* To a solution of 3,5-bis(benzyloxy)-picolinonitrile (**106**) (70.0 g, crude) in dry tetrahydrofuran (700 mL) at −30 °C, methyl magnesium bromide (78.37 mL, 664.5 mmol) was added dropwise over a period of 30 min. The reaction mixture was slowly brought to room temperature and stirred for 2 h. After completion, the reaction was quenched with 6 N hydrochloric acid and stirred for 2 h. The mixture was extracted with ethyl acetate. The organic layer was washed with 1 N sodium hydroxide solution and water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 1-(3,5-bis(benzyloxy)pyridin-2-yl)ethan-1-one (**107**) as a yellow oil. Yield: 82.0 g, crude. MS (ESI) *m*/*z*: 334.16 $[M + 1]^+$.

*1-(3,5-Dihydroxypyridin-2-yl)ethan-1-one (**108**).* A flask containing ethyl acetate (500 mL) was charged with 1-(3,5-bis(benzyloxy)-pyridin-2-yl)ethan-1-one (**107**) (82.0 g, crude) and palladium hydroxide (34.47 g, 50% wet). The reaction was flushed with hydrogen gas twice and stirred at room temperature for 16 h under hydrogen pressure. After completion, the reaction mixture was filtered through Celite and concentrated under reduced pressure to afford 1-(3,5-dihydroxypyridin-2-yl)ethan-1-one (**108**) as a brown oil. Yield: 40.0 g, crude. MS (ESI) *m*/*z*: 153.04 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.06 (s, 1H), 11.25−11.18 (br s, 1H), 7.93 (s, 1H), 6.66 (s, 1H), 2.59 (s, 3H).

*1-(5-(Benzyloxy)-3-hydroxypyridin-2-yl)ethan-1-one (**109**).* A flask containing acetone (250 mL) was charged with 1-(3,5-dihydroxypyridin-2-yl)ethan-1-one (**108**) (40.0 g, crude) and potassium carbonate (72.15 g, 522.1 mmol) under nitrogen. Benzyl bromide (**S47**) (21.7 mL, 31.2 g, 182 mmol) was added, and the mixture was stirred for another 3 h. Then, volatiles were removed under reduced pressure, and the crude residue was suspended in ethyl acetate (200 mL) and washed with water (2 × 150 mL) and brine (150 mL). The organic layer was separated, dried over sodium sulfate, concentrated, and triturated with pentane. The solid was isolated by filtration and dried under vacuum to afford 1-(5-(benzyloxy)-3-hydroxypyridin-2-yl)ethan-1-one (**109**) as a brown solid. Yield: 50.0 g, crude. MS (ESI) *m*/*z*: 244.04 $[M - 1]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 12.26 (s, 1H), 7.99 (s, 1H), 7.46−7.32 (m, 5H), 6.90 (s, 1H), 5.12 (s, 2H), 2.69 (s, 3H).

*(E)-1-(5-(Benzyloxy)-3-hydroxypyridin-2-yl)-3-(4-bromophenyl)-prop-2-en-1-one (**S48**).* To a solution of 1-(5-(benzyloxy)-3-hydroxypyridin-2-yl)ethan-1-one (**109**) (50.0 g, 206 mmol) in methanol (100 mL), sodium hydroxide (24.69 g, 617.3 mmol) was added followed by 4-bromobenzaldehyde (38.06 g, 205.7 mmol). The reaction mixture was heated at 85 °C for 2 h and then cooled to room temperature. The resulting solid was collected by filtration, washed with water, and dried under vacuum to afford (*E*)-1-(5-(benzyloxy)-3-hydroxypyridin-2-yl)-3-(4-bromophenyl)prop-2-en-1-one (**S48**) as a yellow solid. Yield: 50.2 g (122 mmol, 59%). MS (ESI) *m*/*z*: 410.05 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.46 (d, J = 16 Hz, 1H), 7.43−7.18 (m, 11H), 6.24 (s, 1H), 5.00 (s, 2H).

*7-(Benzyloxy)-2-(4-bromophenyl)-3-hydroxy-4H-pyrano[3,2-b]-pyridin-4-one (**110**).* To a solution of (*E*)-1-(5-(benzyloxy)-3-hydroxypyridin-2-yl)-3-(4-bromophenyl)prop-2-en-1-one (**S48**) (20.0 g, 48.7 mmol) in ethanol/dichloromethane (1:1, 100 mL) at room temperature, sodium hydroxide (13.7 g, 343 mmol) was added followed by hydrogen peroxide (15.11 mL 30% aq sln, 5.03 g H_2O_2, 148 mmol). The reaction mixture was stirred for 1 h (reaction is exothermic). Then, the mixture was cooled and neutralized by addition of 6 N hydrochloric acid. The precipitate was collected by filtration and dried under vacuum to afford 7-(benzyloxy)-2-(4-bromophenyl)-3-hydroxy-4*H*-pyrano[3,2-*b*]pyridin-4-one (**110**) as a yellow solid. Yield: 11.0 g (25.9 mmol, 53%). MS (ESI) *m*/*z*: 426.03 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 9.96 (s, 1H), 8.55 (s, 1H), 8.16 (d, J = 8.6 Hz, 2H), 7.92 (s, 1H), 7.89 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 7.5 Hz, 2H), 7.46−7.42 (m, 3H), 5.33 (s, 2H).

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*rac-Methyl (6S,7S,8S,9R)-3-(Benzyloxy)-6-(4-bromophenyl)-9-hydroxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-b]pyridine-8-carboxylate (**S49**).* A solution of 7-(benzyloxy)-2-(4-bromophenyl)-3-hydroxy-4*H*-pyrano[3,2-*b*]pyridin-4-one (**110**) (11.0 g, 25.9 mmol) and methyl cinnamate (**S5**) (42.28 g, 260.7 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated under 400 W UV light for 15 h in a UV reactor flask. Then, the solvent was removed under reduced pressure, and the residue was purified over a plug of silica gel eluting with ethyl acetate. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (6*S*,7*S*,8*S*,9*R*)-3-(benzyloxy)-6-(4-bromophenyl)-9-hydroxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**S49**) as a brown solid Yield: 11.2 g, crude.

*rac-Methyl (5aR,6S,7R,8aR)-3-(Benzyloxy)-5a-(4-bromophenyl)-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**S50**).* The crude *rac*-methyl (6*S*,7*S*,8*S*,9*R*)-3-(benzyloxy)-6-(4-bromophenyl)-9-hydroxy-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-*b*]pyridine-8-carboxylate (**S49**) (11.0 g) was suspended in methanol (100 mL), treated with 25% sodium methoxide in methanol (110 mL, 104 g solution, 26.0 g NaOMe, 481 mmol NaOMe), and heated at 80 °C for 1 h. Then, the solvent was removed under reduced pressure. The crude product was treated with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-3-(benzyloxy)-5a-(4-bromophenyl)-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]-pyridine-7-carboxylate (**S50**) as a brown solid. Yield: 11.0 g, crude.

*rac-Methyl (5aR,6S,7R,8R,8aS)-3-(Benzyloxy)-5a-(4-bromophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**111**).* The crude methyl (5a*R*,6*S*,7*R*,8a*R*)-3-(benzyloxy)-5a-(4-bromophenyl)-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]-pyridine-7-carboxylate (**S50**) (11.0 g) was added to a solution of sodium triacetoxyborohydride (23.4 g, 110 mmol) in acetonitrile (100 mL) and acetic acid (11.3 mL, 188 mmol), and the resulting mixture was stirred for 4 h at room temperature. It was then partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure obtain the crude product, which was purified by silica gel column chromatography eluting with 50% ethyl acetate in hexanes. The desired fractions were concentrated to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-(benzyloxy)-5a-(4-bromophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**111**) as a light yellow solid. Yield: 5.7 g (9.7 mmol, 38% over three steps). MS (ESI) *m*/*z*: 588.38 $[M + 1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.95 (d, J = 2.0 Hz, 1H), 7.56−7.48 (m, 2H), 7.44−7.40 (m, 2H), 7.37−7.36 (m, 1H), 7.28−7.18 (m, 3H), 7.09−6.95 (m, 7H), 5.88 (s, 1H), 5.57−5.56 (br s, 1H), 5.20 (s, 2H), 4.63 (s, 1H), 4.43−4.40 (m, 1H), 4.11−4.10 (m, 1H), 3.55 (s, 3H).

*rac-Methyl (5aR,6S,7R,8R,8aS)-3-(Benzyloxy)-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**S51**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-(benzyloxy)-5a-(4-bromophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**111**) (5.0 g, 8.5 mmol) in *N*,*N*-dimethylformamide (50.0 mL) at room temperature, zinc cyanide (6.12 g, 52.1 mmol) and zinc dust (0.055 g, 0.841 mmol) were added. The mixture was degassed with argon for 15 min. Then, 1,1′-bis-(diphenylphosphino) ferrocene (0.124 g, 0.224 mmol) and tris-(dibenzylideneacetone)dipalladium (0.233 g, 0.254 mmol) were added, degassing was continued for 5 min, and the mixture was heated to 120 °C for 2 h. After completion, the reaction mixture was cooled to room temperature, filtered through Celite, concentrated, and treated with ice-cold water. The precipitate was collected by filtration and dried under vacuum to afford methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-(benzyloxy)-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S51**) as a brown solid. Yield: 4.4 g (8.2 mmol, 97%). MS (ESI) *m*/*z*: 534.18 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.97 (s, 1H), 7.58−7.48 (m, 3H), 7.46−7.40 (m, 2H), 7.37−7.34 (m, 1H), 7.29−7.27 (m, 2H), 7.16−6.93 (m, 7H), 5.99 (s, 1H), 5.63 (s, 1H), 5.20 (s, 2H), 4.64−4.62 (m, 1H), 4.51−4.47 (m, 1H), 4.20−4.16 (m, 1H), 3.57 (s, 3H).

*rac-Methyl (5aR,6S,7R,8R,8aS)-5a-(4-Cyanophenyl)-3,8,8a-trihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**S52**).* A flask containing ethyl acetate (50 mL) was charged with *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-(benzyloxy)-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S51**) (2.5 g, 4.68 mmol) and palladium hydroxide (1.66 g, 11.8 mmol, 50% wet) at room temperature. The reaction mixture was flushed with hydrogen gas twice and stirred at room temperature for 16 h under hydrogen pressure. The mixture was filtered through Celite bed, and the filtrate was concentrated under reduced pressure to afford methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-cyanophenyl)-3,8,8a-trihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S52**) as a brown oil. Yield: 2.01 g (4.52 mmol, 97%), MS (ESI) *m*/*z*: 443.15 $[M - 1]^-$.

*rac-Methyl (5aR,6S,7R,8R,8aS)-5a-(4-Cyanophenyl)-8,8a-dihydroxy-6-phenyl-3-((trifluoro-methyl)sulfonyl)oxy)-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**S53**).* A flask containing dichloromethane (200 mL) was charged with *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-cyanophenyl)-3,8,8a-trihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S52**) (2.01 g, 4.52 mmol) under nitrogen, and *N*, *N*-diisopropylethylamine (0.57 g, 4.4 mmol) was added at −78 °C, followed by triflic anhydride (1.06 mL, 1.78 g, 6.31 mmol). The reaction mixture was stirred at −78 °C for 45 min. Then, the reaction mixture was quenched with saturated $NaHCO_3$ solution at 0 °C and extracted with dichloromethane (100 mL). The organic layer was separated, washed with water (2 × 50 mL), and washed with brine (50 mL) and then dried over sodium sulfate, concentrated, and triturated with pentane. The precipitate was collected by filtration and dried under vacuum to afford methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-3-((trifluoromethyl)-sulfonyl)oxy)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S53**) as a yellow solid. Yield: 2.01 g (3.49 mmol, 77%). MS (ESI) *m*/*z*: 577.1 $[M + 1]^+$.

*rac-Methyl (5aR,6S,7R,8R,8aS)-3-Cyano-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]-furo[3,2-b]pyridine-7-carboxylate (**S54**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-3-(((trifluoromethyl)sulfonyl)oxy)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S53**) (2.0 g, 3.47 mmol) in *N*,*N*-dimethylformamide (20.0 mL) at room temperature, zinc cyanide (2.4 g, 20.43 mmol) and zinc (0.027 g, 0.413 mmol) were added. The reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (51.0 mg, 0.092 mmol) and tris-(dibenzylideneacetone) dipalladium (95 mg, 0.10 mmol) were added, degassing was continued for 5 min, and the mixture was heated at 100 °C for 3 h. The reaction was cooled to room temperature and filtered through Celite. The filtrate was concentrated and treated with ice-cold water. The precipitate was collected by filtration and dried under vacuum to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-cyano-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S54**) as a yellow solid. Yield: 1.9 g, crude. MS (ESI) *m*/*z*: 454.38 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.64 (s, 1H), 8.05 (s, 1H), 7.98 (s, 1H), 7.47 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.06−6.92 (m, 4H), 6.47 (s, 1H), 5.91−5.86 (m, 1H), 4.60−4.57 (m, 1H), 4.51−4.95 (m, 1H), 4.29−4.21 (m, 1H), 3.58 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-3-Cyano-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylic Acid (**S55**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-cyano-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (1.9 g, crude) in methanol/water (3:1, 12 mL), lithium hydroxide (0.237 g, 9.90 mmol) was added. The reaction mixture was stirred for 6 h at room temperature and then cooled to 0 °C and

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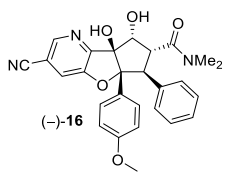
acidified with 1 N hydrochloric acid to pH ≈ 3. The precipitate was collected by filtration and dried under vacuum to afford (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-cyano-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S55**) as a yellow solid. Yield: 0.55 g (1.3 mmol, 37% over two steps). MS (ESI) *m*/*z*: 438.32 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.0−13.0 (br s, 1H), 8.63 (s, 1H), 8.13 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.06−6.98 (m, 5H), 6.40 (s, 1H), 4.66−4.65 (m, 1H), 4.57−4.54 (m, 1H), 4.11−4.07 (m, 1H).

*(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-Cyano-5a-(4-cyanophenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**9**).* A flask containing dichloromethane (10 mL) was charged with (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-cyano-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (0.5 g, 1.1 mmol). Triethylamine (0.46 mL, 3.3 mmol) and dimethylamine hydrochloride (0.139 g, 1.70 mmol) were added at 0 °C. The mixture was stirred for 5 min, treated with propylphosphonic anhydride (50% in ethyl acetate; 0.139 mL, 0.149 g solution, 74.2 mg PPA, 0.234 mmol) at the same temperature, and then stirred for 4 h at room temperature. The reaction mixture was then diluted with dichloromethane and washed with cold water. The organic layer was separated and dried over sodium sulfate, filtered, and concentrated to give a crude product, which was purified by silica gel column chromatography eluting with 70−90% ethyl acetate in hexanes to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-cyano-5a-(4-cyanophenyl)-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*b*]pyridine-7-carboxamide (*rac*-**9**) as a white solid. Yield: 160 mg (0.342 mmol, 31%). The enantiomers were separated by chiral preparative HPLC [Chiralpak IB (4.6 × 250) mm]. Peak 1 (35 mg, (−)-**9**), $[\alpha]_D$ −202.0° (*c* 0.1, $CHCl_3$), R_t 5.99 min, ee >99%, ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.63 (d, *J* = 1.6 Hz, 1H), 8.05 (d, *J* = 1.6 Hz, 1H), 7.5 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.03 (t, *J* = 7.2 Hz, 2H), 6.95 (t, *J* = 8.8 Hz, 3H), 6.37 (s, 1H), 5.45 (d, *J* = 5.6 Hz, 1H), 4.76 (t, *J* = 5.2 Hz, 1H), 4.70 (d, *J* = 13.2 Hz, 1H), 4.36 (dd, *J* = 13.6, 4.8 Hz, 1H), 3.28 (s, 3H), 2.79 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 167.82, 155.54, 152.10, 145.69, 141.76, 137.97, 130.28, 128.45, 127.80, 127.54, 125.92, 119.66, 118.75, 117.08, 109.20, 108.70, 101.63, 91.67, 77.99, 56.58, 48.95, 36.62, 35.28. MS (ESI) *m*/*z*: 467.37 $[M + 1]^+$; HRMS (ESI): calcd, 467.1714 $[M + H]^+$; found, 467.1709; UPLC: 98.66%. Peak-2 (26 mg, (+)-**9**), $[\alpha]_D$ +242° (*c* 0.1, $CHCl_3$), R_t 8.46 min, ee >95%, ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.63 (d, *J* = 1.6 Hz, 1H), 8.05 (d, *J* = 1.6 Hz, 1H), 7.5 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.03 (t, *J* = 7.2 Hz, 2H), 6.95 (t, *J* = 9.2 Hz, 3H), 6.37 (s, 1H), 5.46 (d, *J* = 6 Hz, 1H), 4.76 (t, *J* = 5.2 Hz, 1H), 4.70 (d, *J* = 13.2 Hz, 1H), 4.37 (dd, *J* = 13.2 Hz, 4.4 Hz, 1H), 3.28 (s, 3H), 2.78 (s, 3H), MS (ESI) *m*/*z*: 467.37 $[M + 1]^+$, UPLC: 99.95%.

Synthesis of (5aR,6S,7R,8R,8aS)-3-Cyano-8,8a-dihydroxy-5a-(4-methoxyphenyl)-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-



*cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**16**).* *(E)-1-(5-(Benzyloxy)-3-hydroxypyridin-2-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (**S56**).* To a solution of 1-(5-(benzyloxy)-3-hydroxypyridin-2-yl)ethan-1-one (**109**) (42.0 g, 173 mmol) in MeOH (200 mL), sodium hydroxide (20.97 g, 524.3 mmol) was added followed by 4-methoxybenzaldehyde (**61a**) (31.97 g, 234.8 mmol). The reaction mixture was heated to reflux for 30 min AND then cooled. The resulting solid was collected by filtration, washed with water, and dried under vacuum to afford (*E*)-1-(5-(benzyloxy)-3-hydroxypyridin-2-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (**S56**) as a yellow solid. Yield: 62.3 g (crude). MS (ESI) *m*/*z*: 362.32 $[M + 1]^+$, UPLC: 50%. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.88 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.51−7.31 (m, 6H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.25 (s, 1H), 5.08 (s, 2H), 3.78 (s, 3H).

*7-(Benzyloxy)-3-hydroxy-2-(4-methoxyphenyl)-4H-pyrano[3,2-b]pyridin-4-one (**112**).* To a solution of (*E*)-1-(5-(benzyloxy)-3-hydroxypyridin-2-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (**S56**) (54.0 g, crude) in ethanol (300 mL) at room temperature, sodium hydroxide (47.8 g, 1.19 mol) was added followed by hydrogen peroxide (30% aq sln, 27.6 mL, 9.19 g H_2O_2, 270 mmol). The reaction mixture was stirred for 1 h (reaction is exothermic!). After completion, reaction mass was cooled and neutralized to pH ≈ 7 with 6 N HCl at 0 °C. The solid precipitate was collected by filtration and dried under vacuum to afford 7-(benzyloxy)-3-hydroxy-2-(4-methoxyphenyl)-4*H*-pyrano[3,2-*b*]pyridin-4-one as a pale yellow solid. Yield: 20.5 g (crude). UPLC: 59.5%, MS (ESI) *m*/*z*: 376.11 $[M + 1]^+$, ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.52 (s, 1H), 7.54 (d, *J* = 7.2 Hz, 2H), 7.49−7.33 (m, 5H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.67 (s, 1H), 5.33 (s, 2H), 3.84 (s, 3H).

*rac-Methyl (5aR,6S,7R,8R,8aS)-3-(Benzyloxy)-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-carboxylate (**113**).* A solution of 7-(benzyloxy)-3-hydroxy-2-(4-methoxyphenyl)-4*H*-pyrano[3,2-*b*]-pyridin-4-one (**112**) (18.0 g, crude) and methyl cinnamate (**55**) (77.8 g, 480 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated with 400 W UV light for 15 h in a UV reactor flask. Then, the solvent was removed under reduced pressure, and the residue was purified over a plug of silica gel eluting with ethyl acetate. The desired fractions were concentrated under reduced pressure to afford product **S57** (15.0 g, crude). The crude compound (**S57**) was suspended in methanol (30 mL), treated with 25% sodium methoxide in methanol (30 mL, 28 g solution; 7.0 g, 0.13 mol NaOMe), and the mixture was heated at 70 °C for 1 h. Then, the solvent was removed under reduced pressure. The crude product was treated with ammonium chloride solution and extracted with EtOAc. The organic phase was dried over sodium sulfate and concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-3-(benzyloxy)-8a-hydroxy-5a-(4-methoxyphenyl)-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*b*]pyridine-7-carboxylate (**S58**) (12.5 g, crude). The crude product (**S58**) was added to a solution of sodium triacetoxyborohydride (14.8 g, 69.8 mmol) in acetonitrile (130 mL) and acetic acid (13.93 mL, 23.27 mmol). The resulting mixture was stirred for 6 h at room temperature, then partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography eluting with 50−70% ethyl acetate in hexanes. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-(benzyloxy)-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*b*]pyridine-7-carboxylate (**113**) as a pale brown solid. Yield: 4.5 g. UPLC: 70.6%; MS (ESI) *m*/*z*: 540.25 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.94 (d, *J* = 2.4 Hz, 1H), 7.68−7.34 (m, 5H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.09−6.92 (m, 5H), 6.79 (d, *J* = 8.4 Hz, 2H), 6.59 (d, *J* = 8.8 Hz, 2H), 5.72 (s, 1H), 5.50 (d, *J* = 5.2 Hz, 1H), 4.96 (s, 2H), 4.67 (t, *J* = 5.6 Hz, 1H), 4.34 (d, *J* = 14.0 Hz, 1H), 4.03 (dd, *J* = 5.6 Hz, 14.0 Hz, 1H), 3.36 (s, 3H), 3.32 (s, 3H).

*rac-Methyl (5aR,6S,7R,8R,8aS)-3,8,8a-Trihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo-[3,2-b]pyridine-7-carboxylate (**S59**).* A flask was charged with *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-(benzyloxy)-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*b*]pyridine-7-carboxylate (**113**) (3.0 g, from previous step; used without further purification) in ethyl acetate (300 mL) at room temperature, and palladium(II) hydroxide (50% wet) (0.195 g) was added. The reaction mixture was flushed with hydrogen twice and stirred under hydrogen pressure at room temperature for 16 h. Then, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to afford methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3,8,8a-trihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-

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tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S59**) as a brown solid. Yield: 2.8 g (6.2 mmol, 7% over steps). UPLC: 99.0%; MS (ESI) *m*/*z*: 450.17 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 9.95 (s, 1H), 7.77 (s, 1H), 7.06−6.97 (m, 5H), 6.91 (d, *J* = 7.6 Hz, 2H), 6.08 (s, 1H), 6.58 (d, *J* = 8.8 Hz, 2H), 5.61 (s, 1H), 5.41 (d, *J* = 5.2 Hz, 1H), 4.66 (t, *J* = 5.6 Hz, 1H), 4.30 (d, *J* = 14.0 Hz, 1H), 4.04 (dd, *J* = 5.2 Hz, 13.6 Hz, 1H), 3.58 (s, 3H), 3.54 (s, 3H).

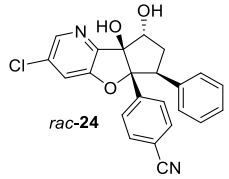
*rac-Methyl (5aR,6S,7R,8R,8aS)-8,8a-Dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-3-((trifluoromethyl)sulfonyl)oxy)-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**S60**).* A flask containing methylene chloride (300 mL) was charged with methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3,8,8a-trihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S59**) (2.2 g, 5.0 mmol), and DIPEA (0.94 g, 7.3 mmol) was added under nitrogen. The mixture was cooled to −78 °C, and triflic anhydride (1.79 g, 6.34 mmol) was added slowly. The reaction mixture was stirred for 30 min at −78 °C, brought to room temperature, and then stirred for 1 h. Then, the reaction was quenched with saturated $NaHCO_3$ solution at 0 °C. Methylene chloride (300 mL) was added. The organic layer was separated and washed first with water (2 × 50 mL) and then with brine (50 mL). The organic layer was separated again, dried over sodium sulfate, and concentrated. The solid was triturated with pentane, filtered, and dried under vacuum to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-3-((trifluoromethyl)sulfonyl)oxy)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S60**) as a brown solid. Yield: 2.5 g, crude. LCMS: 72.6%; MS (ESI) *m*/*z*: 582.05 $[M + 1]^+$.

*rac-Methyl (5aR,6S,7R,8R,8aS)-3-cyano-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-carboxylate (**S61**).* To a solution of crude methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-3-((trifluoromethyl)sulfonyl)oxy)-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S60**) (0.5 g) in dimethylformamide at room temperature, zinc cyanide (0.6 g, 5.1 mmol) and zinc (0.067 g, 0.102 mmol) were added. The reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (0.023 g, 0.041 mmol) and tris-(dibenzylideneacetone)dipalladium (0.025 g, 0.027 mmol) were added. Degassing was continued for 5 min, after which the mixture was heated at 140 °C for 1 h. After this time, the reaction was cooled to room temperature and filtered through Celite. The filtrate was concentrated and treated with ice-cold water. The resulting precipitate was collected by filtration and purified by reverse-phase prep HPLC. The desired fractions were concentrated under vacuum to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-cyano-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate as a yellow solid. Yield: 150 mg. UPLC: 82.1%; MS (ESI) *m*/*z*: 459.19 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.59 (s, 1H), 7.96 (s, 1H), 7.06−7.02 (m, 2H), 6.96−6.89 (m, 5H), 6.56 (d, *J* = 9.2 Hz, 2H), 6.19 (s, 1H), 5.78 (d, *J* = 5.2 Hz, 1H), 4.66 (d, *J* = 4.4 Hz, 1H), 4.46 (d, *J* = 13.6 Hz, 1H), 4.11 (t, *J* = 4.8 Hz, 1H), 3.56 (s, 6H).

*rac-(5aR,6S,7R,8R,8aS)-3-Cyano-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylic Acid (**S62**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-cyano-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S61**) (0.42 g, from previous step; used without further purification) in tetrahydrofuran and water (3:1, 12 mL), lithium hydroxide (0.066 g, 2.76 mmol) was added. The reaction mixture was stirred for 6 h at room temperature, then cooled to 0 °C, and acidified with 1 N citric acid to pH ≈ 5. The resulting precipitate was collected by filtration and dried under vacuum to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-cyano-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid as an off-white solid. Yield: 0.3 g (crude). UPLC: 49%; MS (ESI) *m*/*z*: 443.19 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.1 (br s, 1H), 8.60 (s, 1H), 8.11 (s, 1H), 7.41−6.79 (m, 7H), 6.57 (d, *J* = 8.8 Hz, 2H), 6.16 (s, 1H), 5.75 (br s, 1H), 4.66 (s, 1H), 4.44 (d, *J* = 14.0 Hz, 1H), 4.04 (dd, *J* = 4.8 Hz, 13.6 Hz, 1H), 3.59 (s, 3H).

*(5aR,6S,7R,8R,8aS)-3-Cyano-8,8a-dihydroxy-5a-(4-methoxyphenyl)-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**16**).* To a solution of crude *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-cyano-8,8a-dihydroxy-5a-(4-methoxyphenyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**S62**) (0.3 g) in methylene chloride (30 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (0.388 g, 2.50 mmol), hydroxybenzotriazole (0.27 g, 2.0 mmol) and DIPEA (0.52 mg, 4.02 mmol) were added. The mixture was stirred for 5 min. Dimethylamine hydrochloride (0.274 g, 3.36 mmol) was then added at same temperature and the mixture was stirred for 12 h at room temperature. Then, the reaction mass was diluted with methylene chloride and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to give the crude product, which was purified by silica gel column chromatography eluting with 70−90% ethyl acetate in hexanes to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-cyano-8,8a-dihydroxy-5a-(4-methoxyphenyl)-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (*rac*-**16**) as a white solid. Yield: 250 mg (0.530 mmol, 19% over 4 steps). The enantiomers were separated by chiral preparative HPLC [Chiralpak IB (4.6 × 250) mm]. Peak 1 (35 mg, (−)-**16**), $[\alpha]_D$ −172.0° (*c* 0.1, $CHCl_3$), R_t 6.54, ee >99%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.60 (s, 1H), 8.00 (s, 1H), 7.07−7.00 (m, 4H), 6.97 (d, *J* = 7.0 Hz, 1H), 6.91 (d, *J* = 7.2 Hz, 2H), 6.09 (s, 1H), 5.34 (d, *J* = 5.4 Hz, 1H), 4.76 (s, 1H), 4.54 (d, *J* = 12.8 Hz, 1H), 4.25 (dd, *J* = 13.5, 5.2 Hz, 1H), 3.59 (s, 3H), 3.26 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.12, 157.65, 156.18, 152.31, 145.25, 138.57, 128.52, 127.91, 127.62, 127.37, 125.68, 119.41, 117.21, 111.96, 108.53, 101.95, 90.83, 78.05, 56.19, 54.77, 48.55, 36.58, 35.24; MS (ESI) *m*/*z*: 472.33 $[M + 1]^+$; HRMS (ESI): calcd, 472.1867 $[M + H]^+$; found, 472.1863; UPLC: 98.98%. Peak-2 (35 mg, (+)-**16**), $[\alpha]_D$ +152.0° (*c* 0.1, $CHCl_3$), R_t 10.65, ee >99%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.60 (d, *J* = 1.4 Hz, 1H), 8.00 (d, *J* = 1.4 Hz, 1H), 7.05−7.01 (m, 4H), 6.97 (d, *J* = 7.2 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 2H), 6.61 (d, *J* = 8.8 Hz, 2H), 6.09 (s, 1H), 5.34 (d, *J* = 5.6 Hz, 1H), 4.76 (t, *J* = 5.2 Hz, 1H), 4.54 (d, *J* = 13.2 Hz, 1H), 4.25 (dd, *J* = 13.2, 5.2 Hz, 1H), 3.59 (s, 3H), 3.26 (s, 3H), 2.77 (s, 3H); MS (ESI) *m*/*z*: 472.34 $[M + 1]^+$; UPLC: 99.58%.

Synthesis of rac-(5aR,6S,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-b]-



rac-**24**

*pyridine-8,8a-diol (rac-**24**). rac-2-Thioxopyridin-1(2H)-yl (5aR,6S,7R,8R,8aS)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]-pyridine-7-carboxylate (**115**).* To a mixture of *rac*-(5a*R*,6*S*,7*R*,8-*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**104**) (350 mg, 0.70 mmol) and 1-hydroxypyridine-2(1*H*)-thione (**114**) (443 mg, 3.48 mmol) in DCM (10 mL) was added *N*,*N*′-Dicyclohexylcarbodiimide (0.16 mL, 1.04 mmol), and the mixture was stirred vigorously for 4 h. LCMS analysis showed complete consumption of the acid starting material and desired product was observed. The reaction mixture was filtered to remove the urea and concentrated to provide the crude desired product, *rac*-2-thioxopyridin-1(2*H*)-yl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**115**). MS (ESI) *m*/*z*: 611.2 $[M + 1]^+$. The crude product was used directly in the following step.

*rac-(5aR,6S,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-b]pyridine-8,8a-diol (**116**).* The crude *rac*-2-thioxopyridin-1(2*H*)-yl (5a*R*,6*S*,7*R*,8-

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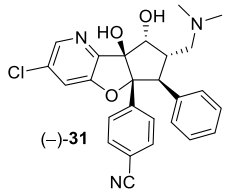
R,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (115) in benzene (50 mL) was treated with tributylstannane (0.55 mL, 2.03 mmol) and azobisisobutyronitrile (22 mg, 0.14 mmol). The mixture was heated at 80 °C and stirred vigorously in the absence of light for 3 h. After this time, the reaction mixture was concentrated *in vacuo*, redissolved in *N*,*N*-dimethylformamide, and filtered through a 5-μm membrane. The crude material was purified by reverse-phase HPLC to afford *rac*-(5a*R*,6*S*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-8,8a-diol (116) as a white solid. Yield: 0.031 g (0.068 mmol, 10%). MS (ESI) *m*/*z*: 460.1 $[M + 1]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 8.23 (s, 1H), 7.69 (s, 1H), 7.30−7.26 (m, 2H), 7.21−7.13 (m, 3H), 7.05−7.01 (m, 4H), 5.01 (dd, *J* = 5.7, 3.4 Hz, 1H), 4.20 (dd, *J* = 11.6, 6.7 Hz, 1H), 2.89−2.78 (m, 1H).

*rac-4-((5aR,6S,8R,8aS)-3-Chloro-8,8a-dihydroxy-6-phenyl-6,7,8,8a-tetrahydro-5aH-cyclopenta[4,5]furo[3,2-b]pyridin-5a-yl)-benzonitrile (rac-**24**).* To a solution of *rac*-(5a*R*,6*S*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-8,8a-diol (**116**) (10.9 mg, 0.0238 mmol) in *N*,*N*-dimethylformamide (3 mL), zinc cyanide (17 mg, 0.14 mmol) and zinc (1 mg, 0.015 mmol) were added and the mixture was degassed with nitrogen for 15 min. 1,1′-Bis(diphenylphosphino)-ferrocene (1 mg, 0.0015 mmol) and tris(dibenzylideneacetone)-dipalladium (1 mg, 0.0011 mmol) were added to the above reaction, and degassing was continued for another 5 min followed by heating at 140 °C for 1 h. After completion, the reaction mixture was cooled to room temperature and filtered. The filtrate was purified by reverse-phase prep HPLC to provide the desired product then purified by preparatory thin-layer chromatography (DCM/MeOH) and prep HPLC to afford *rac*-4-((5a*R*,6*S*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-6-phenyl-6,7,8,8a-tetrahydro-5a*H*-cyclopenta[4,5]furo[3,2-*b*]pyridin-5a-yl)benzonitrile (*rac*-**24**) as a white powder. Yield: 0.0015 g (0.0037 mmol, 16%). MS (ESI) *m*/*z*: 405.1 $[M + 1]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 8.21 (s, 1H), 7.62 (s, 1H), 7.47−7.38 (m, 2H), 7.36−7.26 (m, 2H), 7.17−7.12 (m, 3H), 7.01−6.97 (m, 2H), 5.00 (dd, *J* = 5.7, 2.7 Hz, 1H), 4.23 (dd, *J* = 12.4, 6.7 Hz, 1H), 2.87 (td, *J* = 13.2, 5.6 Hz, 1H), 2.38−2.30 (m, 1H).

Synthesis of (5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-



*cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**31**). rac-(5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]-furo[3,2-b]pyridine-7-carboxamide (**S63**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**104**) (5.0 g, 10.0 mmol) in dichloromethane (100 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (5.73 g, 36.9 mmol), hydroxybenzotriazole (4.58 g, 29.9 mmol), and *N*,*N*-diisopropylethylamine (12.16 mL, 9.023 g, 69.80 mmol) were added. The mixture was stirred for 5 min. Dimethylamine hydrochloride (4.06 g, 49.8 mmol) was then added at the same temperature, and the reaction was stirred for 16 h at room temperature. The reaction mass was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, which was purified by silica gel column chromatography eluting with 1−5% methanol in dichloromethane. The desired fractions were concentrated to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (**S63**) as a white solid. Yield: 4.0 g (7.6 mmol, 76%). MS (ESI) *m*/*z*: 529.16 $[M + 1]^+$. 1H NMR (400 MHz, DMSO-d_6): δ/ppm 8.19 (s, 1H), 7.69 (s, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.09−7.02 (m, 4H), 6.97 (d, *J* = 6.9 Hz, 1H), 6.92 (d, *J* = 6.9 Hz, 1H), 6.04 (s, 1H), 5.75 (s, 1H), 5.28 (d, *J* = 5.6 Hz, 1H), 4.72 (d, *J* = 5.2 Hz, 1H), 4.57 (d, *J* = 13.0 Hz, 1H), 4.25 (dd, *J* = 14.1 Hz, 5.3 Hz, 1H), 3.26 (s, 3H), 2.77 (s, 3H).

*rac-(5aR,6S,7S,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-7-((dimethylamino)methyl)-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-b]pyridine-8,8a-diol (**117**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxamide (**S63**) (2.0 g, 3.8 mmol) in dry tetrahydrofuran (30 mL) at 0 °C, borane dimethyl sulfide complex (3.59 mL, 3.16 g, 41.6 mmol) was added dropwise over a period of 5 min. The reaction mixture was slowly brought to room temperature and stirred for additional 16 h. After this time, the reaction mixture was quenched with methanol at 0 °C and heated to reflux for 5 h. Then, solvent was removed under reduced pressure, and the residue was purified over a plug of silica gel eluting with 1−5% methanol in dichloromethane. The desired fractions were concentrated under reduced pressure to afford *rac*-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-7-((dimethylamino)methyl)-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-8,8a-diol (**117**) as a white solid. Yield: 1.2 g (2.3 mmol, 61%). MS (ESI) *m*/*z*: 515.32 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.16 (s, 1H), 7.92 (s, 1H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.12-7.08-7.02 (m, 7H), 6.01 (s, 1H), 4.45 (s, 1H), 3.87 (d, *J* = 14.1 Hz, 1H), 3.31−3.19 (m, 1H), 2.73−2.66 (m, 1H), 2.25 (s, 6H), 2.02−1.92 (m, 1H)

*4-((5aR,6S,7S,8R,8aS)-3-Chloro-7-((dimethylamino)methyl)-8,8a-dihydroxy-6-phenyl-6,7,8,8a-tetrahydro-5aH-cyclopenta[4,5]-furo[3,2-b]pyridin-5a-yl)benzonitrile ((−)-**31**).* To a solution of *rac*-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-7-((dimethylamino)methyl)-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-8,8a-diol (**117**) (1.2 g, 2.3 mmol) in *N*,*N*-dimethylformamide (48 mL) at room temperature, zinc cyanide (0.273 g, 2.32 mmol) and zinc dust (0.304 g, 4.65 mmol) were added. The reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (0.025 g, 0.046 mmol) and tris(dibenzylideneacetone)dipalladium (0.064 g, 0.069 mmol) were added to the reaction. Degassing was continued for an additional 5 min, and the mixture was heated at 130 °C for 4 h. After this time, the reaction mixture was diluted with ethyl acetate and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to give the crude product which was purified by silica gel column chromatography eluting with 2−3% methanol in dichloromethane. The desired fractions were concentrated to afford 4-((5a*R*,6*S*,7*S*,8*R*,8a*S*)-3-chloro-7-((dimethylamino)methyl)-8,8a-dihydroxy-6-phenyl-6,7,8,8a-tetrahydro-5a*H*-cyclopenta[4,5]furo[3,2-*b*]-pyridin-5a-yl)benzonitrile (*rac*-**31**) as a white solid. Yield: 0.49 g (1.1 mmol, 46%). MS (ESI) *m*/*z*: 462.23 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.18 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.12−6.95 (m, 5H), 6.13 (s, 1H), 5.34 (br s, 1H), 4.44 (br s, 1H), 3.94 (d, *J* = 13.2 Hz, 1H), 3.28−3.17 (m, 1H), 2.61 (dd, *J* = 12.3, 10.0 Hz, 1H), 2.21 (s, 6H), 1.97 (dd, *J* = 12.3, 3.0, 1H);

^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 153.09, 150.08, 142.20, 140.44, 136.87, 130.61, 130.17, 128.76, 128.39, 127.75, 126.35, 118.84, 116.68, 109.02, 102.85, 91.17, 78.26, 57.75, 56.27, 45.93, 43.92. The enantiomers were separated by chiral HPLC [Chiralpak IA (4.6 × 250) mm, 5μ], *n*-hexane/EtOH 20/80 V/V. Peak-1 (137 mg, (−)-**31**), $[\alpha]_D$ −110.4° (*c* 0.26, $CHCl_3$), R_t 4.580 min, ee: 98.5% MS (ESI) *m*/*z*: 462.23 $[M + 1]^+$; HRMS (ESI): calcd, 462.1579 $[M + H]^+$; found, 462.1581; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.18 (d, *J* = 1.6 Hz, 1H), 7.63 (d, *J* = 1.7 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.15−6.98 (m, 5H), 6.12 (s, 1H), 5.41 (br s, 1H), 4.45 (s, 1H), 3.93 (d, *J* = 13.9 Hz, 1H), 3.24 (br s, 1H), 2.66 (s, 1H), 2.59 (s, 1H), 2.25 (s, 6H). Peak-2 (133 mg, (+)-**31**), $[\alpha]_D$ +105.4° (*c* 0.25, $CHCl_3$), R_t 12.693 min, ee: 99.9%, MS (ESI) *m*/*z*: 462.23 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.18 (d, *J* = 1.6 Hz, 1H), 7.63 (d, *J* = 1.7 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.15−6.98 (m, 5H), 6.12 (s, 1H), 5.41 (br s, 1H), 4.45 (s, 1H), 3.93

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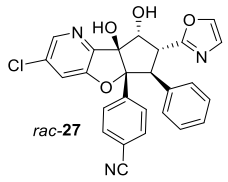
(d, J = 13.9 Hz, 1H), 3.24 (br s, 1H), 2.66 (s, 1H), 2.59 (s, 1H), 2.25 (s, 6H).

Synthesis of 4-((5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-7-(oxazol-2-yl)-6-phenyl-6,7,8,8a-tetrahydro-5aH-cyclopenta[4,5]-



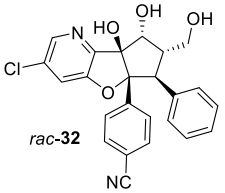
*furo[3,2-b]pyridin-5a-yl)benzonitrile (rac-**27**).* *rac-(5aR,6S,7R,8-R,8aS)-5a-(4-Bromophenyl)-3-chloro-N-(2,2-diethoxyethyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo-[3,2-b]pyridine-7-carboxamide (**119**).* To a solution of (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**104**) (1.4 g, 2.8 mmol) in dichloromethane (20 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (1.6 g, 8.3 mmol), 1-hydroxybenzotriazole (1.13 g, 8.36 mmol), and *N*,*N*-diisopropylethylamine (2.88 mL, 2.14 g, 16.5 mmol) were added. The reaction mixture was stirred for 5 min. Then, 2,2-diethoxyethan-1-amine (**118**) (2.35 g, 17.6 mmol) was added at same temperature and the reaction mixture was stirred at 35 °C for 16 h. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by Combiflash (12 g, RediSep column) using 2% methanol in dichloromethane as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-*N*-(2,2-diethoxyethyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (**119**) as a light brown oil. Yield: 1.1 g (1.8 mmol, 64%). MS (ESI) m/z: 617.12 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.35 (t, J = 5.6 Hz, 1H), 8.19 (d, J = 1.8 Hz, 1H), 7.68 (d, J = 1.9 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H), 7.07−6.98 (m, 7H), 6.07 (s, 1H), 5.09 (d, J = 4.2 Hz, 1H), 4.54−4.51 (m, 2H), 4.36 (t, J = 5.3 Hz, 1H), 4.3 (dd, J = 14.0, 4.0 Hz, 1H), 3.55−3.49 (m, 2H), 3.42−3.35 (m, 2H), 3.17−3.07 (m, 2H), 1.12−1.05 (m, 6H).

*rac-(5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-8,8a-dihydroxy-N-(2-oxoethyl)-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide (**S65**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-*N*-(2,2-diethoxyethyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (**119**) (1.0 g, 1.6 mmol) in tetrahydrofuran (5.0 mL), 2 N hydrochloric acid (5.0 mL) was added. The reaction mixture was stirred for 4 h at room temperature. After this time, the reaction mass diluted with ethyl acetate and the organic layer was separated and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-*N*-(2-oxoethyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (**S65**) as a white solid. Yield: 0.91 g, crude, MS (ESI) m/z: 543.23 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 9.32 (s, 1H), 8.68 (t, J = 5.3 Hz, 1H), 8.2 (d, J = 1.9 Hz, 1H), 7.69 (d, J = 1.9 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H), 7.08−6.95 (m, 7H), 6.09 (br s, 1H), 4.6−4.53 (m, 2H), 4.1−4.03 (m, 1H), 3.84−3.81 (m, 2H).

*rac-(5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-7-(oxazol-2-yl)-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-b]-pyridine-8,8a-diol (**S66**).* To a solution of crude *rac*-(5a*R*,6*S*,7*R*,8-*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-*N*-(2-oxoethyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (**S65**) (0.9 g) in dichloromethane (20.0 mL), triphenylphosphine (0.87 g, 3.3 mmol), iodine (0.83 g, 3.3 mmol) and triethylamine (0.86 mL, 0.62 g, 6.2 mmol) were added. The reaction mixture was stirred at room temperature for 16 h. After this time, the reaction mixture was diluted with dichloromethane and the organic layer was washed with water (2 × 20 mL) and brine (20 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated to dryness. The crude product was purified by Combiflash (4 g, RediSep column) using 2% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-7-(oxazol-2-yl)-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-8,8a-diol (**S66**) as an off-white solid. Yield: 0.18 g (0.34 mmol, 21% over two steps). MS (ESI) m/z: 525.15 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.19 (s, 1H), 7.92 (s, 1H), 7.71 (s, 1H), 7.21 (d, J = 8.4 Hz, 2H), 7.1 (d, J = 8.4 Hz, 2H), 7.04−7.0 (m, 3H), 6.96 (d, J = 6.4 Hz, 3H), 6.24 (s, 1H), 5.52 (d, J = 5.0 Hz, 1H), 4.79 (d, J = 14.4 Hz, 1H), 4.61−4.58 (m, 1H), 3.10 (br s, 1H).

*rac-4-((5aR,6S,7R,8R,8aS)-3-Chloro-8,8a-dihydroxy-7-(oxazol-2-yl)-6-phenyl-6,7,8,8a-tetrahydro-5aH-cyclopenta[4,5]furo[3,2-b]-pyridin-5a-yl)benzonitrile (rac-**27**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-7-(oxazol-2-yl)-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-8,8a-diol (**S65**) (0.06 g, 0.11 mmol) in *N*,*N*-dimethylformamide (1.0 mL) at room temperature, zinc cyanide (0.012 g, 0.10 mmol) and zinc (0.014 g, 0.21 mmol) were added. The mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (0.0013 g, 0.024 mmol) and tris(dibenzylideneacetone)-dipalladium (0.0026 g, 0.0028 mmol) were added to the reaction mixture, and degassing was continued for another 5 min. The reaction mixture was heated at 150 °C for 2 h. After this time, the reaction was cooled to room temperature and filtered with Celite. The filtrate was diluted with ethyl acetate and washed with water. The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure to obtain the crude product, which was purified by Combiflash (4 g, RediSep column) using 2% methanol in dichloromethane as the eluent. The desired fractions were concentrated under reduced pressure. The compound thus obtained was further purified by reverse-phase HPLC. The desired fractions were collected and lyophilized to afford *rac*-4-((5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-7-(oxazol-2-yl)-6-phenyl-6,7,8,8a-tetrahydro-5a*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridin-5a-yl)benzonitrile (*rac*-**27**) as a white solid. Yield: 0.012 g (0.025 mmol, 23%). MS (ESI) m/z: 472.40 $[M + 1]^+$; HRMS (ESI): calcd, 472.1059 $[M + H]^+$; found, 472.1064; UPLC: 99.63%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (d, J = 2.0 Hz, 1H), 7.94 (s, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.04−6.94 (m, 6H), 6.36 (br s, 1H), 5.60 (br s, 1H), 4.85 (d, J = 14.0 Hz, 1H), 4.68 (dd,, J = 14.0, 4.2 Hz, 1H), 4.60 (d, J = 4.1 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 161.42, 153.44, 149.12, 141.78, 140.83, 139.60, 136.85, 131.01, 130.30, 128.39, 128.01, 127.69, 126.85, 126.28, 118.74, 117.11, 109.24, 102.04, 91.32, 79.66, 56.26, 46.05.

Synthesis of rac-((5aR,6S,7S,8R,8aS)-3-Chloro-8,8a-dihydroxy-7-(hydroxymethyl)-6-phenyl-6,7,8,8a-tetrahydro-5aH-cyclopenta-



*[4,5]furo[3,2-b]pyridin-5a-yl)benzonitrile (rac-**32**).* *rac-(5aR,6S,7S,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-7-(hydroxymethyl)-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-b]-pyridine-8,8a-diol (**S64**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8-*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**103**) (320 mg, 0.619 mmol) in tetrahydrofuran (4 mL) at 0 °C was added lithium aluminum hydride (LAH) (27 mg, 0.71 mmol) and the mixture was stirred at 0 °C for 30 min and then warmed up to rt. After another 1.5 h, another 13 mg (0.34 mmol) of LAH was added and stirring at room temperature was continued. After another 30 min, another 13 mg (0.34 mmol) of LAH was added. After 3 h (total reaction time), water and brine were carefully added, and the mixture

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was diluted with ethyl acetate. The phases were separated and the aq phase was extracted with ethyl acetate thrice. The combined organic phases were washed with brine, then dried (sodium sulfate), filtered, and concentrated. The crude product was purified by column chromatography (silica, methanol/dichloromethane, product eluted at 5% methanol). Yield: 165 mg, *ca.* 90% pure, *ca.* 49% yield; *ca.* 25 mg of this material were repurified by HPLC (C18, acetonitrile/water +0.1% trifluoroacetic acid) to give *rac*-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-7-(hydroxymethyl)-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-8,8a-diol (**S64**) as a fluffy white solid. MS (ESI) *m*/*z*: 487.9 $[M + 1]^+$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.17 (d, *J* = 2.1 Hz, 1H), 7.61 (d, *J* = 2.1 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.14−6.97 (m, 7H), 4.50 (d, *J* = 3.8 Hz, 1H), 3.88 (d, *J* = 14.2 Hz, 1H), 3.55 (dd, *J* = 10.6, 9.1 Hz, 1H), 3.43 (dd, *J* = 10.6, 3.1 Hz, 1H), 3.21−3.09 (m, 1H).

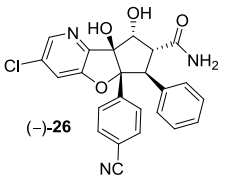
*rac-4-((5aR,6S,7S,8R,8aS)-3-Chloro-8,8a-dihydroxy-7-(hydroxymethyl)-6-phenyl-6,7,8,8a-tetrahydro-5aH-cyclopenta[4,5]furo[3,2-b]pyridin-5a-yl)benzonitrile (rac-**32**).* In a 0.5−2 mL microwave vial, *rac*-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-7-(hydroxymethyl)-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-8,8a-diol (**S64**) (24.7 mg, 0.0505 mmol) was dissolved in *N*,*N*-dimethylformamide (0.50 mL) and water (0.05 mL). Zinc cyanide (19 mg, 0.16 mmol) and zinc (1.8 mg, 0.028 mmol) were added, and the mixture was degassed by bubbling argon through it for 5 min. 1,1′-Bis(diphenylphosphino)ferrocene (2.7 mg, 0.0049 mmol) and tris(dibenzylideneacetone)dipalladium(0) (2.8 mg, 0.0030 mmol) were added, and the mixture was incubated at 100 °C for 30 min. Then, the mixture was diluted with ethyl acetate and washed with water. The organic phase was dried (sodium sulfate), filtered, and concentrated. Purification by column chromatography (silica, methanol/dichloromethane, product eluted at 5% methanol) and subsequently by HPLC (C18, acetonitrile/water +0.1% trifluoroacetic acid) gave *rac*-4-((5a*R*,6*S*,7*S*,8*R*,8a*S*)-3-chloro-8,8a-dihydroxy-7-(hydroxymethyl)-6-phenyl-6,7,8,8a-tetrahydro-5a*H*-cyclopenta[4,5]furo[3,2-*b*]pyridin-5a-yl)benzonitrile (*rac*-**32**). Yield: 15.5 mg (0.0356 mmol, 71%); MS (ESI) *m*/*z*: 435.3 $[M + 1]^+$; HRMS (ESI): calcd, 435.1106 $[M + H]^+$; found, 435.1112; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.19 (d, *J* = 2.0 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.14−6.96 (m, 5H), 4.52 (d, *J* = 3.9 Hz, 1H), 3.94 (d, *J* = 14.1 Hz, 1H), 3.57 (dd, *J* = 10.7, 9.6 Hz, 1H), 3.45 (dd, *J* = 10.7, 2.9 Hz, 1H), 3.26−3.14 (m, 1H).

*Synthesis of (5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**26**).* *rac-Methyl (5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylate (**S67**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**103**) (0.45 g, 0.87 mmol) in *N*,*N*-dimethylformamide (5 mL) at room temperature, zinc cyanide (0.113 g, 0.962 mmol) and zinc (0.28 g, 4.2 mmol) were added. The mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (0.012 g, 0.022 mmol) and tris(dibenzylideneacetone)dipalladium (0.023 g, 0.025 mmol) were added to the reaction mixture, and degassing was continued for 5 min. The reaction mixture was heated at 125 °C for 3 h. After this time, the reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated to obtain the crude product. This was purified by Combiflash (12 g, RediSep column) using 70% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S67**) as a white solid. Yield: 0.31 g (0.67 mmol, 77%). MS (ESI) *m*/*z*: 463.15 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.21 (s, 1H), 7.72 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.08−6.87 (m, 5H), 6.26 (s, 1H), 5.80 (d, *J* = 5.7 Hz, 1H), 4.65−4.63 (m, 1H), 4.58−4.54 (m, 1H), 4.26−4.21 (m, 1H), 3.58 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxylic Acid (**120**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**S67**) (0.3 g, 0.6 mmol) in methanol and water (3:1, 10 mL), lithium hydroxide (0.077 g, 3.2 mmol) was added. This reaction mixture was stirred for 6 h at room temperature. After completion, the reaction mixture was cooled to 0 °C and acidified with 5% citric acid to pH ≈ 6. The resulting precipitate was collected by filtration and dried under vacuum to afford *rac*-5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**120**) as a white solid. Yield: 0.21 g (0.47 mmol, 78%). MS (ESI) *m*/*z*: 449.0 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (s, 1H), 7.71 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.08−6.97 (m, 5H), 6.19 (s, 1H), 4.62 (d, *J* = 4 Hz, 1H), 4.53 (d, *J* = 13.8 Hz, 1H), 4.06 (d, *J* = 12.6 Hz, 1H), 3.60 (br s, 1H)

*rac-(5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**26**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylic acid (**120**) (0.18 g, 0.40 mmol) in dichloromethane (5 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.16 g, 0.83 mmol), 1-hydroxybenzotriazole (0.108 g, 0.799 mmol), and *N*,*N*-diisopropylethylamine (0.2 mL, 0.1 g, 1 mmol) were added. The reaction mixture was stirred for 5 min. Then, ammonium chloride (0.21 g, 3.9 mmol) was then added at same temperature and the mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by Combiflash (4 g, RediSep column) using 70% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated under reduced pressure to afford racemic (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxamide (*rac*-**26**) as an off-white solid. Yield: 0.14 g (0.31 mmol, 78%). MS (ESI) *m*/*z*: 448.12 $[M + 1]^+$. The enantiomers were separated by chiral preparative HPLC [Chiralpak IB (4.6 × 250) mm]. Peak-1 (5 mg, (−)-**26**); $[\alpha]_D$ −184.2° (*c* 0.27, DMSO); R_t 6.41 min, ee >99%; MS (ESI) *m*/*z*: 448.38 $[M + 1]^+$; HRMS (ESI): calcd, 448.1059 $[M + H]^+$; found, 448.1078; UPLC 97.6%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (d, *J* = 1.8 Hz, 1H), 7.70 (d, *J* = 1.8 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.10−6.96 (m, 5H), 6.16 (s, 1H), 5.31 (d, *J* = 4.5 Hz, 1H), 4.58−4.55 (m, 1H), 3.97 (dd, *J* = 14.0, 4.1 Hz, 1H). Peak-2 (7 mg, (+)-**26**); $[\alpha]_D$ +128.8° (*c* 0.26, DMSO); R_t 11.06 min, ee >99%; MS (ESI) *m*/*z*: 448.37 $[M + 1]^+$; UPLC 99.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 (d, *J* = 1.9 Hz, 1H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.09−6.96 (m, 5H), 6.16 (s, 1H), 5.31 (d, *J* = 4.5 Hz, 1H), 4.57 (m, *J* = 7.8 Hz, 2H), 3.97 (dd, *J* = 13.8, 4.2 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.45, 153.44, 149.22, 142.05, 140.64, 137.45, 130.93, 130.27, 128.16, 127.93, 127.60, 126.16, 118.73, 117.04, 109.16, 102.16, 91.48, 79.47, 56.08, 50.96.

*Synthesis of (5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-N-methyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**25**).* *(5aR,6S,7R,8R,8aS)-3-Chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-N-methyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-carboxamide ((−)-**25**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-



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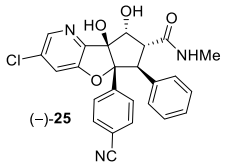
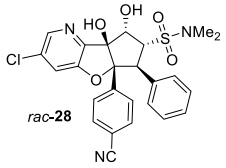


(−)-**25**

carboxylic acid (**120**) (0.13 g, 0.29 mmol) in dichloromethane (10 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.13 g, 0.67 mmol), 1-hydroxybenzotriazole (0.12 g, 0.89 mmol) and *N*,*N*-diisopropylethylamine (0.5 mL, 0.4 g, 3 mmol) were added. The reaction mixture was stirred for 5 min. Then, methylamine hydrochloride (0.097 g, 1.4 mmol) was added at same temperature and the mixture was stirred for 16 h at 40 °C. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford racemic (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-*N*-methyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]-pyridine-7-carboxamide (*rac*-**25**) as a brown solid. Yield: 120 mg (0.260 mol, 90%). The enantiomers were separated by chiral preparative HPLC [Chiralpak IC (4.6 × 250) mm]. Peak 1 (22 mg, (+)-**25**); $[\alpha]_D$ +51.4° (*c* 0.14, $CHCl_3$); R_t 5.66 min, ee >99%; MS (ESI) *m*/*z*: 462.41 $[M + 1]^+$; UPLC: 99.09%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (d, *J* = 2.0 Hz, 1H), 8.17 (q, *J* = 4.3 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.08−6.96 (m, 5H), 6.19 (s, 1H), 5.29 (d, *J* = 4.5 Hz, 1H), 4.61 (d, *J* = 14.0 Hz, 1H), 4.52 (t, *J* = 4.4 Hz, 1H), 3.95 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.55 (d, *J* = 4.5 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 169.78, 153.41, 149.21, 141.98, 140.66, 137.32, 130.94, 130.27, 128.17, 127.88, 127.65, 126.21, 118.72, 117.05, 109.18, 102.10, 91.31, 79.51, 55.96, 51.24, 25.72. Peak-2 (18 mg, (−)-**25**); $[\alpha]_D$ −178° (*c* 0.13, $CHCl_3$); R_t 7.24 min, ee >99%; MS (ESI) *m*/*z*: 462.42 $[M + 1]^+$; HRMS (ESI): calcd, 462.1215 $[M + H]^+$; found, 462.1223; UPLC: 99.61%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (d, *J* = 2.0 Hz, 1H), 8.17 (q, *J* = 4.3 Hz, 1H), 7.71 (d, *J* = 1.9 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.08−6.96 (m, 5H), 6.19 (s, 1H), 5.29 (d, *J* = 4.5 Hz, 1H), 4.61 (d, *J* = 14.0 Hz, 1H), 4.52 (t, *J* = 4.4 Hz, 1H), 3.96 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.56 (d, *J* = 4.6 Hz, 3H).

Synthesis of (5aR,6S,7R,8S,8aS)-3-Chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-



rac-**28**

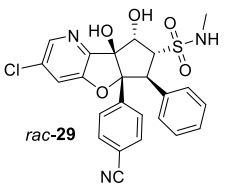
*cyclopenta[4,5]furo[3,2-b]pyridine-7-sulfonamide (rac-**28**). (6S,7S,8S,9R)-6-(4-Bromophenyl)-3-chloro-9-hydroxy-N,N-dimethyl-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-b]-pyridine-8-sulfonamide (**S68**).* A solution of 2-(4-bromophenyl)-7-chloro-3-hydroxy-4*H*-pyrano[3,2-*b*]pyridin-4-one (**102**) (1.5 g, 4.3 mmol) and (*E*)-*N*,*N*-dimethyl-2-phenylethene-1-sulfonamide (**121**) (4.50 g, 21.3 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated for 72 h under 400 W UV light in a UV reactor flask. After this time, the solvent was removed under reduced pressure. The crude product was purified by Combi-flash (4 g, RediSep column) using ethyl acetate as the eluent. The desired fractions were concentrated under reduced pressure to afford 5a-(4-bromophenyl)-3-chloro-7a-hydroxy-*N*,*N*-dimethyl-8-oxo-6-phenyl-5a,6,7a,8-tetrahydro-7*H*-cyclobuta[5,6]pyrano[3,2-*b*]pyridine-7-sulfonamide (**S68**) as a brown solid. Yield: 0.7 g, crude.

*rac-(5aR,6S,7R,8aR)-5a-(4-Bromophenyl)-3-chloro-8a-hydroxy-N,N-dimethyl-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-sulfonamide (**S69**).* The crude 5a-(4-bromophenyl)-3-chloro-7a-hydroxy-*N*,*N*-dimethyl-8-oxo-6-phenyl-5a,6,7a,8-tetrahydro-7*H*-cyclobuta[5,6]pyrano[3,2-*b*]pyridine-7-sulfonamide (**S68**) (0.7 g) was suspended in methanol (20 mL) and treated with 25% sodium methoxide (25% in methanol, 10 mL, 9.5 g solution, 2.4 g NaOMe, 44 mmol). The reaction mixture was heated at 80 °C for 2 h. Then, the solvent was removed under reduced pressure, and the reaction mixture was treated with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure to afford *rac*-(5a*R*,6*S*,7*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-*N*,*N*-dimethyl-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*b*]pyridine-7-sulfonamide (**4**) as a brown solid. Yield: 0.35 g, crude.

*rac-(5aR,6S,7R,8S,8aS)-5a-(4-Bromophenyl)-3-chloro-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-sulfonamide (**122**).* To a solution of sodium triacetoxyborohydride (1.27 g, 3.73 mmol) and crude (5a*R*,6*S*,7*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-*N*,*N*-dimethyl-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*b*]pyridine-7-sulfonamide (**S69**) (0.35 g) in acetonitrile (20 mL), acetic acid (4.0 mL, 4.2 g, 70 mmol) was added. The resulting mixture was stirred for 15 h at room temperature. After this time, reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure to obtain the crude product, which was purified by Combi-flash (4 g, RediSep column) using 50% ethyl acetate in hexanes as the eluent. The compound was further purified by reverse-phase HPLC. The desired fractions were concentrated under reduced pressure to afford *rac*-(5a*R*,6*S*,7*R*,8*S*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*b*]pyridine-7-sulfonamide (**122**) as a light yellow solid. Yield: 0.04 g (0.07 mmol, 2% over three steps). MS (ESI) *m*/*z*: 565.06 $[M + 1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.19 (s, 1H), 7.65 (s, 1H), 7.21 (s, 5H), 7.14−7.02 (m, 4H), 6.35 (br s, 1H), 5.91 (br s, 1H), 4.85 (dd, *J* = 13.4, 3.1 Hz, 1H), 4.64 (br s, 1H), 4.52 (d, *J* = 13.6, Hz, 1H), 2.44 (s, 6H).

*rac-(5aR,6S,7R,8S,8aS)-3-Chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-sulfonamide (rac-**28**).* To a solution of (5a*R*,6*S*,7*R*,8*S*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*b*]pyridine-7-sulfonamide (**122**) (0.03 g, 0.053 mmol) in *N*,*N*-dimethylformamide at room temperature, zinc cyanide (0.005 g, 0.043 mmol) and zinc (0.001 g, 0.015 mmol) were added. The reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (0.001 g, 0.001 mmol) and tris-(dibenzylideneacetone)dipalladium (0.002 g, 0.002 mmol) were added to the reaction mixture, and degassing was continued for 5 min. The reaction mixture was heated at 140 °C for 1 h. After this time, the reaction mixture was cooled to room temperature and filtered with Celite. The filtrate was purified by Combi-flash (4 g, RediSep column) using 10% methanol in dichloromethane as the eluent. Finally, the compound was purified by reverse-phase HPLC. The desired fractions were concentrated under reduced pressure to afford *rac*-(5a*R*,6*S*,7*R*,8-*S*,8a*S*)-3-chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-sulfonamide (*rac*-**28**) as an off-white solid. Yield: 0.002 g (0.004 mmol, 7%). MS (ESI) *m*/*z*: 512.45 $[M + 1]^+$; HRMS (ESI): calcd, 512.1041 $[M + H]^+$; found, 512.1039; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.20 (d, *J* = 1.9 Hz, 1H), 7.69 (d, *J* = 1.9 Hz, 1H), 7.49 (dd, *J* = 14.6 Hz, 8.9 Hz, 4H), 7.14 (d, *J* = 7.2 Hz, 2H), 7.08−6.99 (m, 3H), 6.44 (s, 1H), 5.97 (d, *J* = 6.2 Hz, 1H), 4.95 (dd, *J* = 13.8, 4.0 Hz, 1H), 4.65 (t, *J* = 6.0 Hz, 1H), 4.58 (d, *J* = 13.6, Hz, 1H), 2.46 (s, 6H).

Synthesis of (5aR,6S,7R,8S,8aS)-3-Chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-N-methyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-



rac-**29**

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*cyclopenta[4,5]furo[3,2-b]pyridine-7-sulfonamide (rac-**29**). (E)-N-Benzyl-N-methyl-2-phenylethene-1-sulfonamide (**123**).* (1) To a solution of styrene (**1**, 55.00 g, 528.1 mmol) in *N*,*N*-dimethylformamide (50 mL) at 0 °C, sulfuryl chloride (142.0 g, 1052 mmol) was added. This reaction mixture was stirred at room temperature for 2 h. After this time, the mixture was quenched with ice-cold water (500 mL) and extracted with ethyl acetate (1000 mL). The organic layer was washed with water and brine, separated, and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford (*E*)-2-phenylethene-1-sulfonyl chloride (**S71**) as a white solid. Yield: 90.0 g, crude. (2) To a solution of crude (*E*)-2-phenylethene-1-sulfonyl chloride (**S71**) (35.00 g) in dichloromethane (100 mL), triethylamine (25.0 mL, 18.1 g, 179 mmol) and *N*-methyl-1-phenylmethanamine (**S72**) (20 mL, 19 g, 160 mmol) were added. The reaction mixture was stirred at room temperature for 16 h. After this time, the solvent was removed under reduced pressure. The mixture was quenched with ice-cold aqueous sodium bicarbonate solution (300 mL) and extracted with ethyl acetate (1000 mL). The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product. This was purified by silica gel (100−200 mesh) column chromatography using 50% ethyl acetate in hexanes as eluents. The desired fractions were concentrated under reduced pressure to afford (*E*)-*N*-benzyl-*N*-methyl-2-phenylethene-1-sulfonamide (**123**) as a white solid. Yield: 9.0 g (31 mmol, 18%); MS (ESI) *m*/*z*: 288.23 $[M + 1]^+$.

*rac-(7S,8S,9R)-N-benzyl-6-(4-Bromophenyl)-3-chloro-9-hydroxy-N-methyl-10-oxo-7-phenyl-6,7,8,9-tetrahydro-6,9-methanooxepino[3,2-b]pyridine-8-sulfonamide (**S73**).* A solution of 2-(4-bromophenyl)-7-chloro-3-hydroxy-4*H*-pyrano[3,2-*b*]pyridin-4-one (**102**) (3.0 g, 8.5 mmol) and (*E*)-*N*-benzyl-*N*-methyl-2-phenylethene-1-sulfonamide (**123**) (7.0 g, 24 mmol) in dichloromethane (100 mL), acetonitrile (50 mL), and methanol (50 mL) was irradiated under 400 W UV light for 96 h in a UV reactor flask. After this time, the solvent was removed under reduced pressure and the crude product was purified over a plug of silica gel (100−200 mesh) eluting with ethyl acetate. The desired fractions were concentrated under reduced pressure to afford compound **S73** as a sticky brown solid. Yield: 1.3 g, crude.

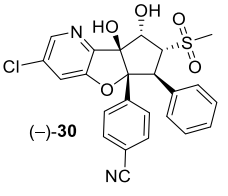
*rac-(5aR,6S,8aR)-N-Benzyl-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-N-methyl-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-sulfonamide (**S74**).* The crude product from the previous step (**S73**) (1.30 g) was suspended in methanol (15 mL) and treated with 25% sodium methoxide in methanol (15 mL, 14 g solution, 3.5 g NaOMe, 66 mmol). The reaction was heated at 90 °C for 3 h. After this time, the solvent was removed under reduced pressure. The crude product was diluted with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford *rac*-(5a*R*,6*S*,8a*R*)-*N*-benzyl-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-*N*-methyl-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-sulfonamide (**S74**) as a sticky brown solid. Yield: 1.3 g, crude.

*rac-(5aR,6S,7R,8S,8aS)-N-Benzyl-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-N-methyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-7-sulfonamide (**124**).* To a solution of sodium triacetoxyborohydride (1.20 g, 5.66 mmol) and crude (5a*R*,6*S*,8a*R*)-*N*-benzyl-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-*N*-methyl-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-sulfonamide (**S74**) (0.6 g) in acetonitrile (10 mL), acetic acid (0.56 g, 9.3 mmol) was added. The resulting mixture was stirred for 16 h at room temperature. After this time, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product, which was purified by Combi-flash (12 g RediSep column) using 50% ethyl acetate in hexanes as eluents. The desired fractions were concentrated under reduced pressure to afford *rac*-(5a*R*,6*S*,7*R*,8*S*,8a*S*)-*N*-benzyl-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-*N*-methyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-sulfonamide (**124**) as a brown solid. Yield: 0.23 g (0.36 mmol, 9% over three steps); MS (ESI) *m*/*z*: 641.12 $[M + 1]^+$.

*rac-(5aR,6S,7R,8S,8aS)-5a-(4-Bromophenyl)-3-chloro-8,8a-dihydroxy-N-methyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-sulfonamide (**S75**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*S*,8a*S*)-*N*-benzyl-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-*N*-methyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]-furo[3,2-*b*]pyridine-7-sulfonamide (**124**) (0.190 g, 0.296 mmol) in dichloromethane (2 mL), trifluoroacetic acid (2.0 mL, 3.0 g, 26 mmol) and triflic acid (2.0 mL, 3.4 g, 23 mmol) were added. This reaction mixture was stirred for 3 h at room temperature. Then, the reaction was diluted with dichloromethane and washed with cold sodium bicarbonate aqueous solution. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford *rac*-(5a*R*,6*S*,7*R*,8*S*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-*N*-methyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-sulfonamide (**9**) as a brown solid. Yield: 0.18, crude. MS (ESI) *m*/*z*: 551.36 $[M + 1]^+$,^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.19 (s, 1H), 7.77 (s, 1H), 7.44−7.42 (m, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 7.5 Hz, 2H), 7.00−6.84 (m, 3H), 6.28 (m, 1H), 5.84 (d, *J* = 5.3 Hz, 1H), 4.90 (m, 1H), 4.63 (m, 1H), 4.57 (d, *J* = 13.1 Hz, 1H), 2.81 (s, 3H).

*rac-(5aR,6S,7R,8S,8aS)-3-Chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-N-methyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-b]pyridine-7-sulfonamide (rac-**29**).* To a solution of crude *rac*-(5a*R*,6*S*,7*R*,8*S*,8a*S*)-3-chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-*N*-methyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]-furo[3,2-*b*]pyridine-7-sulfonamide (**S75**) (0.065 g) in *N*,*N*-dimethylformamide (3.0 mL) at room temperature, zinc cyanide (0.028 g, 0.24 mmol) and zinc dust (0.031 g, 0.47 mmol) were added. This reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (1 mg, 0.002 mmol) and tris-(dibenzylideneacetone)dipalladium (2 mg, 0.002 mmol) were added to the reaction mixture which was then degassed for an additional 5 min and heated at 125 °C for 6 h. After this time, the reaction mixture was diluted with ethyl acetate and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by Combi-flash (12 g RediSep column) using 3% methanol in dichloromethane as the eluent. The product was further purified by reverse preparative HPLC. The desired fractions were lyophilized to afford racemic (5a*R*,6*S*,7*R*,8-*S*,8a*S*)-3-chloro-5a-(4-cyanophenyl)-8,8a-dihydroxy-*N*-methyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-sulfonamide (*rac*-**29**) as an off-white solid. Yield: 4 mg (0.008 mol, 8% over two steps). MS (ESI) *m*/*z*: 498.17 $[M + 1]^+$; HRMS (ESI): calcd, 498.0885 $[M + H]^+$; found, 498.0892; UPLC 98.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.21 (s, 1H), 7.70 (s, 1H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 7.4 Hz, 2H), 7.01 (t, *J* = 7.2 Hz, 3H), 6.41 (s, 1H), 6.30 (d, *J* = 4.3 Hz, 1H), 5.90 (d, *J* = 5.9 Hz, 1H), 4.90 (dd, *J* = 4.0 Hz, 13.4 Hz, 1H), 4.69 (m, 1H), 4.60 (d, *J* = 13.8, 1H), 2.50 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 153.18, 148.97, 141.07, 140.89, 134.94, 131.05, 130.19, 129.41, 127.16, 126.72, 118.74, 117.20, 115.84, 109.38, 102.38, 89.38, 78.67, 65.42, 56.58, 28.79.

Synthesis of 4-((5aR,6S,7R,8S,8aS)-3-Chloro-8,8a-dihydroxy-7-(methylsulfonyl)-6-phenyl-6,7,8,8a-tetrahydro-5aH-cyclopenta-



*[4,5]furo[3,2-b]pyridin-5a-yl)benzonitrile ((−)-**30**). rac-(5aR,6S,8aR)-5a-(4-Bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-5a,6,7,8a-tetrahydro-8H-cyclopenta[4,5]furo[3,2-b]pyridin-8-one (**126**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-

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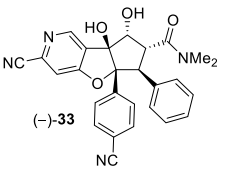
6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-7-carboxylate (**125**) (3.0 g, 5.8 mmol) in dimethylsulfoxide (60 mL), lithium chloride (27.2 g, 0.642 mol) was added, and the mixture was stirred at 150 °C for 24 h. After this time, ice-cold water was added and the precipitate was isolated by filtration. The solid was dissolved in dichloromethane (100 mL) and washed with water (2 × 30 mL) and brine (20 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated. The so-obtained crude product was purified by Combi-flash (12 g, RediSep column) using 20% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-(5a*R*,6*S*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-5a,6,7,8a-tetrahydro-8*H*-cyclopenta[4,5]furo[3,2-*b*]pyridin-8-one (**126**) as an off-white solid. Yield: 0.85 g (1.9 mmol, 33%). MS (ESI) *m*/*z*: 455.92 $[M + 1]^+$.

*rac-(5aR,6S,8aR)-5a-(4-Bromophenyl)-3-chloro-8a-hydroxy-7-(methylsulfonyl)-6-phenyl-5a,6,7,8a-tetrahydro-8H-cyclopenta-[4,5]furo[3,2-b]pyridin-8-one (**S77**).* To a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (3.0 mL, 20 mmol) in DMSO (10 mL) at room temperature, copper(II) bromide (51 mg, 0.23 mmol) was added under air. Then, (5a*R*,6*S*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-6-phenyl-5a,6,7,8a-tetrahydro-8*H*-cyclopenta[4,5]-furo[3,2-*b*]pyridin-8-one (**126**) (1.5 g, 3.3 mmol) and sodium methanesulfinate (**S76**) (3.36 g, 32.9 mmol) in DMSO (10.0 mL) at room temperature were added dropwise to the reaction mixture in under air. The reaction mixture was stirred at room temperature for 1 h. After completion (as determined by mass spectrometry), the reaction mixture was diluted with ethyl acetate and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford (5a*R*,6*S*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-7-(methylsulfonyl)-6-phenyl-5a,6,7,8a-tetrahydro-8*H*-cyclopenta[4,5]furo[3,2-*b*]-pyridin-8-one (**S77**) as a brown semisolid. Yield: 0.5 g, crude. MS (ESI) *m*/*z*: 532 $[M - 1]^-$.

*rac-(5aR,6S,7R,8S,8aS)-5a-(4-Bromophenyl)-3-chloro-7-(methylsulfonyl)-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo-[3,2-b]pyridine-8,8a-diol (**127**).* To a solution of sodium triacetoxyborohydride (1.19 g, 5.61 mmol) and crude *rac*-(5a*R*,6*S*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-7-(methylsulfonyl)-6-phenyl-5a,6,7,8a-tetrahydro-8*H*-cyclopenta[4,5]furo[3,2-*b*]pyridin-8-one (**S77**) (0.5 g) in acetonitrile (25 mL), acetic acid (0.56 mL, 0.59 g, 9.8 mmol) was added. The resulting mixture was stirred for 6 h at room temperature. After this time, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the crude product, which was purified by Combiflash (12 g, RediSep column) using 60% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-(5a*R*,6*S*,7*R*,8-*S*,8a*S*)-5a-(4-bromophenyl)-3-chloro-7-(methylsulfonyl)-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-8,8a-diol (**127**) as a white solid. Yield: 70 mg (0.13 mmol, 4% over two steps). MS (ESI) *m*/*z*: 536.08 $[M + 1]^+$; UPLC 99.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.21 (d, *J* = 2.0 Hz, 1H), 7.67 (d, *J* = 2.0 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.19−7.16 (m, 4H) 7.08−7.01 (m, 3H), 6.33 (br s, 1H), 6.20 (br s, 1H), 4.83 (dd, *J* = 4.0, 13.5 Hz, 1H), 4.77 (d, *J* = 4.4 Hz, 1H), 4.56 (d, *J* = 13.6 Hz, 1H), 2.84 (s, 3H).

*4-((5aR,6S,7R,8S,8aS)-3-Chloro-8,8a-dihydroxy-7-(methylsulfonyl)-6-phenyl-6,7,8,8a-tetrahydro-5aH-cyclopenta[4,5]furo[3,2-b]-pyridin-5a-yl)benzonitrile ((−)-30) and rac-(5aR,6S,7R,8S,8aS)-5a-(4-cyanophenyl)-8,8a-dihydroxy-7-(methylsulfonyl)-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-b]pyridine-3-carbonitrile (rac-**S78**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*S*,8a*S*)-5a-(4-bromophenyl)-3-chloro-7-(methylsulfonyl)-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-8,8a-diol (**127**) (0.13 g, 0.24 mmol) in *N*,*N*-dimethylformamide (5.0 mL) at room temperature, zinc cyanide (0.033 g, 0.28 mmol) and zinc (0.0016 g, 0.024 mmol) were added. The mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (0.013 g, 0.023 mmol) and tris(dibenzylideneacetone)-dipalladium (0.006 g, 0.007 mmol) were added to the reaction mixture, and degassing was continued for another 5 min. The reaction mixture was heated at 150 °C for 2 h. After this time, the reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was diluted with ethyl acetate and washed with water. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the crude product, which was purified by reverse-phase prep-HPLC to afford *rac*-4-((5a*R*,6*S*,7*R*,8*S*,8a*S*)-3-chloro-8,8a-dihydroxy-7-(methylsulfonyl)-6-phenyl-6,7,8,8a-tetrahydro-5a*H*-cyclopenta[4,5]-furo[3,2-*b*]pyridin-5a-yl)benzonitrile (*rac*-**30**) as an off-white solid (84 mg, 0.17 mmol, 72%) and *rac*-(5a*R*,6*S*,7*R*,8*S*,8a*S*)-5a-(4-cyanophenyl)-8,8a-dihydroxy-7-(methylsulfonyl)-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-3-carbonitrile (*rac*-**S78**) as an off-white solid (15 mg, 0.032 mmol, 13%). The enantiomers of *rac*-**30** were separated by chiral preparative HPLC [Chiralpak ID (4.6 × 250) mm] using 0.1% DEA in *n*-hexane/EtOH = 70/30(v/v) mobile phase. Peak 1 (30 mg, (+)-**30**); $[\alpha]_D$ +48.5° (*c* 0.25, $CHCl_3$); R_t 11.3 min, ee >99%; MS (ESI) *m*/*z*: 483.08 $[M + 1]^+$; UPLC: 99.70%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.22 (d, *J* = 1.92 Hz, 1H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 6.5 Hz, 2H), 7.07−7.00 (m, 3H), 6.45 (s, 1H), 6.26 (d, *J* = 6.2 Hz, 1H), 4.94 (dd, *J* = 4.0, 13.8 Hz, 1H), 4.78 (t, *J* = 6.2 Hz, 1H), 4.61 (d, *J* = 13.7 Hz, 1H), 2.86 (s, 3H). Peak-2 (33.0 mg, (−)-**30**); $[\alpha]_D$ −46.6° (*c* 0.30, $CHCl_3$); R_t 17.2 min, ee >99%; MS (ESI) *m*/*z*: 483.08 $[M + 1]^+$; HRMS (ESI): calcd, 483.0776 $[M + H]^+$; found, 483.0771; UPLC: 99.35%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (d, *J* = 1.8 Hz, 1H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 6.6 Hz 2H), 7.07−7.00 (m, 3H), 6.45 (s, 1H), 6.26 (d, *J* = 6.3 Hz, 1H), 4.94 (dd, *J* = 4.0 Hz, 13.6 Hz, 1H), 4.78 (t, *J* = 4.52 Hz, 1H), 4.62 (d, *J* = 13.8 Hz, 1H), 2.86 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 153.08, 148.72, 140.97, 140.86, 134.31, 131.12, 130.25, 129.67, 128.70, 127.21, 127.04, 118.70, 117.29, 109.55, 102.05, 89.69, 78.13, 66.91, 56.34, 41.96. *rac*-**S78**: MS (ESI) *m*/*z*: 474.11 $[M + 1]^+$; UPLC 99.1%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.66 (d, *J* = 1.4 Hz, 1H), 8.04 (d, *J* = 1.4 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 6.6 Hz, 2H), 7.07−7.02 (m, 3H), 6.66 (s, 1H), 6.38 (d, *J* = 6.3 Hz, 1H), 4.99 (dd, *J* = 3.7 Hz, 13.8 Hz, 1H), 4.83−4.80 (m, 1H), 4.65 (d, *J* = 13.7 Hz, 1H), 2.85 (s, 3H).

Synthesis of (5aR,6S,7R,8R,8aS)-3-Cyano-5a-(4-cyanophenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-



*cyclopenta[4,5]furo[3,2-c]pyridine-7-carboxamide ((−)-**33**). 6-Chloro-N,4-dimethoxy-N-methylnicotinamide (**S79**).* To a solution of 6-chloro-4-methoxynicotinic acid (**128**) (25.0 g, 133 mmol) in dichloromethane (300 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (38.44 g, 200.5 mmol), 1-hydroxybenzotriazole (30.40 g, 199.0 mmol), and DIPEA (69.8 mL, 51.8 g, 401 mmol) were added. The mixture was stirred for 5 min. Then, *N*,*O*-dimethylhydroxylamine hydrochloride (**129**) (19.56 g, 200.5 mmol) was added at same temperature and the mixture was stirred for 16 h at room temperature. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated and dried over sodium sulfate, filtered, and concentrated to give the crude product, which was recrystallized from ethanol to afford 6-chloro-*N*,4-dimethoxy-*N*-methylnicotinamide (**S79**) as a white solid. Yield: 19.3 g (83.7 mmol, 63%). MS (ESI) *m*/*z*: 231.17 $[M + 1]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 8.19 (s, 1H), 6.88 (s, 1H), 3.91 (s, 3H), 3.51 (s, 3H), 3.33 (s, 3H).

*1-(6-Chloro-4-methoxypyridin-3-yl)ethan-1-one (**130**).* To a solution of 6-chloro-*N*,4-dimethoxy-*N*-methylnicotinamide (**S79**) (17.0 g, 73.7 mmol) in dry tetrahydrofuran (200 mL) at 0 °C, methyl magnesium bromide (26.43 mL, 221.7 mmol) was added dropwise over a period of 30 min. The reaction mixture was slowly brought to

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room temperature and stirred for 2 h. Then, the reaction mixture was treated with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 1-(6-chloro-4-methoxypyridin-3-yl)ethan-1-one (**4**) as a yellow solid. Yield: 12.0 g (64.7 mmol, 88%). MS (ESI) m/z: 186.17 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.43 (s, 1H), 7.37 (s, 1H), 3.99 (s, 3H), 2.52 (s, 3H).

*1-(6-Chloro-4-hydroxypyridin-3-yl)ethan-1-one (**131**).* To a solution of 1-(6-chloro-4-methoxypyridin-3-yl)ethan-1-one (**130**) (10.0 g, 53.9 mmol) in acetic acid (30.0 mL), 6 M aq hydrochloric acid (60.0 mL, 360 mmol) was added. The reaction mixture was refluxed at 100 °C for 16 h. Then, it was concentrated under reduced pressure, diluted with water, cooled to 0 °C, basified with 10% NaOH solution to pH ≈ 9−10, and extracted with ethyl acetate. The organic layer was concentrated to recover starting material. The aqueous layer was cooled to 0 °C and acidified with 6 M aq hydrochloric acid. The precipitated solid was collected by filtration and dried to afford 1-(6-chloro-4-hydroxypyridin-3-yl)ethan-1-one (**131**) as a brown solid. Yield: 6.3 g (37 mmol, 68%). MS (ESI) m/z: 170.08 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.43 (s, 1H), 8.65 (s, 1H), 7.06 (s, 1H), 2.49 (s, 3H).

*(E)-3-(4-Bromophenyl)-1-(6-chloro-4-hydroxypyridin-3-yl)prop-2-en-1-one (**S80**).* To a solution of 1-(6-chloro-4-hydroxypyridin-3-yl)ethan-1-one (**132**) (5.5 g, 32 mmol) in methanol (50 mL) and dichloromethane (20 mL), sodium hydroxide (3.84 g, 96.0 mmol) was added, followed by 4-bromobenzaldehyde (6.5 g, 35 mmol). The reaction mixture was heated at 90 °C for 1 h. Then, it was cooled to room temperature and the precipitated solid was collected by filtration, washed with water, and dried under vacuum to afford (*E*)-3-(4-bromophenyl)-1-(6-chloro-4-hydroxypyridin-3-yl)prop-2-en-1-one (**S80**) as a yellow solid. Yield: 10.5 g (31.0 mmol, 97%). MS (ESI) m/z: 338.08 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.38 (d, J = 15.8 Hz, 1H), 8.13 (s, 1H), 7.62−7.55 (m, 4H), 7.42 (d, J = 15.8 Hz, 1H), 6.05 (s, 1H).

*2-(4-Bromophenyl)-7-chloro-3-hydroxy-4H-pyrano[3,2-c]-pyridin-4-one (**132**).* To a solution of (*E*)-3-(4-bromophenyl)-1-(6-chloro-4-hydroxypyridin-3-yl)prop-2-en-1-one (**S80**) (10.0 g, 29.5 mmol) in methanol (150 mL) at room temperature, 10% sodium hydroxide (36 mL, 88.0 mmol) was added followed by hydrogen peroxide (30% aq sln, 6.57 mL, 2.19 g H_2O_2, 64.3 mmol). The reaction mixture was stirred for 1 h (reaction is exothermic!), then cooled, and neutralized with 6 M hydrogen chloride to pH ≈ 7. The precipitated solid was collected by filtration and dried under vacuum to afford 2-(4-bromophenyl)-7-chloro-3-hydroxy-4*H*-pyrano[3,2-*c*]pyridin-4-one (**132**) as a yellow solid. Yield: 3.1 g (8.8 mmol, 30%). MS (ESI) m/z: 350.08 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 9.10 (s, 1H), 8.19 (d, J = 7.9 Hz, 2H), 8.04 (s, 1H), 7.78 (d, J = 8.3 Hz, 2H).

*rac-Methyl (2S,3S,4S,5R)-2-(4-Bromophenyl)-8-chloro-5-hydroxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanooxepino-[3,2-c]pyridine-4-carboxylate (**S81**).* A solution of 2-(4-bromophenyl)-7-chloro-3-hydroxy-4*H*-pyrano[3,2-*c*]pyridin-4-one (**132**) (3.1 g, 8.8 mmol) and methyl cinnamate (**55**) (13.82 g, 85.21 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated for 24 h under 400 W UV light in a UV reactor flask. The solvent was then removed under reduced pressure, and the residue was purified over a plug of silica gel eluting with ethyl acetate. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (2*S*,3*S*,4*S*,5*R*)-2-(4-bromophenyl)-8-chloro-5-hydroxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanooxepino[3,2-*c*]-pyridine-4-carboxylate (**S81**). Yield: 3.1 g, crude.

*rac-Methyl (5aR,6S,7R,8aR)-5a-(4-Bromophenyl)-3-chloro-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]-furo[3,2-c]pyridine-7-carboxylate (**S82**).* The crude *rac*-methyl (2*S*,3*S*,4*S*,5*R*)-2-(4-bromophenyl)-8-chloro-5-hydroxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanooxepino[3,2-*c*]pyridine-4-carboxylate (**S81**) (3.1 g) was suspended in methanol (30 mL) and treated with sodium methoxide (25% in methanol, 20.0 mL, 18.9 g, 4.72 g NaOMe, 87.4 mmol NaOMe). The mixture was heated at 90 °C for 3 h. Then, the solvent was removed under reduced pressure. The mixture was diluted with ammonium chloride solution and extracted with ethyl acetate. The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylate (**S82**). Yield: 2.2 g, crude.

*rac-Methyl (5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]-furo[3,2-c]pyridine-7-carboxylate (**133**).* To a solution of sodium triacetoxyborohydride (5.2 g, 25 mmol) and crude *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylate (**S82**) (2.1 g) in acetonitrile (50 mL), acetic acid (2.4 mL, 2.5 g, 42 mmol) was added. The resulting mixture was stirred for 4 h at room temperature. Then, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure to obtain the crude product, which was purified by silica gel column chromatography eluting with 30% ethyl acetate in hexanes. The desired fractions were concentrated to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*c*]pyridine-7-carboxylate (**133**) as an off-white solid. Yield: 1.21 g (2.34 mmol, 28% over three steps). MS (ESI) m/z: 516.22 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.23 (s, 1H), 7.31 (s, 1H), 7.27 (d, J = 8.3 Hz, 2H), 7.09−7.02 (m, 5H), 6.90 (d, J = 7.0 Hz, 2H), 6.03 (s, 1H), 5.75 (s, 1H), 4.75 (t, J = 6.0 Hz, 1H), 4.17−4.09 (m, 2H), 3.54 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-c]pyridine-7-carboxylic Acid (**S83**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylate (**133**) (1.2 g, 2.3 mmol) in tetrahydrofuran and water (3:1, 15 mL), lithium hydroxide (0.55 g, 23 mmol) was added. The reaction mixture was stirred for 16 h at room temperature, then cooled to 0 °C and acidified with 1 M hydrogen chloride to pH ≈ 3. The precipitated solid was collected by filtration and dried under vacuum to afford (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylic acid (**S83**) as an off-white solid. Yield: 1.05 g (2.09 mmol, 91%). MS (ESI) m/z: 502.06 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.22 (s, 1H), 7.30 (s, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.09−7.01 (m, 5H), 6.92 (d, J = 7.3 Hz, 2H), 5.99 (s, 1H), 4.70 (d, J = 6.0 Hz 1H), 4.15−4.11 (m, 1H), 4.05−3.99 (m, 2H), 3.94−3.90 (dd, J = 5.7 Hz, 13.8 Hz, 1H).

*rac-(5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-c]pyridine-7-carboxamide (**134**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylic acid (**S83**) (0.7 g, 1.39 mmol) in dichloromethane (50 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.8 g, 4 mmol), 1-hydroxybenzotriazole (0.63 g, 4.7 mmol) and DIPEA (1.43 mL, 1.06 g, 8.20 mmol) were added. The mixture was stirred for 5 min. Dimethylamine hydrochloride (0.56 g, 6.9 mmol) was then added at same temperature, and the mixture was stirred for 16 h at 40 °C. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to give the crude product, which was purified by silica gel column chromatography eluting with 70% ethyl acetate in hexanes. The desired fractions were concentrated to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxamide (**134**) as a white solid. Yield: 0.52 g (0.98 mmol, 71%). MS (ESI) m/z: 523.21 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.31 (s, 1H), 7.34−7.30 (m, 3H), 7.11 (d, J = 8.4 Hz, 2H), 7.06−7.00 (m, 3H), 6.83 (d, J = 7.2 Hz, 2H), 5.87 (s, 1H), 5.75 (s, 1H), 4.90 (t, J

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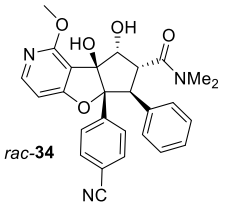
= 6.5 Hz, 1H), 4.20−4.16 (m, 2H), 4.12−4.01 (m, 1H), 3.20 (s, 3H), 2.72 (s, 3H).

*(5aR,6S,7R,8R,8aS)-3-Cyano-5a-(4-cyanophenyl)-8,8a-dihydroxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-c]pyridine-7-carboxamide ((−)-**33**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxamide (**134**) (0.5 g, 0.9 mmol) in *N*,*N*-dimethylformamide (10.0 mL) at room temperature, zinc cyanide (0.66 g, 5.6 mmol) and zinc (0.007 g, 0.11 mmol) were added. The mixture was degassed with argon for 15 min. 1,1′-Bis-(diphenylphosphino)ferrocene (0.013 g, 0.023 mmol) and tris-(dibenzylideneacetone)dipalladium (0.026 g, 0.028 mmol) were added to the mixture and degassing was continued for another 5 min. The reaction mixture was heated at 150 °C for 2 h, then cooled to room temperature and filtered through Celite. The filtrate was diluted with ethyl acetate and washed with water. The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure to obtain the crude product, which was purified by silica gel column chromatography eluting with 70% ethyl acetate in hexanes. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-3-cyano-5a-(4-cyanophenyl)-8,8a-dihydroxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxamide (*rac*-**33**) as a white solid. Yield: 150 mg (0.321 mmol, 36%). The enantiomers were separated by chiral preparative HPLC [Chiralpak IB (4.6 × 250) mm]. Peak 1 (25 mg, (−)-**33**), $[\alpha]_D$ −128.9° (*c* 0.1, $CHCl_3$), R_t 8.28 min, ee >99%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.64 (s, 1H), 7.97 (s, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.06−6.98 (m, 3H), 6.84 (d, *J* = 6.8 Hz, 2H), 6.14 (s, 1H), 5.98 (d, *J* = 6.4 Hz, 1H), 4.96 (t, *J* = 6.8 Hz, 1H), 4.27−4.16 (m, 2H), 3.23 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 167.68, 163.98, 150.72, 140.26, 137.36, 133.18, 130.81, 130.78, 128.44, 127.64, 127.58, 126.36, 118.69, 117.54, 112.97, 109.66, 102.88, 91.43, 77.23, 55.47, 47.28, 36.45, 35.19. MS (ESI) *m*/*z*: 467.43 $[M + 1]^+$; HRMS (ESI): calcd, 467.1714 $[M + H]^+$; found, 467.1729; UPLC: 99.09%. Peak-2 (9.0 mg, (+)-**33**), $[\alpha]_D$ +126° (*c* 0.1, $CHCl_3$), R_t 10.67 min, ee >98%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.64 (s, 1H), 7.97 (s, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.06−6.98 (m, 3H), 6.84 (d, *J* = 6.8 Hz, 2H), 6.14 (s, 1H), 5.98 (d, *J* = 6.4 Hz, 1H), 4.96 (t, *J* = 6.8 Hz, 1H), 4.27−4.16 (m, 2H), 3.23 (s, 3H), 2.73 (s, 3H); MS (ESI) *m*/*z*: 467.47 $[M + 1]^+$; UPLC: 99.17%.

Synthesis of (5aR,6S,7R,8R,8aS)-5a-(4-cyanophenyl)-8,8a-Dihydroxy-1-methoxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-



rac-**34**

*cyclopenta[4,5]furo[3,2-c]pyridine-7-carboxamide (rac-**34**).* *3-Bromo-2-methoxypyridin-4-amine (**136**).* To a solution of 2-methoxypyridin-4-amine (**135**, 20.0 g, 161 mmol) in dichloromethane (200 mL) at 0 °C, *N*-bromosuccinimide (26.6 g, 149 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min. Then, the mixture was quenched with ice-cold water (100 mL) and extracted with dichloromethane (300 mL). The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was triturated with *n*-pentane and diethyl ether to afford 3-bromo-2-methoxypyridin-4-amine (**136**) as a yellow solid. Yield: 30.0 g (0.148 mol, 92%). MS (ESI) *m*/*z*: 203.09 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.59 (d, *J* = 5.6 Hz, 1H), 6.35 (d, *J* = 5.64 Hz, 1H), 6.20 (br s, 2H), 3.80 (s, 3H).

*1-(4-Amino-2-methoxypyridin-3-yl)ethan-1-one (**138**).* To a solution of 3-bromo-2-methoxypyridin-4-amine (**136**) (25.0 g, 123 mmol) in toluene (250 mL) at room temperature, tributyl(1-ethoxyvinyl)stannane (**137**) (67.01 g, 185.5 mmol) was added. The reaction mixture was degassed with argon for 15 min. Then, bis(triphenylphosphine)palladium(II) chloride (8.6 g, 12 mmol) was added to the reaction mixture, degassing was continued for 5 min, and the reaction mixture was heated at 100 °C for 16 h. After this time, the reaction mixture was diluted with ethyl acetate (300 mL) and washed with water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to obtain the crude product. This was treated with 1 N hydrochloric acid (100 mL), and the mixture was stirred at room temperature for 1 h. The mixture was then basified with $NaHCO_3$ solution up to pH ≈ 7, extracted with ethyl acetate (300 mL) and washed with water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by silica gel column chromatography eluting with 10% ethyl acetate in hexane. The desired fractions were concentrated to afford 1-(4-amino-2-methoxypyridin-3-yl) ethan-1-one (**138**) as an off-white solid. Yield: 10.0 g (60.2 mmol, 49%); MS (ESI) *m*/*z*: 167.16 $[M + 1]^+$.

*1-(4-Hydroxy-2-methoxypyridin-3-yl)ethan-1-one (**139**).* To a solution of 1-(4-amino-2-methoxypyridin-3-yl)ethan-1-one (**137**) (10.0 g, 60.2 mmol) in 1,4-dioxane (250 mL) at 0 °C, 50% aq sulfuric acid solution (117.3 g, 1197 mmol) was added dropwise over a period of 30 min. A solution of sodium nitrite in water (16.5 g, 239 mmol) was added dropwise at 0 °C. The reaction mixture was heated at 50 °C for 1 h. After this time, the reaction mixture was quenched with 10% sodium hydroxide solution to pH ≈ 7 and extracted with ethyl acetate (200 mL). The organic layer was separated, washed water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography eluting with 5% ethyl acetate in hexane. The desired fractions were concentrated to afford 1-(4-hydroxy-2-methoxypyridin-3-yl)ethan-1-one (**139**) as a yellow solid. Yield: 3.7 g (22 mmol, 37%). MS (ESI) *m*/*z*: no ionization; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.83 (s, 1H), 8.21 (d, *J* = 5.2 Hz, 1H), 6.60 (d, *J* = 6.0 Hz, 1H), 3.91 (s, 3H), 2.56 (s, 3H).

*(E)-3-(4-Bromophenyl)-1-(4-hydroxy-2-methoxypyridin-3-yl)-prop-2-en-1-one (**S84**).* To a solution of 1-(4-hydroxy-2-methoxypyridin-3-yl)ethan-1-one (**139**) (3.7 g, 22 mmol) in methanol (40 mL), sodium hydroxide (2.6 g, 65 mmol) was added followed by 4-bromobenzaldehyde (4.0 g, 22 mmol). The reaction mixture was heated to reflux for 30 min. Then, the mixture was cooled to room temperature and diluted with water (20 mL). The resulting precipitate was collected by filtration, washed with water and *n*-pentane, and dried under vacuum to afford (*E*)-3-(4-bromophenyl)-1-(4-hydroxy-2-methoxypyridin-3-yl)prop-2-en-1-one (**S84**) as a yellow solid. Yield: 5.0 g (15 mmol, 68%). MS (ESI) *m*/*z*: 334.10 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.33−7.22 (m, 8H), 5.80 (br s, 1H), 3.65 (s, 3H)

*2-(4-Bromophenyl)-3-hydroxy-5-methoxy-4H-pyrano[3,2-c]-pyridin-4-one (**140**).* To a solution of (*E*)-3-(4-bromophenyl)-1-(4-hydroxy-2-methoxypyridin-3-yl)prop-2-en-1-one (**S84**) (6.0 g, 18 mmol) in ethanol (60 mL) and dichloromethane (10 mL) at 0 °C, 10% aq sodium hydroxide (50 mL, 56 g solution, 5.6 g NaOH, 140 mmol) was added followed by 30% aq hydrogen peroxide (4.2 mL, 4.7 g solution, 1.4 g H_2O_2, 41 mmol). The reaction mixture was stirred for 30 min at room temperature (exothermic reaction). Then, the reaction mixture was cooled, neutralized to pH ≈ 7 by the addition of 6 M hydrochloric acid, and extracted with ethyl acetate (100 mL). The organic layer was washed with water and then brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The solid thus obtained was triturated with *n*-pentane and ethanol, filtered, and dried under vacuum to afford 2-(4-bromophenyl)-3-hydroxy-5-methoxy-4*H*-pyrano[3,2-*c*]pyridin-4-one (**140**) as a yellow solid. Yield: 2.0 g (5.7 mmol, 32%). MS (ESI) *m*/*z*: 348.07 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 9.88 (br s, 1H), 8.30 (d, *J* = 6.0 Hz, 1H), 8.13 (d, *J* = 5.62 Hz, 2H), 7.78 (d, *J* = 5.64 Hz, 2H), 7.31 (d, *J* = 6.0 Hz, 1H), 4.07 (s, 3H).

*rac-Methyl (2S,3S,4S,5R)-2-(4-Bromophenyl)-5-hydroxy-6-methoxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanooxepino-[3,2-c]pyridine-4-carboxylate (**S85**).* A solution of 2-(4-bromophenyl)-3-hydroxy-5-methoxy-4*H*-pyrano[3,2-*c*]pyridin-4-one (**140**) (2.0

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g, 5.7 mmol) and methyl cinnamate (**55**) (9.34 g, 57.6 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated for 8 h under 400 W UV light in a UV reactor flask. After this time, the solvent was removed under reduced pressure, and the residue was purified over a plug of silica gel eluting with ethyl acetate. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (2*S*,3*S*,4*S*,5*R*)-2-(4-bromophenyl)-5-hydroxy-6-methoxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanooxepino[3,2-*c*]pyridine-4-carboxylate (**S85**) as a yellow sticky mass. Yield: 1.7 g, crude.

*rac-Methyl (5a*R*,6*S*,7*R*,8a*R*)-5a-(4-Bromophenyl)-8a-hydroxy-1-methoxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-c]pyridine-7-carboxylate (**S86**).* The crude compound **S85** (1.7 g) was suspended in methanol (20 mL) and treated with 25% sodium methoxide in methanol (15 mL 14 g solution, 3.5 g NaOMe, 66 mmol). The reaction mixture was heated at 80 °C for 2 h. Then, the solvent was removed under reduced pressure. The crude product was diluted with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure to afford methyl (5a*R*,6*S*,7*R*,8a*R*)-5a-(4-bromophenyl)-8a-hydroxy-1-methoxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylate (**S86**). Yield: 1.6 g, crude.

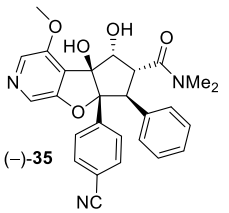
*rac-Methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-Bromophenyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-c]pyridine-7-carboxylate (**141**).* To a solution of sodium triacetoxyborohydride (3.99 g, 18.8 mmol) and crude methyl (5a*R*,6*S*,7*R*,8a*R*)-5a-(4-bromophenyl)-8a-hydroxy-1-methoxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylate (**S86**) (1.6 g) in acetonitrile (20 mL), acetic acid (1.77 g, 29.5 mmol) was added. The resulting mixture was stirred for 12 h at room temperature. After this time, the reaction mixture was partitioned between saturated aq sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product, which was purified by preparative HPLC and lyophilized to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylate (**141**) as a yellowish solid. Yield: 0.03 g (0.06 mmol, 1% over three steps). MS (ESI) *m*/*z*: 512.1 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.02 (d, J = 5.7 Hz, 1H), 7.20 (d, J = 8.8 Hz, 2H), 7.05−6.94 (m, 7H), 6.78 (J = 5.6 Hz, 1H), 5.56−5.53 (m, 2H), 4.65 (br s, 1H), 4.28−4.25 (m, 1H), 4.09−4.08 (m, 1H), 4.38 (s, 3H), 3.56 (s, 3H).

*rac-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-Bromophenyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo-[3,2-c]pyridine-7-carboxylic Acid (**S87**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylate (**141**) (0.03 g, 0.06 mmol) in tetrahydrofuran and water (3:1, 4 mL), lithium hydroxide (0.015 g, 0.63 mmol) was added, and the reaction mixture was stirred for 2 h at room temperature. Then, the reaction mixture was cooled to 0 °C and acidified with 1 M hydrochloric acid to pH ≈ 2−3. The precipitate was collected by filtration and dried under vacuum to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylic acid (**S87**) as a yellow solid. Yield: 0.02 g (0.04 mmol, 67%. MS (ESI) *m*/*z*: 498.24 $[M + 1]^+$.

*rac-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-Bromophenyl)-8,8a-dihydroxy-1-methoxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-c]pyridine-7-carboxamide (**S88**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylic acid (**S87**) (0.02 g, 0.04 mmol) in dichloromethane (2 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (0.019 g, 0.12 mmol), hydroxybenzotriazole (hydrate, 0.018 g, 0.12 mmol), and *N*,*N*-diisopropylethylamine (0.04 g, 0.3 mmol) were added. This reaction mixture was stirred for 5 min. Then, dimethylamine hydrochloride (0.016 g, 0.20 mmol) was added at the same temperature, and the reaction was stirred for 16 h at room temperature. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by silica gel column chromatography eluting with 2−3% dichloromethane in methanol. The desired fractions were concentrated to afford *rac*-(5a*R*,6*S*,7*R*,8-*R*,8a*S*)-5a-(4-bromophenyl)-8,8a-dihydroxy-1-methoxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]-pyridine-7-carboxamide (**S88**) as a yellow sticky mass. Yield: 0.02 g (0.04 mmol, quant.). MS (ESI) *m*/*z*: 525.15 $[M + 1]^+$.

*rac-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-Cyanophenyl)-8,8a-dihydroxy-1-methoxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-c]pyridine-7-carboxamide (rac-**34**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-8,8a-dihydroxy-1-methoxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxamide (**S88**) (0.02 g, 0.04 mmol) in *N*,*N*-dimethylformamide (1.0 mL), zinc cyanide (0.026 g, 0.22 mmol) and zinc (0.001 g, 0.02 mmol) were added at room temperature. The reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (0.5 mg, 0.0009 mmol) and tris(dibenzylideneacetone) dipalladium (1.0 mg, 0.001 mmol) were added, degassing was continued for 5 min, and the reaction mixture was heated at 140 °C for 4 h. After this time, the reaction mixture was diluted with ethyl acetate and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by preparative HPLC and lyophilized to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-cyanophenyl)-8,8a-dihydroxy-1-methoxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*c*]pyridine-7-carboxamide (*rac*-**34**) as a white solid. Yield: 3.5 mg (0.0074 mmol, 19%). MS (ESI) *m*/*z*: 472.44 $[M + 1]^+$; HRMS (ESI): calcd, 472.1874 $[M + H]^+$; found, 472.1867;^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.04 (d, J = 5.6 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.03 (t, J = 8.0 Hz, 2H), 6.96 (t, J = 7.2 Hz, 1H), 6.90 (d, J = 7.6 Hz, 2H), 6.83 (d, J = 5.6 Hz, 1H), 5.61 (s, 1H), 5.10 (br s, 1H), 4.75 (d, J = 5.2 Hz, 1H), 4.44 (d, J = 13.6 Hz, 1H), 4.26 (dd, J = 13.6, 5.2 Hz, 1H), 3.85 (s, 3H), 3.28 (s, 3H), 2.77 (s, 3H).

Synthesis of (4bS,5R,6R,7S,7aR)-7a-(4-cyanophenyl)-4b,5-Dihydroxy-4-methoxy-N,N-dimethyl-7-phenyl-4b,6,7,7a-tetrahydro-5H-



(−)-**35**

*cyclopenta[4,5]furo[2,3-c]pyridine-6-carboxamide ((−)-**35**).* *3-Chloro-5-((4-methoxybenzyl)oxy)isonicotinonitrile (**143**).* To a solution of 3,5-dichloroisonicotinonitrile (**142**) (15.00 g, 86.71 mmol) in tetrahydrofuran (300 mL) at 0 °C, 60% sodium hydride (6.90 g, 174.40 mmol) was added followed by (4-methoxyphenyl)-methanol (13.20 g, 95.53 mmol). The reaction mixture was stirred at room temperature for 2 h. After this time, the mixture was quenched with ice-cold water (100 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with water and then brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford 3-chloro-5-((4-methoxybenzyl)oxy)isonicotinonitrile (**143**) as a white solid. Yield: 18.0 g (65.5 mmol, 76%). Purity: 99.04%. MS (ESI) *m*/*z*: 275.16 $[M + 1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.78 (s, 1H), 8.54 (s, 1H), 7.44 (d, J = 7.0 Hz, 2H), 6.99 (d, J = 7.0 Hz, 2H), 5.38 (s, 2H), 3.76 (s, 3H).

*3-Methoxy-5-((4-methoxybenzyl)oxy)isonicotinonitrile (**144**).* To a solution of 3-chloro-5-((4-methoxybenzyl)oxy)isonicotinonitrile (**143**) (14.00 g, 50.96 mmol) in methanol (160 mL), sodium methoxide (25% in methanol, 20 mL, 19 g solution, 4.7 g NaOMe, 87 mmol) was added. The reaction mixture was refluxed at 80 °C for 2 h. After this time, the solvent was removed under reduced pressure. The

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mixture was quenched with ice-cold water (100 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with water and then brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel column chromatography using 50% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated to afford 3-methoxy-5-((4-methoxybenzyl)oxy)isonicotinonitrile (**144**) as a white solid. Yield: 6.3 g (23.3 mmol, 46%). MS (ESI) m/z: 271.23 $[M + 1]^+$.

*1-(3-Hydroxy-5-methoxypyridin-4-yl)ethan-1-one (**145**).* To a solution of 3-methoxy-5-((4-methoxybenzyl)oxy)isonicotinonitrile (**144**) (6.30 g, 23.3 mmol) in dry tetrahydrofuran (250 mL) at 0 °C, methyl magnesium bromide solution (69.90 mL, 209.7 mmol) was added dropwise over a period of 30 min. The reaction mixture was slowly brought to room temperature and stirred for additional 12 h. After this time, the reaction mixture was quenched with 6 M hydrochloric acid to pH ≈ 3 and stirred for 3 h. The mixture was diluted with ethyl acetate (100 mL) and water (50 mL) and basified with sodium bicarbonate to pH ≈ 10. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography using 60% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated to afford 1-(3-hydroxy-5-methoxypyridin-4-yl)ethan-1-one (**145**) as a light yellow solid. Yield: 2.0 g (12 mmol, 52%). MS (ESI) m/z: 168.17 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 10.52 (s, 1H), 7.96 (s, 1H), 7.93 (s, 1H), 3.85 (s, 3H), 2.41 (s, 3H).

*(E)-3-(4-Bromophenyl)-1-(3-hydroxy-5-methoxypyridin-4-yl)-prop-2-en-1-one (**S89**).* To a solution of 1-(3-hydroxy-5-methoxypyridin-4-yl)ethan-1-one (**145**) (2.00 g, 12.0 mmol) in methanol (10 mL), sodium hydroxide (1.40 g, 35.0 mmol) was added followed by 4-bromobenzaldehyde (2.19 g, 11.8 mmol). The reaction was heated to reflux for 10 min. After this time, the reaction mixture was cooled to room temperature, diluted with water (20 mL), and extracted with 5% methanol in dichloromethane (100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The solid thus obtained was triturated with pentane, filtered, and dried under vacuum to afford (*E*)-3-(4-bromophenyl)-1-(3-hydroxy-5-methoxypyridin-4-yl)prop-2-en-1-one (**S89**) as a yellow solid. Yield: 3.2 g (9.6 mmol, 80%). MS (ESI) m/z: 334.14 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.75 (s, 1H), 7.68−7.58 (m, 5H), 7.25 (d, J = 16.6 Hz, 1H), 7.11 (d, J = 15.7 Hz, 1H), 3.74 (s, 3H).

*(2-(4-Bromophenyl)-3-hydroxy-5-methoxy-4H-pyrano[2,3-c]-pyridin-4-one (**146**).* To a solution of (*E*)-3-(4-bromophenyl)-1-(3-hydroxy-5-methoxypyridin-4-yl)prop-2-en-1-one (**S89**) (4.60 g, 13.8 mmol) in ethanol (70 mL) and dichloromethane (10 mL) at 0 °C, 10% aq sodium hydroxide solution (39 mL, 43 g solution, 4.3 g NaOH, 108 mmol) was added followed by 30% aq hydrogen peroxide (9.80 mL, 10.9 g solution, 1.09 g H_2O_2, 32.0 mmol). The reaction mixture was stirred for 30 min at room temperature (reaction is exothermic). Then, the reaction mixture was cooled and neutralized to pH ≈ 7 by the addition of 6 M hydrochloric acid. The mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with water and then brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The solid thus obtained was triturated with ethanol, filtered, and dried under vacuum to afford (2-(4-bromophenyl)-3-hydroxy-5-methoxy-4*H*-pyrano[2,3-*c*]pyridin-4-one (**146**) as a yellow solid. Yield: 1.4 g (4.0 mmol, 29%). MS (ESI) m/z: 348.07 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 9.90 (br s, 1H), 8.78 (s, 1H), 8.31 (s, 1H), 8.26−8.16 (m, 2H), 7.76−7.64 (m, 2H), 4.02 (s, 3H).

*rac-Methyl (2S,3S,4S,5R)-2-(4-Bromophenyl)-5-hydroxy-6-methoxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanooxepino-[2,3-c]pyridine-4-carboxylate (**S90**).* A solution of (2-(4-bromophenyl)-3-hydroxy-5-methoxy-4*H*-pyrano [2,3-*c*]pyridin-4-one (**146**) (1.40 g, 4.02 mmol) and methyl cinnamate (55) (6.53 g, 40.3 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated under 400 W UV light in a UV reactor flask for 18 h. After this time, solvent was removed under reduced pressure, and the residue was purified over a plug of silica gel eluting the compound with ethyl acetate. The desired fractions were concentrated under reduced pressure to afford compound **S90** as a dark brown solid. Yield: 1.80 g, crude.

*rac-Methyl (4bR,6R,7S,7aR)-7a-(4-Bromophenyl)-4b-hydroxy-4-methoxy-5-oxo-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]-furo[2,3-c]pyridine-6-carboxylate (**S91**).* The crude compound **S90** (1.80 g) was suspended in methanol (25 mL) and treated with 25% sodium methoxide in methanol (15 mL, 14 g solution, 3.5 g NaOMe, 66 mmol). The reaction mixture was heated at 80 °C for 3 h. After this time, the solvent was removed under reduced pressure. The crude was diluted with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure to afford methyl (4b*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b-hydroxy-4-methoxy-5-oxo-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxylate (**S91**) as a brown solid. Yield: 1.4 g, crude.

*rac-Methyl (4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta-[4,5]furo[2,3-c]pyridine-6-carboxylate (**147**).* To a solution of sodium triacetoxyborohydride (3.40 g, 16.0 mmol) and crude methyl (4b*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b-hydroxy-4-methoxy-5-oxo-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxylate (**S91**) (1.40 g) in acetonitrile (20 mL), acetic acid (1.65 g, 27.5 mmol) was added. The resulting mixture was stirred for 4 h at room temperature. After this time, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product, which was purified by silica gel column chromatography using 50% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated under reduced pressure to afford methyl (4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxylate (**147**) as a brown solid. Yield: 0.70 g (1.4 mmol, 35% over three steps). MS (ESI) m/z: 512.2 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.09 (s, 1H) 7.98 (s, 1H), 7.19 (d, J = 8.2 Hz, 2H), 7.70−7.03 (m, 4H), 7.02−6.93 (m, 3H), 5.75 (s, 1H), 5.59 (d, J = 5.6 Hz, 1H), 4.68 (d, J = 4.8 Hz, 1H), 4.32 (d, J = 14.5 Hz, 1H), 4.10−4.01 (m, 1H), 3.87 (s, 3H), 3.56 (s, 3H).

*rac-(4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo-[2,3-c]pyridine-6-carboxylic Acid (**148**).* To a solution of *rac*-methyl (4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxylate (**147**) (0.70 g, 1.4 mmol) in methanol and water (3:1, 20 mL), lithium hydroxide (0.32 g, 13 mmol) was added, and the reaction mixture was stirred for 2 h at room temperature. Then, the reaction mixture was cooled to 0 °C and acidified with 1 M hydrochloric acid to pH ≈ 2−3. The precipitate was collected by filtration and dried under vacuum to afford *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta-[4,5]furo[2,3-*c*]pyridine-6-carboxylic acid (**148**) as a white solid. Yield: 0.53 g (1.1 mmol, 79%). MS (ESI) m/z: 498.08 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.07 (s, 1H) 7.97 (s, 1H), 7.19 (d, J = 7.9 Hz, 2H), 7.07−7.95 (m, 7H), 4.63 (d, J = 4.0 Hz, 1H), 4.30 (d, J = 14.0 Hz, 1H), 3.93−3.82 (m, 4H).

*rac-(4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-4-methoxy-N,N-dimethyl-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo[2,3-c]pyridine-6-carboxamide (**149**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]-furo[2,3-*c*]pyridine-6-carboxylic acid (**148**) (0.53 g, 1.1 mmol) in dichloromethane (25 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (0.49 g, 3.12 mmol), hydroxybenzotriazole (hydrate, 0.48 g, 3.1 mmol), and *N*,*N*-diisopropylethylamine (0.82 g, 6.3 mmol) were added. The mixture was stirred for 5 min. Then, dimethylamine hydrochloride (0.43 g, 5.3 mmol) was added at the same temperature and the mixture was stirred for 28 h at room temperature. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to obtain the crude product. This was purified by silica gel column chromatography using 60−70%

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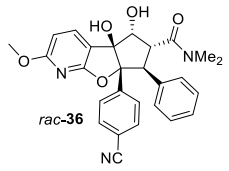
ethyl acetate in hexanes as the eluent. The desired fractions were concentrated to afford *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-*N*,*N*-dimethyl-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxamide (**149**) as a white solid. Yield: 0.38 g (0.72 mmol, 65%). MS (ESI) *m*/*z*: 525.24 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.10 (s, 1H) 7.99 (s, 1H), 7.21 (d, J = 8.5 Hz, 2H), 7.10−7.01 (m, 4H), 6.97−6.94 (m, 1H), 6.90 (d, J = 7.4 Hz, 2H), 5.70 (s, 1H), 5.11 (d, J = 5.4 Hz, 1H), 4.75 (t, J = 5.0 Hz, 1H), 4.40 (d, J = 13.6 Hz, 1H), 4.18 (dd, J = 13.3, 5.1 Hz, 1H), 3.87 (s, 3H), 3.27 (s, 3H), 2.76 (s, 3H).

*(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-Cyanophenyl)-4b,5-dihydroxy-4-methoxy-N,N-dimethyl-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo[2,3-c]pyridine-6-carboxamide ((−)-**35**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-*N*,*N*-dimethyl-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxamide (**149**) (0.38 g, 0.72 mmol) in *N*,*N*-dimethylformamide (5.0 mL) at room temperature, zinc cyanide (0.51 g, 4.3 mmol) and zinc dust (0.005 g, 0.076 mmol) were added. The reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (8 mg, 0.01 mmol) and tris(dibenzylideneacetone)dipalladium (19 mg, 0.02 mmol) were added to the reaction mixture, which was then degassed for an additional 5 min and then heated at 140 °C for 16 h. After this time, the reaction mixture was diluted with ethyl acetate and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by silica gel column chromatography using 2−3% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford racemic methyl (4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-cyanophenyl)-4b,5-dihydroxy-4-methoxy-*N*,*N*-dimethyl-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxamide (*rac*-**35**) as a white solid. Yield: 0.169 g (0.358 mmol, 50%). The enantiomers were separated by chiral preparative HPLC [Chiralpak IB (4.6 × 250) mm]. Peak 1 (31 mg, (+)-**35**), $[\alpha]_D$ +89.6° (*c* 0.1, $CHCl_3$), R_t 7.796 min, ee >99%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.12 (s, 1H), 8.00 (s, 1H), 7.48 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.02 (t, J = 7.3 Hz, 2H), 6.94 (m, 3H), 5.80 (s, 1H), 5.17 (d, J = 5.4 Hz, 1H), 4.76 (t, J = 5.2 Hz, 1H), 4.49 (d, J = 13.4 Hz, 1H), 4.25 (dd, J = 13.4, 5.1 Hz, 1H), 3.87 (s, 3H), 3.29 (s, 3H), 2.77 (s, 3H); MS (ESI) *m*/*z*: 472.43 $[M + 1]^+$; purity: 99.32%. Peak-2 (26 mg, (−)-**35**), $[\alpha]_D$ −89.5° (*c* 0.1, $CHCl_3$), R_t 10.192 min, ee >99%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.12 (s, 1H), 8.00 (s, 1H), 7.48 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.02 (t, J = 7.3 Hz, 2H), 6.94 (m, 3H), 5.8 (s, 1H), 5.16 (d, J = 5.4 Hz, 1H), 4.76 (t, J = 5.2 Hz, 1H), 4.49 (d, J = 13.4 Hz, 1H), 4.25 (dd, J = 13.4, 5.1 Hz, 1H), 3.87 (s, 3H), 3.29 (s, 3H), 2.77 (s, 3H); MS (ESI) *m*/*z*: 472.43 $[M + 1]^+$; HRMS (ESI): calcd, 742.1867 $[M + H]^+$; found, 472.1854; purity: 99.04%.

*Synthesis of (4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-Cyanophenyl)-4b,5-dihydroxy-2-methoxy-N,N-dimethyl-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo[2,3-b]pyridine-6-carboxamide (rac-**36**).*



rac-**36**

*2-Chloro-6-methoxynicotinic Acid (**151**).* To a suspension of 2,6-dichloronicotinic acid (**150**) (20.0 g, 104 mmol) in methanol (250 mL) under nitrogen, potassium *tert*-butoxide (35.0 g, 312 mmol) was added at room temperature. The reaction mixture was stirred at 80 °C for 24 h. After this time, the solvent was removed under reduced pressure and the crude product was treated with 6 M hydrochloric acid. The resulting precipitate was collected by filtration and dried under vacuum to afford 2-chloro-6-methoxynicotinic acid (**2**) as a white solid. Yield: 20.0 g, crude; MS (ESI) *m*/*z*: 188.06 $[M + 1]^+$.

*2-Chloro-N,6-dimethoxy-N-methylnicotinamide (**S92**).* To a solution of crude 2-chloro-6-methoxynicotinic acid (**151**) (20.0 g) in dichloromethane (400 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (30.6 g, 160 mmol), 1-hydroxybenzotriazole (21.6 g, 160 mmol) and *N*,*N*-diisopropylethylamine (46.6 mL, 34.6 g, 268 mmol) were added. This mixture was stirred for 5 min. Then, *N*,*O*-dimethylhydroxylamine hydrochloride (**129**) (12.4 g, 127 mmol) was then added at same temperature and the reaction was stirred at room temperature for 4 h. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to afford 2-chloro-*N*,6-dimethoxy-*N*-methylnicotinamide (**S92**) as a yellow solid. Yield: 18.0 g (0.0781 mol, 75% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 7.56 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 3.52 (s, 3H), 3.34 (s, 3H); MS (ESI) *m*/*z*: 231.15 $[M + 1]^+$.

*1-(2-Chloro-6-methoxypyridin-3-yl)ethan-1-one (**152**).* To a solution of 2-chloro-*N*,6-dimethoxy-*N*-methylnicotinamide (**S92**) (18.0 g, 78.0 mmol) in dry tetrahydrofuran (200 mL), 3 M methyl magnesium bromide in diethyl ether (52.0 mL, 156 mmol) was added dropwise over a period of 30 min at 0 °C. The reaction mixture was slowly brought to room temperature and stirred for 2 h. Then, the reaction mixture was treated with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 1-(2-chloro-6-methoxypyridin-3-yl)ethan-1-one (**152**) as a yellow solid. Yield: 14.0 g, crude; ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 7.97 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 3.99 (s, 3H), 3.68 (s, 3H); MS (ESI) *m*/*z*: 186.14 $[M + 1]^+$.

*1-(6-Methoxy-2-((4-methoxybenzyl)oxy)pyridin-3-yl)ethan-1-one (**S94**).* To a solution of crude 1-(2-chloro-6-methoxypyridin-3-yl)ethan-1-one (**152**) (14.0 g) in tetrahydrofuran (100 mL) under nitrogen at 0 °C, sodium hydride (4.5 g, 190 mmol) was added. This mixture was stirred for 10 min. Then, 4-methoxybenzyl alcohol (**S93**) (11.0 mL, 12.2 g, 88.6 mmol) was added dropwise over a period of 30 min at 0 °C, and the mixture was stirred at room temperature for 2 h. Then, the reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (2 × 150 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product, which was purified by silica gel (100−200 mesh) column chromatography using 20% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated under reduced pressure to afford 1-(6-methoxy-2-((4-methoxybenzyl)oxy)pyridin-3-yl)ethan-1-one (**S94**) as a yellow solid. Yield: 10.5 g (0.0366 mmol, 47% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 8.15 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 6.36 (d, J = 8.4 Hz, 1H), 5.44 (s, 2H), 3.98 (s, 3H), 3.82 (s, 3H), 2.59 (s, 3H); MS (ESI) *m*/*z*: 288.23 $[M + 1]^+$.

*3-Acetyl-6-methoxypyridin-2(1H)-one (**153**).* To a solution of 1-(6-methoxy-2-((4-methoxybenzyl)oxy)pyridin-3-yl)ethan-1-one (**S94**) (10.5 g, 36.5 mmol) in dichloromethane (100 mL) at 0 °C, trifluoroacetic acid (2.0 mL, 3.0 g, 26 mmol) was added. This reaction mixture was stirred at room temperature for 2 h. Then, the mixture was treated with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 3-acetyl-6-methoxypyridin-2(1*H*)-one (**153**) as a yellow solid. Yield: 5.0 g, crude; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 13.12 (br s, 1H), 8.20 (d, J = 8.5 Hz, 1H), 6.37 (d, J = 6.6 Hz, 1H), 3.89 (s, 3H), 2.55 (s, 3H); MS (ESI) *m*/*z*: 168.17 $[M + 1]^+$.

*(E)-3-(3-(4-Bromophenyl)acryloyl)-6-methoxypyridin-2(1H)-one (**S95**).* To a solution of 3-acetyl-6-methoxypyridin-2(1*H*)-one (**153**) (4.5 g, 27 mmol) in methanol (30.0 mL), sodium hydroxide (3.17 g, 79.3 mmol) and 4-bromobenzaldehyde (5.3 g, 28 mmol) were added. The reaction mixture was heated at 80 °C for 2 h. After this time, the reaction mixture was cooled, and the resulting solid was collected by filtration, washed with water, and dried under vacuum to afford (*E*)-3-(3-(4-bromophenyl)acryloyl)-6-methoxypyridin-2(1*H*)-one (**S95**) as a yellow solid. Yield: 8.5 g, crude; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.58 (d, J = 16.0 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 16.0 Hz, 1H), 5.51 (d, J

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= 8.4 Hz, 1H), 3.68 (s, 3H); MS (ESI) m/z: 168.17 $[M + 1]^+$; MS (ESI) m/z: 332.11 $[M - 1]^-$.

*2-(4-Bromophenyl)-3-hydroxy-7-methoxy-4H-pyrano[2,3-b]-pyridin-4-one (**154**).* To a solution of crude (*E*)-3-(3-(4-bromophenyl)acryloyl)-6-methoxypyridin-2(1*H*)-one (**S95**) (6 g) in ethanol and dichloromethane (1:1, 200 mL) at room temperature, sodium hydroxide (10% aq, 50 mL, 56 g solution, 5.6 g NaOH, 140 mmol) was added followed by 30% hydrogen peroxide (14.1 mL, 15.7 g solution, 4.70 g H_2O_2, 138 mmol). The reaction mixture was stirred for 2 h (reaction is very exothermic!). After this time, the reaction mixture was cooled to 0 °C and brought to pH ≈ 8 using 6 M HCl. The solvent was removed under reduced pressure, and the resulting solid was collected by filtration. This solid was suspended in ethanol. This mixture was cooled to 0 °C and neutralized to pH ≈ 6 with 6 M hydrochloric acid. The resulting precipitate was again collected by filtration and dried under vacuum to afford 2-(4-bromophenyl)-3-hydroxy-7-methoxy-4*H*-pyrano[2,3-*b*]pyridin-4-one (**154**) as a yellow solid. Yield: 3.2 g (9.2 mmol, 40% over three steps). MS (ESI) m/z: 348.16 $[M + 1]^+$.

*rac-Methyl (2S,4R,5R)-2-(4-Bromophenyl)-5-hydroxy-8-methoxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanooxepino[2,3-b]-pyridine-4-carboxylate (**S96**).* A solution of 2-(4-bromophenyl)-3-hydroxy-7-methoxy-4*H*-pyrano[2,3-*b*]pyridin-4-one (**11**, 3.0 g, 8.6 mmol) and methyl cinnamate (**55**) (1.4 g, 8.6 mmol) in dichloromethane (200 mL), acetonitrile (100 mL), and methanol (100 mL) was irradiated for 16 h under 400 W UV light in a UV reactor flask. After this time, the solvent was removed under reduced pressure, and the residue was purified by Combi-flash (12 g, RediSep) using ethyl acetate as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-methyl (2*S*,4*R*,5*R*)-2-(4-bromophenyl)-5-hydroxy-8-methoxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanooxepino[2,3-*b*]pyridine-4-carboxylate (**S96**) as a yellow solid. Yield: 1.3 g, crude. MS(ESI) m/z: 508.33 $[M - 1]^-$.

*rac-Methyl (4bR,6R,7S,7aR)-7a-(4-Bromophenyl)-4b-hydroxy-2-methoxy-5-oxo-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]-furo[2,3-b]pyridine-6-carboxylate (**S97**).* The crude methyl (2*S*,4*R*,5*R*)-2-(4-bromophenyl)-5-hydroxy-8-methoxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanooxepino[2,3-*b*]pyridine-4-carboxylate (**S96**) (1.3 g) was suspended in methanol (13.0 mL), treated with sodium methoxide (25% in methanol, 13.0 mL, 12.3 g solution, 3.07 g NaOMe, 56.9 mmol), and heated at 80 °C for 2 h. After this time, the solvent was removed under reduced pressure and the reaction mixture was diluted with ammonium chloride solution and extracted with ethyl acetate. The organic phase was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford *rac*-methyl (4b*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b-hydroxy-2-methoxy-5-oxo-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]-furo[2,3-*b*]pyridine-6-carboxylate (**S97**) as a brown solid. Yield: 1.1 g, crude; MS (ESI) m/z: 508.33 $[M - 1]^-$.

*rac-Methyl (4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-2-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta-[4,5]furo[2,3-b]pyridine-6-carboxylate (**155**).* To a solution of crude *rac*-methyl (4b*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b-hydroxy-2-methoxy-5-oxo-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo-[2,3-*b*]pyridine-6-carboxylate (**S97**) (1.0 g) in acetonitrile (20.0 mL), sodium triacetoxyborohydride (2.7 g, 13 mmol) and acetic acid (1.23 mL, 1.29 g, 21.5 mmol) were added. The resulting mixture was stirred for 4 h at room temperature. After this time, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford *rac*-methyl (4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-2-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*b*]pyridine-6-carboxylate (**155**) as a white solid. Yield: 120 mg (0.234 mmol, 3% over three steps); MS (ESI) m/z: 512.32 $[M + 1]^+$.

*rac-(4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-2-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo-[2,3-b]pyridine-6-carboxylic Acid (**S98**).* To a solution of *rac*-methyl (4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-2-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*b*]-pyridine-6-carboxylate (**16**, 110 mg, 0.215 mmol) in methanol and water (2:1, 6.0 mL), lithium hydroxide (20.0 mg, 0.835 mmol) was added and the reaction was stirred for 16 h at room temperature. After this time, the reaction mixture was cooled to 0 °C and acidified with 1 M hydrochloric acid to pH ≈ 3. The resulting precipitate was collected by filtration and dried under vacuum to afford *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-2-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*b*]pyridine-6-carboxylic acid (**S98**) as a brown solid. Yield: 100 mg (0.201 mmol, 93%); MS (ESI) m/z: 496.16 $[M - 1]^-$.

*rac-(4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-2-methoxy-N,N-dimethyl-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo[2,3-b]pyridine-6-carboxamide (**156**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-2-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]-furo[2,3-*b*]pyridine-6-carboxylic acid (**S98**) (100 mg, 0.201 mmol) in dichloromethane (10.0 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (96.0 mg, 0.501 mmol), 1-hydroxybenzotriazole (76.0 mg, 0.562 mmol), and *N*,*N*-diisopropylethylamine (0.213 mL, 158 mg, 1.22 mmol) were added. This mixture was stirred for 5 min. Dimethylamine hydrochloride (81.0 mg, 0.993 mmol) was then added at same temperature, and the mixture was stirred for 6 h at room temperature. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by Combi-flash (4 g, RediSep) using 70% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-2-methoxy-*N*,*N*-dimethyl-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo-[2,3-*b*]pyridine-6-carboxamide (**156**) as an off-white solid. Yield: 40.0 mg (0.076 mmol, 38%). ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.74 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 7.06−6.99 (m, 3H), 6.84 (d, J = 7.0 Hz, 2H), 6.43 (d, J = 8.1 Hz, 1H), 5.64 (d, J = 6.2 Hz, 1H), 5.45 (s, 1H), 4.88−4.86 (m, 1H), 4.17 (d, J = 13.3 Hz, 1H), 4.05−4.00 (m, 1H), 3.88 (s, 3H), 3.20 (s, 3H), 2.72 (s, 3H); MS (ESI) m/z: 525.28 $[M + 1]^+$.

*rac-(4bS,5R,6R,7S,7aR)-7a-(4-Cyanophenyl)-4b,5-dihydroxy-2-methoxy-N,N-dimethyl-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo[2,3-b]pyridine-6-carboxamide (rac-**36**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-2-methoxy-*N*,*N*-dimethyl-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*b*]pyridine-6-carboxamide (**156**) (40.0 mg, 0.076 mmol) in *N*,*N*-dimethylformamide (5.0 mL), zinc cyanide (18.0 mg, 0.153 mmol) and zinc (25.0 mg, 0.382 mmol) were added at room temperature. The mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (4.0 mg, 0.0072 mmol) and tris(dibenzylideneacetone) dipalladium (7.1 mg, 0.0078 mmol) were added to the reaction mixture and degassing was continued for another 5 min. The reaction mixture was then heated at 140 °C for 6 h. After this time, the mixture was cooled to room temperature and filtered through Celite. The filtrate was diluted with ethyl acetate and washed with water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product, which was purified by reverse-phase HPLC, and the desired fractions were concentrated under reduced pressure to afford *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-cyanophenyl)-4b,5-dihydroxy-2-methoxy-*N*,*N*-dimethyl-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta-[4,5]furo[2,3-*b*]pyridine-6-carboxamide (*rac*-**36**) as an off-white solid. Yield: 8.0 mg (0.017 mmol, 22%). MS (ESI) m/z: 472.44 $[M + 1]^+$; UPLC: 95.37%; HRMS (ESI): calcd, 472.1867 $[M + H]^+$; found, 472.1871; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.75 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.06−6.97 (m, 3H), 6.85 (d, J = 7.1 Hz, 2H), 6.46 (d, J = 8.0 Hz, 1H), 5.69 (d, J = 6.0 Hz, 1H), 5.57 (s, 1H), 4.92 (t, J = 7.7 Hz, 1H), 4.26 (d, J = 13.1 Hz, 1H), 4.12 (dd, J = 13.0, 8.0 Hz, 1H), 3.88 (s, 3H), 3.22 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 168.15, 164.72, 163.48, 141.57, 140.19, 137.99, 130.63, 128.58, 127.53, 127.49,

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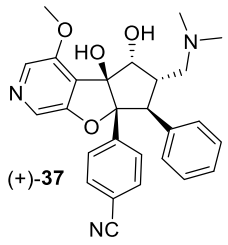
126.12, 118.82, 113.77, 109.20, 102.61, 99.30, 90.89, 77.42, 55.59, 53.59, 46.80, 36.43, 35.15.

Synthesis of 4-((4bS,5R,6S,7S,7aR)-6-((Dimethylamino)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-

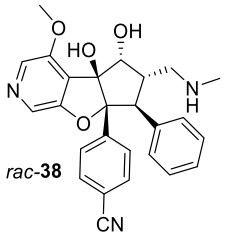


(+)-**37**

*cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((+)-**37**). rac-(4bS,5R,6S,7S,7aR)-7a-(4-Bromophenyl)-6-((dimethylamino)-methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4bH-cyclopenta-[4,5]furo[2,3-c]pyridine-4b,5-diol (**158a**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-*N*,*N*-dimethyl-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo-[2,3-*c*]pyridine-6-carboxamide (**149**) (0.80 g, 1.52 mmol) in dry tetrahydrofuran (20 mL) at 0 °C, borane dimethylsulfide complex (1.30 mL, 1.04 g, 14.7 mmol) was added. The resulting mixture was stirred for 16 h at room temperature. After this time, the reaction mixture was quenched with methanol at 0 °C and refluxed at 80 °C for 6 h. After this time, the reaction mixture was concentrated to give the crude product, which was purified by silica gel column chromatography using 0−5% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-((dimethylamino)methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158a**) as a white solid. Yield: 0.41 g (0.80 mmol, 53%). MS (ESI) *m*/*z*: 511.17 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.02 (s, 1H), 7.95 (s, 1H), 7.21 (d, J = 8.5 Hz, 2H), 7.14−7.07 (m, 4H), 7.02−6.98 (m, 3H), 5.63 (s, 1H), 4.50 (s, 1H), 3.88 (s, 3H), 3.72 (d, J = 13.8 Hz, 1H), 3.16−3.06 (m, 1H), 2.35−2.12 (m, 8H), 2.06−1.90 (m, 1H).

*4-((4bS,5R,6S,7S,7aR)-6-((Dimethylamino)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta-[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((+)-**37**).* To a solution of *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-((dimethylamino)-methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta-[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158a**) (0.4 g, 0.8 mmol) in *N*,*N*-dimethylformamide (10 mL) at room temperature, zinc cyanide (0.45 g, 3.83 mmol) and zinc dust (0.026 g, 0.39 mmol) were added, and the reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (0.021 g, 0.038 mmol) and tris-(dibenzylideneacetone)dipalladium (0.035 g, 0.038 mmol) were added to the reaction mixture, which was then degassed for an additional 5 min and heated at 140 °C for 3 h. After this time, the reaction mixture was diluted with ethyl acetate and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by silica gel column chromatography using 2−3% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford racemic 4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((dimethylamino)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-7a-yl)-benzonitrile (*rac*-**37**) as a white solid. Yield: 0.220 g (0.481 mmol, 60%). MS (ESI) *m*/*z*: 458.31 $[M + 1]^+$. The enantiomers were separated by chiral preparative HPLC [Chiralpak ID (4.6 × 250) mm, 5μ]. Peak 1 (43 mg, (−)-**37**), R_t 10.667 min, ee = 99.24%, ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.04 (s, 1H), 7.96 (s, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.09−7.05 (m, 2H), 7.01−6.97 (m, 3H), 5.73 (s, 1H), 4.48 (d, J = 3.8 Hz, 1H), 3.87 (s, 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.19−3.12 (m, 1H), 2.20 (s, 6H), 1.97 (d, J = 12.8 Hz, 1H), 1.89 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 155.78, 153.46, 142.61, 136.94, 130.13, 128.65, 128.54, 127.70, 127.06, 126.29, 125.45, 123.54, 118.91, 108.90, 101.87, 93.73, 77.44, 57.48, 56.33, 56.17, 45.82, 43.54. Peak-2 (38 mg, (+)-**37**), $[\alpha]_D$ +25.0° (*c* 0.26, $CHCl_3$), R_t 13.904 min, ee >97%; HRMS (ESI): calcd, 458.2074 $[M + H]^+$; found, 458.2078; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.04 (s, 1H), 7.96 (s, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.09−7.05 (m, 2H), 7.01−6.99 (m, 3H), 5.73 (s, 1H), 4.48 (d, J = 4.0 Hz, 1H), 3.87 (s, 3H), 3.78 (d, J = 14 Hz, 1H), 3.19−3.16 (m, 1H), 2.20 (s, 6H), 1.97 (d, J = 12.8 Hz, 1H), 1.88 (s, 2H).

Synthesis of rac-4-((4bS,5R,6S,7S,7aR)-4b,5-Dihydroxy-4-methoxy-6-((methylamino)-methyl)-7-phenyl-4b,5,6,7-tetrahydro-



rac-**38**

*7aH-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile (rac-**38**). rac-(4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-4-methoxy-N-methyl-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta-[4,5]furo[2,3-c]pyridine-6-carboxamide (**157b**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxylic acid (**148**) (2.00 g, 4.01 mmol) in dichloromethane (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrogen chloride (1.54 g, 8.03 mmol), 1-hydroxybenzotriazole (1.08 g, 8.03 mmol), and *N*,*N*-diisopropylethylamine (2.07 g, 16.05 mmol, 2.8 mL) at 0 °C, and the mixture was stirred at 0 °C for 30 min. Then, methanamine (453.66 mg, 4.82 mmol, 33% in methanol) was added and the mixture was stirred at 25 °C for 12 h. LCMS showed that there was desired product detected. The reaction mixture was diluted with dichloromethane (20 mL) and washed with water (60 mL × 3). The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuum. The crude product was purified by column chromatography (dichloromethane/methanol = 20/1) to afford the product *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-*N*-methyl-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta-[4,5]furo[2,3-*c*]pyridine-6-carboxamide (**157b**) as a white solid. Yield: 1.86 g (3.64 mmol, 91%). MS (ESI) *m*/*z*: 511.0 $[M + 1]^+$.

*rac-(4bS,5R,6S,7S,7aR)-7a-(4-Bromophenyl)-4-methoxy-6-((methylamino)methyl)-7-phenyl-5,6,7,7a-tetrahydro-4bH-cyclopenta[4,5]furo[2,3-c]pyridine-4b,5-diol (**158b**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-*N*-methyl-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]-furo[2,3-*c*]pyridine-6-carboxamide (**157b**) (1.86 g, 3.64 mmol) in tetrahydrofuran (40 mL) was added borane dimethyl sulfide complex solution (10 M, 3.64 mL) at 0 °C, and the mixture was stirred at 25 °C for 30 min. Then, the mixture was refluxed at 60 °C for 2 h. TLC (dichloromethane/methanol = 10/1) showed that there was no starting material left. The reaction mixture was quenched with acetic acid (5 mL) at 0 °C, and the mixture was refluxed at 60 °C for 1 h. The reaction mixture was concentrated and washed with petroleum/ethyl acetate = 2: 1 (30 mL) and filtered. The filter-cake was diluted with water (30 mL) and extracted with ethyl acetate (10 mL × 2). The water phase was adjusted pH = 7−8 with saturated sodium bicarbonate and then extracted with ethyl acetate (20 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate and concentrated in vacuum to afford the product *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-4-methoxy-6-((methylamino)methyl)-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158b**) as a white solid. Yield: 1.45 g (2.92 mmol, 80%). MS (ESI) *m*/*z*: 497.0 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.05 (s, 1H), 7.98 (s, 1H), 7.24 (d, J = 8.8 Hz, 2H), 7.13−7.08 (m, 4 H), 7.03−7.01 (m, 3 H), 5.68 (s, 1 H), 4.59 (d, J = 4.0 Hz, 1H), 3.89 (s, 3 H), 3.72 (d, J = 14.4 Hz, 1 H), 3.23−3.17 (m, 3 H), 2.81−2.78 (m, 1 H), 2.57−2.53 (m, 1 H), 2.37 (s, 3 H).

rac-4-((4bS,5R,6S,7S,7aR)-4b,5-Dihydroxy-4-methoxy-6-((methylamino)methyl)-7-phenyl-4b,5,6,7-tetrahydro-7aH-

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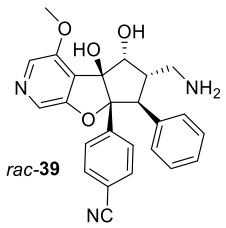
*cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile (rac-**38**).* To a solution of *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-4-methoxy-6-((methylamino)methyl)-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158b**) (300 mg, 0.60 mmol) in DMSO (3 mL) was added zinc cyanide (283 mg, 2.41 mmol) and zinc (79 mg, 1.21 mmol) at 25 °C, and the reaction mixture was degassed with nitrogen for 15 min. 1,1′-Bis-(diphenylphosphino)ferrocene (67 mg, 0.12 mmol) and tris-(dibenzylideneacetone)dipalladium (110 mg, 0.12 mmol) was added, and the mixture was stirred in microwave (100 w, 140 °C, 150 psi) for 2 h. LCMS showed the desired product. The reaction mixture was filtered, and the filtrate was concentrated in vacuum. The crude was purified by column chromatography (dichloromethane/methanol = 10/1) and monitored by LCMS. Then, the crude was purified by Prep-HPLC (Phenomenex Gemini C18 250 × 50 mm × 10 μm; mobile phase: [water (0.05% ammonia hydroxide v/v)−acetonitrile]; B %: 37%−62%, 30 min, 69% min) to afford the product *rac*-4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-4b,5-dihydroxy-4-methoxy-6-((methylamino)methyl)-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-7a-yl)benzonitrile (*rac*-**38**) as a white solid. Yield: 99 mg (0.22 mmol, 37%). MS (ESI) *m*/*z*: 444.2 [M + 1]$^+$; HRMS (ESI): calcd, 444.1918 [M + H]$^+$; found, 444.1931; HPLC: 99.81%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.06 (s, 1H), 7.98 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.09−7.05 (m, 2H), 7.01−6.99 (m, 3H), 5.73 (s, 1H), 4.56 (d, *J* = 3.6 Hz, 1H), 3.89 (s, 3H), 3.82 (d, *J* = 14.0 Hz, 1H), 3.20−3.14 (m, 1H), 2.69−2.66 (m, 1H), 2.27 (s, 3H).

Synthesis of rac-4-((4bS,5R,6S,7S,7aR)-6-(Aminomethyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4bH-



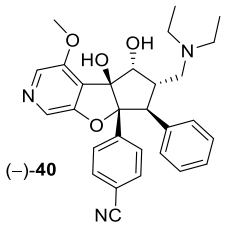
rac-**39**

*cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile (rac-**39**). rac-(4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo[2,3-c]pyridine-6-carboxamide (**157c**).* To a suspension of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxylic acid (**148**) (2.50 g, 5.02 mmol) in dichloromethane (30 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.92 g, 10.03 mmol), 1-hydroxybenzotriazole (1.36 g, 10.03 mmol) and *N*,*N*-diisopropylethylamine (1.95 g, 15.05 mmol). The mixture was stirred at 0 °C for 5 min, then ammonium chloride (322 mg, 6.02 mmol) was added, and the mixture was stirred at 20 °C for 12 h. The mixture was diluted with water (20 mL) and extracted with dichloromethane (60 mL × 2). The organic layer was dried and concentrated under reduced pressure to give a residue, which was purified by silica gel chromatography (dichloromethane: methanol = 20:1 to 10:1) to afford *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxamide (**157c**) as a light yellow solid. Yield: 2.00 g (4.02 mmol, 80%). MS (ESI) *m*/*z*: 497.0 [M + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.07 (s, 1H), 7.97 (s, 1H), 7.71 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.07−6.99 (m, 8H), 5.69 (s, 1H), 5.17 (d, *J* = 4.0 Hz, 1H), 4.60 (t, *J* = 4.4 Hz, 1H), 4.30 (d, *J* = 14.0 Hz, 1H), 3.91−3.90 (m, 1H), 3.87 (s, 3H).

*rac-(4bS,5R,6S,7S,7aR)-6-(Aminomethyl)-7a-(4-bromophenyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4bH-cyclopenta[4,5]furo-[2,3-c]pyridine-4b,5-diol (**158c**).* To a suspension of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxamide (**157c**) (2.00 g, 4.02 mmol) in tetrahydrofuran (40 mL) was added borane dimethyl sulfide complex (10 M, 4.02 mL) at 0 °C, and the mixture was heated to 60 °C for 0.5 h. The mixture was cooled to 0 °C, quenched with methanol (20 mL), and concentrated under reduced pressure to give a crude product, which was triturated in hexane/dichloromethane (10/1, 20 mL) and filtered off solid to afford *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-(aminomethyl)-7a-(4-bromophenyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]-pyridine-4b,5-diol (**158c**) as a white solid. Yield: 1.20 g (2.48 mmol, 62%). MS (ESI) *m*/*z*: 483.1 [M + 1]$^+$.

*rac-4-((4bS,5R,6S,7S,7aR)-6-(Aminomethyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo-[2,3-c]pyridin-7a-yl)benzonitrile (rac-**39**).* A mixture of *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-(aminomethyl)-7a-(4-bromophenyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]-pyridine-4b,5-diol (**158b**) (500 mg, 1.03 mmol), zinc powder (67 mg, 1.03 mmol), zinc cyanide (1.21 g, 10.34 mmol), tris-(dibenzylideneacetone)-dipalladium (95 mg, 103.4 μmol), and 1,1′-bis(diphenylphosphino)ferrocene (57 mg, 103.4 μmol) in DMSO (4 mL) was stirred at 130 °C under nitrogen and microwave irradiated (150 Psi, 40 W) for 1 h. The reaction mixture was purified by silica gel chromatography (dichloromethane/methanol = 20/1 to 10/1) to give the product, which was further purified by prep-HPLC (column: Phenomenex Gemini 150 × 25 mm × 10 μm; mobile phase: [water (0.05% ammonia hydroxide v/v)−acetonitrile]; B %: 40−70%, 10 min) to afford *rac*-4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-(aminomethyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta-[4,5]furo[2,3-*c*]pyridin-7a-yl)benzonitrile (*rac*-**39**) as a light yellow solid. Yield: 22 mg (0.051 mmol, 5%). MS (ESI) *m*/*z*: 430.1 [M + 1]$^+$; HRMS (ESI): calcd, 430.1761 [M + H]$^+$; found, 430.1776; HPLC: 99.89%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.06 (s, 1H), 7.98 (s, 1H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.08−7.04 (m, 2H), 7.01−6.99 (m, 3H), 5.68 (s, 1H), 4.59 (d, *J* = 4.4 Hz, 1H), 3.89 (s, 3H), 3.77 (d, *J* = 14.0 Hz, 1H), 3.06−2.90 (m, 1H), 2.67−2.60 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 155.65, 153.54, 142.57, 136.99, 130.10, 128.67, 128.51, 127.62, 127.04, 126.26, 125.66, 123.73, 118.90, 108.91, 102.22, 93.67, 77.93, 56.71, 56.23, 47.63.

Synthesis of 4-((4bS,5R,6S,7S,7aR)-6-((Diethylamino)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-



(−)-**40**

*cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((−)-**40**). rac-(4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-N,N-diethyl-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta-[4,5]furo[2,3-c]pyridine-6-carboxamide (**157d**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxylic acid (**1**, 1.50 g, 3.01 mmol) in dichloromethane (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbod-iimide hydrogen chloride (1.15 g, 6.02 mmol), 1-hydroxybenzotriazole (813 mg, 6.02 mmol) and *N*,*N*-diisopropylethylamine (2.33 g, 18.06 mmol, 3.15 mL) at 0 °C, and the mixture was stirred at 0 °C for 30 min. Then, *N*-ethylethanamine (495 mg, 4.51 mmol, hydrochloride) was added and the mixture was stirred at 25 °C for 12 h. LCMS showed that there was desired product detected. The reaction mixture was washed with water (30 mL × 3). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuum to give the crude. The crude was purified by column chromatography (dichloromethane/methanol = 20/1) to afford the product *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-*N*,*N*-diethyl-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxamide (**3**) as a yellow solid. Yield: 1.00 g, 55% yield; MS (ESI) *m*/*z*: 555.1 [M + 1] $^+$.

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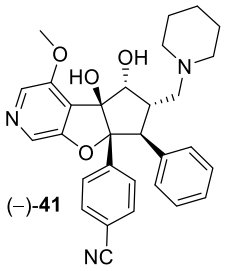
*rac-(4bS,5R,6S,7S,7aR)-7a-(4-Bromophenyl)-6-((diethylamino)-methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4bH-cyclopenta-[4,5]furo[2,3-c]pyridine-4b,5-diol (**158d**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-*N*,*N*-diethyl-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]-furo[2,3-*c*]pyridine-6-carboxamide (**157d**) (1.00 g, 1.81 mmol) dissolved in tetrahydrofuran (10 mL) was added borane dimethyl sulfide complex solution (10 mol/L, 1.81 mL) at 0 °C, and the mixture was stirred at 25 °C for 30 min. Then, the mixture was refluxed at 60 °C for 2 h. LCMS showed that there was no starting material. The reaction mixture was quenched with acetic acid (3 mL) at 0 °C, and the mixture was refluxed at 60 °C for 1 h. LCMS showed that there was desired product detected. The reaction mixture was concentrated, and the residue was washed with petroleum/ethyl acetate = 2:1 (30 mL) and filtered. The filter cake was diluted with water (30 mL) and extracted with ethyl acetate (10 mL × 2). The aqueous layer was adjusted to pH = 7−8 with saturated sodium bicarbonate solution and then extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum to afford the product *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-((diethylamino)methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo-[2,3-*c*]pyridine-4b,5-diol (**158d**) as a white solid. Yield: 620 mg (1.12 mmol, 62%); MS (ESI) *m*/*z*: 539.1 $[M + 1]^+$.

*4-((4bS,5R,6S,7S,7aR)-6-((Diethylamino)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo-[2,3-c]pyridin-7a-yl)benzonitrile ((−)-**40**).* A mixture of *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-((diethylamino)methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo-[2,3-*c*]pyridine-4b,5-diol (**158d**) (30 mg, 55.6 μmol), zinc powder (4 mg, 55.6 μmol), tris(dibenzylideneacetone)dipalladium(0) (5 mg, 5.56 μmol), bis(diphenylphosphino)ferrocene (3 mg, 5.56 μmol), and zinc cyanide (65 mg, 556 μmol) in DMSO (1 mL) was stirred at 130 °C under nitrogen in microwave (150 Psi, 40 W) for 1 h. The reaction mixture was directly purified by silica gel chromatography (dichloromethane/methanol = 20:1 to 10:1) to give the product. The enantiomers were separated by chiral Prep-HPLC (AD-3S_5_40_3.0 mL Column: Chiralpak AD-3 100 × 4.6 mm I.D, 3 μm mobile phase: 40% ethanol (0.05% DEA) in CO_2 flow rate: 3.0 mL/min AD-3S_4_5_40_3 mL; column: Chiralpak AD-3 100 × 4.6 mm I.D, 3 μm mobile phase: iso-propanol (0.05% DEA) in CO_2 from 5 to 40% flow rate: 3 mL/min wavelength: 220 nm) to afford two enantiomers. The two enantiomers were further purified by Prep-HPLC (column: Phenomenex Gemini C_{18} 250 × 21.2 mm × 5 μm; mobile phase: [water (0.05% ammonia hydroxide v/v)−acetonitrile]; B %: 41−71%, 12 min) to give both enantiomeric products. Peak 1 ((−)-**40**, 1.1 mg), yield: 4%; $[\alpha]_D$ −13.228° (*c* 0.08, $CHCl_3$), R_t 0.562 min, ee = 100%; MS (ESI) *m*/*z*: 486.2 $[M + 1]^+$; HRMS (ESI): calcd, 486.2387 $[M + H]^+$; found, 486.2405; HPLC: 99.90%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.05 (s, 1H), 7.97 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.09−7.05 (m, 2H), 7.02−6.99 (m, 3H), 5.71 (s, 1H), 5.20 (s, 1H), 4.50 (d, *J* = 3.2 Hz, 1H), 3.88 (s, 3H), 3.84 (d, *J* = 14.4 Hz, 1H), 3.20−3.16 (m, 1H), 2.62−2.52 (m, 3H), 2.49−2.44 (m, 2H), 2.30−2.25 (m, 1H), 0.94 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 155.86, 153.44, 142.66, 137.06, 130.12, 128.71, 128.53, 127.66, 127.01, 126.28, 125.41, 123.44, 118.91, 108.88, 101.92, 93.70, 77.96, 57.63, 56.14, 50.21, 46.57, 43.96, 11.52. Peak 2 ((+)-**40**, 2.2 mg), yield: 8%; $[\alpha]_D$ +10.096° (*c* 0.08, $CHCl_3$), +3.039° (*c* 0.08, methanol), R_t 1.317 min, ee = 99.72%; MS (ESI) *m*/*z*: 486.2 $[M + 1]^+$; HPLC: 100%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.05 (s, 1H), 7.97 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.09−7.05 (m, 2H), 7.02−6.99 (m, 3H), 5.73 (s, 1H), 5.22 (s, 1H), 4.50 (s, 1H), 3.88 (s, 3H), 3.84 (d, *J* = 14.0 Hz, 1H), 3.31−3.25 (m, 1H), 2.62−2.58 (m, 3H), 2.49−2.44 (m, 2H), 2.30−2.25 (m, 1H), 0.94 (t, *J* = 7.2 Hz, 6H).

*Synthesis of 4-((4bS,5R,6S,7S,7aR)-4b,5-Dihydroxy-4-methoxy-7-phenyl-6-(piperidin-1-ylmethyl)-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((−)-**41**). rac-((4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo[2,3-c]pyridin-6-yl)(piperidin-1-yl)methanone (**157e**).* To a solution of



rac-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]-pyridine-6-carboxylic acid (**148**) (1.0 g, 2.0 mmol) in dichloromethane (25.0 mL), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (1.16 g, 6.05 mmol), hydroxybenzotriazole (0.82 g, 5.4 mmol), and *N*,*N*-diisopropylethylamine (1.5 mL, 1.1 g, 8.6 mmol) were added at 0 °C. This reaction mixture was stirred for 5 min. Then, piperidine (**S99**) (0.297 g, 3.49 mmol) was then added at same temperature, and the reaction was stirred at room temperature for 5 h. After this time, the reaction mixture was diluted with dichloromethane (20 mL) and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by reverse-phase HPLC to afford *rac*-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta-[4,5]furo[2,3-*c*]pyridin-6-yl) (piperidin-1-yl)methanone (**157e**) as a white solid. Yield: 0.80 g (1.4 mmol, 71%). MS (ESI) *m*/*z*: 565.26 $[M + 1]^+$, UPLC: 99.79%, ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.09 (s, 1H), 7.98 (s, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.07−7.02 (m, 4H), 6.97−6.93 (m, 1H), 6.90 (d, *J* = 8.1 Hz, 2H), 5.71 (s, 1H), 5.11 (d, *J* = 5.4 Hz, 1H), 4.67 (t, *J* = 5.1 Hz, 1H), 4.47 (d, *J* = 13.3 Hz, 1H), 4.18 (dd, *J* = 4.9 Hz, 13.2 Hz, 1H), 3.87 (s, 3H), 3.73 (br s, 2H), 3.35 (m, 2H), 1.75−1.64 (m, 4H), 1.46−1.34 (m, 2H).

*rac-(4bS,5R,6S,7S,7aR)-7a-(4-Bromophenyl)-4-methoxy-7-phenyl-6-(piperidin-1-ylmethyl)-5,6,7,7a-tetrahydro-4bH-cyclopenta-[4,5]furo[2,3-c]pyridine-4b,5-diol (**158e**).* To a solution of ((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]-pyridin-6-yl) (piperidin-1-yl)methanone (**157e**) (0.80 g, 1.4 mmol) in tetrahydrofuran at 0 °C, borane dimethylsulfide complex (1.2 mL, 0.96 g, 12.6 mmol) was added. The reaction mixture was stirred for 3 h at room temperature. After this time, the reaction mixture was quenched with methanol at 0 °C and then heated at 60 °C for 4 h. The solvents were concentrated to obtain the crude product which was purified by Combi-flash (4 g, RediSep column) using 7% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-4-methoxy-7-phenyl-6-(piperidin-1-ylmethyl)-5,6,7,7a-tetrahydro-4b*H*-cyclopenta-[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158e**) as a white solid. Yield: 0.4 g (0.7 mmol, 50%). MS (ESI) *m*/*z*: 551.1 $[M + 1]^+$.

*4-((4bS,5R,6S,7S,7aR)-4b,5-Dihydroxy-4-methoxy-7-phenyl-6-(piperidin-1-ylmethyl)-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]-furo[2,3-c]pyridin-7a-yl)benzonitrile ((−)-**41**).* To a mixture of *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-4-methoxy-7-phenyl-6-(piperidin-1-ylmethyl)-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158e**) (0.4 g, 0.7 mmol) in *N*,*N*-dimethylformamide (3.0 mL) at room temperature, zinc cyanide (0.508 g, 4.33 mmol) and zinc (0.047 g, 0.72 mmol) were added at room temperature, and the mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino) ferrocene (0.092 g, 0.166 mmol) and tris(dibenzylideneacetone)dipalladium (0.152 g, 0.166 mmol) were added to the reaction mixture and degassing was continued for another 5 min. The reaction mixture was heated at 140 °C for 2.5 h. After this time, the reaction mixture was cooled to room temperature and filtered with Celite. The filtrate was diluted with ethyl acetate and washed with water. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the crude product which was purified by Combi-flash (12 g, RediSep column) using 0−10% methanol in dichloromethane as the

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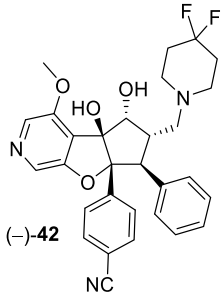
eluent. The product thus obtained was further purified by reverse-phase prep HPLC. The desired fractions were lyophilized to afford *rac*-4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-4b,5-dihydroxy-4-methoxy-7-phenyl-6-(piperidin-1-ylmethyl)-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]-pyridin-7a-yl)benzonitrile (*rac*-**41**) as a white solid. Yield: 0.350 g (0.7 mmol, quant.). The enantiomers were separated by chiral preparative HPLC [Chiralpak IA (4.6 × 250) mm] using 0.1% TEA in *n*-hexane/IPA(80/20) (v/v) mobile phase. Peak 1 (31 mg, (+)-**41**); $[\alpha]_D$ +11.5° (*c* 0.34, $CHCl_3$), R_t 14.5, ee >99%; MS (ESI) *m*/*z*: 498.32 $[M + 1]^+$; UPLC: 97.70%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.04 (s, 1H), 7.96 (s, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.12−7.07 (m, 2H), 7.05−6.99 (m, 3H), 5.72 (s, 1H), 4.50 (d, *J* = 3.6 Hz, 1H), 3.87 (s, 3H), 3.81 (d, *J* = 13.8 Hz, 1H), 2.32−2.27 (m, 3H), 2.09 (d, *J* = 11.6 Hz, 1H), 1.64 (s, 2H), 1.52−1.50 (m, 5H), 1.37 (s, 3H). Peak-2 (17 mg, (−)-**41**); $[\alpha]_D$ −10.4° (*c* 0.23, $CHCl_3$), R_t 22.8, ee >99%; MS (ESI) *m*/*z*: 497.91 $[M + 1]^+$; HRMS (ESI): calcd, 498.2387 $[M + H]^+$; found, 498.2382; UPLC: 99.60%. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.04 (s, 1H), 7.96 (s, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.08−7.05 (m, 2H), 7.01−6.96 (m, 3H), 5.72 (s, 1H), 5.38 (br s, 1H), 4.50 (d, *J* = 3.4 Hz, 1H), 3.87 (s, 3H), 3.80 (d, *J* = 14.0 Hz, 1H), 2.28−2.24 (m, 2H), 2.06 (d, *J* = 11.2 Hz, 1H), 1.88 (s, 4H), 1.59−1.51 (m, 4H), 1.40−1.37 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 155.82, 153.44, 142.64, 137.00, 130.11, 128.69, 128.54, 127.67, 126.97, 126.26, 125.43, 123.47, 118.91, 108.87, 101.94, 93.70, 77.62, 57.46, 56.13, 55.90, 54.73, 25.73, 24.06, 21.43.

Synthesis of 4-((4bS,5R,6S,7S,7aR)-6-((4,4-Difluoropiperidin-1-yl)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((−)-42). *rac-((4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo[2,3-c]pyridin-6-yl)(4,4-difluoropiperidin-1-yl)methanone (157f).* To a solution of (4a*R*,5*S*,6*R*,7*R*,7a*S*)-4a-(4-bromophenyl)-7,7a-dihydroxy-2-(4-methoxybenzyl)-5-phenyl-2,4a,5,6,7,7a-hexahydrocyclopenta[4,5]furo[3,2-*c*]pyrazole-6-carboxylic acid (**148**) (0.9 g, 2 mmol) in dichloromethane (10 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.03 g, 5.37 mmol), 1-hydroxybenzotriazole (0.72 g, 5.41 mmol), and *N*,*N*-diisopropylethylamine (1.65 mL, 1.22 g, 9.44 mmol) were added. This reaction mixture was stirred for 5 min. Then, 4,4-difluoropiperidine hydrochloride (**S100**) (1.4 g, 8.9 mmol) was added at the same temperature, and the mixture was stirred for 16 h at room temperature. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by silica gel column chromatography eluting with 0−4% methanol in dichloromethane. The desired fractions were concentrated to afford ((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-6-yl) (4,4-difluoropiperidin-1-yl)methanone (**157f**) as a white solid. Yield: 0.67 g (1.1 mmol, 55%). ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.10 (s, 1H), 8.00 (s, 1H), 7.20 (d, *J* = 8.36 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 7.1 Hz, 2H), 6.97−6.92 (m, 3H), 5.72 (s, 1H), 5.30 (d, *J* = 5.5 Hz, 1H), 4.73−4.70 (m, 1H), 4.44 (, *J* = 13.2 Hz, 1H), 4.29−4.24 (m, 1H), 4.03−3.98 (m, 1H), 3.88 (s, 3H), 3.78−3.70 (m, 2H), 3.34−3.30 (m, 1H), 2.32−2.20 (m, 2H), 2.03−1.88 (m, 2H); MS (ESI) *m*/*z*: 601.01 $[M + 1]^+$.



(−)-**42**

rac-(4bS,5R,6S,7S,7aR)-7a-(4-Bromophenyl)-6-((4,4-difluoropiperidin-1-yl)methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4bH-cyclopenta[4,5]furo[2,3-c]pyridine-4b,5-diol (158f). To a solution of *rac*-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]-pyridin-6-yl) (4,4-difluoropiperidin-1-yl)methanone (**157f**) (0.6 g, 1 mmol) in dry tetrahydrofuran (25 mL) at 0 °C, borane dimethyl sulfide complex (1.0 mL, 0.80 g, 11 mmol) was added. The resulting mixture was stirred for 16 h at room temperature. After this time, the reaction mixture was quenched with methanol at 0 °C and refluxed at 80 °C for 6 h. Then, the reaction mixture was concentrated to obtain the crude product which was purified by silica gel column chromatography using 1−5% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-((4,4-difluoropiperidin-1-yl)methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta-[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158f**) as a white solid. Yield: 0.560 g (0.953 mmol, 95%); ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.02 (s, 1H), 7.95 (s, 1H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.15−7.12 (m, 2H), 7.10−7.06 (m, 2H), 7.00−6.98 (m, 3H), 5.62 (s, 1H), 5.00 (d, *J* = 5.2 Hz, 1H), 4.49 (s, 1H), 3.87 (s, 3H), 3.72 (d, *J* = 14.0 Hz, 1H), 3.20−3.17 (m, 1H), 2.67−2.60 (m, 4H), 2.14−2.08 (m, 1H), 2.03−1.87 (m, 4H); MS (ESI) *m*/*z*: 587.17 $[M + 1]^+$.

4-((4bS,5R,6S,7S,7aR)-6-((4,4-Difluoropiperidin-1-yl)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((−)-42). To a solution of *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-((4,4-difluoropiperidin-1-yl)methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158f**) (0.50 g, 0.85 mmol) in *N*,*N*-dimethylformamide (10 mL) at room temperature, zinc cyanide (0.59 g, 5.0 mmol) and zinc dust (0.006 g, 0.09 mmol) were added. The reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (0.009 g, 0.02 mmol) and tris(dibenzylideneacetone)dipalladium (0.023 g, 0.025 mmol) were added to the reaction mixture which was degassed for an additional 5 min and then heated at 140 °C for 4 h. After this time, the reaction mixture was diluted with ethyl acetate and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by silica gel column chromatography using 2−4% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford 4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((4,4-difluoropiperidin-1-yl)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-7a-yl)benzonitrile (*rac*-**42**) as a white solid. Yield: 0.325 g (0.609 mmol, 72%) (racemic mixture). The enantiomers were separated by chiral preparative HPLC [Chiralpak IC (4.6 × 250)mm, 5μ] in isocratic *n*-hexane/isopropanol 80/20 v/v. Peak-1 (79 mg, (+)-**42**), $[\alpha]_D$ +10.0° (*c* 0.27, $CHCl_3$), R_t 10.477 min, ee = 99.90%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (s, 1H), 7.97 (s, 1H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.09−6.98 (m, 5H), 5.73 (s, 1H), 5.08 (d, *J* = 5.6 Hz, 1H), 4.51 (s, 1H), 3.88 (s, 3H), 3.80 (d, *J* = 14.0 Hz, 1H), 3.32 (s, 1H), 2.70−2.49 (m, 5H), 2.15 (d, *J* = 9.6 Hz, 1H), 1.97 (br s, 4H). Peak-2 (74 mg, (−)-**42**), $[\alpha]_D$ −4.4° (*c* 0.27, $CHCl_3$), R_t 13.904 min, ee = 99.42%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (s, 1H), 7.97 (s, 1H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.09−6.98 (m, 5H), 5.73 (s, 1H), 5.08 (d, *J* = 5.6 Hz, 1H), 4.51 (s, 1H), 3.87 (s, 3H), 3.80 (d, *J* = 14.0 Hz, 1H), 3.32 (s, 1H), 2.70−2.49 (m, 5H), 2.15 (d, *J* = 9.6 Hz, 1H), 1.97 (br s, 4H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 155.79, 153.41, 142.57, 136.93, 130.09, 128.66, 128.57, 127.70, 126.95, 126.28, 125.47, 123.44, 122.89, 118.90, 108.90, 101.95, 93.78, 77.28, 57.37, 56.12, 54.10, 50.15 (t, *J* = 4.4 Hz), 43.44, 33.63 (t, *J* = 22 Hz); HRMS (ESI): calcd, 534.2199 $[M + H]^+$; found, 534.2214.

Synthesis of 4-((4bS,5R,6S,7S,7aR)-4b,5-Dihydroxy-4-methoxy-6-(morpholinomethyl)-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((−)-43). *rac-((4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo[2,3-c]pyridin-6-yl)(morpholino)methanone (157g).* To a solution of (4a*R*,5*S*,6*R*,7*R*,7a*S*)-4a-(4-bromophenyl)-7,7a-dihydroxy-2-(4-methoxybenzyl)-5-phenyl-2,4a,5,6,7,7a-hexahydrocyclopenta[4,5]furo-

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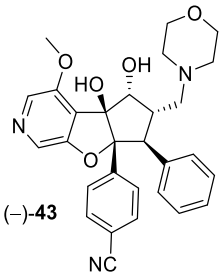


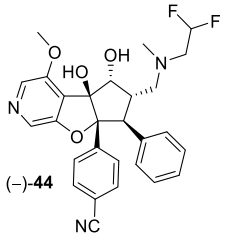
(−)-**43**

[3,2-*c*]pyrazole-6-carboxylic acid (**148**) (1.2 g, 2.4 mmol) in dichloromethane (12 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.37 g, 7.15 mmol), 1-hydroxybenzotriazole (0.97 g, 7.2 mmol) and *N*,*N*-diisopropylethylamine (2.21 mL, 1.64 g, 12.7 mmol) were added. This reaction mixture was stirred for 5 min. Morpholine (**S101**) (0.63 g, 7.2 mmol) was added at same temperature, and the mixture was stirred for 16 h at 40 °C. After completion, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by silica gel column chromatography eluting with 0−4% methanol in dichloromethane. The desired fractions were concentrated to afford *rac*-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta-[4,5]furo[2,3-*c*]pyridin-6-yl) (morpholino)methanone (**157g**) as a white solid. Yield: 0.91 g (1.6 mmol, 67%). MS (ESI) *m*/*z*: 567 [M + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.01 (s, 1H), 7.99 (s, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.09−7.04 (m, 4H), 6.99−6.91 (m, 3H), 5.69 (s, 1H), 5.22 (d, J = 5.4 Hz, 1H), 4.68 (d, J = 5.0 Hz, 1H), 4.45 (d, J = 13.7 Hz, 1H), 4.23−4.19 (m, 1H), 3.88 (s, 4H), 3.78−3.45 (m, 7H).

*rac-(4bS,5R,6S,7S,7aR)-7a-(4-Bromophenyl)-4-methoxy-6-(morpholinomethyl)-7-phenyl-5,6,7,7a-tetrahydro-4bH-cyclopenta[4,5]furo[2,3-c]pyridine-4b,5-diol (**158g**).* To a solution of *rac*-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]-pyridin-6-yl) (morpholino)methanone (**157g**) (0.8 g, 1.4 mmol) in dry tetrahydrofuran (20 mL) at 0 °C, borane dimethyl sulfide complex (1.1 mL, 0.88 g, 12 mmol) was added. The resulting mixture was stirred for 16 h at room temperature. After completion, the reaction mixture was quenched with methanol at 0 °C and refluxed at 80 °C for 6 h. Then, the reaction mixture was concentrated to obtain the crude product which was purified by silica gel column chromatography using 0−5% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-4-methoxy-6-(morpholinomethyl)-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158g**) as a white solid. Yield: 0.65 g (1.2 mmol, 86%). MS (ESI) *m*/*z*: 553.17 [M + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.01 (s, 1H), 7.95 (s, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.13−7.06 (m, 4H), 7.04−6.82 (m, 3H), 5.61 (s, 1H), 5.02 (d, J = 5.0 Hz, 1H), 5.02−4.98 (m, 1H), 3.99 (s, 3H), 3.74 (d, J = 14.0 Hz, 1H), 3.66−3.53 (m, 4H), 3.23−3.12 (m, 1H), 2.60−2.49 (m, 4H), 2.36−2.26 (m, 1H), 2.05 (d, J = 12.6 Hz, 1H).

*4-((4bS,5R,6S,7S,7aR)-4b,5-Dihydroxy-4-methoxy-6-(morpholinomethyl)-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo-[2,3-c]pyridin-7a-yl)benzonitrile ((−)-**43**).* To a solution of *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-4-methoxy-6-(morpholinomethyl)-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158g**) (0.6 g, 1.1 mmol) in *N*,*N*-dimethylformamide (10 mL) at room temperature, zinc cyanide (0.76 g, 6.5 mmol) and zinc dust (0.07 g, 1 mmol) were added. This reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)-ferrocene (0.006 g, 0.01 mmol) and tris(dibenzylideneacetone) palladium (0.003 g, 0.003 mmol) were added to the reaction mixture which was then degassed for an additional 5 min and heated at 140 °C for 3 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by silica gel column chromatography using 3−4% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford racemic 4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-4b,5-dihydroxy-4-methoxy-6-(morpholinomethyl)-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]-pyridin-7a-yl)benzonitrile (*rac*-**43**) as a white solid. Yield: 0.30 g (0.60 mmol, 55%) (racemic mixture). The enantiomers were separated by chiral preparative chiral HPLC [Chiralpak IA (4.6 × 250) mm, 5μ], *n*-hexane/EtOH = 30/70 v/v. Peak-1 (69 mg, (−)-**43**), $[\alpha]_D$ −4.0° (*c* 0.45, $CHCl_3$), R_t 5.548 min, ee >99.88%, ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (s, 1H), 7.96 (s, 1H), 7.49 (d, J = 7.2 Hz, 2H), 7.38 (d, J = 8.0 Hz 2H), 7.09−7.00 (m, 5H), 5.70 (s, 1H), 5.10 (d, J = 4.4 Hz, 1H), 4.50 (s, 1H), 3.88 (s, 3H), 3.81 (d, J = 14.0 Hz, 1H), 3.61 (br s, 4H), 3.31(br s, 1H), 2.62−2.50 (m, 4H), 2.33 (br s, 1H), 2.09 (d, J = 12.0 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 155.81, 153.42, 142.60, 136.94, 130.10, 128.68, 128.56, 127.70, 126.95, 126.29, 125.45, 123.45, 118.91, 108.89, 101.94, 93.74, 77.26, 66.33, 57.31, 56.12, 55.54, 53.91, 42.76. HRMS (ESI): calcd, 500.2180 [M + H]$^+$; found, 500.2185. Peak-2 (60 mg, (+)-**43**), $[\alpha]_D$ +4.3° (*c* 0.28, $CHCl_3$), R_t 8.285 min, ee >95.22%, ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (s, 1H), 7.96 (s, 1H), 7.49 (d, J = 7.2 Hz, 2H), 7.38 (d, J = 8.0 Hz 2H), 7.09−7.00 (m, 5H), 5.70 (s, 1H), 5.10 (d, J = 4.4 Hz, 1H), 4.50 (s, 1H), 3.88 (s, 3H), 3.81 (d, J = 14.0 Hz, 1H), 3.61 (br s, 4H), 3.31(br s, 1H), 2.62−2.50 (m, 4H), 2.33 (br s, 1H), 2.09 (d, J = 12.0 Hz, 1H).

Synthesis of 4-((4bS,5R,6S,7S,7aR)-6-(((2,2-Difluoroethyl)-(methyl)amino)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-



(−)-**44**

*4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)-benzonitrile ((−)-**44**). rac-(4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-N-(2,2-difluoroethyl)-4b,5-dihydroxy-4-methoxy-N-methyl-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo[2,3-c]pyridine-6-carboxamide (**157h**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxylic acid (**148**) (1.0 g, 2.0 mmol) in *N*,*N*- dimethylformamide (20 mL) at 0 °C, 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (2.29 g, 6.02 mmol) and *N*,*N*-diisopropylethylamine (1.8 mL, 1.3 g, 10 mmol) were added. The reaction mixture was stirred for 5 min. Then, 2,2-difluoroethan-1-amine hydrochloride (**S102**) (0.39 g, 4.1 mmol) was added and the reaction mixture was stirred for 4 h at room temperature. After this time, the reaction mixture was diluted with ethyl acetate and washed with cold water. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by Combiflash (12 g, RediSep column) using 3% methanol in dichloromethane as the eluent. Further purification was done on reverse-phase preparative HPLC. The desired fractions were lyophilized to afford (4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-*N*-(2,2-difluoroethyl)-4b,5-dihydroxy-4-methoxy-*N*-methyl-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxamide (**157h**) as a brown solid. Yield: 0.6 g (1.0 mmol, 50%). UPLC: 99.64%; MS (ESI) *m*/*z*: 575.25 [M + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.10 (s, 1H), 8.00 (s, 1H), 7.20 (d, J = 8.5 Hz, 2H), 7.09−7.01 (m, 4H), 6.97 (d, J = 7.0 Hz, 1H), 6.91 (d, J = 7.4 Hz, 2H), 6.56−6.29 (m, 1H), 5.74 (s, 1H), 5.22 (d, J = 5.5 Hz, 1H), 4.79 (t, J = 5.4 Hz, 1H), 4.45 (d, J = 10.0 Hz, 1H), 4.24 (dd, J = 5.0 Hz, 13.6 Hz, 1H), 3.80 (s, 3H), 3.68−3.56 (m, 2H), 3.38 (s, 3H).

rac-(4bS,5R,6S,7S,7aR)-7a-(4-Bromophenyl)-6-(((2,2-difluoroethyl)(methyl)amino)methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4bH-cyclopenta[4,5]furo[2,3-c]pyridine-4b,5-

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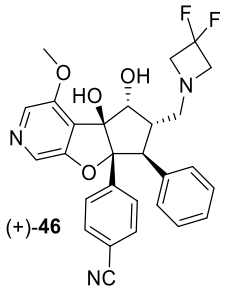
*diol (**158h**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-*N*-(2,2-difluoroethyl)-4b,5-dihydroxy-4-methoxy-*N*-methyl-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]-pyridine-6-carboxamide (**157h**) (0.6 g, 1.0 mmol) in tetrahydrofuran at 0 °C, borane dimethylsulfide (1.0 mL, 0.80 g, 11 mmol) was added. The reaction mixture was heated at 60 °C for 5 h. After this time, the reaction mixture was quenched with methanol at 0 °C and then heated at 80 °C for 6 h. The solvents were concentrated, and the compound was dried to afford *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-(((2,2-difluoroethyl) (methyl)amino)-methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158h**) as a brown solid. Yield: 0.55 g, crude. UPLC: 89.48%; MS (ESI) *m*/*z*: 559.57 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.09 (s, 1H), 8.02 (s, 1H), 7.22−7.03 (m, 9H), 5.96−5.36 (m, 1H), 4.65 (d, *J* = 4.0 Hz, 1H), 3.90 (s, 3H), 3.76−3.70 (m, 2H), 3.18−3.10 (m, 1H), 2.99−2.95 (m, 2 H), 2.74 (s, 3H), 2.38−2.27 (m, 2H).

*4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-(((2,2-Difluoroethyl)(methyl)amino)-methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((−)-**44**).* To a mixture of crude *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-(((2,2-difluoroethyl) (methyl)amino)methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158h**) (0.55 g, from previous step; used without further purification) in *N*,*N*- dimethylformamide (5.0 mL) at room temperature, zinc cyanide (690 mg, 5.88 mmol) and zinc dust (13 mg, 0.20 mmol) were added. The reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (16.0 mg, 0.029 mmol) and tris(dibenzylideneacetone)dipalladium (27.0 mg, 0.029 mmol) were added to the reaction mixture and degassing was continued for another 5 min. The reaction mixture was heated at 140 °C for 6 h. After this time, the reaction was cooled to room temperature and filtered with Celite. The filtrate was concentrated and treated with ice-cold water and the resulting precipitate was collected by filtration. The solid obtained was purified by Combiflash (12 g, RediSep column) using 30% ethyl acetate in hexanes as the eluent. The crude product was purified by reverse-phase preparative HPLC. The desired fractions were lyophilized to afford racemic 4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-(((2,2-difluoroethyl) (methyl)amino)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-7a-yl)benzonitrile (*rac*-**44**) as a white solid. Yield: 0.12 g (0.24 mmol, 24% over two steps). The enantiomers were separated by chiral preparative HPLC [Chiralpak IB (4.6 × 250) mm] using 0.1% TEA in *n*-hexane/IPA = 80/20(v/v) mobile phase. Peak 1 (49 mg, (+)-**44**), $[\alpha]_D$ +48.8° (*c* 0.24, $CHCl_3$), R_t 9.414 min, ee >99%. MS (ESI) *m*/*z*: 508.29 $[M + 1]^+$; UPLC: 99.36%. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.08 (s, 1H), 7.95 (s, 1H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.09−6.98 (m, 5H), 6.33−6.06 (m, 1H), 4.56 (d, *J* = 3.5 Hz, 1H), 3.86 (s, 3H), 3.75 (d, *J* = 14.0 Hz, 1H), 3.31−2.87 (m, 2H), 2.66−2.60 (m, 3H), 2.53 (s, 3H). Peak 2 (49 mg, (−)-**44**), $[\alpha]_D$ −10.8° (*c* 0.24, $CHCl_3$), R_t 14.357 min, ee >99%. MS (ESI) *m*/*z*: 508.29 $[M + 1]^+$; HRMS (ESI): calcd, 508.2042 $[M + H]^+$; found, 508.2051; UPLC: 96.14%. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.09 (s, 1H), 8.02 (s, 1H), 7.51 (d, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 7.1 Hz, 2H), 7.09−7.01 (m, 5H), 6.31−5.17 (m, 1H), 4.53 (d, *J* = 7.0 Hz,1H), 3.90 (s, 3H), 3.79 (d, *J* = 13.8, 1H), 3.15−2.95 (m, 2H), 2.53 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ/ppm 155.66, 153.50, 142.05, 136.15, 130.13, 128.59, 128.41, 127.79, 126.81, 126.54, 125.28, 123.67, 118.82, 109.09, 101.63, 93.79, 76.69, 57.36, 56.25, 54.92, 42.83, 41.31, 40.43.

*Synthesis of 4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((3,3-Difluoroazetidin-1-yl)-methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((+)-**46**).* *rac-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-Bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo[2,3-c]pyridin-6-yl)(3,3-difluoroazetidin-1-yl)methanone (**157i**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]-furo[2,3-*c*]pyridine-6-carboxylic acid (**148**) (1.50 g, 3.01 mmol) in dichloromethane (20 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (1.72 g, 11.1 mmol), hydroxybenzotriazole (1.40 g, 9.14 mmol), and *N*,*N*-diisopropylethylamine (3.20 g, 24.8 mmol) were added. The reaction mixture was stirred for 5 min. Then, 3,3-difluoroazetidine hydrochloride (1.16 g, 8.95 mmol) was added at the same temperature, and the mixture was stirred for 16 h at room temperature. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product which was purified by silica gel column chromatography using 0−5% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo-[2,3-*c*]pyridin-6-yl) (3,3-difluoroazetidin-1-yl)methanone (**157i**) as a white solid. Yield: 1.20 g (2.09 mmol, 69%). MS (ESI) *m*/*z*: 573.18 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.09 (s, 1H), 7.99 (s, 1H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.08−7.03 (m, 4H), 6.99 (m, 3H), 5.67 (s, 1H), 5.34 (d, *J* = 5.2 Hz, 1H), 5.15 (d, *J* = 11.2 Hz, 1H), 4.75 (m, 2H), 4.36 (d, *J* = 13.6 Hz, 1H), 4.22 (br s, 3H), 4.02 (dd, *J* = 13.6, 5.2 Hz, 1H), 3.88 (s, 3H).

*rac-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-Bromophenyl)-6-((3,3-difluoroazetidin-1-yl)methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4bH-cyclopenta[4,5]furo[2,3-c]pyridine-4b,5-diol (**158i**).* To a solution of *rac*-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]-pyridin-6-yl) (3,3-difluoroazetidin-1-yl)methanone (**157i**) (1.20 g, 2.09 mmol) in dry tetrahydrofuran (20 mL) at 0 °C, borane dimethyl sulfide complex (1.90 mL, 1.52 g, 20.0 mmol) was added at the same temperature, and the reaction mixture was stirred for 16 h at room temperature. After this time, the reaction mixture was diluted with methanol at 0 °C and refluxed at 80 °C for 6 h. After this time, the reaction mixture was concentrated to obtain the crude product which was purified by silica gel column chromatography using 0−5% methanol in dichloromethane as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-((3,3-difluoroazetidin-1-yl)methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta-[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158i**) as a white solid. Yield: 0.60 g (1.0 mmol, 51%). MS (ESI) *m*/*z*: 559.24 $[M + 1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.02 (s, 1H), 7.96 (s, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.13−7.08 (m, 4H), 7.02−6.99 (m, 3H), 5.65 (s, 1H), 5.17 (d, *J* = 5.2 Hz, 1H), 4.45 (t, *J* = 4.8 Hz, 1H), 3.87 (s, 3H), 3.69 (d, *J* = 16.0 Hz, 1H), 3.65−3.59 (m, 4H), 2.97 (t, *J* = 10.5 Hz, 1H), 2.76 (t, *J* = 11.4 Hz, 1H), 2.37 (d, *J* = 10.8 Hz, 1H).

*4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((3,3-Difluoroazetidin-1-yl)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((+)-**46**).* To a solution of *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-((3,3-difluoroazetidin-1-yl)methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158i**) (0.60 g, 1.1 mmol) in *N*,*N*-dimethylformamide (10 mL) at room temperature, zinc cyanide (0.60 g, 5.1 mmol) and zinc dust (0.0079 g, 0.12 mmol) were added. The reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (0.012 g, 0.0208 mmol) and tris(dibenzylideneacetone)dipalladium (0.028 g, 0.0312 mmol) were added to the mixture which was degassed for additional 5 min and heated at 140 °C for 1 h. After this time, the reaction mixture was diluted with ethyl acetate and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product which was purified by silica



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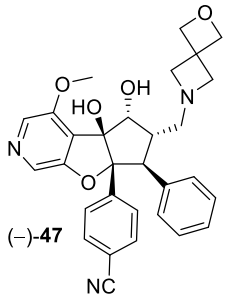
gel column chromatography using 2−3% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((3,3-difluoroazetidin-1-yl)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-7a-yl)benzonitrile (*rac*-**46**) as a white solid. Yield: 0.330 g (0.653 mmol, 59%). MS (ESI) *m*/*z*: 506.27 $[M + 1]^+$. The enantiomers were separated by chiral preparative HPLC [Chiralpak IC (4.6 × 250) mm, 5μ] in isocratic 0.1% triethylamine in hexane/isopropanol 80/20 v/v. Peak 1 (80 mg, (−)-**46**), $[\alpha]_D$ −8.1° (*c* 0.43, $CHCl_3$), R_t 10.350 min, ee = 99.54%, ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.04 (s, 1H), 7.97 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz 2H), 7.10 (m, 2H), 7.02 (m, 3H), 5.74 (s, 1H), 5.23 (d, *J* = 5.2 Hz, 1H), 4.48 (t, *J* = 4.8 Hz, 1H), 3.88 (s, 1H), 3.81 (d, *J* = 14 Hz, 1H), 3.67 (m, 4H), 3.05 (m, 1H), 2.80 (m, 1H), 2.50 (br s, 1H); peak-2 (85 mg, (+)-**46**), $[\alpha]_D$ +9.0° (*c* 0.43, $CHCl_3$), R_t 14.833 min, ee = 99.18%, ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.04 (s, 1H), 7.97 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.10 (m, 2H), 7.02 (m, 3H), 5.74 (s, 1H), 5.23 (d, *J* = 5.2 Hz, 1H), 4.48 (t, *J* = 4.8 Hz, 1H), 3.88 (s, 1H), 3.81 (d, *J* = 14 Hz, 1H), 3.67 (m, 4H), 3.05 (m, 1H), 2.80 (m, 1H), 2.50(br s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 155.79, 153.40, 142.46, 136.66, 130.11, 128.72, 128.56, 127.78, 127.05, 126.37, 125.48, 123.41, 118.89, 117.39, 108.95, 101.80, 93.78, 76.96, 64.37 (t, *J* = 21.6 Hz), 56.99, 56.18, 55.42, 44.65; HRMS (ESI): calcd, 506.1886 $[M + H]^+$; found, 506.1890.

*Synthesis of 4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((2-Oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((−)-**47**).* rac-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-Bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-c]pyridin-6-yl)(2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone (**157j**). To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxylic acid (**148**) (1.0 g, 2.0 mmol) in *N*,*N*- dimethylformamide (20 mL) at 0 °C, HATU (2.29 g, 6.02 mmol) and *N*,*N*-diisopropylethylamine (1.80 mL, 1.33 g, 10.3 mmol) were added. This reaction mixture was stirred for 5 min. Then, 2-oxa-6-azaspiro[3.3]heptane oxalate (**S104**) (1.44 g, 7.61 mmol) was added and the reaction mixture was stirred for 2 h at room temperature. After this time, the reaction mixture was diluted with ethyl acetate and washed with cold water. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product which was purified by Combi-flash (12 g, RedisSep column) using 6% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-6-yl)(2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone (**157j**) as a white solid. Yield: 0.85 g (1.5 mmol, 73%). MS (ESI) *m*/*z*: 579.25 $[M + 1]^+$, ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.08 (s, 1H), 7.98 (s, 1H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.04−7.01 (m, 4H), 6.97−6.90 (m, 3H), 5.68 (s, 1H), 5.16 (d, *J* = 5.3 Hz, 1H), 4.77 (t, *J* = 6.8 Hz, 2H), 4.73−4.70 (m, 2H), 4.67 (d, *J* = 5.4 Hz, 2H), 4.49 (d, *J* = 8.9 Hz, 1H), 4.33 (d, *J* = 13.6 Hz, 1H), 3.97 (s, 2H), 3.87 (s, 3H), 3.83−3.79 (dd, *J* = 5.2, 13.9 Hz, 1H).

*rac-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((2-Oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-7a-(4-bromophenyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4bH-cyclopenta[4,5]furo[2,3-c]pyridine-4b,5-diol (**158j**).* To a solution of *rac*-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-6-yl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone (**157j**) (0.89 g, 1.5 mmol) in tetrahydrofuran (15 mL) at 0 °C, borane dimethylsulfide complex (0.23 mL, 0.18 g, 2.4 mmol) was added. The reaction mixture was stirred for 3 h at room temperature. After this time, the reaction mixture was quenched with methanol at 0 °C and then heated at 60 °C for 4 h. The solvents were concentrated to obtain the crude product which was purified by Combi-flash (4 g, RediSep column) using 7% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((2-oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-7a-(4-bromophenyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158j**) as a white solid. Yield: 0.55 g (0.97 mmol, 65%). MS (ESI) *m*/*z*: 565.72 $[M + 1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.01 (s, 1H), 7.95 (s, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.11−7.07 (m, 4H), 7.02−6.93 (m, 3H), 5.61 (s, 1H), 5.32 (br s, 1H), 4.58 (s, 4H), 4.42 (s, 1H), 3.87 (s, 3H), 3.73−3.63 (m, 1H), 3.3 (s, 4H), 2.88 (br s, 1H), 2.58 (br s, 1H), 2.21 (br s, 1H).

*4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((2-Oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((−)-**47**).* To a mixture of *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((2-oxa-6-azaspiro[3.3]-heptan-6-yl)methyl)-7a-(4-bromophenyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158j**) (0.55 g, 0.97 mmol) in *N*,*N*-dimethylformamide (10.0 mL) at room temperature, zinc cyanide (0.670 g, 5.71 mmol) and zinc dust (0.062 g, 0.95 mmol) were added. This reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino) ferrocene (0.139 g, 0.251 mmol) and tris(dibenzylideneacetone)dipalladium (0.266 g, 0.290 mmol) were added to the reaction mixture and degassing was continued for another 5 min. The reaction mixture was heated at 140 °C for 2.5 h. After this time, the reaction mixture was cooled to room temperature and filtered with Celite. This was diluted with ethyl acetate and washed with water. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the crude product which was purified by reverse-phase prep HPLC. The desired fractions were lyophilized to afford *rac*-4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((2-oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-7a-yl)benzonitrile (*rac*-**47**) as a white solid. Yield: 0.15 g (0.29 mmol, 30%). The enantiomers were separated by chiral preparative HPLC [Chiralpak IA (4.6 × 250) mm] using *n*-hexane/EtOH = 50/50 (v/v) mobile phase. Peak 1 (40 mg, (−)-**47**); $[\alpha]_D$ −99.1° (*c* 0.29, $CHCl_3$), R_t 5.661 min, ee 99.90%. MS (ESI) *m*/*z*: 512.28 $[M + 1]^+$; HRMS (ESI): calcd, 512.2180 $[M + H]^+$; found, 512.2180; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.03 (s, 1H), 7.96 (s, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.09−7.06 (m, 2H), 7.01−6.97 (m, 3H), 5.72 (s, 1H), 5.40 (br s, 1H), 4.58 (d, *J* = 3.2 Hz, 4H), 4.44 (d, *J* = 2.5 Hz, 1H), 3.87 (s, 3H), 3.78 (d, *J* = 14.1 Hz, 1H), 3.29 (s, 4H), 2.94 (s, 1H), 2.69−2.49 (m, 1H), 2.25−2.17 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 155.78, 153.43, 142.52, 136.68, 130.12, 128.68, 128.50, 127.74, 127.03, 126.35, 125.47, 123.44, 118.89, 108.93, 101.80, 93.69, 79.91, 77.64, 63.60, 56.85, 56.16, 55.60, 43.84, 38.59. Peak-2 (34 mg, (+)-**47**); $[\alpha]_D$ +23.0° (*c* 0.259, $CHCl_3$), R_t 22.48 min, ee 99.30%. MS (ESI) *m*/*z*: 512.24 $[M + 1]^+$;^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.03 (s, 1H), 7.96 (s, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.09−7.06 (m, 2H), 7.01−6.97 (m, 3H), 5.72 (s, 1H), 5.39 (br s, 1H), 4.60−4.56 (m, 4H), 4.44 (d, *J* = 2.5 Hz, 1H), 3.87 (s, 3H), 3.78 (d, *J* = 14.1 Hz, 1H), 3.29 (s, 4H), 2.94 (s, 1H), 2.69−2.50 (m, 1H), 2.25−2.17 (m, 1H).

*Synthesis of 4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((tert-Butylamino)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((+)-**48**).* rac-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-Bromophenyl)-N-(tert-butyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-c]pyridine-6-carboxamide (**157k**). To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-



(−)-**47**

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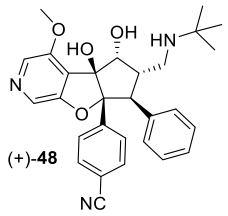


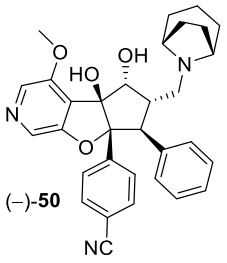
(+)-**48**

7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxylic acid (**148**) (5.0 g, 10.0 mmol) in *N*,*N*-dimethylformamide (50 mL) at 0 °C were added 2-methylpropan-2-amine (6.0 g, 82 mmol), *N*,*N*-diisopropylethylamine (11.0 mL, 8.16 g, 63.2 mmol), *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (5.70 g, 30.0 mmol) and 1-hydroxybenzotriazole (4.50 g, 33.3 mmol), and the reaction mixture was stirred for 16 h at room temperature. After this time, the reaction mixture was diluted with ice cold water. The so-obtained precipitate was isolated by filtration and dissolved in 10% methanol in dichloromethane. The organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated to give the crude product, which was purified by column chromatography using silica gel (100−200 mesh) and 0−4% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-*N*-(*tert*-butyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxamide (**157k**) as a white solid. Yield: 1.80 g (3.25 mmol, 33%); MS (ESI) *m*/*z*: 553.41 $[M + 1]^+$.

*rac-(4bS,5R,6S,7S,7aR)-7a-(4-Bromophenyl)-6-((tert-butylamino)methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4bH-cyclopenta[4,5]furo[2,3-c]pyridine-4b,5-diol (**157k**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-*N*-(*tert*-butyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxamide (**157k**) (1.8 g, 3.3 mmol) in dry tetrahydrofuran (20 mL) at 0 °C was dropwise added borane dimethyl sulfide complex (4.50 mL, 4.05 g, 53.3 mmol), and the reaction mixture was stirred at room temperature for 16 h. Then, the reaction was quenched with methanol at 0 °C and heated to reflux for 6 h. After this time, the solvent was removed under reduced pressure to give the crude product which was purified by column chromatography using silica gel (100−200 mesh) and 0−15% methanol in dichloromethane as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-((*tert*-butylamino)-methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta-[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**157k**) as a white solid. Yield: 1.40 g (2.60 mmol, 79%). MS (ESI) *m*/*z*: 539.45 $[M + 1]^+$.

*(+)-4-((4bS,5R,6S,7S,7aR)-6-((tert-Butylamino)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta-[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((+)-**48**).* To a solution of *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-((*tert*-butylamino)-methyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta-[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158k**) (1.40 g, 2.59 mmol) in *N*,*N*-dimethylformamide (20.0 mL) were added zinc cyanide (1.70 g, 14.5 mmol) and zinc dust (0.081 g, 1.24 mmol), and the reaction mixture was degassed with argon for 15 min. 1,1′-Bis(diphenylphosphino)-ferrocene (0.114 g, 0.206 mmol) and tris(dibenzylideneacetone)-dipalladium (0.14 g, 0.153 mmol) were then added to the mixture. Degassing was continued for additional 5 min, and the mixture was heated at 140 °C for 16 h. After this time, the reaction mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product which was purified by column chromatography using silica gel (100−200 mesh) and 0−15% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((*tert*-butylamino)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-7a-yl)-benzonitrile (*rac*-**48**) as white solid. Yield: 0.820 g (1.69 mmol, 65%). MS (ESI) *m*/*z*: 486.49 $[M + 1]^+$. The enantiomers were separated by chiral SFC [Chiralpak IG (4.6 × 150) mm, 5 μm], CO_2/0.1% TEA in EtOH=(60/40) Peak 1 ((−)-**48**, 55 mg), $[\alpha]_D$ −34.2° (*c* 0.25, $CHCl_3$), R_t 1.73 min, ee: 99.9%; MS (ESI) *m*/*z*: 486.36 $[M + 1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.05 (s, 1H), 7.97 (s, 1H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.09−7.05 (m, 2H), 7.00−6.98 (m, 3H), 5.76 (s, 1H), 5.65 (s, 1H), 4.54 (s, 1H), 3.88 (s, 3H), 3.85 (s, 1H), 3.05−3.01 (m, 1H), 2.62−2.57 (m, 2H), 1.57−1.52 (s, 1H), 0.98 (s, 9H). Peak-2 ((+)-**48**, 58 mg) $[\alpha]_D$ +28.5° (*c* 0.27, $CHCl_3$), R_t 2.42 min, ee: 99.88%; MS (ESI) *m*/*z*: 486.32 $[M + 1]^+$; HRMS (ESI): calcd, 486.2387 $[M + H]^+$; found, 486.2393; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.05 (s, 1H), 7.97 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.09−7.05 (m, 2H), 7.00−6.98 (m, 3H), 5.77 (s, 1H), 5.66 (s, 1H), 4.54 (s, 1H), 3.88 (s, 3H), 3.85 (s, 1H), 3.15−3.10 (m, 1H), 2.62−2.56 (m, 2H), 1.64 (s, 1H), 0.94 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 155.69, 153.49, 142.61, 137.05, 130.09, 128.63, 128.52, 127.64, 126.96, 126.27, 125.60, 123.67, 118.90, 108.88, 102.12, 93.67, 78.49, 56.83, 56.18, 49.87, 45.46, 32.93, 28.54.

Synthesis of 4-((4bS,5R,6S,7S,7aR)-6-(((1R,5S)-8-Azabicyclo-[3.2.1]octan-8-yl)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-



(−)-**50**

*4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)-benzonitrile ((−)-**50**). rac-((1R,5S)-8-Azabicyclo[3.2.1]octan-8-yl)-((4bS,5R,6R,7S,7aR)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo[2,3-c]pyridin-6-yl)methanone (**157l**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxylic acid (**148**) (0.05 g, 0.10 mmol) in dichloromethane (5.0 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (0.043 g, 0.28 mmol), hydroxybenzotriazole (0.04 g, 0.3 mmol), and *N*,*N*-diisopropylethylamine (0.09 mL, 0.07 g, 0.5 mmol) were added. The reaction mixture was stirred for 5 min. Then, 8-azabicyclo[3.2.1]-octane (**S106**) (0.016 g, 0.14 mmol) was added at the same temperature and the reaction mixture was stirred at room temperature for 5 h. After this time, the reaction mixture was diluted with dichloromethane (20 mL) and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by reverse-phase HPLC to afford *rac*-((1*R*,5*S*)-8-azabicyclo[3.2.1]-octan-8-yl) ((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]-furo[2,3-*c*]pyridin-6-yl)methanone (**157l**) as a white solid. Yield: 23.0 mg (0.039 mmol, 39%). MS (ESI) *m*/*z*: 591.18 $[M + 1]^+$; UPLC 99.6%; ^{1}H NMR (400 MHz, DMSO-d_6, at High temperature VT (373 K): δ/ppm 8.11 (s, 1H), 8.01 (s, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 7.05−6.94 (m, 5H), 4.70 (d, *J* = 4.8 Hz, 1H), 4.52 (d, *J* = 13.2 Hz, 1H), 4.09−4.05 (m, 1H), 3.92 (s, 3H), 2.01−1.78 (m, 8H), 1.60−1.55 (m, 4H).

*rac-(4bS,5R,6S,7S,7aR)-6-(((1R,5S)-8-Azabicyclo[3.2.1]octan-8-yl)methyl)-7a-(4-bromophenyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4bH-cyclopenta[4,5]furo[2,3-c]pyridine-4b,5-diol (**158l**).* To a solution of *rac*-((1*R*,5*S*)-8-azabicyclo[3.2.1]octan-8-yl) ((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]-pyridin-6-yl)methanone (**157l**) (0.50 g, 0.85 mmol) in tetrahydrofuran (10 mL) at 0 °C, borane dimethyl sulfide (0.2 mL, 0.2 g, 2.1 mmol) was added. The reaction mixture was stirred for 3 h at room temperature. After this time, the reaction was quenched with methanol (5.0 mL) and again heated for 10 h at 60 °C. The mixture was concentrated to obtain the crude product, which was purified by

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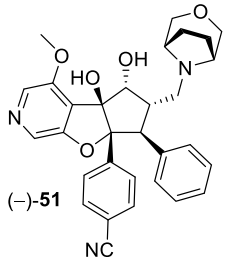
Combiflash (12 g, RediSep column) using 5−20% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-(((1*R*,5*S*)-8-azabicyclo[3.2.1]octan-8-yl)methyl)-7a-(4-bromophenyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158l**) as an off-white solid. Yield: 0.45 g (crude). MS (ESI) *m*/*z*: 577.4 $[M + 1]^+$.

*4-((4bS,5R,6S,7S,7aR)-6-(((1R,5S)-8-Azabicyclo[3.2.1]octan-8-yl)-methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((−)-**50**).* To a solution of crude *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-(((1*R*,5*S*)-8-azabicyclo[3.2.1]octan-8-yl)methyl)-7a-(4-bromophenyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (0.45 g) in *N*,*N*-dimethylformamide (5.0 mL) at room temperature, zinc cyanide (0.543 g, 4.62 mmol) and zinc (0.005 g, 0.08 mmol) were added. The mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (0.130 g, 0.234 mmol) and tris(dibenzylideneacetone)-dipalladium (0.214 g, 0.234 mmol) were added to the reaction and degassing was continued for another 5 min. The reaction mixture was heated at 140 °C for 3 h. After this time, the mixture was cooled to room temperature and filtered with Celite. The filtrate was diluted with ethyl acetate and washed with water. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the crude product, which was purified by Combiflash (4 g, RediSep column) using 0−15% methanol in dichloromethane as the eluent. The desired fractions were concentrated under reduced pressure. The so-obtained material was purified by reverse-phase preparative HPLC, and the desired fractions were lyophilized to afford *rac*-4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-(((1*R*,5*S*)-8-azabicyclo[3.2.1]octan-8-yl)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-7a-yl)benzonitrile as a white solid (*rac*-**50**). Yield: 140 mg (0.267 mmol, 31% over two steps). The enantiomers were separated by chiral preparative HPLC [Chiralpak IA (4.6 × 250) mm, 5μ]; 0.1% TEA in *n*-hexane/IPA = 60/40 (V/V); peak 1 (9 mg, (+)-**50**), $[\alpha]_D$ +33.1° (*c* 0.27, $CHCl_3$), R_t 9.36, ee >99%; MS (ESI) *m*/*z*: 523.93 $[M + 1]^+$; UPLC: 98.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.06 (s, 1H), 7.97 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.09−6.97 (m, 5H), 5.68 (s, 1H), 4.6 (d, *J* = 3.5 Hz, 1H), 3.95 (d, *J* = 13.9 Hz, 1H), 3.88 (s, 3H), 3.13−3.11 (m, 1H), 2.97 (br s, 1H), 1.90 (s, 2H), 1.76 (m, 1H), 1.74−1.31 (m, 10H); peak 2 (8 mg, (−)-**50**), $[\alpha]_D$ −58.9° (*c* 0.25, $CHCl_3$), R_t 14.22, ee >99%; MS (ESI) *m*/*z*: 524.31 $[M + 1]^+$; HRMS (ESI): calcd, 524.2544 $[M + H]^+$; found, 524.2547; UPLC: 97.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.06 (s, 1H), 7.97 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.07−6.98 (m, 5H), 6.05 (s, 1H), 5.69 (s, 1H), 4.6 (s, 1H), 3.95 (m, 1H), 3.88 (s, 3H), 3.12 (br s, 1H), 2.95 (br s, 1H), 2.60 (br s, 2H),1.76 (m, 1H), 1.59−1.14 (m, 10H); 13C NMR (126 MHz, DMSO-d_6): δ/ppm 155.87, 153.46, 142.58, 136.80, 130.07, 128.58, 128.47, 127.74, 127.04, 126.33, 125.46, 123.45, 118.85, 109.52, 108.88, 93.49, 78.92, 60.45, 57.02, 56.15, 50.14, 43.95, 30.69, 25.68, 15.92.

*Synthesis of 4-((4bS,5R,6S,7S,7aR)-6-(((1R,5S)-3-Oxa-8-azabicyclo[3.2.1]octan-8-yl) methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta [4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((−)-**51**).* rac-((1R,5S)-3-Oxa-8-azabicyclo[3.2.1]-octan-8-yl)((4bS,5R,6R,7S,7aR)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta-[4,5] furo[2,3-c]pyridin-6-yl)methanone (**157m**). To a solution of



(−)-**51**

rac-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]-pyridine-6-carboxylic acid (**148**) (1.5 g, 3.0 mmol) in dichloromethane (20 mL) at 0 °C, 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium3-oxide hexafluorophosphate (1.71 g, 4.50 mmol) and *N*,*N*-diisopropylethylamine (3.28 mL, 2.43 g, 18.8 mmol) were added. The reaction mixture was stirred for 5 min. Then, (1*R*,5*S*)-3-oxa-8-azabicyclo[3.2.1]octane hydrochloride (**S107**) (0.9 g, 8.0 mmol) was added at the same temperature and the reaction mixture was stirred for 16 h at room temperature. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product. This was purified by silica gel (100−200 mesh size) column chromatography using 0−5% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-((1*R*,5*S*)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl) ((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-6-yl)methanone (**157m**) as a white solid. Yield: 1.70 g (2.86 mmol, 95%). MS (ESI) *m*/*z*: 593.21 $[M + 1]^+$.^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.10 (s, 1H), 7.99 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.08−6.97 (m, 6H), 6.88 (d, *J* = 7.2 Hz, 1H), 5.73 (d, *J* = 6.8 Hz, 1H), 5.20 (m, 1H), 4.71−4.63 (m, 2H), 4.52−4.46 (m, 1H), 4.31 (br s, 1H), 4.10−4.05 (m, 1H),3.88 (s, 3H), 3.79−3.70 (m, 2H), 3.52 (br s, 2H), 2.08 (br s, 2H), 1.78−1.63 (m, 2H).

*rac-(4bS,5R,6S,7S,7aR)-6-(((1R,5S)-3-Oxa-8-azabicyclo[3.2.1]-octan-8-yl)methyl)-7a-(4-bromophenyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4bH-cyclopenta[4,5]furo[2,3-c] Pyridine-4b,5-diol (**158m**).* To a solution of *rac*-((1*R*,5*S*)-3-oxa-8-azabicyclo[3.2.1]-octan-8-yl) ((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta [4,5] furo[2,3-*c*]pyridin-6-yl)methanone (**157m**) (1.20 g, 2.02 mmol) in dry tetrahydrofuran (20 mL) at 0 °C, borane dimethyl sulfide complex (1.90 mL, 1.52 g, 20.0 mmol) was added dropwise over a period of 5 min. The reaction mixture was slowly brought to room temperature and stirred for an additional 16 h. After this time, the reaction mixture was quenched with methanol at 0 °C and heated to reflux for 10 h. Then, the solvent was removed under reduced pressure, and the residue was purified by silica gel (100−200 mesh size) column chromatography using 0−5% methanol in dichloromethane as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-(((1*R*,5*S*)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl)-7a-(4-bromophenyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*] pyridine-4b,5-diol (**158m**) as a white solid. Yield: 1.0 g (crude). MS (ESI) 579.21 *m*/*z*: $[M + 1]^+$.

*4-((4bS,5R,6S,7S,7aR)-6-(((1R,5S)-3-Oxa-8-azabicyclo[3.2.1]-octan-8-yl) methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta [4,5]furo[2,3-c]pyridin-7a-yl)-benzonitrile ((−)-**51**).* To a solution of *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-(((1*R*,5*S*)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl)-7a-(4-bromophenyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta-[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158m**) (1.0 g, 1.7 mmol) in *N*,*N*-dimethylformamide (10 mL) at room temperature, zinc cyanide (0.98 g, 8.3 mmol) and zinc dust (0.013 g, 0.20 mmol) were added. The reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (0.019 g, 0.034 mmol) and tris-(dibenzylideneacetone)-dipalladium (0.047 g, 0.051 mmol) were added to the reaction mixture which was degassed for an additional 5 min and heated at 130 °C for 2 h. After this time, the reaction mixture was diluted with ethyl acetate and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product. This was purified by silica gel (100−200 mesh size) column chromatography using 2−3% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-(((1*R*,5*S*)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]-furo[2,3-*c*]pyridin-7a-yl)benzonitrile (*rac*-**51**) as a white solid. Yield:

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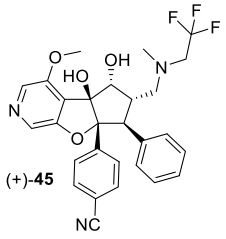
0.30 g (0.57 mmol, 28% over two steps). MS (ESI) *m/z*: 526.36 [M + 1]$^+$. The enantiomers were separated by chiral SFC [CHIRALPAK IA (4.6 × 250) mm, 5μ] in CO_2/0.1% TEA in MeOH (80/20). Peak 1 (72 mg, (−)-**51**), $[\alpha]_D$ −26.5° (*c* 0.25, $CHCl_3$), R_t 6.077 min, ee: 99.84%; MS (ESI) *m/z*: 526.26 [M + 1]$^+$; HRMS (ESI): calcd, 536.2336 [M + H]$^+$; found, 526.2350; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.05 (s, 1H), 7.97 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.09−6.96 (m, 5H), 5.71 (s, 1H), 5.38 (s, 1H), 4.61 (s, 1H), 3.88 (s, 3H), 3.82 (d, *J* = 14.2 Hz, 1H), 3.56 (d, *J* = 7.6 Hz, 2H), 3.50 (t, *J* = 12.0 Hz, 1H), 3.38 (s, 1H), 3.15 (br s, 1H), 2.94 (s, 1H), 2.44−2.41 (m, 2H), 2.23 (d, *J* = 11.2 Hz, 1H), 1.69−1.62 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 155.87, 153.44, 142.63, 136.99, 130.08, 128.64, 128.55, 127.72, 126.97, 126.28, 125.45, 123.49, 118.91, 108.87, 102.04, 93.65, 77.82, 72.63, 72.44, 61.65, 60.02, 56.97, 56.14, 50.58, 44.69, 24.73, 24.49. Peak-2 (104 mg, (+)-**51**), $[\alpha]_D$ +39.2° (*c* 0.258, $CHCl_3$), R_t 7.813 min, ee: 99.68%; MS (ESI) *m/z*: 526.26 [M + 1]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.05 (s, 1H), 7.97 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.11−6.96 (m, 5H), 5.71 (s, 1H), 5.38 (br s, 1H), 4.61 (s, 1H), 3.88 (s, 3H), 3.84 (d, *J* = 13.6 Hz, 1H), 3.56 (d, *J* = 7.6 Hz, 2H), 3.50 (t, *J* = 12.0 Hz, 1H), 3.37 (s, 1H), 3.17 (br s, 1H),3.02 (s, 1H), 2.44−2.41 (m, 2H), 2.23 (d, *J* = 11.2 Hz, 1H), 1.69−1.62 (m, 4H).

*Synthesis of 4-((4bS,5R,6S,7S,7aR)-4b,5-Dihydroxy-4-methoxy-6-((methyl(2,2,2-trifluoroethyl)amino)methyl)-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((+)-**45**).*

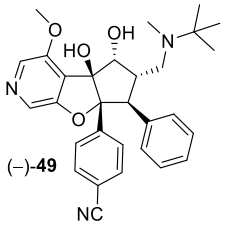


*rac-N-(((4bS,5R,6S,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta-[4,5]furo[2,3-c]pyridin-6-yl)methyl)-2,2,2-trifluoro-N-methylacetamide (**159**).* To a solution of *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-4-methoxy-6-((methylamino)methyl)-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**158b**) (0.8 g, 1.6 mmol) in dichloromethane (5.0 mL) at 0 °C, trifluoroacetic anhydride (0.4 g, 2 mmol) and triethylamine (0.7 mL, 0.5 g, 5 mmol) were added. The reaction mixture was stirred for 5 min at 0 °C, then warmed up to room temperature, and stirred for 30 min. After this time, the mixture was diluted with dichloromethane (20 mL) and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by Combi-flash (12 g RediSep column) using 30% ethyl acetate in hexanes as the eluent. The desired fractions were concentrated to afford *N*-(((4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-6-yl)methyl)-2,2,2-trifluoro-*N*-methylacetamide (**159**) as a yellow solid. Yield: 0.4 g. UPLC: 82.36%; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.05 (s, 1H), 7.99 (s, 1H), 7.27−7.21 (m, 2H), 7.12−7.02 (m, 7H), 5.52 (s, 1H), 5.36 (d, *J* = 5.8 Hz, 1H), 4.38 (br s,1H), 3.88 (s, 3H), 3.84 (d, *J* = 14.0 Hz, 1H), 3.63 (d, *J* = 13.3 Hz, 1H), 3.37−3.06 (m, 5H).

*rac-(4bS,5R,6S,7S,7aR)-7a-(4-Bromophenyl)-4-methoxy-6-((methyl(2,2,2-trifluoroethyl)amino)methyl)-7-phenyl-5,6,7,7a-tetrahydro-4bH-cyclopenta[4,5]furo[2,3-c]pyridine-4b,5-diol (**160**).* To a solution of *N*-(((4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta-[4,5]furo[2,3-*c*]pyridin-6-yl)methyl)-2,2,2-trifluoro-*N*-methylacetamide (**159**) (0.2 g, from previous step; used without further purification) in tetrahydrofuran (20 mL) at 0 °C, borane dimethylsulfide (0.3 mL, 0.2 g, 4 mmol) was added. The reaction mixture was heated at 60 °C for 6 h. After this time, the reaction was quenched with methanol at 0 °C and then heated at 90 °C for 16 h. The solvents were evaporated and the solid thus obtained was dried to afford *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-4-methoxy-6-((methyl(2,2,2-trifluoroethyl)-amino)methyl)-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**160**) as a yellow solid. Yield: 0.15 g (crude). UPLC: 89.22%; MS (ESI) *m/z*: 579.2 [M + 1]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.02 (s, 1H), 7.96 (s, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 7.07−7.00 (m, 5H), 5.62 (s, 1H), 5.04 (d, *J* = 5.5 Hz,1H), 4.48 (br s, 1H), 3.88 (s, 3H), 3.70 (d, *J* = 14.4, 1H), 3.37−3.17 (m, 4H), 2.49 (s, 3H), 2.37−2.32 (m, 1H).

*4-((4bS,5R,6S,7S,7aR)-4b,5-Dihydroxy-4-methoxy-6-((methyl-(2,2,2-trifluoroethyl)amino)-methyl)-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((+)-**45**).* To a mixture of crude *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-4-methoxy-6-((methyl(2,2,2-trifluoroethyl)amino)methyl)-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**160**) (0.15 g) in *N*,*N*- dimethylformamide (10.0 mL) at room temperature, zinc cyanide (182 mg, 1.55 mmol) and zinc (3 mg, 0.05 mmol) were added. The reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (4.0 mg, 0.007 mmol) and tris(dibenzylideneacetone)-dipalladium (7.0 mg, 0.008 mmol) were added to the reaction mixture and degassing was continued for another 5 min. The reaction mixture was heated at 140 °C for 16 h. After this time, the mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated, treated with ice-cold water, and the resulting precipitate was collected by filtration. The crude product was purified by Combi-flash (12 g RediSep column) using 30% ethyl acetate in hexanes as the eluent. Then, it further purified by reverse-phase preparative HPLC. The desired fractions were lyophilized to afford *rac*-4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-4b,5-dihydroxy-4-methoxy-6-((methyl(2,2,2-trifluoroethyl)amino)-methyl)-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-7a-yl)benzonitrile (*rac*-**45**) as a white solid. Yield: 0.10 g (0.19 mmol, 24% over three steps). The enantiomers were separated by chiral preparative HPLC [Chiralpak IB (4.6 × 250) mm] using *n*-hexane/EtOH(90/10) (v/v) mobile phase. Peak 1 (21 mg, (−)-**45**), $[\alpha]_D$ −13.0° (*c* 0.2, $CHCl_3$), R_t 12.65 min, ee >99%. MS (ESI) *m/z*: 526.45 [M + 1]$^+$; UPLC: 99.29%. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.05 (s, 1H), 7.97 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.09−6.97 (m, 5H), 5.72 (s, 1H), 5.11 (d, *J* = 5.7 Hz,1H), 4.59 (t, *J* = 5.0 Hz, 1H), 3.88 (s, 3H), 3.77 (d, *J* = 14.0 Hz, 1H), 3.42−2.75 (m, 4H), 2.46 (s, 3H), 2.39 (d, *J* = 11.0 Hz,1H). Peak-2 (22 mg, (+)-**45**),$[\alpha]_D$ +14.5° (*c* 0.2, $CHCl_3$), R_t 17.019 min, ee >99%. MS (ESI) *m/z*: 526.42 [M + 1]$^+$; HRMS (ESI): calcd, 526.1948 [M + H]$^+$; found, 526.1948; UPLC: 99.42%.^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.04 (s, 1H), 7.97 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.09−6.97 (m, 5H), 5.71 (s, 1H), 5.11 (d, *J* = 5.4 Hz,1H), 4.50 (t, *J* = 5.0 Hz, 1H), 3.88 (s, 3H), 3.77 (d, *J* = 14.0, 1H), 3.42−2.73 (m, 4H), 2.46 (s, 3H), 2.39 (d, *J* = 11.5 Hz,1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 155.80, 153.39, 142.52, 136.83, 130.09, 128.68, 128.60, 127.70, 126.99, 126.44 (q, *J* = 282 Hz), 126.31, 125.44, 123.36, 118.91, 108.92, 101.85, 93.80, 76.97, 57.18, 56.66 (q, *J* = 29 Hz), 56.13, 54.51, 44.03, 43.35.

*Synthesis of 4-((4bS,5R,6S,7S,7aR)-6-((tert-Butyl(methyl)amino)-methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((−)-**49**).*



*4-((4bS,5R,6S,7S,7aR)-6-((tert-Butyl(methyl)amino)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta-[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile ((−)-**49**).* To a solution of *rac*-4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((*tert*-butylamino)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]-

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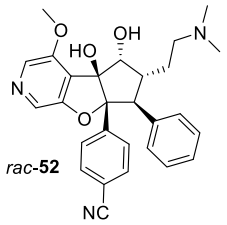
furo[2,3-*c*]pyridin-7a-yl)benzonitrile (*rac*-**48**) (0.41 g, 0.84 mmol) in dichloromethane (10 mL) at 0 °C, 2,6-lutidine (0.24 mL, 0.22 g, 2.1 mmol) and *tert*-butyldimethylsilyltrifluoromethanesulfonate (0.30 mL, 0.35 g, 1.3 mmol) were added. This reaction mixture was stirred for 1 h at room temperature. The reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to 0 °C. *p*-Formaldehyde (0.100 g, 3.33 mmol), sodium acetate (0.68 g, 0.83 mmol), and sodium triacetoxyborohydride (0.711 g, 3.35 mmol) were added. This reaction mixture was stirred at room temperature for 2 h. After this time, the reaction mixture was diluted with water, neutralized with sodium bicarbonate solution, and extracted with 10% methanol in dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by column chromatography using silica gel (100−200 mesh) and 0−6% 7 M methanolic ammonia in dichloromethane as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-4-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-6-((*tert*-butyl(methyl)-amino)methyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-7a-yl)benzonitrile (*rac*-**49**) as a white solid. Yield: 0.230 g (0.460 mmol, 55%). MS (ESI) *m*/*z*: 500.52 $[M + 1]^+$. The enantiomers were separated by chiral HPLC [Chiralpak IC (4.6 × 250)mm, 5μ], 0.1% TEA in *n*-hexane/IPA = 70/30(v/v) peak 1 (50 mg, (+)-**49**), $[\alpha]_D$ +33.2° (*c* 0.28, $CHCl_3$), R_t 7.94 min, ee: 99.88%; MS (ESI) *m*/*z*: 500.37 $[M + 1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.04 (s, 1H), 7.96 (s, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.08−7.05 (m, 2H), 7.02−6.96 (m, 3H), 5.72 (s, 1H), 5.32 (br s, 1H), 4.50 (s, 1H), 3.93 (s, 1H), 3.87 (s, 3H), 3.13 (br s, 1H), 2.73 (br s, 1H), 2.25−2.19 (m, 3H), 1.25−1.22 (m, 1H), 0.94 (s, 9H). Peak-2 (52 mg, (−)-**49**) $[\alpha]_D$ −35.2° (*c* 0.25, $CHCl_3$), R_t 14.67 min, ee: 99.74%; MS (ESI) *m*/*z*: 500.40 $[M + 1]^+$; HRMS (ESI): calcd, 500.2544 $[M + H]^+$; found, 500.2558; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.04 (s, 1H), 7.96 (s, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.44 Hz, 2H), 7.08−7.05 (m, 2H), 7.02−6.98 (m, 3H), 5.72 (s, 1H), 5.32 (br s, 1H), 4.50 (s, 1H), 3.93 (s, 1H), 3.87 (s, 3H), 3.13 (br s, 1H), 2.73 (br s, 1H), 2.25−2.19 (m, 3H), 1.25−1.22 (m, 1H), 0.94 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 155.96, 153.41, 142.72, 137.06, 133.95, 130.09, 128.89, 128.54, 127.62, 127.05, 126.29, 125.35, 123.38, 118.93, 108.85, 101.92, 93.62, 77.85, 57.55, 56.16, 47.87, 44.66, 35.80, 25.76.

*Synthesis of rac-4-((4bS,5R,6R,7S,7aR)-6-(2-(Dimethylamino)-ethyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile (rac-**52**).*



rac-**52**

*rac-(4bS,5R,6S,7S,7aR)-7a-(4-Bromophenyl)-6-(hydroxymethyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4bH-cyclopenta[4,5]furo-[2,3-c]pyridine-4b,5-diol (**161**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-6-carboxylic acid (**148**) (5.0 g, 10 mol) in dry tetrahydrofuran (100 mL) at 0 °C, borane dimethyl sulfide complex (9.52 mL, 7.62 g, 100 mmol) was added dropwise over a period of 5 min. The reaction mixture was heated at 60 °C for 6 h. After completion, the reaction mixture was quenched with methanol at 0 °C and heated to reflux for 16 h. After this time, the solvent was removed under reduced pressure to obtain the crude product which was triturated with diethyl ether, filtered, and dried under vacuum to afford *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-(hydroxymethyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**161**) as a white solid. Yield: 4.5 g (9.3 mmol, 93%). MS (ESI) *m*/*z*: 484.3 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.02 (br s, 1H), 7.96 (br s, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.12−7.06 (m, 4H), 7.01−6.98 (m, 3H), 5.61 (s, 1H), 5.04 (d, *J* = 5.0 Hz, 1H), 4.54 (s, 1H), 4.39−4.34 (m, 2H), 3.86 (s, 3H), 3.66 (d, *J* = 10.3 Hz, 1H), 3.53−3.51 (m, 2H).

*rac-((4bS,5R,6S,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo-[2,3-c]pyridin-6-yl)methyl Methanesulfonate (**S109**).* To a solution of *rac*-(4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-(hydroxymethyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]furo[2,3-*c*]pyridine-4b,5-diol (**161**) (4.5 g, 9.3 mmol) in pyridine (90 mL) at 0 °C, methane sulfonyl chloride (1.60 g, 14.0 mmol) was added. The resulting mixture was stirred at room temperature for 16 h. After this time, the solvent was removed under reduced pressure. The crude product was diluted with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the crude product, which was purified by silica gel (100−200 mesh size) column chromatography using 5% methanol in dichloromethane as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo-[2,3-*c*]pyridin-6-yl)methyl methanesulfonate (**S109**) as a white solid. Yield: 4.20 g (7.47 mmol, 80%). MS (ESI) *m*/*z*: 562.3 $[M + 1]^+$, ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.05 (s, 1H), 7.99 (s, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.20−7.09 (m, 4H), 7.04−7.02 (m, 3H), 5.51 (d, *J* = 5.4 Hz, 1H), 4.52 (s, 1H), 4.29−4.24 (m, 1H), 4.05 (d, *J* = 5.9 Hz, 1H), 3.89 (s, 3H), 3.77 (d, *J* = 14.9 Hz, 1H), 3.77 (d, *J* = 14.9 Hz, 1H), 3.56−3.49 (m, 1H), 3.08 (s, 3H).

*rac-2-((4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo-[2,3-c]pyridin-6-yl)acetonitrile (**162**).* To a solution of *rac*-((4b*S*,5*R*,6*S*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-6-yl)methyl methanesulfonate (**S109**) (4.20 g, 7.47 mmol) in dimethylsulfoxide (84 mL), potassium cyanide (4.86 g, 74.6 mmol) was added. The resulting mixture was heated at 80 °C for 16 h. After this time, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with ice-cold water and then brine. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the crude product which was purified by silica gel (100−200 mesh size) column chromatography using 5% methanol in dichloromethane as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-2-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-6-yl)acetonitrile (**162**) as a yellow-brown solid. Yield: 2.1 g (4.3 mmol, 58%). MS (ESI) *m*/*z*: 493.33 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.07 (s, 1H), 7.99 (s, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.14−7.03 (m, 4H), 6.97−6.95 (m, 3H), 5.75 (s, 1H), 5.58 (d, *J* = 5.9 Hz, 1H), 4.50 (t, *J* = 5.4 Hz, 1H), 3.89 (s, 3H), 3.77 (d, *J* = 13.8 Hz, 1H), 3.50 (s, 1H), 3.39−3.31 (m, 1H), 1.98−1.97 (m, 1H).

*rac-2-((4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo-[2,3-c]pyridin-6-yl)acetic acid (**163**).* To a solution of *rac*-2-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]-pyridin-6-yl)acetonitrile (**162**) (0.8 g, 1.6 mmol) in tetrahydrofuran (4 mL) in a sealed tube, 10% aq sodium hydroxide solution (16 mL) was added. The reaction mixture was heated at 125 °C for 36 h. After this time, the reaction mixture was acidified using 1 N hydrochloric acid, and the resulting precipitate was collected by filtration. The crude product thus obtained was triturated with diethyl ether and dried under vacuum to afford *rac*-2-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-6-yl)acetic acid (**163**) as a white solid. Yield: 0.75 g (1.5 mmol, 94%). MS (ESI) *m*/*z*: 512.3 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.08 (br s, 1H), 8.03 (s, 1H), 7.97 (s, 1H), 7.26−7.24 (m, 2H), 7.13−7.03 (m, 5H), 6.94−6.92 (m, 2H), 5.64 (s, 1H), 5.17 (s, 1H), 4.54 (s, 1H), 3.88 (s, 3H), 3.66 (d, *J* = 13.8 Hz, 1H), 2.07−2.03 (m, 2H).

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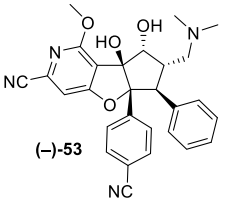
*rac-(3aR,4S,4aR,9bS,9cR)-4a-(4-Bromophenyl)-9b-hydroxy-9-methoxy-4-phenyl-3,3a,4,4a,9b,9c-hexahydro-2H-furo[3″,2″:4′,5′]-cyclopenta[1′,2′:4,5]furo[2,3-c]pyridin-2-one (**164**).* To a solution of *rac*-2-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-6-yl)acetic acid (**163**) (0.45 g, 0.88 mmol) in dichloromethane (9 mL) at 0 °C, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.50 g, 2.6 mmol), hydroxybenzotriazole (0.40 g, 2.6 mmol), and *N*,*N*-diisopropylethylamine (1.09 mL, 0.807 g, 6.24 mmol) were added. The reaction mixture was stirred for 5 min. Then, dimethylamine hydrochloride (0.358 g, 4.19 mmol) was added at the same temperature, and the reaction was stirred for 16 h at room temperature. After this time, the reaction mixture was diluted with dichloromethane and washed with cold water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to obtain the crude product which was purified by silica gel (100−200 mesh) column chromatography using 3% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-3a*R*,4*S*,4a*R*,9b*S*,9c*R*)-4a-(4-bromophenyl)-9b-hydroxy-9-methoxy-4-phenyl-3,3a,4,4a,9b,9c-hexahydro-2*H*-furo[3″,2″:4′,5′]-cyclopenta[1′,2′:4,5]furo[2,3-*c*]pyridin-2-one (**164**) as an off-white solid. Yield: 0.40 g (0.81 mmol, 92%). MS (ESI) *m*/*z*: 494.31 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.17 (s, 1H), 8.12 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.12−7.10 (m, 5H), 6.96 (d, *J* = 5.0, 2H), 6.01 (s, 1H), 5.36 (d, *J* = 6.5 Hz, 1H), 3.96 (s, 3H), 3.80−3.74 (m, 1H), 3.37 (s, 1H), 2.90 (dd, *J* = 7.9, 17.9 Hz, 1H), 1.99 (d, *J* = 17.8 Hz, 1H).

*rac-2-((4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5H-cyclopenta[4,5]furo-[2,3-c]pyridin-6-yl)-N,N-dimethylacetamide (**165**).* To a solution of *rac*-(3a*R*,4*S*,4a*R*,9b*S*,9c*R*)-4a-(4-bromophenyl)-9b-hydroxy-9-methoxy-4-phenyl-3,3a,4,4a,9b,9c-hexahydro-2*H*-furo[3″,2″:4′,5′]-cyclopenta[1′,2′:4,5]furo[2,3-*c*]pyridin-2-one (**164**) (0.25 g, 0.51 mmol) in a 2 M solution of dimethyl amine (20 mL) in tetrahydrofuran, *ca.* 50% propylphosphonic anhydride in ethyl acetate (3.2 mL, 3.4 g solution, 1.7 g propylphosphonic anhydride, 5.4 mmol) was added. The reaction mixture was heated at 80 °C for 16 h. After this time, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the crude product which was purified by silica gel (100−200 mesh size) column chromatography using 5% methanol in dichloromethane as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-2-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]furo[2,3-*c*]-pyridin-6-yl)-*N*,*N*-dimethylacetamide (**165**) as a white solid. Yield: 0.13 g (0.24 mmol, 47%). MS (ESI) *m*/*z*: 539.43 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.03 (s, 1H), 7.96 (s, 1H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.13−7.02 (m, 5H), 6.90 (d, *J* = 6.6 Hz, 2H), 5.59 (s, 1H), 5.06 (s, 1H), 4.49 (s, 1H), 3.87 (s, 3H), 3.67 (d, *J* = 14.6 Hz, 1H), 3.35 (br s, 1H), 2.80−2.79 (m, 6H), 2.79 (s, 3H), 2.00−1.96 (m, 1H), 1.33−1.29 (m, 1H).

*rac-(4bS,5R,6R,7S,7aR)-7a-(4-Bromophenyl)-6-(2-(dimethylamino)ethyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4bH-cyclopenta[4,5]furo[2,3-c]pyridine-4b,5-diol (**166**).* To a solution of *rac*-2-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,6,7,7a-tetrahydro-5*H*-cyclopenta[4,5]-furo[2,3-*c*]pyridin-6-yl)-*N*,*N*-dimethylacetamide (0.13 g, 0.24 mmol) in dry tetrahydrofuran (5.2 mL) at 0 °C, borane dimethyl sulfide complex (0.23 mL, 0.18 g, 2.4 mmol) was added dropwise over a period of 5 min. The reaction mixture was slowly brought to room temperature and stirred for additional 16 h. After this time, the reaction mixture was quenched with methanol (40 mL) at 0 °C and heated to reflux for 24 h. Then, the solvent was removed under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography using 10% methanol in dichloromethane as the eluent. The desired fractions were concentrated under reduced pressure to afford *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-(2-(dimethylamino)-ethyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]-furo[2,3-*c*]pyridine-4b,5-diol (**166**). Yield: 0.09 g (0.17 mmol, 71%); MS (ESI) *m*/*z*: 525.4 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.03 (s, 1H), 7.97 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.13−7.01 (m, 5H), 6.96 (d, *J* = 7.3 Hz, 2H), 5.59 (s, 1H), 4.40 (d, *J* = 4.1 Hz, 1H), 3.89 (s, 3H), 3.39−3.31 (m, 1H), 3.16 (br s, 1H), 2.97−2.94 (m, 1H), 2.27 (br s, 6H), 1.43−1.33 (m, 2H), 1.29−1.10 (m, 2H).

*rac-4-((4bS,5R,6R,7S,7aR)-6-(2-(Dimethylamino)ethyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7aH-cyclopenta-[4,5]furo[2,3-c]pyridin-7a-yl)benzonitrile (rac-**52**).* To a solution of *rac*-(4b*S*,5*R*,6*R*,7*S*,7a*R*)-7a-(4-bromophenyl)-6-(2-(dimethylamino)-ethyl)-4-methoxy-7-phenyl-5,6,7,7a-tetrahydro-4b*H*-cyclopenta[4,5]-furo[2,3-*c*]pyridine-4b,5-diol (0.09 g, 0.17 mmol) in *N*,*N*-dimethylformamide (4 mL) at room temperature, zinc cyanide (0.12 g, 1.0 mmol) and zinc dust (0.00013 g, 0.0020 mmol) were added. This reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino)ferrocene (0.0018 g, 0.0032 mmol) and tetrakis(triphenylphosphine)palladium (0.0046 g, 0.0040 mmol) were added to the reaction mixture which was degassed for an additional 5 min and heated at 140 °C for 8 h. After this time, the reaction mixture was diluted with ethyl acetate and washed with cold water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by silica gel (100−200 mesh size) column chromatography using 6% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-4-((4b*S*,5*R*,6*R*,7*S*,7a*R*)-6-(2-(dimethylamino)ethyl)-4b,5-dihydroxy-4-methoxy-7-phenyl-4b,5,6,7-tetrahydro-7a*H*-cyclopenta[4,5]furo[2,3-*c*]pyridin-7a-yl)benzonitrile (*rac*-**52**) as a white solid. Yield: 0.015 g (0.032 mmol, 19%). MS (ESI) *m*/*z*: 472.28 $[M + 1]^+$; HRMS (ESI): calcd, 472.2231 $[M + H]^+$; found, 472.2251; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 8.05 (s, 1H), 7.97 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.09−7.05 (m, 2H), 7.01−6.96 (m, 3H), 5.68 (s, 1H), 4.42 (d, *J* = 4.0 Hz, 1H), 3.88 (s, 3H), 3.76 (d, *J* = 14.1 Hz, 1H), 3.03 (br s, 1H), 2.41−2.37 (m, 1H), 2.32−2.26 (m, 1H), 2.12 (s, 6H), 1.48 (br s, 1H), 1.41 (br s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 155.64, 153.45, 142.63, 137.11, 130.12, 128.73, 128.52, 127.68, 126.99, 126.28, 125.60, 123.65, 118.91, 108.90, 101.78, 93.86, 77.45, 59.17, 56.98, 56.20, 45.24, 43.53, 24.19.

Synthesis of (5aR,6S,7S,8R,8aS)-5a-(4-Cyanophenyl)-7-((dimethylamino)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-



*5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-c]pyridine-3-carbonitrile ((−)-**53**).* *4-(Benzyloxy)-2,6-dichloropyridine (**168**).* To a solution of 2,4,6-trichloropyridine (**167**) (1.0 kg, 5.5 mol) in *N*,*N*-dimethylformamide (8.0 L) under nitrogen atmosphere at 0 °C, sodium hydride (55% dispersion in paraffin oil, 265.2 g, 6.078 mol) was added. This suspension was held at 0 °C for 15−20 min. Then, benzyl alcohol (596.6 mL, 620.5 g, 5.738 mol) was added, and the reaction mixture was stirred for another 1 h at the same temperature. After this time, the reaction mixture was poured into crushed ice and the resulting precipitate was collected by filtration and washed with water. The solid obtained was stirred in minimum hexane and collected again by filtration. The solid was dried under vacuum to afford 4-(benzyloxy)-2,6-dichloropyridine (**168**) as a white solid. Yield: 1.00 kg (3.94 mol, 72%). MS (ESI) *m*/*z*: 254.32 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.46−7.37 (m, 5H), 7.28 (s, 2H), 5.26 (s, 2H).

*4-(Benzyloxy)-2-chloro-6-methoxypyridine (**169**).* To a solution of 4-(benzyloxy)-2,6-dichloropyridine (1.0 kg, 3.9 mol) in toluene (15.0 L) at room temperature, 25% sodium methoxide in methanol (1.70 L, 1.60 kg solution, 400 g NaOMe, 7.4 mol) was added. The reaction

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mixture was heated at 60 °C for 5 h. After this time, the reaction mixture was cooled to room temperature, poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product, which was recrystallized with chilled hexane to afford 4-(benzyloxy)-2-chloro-6-methoxypyridine (**169**) as a white solid. Yield: 541 g (2.17 mol, 56%). MS (ESI) m/z: 250.35 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.42−7.32 (m, 5H), 6.77 (d, J = 1.3 Hz, 1H), 6.43 (d, J = 1.2 Hz, 1H), 5.17 (s, 2H), 3.80 (s, 3H).

*1-(4-(Benzyloxy)-6-chloro-2-methoxypyridin-3-yl)ethan-1-ol (**170**).* To a solution of 4-(benzyloxy)-2-chloro-6-methoxypyridine (**169**) (541 g, 2.17 mol) in tetrahydrofuran (550 mL) at −78 °C, 2.5 M *n*-buthyl lithium in hexane (1.043 L, 2.608 mol) was added. After this addition was completed, the reaction mixture was stirred at −78 °C for 30 min. Then, acetaldehyde (243.4 mL, 192.3 g, 4.370 mol) was added at the same temperature and the reaction mixture was maintained at that temperature for 2 h. After this time, the reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product, which was purified by silica gel (100−200 mesh) column chromatography using 10−15% ethyl acetate in hexanes as the eluent to afford 1-(4-(benzyloxy)-6-chloro-2-methoxypyridin-3-yl)ethan-1-ol (**170**) as a white crystalline solid. Yield: 414 g (1.41 mol, 65%). MS (ESI) m/z: 294.41 $[M + 1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.46 (d, J = 7.1 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.35 (d, J = 7.0 Hz, 1H), 6.93 (s, 1H), 5.24 (s, 2H), 5.11 (m, 1H), 4.61 (d, J = 6.2 Hz, 1H), 3.83 (s, 3H), 1.38 (m, 3H).

*1-(4-(Benzyloxy)-6-chloro-2-methoxypyridin-3-yl)ethan-1-one (**171**).* To a solution of 1-(4-(benzyloxy)-6-chloro-2-methoxypyridin-3-yl)ethan-1-ol (**170**) (414 g, 1.41 mol) in dichloromethane (8.300 L) at room temperature, water (10 mL) was added followed by the slow addition of Dess−Martin periodinane (719 g, 1.70 mol). The reaction mixture was stirred for 15 min. Then, the reaction mixture was filtered through Celite and washed with an excess of dichloromethane. The filtrate was washed with saturated sodium bicarbonate solution and then brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product, which was purified by silica gel (100−200 mesh) column chromatography using 0−10% ethyl acetate in hexanes as the eluent to afford 1-(4-(benzyloxy)-6-chloro-2-methoxypyridin-3-yl)ethan-1-one (**171**) as a white solid. Yield: 308.0 g (1.06 mol, 75%). MS (ESI) m/z: 292.12 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.4−7.35 (m, 5H), 7.11 (s, 1H), 5.27 (s, 2H), 3.84 (s, 3H), 2.38 (s, 3H).

*1-(6-Chloro-4-hydroxy-2-methoxypyridin-3-yl)ethan-1-one (**172**).* 1-(4-(benzyloxy)-6-chloro-2-methoxypyridin-3-yl)ethan-1-one (**171**) (23.35 g, 80.04 mmol) was dissolved in ethyl acetate (600 mL) under stirring in a 2 L round-bottom flask. A combination vacuum/nitrogen/hydrogen manifold was attached, and the atmosphere in the flask was removed and replaced with argon. Palladium (10%) on carbon (188 mg, 1.88 mmol) was added, and the atmosphere in the flask was removed and replaced with hydrogen. The resulting mixture was stirred vigorously at room temperature under hydrogen for 3 h. The reaction mixture was filtered through Celite, and the filter cake washed thoroughly with EtOAc. The filtrate was concentrated on a rotary evaporator and purified *via* silica gel chromatography (1% ethyl acetate in hexanes isocratic) to afford 1-(6-chloro-4-hydroxy-2-methoxypyridin-3-yl)ethan-1-one (**172**) as a white solid. Yield: 14.15 g (70.19 mmol, 88%). MS (ESI) m/z: 202.2 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 13.02 (s, 1H), 6.70 (s, 1H), 3.91 (s, 3H), 2.53 (s, 3H).

*(E)-3-(4-Bromophenyl)-1-(6-chloro-4-hydroxy-2-methoxypyridin-3-yl)prop-2-en-1-one (**173**).* To a 1 L round-bottom flask with a stir bar was added sequentially 1-(6-chloro-4-hydroxy-2-methoxypyridin-3-yl)ethan-1-one (**172**) (14.13 g, 70.09 mmol) 4-bromobenzaldehyde (13.34 g, 72.13 mmol), *N*,*N*-dimethylformamide (170 mL), and then sodium methoxide (25 wt % in methanol) (48.04 mL, 45.40 g solution; 11.35 g, 210.1 mmol NaOMe). The reaction mixture was stirred vigorously and heated at 50 °C under a reflux condenser for 20 min. The reaction mixture is initially clear and light yellow, but then a lot of solids precipitated. More *N*,*N*-dimethylformamide (50 mL) was added to keep the reaction stirring. The reaction mixture was poured onto a vigorously stirred mixture of 1 N HCl in water (210 mL, 210 mmol) and ice water (500 mL). The resulting light yellow mixture was stirred vigorously for 10 min and then solids were collected by vacuum filtration. The solids were washed with water and dried under high vacuum to afford (*E*)-3-(4-bromophenyl)-1-(6-chloro-4-hydroxy-2-methoxypyridin-3-yl)prop-2-en-1-one (**173**) as a yellow solid. Yield: 25.83 g (70.08 mmol, 100%). MS (ESI) m/z: 368.0, 369.9 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.72−7.67 (m, 2H), 7.65−7.59 (m, 2H), 7.40 (d, J = 16.2 Hz, 1H), 7.17 (d, J = 16.1 Hz, 1H), 6.60 (s, 1H), 3.81 (s, 3H).

*2-(4-Bromophenyl)-7-chloro-3-hydroxy-5-methoxy-4H-pyrano-[3,2-c]pyridin-4-one (**174**).* 10% aq sodium hydroxide (18.1 mL, 49.78 mmol) was added to a stirred mixture (not all dissolved) of (*E*)-3-(4-bromophenyl)-1-(6-chloro-4-hydroxy-2-methoxypyridin-3-yl)prop-2-en-1-one (**173**) (8.31 g, 22.54 mmol) in ethanol (160 mL) and DCM (40 mL) cooled with a room temperature water bath. After 1 min, 30% aq hydrogen peroxide (16.19 mL, 158.5 mmol) was added. The reaction mixture was stirred vigorously while being cooled with a room temperature water bath for 1 h. The reaction mixture was diluted with dichloromethane, poured onto saturated aqueous ammonium chloride (250 mL), and extracted three times with dichloromethane. The organics were concentrated on a rotary evaporator. The residual solids were shaken in a separatory funnel with DCM (1 L) and saturated aqueous ammonium chloride (250 mL). The layers were separated, and the water layer was extracted twice with DCM. The combined organics were dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. Ethyl acetate (10%) in hexanes (100 mL) was added to the residue, and the resulting mixture was heated to reflux with a heat gun. The mixture was capped and let stand 1 h at room temperature. Solids were collected by vacuum filtration, washed with 10% ethyl acetate in hexanes, and dried under high vacuum to afford 2-(4-bromophenyl)-7-chloro-3-hydroxy-5-methoxy-4*H*-pyrano[3,2-*c*]-pyridin-4-one (**174**) as an orange solid. Yield: 1.61 g (4.21 mmol, 19%). MS (ESI) m/z: 382.0, 384.0 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 10.01 (s, 1H), 8.15−8.09 (m, 2H), 7.80−7.75 (m, 2H), 7.55 (s, 1H), 4.02 (s, 3H).

*rac-Methyl (3S,4S,5R)-2-(4-Bromophenyl)-8-chloro-5,10,10-trihydroxy-6-methoxy-3-phenyl-2,3,4,5-tetrahydro-2,5-methanooxepino[3,2-c]pyridine-4-carboxylate (**S110**).* To a 500 mL round-bottom flask were added sequentially a stir bar, 2-(4-bromophenyl)-7-chloro-3-hydroxy-5-methoxy-4*H*-pyrano[3,2-*c*]-pyridin-4-one (**9**, 1.61 g, 4.21 mmol), methyl cinnamate (**10**, 6.83 g, 42.1 mmol), chloroform (80 mL), and TFE (80 mL). The reaction mixture was stirred vigorously and irradiated with 450 W UV light while being cooled with a 0 °C cold bath for 5 h. The reaction mixture was diluted with 3% triethylamine in ethyl acetate (15 mL), concentrated on a rotary evaporator with silica gel, and dried under high vacuum overnight. The residue was loaded into a loading column and purified *via* silica gel chromatography (0-5-100% EtOAc/hexanes) (column was pre-equilibrated with 10% EtOAc in hexanes with 3% triethylamine prior to equilibration with 0% hexanes) to afford 1.67 g of impure *rac*-methyl (3*S*,4*S*,5*R*)-2-(4-bromophenyl)-8-chloro-5,10,10-trihydroxy-6-methoxy-3-phenyl-2,3,4,5-tetrahydro-2,5-methanooxepino[3,2-*c*]pyridine-4-carboxylate (**S110**) an orange residue which was taken on to the next step without further purification. MS (ESI) m/z: 562.3, 564.2 $[M + 1]^+$.

*rac-Methyl (5aR,6S,7R,8aR)-5a-(4-Bromophenyl)-3-chloro-8a-hydroxy-1-methoxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-c]pyridine-7-carboxylate (**S111**).* Sodium methoxide (25 wt % in methanol) (2.03 mL, 1.92 g sln; 0.480 g, 8.89 mmol NaOMe) was added to a stirred solution of impure *rac*-methyl (3*S*,4*S*,5*R*)-2-(4-bromophenyl)-8-chloro-5,10,10-trihydroxy-6-methoxy-3-phenyl-2,3,4,5-tetrahydro-2,5-methanooxepino[3,2-*c*]-pyridine-4-carboxylate (**S110**) (1.67 g) in methanol (60 mL) at room temperature under argon. The clear yellow solution changed to dark

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orange colored. The reaction mixture was heated at 60 °C under a reflux condenser under argon for 40 min and then most of the solvent was removed on a rotary evaporator. The residue was partitioned between saturated aqueous ammonium chloride and ethyl acetate. The organics were washed with brine, dried over $MgSO_4$, filtered, concentrated on a rotary evaporator, and dried under high vacuum to afford impure *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-1-methoxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylate (**S111**) as an orange residue. Yield: 1.57 g (crude). MS (ESI) *m*/*z*: 544.0, 546.1 $[M + 1]^+$. This material was carried on without further purification.

*rac-Methyl (5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-c]pyridine-7-carboxylate (**176**).* To a stirred solution of impure *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-5a-(4-bromophenyl)-3-chloro-8a-hydroxy-1-methoxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylate (**S111**) (1.57 g) in MeCN (50 mL) at room temperature was added acetic acid (1.65 mL, 28.8 mmol) and then sodium triacetoxyborohydride (3.05 g, 14.4 mmol). The resulting reaction mixture was stirred vigorously at room temperature under argon for 40 min. Saturated aqueous ammonium chloride (20 mL) was added slowly dropwise, and the resulting mixture was partitioned between water and ethyl acetate. The organics were washed with saturated aqueous sodium bicarbonate and then brine, dried over $MgSO_4$, filtered, concentrated on a rotary evaporator and purified *via* silica gel chromatography (12−22% EtOAc/hexanes) to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylate (Cpd. no. 136F) as a slightly yellow foam-solid. Yield: 631 mg (1.15 mmol, 27% over three steps). MS (ESI) *m*/*z*: 546.1, 548.1 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.24−7.19 (m, 2H), 7.09−6.92 (m, 8H), 5.70−5.64 (m, 2H), 4.62 (t, *J* = 5.4 Hz, 1H), 4.31 (d, *J* = 13.9 Hz, 1H), 4.09 (dd, *J* = 14.0, 4.9 Hz, 1H), 3.83 (s, 3H), 3.57 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta-[4,5]furo[3,2-c]pyridine-7-carboxylic Acid (**S112**).* To a stirred solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylate (**1**, 1.09 g, 1.99 mmol) in methanol (40 mL) was added water (4 mL) and then lithium hydroxide (477 mg, 19.9 mmol). The resulting yellow reaction mixture was stirred vigorously and heated at 50 °C under a reflux condenser for 4.5 h. The reaction mixture was cooled with a 0 °C cold bath, and 1 N HCl in water (19.9 mL, 19.9 mmol) was added under vigorous stirring. A few more drops of 1 N HCl were added to make the mixture slightly acidic. Most of the methanol was removed on a rotary evaporator. The residue was extracted three times with dichloromethane. The combined organics were washed with brine, dried over $MgSO_4$, filtered, concentrated on a rotary evaporator, and dried under high vacuum at 40 °C overnight to afford crude *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylic acid (**S112**) as a white solid with yellow impurity. Yield: 961 mg (1.80 mmol, 90%). MS (ESI) *m*/*z*: 532.1, 534.0 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.23 (s, 1H), 7.24−7.18 (m, 2H), 7.06 (m, 2H), 7.03−6.94 (m, 5H), 6.93 (s, 1H), 5.62 (d, *J* = 8.3 Hz, 2H), 4.62 (t, *J* = 5.3 Hz, 1H), 4.29 (d, *J* = 13.9 Hz, 1H), 3.95 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.84 (s, 3H).

*rac-(5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-8,8a-dihydroxy-1-methoxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-c]pyridine-7-carboxamide (**S113**).* HATU (686 mg, 1.80 mmol) was added to a stirred solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylic acid (**S112**) (915 mg, 1.72 mmol) in *N*,*N*-dimethylformamide (15 mL) at room temperature under argon. After 2 min, *N*,*N*-diisopropylethylamine (0.45 mL, 2.58 mmol) was added. The resulting reaction mixture was stirred at room temperature under argon for 20 min. Dimethylamine (2 M solution in THF) (2.58 mL, 5.15 mmol) was added, and the reaction mixture was stirred at room temperature under argon for 3 h. The reaction mixture was diluted with 90% ethyl acetate in hexanes, washed three times with water, once with brine, dried over $MgSO_4$, filtered, concentrated on a rotary evaporator, and purified *via* silica gel chromatography (30−100% EtOAc/hexanes) to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-1-methoxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxamide (**S113**) as a white foam-solid. Yield: 917 mg (1.64 mmol, 95%). MS (ESI) *m*/*z*: 559.1, 561.1 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.25−7.20 (m, 2H), 7.07−7.00 (m, 4H), 6.99−6.93 (m, 2H), 6.89 (dt, *J* = 8.2, 1.2 Hz, 2H), 5.62 (s, 1H), 5.19 (d, *J* = 5.7 Hz, 1H), 4.69 (t, *J* = 5.5 Hz, 1H), 4.41 (d, *J* = 13.4 Hz, 1H), 4.18 (dd, *J* = 13.5, 5.2 Hz, 1H), 3.84 (s, 3H), 3.27 (s, 3H), 2.77 (s, 3H).

*rac-(5aR,6S,7S,8R,8aS)-5a-(4-Bromophenyl)-3-chloro-7-((dimethylamino)methyl)-1-methoxy-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-c]pyridine-8,8a-diol (**177**).* Borane dimethyl sulfide complex (1.47 mL, 15.5 mmol) was added to a stirred solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-8,8a-dihydroxy-1-methoxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxamide (**S113**) (866 mg, 1.55 mmol) in THF (30 mL) at room temperature under a reflux condenser under argon. Some bubbling was observed. The reaction mixture was heated at 40 °C under a reflux condenser under argon for 3 h. After cooling to room temperature, wet methanol (20 mL) was added dropwise slowly. The resulting clear colorless reaction mixture was stirred vigorously and heated at 65 °C under a reflux condenser under argon for 36 h. The reaction mixture was loaded onto five 2 g Strata X-C ion exchange columns from Phenomenex. The columns were washed sequentially with acetonitrile, methanol, and then a mixture of 5% ammonium hydroxide in methanol/dichloromethane. Eluent containing the desired product was concentrated on a rotary evaporator and dried under high vacuum at 40 °C to afford *rac*-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-bromophenyl)-3-chloro-7-((dimethylamino)methyl)-1-methoxy-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-8,8a-diol (**177**) as a white solid. Yield: 742 mg (1.36 mmol, 88%). MS (ESI) *m*/*z*: 545.2, 547.3; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.26−7.21 (m, 2H), 7.13−7.05 (m, 4H), 7.04−6.94 (m, 3H), 6.86 (s, 1H), 5.56 (s, 1H), 5.15 (s, 1H), 4.43 (s, 1H), 3.84 (s, 3H), 3.70 (d, *J* = 14.1 Hz, 1H), 3.08 (ddt, *J* = 14.0, 10.0, 3.6 Hz, 1H), 2.56 (m, 1H), 2.19 (s, 6H), 1.94 (d, *J* = 11.1 Hz, 1H).

*(5aR,6S,7S,8R,8aS)-5a-(4-Cyanophenyl)-7-((dimethylamino)-methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-c]pyridine-3-carbonitrile ((−)-**53**).* *rac*-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-Bromophenyl)-3-chloro-7-((dimethylamino)methyl)-1-methoxy-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-8,8a-diol (**177**) (165 mg, 0.300 mmol), zinc cyanide (213 mg, 1.81 mmol), zinc powder (19.8 mg, 0.300 mmol), *N*,*N*-dimethylformamide (0.9 mL), and water (0.09 mL) were combined in a microwave vial with a stir bar. The resulting mixture was sparged with argon gas for 5 min. Pd_2dba_3 (27.7 mg, 0.030 mmol) and dppf (33.5 mg, 0.060 mmol) were added, and the resulting mixture was sparged with argon gas for 5 min. The reaction mixture was sealed, stirred, and microwaved at 120 °C for 2 h. The reaction mixture was diluted with DMSO and methanol, filtered, and purified *via* preparatory HPLC (15−35% acetonitrile in water with 0.1% TFA). Fractions containing the desired product were loaded onto three 2 g Strata X-C ion exchange columns from Phenomenex. The columns were washed sequentially with water, acetonitrile, methanol, and then a mixture of 10% ammonium hydroxide, 20% dichloromethane, and 70% methanol. Fractions containing the desired product were combined, concentrated on a rotary evaporator, and dried under high vacuum at 40 °C to afford *rac*-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-cyanophenyl)-7-((dimethylamino)methyl)-8,8a-dihydroxy-1-methoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]-pyridine-3-carbonitrile (*rac*-**53**) as a white solid. Yield: 91.6 mg (0.190 mmol, 63%). The enantiomers were separated by chiral preparative SFC [Chiralpak IG (4.6 × 250) mm, 5μ] using CO_2:EtOH/TEA (60:40:0.1) mobile phase. Peak 1 ((−)-**53**), $[\alpha]_D$ −36.4° (*c* 0.3,

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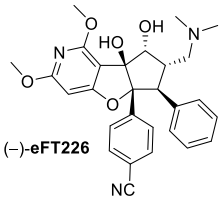
$CHCl_3$), R_t 1.52 min, ee >99%. MS (ESI) m/z: 483.15 $[M + 1]^+$; HRMS (ESI): calcd, 483.2027 $[M + H]^+$; found, 483.2043; UPLC: 99.75; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.61−7.51 (m, 3H), 7.37 (d, J = 8.2 Hz, 2H), 7.10−7.06 (m, 2H), 7.02−6.98 (m, 3H), 5.86 (s, 1H), 5.35 (br s, 1H), 4.51 (s, 1H), 3.89 (s, 3H), 3.79 (d, J = 13.9 Hz, 1H), 3.17−3.16 (m, 1H), 2.62−2.60 (m, 1H), 2.23 (br s, 6H). 1.98 (br s, 1H). Peak 2 ((+)-**53**), SOR (not recorded, solubility issues) R_t 2.04 min, ee >99%. MS (ESI) m/z: 483.15 $[M + 1]^+$; UPLC: 99.78%.^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.54−7.50 (m, 3H), 7.35 (d, J = 8.2 Hz, 2H), 7.09−7.06 (m, 2H), 7.01−6.88 (m, 3H), 5.85 (s, 1H), 5.42 (br s, 1H), 4.59 (d, J = 3.0 Hz, 1H), 3.89 (s, 3H), 3.77 (d, J = 14.0 Hz, 1H), 3.18−3.16 (m, 1H), 2.58−2.50 (m, 1H), 2.21 (s, 6H), 1.96 (d, J = 10.3 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 165.96, 162.09, 141.54, 136.44, 130.27, 129.89, 128.63, 128.32, 127.74, 126.47, 118.77, 117.48, 114.85, 109.21, 108.53, 103.63, 92.62, 77.17, 57.40, 56.20, 53.88, 45.77, 43.40.

*Synthesis of 4-((5aR,6S,7S,8R,8aS)-7-((Dimethylamino)methyl)-8,8a-dihydroxy-1,3-dimethoxy-6-phenyl-6,7,8,8a-tetrahydro-5aH-cyclopenta[4,5]furo[3,2-c]pyridin-5a-yl)benzonitrile ((−)-**eFT226**).*



(−)-eFT226

*2-(4-Bromophenyl)-3-hydroxy-5,7-dimethoxy-4H-pyrano[3,2-c]-pyridin-4-one (**175**).* To a stirred solution of 2-(4-bromophenyl)-7-chloro-3-hydroxy-5-methoxy-4*H*-pyrano[3,2-*c*]pyridin-4-one (**174**) (32.0 g, 83.6 mmol) in *N*,*N*-dimethylformamide (320 mL) at room temperature, 25% sodium methoxide in methanol (180.4 mL, 170.5 g solution, 42.62 g NaOMe, 789.0 mmol) was added under argon. The reaction mixture was heated at 80 °C for 1 h under an argon atmosphere. After this time, the reaction mixture was poured in ice-cold water and acidified up to pH ≈ 6 using 6 N hydrochloric acid. The resulting precipitate was collected by filtration, washed with water, and dried under vacuum. The solid thus obtained was stirred in diethyl ether, filtered, and dried under vacuum to afford 2-(4-bromophenyl)-3-hydroxy-5,7-dimethoxy-4*H*-pyrano[3,2-*c*]pyridin-4-one (**175**) as a beige solid. Yield: 31.0 g (82.0 mmol, 98%); MS (ESI) m/z: 378.04 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.66 (br s, 1H), 8.10 (d, J = 8.00 Hz, 2H), 7.75 (d, J = 9.6 Hz, 2H), 6.61 (s, 1H), 4.02 (s, 3H), 3.95 (s, 3H).

*rac-Methyl (2R,3S,4R,5R)-2-(4-Bromophenyl)-5-hydroxy-6,8-dimethoxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanooxepino[3,2-c]pyridine-4-carboxylate (**S114**).* A suspension of 2-(4-bromophenyl)-3-hydroxy-5,7-dimethoxy-4*H*-pyrano[3,2-*c*]pyridin-4-one (**175**) (31.0 g, 82.0 mmol) and methyl cinnamate (**55**) (132.95 g, 819.72 mmol) in chloroform (1000 mL) and TFE (1000 mL) was stirred vigorously in a UV reactor flask and irradiated with 400 W UV light for 48 h at 0−5 °C. After this time, the reaction mixture became a clear solution. The reaction mixture was diluted with 3% triethylamine in ethyl acetate (100 mL) and then concentrated under reduced pressure. The residue was purified by column chromatography eluting with 0−100% ethyl acetate in hexanes. The desired fractions were concentrated to afford *rac*-methyl (2*R*,3*S*,4*R*,5*R*)-2-(4-bromophenyl)-5-hydroxy-6,8-dimethoxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanooxepino[3,2-*c*]pyridine-4-carboxylate (**S114**) as a sticky light brown solid. Yield: 39 g, crude MS (ESI) m/z: 540.12 $[M + 1]^+$.

*rac-Methyl (5aR,6S,7R,8aR)-5a-(4-Bromophenyl)-8a-hydroxy-1,3-dimethoxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-c]pyridine-7-carboxylate (**S115**).* To a stirred solution of crude *rac*-methyl (2*R*,3*S*,4*R*,5*R*)-2-(4-bromophenyl)-5-hydroxy-6,8-dimethoxy-10-oxo-3-phenyl-2,3,4,5-tetrahydro-2,5-methanooxepino[3,2-*c*]pyridine-4-carboxylate (**S114**) (39 g) in methanol (390 mL) at room temperature, 25% sodium methoxide (46.8 mL, 44.2 g solution, 11.1 g NaOMe, 205 mmol) was added under argon. The reaction mixture was heated at 80 °C for 45 min under an argon atmosphere. After this time, the reaction mixture was concentrated to dryness under vacuum, and the residue was partitioned between saturated aqueous ammonium chloride and ethyl acetate. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate, filtered, concentrated on a rotary evaporator, and dried under high vacuum to afford *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-5a-(4-bromophenyl)-8a-hydroxy-1,3-dimethoxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]-pyridine-7-carboxylate (**S115**) as an orange foam. Yield: 38.0 g, crude. MS (ESI) m/z: 540.21 $[M + 1]^+$.

*rac-Methyl (5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-8,8a-dihydroxy-1,3-dimethoxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-c]pyridine-7-carboxylate (**178**).* To a stirred solution of crude *rac*-methyl (5a*R*,6*S*,7*R*,8a*R*)-5a-(4-bromophenyl)-8a-hydroxy-1,3-dimethoxy-8-oxo-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxylate (**S116**) (38.0 g) in acetonitrile (1140 mL) at 0 °C, acetic acid (42.5 mL, 44.6 g, 743 mmol) and sodium triacetoxyborohydride (74.52 g, 351.6 mmol) were added under an argon atmosphere. The reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, the reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (1000 mL) and partitioned between water and ethyl acetate. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product, which was purified by column chromatography by eluting with 10−50% ethyl acetate in hexanes. The desired fractions were concentrated to afford *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-8,8a-dihydroxy-1,3-dimethoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]-pyridine-7-carboxylate (**178**) as a white solid. Yield: 18.0 g (33.2 mmol, 40% over three steps). MS (ESI) m/z: 542.52 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.20 (d, J = 8.4 Hz, 2H), 7.07−6.96 (m, 5H), 6.93 (d, J = 7.3 Hz, 2H), 6.09 (s, 1H), 5.44−5.41 (m, 2H), 4.60 (s, 1H), 4.27 (d, J = 13.9 Hz, 1H), 4.04 (dd, J = 14.0 Hz, 4.9 Hz, 1H), 3.84 (s, 6H), 3.56 (s, 3H); MS (ESI) m/z: 542.52 $[M + 1]^+$.

*rac-(5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-8,8a-dihydroxy-1,3-dimethoxy-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo-[3,2-c]pyridine-7-carboxylic Acid (**S116**).* To a solution of *rac*-methyl (5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-8,8a-dihydroxy-1,3-dimethoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]-pyridine-7-carboxylate (**178**) (14.80 g, 27.29 mmol) in tetrahydrofuran/methanol/water (2:1:1, 300 mL) at room temperature, lithium hydroxide (6.53 g, 273 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. After completion of reaction, the reaction mixture was concentrated under reduced pressure, and the crude product was diluted with ethyl acetate. The reaction mixture was cooled to 0 °C and acidified to pH ≈ 6 using 6 N hydrochloric acid. The compound was extracted with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-8,8a-dihydroxy-1,3-dimethoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo-[3,2-*c*]pyridine-7-carboxylic acid (**S116**) as a white solid. Yield: 13.50 g (25.5 mmol, 93%); MS (ESI) m/z: 526.21 $[M - 1]^-$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 12.22 (br s, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 7.4 Hz, 2H), 6.99 (d, J = 8.4 Hz, 3H), 6.94 (d, J = 7.4 Hz, 2H), 6.08 (s, 1H), 5.35 (s, 1H), 5.59 (s, 1H), 4.24 (d, J = 14.00 Hz, 1H), 3.91 (d, J = 4.8 Hz, 2H), 3.84 (s, 6H).

*rac-(5aR,6S,7R,8R,8aS)-5a-(4-Bromophenyl)-8,8a-dihydroxy-1,3-dimethoxy-N,N-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6H-cyclopenta[4,5]furo[3,2-c]pyridine-7-carboxamide (**S117**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-8,8a-dihydroxy-1,3-dimethoxy-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta-[4,5]furo[3,2-*c*]pyridine-7-carboxylic acid (**S116**) (13.50 g, 25.55 mmol) in dichloromethane (270 mL) at 0 °C, HATU (14.53 g, 38.21 mmol) and *N*,*N*-diisopropylethylamine (14.20 mL, 10.51 g, 81.30 mmol) were added. This reaction mixture was stirred for 5 min. Then, dimethylamine hydrochloride (10.34 g, 126.8 mmol) was added, and the reaction mixture was stirred for 2 h at room temperature. After this time, the reaction mixture was diluted with water. The organic layer

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was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water and then brine, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product, which was purified by Combi-flash (80 g, RedisSep column) using 1−8% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-8,8a-dihydroxy-1,3-dimethoxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxamide (**S117**) as a white solid. Yield: 13.0 g (23.4 mmol, 92%); MS (ESI) *m*/*z*: 555.61 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.21 (d, J = 8.7 Hz, 2H), 7.05−7.00 (m, 4H), 6.96 (d, J = 6.9 Hz, 1H), 6.86 (d, J = 7.2 Hz, 2H), 6.10 (s, 1H), 5.36 (s, 1H), 4.93 (d, J = 5.1 Hz, 1H), 4.69 (t, J = 5.5 Hz, 1H), 4.35 (d, J = 13.2 Hz, 1H), 4.15−4.10 (m, 1H), 3.84 (s, 6H), 3.26 (s, 3H), 2.76 (s, 3H).

*rac-(5aR,6S,7S,8R,8aS)-5a-(4-Bromophenyl)-7-((dimethylamino)methyl)-1,3-dimethoxy-6-phenyl-5a,6,7,8-tetrahydro-8aH-cyclopenta[4,5]furo[3,2-c]pyridine-8,8a-diol (**179**).* To a solution of *rac*-(5a*R*,6*S*,7*R*,8*R*,8a*S*)-5a-(4-bromophenyl)-8,8a-dihydroxy-1,3-dimethoxy-*N*,*N*-dimethyl-6-phenyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-7-carboxamide (**S118**) (6.00 g, 10.8 mmol) in tetrahydrofuran (120 mL) at 0 °C, borane dimethyl sulfide complex (8.21 g, 108 mmol) was added. The reaction mixture was stirred overnight at room temperature. After this time, the reaction mixture was quenched with methanol at 0 °C and then heated at 60 °C for 16 h. The solvents were concentrated to obtain the crude product, which was purified by Combi-flash (40 g, RediSep column) using 2−10% methanol in dichloromethane as the eluent. The desired fractions were concentrated to afford *rac*-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-bromophenyl)-7-((dimethylamino)methyl)-1,3-dimethoxy-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-8,8a-diol (**179**) as a white solid. Yield: 5.20 g (9.60 mmol, 89%). MS (ESI) *m*/*z*: 541.32 $[M + 1]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.22 (d, J = 8.2 Hz, 2H), 7.11−7.06 (m, 5H), 7.01 (d, J = 6.9 Hz, 1H), 6.95 (d, J = 7.4 Hz, 2H), 6.02 (s, 1H), 5.31 (s, 1H), 4.93 (br s, 1H), 4.41 (d, J = 3.5 Hz, 1H), 3.84 (s, 6H), 3.66 (d, J = 14.0 Hz, 1H), 3.08 (s, 1H), 2.58 (s, 1H), 2.23 (s, 6H).

*4-((5aR,6S,7S,8R,8aS)-7-((Dimethylamino)methyl)-8,8a-dihydroxy-1,3-dimethoxy-6-phenyl-6,7,8,8a-tetrahydro-5aH-cyclopenta[4,5]furo[3,2-c]pyridin-5a-yl)benzonitrile ((−)-**eFT226**).* To a solution of *rac*-(5a*R*,6*S*,7*S*,8*R*,8a*S*)-5a-(4-bromophenyl)-7-((dimethylamino)methyl)-1,3-dimethoxy-6-phenyl-5a,6,7,8-tetrahydro-8a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridine-8,8a-diol (**179**) (8.50 g, 15.7 mmol) in *N*,*N*- dimethylformamide (85.0 mL) at room temperature, zinc cyanide (11.06 g, 94.18 mmol) and zinc (0.103 g, 1.58 mmol) were added. The reaction mixture was degassed with argon for 15 min. Then, 1,1′-bis(diphenylphosphino) ferrocene (1.740 g, 3.139 mmol) and tris(dibenzylideneacetone)dipalladium (1.437 g, 1.569 mmol) were added to the reaction mixture, and degassing was continued for another 5 min. The mixture was heated at 130 °C for 5 h. After this time, the reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was diluted with ethyl acetate and washed with water. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the crude product which was purified by flash column chromatography eluting with 0−10% methanol in dichloromethane. The desired fractions were concentrated to afford *rac*-4-((5a*R*,6*S*,7*S*,8-*R*,8a*S*)-7-((dimethylamino)methyl)-8,8a-dihydroxy-1,3-dimethoxy-6-phenyl-6,7,8,8a-tetrahydro-5a*H*-cyclopenta[4,5]furo[3,2-*c*]pyridin-5a-yl)benzonitrile (*rac*-**eFT226**) as a white solid. Yield: 5.60 g (11.5 mmol, 73%). The enantiomers were separated by chiral SFC [CHIRALPAK IG (4.6 × 250)mm,5μ] in Carbon dioxide/Methanol:Triethylamine (60:40:0.2), peak 1 (1.56 g, (−)-**eFT226**), R_t 1.958 min, ee: 99.74%, $[\alpha]_D$ −38.8° (c 0.25, $CHCl_3$); MS (ESI) *m*/*z*: 488.20 $[M + 1]^+$; HRMS (ESI): calcd, 488.2180 $[M + H]^+$; found, 488.2182; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 7.49 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.08−7.04 (m, 2H), 7.00−6.95 (m, 3H), 6.04 (s, 1H), 5.40 (s, 1H), 5.03 (br s, 1H), 4.42 (d, J = 3.8 Hz, 1H), 3.84 (s, 6H), 3.73 (d, J = 14.0 Hz, 1H), 3.14−3.08 (m, 1H), 2.58−2.56 (m, 1H), 2.20 (s, 6H), 1.96 (d, J = 10.7 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm 169.04, 164.05, 159.31, 142.64, 136.96, 130.12, 128.61, 128.47, 127.69, 126.28, 118.92, 108.87, 103.44, 102.85, 92.22, 83.77, 77.12, 57.21, 56.40, 53.50, 52.85, 45.79, 43.43. Peak-2 (1.55 g, (+)-**eFT226**), R_t 3.90 min, ee: 99.66%, $[\alpha]_D$ +34.5° (c 0.20, $CHCl_3$); MS (ESI) *m*/*z*: 488.20 $[M + 1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.49 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.08−7.04 (m, 2H), 7.00−6.95 (m, 3H), 6.04 (s, 1H), 5.40 (s, 1H), 5.03 (br s, 1H), 4.42 (d, J = 4.1 Hz, 1H), 3.84 (s, 6H), 3.73 (d, J = 14.1 Hz, 1H), 3.14−3.08 (m, 1H), 2.58−2.56 (m, 1H), 2.20 (s, 6H), 1.97 (d, J = 9.7 Hz, 1H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.0c00182.

Synthetic schemes, analytical data, and molecular formula strings for all compounds and molecular model PDB files (PDF)
Molecular formula strings of Figure 9 (CSV)
Molecular formula strings of Figure 10 (CSV)
Molecular formula strings of Figure 12A(CSV)
Molecular formula strings of Figure 12B (CSV)
Molecular formula strings of Figure 13A (CSV)
Molecular formula strings of Figure13B (CSV)
Molecular formula strings of Figure 14A (CSV)
Molecular formula strings of Figure 14B (CSV)
Molecular formula strings (CSV)

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

Ac, acetyl; Bn, benzyl; Bu, butyl; dba, dibenzylideneacetone; DBU, 1,8-diazabucyclo(5.4.0)undec-7-ene; DCC, dicyclohexylcarbodiimide; DCM, dichloromethane; DIPEA, diisopropylethylamine; DMF, dimethylformamide; DMS, dimethylsulfide; DMSO, dimethylsulfoxide; dppf, 1,1′-ferrocenediyl-bis-(diphenylphosphine); EDC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide; Et, ethyl; HATU, 1-[(bis(dimethylamino)-methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate; HOBt, 1-hydroxybenzotriazole; HPLC, high-performance liquid chromatography; LAH, lithium aluminum hydride; Me, methyl; MW, microwave; NMR, nuclear magnetic resonance; Ph, phenyl; PMB, *para*-methoxybenzyl; T3P, propylphosphonic anhydride; TBS, *tert*-butyldimethylsilyl; TEA, triethylamine; TFAA, trifluoroacetic anhydride; TFE, trifluoroethanol; Tf_2O, triflic anhydride; THF, tetrahydrofuran; UV, ultraviolet

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