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Synthesis of Fused Bicyclic Piperidines: Potential Bioactive Templates for Medicinal Chemistry

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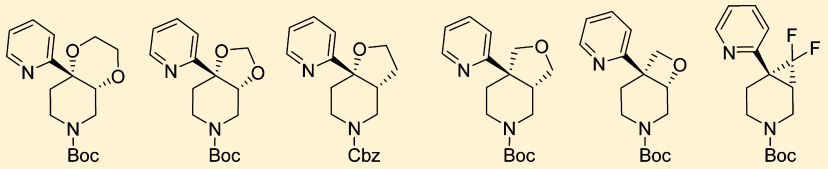
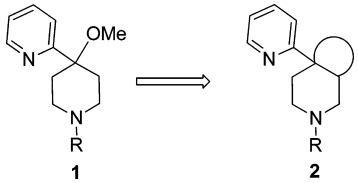
Supporting Information



ABSTRACT: An array of six pyridyl-substituted fused bicyclic piperidines was prepared as novel cores for medicinal chemistry. For maximum diversity, the size of the fused ring varied from three to six atoms and contained up to two oxygen atoms. The pyridine ring was incorporated to improve physicochemical properties and to challenge the robustness of the chemistry. The presence of the pyridine did interfere with our initial approaches to these molecules, and in several instances, a blocking strategy had to be employed. These new scaffolds possess high sp3 character and may prove useful in multiple medicinal chemistry applications.

INTRODUCTION

Medicinal chemistry combines the fields of drug design and synthetic organic chemistry, and the two fields influence each other continually. For example, the advent of highly efficient and reliable sp2−sp2 transition metal-mediated coupling reactions has had such a profound influence on both the design and synthesis elements of medicinal chemistry that it has been implicated as one of the factors leading to an industry-wide trend toward the synthesis of clinical candidates with lower sp3 ratios and higher aromatic ring count.[1] These attributes result in structures with highly planar conformations, which negatively affect water solubility. More importantly, they have also been associated with an increased attrition risk in development,[2] illustrating a need for the preparation of novel druglike scaffolds with improved properties. During the course of a drug discovery program, a series of 4-pyridylpiperidines of the type **1** were identified (Figure 1) as leads. 4-Arylpiperidines have shown activity against a wide range of biological targets, and the substructure is present in six of the top 200 most prescribed drugs,[3] including perhaps the most widely prescribed class, the opiates.[4] In an effort to improve the profile of the lead compounds **1**, including metabolic stability issues, a series of fused bicyclic piperidine templates **2** were designed. Structural rigidification is a common strategy used in medicinal chemistry during lead optimization, and in this case it was combined with increasing sp3 character and 3-dimensionality (i.e., less flat low energy conformations[2]), without increasing lipophilicity. Improved structures of the type **2** may prove more broadly applicable as pharmaceutical intermediates.



1 2

Figure 1. Cyclization strategy to improve profile of lead **1**.

RESULTS

The six ring systems that were targeted are depicted in Figure 2. It was believed that these cores would provide adequate diversity in ring size, conformation, and position of heteroatoms. They also provide numerous new vectors to explore additional, previously inaccessible target space. This feature can best be visualized by the minimized 3-D conformations for four of the targets depicted in Figure 3. It was surprising to find an almost complete lack of literature precedent for these ring systems, regardless of the identity of the aryl ring. We therefore set out to find scalable routes for each of the amine-protected templates. We opted to maintain the aromatic ring as a 2-pyridyl group for several reasons: (1) it was active at our intended target, (2) it reduces the lipophilicity of the final compounds and provides an opportunity for salt formation, and (3) despite adding a significant level of complexity to the syntheses, it represents a more real-world example given the prevalence of heterocyclic systems in medicinal chemistry. Pyridine is, in fact, the most prevalent aromatic heterocycle in approved drugs.[5] Moreover, the 2-pyridyl connectivity, as opposed to the 3- or 4-pyridyl isomers,

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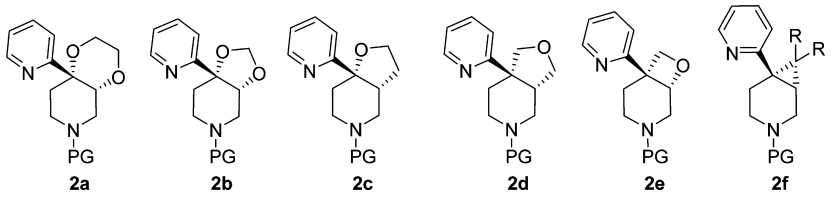


Figure 2. Targeted fused ring systems.

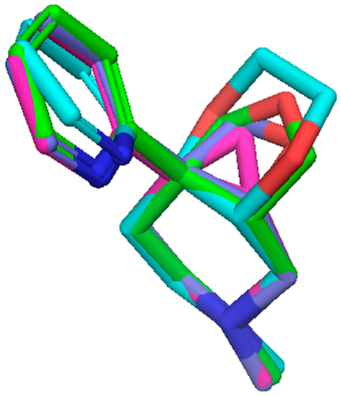
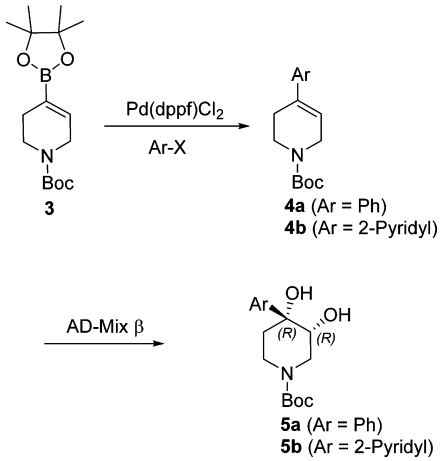


Figure 3. Minimized conformations of **2a** (turquoise, **2d** (green), **2e** (blue), and **2f** (magenta).

is less likely to bind to and inhibit the heme domain of the cytochrome P450 enzymes.[6]

The dioxolane target **2b** was the first to be investigated. The chemistry to prepare **2b** was envisioned to be fairly straightforward given the precedent shown in Scheme 1. It

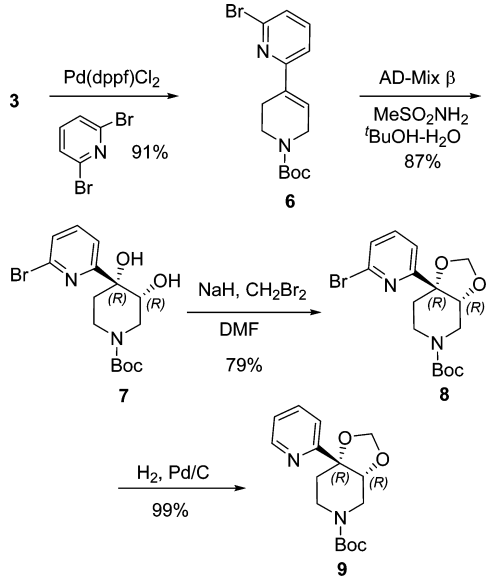
Scheme 1. Sharpless Asymmetric Dihydroxylation



was also attractive from a standpoint of being able to produce both enantiomers in a stereoselective manner. In practice, the synthesis proved to be significantly more challenging than originally anticipated. The preparation of the intermediate olefin **4b** was uneventful starting from commercially available boronic ester **3** under standard Suzuki–Miyaura[7] conditions.

When the aryl ring was phenyl (**4a**) the Sharpless asymmetric dihydroxylation[8] reaction was reported to proceed in 95% yield and >95% ee.[9] These results were reproduced in our project with numerous phenyl-containing substrates. However, when the aryl group was 2-pyridyl, no product was observed using the same conditions developed for the phenyl derivative. Attempts were made to modify the reaction conditions on **4b**, including time, temperature, amount of oxidant, or the addition of accelerants such as methanesulfonamide. In all cases, the use of AD-mix, which is a commercially available premixed reagent composed of $K_2OsO_2(OH)_4$, chiral ligand, $K_3Fe(CN)_6$, and K_2CO_3, did not produce any positive results. To investigate the feasibility of the dihydroxylation reaction it was decided to remove the ligands from the reaction mixture and investigate achiral conditions.[10] Although this protocol resulted in the formation of the desired product, the isolated yield of racemic **5b** was only 7%. The poor reactivity of **4b** was attributed to the potential complexes that the pyridine nitrogen could form with osmium.[11] Apparently, this pyridine–osmium complex was difficult to dissociate and resulted in a stalled reaction and low yield of diol. Given the apparent poisoning of the catalyst, the concept of protecting or shielding the pyridine nitrogen was explored.[12] It was postulated that a bromine at the 6-position of the pyridine ring might serve this role ideally by both sterically shielding the nitrogen and reducing its basicity through inductive effects. Additionally, the bromine atom can be readily removed by reduction, or be used as a handle for further substitution. The revised dioxolane synthesis is shown in Scheme 2.

Scheme 2. Efficient Syntheses of Dioxolane 9



Boronic ester **3** underwent a clean palladium-catalyzed Suzuki–Miyaura coupling reaction with 2,6-dibromopyridine to afford the bromo-substituted pyridine **6**. Compound **6** slowly decomposed to oxidative byproducts that appeared to interfere with subsequent reactions. The olefin was therefore used soon after it was purified and stored under nitrogen in the freezer. As intended, introduction of the bromine greatly improved the

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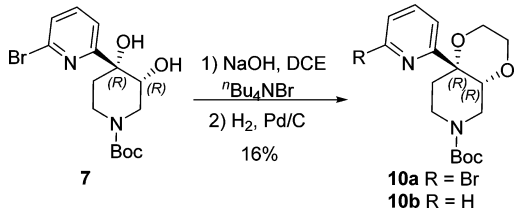
yield of the dihydroxylation reaction (87%) with a high degree of enantioselectivity (95% ee).[13] Diol **7** was converted to the dioxolane **8** using sodium hydride and dibromomethane in DMF in 79% yield. Debromination was efficiently achieved using catalytic hydrogenation conditions to provide **9** in 60% overall yield over the four steps.

With the intermediate diol **7** in hand, the dioxane analogue **10b** could be synthesized as shown in Scheme 3. Alkylation

Scheme 3. Formation of Dioxane Ring

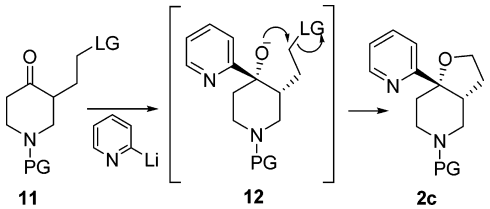


7 **10a** R = Br **10b** R = H

with dichloroethane proved difficult under sodium hydride conditions, but marginal success was realized with a phase-transfer protocol. Thus, treatment of diol **7** with aqueous sodium hydroxide in dichloroethane solvent containing tetrabutylammonium bromide afforded a 17% yield of the dioxane **10a**, with the remainder being unreacted starting material. Reduction of the bromide as before afforded **10b** albeit in significantly lower overall yield relative to the dioxolane.

The synthesis of the tetrahydrofuran (THF) target **2c** is described next. Introduction of the pyridyl group late in the sequence was desirable for efficient analogue generation. As such, the approach shown in Scheme 4 was chosen whereby the aryl ring addition and THF ring-closing reactions would take place in one step.[14]

Scheme 4. General Strategy for Preparing 2c



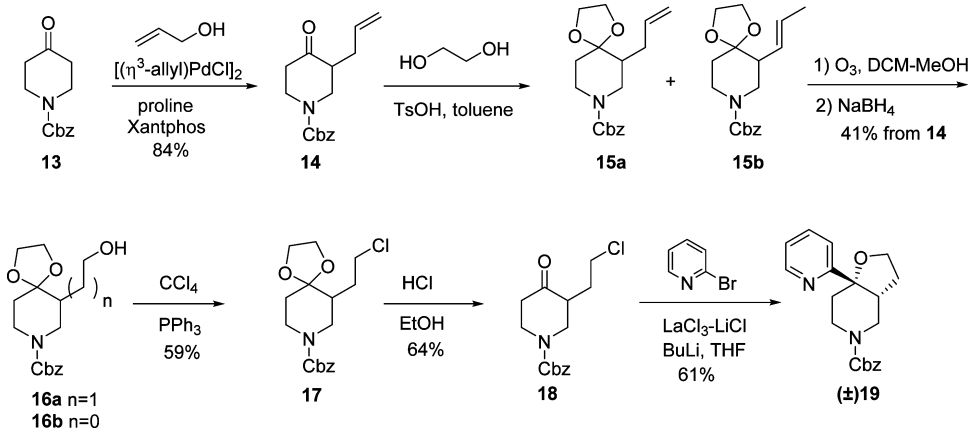
11 **12** **2c**

Starting from commercially available piperidinone **13**, allylation using a Pd-catalyzed coupling with allyl alcohol gave compound **14** (Scheme 5) in good yield. Protection of the ketone as a ketal, ozonolysis of the olefin, and in situ reduction of the ozonide with sodium borohydride provided the alcohol intermediate **16a** in 41% yield for the three steps. The moderate overall yield was largely due to a ~25% isomerization of the olefin which occurred upon ketal formation to give **15b**. The olefin isomers could not be separated at this point, but the structure of **15b** was confirmed by the isolation of **16b** after the ozonolysis and reduction steps. The hydroxyl group in **16a** was converted into a chloride under phosphine-mediated conditions, and the ketal was hydrolyzed in refluxing HCl−EtOH to give the ketone **18**. The racemic final product **19** was formed by the addition of a pyridyllithium species, generated from 2-bromopyridine and *n*-BuLi, to ketone **18** (precomplexed with $LaCl_3$−LiCl)[15] and the subsequent cyclization of the resulting alkoxide. The desired fused THF system **19** was isolated in 61% yield along with 10−15% of the uncyclized chloro alcohol. Use of the $LaCl_3$ complex was necessary to facilitate addition to the ketone and to suppress enolization. Yields without additive averaged 23%. Synthesis of nonracemic product would require access to the single enantiomers of **14** which may be accessible through chiral hydrazone chemistry.[16]

A scalable synthesis was developed to access the regioisomeric THF core **2d** in five steps from the known[17] lactone **20** (Scheme 6). Reduction of pyridine **20** was achieved by a platinum oxide catalyzed hydrogenation to afford the fused piperidine **21** which was protected immediately as a carbamate to facilitate isolation to give **22** in 60% yield for the two steps.[18] Arylation of **22** with 2-bromopyridine was accomplished under modified Buchwald[19] conditions to provide **23** in good yield. It is noted that a variety of aryl or heteroaryl rings could be substituted for pyridine in this step. Lactone reduction with lithium borohydride and Mitsunobu ring closure afforded the THF-fused scaffold **25**.

The oxetane-fused ring system **2e** possessed one of the more interesting structures and also proved to be the most challenging to prepare. Oxetane ring systems have gained popularity in drug discovery in recent years due to their improved stability against oxidative metabolism,[20] publication of novel methods for their preparation,[21] and increased commercial availability of building blocks. Scheme 7 shows several unsuccessful routes that were investigated for the preparation of the key intermediate **26**. Esters **27** and **28** failed

Scheme 5. Synthesis of Tetrahydrofuran Core 19



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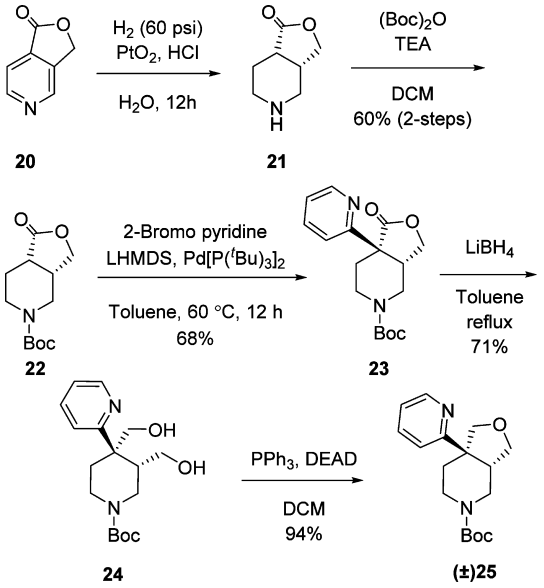
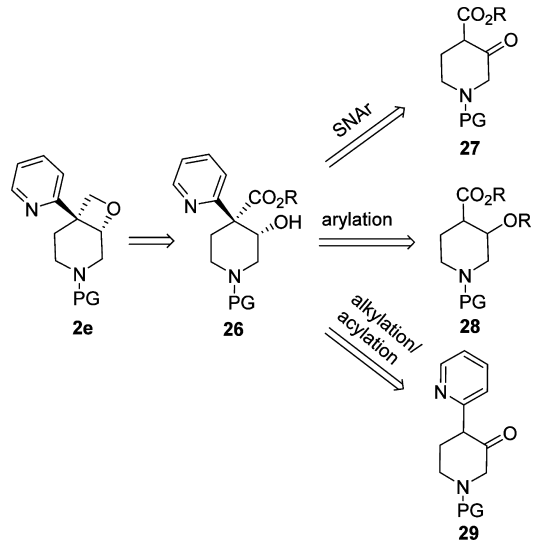
Scheme 6. Preparation of Tetrahydrofuran 25



Scheme 7. Unsuccessful Strategies To Access the Oxetane Bicycle

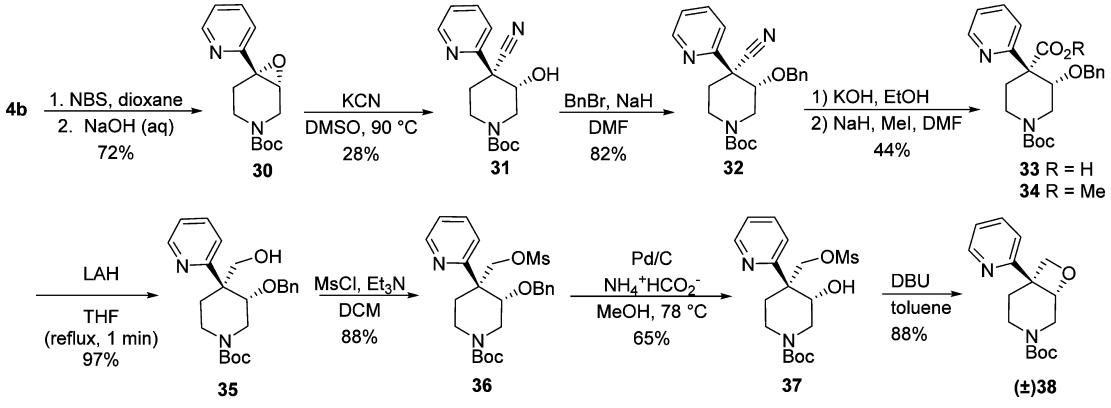


to undergo the arylation reaction despite structural similarity to the successful reaction of **22**. Intermediate **29** was highly unstable and resisted alkylation at the desired most hindered carbon.

The synthesis of the oxetane-fused core was eventually accomplished via the route shown in Scheme 8. Although lengthy, the reaction times are generally short and the entire sequence can be completed rapidly. Once again, the pyridine ring interfered with a reaction in the sequence: in this case, the direct epoxidation of the olefin **4b**. This problem was circumvented by first forming the bromohydrin with *N*-bromosuccinimide followed by base-catalyzed epoxide formation. The key transformation was the unprecedented regio- and syn-selective opening of the epoxide **30** by potassium cyanide. The yield was low but reproducible on scale as long as the rigid reaction conditions were followed. Changing the solvent or even the cyanide counterion was highly detrimental. It was first considered that the regio- and stereoselectivity of the reaction might be the result of anchimeric assistance from the pyridine, or perhaps the *N*-Boc carbonyl. This conclusion was called into doubt after conducting some additional experiments. Compound **31** was isolated containing about 10% of an isomeric cyano alcohol of unknown structure. The isomers could only be separated by reversed-phase HPLC. Curiously, upon concentration, clean fractions of each isomer showed signs of the alternate isomer forming. Moreover, when both compounds were subjected to the original reaction conditions, the same ~10:1 mixture of isomers resulted. These data suggest that the minor isomer is the corresponding trans cyano alcohol and that equilibration is possible through a retro-aldol-like reaction. Given these insights, the exact mechanism of the cyanohydrin-forming reaction cannot be firmly established.

With gram quantities of **31** in hand, the alcohol was protected as a benzyl ether **32** under standard conditions in good yield. The minor trans isomer in compound **31** could be purged at this step. The last major challenge was to convert the nitrile into a primary alcohol. Initial attempts using DIBAL were nonproductive. The transformation was accomplished by first hydrolyzing the nitrile and esterifying the resulting acid, followed by a carefully controlled, selective reduction of the ester to the alcohol **35**. The hindered ester was resistant to reduction with LAH at room temperature, and extended heating times led to over-reduction of the Boc group. It was found that the addition of LAH to a refluxing solution of the ester in THF for 1 min was sufficient to reduce the ester without any appreciable reduction of the carbamate. Mesylation

Scheme 8. Synthetic Route to Oxetane 38



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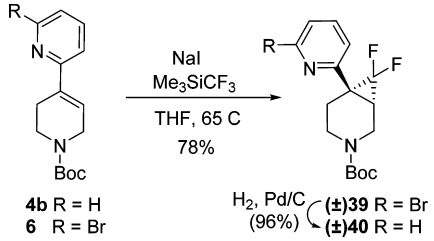
of **35** cleanly gave **36**, and debenzylation was best accomplished under transfer hydrogenation conditions to minimize over-reduction of the mesylate. Finally, ring closure to the oxetane was effected using DBU in toluene providing **38** in high yield.

The synthesis of the cyclopropyl system **2f** was also desired for conformational diversity. Unfortunately, classical Simmons–Smith[22] cyclopropanation conditions (e.g., CH_2I_2, Et_2Zn, TFA) failed in pyridine-containing substrates. Attempts to shield the pyridine nitrogen, as was successfully applied to the preparation of **7** (vide supra), did not provide an advantage here. A solution was found by using a recently described non-metal-catalyzed difluoromethylcarbenoid reagent.[23] Thus, reaction of **6** with trimethyl(trifluoromethyl)silane and sodium iodide in THF afforded a 78% yield of the difluorocyclopropane **39** (Scheme 9). When the same reaction was attempted on the

Scheme 9. Synthesis of Difluorocyclopropane 40



des-bromo substrate **4b**, the yield was only 22%. Removal of the bromine by hydrogenation afforded the desired [4,1,0] ring system **40** in good overall yield.

CONCLUSION

Synthetic routes to six novel fused bicyclic piperidine cores have been developed as potential templates for the synthesis of bioactive molecules. They contain a diverse range of ring sizes and high degrees of sp3 character and 3-dimensionality. In addition, the compounds were all prepared with a pyridine substituent given the frequent use of heterocycles in medicinal chemistry. This choice complicated the chemistry in all six scaffolds, but in most cases, the solution to this problem was to incorporate a bromine deactivating group to shield the strong complexing nature of the pyridine nitrogen atom. The syntheses are amenable to the introduction of a variety of aryl substituents if desired. The time pressures of drug discovery did not allow for these routes to be fully optimized, and some of the yields can doubtless be improved. But given the prevalence of the 4-arylpiperidine pharmacophore, these new ring systems should find utility in many drug discovery programs.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75, 101, or 126 MHz) spectra were obtained as solutions in chloroform-*d* ($CDCl_3$), deuteromethanol (CD_3OD), or dimethyl sulfoxide-d_6 (DMSO). The LC/MS eluting system was 1–99% or 10–99% acetonitrile in H_2O with 0.035% v/v trifluoroacetic acid, 0.035% v/v formic acid, 5 mM HCl, or 5 mM ammonium formate using a 3 or 15 min linear gradient and a flow rate of 12 mL/min. Silica gel chromatography was performed using silica gel-60 with a particle size of 230–400 mesh. All reactions were stirred magnetically under nitrogen unless otherwise noted.

***tert*-Butyl 4-(6-Bromo-2-pyridyl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (6).** A 2 L three-neck RB flask was charged with *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (**3**) (30 g, 0.097 mol) and dimethyl sulfoxide (900 mL). Mechanical stirring commenced, and the vessel was charged with 2,6-dibromopyridine (27.6 g, 0.116 mol) followed by 3 M aqueous potassium carbonate (97 mL) and then finally with dichloro 1,1′-bis(diphenylphosphino)ferrocene palladium(II) dichloromethane adduct (3.6 g, 4.85 mmol, 0.05 equiv). The mixture was heated to a pot temperature of 80 °C for 30 min. The mixture was allowed to cool to rt and then diluted with water (1500 mL) and extracted with ethyl acetate (750 mL). The aqueous layer was extracted with ethyl acetate (2 × 500 mL). The combined organic layers were washed with saturated sodium chloride solution (4 × 500 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography on the Isco (330 g RediSep column) eluting with a gradient of 0–40% EtOAc in hexane to afford *tert*-butyl 4-(6-bromo-2-pyridyl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (**6**) as a clear pale yellow viscous oil (30 g, 91% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, J = 7.8 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.31–7.26 (m, 1H), 6.73–6.67 (m, 1H), 4.14 (dd, J = 5.9, 2.8 Hz, 2H), 3.63 (t, J = 5.7 Hz, 2H), 2.66–2.55 (m, 2H), 1.52–1.46 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 154.8, 141.6, 138.7, 134.0, 126.1, 117.5, 79.8, 44.2, 40.8, 28.5, 25.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{21}BrN_2O_2$ 339.0708, found 339.0700.

(−)-*tert*-Butyl (3*R*,4*R*)-4-(6-Bromo-2-pyridyl)-3,4-dihydroxy-piperidine-1-carboxylate (7). AD-Mix β (33.5 g, 43.0 mmol) and methanesulfonamide (2.3 g, 23.9 mmol) were combined in a mixture of *tert*-butyl alcohol (150 mL) and water (150 mL). The mixture was allowed to stir for 10 min at room temperature before being cooled to 0 °C. *tert*-Butyl 4-(6-bromo-2-pyridyl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (**6**) (8.10 g, 23.9 mmol) was added, and the reaction mixture was stirred at 0 °C for 5 h and 10 °C for 4 h and then warmed to room temperature overnight. Sodium sulfite (22 g) was added to the reaction and allowed to stir for 1 h. The reaction mixture was concentrated to half-volume under reduced pressure, and the remaining suspension was extracted with EtOAc (2× 75 mL). The organic layers were combined, washed with 1 N NaOH (1× 75 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography: 0–25% EtOAc/hexane to afford (−)-*tert*-butyl (3*R*,4*R*)-4-(6-bromo-2-pyridyl)-3,4-dihydroxy-piperidine-1-carboxylate (**7**) (7.72 g, 87%) as a colorless amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (t, J = 7.8 Hz, 1H), 7.45 (dd, J = 10.1, 7.8 Hz, 2H), 4.22 (d, J = 12.3 Hz, 1H), 4.15–3.85 (m, 2H), 3.12 (td, J = 13.0, 2.6 Hz, 1H), 2.95 (t, J = 11.7 Hz, 1H), 1.93–1.82 (m, 1H), 1.77 (dt, J = 13.8, 2.5 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 154.6, 140.6, 139.6, 127.0, 118.8, 79.9, 74.4, 70.0, 45.7, 39.0, 37.3, 28.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{22}BrN_2O_4$ 373.0763, found 373.0769; $[\alpha]_D$ = −7.8 (c 0.78, EtOH).

(+) *tert*-Butyl (3a*R*,7a*R*)-7a-(6-Bromo-2-pyridyl)-3a,4,6,7-tetrahydro[1,3]dioxolo[4,5-*c*]pyridine-5-carboxylate (8). Sodium hydride 60% in mineral oil (3.2 g, 80.4 mol) was added in four equal portions over 15 min to a solution of (−)-*tert*-butyl (3*R*,4*R*)-4-(6-bromo-2-pyridyl)-3,4-dihydroxypiperidine-1-carboxylate (**7**) (5 g, 13.4 mmol) in *N*,*N*-dimethylformamide (50 mL) at 0 °C. After 5 min, dibromomethane (5.6 mL, 80.4 mmol) was added neat via syringe over 5 min. The cooling bath was removed, and the mixture was allowed to warm to rt and continued to stir at rt for 2 h. The reaction mixture was poured over crushed ice/water (150 mL) and then diluted with ethyl acetate (250 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 150 mL). The combined organic layers were washed with water (250 mL) and saturated sodium chloride solution (250 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was adsorbed onto silica gel and purified by silica gel column flash chromatography (80 g RediSep silica gel column) eluting with a gradient of 0–30% EtOAc in hexane to afford (+)-*tert*-butyl (3a*R*,7a*R*)-7a-(6-bromo-2-pyridyl)-3a,4,6,7-tetrahydro[1,3]dioxolo-[4,5-*c*]pyridine-5-carboxylate (**8**) (4.1 g, 79% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.52 (m, 2H), 7.43–7.34 (m, 1H), 5.26 (s, 1H), 4.84 (s, 1H), 4.42–4.34 (m, 1H), 4.06 (m, 1H),

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3.60 (m, 2H), 3.46 (td, J = 12.3, 3.6 Hz, 1H), 2.20 (d, J = 13.9 Hz, 1H), 1.97 (s, 1H), 1.49 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 155.5, 141.8, 139.1, 126.9, 117.8, 93.9, 80.5, 79.6, 77.7, 42.5, 38.1, 33.4, 28.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{22}BrN_2O_4$ 385.0763, found 385.0764; $[\alpha]_D$ = +33.7 (c 0.78, EtOH).

(+) *tert*-Butyl (3a*R*,7a*R*)-7a-(2-Pyridyl)-3a,4,6,7-tetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-5-carboxylate (9). A solution of (+)-*tert*-butyl (3a*R*,7a*R*)-7a-(6-bromo-2-pyridyl)-3a,4,6,7-tetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-5-carboxylate (**8**) (342 mg, 0.88 mmol) was dissolved in absolute ethanol (10 mL) and stirred under nitrogen before the addition of 10% palladium on carbon (473 mg). The reaction mixture was evacuated and put under hydrogen gas (1 atm) for 2 h. The reaction mixture was filtered through a pad of Celite, rinsed with DCM, and concentrated under reduced pressure to provide (+)-*tert*-butyl (3a*R*,7a*R*)-7a-(2-pyridyl)-3a,4,6,7-tetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-5-carboxylate (**9**) (266 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dt, J = 4.7, 1.4 Hz, 1H), 7.70 (td, J = 7.7, 1.8 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.19 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 5.27 (s, 1H), 4.84 (s, 1H), 4.44 (d, J = 14.2 Hz, 1H), 4.07 (m, 1H), 3.70−3.54 (m, 2H), 3.49 (td, J = 12.3, 3.7 Hz, 1H), 2.22 (bs, 1H), 2.11−1.90 (m, 1H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 155.6, 149.4, 136.7, 122.4, 118.9, 93.7, 80.9, 79.5, 42.5, 38.0, 33.6, 28.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{23}N_2O_4$ 307.1658, found 307.1664; $[\alpha]_D$ = +75.9 (c 0.78, EtOH).

(+) *tert*-Butyl (4a*S*,8a*S*)-8a-(6-Bromo-2-pyridyl)-2,3,4a,5,7,8-hexahydro[1,4]dioxino[2,3-*c*]pyridine-6-carboxylate (10a). NaOH (2.6 mL of 50% w/w aqueous solution) was added to a solution of (+)-*tert*-butyl (3*R*,4*R*)-4-(6-bromo-2-pyridyl)-3,4 dihydroxypiperidine-1-carboxylate (**9**) (200 mg, 0.54 mmol) and tetrabutylammonium hydrogen sulfate (52 mg, 0.15 mmol) in dichloroethane (2.6 mL). The reaction mixture was stirred at 35 °C for 48 h, cooled to rt, and diluted with H_2O and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organics were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 4 g, 0−100% EtOAc−hexanes) afforded (+)-*tert*-butyl (4a*S*,8a*S*)-8a-(6-bromo-2-pyridyl)-2,3,4a,5,7,8-hexahydro[1,4]dioxino[2,3-*c*]pyridine-6-carboxylate (**10a**) (36 mg, 17%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.46 (m, 2H), 7.33 (dd, J = 7.2, 1.4 Hz, 1H), 4.39−4.26 (m, 1H), 3.93−3.74 (m, 4H), 3.65 (ddd, J = 11.9, 6.9, 3.4 Hz, 1H), 3.54−3.39 (m, 3H), 2.15 (ddd, J = 13.7, 6.7, 4.1 Hz, 1H), 1.73−1.59 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 140.9, 139.0, 128.3, 126.8, 120.3, 79.6, 75.5, 71.0, 62.4, 62.3, 61.1, 61.0, 33.7, 28.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{17}H_{23}BrN_2O_4Na$ 421.0739, found 421.0733; $[\alpha]_D$ = +1.4 (c 1.0, EtOH).

(−) *tert*-Butyl (4a*S*,8a*S*)-8a-(2-Pyridyl)-2,3,4a,5,7,8-hexahydro[1,4]dioxino[2,3-*c*]pyridine-6-carboxylate (10b). Palladium on carbon (10 wt %) (124 mg, 0.116 mmol) was added to a solution of (+) *tert*-butyl (4a*S*,8a*S*)-8a-(6-bromo-2-pyridyl)-2,3,4a,5,7,8-hexahydro[1,4]dioxino[2,3-*c*]pyridine-6-carboxylate (**10a**) (93 mg, 0.233 mmol) in MeOH (1.5 mL). The mixture was evacuated and put under hydrogen (1 atm). The reaction mixture was stirred for 2 h, purged with nitrogen, diluted with ethyl acetate, and filtered. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 4 g, 0−100% EtOAc−hexanes) afforded (−)-*tert*-butyl (4a*S*,8a*S*)-8a-(2-pyridyl)-2,3,4a,5,7,8-hexahydro[1,4]dioxino[2,3-*c*]pyridine-6-carboxylate (**10b**) (76 mg, 100%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, J = 4.8, 0.8 Hz, 1H), 7.73 (td, J = 7.8, 1.8 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.21 (ddd, J = 7.4, 4.8, 1.0 Hz, 1H), 4.57 (dd, J = 7.3, 4.9 Hz, 1H), 4.07−3.80 (m, 4H), 3.80−3.68 (m, 1H), 3.64−3.37 (m, 3H), 2.22 (dt, J = 13.8, 5.0 Hz, 1H), 1.87−1.67 (m, 1H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9, 155.1, 148.8, 136.8, 122.4, 121.3, 79.6, 70.8, 62.2, 61.2, 43.2, 40.0, 34.3, 28.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{25}N_2O_4$ 321.1809, found 321.1812; $[\alpha]_D$ = −80 (c 0.86, EtOH).

Benzyl 3-Allyl-4-oxopiperidine-1-carboxylate (14). A mixture of benzyl 4-oxopiperidine-1-carboxylate (**13**) (14.0 g, 60.0 mmol), prop-2-en-1-ol (3.4 mL, 50 mmol), pyrrolidine-2-carboxylic acid (1.7 g, 15.0 mmol), and Xantphos (1.45 g, 2.5 mmol) in DMSO (100 mL) was purged with nitrogen for 5 min. The mixture was treated with [(η^3-allyl)PdCl]$_2$ (457 mg, 1.25 mmol) and heated at 75 °C for 72 h. The reaction mixture was cooled to rt and filtered through Celite using ethyl acetate eluent. The filtrate was repartitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (2×). The combined organic layers were washed with water (3×), dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was purified by column chromatography (0−10% ethyl acetate−hexanes) to provide benzyl 3-allyl-4-oxo-piperidine-1-carboxylate (**14**) (11.5 g, 84%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.28 (m, 5H), 5.75 (d, J = 8.2 Hz, 1H), 5.18 (s, 2H), 5.13−4.96 (m, 2H), 4.36−4.01 (m, 2H), 3.42 (s, 1H), 3.07 (s, 1H), 2.50 (m, 4H), 2.18−1.92 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2, 155.2, 136.4, 134.7, 128.6, 128.2, 128.1, 128.0, 117.4, 67.6, 49.4, 47.9, 43.8, 40.7, 31.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{20}O_3N$ = 274.1438, found 274.1431.

Benzyl 6-(2-Hydroxyethyl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (16a). Ethylene glycol (1.23 mL, 22.0 mmol) was added to a solution of benzyl 3-allyl-4-oxo-piperidine-1-carboxylate (**14**) (6.01 g, 22.0 mmol) in toluene (100 mL) followed by the addition of *p*-TsOH hydrate (628 mg, 3.30 mmol). The flask was equipped with a Dean−Stark trap and heated at reflux overnight. The reaction mixture was cooled to rt, washed with saturated sodium bicarbonate (2×) and saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material containing a mixture of benzyl 6-allyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (**15a**) and benzyl (*E*)-6-(prop-1-en-1-yl)-1,4-dioxa-8-azaspiro[4.5]-decane-8-carboxylate (**15b**) (5.4 g) was used directly in the next step without further purification.

A solution of benzyl 6-allyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (**15a**) and benzyl (*E*)-6-(prop-1-en-1-yl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (**15b**) (3.2 g, 10.0 mmol) in DCM (30 mL) was cooled to −78 °C. Ozone was bubbled through the solution for 10 min until a light blue color persisted. The blue solution was then bubbled with nitrogen gas for 10 min to remove the excess ozone. MeOH (30 mL) was added followed by the addition of sodium borohydride (380 mg, 10.0 mmol). The mixture was stirred at rt for 5 min and repartitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was purified by column chromatography (30−40% ethyl acetate−hexanes) to provide benzyl 6-(2-hydroxyethyl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (**16a**) (1.7 g, 53%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.26 (m, 5H), 5.12 (t, J = 10.5 Hz, 2H), 3.99 (m, 4H), 3.90−3.51 (m, 4H), 3.42 (ddd, J = 13.1, 8.9, 3.8 Hz, 1H), 3.28 (dd, J = 13.3, 8.2 Hz, 1H), 1.83 (m, 4H), 1.38 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 136.8, 128.5, 128.0, 127.9, 108.6, 67.2, 64.8, 64.6, 61.3, 46.4, 42.0, 41.3, 29.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{24}O_5N$ 322.1649, found 322.1644. In addition, benzyl 6-(hydroxymethyl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (**16b**) (522 mg, 17%) was also isolated: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.3 (m, 5H), 5.17 (s, 2H), 4.03 (m, 4H), 3.79−3.42 (m, 6H), 2.0 (m, 2H), 1.78 (m, 1H); ESI-MS m/z [M + H]$^+$ calcd 307.1, found 308.7.

Benzyl 10-(2-Chloroethyl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (17). Carbon tetrachloride (428 μL, 4.43 mmol) was added to a solution of benzyl 10-(2-hydroxyethyl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (**16a**) (950 mg, 2.96 mmol) and triphenylphosphine (930 mg, 3.55 mmol) in DMF (20 mL). The mixture was stirred at rt in the dark overnight. The mixture was repartitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with water (3×) and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was purified by column chromatography (10−20% EtOAc−Hex) to provide benzyl 10-(2-

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chloroethyl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (**17**) (595 mg, 59%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.28 (m, 5H), 5.15 (d, J = 3.5 Hz, 2H), 4.00 (dd, J = 2.5, 1.5 Hz, 4H), 3.87−3.39 (m, 5H), 3.32 (dd, J = 13.1, 7.8 Hz, 1H), 2.17−1.85 (m, 2H), 1.88−1.45 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 136.7, 128.5, 128.1, 127.9, 108.4, 67.3, 64.8, 64.6, 45.4, 43.2, 41.9, 41.1, 29.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{23}O_4NCl$ = 340.1340, found 340.1298.

Benzyl 3-(2-Chloroethyl)-4-oxopiperidine-1-carboxylate (18). Aqueous HCl (1 M, 6.6 mL 6.62 mmol) was added to a solution of benzyl 10-(2-chloroethyl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (**17**) (450 mg, 1.32 mmol) in EtOH (6.6 mL). The mixture was heated in a sealed vial at 70 °C for 2 h. The volume was reduced to 1/3, and the residue was repartitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (2×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was purified by column chromatography on silica gel eluting with 0−40% EtOAC/heptanes to provide benzyl 3-(2-chloroethyl)-4-oxo-piperidine-1-carboxylate (**18**) (250 mg, 64%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.32 (m, 5H), 5.21 (s, 2H), 4.52−4.18 (m, 2H), 3.64 (t, J = 6.5 Hz, 2H), 3.35 (ddd, J = 13.4, 10.3, 4.4 Hz, 1H), 3.13−2.89 (m, 1H), 2.88−2.67 (m, 1H), 2.65−2.39 (m, 2H), 2.29 (ddt, J = 14.6, 7.3, 6.2 Hz, 1H), 1.82−1.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 208.1, 155.0, 136.2, 128.6, 128.3, 128.1, 67.8, 48.3, 47.0, 43.9, 42.5, 41.0, 29.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{19}O_3NCl$ = 296.1048, found 296.1036.

(±)-(3a*R*,7a*S*)-Benzyl 7a-(Pyridin-2-yl)hexahydrofuro[3,2-*c*]-pyridine-5(6*H*)-carboxylate (19). Lanthanum trichloride−lithium chloride complex (789 μL of a 0.6 M solution in THF, 0.473 mmol) was added to a solution of benzyl 3-(2-chloroethyl)-4-oxopiperidine-1-carboxylate (**18**) (140 mg, 0.473 mmol) in dry THF (1 mL) at rt and allowed to stir for 20 min. In a separate flask, *n*-butyllithium (236 μL of a 2.2 M solution in hexanes, 0.521 mmol) was added dropwise to a solution of 2-bromopyridine (49.6 μL, 0.521 mmol) in dry THF (3 mL) at −78 °C. Immediately, the mixture turned a light brown color, and after being stirred for 5 min, the contents of the first flask were added dropwise via syringe. The reaction was allowed to slowly warm to ambient temperature over 2 h. After 15 h at rt, the reaction was quenched by the addition of water and ammonium chloride solution and extracted with EtOAc (2×). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (SiO_2, 4g column) eluting with a gradient of 0−40% EtOAc/heptane to afford (±)-(3a*R*,7a*S*)-benzyl 7a-(pyridin-2-yl)hexahydrofuro[3,2-*c*]pyridine-5(6*H*)-carboxylate (**19**) (98 mg, 61%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (ddd, J = 4.8, 1.8, 1.0 Hz, 1H), 7.68 (td, J = 7.6, 1.8 Hz, 1H), 7.59 (dt, J = 7.9, 1.2 Hz, 1H), 7.47−7.29 (m, 5H), 7.16 (ddd, J = 7.4, 4.8, 1.3 Hz, 1H), 5.18 (d, J = 6.3 Hz, 2H), 4.17−3.91 (m, 3H), 3.84 (td, J = 8.7, 5.5 Hz, 1H), 3.37−2.93 (m, 3H), 2.16 (ddd, J = 14.3, 12.3, 5.2 Hz, 1H), 1.97−1.54 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 165.0, 155.7, 149.1, 136.9, 136.6, 128.5, 127.9, 127.87, 121.8, 119.2, 84.8, 67.0, 65.8, 43.8, 40.7, 39.6, 34.0, 29.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{23}O_3N_2$ = 339.1703, found 339.1689.

(±)-(3a*S*,7a*S*)-*tert*-Butyl 1-Oxohexahydrofuro[3,4-*c*]pyridine-5(3*H*)-carboxylate (22). A solution of 3*H*-furo[3,4-*c*]pyridin-1-one (**20**) (3.2 g, 23.7 mmol) in HCl (17 mL of 1 M, 17 mmol) and water (17 mL) in a Parr shaker was treated with PtO_2 (696 mg, 3.06 mmol). The mixture was hydrogenated at 55 psi overnight. The catalyst was filtered off and the filtrate concentrated to afford a yellow oil. The resulting oil was diluted with DCM (230 mL) and MeOH (35 mL) and was treated with TEA (8.3 mL, 59.2 mmol) followed by Boc-anhydride (5.7 g, 26.1 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with water and extracted with DCM (3×). The combined organics were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2-24 g, 30−100% EtOAc−hexanes) afforded (±)-(3a*S*,7a*S*)-*tert*-butyl 1-oxohexahydrofuro[3,4-*c*]pyridine-5(3*H*)-carboxylate (**22**) (3.1 g, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (dd, J = 9.4, 5.6 Hz, 1H), 3.97 (dd, J = 9.5, 2.0 Hz, 2H), 3.73 (s, 1H), 2.96−2.76 (m, 3H), 2.72−2.68 (m, 1H), 2.01 (dq, J = 13.9, 3.6 Hz, 1H), 1.90−1.82 (m, 1H), 1.44 (s, 9H); ESI-MS m/z calc. 241.1, found 242.5 (M + 1)$^+$.

(±)-(3a*S*,7a*S*)-*tert*-Butyl 1-Oxo-7a-(pyridin-2-yl)hexahydrofuro[3,4-*c*]pyridine-5(3*H*)-carboxylate (23). In an oven-dried flask was added (±)-(3a*S*,7a*S*)-*tert*-butyl 1-oxohexahydrofuro[3,4-*c*]pyridine-5(3*H*)-carboxylate (**22**) (410 mg, 1.70 mmol), which was then was put under an inert atmosphere (nitrogen) and diluted with toluene (2 mL). The mixture was treated with $Pd[P(tBu)_3]_2$ (43 mg, 0.08 mmol) and LiHMDS (2.0 mL of 1 M, 2.0 mmol), followed by 2-bromopyridine (0.24 mL, 2.5 mmol). The reaction mixture was warmed to 50 °C, stirred for 20 h, cooled to rt, diluted with saturated aqueous ammonium chloride, and extracted with ethyl acetate (3×). The combined organics were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by reversed-phase HPLC (1−100% ACN/H_2O) afforded (±)-(3a*S*,7a*S*)-*tert*-butyl 1-oxo-7a-(pyridin-2-yl)hexahydrofuro[3,4-*c*]-pyridine-5(3*H*)-carboxylate (**23**) (541 mg, 68%) as a colorless amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (ddd, J = 4.8, 1.7, 0.8 Hz, 1H), 7.73 (td, J = 7.8, 1.8 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.25 (ddt, J = 4.9, 2.9, 2.5 Hz, 1H), 4.33 (dd, J = 9.2, 6.4 Hz, 1H), 4.03 (dd, J = 9.2, 4.2 Hz, 1H), 3.93 (dd, J = 13.9, 5.4 Hz, 1H), 3.63−3.49 (m, 2H), 3.29−3.23 (m, 2H), 2.26 (ddd, J = 14.0, 5.2, 4.0 Hz, 1H), 2.20−2.06 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7, 158.1, 154.8, 149 0.1, 137.1, 122.8, 121.6, 80.0, 68.6, 52.1, 42.2 (broad signal), 41.0 (broad signal), 38.7, 30.7, 28.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{23}O_4N_2$ = 319.1652, found 319.1651.

(±)-(3*S*,4*S*)-*tert*-Butyl 3,4-Bis(hydroxymethyl)-4-(pyridin-2-yl)piperidine-1-carboxylate (24). A solution of (±)-(3a*S*,7a*S*)-*tert*-butyl 1-oxo-7a-(pyridin-2-yl)hexahydrofuro[3,4-*c*]pyridine-5(3*H*)-carboxylate (**23**) (0.56 g, 1.76 mmol) in THF (6.5 mL) and toluene (2 mL) was treated with lithium borohydride (153 mg, 7.04 mmol). The reaction mixture was heated to reflux for 2 h. The reaction was quenched with saturated aqueous ammonium chloride and 1 M HCl, and the pH was adjusted to 8 with saturated aqueous sodium bicarbonate. The mixture was extracted with DCM (3×), and the combined organics were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2-24 g, 40−100% ethyl acetate−DCM) afforded (±)-(3*S*,4*S*)-*tert*-butyl 3,4-bis(hydroxymethyl)-4-(pyridin-2-yl)piperidine-1-carboxylate (**24**) (400 mg, 71%) as a colorless amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (dd, J = 4.9, 0.9 Hz, 1H), 7.83−7.67 (m, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.22 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 4.29−2.73 (m, 10H), 2.28 (s, 1H), 2.00−1.88 (m, 1H), 1.73 (ddd, J = 14.0, 4.7, 3.5 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 155.2, 148.1, 137.4, 121.8, 121.3, 79.8, 64.0, 61.1, 46.2, 44.7 (broad peak), 42.7 (broad peak), 40.0 (broad peak), 33.4 (broad peak), 28.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{27}O_4N_2$ = 323.1965, found 323.1973.

(±)-(3a*S*,7a*S*)-*tert*-Butyl 7a-(Pyridin-2-yl)hexahydrofuro[3,4-*c*]pyridine-5(3*H*)-carboxylate (25). DEAD (196.5 μL, 1.24 mmol) was added to a solution of (±)-(3*S*,4*S*)-*tert*-butyl 3,4-bis-(hydroxymethyl)-4-(pyridin-2-yl)piperidine-1-carboxylate (**24**) (400 mg, 1.24 mmol) and triphenylphosphine (391 mg, 1.49 mmol) in THF (12 mL) at 0 °C. The reaction mixture was stirred for 1 h, allowed to warm to rt, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 4 g, 30−100% EtOAc−hexanes) afforded (±)-(3a*S*,7a*S*)-*tert*-butyl 7a-(pyridin-2-yl)-hexahydrofuro[3,4-*c*]pyridine-5(3*H*)-carboxylate (**25**) (354 mg, 94%) as a colorless glass: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (dd, J = 4.8, 0.9 Hz, 1H), 7.60 (td, J = 7.8, 1.9 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.10 (ddd, J = 7.5, 4.8, 0.9 Hz, 1H), 4.04 (t, J = 8.6 Hz, 1H), 3.90 (d, J = 8.3 Hz, 1H), 3.82−3.69 (m, 4H), 3.45−3.28 (m, 1H), 3.02−2.92 (m, 1H), 2.81 (br s, 1H), 2.15−1.94 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 155.3, 149.2, 136.5, 121.7, 121.2, 79.5, 79.0, 70.4 (broad), 49.6, 41.3, 40.6 (broad), 40.0 (broad), 31.2, 28.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{25}O_3N_2$ = 305.1860, found 305.1851.

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(±)-(1*R*,6*R*)-*tert*-Butyl 6-(Pyridin-2-yl)-7-oxa-3-azabicyclo-[4.1.0]heptane-3-carboxylate (30). A solution of *tert*-butyl 4-(2-pyridyl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (**4b**) (15.1 g, 58.1 mmol) in 1,4-dioxane (100 mL) and water (150 mL) was treated with *N*-bromosuccinimide (15.5 g, 87.1 mmol). The reaction mixture was allowed to stir at rt for 1 h. An aqueous solution of sodium hydroxide (116 mL of 1 M, 116 mmol) was added, and the reaction mixture was stirred for an additional 15 min. The mixture was extracted with ethyl acetate (3 × 75 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting orange oil was purified by silica gel column chromatography: 220 g of silica gel column, 0−40% ethyl acetate/hexane gradient to provide (±)-(1*R*,6*R*)-*tert*-butyl 6-(pyridin-2-yl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (**30**) (11.5 g, 72%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 4.1 Hz, 1H), 7.70 (td, J = 7.8, 1.8 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.22 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 3.90 (m, 2H), 3.66 (s, 1H), 3.30 (d, J = 2.4 Hz, 2H), 2.83 (s, 1H), 2.16 (s, 1H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, DMSO) δ 158.6, 154.0. 148.6, 137.1, 122.9, 118.9, 78.9, 59.1, 58.8, 42.4, 41.8, 37.4, 28.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{21}N_2O_3$ = 277.1547, found 277.1548.

(±)-(3*S*,4*S*)-*tert*-Butyl 3-(Benzyloxy)-4-cyano-4-(pyridin-2-yl)-piperidine-1-carboxylate (32). Potassium cyanide (10.2 g, 157 mmol) was added to a solution of (±)-(1*R*,6*R*)-*tert*-butyl 6-(pyridin-2-yl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (**30**) (14.4 g, 52.2 mmol) in DMSO (220 mL). The mixture was heated at 90 °C for 24 h, cooled to rt, and partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3×). The combined organic layers were washed with water (3×) and saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was purified by column chromatography (SiO_2, 80 g, 0−100% ethyl acetate−hexanes) to provide (±)-(3*S*,4*S*)-*tert*-butyl 4-cyano-3-hydroxy-4-(pyridin-2-yl)piperidine-1-carboxylate (**31**) (4.45 g, 28%) as a colorless solid and ∼10:1 mixture of (3*S*,4*S*) and (3*R*,4*S*) isomers. The material was used directly in the next step without further purification.

Sodium hydride (60% in mineral oil, 340 mg, 8.5 mmol) was added to a solution of (±)-(3*S*,4*S*)-*tert*-butyl 4-cyano-3-hydroxy-4-(pyridin-2-yl)piperidine-1-carboxylate (2.2 g, 7.1 mmol) in DMF (20 mL). The mixture was stirred at rt for 15 min and was treated with benzyl bromide (1.0 mL, 8.5 mmol). The mixture was stirred at rt overnight and then partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3×), and the combined organic layers were washed with water (3×) and saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was purified by column chromatography on silica gel (0−20% ethyl acetate−hexanes) to provide (±)-(3*S*,4*S*)-*tert*-butyl 3-(benzyloxy)-4-cyano-4-(pyridin-2-yl)piperidine-1-carboxylate (**32**) (2.3 g, 82%) as a yellow oil: ^{1}H NMR (400 MHz, DMSO) δ 8.58 (ddd, J = 4.7, 1.9, 0.9 Hz, 1H), 7.90 (td, J = 7.8, 1.9 Hz, 1H), 7.67 (dd, J = 7.9, 1.1 Hz, 1H), 7.42 (ddd, J = 7.6, 4.7, 1.0 Hz, 1H), 7.30−7.10 (m, 3H), 7.04−6.80 (m, 2H), 4.62−3.87 (m, 5H), 3.15−2.74 (m, 2H), 2.16 (ddd, J = 13.9, 12.4, 4.4 Hz, 1H), 2.04 (dt, J = 13.9, 2.8 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 155.5, 153.5, 149.4, 137.6, 137.3, 128.1, 127.6, 127.4, 123.5, 121.8, 119.3, 79.5, 76.0, 71.2, 52.2, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 27.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{28}N_3O_3$ = 394.2131, found 394.2123.

(±)-(3*S*,4*R*)-1-*tert*-Butyl 4-Methyl 3-(benzyloxy)-4-(pyridin-2-yl)piperidine-1,4-dicarboxylate (34). KOH (20 mL of 50%w/w in water) was added to a solution of (±)-(3*S*,4*S*)-*tert*-butyl 3-(benzyloxy)-4-cyano-4-(pyridin-2-yl)piperidine-1-carboxylate (**32**) (2.4 g, 6.1 mmol) in EtOH (20 mL) at rt. The mixture was heated at 120 °C for 25 h, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×), and the combined organic layers were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude product (±)-(3*S*,4*R*)-3-(benzyloxy)-1-(*tert*-butoxycarbonyl)-4-(pyridin-2-yl)piperidine-4-carboxylic acid (**33**) (2.4 g, 5.82 mmol) was dissolved in DMF (30 mL) and treated with 60% sodium hydride in mineral oil (350 mg, 8.7 mmol). The mixture was stirred at rt for 15 min and was treated with iodomethane (543 μL, 8.73 mmol). The mixture was stirred at rt for 2 h and partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (3×), and the combined organic layers were washed with water (3×) and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was purified by column chromatography (0−20% EtOAc−Hex) to provide (±)-(3*S*,4*R*)-1-*tert*-butyl 4-methyl 3-(benzyloxy)-4-(pyridin-2-yl)piperidine-1,4-dicarboxylate (**34**) (1.1 g, 44%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68−8.55 (m, 1H), 7.69 (td, J = 7.8, 1.9 Hz, 1H), 7.44−7.15 (m, 7H), 4.90−4.70 (m, 2H), 4.60−4.28 (m, 2H), 4.18−3.85 (m, 1H), 3.55 (s, 3H), 3.32−3.06 (m, 1H), 2.73−2.29 (m, 3H), 1.39 (s, 9H) (rotamers observed). ^{13}C NMR (126 MHz, DMSO) δ 173.3, 157.4, 155.1, 149.4, 138.7, 137.8, 128.6, 127.9, 123.1, 122.6, 79.3, 75.5, 71.2, 56.4, 52.3, 28.5, 27.7; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{31}N_2O_5$ = 427.2233, found 427.2227.

(±)-(3*S*,4*S*)-*tert*-Butyl 3-(benzyloxy)-4-(((methylsulfonyl)-oxy)methyl)-4-(pyridin-2-yl)piperidine-1-carboxylate (36). Lithium aluminum hydride (1.5 mL of 2 M in THF, 3.1 mmol) was added to a refluxing solution of (±)-(3*S*,4*R*)-1-*tert*-butyl 4-methyl 3-(benzyloxy)-4-(pyridin-2-yl)piperidine-1,4-dicarboxylate (**34**) (1.1 g, 2.6 mmol) in THF (30 mL). The mixture was heated at reflux for 1 min and then cooled to 0 °C. The reaction was quenched with water (5 drops), 15% NaOH (5 drops), and water (15 drops). The white precipitate was removed via filtration and washed with EtOAc. The filtrate was dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was used directly in the next step without further purification.

Triethylamine (210 μL, 1.51 mmol) was added to a solution of (±)-(3*S*,4*S*)-*tert*-butyl 3-benzyloxy-4-(hydroxymethyl)-4-(2-pyridyl)-piperidine-1-carboxylate (**35**) (200 mg, 0.50 mmol) in dichloromethane (10 mL) followed by the addition of methanesulfonyl chloride (58 μL, 0.75 mmol). The mixture was stirred at rt for 5 min, diluted with dichloromethane, washed with water (3×), dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was purified by column chromatography (24 g silica, 20−80% ethyl acetate in hexanes over) to provide (±)-(3*S*,4*S*)-*tert*-butyl 3-(benzyloxy)-4-(((methylsulfonyl)oxy)methyl)-4-(pyridin-2-yl)piperidine-1-carboxylate (**36**) (210 mg, 0.44 mmol, 88%) as a colorless oil: ^{1}H NMR (400 MHz, DMSO) δ 8.60 (dd, J = 4.8, 1.1 Hz, 1H), 7.83 (td, J = 7.8, 1.9 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.41−7.23 (m, 6H), 4.72 (d, J = 11.2 Hz, 1H), 4.58−4.38 (m, 1H), 4.49 (d, J = 9.4 Hz, 1H), 4.37 (d, J = 2.9 Hz, 1H), 4.28 (d, J = 9.4 Hz, 1H), 4.23−4.08 (m, 1H), 3.92−3.71 (m, 1H), 2.91−2.74 (m, 4H), 2.67−2.56 (m, 1H), 2.27 (d, J = 14.3 Hz, 1H), 1.85 (td, J = 13.1, 4.1 Hz, 1H), 1.4−1.25 (m, 9H) (rotamers observed). ^{13}C NMR (126 MHz, DMSO) δ 159.2, 155.1, 149.3, 138.7, 137.3, 128.6, 127.9, 123.1, 122.7, 79.5, 75.1, 74.2, 71.1, 48.1, 36.7, 28.4, 26.7; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{33}N_2O_6S$ 477.2059, found 477.2047.

(±)-(3*S*,4*S*)-*tert*-Butyl 3-Hydroxy-4-(((methylsulfonyl)oxy)-methyl)-4-(pyridin-2-yl)piperidine-1-carboxylate (37). Ammonium formate (530 mg, 8.4 mmol) and 10% Pd/C (92 mg) were added to a solution of (±)-(3*S*,4*S*)-*tert*-butyl 3-(benzyloxy)-4-(((methylsulfonyl)oxy)methyl)-4-(pyridin-2-yl)piperidine-1-carboxylate (**36**) (200 mg, 0.42 mmol) in MeOH (20 mL). The mixture was heated at reflux for 10 min. The catalyst was removed via filtration through Celite and washed with MeOH. The filtrate was concentrated to dryness. The residue was purified by column chromatography (24 g silica, 20−50% ethyl acetate in hexanes over 20 min) to provide (±)-(3*S*,4*S*)-*tert*-butyl 3-hydroxy-4-(((methylsulfonyl)oxy)methyl)-4-(pyridin-2-yl)piperidine-1-carboxylate (**37**) (105 mg, 65%) as a colorless oil: ^{1}H NMR (400 MHz, DMSO) δ 8.59 (dd, J = 4.8, 1.1 Hz, 1H), 7.80 (td, J = 7.8, 1.9 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.29 (ddd, J = 7.5, 4.8, 0.8 Hz, 1H), 5.30 (d, J = 4.8 Hz, 1H), 4.55 (d, J = 9.6 Hz, 1H), 4.42−4.34 (m, 1H), 4.30−4.24 (m, 1H), 3.66−3.52 (m, 2H), 3.07 (d, J = 12.9 Hz, 1H), 3.04−2.87 (m, 1H), 2.97 (s, 3H), 2.21−2.13 (m, 1H), 1.90 (ddd, J = 13.6, 9.8, 4.0 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 160.1, 155.6, 155.2, 149.2, 137.3, 123.1, 122.7, 79.4, 74.9, 74.5, 67.0, 66.8, 47.5, 36.5, 28.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{27}N_2O_6S$ 387.1584, found 387.1588.

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(±)-(1*S*,6*S*)-*tert*-Butyl 6-(Pyridin-2-yl)-8-oxa-3-azabicyclo-[4.2.0]octane-3-carboxylate (38). DBU (18.6 μL, 0.12 mmol) was added to a solution of (±)-(3*S*,4*S*)-*tert*-butyl 3-hydroxy-4-(((methylsulfonyl)oxy)methyl)-4-(pyridin-2-yl)piperidine-1-carboxylate (40 mg, 0.10 mmol) in anhydrous toluene (2.5 mL) at room temperature, and the resulting mixture was heated at reflux temperature for 22 h. After being cooled to room temperature, the reaction mixture was diluted with ethyl acetate (25 mL), washed with water (2 × 25 mL) and brine (25 mL), dried over $MgSO_4$, and concentrated. Purification by silica gel chromatography (12 g silica, 20−50% ethyl acetate in hexane, then isocratic at 50%) afforded (±)-(1*S*,6*S*)-*tert*-butyl 6-(pyridin-2-yl)-8-oxa-3-azabicyclo[4.2.0]-octane-3-carboxylate (22 mg, 0.08 mmol, 73%) as a colorless oil: ^{1}H NMR (400 MHz, DMSO) δ 8.56 (d, *J* = 4.3 Hz, 1H), 7.80 (td, *J* = 7.7, 1.7 Hz, 1H), 7.32−7.24 (m, 2H), 5.18 (d, *J* = 15.2 Hz, 1H), 4.80 (d, *J* = 6.1 Hz, 1H), 4.67−4.60 (m, 1H), 3.88−3.64 (m, 3H), 3.45−3.37 (m, 1H), 2.10−1.95 (m, 2H), 1.43 (d, *J* = 7.5 Hz, 9H); ^{13}C NMR (101 MHz, DMSO) δ 163.2, 154.9, 154.8, 149.0, 137.0, 121.9, 120.0, 82.1, 81.9, 78.6, 74.9, 74.8, 44.7, 44.4, 44.3, 43.8, 38.4, 30.8, 30.5, 28.2 (rotamers observed); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{23}N_2O_3$ 291.1703, found 291.1705.

(±)-(1*S*,6*S*)-*tert*-Butyl 7,7-Difluoro-6-(pyridin-2-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (40). Sodium iodide (55.9 mg, 0.373 mmol) was added to a solution of *tert*-butyl 4-(6-bromo-2-pyridyl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (**6**) (380 mg, 1.12 mmol) in anhydrous THF (2.5 mL) under nitrogen atmosphere. Trimethyl(trifluoromethyl)silane (579 μL, 3.92 mmol) was added, and the reaction vessel was sealed and heated to 65 °C for 17 h, at which time LCMS indicated complete conversion. The residue was filtered and subjected to flash chromatography on silica gel (4 g column) using a gradient of 0 to 60% EtOAc in hexanes to provide (±)-(1*S*,6*S*)-*tert*-butyl 6-(6-bromopyridin-2-yl)-7,7-difluoro-3-azabicyclo[4.1.0]-heptane-3-carboxylate (**39**) (339 mg, 78%) as a yellow oil which was used directly in the next reaction.

Sodium acetate (33 mg, 0.398 mmol) was added to a solution of (±)-(1*S*,6*S*)-*tert*-butyl 6-(6-bromopyridin-2-yl)-7,7-difluoro-3-azabicyclo[4.1.0]heptane-3-carboxylate (**39**) (155 mg, 0.398 mmol) in EtOH, followed by palladium on carbon (10% wet Degussa) (21 mg, 0.2 mmol). The mixture was degassed and purged with hydrogen using a balloon as source of hydrogen for 10 min. The mixture was kept under hydrogen atmosphere for 5 h and was filtered through Celite and washed with EtOH. The filtrate was concentrated to give (±)-(1*S*,6*S*)-*tert*-butyl 7,7-difluoro-6-(pyridin-2-yl)-3-azabicyclo-[4.1.0]heptane-3-carboxylate (**40**) (119 mg, 96%) as a colorless oil: ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (dd, *J* = 5.1, 1.7 Hz, 1H), 7.82 (td, *J* = 7.7, 1.9 Hz, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.33 (dd, *J* = 7.4, 4.9 Hz, 1H), 4.02−3.87 (m, 1H), 3.80 (ddd, *J* = 14.3, 6.8, 2.6 Hz, 1H), 3.59 (d, *J* = 13.1 Hz, 1H), 3.05 (s, 1H), 2.45 (dd, *J* = 14.1, 6.7 Hz, 1H), 2.33 (td, *J* = 12.8, 10.7, 5.0 Hz, 1H), 2.06 (dq, *J* = 14.5, 4.1 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 158.6, 156.4, 150.2, 139.0, 124.5, 124.0, 114.8, 81.5, 41.2, 40.3, 37.3, 36.3, 33.5, 28.7; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{21}N_2O_2F_2$ 311.1571, found 311.1566.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of all ^{1}H and ^{13}C NMR spectra and selected LCMS traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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