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# Asymmetric Synthesis of the Major Metabolite of a CGRP Receptor Antagonist and Mechanism of Epoxide Hydrogenolysis

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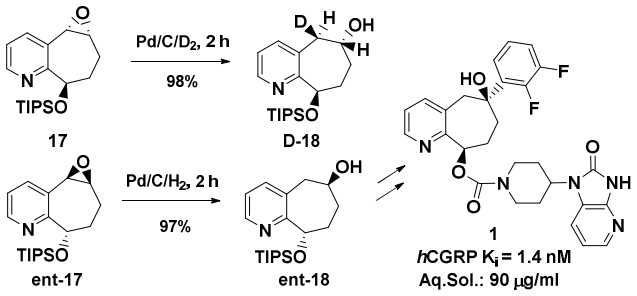
## ABSTRACT




An asymmetric synthesis of the major metabolite of the CGRP recepotor antagonist BMS-846372 is presented. The variously substituted cyclohepta[b]pyridine ring system represents an under-explored ring system, and showed some unexpected chemistry. Reactivities of epoxide and ketone

functional groups on cycloheptane ring were greatly controlled by a remote bulky TIPS group. The rate difference of the hydrogenolysis between two diastereomeric epoxide intermediates shed some light on the mechanism of epoxide hydrogenolysis, and further deuterium labeling studies unravelled more mechanistic details on this well known chemical transformation for the first time.

## INTRODUCTION

Migraine is a very common and disabling medical illness that affects approximately 12% of the adult population.[1] The current standard of care for migraneurs is the use of the triptan class of drugs, which are vasoconstrictors and suffer from mechanism-based cardiovascular risks.[2] Calcitonin gene-related peptide (CGRP), a 37-amino acid peptide, is closely associated with the pathophysiology of migraine.[3] Small molecule inhibitors of the CGRP receptor have been clinically shown to be effective and safe treatment for people who suffer from migraine.[4] In contrast to the triptans, CGRP receptor antagonists should inhibit vasodilation, rather than directly constrict dilated arteries, thereby circumventing cardiovascular risks.[5] Effective treatment of migraine by CGRP receptor antagonists have been clinically proven by numerous small molecules, but so far none has reached the market.[5,6] In one of our medicinal chemistry programs directed at discovering novel CGRP receptor antagonists for the treatment of migraine, BMS-846372 (Figure 1) emerged as a potential clinical candidate.[7] An enantioselective synthesis of BMS-846372 has recently been reported.[8] During preclinical studies, compound **1** (Figure 1) was proposed as the major metabolite of BMS-846372 in various animal species (data not shown). A synthesis of **1** would not only verify the structure of the major metabolite of BMS-846372, but could also determine if it were an active metabolite, which with the added -OH group, might have increased aqueous solubility. This was the key issue that complicated further development of BMS-846372.

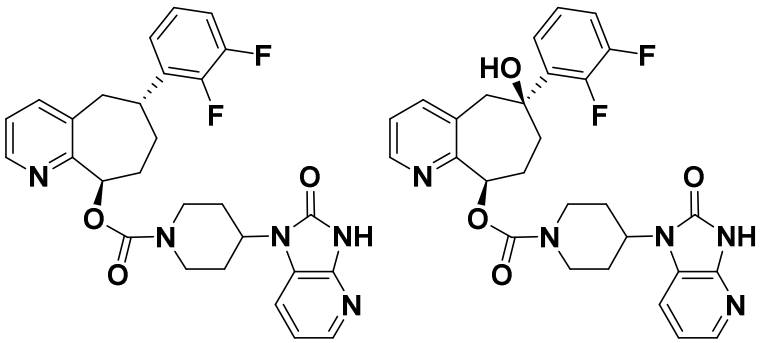



**Figure 1.** CGRP antagonist BMS-846372 and its major metabolite **1**.

## RESULTS AND DISCUSSION

A brief retrosynthetic analysis of **1** led to the diol **2**, from which selective carbamate formation at the secondary alcohol should be straightforward (Figure 2). The tertiary alcohol could come from the key cyclohepta[b]pyridine hydroxyl ketone intermediate **3** by a reaction with an appropriate aryl anion. By choosing a bulky TIPS protecting group, an aryl lithium anion might attack the ketone group from the opposite face to achieve the desired relative stereochemistry as shown.[8] Furthermore, we envisioned that the desired ketone **3** could be transposed from the chiral ketone **5**[8] *via* an epoxide intermediate **4** (Figure 2).

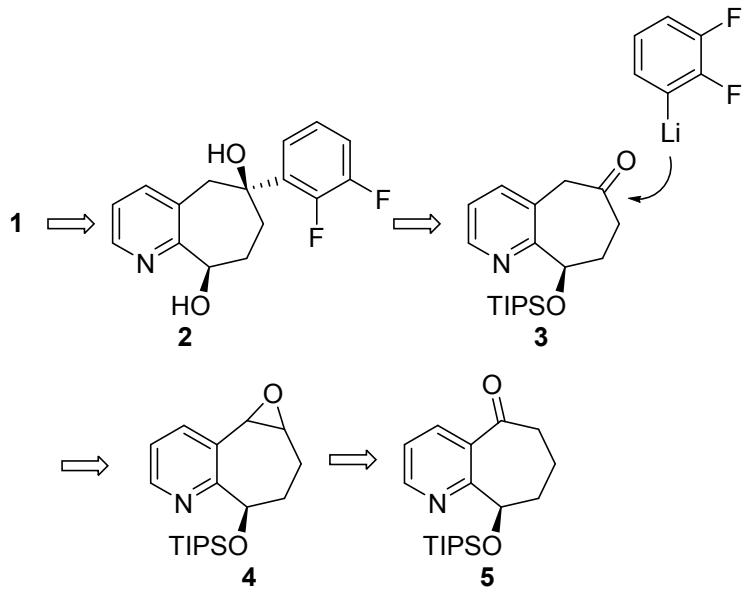
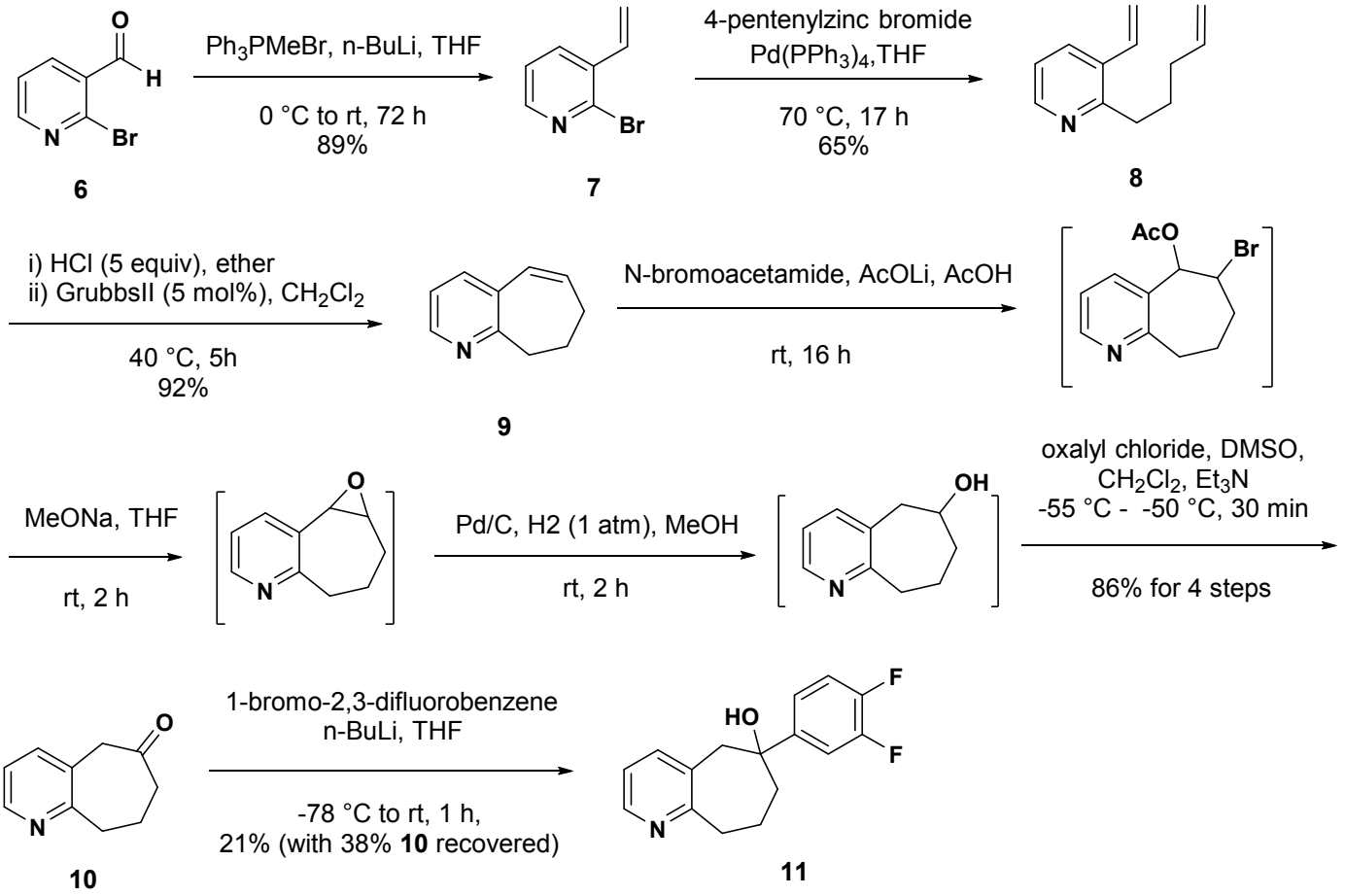



**Figure 2.** Retrosynthetic analysis of **1**.

To test the reactions of epoxide formation and opening, and the aryl lithium addition to the ketone in which the enolizable ketone might be an issue, we pursued a model reaction before starting with the chiral material. As a simpler version of **3**, compound **10** was prepared as shown in Scheme 1. Starting with the commercially available aldehyde **6**, Wittig reaction with methyltriphenylphosphonium bromide treated with n-BuLi afforded vinyl pyridine **7** in 89% yield.[9] A Negishi reaction of **7** with commercially available 4-pentenyl zinc bromide provided the diene **8** in 65% yield. The free base **8** failed RCM, but with its *in situ* prepared HCl salt,[10] diene **8** cyclized smoothly under Grubbs-II catalysis conditions to afford the cycloheptene **9** in excellent yield. Compound **9** was converted to the desired ketone **10** in a straightforward 4-step sequence in 86% overall yield requiring no chromatographic purification. That is, the double bond was first converted to the bromohydrin intermediate, followed by MeONa treatment to form the epoxide. The epoxide was regioselectively opened by hydrogenolysis to generate the alcohol intermediate, which was oxidized by Swern oxidation to **10**. Hydrogenolysis was exceptionally easy

(Pd/C with 1 atm. $H_2$, 2 h), and each of the four steps was essentially spot-to-spot conversion by TLC analysis. With **10** available, we tested the aryl addition reaction. Indeed, the enolizable ketone posed a problem, and the reaction stalled after some conversion. Nonetheless the tertiary alcohol **11** was obtained in 21% yield with 38% recovered ketone.

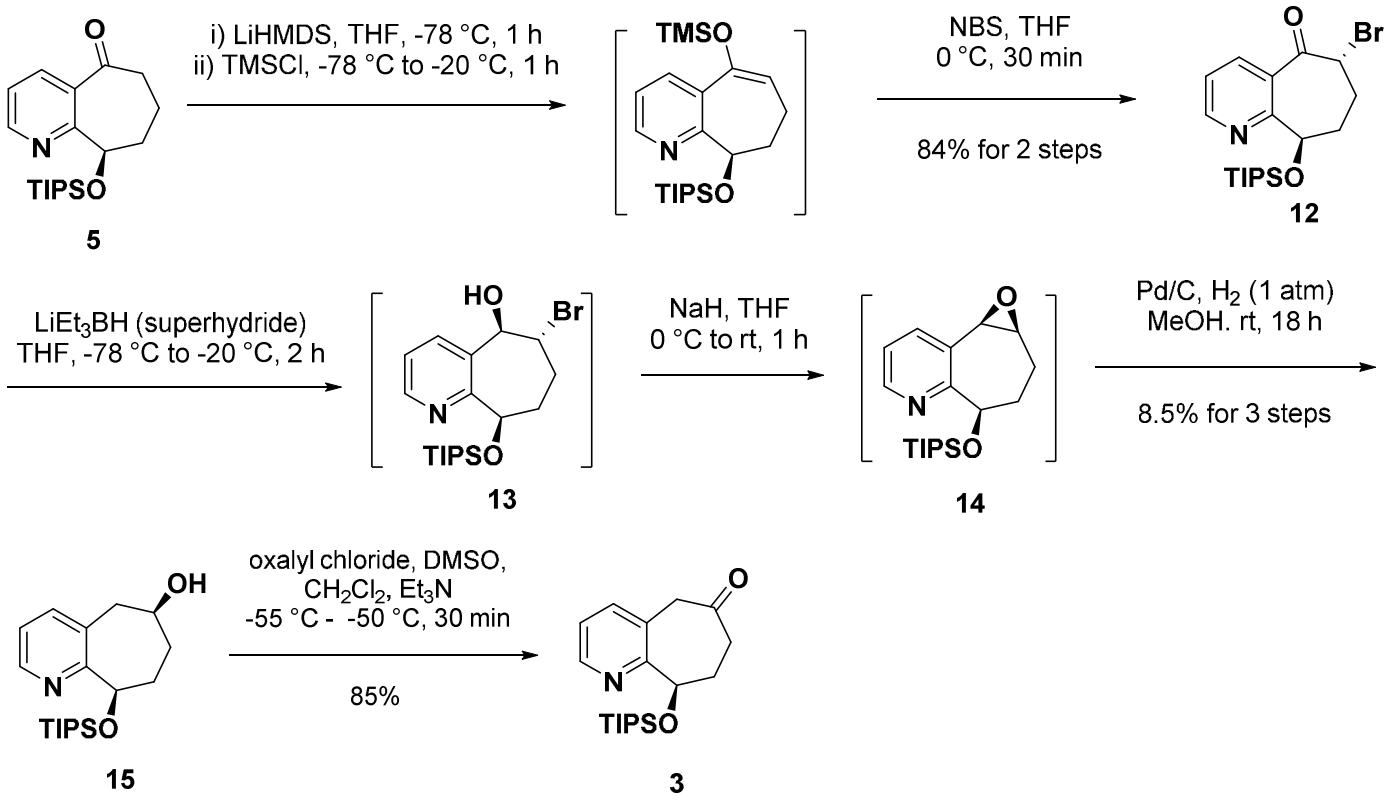
**Scheme 1.** Synthesis of model compound **11**




The first synthesis of the transposed ketone compound **3** was accomplished as shown in Scheme 2. The TMS enol ether was obtained by treating the ketone **5**[8] with LiHMDS followed by quenching with TMSCl. After brief workup and with no purification, treatment of the TMS enol ether intermediate with NBS afforded the bromo-ketone **12** as a single diastereomer in 84% yield. It is conceivable that

NBS reacted from the side opposite to the bulky TIPS protected alcohol. Stereospecific reduction of the ketone group of **12** by superhydride ($LiEt_3BH$) also occurred from the opposite face of the TIPSO group to afford stereospecifically the bromohydrin **13**, which upon treatment with NaH gave the epoxide **14** in excellent yield. However, it was very surprising and interesting to find out that this *cis*-epoxide was very much resistant to typical hydrogenolysis conditions, especially as compared to the hydrogenation reaction shown in Scheme 1. Only 8.5% desired alcohol **15** was obtained, even with prolonged reaction time (18 h, with partial pyridine ring reduction and 36% recovered **14**). The alcohol **15** was then converted to the desired ketone **3** under Swern oxidation condition in good yield.

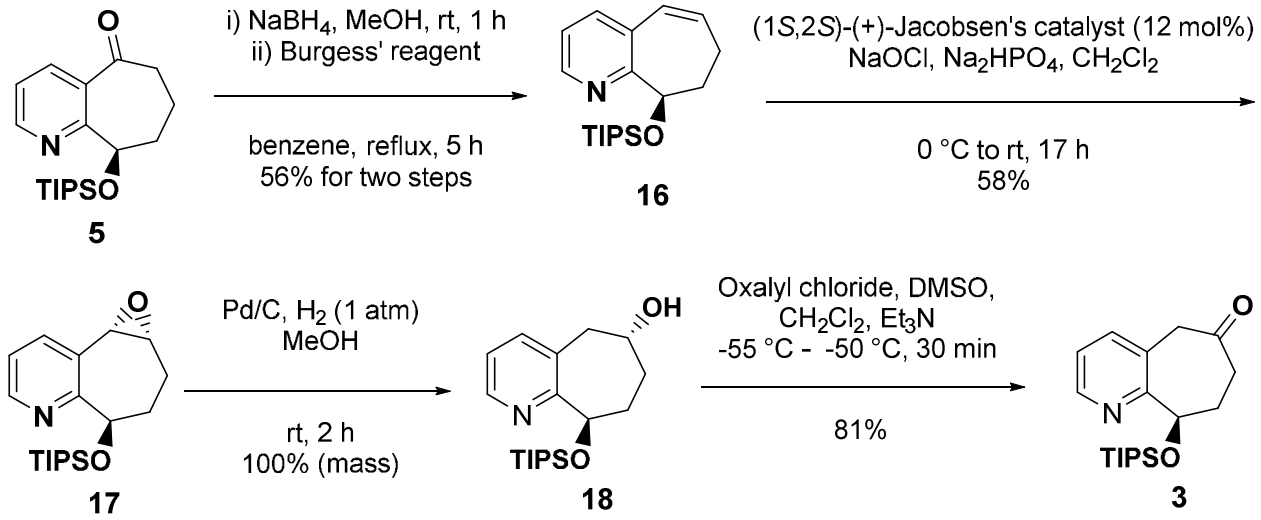
**Scheme 2.** Synthesis of the intermediate ketone **3**




Intrigued by the cause of very low reactivity of the chiral epoxide **14** towards hydrogenolysis, we intended to prepare the diasteromer of **14**, as shown in Scheme 3 for comparison. Nonselective

reduction of **5** by $NaBH_4$, followed by dehydration with Burgess' reagent ((Methoxycarbonylsulfamoyl)-triethylammonium hydroxide, inner salt) afforded the chiral cycloheptene derivative **16** in 56% yield. Stereoselective epoxidation of **16** under Jacobsen's conditions with (1*S*, 2*S*)-(+)-[1,2-cyclohexanediamino-*N*,*N*'-bis(3,5-di-*t*-butylsalicylidene)] manganese (III) chloride,[11] as a match case, afforded **17** in 58% yield. Gratifyingly hydrogenolysis of **17** went smoothly to **18** (diastereomer of **15** with distinctive $^1$H NMR) in quantitative yield. Similar to **15**, alcohol **18** was converted to the desired ketone **3** by Swern oxidation in good yield. To definitively determine the relative stereochemistry of **17**/**18** and **14**/**15**, an x-ray structure of **18** was obtained.[12]

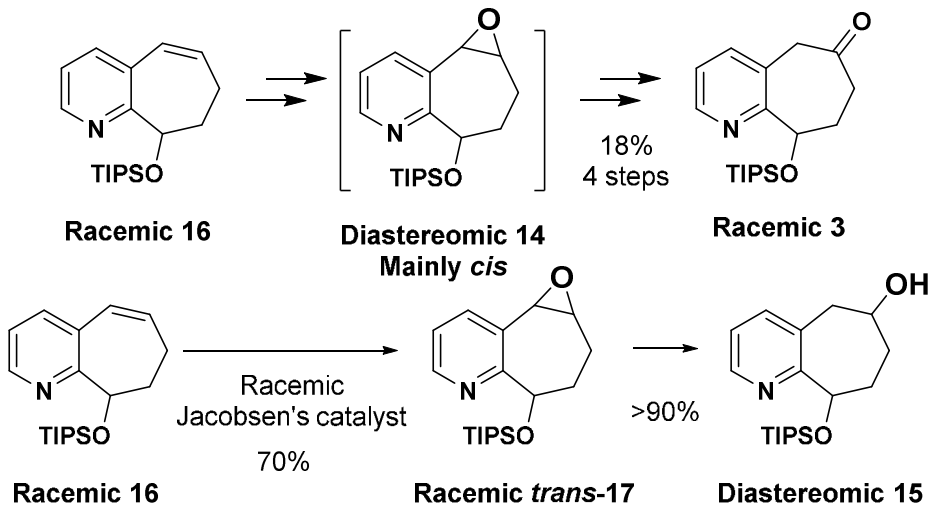
**Scheme 3.** Synthesis of the epoxide **17** and its hydrogenolysis




The drastically different rates of hydrogenolysis of the diastereomeric epoxides **14** and **17** helped to explain some experimental results that had puzzled us. In a previous racemic synthesis of BMS-846372, **16** served as an important intermediate,[7] which, following the 4-step reaction sequence as shown in Scheme 1, afforded racemic **3** in only 18% yield (Scheme 4). The reason for the poor conversion is clear now, as the sequence likely generated more *cis*-epoxide **14** (as a racemate) than *trans*-epoxide **17**. The yield was greatly improved by using racemic Jacobsen's catalysts (equal mixture of the commercial (1*S*, 2*S*)- and (1*R*, 2*R*)-(±)-[1,2-cyclohexanediamino-N,N'-bis(3,5-di-t-

butylsalicylidene)]manganese (III) chloride) but not the chiral form).[7] It is apparent now that the *trans*-epoxide **17** (as a racemate) was mostly formed in the latter case (Scheme 4).

**Scheme 4.** Synthesis and reactivity of diastereomeric/racemic epoxides




Reductive opening of epoxide by hydrogen catalyzed by palladium on carbon is an important reaction in organic chemistry,[13] but its mechanism remains under-investigated. On the other hand, catalytic hydrogenation of alkenes by Pd/C had been well studied.[14] Presumably the oxygen atom of the epoxide is absorbed onto the catalyst surface with either of its two electron pairs and a nearby Pd-bound hydride attacks the weaker C-O bond to open the epoxide ring (Figure 3). For **17**, binding of oxygen and attack of hydride pose no problem as the oxygen is unencumbered on both sides of the epoxy ring similar to the simpler epoxide in Scheme 1. For epoxide **14**, however, binding of the oxygen to the catalyst must occur opposite to the bulky TIPS group, but this should pose no problem and be even more facile than **17** if the hydride comes from nearby same site. The fact that **14** reacted much more slowly might indicate that binding and delivery of hydride occur from different sites and the hydride was delivered

from the side opposite that where Pd-O binding occurs, and which would be significantly hampered by the presence of bulky TIPS group.

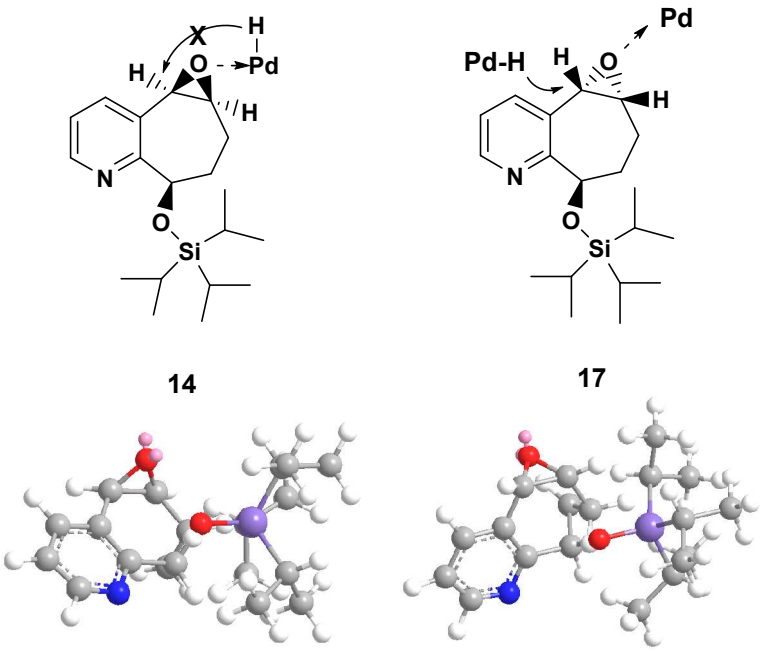



**Figure 3.** Hydrogenolysis of diastereomeric epoxides **14** and **17**. The ball-stick structures were generated by ChemBio3D Ultra without energy minimization and the electron long pairs were depicted as the pink balls.

To further investigate the epoxide hydrogenolysis mechanism, deuterium labeling studies were carried out. Both epoxides **14** and **17** were treated with deuterium gas over Pd/C as before. For epoxide **17**, reaction was complete in 2 h and deuterium was incoported almost exclusively in an $S_N2$ fashion, clearly indicated by the $^1$H NMR coupling patterns of **18** and **D-18** (Figures 4).[15] On the other hand, reaction of **14** was again extremely slow (requiring 18 h) and over-reduction of the pyridine was a competing reaction. Nontheless, desired product **D-15** was obtained. Deuterium incorporation in **D-15** was approximately 60%, but also occurred stereospecifically in an $S_N2$ fashion as indicated by $^1$H NMR analysis (Figures 4).[15] Careful purification of the hydrogenolysis products of **14** also provided the other isomeric alcohol product **19** (Figure 5).[16] Originally we thought that **19** was formed as the completing

hydrogenolysis of the other C-O bond. In the deuteration reaction of **14**, we purified **19** as well. Surprisingly there was no incorporation of deuterium in **19** as shown by $^1$H NMR analysis.[12] It is reasonable to propose that some Pd itself may serve simply as a reducing reagent to the epoxide **14** as a slower competing pathway, which after protonolysis by MeOH generates **19** without deuterium incorporation (Figures 4). This pathway likely also generated the other 40% of **15**, which had no deuterium incorporation. With regard to epoxide hydrogenolysis, these experiments clearly indicated an $S_N2$ mechanism, as the hydride/deuteride must approach from the opposite face of the broken C-O bond. As in the case of **14**, the bulky TIPS group potentially forced catalyst adsorption chelation onto the opposite side, sterically blocking potential $S_N2$ reaction. But with the higher energy transition states where **14** was adsorbed onto the more hindered TIPSO face, $S_N2$ hydrogenolysis occurred, to generate stereospecific **D-15**. In the case of **17**, both sides of the epoxide were open for adsorption but $S_N2$ hydrogenolysis proceeded rapidly and productively. In a previous publication regarding hydrogenolysis of aziridines, the stereochemical outcome appeared to be solvent-dependent.[17] In our case, runing the reaction of **14** in MeOH or EtOH did not affect the reaction rates. In ethyl acetate the conversion was even lower (3.6% yield) for the same amount of time, but cleaner with mainly starting material remaining. Deuterium labeling study of **14** was only carried out in MeOH. With regard to **17**, reaction rate was also significantly slower in EtOAc. Deuterium reaction of **17** was also carried out in EtOAc. For the 2 h reaction time, there was only around 1/3 conversion and 35% of **D-18** was obtained. $^1$H NMR indicated that the deuterium labeling outcome was the same as in MeOH.

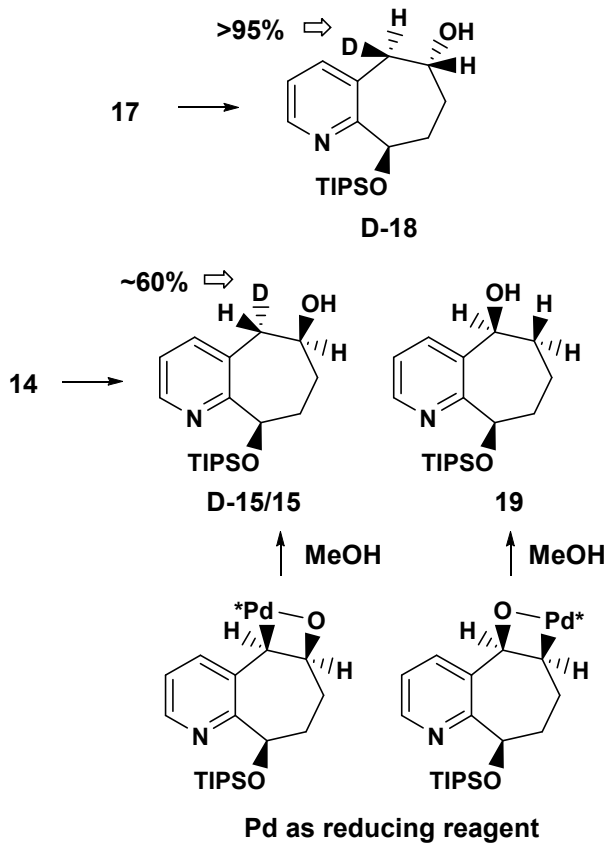
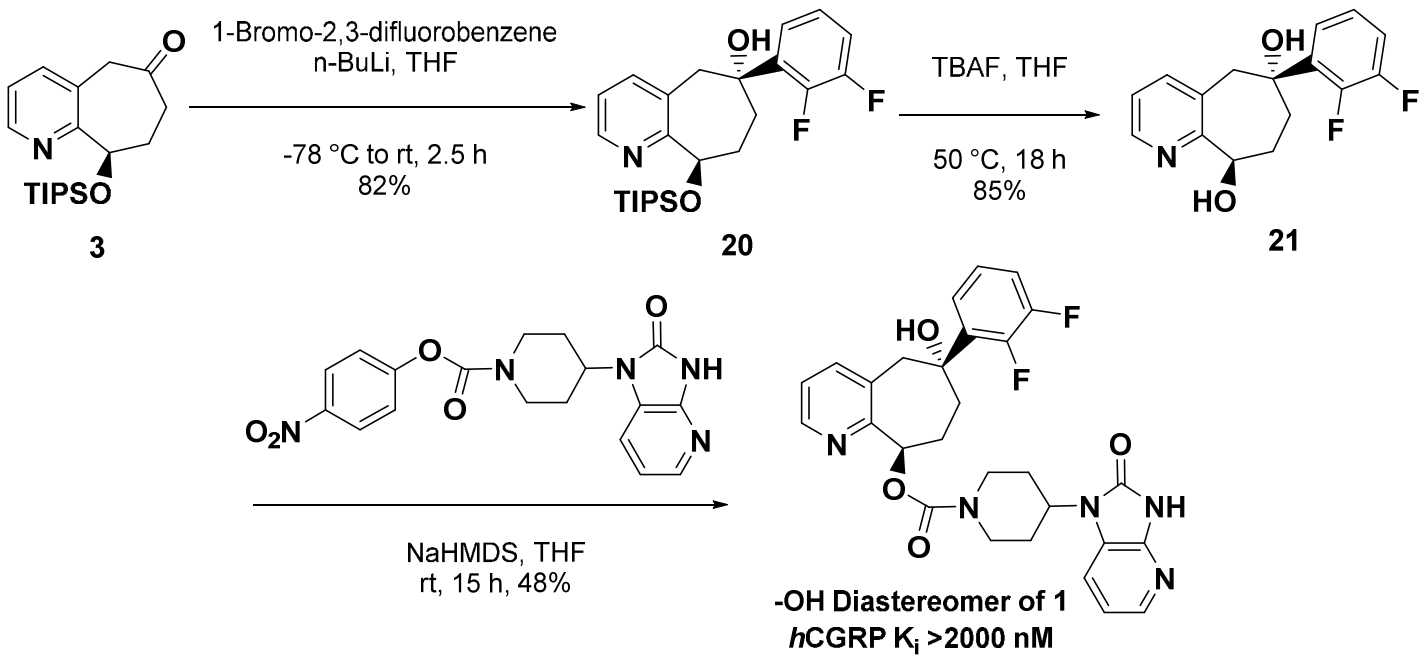



**Figure 4.** Stereospecific incoporation of deuterium and proposed competing mechanism for **14**.

With ketone **3** in hand, aryl addition was performed as shown in Scheme 5. In the presence of the bulky TIPS group, enolization of ketone **3** may have been prevented, and a single diastereomerically pure alcohol **20** was formed in 82% yield. The TIPS group was removed by treatment with TBAF at elevated temperature overnight to afford the diol **21** in good yield. Following previously reported conditions,[7] selective carbamate formation at the secondary alcohol was achieved in good yield. However this product did not match the analytical data of the major metabolite of BMS-846372. Furthermore this product was inactive in a *h*CGRP binding assay. This compound was believed to be the -OH diastereomer of **1** as drawn in Scheme 5.

**Scheme 5.** Synthesis of diastereomeric **1**




It was surprising that the aryllithium attacked the ketone exclusively from the seemingly more crowded face occupied by the bulky TIPS group (TIPS is likely too bulky to allow O-mediated reaction) as compared with the formation of bromide **12** and the arylation of a previously reported isomeric α-ketone[8]. Simple modeling of compound **3** could not easily explain why the aryllithium species would attack exclusively from *Si* face, but probably the ketone group adopted a conformation with *Si* face fully exposed as shown by a simple ball-stick structure generated by ChemDraw3D (Figure 5).

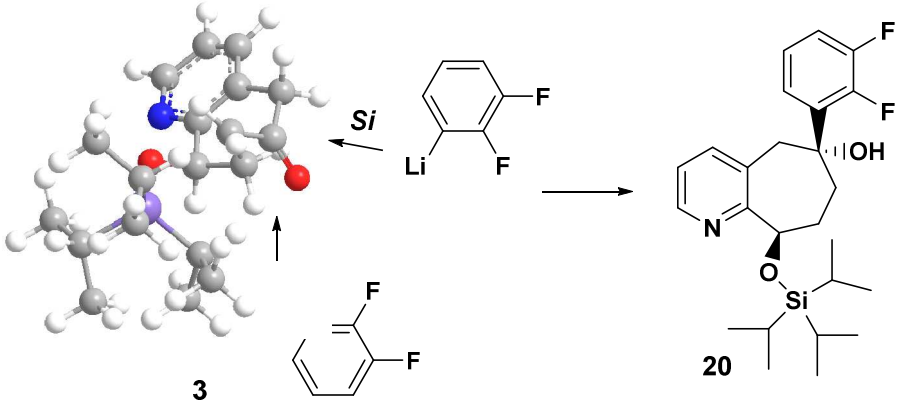
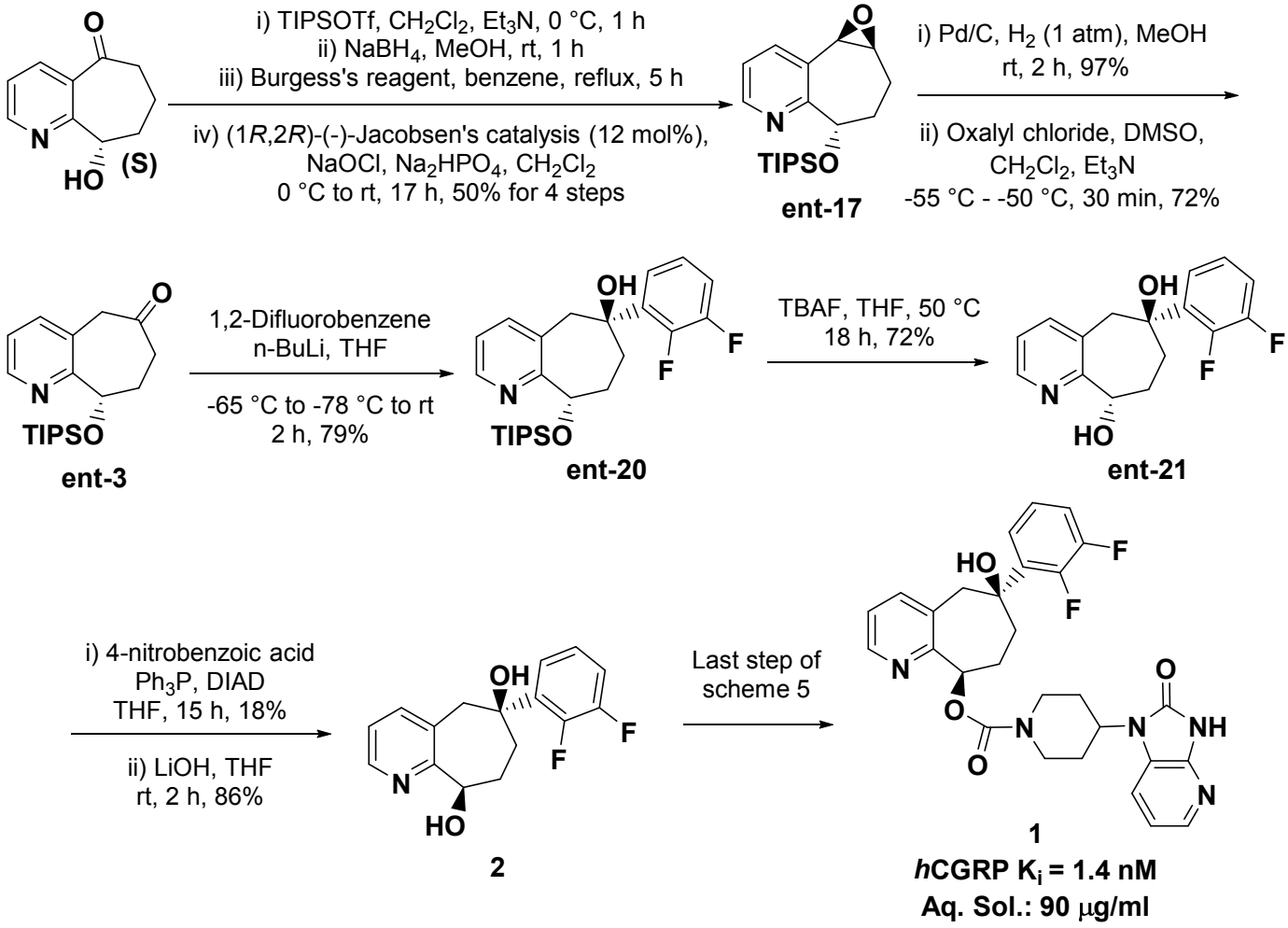


**Figure 5.** *Si* face attack on compound **3** by 2,3-difluorophenyllithium. The ball-stick structure of **3** was generated by ChemBio3D Ultra without energy minimization and Si face of the ketone was fully exposed.

The absolute stereochemistry of the tertiary alcohol was determined by the stereochemistry of the TIPS protected alcohol, albeit not the isomer/metabolite desired. Thus, if we started with the enantiomer of **5**, we should be able to set the desired correct absolute stereochemistry of the tertiary alcohol for metabolite **1**, and then correct the stereochmistry of the secondary alcohol by a simple Mitsunobu inversion. Stereospecific synthesis of **1** was finally achieved as shown in Scheme 6. Following the synthesis described for **17**, the (*S*)-chiral hydroxyl ketone[18] was converted to ent-**17** after the alcohol group was protected with TIPS, and epoxidized with the matched (1*R*, 2*R*)-Jacobsen's catalyst in the epoxidation step. Following previously described conditions, ent-**3** was obtained in good yield. Aryllithium addition proceeded smoothly with the lithium species generated directly from 1,2-difluorobenzene.[19] After TBAF deprotection, ent-**21** was obtained in good yield. Mitsunobu reaction of ent-**21** with 4-nitrobenzoic acid afforded the desired 4-nitrobenzoate in 18%. The major side product was the bridged ether (not unexpected from the relative stereochemistry of the diol ent-**21**), and some dehydration products were obtained as well. After hydrolysis of the 4-nitrobenzoate by LiOH, diol **2** was obtained in 86% yield. An X-ray structure of **2** was obtained,[12] which proved proof of the relative stereochemistry of all previous intermediates and the final products. Finally, carbamate formation went smoothly to afford the desired product **1**. This product matches in every respect the major metabolite of BMS-846372 and demonstrated *h*CGRP receptor binding of 1.4 nM, 20-fold less potent than the parent compound (BMS-846372: *h*CGRP receptor $K_i$ = 0.070 nM). More interestingly, the aqueous solubility was greatly improved to 90 μg/ml for **1** (compared with < 2 μg/ml for BMS-846372).[7]

**Scheme 6.** Synthesis of **1**




In conclusion, a stereospecific synthesis of a potential metabolite of BMS-846372 was accomplished. Some interesting, and unexpected chemistry around the under-explored cyclohepta[b]pyridine ring system was discovered. Two diastereomeric epoxides were excellent substrates for studying the epoxide hydrogenolysis mechanism, and deutorium labeling studies clearly indicated an $S_N2$ mechanism and necessary separation of the adsorption site and reaction site. Even though compound **1** did show only nanomolar potency (1.4 nM – 20-fold less potent than its' parent) against the CGRP receptor, installation of the -OH group improved intrinsic solubility and led to further modifications of BMS-846372, ultimately leading to the discovery an improved CGRP receptor antagonist that has progressed into clinical development. [20]

## Experimental Section

**General information.** $^{1}H$ and $^{13}C$ NMR spectra were recorded on a 400 MHz or 500 MHz Bruker spectrometer. In $^{1}H$ and $^{13}C$ NMR spectra, chemical shifts were expressed in δ (ppm) downfield from $CHCl_3$ (7.26 ppm) and $CDCl_3$ (77.0 ppm), respectively. Mass spectra were recorded by electron impact or chemical ionization. High resolution mass spectrometry (HRMS) analyses were performed on a Fourier Transform Orbitrap mass spectrometer (Exactive, Thermo Fisher Scientific, San Jose, CA) in positive or negative ionization electrospray mode operating at 25,000 resolution (full width at half height maximum, FWHM). The instrument was daily calibrated according to manufacturer's specifications resulting in mass accuracy of or better than 5 ppm. The operating software Xcalibur was used to calculate theoretical mass-to-charge values and to process the obtained data. Column chromatography was performed on silica gel packed in Biotage Horizon columns. 2-Bromonicotinaldehyde (**6**) was commerically available from Aldrich and was directly used. Deuterium gas was purchased from Aldrich with 99.96% purity.

**2-Bromo-3-vinylpyridine (7)**.[9] Butyllithium (22.75 mL, 59.1 mmol) was added to the THF (450 mL) suspension of methyltriphenylphosphonium bromide (21.13 g, 59.1 mmol) at 0 °C. The solution turned to orange and the reaction was lift to room temperature for 30 min before cooled it back to 0 °C. 2-bromonicotinaldehyde (10 g, 53.8 mmol) in 50 mL THF was added through canula to the reaction solution. The precipitate was formed and the reaction was lift to room temperature. The color of the reaction turned to green. After a while, the color of te reaction became orange again. The reaction was stirred at room temperature over weekend. The solvent was removed mostly via vacuum and the crude was partitioned between water and diethyl ether. The organic layer was separated and the aqueous layer was extract twice with diethyl ether. The diethyl ether layer was combined, dried ($Na_2SO_4$), filtered and

concentrated. The product was obtained by flash column eluted with ethyl acetate in hexane (10%) as yellow oil (8.78 g, 89%): MS(ESI) [M+H$^+$] = 184.04; $^1$H NMR δ ppm (400 MHz, CHLOROFORM-*d*) 8.21 - 8.29 (m, 1 H), 7.78 (dd, *J* = 7.68, 1.89 Hz, 1 H), 7.20 - 7.28 (m, 1 H), 6.96 (dd, *J* = 17.37, 11.08 Hz, 1 H), 5.72 (d, *J* = 17.37 Hz, 1 H), 5.46 (d, *J* = 11.08 Hz, 1 H). The proton NMR data matached that of the literature report.[9]

**2-(Pent-4-enyl)-3-vinylpyridine (8)**. In a 500 mL round-bottomed flask was 2-bromo-3-vinylpyridine (4.151 g, 22.56 mmol) (azeotroped with dry benzene) in THF (40 mL) to give a colorless solution. $Pd(Ph_3P)_4$ (0.782 g, 0.677 mmol) was added under nitrogen. While stirring under nitrogen, 4-pentenylzinc bromide (46 mL, 23.00 mmol) was added via syringe, and the resulted dark mixture was stirred at rt for 5 min. It was then heated at reflux (70 °C) overnight. After 17 h, LCMS indicated a complete conversion to the desired product. THF was stripped off. The reaction was quenched with $NH_4Cl$ solution and diluted with EtOAc. The layers were separated and the organic layer was washed with brine, dried and concentrated to a yellow oil. FCC up to 30% EtOAc/hexane afforded the desired product as a colorless oil (2.54 g, 65%): MS(ESI) [M+H$^+$] = 174.10; $^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.39 (dd, *J* = 4.78, 1.51 Hz, 1 H), 7.69 (dd, *J* = 7.81, 1.76 Hz, 1 H), 7.07 (dd, *J* = 7.81, 4.78 Hz, 1 H), 6.89 (dd, *J* = 17.37, 11.08 Hz, 1 H), 5.80 (dddd, *J* = 17.06, 10.26, 6.67, 6.55 Hz, 1 H), 5.62 (d, *J* = 17.37 Hz, 1 H), 5.34 (d, *J* = 11.08 Hz, 1 H), 4.85 - 5.09 (m, 2 H), 2.76 - 2.92 (m, 2 H), 2.11 (q, *J* = 7.13 Hz, 2 H), 1.67 - 1.83 (m, 2 H); $^{13}$C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 159.2, 148.3, 138.4, 133.2, 133.2, 131.7, 121.4, 117.2, 114.9, 35.0, 33.6, 28.6.

**(*Z*)-8,9-Dihydro-7H-cyclohepta[b]pyridine (9)**. In a 2 L round-bottomed flask was 2-(pent-4-enyl)-3-vinylpyridine (2.1 g, 12.12 mmol) in ether (4 mL) to give a colorless solution. HCl (30 mL, 60.0 mmol) was added, and the mixture was stirred for 5 min. The volatiles were evaporated to give a colorless oil, which was then azeotroped with dry benzene to a white solid. It was then dissolved in $CH_2Cl_2$ (1 L) (degassed with argon) to give a colorless solution. GrubbsII (0.515 g, 0.606 mmol) was

added, and the mixture was heated at a 40 °C oil bath with stirring under nitrogen for 5 h. LCMS indicated complete conversion. The mixture was concentrated to a tan oil. It was dissolved EtOAc and washed with saturated $NaHCO_3$ solution, brine, dried with $Na_2SO_4$, and concentrated to a tan oil. FCC up to 40% EtOAc/hexane afforded the desired product as a tan oil (1.79 g, 92%): MS(ESI) [$M+H^+$] = 146.06; $^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.20 (d, *J* = 4.78 Hz, 1 H), 7.32 (d, *J* = 7.55 Hz, 1 H), 6.99 (dd, *J* = 7.55, 5.04 Hz, 1 H), 6.21 (dt, *J* = 12.28, 2.05 Hz, 1 H), 5.90 (dt, *J* = 12.34, 4.41 Hz, 1 H), 2.93 - 3.06 (m, 2 H), 2.30 - 2.49 (m, 2 H), 1.82 - 2.02 (m, 2 H); $^{13}$C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 160.6, 146.3, 137.8, 134.2, 131.3, 127.2, 121.2, 39.1, 32.5, 24.9.

**8,9-Dihydro-5H-cyclohepta[b]pyridin-6(7H)-one (10)**. This compound was prepared through 4-step telescoped reactions. 1. 6-Bromo-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-5-yl acetate (unpurified intermediate): In a 500 mL round-bottomed flask was intermediate **9** (5.16 g, 35.5 mmol), lithium acetate (9.38 g, 142 mmol) in acetic acid (100 mL) to give a tan suspension under nitrogen. *N*-bromoacetamide (5.00 g, 36.2 mmol) was added. The flask was wrapped with aluminum foil and the mixture was stirred at rt for 16 h. There was no solids left and LCMS showed complete conversion to the desired more polar product as a major peak. AcOH was stripped off under high vacuum. The residue was diluted with water and EtOAc. $Na_2CO_3$ was added to neutralize the mixture till no gas evolved. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried with $Na_2SO_4$, and concentrated to a dense tan oil (10.5 g, 100%): MS(ESI) [$M+H^+$] = 284.17. The crude was used as it was in the next step.

2. 6-Bromo-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-5-yl acetate epoxide (unpurified intermediate): In a 500 mL round-bottomed flask was previous crude intermediate (10.09 g, 35.5 mmol) (azeotroped with dry benzene) in THF (100 mL) to give a tan solution. Sodium methoxide (9.59 g, 178 mmol) was added, and the mixture was stirred at rt under nitrogen for 2 h. TLC showed complete conversion to the more polar product spot. THF was stripped off and the residue was partitioned

between water and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried with $Na_2SO_4$, and concentrated to a tan oil (5.72 g, 100%): MS(ESI) $[M+H^+]$ = 162.21, which was directly used in the next reaction.

3. 6,7,8,9-Tetrahydro-5H-cyclohepta[b]pyridin-6-ol (unpurified intermediate): In a 500 mL round-bottomed flask was the previous epoxide (5.72 g, 35.5 mmol) and Pd/C (1.889 g, 1.775 mmol) in MeOH (100 mL) to give a black suspension. It was stirred under 1 atm hydrogen (balloon) for 2 h. It was filtered and concentrated to a tan oil (6 g, 100%). It was used in the next reaction without further purification and characterizations.

4. In an oven-dried 500 mL round-bottomed flask was oxalyl chloride (3.42 mL, 39.1 mmol) in $CH_2Cl_2$ (100 mL) to give a colorless solution at -55 °C under nitrogen. DMSO (5.54 mL, 78 mmol) was added dropwise over 10min. After the solution was stirred for an additional 30 min, previous crude intermediate (5.79 g, 35.5 mmol) (azeotroped with dry benzene) dissolved in 20 mL $CH_2Cl_2$ (plus 20 mL rinse) was added via canuula over 5 min. The reaction mixture was stirred at -50 - -55 °C for an additional 40 min (the solution became milky). $Et_3N$ (24.74 mL, 178 mmol) was added via syringe at -50 °C and the reaction mixture was stirred for 30 min. Water (100 mL) was added, and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (2x100 ml). The combined organic layers were dried with $Na_2SO_4$, and concentrated to a tan oil with some solids. Purification by FCC up to 10% MeOH/$CH_2Cl_2$ afforded the desired product as an orange oil (4.947 g, 86% for 4 steps): $^1$H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.33 (dd, *J* = 4.3, 2.2 Hz, 1H), 7.37 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.05 (ddd, *J* = 6.9, 4.9, 1.6 Hz, 1H), 3.65 (d, *J* = 1.5 Hz, 2H), 3.19 – 3.10 (m, 2H), 2.54 (dd, *J* = 3.4, 1.7 Hz, 2H), 2.01 (pd, *J* = 6.6, 1.7 Hz, 2H); $^{13}$C NMR (126 MHz, CHLOROFORM-*d*) δ ppm 207.2, 160.2, 148.0, 137.2, 128.8, 122.2, 48.9, 43.9, 36.1, 24.7.

**6-(2,3-Difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-6-ol (11)**. In an oven-dried 500 mL round-bottomed flask was BuLi (17.19 mL, 43.0 mmol) in THF (100 mL) to give a colorless

solution at -78 ºC under nitrogen. 1-Bromo-2,3-difluorobenzene (4.81 mL, 43.0 mmol) was added dropwise via syringe. The mixture was stirred at -78 ºC for 20 min, and intermediate **10** (4.947 g, 30.7 mmol) (azeotroped with dry benzene and dried under high vac) dissolved in 10 mL THF was added dropwise via canuula (plus 10 mL THF rinse). The mixture was warmed up to rt in 1 h. TLC showed some conversion to a slightly more polar spot. After quenched with saturated $NH_4Cl$ solution, THF was stripped off. The remaining mixture was partitioned between water and EtOAc. The layers were separated and the organic layer was washed with brine, dried with $Na_2SO_4$, and concentrated to a dark oil. The residue was purified by FCC up to 10% MeOH/$CH_2Cl_2$. The impure fractions were pooled and purified by FCC with EtOAc/$CH_2Cl_2$ up to pure EtOAc. Some starting material was recovered (1.88 g, 38%). The product fractions were pooled and concentrated to a tan solid, which were washed repeatedly with $Et_2O$ to a tan solid (1.79 g, 21%): $^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.27 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.46 – 7.38 (m, 1H), 7.34 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.12 – 6.99 (m, 3H), 3.93 (dd, *J* = 14.4, 2.7 Hz, 1H), 3.18 – 3.04 (m, 2H), 2.86 (dd, *J* = 14.4, 2.0 Hz, 1H), 2.68 – 2.52 (m, 1H), 2.50 – 2.39 (m, 1H), 1.94 – 1.84 (m, 1H), 1.83 – 1.68 (m, 1H); HRMS (ESI), m/z calcd for $C_{16}H_{16}NOF_2$ $[M+H]^+$ 276.1197, found 276.1185.

**(6*R*,9*R*)-6-Bromo-9-(triisopropylsilyloxy)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-5-one (12)**. In a 100 mL round-bottomed flask was compound **5** (2.01g, 6.03 mmol) in THF (20 mL) to give a colorless solution. After cooling to -78 °C, LiHMDS (6.63 mL, 6.63 mmol) (1.0M in THF) was added dropwise via syringe. After stirring for 60min at -78 °C, TMS-Cl (1.078 mL, 8.44 mmol) was added. The stirring was continued for 1h while bath temperature gradually warmed up to -20 °C. TLC (4/1 hexane/EtOAc) showed complete conversion to a less polar spot. The reaction was quenched with saturated $NaHCO_3$ solution and diluted with EtOAc. The layers were separated. The organic layer was washed with brine, dried with $Na_2SO_4$, and concentrated to a light yellow oil (2.447 g), which was directly used in the next step.

In a 250 mL round-bottomed flask was previous crude intermediate (2.447 g, 6.03 mmol) in THF (30 mL) to give a slightly yellow solution. After cooling to 0 °C, NBS (1.084 g, 6.09 mmol) was added in one portion. The mixture was stirred at 0 °C for 30 min. TLC (spot between the TMS ether and starting ketone) (Rf = 0.47 with 20% EtOAc/hexane) and LCMS showed complete conversion. Cooling bath was removed and the mixture was stirred at rt for another 10 min. The reaction was quenched with saturated $NaHCO_3$ solution. The volatiles were stripped off *in vacuo* and the residue was partitioned between water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried with $Na_2SO_4$, and concentrated to a slightly yellow oil. Purification by FCC up to 40% EtOAc/hexane afforded the desired product **12** (2.087 g, 84% for 2 steps) as a colorless dense oil: MS(ESI) $[M+H^+]$ = 414.30; $^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.56 (dd, *J* = 5.04, 1.76 Hz, 1 H), 7.83 (dd, *J* = 7.55, 1.76 Hz, 1 H), 7.25 - 7.32 (m, 1 H), 5.15 (dd, *J* = 4.78, 2.27 Hz, 1 H), 4.99 (dd, *J* = 8.06, 3.02 Hz, 1 H), 2.80 - 2.99 (m, 1 H), 2.30 - 2.39 (m, 1 H), 2.19 - 2.30 (m, 1 H), 2.02 - 2.14 (m, 1 H), 0.94 - 1.08 (m, 3 H), 0.88 - 0.95 (m, 9 H), 0.84 (d, *J* = 7.30 Hz, 9 H); $^{13}$C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 199.0, 160.3, 150.2,137.9, 132.4, 122.9, 75.9, 54.7, 30.4, 30.1, 17.8, 17.7, 12.0.

**(5*R*,6*R*,9*R*)-6-Bromo-9-(triisopropylsilyloxy)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-5-ol (13)**. In a 500 mL round-bottomed flask was previous intermediate **12** (2.087 g, 5.06 mmol) (azeotroped with dry benzene) in THF (16 mL) to give a colorless solution. After cooling to -78 °C under nitrogen, Superhydride (5.06 mL, 5.06 mmol) (1.0M in THF) was added dropwise via syringe. The resulted yellow mixture was gradually warmed up to -60 °C in 2 h. LCMS showed good conversion (might have a minor cis-bromohydrin and partially cyclized to epoxide). After 2.5 h, the reaction was quenched with water. The solvent was removed and the residue was partitioned between EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried with $Na_2SO_4$, and concentrated to a slighly yellow oil. The residue was further

dried overnight (2.097 g): MS(ESI) [M+H$^+$] = 416.30. It was directly carried onto next reaction without further purification and characterizations.

**(1a*S*,4*R*,8b*R*)-4-((Triisopropylsilyl)oxy)-1a,3,4,8b-tetrahydro-2H-oxireno[2',3':3,4]cyclohepta[1,2-b]pyridine (14).** In a 250 mL round-bottomed flask was intermediate **13** (2.097 g, 5.06 mmol) (azeotroped with dry benzene) in THF (20 mL) to give a colorless solution. After cooling to 0 °C, NaH (0.486 g, 20.24 mmol) (excess) was added (Caution: gas evolves). The cooling bath was removed and the mixture was stirred at rt for 1 h. TLC showed complete conversion to a major more polar spot (Rf = 0.32 with 20% EtOAc/hexane). After another 1 h, the reaction was slowly quenched with water (gas evolves!) and THF was removed. The residue was partitioned between EtOAc and brine. The layers were separated. The organic layer was dried with $Na_2SO_4$, concentrated to a yellow oil (1.8 g, LCMS showed 83% purity after two steps), which was directly carried onto next reaction without further purification and characterizations. In a separate experiment, **14** was purified and characterized: $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.54 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.89 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.30 (dd, *J* = 7.6, 4.9 Hz, 1H), 5.19 (t, *J* = 3.4 Hz, 1H), 3.18 (ddd, *J* = 18.3, 13.0, 2.4 Hz, 1H), 2.60 (ddd, *J* = 18.3, 6.2, 2.4 Hz, 1H), 2.16 (ddt, *J* = 7.1, 5.3, 3.8 Hz, 2H), 2.02 (dddt, *J* = 10.7, 8.7, 6.8, 3.4 Hz, 1H), 1.64 (ddtd, *J* = 17.2, 13.1, 8.3, 2.3 Hz, 1H), 1.03 – 0.93 (m, 3H), 0.91 (d, *J* = 7.0 Hz, 9H), 0.84 (d, *J* = 7.1 Hz, 9H); $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 161.7, 150.2, 136.8, 134.0, 123.0, 76.9, 40.73, 32.9, 19.9, 17.8, 17.7, 12.1, 11.9; HRMS (ESI), m/z calcd for $C_{19}H_{32}NO_2Si$ [M+H]$^+$ 334.2197, found 334.2182; $\alpha D^{20}$ +163.9 (c 3.00 $CHCl_3$).

**(6*S*,9*R*)-9-(Triisopropylsilyloxy)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-6-ol (15)**. In a 250 mL round-bottomed flask was epoxide **14** (1.688 g, 5.06 mmol) in MeOH (30 mL) (crude: 83% purity) to give a yellow solution. Pd/C (0.269 g, 0.253 mmol) was added. The mixture was stirred under hydrogen (balloon) at rt for 2 h. LCMS showed only 10% conversion. Another 269 mg of Pd/C was added and the reaction continued overnight for 18 h. It was filtered and washed with MeOH. The

combined organic solution was concentrated to a colorless oil. It was purified by FCC first up to 50% EtOAC/hexane to obtain the starting material (0.6 g, 36%, not pure, contained impurity later shown to be intermediate **19**) and then up to pure EtOAc to elute the desired product (0.145 g, 8.5% for 3 steps): $^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.28 (dd, *J* = 4.91, 1.38 Hz, 1 H), 7.37 - 7.52 (m, 1 H), 7.08 (dd, *J* = 7.43, 4.91 Hz, 1 H), 5.09 (d, *J* = 6.55 Hz, 1 H), 3.50 - 3.78 (m, 2 H), 2.71 (d, *J* = 12.84 Hz, 1 H), 2.51 - 2.65 (m, 1 H), 2.44 (d, *J* = 13.09 Hz, 1 H), 2.09 - 2.26 (m, 1 H), 1.90 - 2.05 (m, 1 H), 1.73 (d, *J* = 3.02 Hz, 1 H), 1.02 - 1.18 (m, 3 H), 0.94 - 1.00 (m, 9 H), 0.90 (d, *J* = 7.05 Hz, 9 H); $^{13}$C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 162.6, 145.8, 138.8, 132.3, 122.7, 77.0, 70.8, 43.0, 33.8, 30.9, 18.0, 17.8, 12.1; HRMS (ESI), m/z calcd for $C_{19}H_{34}NO_2Si$ $[M+H]^+$ 336.2353, found 336.2339; $\alpha D^{20}$ +34.2 (c 1.61 $CHCl_3$).

**(*R*)-9-(Triisopropylsilyloxy)-8,9-dihydro-5H-cyclohepta[b]pyridin-6(7H)-one (3)**. In an oven-dried 100 mL round-bottomed flask was oxalyl chloride (0.951 mL, 0.951 mmol) in $CH_2Cl_2$ (4 mL) to give a colorless solution at -55 °C under nitrogen. DMSO (0.135 mL, 1.901 mmol) was added dropwise slowly over 2 min. After the solution was stirred for an additional 30 min, intermediate **15** (145 mg, 0.432 mmol) (azeotroped with dry benzene) dissolved in 2 mL $CH_2Cl_2$ (plus 2 mL rinse) was added via canuula over 5 min. The reaction mixture was stirred at -50 - -55 °C for an additional 40 min. $Et_3N$ (0.301 mL, 2.161 mmol) was added via syringe at -50 °C and the reaction mixture was gradually warmed up to -20 °C for 30 min. LCMS showed good conversion. Water and EtOAc were added, and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were dried with $Na_2SO_4$, and concentrated to a tan oil. Purification by FCC up to 50% EtOAc/hexane afforded the desired product as an colorless oil (122 mg, 85%): MS(ESI) $[M+H^+]$ = 334.34; $^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.39 (d, *J* = 5.04 Hz, 1 H), 7.49 (d, *J* = 7.55 Hz, 1 H), 7.19 (dd, *J* = 7.55, 4.78 Hz, 1 H), 5.26 (dd, *J* = 4.78, 2.27 Hz, 1 H), 4.69 (d, *J* = 14.35 Hz, 1 H), 3.29 (d, *J* = 14.35 Hz, 1 H), 3.02 (ddd, *J* = 12.15, 9.00, 6.04 Hz, 1 H), 2.45 - 2.59 (m, 1 H), 2.31 - 2.45 (m, 1 H), 2.06 -

2.25 (m, *J* = 8.53, 8.53, 5.98, 2.39 Hz, 1 H), 1.06 - 1.19 (m, 3 H), 1.01 (d, *J* = 7.30 Hz, 9 H), 0.89 - 0.97 (m, 9 H); $^{13}$C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 206.9, 160.5, 146.7, 138.4, 128.7, 123.3, 48.4, 39.9, 33.6, 17.9, 17.8, 12.1; HRMS (ESI), m/z calcd for $C_{19}H_{32}O_2NSi$ $[M+H]^+$ 334.2197, found 334.2186.

**(5*S*,9*R*)-9-((Triisopropylsilyl)oxy)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-5-ol (19)**. After the hydrogenolysis reaction of **14**, in addition to **15**, intermediate **19** was also purified and characterized. The crude product (on 1.357 g, 4.07 mmol reaction scale) was loaded onto a flash column and eluted with 0 – 100% $CH_2Cl_2$/hexane to obtain the recovered starting material **14** (670 mg, 49% recovered), and then the title product **19** (131 mg, 9.6%). The column was further eluted with 0 – 50% EtOAc/hexane to obtain the intermediate **15** (117 mg, 8.5%). **19**: $^1$H NMR (400MHz, CHLOROFORM-d) δ 8.38 (dd, *J* = 4.9, 1.6 Hz, 1 H), 7.59 (dd, *J* = 7.5, 1.3 Hz, 1 H), 7.17 (dd, *J* = 7.5, 4.8 Hz, 1 H), 5.33 (d, *J* = 11.5 Hz, 1 H), 5.19 (d, *J* = 6.5 Hz, 1 H), 4.64 (dd, *J* = 11.5, 6.0 Hz, 1 H), 2.70 - 2.54 (m, 1 H), 2.32 - 2.22 (m, 2 H), 1.82 - 1.62 (m, 3 H), 1.22 - 1.12 (m, 3 H), 1.06 - 1.01 (m, 9 H), 1.01 - 0.95 (m, 9 H); $^{13}$C NMR (101MHz, CHLOROFORM-d) δ 161.1, 146.5, 138.8, 137.3, 122.7, 78.9, 74.2, 34.2, 32.6, 17.5, 17.3, 17.1, 11.8; HRMS (ESI), m/z calcd for $C_{19}H_{34}NO_2Si$ $[M+H]^+$ 336.2353, found 336.2338; $\alpha D^{20}$ +33.5 (c 3.65 $CHCl_3$).

**(*R*,*Z*)-9-(Triisopropylsilyloxy)-8,9-dihydro-7H-cyclohepta[b]pyridine (16).** In a 250 mL round-bottomed flask was compound **5** (1.97 g, 5.91 mmol) in MeOH (20 mL) to give a colorless solution. $NaBH_4$ (0.223 g, 5.91 mmol) was added, and the mixture was stirred at rt for 1 h. LCMS indicated complete conversion. MeOH was stripped off and the residue was partitioned between water and EtOAc. The layers were separated. The organic layer was washed with brine, dried with $Na_2SO_4$, and concentrated to a colorless oil (2 g, 100%), which was carried onto next reaction without further purification and characterizations. In a 250 mL round-bottomed flask was the previous crude alcohol

(2.93 g, 8.74 mmol) and (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt (3.12 g, 13.11 mmol) in benzene (80 mL) to give a suspension. It was heated at reflux (preheated oil bath of 85 °C) with stirring under nitrogen for 5 h. LCMS showed good conversion. Volatiles were stripped off and the residue was partitioned between water and EtOAc. The layers were separated. The organic layer was washed with brine, dried and concentrated. Purification by FCC up to 30% EtOAc/hexane afforded the desired product as a colorless oil (1.64 g, 56.4% for 2 steps): MS(ESI) [M+H$^+$] = 318.38; $^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.25 (d, *J* = 4.53 Hz, 1 H), 7.41 (d, *J* = 7.81 Hz, 1 H), 6.96 - 7.15 (m, 1 H), 6.20 (d, *J* = 12.59 Hz, 1 H), 5.85 - 6.02 (m, 1 H), 5.25 (d, *J* = 7.30 Hz, 1 H), 2.73 - 2.93 (m, 1 H), 2.35 (dd, *J* = 19.39, 4.03 Hz, 1 H), 2.17 - 2.29 (m, 1 H), 1.87 (td, *J* = 13.53, 4.41 Hz, 1 H), 1.01 - 1.11 (m, 3 H), 0.93 - 1.00 (m, 9 H), 0.79 - 0.89 (m, 9 H); $^{13}$C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 161.1, 145.2, 138.8, 135.0, 131.1, 125.8, 122.4, 76.1, 29.8, 26.3, 18.0, 17.8, 12.4.

**(1a*R*,4*R*,8b*S*)-4-((Triisopropylsilyl)oxy)-1a,3,4,8b-tetrahydro-2H-oxireno[2',3':3,4]cyclohepta[1,2-b]pyridine (17).** In a 1 L round-bottomed flask was sodium hypochlride (191 mL, 166 mmol). Sodium phophate, dibasic (0.880 g, 6.20 mmol) was added. After cooling to 0°C, intermediate **16** (1.64 g, 5.16 mmol) and (1*S*,2*S*)-(+)-[1,2-cyclohexanediamino-*N*,*N*'-bis(3,5-di-t-butylsalicylidene)]manganese (III) chloride (0.394 g, 0.620 mmol) dissolved in $CH_2Cl_2$ (40 mL) was added dropwise over 1 h. The dark reaction mixture was allowed to slowly warm to rt and stirred overnight for 17 h. LCMS showed good conversion to the desired product. The mixture was diluted with water and $Et_2O$. The layers were separated and the aqueous layer was extracted with $Et_2O$ twice. The combined organic layers were dried with celite and $Na_2SO_4$, filtered, and concentrated to a tan oil. Purification by FCC up to 50% EtOAc/hexane afforded the desired product as a light yellow oil (1.00 g, 58%): $^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.25 - 8.44 (m, 1 H), 7.81 (d, *J* = 8.31 Hz, 1 H), 7.13 (td, *J* = 7.05, 3.53 Hz, 1 H), 4.94 - 5.16 (m, 1 H), 3.88 - 4.04 (m, 1 H), 3.25 - 3.48 (m, 1 H), 2.18 - 2.38 (m, 1 H), 1.89 - 2.11 (m, 2 H), 1.11 - 1.29 (m, 1 H), 0.62 - 1.10 (m, 21 H); $^{13}$C NMR

(101 MHz, CHLOROFORM-*d*) δ ppm 159.9, 147.7, 139.1, 131.1, 122.7, 76.4, 55.4, 54.3, 30.3, 25.5, 17.9, 17.7, 12.0; HRMS (ESI), m/z calcd for $C_{19}H_{32}NO_2Si$ $[M+H]^+$ 334.2197, found 334.2183; $\alpha D^{20}$ +16.2 (c 3.00 $CHCl_3$).

**(6*R*,9*R*)-9-(Triisopropylsilyloxy)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-6-ol (18).** In a 250 mL round-bottomed flask was intermediate **17** (1.00 g, 3.00 mmol) in MeOH (20 mL) to give a yellow solution. Pd/C (0.160 g, 0.150 mmol) was added. The mixture was stirred under hydrogen (balloon) at rt for 2 h. LCMS showed complete conversion. It was filtered and washed with MeOH. The combined organic solution was concentrated to a light yellow oil (1.01g, 100%): $^1$H and $^{13}$C NMR were obtained (very different from **15**, cis-alcohol): $^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.19 - 8.27 (m, 1 H), 7.44 (d, *J* = 7.30 Hz, 1 H), 7.06 (dd, *J* = 7.43, 4.91 Hz, 1 H), 5.06 - 5.14 (m, 1 H), 4.21 (br. s., 1 H), 3.68 (d, *J* = 14.10 Hz, 1 H), 3.37 (s, 1 H), 2.76 (dd, *J* = 14.10, 6.55 Hz, 1 H), 2.39 - 2.54 (m, 1 H), 1.88 - 2.01 (m, 2 H), 1.73 - 1.89 (m, 1 H), 1.00 - 1.17 (m, 3 H), 0.92 - 0.99 (m, 9 H), 0.81 - 0.91 (m, 9 H); $^{13}$C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 162.2, 145.2, 140.6, 132.6, 122.5, 77.2, 66.9, 39.7, 31.3, 26.7, 18.0, 17.8, 12.1; HRMS (ESI), m/z calcd for $C_{19}H_{34}NO_2Si$ $[M+H]^+$ 336.2353, found 336.2339; $\alpha D^{20}$ +58.9 (c 3.10 $CHCl_3$).

**(*R*)-9-(Triisopropylsilyloxy)-8,9-dihydro-5H-cyclohepta[b]pyridin-6(7H)-one (3).** In an oven-dried 250 mL round-bottomed flask was oxalyl chloride (3.30 mL, 6.60 mmol) in $CH_2Cl_2$ (14 mL) to give a colorless solution at -55 °C under nitrogen. DMSO (0.937 mL, 13.20 mmol) was added dropwise slowly over 2 min. After the solution was stirred for an additional 30 min, crude intermediate **18** (1.01 g, 3.00 mmol) (azeotroped with dry benzene) dissolved in 4 mL $CH_2Cl_2$ (plus 6 mL rinse) was added via canuula over 5 min. The reaction mixture was stirred at -50 - -55 °C for an additional 40 min. $Et_3N$ (2.091 mL, 15.00 mmol) was added via syringe at -50 °C and the reaction mixture was gradually warmed up to -20 °C for 30 min. TLC showed complete conversion. Water and EtOAc were added, and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers

were dried with $Na_2SO_4$, and concentrated to a tan oil. Purification by FCC up to 50% EtOAc/hexane afforded the desired product as an colorless oil (814 mg, 81% for 2 steps). $^1$H NMR was taken and was the same as that made from intermediate **15**.

***Preparation of* D-15 *and* D-18**. The deuterium labeling experiments were carried out following the same procedures described for preparation of **15** and **18** by using deuterium gas in a small balloon. The compounds were purified and 1H NMR were obtained. The spectra difference were shown in Figure 4. **D-15**: HRMS (ESI), m/z calcd for $C_{19}H_{33}DNO_2Si$ $[M+H]^+$ 337.2416, found 337.2397. **D-18**: HRMS (ESI), m/z calcd for $C_{19}H_{33}DNO_2Si$ $[M+H]^+$ 337.2416, found 337.2404.

**(6*R*,9*R*)-6-(2,3-Difluorophenyl)-9-(triisopropylsilyloxy)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-6-ol (20).** In an oven-dried 250 mL round-bottomed flask was 1-bromo-2,3-difluorobenzene (1.036 g, 5.37 mmol) in THF (10 mL) under nitrogen. After cooling to -78 °C, n-BuLi (1.757 mL, 4.39 mmol) was added dropwise via syringe (color turned to faint yellow). After 10 min, a solution of intermediate **3** (814 mg, 2.440 mmol) in THF (4 mL plus 4 mL rinse) was added via syringe and the reaction was stirred at -78 °C for 1 h. LCMS indicated very good conversion. The reaction flask was raised from the cooling bath and stirred at rt for 1.5 h. The reaction was quenched by saturated $NH_4Cl$ solution. THF was stripped off and the residue was partitioned between water and EtOAc. The layers were separated. TLC (1/1 EtOAc/hexane) showed a much less polar minor spot as starting material and a more polar major spot (Rf = 0.28). The organic layer was washed with brine, dried with $Na_2SO_4$, and concentrated to a tan oil. Purification by FCC up to 80% EtOAc/hexane afforded the recovered starting material (148 mg, 18%) as a yellow oil, as well as the desired product (900 mg, 82%) as a colorless oil: MS(ESI) $[M+H^+]$ = 448.36; $^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.26 (d, *J* = 3.53 Hz, 1 H), 7.42 (t, *J* = 6.42 Hz, 1 H), 7.35 (d, *J* = 7.30 Hz, 1 H), 6.99 - 7.13 (m, 3 H), 5.16 (br. s., 1 H), 4.63 (d, *J* = 13.85 Hz, 1 H), 3.02 - 3.28 (m, 1 H), 2.71 (d, *J* = 14.10 Hz, 1 H), 2.34 (d, *J* = 4.03

Hz, 1 H), 2.02 - 2.15 (m, 2 H), 1.75 (d, *J* = 13.85 Hz, 1 H), 1.06 - 1.19 (m, 3 H), 0.97 - 1.07 (m, 9 H), 0.84 - 0.97 (m, 9 H). The compound appeared to be a single diastereomer.

**(6*R*,9*R*)-6-(2,3-Difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-6,9-diol (21).** In a 100 mL round-bottomed flask was intermediate **20** (900 mg, 2.011 mmol) in THF (10 mL) to give a colorless solution. TBAF (2.413 mL, 2.413 mmol) was added, and the mixture was stirred at 50 °C overnight for 18 h. LCMS indicated complete conversion. THF was stripped off and the residue was partitioned between water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried with $Na_2SO_4$, and concentrated to a tan oil. Purification by FCC afforded the desired product as a white crystalline solid (497 mg, 85%): MS(ESI) $[M+H^+]$ = 292.26; $^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.05 (d, *J* = 3.78 Hz, 1 H), 7.37 (d, *J* = 7.55 Hz, 1 H), 7.06 - 7.21 (m, 1 H), 6.81 - 7.05 (m, 3 H), 5.63 (br. s., 1 H), 4.82 - 4.97 (m, 1 H), 3.68 - 4.11 (m, 2 H), 3.00 (d, *J* = 14.35 Hz, 1 H), 2.77 (t, *J* = 10.58 Hz, 1 H), 2.13 (t, *J* = 11.21 Hz, 1 H), 1.87 - 2.03 (m, 1 H), 1.69 - 1.86 (m, 1 H); $^{19}$F NMR (376 MHz, CHLOROFORM-*d*) δ ppm -137.37 (br. s.), -137.99 (d, *J* = 15.52 Hz); $^{13}$C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 160.5, 152.4 - 149.9 (dd, *J* = 13.87 and 248 Hz), 149.9 (dd, *J* = 12.33 and 249 Hz), 145.3, 139.3, 136.0, 130.7, 123.8, 123.7, 122.6, 121.7, 116.3 (d, *J* = 16.95 Hz), 73.1, 72.5, 53.5, 44.4, 44.4, 37.8; HRMS (ESI), m/z calcd for $C_{16}H_{16}O_2NF_2$ $[M+H]^+$ 292.1144, found 292.1136.

**(6*R*,9*R*)-6-(2,3-Difluorophenyl)-6-hydroxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (Diastereomeric 1).** In an oven-dried 100 mL round-bottomed flask was intermediate **21** (47.2 mg, 0.162 mmol) (azeotroped with dry benzene) and 4-nitrophenyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (93 mg, 0.243 mmol) in DMF (2 mL) to give a light yellow suspension under nitrogen. NaHMDS (0.648 mL, 0.648 mmol) was added dropwise. The resulted yellow suspension was stirred under nitrogen at rt overnight for 15 h. LCMS showed the desired product (M + H = 536.27). The

reaction was quenched with saturated $NaHCO_3$ and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water (yellow), brine, dried with $Na_2SO_4$, and concentrated to a yellow oil. Purification by FCC up to 10% MeOH/$CH_2Cl_2$ afforded one major peak (55 mg) as white foam/solid. It was then further purified by prep-HPLC (30x150mm AXIA LUNA C18 5um Phenominex column, 220nM, 30ml/min, 20-90%B over 17min, then 100%B for 3 min, A: 95% $H_2O$/5% MeCN;10mM Ammonium Acetate; B: 95% MeCN/5% H2O;10 mM Ammonium Acetate) to afford the desired product (41.3 mg, 48%) as a dense colorless oil: $^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 11.80 - 10.50 (br. s., 1 H), 8.44 (br. s., 1 H), 8.03 (br. s., 1 H), 7.47 (d, *J* = 6.80 Hz, 2 H), 6.83 - 7.31 (m, 5 H), 6.09 (br. s., 1 H), 4.29 - 4.70 (m, 4 H), 2.84 (d, *J* = 14.60 Hz, 6 H), 2.11 - 2.52 (m, 4 H), 1.82 - 2.01 (m, 2 H); $^{19}$F NMR (376 MHz, CHLOROFORM-*d*) δ ppm -138.31 (d, J = 22.56Hz), -139.80 (dd, J = 18.80 and 131.60 Hz), $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 158.2, 153.7, 153.1, 151.9 - 149.3 (dd, J = 18.23, 308.09 Hz), 148.5 – 145.9 (dd, J = 17.61, 306.83 Hz), 146.6, 142.9, 140.1, 139.8, 138.3 - 138.1 (d, J = 13.83 Hz), 131.4, 123.8, 122.9, 122.8, 120.3, 116.4, 115.8 - 115.6 (d, J = 21.38 Hz), 115.0, 79.1, 72.5, 49.9, 43.3, 43.2, 35.4, 29.0, 24.9; HRMS (ESI), m/z calcd for $C_{28}H_{28}O_4N_5F_2$ $[M+H]^+$ 536.2104, found 536.2088; $\alpha D^{20}$ +45.99 (c 3.20 $CHCl_3$).

**(1a*S*,4*S*,8b*R*)-4-((triisopropylsilyl)oxy)-1a,3,4,8b-tetrahydro-2H-oxireno[2',3':3,4]cyclohepta[1,2-b]pyridine (ent-17).** 1. In an oven-dried 250 mL round-bottomed flask was 5(S)-9-hydroxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-5-one (3.16 g, 17.83 mmol) in $CH_2Cl_2$ (50 mL) to give a tan solution. After cooling to 0 °C, TIPS-OTf (4.84 mL, 17.83 mmol) and $Et_3N$ (4.97 mL, 35.7 mmol) were added via syringe, and the mixture was stirred at 0 °C for 1h. LCMS indicated complete conversion. Volatiles were stripped off and the residue was partitioned between $NaHCO_3$ solution and EtOAc. The layers were separated and the organic layer was washed with brine, dried and concentrated to a tan oil. The crude was directly used in next reaction. MS(ESI) $[M+H^+]$ = 334.28.

2. In a 250 mL round-bottomed flask was previous crude material (5.95 g, 17.83 mmol) in MeOH (50 mL) to give a tan solution. $NaBH_4$ (0.675 g, 17.83 mmol) was added, and the mixture was stirred at rt for 1 h. LCMS indicated complete conversion. MeOH was stripped off and the residue was partitioned between water and EtOAc. The layers were separated. The organic layer was washed with brine, dried with $Na_2SO_4$, and concentrated to a tan oil, which was carried onto next reaction without further purification and characterizations. MS(ESI) $[M+H^+]$ = 336.28 (LCMS showed two diastereomers).

3. In a 250 mL round-bottomed flask was previous crude material (5.98 g, 17.83 mmol) and (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt (6.37 g, 26.7 mmol) in benzene (100 mL) to give a suspension. It was heated at reflux (preheated oil bath of 85 °C) with stirring under nitrogen for 5 h. LCMS showed complete conversion. Volatiles were stripped off and the residue was partitioned between water and EtOAc. The layers were separated. The organic layer was washed with brine, dried and concentrated to a tan oil (5.66 g), which was directly used in the next step without further purification and characterizations. MS(ESI) $[M+H^+]$ = 318.32.

4. In a 2 L round-bottomed flask was sodium hypochlorite (658 mL, 574 mmol). Sodium phosphate, dibasic (3.04 g, 21.40 mmol) was added. After cooling to 0 °C, previous crude material (5.66 g, 17.83 mmol) and manganese(III) 6,6'-(1*E*,1'*E*)-(1*R*,2*R*)-cyclohexane-1,2-diylbis(azan-1-yl-1-ylidene) bis(methan-1-yl-1-ylidene)bis(2,4-di-*tert*-butylphenolate) chloride (1.359 g, 2.140 mmol) dissolved in $CH_2Cl_2$ (140 mL) was added dropwise over 1 h. The dark reaction mixture was allowed to slowly warm to rt and stirred overnight for 20 h. LCMS showed good conversion to the desired product. The mixture was diluted with water and $Et_2O$. The layers were separated and the aqueous layer was extracted with $Et_2O$ twice. The combined organic layers were washed with water, brine, dried with celite, filtered, and concentrated to a dark oil. Purification by FCC up to 50% EtOAc/hexane afforded the desired product as a light yellow oil (2.98 g, 50% for 4 steps): MS(ESI) $[M+H^+]$ = 334.35; $^1$H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.25 - 8.44 (m, 1 H), 7.81 (d, *J* = 8.31 Hz, 1 H), 7.13 (td, *J* = 7.05, 3.53 Hz,

1 H), 4.94 - 5.16 (m, 1 H), 3.88 - 4.04 (m, 1 H), 3.25 - 3.48 (m, 1 H), 2.18 - 2.38 (m, 1 H), 1.89 - 2.11 (m, 2 H), 1.11 - 1.29 (m, 1 H), 0.62 - 1.10 (m, 21 H).

**(6*S*,9*S*)-9-(Triisopropylsilyloxy)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-6-ol (ent-18).** In a 500 mL round-bottomed flask was intermediate **17** (2.98 g, 8.93 mmol) in MeOH (60 mL) to give a yellow solution. Pd/C (0.475 g, 0.447 mmol) was added. The mixture was stirred under hydrogen (balloon) at rt for 2 h. LCMS showed very good conversion. After another 1 h, the mixture was filtered and washed with MeOH. The combined organic solution was concentrated to a light yellow oil, and further dried over 3 days to a light yellow solid (2.91 g, 97%): MS(ESI) $[M+H^+]$ = 336.35, which was used in the next step without further purification and characterizations.

**(*S*)-9-(Triisopropylsilyloxy)-8,9-dihydro-5H-cyclohepta[b]pyridin-6(7H)-one (ent-3).** In an oven-dried 250 mL round-bottomed flask was oxalyl chloride (9.54 mL, 19.08 mmol) in $CH_2Cl_2$ (40 mL) to give a colorless solution at -55 °C under nitrogen. DMSO (2.71 mL, 38.2 mmol) was added dropwise slowly over 2 min. After the solution was stirred for an additional 30 min, intermediate **ent-18** (2.91 g, 8.67 mmol) (azeotroped with dry benzene) dissolved in 8 mL $CH_2Cl_2$ (plus 8 mL rinse) was added via canuula over 5 min. The reaction mixture was stirred at -50 - -55 °C for an additional 40 min. $Et_3N$ (6.04 mL, 43.4 mmol) was added via syringe at -50 °C and the reaction mixture was gradually warmed up to -20 °C for 30 min. TLC showed complete conversion. Water and EtOAc were added, and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were dried with $Na_2SO_4$, and concentrated to a tan oil. Purification by FCC up to 50% EtOAc/hexane afforded the desired product as a light yellow oil (2.08 g, 72%): MS(ESI) $[M+H^+]$ = 334.35; $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.39 (dt, *J* = 5.0, 1.3 Hz, 1H), 7.53 – 7.45 (m, 1H), 7.19 (dd, *J* = 7.6, 4.9 Hz, 1H), 5.26 (dd, *J* = 4.8, 2.3 Hz, 1H), 4.69 (d, *J* = 14.3 Hz, 1H), 3.29 (dd, *J* = 14.5, 1.3 Hz, 1H), 3.02 (ddd, *J* = 12.1, 9.0, 6.2 Hz, 1H), 2.56 – 2.46 (m, 1H), 2.39 (dtd, *J* = 14.2, 6.3, 4.8 Hz, 1H), 2.14 (dddd, *J* = 14.4, 9.1, 5.8, 2.3 Hz, 1H), 1.13 (ddt, *J* = 13.8, 8.6, 6.6 Hz, 3H), 1.01 (d, *J* = 7.3 Hz, 9H), 0.95 (d, *J* = 7.3 Hz, 9H);

$^{13}$C NMR (101 MHz, Chloroform-*d*) δ 206.6, 160.0, 146.3, 138.1, 128.4, 122.9, 47.9, 39.4, 33.2, 17.5, 17.4, 11.6; HRMS (ESI), m/z calcd for $C_{19}H_{32}O_2NSi$ $[M+H]^+$ 334.2197, found 334.2186; $\alpha D^{20}$ -85.12 (c 5.45 $CHCl_3$).

**(6*S*,9*S*)-6-(2,3-Difluorophenyl)-9-(triisopropylsilyloxy)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-6-ol (ent-20).** In an oven-dried 250 mL round-bottomed flask was 1,2-difluorobenzene (0.680 mL, 6.90 mmol) in THF (12 mL) under nitrogen. After cooling to -65 °C, n-BuLi (2.208 mL, 5.52 mmol) was added dropwise via syringe. After the mixture was stirred between -65 and -60 °C for 30 min (very faint yellow), it was cooled down to -78 °C. A solution of intermediate **ent-3** (920.5 mg, 2.76 mmol) in THF (4 mL plus 4 mL rinse) was added via syringe (turned to yellow) and the reaction was stirred at -78 °C for 1 h (yellow), and at rt for 30 min (red). LCMS indicated good conversion. The reaction was quenched by saturated $NH_4Cl$ solution. THF was stripped off and the residue was partitioned between water and EtOAc. The layers were separated. The organic layer was washed with brine, dried with $Na_2SO_4$, and concentrated to a tan oil. Purification by FCC up to 80% EtOAc/hexane afforded the recovered starting material (197 mg, 21 %) as a yellow oil, as well as the desired product (977 mg, 79 %) as a colorless oil: MS(ESI) $[M+H^+]$ = 448.33; $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.38 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.17 – 7.07 (m, 3H), 5.23 – 5.18 (m, 1H), 4.66 (d, *J* = 13.9 Hz, 1H), 3.19 (ddd, *J* = 14.1, 11.7, 5.3 Hz, 1H), 2.75 (dd, *J* = 14.1, 2.1 Hz, 1H), 2.17 – 2.09 (m, 2H), 1.79 (dtd, *J* = 13.9, 3.5, 1.9 Hz, 1H), 1.21 – 1.13 (m, 3H), 1.05 (d, *J* = 7.4 Hz, 9H), 0.97 (d, *J* = 7.3 Hz, 9H).

**(6*S*,9*S*)-6-(2,3-Difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-6,9-diol (ent-21).** In a 250 mL round-bottomed flask was intermediate **ent-20** (977 mg, 2.183 mmol) in THF (10 mL) to give a colorless solution. TBAF (4.80 mL, 4.80 mmol) was added, and the mixture was stirred at 50 °C overnight for 16 h. LCMS indicated good conversion with a little starting material left. Another 0.2 equiv of TBAF was added and the reaction continued at 50 °C for 2 h. THF was stripped off and the

residue was partitioned between water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried with $Na_2SO_4$, and concentrated to a tan oil. Purification by FCC up to 10% MeOH/$CH_2Cl_2$ afforded the desired product as a white solid (458 mg, 72 %): MS(ESI) [M+H$^+$] = 292.21; $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.09 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.19 – 7.10 (m, 1H), 7.04 – 6.88 (m, 3H), 5.58 (s, 1H), 4.92 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.99 (d, *J* = 14.4 Hz, 1H), 3.73 (s, 1H), 3.03 (d, *J* = 14.4 Hz, 1H), 2.77 (ddd, *J* = 13.5, 9.1, 3.1 Hz, 1H), 2.16 (ddt, *J* = 11.8, 9.2, 3.0 Hz, 1H), 1.98 (ddd, *J* = 17.5, 7.4, 3.5 Hz, 1H), 1.80 (dtd, *J* = 13.1, 8.1, 2.6 Hz, 1H); $^{19}$F NMR (376 MHz, Chloroform-*d*) δ -137.39 (d, *J* = 19.6 Hz), -137.67 – -138.28 (m), HRMS (ESI), m/z calcd for $C_{16}H_{16}O_2NF_2$ [M+H]$^+$ 292.1144, found 292.1134.

**(6*S*,9*R*)-6-(2,3-Difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-6,9-diol (2).** 1. In a 250 mL round-bottomed flask was previous intermediate **ent-21** (458 mg, 1.572 mmol) (azeotroped with dry benzene) in THF (8 mL) to give a light orange solution. 4-Nitrobenzoic acid (394 mg, 2.358 mmol) and $Ph_3P$ (619 mg, 2.358 mmol) were added under nitrogen. Diisopropyl azodicarboxylate (0.464 mL, 2.358 mmol) was added dropwise. The mixture was allowed to stir overnight for 15 h. LCMS showed complete conversion, but the desired product was a minor. It was concentrated to a light yellow oil and directly purified by FCC (5% EtOAC/hexanes to 100%) to afford the desired product (6*S*,9*R*)-6-(2,3-Difluorophenyl)-6-hydroxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl 4-nitrobenzoate (125 mg, 18%) as a white solid; MS(ESI) [M+H$^+$] = 441.20. The intermediate was directly used in the next step without further characterizations.

2. In a 250 mL round-bottomed flask was previous 4-nitrobenzoate (125 mg, 0.284 mmol) in THF (2 mL) to give a colorless solution. LiOH (0.568 mL, 0.568 mmol) was added, and the mixture was stirred at rt for 2 h. LCMS indicated complete conversion. It was diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were

washed with brine, dried, and concentrated to a white solid. Purification by FCC up to 6% MeOH/$CH_2Cl_2$ afforded the desired product as a white crystalline solid (71 mg, 86 %). A few crystals were picked up and X-ray structure was obtained to confirm the cis-diol stereochemistry. MS(ESI) [M+$H^+$] = 292.21; $^1$H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.44 (d, *J* = 4.58 Hz, 1 H), 7.38 - 7.51 (m, 2 H), 7.19 (dd, *J* = 7.48, 5.04 Hz, 1 H), 7.04 - 7.16 (m, 2 H), 5.99 (br. s., 1 H), 4.90 (dd, *J* = 11.29, 2.14 Hz, 1 H), 3.80 - 3.91 (m, 1 H), 2.92 (dd, *J* = 14.65, 2.14 Hz, 1 H), 2.57 - 2.70 (m, 1 H), 2.37 (br. s., 1 H), 2.11 (ddd, *J* = 14.19, 5.95, 3.97 Hz, 1 H), 1.96 - 2.06 (m, 1 H), 1.74 - 1.91 (m, 1 H); $^{19}$F NMR (470 MHz, CHLOROFORM-*d*) δ ppm -138.91 - -138.74 (m), -139.22 - -139.06 (m); $^{13}$C NMR (126 MHz, CHLOROFORM-*d*) δ ppm 160.6, 152.0 - 150.1 (dd, J = 21.42 and 254.52 Hz), 148.8 - 146.7 (dd, *J* = 11.52 and 244.44 Hz), 145.6, 139.9, 138.4 (d, *J* = 8.64 Hz), 129.4, 123.9 - 124.6 (m), 122.5, 120.8, 116.2 (d, *J* = 17.28 Hz), 71.8, 71.7, 44.3, 44.3, 39.7, 31.3; HRMS (ESI), m/z calcd for $C_{16}H_{16}O_2NF_2$ [M+H]$^+$ 292.1144, found 292.1132.

**(6*S*,9*R*)-6-(2,3-Difluorophenyl)-6-hydroxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (1).** In an oven-dried 100 mL round-bottomed flask was previous intermeidiate **2** (71 mg, 0.244 mmol) (azeotroped with dry benzene) and 4-nitrophenyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (121 mg, 0.317 mmol) in DMF (2 mL) to give a light yellow suspension under nitrogen. NaHMDS (0.926 mL, 0.926 mmol) was added dropwise. The resulted yellow suspension was stirred under nitrogen at rt for 3.5 h. LCMS showed complete conversion. The reaction was quenched with saturated $NaHCO_3$ and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (LCMS showed no product left in the aqueous). The combined organic layers were washed with water (yellow), brine, dried with $Na_2SO_4$, and concentrated to a yellow oil. Purification by FCC up to 10% MeOH/$CH_2Cl_2$ afforded the desired product (131 mg, 100 %) as a white powder. LCMS and HPLC showed >99% purity. MS(ESI) [M+$H^+$] = 536.26; $^1$H NMR (500 MHz,

CHLOROFORM-*d*) δ ppm 11.31 (br. s., 1 H), 8.35 - 8.50 (m, 1 H), 7.97 - 8.11 (m, 1 H), 7.31 - 7.60 (m, 3 H), 7.02 - 7.18 (m, 3 H), 6.98 (dd, *J* = 7.48, 5.34 Hz, 1 H), 6.03 (d, *J* = 10.68 Hz, 1 H), 4.60 (br. s., 2 H), 4.40 (br. s., 1 H), 3.97 (d, *J* = 14.34 Hz, 1 H), 2.80 - 3.20 (m, 4 H), 2.67 (t, *J* = 11.75 Hz, 2 H), 2.17 - 2.40 (m, 2 H), 2.08 (t, *J* = 12.67 Hz, 2 H), 1.89 (d, *J* = 11.29 Hz, 2 H); $^{19}$F NMR (470 MHz, CHLOROFORM-*d*) δ ppm -138.72, -138.69; $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 159.5, 155.1, 153.8, 152.2 - 150.1 (dd, J = 16.35, 248.99 Hz), 148.8 – 146.7 (dd, J = 15.72, 248.99 Hz), 147.2, 143.6, 140.1, 139.7, 138.2, 128.9, 124.1, 123.4, 122.2, 121.0, 116.7, 116.3 – 116.2 (d, J = 16.35 Hz), 115.7, 75.8, 71.8, 50.5, 44.2, 44.0, 39.6, 29.4, 28.2; HRMS (ESI), m/z calcd for $C_{28}H_{28}O_4N_5F_2$ $[M+H]^+$ 536.2104, found 536.2087; $\alpha D^{20}$ -50.21 (c 4.05 $CHCl_3$).

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**Supporting Information Available:** $^{1}$H, $^{13}$C, $^{19}$F NMR spectra for most of the new compounds, HPLC/LCMS analysis of products diastereomeric-**1** and **1**, and $^{1}$H NMR comparison of intermediates **18**, **15**, and **19** from hydrogen and deuterium experiments. This material is available free of charge via the Internet at http://pubs.acs.org. Crystal structure information files (CIF) of intermediate **2** (CCDC 1528188) and intermediate **18** (CCDC 1528189) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures or from the publisher at http://pubs.acs.org.

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15. In $^{1}$H NMR spectra, benzylic-like protons of both **15** and **18** showed typical coupling patterns in coupling with themselves and adjacent proton connected with OH: one is a doublet which is assigned to the proton cis- to the alcohol proton and the other is a doublet of doublet which is assigned as anti- to the alcohol proton.

16. Alcohol **19** was much less polar than alcohol **15**. It was slightly more polar than **14** and difficult to separate from **14**. See Supplementary Information for details.

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