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Discovery of (5*S*,6*S*,9*R*)-5-Amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl 4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxylate (BMS-927711): An Oral Calcitonin Gene-Related Peptide (CGRP) Antagonist in Clinical Trials for Treating Migraine

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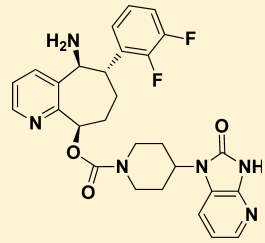
Supporting Information

ABSTRACT: Calcitonin gene-related peptide (CGRP) receptor antagonists have demonstrated clinical efficacy in the treatment of acute migraine. Herein, we describe the design, synthesis, and preclinical characterization of a highly potent, oral CGRP receptor antagonist BMS-927711 (**8**). Compound **8** has good oral bioavailability in rat and cynomolgus monkey, attractive overall preclinical properties, and shows dose-dependent activity in a primate model of CGRP-induced facial blood flow. Compound **8** is presently in phase II clinical trials.



8, CGRP K_i = 0.027 nM

INTRODUCTION

Migraine is a painful, incapacitating disease, that affects a large portion (12%) of the adult population and imposes a substantial economic burden on society (estimated to be $13 billion per year).[1] It is characterized by recurrent unilateral headaches often accompanied by nausea, vomiting, photophobia, and phonophobia. Much remains to be learned about the underlying pathophysiology of migraine. One prominent hypothesis is that migraine headache is initiated with the dilation of cranial blood vessels.[2] Additional contemporary work has focused on neural processes and the potential roles of peripheral[3] and possibly central sensitization[4] in the neurobiology of headache. The current standard of care is the triptan class of 5-$HT_{1B/1D}$ receptor agonists, which are believed to act by constriction of the cranial blood vessels.[3] However, because they cause nonselective smooth muscle vasoconstriction, they are associated with a number of unpleasant, and potentially dangerous, cardiovascular side effects, and the triptans have labeled contraindications against use in patients with heart disease and hypertension.[4] A novel class of drugs for migraine treatment that are devoid of direct vasoconstriction would offer a significant therapeutic advantage over the current standard of care.

Calcitonin gene-related peptide CGRP is a 37 amino acid peptide that is widely distributed in the nervous system.[5] It is an extremely potent vasodilator that has been directly implicated in the pathogenesis of migraine.[6] Studies have shown that plasma levels of CGRP are elevated during migraine attacks, and these levels are normalized by sumatriptan in connection with the relief of headache.[4] CGRP receptors are G-coupled cell surface receptors composed of the calcitonin receptor-like receptor (CLR), receptor activity modifying protein 1 (RAMP1), and the receptor component protein (RCP).[7]

CGRP receptor antagonists are a new therapeutic target for the treatment of migraine. Proof of mechanism in the clinic was first demonstrated with intravenous administration of olcegepant (BIBN4096BS) (**1**, Figure 1), where alleviation of pain in migraneurs was significantly superior over placebo.[8,9] Importantly, cardiovascular side effects associated with sumatriptan were not observed with the CGRP receptor antagonist **1**. More recently, an oral CGRP receptor antagonist, telcagepant (MK-0974)[10] (**2**, Figure 1), showed efficacy in multiple phase II and phase III trials but was discontinued following a larger study.[11] Two later oral CGRP receptor antagonists, MK-3207[12] and BI-44370[13] (**3** and **4**, Figure 1), were efficacious in various phase II trials, but are not currently in clinical development.[14]

A recent publication from our laboratory disclosed the potent, oral CGRP receptor antagonist, BMS-846372, which contained a cyclohepta[*b*]pyridine core (**5**, Figure 1) and was an attractive preclinical lead.[15] However, the compound was highly crystalline with very low aqueous solubility (<2 μg/mL), and this created a significant challenge for further clinical development. Formation of useful salts of the core pyridine ($pK_a \sim 4$) was not feasible

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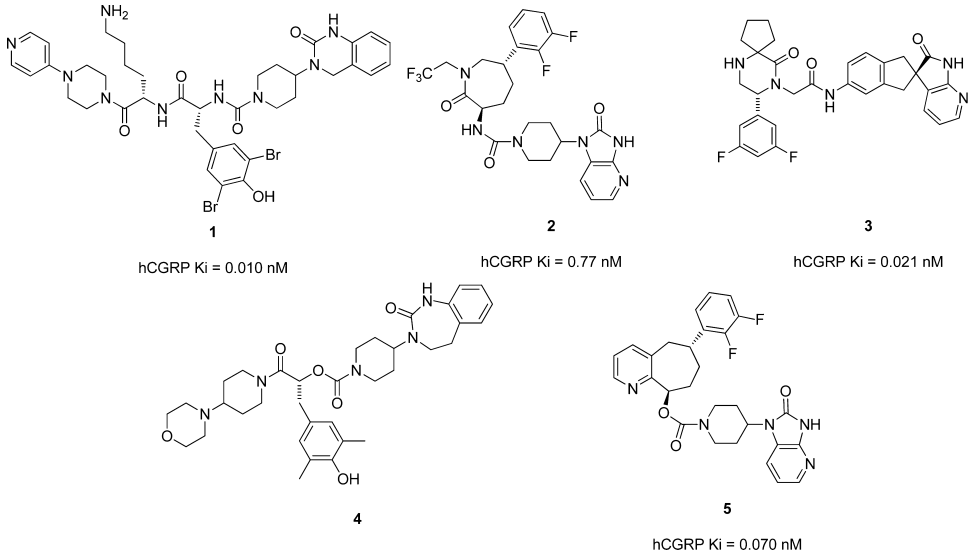

Figure 1. Selected CGRP receptor antagonists.

because strong acids led to hydrolysis of the carbamate. A limited number of phosphate-related prodrugs were attempted, but they were not progressable.[16] We realized that one way to increase the aqueous solubility of an organic molecule was to add hydrophilic groups. We hypothesized that the addition of small, polar groups such as OH or NH_2 would provide "helpful polarity," improving the solubility while maintaining the attractive properties of **5**. In this vein, two target alcohols, **6** and **7** (Figure 2), were prepared

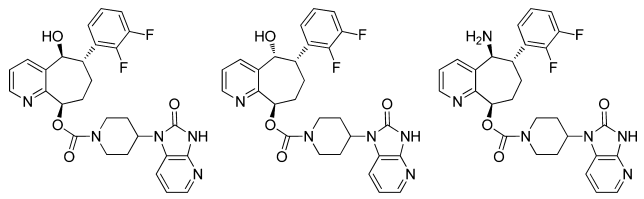

Figure 2. Proposed target CGRP receptor antagonists **6**, **7**, and **8**.

to test this hypothesis. These more polar analogues of **5** (**6** and **7**) maintained their potency as CGRP receptor antagonists, and this encouraged us to make the primary amine analogue **8** (Figure 2). A primary amine would also allow salt formation that might not facilitate decomposition of the carbamate linker. Accordingly, herein we describe the discovery of a potent, aqueous soluble, orally active CGRP receptor antagonist BMS-927711 (**8**) (Figure 2), which is presently in phase II clinical trials.

CHEMISTRY

We recently reported a stereoselective synthesis of **5**,[17] in which ketone **9** (Scheme 1) was prepared as a key intermediate. It was also useful for the formation of our present targets, compounds **6**, **7**, and **8**. The syntheses of the desired alcohols, **6** and **7** are shown in Scheme 1. Careful deprotection of **9** by TBAF afforded the rather unstable hydroxyl ketone intermediate **10** in 62% yield. Carbamate formation with **11** under previously reported conditions[18] using NaHMDS as the base at low temperature afforded the intermediate ketone **12** in 29% yield. Reduction of the ketone **12** by $NaBH_4$ afforded three alcohols, **6**, **7**, and **13**, after careful purifications using preparative HPLC and flash column chromatography.

To assign relative stereochemistry, ketone mixture **9** was directly reduced by $NaBH_4$ to the diastereomeric mixture **14** (Scheme 2). Treatment of **14** with TBAF at room temperature left **16** untouched while removing the TIPS protecting group from the major and minor diastereomers, **15** and **17**. All three components were easily separable at this stage. The major diastereomer, **15**, was obtained in 65% yield. An X-ray structure of **15** was obtained and identified its relative stereochemistry (as shown in Scheme 2).[19] The protected diasteromer **16** was further treated with TBAF at elevated temperature to afford the diol **18**. An X-ray structure of **18** was also obtained, showing its relative stereochemistry (as shown in Scheme 2).[19] The relative stereochemistry of diol **17** was not determined.[20]

On the basis of the stereochemical information and product distribution ratio (compounds **6** and **15** were major products from both $NaBH_4$ reductions) obtained from **15** and **18**, the absolute stereochemistry of compound **6** was assigned as shown in Scheme 1. To further confirm the stereochemistry of **6**, a stereoselective synthesis of compound **6** was carried out (Scheme 3). Enantiomerically pure **19** was available from ketone **9** through dynamic resolution and diastereoselective reduction.[17] Protection of alcohol **19** as the acetate afforded **20**, which after TBAF deprotection, afforded the desired alcohol **21**. When **21** was subjected to the coupling conditions described in Scheme 1, compound **22** was obtained. Under the basic conditions, partial hydrolysis of **22** occurred to generate the final product **6**. After separation, treatment of **22** with K_2CO_3 in MeOH resulted in complete conversion to compound **6**, which was identical in every respect with that generated in Scheme 1.

With the absolute stereochemistry of the more active alcohol **6** established (Table 1), we prepared the primary amine analogue with the same configuration. The stereospecific synthesis of **8** was achieved as shown in Scheme 4.[20] On the basis of the stereochemistry of alcohol **19**, a double inversion strategy was used to preserve the absolute configuration of **6**. Thus, alcohol **19** was first converted to the chloride **23** with inversion of the chiral center. The second inversion was achieved by treating **23** with NaN_3 to obtain **24**. After TIPS removal, the alcohol **25** was coupled with **11**, as described in Scheme 1, to give the azide **26**. This was converted to the amine **8** by treatment with Me_3P (Scheme 4).

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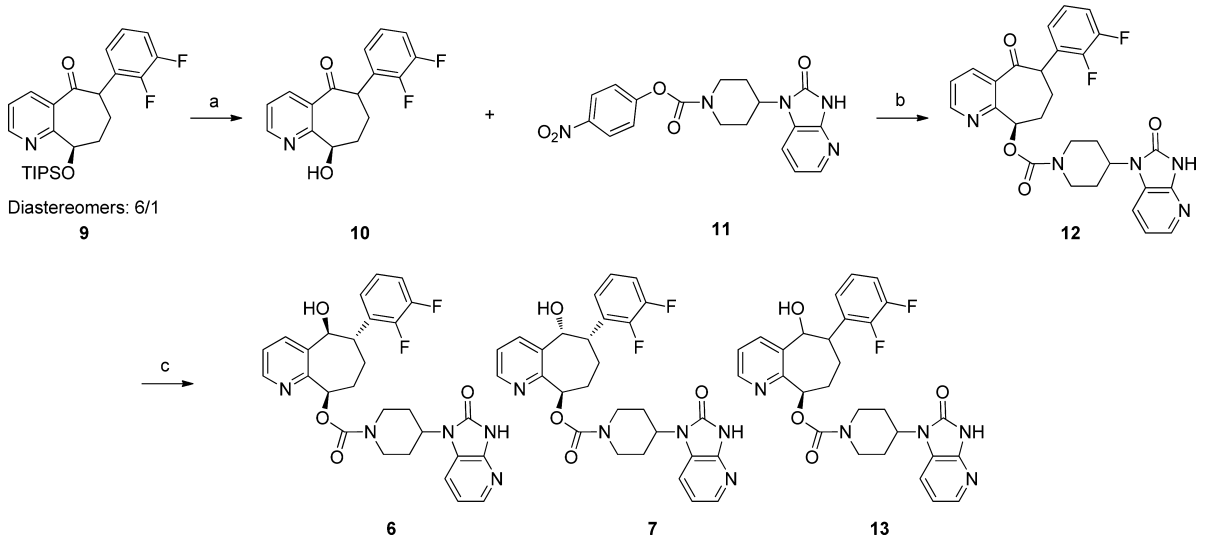
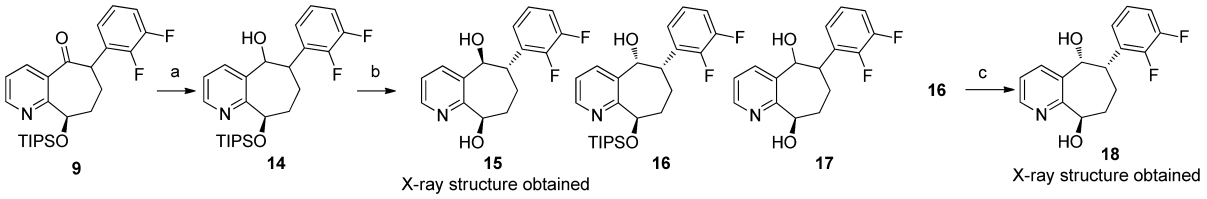
Scheme 1. Synthesis of Alcohols 6 and 7[a]



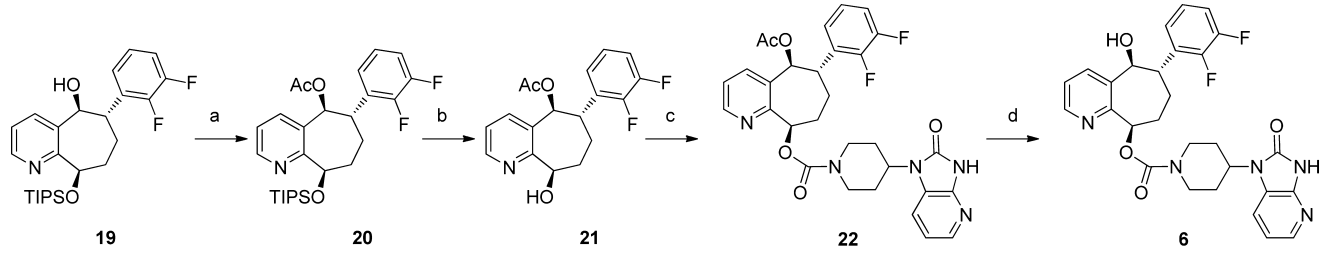
[a]Reagents and conditions: (a) THF, TBAF, −15 °C, 1 h (62%); (b) DMF, NaHMDS, −15 to −5 °C, 1.5 h (29%); (c) MeOH, $NaBH_4$, rt, 30 min, **6** (14%), **7** (12%), **13** (6%).

Scheme 2. Absolute Stereochemistry of Diols 15 and 18[a]



[a]Reagents and conditions: (a) MeOH, $NaBH_4$, rt, 1 h (96%); (b) THF, TBAF, rt, 2 h, **15** (65%), **16** (17%), **17** (12%); (c) THF, TBAF (2.5 equiv), 50 °C, 18 h, (94%).

Scheme 3. The Stereospecific Synthesis of 6[a]



[a]Reagents and conditions: (a) CH_2Cl_2, Ac_2O, Et_3N, DMAP, rt, 2 h; (b) THF, TBAF, rt, 2h (87% for 2 steps); (c) **11**, DMF, NaHMDS, −15 to 0 °C, 2 h (30% + 13% of **6**); (d) MeOH, K_2CO_3, rt, 1 h (56%).

Table 1. In Vitro Data for hCGRP Receptor Antagonists

compd	hCGRP K^i (nM)	cAMP EC_{50} (nM)	human f_u (%)	protein adjusted K_i (nM)[a]	aq soln (crystalline) (μg/mL)	HMetStab $T_{1/2}$ (min)
5[15]	0.070 (±0.021)	0.22	2.3	3.0	<2	24
6	0.081 (±0.034)		4.1	2.0	66[b]	70
7	4.3 (±0.7)					
8	0.027 (±0.009)	0.14	6.9	0.39	50	83
13	0.67 (±0.01)					
26	0.066 (±0.018)					

[a]Protein adjusted K_i was defined as K_i/human f_u. [b]Amorphous.

RESULTS AND DISCUSSION

Binding affinities for the human CGRP receptor were determined by inhibition of ^{125}I-CGRP binding to SK-N-MC cell membranes, which endogenously express receptor.[21] Alcohol **6** demonstrated potent CGRP receptor binding (K_i = 0.081 ± 0.034 nM (n = 8), Table 1), comparable to previously reported

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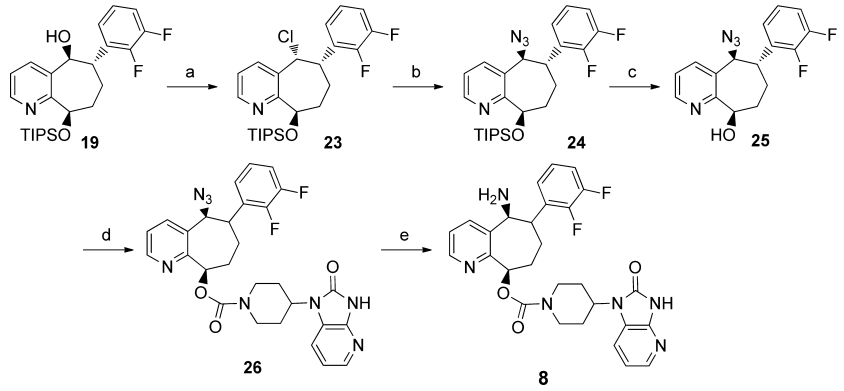
Scheme 4. The Stereospecific Synthesis of 8[a]



[a]Reagents and conditions: (a) NCS, Ph_3P, THF, rt, 5 h (83%); (b) NaN_3, DMF, 50 °C, 15 h; (c) TBAF, THF, rt, 1.5 h; (d) **11**, DMF, NaHMDS, −15 °C to rt, 4 h (73% for 3 steps); (e) PMe_3, THF, H_2O, rt, 5 h (85%).

antagonist **5**[15] (K_i = 0.070 ± 0.021 nM). In addition, the presence of the hydroxyl group in **6** improved aqueous solubility (66 μg/mL), reduced human plasma protein binding (f_u = 4.1%), and improved human microsomal stability (HLM $T_{1/2}$ = 70 min.) relative to **5**. The diastereomeric alcohols **13** and **7** (K_i = 0.67 and 4.3 nM, respectively) were successively less potent than **5** (Table 1).

The corresponding primary amine **8** demonstrated even better in vitro properties relative to **5** (Table 1). Because of its higher human plasma free fraction and more potent CGRP receptor binding, the protein-adjusted K_i for **8** was improved by 8-fold in comparison with **5**. There was also a further improvement in HLM stability ($T_{1/2}$ = 83 min). Functional receptor antagonism for **8** was determined by measuring inhibition of CGRP-stimulated cAMP production in SK-N-MC cells. Compound **8** was shown to be a full, competitive antagonist with IC_{50} = 0.14 ± 0.01 nM (n = 2). Despite the additional polarity of the primary amine, permeability of **8** in the parallel artificial membrane permeability assay (PAMPA) was excellent (190 and 320 nm/s at pH 5.5 and 7.4, respectively). The solubility of crystalline **8** was very good (50 μg/mL) and a good portent of a straightforward pharmaceutics development.

A novel noninvasive marmoset recovery model for in vivo efficacy assessment of CGRP receptor antagonists was developed in our laboratories, which utilizes laser Doppler facial blood flow as a surrogate for intracranial artery diameter.[15,21] Briefly, marmosets were anesthetized and facial blood flow was increased by four intravenous (IV) administrations of hαCGRP (10 μg/kg) delivered at 45 min intervals (−30, 15, 60, and 105 min). The effect of antagonist, delivered subcutaneously (SC) at 0 min, on the hαCGRP-induced changes in facial blood flow was measured by laser Doppler flowmetry. In this model, compound **8** inhibited hαCGRP-induced increases in marmoset facial blood flow upon subcutaneous (SC) dosing.[22] Compared to predose hCGRP control (−30 min), strong (>50%) inhibition of CGRP-induced effects on facial blood flow were observed with **8** dosed sc at 7 mg/kg at 15, 60, and 105 min postdose (Figure 2). Comparing activity versus exposure 15 min postdose, plasma levels of approximately 400 nM were associated with strong in vivo efficacy (>65% inhibition). In comparison, plasma levels of **5** above 1000 nM were needed for similar efficacy in this model.[15,21] Peak inhibition for **8** was very strong at 75−80% at 60 and 105 min postdose, with corresponding plasma levels just below 800 nM (Figure 3).[22]

Compound **8** exhibited good oral bioavailability in the rat (F_{PO} = 45%) and cynomolgus monkey (F_{PO} = 67% as a solution).

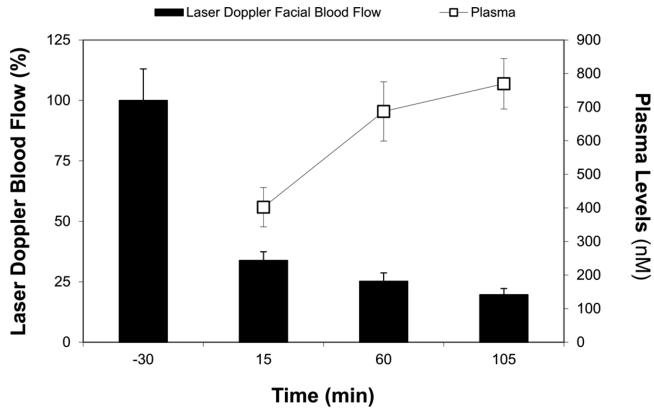


Figure 3. Marmoset facial blood flow at 7 mg/kg, SC: 30 min represents the increased facial blood flow caused for hCGRP (10 μg/kg IV); 7 mg/kg **8** (SC) delivered at time = 0 min. At 15, 60, and 105 min, hCGRP challenge (10 μg/kg IV) was administered and reduction of facial blood flow and plasma levels of **8** were measured.

When dosed as a free base suspension of crystalline material, the oral bioavailability of **8** in the monkey remained good at 48%.

Against a panel of eight recombinant hCYP isoforms, **8** showed low levels of inhibition: $IC_{50} \geq 20$ μM for all except CYP3A4 (IC_{50} = 17 μM). In addition, **8** showed no significant potential for off-target liabilities in a panel of 45 receptor and ion channel binding and enzyme activity assays. No cardiovascular liability was identified in vitro. At 10 and 30 μM, **8** caused less than 30% inhibition of the hERG potassium channel alpha subunit expressed in HEK-293 cells, and no significant effect was seen on L-type sodium or calcium channels expressed in these cells. The compound was not mutagenic in an exploratory Ames study.

On the basis of favorable prenomination and pre-IND toxicological studies, **8** was chosen for clinical development. Initial phase I human PK results have been in good agreement with preclinical human PK projections, giving exposures at a 75 mg dose that are expected to prove efficacious. No significant adverse effects were encountered up to 600 mg. Compound **8** is presently in phase II studies, and the results of those studies will be reported in due course.

CONCLUSION

Compound **8** is a highly potent CGRP receptor antagonist, with very good metabolic stability, acceptable CYP inhibition profile,

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good animal PK, and a favorable predictive toxicological profile. The presence of a primary amino group greatly improved aqueous solubility without compromising bilayer permeability, resulting in enhanced ADME properties. More detailed pharmacological and clinical results for **8** will be reported in due course.

EXPERIMENTAL SECTION

General Procedures. All commercially available reagents and solvents were used without further purification unless otherwise stated. All reactions were carried out under an inert atmosphere of dry nitrogen in oven- or flame-dried glassware unless otherwise stated. Flash column chromatography was performed using 40−60 μm Silica Gel 60 (EMD Chemicals, Inc.) as the stationary phase or prepacked columns from ISCO Inco., Biotage, or Thomson Instrument Co. ^{1}H NMR spectra were recorded on a Bruker 400 or 500 MHz machine with tetramethylsilane or residual protiated solvent used as a reference. ^{13}C NMR were recorded on a Bruker DRX-500 instrument operating at 125 MHz with residual ^{12}C solvent used as a reference. Low resolution mass spectra were recorded using a Waters Micromass ZQ with electrospray ionization. High resolution mass spectra were recorded using a Waters Micromass LCT time-of-flight mass spectrometer with electrospray ionization. The purity of all compounds was determined by either liquid chromatography−mass spectrometry (LCMS) or analytical HPLC and was confirmed to be greater than 95% purity.

(5*S*,6*S*,9*R*)-6-(2,3-Difluorophenyl)-5-hydroxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl 4-(2-Oxo-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-1-yl)piperidine-1-carboxylate (6), (5*R*,6*S*,9*R*)-6-(2,3-Difluorophenyl)-5-hydroxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]-pyridin-9-yl 4-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-piperidine-1-carboxylate (7), and (5*S*,6*R*,9*R*)-6-(2,3-Difluorophenyl)-5-hydroxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl 4-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxylate (13). In a 100 mL round-bottom flask was dissolved **12** (44.4 mg, 0.083 mmol) in MeOH (1 mL) to give a colorless solution. $NaBH_4$ (6.30 mg, 0.166 mmol) was added, and the mixture was stirred at rt for 30 min. LCMS indicated complete conversion, showing three peaks, all with the desired MW (M + H = 536). The mixture was concentrated and directly purified by prep-HPLC (0.1% TFA−MeOH−water system) to afford three components. They were individually purified by flash column chromatography using 0−10% MeOH/CH_2Cl_2 to afford the products **6** (6.7 mg, 14%), **7** (5.5 mg, 12%), and **13** (3.0 mg, 6%) as white solids. The relative stereochemistry was not strictly assigned at this stage. Product **6**: ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 10.21 (br s, 1 H), 8.52 (d, *J* = 3.53 Hz, 1 H), 7.97−8.16 (m, 2 H), 7.47 (br s, 1 H), 7.27−7.37 (m, 1 H), 6.90−7.22 (m, 4 H), 5.97 (d, *J* = 10.32 Hz, 1 H), 5.32 (d, *J* = 10.4 Hz, 1 H), 4.26−4.74 (m, 3 H), 2.55−3.29 (m, 3 H), 2.18−2.49 (m, 4 H), 2.07−2.17 (m, 1 H), 1.59−2.02 (m, 4 H); ^{19}F NMR (376 MHz, chloroform-*d*) δ ppm −137.26 to −136.84 (m, 1 F), −142.46 to −142.13 (m, 1 F). Product **7**: ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 10.04 (br s, 1 H), 8.60 (dd, *J* = 4.78, 1.26 Hz, 1 H), 8.05 (br s, 1 H), 7.66 (d, *J* = 6.55 Hz, 1 H), 7.31 (dd, *J* = 7.43, 4.91 Hz, 3 H), 7.03−7.17 (m, 2 H), 6.91−7.03 (m, 1 H), 6.25 (d, *J* = 5.79 Hz, 1 H), 4.80 (d, *J* = 8.56 Hz, 1 H), 4.18−4.66 (m, 3 H), 3.38−3.58 (m, 2 H), 3.02 (d, *J* = 6.29 Hz, 2 H), 2.68 (d, *J* = 13.60 Hz, 2 H), 2.05−2.45 (m, 3 H), 1.93 (br s, 3 H); ^{19}F NMR (376 MHz, chloroform-*d*) δ ppm −138.28 (m, 1 F), 143.94 (m, 1 F). Product **13**: ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 9.47 (br s, 1 H), 8.50 (dd, *J* = 4.78, 1.26 Hz, 1 H), 8.03 (dd, *J* = 5.16, 1.13 Hz, 1 H), 7.35−7.55 (m, 3 H), 7.04−7.15 (m, 3 H), 7.00 (dd, *J* = 7.55, 5.29 Hz, 1 H), 6.58 (br s, 1 H) 4.85 (s, 1 H), 4.61 (br s, 3 H), 3.36 (br s, 1 H), 2.55−3.15 (m, 3 H), 2.35 (br s, 1 H), 1.83−2.04 (m, 3 H), 1.57−1.80 (m, 4 H); ^{19}F NMR (376 MHz, chloroform-*d*) δ ppm −138.49 (br s, 1 F), −144.30 (m, 1 F).

(5*S*,6*S*,9*R*)-6-(2,3-Difluorophenyl)-5-hydroxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl 4-(2-oxo-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-1-yl)piperidine-1-carboxylate (6). In a 250 mL round-bottom flask was dissolved **22** (51 mg, 0.088 mmol) (acetate-protected product from above) in MeOH (1 mL) to give a colorless solution. K_2CO_3 (122 mg, 0.883 mmol) was added, and the mixture was stirred at rt for 1 h. LCMS indicated complete conversion. MeOH was removed in vacuo. The residue was partitioned between water and EtOAc. The phases were separated. The organic layer was washed with brine, dried, and concentrated to a white solid. Purification by flash column chromatography using 0−10% MeOH/CH_2Cl_2 afforded the desired product (28 mg, 56%) as a light-yellow solid. ^{1}H and ^{19}F NMRs were obtained and matched that of the previous product **6**.

(5*S*,6*S*,9*R*)-5-Amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl 4-(2-Oxo-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-1-yl)piperidine-1-carboxylate (8). In a 100 mL round-bottom flask was dissolved **26** (620 mg, 1.106 mmol) in THF (5 mL) to give a colorless solution. Trimethylphosphine (3.32 mL, 3.32 mmol, 1.0 M in toluene) was added. The mixture was stirred at rt. After 2 h, LCMS indicated complete conversion. Water (0.080 mL, 4.42 mmol) was added, and the mixture was stirred for another 3 h. LCMS showed complete conversion to the desired product. Volatile components were removed in vacuo, and the residue was directly purified by flash column chromatography using 0−10% MeOH in CH_2Cl_2 to afford the product (510 mg, 85%) as a white solid, which was recrystallized from EtOH: MS (ESI) [M + H$^+$] = 535.23. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 10.39 (br s, 1 H), 8.52 (d, *J* = 3.78 Hz, 1 H), 8.09 (d, *J* = 5.04 Hz, 2 H), 7.46 (br s, 1 H), 7.26−7.38 (m, 1 H), 7.06−7.20 (m, 3 H), 6.94−7.05 (m, 1 H), 6.06−6.23 (m, 1 H), 4.31−4.78 (m, 4 H), 4.05 (spt, *J* = 6.13 Hz, 1 H), 2.57−3.25 (m, 3 H), 2.17−2.38 (m, 3 H), 1.42−2.04 (m, 6 H); ^{19}F NMR (376 MHz, chloroform-*d*) δ ppm −136.90 (br s, 1 F), −142.48 to −142.21 (m, 1 F); $[\alpha]_D^{23}$ = −86.36° (*c* = 5.71 mg/mL, methanol). Elemental Analysis: Calcd for $C_{28}H_{28}N_6$·0.01EtOH: C 62.90, H 5.29, N 15.70. Observed: C 63.03, H 5.26, N 15.62.

(9*R*)-6-(2,3-Difluorophenyl)-9-hydroxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-5-one (10). In a 250 mL round-bottom flask was dissolved **9** (0.218 g, 0.49 mmol) in THF (5 mL) to give a colorless solution. After cooling to −15 °C (ice/MeOH bath) under nitrogen, TBAF (0.490 mL, 0.490 mmol) was added, and the resulting bright-yellow solution was stirred at −15 °C for 1 h. The reaction was quenched with $NaHCO_3$ solution and diluted with EtOAc. The phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried, and concentrated to give a tan oil. Purification by flash column chromatography using EtOAc/hexane afforded a mixture of two diastereomers (87 mg, 62%). Major component: ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.53 (dd, *J* = 4.91, 1.64 Hz, 1 H), 7.85 (dd, *J* = 7.68, 1.64 Hz, 1 H), 7.34 (dd, *J* = 7.68, 4.91 Hz, 1 H), 7.00−7.16 (m, 3 H), 5.32 (s, 1 H), 4.94−5.04 (m, 1 H), 4.48 (dd, *J* = 11.83, 3.02 Hz, 1 H), 2.14−2.48 (m, 4 H); ^{19}F NMR (376 MHz, chloroform-*d*) δ ppm −138.24 to −138.07 (m, 1 F), −140.70 to −140.50 (m, 1 F).

(9*R*)-6-(2,3-Difluorophenyl)-5-oxo-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl 4-(2-Oxo-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-1-yl)piperidine-1-carboxylate (12). In an oven-dried 100 mL round-bottom flask was added **10** (112 mg, 0.389 mmol) (azeotroped with dry benzene) and **11**[17] (224 mg, 0.583 mmol) in DMF (3 mL) to give a light-yellow suspension under nitrogen. After cooling to −15 °C (ice/MeOH bath), NaHMDS (1.55 mL, 1.55 mmol, 1.0 M in THF) was added dropwise. The resulting yellow solution was stirred under nitrogen at −15 °C for 1 h. After gradually warming to −5 °C over 30 min, the reaction was quenched with $NaHCO_3$ solution and diluted with EtOAc. The phases were separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated to give a yellow oil. Purification by flash column chromatography using 0−10% MeOH/CH_2Cl_2 afforded the product (60 mg, 29%) as a white solid. Major component: ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 11.35 (br s, 1 H), 8.76 (br s, 1 H), 8.00−8.17 (m, 1 H), 7.88−8.00 (m, 1 H), 7.29−7.55 (m, 2 H), 6.82−7.19 (m, 4 H), 6.20 (br s, 1 H), 4.58 (br s, 1 H), 4.24−4.51 (m, 2 H), 4.12 (q, *J* = 7.22 Hz, 1 H), 2.75−3.17 (m, 2 H), 2.02−2.68 (m, 6 H), 1.89 (br s, 2 H).

(9*R*)-6-(2,3-Difluorophenyl)-9-(triisopropylsilyloxy)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-5-ol (14). In a 100 mL round-bottom flask was dissolved ketone **9** (510 mg, 1.144 mmol) (mainly trans with a trans/cis ratio of ~6/1) in MeOH (5 mL) to give a colorless solution. $NaBH_4$ (87 mg, 2.289 mmol) was added, and the mixture was stirred at rt for 1 h. LCMS indicated complete conversion. MeOH was

removed in vacuo, and the residue was partitioned between water and EtOAc. The phases were separated. The organic layer was washed with brine, dried, and concentrated to **14** (492 mg, 96%) as a light-yellow oil. The crude product was carried onto the next reaction without further purification and characterization.

(5*S*,6*S*,9*R*)-6-(2,3-Difluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-5,9-diol (15), (5*R*,6*S*,9*R*)-6-(2,3-Difluorophenyl)-9-((triisopropylsilyl)oxy)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-5-ol (16), and (5*S*,6*R*,9*R*)-6-(2,3-Difluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-5,9-diol (17). In a 100 mL round-bottom flask was dissolved **14** (224.3 mg, 0.501 mmol) in THF (4 mL) to give a colorless solution. TBAF (0.752 mL, 0.752 mmol) was added, and the mixture was stirred at rt for 2 h. LCMS indicated complete conversion of the major component while the minor one did not change. THF was removed in vacuo, and the residue was partitioned between water and EtOAc. The phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated to give a tan oil. Flash column chromotagraphy using 0−50% EtOAc/hexane afforded intermediate **16** unchanged (38 mg, 17%) as a white crystalline solid and intermediate **15** (95 mg, 65%) as a colorless oil that solidified upon standing. Further elution up to 100% EtOAc afforded **17** (17.3 mg, 12%) as a colorless oil. Intermediate **15** was further crystallized, and single crystals were obtained. Its relative stereochemistry was proven by X-ray studies. **15**: MS (ESI) $[M + H^+]$ = 292.26; ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.45 (dd, *J* = 4.78, 1.26 Hz, 1 H), 8.10 (d, *J* = 7.81 Hz, 1 H), 7.24−7.36 (m, 1 H), 6.97−7.18 (m, 3 H), 5.77−6.44 (m, 1 H), 5.08 (d, *J* = 10.07 Hz, 1 H), 4.70−4.84 (m, 1 H), 2.93−3.08 (m, 1 H), 2.55 (br s, 1 H), 2.17−2.38 (m, 2 H), 2.04−2.13 (m, 1 H), 1.39−1.58 (m, 1 H); ^{19}F NMR (376 MHz, chloroform-*d*) δ ppm −137.35 to −136.88 (m, 1 F), −142.50 to −142.13 (m, 1 F); ^{13}C NMR (101 MHz, chloroform-*d*) δ ppm 157.58 (s, 1 C), 150.05−152.35 (dd, J = 12.5 and 199 Hz, 1 C), 147.63−149.87 (dd, J = 13.0 and 197 Hz, 1 C), 145.43 (s, 1 C), 136.62 (s, 1 C), 133.15 (s, 1 C), 132.69 (d, *J* = 11.56 Hz, 1 C), 124.36−124.79 (m, 1 C), 123.71 (br s, 1 C), 122.74 (s, 1 C), 115.75 (d, *J* = 16.96 Hz, 1 C), 71.37 (s, 1 C), 71.12 (s, 1 C), 46.21 (br s, 1 C), 35.70 (s, 1 C), 32.83 (s, 1 C). **16**: MS (ESI) $[M + H^+]$ = 448.43; ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.34−8.48 (m, 1 H), 7.62 (d, *J* = 7.55 Hz, 1 H), 7.15 (dd, *J* = 7.81, 4.78 Hz, 1 H), 6.89−7.05 (m, 1 H), 6.67−6.82 (m, 1 H), 6.24 (br s, 1 H), 5.81 (br s, 1 H), 5.38 (d, *J* = 4.78 Hz, 1 H), 3.93 (br s, 1 H), 2.59 (br s, 1 H), 2.31 (d, *J* = 4.53 Hz, 1 H), 2.13−2.25 (m, 1 H), 2.01−2.12 (m, *J* = 14.20, 7.07, 7.07, 3.65 Hz, 1 H), 1.85−2.01 (m, 1 H), 1.10−1.23 (m, 3 H), 1.02−1.08 (m, 9 H), 0.93−1.00 (m, 9 H). **17**: ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.11 (dd, *J* = 5.04, 1.51 Hz, 1 H), 7.55 (dd, *J* = 7.55, 1.51 Hz, 1 H), 7.43−7.51 (m, 1 H), 7.28 (s, 1 H), 6.99−7.16 (m, 3 H), 5.92 (br s, 1 H), 5.12 (d, *J* = 6.04 Hz, 1 H), 4.63 (br s, 1 H), 3.40 (d, *J* = 12.09 Hz, 1 H), 2.76−2.98 (m, 1 H), 2.33−2.54 (m, 1 H), 1.90−2.03 (m, 1 H), 1.76−1.90 (m, 1 H); ^{19}F NMR (376 MHz, chloroform-*d*) δ ppm −138.96 to −138.49 (m, 1 F), −145.03 to −144.50 (m, 1 F).

((5*R*,6*S*,9*R*)-6-(2,3-Difluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-5,9-diol (18). In a 100 mL round-bottom flask was dissolved **16** in THF (2 mL) to give a colorless solution. TBAF (0.407 mL, 0.407 mmol) was added, and the mixture was heated at 50 °C for 18h. LCMS showed complete conversion. The mixture was diluted with EtOAc and water. The phases 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 give a tan oil. Flash column chromotagraphy using 0−50% EtOAc/hexane afforded the desired product (56 mg, 94%) as a white crystalline solid. Intermediate **18** was further crystallized, and single crystals were obtained. Its relative stereochemistry was proven by X-ray studies. MS (ESI) $[M + H^+]$ = 292.26; ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.37 (dd, *J* = 5.04, 1.51 Hz, 1 H), 7.52 (dd, *J* = 7.55, 1.51 Hz, 1 H), 7.37−7.49 (m, 1 H), 7.19 (dd, *J* = 7.30, 5.04 Hz, 1 H), 7.00−7.15 (m, 2 H), 5.96 (br s, 1 H), 5.23 (dd, *J* = 11.58, 2.27 Hz, 1 H), 4.78 (s, 1 H), 3.22−3.32 (m, 1 H), 3.10 (br s, 1 H), 2.74−2.89 (m, 1 H), 2.29 (dddd, *J* = 13.60, 5.16, 2.77, 2.64 Hz, 1 H), 1.77−1.91 (m, 1 H), 1.47−1.67 (m, 1 H); ^{19}F NMR (376 MHz, chloroform-*d*) δ ppm −138.73 to −138.11 (m, 1 F), −144.45 to −144.03 (m, 1 F); ^{13}C NMR (101 MHz, chloroform-*d*) δ ppm 160.75 (s, 1 C), 149.14−151.82 (dd, J = 14.0 and 246 Hz, 1 C), 146.49−149.15 (dd, J = 12.0 and 244 Hz, 1 C), 146.14 (s, 1 C), 136.75 (s, 1 C), 135.45 (s, 1 C), 134.93 (d, *J* = 10.79 Hz, 1 C), 123.79−124.30 (m, 1 C), 123.38 (s, 1 C), 122.20 (s, 1 C), 115.24 (d, *J* = 16.96 Hz, 1 C), 77.94 (s, 1 C), 70.62 (s, 1 C), 40.42 (s, 1 C), 36.62 (s, 1 C), 26.81 (s, 1 C).

(5*S*,6*S*,9*R*)-6-(2,3-Difluorophenyl)-9-(triisopropylsilyloxy)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-5-yl acetate (20). In a 250 mL round-bottom flask was dissolved **19** (1.0 g, 2.243 mmol) in CH_2Cl_2 (20 mL) to give a colorless solution. Acetic anhydride (0.423 mL, 4.49 mmol) and triethylamine (0.938 mL, 6.73 mmol) were added, followed by DMAP (0.055 g, 0.449 mmol). The mixture was stirred at rt under nitrogen. After 2 h, LCMS showed complete conversion. The mixture was quenched with $NaHCO_3$ solution and diluted with EtOAc. The phases were separated. The organic layer was washed with brine, dried, and concentrated to give a colorless oil (100%), which was immediately carried onto the next reaction without further purification and characterization. MS ESI) $[M + H^+]$ = 490.26.

(5*S*,6*S*,9*R*)-6-(2,3-Difluorophenyl)-9-hydroxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-5-yl Acetate (21). In a 100 mL round-bottom flask was dissolved **20** (1.1 g, 2.243 mmol) (azeotroped with dry benzene) in THF (20 mL) to give a colorless solution. TBAF (2.69 mL, 2.69 mmol) was added, and the resulting light-yellow solution was stirred at rt for 2 h. LCMS indicated complete conversion. THF was removed in vacuo, and the residue was diluted with water and EtOAc. The phases were separated. The organic layer was washed with brine, dried, and concentrated to give a colorless oil. Purification by flash column chromotagraphy using 0−70% EtOAc/hexane afforded the desired product (648 mg, 87% for 2 steps) as a colorless oil. MS (ESI) $[M + H^+]$ = 334.21; ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.47 (dd, *J* = 4.78, 1.51 Hz, 1 H), 7.69 (d, *J* = 7.30 Hz, 1 H), 7.28 (dd, *J* = 7.81, 5.04 Hz, 1 H), 6.94−7.10 (m, 3 H), 6.20 (d, *J* = 10.32 Hz, 1 H), 5.95 (br s, 1 H), 4.95 (dd, *J* = 11.21, 1.64 Hz, 1 H), 3.16−3.31 (m, 1 H), 2.27−2.41 (m, 2 H), 2.06−2.19 (m, 1 H), 1.80 (s, 3 H), 1.48−1.63 (m, 1 H); ^{13}C NMR (101 MHz, chloroform-*d*) δ ppm 168.96 (s, 1 C), 157.96 (s, 1 C), 149.66−151.75 (d, J = 12.6 and 199 Hz, 1 C), 147.21−149.29 (d, J = 13 and 198 Hz, 1 C), 146.00 (s, 1 C), 133.43 (s, 1 C), 132.23 (d, *J* = 11.56 Hz, 1 C), 131.99 (s, 1 C), 123.90−124.24 (m, 1 C), 122.89 (br s, 1 C), 122.66 (s, 1 C), 115.36 (d, *J* = 16.95 Hz, 1 C), 72.77 (s, 1 C), 71.14 (s, 1 C), 42.12 (br s, 1 C), 35.66 (s, 1 C), 32.68 (s, 1 C), 20.28 (s, 1 C); ^{19}F NMR (376 MHz, chloroform-*d*) δ ppm −138.20 to −137.93 (m, 1 F), −143.38 to −143.16 (m, 1 F).

(5*S*,6*S*,9*R*)-5-Acetoxy-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl 4-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxylate (22). In an oven-dried 100 mL round-bottom flask was added **21** (96.7 mg, 0.290 mmol) (azeotroped with dry benzene) and 4-nitrophenyl 4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxylate (167 mg, 0.435 mmol) in DMF (3 mL) to give a light-yellow suspension under nitrogen. After cooling to −15 °C (ice/MeOH bath), NaHMDS (0.870 mL, 0.870 mmol) was added dropwise. The resulting dark-red solution was stirred under nitrogen at −15 to 0 °C for 1 h. LCMS showed the desired product along with possible hydrolyzed product. After another 1 h at rt, complete hydrolysis was not achieved. The reaction was quenched with $NaHCO_3$ solution and volatile components removed in vacuo. The mixture was diluted with EtOAc. The phases were separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated to give a yellow oil. Purification by flash column chromotagraphy using 0−10% MeOH/CH_2Cl_2 afforded the acetate-protected product (51 mg, 30%) as well as the final product alcohol **6** (20 mg, 13%).

(5*R*,6*S*,9*R*)-5-Chloro-6-(2,3-difluorophenyl)-9-(triisopropylsilyloxy)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (23). In an oven-dried 250 mL round-bottom flask was added *N*-chlorosuccinimide (0.751 g, 5.62 mmol) in THF (15 mL) to give a colorless suspension. Ph_3P (1.475 g, 5.62 mmol) was added. After stirring under nitrogen for 5 min, **19** (1.0 g, 2.250 mmol) was added in one portion to the gray suspension. The resulting reddish suspension was stirred at rt. The solids gradually dissolved to give a tan solution. After 5 h, LCMS indicated complete conversion. THF was removed in vacuo. The remaining red oil

was directly purified by flash column chromatography (240 g silica column) using 10−100% EtOAc/hexane and then using 10% MeOH (with 2.0 M NH_4OH) in CH_2Cl_2. The product fractions were combined and repurified by flash column chromatography using 0−50% EtOAc/hexane to afford the desired product as a colorless oil (869 mg, 83%). MS (ESI) $[M + H^+]$ = 466.22; ^1H NMR (400 MHz, chloroform-*d*) δ ppm 8.55 (d, *J* = 3.53 Hz, 1 H), 7.63 (br s, 1 H), 7.20 (dd, *J* = 7.68, 4.91 Hz, 1 H), 7.01−7.15 (m, 1 H), 6.90−7.01 (m, 1 H), 6.66−6.90 (m, 1 H), 5.55−5.85 (m, 1 H), 5.40−5.56 (m, 1 H), 3.96−4.33 (m, 1 H), 2.33 (br s, 3 H), 2.09−2.20 (m, 1 H), 1.14−1.23 (m, 3 H), 1.04−1.14 (m, 9 H), 1.01 (d, *J* = 7.30 Hz, 9 H).

(5*S*,6*S*,9*R*)-5-Azido-6-(2,3-difluorophenyl)-9-(triisopropylsilyloxy)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (24). In a 100 mL round-bottom flask was dissolved **23** (566 mg, 1.214 mmol) in DMF (5 mL) to give a colorless solution. Sodium azide (474 mg, 7.29 mmol) was added, and the mixture was stirred at rt under nitrogen for 2.5 h. LCMS indicated only very little reaction. The mixture was heated at 50 °C overnight. After 15 h, LCMS indicated complete conversion with some elimination product. The mixture was diluted with water and EtOAc. The phases were separated. The organic layer was washed with brine, dried, and concentrated to a colorless oil. The crude product was carried onto the next reaction without further purification and characterization. Smaller scale purification afforded an analytical sample: MS (ESI) $[M + H^+]$ = 473.27; ^1H NMR (400 MHz, chloroform-*d*) δ ppm 8.52−8.63 (m, 1 H), 7.75 (d, *J* = 7.81 Hz, 1 H), 7.23−7.36 (m, 1 H), 6.95−7.17 (m, 2 H), 6.89 (br s, 1 H), 5.28 (d, *J* = 4.03 Hz, 1 H), 4.90 (d, *J* = 9.07 Hz, 1 H), 3.79 (t, *J* = 9.44 Hz, 1 H), 1.86−2.23 (m, 4 H), 1.16−1.30 (m, 3 H), 0.98−1.15 (m, 18 H); ^{19}F NMR (376 MHz, chloroform-*d*) δ ppm −137.68 to −137.36 (m, 1 F), −141.78 to −141.54 (m, 1 F).

(5*S*,6*S*,9*R*)-5-Azido-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-ol (25). In a 100 mL round-bottom flask was dissolved **24** (0.732 g, 1.549 mmol) (crude) in THF (8 mL) to give a colorless solution. TBAF (1.859 mL, 1.859 mmol) was added, and the resulting light-yellow solution was stirred at rt for 1.5 h. LCMS indicated complete conversion. THF was removed in vacuo, and the residue was diluted with water and EtOAc. The phases were separated. The organic layer was washed with brine, dried, and concentrated to a light-yellow oil. Purification by flash column chromatography using 0−60% EtOAc/hexane afforded the desired product (crude weight 480 mg) as a colorless oil. Smaller scale purification afforded an analytical sample: MS (ESI) $[M + H^+]$ = 317.22; ^1H NMR (400 MHz, chloroform-*d*) δ ppm 8.51 (dd, *J* = 4.91, 1.38 Hz, 1 H), 7.99 (d, *J* = 7.30 Hz, 1 H), 7.35 (dd, *J* = 7.81, 5.04 Hz, 1 H), 7.06−7.20 (m, 2 H), 6.94−7.05 (m, 1 H), 5.91 (br s, 1 H), 5.03 (d, *J* = 10.32 Hz, 1 H), 4.92 (dd, *J* = 11.21, 2.39 Hz, 1 H), 2.84−3.02 (m, 1 H), 2.37−2.49 (m, 1 H), 2.25−2.36 (m, 1 H), 2.07−2.17 (m, *J* = 14.38, 4.94, 3.05, 3.05 Hz, 1 H), 1.40−1.64 (m, 1 H); ^{13}C NMR (101 MHz, chloroform-*d*) δ ppm 158.48 (s, 1 C), 152.19−149.87 (dd, *J* = 13.10 and 221 Hz, 1 C), 149.72−147.42 (dd, *J* = 13.87 and 219 Hz, 1 C), 146.16 (s, 1 C), 133.67 (s, 1 C), 133.23 (s, 1 C), 132.66 (d, *J* = 10.79 Hz, 1 C), 124.43 (dd, *J* = 6.94, 3.85 Hz, 1 C), 123.84 (br s, 1 C), 122.89 (s, 1 C), 115.98 (d, *J* = 17.73 Hz, 1 C), 70.94 (s, 1 C), 65.67 (s, 1 C), 45.43 (br s, 1 C), 35.71 (s, 1 C), 33.45 (s, 1 C); ^{19}F NMR (376 MHz, chloroform-*d*) δ ppm −137.55 to −137.20 (m, 1 F), −142.28 to −141.89 (m, 1 F).

(5*S*,6*S*,9*R*)-5-Azido-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl 4-(2-Oxo-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-1-yl)piperidine-1-carboxylate (26). In a 100 mL round-bottom flask was added **25** (0.490 g, 1.549 mmol) (azeotroped with dry benzene) and 4-nitrophenyl 4-(2-oxo-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-1-yl)piperidine-1-carboxylate (0.713 g, 1.859 mmol) in DMF (8 mL) to give a light-yellow suspension under nitrogen. After cooling to −15 °C (ice/MeOH bath), NaHMDS (4.18 mL, 4.18 mmol) was added dropwise. The resulting tan solution was stirred under nitrogen at −10 to 0 °C for 2 h and at rt for 2 h. LCMS showed complete conversion. The reaction was quenched with $NaHCO_3$ solution. The mixture was diluted with EtOAc. The phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water, brine, dried with Na_2SO_4, and concentrated to give a tan oil. Purification by flash column chromatography using 0−8% MeOH/CH_2Cl_2 afforded the desired product (632 mg, 73% for 3 steps) as a light-yellow foam. MS (ESI) $[M + H^+]$ = 561.27; ^1H NMR (400 MHz, chloroform-*d*) δ ppm 11.50 (br s, 1 H), 8.58 (d, *J* = 3.78 Hz, 1 H), 8.11 (d, *J* = 5.04 Hz, 1 H), 7.91 (d, *J* = 7.30 Hz, 1 H), 7.33 (br s, 2 H), 7.07−7.19 (m, 2 H), 6.92−7.06 (m, 2 H), 6.10 (d, *J* = 9.32 Hz, 1 H), 5.23 (d, *J* = 10.07 Hz, 1 H), 4.26−4.84 (m, 3 H), 2.46−3.34 (m, 4 H), 2.20−2.43 (m, 3 H), 2.01−2.13 (m, 1 H), 1.94 (d, *J* = 12.34 Hz, 3 H); ^{19}F NMR (376 MHz, chloroform-*d*) δ ppm −137.30 to −137.01 (m, 1 F), −142.32 to −142.03 (m, 1 F).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray structures of intermediates **15** and **18** and biology experimental. 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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■ ABBREVIATIONS USED

CGRP, calcitonin gene-related peptide; CLP, calcitonin receptor-like receptor; RAMP1, receptor activity modifying protein 1; RCP, receptor component protein; TBAF, tetrabutylammonium fluoride; PAMPA, parallel artificial membrane permeability assay; IV, intravenous; F_{po}, oral bioavailability; SC, subcutaneous

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(19) See Supporting Information for details.

(20) The relative stereochemistry of **17** and **13** were not rigorously established. The absolute stereochemistry of **8** was established through extensive X-ray analysis of **8** and intermediate **23** : QiG. Unpublished results.

(21) Compound **8** had marmoset CGRP receptor K_i of 0.0921 ± 1.5 nM (n = 2). For the description of all biologic assays, see also: Degnan, A. P.; Chaturvedula, P. V.; Conway, C. M.; Cook, D.; Davis, C. D.; Denton, R.; Han, X.; Macci, R.; Mathias, N. R.; Moench, P.; Pin, S. S.; Ren, S. X.; Schartman, R.; Signor, L.; Thalody, G.; Widmann, K. A.; Xu, C.; Macor, J. E.; Dubowchik, G. M. Discovery of (*R*)-4-(8-Fluoro-2-oxo-1,2-dihydroquinazolin-3(4*H*)-yl)-*N*-(3-(7-methyl-1*H*-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)-propan-2-yl)piperidine-1-carboxamide (BMS-694153): A Potent Antagonist of the Human Calcitonin Gene-Related Peptide Receptor for Migraine with Rapid and Efficient Intranasal Exposure. *J. Med. Chem.* **2008**, *51*, 4858−4861.

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