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Practical asymmetric synthesis of a CGRP receptor antagonist ubrogepant

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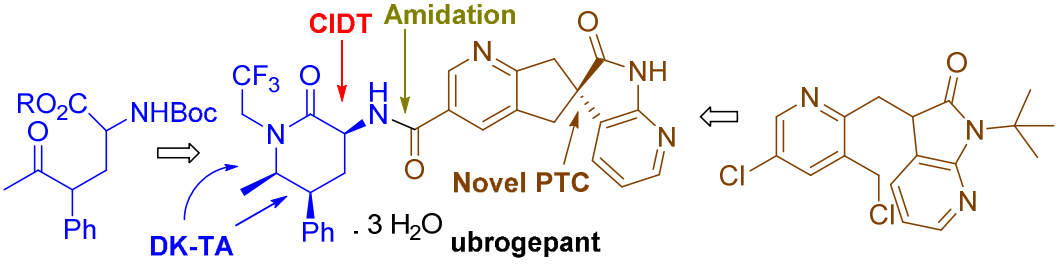


ABSTRACT: The development of a scalable asymmetric route to a new calcitonin gene-related peptide (CGRP) receptor antagonist is described. The synthesis of the two key fragments was redefined, and the intermediates accessed through novel chemistry. Chiral lactam **2** was prepared by an enzyme mediated dynamic kinetic transamination which simultaneously set two stereocenters. Enzyme evolution resulted in an optimized transaminase providing the desired configuration in >60:1 *syn:anti*. The final chiral center was set *via* a crystallization induced diastereomeric transformation. The asymmetric spirocyclization to form the second fragment, chiral spiro acid intermediate **3**, was catalyzed by a novel doubly quaternized phase transfer catalyst and provided optically pure material on isolation. With the two fragments in hand, development of their final union by amide bond formation and subsequent direct isolation is described. The described chemistry has been used to deliver over 100 kg of our desired target, ubrogepant.

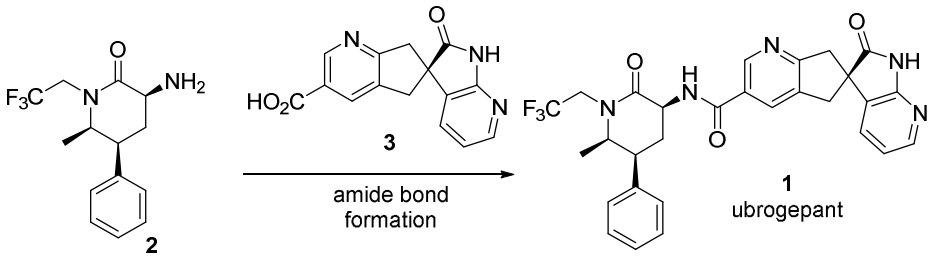
Key words: dynamic kinetic transamination; phase transfer catalyst; crystallization induced diastereomeric transformation; CGRP receptor antagonist

Introduction

Migraine is a chronic neurovascular disorder, characterized by attacks of moderate to severe headache.[1] A recent survey indicated that greater than 10% of the world-wide population suffer from bouts of migraine.[2] The current standard treatments are 5-$HT_{1B/1D}$ agonists commonly known as triptans. Unfortunately, the inherent vasoconstrictive activity of triptans makes them unsuitable for use in patients with pre-existing cardiovascular disease.[3] Therefore, there is a need for alternative therapies for migraine which possess an improved cardiovascular safety profile, to ultimately fill this unmet medical need.

Although the underlying mechanisms of migraine pathogenesis are complex and have not been fully elucidated to date, calcitonin gene-related peptide (CGRP) is a 37-amino acid neuropeptide that has long been postulated to play an important role in treatment of migraine headaches. The clinical effectiveness of antagonizing the CGRP receptor for relief of migraine pain has also been demonstrated.[4]

Recently a new CGRP receptor antagonist, ubrogepant has been identified and advanced into clinical studies.[5] Whilst ubrogepant could be prepared by a simple amide bond formation reaction, between the corresponding amino lactam **2** and the spiro acid **3** (Scheme 1), the preparation of the two key coupling partners provided a significant synthetic challenge.[5b] As the compound moved through the development phases, the discovery and development of efficient and economical large scale routes to these two key intermediates became essential to ensure successful advancement of the program into clinical studies. Herein, we report the asymmetric synthesis of lactam **2** using a dynamic kinetic transamination (DK-TA) approach. We also describe the asymmetric synthesis of key fragment **3** employing a novel doubly quaternized phase transfer catalyst (PTC) spirocyclization to set the chiral all carbon quaternary stereocenter.

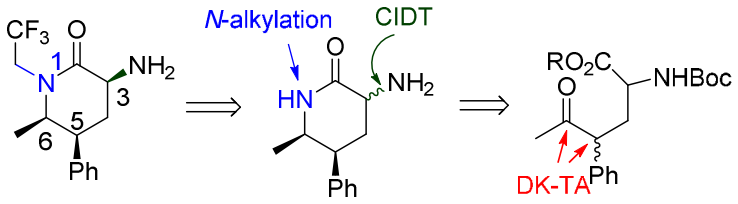


Scheme 1. Final amide bond formation; synthesis of ubrogepant (**1**)

Results and Discussion

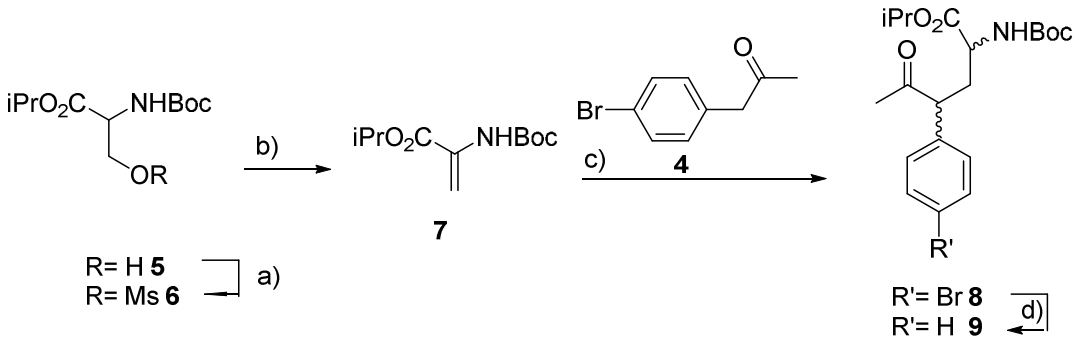
Chiral Synthetic Route to Lactam 2. The core framework of the lactam contains three chiral centers including a pendant phenyl ring. The original synthetic route to **2** used a chiral serine derivative. However, this route ultimately provided the product as racemic mixture which required a chiral SFC separation.[5b]

Our strategy to address these synthetic limitations is summarized in Scheme 2. Control of the C-5 and C-6 contiguous chiral centers was deemed the most challenging task in the lactam synthesis. We decided to evaluate a DK-TA setting both chiral centers simultaneously to achieve this goal.[6] With a judicious selection of the ester, we envisioned that lactam formation would occur during the transamination process. The N-1 side chain could be introduced by alkylation after lactam formation. Finally, the stereochemistry at the C-3 position was expected to be controlled by a thermodynamically driven crystallization induced diastereomeric transformation (CIDT) with appropriate choice of salt.[7]



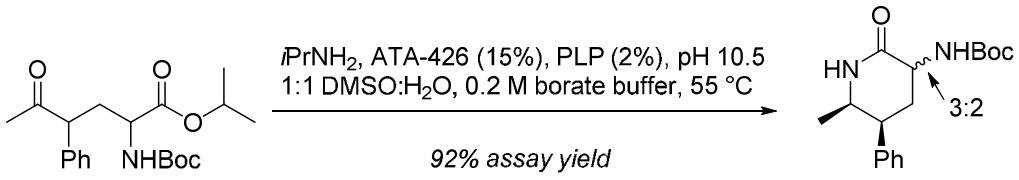
Scheme 2. Retrosynthesis of the lactam

Early development of this strategy was accomplished using 4-bromophenylacetone (**4**).[8] The isopropyl ester was selected for development as this provided a balance between stability with respect to hydrolysis during the transaminase reaction and reactivity in the cyclization to form our desired lactam. The synthesis of ketone **9** began with mesylation of *N*-Boc serine isopropyl ester **5** (Scheme 3). Alkylation of **4** with the mesylate **6** was sluggish. It was subsequently found that mesylate **6** was rapidly converted to alkene **7** under the alkylation conditions. The modest yields of the desired adduct **8** were actually the result of product formed from the conjugate addition of the enolate anion of **4** to the activated alkene **7**. Since the mesylate anion could potentially compete with the enolate anion of **4**, it was removed by isolation of **7**. This was found to significantly improve the alkylation step offering an 85% yield when enolization was performed with 0.5 equiv of Cs_2CO_3 in DMSO. Transfer hydrogenation mediated by Pd/C of bromide **8** provided our key substrate **9** in 71% yield for transamination development.



Scheme 3. Preparation of transamination substrate **9**. Reagents and conditions: a) MsCl (1.1 equiv), TEA (1.1 equiv), DCM, rt, 1 h, 92%; b) MsCl (1.3 equiv), TEA (2.5 equiv), DMF, 0 °C then rt, overnight, 93%, c) Cs_2CO_3 (0.5 equiv), DMSO, rt, 79%; d) 10 % Pd/C, HCO_2K, K_2CO_3, iPA, 60 °C, 2 h, 71%.

Screening of a transaminase panel from Codexis, Inc. was carried out under previously established conditions for DK transaminations at pH 10.5 to promote epimerization of the starting material.[6b-c] The initial results confirmed the feasibility of a dynamic kinetic reaction and delivered diverse selectivity. The appropriate choice of enzyme enabled access to either the *syn*- or *anti*-epimer with (*R*)-configuration at C-6 (Table 1, entries 1 and 2), demonstrating enzymatic catalysis as a powerful methodology for asymmetric synthesis setting multiple stereocenters. We identified ATA-301 as an initial lead providing the desired *syn*-lactam **10** with 7:1 diastereomeric ratio (dr) and >99%ee at C-6. Unfortunately, the activity of the enzyme was low and afforded only 38% conversion even at high loading. Given the recent development and success of protein engineering technologies,[9] we envisioned improving the activity and diastereoselectivity of the selective transaminase by directed evolution.



Scheme 4. Optimized DK transaminase conditions

Table 1. DK transaminase process improvements through enzyme evolution

TA variant	**9** Conc. g/L	E.L.[a] wt%	DMSO: H_2O	Conv. %[b,c]	*syn:anti*[d]
CDX-017	5	300	1:4	94	1:5
ATA-301	5	300	1:4	38	7:1
ATA-401	5	300	1:4	95	61:1
ATA-404	5	100	1:2.3	90	61:1
ATA-412	50	50	1:1	95	61:1
ATA-426	50	15	1:1	95[e]	61:1

[a] Enzyme loading relative to **9**. [b] DMSO-H_2O, 0.2 M borate buffer pH 10.5, 1 M *i*$PrNH_2$, 1 g/L PLP, 45 °C. [c] Determined by HPLC. [d] *syn* and *anti* of C-5 and C-6 chiral centers. [e] 55 °C.

In collaboration with Codexis, initial enzyme evolution efforts targeted improving the selectivity at the C-5 and C-6 chiral centers. The first round of evolution resulted in a variant that produced **10** with a ~9 fold increase in dr to 61:1. This new variant also improved activity by 2.5 fold (Table 1, entry 3). In the subsequent rounds of evolution, we continuously improved the transaminase's reactivity, leading to reactions run at higher substrate concentrations. In parallel, the enzyme was engineered to tolerate higher DMSO concentration in order to avoid limitations due to low substrate solubility under the more aqueous conditions used previously. An additional increase in temperature stability resulted in a ~2 fold faster reaction rate of final variant ATA-426 which afforded the desired lactam **10** in 92% assay yield and 61:1 dr in <24 hours (Scheme 4).[10]

The lactam product **10** was finally isolated as a crystalline 3:2 (β:α) diastereomeric mixture at the C-3 position. The C-3 position was prone to epimerization favoring the desired β-isomer under basic conditions, and therefore epimerization also occurred during the *N*-alkylation. This led us to perform the *N*-alkylation on the diastereomeric mixture of lactam **10**.

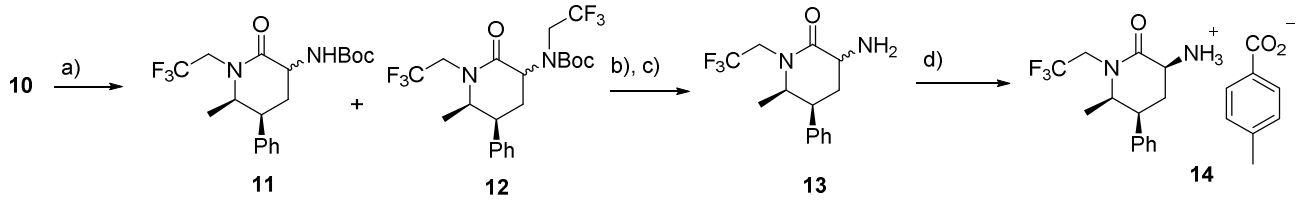
A highly reactive alkylating reagent, trifluoroethyl triflate, was required for *N*-alkylation.[11] Selective mono *N*-alkylation of **10** was not trivial and the undesired *N*,*N'*-dialkyl byproduct **12** was formed

competitively even before complete consumption of **10**. An extensive screen of bases revealed that the best base was lithium *tert*-butoxide.

With both base and alkylating reagent identified, optimization showed that an excess of LiO^tBu and triflate were required to achieve a high conversion in THF. The reaction was sensitive to temperature and it was found that best results were achieved when it was performed at sub-ambient temperatures. Under these conditions optimal levels of selectivity were observed, with the reaction affording a 94% conversion after 18 h. The ratio of **11** to **12** was 9.3 to 1 and the yield of **11** was 87% (Scheme 5).

Crude isolation of compound **11** still showed unreacted **10** and dialkylated **12** as impurities. However, Boc deprotection and isolation of the free amine as a salt led to removal of these main impurities. The desired product **13** was then recovered in 96% yield as a 4:1 diastereomeric mixture in favour of the β isomer at the C-3 position.

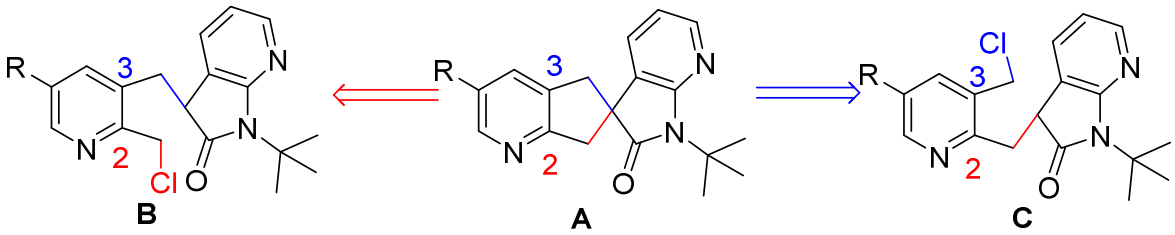
The stereochemistry of the C-3 center in **13** was set by a crystallization induced diastereoselective transformation (CIDT). After salt screening, *p*-toluic acid salt was selected for further development.[12] From the literature, CIDT based epimerizations, can be mediated by aromatic aldehydes.[7] Indeed, when crude **13** was treated with *p*-toluic acid in the presence of 1 mol% of 3,5-dichlorosalicyaldehyde at 50 °C, crystals precipitated as the pure β-isomer of the *p*-toluic acid salt **14** in 86% yield and with a 99.6% de. The salt **14** was suitable for use in the final coupling step after a salt break.



Scheme 5. *N*-Alkylation, stepwise deprotection and dynamic crystallization. Reagents and conditions: a) CF_3CH_2OTf (1.3 equiv), LiO^tBu (1.2 equiv), THF, 16-22 °C, 18 h, 87%, b) 3 N HCl, TBABr (3.8 mol%), toluene, 35 °C, 3 h, c) 4.5 N HCl, MTBE/MeOH, 50 °C, 5 h, 96%, d) *p*-toluic acid (1.0 equiv), 3,5-dichorosalicyaldehyde (1 mol%), 50 °C, 3-5 h, 86%.

Initial Medicinal Chemistry Route for Spiro Acid 3. The original route to **3** was racemic and suffered from polymerization when the previously described[5] double alkylation sequence was used to form the spirocycle. Furthermore, this method required SEM protection on the nitrogen atom at the azaindolone and SFC separation of a racemic mixture of the ester after spirocyclization. Thus, it became evident that a more efficient, practical asymmetric synthesis of **3** would be required.

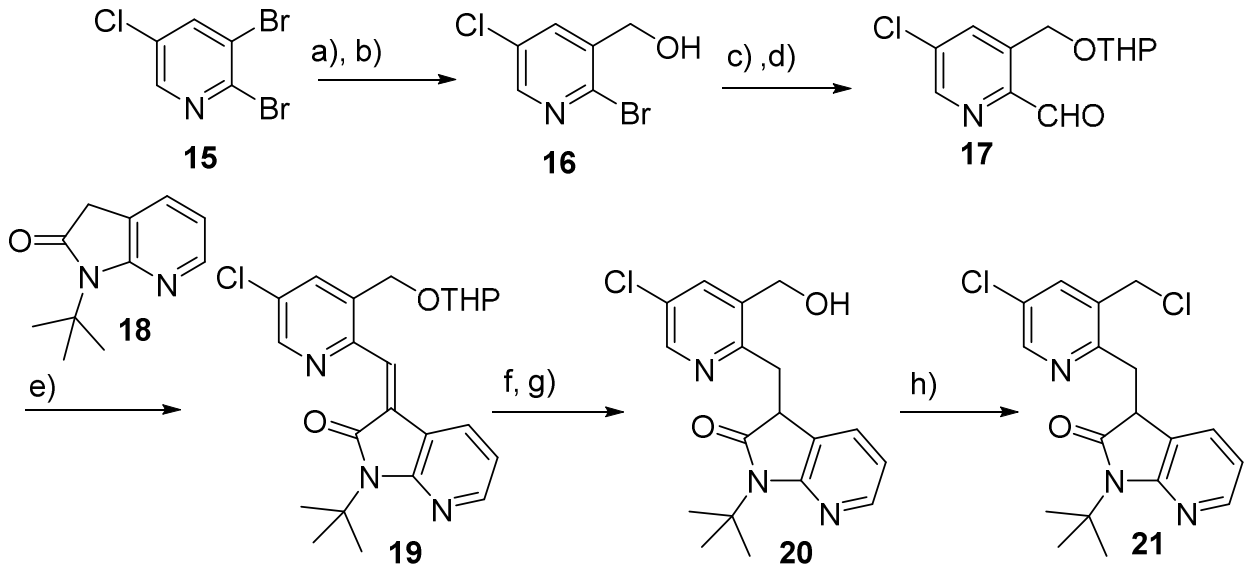
Chiral Synthetic Route to Spiro Acid 3. During a re-design of the synthesis of **3**, a number of key objectives were addressed. First, the *N*-protecting group was switched from the relatively expensive SEM group to *tert*-butyl. Next, to avoid polymerization during the spirocyclization, we decided to disconnect the key quaternary center in order to make each bond in a step-wise fashion. This provided us with two alternatives for ring closure and both these key intermediates, **B** and **C**, (Scheme 6) were independently prepared (R=Br). When **B** and **C** were independently subjected to the second alkylation to form spirocycle **A**, a clear difference was observed. Upon spirocyclization, intermediate **C**, the 3-isomer, proceeded smoothly under phase transfer conditions, whilst cyclization of the corresponding 2-isomer **B** was substantially worse. Therefore, spirocyclization from modified precursors of intermediate **C** was selected for further optimization.



Scheme 6. Retrosynthetic analysis of spiro acid

The practical synthesis of a suitable derivative of the 3-isomer **C** became our initial target for developing a scalable synthesis of spiro acid **2**. 2,3,5-Tribromopyridine was initially considered as the starting material, however chemoselectivity between C-2 and C-5 became a serious issue, therefore, 2,3-dibromo-5-chloropyridine (**15**) was selected as the starting material (Scheme 7). A regioselective transmetallation of the bromide at C-3 of **15** proceeded as expected[13] to provide C-3 aldehyde, after

quenching with DMF. The aldehyde was readily reduced to the corresponding alcohol **16**. The alcohol **16** was protected with a THP group, followed by a second selective transmetallation with *i*PrMgCl in toluene. The resulting anion was converted to the corresponding C-2 aldehyde **17** in high yield by addition of DMF. Condensation of aldehyde **17** with *N*-*tert*-butyl azaindolone **18** provided the highly crystalline alkene as its *Z*-isomer **19**. The alkene was reduced with $NaBH_4$ which was followed by THP deprotection to afford the primary alcohol **20**. Chlorination of **20** with $SOCl_2$ in presence of DMF provided **21**, the chloro variant of the desired intermediate **C**, in high yield.



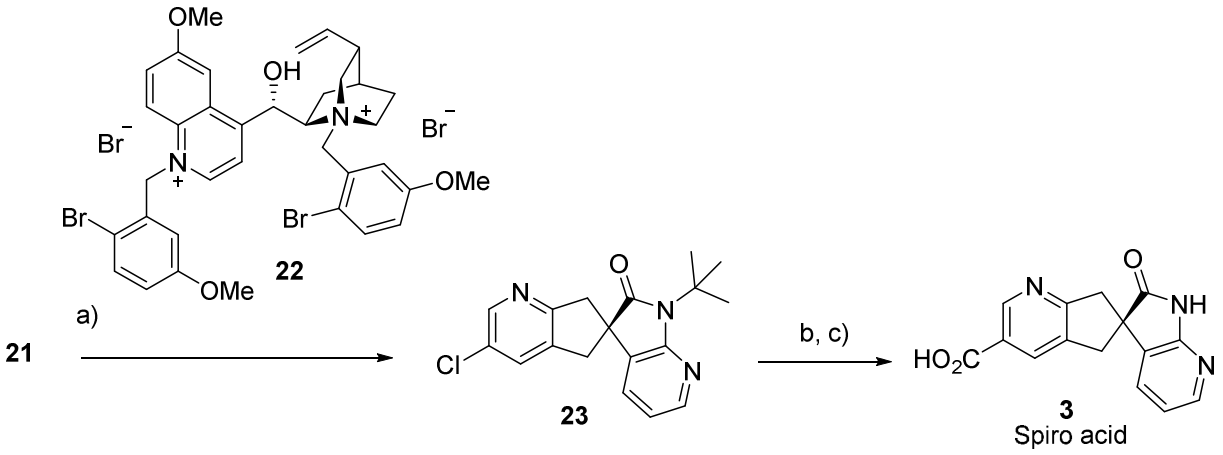
Scheme 7. Preparation of benzyl chloride **21** from **15**. Reagents and conditions: a) *i*PrMgCl LiCl, THF, -40 °C, 30 min, then DMF; b) $NaBH_4$, MeOH, rt, 30 min, 93%; c) DHP, conc. H_2SO_4, 2-MeTHF, rt, 10 min; d) *i*PrMgCl, toluene-THF, 0 °C, 2 h, then DMF, 0 °C, 1 h, 97%; e) **18** (1.1 equiv), DBU (5 mol%), iPA, -2 °C 2 h then rt 3 h, 87%; f) $NaBH_4$, EtOH, rt, 1 h; g) HCl, iPA, 40 °C, 3 h, 86%; h) $SOCl_2$, CH_2Cl_2, 5 °C, 30 min, 93%.

With intermediate **21** in hand the stage was now set to evaluate the key spirocyclization. The ultimate goal was to identify conditions which would provide some asymmetric introduction during this step. The spirocyclization of **21** proceeded well under standard PTC conditions. We therefore screened the

spirocyclization of **21** against a library of chiral PTCs (mainly cinchona alkaloid derivatives). As a result, the novel *N*,*N*'-doubly quaternized PTC **22** was serendipitously discovered as the most potent catalyst.[14]

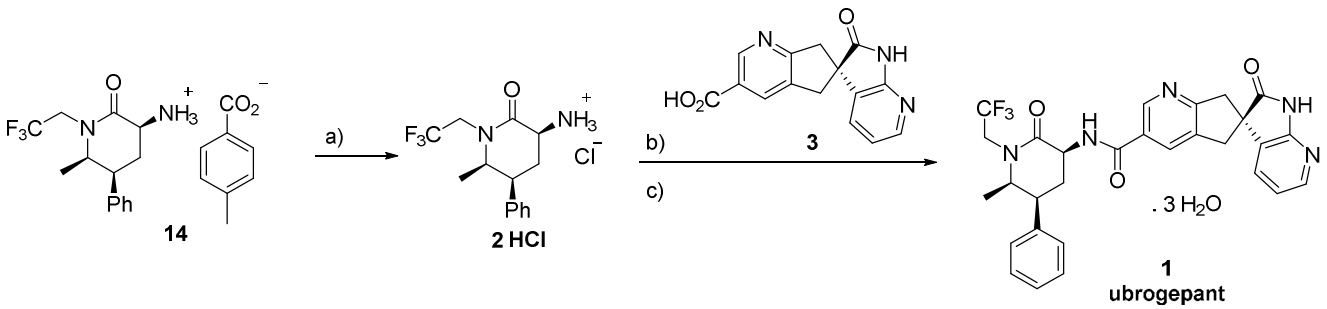
The spirocyclization of **21** was further optimized with PTC **22**. When employing this new catalyst, less solvent and only a slight excess of base were required. The ease of reaction is in direct contrast to mono-quaternized PTC catalyzed reactions which often require strict reaction conditions, such as well controlled stirring rate, temperature, high base concentrations and high catalyst loading; this novel bis-quaternary PTC reaction is mild, fast, robust and highly reproducible. Employing these conditions on scale gave the desired spiro compound **23** (94.4% ee with 100% assay yield) in an 87% isolated yield. The optical purity of the material isolated by crystallization was measured at 99.5% ee.

With optically pure **23** in hand, we were now in a position to complete the synthesis of the spiro acid fragment **3**. Carbonylation of **23** under conditions exemplified by the Buchwald group gave the intermediate acid.[15] Finally the *tert*-butyl protecting group was removed under acidic conditions, either HCl or H_2SO_4 were found to be suitable (Scheme 8). Ultimately the spiro acid **3** was prepared from **15** in 11 synthetic steps in a 43 % overall yield. This process is extremely robust and has successfully produced over 100 kg of **3**.



Scheme 8. Completion of the spiro acid synthesis. Regents and conditions: a) **22** (0.3 mol%), 0.3 N NaOH (1.1 equiv), toluene, -1 °C, 3 h, 83%; b) $Pd(OAc)_2$ (1 mol%), DCPP (2 mol%), K_2CO_3, NMP, CO (30 psi), 120 °C, 24 h, 95%; c) conc. HCl, 94 °C, 48 h, 94%.

With new robust syntheses of lactam **2** and spiro acid **3** in hand, the final coupling reaction and isolation conditions were optimized (Scheme 9). After a salt break of **14**, the HCl salt of lactam **2** in the aqueous layer was directly used for the coupling in aqueous acetonitrile. The coupling reaction proceeded smoothly with EDC (1.2 equiv) and catalytic amount of HOPO, without epimerization at the α carbon center of the newly formed amide bond.[16] After the reaction was complete, the product could be directly crystallized by slow addition of the crude reaction stream into a mixture of ethanol and water. Ubrogepant **1** was isolated directly as its trihydrate in a 95% yield with excellent optical and chemical purities.



Scheme 9. Preparation of ubrogepant **1**. Reagents and conditions: a) 0.6 N HCl (1.2 equiv), MTBE, b) **3** (1.0 equiv), EDC (1.2 equiv), HOPO (0.1 equiv), MeCN, H_2O, pH 6.0-6.5, rt, 6-12 h, c) EtOH, H_2O, 95%.

Conclusion

A new economical route to a highly potent CGRP receptor antagonist, ubrogepant, currently in phase 3 studies for acute treatment of migraine, is described. New asymmetric routes to the two main fragments were developed in order to establish the four chiral centers. Highlights include setting both

the C-5 and C-6 chiral centers of fragment **2** in a single transformation by an enzymatic DK-TA. The final chiral center at C-3 could be established by an aldehyde initiated CIDT. The spiro acid **3** was prepared by a stepwise bond formation sequence. A highly productive asymmetric spiro cyclization was accomplished using a novel doubly quaternized PTC to set the challenging key quaternary stereogenic carbon center. The final coupling conditions were modified to avoid epimerization with an EDC mediated coupling with catalytic amounts of HOPO. These conditions allowed the direct isolation of the target compound from the reaction medium in high yield and with high purity.

Experimental Section

All reagents and solvents were purchased from commercial suppliers and used without further purification, unless otherwise specified. All transaminase variants in Table 1 were purchased from Codexis Inc. Column chromatography was performed on Merck Silica Gel 60 Å (230 X 400 meshes). Reactions were typically monitored by HPLC analysis using an Agilent 1100 with reverse phase columns unless otherwise specified.

^{1}H and ^{13}C NMR spectra were recorded using Bruker-500, Bruker-400 and Agilent-500 MHz spectrometers. For ^{1}H NMR, chemical shifts are reported relative to residual protonated solvent peaks (δ 7.27, 2.50, and 1.94 ppm for $CDCl_3$, $(CD_3)_2SO$ and CD_3CN, respectively). ^{13}C NMR spectra were measured at either 126 MHz or 100 MHz on the same instruments noted above for recording ^{1}H NMR spectra. Chemical shifts were again reported in accordance to residual protonated solvent peaks (δ 77.23, 39.51, and 118.69 ppm for $CDCl_3$, $(CD_3)_2SO$ and CD_3CN, respectively). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, om = overlapped multiplet, br = broad resonance.

Mass spectral data were obtained on Waters SYNAPT G1 ESI-TOF HRMS and Waters Micromass ZQ ESI-TOF LCMS. Optical purities were measured using a HPLC (Agilent 1100) or a SFC (Aurora SFC/Agilent 1100) using chiral columns.

Isopropyl 2-((*tert*-butoxycarbonyl)amino)-4-oxo-3-phenylpentanoate (**9**)

To Cs_2CO_3 (7.38 g, 22.7 mmol) was added DMSO (45.7 mL) at room temperature and stirred at room temperature for 2 h under N_2 atmosphere. To the suspension was added phenylacetone (6.94 g, 90.3% purity, 46.7 mmol) and stirred at 18-22 °C for 40 min. To the reaction mixture was added a solution of isopropyl 2-((*tert*-butoxycarbonyl)amino)acrylate (**7**)[17] (10.2 g, 44.5 mmol) in DMSO (28.8 mL) over 1 h and the mixture was stirred at the same temperature for 1 h. MTBE (110 mL) was added to the reaction mixture. The solid was removed by filtration and rinsed with MTBE (48 mL). The filtrate and rinse were combined, washed with 5% aqueous NaCl twice (80 mL then 70 mL). The organic layer was concentrated and was used in the next reaction without purification (assay yield was 76.7%). Two diastereomers can be separated for analysis by silica gel column chromatography with EtOAc-hexanes (0% to 20%). In $CDCl_3$, both diastereomers show rotamers and mainly enol forms. NMR data is reported for each major rotamer.

Isomer A; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31 (t, *J*=7.4 Hz, 2H), 7.27-7.17 (m, 3H), 5.06 (m, 1H), 4.66 (dd, *J*=11.9, 4.7 Hz, 1H), 3.24 (ddq, *J*=16.1, 11.9, 2.3 Hz, 1H), 2.76 (ddq, *J*=16.1, 4.0, 1.9 Hz, 1H), 2.31 (s, 3H), 1.47 (s, 9H), 1.25 (d, *J*=6.5 Hz, 3H), 1.23 (d, *J*=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.8, 152,1, 135.9, 128.2, 127.7, 126.2, 80.8, 68.6, 59.1, 35.6, 28.3, 21.7, 14.5; HRMS: $C_{20}H_{29}NNaO_5$ 386.1938 (M+Na); found 386.1947.

Isomer B; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (t, *J*=7.4 Hz, 2H), 7.24 - 7.15 (m, 3H), 5.07 (hept, *J*=6.3 Hz, 1H), 4.67 (dd, *J*=11.9, 4.7 Hz, 1H), 3.24 (ddq, *J*=15.8, 12.0, 2.3 Hz, 1H), 2.77 (ddq, *J*=15.8, 3.9, 1.9 Hz, 1H), 2.32 (b, 3H), 1.47 (s, 9H), 1.28 (d, *J*=6.3 Hz, 3H) 1.20 (d, *J*=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.8$_3$, 171.7$_6$, 152.1, 136.0, 128.2, 127.7, 126.2, 115.6, 80.8, 68.6, 59.1, 35.6, 28.3, 21.7, 14.5.

Isopropyl 4-(4-bromophenyl)-2-((*tert*-butoxycarbonyl)amino)-5-oxohexanoate (**8**)

Compound **8** was prepared in the similar manner for **9**. The crude mixture of **8** was converted to **9** under transfer hydrogenation conditions (HCO_2K, K_2CO_3, iPA, 10% Pd/C, at 60 °C for 2 h). The crude **9** was used in next reaction without further purification.

Diastereoisomers of **8** can be separated by silica gel column chromatography using EtOAc hexanes (0 to 20 v/v%). In $CDCl_3$, both isomers (**8**) show rotamers and mainly ketone forms. NMR data is reported for each major rotamer.

Isomer A; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44 (d, *J*=8.3 Hz, 2H), 7.07 (d, *J*=8.3 Hz, 2H), 5.10 (d, *J*=7.1 Hz, 1H), 4.95 (hept, *J*=6.3 Hz, 1H), 4.18 (q, *J*=7.5 Hz, 1H), 3.76 (dd, *J*=8.9, 5.3 Hz, 1H), 2.64 (b, 1H), 2.06 (s, 3H), 1.68 (b, 1H), 1.43 (s, 9H), 1.24 (d, *J*=6.3 Hz, 3H), 1.21 (d, *J*=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 206.3, 171.7, 155.4, 137.3, 132.2, 131.1, 130.0, 121.8, 79.9, 69.4, 54.7, 52.0, 35.7, 29.1, 28.3, 21.7.

Isomer B; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46 (d, *J*=8.3 Hz, 2H), 7.09 (d, *J*=8.3 Hz, 2H), 4.98 (m, 1H), 4.89 (d, *J*=7.5 Hz, 1H), 4.07 (b, 1H), 3.76 (t, *J*=6.9 Hz, 1H), 2.37 (br, 1H), 2.08 (m, 1H), 2.04 (s, 3H), 1.42 (s, 9H), 1.22 (d, *J*=6.6 Hz, 3H), 1.20 (d, *J*=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 206.8, 171.7, 155.4, 137.0, 132.3, 130.0, 121.8, 80.0, 69.3, 55.5, 52.3, 34.7, 29.2, 28.3, 21.7.

tert-Butyl ((5*S*,6*R*)-6-methyl-2-oxo-5-phenylpiperidin-3-yl)carbamate (**10**)

Sodium tetraborate decahydrate (26.7 g) was dissolved in water (1.4 L). After all solids were dissolved, isopropylamine (82.8 g) was added. The pH of the buffer was adjusted to pH 10.5 using 6 N HCl. The buffer was cooled to room temperature. Then, pyridoxal-5-phosphate (2.8 g) and SEQ ID NO: 1 (70 g) were added and slowly dissolved at room temperature. The solution of **9** (197.9 g, 70.7wt%, 385 mmol) in DMSO (1.4 L) was added to the flask over 5-10 min and the reaction was heated to 55 °C. The pH was adjusted to 10.5 according to a handheld pH meter and controlled overnight with an automated pH controller using 8 M aqueous isopropylamine. The reaction was aged for 24 h. After confirmation of >95A% conversion by HPLC, the reaction was extracted by first adding 2.8 L of a mixture of iPA:IPAc (3:4) and stirring for 20 min. The phases were separated and the aqueous layer was back extracted with 2.8 L of a mixture of iPA:IPAc (2:8). The phases were separated; the organic layers were combined and washed with DI water (0.5 L). The HPLC based assay yield in the organic layer was **10** (114.6 g) with >60:1 dr at the positions C-5 and C-6. The ratio of stereoisomers at position C-3 was ~1:1. The extract was concentrated and dissolved in CH_2Cl_2. The organic solution was washed with water then sat. NaCl

aq, concentrated and crystallized from MTBE/*n*-hexane (2:3). The crystals were filtered at room temperature and washed with MTBE/*n*-hexane (2:3) and dried to afford a *cis* and *trans* mixture (~1 :1.2) of the lactam **10** (99.6 g, 80.0 %).

cis:trans (~1: 1.2) mixture but NMR integration was reported as 1:1 (for proton number counts)

Mp 87-90.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.20 (m, 8H, *cis* and *trans*), 7.16-7.12 (m, 2H, *cis* and *trans*); 6.56 (broad s, 1H, *trans*), 6.35 (broad s, 1H, *cis*), 5.57 (broad d, *J*=4.6 Hz, 1H, *cis*), 5.34 (broad d, *J*= 5.7 Hz, 1H, *trans*), 4.33-4.15 (m, 2H, *cis* and *trans*), 3.93 (m, 1H, *trans*), 3.81 (m, 1H, *cis*), 3.41 (dt, *J*= 11.8, 5.0 Hz, 1H, *cis*), 3.29 (dt, *J*=8.0, 4.4 Hz, 1H, *trans*), 2.74 (m, 1H, *cis*), 2.57 (m, 1H, *trans*), 2.23 (ddd, *J*=13.5, 8.0, 4.4 Hz, 1H, *trans*), 2.07 (q, *J*=11.8 Hz, 1H, *cis*), 1.46 (s, 9H, *cis*), 1.42 (s, 9H, *trans*), 1.05 (d, *J*=6.9 Hz, 3H, *trans*), 0.89 (d, *J*=6.9 Hz, 3H, *cis*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5_2 (*cis*), 171.4_6 (*trans*), 156.0_4 (*cis* or *trans*), 155.9_3 (*cis* or *trans*), 140.8 (*cis*), 139.9 (*trans*), 128.8 (*trans*), 128.7 (*cis*), 128.6 (*trans*), 128.1 (*cis*), 127.2_5 (*trans*), 127.1_8 (*cis*), 79.9_8 (*trans*), 79.9_1 (*cis*), 52.4 (*trans*), 51.8 (broad, *cis*), 51.7 (*cis*), 49.0 (broad, *trans*), 42.1 (*cis*), 41.9 (*trans*), 32.4 (broad, *trans*), 30.1 (*cis*), 28.5_7 (*cis* or *trans*), 28.5_3 (*cis* or *trans*), 18.3 (*cis*), 18.1 (broad, *trans*); HRMS m/z cacld. for $C_{17}H_{24}N_2NaO_3$ 327.1679 (M+Na); found 327.1696.

(5*S*,6*R*)-3-Amino-6-methyl-5-phenyl-1-(2,2,2-trifluoroethyl)piperidin-2-one (**13**)

To a mixture of **10** (20.0 g, 65.7 mmol) and $Na_2S_2O_3$ (0.52 g, 3.3 mmol) in THF (200 mL) was added *tert*-BuOLi (6.8 g, 85 mmol) at 20 ^{o}C. The mixture was stirred at 20 ^{o}C for 15 min followed by addition of trifluoroethyl trifluoromethanesulfonate (20.6 g, 89 mmol) in one portion. The resulting mixture was stirred for 18 h at 20 ^{o}C. The reaction mixture was then quenched by addition of toluene (70 mL) followed by 0.5 N HCl solution (50 mL). The aqueous layer was separated and extracted with toluene (20 mL). The combined organic layer contained 87% of **11**, 6% of **12** and 6% of **10** by HPLC and yield for the desired product **11** was 87%.

Analytically pure *cis* and *trans* isomers **11** were isolated by chromatography on silica gel with ethyl acetate and heptane as eluant.

11 (*cis*); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31 (m, 2H), 7.23 (m, 1H), 7.17 (m, 2H), 5.75 (s, broad, 1H), 4.85 (m, 1H), 4.15 (m, 1H), 3.80 (m, 1H), 3.50 (m, 1H), 3.17 (m, 1H), 2.45 (m, 2H), 1.45 (s, 9H), 0.93 (d, *J*=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 155.9, 140.0, 128.6, 127.6, 127.1, 124.6 (q, *J*=279 Hz), 79.7, 58.7, 52.2, 45.3 (q, *J*=33.7 Hz), 41.9, 28.3, 27.4, 13.4; HRMS: m/z calcd for $C_{19}H_{26}F_3N_2O_3$ 387.1890 (M+H); found: 387.1899.

11 (*trans*); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 (m, 2H), 7.30 (m, 3H), 5.55 (br, 1H), 4.53 (br, 1H), 4.45 (m, 1H), 3.78 (m 2H), 3.45 (m, 1H), 3.00 (m, 1H), 2.12 (m, 1H), 1.46 (s, 9H), 1.12 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 155.9, 139.6, 128.7, 127.9, 127.4, 124.3 (q, *J*=279 Hz), 80.0, 59.6, 49.1, 46.9 (q, *J*=34.0 Hz), 42.1, 28.3, 25.3, 13.4; HRMS: m/z calcd for $C_{19}H_{26}F_3N_2O_3$ 387.1890 (M+H); found 387.1901.

The organic layer was then stirred with 3 N HCl solution (80 mL) and tetrabutylammonium bromide (0.8 g, 2.48 mmol) at 35 °C for about 3 h until HPLC analysis indicated selective removal of the Boc group in the unreacted **10** was complete. The aqueous layer was removed. The organic layer containing **11** and **12** was then concentrated under vacuum at 60 ^{o}C to remove most of solvent. The residue was dissolved in a mixture of MTBE (60 mL), MeOH (10 mL), and 4.5 N HCl solution (64 mL). The diphasic solution was agitated vigorously at 50 ^{o}C for about 5 h until the deprotection of **11** was complete while **12** was mainly intact. After addition of heptane (30 mL) to the mixture, the organic layer was separated at 45 ^{o}C. The aqueous layer was diluted with water (60 mL) and then washed with heptane (20 mL) and MTBE (10 mL) at 45 ^{o}C. The combined organic layer was extracted with 0.5 N HCl solution (20 mL). The combined aqueous solution was then mixed with MTBE (100 mL) and basified with 10 N NaOH solution until the pH of the mixture was about 10. The organic layer was separated and the aqueous layer was back-extracted with MTBE (60 mL). The combined organic layers were washed with brine (60 mL). The resulting organic solution was suitable for the next reaction. The

solution contained **13** (15.6 g, 83% from **10**) with 97% LC purity as a mixture of two diastereomers (*cis* and *trans*) in 4 to 1 ratio, which was used in the next reaction without further purification.

(3*S*,5*S*,6*R*)-6-Methyl-2-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)piperidin-3-aminium 4-methylbenzoate (**14**)

To a suspension of 4-methylbenzoic acid (6.8 g, 49.9 mmol) and 3,5-dichlorosalicylaldehyde (93 mg, 0.49 mmol) in MTBE (40 mL) was added a solution of **13** (13.9 g, 48.5 mmol) in MTBE (about 150 mL) over 1 h at 50 ^{o}C. The resulting suspension was agitated for about 3 h at 50 ^{o}C. The solids were collected by filtration after cooling to -5 ^{o}C over 1 h. The cake was washed with MTBE (50 mL). The crystalline solids were dried in a vacuum oven to give **14** (17.6 g, 86%) with 99.5% LC purity and 99.6% de. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.85 (d, *J*=8.1 Hz, 2H), 7.40 (m, 2H), 7.25 (m, 5H), 6.42 (br, 3H), 4.65 (m, 1H), 3.82 (m, 1H), 3.76 (m, 1H), 3.62 (m, 1H), 3.50 (m, 1H), 2.35 (s, 3H), 2.30 (m, 1H), 2.15 (m, 1H), 0.88 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 172.4, 168.5, 142.1, 141.1, 130.9, 129.7, 129.2, 129.0, 128.0, 125.5 (q, *J*=279 Hz), 59.1, 51.6, 45.1 (q, *J*=32 Hz), 41.6, 28.0, 21.5, 13.9. HRMS: m/z calcd for $C_{14}H_{18}F_3N_2O^+$ 287.1366 (M+H); found 287.1359.

Preparation of compounds **16, 17, 18, 19, 20, 21, 22**, and **23** has been reported.[14]

(*S*)-2'-Oxo-1',2',5,7-tetrahydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxylic acid (**3**)

A mixture of **23** (5.0 g, 14.5 mmol), K_2CO_3 (5.01 g, 36.2 mmol), $Pd(OAc)_2$ (33 mg, 0.145 mmol), 1,3-bis(dicyclohexylphosphino)propane (DCPP, 127 mg, 0.290 mmol) and water (0.522 mL, 29.0 mmol) in NMP (32 mL) was heated at 120 °C under 30 psi of CO for 24 h. After cooling to room temperature, the resulted slurry was diluted with water (100 mL). The pH was slowly adjusted to 3~4 with 2 N HCl. The slurry was aged at room temperature for 1 h, filtered, rinsed with water (40 to 50 mL), dried under oven at 60 °C to give *N*-*tert*-butyl carboxylic acid (4.64 g, 95%) as a solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.90 (s, 1H), 8.19 (d, *J*=5.2 Hz, 1H), 7.54 (d, *J*=7.3 Hz, 1H), 6.99 (dd, *J*=7.3, 5.2 Hz, 1H), 3.33 (m, 4H), 1.72 (s, 9H); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 180.2, 167.4, 167.0, 158.1, 149.8, 146.6, 135.4, 133.1,

130.4, 128.8, 125.5, 118.4, 58.2, 51.1, 44.6, 41.2, 28.9; HRMS: m/z calcd for $C_{19}H_{20}N_3O_3^+$: 338.1499 (M+H); found: 338.1496.

To the *N*-*tert*-butyl carboxylic acid (4 g, 97%wt, 11.5 mmol) was charged 37% HCl (40 to 44 mL). The slurry was heated at 94 °C for 48 h, cooled to room temperature. The solvent was partially removed by reducing pressure to about total 2 vol (~ 4 mL water remained). The residue was diluted with water (20 mL) followed by adjusting pH to 2.6 with NaOH (3.5 N, 4.5 mL). The thick slurry was aged for 1 to 2 h, filtered, rinsed with water (2 x 8 mL), followed by water/acetone (1:1, 8 mL). The wet cake was dried to give compound **3** (3.1 g, 98%wt, 94%) as crystals. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 13.31 (br, 1H), 11.14 (s, 1H), 8.91 (s, 1H), 8.19 (s, 1H), 8.11 (m, 2H), 7.49 (dd, *J*=7.3, 1.3 Hz, 1H), 6.93 (dd, *J*=7.3, 5,3 Hz, 1H), 3.36 (m, 4H); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 181.1, 167.4, 167.0, 156.8, 149.8, 147.3, 135.4, 133.2, 130.7, 128.9, 125.5, 118.5, 51.8, 44.1, 40.7; HRMS: m/z calcd for $C_{15}H_{10}N_3O_3^-$: 280.0728 (M-H); found: 280.0725.

(*S*)-*N*-((3*S*,5*S*,6*R*)-6-Methyl-2-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)piperidin-3-yl)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxamide trihydrate (**1**)

To a suspension of **14** (10.0 g, 98wt%, 23.2 mmol) in MTBE (70 mL) was added 0.6 N HCl (42 mL, 25.2 mmol). The mixture was stirred for 5 min. The organic layer was separated and extracted with another 0.6 N HCl (8 mL, 4.8 mmol). The combined aqueous solution was washed with MTBE three times (3 X 10 mL). The resulting aqueous solution was mixed with acetonitrile (35 mL) and **3** (6.66 g, 99wt%, 23.5 mmol) was added. To the resulting suspension was added 29% NaOH solution (4.25 g, 1.33 equiv) dropwise in a few min to pH 6.0-6.5. After the mixture was stirred for 15 min at room temperature, HOPO (0.26 g, 2.34 mmol) was added followed by EDC hydrochloride (5.34 g, 27.9 mmol). The mixture was stirred at room temperature for 6-12 h until the conversion was complete. Ethanol (30 mL) was added and the mixture was stirred at 35 ^{o}C for 10 min. The resulting solution was cooled to room temperature and filtered. To another three neck flask was added ethanol (10 mL) and water (30 mL) followed by **1** seeds (0.4 g). The resulting suspension was stirred for 10 min. Part of the

filtrate (10 mL) was transferred into a syringe and added to the agitated suspension slowly via a syringe pump over 1 h. The flask was then equipped with two additional funnels. The rest of the filtrate was transferred into one additional funnel while the other funnel was charged water (70 mL). The contents in both funnels were charged into the suspension at the same time over an hour at room temperature. The suspension was then cooled to 5 ^{o}C over 30 min. The suspension was filtered and washed with ethanol/water mixture (40 mL, 1:3). The cake was dried in a vacuum oven at 40 ^{o}C, to give 13.7 g of white solids as **1** trihydrate (95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.15 (br s, 1H); 8.91 (br s, 1H); 8.21 (d, *J*=6.0 Hz, 1H); 8.16 (dd, *J*=5.3, 1.5 Hz, 1H); 8.01 (br s, 1H); 7.39-7.33 (m, 2H); 7.31-7.25 (m, 1H); 7.22-7.20 (m, 2H); 7.17 (dd, *J*=7.4, 1.6 Hz, 1H); 6.88 (dd, *J*=7.4, 5.3 Hz, 1H); 4.94 (dq, *J*=9.3, 7.6 Hz, 1H); 4.45-4.37 (m, 1H); 3.94-3.87 (m, 1H); 3.72 (d, *J*=17.2 Hz, 1H); 3.63-3.56 (m, 2H); 3.38-3.26 (m, 1H); 3.24 (d, *J*=17.3 Hz, 1H); 3.13 (d, *J*=16.5 Hz, 1H); 2.78 (q, *J*=12.5 Hz, 1H); 2.62-2.56 (m, 1H); 1.11 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 181.4, 170.6, 166.7, 166.6, 156.9, 148.6, 148.1, 141.7, 135.8, 132.1, 131.1, 130.1, 129.7, 129.6, 128.8, 128.1, 126.3 (q, *J*=280.1 Hz), 119.4, 60.1, 53.1, 52.0, 46.4 (q, *J*=33.3 Hz), 45.2, 42.8, 41.7, 27.8, 13.5; HRMS m/z: calcd for $C_{29}H_{27}F_3N_5O_3$ 550.2061 (M+H): found 550.2059.

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Supporting Information

The supporting Information is available free of charge on the ACS Publications website at DOI:

^{1}H and ^{13}C NMR spectra of compounds **1**, **3**, **8**, **9**, **10**, **11**, and **14**.

Notes

The authors declare no competing financial interest.

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