Organic Process Research & Development

Article

pubs.acs.org/OPRD

Lab-Scale Preparation of a Novel Carbocyclic Chemokine Receptor Antagonist

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Supporting Information

ABSTRACT: The preparation of a novel chemokine receptor type 2 (CCR-2) antagonist is described on a 135 g scale. The synthesis of an all-carbon bicyclic core was accomplished using a radical cyclization strategy using chiral precursors, wherein elaboration led to *N*-Boc carboxylic acid in good yield. After amidation using a traditional coupling reaction, a reductive amination using enantiomerically enriched 3-methoxy-4-pyranone led to the final compound. Although several steps of the syntheses involved reagents that would not be preferred in process and chromatography was used to provide the free-base diastereomer of the final succinate salt, the overall route went through stable intermediates that could be used for future scale-up. This lab-scale synthesis struck a balance between a quick scale-up and a more thorough process review of all possible methods and routes.

INTRODUCTION

Antagonists of the CC-chemokine receptor 2 (CCR-2) have been vigorously pursued by a number of pharmaceutical companies as a target for drug discovery, in that compounds could have the potential for use in the acute and chronic conditions of inflammatory and autoimmune diseases associated with infiltration of monocytes, macrophages, lymphocytes, dendritic cells, NK cells, eosinophils, basophils, natural killer (NK cells), and memory T-cells. A compound of interest that was discovered in the Janssen laboratories that met the initial criteria set out during the in vitro screening phase of drug discovery was bicyclic **1**.[1,2] The Discovery Chemistry team charged us with up-scaling the preparation of **1** to 135 g for use in a 14-day tox/tolerability study. Although we realized that we may have to incorporate some process-unfriendly techniques, we had to do a meld of discovery/process that matched the best of pure speed of preparation with work-arounds to allow us to start thinking of a future process. For the scale-up of **1**, we took advantage of the process innovations which we uncovered during the course of our investigations and are reported here.

The Discovery Chemistry retrosynthesis of **1** in Figure 1 was reasonable for discovery scale-up and entailed: (1) amide formation between Boc acid **4** with fused piperidine **5**; (2) deprotection of the NHBoc protecting group; (3) reductive amination of the newly revealed amine with the chiral ketone **3**; (4) chiral separation of the reductive amination products to provide diastereomerically pure **1** as the free base; and (5) salt formation with succinic acid to give final compound **1**. This general synthesis strategy of these final steps to arrive at **1** could not be altered under the time constraints of the project.

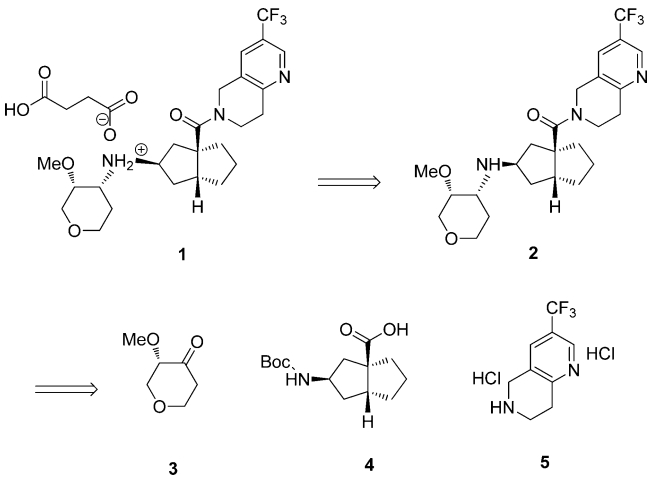


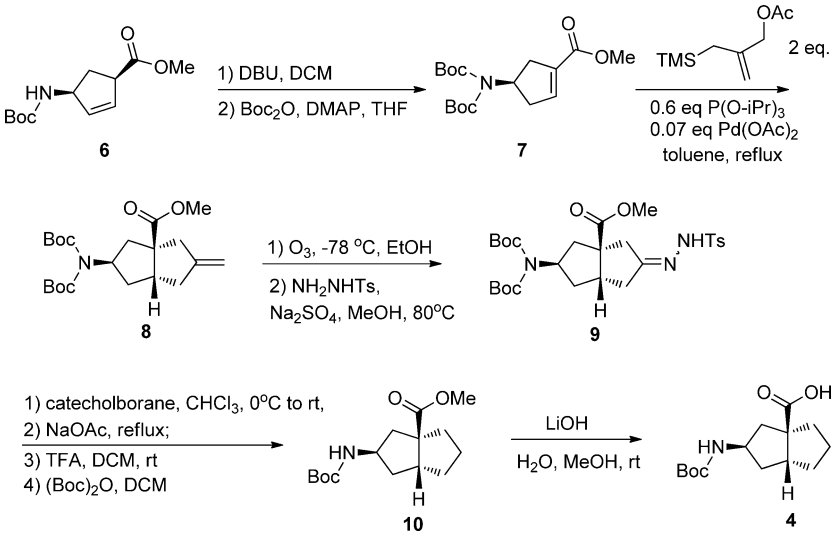
Figure 1. Retrosynthesis of CCR2 antagonist compound **1**.

A time factor that had to be considered was chiral chromatography of the reductive amination product **2**. Several quick attempts were made to form salts of the crude reduction product **2** with ∼10% of two diastereomers, in the hope that crystallization could render the product free of the diastereomeric contaminants (described later). However, there were no hits or enrichment of pure diastereomer **2** in this investigation, so chiral chromatography of the reductive amination product was accepted as the only sure-fire method to obtain diastereomerically pure product. Several preparations of the

Received: July 17, 2014

dx.doi.org/10.1021/op500265z | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

Scheme 1. Discovery Chemistry route to all-carbon core acid 4



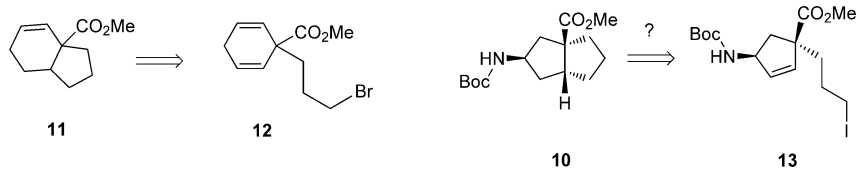
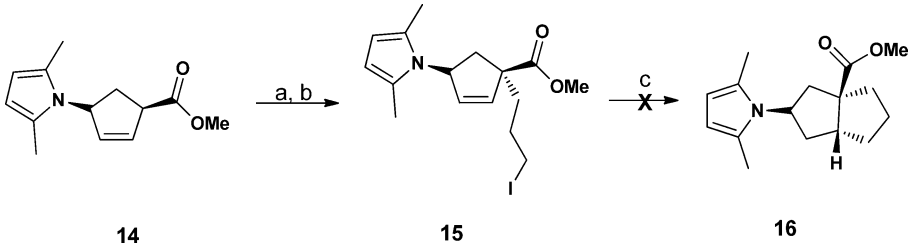


Figure 2. Background of bicyclic ethers and alkanes and proposed disconnection for **10**.

Scheme 2. Attempted radical cyclization for the formation of 16



[a]$I(CH_2)_3Cl$, LiHMDS, THF, −20 to 0 °C (66%). [b]NaI, acetone, 60 °C (90%). [c]AIBN/$(TMS)_3SiH$ or Bu_3Sn/benzene, 80 0 °C.

enantiomer of **3** have been described,[3] and so access to ketone **3** was expected with some slight variations.[4] The chiral purity of **3** that we had was ∼86−95% ee, thus leading to the earlier described diastereomers of **2**. This confirmed the decision to use chiral chromatography to arrive at diastereomerically pure **2**.

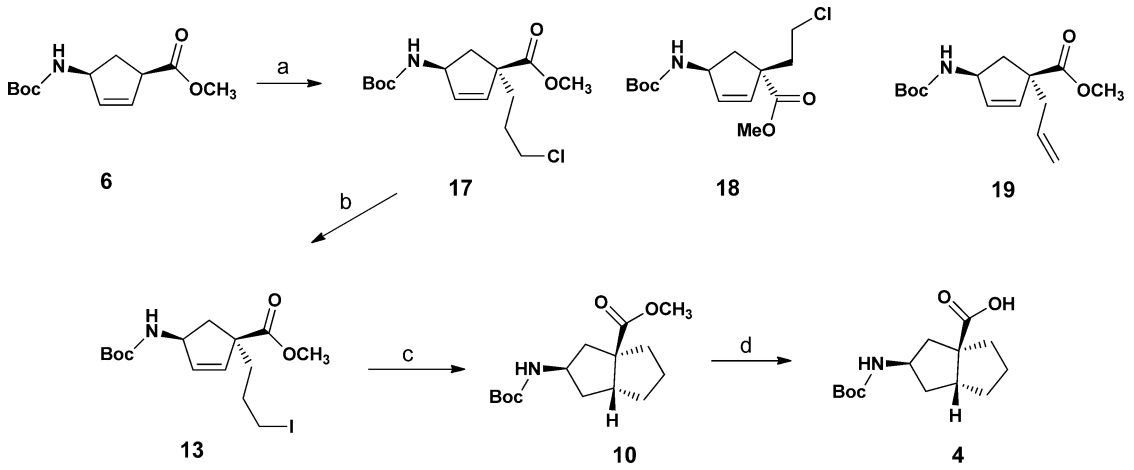
The acid **4** was previously described in both chiral and racemic form.[1] The absolute stereochemistry of **4** was based on an X-ray crystal structure performed on the final compound **1** and confirmed the positional relationships of the groups on a [3.3.0]-bicyclic carbon core. Although the chiral route (Scheme 1) was justifiable to obtain acid **4** and the precursor ester **10** in chiral form on a discovery scale, the reductive cleavage of the exo-olefin was cumbersome and not amenable to scale-up. This 3 + 2 cycloaddition strategy, as well other work in the area,[5] demonstrated that the −NHBoc group was effective to direct chemistry to the anti- face of the cyclopentene ring, and so we looked into other prominent ring-closing strategies for the formation of bicyclic ring systems.

Bicyclic alkanes, such as the [4.3.0] ring system exemplified by **11**, have been prepared by free-radical cyclization based on the pioneering work of Beckwith and Roberts,[6] utilizing alkyl bromide **12** and a trialkylstannane/free-radical initiator method (Figure 2). In addition, this general strategy has been used to synthesize closely related bicyclic systems.[7] It is easy to see the radical cyclization method applied to iodide precursor **13**, although use of trialkylstannane reagent would not be acceptable for any scale-up. Hence, the synthesis of ester **10** represented a unique challenge with the nitrogen side chain protecting group.

Chiral nitrogen protected cyclopentenes have been featured as intermediates in the syntheses of nucleosides as inhibitors of γ-aminobutyric acid aminotransferase and as antagonists of chemokine receptor antagonists.[8,9] In particular, pyrrole protected **14**[3c] has been used as an intermediate in the preparation of MK-0812,[10] because of its ability to provide excellent diastereoselectivity in the alkylation with electrophiles. We confirmed the high diastereoselectivity seen in the alkylation of **14** upon treatment with 1.6 equiv of LHMDS, followed by 3-chloro-1-iodopropane, which, after the Finkelstein reaction, provided iodide **15** as the necessary precursor for radical cyclization (Scheme 2). The reaction sequence gave

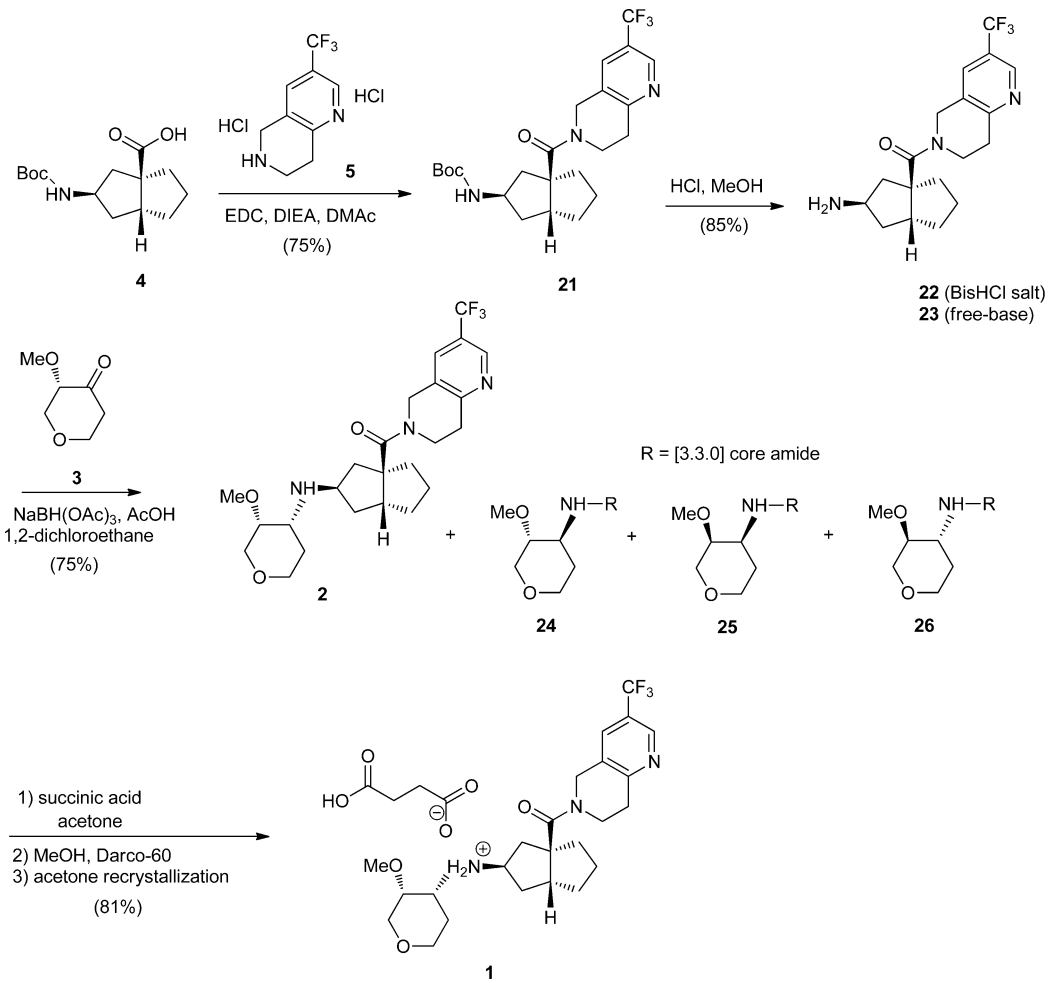
dx.doi.org/10.1021/op500265z | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 3. Prepartion of acid 4



[a]$I(CH_2)_3Cl$, LiHMDS, THF, −70 to 0 °C (25−65%, see discussion). [b]NaI, acetone, 60 °C (96%). [c]TMS_3SiH AIBN, PhMe, 80 °C (63%). [d]10N NaOH, MeOH, H_2O, 60 °C (93%).

Scheme 4. Steps of final compound 1



predominantly one isomer which was used to investigate the downstream chemistry.

Upon subjecting **15** to radical cyclization conditions (AIBN/$(TMS)_3SiH$ or Bu_3SnH/benzene/80 °C), we failed to isolate any **16**, only detecting deiodinated starting material by LCMS, probably due to radical quenching by the electron-rich pyrrole group.[11] The *N*-phthalimide protecting group as a replacement for the 2,5-dimethylpyrrole group was briefly investigated but was unstable under the alkylation conditions. Finally we changed to the ester **6**,[8] and this allowed us to complete the synthesis. As shown in Scheme 3, *N*-Boc ester **6** was a competent alkylation nucleophile, whereupon treatment with

dx.doi.org/10.1021/op500265z | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

2.2 equiv of LHMDS gave the expected dianion that, upon reaction with 3-chloro-1-iodopropane, provided alkylation products **17** and **18**, favoring the desired isomer in a ratio of 6:1. The same β-facial selectivity was seen for this reaction, in concert with that observed for 2,5-dimethylpyrrole protected **14**, although the diastereoselectivity was lower for the Boc group.

The reaction worked better using an inverse addition, whereby the preformed dianion was added to a chilled solution of the electrophile. Yields were better with reverse addition, even though this was more difficult operationally. Two additional parameters were the key to reproducible yields: (1) it was important to maintain an inert atmosphere over both the anion and electrophile flasks during the course of the reaction, and this was effectively accomplished with high flow nitrogen sweeps; (2) a gradual temperature increase from −70 to 0 °C after cannulation of the anion into the electrophile was required for good results.[12] When these two precautions were not taken, the yield dropped from 65% to 25−33%.

Side products for the early low-yielding reactions were not investigated once the key parameters were identified. The alkylation reaction also produced some chain-elimination product **19**; this was easy to remove relative to the close-eluting **17** (less polar) and **18** (more polar) products on silica gel. In the mass balance analysis, when alkylation was incomplete, the starting material with the double bond moving into conjugation with the ester was detected but never to such an amount that separation was an issue. Poor results were seen when 1,3-dibromopropane was used, favoring **19** as the major product. Alkylation products **17** and **18** were oils on initial isolation, although higher purity batches of **17** did slowly crystallize to a low-melting solid on standing. No follow-up work was done to take advantage of this property. Although useful for this lab campaign to obtain the required materials, this alkylation sequence will require alterations if considered for further scaling.

The Finkelstein reaction (NaI/acetone/65 °C) of chloride **17** provided iodide **13** in high yield. Gratifyingly, the reaction of **13** under radical cyclization using tin-free radical precursor tris(TMS)silane gave [3.3.0] alkane **10** in 63% yield. The cyclization proceeded with the expected diastereoselectivity, providing the cis-fused bicyclic ring, owing to the short chain length. There may have been a small amount of trans-fused ring product from the reaction but was not investigated to determine if it came from trans-cyclization or if it came as a result of contamination of **18** in the chromatographed **17** product.

A through-process utilizing a mixture of alkylation isomers **17** and **18** directly into the radical cyclization was considered but was ruled out since, under the time constraints of the project, it was too risky to rely on one chromatography column to effectively separate isomers at the methyl ester stage. With a single isomer ester **10** in hand, hydrolysis of the ester gave acid **4** in 93% yield. The sequence was viable towards accomplishing our goal, with the scalability of the reactions highlighted by a radical cyclization reaction conducted on a 385 g scale.

With quantities of acid **4** in hand, the final steps were identical to that reported by the Discovery Chemistry team. Amide formation between acid **4** and fused piperidine **5**[13] utilized a standard reagent combination of EDC/HOBt/Et_3N in THF and required concentration before workup. We felt that the reagents were satisfactory for scale-up, incorporating only a minor change in bases (Scheme 4). We did change the reaction solvent to DMAc, which allowed for isolation of amide **21** by filtration from an aqueous solution of 5% sodium bicarbonate that was used to quench and workup the reaction. A 75% yield was obtained for the filtered coupling product, which was considered acceptable taking into account that the revised procedure saved time by eliminating purification by column chromatography.

Deprotection of the Boc group in amide **21** was originally performed using mixtures of TFA in DCM. Aside from the fact that the TFA salt of **23** was an oil after concentration of the reaction mixture, we observed some variation in the rate of the reaction depending on the charge of TFA. Deprotections using DCM mixtures of **21** with 6−20 equiv of TFA were only 80% complete at rt overnight. Heating to 50 °C while concentrating the reaction solution as part of the workup led the reaction to completion. As such, we changed the deprotection conditions to 1.25 M HCl in MeOH which rendered the bis HCl salt **22** as a solid. The reaction was heated from 40 to 60 °C, at which temperature the reaction did have a vigorous off-gassing. At lab scale (220 g), nonrestrictive venting was used on the outflow of the inert gas sweep to prevent pressure build-up. After 40 min hold, the reaction had a clean HPLC profile for completion, and the reaction was evaporated.

Choice of the bis-HCl salt product **22** was fortuitous in that it was easily rendered as a filterable solid upon trituration with *i*-PrOH at 40 °C. Addition of heptane facilitated higher recoveries of the product in the ensuing filtration. The HCl salt **22** was isolated as a yellow solid in 85% yield. The color of the solid did seem to have some variation depending on the color of the starting **21** used for the reaction. An attempt was made to use 5−6 M HCl in *i*-PrOH for the deprotection; the reaction again required heating and was efficient in the conversion to product, but the solid form that was initially obtained (without the heptane treatment) was not as filterable as the solid obtained by the HCl/MeOH method.

The reductive amination reaction between newly revealed amine and the chiral ketone **3** was the most challenging step of this scale-up. We were specifically worried about several aspects of this reaction: (a) the reaction was performed in DCM, which could have the possibility to react in some cases with amines;[14] (b) chiral ketone **3** was prone to racemization in the presence of base; (c) the reductive amination of amines with ketones are not unprecedented but generally less prevalent than amine/aldehyde combinations;[15] (d) the reductive amination was found to be cis-selective (with respect to the α-OMe group) but not exclusive, meaning that there was some detectable amounts of the trans-reductive amination product formed; and finally, (e) the chirality of the ketone **3** was not 100% ee, thus leading to the above-described diastereomers.

Addressing these concerns in this reaction, we reasoned that changing the DCM solvent to 1,2-dichloroethane (DCE) was an acceptable replacement that would not alter the overall reaction. The discovery team had performed the reductive amination using the TFA salt of amine **23** and excess tertiary amine which caused an increase in the unwanted diastereomers from ketone racemization. To eliminate this complication, we chose to free-base the HCl salt **22** as a separate operation; ideally the free-basing would be done using DCE in the extraction step, so a through-process could be used. The process worked well except that we encountered a heavy rag interface between the DCE and the aqueous NaOH used for the neutralization. This required a filtration of the DCE layer through Celite to achieve a clear organic solution. After drying

dx.doi.org/10.1021/op500265z | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

the DCE layer with drying agent, Karl Fischer titration indicated the organic layer had ∼2% water which was not controlled to any strict level. The reductive amination was carried out using the DCE solution of free-base **23**, along with glacial AcOH (2 equiv), sodium triacetoxyborohydride (STAB) (1.4 equiv) followed by charging a DCE solution of **4** (1.4 equiv) at 0 °C. After 1 h, some **23** was still found to be present, so an additional 5% charge of **4** was made before the reaction was allowed to warm to rt overnight. The presence of the trans-product **24** was detected at 2.5% in the first hour of the reaction and had increased to 4.6% at the end of the reaction (24 h). The reaction was stopped with <0.5% **23** left unreacted. Also detected in the crude reaction product was ∼5% of **25**, which was present as a consequence of the ketone enantiomer present in the batches of **4** used for the scale-up. We did not have access to enantiopure **4**, so the presence of **25** was understandable but also unavoidable. The presence of diastereomer **26** was theoretically possible based on the reactants but was not quantitated in the crude product mixture. As discussed earlier, chiral chromatography rendered the pure diastereomer **3** in 97.6% de and in 75% yield as an oil that retained about 3% w/w EtOH.

Polymorph screening of the succinate salt **1** revealed that acetone was a good solvent to provide a crystalline solid (as judged by XRPD) that was required for testing in the tox/tolerability studies. The salt formation procedure was straightforward: a heated solution of **3** with an eqimolar equivalent of succinic acid which resulted in a clear solution, which on seeding at 50 °C was allowed to cool to rt. After chilling to 0 °C, filtration, washing and drying provided the product. The succinate salt **1** directly obtained using chromatographed amine was ivory-colored, despite some color being retained in the mother liquors and was not brilliant-white as seen in earlier lots, so a decolorization procedure was required. The salt **1** was dissolved in MeOH, treated with 20% w/w Darco-60 charcoal, and warmed to 50 °C. Filtration and concentration gave a foam that was again recrystallized from acetone (6 vol). Seeding was not required, and upon cooling/filtration/washing and vacuum oven drying, there was obtained **1** in 81% yield in the chiral purity of 99.5% de and 99.1% HPLC purity. The API met the team's requirements for use in the tox/tolerability studies. Results of these tests will be reported elsewhere.

CONCLUSION

We have described the scale-up of CCR-2 antagonist **1** as its succinate salt in 135 g quantity that met the purity and polymorph specifications and achieved the goal of making the required amount within an aggressive timeline. The process for the formation of **1** involved a new method relative to the initial discovery chemistry route and focused on the preparation of all-carbon NHBoc acid **4** in 36% overall yield from starting **6**. The process involved diastereoselective enolate alkylation that led to an iodide precursor **13** that underwent a radical cyclization using tin-free conditions to intersect the previously known **10**. The final steps involved a sequence identical to the discovery route, coupling of acid **4** with amine **5**, Boc deprotection of **21**, reductive amination with **3**, chromatographic enrichment for the desired diastereomer **2**, and succinate salt formation completed the synthesis of final compound **1** in 8 steps overall and 14% yield from **6**. Additional work in the exploration of alternate cyclization strategies directed toward the preparation of other complex CCR-2 antagonists can be found in our companion paper.[2]

EXPERIMENTAL SECTION

(1*R*, 4*S*)-Methyl-1-(3-chloropropyl)-4-(2,5-dimethyl-1*H*-pyrrol-1-yl)cyclopent-2-enecarboxylate (15). To a solution of LHMDS (1 M in THF, 36.5 mL, 36.5 mmol, 1.6 equiv) cooled to −20 °C was added a solution of **14**[3c] (5 g, 22.8 mmol) in THF (23 mL) over 20 min. The anion was stirred for 20 min at −20 °C, cooled to −70 °C (dry ice/acetone), and 1-chloro-3-iodopropane (3.4 mL, 31.6 mmol, 1.4 equiv) was added quickly and the resulting solution stirred for 1 h at −70 °C. The bath was replaced by an ice bath, and the temperature was allowed to rise to 0 °C and stirred for 3 h at this temperature. The reaction was quenched by addition of aqueous NH_4Cl (6%, 25 mL) and isopropyl acetate (*i*PAc, 50 mL). The organic layer was separated and washed with aqueous NH_4Cl (6%, 25 mL) and brine (2 × 25 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated and gave (1*R*,4*S*)-methyl-1-(3-chloropropyl)-4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-cyclopent-2-enecarboxylate (4.42 g) as a brown oil in 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 6.03−6.05 (m, 2 H), 5.74 (s, 2 H), 5.30 (s, 1 H), 3.68−3.75 (m, 3 H), 3.54 (t, J = 6.2 Hz, 2 H), 2.30−2.49 (m, 2 H), 2.20 (s, 6 H), 1.67−1.91 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.22, 134.56, 133.51, 128.17, 106.35, 60.07, 58.52, 52.21, 44.82, 40.34, 35.83, 28.80, 13.83; LCMS (m/z): 296 (M + H, 100); exact mass calc for $C_{16}H_{23}ClNO_2^+$: 296.1412, found 296.1410.

To part of the above isolated chloride (1.15 g, 3.89 mmol) in acetone (14 mL) was added NaI (2.90, 19.4 mmol, 6 equiv), and the mixture was heated to 60 °C for 5.5 h. The reaction was cooled to rt and diluted with water (20 mL) and EtOAc (25 mL). The layers were separated, the aqueous layer extracted with EtOAc (20 mL), and the combined organics washed with brine (25 mL) and dried (Na_2SO_4). After filtration, the volatiles were removed on a rotary evaporator (29 in Hg, 40 °C), and the product **15** (1.36 g) was isolated as a red oil in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 5.97 (s, 2 H), 5.74 (s, 2 H), 5.30 (t, J = 8.3 Hz, 1 H), 3.69−3.77 (m, 3 H), 3.13−3.21 (m, 2 H), 2.31−2.51 (m, 2 H), 2.20 (s, 6 H), 1.76−1.87 (m, 2 H);); ^{13}C NMR (100 MHz, $CDCl_3$) 175.15, 134.56, 133.52, 128.16, 106.33, 60.01, 58.38, 52.22, 40.30, 39.24, 29.45, 13.82, 5.95; LCMS (m/z): 388 (M + H, 100); exact mass calc for $C_{16}H_{23}INO_2^+$: 388.0768, found 388.0621.

Alkylation of Ester 6 with 3-Chloro-1-iodopropane. LHMDS in THF (1M, 1.24 L, 1.24 mol) was quickly measured into a graduated cylinder under vigorous stream of N_2, transferred to a reaction flask, and cooled to −73 °C. A solution of **6**[8] (136 g, 0.564 mol) in THF (544 mL) was added at < − 67 °C. The resulting orange anion solution was stirred for 1.5 h at −70 °C. Another flask was charged with 3-chloro-1-iodopropane (85 mL, 0.789 mol) in THF (136 mL) and cooled to −69 °C. The orange anion solution was transferred over 30 min while keeping the temperature about −55 °C. The reaction was warmed to −40 °C and held for 30 min, −20 °C and held for 30 min, and then 0 °C for 30 min. Progress of the reaction was evaluated by TLC and NMR (quench aliquot): (20% EtOAc/heptanes, R_f **17** = 0.1; R_f **18** just below **17**; R_f **19** just above **18**; R_f **6** (conjugated) just above **19**; Ceric Ammonium Molybdate) [If the reaction is dark green or dark brown in color at this point, typically this was the result of an inadequate nitrogen sweep]. The reaction was carefully poured into a 4 L beaker which contained ice (750 g) and aqueous HCl (2 M, 1

dx.doi.org/10.1021/op500265z | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

L). The layers were separated in a separatory flask, and the aqueous was extracted with toluene (2 × 500 mL). The organic layers were combined, washed with H_2O (1 L and 500 mL) and brine (1 L and 500 mL), dried over Na_2SO_4, filtered, and evaporated (rotary evaporator, 29 in Hg, 40 °C) to afford 169 g of crude red oil. Purification by flash chromatography (2.5 kg) using the following conditions: a prewetted column with heptane (4 L) was loaded with crude product in CH_2Cl_2 (100 mL), eluted with heptane (4 L), 10% EtOAc/heptane (16 L), and 15% EtOAc/heptane (16 L). There was provided **17** (116.7 g, 65%) as a slowly crystallizing solid on standing; **18** was not isolated in this run but typically isolated in a mass recovery of 25%. The NMR ratios of **17**/**18** were seen in the range of 3.8:1 to 16:1 depending on the scale and variability of the run. **19** was only isolated for identification purposes and not fully characterized.

(1*R*,4*S*)-Methyl-4-(*tert*-butoxycarbonylamino)-1-(3-chloropropyl)cyclopent-2-ene-carboxylate (17). mp 52.8−61.3 °C, ^{1}H NMR (400 MHz, DMSO-d_6) 6.84 (d, J = 7.6 Hz, 1 H), 5.73 (dd, J = 2.1, 5.5 Hz, 1 H), 5.56−5.65 (m, 1 H), 4.37−4.50 (m, 1 H), 3.45−3.56 (m, 5 H), 2.07 (dd, J = 7.9, 13.6 Hz, 1 H), 1.88 (d, J = 6.8 Hz, 1 H), 1.43−1.65 (m, 1 H), 1.28 (s, 9 H); ^{13}C NMR (100 MHz, DMSO-d_6) 175.03, 155.00, 134.47, 133.89, 77.68, 57.72, 51.85, 45.24, 35.27, 28.21, 28.15; $[\alpha]_D^{25}$ −39.64 (c 1.1, MeOH), Anal. Calcd for $C_{15}H_{24}ClNO_4$: C, 56.69; H, 7.61; Cl, 11.16; N, 4.41. Found: C, 56.80; H, 7.85; Cl, 10.34; N, 4.43.

(1*S*,4*S*)-Methyl-4-(*tert*-butoxycarbonylamino)-1-(3-chloropropyl)cyclopent-2-ene-carboxylate (18). ^{1}H NMR (400 MHz, DMSO-d_6) 7.06 (d, J = 7.6 Hz, 1 H), 5.75 (s, 1 H), 5.67−5.74 (m, 2 H), 4.59 (d, J = 7.6 Hz, 1 H), 3.56−3.66 (m, 5 H), 2.65 (dd, J = 8.1, 13.2 Hz, 1 H), 1.78−1.92 (m, 1 H), 1.56−1.77 (m, 3 H), 1.47 (dd, J = 7.0, 13.3 Hz, 1 H), 1.38 (s, 9 H); ^{13}C NMR (100 MHz, DMSO-d_6) 174.84, 155.00, 134.62, 134.33, 77.67, 58.29, 55.73, 54.87, 51.94, 51.85, 45.41, 45.24, 35.27. 28.23, 28.05; $[\alpha]_D^{25}$ −112.61 (c 1.15, MeOH); Anal. Calcd for $C_{15}H_{24}ClNO_4$: C, 56.69; H, 7.61; Cl, 11.16; N, 4.41. Found: C, 56.59; H, 7.84; Cl, 11.08; N, 4.35.

(1*R*, 4*S*)-Methyl-4-(*tert*-butoxycarbonylamino)-1-(3-iodopropyl)cyclopent-2-ene-carboxylate (13). A solution of **17** (311 g, 0.978 mol) in acetone (3.7 L)was treated with NaI (741 g, 4.89 mol, 5 equiv) portion-wise, and the reaction was heated to 60 °C for 18 h (The progress of the reaction was monitored by NMR (DMSO-d_6 400 MHz) observing the disappearance of the triplet at 3.58 ppm for **17** and the appearance of the signal at 3.13 ppm for **13**). The reaction was cooled to rt, diluted with EtOAc (4 L), and washed with brine (2 L). The organic was rotary evaporated (29 in Hg, 40 °C) to a residue which contained water. EtOAc (1 L) was added to the residue, and the layers were allowed to separate. The separated organic layer was dried over Na_2SO_4, filtered, and concentrated to afford **13** (386 g) in 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 5.74−5.84 (m, 2 H), 4.69−4.98 (m, 2 H), 3.72 (s, 3 H), 3.14 (t, J = 6.5 Hz, 2 H), 2.07−2.26 (m, 2 H), 1.83−1.98 (m, 1 H), 1.59−1.83 (m, 3 H), 1.44 (s, 9 H), $[\alpha]_D^{25}$ −47.64° (c 1.5, MeOH); Anal. Calcd for $C_{15}H_{24}INO_4$ × 0.5 H_2O × 0.28 EtOAc: C, 44.53; H, 6.11; I, 29.18; N, 3.22; KF, 0.21. Found: C, 44.92; H, 6.39; I, 29.53; N, 3.36; KF, 0.20.

(2*R*,3a*R*,6a*R*)-Methyl-2-(*tert*-butoxycarbonylamino)-octahydropentalene-3a-carboxylate (10). A solution of **13** (385 g, 0.941 mol) and toluene (8.5 L) was heated to 78 °C. In a separate flask was added 2,2′-azo-bis-isobutyronitrile (16 g, 0.094 mol, 0.1 equiv), tris(trimethylsilyl)silane (377 mL, 1.213 mol, 1.28 equiv), and toluene (850 mL) and stirred until homogeneous. This homogeneous solution was added dropwise to the reaction flask over 1 h at >82 °C. The reaction was stirred for 2 h. (The progress of the reaction was monitored by TLC (20% EtOAc/heptanes, R_f dilane debris = 0.6; R_f **10** = 0.4; R_f cyclization product from iodo-**18** = 0.33; $KMnO_4$ stain). The reaction was cooled to rt, washed with H_2O (2 × 4 L), brine (2 L), dried over Na_2SO_4, filtered, and concentrated to afford crude product (681 g) which contained toluene and TMSI. The crude material was split in two equal portions (loaded in mix of DCM and heptane) and each purified by flash chromatography (5 kg, prewetted with heptane, 8 L) using a isocratic solvent system of 10% EtOAc/heptane and provided **10** (166.7 g) as a clear oil in 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 4.88 (br. s., 1 H), 4.08 (d, J = 7.1 Hz, 1 H), 3.69 (s, 3 H), 2.69−2.84 (m, 1 H), 2.13−2.24 (m, 1 H), 2.08 (dd, J = 7.0, 13.1 Hz, 1 H), 1.71−1.95 (m, 4 H), 1.48−1.71 (m, 3 H), 1.33−1.47 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) 179.3, 155.5, 79.1, 58.3, 52.2, 52.1, 47.5, 43.6, 40.3, 38.7, 34.0, 28.4, 26.2; $[\alpha]_D^{25}$ +17.13° (c 1.0) (MeOH), Anal. Calcd for $C_{15}H_{25}NO_4$ × 0.1 H_2O: C, 63.18; H, 8.91; N, 4.91. Found: C, 62.96; H, 9.01; N, 4.89; LCMS (m/z): 183 (M-Boc, 100), 305 (M + Na, 60).

(2*R*,3a*R*,6a*R*)-2-(*tert*-Butoxycarbonylamino)octahydropentalene-3a-carboxylic Acid (4). A solution of **10** (166 g, 0.585 mol), MeOH (930 mL), and H_2O (300 mL) was treated with 10 M NaOH (234 mL) and the reaction was heated to 65 °C for 2 h. The reaction was cooled to 10 °C and acidified with conc. HCl until pH = 3; H_2O (1.8 L) was added to the slurry and stirring continued for 1/2 h. The slurry was extracted with CH_2Cl_2 (2 L; 2 × 1 L), washed with brine (1 L), dried over Na_2SO_4, filtered and evaporated (29 in Hg, 40 °C) to afford **4** (146.1 g) as a white foam in 93% yield.

^{1}H NMR (400 MHz, DMSO-d_6) 12.09 (s, 1 H), 6.80 (br. s., 1 H), 3.75−3.92 (m, 1 H), 2.56−2.70 (m, 1 H), 2.11 (br. s., 1 H), 1.90 (br. s., 2 H), 1.72 (br. s., 1 H), 1.51−1.67 (m, 3 H), 1.37 (s, 11 H), 1.21 (br. s., 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) 179.05, 154.95, 77.38, 56.99, 50.59, 45.64, 42.63, 38.84, 38.51, 34.26, 28.18, 26.29; Anal. Calcd for $C_{14}H_{23}NO_4$ × 0.07 CH_2Cl_2 × 0.14 H_2O: C, 60.91; H, 8.49; N, 5.05; KF, 0.78. Found: C, 60.99; H, 8.54; N, 5.01; Karl Fischer, 0.79; $[\alpha]_D^{25}$ +13.94° (1.05) (MeOH); LCMS (m/z): 196 (M-Boc, 80), 291 (M + Na, 100).

***tert*-Butyl-(2*R*,3a*R*,6a*R*)-3a-(3-(Trifluoromethyl)-5,6,7,8-tetrahyro-1,6-naphthyridine-6-carbonyl)-octahydrentalen-2-yl-carbamate (21).** A solution of **4** (326 g, 1.21 mol) and *N*,*N*-dimethylacetamide (3.3 L) was treated with 1-hydroxybenzotriazole (217 g, 1.57 mol) and **5** (400 g, 1.45 mol). The slurry was cooled to 10 °C, followed by portionwise addition of EDC (354 g, 1.82 mol) at <20 °C. DIEA (634 mL, 3.63 mol) was added dropwise while maintaining a temperature <20 °C. The reaction was stirred for 2 h and quenched into *ice-cold* 5% $NaHCO_3$ (8.7 L). The above reaction mixture was stirred, and after a 15 min, a precipitate formed, and the slurry was stirred for 1 h. The solid was filtered and washed with aqueous 5% $NaHCO_3$ solution (4 × 2 L), H_2O (2 × 3 L), and heptane (2 × 2 L). The solid was placed into vacuum oven (29 in Hg) for 18 h at 40 °C and afforded **21** (413.6 g) as an off-white solid in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 8.70 (s, 1H), 7.69 (s, 1H), 4.90−4.68 (m, 2H), 4.60 (d, J = 7.3 Hz, 1H), 4.13 (d, J = 6.6 Hz, 1H), 4.02−3.83 (m, 2H), 3.55 (t, J = 5.7 Hz, 1H), 3.12 (br. s., 2H), 2.21 (dd, J = 5.7, 12.8 Hz, 1H), 1.95 (br. s., 1H), 1.92−

dx.doi.org/10.1021/op500265z | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

1.78 (m, 3H), 1.78−1.49 (m, 5H), 1.38 (s, 9H); $[\alpha]_D^{25}$ +47.69° (*c* 0.98) (MeOH), Anal. Calcd for $C_{23}H_{30}F_3N_3O_3 \times 0.35\ H_2O \times 0.25$ DMAc: C, 59.67; H, 6.84; F, 11.66; N, 9.52; KF, 1.32. Found: C, 60.05; H, 6.96; F, 11.27; N, 9.41; KF, 1.33; HPLC (Zorbax SD): 5.97 min, 86%; LCMS (*m*/*z*): 353 (M-Boc, 100), 476 (M + Na, 20).

(2*R*,3a*R*,6a*R*)-2-Aminooctahydropentalen-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthridine-6(5*H*)-yl)methanone Dihydrochloride (22). **CAUTION**: non-restricting venting should be used, as there was a vigourous outflow of gas during this reaction. A mixture of **21** (222.7 g, 0.491 mol) in HCl in MeOH (1.25 M, 4 L, 4.91 mol) was heated in stages, first to 40 °C in 10 min, then to 50 °C in 10 min, and finally to 60 °C in 10 min, at which point the reaction was held for 40 min. Vigorous off-gassing ceased after 40 min. The reaction was cooled and evaporated (10 mm Torr) to dryness at 40 °C. MeOH (1 L) was added, the contents swirled until dissolved, and the volatiles removed under vacuum. This MeOH treatment was repeated one more time. The orange contents were suspended in *i*-PrOH (620 mL) at 40 °C for 15 min, and heptane (1.75 L) was added to the suspension. Cooling the bath with ice commenced, and the suspension was swirled for 20 min at 21 °C. The light yellow solid was filtered, washed with 20% IPA/heptane (500 mL), and allowed to air-dry at rt overnight and afforded **22** (186.5 g) as a yellow solid in 89% yield. mp 193.0−195.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) 8.83 (s, 1H), 8.29 (br. s., 4H), 7.19 (br. s., 3H), 4.85 (d, *J* = 17.6 Hz, 1H), 4.74 (d, *J* = 18.1 Hz, 1H), 3.85 (br. s., 2H), 3.56 (br. s., 1H), 3.46−3.30 (m, 1H), 3.05 (br. s., 2H), 2.40 (dd, *J* = 7.1, 13.0 Hz, 1H), 1.91−1.72 (m, 4H), 1.70−1.59 (m, 2H), 1.44−1.21 (m, 2H); ^{19}F NMR (376 MHz, DMSO-d_6)−60.63; ^{13}C NMR (101 MHz, DMSO-d_6) 174.58, 143.16, 132.66, 130.30, 124.94, 123.45, 123.13, 122.24, 96.23, 89.20, 58.01, 50.62, 45.46, 41.92, 38.67, 35.78, 32.46, 31.19, 26.45; Anal. Calcd for $C_{18}H_{22}F_3N_3O \times 2HCl \times 0.35\ H_2O$: C, 49.97; H, 5.75; F, 13.17; Cl, 16.39; N, 9.71; 1.46; Found: C, 50.04; H, 5.73; F, 12.74; Cl, 16.61; N, 9.67; KF, 1.36; HPLC (eclipLO): 8.76 min, 98%; LCMS (*m*/*z*): 354 (M + H, 100).

((2*R*,3a*R*,6a*R*)-2-((3*R*,4*R*)-3-Methoxytetrahydro-2*H*-pyran-4-ylamino)octahydropentalen-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone (2). A solution of **22** (80 g, 0.187 mol), 1,2-dichloroethane (400 mL), and water (140 mL) at 0 °C was neutralized by careful addition of aqueous NaOH (1M, 140 mL) over 10 min, at <6 °C. The mixture was stirred for 2 min, and an attempt was made to separate the layers; water (50 mL) and brine (50 mL) were added, but a clean interface could not be achieved. The biphasic mixture was filtered with Celite. A minimum of dichloroethane should be used here to rinse the filter-aid. The aqueous layer was drawn off and shaken with 1,2-dichoroethane (200 mL), and this mixture was filtered through the original Celite pad. The combined organic layers were washed with aqueous $NaHCO_3$ (saturated, 25 mL), dried (Na_2SO_4), and filtered (washing the drying agent with 2 × 25 mL fresh DCE), and the solution containing **23** was used directly in the next reaction. A KF analysis of the solution was found to be 1.99% water.

A solution of **23** (675 mL solution, assumed 66.5 g, 0.187 mol) was chilled to 0 °C. Acetic acid (glacial, 22 mL) was added, followed by solid $Na(AcO)_3BH$ (56.05 g, 0.264 mol), and the resulting suspension was stirred for 5 min. A solution of **3** (33.05 g, 0.254 mol, 86.5% ee) in 1,2-dichloroethane (200 mL) was added over 20 min, and a rise of 4 °C was noted. The reaction was stirred for 0.75 h at 0 °C; HPLC showed **23** to still be present (16.1%, compared to 79% for **2**, along with 2.4% trans isomer **24**). A second charge of **3** (3.75 g) in 1,2-dichloroethane (20 mL) was made. HPLC after 30 min showed a reduction of **23** to 1.3%, and after allowing the reaction to warm to rt overnight, the amount of **23** was reduced to 0.45% (although the trans isomer **24** increased to 4.6%). The reaction was chilled in an ice bath, aqueous NaOH (3N, 430 mL) was added. The layers were separated, and the aqueous layer (pH 13) was extracted with DCE (1 × 100 mL), upon which a second extraction with DCE (100 mL) produced an emulsion that required filtration through Celite. The combined organic layers were dried (Na_2SO_4) and filtered, and the volatiles were evaporated under reduced pressure. The crude product was obtained as a red thick oil (98.3 g, 111% isolated yield). The crude products from two other similar runs were combined (totaling 183 g) and sent for chromatographic separation: first, using the reverse phase to remove a small amount of **23**, and the trans reductive amination isomer **24** (minor), followed by Chiralpak AD, using 2:1:1 IPA/EtOH/heptane to remove the cis-reductive amination product **25** and provided 150 g of red oil (residual EtOH detected). After treating to high vacuum with heat (5 mm, 50 °C) there was provided **2** (137.7 g) in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 8.70 (s, 1H), 7.68 (s, 1H), 4.78 (d, *J* = 6.4 Hz, 2H), 4.11−3.81 (m, 5H), 3.74 (s, 2H), 3.61−3.47 (m, 2H), 3.43−3.23 (m, 8H), 3.12 (br. s., 2H), 2.82−2.71 (m, 1H), 2.21−1.85 (m, 3H), 1.82−1.48 (m, 15H), 1.35−1.20 (m, 1H). HPLC (EclipLO): 9.40 min, 98.2%.

((2*R*,3a*R*,6a*R*)-2-((3*R*,4*R*)-3-Methoxytetrahydro-2*H*-pyran-4-ylamino)octahydropentalen-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone Semisuccinate (1). A solution of **2** (137.7 g, 0.284 mol) and acetone (660 mL) was warmed to 50 °C, and succinic acid (34.9 g, 0.295 mol) was added in one portion. The temperature jumped to 55 °C, the solution cleared immediately, and after settling back to 50 °C, no precipitate was evident. The solution was seeded, and within a few minutes, cloudiness ensued, followed by precipitation. The heating was continued for 1.25 h total. The heat was removed, and the suspension was allowed to come to rt over ∼1 h. The suspension was chilled in an ice bath to 0 °C and filtered through paper, and the solid was washed with ice-cold acetone (150 mL), followed by room temperature acetone (50 mL). After drying the isolated solid in a vacuum oven (29 mmHg, 27 °C), the batch was deemed unacceptable for delivery because of the ivory-tinge color (139.2 g) and was not identical to the brilliant white color of lots delivered previously.

Decolorization Procedure. A solution of **1** (139.2 g) and MeOH (2.1 L) was treated with Darco G-60 charcoal (Aldrich cat. # 242276−250 g, Lot # 04916KD) and the contents warmed with 50 °C for 10 min. Hot filtration through Celite proceeded, followed by washing the plug with MeOH (rt, 200 mL). The filtrate was evaporated (29 in Hg, 40 °C), and the resulting white foam (159 g) was suspended in acetone (720 mL) and swirled at 50 °C for 45 min. In about 10 min of swirling the hazy liquid, crystals started to form on the top of the liquid surface; in 20 min, copious solid formed, and within 30 min, a solid was thick and required mechanical scraping to free from the sides of the flask. After 45 min, the heat was turned off; ice was added to the bath, and (when the flask was cold to the touch) the solid was filtered, washed with rt acetone (150 mL), and the solid dried in a vacuum oven (27 °C, 30″ Hg) for 60 h. The white solid **1** (135.1 g) was obtained in 81%

dx.doi.org/10.1021/op500265z | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

yield. mp: 166.5−168.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) 10.81−9.06 (m, 2H), 8.78 (s, 1H), 8.19 (br. s., 1H), 4.90−4.61 (m, 2H), 3.95 (d, J = 12.5 Hz, 1H), 3.85 (br. s., 2H), 3.80−3.60 (m, 1H), 3.54−3.32 (m, 3H), 3.32−3.15 (m, 5H), 3.01 (br. s., 3H), 2.42−2.23 (m, 5H), 2.04−1.81 (m, 2H), 1.78−1.68 (m, 2H), 1.67−1.48 (m, 4H), 1.45−1.33 (m, 1H), 1.33−1.14 (m, 1H); ^{19}F NMR (376 MHz, DMSO-d_6) −60.6 ppm; ^{13}C NMR (101 MHz, DMSO-d_6) 175.22, 174.26, 143.91, 131.69, 129.88, 125.16, 123.14, 122.82, 122.50, 122.46, 74.14, 64.89, 64.83, 57.82, 55.61, 55.09, 53.54, 45.34, 43.91, 39.00, 37.21, 32.76, 30.34, 27.13, 26.50; $C_{28}H_{38}F_3N_3O_7$: C, 57.43; H, 6.54; F, 9.73; N, 7.18; Found: °C, 57.33; H, 6.53; F, 9.50; N, 7.09; KF <0.1%; $[\alpha]_D^{25}$ +26.5° (c 1.0) (MeOH); HPLC (eclipLO): 9.33 min, 99.1%; HPLC (genpur01): 13.17 min, 96.1%; Chiral HPLC (xlb5): 6.31 min, 99.5%.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR for all reported compounds and all HPLC and chiral HPLC methods. 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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(12) We would like to thank Dr. Wim Aelterman for these suggestions.

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