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Practical Asymmetric Synthesis of RO5114436, a CCR5 Receptor Antagonist

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Abstract:

A practical asymmetric synthesis of a 3,7-diazabicyclo[3.3.0]octane derivative (1), a representative of a new class of potent CCR5 receptor antagonists, is described. The benzylamine stereogenic center of 1 was introduced by a ruthenium-catalyzed asymmetric reductive amination using (*R*)-MeOBIPHEP as ligand. Aldehyde 4, prepared by Parikh−Doering oxidation, was used without workup in the reductive amination reaction, which not only simplified the process but also overcame the instability of 4. The 3,7-diazabicyclo[3.3.0]octane core was obtained by a [3 + 2] cycloaddition.

1. Introduction

The chemokine receptor CCR5 is a clinically validated target for Human Immunodeficiency Virus (HIV) disease and a potentially interesting target for the inflammation therapy area. The first small-molecule CCR5 antagonist on the market, maraviroc (Selzentry), was approved by the FDA for treatment of HIV-1 infection.[1] Medicinal chemistry research at Roche led to the discovery of a series of 3,7-diazabicyclo[3.3.0]octane compounds,[2] represented by **RO5114436** (**1**), that are potent CCR5 antagonists. Compound **1** also showed high potency in functional assays for inflammation. The PK properties of **1** were superior to those of maraviroc in preclinical species, including rat, dog, and monkey. In order to satisfy our need for kilogram amounts of **1** for toxicity studies, an enantioselective synthesis was envisioned.

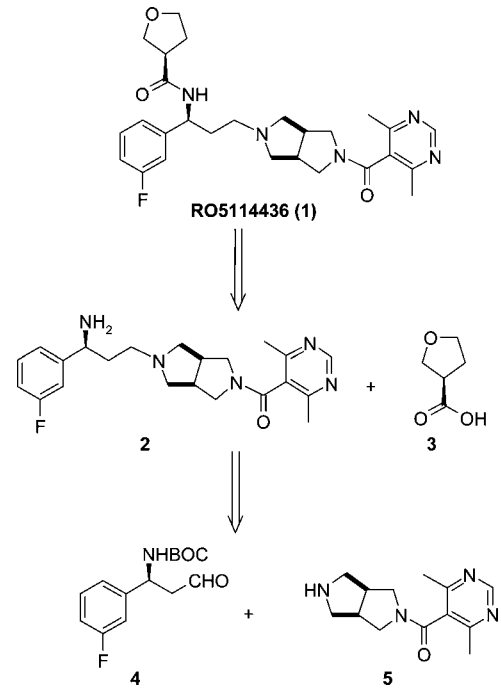
We disclose herein our studies on the practical synthesis of **1**. We focused on the set of retrosynthetic disconnection shown in Scheme 1. Peptide coupling between primary amine **2** and acid **3** would give the final active pharmaceutical ingredient (API). Amine **2** could be synthesized by reductive amination of aldehyde **4** with amine **5**.

2. Results and Discussion

2.1. Synthesis of aldehyde 4. Medicinal chemists had prepared aldehyde **4** from BOC-protected β-aminoester **7** by DIBAL-H reduction (Scheme 2). Ester **7** was prepared from the corresponding acid **6**, which was commercially available but very expensive.

The enantioselective synthesis of β-aminoester **12** was investigated in order to satisfy our needs for large amounts

Scheme 1. **Retrosynthetic analysis of 1**



(Scheme 3). Claisen condensation between commercially available ester **8** and EtOAc in the presence of potassium *tert*-butoxide produced β-ketoester **9** in near-quantitative yield. β-Ketoester **9** was a liquid, which was used as crude in the next step after aqueous workup with 3 N HCl. At least 2.5 equiv of potassium *tert*-butoxide was required for full conversion (3.0 equiv of potassium *tert*-butoxide was used for pilot-plant-scale preparations). It was also very important to add EtOAc last to achieve full conversion. The major byproduct in the crude product mixture was ethyl acetoacetate, which can be minimized by lowering the reaction temperature from ambient to 0 °C. β-Ketoester **9** was also prepared in quantitative yield by the condensation of *m*-fluoroacetophenone with diethylcarbonate using sodium hydride in THF. However, the cost of *m*-fluoroactophenone was much higher than that of ethyl 3-fluorobenzoate (**8**);[3] thus, this route was not selected.

The preparation of enantiomerically pure **12** was a key transformation for the whole process. One approach for the transformation could be the resolution of (±)-**12** via diastereomeric salt formation. Other possible approaches included an asymmetric Michael addition reaction to an appropriately substituted cinnamic acid ester,[4] and the enantioselective

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(1) (a) Haycock-Lewandowski, S. J.; Wilder, A.; Åhman, J. *Org. Process Res. Dev.* **2008**, *12*, 1094–1103. (b) Åhman, J.; Birch, M.; Haycock-Lewandowski, S. J.; Long, J.; Wilder, A. *Org. Process Res. Dev.* **2008**, *12*, 1104–1113, and references therein.

(2) Lee, E. K.; Melville, C. R.; Rotstein, D. M. *Chem. Abstr.* **2005**, *144*, 69821. PCT Int. Publication Number WO/2005/121145 A2, 2005.

(3) The list price was $245/100 g for *m*-fluoroactophenone and $71/100 g for ethyl 3-fluorobenzoate (**8**) at Fluorochem.

(4) See for example, Davies, S. G.; Ichihara, O.; Lenior, I.; Walters, I. A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1411.

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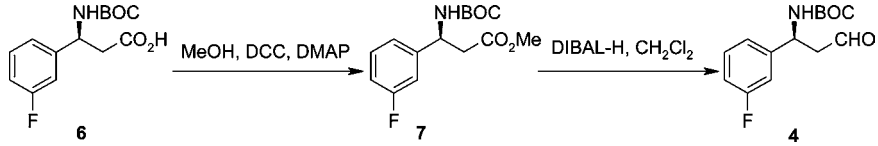
10.1021/op100020z

Scheme 2. **Medicinal chemistry synthesis of 4**



Scheme 3. **Synthesis of β-aminoester 12**

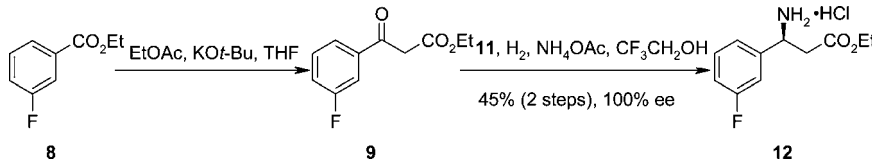
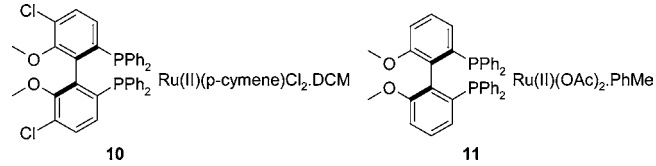


Table 1. **Reductive amination results for converting 9 into 12[a]**



entry	catalyst/(loading)	solvent/(vol)	NH_4OAc (equiv)	T (°C)	time (h)	H_2 (psig)	conv.[b] (%)	yield[c]/(ee)[d], (%/%)
1	**10**(2.5%)	TFE/(38)	5	80	16	40	100	52[e]/(99.6)
2	**11**(2%)	TFE/(10)	5	80	16	40	100	55[e]/(99.8)
3	**11**(2%)	MeOH/(10)	5	67	24	45	78	2.1
4	**11**(2%)	EtOH/(10)	5	80	16	45	77	4.4
5	**11**(2%)	IPA/(10)	5	85	16	45	76	3.4
6	**11**(2%)	TFE/(20)	5	80	16	45	100	46
7	**11**(2%)	TFE/(10)	5	80	16	45	100	46
8	**11**(2%)	TFE/(5)	5	80	16	45	95	38
9	**11**(2%)	TFE/(10)	2	80	16	45	100	45
10	**11**(2%)	TFE/(10)	7.5	80	16	45	100	41
11	**11**(2%)	TFE/(10)	10	80	16	45	92	30
12	**11**(2%)	TFE/(10)	5	80	16	100	100	44
13	**11**(2%)	TFE/(10)	5	80	16	200	100	45
14	**11**(2%)	TFE/(10)	5	80	16	300	100	43
15	**11**(1%)	TFE/(10)	5	75	16	100	100	47[e]
16	**11**(0.5%)	TFE/(10)	5	75	16	100	90	26[e]/(99.7)
17	**11**(2%)	TFE/(10)	5	70	16	100	93	38
18	**11**(2%)	TFE/(10)	5	60	16	100	78	17
19[f]	**11**(2%)	TFE/(10)	4	75	30	100	100	45[e]/(100)

[a] Conditions: Ru catalyst, NH_4OAc, H_2, (TFE), heat. [b] Conversion was determined on the basis of area % by HPLC (210 nm). [c] Yield was determined on the basis of area % by HPLC (210 nm). [d] Ee for the HCl salt of **12** is shown in parentheses. [e] Isolated yield. [f] Pilot-plant run (1.6 kg).

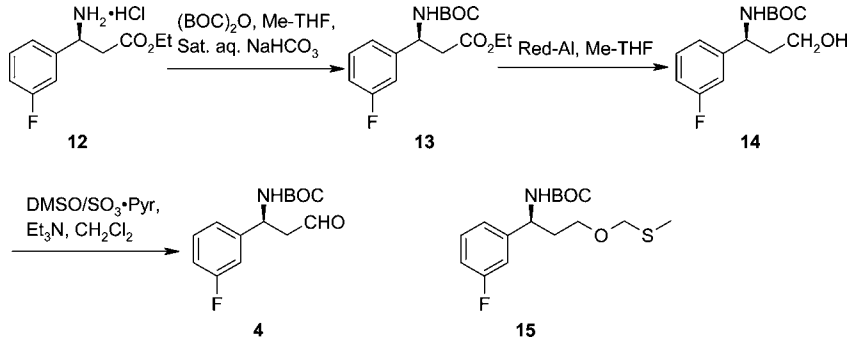
hydrogenation of a corresponding enamine.[5] The preliminary efforts for the chiral resolution of (±)-**12** and the enantioselective hydrogenation of the unprotected enamine were unsuccessful. The direct conversion of β-ketoesters to chiral β-aminoesters by catalytic asymmetric hydrogenation has been described in the literature.[6] The catalytic asymmetric amination and hydrogenation of ketoester **9** was investigated, and the results are summarized in Table 1. The reaction was first carried out following the literature procedure using the Ru-ClMeOBIPHEP catalyst **10**. Full conversion was achieved, and β-aminoester **12** was isolated in 52% yield and 99.6% ee after recrystallization from hexane as an acetic acid salt (entry 1, crude mixture has ~98% ee). The absolute configuration of **12** was confirmed by comparing BOC-protected **13** to the ethyl ester derivative of commercially available **6**. We then turned our attention to a similar catalyst, Ru-MeOBIPHEP catalyst **11**, which is more readily available to us.[7] The reductive amination performed equally well with catalyst **11**, giving product **12** in 55% isolated yield and 99.8% ee as a HCl salt after a single recrystallization from isopropyl acetate (entry 2, crude mixture has ~96% ee). We tested different solvents, including MeOH, EtOH, isopropanol (IPA), and 2,2,2-trifluoroethanol (TFE) (entries 2−5). TFE was the only solvent to give reasonable yields. The reasons for the beneficial results of using TFE were not disclosed in the literature.[6] Ten volumes of TFE were required to give full conversion and reasonable yield (entries 6−8). It was found

(5) (a) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D., III; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918–9919. (b) Hansen, K. B.; Hsiao, Y.; Xu, F.; Rivera, N.; Clausen, A.; Kubryk, M.; Krska, S.; Rosner, T.; Simmons, B.; Balsells, J.; Ikemoto, N.; Sun, Y.; Spindler, F.; Malan, C.; Grabowski, E. J. J.; Armstrong, J. D., III. *J. Am. Chem. Soc.* **2009**, *131*, 8798–8804.

(6) Bunlaksananusorn, T.; Rampf, F. *Synlett* **2005**, 2682–2684.

(7) Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370–389. We have multikilograms of catalyst **11** in Roche stock.

Scheme 4. **Synthesis of aldehyde 4**



that the equivalency of ammonium acetate was very important for this transformation (entries 7, 9−11). Greater than 7.5 equivalents of ammonium acetate led to lower conversion. It was unclear why the conversion was affected. Four equivalents of ammonium acetate were used for the final scale-up studies. Hydrogen pressure (40−300 psig) was not critical to the outcome of the reaction (entries 7, 12−14). A middle point of hydrogen pressure at 100 psig was applied for the large-scale synthesis. The effect of catalyst loading was also investigated (entries 12, 15−16). Greater than 1 mol % catalyst was required to achieve good conversion and 2 mol % of catalyst **11** was used in the scale-up run. The reaction was very slow when the temperature was lower than 70 °C (entries 17−18). Since lower temperature gave less byproduct, the temperature for the large-scale synthesis was set at 75 °C. Different additives were tested, including acetic acid, *p*-toluenesulfonic acid, methanesulfonic acid, pyridine, triethylamine, di-*tert*-butyldicarbonate. All these additives led to either lower conversion and/or decreased yields. The pilot-plant run, using 2 mol % catalyst **11**, 4 equiv of ammonium acetate, 10 volumes of TFE, hydrogen at 75 °C and 100 psig, gave chiral amine **12** in 45% isolated yield and 100% ee as the hydrochloride salt (entry 19). The major byproduct was the cinnamic acid ethyl ester by the elimination of ammonia from product **12**, which was confirmed by ^{1}H NMR analysis. A dimer byproduct was also observed by LC−MS. Even though the yield was moderate (45% over two step), large amounts of enantiomerically pure **12** could be prepared in two steps from readily available starting materials, which satisfied our needs at the moment.

BOC protection of the primary amine **12** followed by DIBAL-H reduction of **13** was investigated for the synthesis of aldehyde **4** following Medicinal Chemistry procedures. The DIBAL-H reduction gave inconsistent results, with a mixture of desired aldehyde **4**, over-reduced alcohol **14**, and some starting ester **13**. In one of the better cases, when 2.4 equiv of DIBAL-H was used, aldehyde **4** was isolated in 82% yield, along with 13% of alcohol **14** after flash chromatography. The need to conduct this reaction at −78 °C also encouraged exploration of alternate routes. A two-step process, reduction of **13** to alcohol **14** followed by oxidation of **14** to aldehyde **4**, was employed (Scheme 4). Several conditions were tried for the reduction of ester **13** to alcohol **14** including sodium borohydride in EtOH under reflux, and lithium aluminum hydride in cold (0 °C) THF. Sodium borohydride gave inconsistent results, but lithium aluminum hydride gave **14** in near quantitative yield. Red-Al (Vitride) was the reagent of choice for scale-up because, as a convenient 65% solution in toluene, it is a less hazardous reagent, and it gave the same clean, full conversion of **14**. The amount of 2-methoxyethanol, which was generated on workup for Red-Al reduction, was not significant since no adduct peak with amine **5** was observed after oxidation and reductive amination. The fact that there were five following steps and three isolations also made 2-methoxyethanol not a residue of concern. Process-friendly nitroxyl radical (TEMPO)-based oxidation was investigated first for the conversion of alcohol **14** to aldehyde **4**. It also gave inconsistent results and was hard to drive to high conversion; overoxidation to the corresponding acid was significant. We examined a stabilized formulation of IBX (SIBX) to oxidize **14** in acetone.[8] About 90% conversion was achieved, with no overoxidation to the corresponding acid when 1.2 equiv of SIBX was used. However, SIBX is expensive ($1750/kg, quoted for 4 kg from SIMAFEX in September, 2007), and the safety issues about using it in the pilot plant were still a concern. We finally turned our attention to activated DMSO oxidation procedures. It was quickly realized that Parikh−Doering oxidation (SO_3•py, DMSO, and Et_3N) was the preferred method for this transformation.[9] Aldehyde **4** was usually obtained in greater than 90% yield based on HPLC. Methylsulfanylmethyl ether **15** (4−8%) was the major byproduct for this process. The purification of aldehyde **4** was difficult since it was not a crystalline compound and was unstable in air. This problem was addressed by using the oxidation reaction mixture directly to the next (reductive amination) step without workup. The reaction performed equally well as when using purified **4**. The dimethylsulfide (DMS) byproduct was carried to the next step and purged off with nitrogen after the reductive amination, using bleach as a trap. This procedure was carried out in the pilot plant, and the odor from DMS was well-contained.

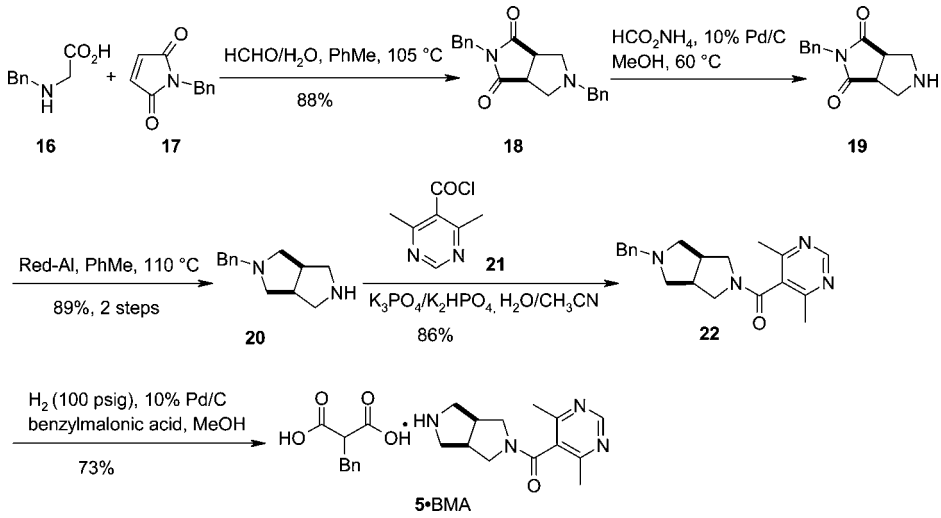
2.2. Synthesis of Amine 5. The synthesis of amine **5** started with *N*-benzylglycine (**16**) and *N*-benzylmaleimide (**17**) (Scheme 5). The bicyclic core was created by a [3 + 2] cycloaddition of **16**, **17**, and formaldehyde.[10] Despite what might be expected by the mechanisms proposed in the literature, which involve evolution of water, it was found that aqueous formaldehyde

(8) Ozanne, A.; Pouyse'gu, L.; Depernet, D.; François, B.; Quideau, S. *Org. Lett.* **2003**, *5*, 2903.

(9) Parikh, J. P.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

(10) Pennell, A. M. K.; Aggen, J. B.; Wright, J. J. K.; Sen, S.; Chen, W.; Dairaghi, D. J.; Zhang, P. *Chem. Abstr.* **2005**, *143*, 306291. PCT Int. Publication Number WO/2005/084667 A1, 2005.

Scheme 5. **Synthesis of amine 5**



(formalin) was a better source of formaldehyde for this particular [3 + 2] cycloaddition. The use of paraformaldehyde was not preferred because of the sublimation of paraformaldehyde to the condenser. The reaction was carried out at the boiling point of the toluene/water mixture, with formalin being added slowly to control reaction/distillation rate. Chemoselective debenzylation of *N*-benzyl tertiary amines in **18**, using ammonium formate in MeOH catalyzed by Pd/C, gave **19**. Electronic factors must have played a pivotal role in determining the selectivity of the debenzylation reaction. Red-Al reduction under forcing conditions (105 °C) converted **19** to the monobenzyl protected diamine **20**. Crude **20** was coupled with acid chloride **21** under Schotten−Baumann conditions to give amide **22**,[11] which was an oil and used in the next step without purification. EDCI-mediated coupling of **20** with 4,6-dimethylpyrimidine-5-carboxylic acid also successfully produced **22**.[12]

Deprotection of **22** was complicated by undesired side reactions and the fact that the product was an oil that was difficult to isolate. The *N*-methyl analogue of **5** was the major side product, along with unidentified impurities on the baseline. Transfer hydrogenation of **22** with ammonium formate required forcing conditions to reach completion and generated the *N*-methyl analogue of **5** as a significant impurity that carried through the synthesis. An extensive screen of classical hydrogenation conditions including solvent and catalyst showed that 10% Pd/C with acetic acid in MeOH worked best. Under these conditions, both temperature and hydrogen pressure could be raised to achieve a faster reaction rate, without the generation of the *N*-methyl impurity. Unfortunately, the acetic acid salt of **5** failed to crystallize despite extensive solvent screening. A search was conducted to find an acid additive that would, in addition to accelerating the debenzylation of **22**, provide a crystalline product to enable purification of **5** and be suitable for scale-up. Screening of acids revealed that, while some additives expedited the hydrogenation, only benzylmalonic acid also afforded a crystalline product (Table 2). Hydrogenolysis needed to be conducted in a solvent that the product was soluble in so that it could be filtered away from the catalyst. MeOH was chosen as the solvent because the resulting salt was soluble in MeOH at room temperature but not in IPA. IPA proved to be a good recrystallization solvent.

Table 2. **Effect of acid additives on hydrogenation of 22**[a]

acid	conversion[b] (%)	product form
acetic	100	oil
oxalic	45	oil
succinic	100	oil
phenylsuccinic	100	oil
benzylsuccinic	100	oil
glutaric	100	oil
L-tartaric	58	oil
citric	75	oil
salicyclic	100	oil
malonic	100	oil
phenylmalonic	60	oil
benzylmalonic	100	solid[c]
tartronic	69	oil
2,5-dihydroxybenzoic	100	oil
1-naphthoic	0	oil
tricarballylic	96	oil

[a] Reaction was performed with 1.0 equiv of acid in MeOH (10 vol) at 40 °C under H_2 (50 psig) with 10% Pd/C (10 wt %) for 24 h. [b] Conversions were determined by HPLC area % (210 nm). [c] Crystallized from 2-propanol.

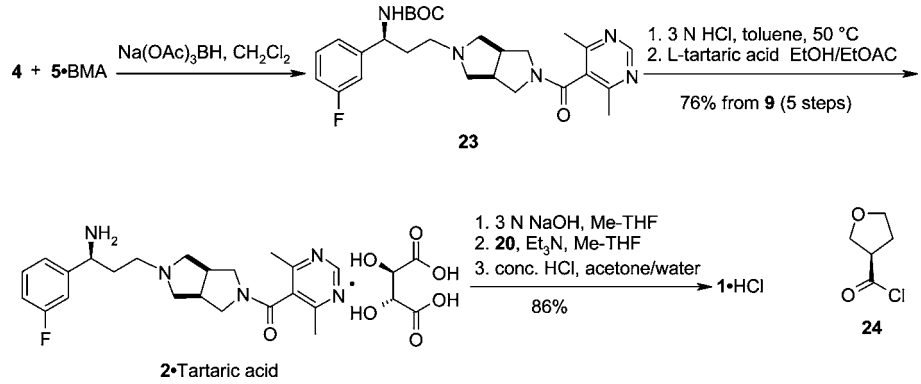
2.3. Coupling of 4 and 5. Reductive amination of aldehyde **4** with amine **5** was carried out using sodium triacetoxyborohydride (STAB) in dichloromethane (Scheme 6).[13] Aldehyde **4** was used as the crude reaction mixture from the Parikh−Doering oxidation without workup. Amine **5** was used directly as the benzylmalonic acid (BMA) salt, avoiding a low-yielding (due to the high water solubility of **5**) free amine formation step. The BOC-protected amine **23** was not crystalline; therefore, after workup it was used directly in the next step without purification. Deprotection of **23** was accomplished using aqueous HCl/toluene at 50 °C, giving amine **2** as a dry foam. An

(11) Kuo, S.-C.; Tsai, D. J.-S.; Liao, H. *Chem. Abstr.* **2006**, *145*, 124603. PCT Int. Publication Number WO/2006/074264 A2, 2006.

(12) (a) McCombie, S.; Tagat, J. R.; Vice, S.; Lin, S.-I.; Steensma, R.; Palani, A.; Neustadt, B.; Baroudy, B.; Strizki, J.; Endres, M.; Cox, K.; Dan, N.; Chou, C.-C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 567–571. (b) Palani, A.; Shapiro, S.; Clader, J. W.; Greenlee, W. J.; Vice, S.; McCombie, S.; Cox, K.; Strizki, J.; Baroudy, B. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 709–712. (c) Draper, R. W. *Chem. Abstr.* **2005**, *142*, 176442. PCT Int. Publication Number WO/2005/007608 A2, 2005.

(13) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.

Scheme 6. **Coupling of the fragments**



extensive effort to find a solid derivative of **2** to effect purification and facilitate isolation resulted in the finding that a 1:1 mixture of **2** and L-tartaric acid gave a nicely behaved solid in good yield. Although the purity of **2** was modestly improved, X-ray powder diffraction analysis showed that this salt was completely amorphous. A crystalline derivative was not found. Thus, amine **2** was treated with L-tartaric acid in a mixture of EtOH and EtOAc to afford the tartaric acid salt of **2** in 76% over all yield for five steps.

Completion of the synthesis required coupling of acid **3** with amine **2**. Acid **3** was converted to acid chloride **24** by reaction with oxalyl chloride (cat. DMF) and isolation as a stable toluene concentrate. The tartaric acid salt of amine **2** was converted to its free base using Me-THF/3 N NaOH. Acylation of free amine **2** in Me-THF with the toluene solution of acid chloride **24** in the presence of triethylamine gave the free base of API **1**. Despite a considerable effort, of the two salts found, only the HCl salt of **1** was found to be useful. Treatment of an acetone/water (95/5) solution of **1** with conc. HCl gave a nicely crystalline solid (**1**·HCl, 1:1 molar ratio, mp 149−150 °C) in 86% yield that proved to be a stable monohydrate.

3. Conclusion

In summary, a convergent 13-step route (8 longest linear steps) to **1** was developed and used to produce highly chemical and chiral pure material suitable for toxicity studies. All the chromatographic purifications were removed. The chiral amine center was produced by a highly enantioselective reductive amination reaction using chiral ruthenium catalyst **11** (95−96% ee for crude mixture, and >99.5% ee after isolation). The Parikh−Doering oxidation was used to efficiently produce aldehyde **4**, which was used for the next reductive amination reaction directly without workup. This process was critical since it not only simplified the overall process but also overcame the instability of aldehyde **4**. The overall yield for this process was about 29% starting from ethyl 3-fluorobenzoate (**8**).

4. Experimental Section

General. HPLC analysis was performed using the following system: Waters 2690 HPLC with Zorbax SB-C8 column 4.6 mm × 75 mm, 3.5 μm particles; mobile phase consisting of solvent A, 0.1% trifluoroacetic acid in water, solvent B, 0.1% trifluoroacetic acid in MeCN. Gradient from 10−90% mobile phase B in 10 min; λ = 210 nm. Chiral purity was monitored by SFC as the trifluoroacetamide using the following system: Mettler-Toledo/Berger Analytical SFC with (R,R)-Whelk-O1 column, 4.6 mm × 250 mm, 5 um particles. Mobile phase consisted of 95% carbon dioxide and 5% ethanol containing 0.4% (v/v) isopropylamine at a flow rate of 2.5 mL/min and 125 bar backpressure. Column temperature was 40 °C, detection was UV at 262 nm. Run time was 6 min.

3-(3-Fluorophenyl)-3-oxopropionic Acid Ethyl Ester (9). To a stirred and cooled (−10 °C) solution of potassium *tert*-butoxide in THF (1.0 M, 33.77 kg, 37.44 mol) in an 80-L glass-lined reactor was added ethyl 3-fluorobenzoate **8** (2.11 kg, 12.55 mol). EtOAc (3.01 kg, 34.16 mol) was added to the cooled (−10 °C) solution over 90 min at −10 to −5 °C. After 1 h, the mixture was treated with 3 N HCl (15.0 kg, 42.9 mol) and concentrated under reduced pressure (30−125 Torr) at 25−30 °C to remove the solvents with low boiling points. The mixture was extracted with MTBE (16.5 kg), and the organic layer was washed with water (15.3 kg), a mixture of saturated aqueous $NaHCO_3$ (5.0 kg)/saturated aqueous Na_2CO_3 (10.0 kg), and with brine (10.0 kg). Solvents were removed under reduced pressure (30−125 Torr) to give **9** (2.90 kg, 90% pure, 2:1 ketone/enol form based on ^{1}H NMR, ∼99% yield) as an oil,[14] which was used directly to the next chemical step. An analytically pure sample of **9** was obtained by column chromatography and characterized. ^{1}H NMR (300 MHz, $CDCl_3$) 1.27 (t, J = 7.16 Hz, 2 H), 1.35 (t, J = 7.16 Hz, 1 H), 3.98 (s, 1.4 H), 4.17−4.35 (m, 2 H), 5.66 (s, 0.3 H), 7.11−7.22 (m, 0.3 H), 7.27−7.79 (m, 3.7 H), 12.56 (s, 0.3 H). MS m/z 211.1 $[M + H]^+$. HPLC t_R = 7.12, 8.96 min.

(*S*)-3-Amino-3-(3-fluorophenyl)propionic Acid Ethyl Ester Hydrochloride Salt (12·HCl). Ketoester **9** (3.38 kg, ca. 90%, pure, ∼14.5 mol) and TFE (48 kg) were added successively to a nitrogen-inerted 40-L glass-lined reactor with NH_4OAc (2.46 kg, 57.9 mol) and Ru[(*R*)-MeOBIPHEP](OAc)$_2$ (**11,** 68 g, 0.072 mol),. The mixture was heated at 75 °C under hydrogen at 100 psig. After 30 h, the reaction achieved full conversion. The solvents was removed under reduced pressure (30−125 Torr). Isopropyl acetate (37 kg) was added, and the mixture was washed with saturated aqueous Na_2CO_3 (25 kg, pH = 9) and 1:1 brine/water (22 kg). HCl in IPA (4.82 N, 2.8 kg, 14.8 mol) was added to the organic phase, and the solvent

(14) Several stripping to dryness operations remain that can be optimized for mulitkilogram scale by using solvent exchange operations. This was not completed due to the termination of the work.

was removed under reduced pressure (30−125 Torr) at 45 °C until the volume was reduced to about 10 L. The mixture was slowly cooled to −10 °C and filtered, and the solids were washed with isopropyl acetate and dried in an oven under reduced pressure (30−50 Torr) to give **12**·HCl (1.60 kg, 45% yield, 100% ee) as a white solid. Mp 156.0−159.0 °C. IR ν_{max} (KBr) 3432, 2894, 2700, 1738, 1596, 1524, 1266, 1028 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 1.16 (t, J = 7.16 Hz, 3 H), 3.01 (dd, J = 16.58, 7.91 Hz, 1 H), 3.15−3.33 (m, 1 H), 4.05 (q, J = 7.16 Hz, 2 H), 4.78 (br s, 1 H), 6.95−7.13 (m, 1 H), 7.27−7.40 (m, 3 H), 8.84 (br s, 3 H). MS m/z 212.1 $[M + H]^+$. $[\alpha]^{20}_D$ = +4.9 (CH_3OH). HPLC t_R = 4.0 min.

(*S*)-3-*tert*-Butoxycarbonylamino-3-(3-fluorophenyl)propionic Acid Ethyl Ester (13). To a 40-L glass-lined reactor was added successively amine **12** (460 g, 1.86 mol), Boc_2O (405 g, 1.86 mol), Me-THF (4.6 L), and saturated aqueous $NaHCO_3$ (2.66 kg, 2.79 mol) at ambient temperature. After stirring overnight, the two phases were separated, and the organic layer was washed with water (4.6 L) and brine (4.6 L). The organic layer was distilled under atmosphere pressure to give **13** (97% purity by HPLC area), which was used to the next step without further purification. An analytically pure sample of **13** was obtained by recrystallization from heptane and characterized. Mp 56.0−57.0 °C. ^1H NMR (300 MHz, $CDCl_3$) 1.17 (t, J = 7.16 Hz, 3 H), 1.42 (s, 9 H), 2.63−3.03 (m, 2 H), 4.07 (q, J = 7.16 Hz, 2 H), 5.07 (br. s., 1 H), 5.58 (br. s., 1 H), 6.88−7.11 (m, 3 H), 7.28−7.34 (m, 1 H). MS m/z 256.1 $[M - t\text{-Bu} + 2H]^+$. Anal. Calc'd for $C_{16}H_{22}FNO_4$: C, 61.72; H, 7.12; N, 4.50. Found: C, 61.97; H, 7.03; N, 4.70.

[(*S*)-1-(3-Fluorophenyl)-3-hydroxypropyl]carbamic Acid *tert*-Butyl Ester (14). Red-Al (65 wt % in toluene, 1.19 kg, 3.83 mol) over 15 min was added to a stirred and cooled (0−15 °C) solution of **13** (ca. 1.86 mol) in Me-THF (6.9 L) in a 40-L glass-lined reactor. The mixture was warmed to 24 °C after addition. After 5 h, the reaction mixture was cooled to 10 °C, quenched with 10% aqueous NaOH (4.6 L), and extracted with toluene (4.6 L). The organic layer was washed with 10% aqueous NaOH (2.3 L) and two times with brine (2 × 4.6 L). The organic layer was concentrated under reduced pressure (30−125 Torr) to give crude **14** (97% purity by HPLC area) as a colorless viscous oil, which was used in the next step directly. An analytically pure sample of **14** was obtained by column chromatography over silica gel and characterized. ^1H NMR (300 MHz, $CDCl_3$) 1.44 (s, 9 H), 1.69−1.90 (m, 1 H), 1.93−2.30 (m, 1 H), 2.89 (br s, 1 H), 3.56−3.79 (m, 2 H), 4.79−4.98 (m, 1 H), 5.12 (dd, J = 8.57, 4.05 Hz, 1 H), 6.89−7.14 (m, 3 H), 7.28−7.38 (m, 1 H). MS m/z 214.1 $[M - t\text{-Bu} + 2H]^+$.

[(*S*)-1-(3-Fluorophenyl)-3-oxo-propyl]carbamic Acid *tert*-Butyl Ester (4). Triethylamine (0.75 kg, 7.4 mol) was added to a stirred and cooled (0 °C) solution of crude **14** (∼1.86 mol) in DMSO (1.0 L, 13.9 mol) and DCM (2.5 L) in a 40-L glass-lined reactor. In another 5-L flask, DMSO (1.0 L, 13.9 mol) and pyridine (0.45 L, 5.6 mol) were added to sulfur trioxide pyridine complex (45% SO_3, 0.89 kg, 5.6 mol) at ambient temperature. After agitating for 20 min, the resulting suspension was added to the previously formed, cooled solution of alcohol **14** over 15 min. The mixture was warmed to 20 °C and stirred overnight. The reaction achieved full conversion to give aldehyde **4** (88% purity by HPLC area), which was used directly in the next step. An analytically pure sample of **4** was obtained by column chromatography over silica gel and characterized. Mp 63.7−66.2 °C. ^1H NMR (300 MHz, $CDCl_3$) 1.42 (s, 9 H), 2.79−3.15 (m, 2 H), 5.19 (br s, 2 H), 6.91−7.16 (m, 3 H), 7.31 (dt, 1 H), 9.74 (dd, J = 2.26, 1.51 Hz, 1 H). MS m/z 212.1 $[M - t\text{-Bu} + 2H]^+$.

2,5-Dibenzyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3-dione (18). Toluene (42 kg) was added to a mixture of *N*-benzylglycine (**16**, 2.16 kg, 13.11 mol) and *N*-benzylmaleimide (**17**, 1.76 kg, 9.38 mol) in a 120-L glass-lined reactor, and the resulting solution was heated to just under reflux (∼105 °C). Formaldehyde/water (1.06 kg, 37% w/w, 13.1 mol) was added at a rate of 300 mL/h while collecting toluene/water distillate. After the completion of the reaction, the reaction mixture was cooled, and the solvent was distilled under reduced pressure (30−125 Torr) at 50 °C. MeOH (28 L) was added and then distilled off, the mixture was cooled to ambient temperature, and more MeOH (22.4 L) was added. Water (15 L) was slowly added to the solution over 2 h, and the slurry was stirred at ambient temperature overnight and then filtered. The solid was washed with MeOH/water (3 × 4 L, 60:40 v/v) and dried at 50 °C under reduced pressure (30−50 Torr) to give **18** (2.65 kg, 88% yield, 99% purity by HPLC area) as a light-gray solid. ^1H NMR (300 MHz, $CDCl_3$) 2.13−2.58 (m, 2 H), 3.07−3.25 (m, 2 H), 3.30 (d, J = 10.2 Hz, 2 H), 3.55 (s, 2 H), 4.69 (s, 2 H), 6.90−7.67 (m, 10 H). MS m/z 321.1 $[M + H]^+$.

2-Benzyloctahydropyrrolo[3,4-*c*]pyrrole (20). A mixture of **18** (2.62 kg, 8.18 mol), ammonium formate (0.57 kg, 0.90 mol), 10% Pd/C (0.26 kg, 62.4% water wet) and MeOH (21 kg) was heated at 60 °C. After 5 h, the reaction mixture was cooled to ambient temperature, and the catalyst was filtered off through a pad of Solka Floc. The solvent was removed under reduced pressure (30−125 Torr) at 40 °C, and the residue was treated with toluene (23 kg). The mixture was washed with water, and the organic layer was concentrated to about half volume under reduced pressure (30−125 Torr). The solution (containing crude **19**) was added slowly to a Red-Al solution (4.13 kg, 65% in toluene, 13.3 mol) in toluene (2.6 L) at 50 °C. The reaction mixture was stirred under reflux, achieving full conversion in 5 h. The mixture was cooled to 0 °C and slowly treated with 15% aqueous NaOH solution. The organic layer was concentrated under reduced pressure (30−125 Torr) at 50 °C to give **20** (1.47 kg, ∼89% yield, 81% purity by HPLC area) as an oil. ^1H NMR (300 MHz, $CDCl_3$) 2.09−2.46 (m, 2 H), 3.52−2.92 (m, 8 H), 3.52 (s, 2 H), 7.13−7.38 (m, 5 H). MS m/z 203.1 $[M + H]^{+1}$.

(5-Benzylhexahydropyrrolo[3,4-*c*]pyrrol-2-yl)-(4,6-dimethylpyrimidin-5-yl)methanone (22). To a suspension of commercially available 4,6-dimethylpyrimidine-5-carboxylic acid[11] (1.015 kg, 6.67 mol) and DMF (5.6 mL) in acetonitrile (7.1 L) was added oxalyl chloride (0.89 kg, 7.0 mol) at such a rate as to maintain the reaction temperature between −5 to 5 °C. The mixture was then aged at 0 °C for 2 h to give a solution of acid chloride **21**.

In another reactor, to a heterogeneous mixture of K_3PO_4 (1.56 kg, 7.34 mol) and K_2HPO_4 (2.09 kg, 12.0 mol) in water

(3.4 L) and acetonitrile (6 L) at 0 °C was added a solution of **20** (1.484 kg, 81% purity by HPLC area) in acetonitrile (1.7 L).[5] After 2 h at 0 °C, the solution of acid chloride **21** prepared above was added at such a rate as to maintain the temperature below 10 °C. After stirring at 10 °C overnight, water was added (10 L). The organic phase was distilled under reduced pressure (30−125 Torr), and EtOAc (11 L) was added. The mixture was washed with 50% K_2HPO_4 aqueous solution (2 × 3 L), water (6 L), and brine (6 L). The organic layer was decolorized with charcoal (500 g) overnight. The mixture was then filtered through Solka Floc, and the cake was washed with EtOAc (1 L). The filtrate was concentrated under reduced pressure (30−125 Torr) to give **22** (1.92 kg, ∼86% yield, 84% purity by HPLC area) as a honey-colored oil. An analytical pure sample of **22** was obtained by column chromatography over silica gel and characterized. ^{1}H NMR (300 MHz, $CDCl_3$) 2.36−2.68 (m, 4 H), 2.43 (s, 3 H), 2.48 (s, 3 H), 2.75−3.03 (m, 3 H), 3.35 (dd, J = 11.11, 8.10 Hz, 1 H), 3.50−3.65 (m, 2 H), 3.70−3.91 (m, 2 H), 7.13−7.43 (m, 5 H), 8.94 (s, 1 H). MS m/z 337.2 $[M + H]^+$.

4,6-Dimethylpyrimidin-5-yl)(hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)methanone Benzylmalonic Acid Salt (5·BMA). A nitrogen-inerted 1-L high-pressure reactor was charged with **22** (100 g, 0.298 mol), benzylmalonic acid (69 g, 0.357 mol), 10% Pd/C (10 g), and MeOH (0.5 L). The mixture was purged with nitrogen, heated to 60 °C, and pressurized to 100 psig with hydrogen. Upon reaction completion by HPLC the reaction mixture was cooled to ambient temperature, filtered through Solka Floc (40 g) and rinsed with MeOH (0.25 L). MeOH was replaced with IPA (0.25 L) by atmospheric-pressure distillation and the mixture aged at 25 °C for 18 h. The crystals were filtered to provide **5** as the benzylmalonic acid salt (97 g, 73% yield, 100% purity by HPLC area). An analytical pure sample of free amine **5** was obtained by column chromatography over silica gel and characterized. ^{1}H NMR (300 MHz, $CDCl_3$) 2.07 (s, 1 H), 2.45 (s, 3 H), 2.48 (s, 3 H), 2.66 (dd, J = 10.93, 4.14 Hz, 1 H), 2.76−3.01 (m, 4 H), 3.12 (dd, J = 10.74, 6.97 Hz, 1 H), 3.21 (dd, J = 10.74, 6.97 Hz, 1 H), 3.39 (dd, J = 11.30, 7.91 Hz, 1 H), 3.60−3.74 (m, 1 H), 3.83−3.99 (m, 1 H), 8.95 (s, 1 H). ^{1}H NMR (BMA salt, 300 MHz, DMSO-d_6) 2.35 (s, 3 H), 2.38 (s, 3 H), 2.81−3.89 (m, 13 H, 3 H from BMA), 6.89−7.37 (m, 5 H, all from BMA), 8.94 (s, 1 H). MS m/z 247.1 $[M + H]^+$.

[(*S*)-3-[5-(4,6-Dimethylpyrimidine-5-carbonyl)hexahydropyrrolo[3,4-*c*]pyrrol-2-yl]-1-(3-fluorophenyl)propyl]carbamic Acid *tert*-Butyl Ester (23). Sodium triacetoxyborohydride (0.59 kg, 2.8 mol) was added to a stirred and cooled (0 °C) slurry of **5**·BMA salt (0.82 kg, 1.86 mol) in dichloromethane (5.6 L) in a 40-L glass-lined reactor, followed by addition of the crude **4** (∼1.86 mol) solution from the previous step over 30 min (<10 °C). After 2 h at ambient temperature, the mixture was warmed to 60 °C and stirred for another 2 h. The reaction mixture was cooled to ambient temperature and quenched with saturated aqueous $NaHCO_3$ (15 kg) over 20 min. The mixture was purged with a nitrogen stream overnight, using a bleach trap, to remove most of the dimethylsulfide. The mixture was extracted twice with toluene (6 and 2 kg). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (10 kg) and brine (11 kg) to give a solution of adduct **23** (∼898 g, 89% purity by HPLC area), which was used in the next step directly. ^{1}H NMR (300 MHz, $CDCl_3$, ∼1:1 rotamers) 1.42 (br s, 9 H), 1.80−1.95 (m, 1 H), 2.23−3.14 (m, 18 H), 3.39 (ddd, J = 11.30, 8.10, 6.03 Hz, 1 H), 3.52−3.78 (m, 1 H), 3.84−4.18 (m, 0.5 H), 5.82 (d, J = 7.35 Hz, 0.5 H), 6.84−7.10 (m, 3 H), 7.20−7.41 (m, 1 H), 8.96 (s, 1 H). MS m/z 498.2 $[M + H]^+$.

{5-[(*S*)-3-Amino-3-(3-fluorophenyl)-propyl]hexahydropyrrolo[3,4-*c*]pyrrol-2-yl}-(4,6-dimethylpyrimidin-5-yl)methanone Tartaric Acid Salt (2·Tartaric Acid). A solution of **23** in toluene (∼898 g, 1.81 mol, 89% pure by HPLC area) was filtered to a 40-L glass-lined reactor through Solka Floc (300 g) to remove trace insoluble impurities. The solvent level was reduced to 2.7 L by vacuum distillation, followed by the addition of 3 N HCl (1.8 kg) at 25 °C. The reaction mixture was then heated to 35 °C and stirred. Upon completion (HPLC), the mixture was cooled, and the layers were separated. The aqueous layer was stirred with toluene (1 kg) for 5 min and separated. The aqueous layer was basified with 50% aqueous NaOH solution (800 g) and extracted with Me-THF (2 × 1.1 kg). The Me-THF layer was filtered through Solka Floc (300 g) to remove insoluble impurities. Me-THF was replaced with EtOAc (12.5 kg) by atmospheric pressure distillation until less than 1% Me-THF remained by GC analysis. L-Tartaric acid (272 g, 1.81 mol), as a solution of EtOH (2.86 kg) was slowly added with rapid stirring. Once addition was complete, the solution was cooled to 25 °C and filtered. The cake was immediately rinsed with MTBE (2.7 kg) and dried in a vacuum oven at 50 °C, 30−50 Torr to constant weight, to give **2** as a tartaric acid salt (810 g, 76% yield over five steps, 96% purity by HPLC area). Mp 180−186 °C (amorphous solid). ^{1}H NMR (300 MHz, D_2O) 2.37 (s, 3 H), 2.38 (s, 3 H), 2.39−2.58 (m, 3 H), 2.88 (td, J = 11.59, 4.33 Hz, 1 H), 3.12−3.81 (m, 8 H), 3.88−4.04 (m, 1 H), 4.34−4.48 (m, 5 H), 7.10−7.32 (m, 3 H), 7.37−7.59 (m, 1 H), 8.86 (s, 1 H). ^{1}H NMR (free amine **2**, 300 MHz, $CDCl_3$) 1.70−2.07 (m, 2 H), 2.23−2.66 (m, 13 H), 2.70−3.07 (m, 3 H), 3.37 (dd, J = 11.30, 8.29 Hz, 1 H), 3.63−4.08 (m, 4 H), 6.82−7.13 (m, 3 H), 7.21−7.38 (m, 1 H), 8.95 (s, 1 H). MS m/z 398.2 $[M + H]^+$.

(*R*)-Tetrahydrofuran-3-carboxylic acid [(*S*)-3-[5-(4,6-dimethylpyrimidine-5-carbonyl)hexahydropyrrolo[3,4-*c*]pyrrol-2-yl]-1-(3-fluorophenyl)propyl]amide Hydrochloride Salt (1·HCl).[15] Oxalyl chloride (46.0 g, 36.2 mmol) was added over 1 h to a solution of (*R*)-tetrahydrofuran-3-carboxylic acid **3**[16] (40.1 g, 34.5 mmol) in toluene (310 mL) containing DMF (0.5 mL) with stirring, while maintaining the temperature at 10 °C with an ice bath. After 40 min the ice bath was removed and the solution allowed to warm to ambient temperature and stir overnight. The light-yellow solution was partially evaporated at 40 °C, gradually reducing the pressure to 30−35 Torr. The precipitated Vilsmeier reagent was removed by filtration, leaving

(15) The scale-up study was not conducted for this final process due to the termination of the program.

(16) (*R*)-Tetrahydrofuran-3-carboxylic acid **3** of 98% ee was purchased from Chirotech Technology Ltd. For preparation, see: Johnson, N. B.; Lennon, I. C.; Moran, P. H.; Ramsden, J. A. *Acc. Chem. Res.* **2007**, *40*, 1291–1299.

92.1 g of a gold-colored solution of acid chloride **24** (0.504 g per g of solution) that was stored under nitrogen in a freezer until used.

2·tartaric acid salt (14.54 g, 26.54 mmol, 95.8% pure by HPLC area) was stirred with Me-THF (140 mL) and 3 N NaOH (21.5 mL) until the solids dissolved. The organic phase was washed with 3 N NaOH (14 mL) and clarified by filtration through a medium porosity fritted glass filter. Solvent evaporation at 40 °C gave a gold-colored oil. To the oil dissolved in Me-THF (95 mL) was added triethylamine (8.06 g, 79.62 mmol), and the resulting solution was cooled in an ice bath. Acid chloride **24** (9.93 g of the solution prepared above, 5.00 g of acid chloride, 37.18 mmol) was added over 30 min. The ice bath was removed and the mixture allowed to stir overnight. The reaction mixture was quenched by the addition of 3 N NaOH (100 mL) and stirring for 1 h. The aqueous phase was extracted with Me-THF (20 mL), and the combined organic phase was evaporated at 40 °C to give the free base of **1** (11.44 g, 23.08 mmol) as a slightly tacky dry foam.

A solution of the free base of **1** (11.44 g, 23.08 mmol) in acetone (57.4 mL) and water (1.45 mL) was acidified with 12 N HCl (2.42 mL, 29.0 mmol). The clear solution was seeded with authentic product and stirred for 3.5 h, after which the resulting slurry was filtered and washed with ice-cold acetone (12 mL in two portions). Drying in a vacuum oven at 68 °C, 30−50 Torr gave **1**·HCl as a dry, white powder (10.57 g, 86.1% theory, 97.8% purity by HPLC area). Analytical data for **1**·HCl salt: mp 149−150 °C. ^{1}H NMR (300 MHz, D_2O) 1.73−1.91 (m, 1 H), 1.98−2.26 (m, 3 H), 2.34 (s, 3 H), 2.37 (s, 3 H), 2.82−3.37 (m, 8 H), 3.40−4.10 (m, 9 H), 4.81 (t, J = 7.54 Hz, 1 H), 6.93−7.13 (m, 3 H), 7.33 (td, J = 7.82, 5.84 Hz, 1 H), 8.83 (s, 1 H). MS m/z 496.2 $[M + H]^+$.

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