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Synthesis of a Histamine H_3 Receptor Antagonist—Manipulation of Hydroxyproline Stereochemistry, Desymmetrization of Homopiperazine, and Nonextractive Sodium Triacetoxyborohydride Reaction Workup

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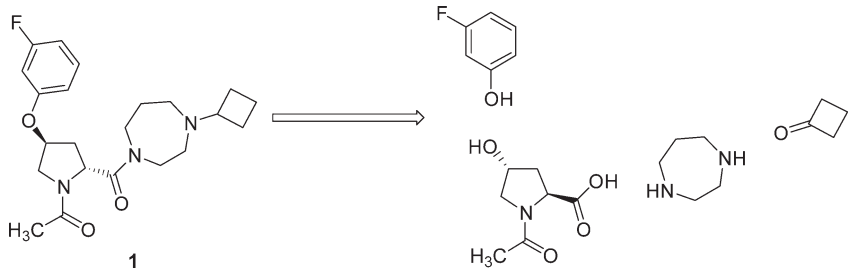

We have recently completed the synthesis of 1-[2-(4-cyclobutyl-[1,4]diazepane-1-carbonyl)-4-(3-fluoro-phenoxy)-pyrrolidin-1-yl]-ethanone, a hydroxyproline-based H_3 receptor antagonist, on 100 g scale. The synthesis proceeds through four steps and route selection was driven by a desire to minimize the cost-of-goods. Naturally occurring *trans*-4-hydroxy-L-proline was chosen as the precursor to the target's core, which necessitated an inversion at both stereogenic centers. The inversions were accomplished through strategic employment of La Rosa's lactone and a late-stage Mitsunobu reaction. A first generation synthesis that employed *N*-Boc-homopiperazine was improved in a second generation approach wherein homopiperazine was directly desymmetrized. Finally, the water solubility of a key intermediate necessitated the development of a nonextractive workup for the sodium triacetoxyborohydride reduction.

Introduction

Histamine H_3 antagonists have the potential to play a therapeutic role in a range of CNS disorders, including narcolepsy, cognition, ADHD (attention-deficit hyperactivity disorder), and suppression of food intake.[1] Medicinal chemistry efforts from our laboratories have afforded several series of potent and selective small molecule antagonists.[2] Most recently, this has led to a class of hydroxyproline-based amides, exemplified by **1** (Figure 1).[2b] This molecule is similar to other known H_3 antagonists in that it possesses a basic amine portion (the tertiary amine), a spacer, a central core, and a lipophilic end group (the fluorophenyl ether).[3] As early-stage process development chemists, we were charged with the dual responsibilities of (a) providing 100 g of **1** for preclinical toleration studies and (b) determining and validating a synthetic route for **1** that would be suitable for further up-scaling. The challenges associated with the synthesis of this molecule consist primarily of setting the configurations about the hydroxyproline core, differentially substituting the symmetrical homopiperazine diamine, and dealing with water-soluble intermediates.

(1) Leurs, R.; Bakker, R. A.; Timmerman, H.; de Esch, I. J. P. *Nat. Rev. Drug Discov.* **2005**, *4*, 107–120.

(2) (a) Bonaventure, P.; Letavic, M.; Dugovic, C.; Wilson, S.; Aluisio, L.; Pudiak, C.; Lord, B.; Mazur, C.; Kamme, F.; Nishino, S.; Carruthers, N.; Lovenberg, T. *Biochem. Pharmacol.* **2007**, *73*, 1084–1096. (b) Stocking, E. M.; Aluisio, L.; Atack, J. R.; Bonaventure, P.; Carruthers, N. I.; Dugovic, C.; Everson, A.; Fraser, I.; Jiang, X.; Leung, P.; Lord, B.; Ly, K. S.; Morton, K. L.; Nepomuceno, D.; Shah, C. R.; Shelton, J.; Soyode-Johnson, A.; Letavic, M. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2755–2760.

(3) For a review that discusses the pharmacophore model for the H_3 receptor, see: Celanire, S.; Wijtmans, M.; Talaga, P.; Leurs, R.; de Esch, I. J. P. *Drug Disc. Today* **2005**, *10*, 1613–1627.

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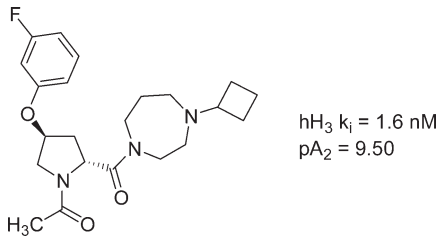


1

FIGURE 1. Structure of potent and selective H_3 receptor antagonist (2*R*-4*S*)-**1**.

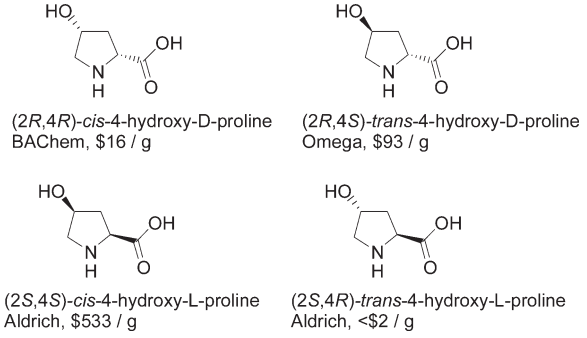


FIGURE 2. Four stereoisomers of 4-hydroxyproline and their commercial cost normalized to a per gram basis.

Hydroxyproline derived *N*,*N*-disubstituted amides have been the focus of recent interest in drug discovery and organocatalysis.[4,5] In most reports, relevant molecules have possessed the *S* configuration at the carboxamide-bearing carbon. This is likely due to the fact that (2*S*,4*R*)-*trans*-4-hydroxy-L-proline occurs naturally and is readily available. The other possible isomers of hydroxyproline are also commercially available, but at a substantially higher cost (Figure 2).

Compound **1** possesses an absolute configuration of (2*R*,4*S*), and consequently, its synthesis could conceivably proceed through any of the following strategies: (1) from (2*R*,4*R*)-*cis*-4-hydroxy-D-proline with inversion at the 4-position and retention at the 2-position, (2) from (2*R*,4*S*)-*trans*-4-hydroxy-D-proline with retention at both stereogenic centers, or (3) from (2*S*,4*R*)-*trans*-4-hydroxy-L-proline with inversion at both stereogenic centers. Prior to our involvement, medicinal chemists had employed both strategies 1 and 2 for the synthesis of **1**. The initial synthesis of **1** utilized standard coupling chemistry to form the requisite carboxamide from *cis*-4-hydroxy-D-proline and cyclobutylhomopiperazine. A subsequent Mitsunobu reaction inverted the configuration at C-4; customary chemistry to transform the *N*-Boc group to the desired *N*-acetyl group completed the synthesis (Figure 3).[2b] A more elegant approach was developed as analogue synthesis gave way to focused production of several key target molecules. Specifically, after carboxamide formation, copper-mediated aryl iodide/hydroxyproline coupling gave rise to **1** in high yield (Figure 4).[2b] Despite these successes, our focus on cost-of-goods for a potential downstream manufacturing process pushed us to consider *trans*-4-hydroxy-L-proline as our core building block.

Having committed to the pursuit of a double-inversion strategy for the synthesis of **1**, our retrosynthetic analysis honed in on another opportunity for long-term cost savings. Specifically, if homopiperazine could be desymmetrized during the course of our synthesis, it would obviate employment of the nonsymmetric *N*-Boc-homopiperazine, which is 25 times more expensive than homopiperazine on a molar basis.[6] In addition, this approach would eliminate a synthetic step, namely Boc group removal. With the preferred starting materials in mind, we devised the retrosynthetic analysis shown in Scheme 1. One potential pitfall of this approach was the suspected water solubility of the final two intermediates. This water solubility was ultimately verified and addressed.

Results and Discussion

As discussed above, our first goal was to determine an efficient approach for the epimerization of the C-2 carbon. Historically, this transformation has been accomplished through heating *trans*-hydroxy-L-proline (**2**) to reflux in a mixture of acetic acid and acetic anhydride. The resulting mixture can then be concentrated and treated with refluxing 2 M $HCl_{(aq)}$ to provide the C-2 epimer of the starting material, *cis*-hydroxy-D-proline.[7] A particularly appealing alternative, however, is a method developed by La Rosa, which accomplishes not only the C-2 inversion but also concomitantly *N*-acetylates the proline and activates the carboxylic acid for amide bond formation.[8] During the course of their studies on mesoionic compounds, La Rosa's group reported that heating of *trans*-4-hydroxy-L-proline (**2**) or *N*-acetyl-*trans*-4-hydroxy-L-proline (**3**) in acetic anhydride at 90 °C provided the bicyclic lactone (1*R*, 4*R*)-*N*-acyl-2-oxa-5-azabicyclo[2.2.1]heptan-3-one (**4**). The workers proposed a mechanism in which the acetyl group on nitrogen assists with the epimerization of C2. The inversion is driven to completion as only one of the two epimers at C2 is suitable for lactone formation with the *R*-configured hydroxyl at C4 (Scheme 2).

Because we considered La Rosa's lactone **4** to be the foundation of our synthesis of **1**, we invested resources into the optimization of its formation. The reaction was performed at various concentrations and temperatures with

(4) Yea, C. M.; Allan, C. E.; Ashworth, D. M.; Barnett, J.; Baxter, A. J.; Broadbridge, J. D.; Franklin, R. J.; Hampton, S. L.; Hudson, P.; Horton, J. A.; Jenkins, P. D.; Penson, A. M.; Pitt, G. R. W.; Riviere, P.; Robson, P. A.; Rooker, D. P.; Semple, G.; Sheppard, A.; Haigh, R. M.; Roe, M. B. *J. Med. Chem.* **2008**, *51*, 8124–8134. Shu, C.; Zeng, X.; Hao, M.-H.; Wei, X.; Yee, N. K.; Busacca, C. A.; Han, Z.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 1303–1306. For a case with a *R* configuration at C-2 (starting from *cis*-4-hydroxy-D-proline), see: Bradbury, R. H.; Halsall, C. T.; Hennequin, L. F. A.; Kettle, J. G.; Plowright, A. WO 030757, 2005. Mayer, S. C.; Ramanjulu, J.; Vera, M. D.; Pfizenmayer, A. J.; Joullie, M. M. *J. Org. Chem.* **1994**, *59*, 5192–5205. Lubisch, W.; Oost, T.; Wernet, W.; Unger, L.; Hornberger, W.; Geneste, H. WO 072458, 2006. Within this class of pharmaceuticals, meropenem is the most famous. Process patents for the key hydroxy proline piece include: Zhang, F.; Ju, Y.; Pan, H.; Wang, G.; Xie, M. Chinese Patent 101033209, 2007. Miki, T.; Yamauchi, K. WO 052517, 2007. Chaturvedi, N. C.; Mukhopadhyay, M. Rao, A. V. S. Indian patent 183459, 2000. Related hydroxyproline derived *N*-monosubstituted amides are even more common; see, for example: Yee, N. K.; Farina, V.; Houpis, I. N.; Haddad, N.; Frutos, R. P.; Gallou, F.; Wang, X.-J.; Wei, X.; Simpson, R. D.; Feng, X.; Fuchs, V.; Xu, Y.; Tan, J.; Zhang, L.; Xu, J.; Smith-Keenan, L. L.; Vitous, J.; Ridges, M. D.; Spinelli, E. M.; Johnson, M. *J. Org. Chem.* **2006**, *71*, 7133–7145.

(5) Xin, J.; Chang, L.; Hou, Z.; Shang, D.; Liu, X.; Feng, X. *Chem.—Eur. J.* **2008**, *14*, 3177–3181. Palomo, C.; Vera, S.; Mielgo, A.; Gomez-Bengoa, E. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 5984–5987. Clapham, B.; Cho, C.-W.; Janda, K. D. *J. Org. Chem.* **2001**, *66*, 868–873.

(6) Standard Sigma-Aldrich pricing: *N*-Boc-homopiperazine, $3180/mol; homopiperazine $124/mol.

(7) Baker, G. L.; Fritschel, S. J.; Stille, J. R.; Stille, J. K. *J. Org. Chem.* **1981**, *46*, 2954–2960. Robinson, D. S.; Greenstein, J. P. *J. Biol. Chem.* **1952**, *195*, 383.

(8) Croce, P. D.; La Rosa, C. *Tetrahedron: Asymmetry* **2002**, *13*, 197–201.

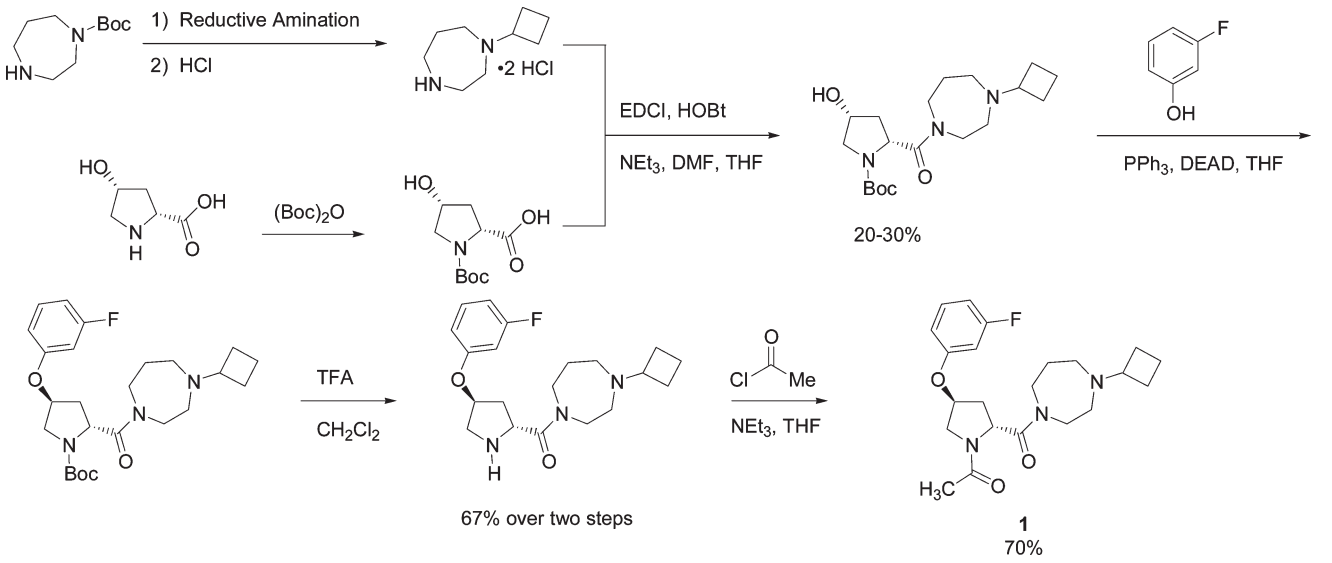


FIGURE 3. Synthesis of **1** from *cis*-4-hydroxy-D-proline.

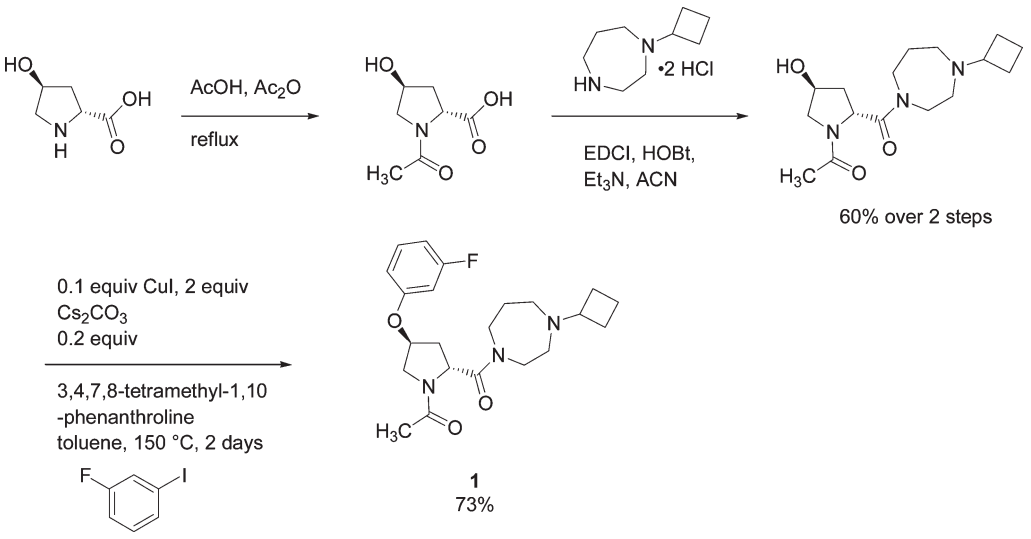
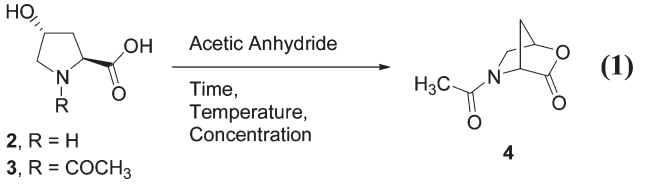


FIGURE 4. Synthesis of **1** from *trans*-4-hydroxy-D-proline.

both *trans*-4-hydroxy-L-proline (**2**) and *N*-acetyl-*trans*-4-hydroxy-L-proline (**3**) employed as starting materials (eq 1).



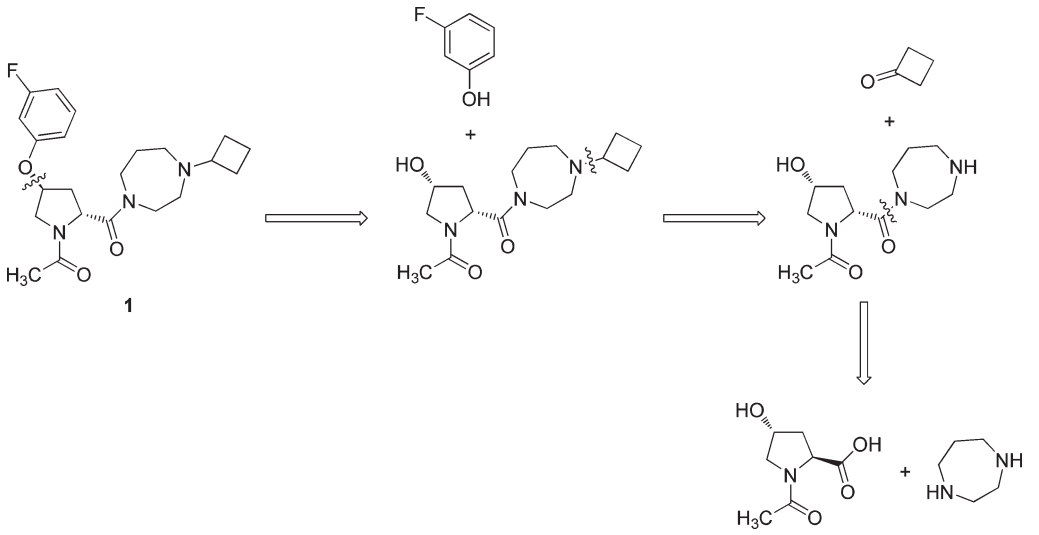
(1)

We started by analyzing the effect of concentration on the course of the reaction between *trans*-4-hydroxy-L-proline (**2**) and acetic anhydride (Figure 5). The yields shown were calculated using *o*-terphenyl as an internal standard after quantification of its HPLC response relative to **4**. Although reactions at higher concentrations (1.75 and 3.5 M) did proceed more rapidly, final yields were highest in the cases of lower concentrations (1.15 and 0.87 M). We next attempted to differentiate between reactions of **2** executed at 60 and 90 °C (Figure 6). Reactions at 90 °C were found to be substantially more rapid than those at 60 °C; however, the ultimate end points were essentially identical at either temperature. Finally, based on La Rosa's reports that *N*-acetyl-4-hydroxyproline **3** was also a competent substrate for the synthesis of **4**, we undertook a head-to-head comparison of the two starting materials (Figure 7).[9] The *N*-acetyl substrate **3** did form product **4** more rapidly than in the case of unprotected **2**, but both substrates ultimately reached a similar end point at a given concentration.

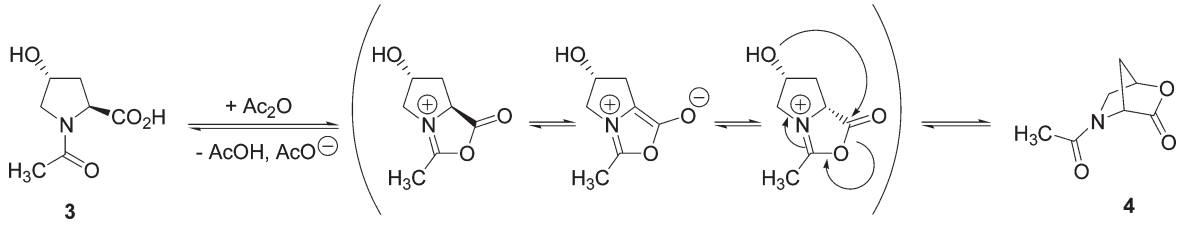
With the results of these optimization experiments in hand, we chose to form **4** from **2** and **3** at 90 °C, at concentrations of 1 M on a 1 mol scale. After recrystallization from 2-propanol, the desired product was obtained in 52% from **2** and 41% yield from **3** (eq 2). The recrystallization remains unoptimized with substantial quantities of product remaining in the mother liquors. To convince ourselves of the stereochemical purity of this key intermediate, we also prepared the opposite enantiomer through an identical reaction starting with *trans*-4-hydroxy-D-proline. Having both enantiomers in hand permitted the development of

(9) We were able to purchase 1 kg of *N*-acetylated **4** for less than $1/g.

SCHEME 1. Retrosynthetic Analysis for 1



SCHEME 2. Mechanism Proposed by La Rosa's Group for Key Transformation from 3 to 4



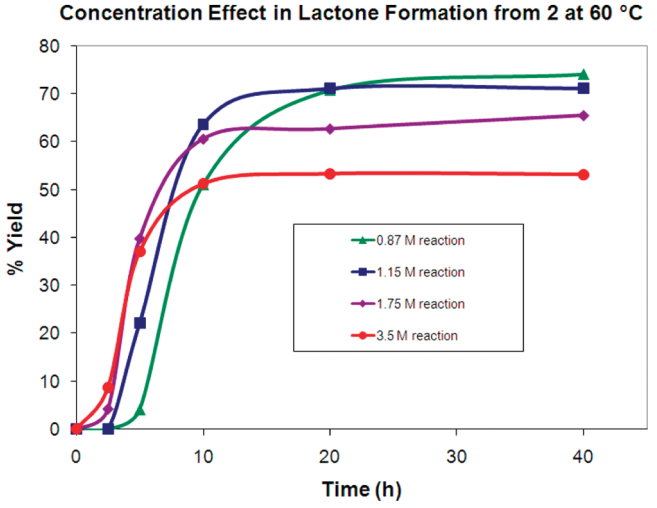


FIGURE 5. Effect of concentration on the synthesis of **4**.

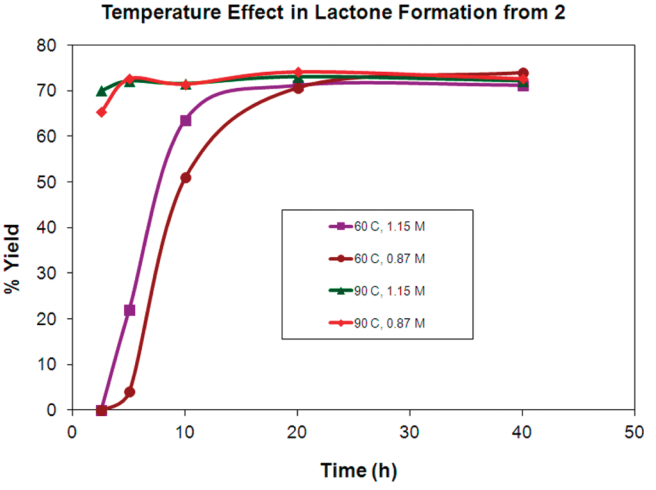
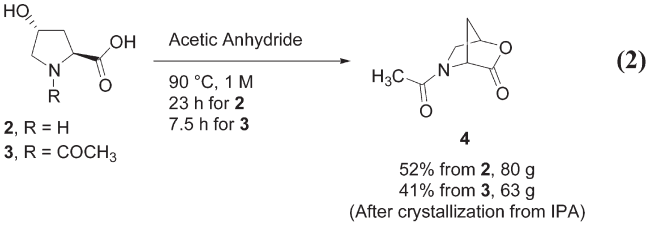


FIGURE 6. Effect of temperature on the synthesis of **4**.

a chiral HPLC method, which revealed that the procedure provides enantiomerically pure lactone.[10]



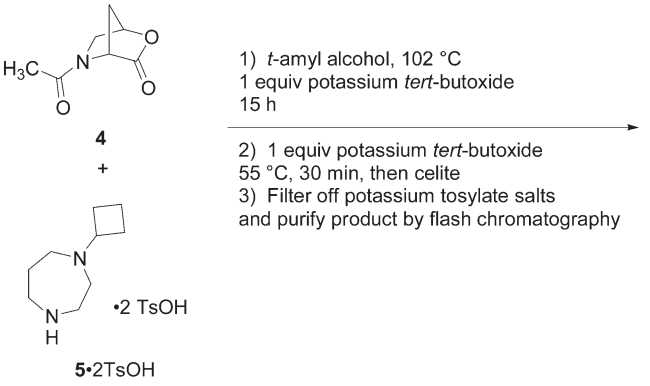
(2)

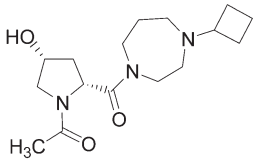
With the epimerization and carboxylate activation accomplished, we turned our attention toward lactone opening to furnish the desired amide linkage. Despite the obvious utility of La Rosa's lactone as a synthetic intermediate, reports of its application have been somewhat scarce.[11] In fact, we were aware of no examples of its opening with dialkyl secondary amines. Thus, although our ultimate goal was a direct reaction with homopiperazine, our first-generation experiments were

(10) AS-H column, 85/15 hexanes/ethanol, 1 mL min flow rate, (*S*,*S*) enantiomer retention time 39 min, (*R*,*R*) enantiomer 42 min.

(11) Zheng, C.; Li, Y.; Yang, Y.; Wang, H.; Cui, H.; Zhang, J.; Zhao, G. *Adv. Synth. Catal.* **2009**, *351*, 1685–1691. Chorghade, M. S.; Debendra, K. M.; Sahoo, G.; Gurjar, M.; Mandlech, M. V.; Bhoite, N.; Moghe, S.; Raines, R. T. *J. Fluorine Chem.* **2008**, *129*, 781–784. Ma, Z.; Zhai, H. *Synlett* **2007**, 161–163. Ma, Z.; Hu, H.; Xiong, W.; Zhai, H. *Tetrahedron Lett.* **2007**, *63*, 7523–7531. Li, Y.; Liu, X.; Yang, Y.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 288–291.

performed with a substrate for which we believed there existed a high probability of success—cyclobutylhomopiperazine as its ditosylate (**5**·2TsOH).[12] Reactions in *tert*-amyl alcohol at 80 °C in the presence of 0 or 2 equiv of potassium *tert*-butoxide were not nearly as effective as reaction with 1 equiv of potassium *tert*-butoxide. Additionally, a reaction with 3 equiv of potassium carbonate in acetonitrile was inferior to the potassium *tert*-butoxide variant. Eventually, the reaction with 1 equiv of potassium *tert*-butoxide was scaled to 10 g, and the product was provided in 62% isolated yield (eq 3). Due to the water solubility of the amide product, an aqueous workup was not possible. Instead, at the conclusion of the reaction, the mixture was cooled and a second equiv of potassium *tert*-butoxide was added. The potassium tosylate salts were then filtered off, and the filtrate was concentrated and purified by flash chromatography.

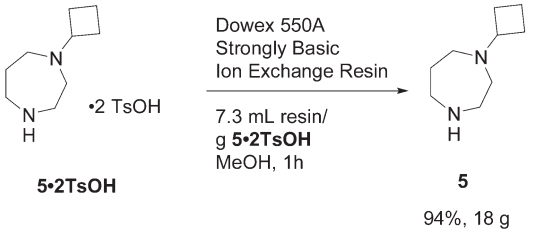




6
62%, 10 g

(3)

Although it was possible to remove the tosylate counterion at the conclusion of the ring-opening reaction, we were also interested in performing the lactone-opening with the cyclobutylhomopiperazine free base. Because the water solubility of this free base made it difficult to isolate after an extractive workup, we opted for a resin-mediated free-basing strategy. Simply mixing the ditosylate in methanol with Dowex 550A OH strongly basic ion-exchange resin and then filtering off the resin provided the desired free base in 94% yield after concentration (eq 4).



(4)

Through model studies with hexamethylene imine and homopiperazine, we determined that no exogenous acid or base was required to achieve high yields of the desired amide in reactions directly between **4** and secondary amine free bases. Thus, heating the [2.2.1] lactone with cyclobutyhomopiperazine in *tert*-amyl alcohol at 102 °C for 10 h and then concentrating under reduced pressure provided the desired *cis*-hydroxy amide in a quantitative crude yield with a purity estimated at greater than 85% (eq 5). This material was subsequently used directly.

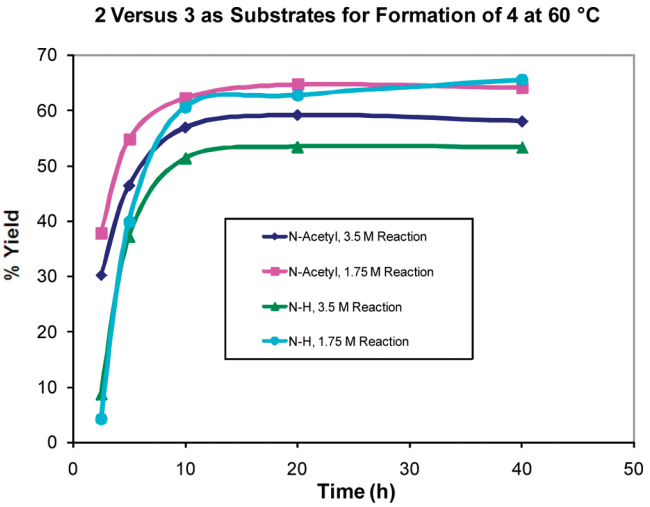
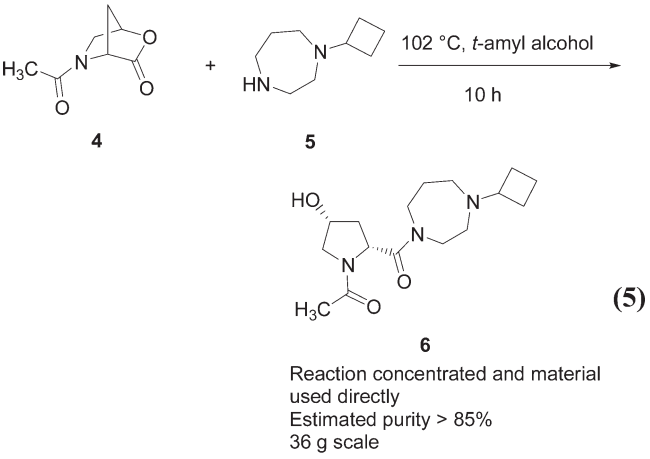


FIGURE 7. Effect of substrate *N*-acetylation on the formation of **4**.



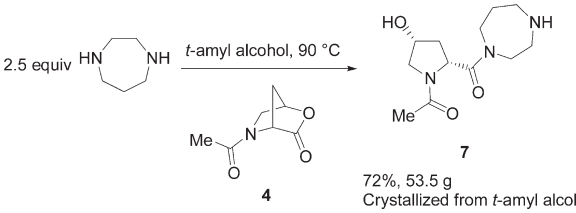
(5)

Having demonstrated that La Rosa's lactone **4** was a suitable substrate for ring-opening with the dialkylamine cylcobutylhomopiperazine, we turned our attention toward direct reaction with homopiperazine. Desymmetrization of the more common piperazine is not a trivial problem and has been the focus of several publications.[13] Gratifyingly, in our case, 2.5 equiv of homopiperazine could be utilized in the ring opening of **4** to provide **7** in 72% yield on 53 g scale after crystallization from IPA/ethyl acetate or directly from *tert*-amyl alcohol (eq 6). As **7** possesses a high degree of aqueous solubility,

(12) As shown in Figures 3 and 4, initial medicinal chemistry efforts utilized the di-HCl salt of cyclobutylhomopiperazine for the synthesis of **1**. We found the ditosylate to be less hygroscopic and, thus, more suitable for benchtop handling. See the Experimental Section for details on the synthesis of cyclobutylhomopiperazine ditosylate.

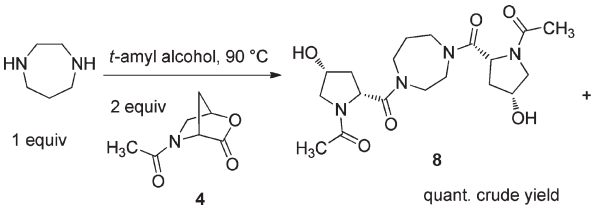
(13) Wang, T.; Zhongxing, Z.; Meanwell, N. A. *J. Org. Chem.* **2000**, *65*, 4740–4742. Chou, W.-C.; Tan, C.-W.; Chen, S.-F.; Ku, H. *J. Org. Chem.* **1998**, *63*, 10015–10017.

the obviation of an aqueous workup through crystallization was significant.



(6)

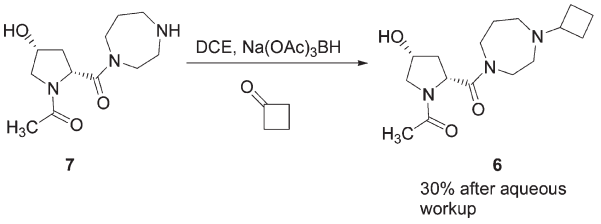
Reaction between 1 equiv of homopiperazine and 2 equiv of lactone **4** provided primarily the potential dimer byproduct, **8**, as well as a small amount of **7** (eq 7).



(7)

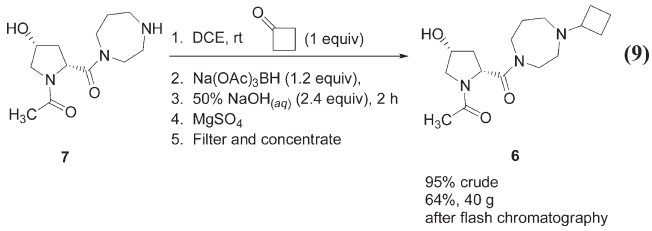
With the characteristic ^{1}H NMR shifts for **8** in hand, ^{1}H NMR analysis of crystalline **7** revealed the material to contain 2.3 wt % residual solvent, 1.5 wt % homopiperazine, no detectable levels of **8**, and 96.2 wt % **7**.[14]

Despite the successful ring-opening of **4** with homopiperazine, transformation of **7** to **6** was still undocumented. Our initial attempt using standard reductive amination technology provided a disappointingly low yield of the desired product: 30% (eq 8). The low yield was found to result primarily from the water solubility of **6**.



(8)

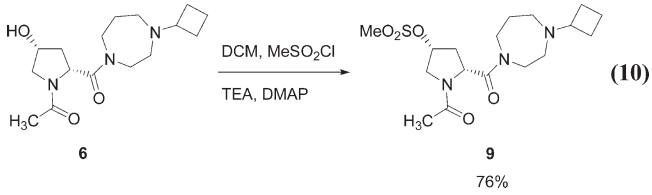
Despite a myriad of applications since the introduction of sodium triacetoxyborohydride (STAB-H) in 1996, we are unaware of any widely utilized nonextractive workup protocol for these reductions.[15] We reasoned that the unwanted components of the crude reaction mixture (sodium acetate, $(OAc)_2BOH$, and excess STAB-H) could be further transformed into sodium acetate and boric acid ($B(OH)_3$) through the addition of the proper quantity of NaOH. Because boric acid and sodium acetate are known to be only marginally soluble in ether and alcohol, respectively, we thought it might be possible to simply filter away the undesired components of the reaction mixture.[16] As we planned to add sodium hydroxide as a 50% aqueous solution, we also thought it reasonable to add anhydrous magnesium sulfate prior to filtration.[17] To our satisfaction, this approach was successfully applied to the synthesis of **6** from **7** (eq 9). The crude yield was excellent, and elemental analysis indicated less than 20 ppm boron, 40 ppm magnesium, and 0.4% sodium. In this particular case, we did choose to remove minor impurities, including some acetate, by flash chromatography prior to the final step.[18]



(9)

Overall, this second-generation synthesis of **6** via homopiperazine was superior to the alternative route proceeding via cyclobutyl homopiperazine. In the cyclobutyl homopiperazine case, four total steps are required to prepare the key intermediate (reductive amination of Boc-homopiperazine with cyclobutanone, Boc removal, ion-exchange resin freebasing of the resulting salt, and lactone opening). The alternative route reduces the number of steps to two, proceeds via a crystalline intermediate, and utilizes a starting material that is significantly less expensive.

The final step of our synthesis of **1** required activation and invertive substitution of the proline C4-hydroxyl group. In parallel, we pursued both a mesylation/displacement strategy and a Mitsunobu reaction strategy. In both cases, the propensity of the activated alcohol to eliminate under displacement conditions represented the most significant challenge. Mesylate formation proceeded in 76% yield from the alcohol (eq 10). A variety of conditions were screened for displacement; in each case, MS ratios indicated substantial quantities of the elimination byproduct(s) **10a** and/or **10b** (Table 1).[19,20]



(10)

More fruitful was the pursuit of a Mitsunobu strategy for the synthesis of **1**. In this case, the ratio of desired product to elimination byproducts reached 6:1. Using free triphenylphosphine, DBAD and methylene chloride were found to be efficient. With resin-bound triphenylphosphine, DEAD or

(14) See the Supporting Information for characterization related to the crude mixture **8** and **7**.

(15) For lead references on STAB-H reductions, see: Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849. Abdel-Magid, A. F.; Mehrman, S. J. *Org. Process Res. Dev.* **2006**, *10*, 971–1031. For an example of a polymer-supported variant of triacetoxyborohydride, which can be utilized in reductions that require no aqueous workup, see: Bhattacharyya, S.; Rana, S.; Gooding, O. W.; Labadie, J. *Tetrahedron Lett.* **2003**, *44*, 4957–4960.

(16) *The CRC Handbook*, 72nd ed. reports a solubility of 8 mg/100 mL of boric acid in diethyl ether and slight solubility of sodium acetate in alcohol. *The CRC Handbook*; CRC Press: Boca Raton, 1991

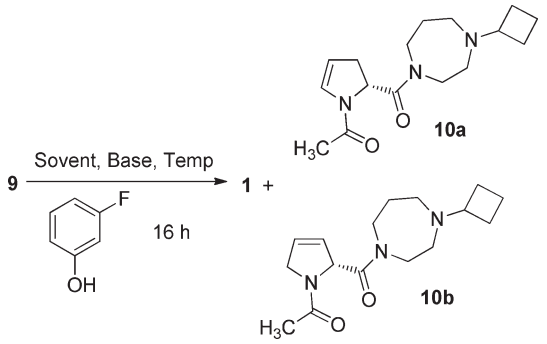
(17) We theorized that a minimum of 1/7 equiv of anhydrous magnesium sulfate (relative to water) was required for the quench, as magnesium sulfate forms a heptahydrate with water.

(18) Because our final step ultimately employed Mitsunobu conditions, complete removal of the potentially nucleophilic acetate was necessary. Peak shaving to remove minor impurities resulted in the substantial decrease in yield from crude to purified **6**.

(19) The actual structure(s) of the elimination byproduct(s) was not proven. Elimination reactions at C4 of various proline analogues have been shown to provide both potential product regioisomers. Zhao, X.; Zhuang, W.; Fang, D.; Xue, X.; Zhou, J. *Synlett* **2009**, 779–782. Brackmann, F.; Schill, H.; de Meijere, A. *Chem.—Eur. J.* **2005**, *11*, 6593–6600.

(20) Similar reactions utilizing the corresponding tosylate and nosylate were equally fruitless.

TABLE 1. Mesylate Displacement Strategy for the Synthesis of 1



solvent	base	temp (°C)	MS product ratio (1:10:9)[a]
acetonitrile	Na_2CO_3	80	0:0:1
acetonitrile	K_2CO_3	80	1:0.5:0.4
acetonitrile	Cs_2CO_3	80	1:0.7:0
THF	KO-*t*-Bu	80	1:0.9:0.5
tert-amylOH	KO-*t*-Bu	80	1:1:0.2
tert-amylOH	KOH[b]	60	1:0.4:0.2
DMF	CsF	50	1:1:0

[a]Product/elimination ratios are based on TIC from ESI (positive mode) MS. [b]With 0.1 equiv of tetrabutylbenzylammonium chloride.

DIAD with toluene or methylene chloride as a solvent was found to be optimal (Table 2).

During our studies on the workup of these reactions, we discovered that at neutral pH, the elimination byproduct(s) are water-soluble, while the desired **1** is organic soluble (MTBE). Nonetheless, as final drug substance, **1** was also purified by flash chromatography as no crystalline form has currently been discovered. Our initial scale-up of the reaction gave rise to the desired product in 40% yield on 20 g scale. An analytical chiral-SFC method capable of separating all four potential stereoisomers of **1** revealed that our final product from this synthetic route was both diastereomerically and enantiomerically pure.[21] After isolation of the desired free base of **1**, an amorphous mono-HCl salt was formed through reaction with 1 equiv of aqueous HCl and lyophilization. The solution structures of both free base **1** and **1**·**HCl** are interesting in that they show a mixture of major conformers—approximately 9:1 in the case of the former and approximately 3:1 in the case of the latter.

Conclusion

Having established a valid route for the synthesis of **1**, the chemistry was repeated on a larger scale. The results and quantities synthesized are shown in Scheme 3. The synthesis proceeds through four total steps and two crystalline intermediates. Highlights include the following: (1) capitalizing on the utility of La Rosa's lactone for concomitant C2-inversion/activation of the hydroxyproline—a strategy that has implications for useful pharmacophores and organic catalysts, (2) direct desymmetrization of homopiperazine—a useful addition to the recent work in piperazine chemistry, and (3) a novel nonextractive workup for the reductive amination—an approach that could well gain widespread use in light of the frequent aqueous solubility of reductive amination products. Additional work aimed at the discovery of crystalline salt forms for both **6** and **1** would likely render this synthesis suitable for further scale-up.

(21) All four possible stereoisomers of this compound were prepared, and a method was developed for their analytical separation: AD-H column, 80/20 CO_2/methanol with 0.2% TEA for 10 min, ramping over 5 min to 50/50 CO_2/methanol with 0.2% TEA and then holding for 20 min, 2 mL/min flow rate, (2*R, 4S*) isomer retention time 5.3 min, (2*R*, 4*R*) isomer retention time 11.5 min, (2*S*, 4*S*) isomer retention time 24.3 min, (2*S*, 4*R*) isomer retention time 31.6 min.

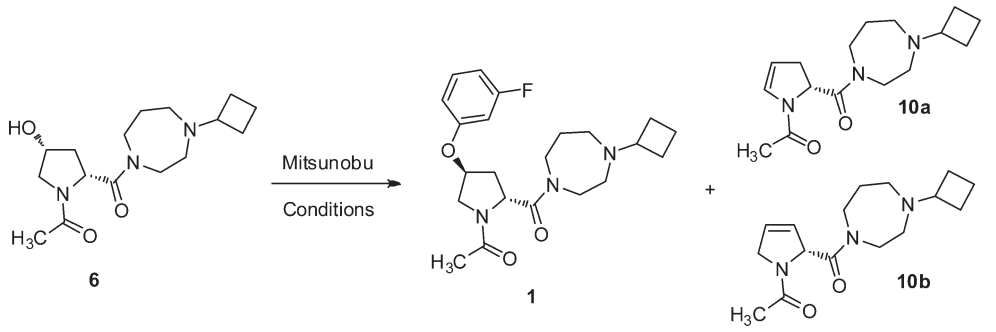
Experimental Section

General Experimental Chemical Procedures. Nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) spectra were recorded on a 400, 500, or 600 MHz spectrometer. Flash chromatography was performed on an automated system. All reagents were used as received from commercial sources. DCE, DCM, THF, MTBE, and MeOH were purchased in anhydrous form and passed through two columns of neutral alumina. Toluene was passed through one column of neutral alumina and one column of Q5 oxygen scavenger. 2-Me-THF and *tert*-amyl alcohol were used directly.

1-Cyclobutyl[1,4]diazepane (5). To a 2-L, three-necked, round-bottomed flask equipped with mechanical stirrer and nitrogen inlet was added 1-Boc-homopiperazine (50 mL, 253.6 mmol) in 2-methyl-THF (850 mL). Cyclobutanone (19 mL, 253.6 mmol) was added, and the solution was allowed to stir for 1 h. Sodium triacetoxyborohydride (64.5 g, 304 mmol) was then added in four equal portions over 2 h. The reaction mixture was allowed to stir for 24 h and then quenched with 500 mL of a 1 N $NaOH_{(aq)}$ solution. After the mixture was stirred for 30 min, the layers were separated and the aqueous layer was extracted with methylene chloride (2 × 400 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to provide 4-cyclobutyl-[1,4]diazepane-1-carboxylic acid *tert*-butyl ester as a yellow oil (64.5 g, quant yield). To a 2-L, three-necked, round-bottomed flask equipped with mechanical stirrer, reflux condenser, temperature probe, and nitrogen inlet were added tosic acid (96.5 g, 507 mmol) and a solution of 4-cyclobutyl[1,4]diazepane-1-carboxylic acid *tert*-butyl ester (64.5 g, 253.6 mmol) in 2-methyl-THF (1 L). The resulting solution was warmed to 70 °C and stirred for 10 h, during which time the desired product precipitated out. The resulting solids were filtered through a coarse frit and washed with 2-methyl-THF to provide 1-cyclobutyl[1,4]diazepane·2TsOH as an off-white solid that was directly free-based. To a 3-L, three-necked, round-bottomed flask equipped with mechanical stirrer and nitrogen inlet were added Dowex Monosphere 550A hydroxide (924 mL resin, 1.1 equiv/L, prewashed with 1 N NaOH and MeOH), 1-cyclobutyl-[1,4]diazepane·2TsOH from the previous step, and MeOH (2 L). The mixture was stirred for 2 h, and then the resin was removed by filtration. The filtrate was concentrated to provide the title compound **5** as a clear oil (37.53 g, quant): ^{1}H NMR (600 MHz, MeOD) δ 3.05−2.85 (m, 5H), 2.62−2.47 (m, 4H), 2.14−2.01 (m, 2H), 1.94−1.77 (m, 4H), 1.75−1.61 (m, 2H); ^{13}C NMR (151 MHz, MeOD) δ 61.1, 54.7, 52.0, 48.0, 47.5, 29.6, 28.7, 14.24. Anal. Calcd for $C_9H_{18}N_2 \cdot 0.25H_2O$: C, 68.09; H, 11.75; N, 17.65. Found: C, 67.96; H, 11.57; N, 17.60.

(1*R*,4*R*)-5-Acetyl-2-oxa-5-azabicyclo[2.2.1]heptan-3-one (4) from 3. To a 3-L, three-necked, round-bottomed flask equipped with an overhead mechanical stirrer, nitrogen inlet, reflux condenser, thermocouple probe, and heating mantle were added (2*S*,4*R*)-1-acetyl-4-hydroxypyrrolidine-2-carboxylic acid (400 g, 2.31 mol) and acetic anhydride (2 L). The mixture was warmed to 90 °C for 7 h and then cooled to room temperature and stirred for 64 h. The reaction mixture was then concentrated under reduced pressure to a mass of 427.43 g and stirred in IPA (537 mL) at room temperature for 45 min. After the mixture was cooled to 0 °C and stirred for an additional 4 h, the resulting solids were filtered, washed with 150 mL of cold IPA, and dried on the filter to provide the title compound as an off-white crystalline solid (159.63 g, 45%). The spectral data of **4** are identical to those reported:[6] ^{1}H NMR (500 MHz, $CDCl_3$) 5.20−5.16 (m, 1H), 5.09 (s, 0.36H), 4.45 (s, 0.64H), 3.72−3.52 (m, 2H), 2.36−2.25 (m, 1H), 2.19 (s, 1.91H), 2.15−2.10 (m, 0.64H), 2.07 (s, 1.09H), 2.0−1.95 (m, 0.36H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (170.6 and 170.5), (169.5 and 168.9), (78.7 and 78.4),

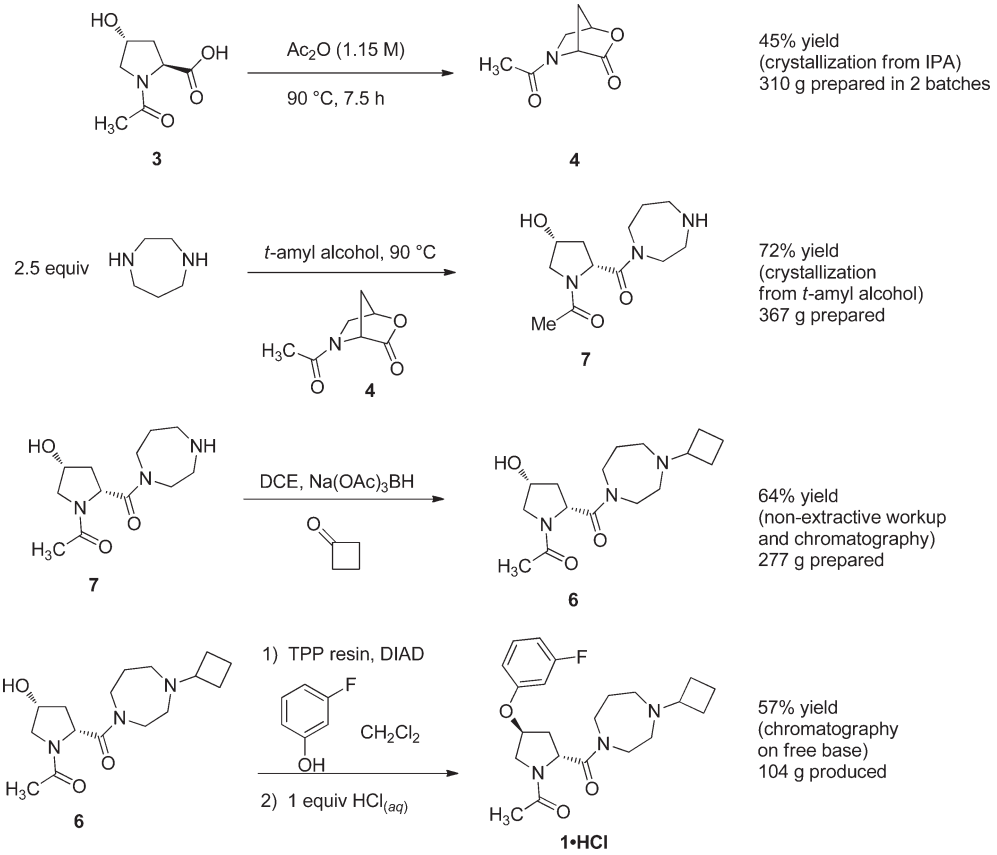
TABLE 2. Mitsunobu Strategy for the Synthesis of 1



reagent combination	solvent	result[a]
PL-TPP resin/DEAD[b]	toluene, 0 °C to rt	~4: 1 product/elimination
PL-TPP resin/DEAD	toluene	~6:1 product/elimination
PL-TPP resin/DIAD	THF	~2: 1 product/elimination
PL-TPP resin/DIAD	CH_2Cl_2	~4: 1 product/elimination
PL-TPP resin/DIAD	Toluene	~5: 1 product/elimination
PL-TPP resin/DBAD	THF	no reaction
PBu_3/DIAD	THF	messy reaction
TPP/DBAD	CH_2Cl_2	~5: 1 product/elimination
TPP/DIAD	THF	DIAD displacement of OH

[a]Product/elimination ratios are based on TIC from ESI (positive mode) MS. [b]PL-TPP resin refers to commercially available polymer-bound triphenylphosphine.

SCHEME 3. Ultimate Scale up Synthesis of 1 To Form Greater than 100 g



(59.2 and 55.8), (50.7 and 49.6), (39.6 and 38.3), 22.0. Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 53.88; H, 6.21; N, 8.83.

(1*R*,4*R*)-*N*-Acetyl-2-oxa-5-azabicyclo[2.2.1]heptan-3-one (4) from 2. To a 2-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, temperature probe, and nitrogen inlet were added *trans*-4-hydroxy-L-proline (129.2 g, 985 mmol, 1.0 equiv) and 1 L of acetic anhydride. The mixture was stirred at 90 °C for 24 h and then cooled to room temperature. After concentration under reduced pressure, IPA (230 mL) was added, and the mixture was

stirred at room temperature for 30 min. After the mixture was stirred at 0 °C for an additional 2 h, the resulting solids were collected by filtration and washed with 90 mL of IPA to provide the title compound as a white solid (80 g, 52%).

(2*R*,4*R*)-1-[2-([1,4]Diazepane-1-carbonyl)-4-hydroxypyrrolidin-1-yl]ethanone (7). To a 5-L jacketed reactor equipped with an overhead mechanical stirrer, nitrogen inlet, thermocouple probe, and reflux condenser were added (1*R*,4*R*)-*N*-acyl-2-oxa-5-azabicyclo[2.2.1]heptan-3-one (310.3 g, 2 mol), homopiperazine (500.85 g, 5 mol), and *tert*-amyl alcohol (3 L). The mixture was warmed to 90 °C for 15 h and then cooled to room temperature. The mixture was then concentrated under reduced pressure to a mass of 1280.16 g. During concentration, white solids formed. The solids were filtered, washed with 1 L of ethyl acetate, and dried on the filter to provide the title compound as a white crystalline solid (379.7 g, 1.6 wt % *tert*-amyl alcohol, 1.8 wt % homopiperazine, 96.6 wt % **7** (367 g, 72%)): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (s, 1H), 4.88 (dd, J = 14.5, 9.7, 1H), 4.42 (bs, 1H), 3.91−3.63 (m, 5H), 3.54−3.40 (m, 1H), 3.28 (ddd, J = 13.7, 7.3, 4.5, 0.44H), 3.12−2.74 (m, 4H), 2.27 (ddd, J = 14.7, 10.2, 5.2, 1H), 2.17−1.95 (m, 4.56H), 1.82−1.72 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 170.3, (72.1 and 72.1), (58.50 and 58.46), (55.52 and 55.48), (51.6, 50.2, 49.3, 48.9, 48.5, 48.3, 48.0, 47.0 signals for 4 carbons), (37.58 and 37.55), (30.6 and 29.9), 22.8. Anal. Calcd for $C_{12}H_{21}N_3O_3$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.33; H, 8.46; N, 16.27.

(2*R*,4*R*)-1-[2-(4-Cyclobutyl[1,4]diazepane-1-carbonyl)-4-hydroxypyrrolidin-1-yl]ethanone (6). To a 5-L jacketed reactor equipped with an overhead mechanical stirrer, nitrogen inlet, and thermocouple probe were added (2*R*,4*R*)-1-[2-([1,4]diazepane-1-carbonyl)-4-hydroxypyrrolidin-1-yl]ethanone (370 g, 1.4 mol **7**, 0.07 mol homopiperazine), cyclobutanone (137 mL, 1.84 mmol), and 1,2-dichloroethane (3.7 L). The mixture was stirred for 1 h, and then sodium triacetoxy borohydride (422.4 g, 1.99 mol) was added in five portions over 2 h. After the reaction mixture was stirred overnight at room temperature, the mixture was quenched with 50% $NaOH_{(aq)}$ (318.4 g solution, 3.98 mol). After the mixture was stirred for 2 h, magnesium sulfate was added (264.19 g). After an additional 1.5 h of stirring, the solids were removed by filtration and the filtrate was dried with additional magnesium sulfate, filtered, and concentrated to a final mass of 435.57 g, ∼73 wt % **6** (318 g, 73%). Additional purification was achieved by flash chromatography (2.5 kg of silica gel, 5% 2 M NH_3 in MeOH/95% DCM) to give the title compound as an oil (277.4 g, 64%). To remove all traces of methanol prior to the final step, the compound was taken up in THF and reconcentrated: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16−5.95 (m, 1H), 4.90 (dd, J = 9.6, 4.6, 1H), 4.49−4.32 (m, 1H), 3.99−3.55 (m, 5.5H), 3.53−3.42 (m, 0.5H), 2.90 (tt, J = 15.7, 8.0, 1H), 2.72 (ddd, J = 13.0, 7.5, 2.5, 0.5H), 2.63−2.34 (m, 3.5H), 2.26 (ddd, J = 14.4, 9.7, 5.0, 1H), 2.11−1.50 (m, 12H); ^{13}C NMR (151 MHz, $CDCl_3$) two major conformers, δ (173.8 and 173.6), (169.9 and 169.8), 71.7, (59.6 and 59.5), (55.1 and 55.0), (52.4 and 52.0), (50.4 and 50.3), (48.5 and 47.3), (46.4 and 45.5), (37.2 and 37.1), (28.02, 28.00, 27.95, and 26.8, signals for 2 carbons), 22.4, (13.42, 13.39). Anal. Calcd for $C_{16}H_{17}N_3O_3$: C, 62.11; H, 8.80; N, 13.58. Found: C, 61.28; H, 8.79; N, 13.70.

(2*R*,4*S*)-1-[2-(4-Cyclobutyl[1,4]diazepane-1-carbonyl)-4-(3-fluorophenoxy)pyrrolidin-1-yl]ethanone (1·HCl). To a 5-L jacketed reactor equipped with an overhead mechanical stirrer, nitrogen inlet, and thermocouple probe were added (2*R*,4*R*)-1-[2-(4-cyclobutyl[1,4]diazepane-1-carbonyl)-4-hydroxypyrrolidin-1-yl]ethanone (138.77 g, 448.5 mmol) and dichloromethane (4.3 L). To the stirring solution were added 3-fluorophenol (41.83 mL, 462.0 mmol) and resin-supported triphenylphosphine (339.33 g, Polymer Laboratories, PL-TPP, 1.52 mmol/g, 515.8 mmol). Finally, diisopropyl azodicarboxylate (91 mL, 462.0 mmol) was added dropwise over 15 min. The mixture was allowed to stir at room temperature for 15 h, and then the resin was removed by filtration and washed with dichloromethane (4 L). The resulting filtrate was concentrated to dryness and partitioned between water (2 L) and MTBE (2 L). After separation of the layers, the aqueous layer was further extracted with MTBE (2 × 1.8 L). The combined organics were concentrated to 2 L and then extracted with 1 N HCl (2 L). The acidic aqueous layer was washed once with MTBE (1 L) and then basified to pH > 12 with 50% $NaOH_{(aq)}$ (118 mL). The aqueous layer was extracted with dichloromethane (2 × 1.5 L), and the combined organics were dried over $MgSO_4$, filtered, and concentrated to a yellow oil (129.0 g, 16.9 wt % dichloromethane, 1.4 wt % MTBE, 1.1 wt % DIAD byproduct, 80.5 wt % **1** (103.8 g, 57%). The material was purified further through flash chromatography (0−5% 2 M NH_3 in MeOH/DCM) (96.3 g, 53%). The material was taken up into ethanol and concentrated to remove all dichloromethane and methanol. Finally, dissolution into water with 1 equiv of 1 N $HCl_{(aq)}$ and lyophilization provided **1·HCl** as a somewhat hygroscopic, noncrystalline, white solid (with ∼10000 ppm EtOH): ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.38 (bs, 1H), 7.28−7.20 (m, 1H), 6.75−6.67 (m, 1H), 6.67−6.61 (m, 1H), 6.61−6.53 (m, 1H), 5.06 (bs, 1H), 4.90−4.65 (m, 1H), 4.40−4.23 (m, 1H), 4.22−4.06 (m, 1H), 4.06−3.90 (m, 1.25H), 3.80−3.73 (m, 1H), 3.66−3.46 (m, 2H), 3.46−3.18 (m, 3.5H), 3.06−2.93 (m, 1.25H), 2.93−2.62 (m, 3H), 2.53−2.37 (m, 1H), 2.37−2.10 (m, 4H), 2.07−2.04 (m, 3H), 1.98−1.87 (m, 1H), 1.76−1.57 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) two major conformers δ (172.3 and 171.9), 169.5, 163.3 (d, J_{C-F} = 246 Hz), (157.7 [d, J_{C-F} = 11 Hz] and 157.8 [d, J_{C-F} = 11 Hz]), 130.5 (d, J_{C-F} = 10 Hz), 110.9, (108.32 [d, J_{C-F} = 21 Hz] and 108.28 [d, J_{C-F} = 21 Hz]), (103.2 [d, J_{C-F} = 25 Hz] and 103.1 [d, J_{C-F} = 25 Hz]), 76.1, (60.1 and 60.0), (54.8 and 54.3), (53.45 and 53.39), (51.2, 50.9), (49.4 and 48.9), (45.2 and 43.2), (43.4 and 41.3), (35.1 and 34.9), (25.70, 25.67, 25.50, and 25.48), (23.5 and 22.2), 22.2, (12.9 and 12.8). Anal. Calcd for $C_{22}H_{31}ClFN_3O_3 \cdot 0.15H_2O$: C, 59.69; H, 7.13; N, 9.49; Cl, 8.01. Found: C, 59.56; H, 7.24; N, 9.37; Cl, 8.14.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for **1·HCl** and **4**−**7**, DSC traces for **4** and **7**, HPLC/SFC chromatograms for **4** and **1** (including chiral stationary phase traces), ^{1}H NMR for **1** free base, and check for byproduct **8** in **7**. This material is available free of charge via the Internet at http://pubs.acs.org.