Organic Process Research & Development **2006**, *10,* 262–271

Stereoselective Process for a CCR3 Antagonist

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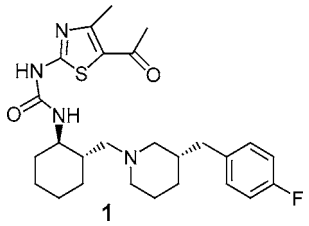
Abstract:

A convergent, multikilogram, stereoselective synthesis of 1 is described. A key fragment, (*S*)-3-(4-fluorobenzyl)piperidine (2) was synthesized from valerolactam in three steps using our recently discovered Ir−BDPP-catalyzed asymmetric hydrogenation. Another key fragment, (1*R*,2*R*)-2-(benzyloxycarbonylamino)cyclohexanecarboxaldehyde (3) was synthesized from *meso*-hexahydrophthalic anhydride in seven steps. The stereochemistry was set in the first step of this sequence via a quinidine-mediated desymmetrization of the *meso*-anhydride. Coupling of the fragments 2 and 3 followed by deprotection provided the penultimate 23. The active pharmaceutical ingredient (API) free base 1 was obtained by treatment of 23 with the aminothiazole fragment 4 under mild conditions.

Introduction

Many APIs contain multiple stereogenic centers which present synthetic challenges to process chemists. The advances in stereoselective synthesis and catalysis and their applications are increasingly evident in the process development of pharmaceuticals.[1] An example is our target molecule **1**,



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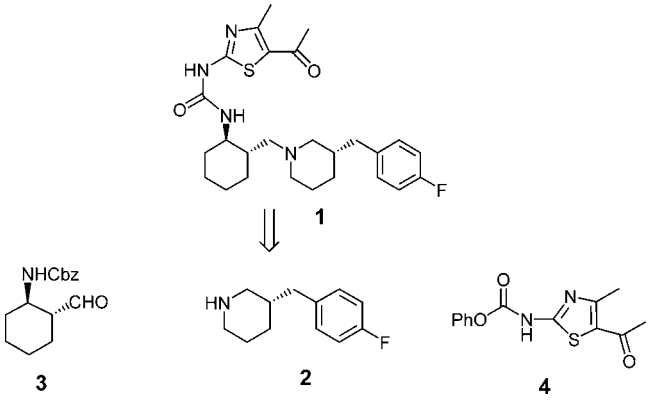
a CCR3 antagonist, which has potential in the prevention of inflammation in asthma and allergic rhinitis.[2] A stereoselective synthesis and the scale-up issues associated with a 20-kg pilot-plant manufacturing campaign are described herein.

Scheme 1. **Retrosynthetic analysis**



3 **2** **4**

Results and Discussion

Discovery Chemistry Synthesis. Our Discovery Chemistry colleagues employed a convergent synthesis for **1** from three fragments, the enantiopure 3-(4-fluorobenzyl)piperidine (**2**), enantiopure cyclohexane aminoaldehyde **3**, and aminothiazole fragment **4**.[2] Our process research efforts focused on the development of efficient and scalable synthetic routes to the two enantiopure fragments **2** and **3**. The union of these fragments could be achieved by a reductive amination reaction between **2** and **3**, followed by urea formation with fragment **4** (Scheme 1).

Synthesis of Enantiopure Piperidine Fragment 2. Several syntheses of the optically active piperidine **2** have been reported.[2−4] Reduction of *N*-Boc-3-(4-fluorobenzylidene)-piperidine followed by deprotection gave the racemic piperidine **2**, which was then resolved by treatment with (*R*)-mandelic acid in acetonitrile.[3] Alternatively, hydrogenation of the hydrochloride salt of (4-fluorophenyl)(pyridine-3-yl)-

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(1) (a) Blaser, H. U.; Spindler, F.; Studer, M. *Appl. Catal., A.* **2001**, *221*, 119−143. (b) Hawkins, J. M.; Watson, T. J. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3224−3228. (c) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Stuermer, R.; Zelinski, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 788−824.

(2) De Lucca, G. V.; Kim, U. T.; Vargo, B. J.; Duncia, J. V.; Santella, J. B.; Gardner, D. S.; Zheng, C.; Liauw, A.; Wang, Z.; Emmett, G.; Wacker, D. A.; Welch, P. K.; Covington, M.; Stowell, N. C.; Wadman, E. A.; Das, A. M.; Davies, P.; Yeleswaram, S.; Graden, D. M.; Solomon, K. A.; Newton, R. C.; Trainor, G. L.; Decicco, C. P.; Ko, S. S. *J. Med. Chem.* **2005**, *48*, 2194−2211.

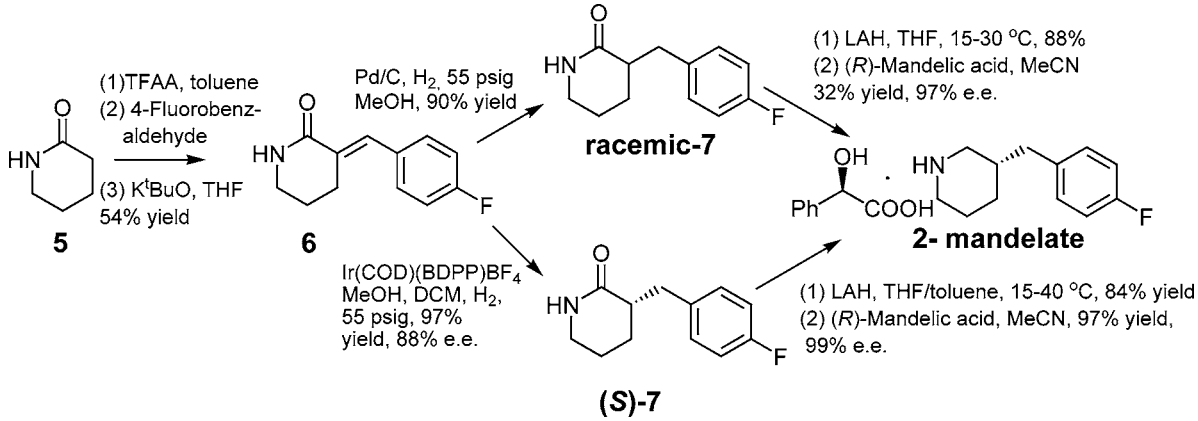
(3) Varnes, J. G.; Gardner, D. S., Santella, J. B.; Duncia, J. V.; Estrella, M.; Watson, P. S.; Clark, C. M.; Ko, S. S.; Welch, P.; Covington, M.; Stowell, N.; Wadman, E.; Davies, P.; Solomon, K.; Newton, R. C.; Trainor, G. L., Decicco, C. P.; Wacker, D. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1645−1649.

(4) Emmett, G. C.; Cain, G. A.; Estrella, M. J.; Holler, E. R.; Piecara, J. S.; Blum, A. M.; Mical, A. J.; Teleha, C. A.; Wacker, D. A. *Synthesis* **2005**, 92−96.

Published on Web 01/12/2006

10.1021/op050202l CCC: $33.50

Scheme 2. **Synthesis of (*S*)-3-(4-fluorobenzyl)piperidine (2)**



methanol using 5% PtO_2 in ethanol gave (4-fluorophenyl)-(piperidinyl-3-yl)methanol which was then treated with trimethylsilyl iodide to afford the racemic piperidine **2**, which was resolved similarly.[4]

We envisioned that inexpensive and readily available valerolactam could serve as a good starting material for the multikilogram synthesis of piperidine **2**. Valerolactam **5** can be readily converted to the exocyclic olefin **6** using a literature procedure.[5] Benzylidenelactam **6** can be conveniently reduced to the benzyllactam **7** via catalytic hydrogenation. The benzyllactam **7** can be converted to racemic piperidine **2** by lithium aluminum hydride reduction. Chemical resolution by diastereomeric salt formation would then furnish enantiopure piperidine **2**. To improve the overall efficiency of this process, asymmetric hydrogenation of olefin **6** was also pursued. A comparison of the chemical resolution and asymmetric catalysis routes is discussed below (Scheme 2).

Racemic Hydrogenation of 6 and Resolution of 7. Preparation of arylidenelactams by aldol condensation of *N*-acetyllactams and benzaldehydes under basic conditions (potassium *tert*-butoxide or sodium hydride) in modest yields (20−45%) has been reported.[5] The low yields were attributed to an undesired competing aldol reaction of the acetyl group.[5] Changing the protecting group to trifluoroacetyl eliminated this undesired aldol reaction and perhaps also increased the acidity of the α-proton. Preparation of **6** thus involved protection of valerolactam with trifluoroacetic anhydride (TFAA) in toluene.[6] Removal of the trifluoroacetic acid (TFA) byproduct was carried out by vacuum distillation, and the TFA content was monitored by ^{19}F NMR. The TFA-protected valerolactam was mixed with 4-fluorobenzaldehyde, and the resultant mixture was charged to a 1.0 M solution of potassium *tert*-butoxide in THF. The crude product **6** was readily isolated by filtration after the reaction mixture was quenched by addition of water. Reslurry purification of the crude product in a mixture of isopropyl acetate and heptane improved the purity from 70.3 to 99.1 wt % and afforded benzylidenelactam **6** in 54% isolated yield.

Hydrogenation of benzylidenelactam **6** was carried out in methanol using 10% Pd/C under 55 psig pressure to give racemic benzyllactam **7** in 90% yield. The benzyllactam **7** was converted to racemic piperidine **2** by reduction with lithium aluminum hydride (LAH) in THF. Rochelle's salt solution was identified as the best quench for the LAH reaction mixture in terms of ease of phase separation and control of heat evolution. The racemic piperidine **2** was extracted into ethyl acetate (solution yield 88%). Our medicinal chemistry collegues had shown that mandelic acid salt formation in acetonitrile provided optimal resolution for racemic piperidine **2** after screening some chiral acids and solvents.[4] Following that procedure, a solvent switch from ethyl acetate to acetonitrile was carried out to prepare for the mandelic acid salt formation. Our studies on the stoichiometry of mandelic acid and the isolation temperature showed 0.7 equiv and isolation at 50 °C gave optimal product purity and recovery. The de of the crude mandelic acid salt of piperidine **2** was observed to be 84%, and was readily upgraded to 97% by reslurry in acetonitrile at 50 °C. The overall yield of enantiopure piperidine **2** from olefin **6** was 25%.

Asymmetric Hydrogenation of 6. Although the Pd/C catalysed hydrogenation and chemical resolution sequence provided a practical scale-up for piperidine **2**, improvement in the yield and efficiency was highly desirable. In our effort to identify suitable catalysts for the asymmetric hydrogenation of the benzylidenelactam **6**, a 256-variation catalyst screen was run.[6] After the initial hits, the screen was refined by focusing on additives and solvents. A cationic Ir−BDPP complex was identified to have the best selectivity (90% ee) under practical loading (0.2−1.0 mol %).[6] Recrystallization of the hydrogenation substrate **6** from IPA/water mixture was routinely carried out to remove any traces of potential poisons to ensure catalyst performance. Process development of this new technology indicated the robustness of this reaction. The Ir−BDPP catalyst was readily generated in situ from $[(COD)_2Ir]BF_4$ and (2*S*,4*S*-BDPP). The reaction kinetics and selectivity were almost identical for runs carried out in 1-L laboratory reactor and a 400-L reactor under the same reaction conditions (20 °C, 55 psig hydrogen pressure, 0.25 mol % catalyst loading, 10 volumes of 1:1 DCM/methanol). The reaction solvent was chosen for its good solubility of

(5) Bose, A. K.; Fahey, J. L.; Manhas, M. S. *Tetrahedron* **1974**, *30*, 3−9.
(6) For a detailed screening protocol, see the Supporting Information for Yue, T.-Y.; Nugent, W. A. *J. Am. Chem. Soc.* **2002**, *124*, 13692−13693.

Scheme 3. **Discovery chemistry synthesis of aminoaldehyde 3**

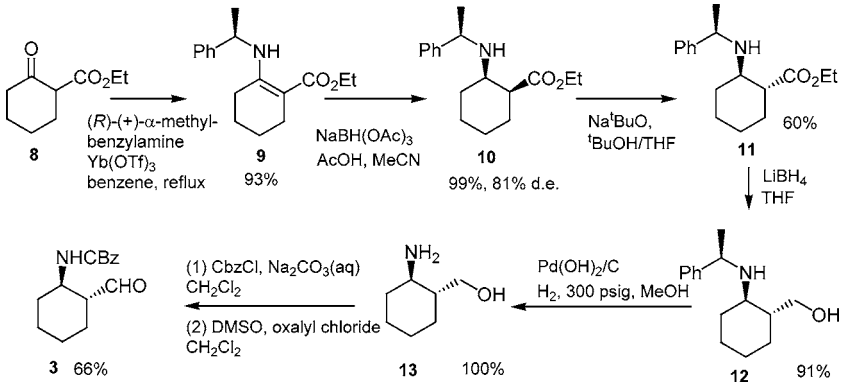
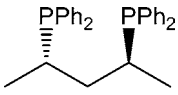


Table 1. **Comparison of the Pd/C and Ir−BDPP Hydrogenation Processes**

	10% Pd/C, 50% wet Degussa type E101	Ir-BDPP
enantiomeric ratio (as is from reduction)	1:1	20:1
reaction temperature	20 °C	20 °C
pressure	55 psig	55 psig
solvent	methanol	methanol/DCM (1:1 v/v)
concentration	0.2 kg/L	0.1 kg/L
reaction time	6 h	14 h
overall yield from **6** to **2**	25%	79%
optical purity of **2** (after salt formation)	97% ee	99% ee

the substrate **6**. The catalyst was removed by filtration through silica gel and Celite, and recovery was not attempted. Crystallization of the benzyllactam **7** (88% ee) from a number of solvents did not improve the enantiomeric purity. Benzyllactam **7** was converted to the piperidine **2** (LAH in THF/toluene) without any loss in enantiomeric purity. The formation of the mandelic acid salt of piperidine **2** further enhanced the ee of the derived free base to 99%, and the salt was readily isolated by filtration.[2,3,4] The overall yield of enantiopure piperidine **2** from olefin **6** was 79%. Table 1 shows a comparison of the Pd/C and Ir−BDPP processes.



(*2S,4S*)-BDPP

Synthesis of Enantiopure Aminoaldehyde Fragment 3. Enantiopure 2-aminocycloalkanecarboxylic acids and their derivatives are common structural units in many natural products and biologically active compounds. The synthesis of this class of β-amino acids has attracted considerable attention.[7]

A synthesis of the aminoaldehyde **3** based on the stereoselective reduction of a chiral enamino-ester **9**[8] has been published by our Discovery Chemistry group (Scheme 3).[2] The known amino alcohol **13**[8c] was protected as its benzyl carbamate and was then subjected to Swern oxidation conditions to furnish the aldehyde **3**.[2] Preparation of the alcohol **13** from the readily available keto-ester **8** was described by Corey et al.[8c] The moderate diastereoselectivity (de = 81%) in the formation of the amino ester **10** and the need for chromatographic purification of intermediates **10** and **11** prompted us to consider an alternative synthesis.

A selective synthesis utilizing desymmetrization of a *meso*-cyclic anhydride by ring-opening was envisioned.[9] The use of cinchona alkaloids as chiral mediators in these reactions is well documented.[10] This synthetic route, shown in Scheme 4, was evaluated and found to be more efficient in pilot-plant operations compared to the route outlined in Scheme 3.

Using a procedure similar to that described by Bolm et al,[10c] opening of the *meso*-hexahydrophthalic anhydride (**14**) by ethanol in the presence of quinidine (1.3 equiv) furnished enantiomerically enriched *cis*-hemi-ester **15** (87% ee) in good conversion (99%). Quinidine was removed by extraction with aqueous sulfuric acid, which allowed for recycling of this alkaloid to reduce cost. The toluene solution containing *cis*-hemi-ester **15** was used without further purification in the epimerization step after removal of the residual water and ethanol by distillation. Epimerization of the *cis*-hemi-ester **15** to its *trans*-isomer **16** was carried out at −15 °C using potassium *tert*-amylate as the base. The reaction was considered complete when equilibrium was reached at less than 4% *cis*-hemi-ester **15**. A multistage quench using glacial acetic acid followed by aqueous hydrochloric acid eliminated hydrolysis on workup. Isolation of the *trans*-ester **16** as its (*R*)-α-methylbenzylamine salt **17** improved the ee from 87% to greater than 99% in 65% yield over the three steps from anhydride **14**.

The *trans*-hemi-ester **16** was liberated from the salt **17** by treatment with aqueous hydrochloric acid and extracted into toluene. The toluene solution of **16** was distilled to a water content of less than 0.1% to minimize the potential for generation of hydrazoic acid by hydrolysis. The resultant

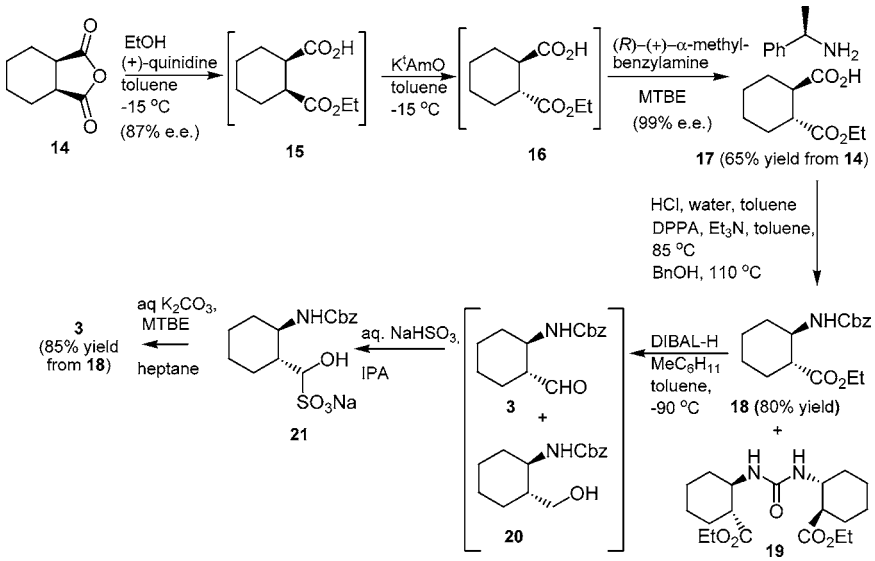
(7) For a review: Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181.

(8) (a) Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem*. **1994**, *59*, 5328−5335. (b) Cimarelli, C.; Palmieri, G.; Bartoli, G. *Tetrahydron: Asymmetry* **1994**, *5*, 1455−1458. (c) Hayashi, Y.; Rhode, J. J.; Corey, E. J. *J. Am. Chem. Soc*. **1996**, *118*, 5502−5503

(9) For a review: Spivey, A. C.; Andrew, B. I. *Angew. Chem., Int. Ed*. **2001**, *40*, 3131.

(10) (a) Hiratake, J.; Yamamoto, Y.; Oda, J., *J. Chem. Soc., Chem. Commun*. **1985**, 1717. (b) Hiratake, J.; Inagaki, M.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1053. (c) Bolm, C.; Gerlach, A.; Dinter, C. L. *Synlett* **1999**, 195.

Scheme 4. **Synthesis of aminoaldehyde 3 from *meso*-anhydride (14)**



16 was subjected to Curtius rearrangement conditions similar to those described by Mittendorf et al.[11] The toluene solution containing **16** was treated with triethylamine and heated to 85 °C. Diphenyl phosphoryl azide (DPPA) in toluene was charged to this mixture at a rate to control the batch temperature between 85 and 90 °C. Consumption of the *trans*-hemi-ester **16** (over 98% as evident by HPLC) was observed in 30 min, and benzyl alcohol was added to the intermediate isocyanate to give the Cbz-protected amino-ester **18** in 80% isolated yield. In this reaction only a small amount (up to 0.5 area %) of the symmetrical urea **19** was formed, which was removed by an 2-propanol/water recrystallization to a very low level (0.1 area %).

Important Safety Information. With respect to the safety issues of this reaction involving DPPA, we carried out thermochemical studies which showed the heat flow of the reaction between **16** and DPPA is addition controlled. Analysis by React-IR showed that no buildup of the potentially dangerous acylazide occurred under these reaction conditions. The complete consumption of **6** and production of one equivalent of nitrogen gas (with respect to DPPA) under the dry reaction conditions (less than 0.1% water) suggested that the hydrolysis of DPPA to hydrazoic acid by residual water is slow. However, as the formation of hydrazoic acid in this reaction was not thoroughly investigated, we had taken measures to ensure low water content in the reaction mixture in pilot-plant runs. Also see caution in Experimental Section.

Amino-ester **18** was reduced to the aminoaldehyde **3** by treatment with DIBAL-H in toluene/methylcyclohexane at −90 °C. Formation of the over-reduction product, the amino alcohol **20**, was suppressed to 4.4% at this low temperature as compared to 12.5% at −78 °C. The product isolation and purity were improved by formation of the bisulfite adduct **21**. Unreacted starting material **18** and the amino alcohol **20** were selectively removed in the mother liquors. After liberation of the aminoaldehyde **3** from the bisulfite adduct **21** with aqueous potassium carbonate, the yield of the aminoaldehyde **3** was 85%.

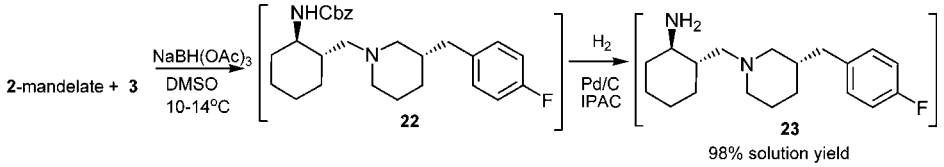
The overall yield from the anhydride **14** to the aminoaldehyde **3** was 44%. The desymmetrization reaction was shown to be robust on scale-up and consistent in enantioselectivity. The sequence involves four isolations, and the crystalline intermediates **17**, **18** , and **21** provided convenient purification points.

Formation of the Penultimate (23) and API (1). With the enantiopure benzylpiperidine **2**-mandelate and aminoaldehyde **3** in hand, the emphasis of development work turned to the coupling reactions to bring the fragments together, while maintaining the overall chiral purity (Schemes 5, 6). The reaction sequence followed the Discovery Chemistry synthesis.[2] The reductive amination conditions developed and scaled utilized sodium triacetoxyborohydride (STAB) in DMSO at 10−14 °C, with a slow addition of the substrates to the STAB solution to control the reaction temperature. No epimerization of the stereogenic centers was observed under these conditions. The coupled product **22** was worked up with aqueous NaOH and extracted into isopropyl acetate (*i*PrOAc). It was readily deprotected by either of two methods. Treatment of **22** with hydrobromic acid in acetic acid/*i*PrOAc furnished the deprotected diamine **23** and was isolated as its bis-hydrobromide salt. However, the byproduct benzyl bromide is a lachrymator and poses hazards in operations. Hydrogenolysis was used as a greener alternative. An *i*PrOAc solution of **22** was hydrogenated in the presence of palladium on carbon under 55 psig pressure for 4 h to remove the Cbz-group to give the penultimate **23** (see Scheme 5). The Pd catalyst was removed by filtration, and the *i*PrOAc solution of the penultimate **23** was dried by azeotropic distillation to set the stage for the final API formation step.

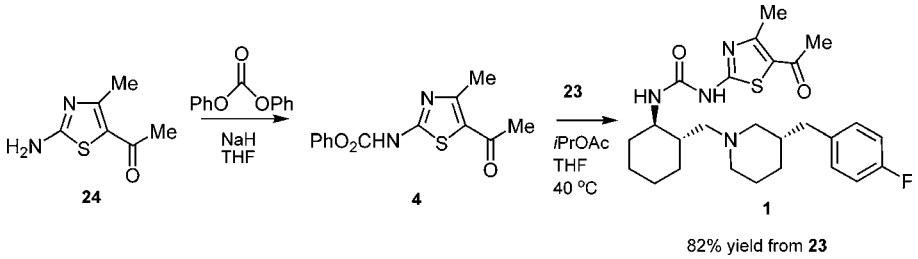
The thiazolecarbamate fragment **4** was prepared in 78% isolated yield by treatment of a suspension of aminothiazole **24** and diphenyl carbonate in THF with sodium hydride as reported in the literature (Scheme 6).[2] A suspension of sodium hydride in mineral oil (60 wt %) was added in

(11) Mittendorf, J.; Benet-Buchholz, J.; Fey, P.; Mohrs, K.-H. *Synthesis* **2003**, *1*, 136.

Scheme 5. **Formation of the penultimate 23**



Scheme 6. **Formation of the API**



multiple portions to control heat and gas evolution. Thermal conditions (e.g., 100 °C in DMSO, NMP, and toluene) and other basic conditions (*n*-BuLi in THF, NaHMDS or LiHMDS in THF) were attempted; however, all gave low conversion or complex reaction mixtures.

The thiazole carbamate **4** was dissolved in THF and added to the *i*PrOAc solution of the penultimate **23** at 40 °C. Upon reaction completion, the THF/*i*PrOAc solvent mixture was switched to IPA by distillation. The free base API **1** was crystallized from a mixture of 2-propanol and water. The isolated yield of the API **1** was 80% from **2** and **3**.

The API free base **1** unexpectedly gave a new polymorph on large scale (1000 L). The new polymorph was shown to be higher melting by DSC. The low solubility of this new form (18 vs 38 mg/mL) led to difficulties in making the fumarate salt which was the desired solid form of this compound. The free base **1** was dissolved in 1-methoxy-2-propanol at 70 °C and a solution of fumaric acid (0.2 equiv to the free base **1**) in 1-methoxy-2-propanol was added while maintaining the batch temperature at 70 °C. Seed crystals were charged to this clear solution. Once the fumarate salt had started to crystallize, the remaining fumaric acid (0.8 equiv) in 1-methoxy-2-propanol was added. The batch was then cooled to 20 °C, and the product was collected by filtration. This process gave an 86% yield of the final product with higher than 99.5% purity. The dried final product was analyzed by XRPD and DSC and was shown to be the desired form.

Conclusion

The target compound **1** was synthesized in multikilogram quantities by a convergent synthesis from readily available starting materials. The stereochemistry of the key piperidine fragment **2** was established by our recently reported Ir−BDPP-catalyzed asymmetric hydrogenation,[6] and its preparation from valerolactam involved four steps with two isolations in 43% overall yield. The preparation of another key fragment **3** followed the well-known desymmetrization of a *meso*-anhydride, which was shown to be practical and robust. This sequence starting from *meso*-hexahydrophthalic anhydride involved seven steps with four isolations and 44% overall yield. The coupling of these fragments followed standard chemistry. The API formation procedure was shown to be robust in producing the desired solid form.

Experimental Section

Chiral HPLC analytical methods were developed using authentic racemic samples. The Chiralpak AS and Chiralpak OD columns used to determine enantiomeric purity of the products were purchased from Chiral Technologies, Inc., Exton, PA. NMR spectra were obtained at 25 °C in $CDCl_3$ except as indicated, and field strengths for the various nuclei were as follows: ^{1}H (400.1 MHz), ^{13}C (100.6 MHz), ^{19}F (376.5 MHz), ^{31}P (162.0 MHz). Coupling constants (*J*) are given in Hertz.

3-(4-Fluorobenzylidene)-2-piperidone (6). A 30-gal (120-L) glass-lined reactor was charged with valerolactam (18.0 kg, 182 mol) and toluene (42.0 kg). Trifluoroacetic anhydride (42.0 kg, 200 mol) was added below 25 °C over 30 min, and the mixture was stirred for an additional 60 min. Volatiles were distilled off at 60−70 ° C at 140 Torr. Toluene (50.0 kg) was added, and the mixture was further distilled until approximately 27 L remained in the pot; this process was repeated twice. To the residue was added *tert*-butyl alcohol (18.8 kg) and 4-fluorobenzaldehyde (20.3 kg, 164 mol). The resultant solution was slowly transferred to a 100-gal (400-L) glass-lined reactor containing potassium *tert*-butoxide in tetrahydrofuran (122 kg of a 20% solution, 218 mol). The mixture was warmed to 60 °C for 1 h. Volatiles were distilled at 40−50 °C at 250 Torr to a volume of approximately 100 L. Water (180 L) was added to the slurry at 40 °C, the mixture was cooled to 5 °C for 2 h, and the solid was collected by filtration. The wet cake was washed and reslurried with water (3 × 200 L) and dried in a tray dryer (50 °C, 50 Torr) to afford crude 3-(4-fluorobenzylidene)-2-piperidone (32.6 kg); the purity by HPLC was 70.3 wt % (95.4 area %).

The crude product **6** (32.6 kg) was charged to a 100-gal (400-L) glass-lined reactor with isopropyl acetate (80 kg). Residual water was removed by distillation at atmospheric pressure to a volume of 70 L. Heptane (56 kg) was added at 80 °C, and the slurry was cooled to 5 °C. Filtration, washing

with a mixture of isopropyl acetate (8 kg) and heptane (62 kg) at 5 °C, and drying (50 °C, 50 Torr) afforded purified 3-(4-fluorobenzylidene)-2-piperidone **6** (20.0 kg, 54% yield) which by HPLC analysis has a purity of 99.1 wt % (99.6 area %). To ensure the material was free from catalyst poisons, the majority of the product (19.7 kg) was further crystallized by dissolution in 2-propanol (61.9 kg) and water (20 L) at 75 °C. The mixture was seeded at 70 °C and cooled to 30 °C, whereupon water (140 L) was added. After standing overnight, the mixture was cooled to 2 °C, and the product was collected by filtration, washed with 10% 2-propanol in water (88 L), and dried (65 °C, 50 Torr). This afforded crystalline 3-(4-fluorobenzylidene)-2-piperidone (**6**, 19.5 kg, 54% yield from valerolactam). Mp 170 °C. ^{19}F NMR (376 MHz, $CDCl_3$) δ 112.99. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (m, 2H), 2.80 (m, 2H), 3.45 (m, 2H), 7.08 (m, 3H), 7.40 (m, 2H), 7.77 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.2, 26.4, 42.2, 115.6 (d, J = 21 Hz, C-3′), 129.5(C-3), 131.8 (d, J = 8 Hz, C-2′), 132.1 (d, J = 4 Hz, C-1′), 134.7 (olefinic), 162.5 (d, J = 249 Hz, C-4′), 167.0 (C-2). Anal. Calcd. for $C_{12}H_{12}FNO$: C, 70.23; H, 5.89; N, 6.82. Found: C, 70.07; H, 5.86; N, 6.79.

Racemic 3-(4-Fluorobenzyl)-2-piperidone (7). A 50-gal, stainless steel reactor was charged with 3-(4-fluorobenzylidene)-2-piperidone (**6**, 30.0 kg, 146 mol), 10% Pd on carbon (3.12 kg), and methanol (118 kg). The reactor was purged with nitrogen to a pressure of 30 psig and vented, with the purge/vent cycle being carried out four times in total. The reactor was then pressurized with hydrogen to 55 psig and 25 °C. After approximately 6 h reaction time, the batch was sampled, analyzed by HPLC, and shown to contain <1 area % of **6.** The batch was filtered through a bag filter to remove the catalyst. The filtrate was concentrated to a volume of about 70 L by distillation under atmospheric pressure at 65−66 °C. Toluene (104 kg) was charged to the reactor and distilled under atmospheric pressure to remove approximately 145 L of distillate. Toluene (77.8 kg) was again charged and concentrated to collect approximately 80 L of distillate. The concentrate in the reactor was sampled and shown to contain less than 2 vol % of methanol in toluene. Heptane (152 kg) was charged to the toluene solution at about 80 °C. The batch was cooled to 0 °C over 2 h and then held at 0 °C for 1 h. The slurry was filtered in a 30-in. diameter filter. The cake was washed with a mixture of heptane (51.5 kg) and toluene (7.2 kg) at 0 °C. The wet cake was dried in a tray dryer at 50 °C and 50 Torr to a constant weight of 27.5 kg, and the yield of **7** was 90%. Mp 127 °C. ^{19}F NMR (376 MHz, $CDCl_3$) δ −117.63. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (m, 1H), 1.57−1.89 (m, 3H), 2.50 (m, 1H), 2.71 (m, 1H), 3.29 (m, 3H), 6.01 (br s, 1H), 6.98 (m, 2H), 7.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 24.3, 35.6, 41.3, 41.8, 114.1 (d, J = 21 Hz), 129.6, 134.4, 160.4 (d, J = 241 Hz), 173.5.

***(S)*-3-(4-Fluorobenzyl)piperidine (2) Mandelate.** To a 200-gal glass-lined reactor were charged racemic 3-(4-fluorobenzyl)-2-piperidone (**7**, 27.5 kg, 133 mol) and THF (254 kg). The resulting solution was cooled to 15−20 °C with stirring. A solution of lithium aluminum hydride (50.3 kg, 10 wt % in THF, 133 mol) was added to the reaction solution at such a rate that the temperature of the reaction solution did not exceed 20 °C. Upon complete addition of the LAH solution, the batch was heated to 30 °C and stirred for 2 h. The batch was sampled and analyzed by HPLC and shown to contain less than 1.0 area % of **7**. To a 300-gal glass-lined reactor was added Rochelle salt (sodium potassium tartrate tetrahydrate, 112 kg, 397 mol) and water (358 L). The reaction mixture was quenched by slow addition to the Rochelle's salt solution. The transfer line was rinsed with THF (25 kg). The quenched mixture was stirred for 15 min, and the aqueous phase, containing lithium and aluminum salts, was transferred to the 200-gal reactor for back extraction. Ethyl acetate (189 kg) was added to the aqueous layer, the mixture was agitated at room temperature and allowed to settle. The aqueous layer was split away for disposal. The ethyl acetate layer was transferred to the 300-gal reactor and mixed with the THF layer. Additional water separated and was removed for disposal. Distillation was used to replace the THF with ethyl acetate. In the first batch, the ethyl acetate/THF mixture was distilled at atmospheric pressure until ca. 170 L of distillate was collected. Ethyl acetate (146 kg) was added to the reactor and distilled again until ca. 170 L of distillate was collected. A sample of the bottoms showed 40% residual THF. Ethyl acetate (50 kg) was charged to the reactor, and the distillation was repeated. Following the distillation, the ethyl acetate solution was washed twice with 10% brine (100 kg each wash). The phases split readily. The solution of racemic 3-(4-fluorobenzyl)piperidine (**2**) in ethyl acetate was drummed, weighed, and sampled. The solution yield of racemic 3-(4-fluorobenzyl)-piperidine (**2**) was 22.5 kg (88%) by HPLC assay.

The solution of racemic piperidine **2** (22.5 kg, 117 mol contained) in ethyl acetate was charged to a 200-gal glass-lined reactor. Atmospheric distillation was used to replace the ethyl acetate with acetonitrile as the solvent. Residual ethyl acetate in acetonitrile was shown to be less than 5 v/v%. (*R*)-(−)-Mandelic acid (12.4 kg, 81.6 mol, 0.7 equiv based on racemic piperidine **2** solution yield) and acetonitrile (137 kg) were charged to a 300-gal glass-lined reactor. The racemic piperidine **2** solution and the mandelic acid solution were separately heated to 78 °C. The racemic piperidine **2** solution was transferred to the mandelic acid solution, keeping the temperature above 75 °C. Acetonitrile (20 kg) was used to rinse the transfer line. The resulting mixture was aged for 1 h at 78−80 °C, cooled to 65 °C over 3 h, cooled to 50 °C over 3 h, and held at 50 °C for 2 h. The slurry was sampled and filtered, and the wet cake was analyzed for ee. The ee of the solid from the slurry was 84%. The batch was filtered at 50 °C. The wet cake was washed with acetonitrile (85 kg) at 50 °C and dried with nitrogen to remove as much liquor as possible. The wet cake was sampled and transferred to a 300-gal glass-lined reactor. The ee of the wet cake was 91%. To the wet cake in the 300-gal reactor was added acetonitrile (15 L per kg of contained piperidine **2**). The slurry was heated to 80 °C and held for 4 h with agitation. The solids did not all dissolve. The batch was then cooled to 50 °C over 3 h. The slurry was filtered

in a Nutsche at 50 °C and washed with acetonitrile (45 kg) at 50 °C. The product was dried at 50 °C and 50 Torr in a tray dryer. The yield of **2**-mandelic acid salt was 12.8 kg (32%), and the ee was 97%. Chiral HPLC method, Chiralpak AS (250 mm × 4.6 mm, 10-μm particle size); 1.0 mL/min, 30 °C; 265 nm; mobile phase, 95% (v/v) heptane, 4.5% (v/v) ethanol, 0.25% (v/v) trifluoroacetic acid, 0.25% (v/v) *n*-hexylamine. The retention times for the desired (*S*)-**2** enantiomer and the undesired (*R*)-**2** enantiomer are 10.1 and 12.8 min, respectively. Mp 172 °C. ^{19}F NMR (376 MHz, DMSO-d_6) δ −117.50. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08 (m, 1H), 1.48 (m, 1H), 1.62 (m, 2H), 1.84 (m, 1H), 2.45 (m, 5H), 2.62 (m, 1H), 2.96 (d, J = 13 Hz, 1H), 3.08 (d, J = 13 Hz, 1H), 7.17 (m, 7H), 7.37 (m, 2H).^{13}C NMR (100 MHz, DMSO-d_6) δ 22.1, 28.5, 35.2, 38.6, 43.4 47.8, 73.9, 115.2 (d, J = 21 Hz, C-3′), 126.5, 126.6, 127.8, 131.0 (d, J = 8 Hz, C-2′), 135.4 (d, J = 3 Hz, C-1′), 143.9, 161.1 (d, J = 240 Hz, C-4′), 175.9. Anal. Calcd for $C_{20}H_{24}FNO_3$: C, 69.55; H, 7.00; N, 4.06; found: C, 69.53; H, 7.00; N, 3.99.

(*S*)-3-(4-Fluorobenzyl)-2-piperidone (7) by Asymmetric Hydrogenation. A 100-gal (400-L) glass-lined reactor was charged with recrystallized 3-(4-fluorobenzylidene)-2-piperidone (**6**, 19.5 kg, 95.0 mol), methanol (75 kg), and dichloromethane (126 kg). (2*S*,4*S*)-(−)-2,4-Bis(diphenylphosphino)pentane (97 g, 0.25 mol %) and bis(1,5-cyclooctadiene)iridium(I) tetrafluoroborate (109 g, 0.25 mol %) was added to the stirred solution under nitrogen. The reactor was pressured to 55 psig hydrogen and stirred for 13 h at which time no starting material remained. The solvent was replaced with toluene by successive vacuum distillation and toluene charges, and the resultant solution was filtered through a bed of charcoal (Darco G-60) and silica gel 60. The resultant solution contained (*S*)-**7** (19.1 kg, 97% solution yield, 88% ee). Chiral HPLC analysis, Chiralpak AS (250 mm × 46 mm; 10-μm particle size); 1.0 mL/min, 40 °C; 210 nm; mobile phase, 60% (v/v) heptane, 39.2% (v/v) 2-propanol, 0.4% (v/v) trifluoroacetic acid, 0.4% (v/v) *n*-hexylamine; retention times of the desired (*S*)-**7** enantiomer and the undesired (*R*)-**7** enantiomer are 15.6 and 10.6 min, respectively. ^{19}F NMR (376 MHz, $CDCl_3$) δ −117.63. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (m, 1H), 1.57−1.89 (m, 3H), 2.50 (m, 1H), 2.71 (m, 1H), 3.29 (m, 3H), 6.01 (br s, 1H), 6.98 (m, 2H), 7.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 24.3, 35.6, 41.3, 41.8, 114.1 (d, J = 21 Hz), 129.6, 134.4, 160.4 (d, J = 241 Hz), 173.5.

(*S*)-3-(4-Fluorobenzyl)piperidine (2) Mandelate. A solution of (*S*)-3-(4-fluorobenzyl)-2-piperidone (**7**, 6.4 kg, 30.8 mol) in 120 L of toluene was cooled to 10 °C. Lithium aluminum hydride bis(tetrahydrofuran) solution in toluene (1.0 M, 27.8 kg, 31.8 L, 31.8 mol) was added at a temperature below 15 °C. The batch was heated to 40 °C and stirred for 3 h. The batch was quenched by slow addition to a Rochelle salt solution (16.4 kg in 90 L of water) and stirred for 15 min. The organic phase was washed with 10% brine followed by water. The toluene solution was concentrated by vacuum distillation to a volume of about 60 L. The resultant solution contained (*S*)-**2** (5.0 kg, 25.9 mol, 84% solution yield). Chiral HPLC analysis (as described above) indicated that the ee was 90%.

A solution of (*S*)-3-(4-fluorobenzyl)piperidine (**2**, 12.2 kg contained, estimated by HPLC assay, 63.1 mol at 90% ee) in 120 L of toluene was heated to 70 °C. To this hot solution was added a hot solution (at 70 °C) of (*R*)-(−)-mandelic acid (10.1 kg, 66.4 mol) in acetonitrile (50 L). The resulting mixture was stirred for 1 h at 70 °C, cooled to 25 °C over 2 h, and then held for 2 h. The slurry was filtered, washed with acetonitrile, and dried in a vacuum-dryer. The yield of **2**-mandelate was 21.1 kg (97%). Chiral HPLC analysis indicated that the ee was 99%.

2-(Phenoxycarbonyl)amino-4-methyl-5-acetylthiazole (4). The two solids, 2-amino-4-methyl-5-acetylthiazole (**24**, 10.5 kg, 67.2 mol) and diphenyl carbonate (14.5 kg, 67.7 mol) were each charged to a 100-gal glass-lined reactor, followed by pump charging of THF (178 kg). The mixture was heated to 30 °C and mixed for an additional 15 min. Sodium hydride (60% dispersion in mineral oil, 3.5 kg, 87.5 mol) was added in 15 portions through a charge lock under argon. The liberated hydrogen gas from the reaction was vented to a flame-arrestor. After 2 h aging at 30 °C, the reaction mass was sampled for reaction completion. A solution of phenol (1.3 kg, 13.8 mol) in THF (5 kg) was then pressure transferred from a pressure cylinder to the 100-gal reactor. After aging for another 30 min, the reaction mass was cooled to 15 °C and filtered through a bag filter and a cartridge filter in series to remove residue particles, followed by concentrating to 25% of initial volume in a glass-lined reactor at 125 Torr pressure and 25 °C.

To a clean 100-gal glass-lined reactor was added purified water (240 L). The concentrate was transferred into the 100-gal reactor, while maintaining the pot temperature at 25 °C. Solids started to form in the reactor. An aqueous solution of 6 N HCl was then added to the slurry, followed by a 1 N HCl solution to fine-tune the pH of the aqueous solution to between 4 and 7. The resulting slurry was held at 25 °C for 1 h and filtered on a 36-in. Nutsche installed with a filter cloth. The wet cake was washed with 120 L of purified water and dried in a pan-dryer for 12 h at 40 °C under 50 Torr.

The crude product was transferred back to the 100-gal glass-lined reactor for reslurrying by charging a mixture of 140 kg of *n*-heptane and 10 kg of THF (5 vol % THF in *n*-heptane). After aging at 25 °C for 1 h at 60 rpm, the slurry was sampled for solid purity and then filtered on the 36-in. Nutsche installed with a new filter cloth. The wet cake was washed with a solution of 5% THF in *n*-heptane and dried in a pan-dryer for 12 h at 40 °C under 50 Torr. The yield was 13.5 kg (78%). Mp 189 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 2.75 (s, 3H), 7.20 (m, 2H), 7.29 (m, 1H), 7.41 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 30.7, 121.4, 125.7, 126.8, 129.9, 150.0, 152.3, 155.5, 162.7, 190.6. HRMS Calcd for $C_{13}H_{12}N_2O_3S$: 277.0647 [M + 1]; found: 277.0652 [M + 1]. Anal. Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14; found: C, 56.45; H, 4.24; N, 10.06.

(1*R*,2*R*)-Cyclohexane-1,2-carboxylic Acid Monoethyl Ester (*R*)-(+)-α-Methylbenzylamine Salt (17) via *cis*-Hemi-ester (15) and *trans*-Hemi-ester (16). To a 50-gal glass-lined reactor was charged toluene (32.6 kg), followed by anhydrous (water content < 400 ppm) ethanol (12.6 kg, 274 mol). The mixture was cooled to and maintained at −20 °C. To a 300-gal glass-lined reactor was charged (+)-quinidine (89.3 kg, 275 mol), followed by toluene (242.5 kg) and *meso*-hexahydrophthalic anhydride (**14**, premelted at 50 °C, 35.0 kg, 227 mol). The resulting slurry was cooled to −20 °C. The ethanol/toluene mixture from the 50-gal reactor was transferred to that slurry at a rate (approximately 0.2 L/min) to maintain batch temperature in the 300-gal reactor below −15 °C. The transfer time was about 2.5 h. After an additional 2 h aging at −15 °C, HPLC analysis showed 99% conversion. To quench the reaction, the batch was warmed to room temperature and charged with 230 kg of 3 M sulfuric acid solution. After extraction and phase separation, the organic layer was washed twice with 100 L of purified water and then distilled at 35−40 °C and 35−50 Torr to approximately 178 L. GC analysis and Karl Fischer titration showed completion of distillation: less than 0.5 v/v % ethanol and less than 400 ppm water content in the *cis*-hemi-ester **15** toluene solution. The batch was cooled to −20 °C and used directly in the next step. The ee of the *cis*-hemi-ester **15** was determined by chiral HPLC to be 87%. Chiral HPLC method: Chiralcel OJ-R (150 mm × 4.6 mm; 5-μm particle size); 0.5 mL/min; 20 °C; 210 nm; mobile phase: 70% 0.1% phosphoric acid in water−30% acetonitrile. Retention times of the desired (1*R*,2*S*)-**15** enantiomer and undesired (1*S*,2*R*)-**15** enantiomer were 8.4 and 9.9 min, respectively. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7 Hz, 3H), 1.38−1.62 (m, 4H), 1.78 (m, 2H), 2.02 (m, 2H), 2.83 (m, 2H), 4.12 (q, J = 7 Hz, 2H).

To a 100-gal glass-lined reactor was charged 146.1 kg of a toluene solution containing 25 wt % potassium *tert*-amylate (contained 36.5 kg, 289 mol), followed by toluene (392.0 kg). The mixture was cooled to −20 °C. The toluene solution of *cis*-hemi-ester **15** was added at −10 to −15 °C, at a rate so that the temperature of reaction did not exceed −10 °C. The addition took approximately 3 h. After an additional 1 h aging, the reaction reached 96% conversion to the *trans*-hemi-ester **16** based on HPLC analysis. To quench the reaction, glacial acetic acid (45.2 kg) was added over 1 h while keeping the batch temperature below −5 °C. Hydrochloric acid solution (3 N, 144.0 kg) was charged to the vessel, followed by 33.0 L of purified water, while maintaining the pot temperature below 10 °C. After extraction and phase separation, the organic layer was washed once with 180 L of purified water and then distilled at 35−45 °C under 35−50 Torr until approximately 60 L was left in the reactor. An additional amount of toluene (50 kg each) was charged twice, and each time the batch was distilled to approximately 60 L. The distillation reached end-point when the acetic acid and amyl alcohol contents in the pot were below 4.0 and 0.8 v/v %, respectively, by GC analysis. The toluene solution of *trans*-hemi-ester **16** was used directly in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J = 7 Hz, 3H), 1.35 (m, 4H), 1.81 (m, 2H), 2.11 (m, 2H), 2.61 (m, 2H), 4.14 (q, J = 7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 25.3, 25.4, 28.96, 29.04, 44.78, 44.83, 60.7, 175.1, 181.5.

A 300-gal glass-lined reactor containing *trans*-hemi-ester **16** toluene concentrate was charged with MTBE (470.0 kg). The batch was heated to 40 °C. (*R*)-(+)-(α)-Methylbenzylamine (25.6 kg, 211 mol) was added. After seeding at 40 °C with 420 g of the salt **17** suspended in *n*-heptane (3 L), the batch was cooled to 33−34 °C at 0.2 °C/min ramping and was aged for 30 min at this temperature. The batch was then heated to 42−43 °C and held for 2 h. It was again cooled to 20 °C at a rate of 0.2 °C/min and held for 12 h. After the holding, *n*-heptane (100 kg) was charged at 20 °C. The batch was cooled to −15 to −20 °C at the same cooling rate. The batch was harvested on a centrifuge. About 50% of recovered mother liquors was recycled to the vessel to thin out the slurry. The wet cake was washed with 150 kg of cold *n*-heptane (−10 °C) and dried on a tray dryer at 50 °C under 50 Torr. The yield of **17** was 19.5 kg (65% from anhydride **14**). The ee was determined by chiral HPLC to be higher than 99%. Chiral HPLC method: the same method as described for the *cis*-hemi-ester **15**. The retention times for the desired (1*R*,2*R*)-**17** enantiomer and the undesired (1*S*,2*S*)-**17** enantiomer were 8.5 and 7.3 min, respectively. Mp Form I 99 °C (MTBE, *n*-heptane), mp Form II 107 °C (MTBE, *n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90−1.28 (m, 7H), 1.50 (d, J = 7 Hz, 3H), 1.57 (m, 1H), 1.70 (m, 2H), 1.89 (m, 1H), 2.14 (m, 1H), 2.34 (m, 1H), 3.96 (m, 1H), 4.02 (m, 1H), 4.22 (q, J = 7 Hz), 1H), 7.27 (m, 1H), 7.32 (m, 2H), 7.42 (m, 2H), 8.18 (br, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 22.4, 25.7, 25.9, 29.3, 29.5, 46.0, 47.0, 51.1, 60.0, 126.7, 128.0, 128.9, 141.6, 176.6, 181.3. HRMS Calcd for the acid **16**, $C_{10}H_{16}O_4$: 199.0970 [M − 1]; found: 199.0973 [M − 1]. Anal. Calcd for the salt **17**, $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36; found: C, 67.34; H, 8.61; N, 4.38.

Ethyl(1*R*, 2*R*)-2-(Benzyloxycarbonylamino)cyclohexanecarboxylate (18). ***CAUTION!*** Although diphenyl phosphoryl azide (DPPA) is widely utilized in multikilogram quantities,[11] prudent safety practices for its use are clearly indicated. DPPA itself is thermally stable and is often purifed by vacuum distillation (137 °C, 0.2 Torr).[12] However, adventitious moisture might hydrolyze the reagent, forming volatile (bp 37 °C) anhydrous hydrazoic acid. At least in principle, HN_3 could collect in a cool region of the reactor and present an explosion hazard. A scrutiny of the literature did not reveal any incidents based on this eventuality. However, several sensible measures were taken to circumvent any potential problems. (1) Karl Fischer titration was used to monitor water levels, and these were kept below 0.1%. (Others have recommended still lower water levels.[13]) (2) Excess triethylamine was employed. Any traces of strongly acidic hydrazoic acid should be retained in solution as the triethylammonium salt. (3) Cooling to the reactor condensor

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was not turned on to maximize the likelihood of HN_3 vapor being flushed from the system.

To a 100-gal vessel were charged (1*R*,2*R*)-cyclohexane-1,2-carboxylic acid monoethyl ester, (*R*)-(+)-α-methylbenzyl-amine salt (**17**, 55.0 kg, 172 mol), water (77.0 L), and toluene (119 kg). To the above suspension was added a 37% aqueous solution of HCl (22.0 kg). The phases were cut, and the toluene solution was distilled to a volume of about 120 L to remove water to under 1000 ppm. The solution was cooled to 20 °C, and triethylamine (26.0 kg, 257 mol) was added. The mixture was heated to 85 °C. A solution of diphenylphosphoryl azide (DPPA, 45.4 kg, 165 mol) in toluene (44.0 kg) was added to the mixture at a rate to maintain the temperature at 83−87 °C. The reaction was stirred for 30 min after the addition was complete and after a sample showed the reaction was complete (>98% conversion by HPLC, analysed as *N*-benzyl urea derivative of the isocyanate). To the above mixture was added benzyl alcohol (17.7 kg, 164 mol), and the mixture was heated to reflux at 110 °C for 5 h. When the reaction was complete, it was cooled to 20−25 °C and washed with water (50 L) and then twice with 10% brine (50 L). The toluene solution was solvent switched first to 2-propanol and then to *n*-heptane by vacuum distillation (to an end-point of less than 2% IPA in the *n*-heptane in the pot). The mixture was cooled to 50 °C, seeded with 200 g of **18** suspended in *n*-heptane (300 mL), and then cooled to 20 °C at 0.2 °C/min. After 8 h at this temperature the mixture was cooled further to −5 °C and filtered on a 36-in. Nutsche. The cake was washed with *n*-heptane and dried in a vacuum oven. The yield of **18** was 44.7 kg (80%). The crude product contained 0.5 area % of the symmetrical urea impurity **19**, and had a purity of 96.6 area % and 96.5 wt %.

The dried crude product **18** (37.0 kg) was charged to a 200-gal glass-lined reactor, followed by IPA (87.1 kg). The solid dissolved after mixing at 40 °C for 15 min. After an additional 15-min hold, the batch was cooled to 22 °C without ramping. Crystals formed in the batch without seeding. Water (167 L) was charged to the reactor over a 2 h period (about 1.4 kg/min). After a 30-min hold, the solid was filtered in two drops on a 36-in. diameter, glass-lined Nutsche and washed with a mixture of IPA (62.0 kg) and water (130 kg). The washed cake was dried in a tray dryer. The level of symmetrical urea impurity **19** was lowered from 0.5 area % to 0.1 area %. The yield of pure **18** was 32.0 kg (87%). Mp 81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12−1.28 (m, 2H), 1.18 (t, J = 7 Hz, 3H), 1.39 (m, 1H), 1.56 (m, 1H), 1.72 (m, 1H), 1.93 (m, 1H), 2.08 (m, 1H), 2.23 (m, 1H), 3.71 (m, 1H), 4.08 (q, J = 7 Hz, 2H), 4.84 (br, 1H), 5.06 (s, 2H), 7.25−7.38 (m, 5H).^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.3, 24.6, 24.8, 28.8, 33.2, 50.1, 51.9, 60.7, 66.7, 128.2, 128.7, 136.8, 155.6, 174.1. HRMS Calcd for $C_{17}H_{23}NO_4$: 306.1705 [M + 1]; found: 306.1704 [M + 1]. Anal. Calcd For $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59; found: C, 66.89; H, 7.68; N, 4.53.

(1*R*,2*R*)-2-(Benzyloxycarbonylamino)cyclohexanecarboxaldehyde (3). In a 600-L reactor, ethyl (1*R*,2*R*)-2-(benzoloxycarbonylamino)cyclohexanecarboxylate (**18**, 17.5 kg, 57.3 mol) was dissolved in toluene (167 kg) and methylcyclohexane (27.0 kg). The mixture was cooled to −90 to −96 °C. A 20 wt % solution of diisobutylaluminum hydride (DIBAL-H) (90.1 kg, 18.0 kg contained 127 mol) in hexanes was added at a rate that kept the temperature below −90 °C. After the addition the mixture was held for an additional 30 min, and a solution of 2-propanol (13.8 kg) and *n*-heptane (23.0 kg) was added to quench the excess DIBAL-H. The mixture was then transferred to a 1000-L reactor containing a solution of citric acid (54.3 kg, 258 mol) and water (112 L), keeping the temperature below 30 °C. The phases were cut, and the organic was washed with 5% aqueous sodium bicarbonate (147 kg) and 10% brine (150 kg). 2-Propanol (27.5 kg) was added to the organic solution. To the organic solution was added sodium bisulfite (11.9 kg, 62.6 mol) in water (24.5 L), and solids separated. The aldehyde **3**−bisulfite adduct was isolated in a centrifuge. Mp 141 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.95−1.25 (m, 4H), 1.59 (t, J = 12 Hz, 2H), 1.84 (m, 2H), 2.19 (d, J = 13 Hz, 1H), 3.28 (m, 1H), 4.17 (d, J = 5 Hz, 1H), 4.90 (d, J = 6 Hz, 1H), 4.99 (q, J = 13 Hz, 2H), 7.10 (d, J = 9 Hz, 1H), 7.35 (m, 5H).^{13}C NMR (100 MHz, DMSO-d_6) δ 23.9, 25.4, 25.5, 34.0, 43.5, 51.0, 65.4, 81.9, 127.97, 128.02, 128.7, 137.7, 156.1. The wet cake of the aldehyde **3**−bisulfite adduct was charged back to the 1000-L reactor for acid treatment without further purification. Water (140 L), MTBE (90.9 kg), and 50% aqueous potassium carbonate solution (40.8 kg) were charged in that order to the 1000-L reactor. The mixture was stirred until the solids dissolved, and then the aqueous phase was removed. The organic phase was washed twice with 15% aqueous brine (180 kg) The organic phase was solvent switched to *n*-heptane (final volume about 88 L) by vacuum distillation. The product aldehyde **3** crystallized out and was filtered. The solid was dried in a vacuum oven at 30 °C, and the yield of **3** was 12.75 kg (85%). Mp 67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14−1.53 (m, 4H), 1.68−1.83 (m, 3H), 2.00 (m, 1H), 2.15 (m, 1H), 3.82 (m, 1H), 4.98−5.13 (m, 3H), 7.26−7.38 (m, 5H), 9.58 (d, J = 4 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 24.7, 25.6, 32.5, 49.6, 56.6, 67.0, 128.26, 128.34, 128.7, 136.5, 155.9, 203.7. HRMS Calcd for $C_{15}H_{19}NO_3$: 262.1443 [M + 1]; found 262.1436 [M + 1]. Anal. Calcd for: $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36; found: C, 68.92; H, 7.39; N, 5.23.

***N*-(5-Acetyl-4-methyl-1,3-thiazol-2-yl)-*N*′-((1*R*,2*S*)-2-{[3(*S*)-(4-fluorobenzyl)piperidinyl]methyl}cyclohexyl)-urea (1).** In a 100-gal glass reactor were warmed sodium triacetoxyborohydride (18.5 kg, 87.3 mol) and DMSO (71 kg) to 40 °C until homogeneous. The batch was cooled to 12 °C, and (*S*)-3-(4-fluorobenzyl)piperidine **2**-(*R*)-mandelate salt (20.2 kg, 58.5 mol) was added. In a separate reactor, (1*R*,2*R*)-2-(benzyloxycarbonylamino)cyclohexanecarboxaldehyde **(3**, 15.3 kg, 58.5 mol) and DMSO (33 kg) were mixed to give a homogeneous solution. The aldehyde **3** solution was added over 2 h to the piperidine **2** solution while keeping the temperature at 10−14 °C. After the addition the reaction was stirred for an additional hour and then quenched with 6 N aqueous HCl solution (8.4 kg) at 20−24 °C. To

the quenched reaction mass were sequentially added *i*PrOAc (59 kg), water (67 kg), and 15% aqueous sodium hydroxide solution (50 kg). The mandelic acid was removed in the aqueous solution. The product was extracted into the *i*PrOAc, which was washed with 10% brine (40 kg) and water (45 kg). This *i*PrOAc solution containing (1*R*,2*S*)-1-(benzyloxycarbonyl)amino-2-{[3(*S*)-(4-fluorobenzyl)piperidinyl]methyl}-cyclohexane (**22**) was carried forward into the next step without further purification.

To a 100-gal glass reactor was charged palladium on carbon (5% Pd, 50% wet, 6.3 kg) followed by the *i*PrOAc solution of **22** and *i*PrOAc (120 kg). The reactor was inerted and then pressurized with 55 psig hydrogen and stirred for 4 h at 25 °C. When the reaction was complete, the catalyst was filtered through a 1-μm bag filter followed by 0.5-μm and 0.2-μm cartridge filters. The resulting solution was distilled to a volume of about 100 L and a water content of less than 500 ppm. The penultimate, **(**1*R*,2*S*)-1-amino-2-{[3(*S*)-(4-fluorobenzyl)piperidinyl]methyl}cyclohexane (**23**), was used in the next step without further purification**.** ^{19}F NMR (376 MHz, $CDCl_3$) δ −118.22. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (m, 2H), 1.15 (m, 3H), 1.36 (m, 1H), 1.46 (m, 1H), 1.65−1.85 (m, 7H), 2.08 (dd, J = 4, 12 Hz, 1H), 2.28 (m, 3H), 2.44 (m, 3H), 2.67 (d, J = 10 Hz, 1H), 3.01 (d, J = 11 Hz, 1H), 6.96 (t, J = 9 Hz, 2H), 7.08 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 25.5, 26.2, 30.8, 31.2, 36.6, 38.9, 40.7, 41.2, 54.4, 57.3, 62.1, 67.0, 115.3 (d, J = 21 Hz), 130.7 (d, J = 8 Hz), 136.5 (d, J = 3 Hz), 161.6 (d, J = 242 Hz).

The solution containing the penultimate **23** (17.5 kg contained by HPLC assay, 57.5 mol) from the previous step was heated to 40 °C, and a solution of 2-(phenoxycarbonyl)-amino-4-methyl-5-acetylthiazole (**4**, 16.2 kg, 58.6 mol) in THF (105 kg) was added in portions while monitoring reaction completion. When 95% of the thiazole **4** had been added, less than 1.0 area % of **23** was present by HPLC, and the reaction was considered complete. The reaction solvent was switched to IPA through distillations to a volume of about 114 L (with THF and *i*PrOAc level <1 v/v % in IPA by GC analysis). Water (88 L) was added as an anti-solvent, and the mixture cooled to 0 °C. The crude product was filtered. It was dissolved in a mixture of IPA (95 kg) and water (15 kg) at 80 °C. The solution was then cooled to 55 °C and held for 1 h and cooled further to 30 °C. Water (120 kg) was added, and the mixture was cooled to 0 °C. The solids were filtered and dried in a vacuum oven at 50 °C and under 50 Torr. The yield of the API free base **1** was 22.8 kg (80% from **2** and **3**). Mp Form I 181 °C, Form II 199 °C.^{19}F NMR (376 MHz, $CDCl_3$) δ −117.58. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80−1.48 (7H, m), 1.55−1.79 (8H, m), 2.08 (dd, J = 3, 13 Hz, 1H), 2.25−2.34 (2H, m), 2.38 (d, J = 7 Hz, 2H), 2.49 (3H, s), 2.56 (d, J = 9 Hz, 1H), 2.65 (3H, s), 2.91 (d, J = 11 Hz, 1H), 3.29 (dt, J = 4, 11 Hz, 1H), 6.79 (t, J = 9 Hz, 2H), 6.96−7.03 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 24.5, 25.1, 25.7, 30.4, 30.5, 30.7, 33.3, 38.6, 38.8, 40.0, 54.0, 57.7, 60.8, 64.8, 115.0 (d, J = 21 Hz), 123.552, 130.0 (d, J = 8 Hz), 135.3 (d, J = 3 Hz), 154.318,161.3 (d, J = 242 Hz) 162.578, 190.488. HRMS Calcd for $C_{26}H_{35}FN_4O_2S$: 487.2543 [M − 1]; found: 487.2533 [M − 1]. Anal. Calcd for $C_{26}H_{35}FN_4O_2S$: C, 64.17; H, 7.25; N, 11.51; found: C, 64.21; H, 7.28; N, 11.53.

***N*-(5-Acetyl-4-methyl-1,3-thiazol-2-yl)-*N*′-((1*R*,2*S*)-2-{[3-(*S*)-(4-fluorobenzyl)-piperidinyl]methyl}cyclohexyl)-urea, Fumarate Salt (1-Fumarate).** In a 50-gal glass reactor the API free base **1** (11.0 kg, 22.6 mol) was charged followed by 1-methoxy-2-propanol (147.1 kg). The mixture was heated to 70 °C, stirred for 30 min, and filtered through a 0.45-μm filter into a 100-gal reactor. To the 50-gal reactor were charged fumaric acid (3.1 kg, 26.7 mol) and 1-methoxy-2-propanol (45.8 kg). The mixture was heated to 60 °C, and the first 20% was added to the API free base **1** solution. The batch was seeded with 1 wt % of seeds suspended in 1-methoxy-2-propanol. Then the remainder (80%) of the fumaric acid solution was added to the batch. The batch was cooled to 20 °C over 6 h and was held at that temperature for 2 h. The solids were filtered and dried in a vacuum oven at 50 °C and under 50 Torr. The yield of the dried product **1**-fumarate was 11.7 kg (86%). Mp 209 °C. ^{19}F NMR (376 MHz, DMSO-d_6), δ −117.91. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.95−1.03 (m, 3H), 1.21 (m, 3H), 1.43−1.75 (m, 6H), 1.87 (m, 3H), 2.15 (t, J = 12 Hz, 1H), 2.34 (m, 1H), 2.42 (s, 3H), 2.51 (s, 3H), 2.53 (m, 2H), 2.74 (m, 2H), 3.10 (br, 2H), 3.24 (br, 1H), 6.58 (s, 2H), 7.02 (m, 2H), 7.16 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 18.5, 23.2, 24.9, 28.5, 30.2, 30.7, 33.3, 36.2, 38.5, 38.8, 52.2, 54.1, 56.4, 57.9, 61.3, 105.0 (d, J = 21 Hz), 124.5, 130.9 (d, J = 8 Hz), 135.2, 135.6, 154.0, 155.1, 161.1 (d, J = 240 Hz), 162.5, 168.0, 190.4. Anal. Calcd for: $C_{30}H_{39}FN_4O_6S$, C, 59.78; H, 6.52; N, 9.30; found: C, 59.72; H, 6.70; N, 9.10.

Acknowledgment

We are grateful to Dr. Pat N. Confalone for helpful discussions. Thanks are due to Dr. Percy H. Carter and Dr. Richard H. Mueller for useful comments on the manuscript. We thank Mr. Michael Peddicord and Dr. John Castoro for assistance with mass spectrometry. Thanks are also due to Mr. Thomas Smyser and Ms. Wei Wu for skilled technical assistance.

Received for review October 17, 2005.

OP050202L