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An Efficient Synthesis of an $\alpha_v\beta_3$ Antagonist

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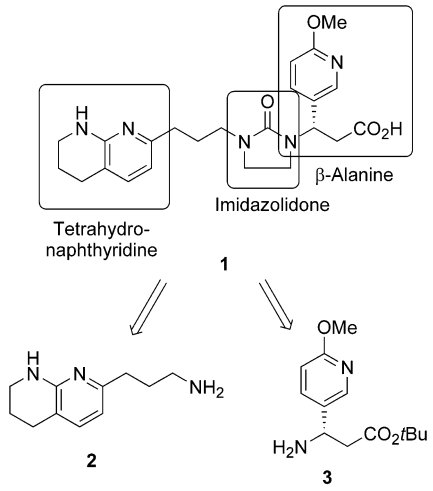
A practical preparation of an $\alpha_v\beta_3$ antagonist is reported. The antagonist consists of three key components, a tetrahydronaphthyridine moiety, a β-alanine moiety, and a central imidazolidone moiety. The tetrahydronaphthyridine component was prepared using two different methods, both of which relied on variations of the Friedländer reaction to establish the desired regiochemistry. The β-alanine component was prepared using Davies' asymmetric 1,4-addition methodology as the key stereo-defining step. The central imidazolidone portion was created from these two components using an effective three-step cyclization protocol. Thus, a highly convergent process for the drug candidate was defined.

Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass resulting in increased risk of debilitating fractures. In healthy adults, bone mass is maintained by a homeostatic balance between the processes of bone resorption and bone formation. The most common cause of osteoporosis in women is the decrease in estrogen that accompanies menopause.[1] Estrogen loss is associated with elevated bone resorption caused by a rise in the number of osteoclasts, cells which resorb bone. Osteoclasts highly express the $\alpha_v\beta_3$ integrin, which binds to a variety of extracellular matrix proteins through their RGD domains.[2] RGD-containing peptides, RGD-mimetics, and $\alpha_v\beta_3$-blocking antibodies inhibit bone resorption in vitro and in vivo, suggesting that this integrin plays an important role in osteoclast function.[3,4] A number of reports from our laboratories and others have focused on the design of $\alpha_v\beta_3$ antagonists.[5,6] To provide research programs with sufficient drugs to carry out toxicity and clinical studies, efficient syntheses of developmental drug candidates are required. We report herein a highly convergent and practical synthesis of the Merck $\alpha_v\beta_3$ integrin antagonist **1**.

SCHEME 1



Results and Discussion

Retrosynthetic Analysis. The $\alpha_v\beta_3$ antagonist **1** consists of three key domains, a tetrahydronaphthyridine, an imidazolidone, and a β-alanine (Scheme 1). To accomplish the most convergent synthesis, we planned to prepare the tetrahydronaphthyridine-propylamine[7] portion (**2**) and β-alanine portion (**3**) first, followed by the construction of the central imidazolidone portion. Sequential N-alkylations on imidazolidone and/or 2,3-

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† Current address: Johnson & Johnson, Pharmaceutical Research & Development, L.L.C., 1000 Route 202, P.O. Box 300, OMP-B145, Raritan, NJ 08869.

(1) Rodan, G. A.; Martin, T. J. *Science* **2000**, *289*, 1508.

(2) Duong, L. T.; Rodan, G. A. *J. Bone Miner. Metab.* **1999**, *17*, 1.

(3) Yamamoto, M.; Fisher, J. E.; Gentile, M.; Seedor, J. G.; Leu, C.-T.; Rodan, S. B.; Rodan, G. A. *Endocrinology* **1998**, *139*, 1411.

(4) Lark, M. W.; Stroup, G. B.; Dodds, R.a.; Kapadia, R.; Hoffman, S. J.; Hwang, S. M.; James, I. E.; Lechowska, B.; Liang, X.; Rieman, D. J.; Salyers, K. L.; Ward, K.; Smith, B. R.; Miller, W. H.; Huffman, W. F.; Gowen, M. *J. Bone Miner. Res.* **2001**, *16*, 319.

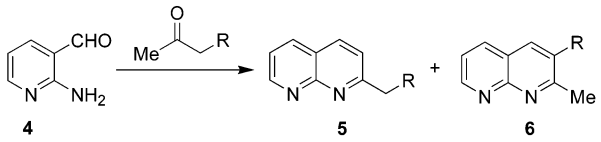
(5) Duggan, M. D.; Duong, L. T.; Fisher, J. E.; Hamill, T. G.; Hoffman, W. F.; Huff, J. R.; Ihle, N. C.; Leu, C.-T.; Nagy, R. M.; Perkins, J. J.; Rodan, S. B.; Wesolowski, G.; Whitman, D. B.; Zartman, A. E.; Rodan, G. A.; Hartman, G. D. *J. Med. Chem.* **2000**, *43*, 3736.

(6) Brashear, K. M.; Hunt, C. A.; Kucer, B. T.; Duggan, M. E.; Hartman, G. D.; Rodan, G. A.; Rodan, S. B.; Leu, C.-T.; Prueksaritanont, T.; Fernandez-Metzler, C.; Barrish, A.; Homnick, C. F.; Hutchinson, J. H.; Coleman, P. J. *Bioorg. Med. Chem. Lett.* **2002**, 3483.

(7) Preparation of **2** via a Chichibabin cyclization has been reported. Palucki, M.; Hughes, D. L.; Yasuda, N. Y.; Yang, C.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6811.

10.1021/jo030297u CCC: $27.50
Published on Web 02/18/2004

SCHEME 2



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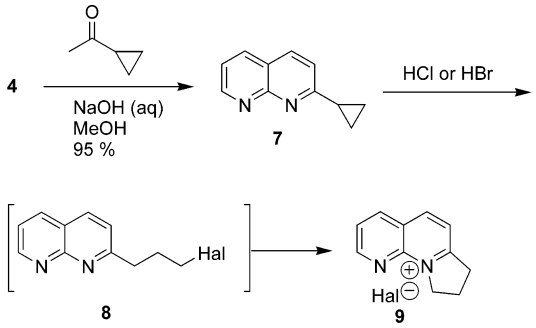

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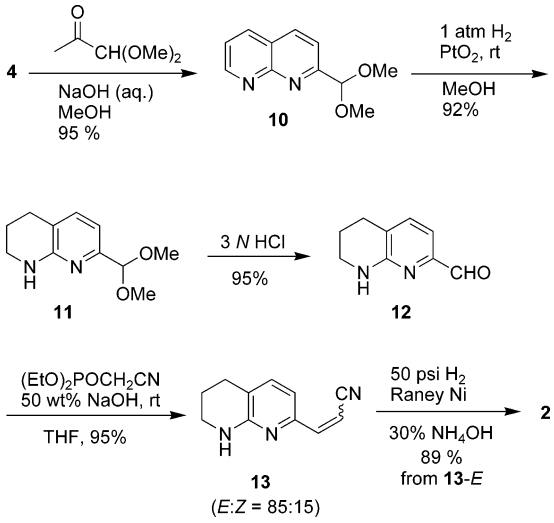


dihydro-1*H*-imidazol-2-one were also attempted. However, investigations on these routes were abandoned due to the difficulties associated with the N-alkylations (vida infra) and the less convergent nature of these routes.

Preparation of Tetrahydronaphthyridine 2. One of the most traditional approaches for the preparation of [1,8]naphthyridine derivatives[8] utilizes the Friedländer reaction between 2-amino-3-formylpyridine (**4**)[9] and methyl ketones. However, the lack of regiocontrol is a prominent problem associated with this approach (Scheme 2).[10] To address this issue, two methods were developed.

The first approach was to employ an α,α-disubstituted methyl ketone. By doing so, the formation of the undesired regioisomer **6** would be prohibited because the initial adduct, which would eventually lead to **6**, could not aromatize. Since the steps prior to aromatization are presumed to be reversible,[11] this pathway would be eliminated. Therefore, only the desired product **5** would be obtained. The first attempt at this approach was the Friedländer reaction between amino-aldehyde **4** and cyclopropyl methyl ketone. As expected, the reaction proceeded smoothly in the presence of aqueous sodium hydroxide and provided the desired 2-cyclopropyl[1,8]-naphthyridine (**7**) as the sole product in high yield (Scheme 3). We planned to open the cyclopropane ring of **7** with acids such as HCl and/or HBr, producing the corresponding 3-halopropyl derivative **8**, which would allow us to install the imidazolidone moiety by N-alkylation. NMR studies confirmed that **8** was initially formed but rapidly cyclized to the corresponding five-membered ammonium compound **9**. Ammonium salt **9** was stable, and no reaction was observed when **9** was treated with NaN_3 under several different conditions. A similar phenomenon was observed in the corresponding tetrahydronaphthyridine series.

To avoid the difficulties of the cyclopropane ring opening, 1,1-dimethoxyacetone was used as the starting methyl ketone, anticipating that the proper side chain could be installed on the latent aldehyde after formation of the naphthyridine ring. Friedländer reaction between **4** and 1,1-dimethoxyacetone gave the desired crystalline 2-(dimethoxy)methyl[1,8]naphthyridine (**10**) in 95% yield as the sole regioisomeric product. Partial reduction of **10** in the presence of PtO_2 was highly selective due to the steric hindrance of the one ring as well as the electron-donating nature of the dimethoxymethyl group. Crystalline tetrahydronaphthyridine **11** was isolated in 92% yield. Installation of the propylamine side chain was accomplished in three steps. The acetal was removed under acidic conditions to provide crystalline aldehyde **12**. Horner−Emmons reaction of **12** with diethyl cyanomethylphosphonate gave a *E*/*Z* (85:15) mixture of acrylonitrile derivatives **13**-*E* and **13**-*Z*. Isomer **13**-*E* is a crystalline compound, and **13**-*Z* slowly isomerizes to **13**-*E*. Finally, reduction of the acrylonitrile moiety of **13**-*E* in the presence of Raney-Ni in ammonium hydroxide[12] provided the desired tetrahydronaphthyridine amine **2** as a crystalline compound (Scheme 4).[13]

This route was very effective on a kilogram scale but had several drawbacks. The process was linear, relied on an expensive Horner−Emmons reagent, and possessed an *E*/*Z* selectivity issue, and the reduction of the nitrile required an excess of Raney-Ni. To eliminate these problems, a more convergent route, which relied on another modification of the Friedländer reaction to address regioselectivity,[14] was developed. This new method was based on increasing the difference in the pK_a of the α and α′ protons of the ketone partner by introduction of

(8) Lowe, P. A. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; The Pergamon Press: Oxford, England, 1984; Vol. 2, Chapter 2.11.

(9) Rivera, N. R.; Hsiao, Y.; Cowen, J. A.; McWilliams, C.; Armstrong, J.; Yasuda, N.; Hughes, D. L. *Synth. Commun.* **2001**, *31*, 121 and references therein.

(10) A highly selective Friedländer has recently been reported: Dormer, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G. R.; McWilliams, J. C.; Reider, P. J.; Sager, J. W.; Volante, R. P. *J. Org. Chem.* **2003**, *68*, 467.

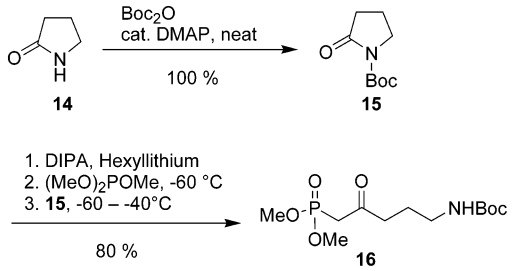
(11) Cheng, C.-C.; Yan, S.-J. The Friedlander Synthesis of Quinolines. In *Organic Reactions;* Daube, W. C., Ed.; J. Wiley & Sons: New York, 1982; Vol. 28, p 37.

(12) Ammonium hydroxide was used as a solvent to prevent the formation of the corresponding dimer secondary amine. For an example, see: Journet, M.; Cai, D.; DiMichele, L. M.; Hughes, D. L.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2411.

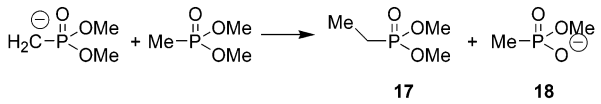
(13) Reduction of **13**(*Z*) is not as clean as that of **13**(*E*).

(14) Hsiao, Y.; Rivera, N. R.; Yasuda, N.; Hughes, D. L.; Reider, P. J. *Org. Lett.* **2000**, *3*, 1101 and references therein.

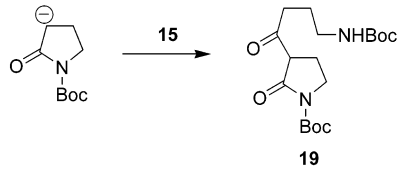
SCHEME 5



SCHEME 6



SCHEME 7



a phosphonate group at one of the α-positions of the ketone (**16**). Using this Horner−Emmons type of reagent allowed the regioselectivity of the Friedländer reaction to be perfectly controlled. The preparation of **16** is summarized in Scheme 5. In the presence of a catalytic amount of DMAP, *N*-Boc-2-pyrrolidone (**15**) was prepared from 2-pyrrolidone (**14**) and di-*tert*-butyl dicarbonate neat in quantitative yield. The pyrrolidone ring of **15** was opened with the anion derived from dimethyl methylphosphonate to yield **16** in 80−85% isolated yield.[15] Isolated crude **16** was suitable for the next reaction without purification.

Success in the preparation of **16** relies on several factors.[16] It was found that dimethyl methylphosphonate must be added to a solution of LDA at low temperature. Reversing the mode of addition instantly generates a mixture of dimethyl ethylphosphonate (**17**) and monomethyl methylphosphonate lithium salt (**18**) even at −60 °C (Scheme 6).[17] Also, maintaining a lower temperature throughout the course of the whole ring-opening reaction sequence was critical. At about −40 °C, deprotonation of an α-proton of **15** occurs and the resulting anion reacts with **15** to form dimer **19** (Scheme 7). Contamination of **19** in the Friedländer reaction created difficulties in the crystallization of tetrahydronaphthyridine **24**.

The modified Friedländer reaction of **4** and **16** proceeded smoothly in methanol with aqueous sodium hydroxide to provide naphthyridine **20** in 90% isolated yield. When the reaction was run in THF, compound **21** was produced. Subjection of **21** to the standard reaction conditions in methanol gave the desired **20**. We speculate

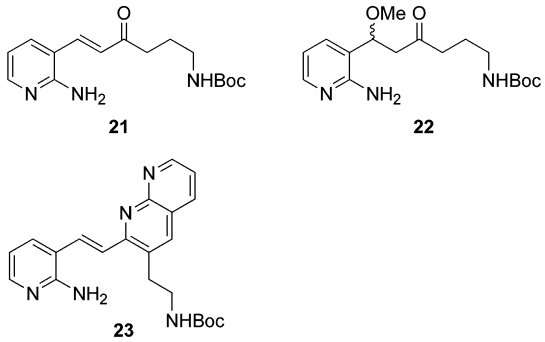
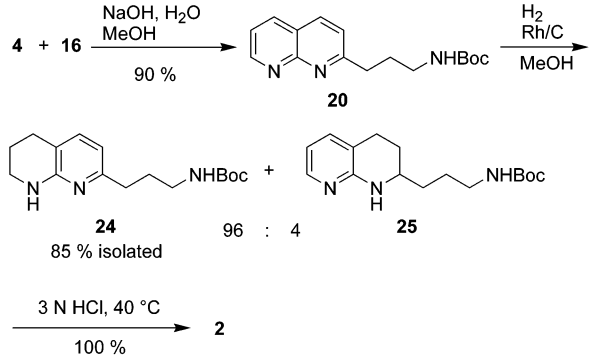


FIGURE 1. Intermediates and impurity of the Friedländer reaction.

SCHEME 8



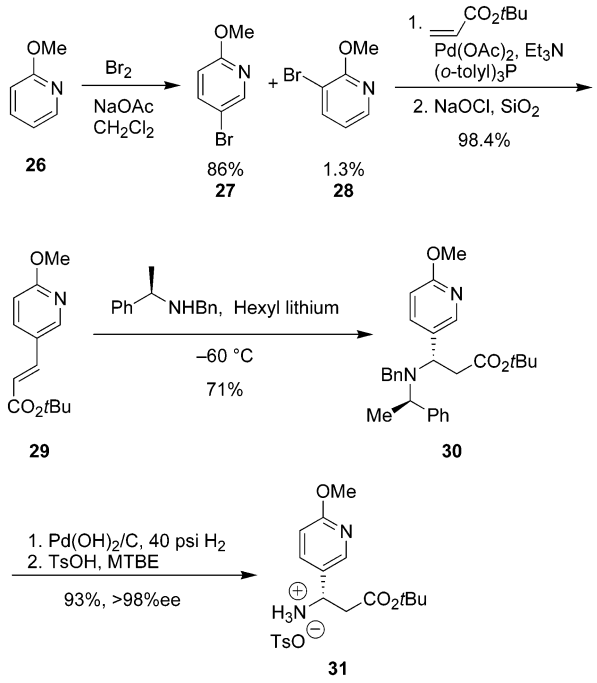
that the methanol adduct (**22**) of **21** plays a pivotal role in the cyclization sequence.[15] By careful monitoring (HPLC) of the reaction as it proceeded, intermediate **21** could be observed even under standard reaction conditions in methanol. To avoid further Friedländer reaction between **21** and amino-aldehyde **4**, generating impurity **23**, the concentration of **4** in the reaction medium was maintained at a low level by addition of amino-aldehyde **4** in two portions (Scheme 8 and Figure 1). In this way, formation of **23** was completely suppressed.

The next step was the partial reduction of **20**. Several catalysts were screened for this purpose. Under the best conditions (Rh/C, 40 psi H_2, 5 °C, MeOH), a 96:4 mixture of **24** and **25** was obtained. After catalyst removal, compound **24** was crystallized from aqueous MeOH to provide material that was 99.8 wt % pure in 85% isolated yield. Deprotection of **24** proceeded smoothly in aqueous HCl and provided **2** in quantitative yield.

Preparation of *β*-Alanine 3. *β*-Alanine **3** was prepared as shown in Scheme 9, with Davies' chiral amine Michael addition[18] as the key reaction. Using a modification of a literature procedure,[19] 5-bromo-2-methoxypyridine (**27**) was prepared from 2-methoxypyridine (**26**). In the reported procedure, the bromination was run using Br_2, AcOH, and AcONa to provide **27** in 68% isolated yield. We found that the presence of AcOH decreased the reaction rate. Therefore, the reaction was carried out via addition of Br_2 to a suspension of NaOAc in **26** and CH_2Cl_2. Using this protocol afforded smooth reaction, and **27**

(15) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.
(16) Analytical method development for this reaction: Buote, A.; Kelly, J.; Hsiao, Y.; Yasuda, N.; Antonucci, V. *J. Chromat. A* **2002**, *978*, 177.
(17) Teulade reported that this anion is stable at 0 °C for 5 min prior to dimerization. We could not repeat these data. Teulade, M.-P.; Savignac, P. *J. Organomet. Chem.* **1986**, *312*, 283.
(18) Davies, S. G.; Ichihara, O. *Tetrahedron Asymmetry* **1991**, *2*, 183.
(19) Butora, G.; Reed, J. W.; Hudlicky, T.; Brammer, L. E. J.; Higgs, P. I.; Simmons, D. P.; Heard, N. E. *J. Am. Chem. Soc.* **1997**, *119*, 7694.

SCHEME 9



was isolated in 86% yield after distillation.[20] Distilled **27** contained 1.3% of the 3-bromo isomer **28**.[21,22] Heck reaction of **27** and *tert*-butyl acrylate in the presence of the preactivated catalyst from $Pd(OAc)_2$ and tri-*o*-tolylphosphine and NMP provided ester **29** in over 98% yield. The choice of alkyl esters was found to greatly affect the selectivity of subsequent Michael addition. To avoid 1,2-addition, the *tert*-butyl ester was chosen. Since the Heck reaction was exothermic,[23] it was controlled by the addition rate of *tert*-butyl acrylate to the reaction mixture at 90 °C. The crude mixture was treated with aqueous NaOCl to oxidize tri-*o*-tolylphosphine, which was found to be a poison in the subsequent catalytic hydrogenation reaction. The resulting phosphine oxide was easily removed by filtering the product through a pad of silica gel. Michael addition of the lithium salt of (*R*)-(+)-*N*-benzyl-α-methylbenzylamine was accomplished at −60 °C. This low reaction temperature gave the best diastereoselectivity. The benzyl and methyl benzyl groups of the crude product **30** were removed by hydrogenolysis. Amine **3** was typically isolated in 97% yield and 95−96% ee. When **3** was crystallized as tosylate salt **31**, all impurities, including those generated from the 3-position isomer **28**, were rejected. The crystallization proceeded in 97% yield while upgrading the ee of **31** to >98%.

Construction of Imidazolidone. To construct the imidazolidone ring from the two primary amine intermediates **2** and **31**, a two carbon unit and a carbonyl group had to be installed as shown in Figure 2. It was anticipated that the carbonyl would originate as phosgene or an equivalent[24] and that the two-carbon unit would be introduced as either a 1,2-dihaloethane or glyoxal. Several different strategies were examined to join these four components. N,N′-Dialkylation of an unsymmetric urea to complete the imidazolidone (initial formation of b_1 and b_2, followed by a_1 and a_2) was briefly investigated. The result of this approach was an interesting rearrangement via O-alkylation.[25] Another approach used dimethoxyacetaldehyde as the C_1-C_2 unit, with bonds a_1 and a_2 being formed by sequential reductive aminations. In this strategy the carbonyl would be installed last. The first reductive amination proceeded smoothly to form either bond a_1 or a_2. However, the second reductive amination was low yielding and had poor reproducibility. These difficulties led to the another change in strategy.

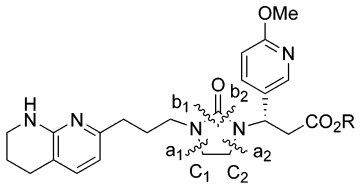


FIGURE 2. Construction of the imidazolidone ring.

In the most successful route, a_2 was forged first via reductive amination with dimethoxyacetaldehyde and then in a high-yielding one-pot sequence, b_2, b_1, and then a_1 were formed. This strategy overcame the problem of the second reductive amination seen earlier by forming the final C−N bond (a_1) using an intramolecular amina-

(20) Distillation residue from this reaction has an exothermic nature (initiation temperature = 74.2 °C; maximum temperature of the exothermic reaction = 386.1 °C; maximum rate of temperature increase = 1104.6 °C/min).

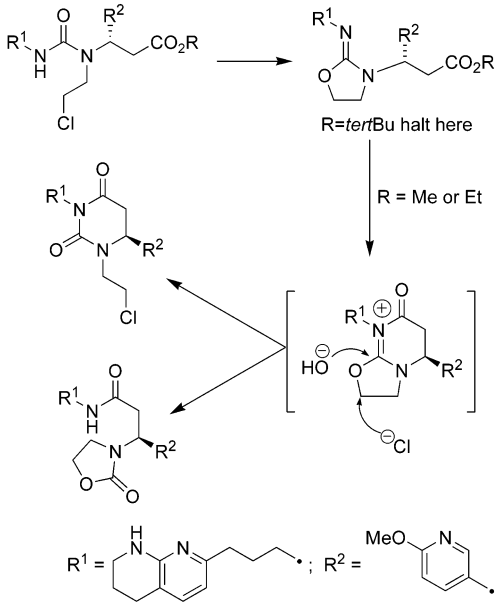
(21) Shiao, M.-J.; Tarng, K.-Y. *Heterocycles* **1990**, *31*, 819.

(22) Boucher, É.; Simard, M.; Wuest, J. D. *J. Org. Chem*. **1995**, *60*, 1408.

(23) Heat of reaction of this reaction as measured using an RC-1 reaction apparatus is −48.8 Kcal.

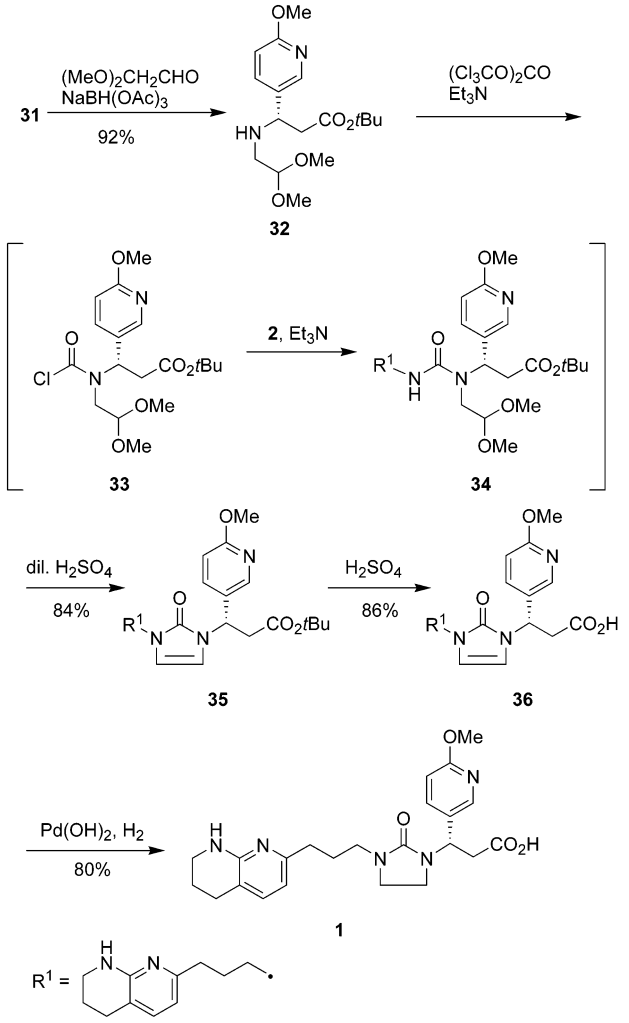
(24) The corresponding *p*-nitrophenylcarbamate is extremely unreactive. No reaction was observed in the presence of excess benzylamine even at elevated temperature.

(25) Intramolecular cyclization of *N*-(2-chloroethyl)urea did not provide the desired imidazolidone. Instead, the reaction provided two major byproducts in the case of methyl and ethyl esters. In the case of *tert*-butyl ester, the reaction stopped after the initial O-alkylation due to steric hindrance.



O-Alkylation of *N*-(2-haloethyl)urea with KF/SiO_2 has been reported. Wong, W. C.; Wang, D.; Forray, C.; Vaysse, P. J.-J.; Branchek, T. A.; Gluchowki, C. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2317.

SCHEME 10



tion.[26] Several issues were considered while planning this route. We decided to avoid treatment of **2** in any form with phosgene or an equivalent. Doing so could lead to competing reactions of the intermediate chlorocarbamate, or isocyanate, with the tetrahydronaphthyridine. We also wanted to avoid treatment of amine **31** with phosgene. This could lead to the formation of an isocyanate and the scrambling of the then acidic asymmetric center. Instead, initial reductive amination of **31** with the glyoxal equivalent followed by phosgene would prevent isocyanate formation as well as the potential epimerization. This reasoning lead to an initial reductive amination of **31** with dimethoxyacetaldehyde followed by treatment with bis(trichloromethyl) carbonate.[27] Amine **2** would then be introduced followed by cyclization. The optimized route is summarized in Scheme 10.

The reductive amination of **31** proceeded well using sodium triacetoxyborohydride to provide the two-carbon homologated β-alanine **32** in 92% isolated yield. Secondary amine **32** was converted to the chlorocarbamate **33** by treatment with bis(trichloromethyl) carbonate (triphosgene) and triethylamine in THF. Chlorocarbamate **33** was reasonably stable in the reaction mixture and directly reacted with **2** in the presence of triethylamine at 45 °C to afford the unsymmetric urea **34**. Addition of sulfuric acid to the reaction mixture initiated the cyclization of urea **34** to provide imidazoline-2-one **35**, which was isolated in 84% overall yield from **32**.

With **35** in hand, two steps remained: the olefin reduction and removal of the ester. Reduction of the double bond proceeded well under catalytic hydrogenation to provide the corresponding imidazolidone in high yield as an oil. Solvolysis of the ester provided the antagonist **1** in excellent yield as a crystalline solid. When the order of the final two steps was reversed, the reactions were equally efficient and both products were isolated as crystalline solids. Having a crystalline penultimate is advantageous. The crystallization can be used as a purification event, and storage of a crystalline penultimate is typically favored. Thus, treatment of an IPAC solution of ester **35** with 3 M sulfuric acid provided carboxylic acid **36**, which was isolated as a crystalline solid in 86% yield. The enantiopurity of **36** was easily upgraded to >99.8% ee by this simple crystallization. Finally, carboxylic acid **36** was dissolved in 5 M NaOH and reduced by hydrogenation in the presence of $Pd(OH)_2$ at 120 psi. After removal of catalyst, **1** was crystallized by adjusting the pH to 6.4 with concentrated aqueous HCl to provide the drug candidate in high yield and high purity.

In conclusion, a practical preparation of $\alpha_v\beta_3$ antagonist **1** has been defined and demonstrated on multikilogram scale. The retrosynthetic analysis for this route divided the antagonist into three key components: a tetrahydronaphthyridine moiety, a β-alanine moiety, and a central imidazolidone moiety. The tetrahydronaphthyridine portion was prepared using two different methods, both of which relied on variations of the Friedländer reaction to effect the desired regioselectivity. The β-alanine portion was prepared via Davies' asymmetric 1,4-addition methodology as the key stereodefining step. The central imidazolone portion was created from these two components using a highly effective three-step cyclization protocol.

Experimental Section

2-(Cyclopropyl)-1,8-naphthyridine (7). A solution of 2-aminonicotinaldehyde **4** (15 g, 0.123 mol), ethanol (100 mL), water (50 mL), cyclopropyl methyl ketone (13.6 g, 0.16 mol), and NaOH (6.4 g, 0.16 mol) was heated at reflux temperature for 1 h. Removal of the ethanol under reduced pressure gave the title compound as colorless crystals (20.5 g, 98%): mp 99.5−101.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (dd, J = 4.3, 2.0 Hz, 1H), 7.88 (dd, J = 8.0, 2.0 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.14 (dd, J = 8.0, 4.3 Hz, 1H), 2.07−2.00 (m, 1H), 1.24−1.20 (m, 2H), 0.96−0.91 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 155.9, 152.9, 136.6, 136.2, 121.7, 120.8, 120.6, 18.1, 11.6.

2-(3-Chloropropyl)-1,8-naphthyridine (8). 2-(3-Chloropropyl)-1,8-naphthyridine was prepared by treatment of **7** (100 mg) with concentrated HCl (1.0 mL). Since **8** quickly ring closes to produce **9**, identification of these compounds was established by ^{1}H NMR and ^{13}C NMR analysis of the mixture (See Supporting Information).

2-(Dimethoxymethyl)-1,8-naphthyridine (10). To a 6 °C solution of 2-aminonicotinaldehyde **4** (40.0 g, 0.316 mol), ethanol (267 mL), water (41 mL), and 1,1-dimethoxyacetone (51.3 mL, 0.411 mol) was added 5 M NaOH (82.3 mL, 0.411 mol) at a rate such that the internal temperature remained

(26) Wright, W. B. J.; Brabander, H. J.; Hardy, R. A. J. *J. Med. Chem.* **1966**, *9*, 858.
(27) For review: Cotarca, L.; Delogu, P.; Nardelli, A.; Šunjić, V. *Synthesis* **1996**, 553.

lower than 20 °C. After the addition, the mixture was stirred at ambient temperature for 1 h. Ethanol was then removed under vacuum, and IPAC (100 mL) and NaCl (55 g) were added. After agitation, the layers were separated and the aqueous layer was extracted with IPAC (2 × 100 mL). The organic layers were combined and filtered through a pad of silica gel (90 g), and the pad was rinsed with IPAC (1 L). The combined filtrate was concentrated to 200 mL at 38 °C. To the solution was slowly added hexane (400 mL). The resulting suspension was cooled to 10 °C and aged for 30 min. The resulting suspension was filtered, and the collected solids were dried under vacuum to provide **10** (54.2 g, 84%) as colorless crystals. To the mother liquors was added additional hexane (100 mL), and another 7.2 g (11%) of **10** was isolated: mp 53.5−55.5 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.89 (dd, J = 4.3, 2.0 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.98 (dd, J = 8.1, 2.0 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.26 (dd, J = 8.1, 4.3 Hz, 1H), 5.28 (s, 1H), and 3.30 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 161.3, 155.0, 153.5, 137.9, 136.8, 122.5, 122.3, 119.4, 105.9, and 54.9. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.71. Found: C, 64.50; H, 6.15; N 13.48.

7-(Dimethoxymethyl)-1,2,3,4-tetrahydro-1,8-naphthyridine (11). A solution of acetal **10** (20.0 g, 97.9 mmol) and ethanol (400 mL) was hydrogenated in the presence of PtO_2 (778 mg) under 1 atm of hydrogen at room temperature for 18 h. The reaction mixture was filtered through Solka Flok, and the filter cake was washed with a mixture of ethanol−H_2O (1:2 v/v). The filtrate and wash were combined and concentrated in vacuo to remove ethanol. The product crystallized as the ethanol was removed. The crystals were collected by filtration and dried in vacuo to give **11** (18.7 g, 92%): mp 91−92.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 7.4 Hz, 1H), 6.62 (d, J = 7.4 Hz, 1H), 5.07 (s, 2H, 1H exchangeable with D_2O), 3.37−3.29 (m, 2H), 3.29 (s, 6H), 2.64 (t, J = 6.3 Hz, 2H), and 1.86−1.78 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.9, 153.0, 136.3, 116.0, 109.8, 103.9, 53.3, 41.5, 26.6, and 21.2. Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.68; H, 7.68; N, 13.42.

5,6,7,8-Tetrahydro-1,8-naphthyridine-2-carbaldehyde (12). To a mixture of the acetal **11** (35 g, 0.16 mol) and cold water (∼5 °C, 90 mL) was added concentrated aqueous HCl (30 mL, 0.36 mol). The resulting solution was heated at 85 °C for 2.5 h. The mixture was cooled to 13 °C, and IPAC (60 mL) was added. Aqueous NaOH (50 wt %) was added slowly to pH 11, keeping the internal temperature below 25 °C. The layers were separated, and the aqueous layer was extracted with IPAC (2 × 120 mL). The organic layers were combined and concentrated in vacuo to give a reddish oil (26 g, 87.5 wt %, 95.3%), which was used in the next reaction without further purification. An authentic sample was prepared by crystallization from THF: mp 63.5−64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.17 (d, J = 7.3 Hz, 1H), 7.03 (d, J = 7.3 Hz, 1H), 5.94 (bs, 1H), 3.39−3.33 (m, 2H), 2.69 (t, J = 6.3 Hz, 2H), and 1.84−1.80 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 192.8, 156.8, 149.5, 136.2, 122.5, 113.4, 41.4, 27.2, and 20.6. Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.69; H, 6.28; N, 17.17.

3-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)prop-2-enenitrile (13). To a solution of aldehyde **12** (26.0 g, 87.5 wt %, 140 mmol), diethyl (cyanomethyl)phosphonate (26.7 mL, 140 mmol), and THF (260 mL) was added 50 wt % aqueous NaOH (14.8 g, 174 mmol) at a rate such that the internal temperature remained below 26 °C. After the mixture was stirred at room temperature for 1 h, IPAC (260 mL) was added. The layers were separated, and the organic phase was concentrated in vacuo to give **13** as a yellow solid (31.6 g, 84.6 wt %, 90% yield from **11**; the *E*:*Z* ratio was ∼9:1 at the end of the reaction, and slow isomerization occurred to give the single E isomer). Authentic *E* sample was prepared by flash chromatography on silica gel: mp 103.7−104.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 16.0 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 6.48 (d, J = 7.2 Hz, 1H), 6.33 (d, J = 16.0 Hz, 1H), 5.12 (bs, 1H), 3.41−3.36 (m, 2H), 2.72 (t, J = 6.3 Hz, 2H), 1.93−1.84 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.1, 149.4, 147.4, 136.3, 120.1, 118.8, 114.8, 97.7, 41.4, 27.0, 21.0. Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.26; H, 6.03; N, 22.67.

3-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)propane-1-amine (2). A slurry of nitrile **13** (648 g, 3.50 mol) and saturated aqueous ammonium hydroxide (7 L) was hydrogenated under 40 psi of hydrogen at 50 °C for 16 h in the presence of Raney nickel 2800 (972 g). The mixture was filtered through Solka Flok, and the pad was rinsed with water (2 × 1 L). After addition of NaCl (3.2 kg), the mixture was extracted with CH_2Cl_2 (3 × 5 L). The combined organic phases were concentrated to provide an oil. The oil was dissolved in MTBE (1 L) and seeded. The resulting suspension was slowly evaporated to provide the amine **2** as a colorless crystalline solid (577 g, 89%): mp 66−68.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 7.3 Hz, 1H), 6.33 (d, J = 7.3 Hz, 1H), 4.88 (bs, 1H), 3.37 (t, J = 5.3 Hz, 2H), 2.72 (t, J = 6.9 Hz, 2H), 2.67 (t, J = 6.3 Hz, 2H), 2.57 (t, J = 7.5 Hz, 2H), 1.88 (m, 2H), 1.79 (m, 2H), 1.76 (bm, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 155.7, 136.6, 113.1, 111.2, 41.8, 41.5, 35.1, 33.7, 26.3, 21.5. Anal. Calcd for $C_{11}H_{17}N_3 \cdot 0.3H_2CO_3$: C, 64.67; H, 8.45; N, 20.02. Found: C, 64.66; H, 8.13; N, 19.71.

***tert*-Butyl 2-Oxopyrrolidine-1-carboxylate (15).**[28] To a solution of 2-pyrrolidone (**14**, 33.8 mL, 444 mmol) and di-*tert*-butyl dicarbonate (97.0 g, 444 mmol) was added *N*,*N*-(dimethylamino)pyridine (92 mg, 0.75 mmol), and the mixture was stirred at 25−27 °C for 16 h. After the reaction was complete, the mixture was distilled at 40 mmHg, maintaining a constant volume by slow addition of toluene (100 mL). No *tert*-butyl alcohol was detected by GC or ^{1}H NMR. The resulting oil (86.0 g) contained 79.5 g of **15** (97% yield) and 7.6 wt % toluene. The solution was used for the next reaction without any further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (t, J = 7.2 Hz, 2H), 2.48 (t, J = 8.1 Hz, 2H), 1.97 (quintet, J = 7.5 Hz, 2H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 150.1, 82.6, 46.3, 32.8, 27.9, 17.3.

Dimethyl 5-[(*tert*-Butoxycarbonyl)amino]-2-oxopentylphosphonate (16).[29] To a solution of diisopropylamine (48.8 mL, 346 mmol) and dry THF (480 mL) was added hexyllithium (2.4 M in hexanes, 133.6 mL, 320.6 mmol) below −10 °C. After the reaction mixture was aged for 30 min, a solution of dimethyl methylphosphonate (65.2 mL, 333.4 mmol) in dry THF (128 mL) was slowly added, maintaining the temperature at −60 °C. After the reaction mixture was aged for 1 h at −60 °C, a solution of **15** (50.0 g, 95 wt %, 256.5 mmol) and dry THF (32 mL) was slowly added, maintaining the reaction temperature below −58 °C. The solution was stirred at −60 °C for 1 h and at −45 °C for 1 h. To the solution was added sulfuric acid (2 N, 333.4 mL). The mixture was allowed to warm to 0 °C. The organic layer was separated and concentrated in vacuo. The residue was dissolved in methanol (150 mL) and used at the next reaction without further purification. The isolated yield was 80%. An analytical standard was prepared by silica gel column chromatography: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (broad s, 1H), 3.62 (d, J = 11.2 Hz, 6H), 2.96 (d, J = 22.0 Hz, 2H), 3.00−2.90 (m, 2H), 2.51 (t, J = 7.0 Hz, 2H), 1.60 (quintet, J = 6.8 Hz, 2H), 1.26 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9 (d, J = 6.0 Hz), 155.5, 77.9, 52.3 (d, J = 6.4 Hz), 40.6 (d, J = 127.7 Hz), 40.3, 38.8, 27.7, 23.1.

***tert*-Butyl 3-(1,8-Naphthyridin-2-yl)propylcarbamate (20).** To a solution of 2-aminonicotinaldehyde (**4**, 21.8 g, 179 mmol) and β-keto phosphonate (**16**, 77.5 g, 95 wt %, 238 mmol) and methanol (400 mL) was added aqueous sodium hydroxide (50 wt %, 13.7 mL). The mixture was stirred at 40−50 °C for 30 min. Additional aldehyde **4** (5.4 g, 44 mmol) was added to the mixture with 100 mL of methanol. The mixture was stirred

(28) For other synthesis and physical data: Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228.

(29) Similar ring opening was reported: Lieb, F. DE Patent 27 11 010, 1978.

at 40−50 °C for 16 h. The mixture was concentrated in vacuo. The residue was partitioned between ethyl acetate (270 mL) and water (135 mL). The organic layer was washed with water (150 mL) and concentrated in vacuo. The residue was dissolved in methanol (300 mL) and used in the next step without further purification. Assay of the methanol solution indicated a 90% yield. An analytical standard was prepared by silica gel column chromatography: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (dd, J = 4.2, 2.0 Hz, 1H), 8.07 (dd, J = 8.1, 2.0 Hz, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.35 (dd, J = 8.1, 4.2 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 4.93 (broad s, 1H), 3.15 (quartet, J = 6.5 Hz, 2H), 3.00 (t, J = 7.6 Hz, 2H), 2.03 (quintet, J = 7.2 Hz, 2H), 1.34 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 155.9, 155.7, 153.1, 137.0, 136.7, 122.5, 121.4, 120.9, 78.7, 39.9, 36.1, 29.1, 28.3.

***tert*-Butyl 3-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)-propylcarbamate (24).** A solution of naphthyridine **20** (2.72 g, 9.5 mmol) and methanol (20 mL) was hydrogenated in the presence of 5% rhodium on carbon (2.1 g, containing 63% water) under 40 psi of hydrogen at 5 °C for 10 h. The catalyst was removed by filtration through Solka Floc, and the filter cake was rinsed with methanol (2 × 25 mL). The filtrate and washings were combined, concentrated in vacuo, and dissolved in methanol (6.8 mL). To the combined filtrate was added water (6.8 mL) slowly at room temperature to induce crystallization. The resulting solid was collected by filtration, washed with a mixture of water and methanol (2:1 v/v, 5 mL), and dried under vacuum to give tetrahydronaphthyridine **24** (2.33 g, 85%). The mother liquor loss was 5%: mp 95.2−96.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 7.4 Hz, 1H), 6.33 (d, J = 7.3 Hz, 1H), 5.45 (bs, 1H), 4.92 (bs, 1H), 3.39 (m, 2H), 3.16 (bm, 2H), 2.68 (t, J = 6.2 Hz, 2H), 2.59 (t, J = 7.3, 2H), 1.89 (m, 2H), 1.83 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.1, 156.0, 155.4, 136.7, 113.4, 111.3, 78.6, 41.4, 40.3, 35.0, 29.4, 28.4, 26.2, 21.3. Anal. Calcd for $C_{16}H_{25}N_3O_2$: C, 65.95; H, 8.65; N, 14.42. Found: C, 66.09; H, 8.62; N, 14.44.

5-Bromo-2-methoxypyridine (27). To a suspension of 2-methoxypyridine (**26**, 3.96 kg, 36.3 mol), NaOAc (3.57 kg, 39.9 mol), and dichloromethane (22 L) was added a solution of bromine (2.06 L, 39.9 mol) and dichloromethane (2 L), maintaining the reaction temperature below 7 °C over 2−3 h. The mixture was aged for 1 h at 0−7 °C and stirred at room temperature for 16 h. The reaction mixture was filtered, and the filter cake was rinsed with dichloromethane (5 L). The filtrate and washings were combined and extracted with cold 2 M NaOH (22 L, pH should be below 8), maintaining the temperature below 10 °C, and with cold water (11 L). The organic layer was concentrated under reduced pressure to give crude **27** (6.65 kg), which was purified by vacuum distillation to give pure **27** (5.90 kg, 86%) along with 1.3% of **28**. **27**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.18 (d, J = 2.5 Hz, 1H), 7.61 (dd, J = 8.8, 2.5 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), and 3.89 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 162.9, 147.5, 141.0, 112.6, 111.7, 53.7.

***tert*-Butyl (2*E*)-3-(6-methoxypyridin-3-yl)prop-2-enoate (29).** A mixture of *tert*-butyl acrylate (137 mL, 916 mmol), triethylamine (100 mL, 720 mmol), tri-*O*-tolylphosphine (6.30 g, 20 mmol), $Pd(OAc)_2$ (1.80 g, 8 mmol), and NMP (90 mL) was degassed three times. The mixture was heated to 90 °C, and a solution of **27** (50.0 g, 266 mmol) and NMP (10 mL) was added via addition funnel over 1 h, maintaining the reaction temperature at 90 °C. After an additional 12 h at 90 °C, the mixture was cooled to room temperature. Toluene (400 mL) was added, and the resulting solution was passed through a pad of Solka Flok. The filter cake was washed with toluene (270 mL). The combined toluene solution was extracted with water (3 × 540 mL). An aqueous solution of NaClO (2.5%, 200 mL) was slowly added to the toluene solution, keeping the temperature at about 30 °C. The reaction was stirred vigorously for 50 min. The organic layer was separated and washed with water (3 × 540 mL) and saturated aqueous NaCl (270 mL). The organic layer was concentrated to an oil. The oil was dissolved in hexanes (270 mL) and loaded onto to a silica gel pad (90 g). The silica gel pad was eluted with hexanes (73 mL) followed by EtOAc/hexane (1:8, v/v, 730 mL). The rich cut was concentrated to provide an oil (126 g, 49.2 wt %, 98.4% yield). The crude oil was used for the next reaction without further purification. An authentic crystalline sample was obtained by further concentration of the oil: mp 44−45 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.23 (d, J = 2.4 Hz, 1H), 7.73 (dd, J = 8.7 and 2.4 Hz, 1H), 7.50 (d, J = 16.0 Hz, 1H), 6.73 (d, J = 8.7 Hz, 1H), 6.25 (d, J = 16.0 Hz, 1H), 3.94 (s, 3H), and 1.51 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.1, 165.1, 148.1, 139.9, 136.3, 124.0, 119.1, 111.5, 80.6, 53.7, and 28.2. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.35; H, 7.43; N, 5.79.

***tert*-Butyl (3*S*)-3-{Benzyl[(1*R*)-1-phenylethyl]amino}-3-(6-methoxypyridin-3-yl)propanoate (30).** To a solution of (*R*)-(+)-*N*-benzyl-α-methylbenzylamine (88 mL, 0.42 mol) and anhydrous THF (1 L) was added *n*-BuLi (2.5 M in hexanes, 162 mL, 0.41 mol) over 1 h at −30 °C. The solution was cooled to −65 °C, and a solution of *tert*-butyl ester **29** (65.9 g, 0.28 mol) and anhydrous THF (0.5 L) was added over 90 min during which the temperature rose to −57 °C. After the reaction was complete, the reaction solution was poured into a mixture of saturated aqueous NH_4Cl (110 mL) and EtOAc (110 mL). The organic phase was separated and washed sequentially with aqueous AcOH (10%, 110 mL), water (110 mL), and saturated aqueous NaCl (55 mL). The organic layer was concentrated in vacuo to provide a crude oil. The crude oil was purified by passing through a silica gel (280 g) pad eluting with 95:5 hex/EtOAc. The product-containing fractions were combined and concentrated in vacuo to give an oil. The resulting oil was used directly in the next step. The oil contained 91 g (0.20 mol, 71%) of the product **30**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 2.4 Hz, 1H), 7.65 (dd, J = 8.8, 2.4 Hz, 1H), 7.40 (m, 2H), 7.34 (m, 2H), 7.30−7.16 (m, 6 H), 6.74 (d, J = 8.8 Hz, 1H), 4.39 (dd, J = 9.8, 5.3 Hz, 1H), 3.97 (q, J = 6.6 Hz, 1H), 3.94 (s, 3H), 3.67 (s, 2H), 2.52 (dd, J = 14.9, 5.3 Hz, 1H), 2.46 (dd, J = 14.9, 9.8 Hz, 1H), 1.30 (d, J = 6.6 Hz, 3H), 1.26 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 163.3, 146.4, 143.8, 141.3, 138.6, 130.0, 128.24, 128.19, 127.9, 127.7, 127.0, 126.6, 110.4, 80.5, 57.4, 56.6, 53.4, 50.7, 37.5, 27.8, 17.3. Anal. Calcd for $C_{28}H_{34}N_2O_3$: C, 75.31; H, 7.67; N, 6.27. Found: C, 75.13; H, 7.75; N, 6.17.

***tert*-Butyl (3*S*)-3-Amino-3-(6-methoxypyridin-3-yl)propanoate 4-Methylbenzenesulfonate (31).** The thick oil (**30**, containing 80.3 g, 0.18 mol) was hydrogenated in the presence of $Pd(OH)_2$ (20 wt % on carbon, 8.0 g) in a mixture of EtOH (400 mL), AcOH (40 mL), and water (2 mL) under 40 psi of hydrogen at 35 °C for 8 h. The reaction mixture was filtered through a pad of Solka Flok, and evaporated to a thick oil in vacuo. MTBE (2L) was added, and the resulting solution was evaporated to provide an oil. This was repeated several times. A hot solution (40 °C) of *p*-toluenesulfonic acid (*p*-TsOH, 41.7 g, 0.22 mol) and MTBE (400 mL) was added slowly to the warm solution of the amine. After ∼30% of the *p*-TsOH solution had been added, the solution was seeded and a thick slurry formed. The remaining *p*-TsOH was added over 2 h. The resulting suspension was aged for 3 h at 45 °C. The suspension was then slowly cooled to room temperature. After 12 h at room temperature, the mixture was cooled to 6 °C. The solids were collected on a frit, rinsed with MTBE (100 mL), and dried under vacuum at 35 °C to give **31** (71.0 g, 93%, >98% ee): mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (bs, 3H), 8.22 (s, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 6.65 (d, J = 8.8 Hz, 1H), 4.63 (m, 1H), 3.91 (s, 3H), 3.09 (dd, J = 16.5 and 6.0 Hz, 1H), 2.87 (dd, J = 16.5, 8.8 Hz, 1H), 2.36 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 164.2, 146.8, 140.9, 140.4, 137.8, 128.8, 125.8, 124.3, 111.0, 81.6, 53.5, 49.6, 39.3, 27.8, 21.3. Anal. Calcd for $C_{20}H_{28}N_2O_6S$: C, 56.59; H, 6.65; N, 6.60; S, 7.55. Found: C, 56.61; H, 6.76; N, 6.56; S, 7.59. Chiral HPLC analysis: Chirobiotic V (4.6 × 250 mm); 0.01 % vol HOAc and

0.01 % vol TFA in MeOH; 1.0 mL/min; 13.9 min (desired enantiomer) and 17.4 min (undesired).

***tert*-Butyl (3*S*)-3-[(2,2-Dimethoxyethyl)amino]-3-(6-methoxypyridin-3-yl)propanoate (32).** To a solution of **31** (100 g, 239 mmol) and dimethoxyacetaldehyde (60 wt % in water, 39.3 mL, 261 mmol) and THF (400 mL) was added a suspension of sodium triacetoxyborohydride (95 wt %, 79 g, 354 mol) and THF (200 mL) over 1 h, maintaining the reaction temperature below 10 °C. The residual sodium triacetoxyborohydride was rinsed into the reaction mixture with THF (40 mL). The mixture was stirred at 5−10 °C for 30 min and then at room temperature for 30 min. After the mixture was cooled to below 10 °C, aqueous Na_2CO_3 (10 wt %, 120 mL) was added maintaining the temperature below 10 °C. The mixture was extracted with EtOAc (750 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (600 mL) and water (500 mL) and concentrated in vacuo to give crude **32** (88.4 g, 83.9 wt %, 92.2%). An analytical sample was prepared by silica gel column chromatography: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 2.4 Hz, 1H), 7.61 (dd, J = 8.4, 2.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 4.41 (t, J = 5.6 Hz, 1H), 4.00 (dd, J = 8.2, 6.0 Hz, 1H), 3.93 (s, 3H), 3.35 (s, 3H), 3.31 (s, 3H), 2.67 (dd, J = 15.3, 8.2 Hz, 1H), 2.60 (dd, J = 12.0, 5.6 Hz, 1H), 2.51 (dd, J = 12.0, 5.6 Hz, 1H), 2.49 (dd, J = 15.3, 6.0 Hz, 1H), 1.40 (s 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 163.8, 145.9, 137.4, 130.4, 110.9, 103.5, 80.9, 56.9, 53.71, 53.68, 53.4, 48.6, 43.8, 28.0.

***tert*-Butyl (3*S*)-3-(6-Methoxypyridin-3-yl)-3-{2-oxo-3-[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-2,3-dihydro-1*H*-imidazol-1-yl}propanoate (35).** A solution of **24** (10.4 g, 35 mmol) and 6 M HCl (18 mL) was stirred at 35 °C for 1.5 h. The pH of the reaction mixture was adjusted at 7 with 50 wt % NaOH. After addition of *sec*-butanol (35 mL), the pH of the aqueous layer was adjusted at 11.5 with 50 wt % NaOH. The organic layer was separated, washed with saturated aqueous NaCl (10 mL), and concentrated in vacuo to remove water to yield a dry solution of amine **2** (35 mmol) and *sec*-butanol.

A solution of **32** (10 g as pure, 29 mmol), triethylamine (5.5 mL, 40 mmol), and THF (45 mL) was added to a cold solution of bis(trichloromethyl)carbonate (3.51 g, 12 mmol) and THF (75 mL) over 30 min, maintaining the temperature below 0 °C. The mixture was stirred for 2 h at room temperature to yield chlorocarbamate **33**. The solution of **2**, prepared above, and triethylamine (5.5 mL, 40 mmol) was added to the reaction mixture containing **33**. The resulting mixture was stirred at 45 °C for 3 h. To the mixture was added water (20 mL). The phases were separated, and the organic layer, which contained urea **34**, was retained. To the organic layer was added 2 M sulfuric acid (40 mL), and the mixture was stirred for 18 h at room temperature. To the mixture was added iPAc (50 mL). The organic layer was separated and extracted with 2 M sulfuric acid (20 mL). The aqueous layers were combined and extracted with iPAc (50 mL). iPAc (80 mL) was added to the aqueous phase, and the two-phase mixture was cooled to 0 °C. The pH was adjusted to 8.3 by addition of 5 M NaOH (~40 mL). The organic layer was separated and washed with water (3 × 45 mL). The solution containing **35** (12.0 g, 84%) was used for the next step without further purification. An analytical sample was prepared by silica gel column chromatography: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.05 (d, J = 2.5 Hz, 1H), 7.53 (dd, J = 8.6, 2.5 Hz, 1H), 6.95 (d, J = 7.3 Hz, 1H), 6.63 (d, J = 8.6 Hz, 1H), 6.25 (d, J = 7.3 Hz, 1H), 6.16 (d, J = 3.0 Hz, 1H), 6.12 (d, J = 3.0 Hz, 1H), 5.53 (t, J = 8.1 Hz, 1H), 4.90 (bs, 1H), 3.82 (s, 3H), 3.54 (t, J = 7.1 Hz, 2H), 3.32−3.23 (m, 2H), 3.04 (dd, J = 15.5, 8.3 Hz, 1H), 2.90 (dd, J = 15.5, 7.9 Hz, 1H), 2.59 (t, J = 6.3 Hz, 2H), 2.46 (t, J = 7.5 Hz, 2H), 1.93 (m, 2H), 1.80 (m, 2H), 1.27 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 168.6, 163.6, 156.6, 155.5, 152.1, 145.1, 137.6, 136.5, 127.6, 113.2, 111.1, 110.8, 110.7, 107.4, 81.1, 53.3, 51.2, 42.8, 41.3, 39.6, 34.4, 29.1, 27.6, 26.1, 21.2.

(3*S*)-3-(6-Methoxypyridin-3-yl)-3-{2-oxo-3-[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-2,3-dihydro-1*H*-imidazol-1-yl}propanoic Acid (36). To a solution of **35** and iPAc (140 mg/mL, 220 mL, 30.8 g, 62.4 mmol) was added 3.06 M sulfuric acid (150 mL). The aqueous layer was separated and stirred at 40 °C for 3 h. The mixture was cooled to 10 °C. The pH of the solution was adjusted to about 2 with 50 wt % NaOH. To the solution was added SP207 resin[30] (310 mL). The pH of the suspension was adjusted to 5.9 with 50 wt % NaOH and stirred at room temperature for 4 h. The suspension was filtered, and the resin was washed with water (930 mL) and then with 70 v/v % acetone−water (1.5 L). The fractions containing **36** were combined and concentrated to remove acetone. The resulting suspension was cooled to 5 °C. Crystals were collected by filtration, washed with cold water (20 mL), and dried at 30 °C under vacuum to provide **36** (23.5 g, 86%) as crystals. Recrystallization from aqueous iPA gave a thermodynamically more stable crystal form: mp 123 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (d, J = 2.6 Hz, 1H), 7.73 (dd, J = 8.6, 2.6 Hz, 1H), 7.45 (d, J = 7.4 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.54 (d, J = 3.1 Hz, 1H), 6.53 (d, J = 7.4 Hz, 1H), 6.50 (d, J = 3.1 Hz, 1H), 5.70 (dd, J = 11.6, 4.2 Hz, 1H), 3.90 (s, 3H), 3.76 (ddd, J = 14.0, 9.7, 4.3 Hz, 1H), 3.51 (dt, J = 14.0, 5.0 Hz, 1H), 3.46 (m, 2H), 2.99 (dd, J = 14.0, 11.6 Hz, 1H), 2.85 (dd, J = 14.0, 4.2 Hz, 1H), 2.77 (t, J = 6.2 Hz, 2H), 2.70 (ddd, J = 13.5, 7.5, 5.3 Hz, 1H), 2.50 (dt, J = 15.3, 8.2 Hz, 1H), 2.14−1.87 (m, 4H); ^{13}C NMR (101 MHz, CD_3OD) δ 177.6, 163.9, 153.8, 152.2, 148.8, 145.0, 140.1, 137.9, 128.6, 118.2, 111.1, 110.4, 109.5, 108.6, 52.7, 52.1, 41.5, 40.8, 40.3, 28.9, 28.1, 25.1, 19.4. Anal. Calcd for $C_{23}H_{27}N_5O_4 \cdot 0.5\ H_2O$: C, 61.87; H, 6.30; N, 15.64. Found C, 61.76; H, 6.12; N, 15.71. KF 1.97%.

(3*S*)-3-(6-Methoxypyridin-3-yl)-3-{2-oxo-3-[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]imidazolidin-1-yl}propionic Acid (1). A suspension of **36** (105 g, 240 mmol), water (247 mL), 5 M NaOH (84 mL), and 20 wt % $Pd(OH)_2$/C (21 g) was hydrogenated at 120 psi of hydrogen at 80 °C for 18 h. The pH was adjusted to 9.0 with concentrated HCl, and the catalyst was removed by filtration through a pad of Solka Flok (13 g). The filter cake was rinsed with water (200 mL), and the combined filtrate was adjusted to pH 6.4 with concentrated HCl. The solution was seeded and stirred at 0 °C for 1 h. The resulting crystals were collected by filtration and dried under nitrogen to provided **1** as a hemihydrate (84.5 g, 80%): mp 122 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.08 (d, J = 2.4 Hz, 1H), 7.66 (dd, J = 8.7, 2.4 Hz, 1H), 7.45 (d, J = 7.2 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 6.53 (d, J = 7.2 Hz, 1H), 5.48 (dd, J = 12.3, 3.6 Hz, 1H), 3.89 (s, 3H), 3.64 (q, J = 9.2 Hz, 2H), 3.50 (m, 1H), 3.45 (m, 2H), 3.34 (ddd, J = 14.1, 12.1, 3.9 Hz, 1H), 3.16 (q, J = 9.1 Hz, 1H), 2.98 (m, 1H), 2.97 (t, J = 12.3 Hz, 1H), 2.81 (dt, J = 14.1, 4.0 Hz, 1H), 2.75 (m, 3H), 2.65 (ddd, J = 14.4, 11.2, 5.0 Hz, 1H), 2.55 (dd, J = 12.3, 3.4 Hz, 1H), 2.06 (m, 1H), 1.92 (m, 2H), 1.82 (m, 1H); ^{13}C NMR (125.7 MHz, CD_3OD) δ 180.7, 165.1, 162.6, 153.3, 150.2, 146.6, 141.4, 139.7, 130.0, 119.6, 111.6, 110.7, 54.1, 53.1, 42.2, 41.6, 41.0, 38.7, 38.6, 29.1, 27.9, 26.6, 20.7. Anal. Calcd for $C_{23}H_{29}N_5O_4$: C, 62.85; H, 6.65; N, 15.94. Found C, 62.51; H, 6.76; N, 16.04. Chiral HPLC analysis: Chiralpack AD (4.6 × 250 mm); 0.045 % vol TFA and 0.023 % vol diethylamine in hexanes, EtOH, and MeOH (14:3:3); 1.0 mL/min; 7.3 min (undesired enantiomer) and 8.9 min (desired).

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Supporting Information Available: Copies of ^{1}H NMR of **7**, a mixture of **8** and **9**, **16**, **19**−**21**, **23**, **32**, and **35** and ^{13}C NMR of **7**, a mixture of **8** and **9**, **16**, **19**−**21**, **32**, and **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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