Stereoselective Synthesis of Furo[2,3-*c*]pyridine Pyrimidine Thioethers, A New Class of Potent HIV-1 Non-nucleoside Reverse Transcriptase Inhibitors

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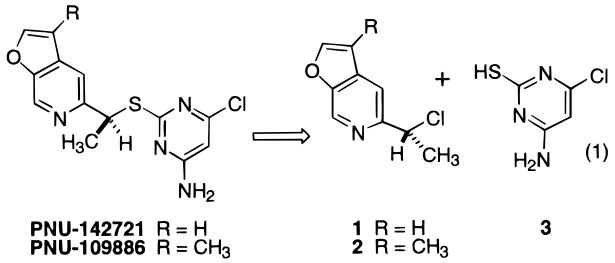
An efficient stereoselective total synthesis of the furo[2,3-*c*]pyridine thiopyrimidine HIV-1 reverse transcriptase inhibitors, PNU-142721 and PNU-109886, has been developed. A convergent approach was utilized, providing direct access to the desired (*S*)-configuration of the molecule by making use of the alkylation of 4-amino-6-chloro-2-thiopyrimidine with the appropriate (*R*)-1-chloroethyl furo[2,3-*c*]pyridine intermediates. The successful preparation makes use of an efficient enzymatic kinetic resolution of the key 1-hydroxyethyl furo[2,3-*c*]pyridine intermediates to establish stereochemical control of the respective stereogenic centers. In addition, a workable asymmetric reduction strategy was developed for the synthesis of PNU-109886. Prudent reagent selection for the chlorination required for the final coupling reactions allowed for maintenance of the stereochemical integrity of the target compounds. Structural assignment of the absolute configuration of PNU-142721 and PNU-109886 as the (*S*)-enantiomer was confirmed by X-ray crystallographic analysis.

The search for new and more potent nonnucleoside reverse transcriptase inhibitors (NNRTIs) targeting drug-resistant variants of HIV-1 of specific genotypes has led to the discovery of the furo[2,3-*c*]pyridine thiopyrimidine ethers.[1,2] A major outcome of an intensive evaluation of this class of NNRTIs has been the recent selection of PNU-142721 as a candidate for clinical development for the treatment of HIV infection and AIDS.[3] PNU-142721 offers a significantly improved profile relative to the currently marketed NNRTI, delavirdine. In addition to being 50 times more potent against a laboratory strain of wild type HIV-1, PNU-142721 is extremely potent against variant virus selected for by delavirdine and other NNRTIs.[4] Another member of this class of current interest is the corresponding 3-methyl furopyridine derivative, PNU-109886, which displays increased potency against variant virus conferring the Y181C mutation.[1,5] However, PNU-109886 is characterized by a somewhat less favorable pharmacokinetic profile in the rat relative to PNU-142721.[1]

An examination of the SAR associated with the furopyridine pyrimidine thioether NNRTIs led to the conclusion that incorporation of the methyl group on the carbon adjacent to the sulfur has an extremely positive effect on the antiviral potency of these derivatives.[1] Moreover, it was apparent that this effect is stereoselective, with the broad antiviral activity associated primarily with the (*S*)-enantiomer. PNU-142721, whose structural (*S*)-configuration was determined by X-ray crystallographic analysis, was found to be at least 100 times more potent than the corresponding (*R*)-enantiomer against variant virus selected for by the NNRTI L-697,661.[3]

PNU-142721 was originally prepared as its racemate and was resolved using preparative chiral HPLC.[3] In support of a more thorough preclinical evaluation of PNU-142721, as well as PNU-109886, we required the development of a general stereoselective synthesis of this class of NNRTIs. A concise retrosynthetic analysis for the preparation of PNU-142721 and PNU-109886 specified for the alkylation of thiopyrimidine **3** with the (*R*)-1-chloroethyl furopyridine intermediates **1** and **2** (eq 1).



PNU-142721 R = H
PNU-109886 R = CH_3

1 R = H
2 R = CH_3

3

This convergent approach, expected to proceed with inversion of configuration at the key stereogenic center, provided direct access to the desired (*S*)-configuration of the molecule. Herein, we present our synthetic studies in this area, culminating in a stereoselective total

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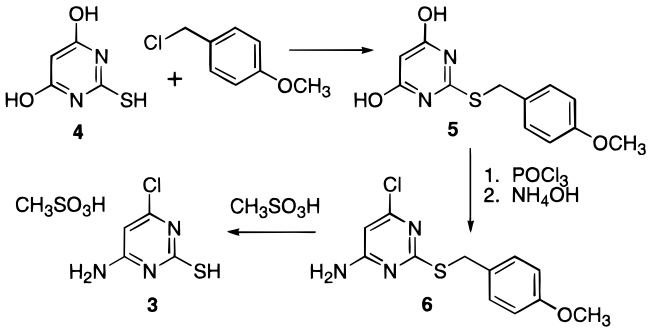
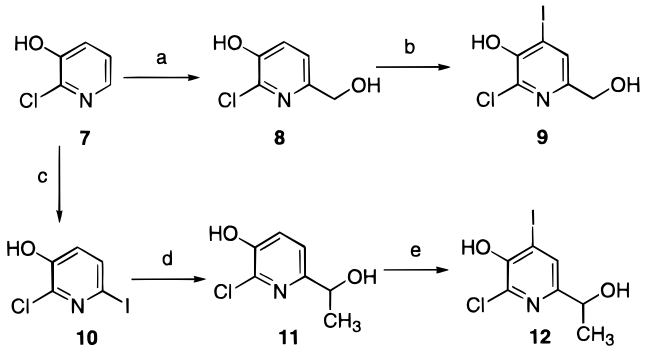
Scheme 1



Scheme 2



(a) $NaHCO_3$, aq. formaldehyde, 81%; (b) I_2, aq. $NaHCO_3$, 74%; (c) I_2, aq. K_2CO_3, 71%; (d) i. LiH; ii. nBuLi; iii. CH_3CHO; 62%; (e) I_2, aq. K_2CO_3, 62%.

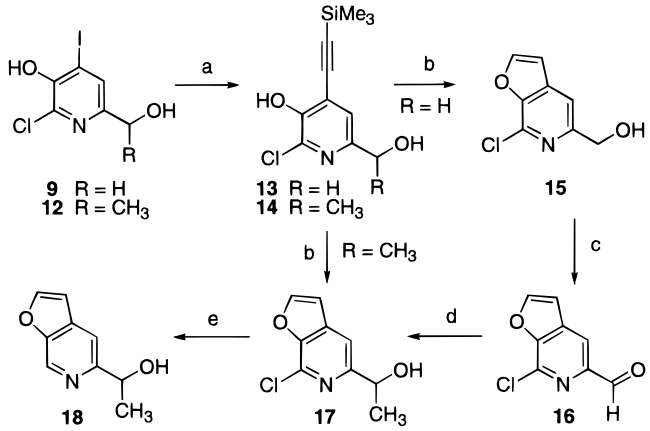
synthesis of PNU-109886 and the clinical candidate PNU-142721.

Results and Discussion

Thiopyrimidine Synthesis. The required thiopyrimidine **3** was synthesized in four steps starting with 4,6-dihydroxy-2-thiopyrimidine (**4**) by variation of the methodology described by d'Atri (Scheme 1).[6] Protection of the 2-thiol of **4** with a *p*-methoxybenzyl group provided **5**, which upon subsequent (bis)chlorination with $POCl_3$ and monoamination gave the 4-amino-6-chloro derivative **6** in good yield. Deprotection of **6** with CH_3SO_3H afforded **3** which was isolated and utilized as its methanesulfonate salt.

Furo[2,3-*c*]pyridine Synthesis. Our synthetic strategy served to complete the elaboration of the carbon framework of the furo[2,3-*c*]pyridine entity prior to establishment of the essential chirality in the side chain of the molecule. Several routes directed toward construction of the furo[2,3-*c*]pyridine nucleus were examined starting from two related functionally advanced pyridine intermediates.[7] The synthesis of these pyridine homologues, **9** and **12**, started from commercially available 2-chloro-3-hydroxypyridine (**7**) (Scheme 2). By blocking access to the 2-position, the chloro substituent of **7** served to direct subsequent electrophilic reactions of the pyridine to the 6-position and was readily removed at a later stage in the synthesis. Base-promoted hydroxymethylation of

Scheme 3



(a) TMS-acetylene, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, $CHCl_3$/THF; (b) CuI, Et_3N, EtOH; (c) oxalyl chloride, DMSO, -60°C, 95%; (d) CH_3MgBr, THF, 80%; (e) cyclohexene, 20% $Pd(OH)_2$/C, MeOH, reflux, 77%.

7 afforded **8**,[8] which was cleanly iodinated to give the 4-iodo derivative **9** in 60% overall yield. Alternatively, **7** was first iodinated to produce **10**, as a prerequisite for the direct introduction of the 1-hydroxyethyl side chain. Initial deprotonation of the pyridyl alcohol of **10** with LiH then allowed for the subsequent lithium−halogen exchange with ^{n}BuLi and quenching with acetaldehyde to afford **11** in 62% yield. Finally, iodination of **11** produced the 1-hydroxyethyl pyridine intermediate **12**.

The *o*-hydroxy iodide functionality of **9** and **12** provided ready access to the construction of the unsubstituted fused furan ring of PNU-142721 (Scheme 3). Palladium−copper cross-coupling reactions of **9** and **12** with TMS-acetylene afforded 92% and 81% yields of the 4-acetylenic pyridines **13** and **14**, respectively.[9] Cyclization of **14** utilizing the CuI catalysis conditions reported by Houpis produced the desired furopyridine **17** in 86% yield.[10] Alternatively, **13** was cyclized in a fashion similar to give the 5-(hydroxymethyl)furopyridine **15** (80%). A one-carbon homologation of the side chain of **15** was accomplished by initial Swern oxidation[11] to aldehyde **16**, followed by treatment with CH_3MgBr, to afford **17** in 76% overall yield. The chloro substituent of **17** was readily removed under transfer hydrogenolysis conditions, producing a 77% recovery of the desired racemic furopyridine intermediate **18**.

The *o*-hydroxypyridyl iodide **12** also served as the source for the corresponding 3-methylfuropyridine intermediate necessary for the synthesis of PNU-109886 (Scheme 4). A rapid entry to the this ring system was realized through initial allylation of **12** followed by palladium acetate catalyzed cyclization of the resultant allyloxypyridyl iodide **19** to provide a modest 29−36% yield of **20**.[12] Subsequent hydrodechlorination of **20** afforded a 97% recovery of **21**. A more efficient ring closure of **19** was identified through the use of ^{n}Bu_3SnH which provided an 88% yield of the corresponding 2,3-

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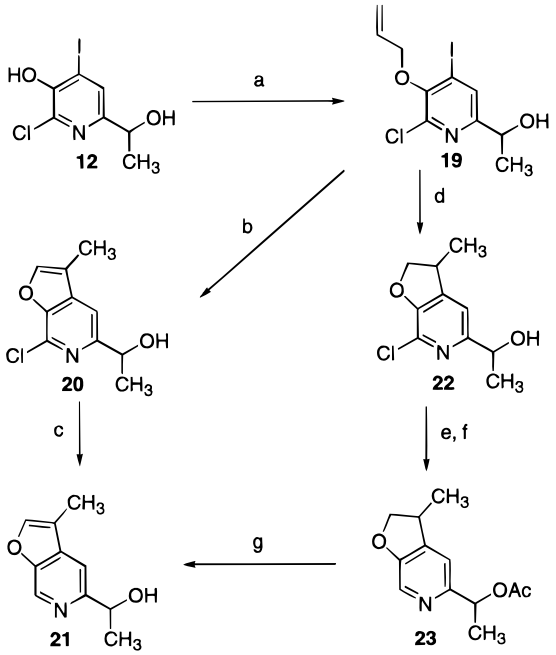
Scheme 4

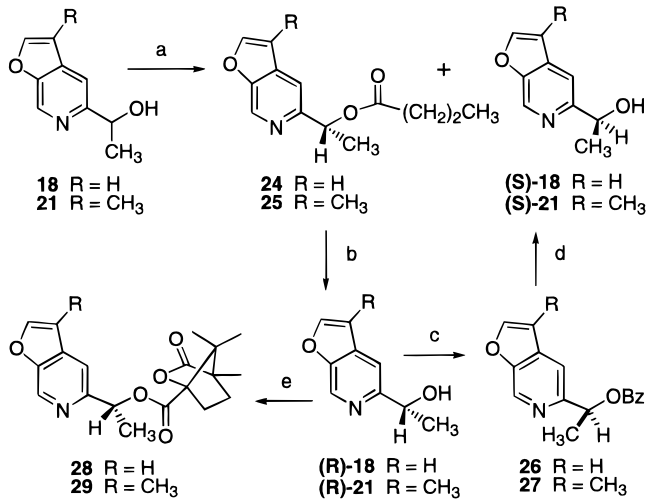


(a) NaH, allyl bromide, 93%; (b) $Pd(OAc)_2$, HCO_2Na, nBu_4NCl, Na_2CO_3, DMF, 60°C, 29%; (c) 20% $Pd(OH)_2/C$, 1,4-cyclohexadiene, EtOH, reflux, 97%; (d) nBu_4SnH, AIBN, 88%; (e) H_2, 20% $Pd(OH)_2/C$, 93%; (f) Ac_2O, 100%; (g) i. chloranil; ii. NaOH, 94%.

dihydrofuropyridine intermediate **22**.[13] Conversion of **22** to **21** was accomplished in three high-yielding steps. Following hydrodechlorination of **22**, acetylation of the secondary alcohol affording **23** was required in order to achieve a successful oxidation of the 2,3-dihydrofuran. Thus, treatment of **23** with chloranil followed by acetate removal upon workup produced a 90% yield of **21**. The use of DDQ for this oxidation proceeded in somewhat lower yield due to complications realized during the workup of the reaction. Although five steps were required, the latter route for the preparation of **21** from **19** proved to be more efficient considering both the higher overall yield (77% vs 26%) and lack of chromatography required for the purification of intermediates.

Enzymatic Resolution of Furo[2,3-*c*]pyridines 18 and 21. Textbook resolution proved achievable by a process employing the enzymatic esterification of the furo[2,3-*c*]pyridine intermediates **18** and **21** (Scheme 5).[14] Exposure of **18** to excess (2,2,2-trifluoroethyl)butyrate in the presence of porcine pancreatic lipase (type II) for 9 days allowed for complete reaction affording a 44.5% recovery of (*S*)-**18** along with 46.5% of the (*R*)-butyric ester **24**.[15] The enantiomeric purity of (*S*)-**18** was established as >99% ee by comparison of the chiral HPLC analysis of its corresponding acetate derivative with an independently prepared racemic sample. A similar chiral HPLC analysis was performed for butyrate **24** (>99% ee). Hydrolysis of **24** with aqueous NaOH afforded (*R*)-**18** in 89% yield. The stereochemistry of (*R*)-**18** was determined

Scheme 5



(a) trifluoroethylbutyrate, porcine pancreatic lipase type II, Et_2O, rt; (b) 2N NaOH, MeOH; (c) Ph_3P, DEAD, BzOH; (d) 2N NaOH, MeOH; (e) (-)-(1S)-camphanic chloride.

by the X-ray crystallographic analysis of its corresponding (1*S*)-camphanic ester derivative **28**.[16]

To realize maximum overall efficiency from the resolution process, methodology was examined to invert the stereocenter of (*R*)-**18**. Mitsunobu treatment of (*R*)-**18** with benzoic acid in the presence of Ph_3P and diethyl azodicarboxylate produced a 90% yield of benzoate **26**.[17] Subsequent hydrolysis of **26** with aqueous NaOH gave (*S*)-**18** in 94% yield. Analysis of the corresponding acetate of (*S*)-**18** showed the optical purity of this sample to be 99% ee. Taking into account both the (*S*)-**18** lots obtained from the enzymatic resolution and that received from the Mitsunobu inversion, the total amount of resolved (*S*)-**18** obtained through this process was 80% of the theoretical yield. A similar sequence and analysis was used for the resolution of the corresponding 3-methylfuro[2,3-*c*]pyridine intermediate **21** to afford the desired (*S*)-enantiomer in 87% overall yield (Scheme 5).

Asymmetric Reduction Route to Furo[2,3-*c*]pyridine (*S*)-21. The hydroxyethyl substrates **20** and **22** served as sources of the methyl ketone intermediates needed to examine a potential asymmetric reduction strategy for the production of (*S*)-**21** (Scheme 6). Swern oxidation of **20** and **22** afforded methyl ketones **30** and **31** in 90% and 84% yields, respectively.[11] Reduction of **30** with (−)-chlorodiisopinocampheylborane [(−)-Dip-Cl] was carried out in THF at room temperature overnight.[18] Following a prescribed oxidative workup, there was obtained a 94% yield of alcohol (*S*)-**20**. Chiral HPLC analysis and comparison of the corresponding acetate of (*S*)-**20** with an independently prepared racemic sample showed the alcohol to be 92% ee. Recrystallization of this material from Et_2O/hexane provided a 78% recovery of (*S*)-**20** with >99% ee. The subsequent hydrodechlorination of (*S*)-**20** under transfer hydrogenolysis conditions

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(16) *ORTEP* drawing of and atomic coordinate information for this compound can be obtained from Supporting Information.

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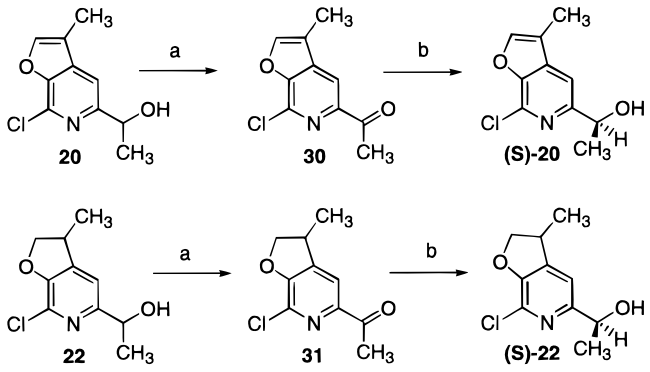
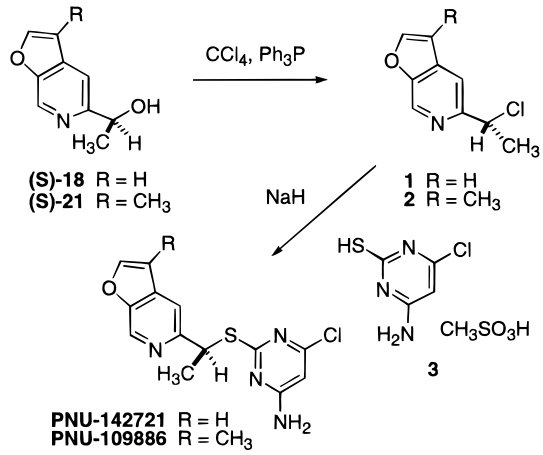
Scheme 6



(a) oxalyl chloride, DMSO, -60°C; (b) (-)-Dip-Cl, THF, rt.

Scheme 7



described for the racemic material afforded an 88% yield of (*S*)-**21** (>99% ee).

A related reduction of the 3-methyldihydrofuropyridine derivative **31** with (−)-Dip-Cl afforded a 99% yield of (*S*)-**22**. Analysis of the enantiopurity of this material was complicated due to the formation of a diastereomeric mixture. Conversion of (*S*)-**22** to (*S*)-**21** as outlined for the corresponding racemic series (Scheme 4) proceeded in 79% overall yield and with 89% ee.

Synthesis of PNU-142721 and PNU-109886. The synthetic plan for the coupling of (*S*)-**18** and (*S*)-**21** with **3** called for a double inversion process that included the stereocontrolled chlorination of the hydroxyl group followed by displacement with the thiopyrimidine anion. We had previously examined the reaction of 4-ethyl-2-(1(*S*)-hydroxyethyl)pyridine with $SOCl_2$ which cleanly afforded the inverted (*R*)-chloride in high yield (>99% ee).[19] This outcome was consistent with the classical reaction of secondary alcohols with $SOCl_2$ that produce chlorides with inversion of configuration in the presence of pyridine and chlorides with retention of configuration (S_Ni mechanism) in the absence of base.[20] However, the corresponding reaction of (*S*)-**21** with $SOCl_2$ with pyridine proved to be more problematic, producing chloride **2** with a modest 42% ee (70% yield) (Scheme 7). A related transformation in the absence of pyridine with the corresponding (*R*)-**21** alcohol gave chloride with an equal but opposite rotation. Turning to the use of other methods to accomplish this transformation, we saw some improvement in the enantiopurity of the product chloride (79% ee, 70% yield) through the use of the conditions of Meyers and Collington (MsCl, LiCl).[21] Fortunately, the use of Ph_3P/CCl_4 resulted in a complete inversion of the stereogenic center, providing chloride **2** in 75−89% yields (>97% ee).[22] Similar results were obtained for the conversion of (*S*)-**18** to chloride **1**.

The alkylation of the mesylate salt of thiopyrimidine **3** with chlorides **1** and **2** was performed by initial formation of the thiolate anion with 2 equiv of NaH in DMF. With **1**, an 89% initial chromatographed yield of PNU-142721 was obtained with 97.6% ee. Recrystallization of this material afforded a final 64% recovery of PNU-142721 that was determined to be >99% ee by chiral HPLC analysis. Similar results of 61% yield (98% ee) were obtained for the preparation of PNU-109886 from chloride **2**. Definitive proof for the proposed outcome of overall retention of configuration resulting from the chlorination−alkylation sequence was afforded by X-ray crystallographic analysis of the final products. These determinations of absolute configuration by X-ray provided confirmation of the (*S*)-configuration assignment to the stereogenic centers of PNU-142721[3] and PNU-109886.[16]

Conclusion

An efficient stereoselective synthesis of the furo[2,3-*c*]pyridine thiopyrimidine HIV-1 RTIs, PNU-142721 and PNU-109886, has been developed. The successful preparation makes use of an efficient enzymatic kinetic resolution of the key alcohol intermediates, **18** and **21**, to establish stereochemical control of their respective stereogenic centers. In addition, a workable asymmetric reduction strategy was examined for the synthesis of PNU-109886. Prudent reagent selection for the chlorination reaction required for the coupling of (*S*)-**18** and (*S*)-**21** with thiopyrimidine **3** allowed for maintenance of the stereochemical integrity of the final products. Finally, structural assignment of the absolute configuration of PNU-142721 and PNU-109886 as the (*S*)-enantiomer was confirmed by X-ray crystallographic analysis.

Experimental Section

4-Amino-6-chloro-2-thiopyrimidine, Mesylate Salt (3). A solution of 4,6-dichloro-2-(4-methoxybenzyl)thiopyrimidine (19.55 g, 64.9 mmol) in 391 mL of warm CH_3CN was treated with 391 mL of 29% NH_4OH at 75 °C for 9 h and at 40 °C overnight. The contents were cooled to room temperature, filtered, and concentrated in vacuo. The white solid was dissolved in EtOAc and washed once with a mixture of 50 mL of water and 75 mL of saturated brine. The combined aqueous layers were extracted once with EtOAc, and the combined organics were dried over Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in refluxing Et_2O plus a minimum amount of EtOAc, diluted with hexane, and placed in refrigerator to afford 15.0 g (82%) of **6**. Mp: 118.5−119.5 °C; ^1H NMR ($CDCl_3$): δ 7.26 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 6.07 (s, 1H), 4.93 (brs, 2H), 4.23 (s, 2H), 3.72 (s, 3H). Anal. Calcd for $C_{12}H_{12}ClN_3OS$: C, 51.25; H, 4.27; N, 14.95; S, 11.39. Found: C, 51.38; H, 4.54; N, 14.41; S, 11.04.

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A suspension of **6** (10.0 g, 33.22 mmol) in 160 mL of CH_2Cl_2 at room temperature was treated with methanesulfonic acid (31.89 g, 332.2 mmol). After 50 min, 1280 mL of Et_2O was added dropwise (slowly, at first) to precipitate the product as a granular solid. The suspension was stirred overnight at room temperature. The product was collected by filtration and washed with Et_2O to provide 8.62 g of **3**. Mp: 166−167 °C; HRMS: Calcd for $C_5H_8ClN_3O_3S_2$: 160.9814. Found: 160.9822. Anal. Calcd for $C_5H_8ClN_3O_3S_2$ @4.94% H_2O: C, 23.22; H, 3.16; N, 16.25. Found: C, 23.48; H, 3.25; N, 15.70.

2-Chloro-3-hydroxy-6-(hydroxymethyl)pyridine (8). A solution of 2-chloro-3-pyridinol (**7**) (20.0 g, 0.154 mol) and $NaHCO_3$ (19.5 g, 0.232 mol) in 150 mL of H_2O was stirred at room temperature for several minutes and heated to 90 °C. After 5 min at 90 °C, the first of six unequal doses of 37% formaldehyde (40.5 mL, 0.541 mol, 3.5 equiv) was added; 12 mL initially, 3 × 8 mL followed by 1 × 2.2 mL all at 90 min intervals with the final 2.3 mL added after maintaining at 90 °C overnight (15 h). The reaction mixture was heated for an additional 4 h after the last dosing. The mixture was cooled to 0 °C, and 100 mL of crushed ice was added followed by 39 mL of 6 N HCl (to pH 1). The precipitated slurry was stirred for 1.5 h at 0 °C. The undesired precipitated side product was filtered off and washed once with 75 mL of ice−water. The yellow filtrate was extracted seven times with EtOAc. The organic extracts were dried with anydrous Na_2SO_4 and concentrated. Toluene was added, and the mixture was reconcentrated to azeotrope any remaining water. The addition of CH_2Cl_2 to suspend the material followed by reconcentration afforded **8** as a pale yellow solid (19.93 g, 81%). Mp: 133.5−135 °C; ^{1}H NMR (DMSO-d_6): δ 10.47 (brs, 1H), 7.38−7.19 (m, 2H), 5.33 (brs, 1H), 4.38 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 63.7, 121.2, 124.9, 137.0, 148.5, 152.5; UV (λ_{max}, ethanol): 225 (7680), 288 (5930) nm; IR 3055, 3038, 2925, 2956, 1562 cm^{-1}. MS: *m*/*z*(relative intensity %): 159 (41), 158 (42), 132 (31), 130 (100), 94 (34). Anal. Calcd for $C_6H_6ClNO_2$: C, 45.16; H, 3.79; N, 8.78. Found: C, 44,88; H, 3.76; N, 8.57.

2-Chloro-3-hydroxy-6-(hydroxymethyl)-4-iodopyridine (9). A mixture of **8** (11.6 g, 72.7 mmol) and $NaHCO_3$ (18.3 g, 218 mmol) in 200 mL of H_2O was stirred until homogeneous, cooled to 0 °C, and treated with I_2 (19.4 g, 76.3 mmol). The reaction was stirred over the weekend as the cooling bath expired. The pH of the mixture was adjusted to 3 with 2 N $NaHSO_3$, and the mixture was extracted with 4 × 50 mL of EtOAc. The combined organics were dried over anhydrous $MgSO_4$ and were concentrated in vacuo to a yellow solid. The crude solid was washed with EtOAc to provide 12.9 g (62%) of **9** as an off-white solid. The filtrate was concentrated to a small volume and was chromatographed over 250 g of silica gel (230−400 mesh) eluting with EtOAc/CH_2Cl_2/hexane/HOAc 2.5:4.5:4:0.1 to afford an additional 2.4 g (12%) of pure **9**. Mp: 147−149 °C; ^{1}H NMR (DMSO-d_6): δ 4.38 (s, 2H), 7.73 (s, 1H), 10.35 (s, 1H); IR: 3156, 2925, 1541, 1455, 1361, 1248 cm^{-1}; MS: [*m*/*z*](relative intensity): [285](80). Anal. Calcd for $C_6H_5ClINO_2$: C, 25.25; H, 1.77; N, 4.91. Found: C, 25.06 H, 1.81; N, 4.92.

2-Chloro-3-hydroxy-6-iodo-pyridine (10). A solution of 2-chloro-3-pyridinol (**7**) (60 g, 0.46 mole) was dissolved in 700 mL of H_2O containing K_2CO_3 (220 g, 1.6 mol) was treated with I_2 (141 g, 0.56 mol) and stirred for 4 h at room temperature. The excess I_2 was quenched with saturated sodium thiosulfate, and the pH of the mixture was adjusted to 2 with 12 N HCl. The mixture was extracted with 3 × 250 mL of EtOAc, and the combined organics were dried over $MgSO_4$ and were concentrated in vacuo. The crude yellow solid was recrystallized from 150 mL of EtOAc and 700 mL of heptane to give 69 g (58%) of **10** as a crystalline solid. The mother liquor was concentrated to a yellow solid which was recrystallized from 60 mL of EtOAc and 370 mL of heptane to provide 15.5 g (13%) of additional **10**. Mp: 142−143 °C; ^{1}H NMR (DMSO-d_6): δ 6.90 (d, J = 8 Hz, 1H), 7.43 (d, J = 8 Hz, 1H), 10.87 (bs, 1H); ^{13}C NMR (DMSO-d_6): δ 100.7, 126.5, 134.5, 137.6, 150.2; IR: 3056, 2925, 1554, 1289, 1226 cm^{-1}; MS: [*m*/*z*](relative intensity): [255](80). Anal. Calcd for C_5H_3ClINO: C, 23.51; H, 1.18; N, 5.48. Found: C, 23.44; H, 1.22; N, 5.39.

2-Chloro-3-hydroxy-6-(1-hydroxyethyl)pyridine (11). A suspension of LiH (2.5 g, 313 mmol) in 1000 mL of dry THF was treated portionwise with **10** (80 g, 313 mmol) and stirred for 1 h at 45 °C. The solution was cooled to room temperature and then to −78 °C and was treated dropwise with ^{n}BuLi (205 mL, 329 mmol). The suspension was stirred for 1 h at −78 °C and was treated dropwise with acetaldehyde (35 mL, 626 mmol). The mixture was stirred for 1 h at −78 °C and was allowed to slowly warm to −40 °C over 2 h and then to 0 °C. The reaction was quenched with 300 mL of H_2O, and the aqueous layer was washed with 2 × 100 mL of Et_2O. The pH of the aqueous layer was adjusted to 3.5 with 10% HCl, and the mixture was extracted with 4 × 100 mL of EtOAc followed by 2 × 100 mL of 10% MeOH/CH_2Cl_2. The combined organics were dried over $MgSO_4$ and treated with 150 g of silica gel (230−400 mesh), and the volatiles were removed in vacuo. The plug was chromatographed over 600 g of silica gel, eluting with 4 L of 35% EtOAc/hexane, 1 L of 55% EtOAc/hexane, and followed by 2 L of 80% EtOAc/hexane to provide an amber oil which was crystallized from 150 mL of 2:1 $CHCl_3$/hexane to afford 33.8 g (62%) of **11** as a white solid. Mp: 89−92 °C, dec; ^{1}H NMR (DMSO-d_6): δ 1.10 (d, J = 6.5 Hz, 3H), 4.40 (m, 1H), 5.10 (d, J = 4.5 Hz, 1H), 7.12 (s, 2H), 10.27 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 24.0, 68.4, 119.6, 124.6, 136.2, 147.9, 156.0; IR: 3334, 2925, 2569, 1558 cm^{-1}; HRMS: Calcd for $C_7H_8ClNO_2$: 173.0244. Found: 173.0252.

2-Chloro-3-hydroxy-4-iodo-6-(1-hydroxyethyl)pyridine (12). A suspension of **11** (4.5 g, 23.6 mmol) in 70 mL of H_2O was treated successively with K_2CO_3 (6.5 g, 47.2 mmol) and I_2 (12.0 g, 47.2 mmol), and the reaction mixture was stirred for 4 h at room temperature. The excess I_2 was quenched with saturated sodium thiosulfate, and the pH of the reaction mixture was adjusted to 3 with 10% HCl. The solid was collected, washed with H_2O, and dissolved in EtOAc. The organics were dried over $MgSO_4$ and concentrated in vacuo. The yellow solid was washed with $CHCl_3$ and was dried to provide 4.4 g (62%) of **12** as a white solid. Mp: 114−116 °C, dec; ^{1}H NMR (DMSO-d_6): δ 1.10 (d, J = 6.5 Hz, 3H), 4.38 (q, J = 6.5 Hz, 1H), 5.22 (bs 1H), 7.59 (s, 1H), 10.2 (bs, 1H); ^{13}C NMR (DMSO-d_6): δ 24.0, 68.1, 100.1, 129.6, 136.3, 148.1, 157.7; IR: 3078, 2926, 1669, 1537 cm^{-1}; MS: [*m*/*z*](relative intensity): [299](16). Anal. Calcd for $C_7H_7ClINO_2$: C, 28.07; H, 2.36; N, 4.68. Found: C, 27.96; H, 2.28; N, 4.55.

2-Chloro-3-hydroxy-6-(hydroxymethyl)-4-[(trimethylsilyl)ethynyl]pyridine (13). A mixture of **9** (13.9 g, 48.6 mmol), (trimethylsilyl)acetylene (9.6 mL, 68 mmol), bis(triphenylphosphine)palladium dichloride (1.02 g, 1.46 mmol), and CuI (139 mg, 0.73 mmol) in 80 mL of chloroform and 40 mL of THF under N_2 was treated with Et_3N (21 mL, 151 mmol) and was stirred for 3 h at room temperature. The reaction was diluted with 200 mL of $CHCl_3$ and was washed with 2 × 150 mL of 5% HCl. The combined aqueous layers were extracted with 2 × 50 mL of $CHCl_3$, and the combined organics were washed with 100 mL of 50% saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo to an amber oil. The crude material was chromatographed over 350 g of silica gel (230−400 mesh), eluting with 35% EtOAc/hexane to afford 11.4 g (92%) of **13** as a golden solid. Mp: 97−98 °C; ^{1}H NMR (DMSO-d_6): δ 0.28 (s, 9H), 4.63 (s, 2H), 7.24 (s, 1H); ^{13}C NMR (DMSO-d_6): δ −0.4, 63.8, 96.1, 107.4, 119.7, 122.4, 137.4, 147.8, 150.8; IR: 3151, 2924, 1602, 1464 cm^{-1}; MS: [*m*/*z*]-(relative intensity): [255](25). Anal. Calcd for $C_{11}H_{14}ClNO_2$-Si: C, 51.66; H, 5.52; N, 5.48. Found: C, 51.39; H, 5.41; N, 5.37.

2-Chloro-3-hydroxy-6-(1-hydroxyethyl)-4-[(trimethylsilyl)ethynyl]pyridine (14). Following the procedure for the preparation of **13**, starting with 5.99 g (20 mmol) of **12**, there was synthesized 4.35 g (81%) of **14** as a pale yellow solid. Mp: 97−98 °C; ^{1}H NMR ($CDCl_3$, TMS): δ 0.20 (s, 9H), 1.39 (d, J = 6.5 Hz, 3H), 2.77 (bs, 1H), 4.71 (q, J = 6.5 Hz, 1H), 6.07 (bs, 1H), 7.16 (s, 1H); ^{13}C NMR ($CDCl_3$): δ −2, 23.8, 68.8, 96.2, 107.0, 119.6, 121.3, 137.1, 147.6, 154.8; IR: 3155, 2924, 2162, 1598, 1461 cm^{-1}; HRMS: Calcd for $C_{12}H_{16}ClNO_2Si$: 269.0639. Found: 269.0639. Anal. Calcd for $C_{12}H_{16}ClNO_2Si$

@ 0.18% water found: C, 53.32; H, 5.99; N, 5.18. Found: C, 52.85; H, 5.99; N, 5.02.

7-Chloro-5-(hydroxymethyl)furo[2,3-*c*]pyridine (15). **13** (11.4 g, 44.6 mmol) was combined with CuI (424 mg, 2.23 mmol) in 60 mL of EtOH and 60 mL of Et_3N and was warmed to 75 °C for 3 h. The reaction mixture was treated with DARCO, diluted with 60 mL of MeOH, and refluxed for 20 min. The mixture was cooled and filtered through Celite. The filtrate was treated with 25 mL of saturated $NaHCO_3$ and 25 mL of 2 N NaOH (50 mmol) and stirred overnight at room temperature. The volatiles were removed in vacuo, and the residue was partitioned between 250 mL of 50% saturated NaCl and 4 × 75 mL of CH_2Cl_2. The combined organics were dried over anhydrous K_2CO_3 and were concentrated in vacuo to give a crude tan solid. The crude material was chromatographed over 300 g of silica gel (230−400 mesh) eluting with 40% EtOAc/hexane to afford 6.6 g (80%) of **15** as a white solid. Mp: 102−103 °C; ^{1}H NMR ($CDCl_3$): δ 3.37 (bs, 1H), 4.79 (s, 2H), 6.82 (d, J = 2 Hz, 1H), 7.51 (s, 1H), 7.79 (d, J = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 64.6, 107.1, 112.5, 133.1, 136.8, 146.9, 149.3, 153.1; IR: 3312, 3099, 2924, 1611, 1572, 1444 cm^{-1}; MS: [*m*/*z*](relative intensity): [183](53). Anal. Calcd for $C_8H_6ClNO_2$: C, 52.34; H, 3.29; N, 7.63. Found: C, 52.27; H, 3.23; N, 7.57.

7-Chloro-5-formylfuro[2,3-*c*]pyridine (16). A solution of oxalyl chloride (831 μL, 9.5 mmol) in 30 mL of CH_2Cl_2 under N_2 at −60 °C was treated with DMSO (1.34 mL, 18.9 mmol) in 5 mL of CH_2Cl_2 and stirred for 20 min. The solution was treated with **15** (1.5 g, 8.2 mmol) in 2 × 5 mL of CH_2Cl_2 at −60 °C, was stirred for 20 min, and was treated with Et_3N (5.83 mL, 41.8 mmol). The reaction was diluted with 50 mL of CH_2Cl_2 and was washed with 100 mL of 1:1 saturated NaCl/5% HCl. The organics were dried over anhydrous $MgSO_4$ and concentrated in vacuo to give 1.5 g of a crude off-white solid. The crude material was chromatographed over 60 g of silica gel (230−400 mesh), eluting with 25% EtOAc/hexane to provide 1.42 g (95%) of **16**. Mp: 140−142 °C; ^{1}H NMR ($CDCl_3$): δ 7.03 (d, J = 2 Hz, 1H), 7.92 (d, J = 2 Hz, 1H), 8.23 (s, 1H), 10.09 (s, 1H);^{13}C NMR ($CDCl_3$): δ 108.2, 115.2, 134.8, 136.2, 146.9, 150.0, 150.0, 191.3; IR: 2924, 1713, 1407 cm^{-1}; MS: [*m*/*z*](relative intensity): [181](47). Anal. Calcd for $C_8H_4ClNO_2$: C, 52.92; H, 2.22; N, 7.71. Found: C, 52.72; H, 2.37; N, 7.63.

7-Chloro-5-(1-hydroxyethyl)furo[2,3-*c*]pyridine (17). Method A: A combination of **14** (25.3 g, 94.1 mmol) and CuI (896 mg, 4.7 mmol) in 300 mL of 1:1 absolute EtOH/ Et_3N was stirred at 75 °C for 2.5 h, was diluted with 2 N NaOH (94 mL, 188 mmol), and was stirred for 1.5 h at 75 °C. The reaction was diluted with 150 mL of MeOH, was treated with 5 g of DARCO, and was refluxed for 20 min. The DARCO was removed by filtration through Celite, and the filtrate was concentrated in vacuo to a small volume. The residue was partitioned between 100 mL of saturated NaCl and 4 × 60 mL of CH_2Cl_2. The combined organics were washed with 2 × 60 mL of 1:1 saturated NaCl/saturated disodium EDTA, were dried over anhydrous $MgSO_4$, and were concentrated in vacuo to an amber oil. The crude material was chromatographed over 600 g of silica gel (230−400 mesh), eluting with 38% EtOAc/hexane to afford 15.9 g (86%) of **17** as a pale yellow solid. Method B: A solution of **16** (6.47 g, 35.6 mmol) in 105 mL of THF and 155 mL of Et_2O under N_2 was treated dropwise with methylmagnesium bromide (18 mL, 53.4 mmol, 3 M in Et_2O) at room temperature and was warmed to reflux for 2 h. The reaction was cooled to 0 °C and was quenched with 150 mL of 5% HCl. The aqueous layer was washed with 2 × 50 mL of CH_2Cl_2, and the combined organics were dried over anhydrous $MgSO_4$. The organics were concentrated in vacuo. The yellow oil was chromatographed over 300 g of silica gel (230−400 mesh), eluting with 50% EtOAc/hexane, to afford 5.65 g (80%) of **17**. Mp: 71−73 °C; ^{1}H NMR ($CDCl_3$): δ 1.56 (d, J = 6.5 Hz, 3H), 4.96 (q, J = 6.5 Hz, 1H), 6.84 (d, J = 2 Hz,1H), 7.51 (s, 1H), 7.81 (d, J = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 24.4, 69.5, 107.2, 111.3, 132.8, 136.8, 146.8, 149.2, 157.3; IR: 3205, 2925, 1611, 1572 cm^{-1}. MS: [*m*/*z*](relative intensity): [197](3). Anal. Calcd for $C_9H_8ClNO_2$: C, 54.70; H, 4.08; N, 7.09. Found: C, 54.46; H, 4.01; N, 7.04.

5-(1-Hydroxyethyl)furo[2,3-*c*]pyridine (18). A solution of **17** (3.95 g, 20 mmol) in 110 mL of MeOH containing 20% $Pd(OH)_2$ on carbon (1 g) under N_2 was treated with cyclohexene (19.8 mL, 200 mmol) followed by 2 N NaOH (15 mL, 30 mmol), and the reaction was refluxed for 3.5 h. The mixture was cooled and filtered through Celite, and the filter cake was washed well with fresh MeOH. The filtrate was concentrated in vacuo to a yellow paste. The residue was partitioned between 50 mL of water and 4 × 25 mL of CH_2Cl_2, and the organics were dried over K_2CO_3 and were concentrated in vacuo to a pale oil (3.16 g). The crude material was chromatographed over 125 g of silica gel (230−400 mesh), eluting with 60% EtOAC/hexane to give 2.52 g (77%) of **18** as a pale oil. ^{1}H NMR ($CDCl_3$, TMS): δ 1.55 (d, J = 6.5 Hz, 3H), 4.19 (bs, 1H), 5.01 (q, J = 6.5 Hz, 1H), 6.78 (d, J = 2 Hz, 1H), 7.56 (s, 1H), 7.76 (d, J = 2 Hz, 1H), 8.76 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.7, 69.6, 106.1, 111.8, 132.0, 135.0, 148.8, 151.4, 156.5; IR: 3355, 2973, 1614, 1465, 1280 cm^{-1}. HRMS: Calcd for $C_9H_9NO_2$: 163.0633. Found: 163.0646.

3-(Allyloxy)-2-chloro-6-(1-hydroxyethyl)-4-iodopyridine (19). A suspension of 60% NaH (1.2 g, 30 mmol) (washed with 3 × 10 mL of hexane) in 48 mL of dry DMF at 0 °C was treated portionwise with **12** (8.98 g, 30 mmol). The mixture was stirred for 1 h at room temperature and treated with allyl bromide (2.9 mL, 33 mmol), and the reaction was stirred for 4 h. The mixture was diluted with 150 mL of EtOAc, washed with 4 × 25 mL of 50% saturated 1:1 NaCl/$NaHCO_3$, and dried over anhydrous $MgSO_4$/K_2CO_3. The dried organics were concentrated in vacuo to a solid which was washed with hexane to give 9.52 g (93%) of **19** as a white solid. Mp: 89−91 °C; ^{1}H NMR ($CDCl_3$, TMS): δ 1.49 (d, J = 6.6 Hz, 3H), 2.87 (bs, 1H), 4.56 (m, 2H), 4.82 (q, J = 6.6 Hz, 1H), 5.32 (m, 1H), 5.45 (m, 1H), 6.16 (m, 1H), 7.73 (m, 1H); ^{13}C NMR ($CDCl_3$): 24.0, 68.6, 74.4, 105.6, 119.5, 129.6, 132.4, 143.5, 150.5, 159.8; IR 3157, 2928, 1561, 1523 cm^{-1}; MS: [*m*/*z*]-(relative intensity): [339](44). Anal. Calcd for $C_{10}H_{11}ClINO_2$: C, 35.37; H, 3.26; N, 4.12. Found: C, 35.11; H, 3.03; N, 3.98.

7-Chloro-5-(1-hydroxyethyl)-3-methylfuro[2,3-*c*]pyridine (20). A combination **19** (9.52 g, 28 mmol) with ^{n}Bu$_4$NCl (10.6 g, 38 mmol), sodium formate (2.4 g, 35 mmol), Na_2CO_3 (8.9 g, 84 mmol), and $Pd(OAc)_2$ (367 mg, 1.6 mmol) in 60 mL of DMF was warmed to 60 °C for 2 h. The mixture was diluted with 150 mL of EtOAC and extracted with 4 × 50 mL of 50% saturated NaCl. The organics were dried over K_2CO_3 and were concentrated in vacuo to a dark oil. The crude oil was taken up in 60 mL of MeOH, was refluxed with Darco for 10 min, and was filtered through Celite. The filtrate was concentrated in vacuo to a crude dark oil which was chromatographed over 150 g of silica gel (230−400 mesh), eluting with 25% EtOAc/hexane to give 1.71 g (29%) of **20** as a pale yellow solid. Mp: 67−68 °C; ^{1}H NMR ($CDCl_3$, TMS): δ 1.55 (d, J = 6.6 hz, 3H), 2.24 (s, 3H), 3.56 (bs, 1H), 4.96 (q, J = 6.5 Hz, 1H), 7.49 (s, 1H), 7.57 (m, 1H); ^{13}C NMR ($CDCl_3$): 7.9, 24.5, 69.6, 109.7, 116.8, 132.5, 138.2, 145.7, 146.9, 156.9; IR 3293, 2925, 1441 cm^{-1}; MS: [*m*/*z*](relative intensity): [211](4), [196](100). Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.54; H, 4.79; N, 6.52.

7-Chloro-2,3-dihydro-5-(1-hydroxyethyl)-3-methylfuro-[2,3-*c*]pyridine (22). A solution of **19** (40 g, 117.8 mmol) in 260 mL of benzene under N_2 was combined with *N*,*N*′-azobis-(isobutyrylnitrile) (1.94 g, 11.8 mmol). The solution was warmed to reflux and was treated rapidly dropwise with tri-*n*-butyltin hydride (34.2 mL, 127.2 mmol) in 60 mL of dry benzene. The reaction was stirred for 1 h at reflux, was cooled, and the benzene was removed in vacuo. The residue was chromatographed over 750 g of silica gel (230−400 mesh), eluting with 4 L of 10% EtOAc/hexane (including a 2 L forerun), 2 L of 20% EtOAc/hexane, followed by 3 L of 35% EtOAc/hexane to afford 22.2 g (88%) of **22** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, TMS): δ 1.37 (d, J = 7 Hz, 3H), 1.48 (d, J = 6.5 Hz, 3H), 2.91 (bs, 1H), 3.65 (bs, 1H), 4.24 (t, J = 8.8 Hz, 1H), 4.83 (m, 2H), 7.12 (m, 1H); IR 3386, 2971, 1571 cm^{-1};

MS: Calcd for $C_{10}H_{12}NO_2$: 213.0557. Found: 213.0555. Anal. Calcd for $C_{10}H_{12}NO_2$ @0.87% H_2O: C, 55.46; H, 6.15; N, 6.47. Found: C, 55.46; H, 5.63; N, 6.45.

2,3-Dihydro-5-(1-acetoxyethyl)-3-methylfuro[2,3-*c*]pyridine (23). A solution of **22** (26 g, 122 mmol) in 200 mL of MeOH was treated with 5.5 g DARCO and was refluxed for 20 min. The mixture was filtered through Celite, and the filter cake was washed with MeOH. The filtrate was concentrated in vacuo to give 25 g of a pale oil. The oil was dissolved in 160 mL of absolute EtOH, was treated with 5.5 g of 20% $Pd(OH)_2$ on carbon, and was diluted with 60 mL (120 mmol) of 2 N aqueous NaOH. The mixture was hydrogenated at 22 psi for 20 h. The catalyst was removed by filtration, and the filter cake was washed with fresh absolute EtOH. The filtrate was concentrated in vacuo to a pasty residue and was partitioned between 1 × 200 mL of 50% saturated $NaHCO_3$ and 4 × 100 mL of CH_2Cl_2. The organics were dried over K_2CO_3 and were concentrated in vacuo to provide 20.1 g (93%) of 5-(1-hydroxyethyl)-2,3-dihydro-3-methylfuro[2,3-*c*]pyridine as a pale yellow oil. ^{1}H NMR ($CDCl_3$, TMS): δ 1.36 (m, 3H), 1.48 (m, 3H), 3.56 (m, 1H), 4.05 (bs, 1H), 4.13 (m, 1H), 4.86 (t, J = 9 Hz, 1H), 4.87 (q, J = 6.4 Hz, 1H), 7.15 (s, 1H), 8.03 (s, 1H); IR 3368, 2970, 1584, 1488, 1273, 1231, 1118, 959 cm^{-1}; MS: Calcd for $C_{10}H_{13}NO_2$: 179.0946. Found: 179.0949. Anal. Calcd for $C_{10}H_{13}NO_2$ @2.01% H_2O: C, 65.67; H, 7.39; N, 7.66. Found: C, 66.11; H, 7.10; N, 7.66. A solution of of 5-(1-hydroxyethyl)-2,3-dihydro-3-methylfuro[2,3-*c*]pyridine (20.1 g, 112 mmol) in 112 mL of pyridine under N_2 was treated with acetic anhydride (31.2 mL, 336 mmol) and was stirred overnight at room temperature. The pyridine was removed in vacuo, and the residue was taken up in 200 mL of EtOAc. The solution was stirred vigorously for 1 h with 200 mL of saturated $NaHCO_3$ containing 35 g of solid $NaHCO_3$. The organic layer was extracted with 4 × 100 mL of 50% saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give 24.8 g (quant) of **23** as a pale oil. ^{1}H NMR ($CDCl_3$, TMS): δ 1.36 (m, 3H), 1.58 (m, 3H), 2.11 (m, 3H), 3.57 (m, 1H), 4.14 (t, J = 8.4 Hz, 1H), 4.75 (t, J = 8.4 Hz, 1H), 5.89 (q, J = 6.5 Hz, 1H), 7.18 (m, 1H), 8.12 (s, 1H); IR 2980, 1739 cm^{-1}; HRMS: Calcd for $C_{12}H_{15}NO_3$: 221.1052. Found: 221.1054.

5-(1-Hydroxyethyl)-3-methylfuro[2,3-*c*]pyridine (21). Method A: A combination of **20** (1.71 g, 8.1 mmol) and 20% $Pd(OH)_2$ on carbon (1.71 g) in 24 mL of absolute EtOH under N_2 was treated with 1,4 cyclohexadiene (7.6 mL, 81 mmol), and the reaction was warmed to reflux for 2 h. The mixture was filtered through Celite, and the cake was washed well with fresh MeOH. The filtrate was concentrated in vacuo, and the residue was partitioned between 50 mL of saturated $NaHCO_3$ and 4 × 25 mL of CH_2Cl_2. The combined organics were dried over K_2CO_3 and were concentrated in vacuo to provide 1.39 g (97%) of **21** as a colorless oil which crystallized on standing. Method B: A solution of **23** (24.3 g, 110 mmol) and 2,3,5,6-tetrachlorobenzoquinone (29.6 g, 120.4 mmol) in 500 mL of dioxane under N_2 was warmed to a gentle reflux for 24 h. The reaction was cooled to room temperature and was filtered, and the filter cake was washed well with EtOAc. The filtrate was concentrated in vacuo to a reddish brown slurry which was diluted with 100 mL of dioxane and filtered, and the filter cake was washed with Et_2O. The filtrate was concentrated to a brown oil, was diluted with 500 mL of MeOH followed by 185 mL (370 mmol) of 2 N NaOH, and the reaction was stirred for 1 h at room temperature. The MeOH was removed in vacuo, the aqueous residue was diluted with 300 mL of H_2O, and the mixture was extracted with 4 × 100 mL of CH_2Cl_2. The combined organics were backwashed with 2 × 100 mL of 1 N NaOH, dried over K_2CO_3, and concentrated in vacuo to a greenish oil. The oil was dissolved in 200 mL of MeOH and was refluxed with DARCO for 20 min. The mixture was filtered through Celite, the filter cake was washed well with MeOH, and the filtrate was concentrated in vacuo to provide 18.4 g (94%) of **21**. Mp: 56−58 °C; ^{1}H NMR ($CDCl_3$, TMS): δ 1.57 (d, J = 6.5 Hz, 3H), 2.26 (s, 3H), 3.68 (bs, 1H), 5.03 (q, J = 6.5 Hz, 1H), 7.49 (s, 1H), 7.55 (m, 1H), 8.72 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 7.6, 24.7, 69.5, 110.1, 115.4, 131.8, 136.5, 145.3, 151.7, 156.0; IR 3208, 2925, 1621, 1589, 1457 cm^{-1}; MS: [*m*/*z*](relative intensity): [177](3), [162](100). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.65; H, 6.38; N, 7.85.

(−)-(*S*)-5-(1-Hydroxyethyl)furo[2,3-*c*]pyridine ((*S*)-18) and (+)-(*R*)-5-(1-butyryloxy)furo[2,3-*c*]pyridine (24). A combination of **18** (11.3 g, 69.4 mmol), porcine pancreatic lipase type (II) (16.5 g), and 2,2,2 trifluoroethyl butyrate (41.8 mL, 227 mmol) in 226 mL of Et_2O under N_2 was stirred for 9 days at room temperature. The mixture was filtered to remove the enzyme, and the filter cake was washed well with Et_2O. The filtrate was concentrated in vacuo to a pale oil. The residue was azeotroped with 3 × 200 mL of toluene and placed under high vacuum at 40 °C for 3 h. The crude material was chromatographed over 300 g of silica gel (230−400 mesh), eluting with 60% EtOAc/hexane to provide 7.53 g (46.5%) of **24** as a pale oil and 5.03 g, (44.5%) of (−)-(*S*)-**18** as an off-white solid. Data for **24**: $[\alpha]_D = {}^+84.0°$ (c = 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS): δ 0.94 (t, J = 7.4 Hz, 3H), 1.61−1.74 (m, 5H), 2.36 (m, 2H), 6.04 (q, J = 6.6 Hz, 1H), 6.79 (m, 1H), 7.59 (s, 1H), 7.75 (d, J = 2.1 Hz, 1H), 8.85 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.6, 18.5, 21.2, 36.4, 72.7, 106.3, 113.2, 133.0, 134.9, 148.8, 151.5, 153.1, 173.0; IR 2968, 1735, 1611, 1466 cm^{-1}; MS: [*m*/*z*](relative intensity): [233](2), [162](100). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.63; H, 6.39; N, 6.03. Chiral HPLC (0.46 × 25 cm (R,R) Whelk-O1; 1.0 mL/min; 20% 2-propanol in hexane; retention time (*R*)-isomer: 11.7 min, (*S*)-isomer: 8.2 min) indicated the butyrate to be 99.9% ee. Data for (−)-(*S*)-**18**: Mp: 59−61 °C; $[\alpha]_D = -35.8°$ (c = 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS): δ 1.58 (d, J = 6.5 Hz, 3H), 4.24 (bs, 1H), 5.07 (q, J = 6.5 Hz, 1H), 6.84 (m, 1H), 7.61 (s, 1H), 7.84 (d, J = 2.1 Hz, 1H), 8.84 (s, 1H); IR: 3111, 2926, 1612, 1465 cm^{-1}; MS: [*m*/*z*](relative intensity): [163](2), [148](100). Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.13; H, 5.45; N, 8.54. A 50 mg sample of (*S*)-**18** was converted to the corresponding acetate ($[\alpha]_D = -102.2°$ (c = 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS): δ 8.86 (m, 1H), 7.76 (d, J = 2.1 Hz, 1H), 7.60 (m, 1H), 6.80 (m, 1H), 6.03 (q, J = 6.6 Hz, 1H), 2.12 (s, 3H), 1.64 (d, J = 6.5 Hz, 3H). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.05; H, 5.59; N, 6.74) with Ac_2O/pyridine. Chiral HPLC (0.46 × 25 cm (*R*,*R*) Whelk-O1; 1.0 mL/min; 10% 2-propanol in hexane; retention time (*S*)-isomer: 12.1 min, (*R*)-isomer: 17.9 min) indicated the acetate to be 99% ee.

(−)-(*S*)-5-(1-Hydroxyethyl)-3-methylfuro[2,3-*c*]pyridine ((*S*)-21) and (+)-(*R*)-5-(1-butyryloxyethyl)-3-methylfuro[2,3-*c*]pyridine (25). A solution of **21** (2.54 g, 14.35 mmol) in 50 mL of Et_2O at room temperature was treated with 2,2,2-trifluoroethyl butyrate (9.76 g, 57.40 mmol) and porcine pancreatic lipase, type II (3.71 g) and stirred for 7 days. The contents were diluted with 40 mL of Et_2O plus 3 g of Celite, filtered through a pad of Celite (12 g), and washed thoroughly with Et_2O. The filtrate was concentrated in vacuo, and the residue was chromatographed over 70 g of silica gel (230−400 mesh), eluting with acetone−CH_2Cl_2 (1:5), to yield 1.81 g (51%) of **25** and 1.28 g (50%) of (−)-(*S*)-**21**. Data for **25**: $[\alpha]_D = +76.5°$ (c = 1.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$,TMS): δ 8.78 (s, 1H), 7.50 (s, 2H), 6.04 (q, J = 6.6 Hz, 1H), 2.35 (t, J = 7.4 Hz, 2H), 2.23 (s, 3H), 1.72−1.57 (m, 2H), 1.64 (d, J = 4.6 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); HRMS: Calcd for $C_{14}H_{17}NO_3$: 247.1208. Found: 247.1213. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.02; H, 6.88; N, 5.67. Found: C, 67.98; H, 6.97; N, 6.19. Chiral HPLC (0.46 × 25 cm (*R*,*R*) Whelk-O1; 1.0 mL/min; 15% 2-propanol in hexane; retention time (*R*)-isomer: 11.4 min, (*S*)-isomer: 6.7 min) indicated the butyrate to be 99.9% ee. Data for (*S*)-**21**: Mp: 76−78 °C; $[\alpha]_D = -40.8°$ (c = 0.865, $CHCl_3$); ^{1}H NMR ($CDCl_3$,TMS): δ 8.69 (s, 1H), 7.51 (s, 1H), 7.46 (s, 1H), 5.00 (q, J = 6.5 Hz, 1H), 2.23 (s, 3H), 1.55 (d, J = 6.5 Hz, 3H); HRMS: Calcd for $C_{10}H_{11}NO_2$ − H: 176.0712. Found: 176.0709. A 17 mg sample of (*S*)-**21** was converted to the corresponding acetate ($[\alpha]_D = -90.4°$ (c = 0.575, $CHCl_3$); ^{1}H NMR ($CDCl_3$,-TMS): δ 8.78 (s, 1H), 7.51 (m, 2H), 6.03 (q, J = 6.6 Hz, 1H), 2.25 (s, 3H), 2.12 (s, 3H), 1.64 (d, J = 6.5 Hz, 3H); HRMS: Calcd for $C_{12}H_{13}NO_3$: 219.0895. Found: 219.0891) with acetic anhydride/pyridine. Chiral HPLC (0.46 × 25 cm (*R*,*R*) Whelk-O1; 1.0 mL/min; 15% 2-propanol in hexane; retention time (*S*)-

isomer: 8.3 min, (*R*)-isomer: 13.5 min) indicated the acetate to be 99% ee.

(+)-(*R*)-5-(1-Hydroxyethyl)furo[2,3-*c*]pyridine ((*R*)-18). A solution of **24** (7.5 g, 32.2 mmol) in 88 mL of MeOH was treated with 2 N NaOH (35.4 mL, 70.8 mmol) and was stirred for 1 h. The volatiles were removed in vacuo, and the residue was partitioned between 25 mL of CH_2Cl_2 and 100 mL of H_2O. The insoluble material was removed by filtration through Celite. The aqueous layer was extracted with 3 × 25 mL of CH_2Cl_2. The combined organics were dried over K_2CO_3 and were concentrated in vacuo to give 4.68 g (89%) of (*R*)-**18** as a white solid. Mp: 60−61 °C; $[\alpha]_D = +37.0°$ (*c* = 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS): δ 1.55 (d, *J* = 6.5 Hz, 3H), 4.25 (bs, 1H), 5.01 (q, *J* = 6.5 Hz, 1H), 6.81 (m, 1H), 7.55 (s, 1H), 7.78 (d, *J* = 2.1 Hz, 1H), 8.80 (s, 1H); IR 3111, 2928, 1613, 1464 cm^{-1}. Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.46; H, 5.55; N, 8.70.

(+)-(*R*)-5-(1-Hydroxyethyl)-3-methylfuro[2,3-*c*]pyridine ((*R*)-21). Following the procedure for the preparation of (*R*)-**18**, starting with 10.8 g (43.7 mmol) of **25**, there was synthesized 6.94 g (90%) of (*R*)-**21** as a tan solid. Mp: 78−79 °C; $[\alpha]_D = +40.6°$ (*c* = 0.515, $CHCl_3$); ^{1}H NMR ($CDCl_3$,TMS): δ 8.66 (s, 1H), 7.47 (s, 1H), 7.40 (s, 1H), 4.95 (q, *J* = 6.4 Hz, 1H), 3.77 (brs, 1H), 2.19 (s, 3H), 1.50 (d, *J* = 6.4 Hz, 3H); IR 3316, 1615, 1588 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.74; H, 6.16; N, 7.95.

(+)-(*S*)-5-[1-(Benzoyloxy)ethyl]furo[2,3-*c*]pyridine (26). A combination of (*R*)-**18** (4.68 g, 28.7 mmol), benzoic acid (3.86 g, 31.6 mmol), and Ph_3P (8.29 g, 31.6 mmol) in 125 mL of dry THF under N_2 was treated dropwise (moderate add rate, allow some exotherm) with diethyl azodicarboxylate (4.98 mL, 31.6 mmol), and the reaction was stirred for 1.5 h at room temperature. The volatiles were removed in vacuo, the oily residue was diluted successively with equal volumes of Et_2O and hexane, and the white solid was collected by filtration. The filtrate was concentrated in vacuo to an amber oil. The crude material was chromatographed over 250 g of silica gel (230−400 mesh), eluting with 20% EtOAc/hexane to give 6.87 g (90%) of **26**. $[\alpha]_D = +52.7°$ (*c* = 0.67, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS): δ 1.79 (d, *J* = 6.7 Hz, 3H), 6.32 (q, *J* = 6.7 Hz, 1H), 6.80 (m, 1H), 7.41−7.48 (m, 2H), 7.52−7.60 (m, 1H), 7.71 (s, 1H), 7.76 (d, *J* = 2.1 Hz, 1H), 8.12 (m, 2H), 8.95 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.3, 73.6, 106.3, 113.2, 128.4, 128.4, 129.8, 130.1, 130.3, 130.5, 133.0, 135.1, 149.0, 151.6, 152.0, 165.9, 170.2; IR 3062, 1718, 1466, 1450 cm^{-1}; HRMS: Calcd for $C_{16}H_{13}NO_3$: 267.0895. Found: 267.0903.

(+)-(*S*)-5-[1-(Benzoyloxy)ethyl]-3-methylfuro[2,3-*c*]pyridine (27). Following the procedure for the preparation of **26**, starting with 3.9 g (22 mmol) of (*R*)-**21**, there was synthesized 5.57 g (90%) of **27**. $[\alpha]_D = +55.6°$ (*c* = 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$,TMS): δ 8.79 (s, 1H), 8.13 (s, 1H), 8.11 (s, 1H), 7.63−7.38 (m, 5H), 6.30 (q, *J* = 6.6 Hz, 1H), 2.22 (s, 3H), 1.78 (d, *J* = 6.6 Hz, 3H); IR 1717 cm^{-1}; HRMS: Calcd for $C_{17}H_{15}NO_3$: 281.1047. Found: 281.1052.

(−)-(*S*)-5-(1-Hydroxyethyl)furo[2,3-*c*]pyridine ((*S*)-18). A solution of **26** (6.87 g, 25.7 mmol) in 88 mL of MeOH was treated with 2 N sodium hydroxide (28.3 mL, 56.6 mmol), and the reaction was stirred for 2 h at room temperature. The volatiles were removed in vacuo, and the residue was partitioned between 50 mL of H_2O and 4 × 25 mL of CH_2Cl_2. The organics were dried over anhydrous K_2CO_3 and were concentrated in vacuo to an amber oil. The crude material was chromatographed over 150 g of silica gel (230−400 mesh), eluting with 65% EtOAc/hexane to afford 3.96 g (94%) of (*S*)-**18** as a white solid. Mp: 60−61 °C; $[\alpha]_D = -35.3°$ (*c* = 0.51, $CHCl_3$). ^{1}H NMR ($CDCl_3$, TMS): δ 1.56 (d, *J* = 6.5 Hz, 3H), 4.10 (bs, 1H), 5.03 (q, *J* = 6.5 Hz, 1H), 6.82 (m, 1H), 7.57 (s, 1H), 7.81 (d, *J* = 2.1 Hz, 1H), 8.81 (s, 1H).

(−)-(*S*)-5-(1-Hydroxyethyl)-3-methylfuro[2,3-*c*]pyridine ((*S*)-21). Following the procedure for the preparation of (*S*)-**18**, starting with 9.86 g (35 mmol) of **27**, there was synthesized 5.67 g (91%) of (*S*)-**21**. Mp: 78−79 °C; $[\alpha]_D = -41.2°$ (*c* = 0.505, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS): 8.73 (m, 1H), 7.55 (m, 1H), 7.49 (s, 1H), 5.03 (q, *J* = 6.5 Hz, 1H), 3.91 (bs, 1H), 2.25 (s, 3H), 1.56 (d, *J* = 6.4 Hz, 3H); IR: 3317, 1615, 1588, 1462 cm^{-1}. HRMS: Calcd for $C_{10}H_{11}NO_2 - H$: 176.0712. Found: 176.0711. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.77; H, 6.24; N, 8.11.

5-(1-Acetyl)-7-chloro-3-methylfuro[2,3-*c*]pyridine (30). To a solution of oxalyl chloride (0.93 mL, 10.90 mmol) in 45 mL of CH_2Cl_2 at −60 °C was added dimethyl sulfoxide (1.54 mL, 21.80 mmol) in 5 mL of CH_2Cl_2 dropwise over a 7 min period. After 30 min, a solution of **20** (2.00 g, 9.48 mmol) in 8 mL of CH_2Cl_2 was added dropwise to the mixture at −60 °C over a 19 min period. An additional 5 mL of CH_2Cl_2 was added to facilitate stirring. After 15 min, Et_3N (6.6 mL, 47.4 mmol) was added dropwise at −60 °C. After stirring for 1 h at −60 °C, the cooling bath was removed and the reaction was allowed to warm to room temperature. After 1.5 h, the mixture was poured into 50 mL of 50% saturated NaCl and extracted 2× with EtOAc. The combined organics were concentrated, and the mixture (2.0 g) was chromatographed on 200 g of silica gel, eluting with 5% EtOAc/hexane to afford 1.78 g (90%) of **30**. Recrystallization from ether provided an analytical sample. Mp: 115−117 °C; ^{1}H NMR ($CDCl_3$, TMS): δ 8.23 (s, 1H), 7.62 (s, 1H), 2.74 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 198.5, 149.8, 147.2, 145.9, 137.6, 132.8, 117.7, 113.7, 26.2, 7.8; IR: 2924, 1695, 1687, 1407, 1322, 1250 cm^{-1}. Anal. Calcd for $C_{10}H_8NClO_2$: C, 57.29; H, 3.85; N, 6.68. Found: C, 57.37; H, 3.90; N, 6.80.

5-(1-Acetyl)-7-chloro-2,3-dihydro-3-methylfuro[2,3-*c*]-pyridine (31). Following the procedure for the preparation of **30**, starting with 27.9 g (130 mmol) of **22**, there was synthesized 23.2 g (84%) of **31**. Mp: 88−89 °C; ^{1}H NMR ($CDCl_3$, TMS): δ 7.87 (s, 1H), 4.90 (t, *J* = 9.2 Hz, 1H), 4.31 (dd, *J* = 7.5, 9.1 Hz, 1H), 3.68 (m, 1H), 2.64 (s, 3H), 1.38 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 197.7, 156.0, 147.3, 143.6, 131.0, 117.6, 80.0, 36.8, 25.7, 18.8; IR 2926, 1686, 1587, 1476, 1290 cm^{-1}. Anal. Calcd for $C_{10}H_{10}NClO_2$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.76; H, 4.83; N, 6.63.

(−)-(*S*)-7-Chloro-5-(1-hydroxyethyl)-3-methylfuro[2,3-*c*]pyridine ((*S*)-20). To a suspension of **30** (1.64 g, 7.85 mmol) in 15 mL of THF at −30 °C was added a solution of (−)-chlorodiisopinocampheylborane [(−)-DipCl] (5.42 g, 16.90 mmol) in 15 mL of THF dropwise over a 22 min period. After 5 min, the reaction temperature was adjusted to −18 °C and the mixture was stirred at −18 °C for 4 h and at room temperature overnight. The reaction mixture was cooled to −18 °C, and a mixture of 14 mL of saturated $NaHCO_3$ and 4 mL of 30% H_2O_2 was added over a 30 min period. The mixture was stirred at room temperature for 1 h, diluted with EtOAc, and washed with 2 × 50 mL of saturated $NaHCO_3$ and 1 × 50 mL of saturated NaCl. The organics were dried with anhydrous Na_2SO_4 and concentrated to give 6.08 g of a golden oil. Chromatography on 140 g of silica gel (230−400 mesh), eluting with 25% EtOAc/hexane gave 1.56 g (94%) of (*S*)-**20** as a white solid [chiral HPLC of the prepared acetate of (*S*)-**20** as compared to that of the corresponding racemate shows the material to be 92% ee]. Recrystallization of 1.30 g of the chromatographed sample from ether/hexane afforded 1.02 g of white crystals (Chiral HPLC (0.46 × 25 cm (*R*,*R*) Whelk-O1; 0.5 mL/min; 50% 2-propanol in hexane (0.05% TEA); retention time (*S*)-isomer: 10.3 min, (*R*)-isomer: 14.6 min) of the corresponding acetate [optical rotation: $[\alpha]_D = -92.9°$ (*c* = 2.54, $CHCl_3$)] indicated >99% ee). Mp: 99−100 °C; $[\alpha]_D = -26.2°$ (*c* = 1.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS): δ 7.56 (s, 1H), 7.43 (s, 1H), 4.97 (q, *J* = 6.3 Hz, 1H), 3.37 (d, *J* = 5.2 Hz, 1H, OH), 2.23 (s, 3H), 1.54 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): 156.9, 147.0, 145.7, 138.2, 132.6, 116.5, 109.7, 69.6, 24.5, 7.9; IR 3262, 3178, 1617, 1588, 1558, 1459 cm^{-1}. Anal. Calcd for $C_{10}H_{10}NClO_2$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.57; H, 5.11; N, 6.61.

7-Chloro-2,3-dihydro-5-(1(*S*)-hydroxyethyl)-3-methylfuro[2,3-*c*]pyridine ((*S*)-22). Following the procedure for the preparation of (*S*)-**20**, starting with 7.2 g (34 mmol) of **31**, there was synthesized 7.2 g (99%) of (*S*)-**22**. ^{1}H NMR ($CDCl_3$, TMS): δ 7.09 (m, 1H), 4.78 (m, 2H), 4.18 (t, *J* = 8 Hz, 1H), 3.63 (m, 1H), 1.45 (d, *J* = 6.3 Hz, 3H), 1.34 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 156.7, 151.7, 144.5, 130.5, 114.5, 79.2, 69.2, 37.3, 24.2, 18.6; IR 3385, 2972, 1571 cm^{-1}. HRMS: Calcd for $C_{10}H_{12}ClNO_2$: 213.0556. Found: 213.0550.

(+)-(*R*)-5-(1-Chloroethyl)furo[2,3-*c*]pyridine (1). A solution of (*S*)-**18** (9.0 g, 55.2 mmol) in 35 mL of $CHCl_3$ under N_2 was treated with Ph_3P (28.9 g, 110.3 mmol) followed by CCl_4 (106 mL, 1.10 mol), and the reaction was stirred for 24 h at room temperature. The solution was diluted with 35 mL of hexane and stirred for 30 min, and the white precipitate was removed by filtration. The filter cake was washed with 100 mL of 20% Et_2O/hexane, and the filtrate was concentrated to a small volume (not to dryness). The residue was chromatographed over 350 g of silica gel (230−400 mesh), eluting with 15% EtOAc/hexane to afford 8.48 g (83%) of **1** as a low melting off-white solid. Chiral HPLC analysis (0.46 × 25 cm, Chiralcel OD-H, 0.5 mL/min; 2% 2-propanol in hexane; retention time (*R*)-isomer: 14.2 min, (*S*)-isomer: 12.9 min) indicated 97% ee. Mp: 36−38 °C; $[\alpha]_D = +73.0°$ ($c = 0.47$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS): δ 1.93 (d, $J = 6.8$ Hz, 3H), 5.28 (q, $J = 6.8$ Hz, 1H), 6.80 (m, 1H), 7.72 (m, 1H), 7.77 (d, $J = 2.1$ Hz, 1H), 8.83 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 25.5, 59.2, 106.3, 113.7, 132.9, 135.1, 149.0, 151.5, 153.7; IR 2928, 1610, 1466, 1304, 1193 cm^{-1}; MS: [*m*/*z*](relative intensity): [181](4), [146](100). Anal. Calcd for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.33; H, 4.41; N, 7.62.

(+)-(*R*)-5-(1-Chloroethyl)-3-methylfuro[2,3-*c*]pyridine (2). A solution of (*S*)-**21** (5.57 g, 31.4 mmol) and Ph_3P (16.5 g, 62.8 mmol) in 20 mL of $CHCl_3$ at 0 °C was treated with 60 mL of CCl_4 (0.628 mol), and the reaction was stirred at room temperature for 48 h. The mixture was diluted with 20 mL of hexane and filtered. The filtrate was concentrated in vacuo, and the material was chromatographed over 210 g of silica gel (230−400 mesh), eluting with 20% EtOAc/hexanes to give 5.45 g (89%) of **2**. Chiral HPLC analysis (0.46 × 25 cm, Chiralpak AD, 0.25 mL/min; 5% EtOH in hexane; retention time (*R*)-isomer: 22.0 min, (*S*)-isomer: 23.4 min) of a sample from a previous run, having an optical rotation of $[\alpha]_D = +68.4°$ ($c = 1.53$, $CHCl_3$), indicated >97% ee. Data for **2**: Optical rotation: $[\alpha]_D = +65.7°$ ($c = 0.49$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, TMS): δ 8.75 (m, 1H), 7.53 (m, 1H), 7.26 (s, 1H), 5.30 (q, $J = 6.8$ Hz, 1H), 2.25 (s, 3H), 1.94 (d, $J = 6.8$ Hz, 3H); IR 1463, 1313, 1193, 1089 cm^{-1}. Anal. Calcd for $C_{10}H_{10}ClNO$: C, 61.38; H, 5.12; N, 7.16. Found: C, 60.94; H, 5.04; N, 7.06.

(−)-(*S*)-6-Chloro-2-[[1-(furo[2,3-*c*]pyridin-5-yl)ethyl]thio]-4-pyrimidinamine (PNU-142721). A suspension of 60% NaH (3.5 g, 87.5 mmol, washed with 3 × 7 mL of hexane) in 75 mL of dry DMF under N_2 at 0 °C was treated portionwise with 4-amino-6-chloro-2-mercaptopyrimidine mesylate salt (**3**) (10.9 g, 42.3 mmol) and was stirred for 1 h at room temperature. The reaction mixture was treated dropwise with **1** (7.4 g, 40.6 mmol) in 1 × 20 mL of DMF (5 mL rinse) and the mixture was stirred for 5 days at room temperature. The mixture was poured into 400 mL of EtOAc, washed with 4 × 100 mL of 50% saturated NaCl, and was dried over anhydrous K_2CO_3/$MgSO_4$. The dried organics were concentrated in vacuo to an amber oil. The crude material was diluted with acetone/CH_2Cl_2 and was chromatographed over 450 g of silica gel (230−400 mesh), eluting with 45% EtOAc/hexane to give 11.05 g (89%) of **PNU-142721** as a white solid. Chiral HPLC analysis (0.46 × 25 cm, Chiralcel OD-H; 0.5 mL/min; 25% 2-propanol/hexanes; retention time (*S*)-isomer: 13.5 min, (*R*)-isomer: 12.1 min) indicated 97.6% ee. Recrystallization from EtOAc afforded 7.92 g (64%, 99% ee) of **PNU-142721**. Mp: 169−170.5 °C; $[\alpha]_D = -334°$ ($c = 0.68$, $CHCl_3$); ^{1}H NMR (DMSO-d_6): δ 1.70 (d, $J = 7$ Hz, 3H), 5.11 (q, $J = 6.9$ Hz, 1H), 6.15 (s, 1H), 7.00 (m, 1H), 7.30 (bs, 2H), 7.78 (d, $J = 1$ Hz, 1H), 8.20 (d, $J = 2.1$ Hz, 1H), 8.88 (s, 1H); IR 3458, 3114, 2925, 1637, 1572, 1529, 1465, 1282, 1116 cm^{-1}; MS: [*m*/*z*](relative intensity): [306](10), [273](69), [146](100). Anal. Calcd for $C_{13}H_{11}Cl\ N_4OS$: C, 50.90; H, 3.61; N, 18.26. Found: C, 51.16; H, 3.54; N, 18.11.

(−)-(*S*)-6-chloro-2-[[1-(3-methylfuro[2,3-*c*]pyridin-5-yl)-ethyl]thio]-4-pyrimidinamine (PNU-109886). A suspension of NaH (1.25 g, 0.0522 mol, 60% oil dispersion) in 80 mL of DMF at 16 °C was treated with 4-amino-6-chloro-2-mercaptopyrimidine mesylate salt (**3**) (6.71 g, 0.0261 mol), and the reaction mixture was stirred for 15 min. The cooling bath was removed, and the contents were stirred at room temperature for 1.5 h. A solution of **2** (4.86 g, 0.0249 mol) in 15 mL of DMF was added (plus a 10 mL rinse). The reaction mixture was allowed to stir at room temperature for 5 days. The contents were poured into ice−water and extracted two times with Et_2O. The combined organic fractions were dried with anhydrous Na_2SO_4 and concentrated at reduced pressure. Chromatography over 350 g of silica gel, eluting with EtOAc/hexane (2:3) and then (1:1), provided 6.55 g (82%) of **PNU-109886**. Recrystallization from methyl *tert*-butyl ether−methylene chloride−ethyl acetate afforded 4.83 g (61%) of analytical material. Chiral HPLC analysis (0.46 × 25 cm, Chiralcel OD-H; 0.5 mL/min; 25% 2-propanol/ hexanes; retention time (*S*)-isomer: 12.1 min, (*R*)-isomer: 16.8 min) indicated 98% ee. Mp: 156−157 °C; $[\alpha]_D = -270.3°$ ($c = 0.620$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.81 (s, 1H), 7.96 (s, 1H), 7.77 (s, 1H), 7.30 (brs, 2H), 6.15 (q, $J = 7.0$ Hz, 1H), 2.19 (s, 3H), 1.71 (d, $J = 7.0$ Hz, 3H); IR 2925, 1644, 1572, 1537, 1465, 829 cm^{-1}; MS: *m*/*z* (relative intensity %): M^+ 320 (9), 287 (75), 160 (100). Anal. Calcd for $C_{14}H_{13}ClN_4OS$: C, 52.42; H, 4.06; N, 17.47. Found: C, 52.41; H, 4.06; N, 17.31.

Supporting Information Available: Full experimental and spectroscopic data for **5**, **6**, **28**, **29**, (*S*)-**21** (from (*S*)-**20** and (*S*)-**22**), ^{1}H NMR for **11**, **18**, (*S*)-**21**, **23**, **26**, **27**, and ORTEP drawings and atomic coordinate information for **28**, **29**, and **PNU-109886** (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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