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An Efficient and Large-Scale Enantioselective Synthesis of PNP405: A Purine Nucleoside Phosphorylase Inhibitor

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An efficient and large-scale enantioselective synthesis of PNP405 (**1**), a purine nucleoside phosphorylase inhibitor, is described. This synthesis of **1** involved eight steps starting from *o*-fluorophenylacetic acid with a 21.6% overall yield and >99.5% enantiopurity. The key stereogenic center with (*R*)-configuration was created using Evans' asymmetric alkylation methodology. This synthesis also features the racemization-free reductive removal of the chiral auxiliary in **5** using sodium borohydride, protection of the γ-cyano alcohol **6** as the trityl ether by a new water-assisted tritylation with trityl chloride and triethylamine or with trityl alcohol and catalytic trifluoroacetic acid, and an efficient one-pot cyclo-guanidinylation of **10** using cyanamide as the guanidinylating agent.

2-Amino-7-[1-(2-fluorophenyl)-2-(*R*)-hydroxyethyl]-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (**1**; PNP405) is a purine nucleoside phosphorylase (PNP) inhibitor from a 9-deazaguanine structural class. As a potent, orally active PNP inhibitor, it is targeted as a therapy for transplant rejection and potentially for rheumatoid arthritis, autoimmune diseases, and T-cell-mediated inflammatory diseases.[1] Our goal was to develop an economical, efficient, and enantioselective synthesis of PNP405 (**1**) that was suitable for large scale preparation.

Asymmetric alkylation approach[1] using Evans' chiral auxiliary was considered suitable for large scale preparation to create the key stereogenic center with (*R*)-configuration that would also afford the primary alcohol functionality in **1** after reductive removal of the auxiliary. Recently, we developed a one-pot, convenient, and practical method for the N-acylation of 2-oxazolidinones directly with arylacetic acids in the presence of pivaloyl chloride and triethylamine at 80−85 °C in toluene.[2] This new method avoided the necessity of preparing and isolating the acid chloride. Thus, the N-acylation of (*R*)-4-phenyl-2-oxazolidinone (**3**) with *o*-fluorophenylacetic acid (**2**) under these conditions afforded **4** in >85% crude yield, which was recrystallized from *tert*-butyl methyl ether to obtain a 73% yield (Scheme 1). The asymmetric alkylation[3] of **4** with bromoacetonitrile in the presence of sodium bis(trimethylsilyl)amide at −78 °C initially proved problematic with variable diastereoselectivity, perhaps, due to the varying degree of epimerization during quenching of the reaction mixture. Additionally, low-temperature (−78 °C) conditions also presented equipment limitations. We found that the use of 0.97 equiv of commercial lithium bis(trimethylsilyl)amide in THF at −15 to −20 °C followed by a reverse quench of the reaction mixture yielded a highly reproducible diastereomeric ratio of 7:1, and the desired diastereoisomer **5** was obtained in 80% yield with >99% de by a recrystallization from *tert*-butyl methyl ether. Thus, an increase in the temperature of the recation from −78 to −20 °C led to only a slight loss (6%) in the yield of **5** but eliminated equipment limitations. The effect of the substituents in the chiral auxiliary on the diastereoselectivity during the asymmetric alkylation was studied using several auxiliaries. The (*R*)-4-benzyl- and (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinones gave poorer diastereoselectivity (5.3:1 and 3.7:1, respectively) and yield (56 and 52%, respectively, with >99% de). Such a low diastereoselectivity using (4*S*,5*R*)-4-methyl-5-phenyl-2-oxazolidinone was also recently reported[4] during the asymmetric alkylation of (4*S*,5*R*)-*N*-phenylacetyl-4-methyl-5-phenyl-2-oxazolidinone with bromoacetonitrile, affording a 3.9:1 diastereomeric mixture from which the required diastereomer was obtained in 60% yield. The (*R*)-4-isopropyl-2-oxazolidinone afforded the highest diastereoselectivity (13.4:1), but the product purification required a silica gel chromatography and afforded the desired diastereomer in the same yield (81% with >99% de) as with the 4-phenyl substituent. (*R*)-4-Phenyl-2-oxazolidinone (**3**) was used for the large scale preparation because it afforded crystalline intermediate **5** as well as because it is a cheap and commercially readily available chiral auxiliary.

Having developed the highly reproducible asymmetric alkylation conditions, we were ready to carry out the

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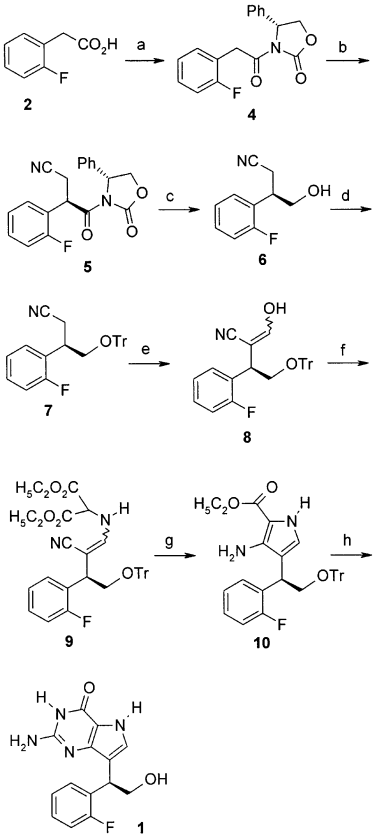
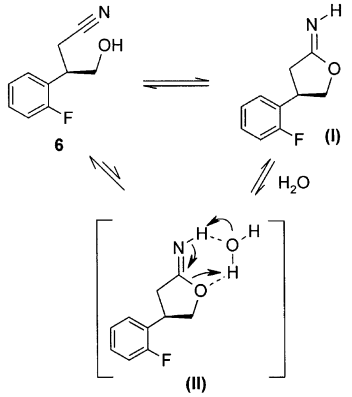
SCHEME 1[a]



[a] Reagents: (a) **3**, Me_3CCOCl, Et_3N, toluene, 80−85 °C (75%); (b) LiHMDS, $BrCH_2CN$, THF, −20 °C (80%); (c) $NaBH_4$, THF−H_2O, 23 °C (100%); (d) Ph_3CCl, Et_3N, toluene, water, 35 °C (66%) or Ph_3COH, TFA, toluene, reflux (73%); (e) LDA, $HCO_2C_2H_5$, THF, −10 °C (100%); (f) diethylaminomalonate hydrochloride, NaOAc, C_2H_5OH, 23 °C (100%); (g) C_2H_5ONa, C_2H_5OH (93%); (h) HCl, C_2H_5OH, 50% aq NH_2CN, aq NaOH (53%).

reductive removal of the chiral auxiliary in **5** to the γ-cyano alcohol **6** with $LiBH_4$. The reported conditions[5] using 1.1 equiv of $LiBH_4$ and 1.1 equiv of water at 0 °C in THF afforded **6** as an oil, but with significant racemization (6%). Further optimization of these conditions revealed that an increase in the rate of reaction by increasing the amount of $LiBH_4$ to 1.5 equiv led to a decrease in the racemization (2%). However, a scale-up of these conditions in the pilot plant led to 10% racemization. The racemization problem as well as the fact that $LiBH_4$ is an expensive and commercially nonreadily available reagent led us to develop an alternative method for this transformation. $LiAlH_4$ has been used in the literature[3] for similar reductions; however, it gave a complex mixture in the case of **5**, perhaps, due to the presence of the nitrile group. We then developed a new, economical, practical, and racemization-free method for the reductive removal of 2-oxazolidinones with inexpensive $NaBH_4$ in a mixture of THF and water at room temperature.[6] This new method afforded the desired γ-cyano alcohol **6** in quantitative yield with undetectable racemization (Scheme 1). The chiral auxiliary was recovered by a simple filtration, and it was also recycled satisfactorily. Although alcohol **6** could be purified by silica gel chromatography, we found that crude **6** could be used in the next step without purification.

SCHEME 2



The next step involved the protection of the primary alcohol **6**. Of a few protecting groups investigated, the trityl group was our choice for further development because the trityl ether **7** was a solid that could be recrystallized from either *tert*-butyl methyl ether or methanol and it was stable in subsequent steps utilizing basic conditions. These recrysallization conditions also efficiently removed any residual chiral auxiliary and the undesired (*S*)-enantiomer, produced by racemization (~10%) when $LiBH_4$ was used in the preceding step in the pilot plant, affording **7** with >99% ee. Surprisingly, the tritylation of **6** with trityl chloride in the presence of Et_3N in toluene was slow and could not be driven to completion, even upon addition of an excess of reagents, and the results varied from batch to batch. A Karl Fischer analysis of three different crude batches of **6** in toluene suggested that more water gave a better conversion. On the basis of these results, we postulated that tritylation of **6** was assisted by water. A highly reproducible process for the tritylation of **6** with trityl chloride (1.52 equiv) in the presence of Et_3N (2.01 equiv) in toluene at 35 °C for 70 h using water (0.55 equiv) as the catalyst was developed to afford **7** in 66% yield that also scaled-up well in the pilot plant. We hypothesized that, due to the presence of the nitrile group, under the basic conditions **6** may exist in equilibrium with the cyclic iminoether **I** (Scheme 2), which may be the reason for the inhibition of the tritylation. Water, perhaps, drives the equilibrium toward **6** by opening **I** back to γ-cyano alcohol **6** via the transition state **II**. Indirect evidence for the suppression of the tritylation by the participation of the nitrile group was obtained by the satisfactory tritylation of (±)-2-phenyl-1-propanol (lacking the nitrile group) without water. Water-assisted reactions have been reviewed recently,[7] and such a tritylation reaction is not reported therein. This new water-assisted tritylation of a γ-cyano alcohol is an interesting addition to the list of water-assisted reactions. Having recognized that the nitrile group may be suppressing the tritylation of **6** under basic conditions, we next studied the tritylation of **6** with trityl

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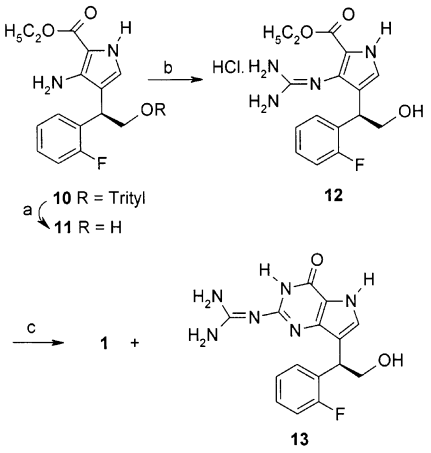
SCHEME 3[a]



[a] Reagents: (a) HCl, C_2H_5OH; (b) concd HCl, 50% aq H_2HCN, C_2H_5OH; (c) aq NaOH.

alcohol under acidic conditions. Thus, treatment of **6** with trityl alcohol (1.1 equiv) in the presence of catalytic amounts of trifluoroacetic acid in refluxing toluene for only 4 h afforded the desired intermdiate **7** in 73% yield. Thus, this method was more efficient than the water-assisted conditions.

Formylation of **7** with ethyl formate using LDA as a base in THF yielded **8** cleanly and in quantitative yield. The reaction of **8** with diethyl aminomalonate hydrochloride in ethanol in the presence of sodium acetate yielded the enamine **9** as a mixture of stereoisomers.[8−10] Some of the pyrrole **10** was also formed under these conditions as observed by HPLC. Treatment of crude **9** with sodium ethoxide in ethanol yielded the pyrrole **10** in high yield (93% overall from **7**). With pyrrole **10** in hand, we next turned our attention toward constructing the six-membered 2-aminopyrimidinone ring. We reasoned that a direct cyclo-guanidinylation approach using cheap and commercially readily available cyanamide[11] as the guanidinylating agent would provide an efficient method for this purpose. Thus, reaction of **10** with 50% aqueous cyanamide in ethanol in the presence of HCl followed by basification with NaOH yielded PNP405 (**1**) efficiently. Initially, the reaction of **10** with HCl led to the deprotection of the trityl group to give alcohol **11** (Scheme 3). The alcohol **11** then reacted with 50% aqueous cyanamide to afford acyclic guanidine **12**, which underwent cyclization with aqueous sodium hydroxide to afford crude **1** in 73% yield. An adjustment of the pH to 12 with aqueous NaOH was critical for the cyclization of **12**. The acyclic guanidine **12** can also be isolated in 85% yield. Attempts to purify the crude **1** by recrystallization from a mixture of methanol and water or ethanol and water not only gave poor recovery of **1** but also did not improve the purity. The major impurity, which was isolated by repetitive HPLC, was characterized as **13** (Scheme 3) on the basis of spectroscopic data. Having identified this impurity, we realized that **13** would be more basic than **1** and should be removed easily as the water-soluble salt at a pH at which **1** does not form the salt. Consequently, we developed conditions for the purification of **1** that involved the treatment of a solution of crude **1** in aqueous sodium hydroxide with acetic acid to adjust the pH to ~4.5. These conditions yielded pure **1** as a crystalline solid in 53% yield and >99% purity. Thus, an efficient one-pot process for the construction of the six-membered 2-aminopyrimidone ring by cyclo-guanidinylation of **10** with cyanamide was developed that also scaled-up well in the pilot plant. To ascertain the enantiomeric purity of **1**, an authentic sample of the (*S*)-enantiomer (*S*)-**1** was also synthesized. A chiral HPLC analysis indicated that the enantiomeric purity of **1** was >99.5%. Thus, an efficient and large-scale enantioselective synthesis of PNP405 (**1**) was developed that was a linear 8-step synthesis with an overall yield of 21.6% (Scheme 1).

In summary, an efficient and large-scale enantioselective synthesis of a purine nucleoside phosphorylase inhibitor, 2-amino-7-[1-(2-fluorophenyl)-2(*R*)-hydroxyethyl]-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (**1**; PNP405) is described. This synthesis of **1** involved eight steps starting from *o*-fluorophenylacetic acid with a 21.6% overall yield and >99.5% enantiopurity. The key stereogenic center with (*R*)-configuration was created using Evans' asymmetric alkylation methodology. This synthesis also features the racemization-free reductive removal of the chiral auxiliary in **5** using sodium borohydride, protection of the γ-cyano alcohol **6** as the trityl ether by a new water-assisted tritylation with trityl chloride and triethylamine or with trityl alcohol and catalytic trifluoroacetic acid, and an efficient one-pot cyclo-guanidinylation of **10** using cyanamide as the guanidinylating agent.

Experimental Section

The enantiopurity of **1** was determined using a Chiralcel OD-R column (4.6 × 250 mm) and a mixture of CH_3CN/0.05 M NH_4OAc buffer (20:80 v/v) as the mobile phase (isocratic at a flow rate of 0.5 mL/min and UV detector at 235 nm) at a column temperature at 40 °C. The retention times of PNP405 (**1**) and its enantiomer (*S*)-**1** were 18 and 16 min, respectively. The diastereomeric purity of **5** was determined using a Waters μ-Bondapak, C-18 column (4.5 × 250 mm) and a mixture of CH_3OH/H_2O (45:55 v/v) as the mobile phase (isocratic at a flow rate of 1.0 mL/min and a UV detector at 210 nm) at a column temperature at 40 °C. The retention times of **5** and its diastereomer (**5a**) were 11 and 14 min, respectively. The enantiopurity of **6** was determined using a Chiralcel OJ column (4.6 × 250 mm) and a mixture of hexane/C_2H_5OH/TFA (93:7:1 v/v/v) as the mobile phase (isocratic at a flow rate of 1 mL/min and UV detector at 260 nm). The retention times of **6** and its enantiomer **(*S*)-6** were 23 and 31 min, respectively. The enantiopurity of **7** was determined using a Chiralcel OD column (4.6 × 250 mm) and a mixture of hexane/2-propanol (95:5 v/v) as the mobile phase (isocratic at a flow rate of 1.0 mL/min and UV detector at 230 nm). The retention times of **7** and its enantiomer (*S*)-**7** were 9.5 and 18 min, respectively.

3-[2-(2-Fluorophenyl)-1-oxoethyl]-4-(*R*)-phenyl-2-oxazolidinone (4). A mixture of *o*-fluorophenylacetic acid (**2**, 107.7 g, 0.7 mol), (*R*)-4-phenyl-2-oxazolidinone (**3**, 100.0 g, 0.613 mol), Et_3N (186.0 g, 1.84 mol), and toluene (1.0 L) was heated to an internal temperature of 80 °C to afford a solution. To this solution was added pivaloyl chloride (88.5 g, 0.734 mol)

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over a period of 30 min with efficient stirring while an internal temperature 80−85 °C was maintained, and the mixture was stirred at this temperature for an additional 2 h. Additional pivaloyl chloride (44.1 g, 0.365 mol) was added over a period of 15 min while an internal temperature 80−85 °C was maintained, and the mixture was stirred at the same temperature for an additional 3 h. The mixture was cooled to an internal temperature of 40 °C, and prewarmed (40 °C) water (300 mL) was added in 2 min while an internal temperature of 40−45 °C was maintained (slightly exothermic reaction). The organic layer was separated and washed with a prewarmed (40 °C) 2.2 N solution of HCl (358 mL) and prewarmed (40 °C) water (100 mL) sequentially while an internal temperature of 40−45 °C was maintained. The organic layer was concentrated under reduced pressure to collect 940 mL of solvent to obtain 3-[2-(2-fluorophenyl)-1-oxoethyl]-4-(*R*)-phenyl-2-oxazolidinone (**4**) as a semisolid. The semisolid was suspended in *tert*-butyl methyl ether (400 mL), and the mixture was heated to reflux to obtain a yellow solution. The solution was cooled to 20−25 °C over a period of 20 min and stirred at this temperture for 4 h. The mixture was further cooled to 5−9 °C and stirred at this temperature for an additional 2 h. The solids were filtered and washed with precooled (5−9 °C) *tert*-butyl methyl ether (3 × 9 mL). The product was dried at 45−50 °C (86−99 mbar) for 12 h to obtain pure 3-[2-(2-fluorophenyl)-1-oxoethyl]-4-(*R*)-phenyl-2-oxazolidinone (**4**, 137.0 g, 75%) as a white solid: mp 110−111 °C; $[\alpha]_D$ −154.8 (c = 1, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (dd, 1H, J = 8.9, 3.8 Hz), 4.28 (dd, 2H, J = 9.3 Hz), 4.54 (t, 1H, J = 8.9 Hz), 5.34 (dd, 1H, J = 8.9, 3.8 Hz), 6.94−7.34 (m, 9H). ^{13}C NMR (300 MHz, DMSO-d_6) δ 169.3, 162.8, 159.5, 153.9, 138.9, 131.8, 129.4, 128.6, 126.2, 124.0, 121.0, 120.8, 115.3, 115.2, 72.3, 57.6, 36.1. Anal. Calcd for $C_{17}H_{14}FNO_3$: C, 68.2; H, 4.68; N, 4.68; F, 6.35. Found: C, 68.33; H, 4.61; N, 4.70; F, 6.55.

***β*-(*R*)-(2-Fluorophenyl)-γ,2-dioxo-4-(*R*)-phenyl-3-oxazolidinebutyronitrile (5).** A solution of 3-[2-(2-fluorophenyl)-1-oxoethyl]-4-(*R*)-phenyl-2-oxazolidinone (**4**, 546.0 g, 1.824 mol) in dry THF (2.18 L) was cooled to an internal temperature of −5 to −8 °C. A solution of lithium bis(trimethylsilyl)amide (1 M in THF, 1.773 L, 1.773 mol) was added over a period of 55 min while an internal temperature of 0 to −5 °C was maintained. The solution was stirred at an internal temperature of 0 to −5 °C for 1 h and then cooled to an internal temperature of −20 °C. To the resulting mixture was added bromoacetonitrile (258.3 g, 2.153 mol) over a period of 40 min while an internal temperature of −15 to −20 °C was maintained. The reaction mixture was stirred at this temperature for 4.5 h and was added to a precooled (0−5 °C) solution of NaCl (478.0 g) in water (2.164 L) and concentrated HCl (214.0 g) over a period of 20 min while the internal temperature was maintained below 9 °C. After addition of THF (500 mL) as a rinse, the slurry was stirred for 15 min at an internal temperature of 5−8 °C and then warmed to room temperature over a period of 30 min. The organic layer was separated, washed with a solution of NaCl (632.0 g) in water (2.180 L), and concentrated under reduced pressure to a final volume of 1.4−1.6 L. To the mixture was added *tert*-butyl methyl ether (2.5 L), and the slurry was vigorously stirred for 1 h at room temperature. The solid was filtered, washed with *tert*-butyl methyl ether (2 × 150 mL), and dried at 45−50 °C (86−95 mbar) for 20 h to obtain *β*-(*R*)-(2-fluorophenyl)-γ,2-dioxo-4-(*R*)-phenyl-3-oxazolidinebutyronitrile (**5**, 480.0 g, 80%) as an off-white crystalline solid: mp 182−3 °C; de >99.0%; $[\alpha]_D$ −234.13 (c = 1, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.0−3.04 (m, 2H), 4.17 (dd, 1H, J = 8.5, 3.3 Hz), 4.69 (t, 1H, J = 8.5 Hz), 5.50 (t, 1H, J = 6.6 Hz), 5.57 (dd, 1H, J = 8.5, 3.3 Hz), 7.20−7.39 (m, 9H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 169.5, 161.7, 158.5, 152.8, 139.3, 130.2, 129.1, 128.8, 128.1, 125.8, 124.7, 123.4, 123.2, 118.3, 115.8, 115.5, 70.5, 57.5, 20.5. Anal. Calcd for $C_{19}H_{15}FN_2O_3$: C, 67.35; H, 4.43; F, 5.61; N, 8.27. Found: C, 67.23, H, 4.31; F, 5.56; N, 8.23.

Chromatography of the mother liquor furnished the diastereomer *β*-(*S*)-(2-fluorophenyl)-γ,2-dioxo-4-(*R*)-phenyl-3-oxazolidinebutyronitrile (**5a**): mp 138−140 °C; $[\alpha]_D$ +118.85 (c = 1, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.96−3.04 (m, 2H), 4.13 (dd, 1H, J = 8.8, 4.6 Hz), 4.76 (t, 1H, J = 8.8 Hz), 5.42 (t, 1H, J = 6.6 Hz), 5.56 (dd, 1H, J = 8.8, 4.6 Hz), 6.74 (t, 1H, J = 6.2 Hz), 7.07−7.40 (m, 8H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 169.4, 161.8, 158.6, 152.8, 138.9, 130.2, 128.7, 128.2, 126.2, 125.7, 124.4, 123.3, 123.1, 118.5, 115.9, 115.6, 70.1, 57.2, 20.1. Anal. Calcd for $C_{19}H_{15}FN_2O_3$: C, 67.35; H, 4.43; F, 5.61; N, 8.27. Found: C, 67.51, H, 4.34; F, 5.76; N, 8.24.

2-Fluoro-(*β*-(*R*)-hydroxymethyl)benzenepropionitrile (6). To a slurry of *β*-(*R*)-(2-fluorophenyl)-γ,2-dioxo-4-(*R*)-phenyl-3-oxazolidinebutyronitrile (**5**, 60.0 g, 0.177 mol) in THF (540 mL) was added a freshly prepared solution of $NaBH_4$ (27.0 g, 0.714 mol) in water (170 mL) over a period of 45 min while an internal temperature 20−25 °C was maintained. The reaction mixture was stirred at 20−25 °C for 1 h. A solution of NaCl (40.0 g) in 2 N HCl (400 mL) was added over a period of 45 min while an internal temperature of 20−25 °C was maintained. The top organic layer was separated, and the aqueous layer was extracted with toluene (175 mL). The combined organic layers were washed with brine (175 mL), filtered, and concentrated (to collect 580 mL of solvent) under reduced pressure. To the residue was added toluene (100 mL), and the mixture was concentrated under reduced pressure to a volume of about 110 mL. The mixture was cooled to 0−5 °C and stirred for 1−2 h. The solid (chiral auxiliary **3**) was filtered and washed with cold (∼5 °C) toluene (3 × 25 mL). The filtrate was concentrated to dryness under reduced pressure to obtain crude 2-fluoro-(*β*-(*R*)-hydroxymethyl)benzenepropionitrile (**6**, 31.8 g, 100%), which was stored below 0 °C and used for the next step as is: oil; ee >99%; $[\alpha]_D$ −37.6 (c = 1, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.66−2.86 (m, 2H), 3.08−3.15 (m, 1H), 3.45−3.58 (m, 1H), 3.70−3.78 (m, 2H), 7.01−7.26 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.3, 159.1, 129.4, 128.7, 124.6, 118.6, 115.9, 63.5, 37.9, 19.3. Anal. Calcd for $C_{10}H_{10}FNO$: C, 66.9; H, 5.5; N, 7.8. Found: C, 66.8; H, 5.56; N, 7.72.

2-Fluoro-*β*-(*R*)-[(triphenylmethyl)oxy]benzenepropionitrile (7). Method A. To a solution of 2-fluoro-(*β*-(*R*)-hydroxymethyl)benzenepropionitrile (**6**, 59.5 g, 0.332 mol) in toluene (500 mL) was added triphenylmethyl chloride (117.65 g, 0.442 mol), and the mixture was stirred at 20−22 °C for 10 min to afford a brown solution. To this solution was added Et_3N (60.0 g, 0.593 mol) rapidly over a period of 10 min while an internal temperature of <30 °C was maintained. The reaction mixture was stirred at an internal temperature of 35 °C for 4 h to obtain a light-brown suspension. Water (1.1 g, 0.061 mol) was added, and the stirring was continued at the same temperature for an additional 20 h. Additional triphenylmethyl chloride (19.0 g, 0.068 mol), Et_3N (7.7 g, 0.076 mol), and water (1.1 g, 0.061 mol) were added. The resulting suspension was stirred for an additional 24 h, additional water (1.1 g, 0.061 mol) was added, and the stirring was continued at 35 °C for an additional 22 h (or until starting material is <10%). The mixture was cooled to room temperature, and methanol (64 mL) was added dropwise over 10 min while an internal temperature of 30−35 °C was maintained. The reaction mixture was stirred for 40 min at an internal temperature of 20−25 °C. The mixture was concentrated under reduced pressure to obtain a red semisolid. The semisolid was suspended in methanol (880 mL). The slurry was stirred at an internal temperature of 50 °C for 1 h and then at 20−22 °C for 30 min. The solid was filtered, washed with methanol (3 × 40 mL), and dried at 45−50 °C (30 mbar) for 4 h or to a constant weight to afford 2-fluoro-*β*-(*R*)-[(triphenylmethyl)oxy]-benzenepropionitrile (**7**, 93.0 g, 66%): mp 145−8 °C; ee >99%; $[\alpha]_D$ −21.93 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65−2.68 (m, 2H), 3.35−3.52 (m, 3H), 6.69−7.37 (m, 19H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.3, 159.1, 143.8, 129.3, 129.1, 128.8, 128.7, 128.5, 127.9, 127.6, 127.3, 127.1, 126.0, 125.9, 125.7, 124.4, 124.3, 118.2, 115.8, 115.5, 87.0, 64.7, 36.4, 19.7. Anal.

Calcd for $C_{29}H_{24}FNO$: C, 82.6; H, 5.6; N, 3.3; F, 4.5. Found: C, 82.4; H, 5.7; N, 3.32; F, 4.55.

Method B. A solution of 2-fluoro-(*β*-(*R*)-hydroxymethyl)-benzenepropionitrile (**6**, 21.2 g, 118.24 mmol) and triphenylmethanol (33.9 g, 130.2 mmol) in toluene (206 mL) was stirred at 20−22 °C for 10 min to obtain a hazy yellow solution. To the resulting solution was added trifluoroacetic acid (0.674 g, 5.91 mmol) dropwise in 5 min. The mixture was heated to an internal temperature of 111−113 °C to achieve a gentle reflux, and refluxing was continued for 4 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to obtain a semisolid. The semisolid was suspended in methanol (300 mL) and heated to an internal temperature of 60−65 °C. The slurry was stirred at 60−65 °C for 1 h, cooled to 20−22 °C, and stirred at this temperature for an additional 1 h. The solid was filtered, washed with methanol (3 × 30 mL), and dried at 45−50 °C (30 mbar) for 4 h or to a constant weight to afford 2-fluoro-*β*-(*R*)-[(triphenylmethyl)oxy]benzenepropionitrile (**7**, 36.0 g, 73%).

2-Fluoro-α-(hydroxymethylidenyl)-*β*-(*R*)-[(triphenylmethoxy)methyl]benzenepropionitrile (8). A mixture of 2-fluoro-*β*-(*R*)-[(triphenylmethyl)oxy]benzenepropionitrile (**7**, 59.81 g, 0.142 mol) and anhydrous THF (300 mL) was stirred at 20−25 °C under nitrogen for 15 min. The yellowish solution was cooled to −10 °C (internal temperature), and a 2.0 M solution of LDA (78.0 mL, 0.156 mol) in heptane/THF was added over a period of 20 min while an internal temperature −10 to −5 °C was maintained. The mixture was stirred at −10 to −5 °C for 15 min, and ethyl formate (26.6 g, 0.359 mol) was added over a period of 20 min while an internal temperature −10 to −5 °C was maintained. The reaction mixture was stirred at −10 to −5 °C for 30 min, and to it was added to a solution of glacial acetic acid (15 mL) and 20% NaCl solution (300 mL) over a period of 20 min while an internal temperature of 0−5 °C was maintained. After the mixture was stirred at 0−5 °C for 15 min, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (150 mL). The combined organic layers were washed with saturated $NaHCO_3$ (300 mL, the pH of the aqueous layer after the wash should be 8−10) and then with brine (300 mL). The organic solution was dried and concentrated to dryness under reduced pressure to obtain crude 2-fluoro-α-(hydroxymethylidenyl)-*β*-(*R*)-[(triphenylmethoxy)methyl]benzenepropionitrile (**8**, 0.142 mole) as an oil, which was used in the next step without purification (the product was unstable and should be stored at 0−4 °C).

2-Fluoro-α-[[[di(ethoxycarbonyl)methyl]amino]-methylidenyl]-*β*-(*R*)-[(triphenylmethyoxy)methyl]benzenepropionitrile (9). A mixture of sodium acetate (34.92 g, 0.426 mol), diethyl aminomalonate hydrochloride (60.06 g, 0.284 mol), and anhydrous 2B ethanol (150 mL) was stirred at 20 to 25 °C for 20 min. A solution of crude 2-fluoro-α-(hydroxymethylidenyl)-*β*-(*R*)-[(triphenylmethoxy)methyl]-benzenepropioni-trile (**8**, 0.142 mol) in anhydrous 2B ethanol (150 mL) was added at 20−25 °C over a period of 20 min. The mixture was stirred at 20−25 °C for 72 h. Ethyl acetate (240 mL) and water (300 mL) were then added, and the mixture was stirred at 20−25 °C for 20 min. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (120 mL). The combined organic layers were washed with saturated $NaHCO_3$ (240 mL) and brine (240 mL) and concentrated to dryness under reduced pressure. To the residue was added toluene (150 mL), and the mixture was stirred at 20−25 °C for 20 min and concentrated to dryness under reduced pressure. This treatment was repeated two additional times with 150 mL of toluene each time to obtain crude 2-fluoro-α-[[[di(ethoxycarbonyl)methyl]amino]-methylidenyl]-*β*-(*R*)-[(triphenylmethyoxy)methyl]benzenepropionitrile (**9**, 0.142 mol) as an oil, which was used in the next step without purification.

3-Amino-4-[1-(2-fluorophenyl)-2-(*R*)-[(triphenylmethoxy)ethyl-2-1*H*-pyrrole-2-carboxylate (10). A mixture of crude 2-fluoro-α-[[[di(ethoxycarbonyl)methyl]amino]-methylidenyl]-*β*-(*R*)-[(triphenylmethyoxy)methyl]benzenepropionitrile (**9**, 0.142 mol) and anhydrous 2B ethanol (240 mL) was stirred for 20 min and cooled to 10 ± 5 °C. A 21% sodium ethoxide solution (80 mL, 0.214 mol) in ethanol was added over a period of 20 min while an internal temperature at 10−20 °C was maintained. The mixture was stirred at 20−25 °C overnight (14 h). The reaction mixture was cooled to −5 to 0 °C, and acetic acid (20 mL) was added at −5 to 0 °C over a period of 15 min. After the mixture was stirred for 20 min, ethyl acetate (300 mL) and 20% NaCl (400 mL) were added (pH of the aqueous layer should be 4−6), and the mixture was stirred for 20 min at the same temperature. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (120 mL). The combined organic layers were washed with saturated $NaHCO_3$ (300 mL) and then with brine (300 mL). The organic layer was filtered and concentrated to dryness under reduced pressure. Anhydrous 3A ethanol (150 mL) was added, and the mixture was stirred for 20 min. The mixture was concentrated to dryness under reduced pressure. This treatment was repeated two additional times with 150 mL of anhydrous 3A ethanol each time. The residue was then dissolved in anhydrous 3A ethanol (180 mL). The resulting solution was added to precooled (0−5 °C) water (600 mL) over a period of 30 min while an internal temperature at 0−5 °C was maintained. The mixture was stirred at 5 ± 5 °C for 1 h, and brine (200 mL) was added. Stirring was continued for an additional 1 h at 5 ± 5 °C. The solid was filtered, washed with water (2 × 100 mL), and dried at room temperature (22−25 °C) under reduced pressure (30 mbar) for 48 h to obtain ethyl 3-amino-4-[1-(2-fluorophenyl)-2-(*R*)-[(triphenylmethoxy)ethyl-2-1*H*-pyrrole-2-carboxylate (**10**, 70.49 g, 93%) as a brown powder: mp 59−62 °C; $[\alpha]_D$ −10.73 (c = 1, CH_3OH); ^{1}H NMR (300 MHz, $DMSOd_6$) δ 1.22 (t, 3H, J = 7.2 Hz), 3.44 (d, 2H, J = 5.8 Hz), 4.18 (q, 2H, J = 7.0 Hz), 4.55 (t, 1H, J = 6.0 Hz), 4.77 (bs, 2H), 6.56 (s, 1H), 7.20−7.29 (m, 19H), 10.66 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.7, 159.5, 144.0, 130.1, 128.7, 128.5, 128.4, 128.3, 127.9, 127.1, 124.3, 124.2, 115.5, 115.2, 86.8, 66.1, 59.6, 34.8, 14.8. Anal. Calcd for $C_{34}H_{31}FN_2O_3$: C, 76.3; H, 5.7; N, 5.2; F, 3.6. Found: C, 76.23; H, 5.96; N, 5.01; F, 3.6.

2-Amino-7-[1-(2-fluorophenyl)-2-(*R*)-hydroxyethyl]-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (1). A mixture of ethyl 3-amino-4-[1-(2-fluorophenyl)-2-(*R*)-[(triphenylmethoxy)-ethyl-2-1*H*-pyrrole-2-carboxylate (**10**, 69.8 g, 0.131 mol) and anhydrous 2B ethanol (300 mL) was stirred at 20−25 °C for 20 min. Concentrated HCl (54 mL) was added at 20−40 °C over a period of 15 min. The mixture was heated to an internal temperature of 40−45 °C and stirred at 40−45 °C for 16 h. The mixture was cooled to 0−5 °C and filtered. The filter cake was washed with 2B ethanol (2 × 50 mL). The filtrate was heated to an internal temperature of 40−45 °C, and a total of 100 mL of 50% (w/w) aqueous solution of cyanamide (1.31 mol) was added in five 20 mL portions at 2 h intervals. The pH was checked after each addition; if the pH was above 2, concentrated HCl (5 mL) was added. The reaction mixture was cooled to 0−5 °C 2 h after the last addition of cyanamide, and 50% (w/w) aqueous NaOH (45 mL) was then added (to adjust the pH to 12) at a rate to maintain the internal temperature below 15 °C. The mixture was cooled to 0−5 °C and stirred at 0−5 °C for 2 h. Concentrated HCl (45 mL) was added (to adjust pH to 2) at a rate to maintain the internal temperature at 5−10 °C. The mixture was concentrated under reduced pressure until the batch volume was about 350 mL. To the residue was added water (200 mL), and the mixture was stirred at 20−25 °C for 20 min. Ethyl acetate (150 mL) was added, and the mixture was again stirred for 20 min. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (100 mL). The aqueous layer was saved. The combined organic layers were washed with 0.1 N HCl (2 × 90 mL). All the aqueous layers were combined and cooled to an internal temperature of 0−5 °C, and 50% (w/w) aqueous NaOH (15 mL) was added (to adjust the pH to 8−9) at a rate to maintain the

internal temperature at 0−15 °C with vigorous agitation. The mixture was stirred at 0−5 °C for 2 h and then at room temperature for 16 h. The solid was filtered, washed with water (2 × 100 mL), and dried at 50 °C (20−45 mbar) for 16 h to afford crude 2-amino-7-[1-(2-fluorophenyl)-2-(*R*)-hydroxyethyl]-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (**1**, 25.7 g, 73%).

A mixture of crude 2-amino-7-[1-(2-fluorophenyl)-2-(*R*)-hydroxyethyl]-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (**1**, 25.7 g) and 1.0 N NaOH (98 mL) was heated to an internal temperature of 40−45 °C and stirred for 30 min to obtain a clear brown solution. Charcoal (1.29 g) was added, and the mixture was stirred at 40−45 °C for 20 min. The mixture was filtered through a pad of Celite (3.0 g). The filter cake was washed with water (20 mL). To the filtrate was added 2B ethanol (120 mL), and the resulting solution was heated to an internal temperature of 35−40 °C. Glacial acetic acid (10.2 mL) was added dropwise at 35−45 °C over 20 min with moderate agitation. The mixture was stirred at 40−45 °C for 2 h, cooled to 20−25 °C over a period of 30 min, and stirred at the same temperature for 4 h. The solid was filtered and washed with 50% aqueous 2B ethanol (2 × 40 mL). The wet cake was suspended in water (150 mL) and stirred for 4 h. The solid was filtered, washed with water (2 × 30 mL), and dried at 50 °C (25−40 mbar) for 16 h to obtain pure 2-amino-7-[1-(2-fluorophenyl)-2-(*R*)-hydroxyethyl]-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (**1**, 20.15 g, 53.5%): mp 267−269 °C; ee >99.5%; $[\alpha]_D$ +34.74 (*c* = 1, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.99 (m, 2H), 4.56 (m, 1H), 5.32 (bs, 1H), 6.10 (bs, 2H), 7.01−7.36 (m, 5H), 10.82 (bs, 1H), 11.47 (bs, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 162.1, 158.9, 154.7, 150.7, 145.1, 130.4, 127.9, 126.2, 124.2, 115.3, 115.0, 112.7, 65.6, 37.4. Anal. Calcd for $C_{14}H_{13}FN_4O_2$: C, 58.25; H, 4.5; F, 6.5; N, 19.4. Found: C, 58.36, H, 4.39; F, 6.63; N, 19.45.

2-Amino-7-[1-(2-fluorophenyl)-2-(*S*)-hydroxyethyl]-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one ((*S*)-1). Prepared from **5a** using the same procedures as described above for **1**. (*S*)-**1**: mp 265−268 °C; ee >99.5%; $[\alpha]_D$ −35.0 (*c* = 1, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.99 (m, 2H), 4.56 (m, 1H), 5.32 (bs, 1H), 6.10 (bs, 2H), 7.01−7.36 (m, 5H), 10.82 (bs, 1H), 11.47 (bs, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 162.1, 158.9, 154.7, 150.7, 145.1, 130.4, 127.9, 126.2, 124.2, 115.3, 115.0, 112.7, 65.6, 37.4. Anal. Calcd for $C_{14}H_{13}FN_4O_2$: C, 58.25; H, 4.5; F, 6.5; N, 19.4. Found: C, 58.42, H, 4.42; F, 6.91; N, 19.11.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **1**, (*S*)-**1a**, **4**−**7**, **5a**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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