Efficient synthesis of the optically active dihydropyrimidinone of a potent α_{1A}-selective adrenoceptor antagonist

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Abstract: The convergent synthesis of a potent α_{1A}-selective adrenoceptor antagonist is described. Salient features of the synthesis include the enzymatic resolution of a racemic dihydropyrimidinone and the use of a palladium coupling reaction in the synthesis of 2,4′-dipyridyl.

Key words: dihydropyrimidinone, enzymatic resolution, palladium coupling.

Résumé : Voici la description de la synthèse convergente d'un puissant antagoniste α_{1A}-sélectif au récepteur adrénergique (adrénorécepteur). Les principales caractéristiques de cette synthèse incluent notamment la résolution enzymatique d'un dihydropyrimidinone racémique et l'utilisation d'une réaction de couplage catalysée par le palladium dans la synthèse du 2,4′-dipyridyle.

Mots clés : dihydropyrimidinone, résolution enzymatique, couplage par le palladium.

[Traduit par la Rédaction]

Introduction

Benign prostatic hyperplasia (BPH) is a common condition afflicting men over the age of 40, with symptoms characterized by urinary obstruction resulting from enlargement of the prostate gland and increased noradrenergic tone in the hyperplastic prostate. Currently, transurethral prostatectomies are the second most common operation performed on males over the age of 65. To avoid surgery, pharmacological approaches are increasingly becoming the first option in treatment (1). Current treatment options include treatment with a 5-α reductase inhibitor, such as finasteride, for relief of symptoms through inhibition of the transformation of testosterone to dihydrotestosterone which results in reduction of prostatic mass (1*f*). The prostate is innervated with adrenergic nerves, which determine smooth muscle tone. The α_1 adrenoceptor has been identified as a target to alleviate the symptoms of BPH through decreasing the adrenergic tone of smooth muscle in the prostate (2). Three subtypes for the α_1 adrenoceptors have been identified (α_{1A}, α_{1B}, and α_{1D}). Selective antagonists for the α_{1A} receptor are expected to be more efficacious and to exhibit fewer side effects (3). The nonselective antagonists terazosin and doxazosin, and more recently tamsulosin, a subtype (α_{1A}/α_{1D})-selective antagonist, are currently in use.

Recently, Merck and Synaptic (4) reported candidate **1** as a new, potent, and selective α_{1A}-adrenoceptor antagonist. The dihydropyrimidinone moiety of **1** is a particularly interesting pharmacophore (3*a*, 5) in that this heterocycle has shown activity in a number of medicinal applications. Here we describe our work on the development of a highly efficient synthesis of the enantiomerically pure form of clinical candidate **1**. Retrosynthetically, the logical approach to **1** would involve the formation of a urea linkage (4,5) between the two penultimate building blocks **2** and **3** (Scheme 1). The preparations of non-racemic dihydropyrimidinone **2** and amine side chain **3**, as well as the formation of the urea linkage, and isolation of a crystalline form of the drug are also described.

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Dedicated to Professor J. Bryan Jones on the occasion of his 65th birthday.

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Results and discussion

Typically, dihydropyrimidinones are constructed through variations of the Biginelli reaction (6). This reaction is a three-component coupling of an aromatic aldehyde, urea, and an acetoacetate to afford the heterocycle in generally moderate yields. The Biginelli reaction has been used in one form or another for over a century using Bronsted acids in protic media (7). In the last decade a number of improvements have been reported for this reaction using polyphosphate esters (8*a*, 8*i*), microwave-assisted synthesis (8*b*, 8*c*),

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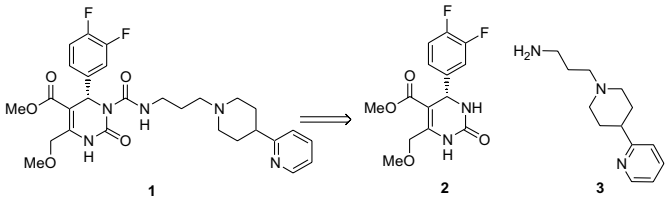
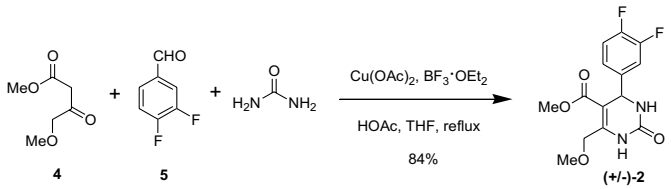
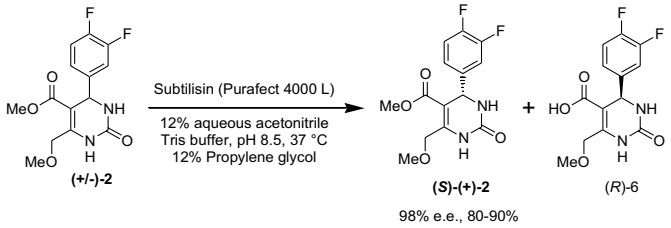
Scheme 1.



Scheme 2.



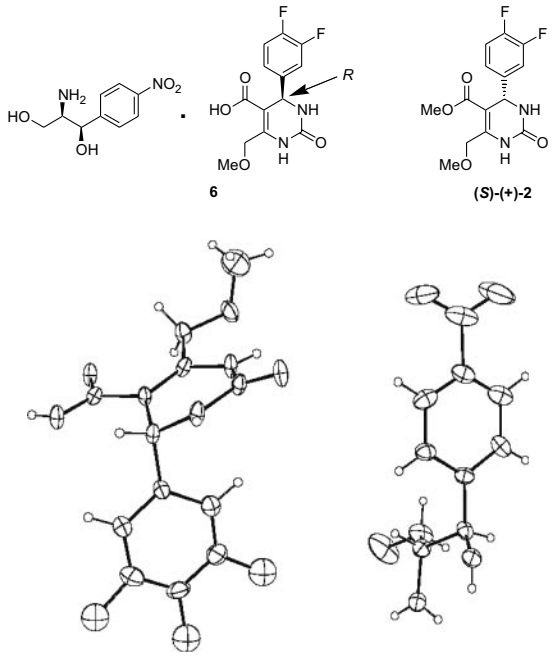
Scheme 3.



solid-phase synthesis (8*d*, 8*e*), solid-acid catalysis (8*f*), and fluorous synthesis (8*g*, 8*h*). A major improvement in the traditional Biginelli protocol was recently reported by us through the application of a Lewis acid catalysis which afforded much improved yields (9*a*). A combination of boron trifluoride etherate with a catalytic amount of acetic acid and a metal salt in THF has vastly improved the reaction. Metal salts such as $Cu(OAc)_2$, CuCl, $CuCl_2$, Cu_2O, $NiBr_2$, and $Pd(OAc)_2$ can be used equally well in this reaction. Alternative Lewis acids, such as $Ln(OTf)_3$ (9*b*), $FeCl_3$ (9*c*), or $InCl_3$ (9*d*) have also been reported for this three-component condensation. We determined that 1.7 equivalents of $BF_3{\cdot}Et_2O$ in combination with 10 mol% acetic acid and 10 mol% $Cu(OAc)_2$ gave the best overall results for this reaction. Heating a mixture of methyl 4-methoxyacetoacetate (**4**), 3,4-difluorobenzaldehyde (**5**), and urea with the acid mixture in THF afforded an 84% isolated yield of the desired dihydropyrimidinone (±)-**2** (Scheme 2).

The only preparation of an optically pure dihydropyrimidinone through an asymmetric variant of the Biginelli reaction was reported by Overman and co-workers (10). Our attempts at diastereoselective Biginelli reactions through cyclization of chiral ester derivatives of methoxyacetoacetate afforded only modest diastereoselectivity. A brief investigation of chiral ligands used in conjunction with the Lewis acid mixture of the boron–copper-mediated Biginelli reaction afforded no enantioselectivity. Most reports on the preparation of non-racemic dihydropyrimidinones have employed either classical resolution through diastereomeric salt crystallization (11) or chiral HPLC separation (12). For our needs, the former would require hydrolysis of the ester to the acid, resolution, and re-esterification, reducing the overall efficiency of the process, and the latter would not be amenable to large-scale preparation.

Fig. 1. Crystal structure of dihydropyrimidinone·D-*threo*-2-amino-1-(4-nitrophenyl)-1,3-propanediol salt (**6**).



A more effective approach for the resolution of **2** would be an enzymatic hydrolysis of the unwanted methyl ester to the acid, allowing easy separation of the enantiomers (Scheme 3) (13). A number of esterases, lipases, and proteases were screened for this reaction. Interestingly, none of the esterases or lipases tested were successful for this procedure (14). The protease enzyme Proteinase K (Sigma), however, gave excellent selectivity for conversion of the undesired methyl ester to the acid. Unfortunately, this enzyme is not widely available and is quite expensive to use in a bulk process. The search for a less expensive, commercially available protease led to the discovery of Subtilisin (Genencor Purafect 4000L) as a highly effective biocatalyst for the resolution of **2** to the desired (+)-methyl ester of the dihydropyrimidinone.

At the time of this work, only the rotation of the desired ester was known, since this material was previously resolved by chiral HPLC (4). Upon successful hydrolysis of the (–)-methyl ester to the free acid, we were able to evaluate the absolute configuration of the 6-aryl moiety. The acid was recovered from the aqueous phase of the resolution after workup, which was then crystallized from ethanol as a D-*threo*-2-amino-1-(4-nitrophenyl)-1,3-propanediol salt **6**. A crystal structure was obtained and the absolute stereochemistry of the 6-position of the acid was assigned as *R* relative to the stereocenters of the amine (Table 1).

By inference we could assign the desired enantiomer of **2** as the (*S*)-(+)-isomer (Fig. 1).

The optimization of the resolution procedure provided the desired (S)-(+)-methyl ester in 40–45% yield or 80–90% of the available enantiomer. The reaction was run with an enzyme loading of 40–50 wt% at ~6 g L^{-1} in a medium of 12% acetonitrile. Acetonitrile was needed to solubilize the ester. Without the co-solvent the reaction was very sluggish

Table 1. Summary of crystal data for **6**.

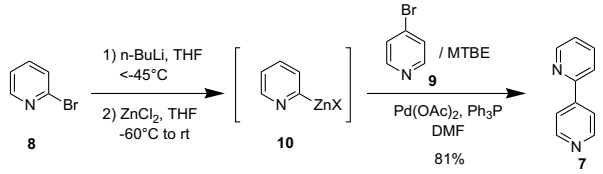
Formula	$C_{23}H_{28}F_2N_4O_9$	Diffractometer	Rigaku AFC5
Fw	542.498	Reflections measured	5888
Crystal colour	Colorless	Data Octants	
Crystal dimen. (mm)	0.08 × 0.33 × 0.35	Scan type	ω–2θ
Lattice symmetry	Orthorhombic	Resolution (Å)	0.80
Space group	$P2_12_12_1$	Unique reflections	5888
a (Å)	18.148(3)	Absorp. corr.	none
b (Å)	22.282(4)	Reflections used	5888
c (Å)	13.372(2)	Refl. obsd. criterion	$>2\sigma(I)$
α (°)	90	Obsd. Reflections	2725
β (°)	90	Variables	648
γ (°)	90	Refined on	F^2
V (Å^3)	5407(3)	*R*	0.105
Z	8	R_w	0.293
$D_{calcd.}$ (Mg m^{-3})	1.328	*S*	0.97
Radiation	Kα Cu	Residual peak (e Å^{-3})	0.8(1)
Wavelength (Å)	1.541838	Computer programs:	
Temperature (K)	294	Solution	SHELXS-86
μ (mm^{-1})	0.96	Refinement	SHELXL-97

(>15 days reaction time); however, as the concentration of acetonitrile was increased to >20%, the enzyme was deactivated. Subtilisin was purchased as a solution containing propylene glycol as a stabilizer. By adjusting the concentration of the glycol to 12% an increased stability in reaction solution was obtained, but as the volume percent was increased to >15%, the additive slowed the rate significantly. The system was buffered at pH 8.5 using a Tris buffer and the reaction required 10–12 days at 37°C to complete. The reaction was stopped once the ee of the unhydrolyzed ester reached 98%. During the course of the reaction the pH of the mixture dropped due to the liberation of acid; therefore, aqueous sodium hydroxide was added to maintain the pH. Interestingly, during the course of the enzymatic resolution very little of the desired (+)-methyl ester was hydrolyzed by the enzyme. There was, however, a small amount of background chemical hydrolysis leading to a slight loss in yield. Upon reaching 98% ee, the reaction was worked up by adding toluene and extracting the methyl ester into the organic phase. The undesired free acid remained in the aqueous phase. The toluene was concentrated and the product was isolated in >40% yield by crystallization from toluene–heptane, with an increase in optical purity to >99% ee.

Synthesis of the second penultimate building block (**3**) required the preparation of the two-ring heterocycle. The original synthesis (4) of **3** was improved to afford a process capable of preparing multi-kilogram quantities of the side chain. Although 2,4′-dipyridyl (**7**) is commercially available, only gram quantities could be obtained. We therefore set out to prepare **7** through a selective coupling process (Scheme 4).

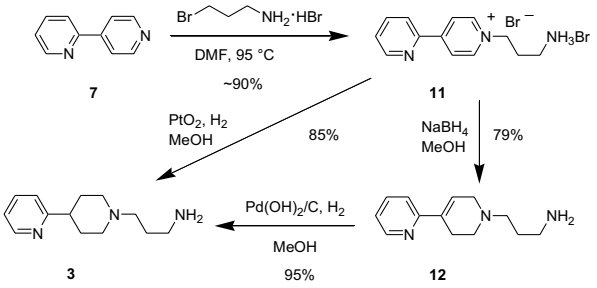
Traditionally, the synthesis of bipyridines has involved the construction of one pyridine ring upon an existing substituted pyridine (15). In recent years, cross coupling through organometallic species has increasingly become more practical (16), especially with the advent of the palladium-catalyzed cross-coupling reactions (17). The preparation of a dipyridyl is often encumbered by the selection of the coupling partners. Generally, the halides are available, which has been exploited by the use of Ullmann-like couplings to

Scheme 4.



prepare the symmetrical bipyridines (18). In the case of unsymmetrical bipyridines, one of the halopyridines needs to be converted to a suitable coupling partner, such as a stannane (19), borane (20), or zinc halide (21). We sought to avoid the synthesis of an intermediate, as is necessary with the stannanes or boranes, and in the case of the former to avoid the use of tin reagents on a large scale. The Negishi coupling protocol (22) provided a straightforward approach using a zinc halide intermediate. Surprisingly, 2,4′-dipyridyl has not been previously prepared with this procedure. Both 2- and 4-bromo pyridines are available, but the better substrate for conversion to the zinc reagent is 2-bromopyridine (**8**). Previous reports show that 2-pyridyl zinc halide can be generated by halogen–metal exchange with either Rieke's zinc (21*d*) or with an alkyl lithium reagent followed by transmetalation with zinc chloride (21*e*, 22*b*). Accordingly, the metal–halogen exchange was carried out on **8** with *n*-BuLi at <–45°C. 2-Pyridyl–lithium was then transmetalated with zinc chloride in THF to afford intermediate **10**. 4-Bromopyridine (**9**) was purchased as its hydrochloride salt, which was partitioned between *tert*-butyl methyl ether (MTBE) and aqueous sodium carbonate to afford the free base in MTBE. The azeotropically dried MTBE solution was added directly to zinc reagent **10** followed by addition of palladium acetate and triphenylphosphine. The coupling reaction was carried out at 50°C. If the temperature exceeded 50°C, an exotherm occurred causing the reaction to reflux. Upon completion of the coupling, the reaction mixture was quenched with ammonium hydroxide and the solvent was concentrated and displaced with DMF. 2,4′-Dipyridyl **7** was obtained as a DMF solution in 81% yield. Alternatively,

Scheme 5.



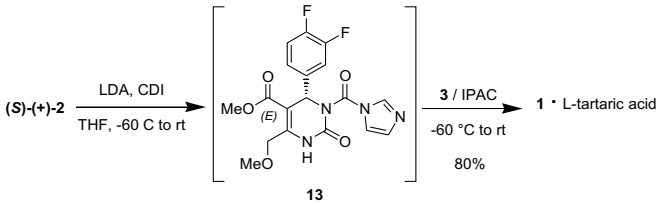
rather than preparing a DMF solution, **7** could be isolated as a solid; however, large losses were incurred during the isolation procedure.

The first step in the conversion of 2,4′-dipyridyl (**7**) to side chain **3** was the selective alkylation at the 4′-position. Heating a mixture of dipyridyl **7** and bromopropylamine hydrobromide in DMF at 95°C resulted in a high conversion to pyridinium salt **11**, with no competing alkylation at the 2-position. Alkylation reactions run at 1 M concentrations in DMF became quite thick, because the pyridinium salt started to crystallize. To alleviate stirring problems, the reaction was run at 0.5 M, but the reaction rate and yield suffered. By adding 10–15% water to the reaction mixture, however, the concentration and rate of reaction was maintained. At the end of the reaction, the water was removed by distillation and pyridinium salt **11** could be isolated in 95% yield after cooling and addition of MTBE.

At this stage, the piperidine ring (**3**) could be obtained by either a one- or two-step reduction process (Scheme 5). In the two-step process, pyridinium salt **11** was dissolved in methanol and 3.3 equivalents of $NaBH_4$ was added to produce tetrahydropiperidine **12** in 79% yield. The remaining olefin was then reduced at 40 psi hydrogen and 20% $Pd(OH)_2/C$ in methanol to afford **3** in 95% assay yield. Unfortunately, amine **3** was not crystalline. To facilitate isolation and handling of the product as a solid it was crystallized as the L-tartrate salt from ethanol in 93% recovery. Alternatively, pyridinium intermediate **11** could be reduced directly to **3** using PtO_2 as catalyst in methanol. In this case, the product could be isolated by crystallization as the dihydrobromide salt in 85% yield upon switching the solvent to a mixture of 2-propanol–hexanes (1:1).

The final coupling step used 1,1′-carbonyldiimidazole (CDI) as the urea linking agent (Scheme 6). The (*S*)-dihydropyrimidinone **2** was deprotonated with LDA in THF at <–55°C. CDI was then added and the mixture was warmed to complete the acylation to **13**. The mixture was then recooled to –60°C and the free base of **3** as an IPAc solution was added. The reaction proceeded regioselectively, with no acylation or coupling observed at the unprotected N-1 position. Following an aqueous work-up, the coupled product was isolated from 2-propanol by addition of L-tartaric acid. A sample of the salt was hydrolyzed and the free base was analyzed by chiral HPLC showing the product **1** to be >99% optically pure. The product L-tartrate salt was obtained as a 2-propanol solvate in 80% yield. Interestingly, this salt was reluctant to crystallize without the presence of 2-propanol. Fortunately, the 2-propanol solvate could be removed by aging the solid as a suspension in ethanol for a few hours. Upon filtration, unsolvated salt **1** was isolated in 80% yield.

Scheme 6.



In conclusion, a highly effective preparation of drug candidate **1** for the treatment of BPH has been designed and demonstrated. The key chiral dihydropyrimidinone was easily prepared in two steps using a Lewis acid-modified Biginelli reaction and a very efficient enzymatic hydrolysis to afford the resolved heterocycle in 67–75% overall theoretical yield. An improved process for preparing the side chain and coupling procedure have also been developed, which allows for the construction of the material in multi-kilogram quantities.

Experimental

(±)-4-(3,4-Difluorophenyl)-1,2,3,4-tetrahydro-6-(methoxymethyl)-2-oxo-5-pyrimidinecarboxylic acid methyl ester (2)

A mixture of 3,4-difluorobenzaldehyde (670 g, 4.7 mol), methyl 4-methoxyacetoacetate (702 g, 4.8 mol), urea (433 g, 7.2 mol), boron trifluoride diethyl etherate (1126 g, 7.9 mol), copper(II) acetate (94 g, 0.5 mol), and acetic acid (36 mL) in THF (7.5 L) was heated at reflux for ~8 h. The mixture was cooled to room temperature and ethyl acetate (8 L) and aqueous citric acid (10%, 7.5 kg) were added. The layers were separated and the aqueous layer was washed with ethyl acetate (4 L). The combined organic layers were washed with aqueous 10% Na_2CO_3 (2 × 5 kg) and 5% brine (5 kg). The organic layer was concentrated to 4.3 L, then toluene (5 L) was added, and the batch was concentrated to ~4 L. The batch was heated to 80°C to dissolve the solids and then cooled to room temperature, whereupon the product crystallized. Hexanes (450 mL) were added and the slurry was aged for 18 h. The solid was filtered and washed with toluene (2.5 L) and dried to afford 1.2 kg of racemic dihydropyrimidinone **2** in 84% yield; mp 92–94°C. IR (cm^{-1}): 3232, 3114, 293, 1695, 1652, 1515, 1435, 1093. ^1H NMR ($CDCl_3$) δ: 7.65 (s, 1H), 7.00 (m, 3H), 6.63 (s, 1H), 5.34 (s, 1H), 4.63 (m, 2H), 3.64 (s, 3H), 3.45 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 165.0, 152.2, 150.3 (dd, J = 249, 13 Hz), 149.8 (dd, J = 249, 13 Hz), 147.5, 140.2, 122.3, 117.4 (d, J = 18 Hz), 115.5 (d, J = 18 Hz), 98.3, 68.4, 59.0, 54.4, 51.3. Anal. calcd. for $C_{14}H_{14}F_2N_2O_4$: C 53.85, H 4.52, N 8.97; found: C 53.80, H 4.48, N 8.84.

(*S*)-4-(3,4-Difluorophenyl)-1,2,3,4-tetrahydro-6-(methoxymethyl)-2-oxo-5-pyrimidinecarboxylic acid methyl ester ((*S*)-2)

A suspension of the racemic dihydropyrimidinone (3.1 kg, 10.2 mol), Trizma hydrochloride (1.3 kg), Trizma base (5.5 kg) in water (992 L), and acetonitrile (110 kg) was heated to 37°C. Purafect 4000L (362 kg) was added and the

suspension was agitated for 10 d. The extent of the optical enrichment was followed by chiral SFC: Chiralcel OD-H (4.6 mm × 25 cm), isocratic elution at 30°C (290 bar), CO_2 with 6% methanol, 2 mL min^{-1}, 280 nm, retention times: (+)-DHP ester = 4.6 min, (–)-DHP ester = 5.3 min, (–)-DHP acid = 11 min; or chiral HPLC: Chiracel OD-H, isocratic elution at ambient temperature with 15% isopropanol in hexanes, 1 mL min^{-1}, 280 nm, retention times: (+)-DHP ester = 7.6 min, (–)-DHP ester = 9.1 min. The reaction was stopped once the DHP methyl ester (*S*)-(+)-**2** had been enriched to >96% ee. The batch was cooled to 20°C, and then toluene (182 kg) was added. The layers were separated and the aqueous layer was washed with toluene (133 kg). The combined organic layers were washed with water (132 L) containing NaCl (32 kg). The organic layer was concentrated to a volume of 4 L and filtered. Toluene was added to bring the volume to 11 L. Heptane (15.8 L) was added to the batch over 10 h with seeding (2 wt%) with pure (*S*)-**2** and aged for 18 h. The solids were filtered, washed with toluene–heptane (40:60, 5.7 L), and dried to afford 1.3 kg of (*S*)-**2** in 40% yield. The optical purity was assayed at >99% (*S*)-(+)-**2**; mp 92–94°C. $[\alpha]_D^{25}$ +89 (*c* 0.5, $CHCl_3$). IR (cm^{-1}): 3232, 3114, 293, 1695, 1652, 1515, 1435, 1093. Anal. calcd. for $C_{14}H_{14}F_2N_2O_4$: C 53.85, H 4.52, N 8.97; found: C 53.76, H 4.34, N8.81.

Dihydropyrimidinone·D-*threo*-2-amino-1-(4-nitrophenyl)-1,3-propanediol salt (6)

Crystals grew from an ethanol solution of **6** held at room temperature. A suitable crystal was selected and reflection data were collected on a point-detector diffractometer. The structure was solved by direct methods and determined to have two independent molecules of **6** present in the lattice along with ethanol molecules and disordered water molecules of solvation. Refinement proceeded normally with the final model using 648 parameters. All non-hydrogen atoms were refined with anisotropic thermal displacements except for the fluorine atoms (one of which is disordered) and those of the solvent molecules. The weighting scheme used was the standard SHELXL function with P^2 and *P* coefficients of 0.2562 and 0.0 respectively. Final agreement statistics are: $R = 0.105$, $wR = 0.371$, $S = 0.97$, $(\Delta/\sigma)_{max} = 0.01$. The maximum peak height in a final difference Fourier map is 0.80 e $Å^{-3}$ and it has no chemical significance.[3]

Preparation of 2,4′-Bipyridine (7)

Lithiation–transmetalation

n-BuLi in hexanes (2.5 M, 4.16 L, 10.4 mol) was added to THF (9.4 L) at <–45°C. 2-Bromopyridine (**8**) (881.4 mL, 9.24 mol) was added to the *n*-BuLi in THF at <–45 C and the mixture was aged for 1.5 h at –55°C. A suspension of zinc chloride (1352 g, 9.92 mol) in THF (9.9 L), previously heated at reflux over molecular sieves in a Soxhlet extractor for 2 h, was added to the batch and the mixture was warmed to room temperature and aged for 2 h.

Salt break of 4-bromopyridine hydrochloride

In a separate flask, 4-bromopyridine hydrochloride (**9**) (1300 g, 6.62 mol) was partitioned between methyl *tert*-butyl ether (MTBE) (6.5 L) and water (1 L). Aqueous Na_2CO_3 (2 M, 4.7 L, 9.4 mol) was added carefully over 10 min and the mixture was well-agitated for 10 min. The layers were separated and the organic phase was diluted with MTBE (6.5 L). The combined organics were azeotropically dried by concentrating to ~6.5 L at 48–54°C.

Coupling

The solution of **8** was added to the 2-pyridyl zinc mixture (**10**) over 10 min. Triphenylphosphine (177 g, 0.67 mol) was added followed by palladium(II) acetate (34.8 g, 0.15 mol). The mixture was then heated and maintained at 50°C. The reaction is exothermic above 50°C. The heating was discontinued, but the reaction temperature rose to 60°C over 10 min. The reaction mixture was cooled to room temperature and concentrated ammonium hydroxide (5 L) was slowly added and the mixture was stirred for 30 min. The layers were separated and the organic layer was washed with brine (4 L). DMF (5 L) was added and the mixture was concentrated to ~2 L. The concentrate contained 837 g of 2,4′-dipyridyl (**7**) (81% assay yield).

1-(3-Aminopropyl)-2,4′-bipyridinium bromide monohydrobromide (11)

To a solution of 2,4′-dipyridyl (**7**) in DMF (1.85 L, 444 mg mL^{-1}, 5.25 mol) was added 3-bromopropylamine-hydrobromide (1400 g, 6.39 mol) and DMF (3.5 L). The mixture was heated to 95°C and aged for 8 h. The reaction mixture was cooled to room temperature and MTBE (3.7 L) was added over 3 h, whereupon the pyridinium salt crystallized. The slurry was aged for 1 h and filtered. The solid was washed with MTBE–DMF (1:1, 4.2 L) and dried to afford 1866 g (95%) of the pyridinium salt **11**; mp 253–256°C. IR (cm^{-1}): 3030, 2933, 1638, 1558, 1506, 1216, 1185, 1149. ^1H NMR (DMSO-d_6) δ: 9.33 (d, J = 6.8 Hz, 2H), 8.82 (d, J = 6.8 Hz, 3H), 8.46 (d, J = 8.1 Hz, 1H), 8.10 (m, 4H), 7.63 (dd, J = 7.5, 4.8 Hz, 1H), 4.87 (t, J = 6.8 Hz, 2H), 2.93 (m, 2H), 2.33 (m, 2H). ^{13}C NMR (DMSO-d_6) δ: 152.8, 150.5, 149.6, 145.2, 138.2, 126.6, 124.4, 123.4, 57.0, 35.5, 34.1, 28.5. Anal. calcd. for $C_{13}H_{17}Br_2N_3$: C 41.63, H 4.57, N 11.20; found: C 41.40, H 4.46, N 11.10.

4-(2-Pyridinyl)-1-piperidinepropanamine (3)

Method A

Pyridinium salt **11** (1840 g, 4.9 mol) was dissolved in methanol (18 L). The slurry was cooled to 5°C and $NaBH_4$ (612 g, 16.2 mol) was added over 2 h. The mixture was concentrated in vacuo and MTBE (10 L) and 20% aqueous NaOH (20 L) were added. The layers were well-stirred and then separated. The aqueous layer was washed with MTBE (10 L). The combined organics were concentrated to afford **12** as a thick oil (836 g, 79% yield). The crude tetrahydropiperidine **12** was dissolved in methanol (8 L). To the methanol solution of crude **12** (812 g, 3.70 mol) was added 20%

[3] Crystallographic information has also been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 177624). Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

$Pd(OH)_2$ (81 g) and the tetrahydropiperidine was hydrogenated at 40 psi hydrogen. The catalyst was removed by filtration through Celite 521 and the solids were rinsed with methanol (3 × 300 mL). The combined filtrates were concentrated to afford amine **3** as a yellow oil (755 g, 93%). Amine **3** (755 g, 3.4 mol) was dissolved in ethanol (8 L) and the solution was warmed to 65°C. A solution of L-tartaric acid (596 g, 3.97 mol) in ethanol (2.1 L) was added over ~1 h with seeding to crystallize the **3**-tartrate salt. The slurry was slowly cooled to ambient temperature over 18 h. The solids were filtered and washed with ethanol (2 × 1 L) and dried to afford the amine **3**-tartrate salt containing 11 wt% residual solvent (1401 g, 97% corrected yield); mp 101–103°C. IR (cm^{-1}): 3372, 2980, 1589, 1386, 1201, 1118. ^1H NMR ($CDCl_3$) δ: 8.48 (d, *J* = 0.3 Hz, 1H), 7.57 (dt, *J* = 7.7, 1.8 Hz,1H), 7.14 (d, *J* = 7.9 Hz, 1H), 7.07 (m, 1H), 3.03 (d, *J* = 11.5 Hz, 2H), 2.70 (m, 3H), 2.40 (m, 2H), 2.1–1.5 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 165.2, 149.1, 136.3, 121.2, 120.5, 56.8, 54.2, 44.7, 41.0, 32.1, 30.9.

Method B

Di-hydrobromide salt: Pyridinium bromide salt **11** (50 g, 0.13 mol) was dissolved in methanol (500 mL) and hydrogenated over PtO_2 (1.0 g) at 40 psi and 20°C. After 6 h, the slurry was filtered through Solka-floc® (powdered-cellulose filter aid) on a sintered glass funnel. The solids were rinsed with methanol (2 × 50 mL), and the solution was concentrated and turned over to 2-propanol by distillation at ambient pressure to a concentration of ca. 7.5 mL 2-propanol per g for a final volume of ca. 375 mL. The suspension was cooled to 20°C, and *n*-heptane (15 mL g^{-1}, 750 mL) was added over 1 h. The resulting slurry was filtered, rinsed with 2-propanol–heptane (1:2, 50 mL) and dried at 40°C in vacuo to afford of the dihydrobromide salt (45.5 g, 90% yield); mp 200–204°C. IR (cm^{-1}): 3411, 2934, 1589, 1472, 1435, 1200, 1146. ^1H NMR (DMSO-d_6) δ: 8.51 (m, 1H), 7.75 (dt, *J* = 7.5, 2.0 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.25 (m, 1H), 3.5–3.0 (br m, 10H), 2.92 (m, 3H), 2.08 (m, 6H). ^{13}C NMR (DMSO-d_6) δ: 162.7, 149.4, 137.3, 122.4, 121.9, 53.5, 52.2, 45.0, 36.7, 28.8, 22.0. Anal. calcd. for $C_{13}H_{23}Br_2N_3 \cdot H_2O$: C 39.12, H 6.31, N 10.53; found: C 39.22, H 6.11, N 10.47.

Salt break

The L-tartrate or dihydrobromide salt of **3** (3.0 mol) was added to 50% NaOH (2.29 kg) diluted with water (6 L). The free amine was extracted with isopropyl acetate (3 × 18 L) and the combined extracts were concentrated to afford 594.1 g of **3** as an oil (90% recovery), which was used without further purification in the following step.

(*S*)-6-(3,4-Difluorophenyl)-1,2,3,6-tetrahydro-4-(methoxymethyl)-2-oxo-1-[[[3-[4-(2-pyridinyl)-1-piperidinyl]propyl]amino]carbonyl]-5-pyrimidinecarboxylic acid methyl ester – tartrate salt

A solution of LDA (2 M in heptane–THF–ethylbenzene, 184 mL, 0.4 mol) was added to a –65°C solution of (*S*)-(+)-**2** (100 g, 0.4 mol) in THF (1 L). After 15 min, carbonyl diimidazole (62.3 g, 0.38 mol) was added in one portion. The resulting slurry was aged at –60°C for 15 min and then warmed to 20°C. After 1 h, the mixture was re-cooled to –60°C. A solution of amine **3** (100 g, 0.45 mol) in isopropyl acetate (IPAc) (300 mL) was added at <–45°C. The mixture was slowly warmed to 20°C. The reaction was quenched with water (1.5 L) and IPAc (1.5 L). The layers were separated and the organic layer was washed with water (2 × 1.5 L). The combined aqueous layers were washed with IPAc (0.5 L). The combined organic layers were extracted with 2 N HCl (1 × 1 L and 1 × 0.5 L). The combined acid extracts were neutralized with solid $NaHCO_3$ (450 g). IPAc (1 L) and water (1 L) were added and the layers were mixed and separated. The aqueous layer was extracted with IPAc (1 L). The combined organic layers were washed with water (2 × 1 L) and concentrated to an oil. The oil was dissolved in 2-propanol (1.27 L). The solution was warmed to 50°C. A solution of L-tartaric acid (38 g, 0.2 mol) in ethanol (175 mL) was added and the mixture was aged for 1 h, whereupon crystals formed. The slurry was cooled to 20°C, aged for 18 h, cooled to 0°C, and then aged for an additional 1 h. The solid was filtered, washed with 2-propanol (300 mL), and dried to afford 195 g of the **1** tartrate salt as a 2-propanol solvate (80% yield). The solvate was broken by stirring the solid in ethanol (975 mL) at 0°C for 2 h. The solid was filtered and dried to afford the L-tartrate salt of **1** (156 g, 80% yield); mp 145–148°C. $[\alpha]_{589}^{20}$ +127.5 (*c* 1.0, CH_3OH). Optical purity >99.9% by chiral HPLC assay. IR (cm^{-1}): 3295, 2946, 1709, 1645, 1516, 1436, 1393. ^1H NMR (DMSO-d_6) δ: 9.98 (br s, 1H), 8.82 (t, *J* = 5.5 Hz, 1H), 8.49 (d, *J* = 4.0 Hz, 1H), 7.72 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.42 (m, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.21 (m, 2H), 7.08 (m, 1H), 6.56 (s, 1H), 4.63 (d, *J* = 13.0 Hz, 1H), 4.42 (d, *J* = 13.0 Hz, 1H), 4.07 (s, 2H), 3.67 (s, 3H), 3.29 (s, 3H), 3.25 (m, 4H), 2.77 (m, 1H), 2.65 (m, 1H), 2.49 (m, 7H), 1.90–1.60 (m, 6H). ^{13}C NMR (DMSO-d_6) δ: 173.9, 164.4, 163.2, 152.9, 152.1, 148.8, 146.7, 138.0, 136.6, 123.1, 123.0, 122.9, 121.6, 121.2, 118.0, 117.7, 115.4, 115.2, 103.1, 71.8, 66.7, 62.0, 58.1, 54.2, 52.1, 51.7, 41.7, 38.0, 29.4, 25.4, 24.7. Anal calcd. for $C_{32}H_{39}F_2N_5O_{11}$: C 54.31, H 5.55, N 9.90; found: C 54.12, H 5.64, N 9.80.

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