Efficient Synthesis of AMP579, a Novel Adenosine A1/A2 Receptor Agonist

Adam W. Sledeski,* Gregory G. Kubiak, Michael K. O'Brien, Matthew R. Powers, Tory H. Powner,† and Larry K. Truesdale‡

Process Chemistry, Rhône-Poulenc Rorer,§ Collegeville, Pennsylvania

adam.sledeski@aventis.com

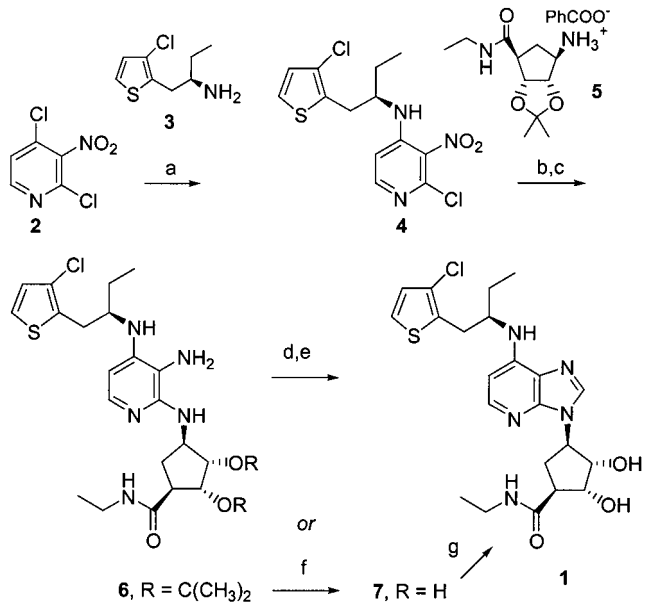
Received July 14, 2000

Introduction

AMP579 (**1**) is a novel adenosine analogue with high affinity for both the A_1 (K_i ∼5 nM) and A_{2a} (K_i ∼56 nM) receptor subtypes and has recently been demonstrated in a clinically relevant manner to have cardioprotective effects in various animal models of myocardial infarction.[1,2] It is currently under development for potential use in cardiovascular therapeutics.[3] Structurally, **1** is distinguished from adenosine by: 5′-*N*-ethylcarboxamide (NECA)[4] replacement for the hydroxyl group, carbocyclic modification of the ribose unit, and 1-deaza N^6-substituted purine[5,6] system.

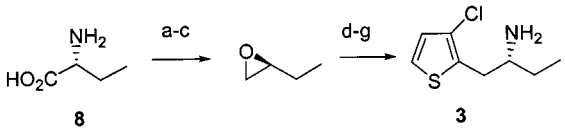
The synthetic route used to generate preclinical material supplies is summarized in Scheme 1.[3] Assembly of two optically pure synthons, thienylamine **3**[5,7] and carbosugar derivative **5**,[8,9] was followed by a sequential condensation of the commercially available 2,4-dichloro-3-nitropyridine **2** with **3** and **5** and then reduction of the nitro group and cyclization to the desired 1-deazapurine heterocycle. Although straightforward and triply convergent, this route suffered from some major drawbacks. First, the preparation of **3** necessitated seven steps, several of which presented scale-up challenges (Scheme 2). Second, the initial condensation step was poorly selective, producing the desired 4-substituted pyridine **4** in ca. 50% yield along with the mixture of the starting materials, 2-thienylamino regioisomer and the diaminated compound A. The monoaminated pyridine **4** could either be purified by chromatography prior to use in the next step, or used crude, in which case impurities **B** and **C** were formed. The second amine introduction and subsequent reduction step proceeded efficiently, however formation of the deazapurine system was again impaired by a regioselectivity issue. A 5:1 ratio of the 2,3:3,4 (**D**) fused systems was obtained, from which the desired 2,3 regioisomer was isolated by chromatography. The hydrolysis of the acetonide moiety was then followed by the isolation of AMP579 (**1**) as the amorphous HCl salt. The overall yield starting from the dichloroaminopyridine **2** was 17%, and the overall yield from the chiral amino acid **8** was only 6%. This route was

Scheme 1[a]

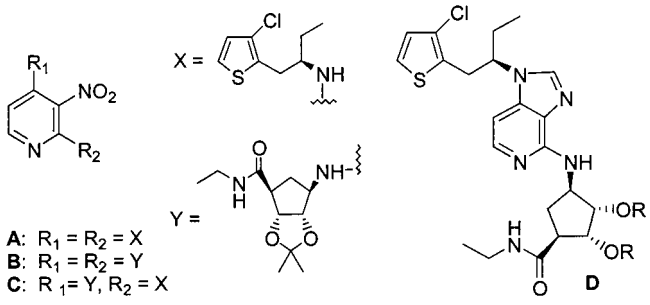


[a] Reagents: (a) **3**, NEt_3, iPrOH, 47%; (b) **5**, NEt_3, BuOH, 92%; (c) H_2, Pt, 87%; (d) formamidine acetate, BuOAc, 55%; (e) aq HCl, THF, 79%; (f) HCl, iPrOH; (g) formamidine acetate.

Scheme 2[a]



[a] Reagents: (a) $NaNO_2$, HCl, 95%; (b) BH_3, THF, 90%; (c) KOH, 56%; (d) 3-chlorothiophene, BuLi, 81%; (e) MsCl, NEt_3; (f) NaN_3, EtOH, 94%; (g) PPh_3, toluene, 99%.



* Corresponding author. Current address: Aventis Pharmaceuticals, N2342, P.O. Box 6800, Bridgewater, NJ 08807.

† Present address: Boehringer Ingelheim Chemicals, Inc., Petersburg, VA.

‡ Present address: Alanex Corp., San Diego, CA.

§ Currently: Aventis Pharmaceuticals.

(1) Merkel, L.; Rojas, C. J.; Jarvis, M. F.; Cox, B. F.; Fink, C.; Smits, G. J.; Spada, A. P.; Perrone, M. H.; Clark, K. L. *Drug. Dev. Res.* **1998**, *45*, 30−43.

(2) McVey, M. J.; Smits, G. J.; Cox, B. F.; Kitzen, J. M.; Clark, K. L.; Perrone, M. H. *J. Cardiovasc. Pharmacol.* **1999**, *33*, 703−710.

(3) Spada, A. P.; Fink, C. A.; Myers, M. R. PCT Int. Appl. WO 9528160, **1995**.

(4) Chen, J.; Grim, M.; Rock, C.; Chan, K. *Tetrahedron Lett.* **1989**, *41*, 5543−5546.

(5) Fink, C. A.; Spada, A. P.; Colussi, D.; Rivera, L.; Merkel, L. *Nucleosides Nucleotides* **1992**, *11*, 1077−1088.

(6) For other examples of carbocyclic and N^6-substituted nucleosides in the adenosine area, see: Siddiqi, S. M.; Jacobson, K. A.; Esker, J. L.; Olah, M. E.; Ji, X.-d.; Melman N.; Tiwari, K. N.; Secrist, J. A., III; Schneller, S. W.; Cristalli, G.; Stiles, G. L.; Johnson, C. R.; Ijizerman, A. P. *J. Med. Chem.* **1995**, *38*, 1174−1188 and references therein.

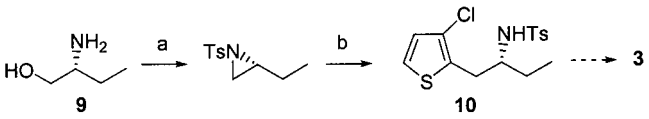
(7) Grondard, L.; Casimir, J.-P.; Leon, P.; O'Brien, M. K.; Powers, M. R.; Robin, D. PCT Int Appl. WO 9811064, 1998.

(8) Bannister, R..; Hanson, C.; Henderson, N.; McCague, R.; Ruecroft, G. *Org. Process Res. Dev.* **1997**, *1*, 415−419.

(9) O'Brien, M.; Leon, P.; Largeau, D.; Powers, M.; Durand, T. US patent 5684159, **1997**.

10.1021/jo001066f CCC: $19.00
Published on Web 10/24/2000

Scheme 3[a]



[a] Reagents: (a) 2.1 equiv of TsCl, aq NaOH, MTBE, 88%; (b) 3-chlorothiophene, BuLi, 90%.

subsequently rendered more practical, after the identification of a crystalline HCl salt of the triamine **7**, and ultimately a crystalline form of AMP579 itself,[10] enabling the elimination of all chromatographic purification steps. Nevertheless, despite extensive optimization, the chemical yield of the first amination step did not exceed 60% and the cyclization proceeded in a 9:1 ratio, indicating inherent limitations of this approach.[11] Attempts to prevent the unwanted cyclization by protecting the 4-NH functionality in **4** failed due to its inertness toward common electrophiles such as Ac_2O, Boc_2O, or TsCl.

An alternative preparation of thienylamine **3** from commercially available and inexpensive (*R*)-(−)-2-amino-1-butanol **9** would only require three steps (Scheme 3).[7] While aziridine formation and the ring opening by the chlorothienyl anion were straightforward, removal of the toluenesulfonyl group was problematic.[12] Since sulfonamides of secondary amines are generally cleaved more readily than those of primary amines,[13] we were intrigued by the idea of reversing the order of the detosylation and aromatic nucleophilic substitution steps. Apart from a net savings of four synthetic steps, this approach would secure the regiospecific formation of the deazapurine if the detosylation was delayed past the cyclization step. The toluenesulfonamide moiety was also likely to impart crystallinity[13] to a larger number of intermediates, which could lead to practical and scalable isolation protocols.

Results and Discussion

To the best of our knowledge, *N*-alkylsulfonamides have not been previously used as nucleophiles in aromatic nucleophilic substitution.[14] Our attempts to react the tosylaziridine **10** with **2** using a variety of bases did not result in any detectable substitution. The required breakthrough occurred only when the electrophile was switched to the more reactive 2,4-difluororo-3-nitropyridine **11**.[15,16] Using potassium carbonate as base in refluxing acetonitrile for 27 h, the desired 4-thienylaminopyridine derivative **12** was formed in ca. 65% yield. Equally encouraging was the lack of evidence at this stage for the formation of the undesired 2-regioisomer[17] or the diaminated pyridine. It is noteworthy that replacing **10** with the corresponding trifluoromethylsulfonamide led to extensive β-elimination, producing the olefin **E** and its double bond isomer in a total of 40% yield. Although methane- and benzene- sulfonamides underwent condensation with **11** with similar efficiency, unlike the toluenesulfonamide, they did not offer crystallinity in the starting material or product. At this point, we decided to focus on using **10** as nucleophile and **11** as electrophile and briefly screened some alternative reaction conditions. The reaction time was drastically reduced by the addition of a catalytic amount of 18-crown-6, or by employing potassium *tert*-butoxide in THF. The latter system turned out to be the most effective, allowing the isolation of crystalline **12** in 83% yield. Although use of isolated 2,4-difluoro-3-nitropyridine led to superior results in terms of impurity profile, from the process development point of view in situ fluorination of **2** followed by the condensation was a viable and attractive alternative. The fully substituted pyridine intermediate **13** was obtained quantitatively by condensing **12** with the carbosugar synthon **5** in the presence of potassium carbonate in *N*-methylpyrrolidinone (NMP) at 80 °C for 1.5 h. Other reaction conditions including potassium carbonate in acetonitrile or in ethyl acetate, triethylamine in acetonitrile or diisopropylethylamine in NMP at 70−80 °C for 1−2 h worked equally well. Reduction of the nitro functionality was then achieved via hydrogenation of **13** in the presence of a catalytic amount of platinum on carbon, affording crude triamine **14** in quantitative yield. Although purification via flash chromatography or recrystallization yielded pure triamine **14** in 95 and 73% respectively, the crude material could be used directly in the next step (Scheme 4).

The stage was now set for the regiospecific formation of the requisite deazapurine ring system. Whereas the parent system **7** (or **8**) underwent formamidine acetate promoted closure in less than 4 h at 90 °C in *n*-butyl acetate, the tosylated derivative **14** required over 40 h at 120 °C to reach approximately 70% conversion when the same reagent/solvent system was employed. Fortunately, an alternative system consisting of a 1:1 (v/v) mixture of triethylorthoformate and acetic anhydride allowed complete conversion in 1 h at 120 °C.[18] The pure deazapurine **15** was isolated directly from the reaction mixture as crystalline solid in 75% yield based on the crude material from the preceding step.

Liberation of AMP579 (**1**) was then accomplished in two steps. First, the toluenesulfonyl protective group was removed using magnesium in a methanol/toluene mixture. The reaction required 5 equiv of magnesium and was completed in 3 h at 40 °C. At higher temperatures

(10) O'Brien, M. K.; Garcia, H.; Leon, P.; Powner, T.; Reilly, L. W.; Shah, H. C.; Thompson, M. D.; Tsuei, C. T.; Vanasse, B. J.; Walther, F. PCT Int Appl. WO 9825921, 1998.

(11) An alternative route avoiding the regioselectivity issue in the first amination step is described in ref 10.

(12) Subsequently, a practical detosylation method was developed.[7]

(13) Greene T. W.; Wuts P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York 1999; pp 603−616.

(14) (a) The closest related literature case involves stoichiometric complexes of Na- and K-phthalimides and saccharinates: Rasshofer, W.; Voegtle, F. *Tetrahedron Lett.* **1979**, 1217−18. Other related processes: (b) *Goldberg coupling reaction* between sulfonamide and aryl bromide: Hall, R. J.; Marchand, J.; Oliveira-Campos, A. M. F.; Queiroz, M.-J. R. P.; Shannon, P. V. R. J. *Chem. Soc. Perkin Trans. 1* **1992**, 3439−3450. (c) Coupling of sulfonamide with phenylboronic acid in the presence of cupric aceate: Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933−2936.

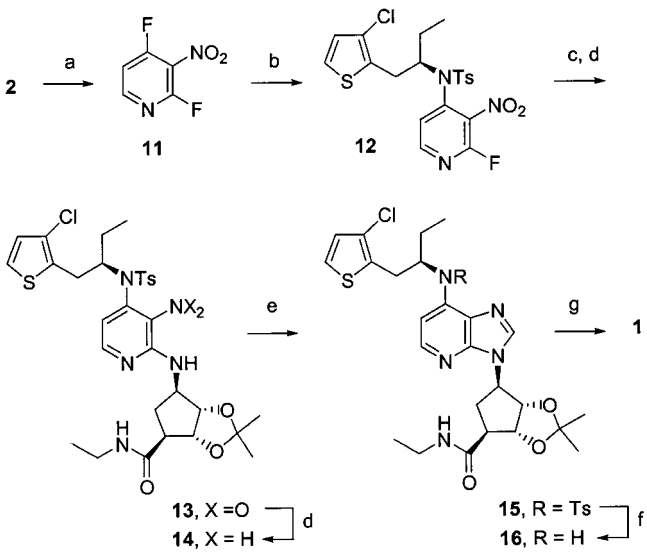
(15) Kroon, C.; Maaseeen van den Brink, A.; Vlietstra, E. J.; Salemink, C. A.. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 127−156. A modified procedure for the large scale prep of **11** is described in the Experimental Section.

(16) For a recent example of a use of aryl fluoride in aromatic nucleophilic substitution with a secondary alkylamine, see: Brown, G. R.; Foubister, A. J.; Ratcliffe, P. D. *Tetrahedron Lett.* **1999**, *40*, 1219−1222.

(17) An indirect evidence for the formation of the small amount of the unwanted 2-regioisomer during the condensation of **2** with **10** was obtained after the next step. When crude (untriturated) **4** was used in condensation with **5**, a ca. 2A% of an isomer of **5** was detected by LC-MS in the crude reaction mixture.

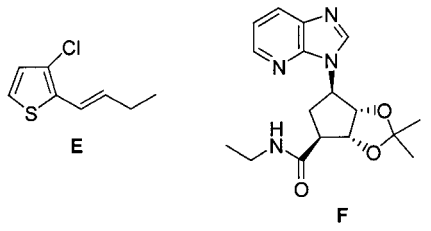
(18) The likely active reagent is diethoxymethyl acetate (DEMA): Montgomery, J. A.; Fitzgibbon, W. E., Jr. In *Nucleic Acid Chemistry vol. 2*; Townsend, L. B., Tipson, R. S., Eds.; John Wiley and Sons: New York, 1978; pp 995−997. Neat DEMA (Aldrich) at 70−80 °C also allowed ring closure of **14** to **15**.

Scheme 4[a]



[a] Reagents: (a) KF, 18-c-6, NMP, 83%; (b) **10**, t-BuOK, THF, 83%; (c) **5**, K_2CO_3, NMP, 99%; (d) H_2, Pt, EtOAc/MeOH, 97%; (e) $HC(OEt)_3$, Ac_2O, 84%; (f) Mg, EtOH, 99% or $LiEt_3BH$, THF, 96% (crude); (g) concd HCl, THF, 75%.

more magnesium was necessary due to the competitive formation of magnesium methoxide.[19] The estimated reaction yield was 84% (99% yield of crude material with a purity of 85%) and the principal side reaction was the cleavage of the N−C(aryl) bond leading to the release of the tosylthienylamine **10** and the deazapurine analogue **F**. Alternatively, the deprotection was cleanly achieved



with lithium triethylborohydride (Super-Hydride)[20,21] in THF at 4 °C to room temperature. We are unaware of any precedent for sulfonamide cleavage using this reagent. In contrast, attempts to use the bis(2-methoxyethoxy)aluminum hydride (Red-Al)[22] in toluene at temperatures between 40 and 108 °C led to mixtures of starting material and several products including only minor amounts of the desired material. Lithium and sodium naphthalenides[13] were also found to be ineffective. It is noteworthy that when either magnesium or Super-Hydride protocols were applied to thienylsulfonamide substrate **10**, no deprotection product was detected. Finally, the acetonide moiety in **16** was hydrolyzed in an aqueous hydrochloric acid/THF mixture, then following the workup and crystallization,[10] the desired AMP579 (**1**) was isolated as a free base in 75% yield.[23]

In summary, we have demonstrated an efficient, highly regioselective route to the adenosine agonist AMP579. The route involves an unprecedented condensation of an alkylsulfonamide with a pyridine synthon, then takes advantage of the sulfonamide protecting group to prevent the undesired cyclization pathway during the deazapurine ring formation. Starting from the (*R*)-(−)-2-amino-1-butanol (**9**), this process affords AMP579 in eight steps and 35% overall yield, whereas the previous one necessitated 12 steps from the amino acid **8** and the overall yield was 6%. In addition, the approach described herein allows concatenation of multiple steps, while offering the flexibility of implementing isolation steps by means of crystallization. The requisite cleavage of the N−Ts bond was facilitated by the aryl substitution and was accomplished using magnesium in methanol or Super-Hydride in THF. The latter constitutes a novel detosylation protocol and should find further applications, since it is well recognized that existing methods are substrate dependent.[24,25]

Experimental Section

General Methods. All substrates and reagents were obtained commercially and used without purification. Nuclear magnetic resonance (NMR) chemical shifts (δ) are reports in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent [^{1}H NMR, C*H*Cl_3 (7.25), C*H*D_2-$SOCD_3$ (2.50); ^{13}C NMR, $CHCl_3$ (77.0), *C*D_3SOCD_3 (39.43)]. Flash chromatography was carried out using Merck Kiesegel 60 F_{254} (230−400 mesh). HPLC analysis was performed using following conditions: Kromasil C8 column (250 × 4.6 mm), flow 1 mL/min, eluent: acetonitrile 70%, water 20%, 20 mM potassium phosphate buffer, pH 3.0, 10%, detection: UV, 230 nm. HPLC results are presented as area percent of the peak (A%) for a particular compound relative to the total area of all the peaks integrated. Melting points are uncorrected.

2,4-Difluoro-3-nitropyridine[15] (11). A mixture of 300 g (1.56 mol, 1 equiv) of 2,4-dichloro-3-nitropyridine (**2**), 1.0 L of 1-methyl-2-pyrrolidinone, 270.5 g (4.65 mol, 2.97 equiv) of potassium fluoride, and 66.0 g (0.25 mol, 0.16 equiv) of 18-crown-6 was heated with stirring at 100 °C for 2 h. The reaction mixture was cooled to 20 °C, and then it was partitioned between 1.75 L of water and 1.75 L of *tert*-butyl methyl ether (TMBE). The organic layer was washed with 300 mL of brine, dried over magnesium sulfate, and concentrated under reduced pressure. **11** (208 g, 83% yield) was obtained as a brown oil with a purity of 97 A% (HPLC). The oil may be used as is or distilled. A 42.61 g portion of the 2,4-difluoro-3-nitropyridine was distilled at 61−64 °C and 4.0 Torr to give the title compound (38.15 g, 90% yield, 99.6 A% (HPLC)) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.45 (1H, app t), 7.28 (1H, dd). MS (EI, 70 eV, relative intensity): 160 (M^+, 75), 114 (25). *Alternatively, the reaction may be performed with 0.3 equiv of tetrabutylammonium bromide, in place of 16-crown-6, in toluene at 110 °C.*

(*R*)-*N*-[1-[(3-Chlorothien-2-yl)methyl]propyl]-*N*-(2-fluoro-3-nitropyrid-4-yl)-4-methylbenzenesulfonamide (12). To the solution of (*R*)-*N*-[1-[(3-chlorothien-2-yl)methyl]propyl]-4-methylbenzenesulfonamide (**10**)[5,7] (43.55 g, 0.127 mol) in 71 mL of tetrahydrofuran (THF) at 4 °C was added dropwise 1.0 M solution of potassium *tert*-butoxide in tetrahydrofuran (138 mL, 0.138 mol). The resulting mixture was stirred for 15 min at 20 °C, and then 23.7 g (0.149 mol) of 2,4-difluoro-3-nitropyridine

(19) In a control experiment **15** was treated with a 10% magnesium methoxide in methanol solution between room temperature and boiling point. No detosylation product under these conditions was detected.

(20) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1−12.

(21) For other synthetic applications of this reagent, see: Zaidlewicz, M.; Brown, H. C. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1995; Vol. 5, pp 3180−3182.

(22) Gold, E. H.; Babad, E. *J. Org. Chem.* **1972**, *37*, 2208.

(23) Promising results were also obtained using a one step detosylation/acetonide hydrolysis protocols such as methanesulfonic acid (see the Acknowledgment) or trimethylsilyl trifluoroacetate in conjunction with trifluoroacetic acid and thioanisole at 70−85 °C. The yields based on compound **15** ranged between 50 and 70%.

(24) Vedejs, E.; Lin, S. *J. Org. Chem.* **1994**, *59*, 1602−1603.

(25) An, H.; Cook, P. D. *Tetrahedron Lett.* **1996**, *40*, 7233.

in 10 mL of tetrahydrofuran was added and the mixture was heated at 65 °C for 1 h. The mixture was cooled to room temperature and partitioned between 150 mL of water and 300 mL of ethyl acetate. The organic layer was washed with water (2 × 150 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was successively slurried with 100 mL of methanol, 150 mL of heptane, and 60 mL of methanol and vacuum-dried at room temperature with a nitrogen bleed to afford the title compound (**12**) (51.1 g, 83% yield, 97.6 A% (HPLC)) as a white solid. MS (ion spray) (relative intensity): 484/486 (75), 312 (100).

A small sample of the crude product was recrystallized from THF/CH_3CN/H_2O. Mp: 139 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.30 (1H, d broad), 7.73 (2H, d broad), 7.38−7.15 (3H, m), 7.16 (1H, d), 6.82 (1H, d), 3.95 (1H, m), 3.27 (1H, dd), 3.02 (1H, dd), 2.45 (3H, s), 1.6 (2H, m broad), 0.70 (3H, t broad). ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.565, 152.696, 148.771, 148.445, 145.131, 132.348, 129.945, 128.224, 127.757, 125.370, 125.267, 123.966, 123.768, 67.078, 32.346, 26.081, 21.648, 11.617. Anal. Calcd for $C_{20}H_{19}ClFN_3O_4S_2$: C, 49.64; H, 3.96; N, 8.68. Found: C, 49.68; H, 3.96; N, 8.76.

[3a*R*-[3aα,4α,6a(*R),6aα]]-6-[4-[[1-[(3-Chlorothien-2-yl)-methyl]propyl] [4-Methylbenzenesulfonyl]amino]-3-nitropyrid-2-ylamino] *N*-Ethyl Tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-carboxamide (13).** A mixture of the monoaminated fluoronitropyridine **12** (123.0 g, 0.254 mol), 3a*R*-[3aα,4α,6a,6aα]-6-amino-*N*-ethyltetrahydro-3,3-dimethyl-2,4-dioxabicyclo [3.3.0]octane-8-carboxamide benzoate (**5**)[8,9] (123.0 g, 0.254 mol), potassium carbonate (325 mesh) (105.3 g, 0.762 mol), and 1-methyl-2-pyrrolidinone (1.0 L) was heated at 85 °C with stirring for 1.5 h. The reaction mixture was cooled to room temperature and poured into 2.5 L of water with stirring. Solid that formed was isolated by filtration, and the filtercake was washed with 10 L of water. The filtercake was air-dried on the filter overnight and then dried under vacuum with a nitrogen bleed for 4 days to provide the title compound (179 g, 100%, 98 A% (HPLC)) as a yellow solid. Mp 90−113 °C. HRMS (FAB): calcd for $C_{31}H_{38}ClN_5O_7S_2$ $(M + H)^+$ 692.1979, found 692.1931. ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of conformational isomers, ratio ca. 7:3, all signals reported): δ 8.33 (d), 8.25 (d, minor conformer), 7.94 (d), 7.87 (d), 7.76 (d), 7.34 (d), 7.30 (d), 7.13 (m), 6.81 (m), 6.56 (d), 6.47 (d, min. conf.), 5.66 (m), 4.81 (d, min. conf.), 4.74 (m), 4.58 (d, min. conf.), 4.56 (d), 3.99 (m), 3.87 (m), 3.35 (m), 3.21 (dd, min. conf.), 3.10 (dd), 2.90 (dd), 2.82 (dd), 2.55 (m), 2.41 (s), 2.13 (d), 1.96 (d, min. conf.), 1.64 (m), 1.60 (s), 1.52 (s), 1.30 (s), 1.22 (s), 1.40−1.20 (m), 1.15 (t), 0.88 (t), 0.64 (t, min. conf.), 0.51 (t). ^{13}C NMR (50 MHz, $CDCl_3$) (mixture of conformational isomers, as above): δ 173.781, 151.181, 144.504, 139.049, 135.972, 133.204, 129.715, 128.772, 128.089, 127.654, 123.641, 123.411, 114.768, 110.787, 86.284, 84.833, 64.913, 57.380, 53.328, 34.788, 32.361, 31.085, 30.680, 26.692, 24.297, 21.632, 14.718, 11.395.

[3a*R*-[3aα,4α,6a(*R),6aα]]-6-[4-[[1-[(3-chlorothien-2-yl)-methyl]propyl] [4-Methylbenzenesulfonyl]amino]-3-aminopyrid-2-ylamino] *N*-Ethyl Tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-carboxamide (14).** A solution of the diaminated nitropyridine **13** (90.0 g, 0.13 mol) in 1.1 L of ethyl acetate was washed with water (3 × 500 mL), and then it was diluted with 300 mL of methanol and hydrogenated in the presence of platinum on carbon (8.8 g, Degussa type F101 RA/W, 5% Pt, 50% water) under 50−55 psi of hydrogen for 24 h at room temperature. The reaction mixture was filtered through a glass microfiber filter, and the filter was washed with 300 mL of hot ethyl acetate. The combined filtrates were evaporated under reduced pressure to give a solid which was then slurried with 800 mL of heptane and isolated by filtration. The filtercake was dried under vacuum with a nitrogen bleed for 2 days to provide the title compound (94.5 g, 109% (crude), 89 A% (HPLC), 97% corrected yield).

A small sample of the oil was triturated with Et_2O to give the title compound as an off-white solid. Mp: 175−177 °C. HRMS (FAB): calcd for $C_{31}H_{41}ClN_5O_5S_2$ $(M + H)^+$ 662.2237, found 662.222. ^{1}H NMR (200 MHz, $CDCl_3$) (mixture of conformational isomers, ratio ca. 7:3, all signals reported): δ 7.75 (d), 7.63 (d), 7.54 (d), 7.27 (d), 7.21 (s), 7.15 (dd), 6.82 (dd), 6.64 (d), 6.48 (d, minor conformer), 5.95 (d, min. conf.), 5.83 (d), 5.80 (br. m), 4.78 (m), 4.60 (m), 4.39 (m), 3.99 (s), 3.75 (s, min. conf.), 3.27 (dt), 3.12 (dd, min. conf.), 2.90−2.45 (m), 2.42 (s), 2.41 (1s, min. conf.), 2.04 (apparent t), 1.81 (s), 1.48 (s), 1.47 (s, min. conf.), 1.55−1.22 (m), 1.30 (s), 1.29 (s, min. conf.), 1.16 (t), 1.15 (t, min. conf.), 1.04 (t), 0.73 (t). ^{13}C NMR (50 MHz, $CDCl_3$) (mixture of conformational isomers, all signals reported): δ 174.97, 174.84, 149.88, 149.53, 143.77, 143.60, 137.42, 136.47, 136.32, 133.45, 131.55, 131.08, 129.66, 129.38, 127.94, 127.73, 127.59, 125.99, 125.88, 123.59, 123.23, 123.10, 114.47, 114.05, 110.71, 86.36, 85.94, 85.13, 84.72, 64.46, 64.20, 56.90, 56.75, 53.99, 53.74, 34.92, 34.83, 32.58, 32.13, 31.23, 26.84, 26.78, 26.05, 24.96, 24.44, 21.59, 14.70, 12.57, 12.08.

[3a*R*-[3aα,4α,6a(*R),6aα]]-6-[7-[[1-[(3-chlorothien-2-yl)-methyl]propyl] [4-Methylbenzenesulfonyl]amino]-3*H*-imidazo[4,5-*b*]pyrid-3-yl] *N*-Ethyl Tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-carboxamide (15).** A mixture of the crude triamine **14** (94.5 g, 0.13 mol), triethylorthoformate (141.0 mL, 0.85 mol), and acetic anhydride (114.0 mL, 1.21 mol) was heated at 100−105 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with 1.0 L of heptane, and stirred for 1 h. The solids formed were isolated by filtration, washed with cold heptane (500 mL), and dried under vacuum with a nitrogen bleed for 2 days to provide the title compound as a white solid (65.0 g, 75% yield, 97.0 A% (HPLC)). MS (ion spray): 672/674 (100). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.38 (1H, d), 8.15 (1H, s), 7.85 (2H, d), 7.25 (1H, s), 7.22 (1H, d), 7.15 (2H, dd), 6.78 (1H, d), 5.85 (1H, t), 5.05 (3H, m), 4.25 (1H, m), 3.28 (3H, m), 2.85 (3H, m), 2.60 (1H, q), 2.40 (3H, s), 1.60 (3H, s), 1.45 (2H, q), 1.25 (3H, s), 1.20 (3H, t), 0.90 (3H,t). ^{13}C NMR (500 MHz $CDCl_3$): δ 171.36, 149.04, 144.51, 143.53, 142.90, 137.70, 136.37, 135.34, 133.86, 129.45, 128.11, 127.46, 123.39, 123.21, 121.08, 114.22, 83.86, 81.88, 64.99, 60.69, 50.24, 34.63, 34.38, 33.35, 27.45, 25.26, 25.07, 21.58, 14.81, 11.64.

A sample of the crude material was recrystallized from ethyl acetate/CH_3CN. Mp: 197−199 °C. The structure of [3a*R*-[3aα,4α,6a(*R**),6aα]]-6-[7-[[1-[(3-chlorothien-2-yl)methyl]propyl] [4-methylbenzenesulfonyl]amino]-3*H*-imidazo[4,5-*b*]pyrid-3-yl] *N*-ethyl tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-carboxamide was confirmed by single-crystal X-ray analysis (see the Supporting Information).

[3a*R*-[3aα,4α,6a(*R),6aα]]-6-[7-[[1-[(3-Chlorothien-2-yl)-methyl]propyl]amino]-3*H*-imidazo[4,5-*b*]pyrid-3-yl] *N*-Ethyl Tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-carboxamide (16). A. Using Magnesium in Methanol.** One or two small crystals of iodine were added to a mechanically stirred suspension of magnesium turnings (3.9 g, 0.16 mol) in methanol (30 mL) under nitrogen. Bubbles rising from the magnesium were observed as the mixture started to warm. A solution containing tosylated compound **15** (20 g, 0.03 mol) in a mixture of 65 mL of methanol and 55 mL of toluene was added over 20 min, while the reaction temperature was maintained at ∼40 °C. The mixture was stirred at ∼40 °C for approximately 3 h, and then it was cooled to room temperature, concentrated to one half of the original volume, and filtered through ca. 50 g of Celite. The filter was washed with 150 mL of ethyl acetate, and the combined filtrate was washed with 150 mL of water and 150 mL of brine. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to provide the title compound (15.4 g, 99% (crude), 85 A%, (HPLC)). MS (FAB): 518/520 (100). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8. 02 (1H, d), 7.90 (1H, s), 7.09 (1H, d), 6.85 (1H, d), 6.34 (1H, d), 6.16 (1H, m), 5.32 (1H, d broad), 5.10−4.85 (3H, m), 3.90 (1H, m), 3.33 (2H, m), 3.09 (2H, d), 2.95−2.50 (3H, m), 2.0−1.5 (2H, m), 1.57 (3H, t), 1.31 (3H, s), 1.17 (3H, t), 1.05 (3H, t).

B. Using Lithium Triethylborohydride. A solution of lithium triethylborohydride (1.0 N in THF, 18.6 mL, 1.86 mmol) was added dropwise to a magnetically stirred solution containing tosylated compound **15** (5.0 g, 7.43 mmol) in 66 mL of THF at about 4 °C under nitrogen. Following the end of the addition, the mixture was stirred at room temperature for 2 h. HPLC showed ≤3 A% of starting material and ca. 90 A% of the detosylated material. Thirty millilters of water and 20 mL of ethyl acetate were added, and the phases were separated. The organic phase was washed with water and with brine, dried ($MgSO_4$), and concentrated under reduced pressure to provide the title compound (3.7 g, 96% (crude), 85 A% (HPLC)) as a light yellow solid.

[1*S*-[1α,2*β*,3*β*,4α(*S)]]-4-[7-[[1-[(3-Chlorothien-2-yl)methyl]propyl]amino]-3*H*-imidazo[4,5-*b*]pyrid-3-yl] *N*-Ethyl 2,3-Dihydroxycyclopentanecarboxamide (1).** A 9.4 mL portion of concentrated (37%) HCl was added to a magnetically stirred mixture of crude detosylated acetonide **16** (14.2 g, ca. 0.027 mol) in THF (32 mL) over 10 min while the mixture temperature was maintained below 35 °C. Following the end of the addition, the mixture was stirred for 3 h at room temperature, after which time a precipitated solid was isolated by filtration. The solid was washed with cold (5−10 °C) ethyl acetate and dried to constant weight to give the title compound as its bis HCl salt. The solid was partitioned between 100 mL of *n*-butyl acetate and 50 mL of a saturated aqueous sodium carbonate solution. The organic phase was washed with water and brine, cooled to room temperature, and stirred for 16 h. The reaction mixture was filtered and the solid was dried at 40−50 °C under reduced pressure to give the title compound (10 g, 75% yield) as the hemihydrate. Anal. Calcd for $C_{22}H_{28}ClN_5O_3S\cdot0.5(H_2O)$: C, 54.26; H, 6.00; N, 14.38; Cl, 7.28. Found: C, 54.06; H, 5.94; N, 14.38; Cl, 7.28. MS (ion spray): 478/480 ($(M + H)^+$, 100), 346 (55). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.23 (1H, s), 8.06 (1H, t), 7.84 (1H, d), 7.42 (1H, d), 6.96 (1H, d), 6.63 (1H, broad d), 6.34 (1H, d), 5.16 (1H, broad d), 4.94(1H, d), 4.76 (1H, q), 4.33 (1H, m), 4.11 (1H, q), 3.12 (2H, q), 3.07 (2H, m), 2.73 (1H, m), 2.51 (1H, m), 2.39 (1H, dt), 2.09 (1H, dt), 1.63 (2H, m), 1.05 (3H, t), 0.92 (3H, t). ^{13}C NMR (50 MHz, DMSO-d_6): δ 172.73 (C), 147.42 (C), 146.12 (C), 144.37 (CH), 138.74 (CH), 134.079 (C), 126.671 (CH), 124.516 (C), 122.779 (C), 121.626 (CH), 96.938 (CH), 75.073 (CH), 73.07 (CH), 58.61 (CH), 54.20 (CH), 48.81 (CH), 33.45 (CH_2), 32.19 (CH_2), 30.06 (CH_2), 27.23 (CH_2), 14.66 (CH_3), 10.40 (CH_3).

Acknowledgment. We thank our colleagues Luc Grondard, Benoît Viguier, and Laurence Pailleres-Hubert from Rhône-Poulenc Rorer, France, for their contributions expanding the scope of this work, and in particular for developing an alternative in situ tetrabutylammonium bromide promoted fluorination/amination and methanesulfonic acid/TFA/thioanisole detosylation procedures.

Supporting Information Available: ^{1}H NMR spectra for compounds **12**−**16**; single-crystal X-ray data for compound **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001066F