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Development of an Enabling Route to PF-00610355: A Novel Inhaled β_2-Adrenoreceptor Agonist

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ABSTRACT: The initial route used to prepare PF-00610355 (**8**) for early clinical development is described. Through careful choice of solvent, an efficient, telescoped route to carboxylic acid **23** was developed, affording this late-stage intermediate in 80% yield over 4 steps. Deprotection of **23** to give sodium salt **24a** and coupling with amine **6**·HCl afforded the desired API. Effective synthetic routes to two of the starting materials, chiral bromide **1** and amine **6**, are also described.

INTRODUCTION

The use of long-acting inhaled β_2-adrenoreceptor agonists is an established therapy for the treatment of respiratory diseases such as asthma and COPD. While both salmeterol and formoterol (Figure 1) are current marketed agents in this class, their duration of action is adequate only for twice-daily administration.[1] As a result, there has been considerable activity to identify novel, ultra-long-acting β_2-adrenoreceptor agonists that are suitable for once-daily dosing, with indacaterol (Figure 1) having been recently approved in the European Union (2009) for once-daily treatment of COPD.[2] Other advanced agents include milveterol (GSK-159797),[3] vilanterol (GSK-642444),[4] and olodaterol (BI-1744-CL).[5] Our efforts in this area[6] resulted in the identification of PF-00610355 (**8**) as a novel, once-daily inhaled β_2-adrenoceptor agonist;[1] herein we describe the development of the route that was used to prepare the first clinical supplies.

The medicinal chemistry route to **8** is shown in Scheme 1, wherein three key building blocks, bromide **1**, amino ester **2**, and amine **6**, are combined in a five-step sequence. The final step is a direct drop deprotection[7] with ammonium fluoride in ethanol, and **8** crystallizes directly from the reaction mixture with suitable purity and solid form properties.[1] A key feature of this initial process was that the crystalline TBS-protected acid **5** was easily purified, thus allowing multiple structural analogues to be prepared in an efficient manner. However, upon closer inspection, several of the yields were low, and multiple chromatographic purifications were employed en route to the desired **8**. In addition, all three building blocks (**1**, **2**, and **6**) were made through multistep sequences that would also require development.

RESULTS AND DISCUSSION

Initial development efforts were focused on developing suitable routes to building blocks **1**, **2**, and **6**. The development of a scaleable route to amino ester **2** has been reported elsewhere;[8] the salient point to note herein is that this process delivered the di(4-toluoyl)-L-tartaric acid (DTTA) salt of the ethyl ester **2a**, rather than the methyl ester **2** shown in Scheme 1.

Chiral bromide **1** was prepared from chiral aniline **13** (Scheme 2), a key building block in the synthesis of (*R*,*R*)-formoterol.[9] However, upon closer examination of the published process to **13**, there was very little detail available on how best to prepare bromoketone **11**. Fortunately, we identified a supplier of 4-hydroxy-3-nitro acetophenone **9** and were rapidly able to develop a scaleable route to bromoketone **11**, as shown in Scheme 2.[10] It is important to note that the bromoketone **11** is prone to halogen exchange, and thus it is essential to avoid contact with chloride sources.[11] Asymmetric reduction of **11** using the published protocol (diethylaniline borane, (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol)[9,12] proceeded smoothly affording the desired bromohydrin **12**. The initial optical purity in solution was around 94% ee; after isolation by crystallization from toluene/heptane, this was usually enhanced to >98% ee. The isolated yield of **12** was also high (95%). If the ee was <98%, a recrystallization from toluene/heptane could be used to increase the optical purity to >99% (85% recovery).[9]

Chemoselective reduction of the nitro functionality of **12** was achieved by hydrogenation over platinum oxide in THF. In contrast to the published processes we did not find it necessary to use toluene as a cosolvent[9] or to use any catalyst poisons.[13] The resulting aniline **13** was not isolated; instead after filtration to remove the catalyst, the THF solution was treated with methanesulfonyl chloride and pyridine to give the sulfonamide **14**. Finally, silylation with TBSCl and imidazole in refluxing CH_2Cl_2 afforded the desired bromide **1** (86% yield). The choice of base and solvent was critical for this final step, as the bromohydrin **14** was prone to cyclization to the unstable epoxide, resulting in decomposition (this was observed in most alternative conditions examined). This process was then successfully outsourced to multiple vendors to supply **1** for this and future manufacturing campaigns.

An alternative literature route to **14** was also examined (Scheme 3)[14] wherein the nitro acetophenone **10** was converted to the sulfonamide **15** prior to bromination. Using our prior

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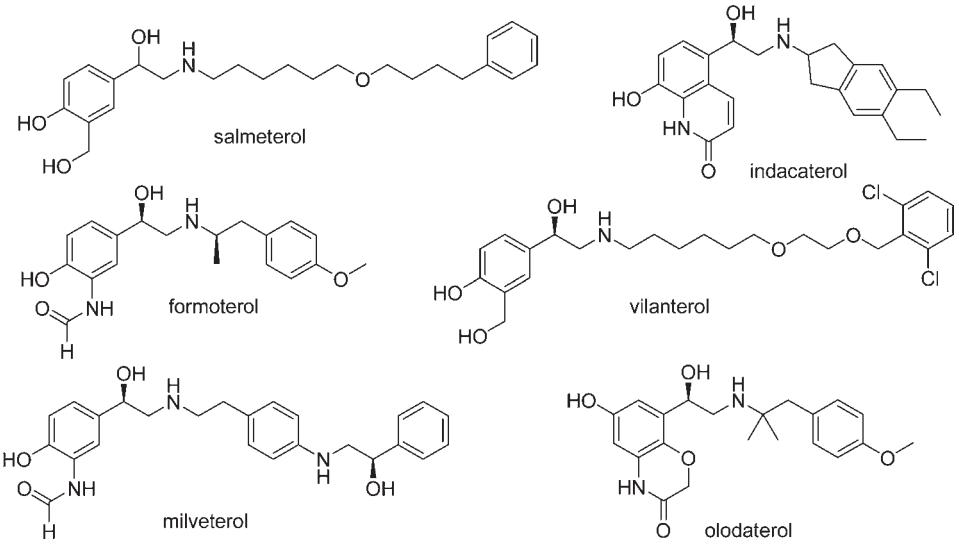
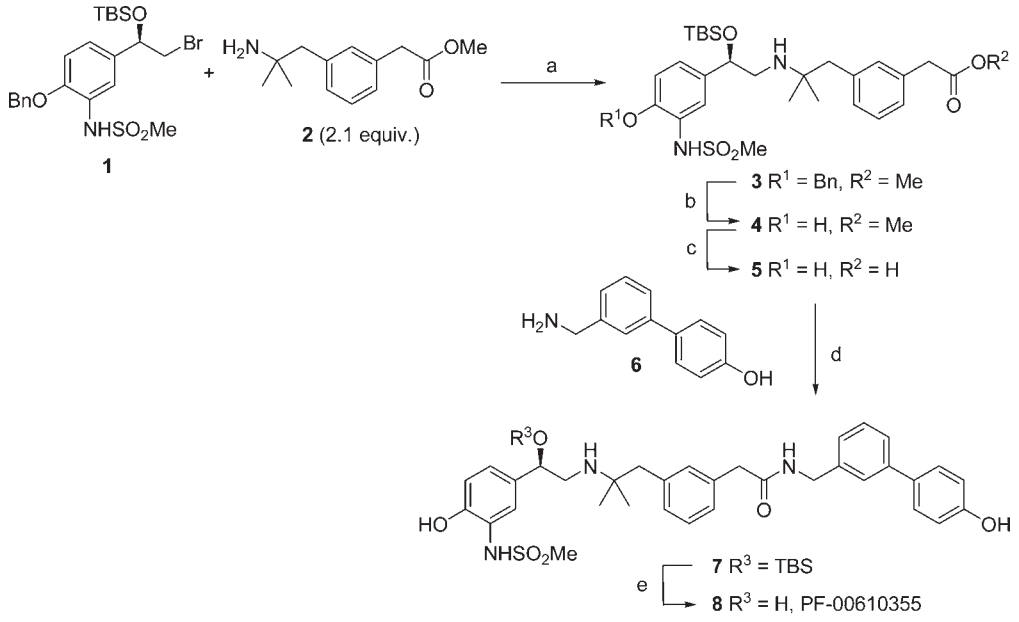


Figure 1. Structures of marketed and developmental long-acting β_2-adrenoreceptor agonists.

Scheme 1. Medicinal Chemistry Route to PF-00610355[a]



[a] Reagents and conditions: (a) (i) neat, 85 °C, 72 h; (ii) chromatography, 80%; (b) (i) ammonium formate, 20% $Pd(OH)_2/C$, ethanol, 85 °C; (ii) chromatography, 65%; (c) LiOH, THF/water, 72 h, 100%; (d) (i) **6**·HCl (1.0 equiv), EDC·HCl, HOBt, Et_3N, DMF; (ii) chromatography, 56%; (e) NH_4F, EtOH/water, 87%.

experience, we modified the reagents slightly and were able to isolate all of the intermediates through simple direct-drop processes, as described in the Experimental Section. However, the published procedure for the asymmetric reduction of **16**[14] provided only ~97% ee bromohydrin **14**, and we were unable to upgrade this to the required >98% ee by crystallization. Alternative reduction conditions did not provide higher optical purity material, and as a result, this process was not developed further.

Amine **6** was prepared from commercially available 3-bromobenzylamine hydrochloride **17**·HCl and 4-hydroxyphenyl boronic acid **19**, as shown in Scheme 4. Boc-protection of **17**·HCl proceeded smoothly, and Suzuki reaction with boronic acid **19** in the presence of $PdCl_2$(dppf) and sodium carbonate afforded the Boc protected biaryl **20**, after carbon treatment to remove palladium residues. Deprotection with 4 M hydrogen chloride (HCl) in 1,4-dioxane afforded amine **6**·HCl, with the hydrochloride salt precipitating from solution to provide a simple isolation process (in around 95% yield). This process was successfully outsourced to provide material for this and subsequent campaigns.[15] However, during one campaign (the largest scale conducted in-house), instead of charging anhydrous 4 M HCl in 1,4-dioxane, 4 M hydrochloric acid in 1,4-dioxane was inadvertently used. As a result of the unexpected water content, the isolated yield of **6**·HCl was rather low (58%). Once the problem had been identified, the mother liquors were reprocessed to provide a further 2.36 kg (37%) of **6**·HCl; this process

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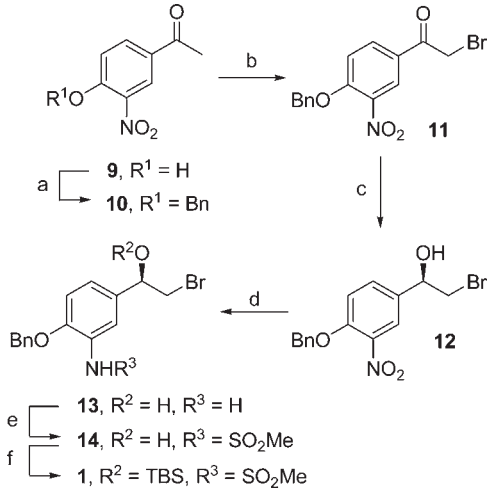
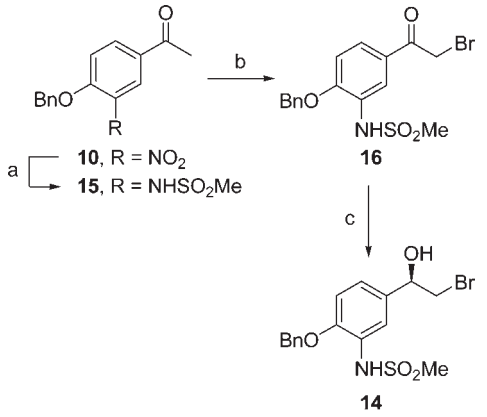
Scheme 2. Synthesis of TBS-Protected Bromohydrin 1[a]



[a] Reagents and conditions: (a) BnBr, *i*-Pr_2NEt, MeCN, reflux; then water, 96%; (b) (i) Bu_4NBr_3, THF/MeOH; then water; (ii) EtOAc recryst, 66%; (c) (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol, diethylaniline borane, THF; then toluene/heptane cryst, 95%, 99% ee; (d) H_2, PtO_2, THF, 20−25 °C; (e) MsCl, pyridine, THF; then toluene cryst, 83% (2 steps) (f) (i) TBSCl, imidazole, CH_2Cl_2, reflux; (ii) iPrOAc/heptane cryst, 86%.

Scheme 3. Alternative Synthesis of Bromohydrin 14 (see Ref 14)[a]

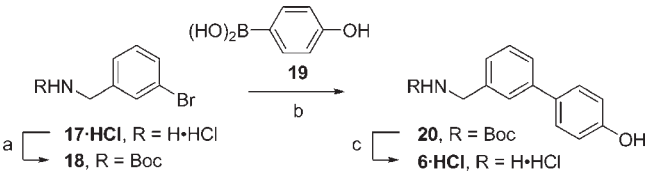


[a] Reagents and conditions: (a) (i) H_2, PtO_2, THF/toluene, 20−25 °C; (ii) MsCl, pyridine, MeCN; then water, 90%; (b) Bu_4NBr_3, THF/MeOH; then water, 100%; (c) (i) (*R*)-(+)-α,α-diphenyl-2-pyrrolidinemethanol, $B(OMe)_3$, $BH_3 \cdot SMe_2$, THF/toluene; (ii) chromatography, 96%, 97% ee.

is reported in the Experimental Section. The free base **6** can be prepared by simply stirring **6**·HCl in aqueous sodium hydroxide, followed by filtration.

Having established routes to the building blocks, we then examined the remainder of the synthesis (Scheme 1). The coupling reaction between amine **2** and bromide **1** was conducted without solvent (neat).[1] While neat reactions have been used successfully on scale,[9] when we examined this reaction, we found the mixture challenging to stir at ambient temperature, both before and after the reaction. Consequently, for practical and safety reasons we elected to add a solvent to the reaction

Scheme 4. Synthesis of Biaryl Amine 6·HCl[a]



[a] Reagents and conditions: (a) Boc_2O, Et_3N, EtOAc; then heptane, 94%; (b) **19**, $PdCl_2(dppf)$, Na_2CO_3, 1,4-dioxane/water, 72%; (c) 4 M HCl in 1,4-dioxane; then acetonitrile, 95%.

mixture. An additional concern was the use of amine **2** as an HBr scavenger in addition to being a coupling partner (2 equiv is used). Since **2** is made by a lengthy route, this was wasteful, and an alternative would be beneficial.

A screen of bases and solvents was carried out, from which acetonitrile (MeCN) was identified as the preferred solvent for the coupling reaction. The screen evaluated five solvents (DMF, CH_2Cl_2, MeCN, THF, and toluene) in combination with 10 bases (K_2CO_3, Ag_2CO_3, Cs_2CO_3, CsOH, K_3PO_4, sodium pentoxide, NaHMDS, imidazole, *i*-Pr_2NEt, and DBU), using a slight excess of **2a** relative to **1**. Although both K_2CO_3 and Ag_2CO_3 in MeCN appeared promising on small scale, unfortunately these did not work as well on larger scale. Consequently, since we were unable to identify a suitable alternative to amine **2a**[16] as the HBr scavenger, we continued to use 2 equiv of **2a** in this step.[17] As the process to amine **2a** afforded the DTTA salt,[8] an initial salt break step was also required (Scheme 5, step a).

Upon detailed investigation of the coupling reaction (Scheme 5, step b), a major issue was encountered, namely, that significant levels of TBS-deprotection of the product **21** to amino alcohol **22** were observed, and as the scale increased, this got worse (>20%). This resulted in substantial material loss during the subsequent chromatographic purification of **21** and clearly was not viable.

Faced with unacceptable yield losses we were forced to modify the synthetic route. Recognizing that we were unable to prevent partial loss of the TBS group during the coupling reaction, we treated the crude product (**21**) mixture with $Et_3N(HF)_3$ to affect complete deprotection, affording amino alcohol **22**. Hydrolysis of the ethyl ester then gave the free acid **23**. After some experimentation, we discovered that a 1:1 1,4-dioxane solvate of **23** crystallized upon neutralization of a basic aqueous solution of **23** in the presence of 1,4-dioxane. Having identified this crystalline intermediate (the remainder were oils), we sought to develop a telescoped process to **23**. Because MeCN is water-miscible, it was not suitable for this purpose; however, the higher homologue, propionitrile (EtCN), is immiscible with water. When we examined EtCN in the coupling step, we discovered that it afforded both a quicker reaction and a superior reaction profile to MeCN. Similarly, we were able to successfully demonstrate the other steps using EtCN.

Consequently, by using EtCN as the common solvent, we were then able to telescope the salt break, coupling, TBS deprotection, and ester hydrolysis steps (Scheme 5, steps a−d). Once the ester hydrolysis was complete, the sodium salt of **23** partitioned into the aqueous phase, and the organic phase could be discarded. The aqueous phase was then diluted with 1,4-dioxane, and hydrochloric acid was added, precipitating pure **23** (dioxane solvate) in 80% yield from bromide **1**. Despite considerable effort, we were unable to recover and recycle the excess **2a**.

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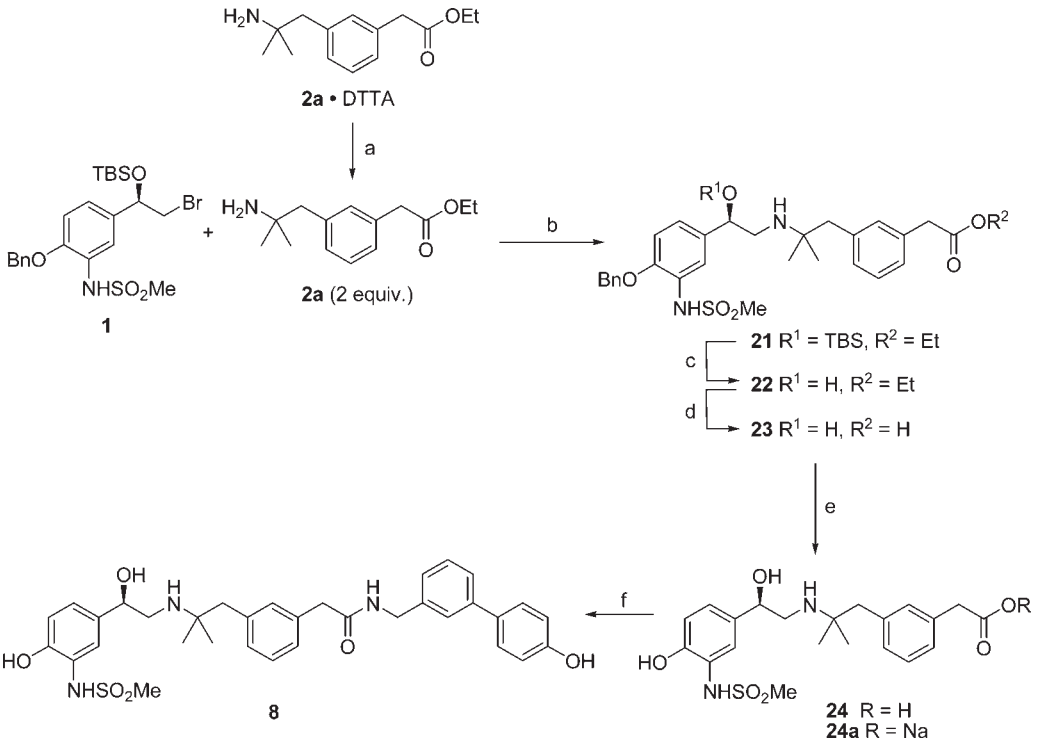
Scheme 5. Large-Scale Route to PF-00610355 (8)[a]



[a] Reagents and conditions: (a) K_2CO_3, EtCN/water; (b) EtCN, reflux; (c) $Et_3N(HF)_3$, EtCN; (d) (i) NaOH, EtCN/water; then HCl/1,4-dioxane; (ii) water reslurry, 80%; (e) NaOH, H_2, 20% $Pd(OH)_2/C$, water; then acetonitrile, 69%; (f) (i) **6**·HCl (1.0 equiv), EDC·HCl, pyridine; then water, 80%; (ii) acetone/water; (iii) MeOH/water reslurry, 45%.

At this point, two alternative sequences were considered: deprotection followed by amide formation or amide formation followed by deprotection. Since **8** has limited solubility in most common organic solvents, we recognized that separating **8** from a heterogeneous hydrogenation catalyst (e.g., Pd/C) would be challenging. In addition, those solvents in which **8** is soluble (DMF, NMP) were prone to leach palladium from the support, and it proved difficult to recover **8** from these solvents (addition of water tended to give gummy residues, and concentration caused decomposition). A final consideration was that **8** was not the only candidate under evaluation, and having a common late-stage intermediate available that would allow us access to other targets in a single step through simply changing the amine coupling partner would be beneficial. Therefore we chose to conduct the deprotection first, followed by amide formation as the final step.

Deprotection of **23** under hydrogenation conditions proceeded smoothly; however, the product (**24**) proved difficult to isolate. Recognizing the challenges of the final coupling step (vide infra), we ideally wanted to isolate a well characterized solid at this stage to ensure that we could determine accurate stoichiometric charges of the other reagents. A further complication was that both the starting material **23** and product **24** are rather insoluble in common hydrogenation solvents. Addition of aqueous ammonia to either methanol or THF slurries of **23** did afford a homogeneous solution; however, during the subsequent hydrogenation significant Pd leaching was observed, resulting in **24** being isolated as a black tar. Addition of acetic acid to either methanol or THF was also successful, but in this case **24** was isolated as the acetate salt, clearly unsuitable for the subsequent coupling step.

A large salt screen, varying the counterion, stoichiometry, and isolation solvent, was carried out on the free acid **24**, and from this screen the monosodium salt **24a** was identified as a suitable, crystalline solid. As **24a** is water-soluble, we elected to conduct the hydrogenolysis in water, followed by solvent exchange to acetonitrile to precipitate **24a**. Conducting the hydrogenolysis in water also helped to minimize the level of Pd leach from the catalyst; an Arbocel treatment was added to ensure acceptable Pd levels were obtained. Since the free acid **24** and the disodium salt were not crystalline, and there were limited options for purging inorganic impurities, it was important that the sodium hydroxide charge was accurate. When conducted with appropriate care, the hydrogenation and isolation proceeded smoothly, affording the desired salt **24a**.[18] This sequence was scaled up in our pilot plant, affording sodium salt **24a** in an acceptable 69% yield from bromide **1**.

The remaining challenge was to couple amine **6** with sodium salt **24a**. Since there are multiple reactive sites in both molecules, we recognized that accurate control of stoichiometry and choice of reagents would be crucial to minimize byproduct formation. In addition, the process used to manufacture **8** would need to include a solution filtration to remove particulate impurities ("speck-free" filtration), as well as provide material suitable for subsequent particle size reduction, required for this inhaled therapeutic agent.[19]

A range of coupling reagents, additives, and solvents were screened, as well as the use of both the free base **6** and the hydrochloride salt **6**·HCl. From this screen, the optimal reaction conditions were identified as coupling amine salt **6**·HCl with sodium salt **24a** using EDC·HCl and HOBt in the presence of

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triethylamine. Due to the low solubility of **8**, only DMF, DMA, DMSO, and pyridine were suitable for the reaction. Initial attempts at isolating **8** from these reactions by precipitation (addition of water or other antisolvents) or an extractive workup were unsuccessful, and removal of the high-boiling-point solvents by distillation caused degradation. However, by using pyridine as the solvent, upon reaction completion we were able to azeotropically distill and replace with ethanol at 50 °C under vacuum (higher temperatures led to significant degradation) and isolate crude **8** by crystallization in 80% yield. Addition of water to the crystallization solvent maximized recovery and purged most of the reagent-related byproducts. In addition, HOBt was not required when using pyridine. One drawback of this process was the lack of a homogeneous solution phase, thus precluding a speck-free filtration at this point. Unfortunately, due to the aforementioned multiple reactive sites in **6**·HCl and sodium salt **24a**, as well as the extended processing times at elevated temperature required to displace pyridine with ethanol, **8** was contaminated with several low-level impurities and required further purification.

An extensive screen of solvents, solvent mixtures, and solvent/water mixtures was carried out to identify a suitable purification strategy.[20] Due to the low solubility and limited stability of **8**, we were forced to adopt a two-stage purification protocol, as follows. Initially, **8** was dissolved in a relatively large volume (36 mL/g) of 10% aqueous acetone at reflux, allowing a speck-free filtration to be carried out. Partially purified **8** was isolated after concentration to half volume and crystallization at 20 °C. A reslurry in 5% aqueous methanol at reflux, followed by granulation at 20 °C, afforded acceptable purity **8**, with suitable solid form properties for downstream processing. However, the overall yield for this purification process was a disappointing 45%. Given the need to deliver material in support of early development work, we used this process to prepare the first batches of material. Subsequent work to develop a more suitable process for long-term manufacture of **8** will be reported in due course.

In conclusion, herein we describe the initial scale-up route used to prepare PF-00610355 (**8**). Through careful choice of solvent, an efficient, telescoped route to carboxylic acid **23** was developed. Deprotection of **23** to give sodium salt **24a** and coupling with amine **6**·HCl afforded the desired API. Effective synthetic routes to two of the key building blocks, chiral bromide **1** and amine **6**, are also described.

EXPERIMENTAL SECTION

4-Benzyloxy-3-nitroacetophenone, 10. 4-Hydroxy-3-nitroacetophenone **9** (200 g, 1.10 mol) was slurried in acetonitrile (2 L) at ambient temperature. *N*,*N*-Diisopropylethylamine (202 mL, 1.16 mol) was added, resulting in a temperature rise of 6 °C, to give a dark orange solution. Benzyl bromide (138 mL, 1.16 mol) was then added over 5 min, and once the addition was complete the reaction mixture was heated to reflux. After 3 h the reaction was complete and the mixture was cooled to 25 °C, some precipitation was noted. Water (2 L) was added over 5 min, and the resulting suspension was stirred at 25 °C for 1 h. The solid was isolated by filtration, washed with water (2 × 500 mL), and then dried under vacuum at 50 °C to afford the product **10** as a pale yellow solid (287 g, 96%). Spectroscopic data were identical to those reported.[10]

1-[4-Benzyloxy)-3-nitrophenyl]-2-bromoethanone, 11. Tetrabutylammonium tribromide (168.5 g, 0.35 mol) was dissolved in THF (250 mL). The resulting solution was added over 2 h to a vigorously stirred suspension of **10** (90.3 g, 0.33 mol) in a mixture of THF (270 mL) and methanol (45 mL). After a further 2 h, HPLC analysis showed that the reaction was complete. Water (630 mL) was added over 20 min, and after a further 1 h the suspension was filtered; the solid was washed with water (2 × 90 mL) and dried under vacuum at 50 °C to give crude **11** as a pale yellow solid (90.6 g). This was suspended in ethyl acetate (317 mL), and the mixture was refluxed until complete dissolution occurred. The solution was then cooled to 25 °C, and the resulting slurry was stirred at 25 °C for 4 h. The solid was isolated by filtration, washing with ethyl acetate (2 × 25 mL), and dried under vacuum oven at 50 °C to give the product **11** as a pale yellow solid (76.5 g, 66%). Spectroscopic data were identical to those reported.[10]

(1*R*)-1-[4-(Benzyloxy)-3-nitrophenyl]-2-bromoethanol, 12 (adapted from ref 12). (1*R*,2*S*)-(+)-*cis*-1-Amino-2-indanol (2.13 g, 0.014 mol) was dissolved in anhydrous THF (300 mL) and cooled to 10 °C. Diethylaniline-borane (38.1 mL, 0.214 mol) was added over 5 min, maintaining the temperature below 12 °C. The resulting solution was stirred at 5−10 °C for 1 h and then cooled to 4 °C. A solution of bromide **11** (100 g, 0.29 mol) in anhydrous THF (900 mL) was added over ∼3 h, maintaining the temperature between 3 and 5 °C. After 30 min, acetone (100 mL) was added over 10 min, maintaining the temperature below 5 °C. The solution was warmed to 20 °C and stirred for 1 h. The solution was concentrated under reduced pressure at 45 °C to 300 mL, and toluene (700 mL) was added. The organic solution was washed with 10% aqueous sulfuric acid (2 × 300 mL), followed by water (120 mL), and was concentrated under reduced pressure at 50 °C to 300 mL. The solution was cooled to 20 °C and stirred for 1 h, and then a seed of **12** (0.25 g) was added. A suspension quickly formed and was stirred at 20 °C for 1 h and then at 15 °C for 1 h. Heptane (200 mL) was added over 15 min, maintaining the temperature at 15−18 °C. The slurry was stirred at 15−18 °C for 1 h, and then the solid was isolated by filtration, washing with heptane (2 × 100 mL). The resulting filter cake was dried under vacuum at 45 °C to give **12** as an off-white solid (95.6 g, 95% yield, 98.6% ee). If the optical purity is not suitable (>98% ee), the product can be recrystallized as follows: Dissolve bromohydrin **12** in toluene (4 mL/g) at 40 °C. Once all the material has dissolved, cool the solution to 20 °C and seed with optically pure **12** (0.0025 g/g input). Stir the resulting suspension at 20−25 °C for 1 h, then add heptane (2 mL/g) over 10 min, and then stir at 20−25 °C for 1 h. Isolate the solid by filtration, washing with heptane (2 × 1 mL/g), and dry at 45 °C under vacuum to obtain optically pure **12** as an off-white solid (85% recovery, 100% ee). Spectroscopic data were identical to those reported.[9,10]

***N*-(2-(Benzyloxy)-5-(2-bromoacetyl)phenyl)methanesulfonamide, 16 (adapted from ref 14).** PtO_2 (200 mg; 0.5% w/w) was added to a solution of acetophenone **10** (38.7 g, 142.7 mmol) in THF (387 mL) and toluene (194 mL). The reaction mixture was stirred under 1.03 bar of hydrogen at 25 °C for 24 h. The mixture was filtered through Celite and concentrated to dryness, affording a sticky orange solid (32.8 g). This solid was dissolved in refluxing isopropyl acetate (66 mL), cooled to 25 °C, and stirred for 4 h. The solid was isolated by filtration, washed with isopropyl acetate (16 mL), and dried under vacuum at 50 °C for 12 h to give the aniline intermediate as an orange solid (27.6 g). This was suspended in acetonitrile (138 mL), pyridine

(18.5 mL; 228.5 mmol) was added, followed by methanesulfonyl chloride (10.6 mL; 137.1 mmol), and the resulting mixture was stirred at 25 °C for 1 h. Water (207 mL) was added over 5 min, and the resulting suspension was stirred at 25 °C for 1 h. The solid was isolated by filtration, washed with water (2 × 28 mL), and dried under vacuum at 50 °C for 12 h to give sulfonamide **15** as an orange solid (34.4 g, 75%).

A solution of tetrabutylammonium tribromide (70.8 g, 146.9 mmol) in THF (92 mL) was added over 45 min to a suspension of sulfonamide **15** (46 g, 144.0 mmol) in methanol (460 mL) at 25 °C to give an orange solution. After a further 1 h at 25 °C, HPLC analysis indicated complete reaction. Water (690 mL) was added over 20 min, and the resulting suspension was stirred at 25 °C for 1 h. The solid was isolated by filtration, washed with water (2 × 230 mL), and dried under vacuum at 50 °C for 12 h to give bromoketone **16** as a pale yellow solid (57.1 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (1H, d, J = 1.8 Hz), 7.84 (1H, dd, J = 8.6, 1.8 Hz), 7.44 (5H, m), 7.11 (1H, d, J = 8.6 Hz), 6.90 (1H, s), 5.23 (2H, s), 4.42 (2H, s), 3.02 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.7, 152.6, 134.7, 129.1, 127.9, 127.7, 127.1, 126.8, 121.0, 112.0, 71.5, 39.8, 30.4. LCMS: found m/z 415.05/417.05 $[M + NH_4]^+$. Anal. Calcd For $C_{16}H_{16}BrNO_4S$: C, 48.25; H, 4.05; N, 3.52; S, 8.05. Found: C, 47.96; H, 3.95; N, 3.49; S, 8.18.

***N*-{2-(Benzyloxy)-5-[(1*R*)-2-bromo-1-hydroxyethyl]phenyl}methanesulfonamide, 14.** *Method A.* PtO_2 (0.40 g, 1 wt %/wt) was added to a solution of bromohydrin **12** (40 g, 113.6 mmol; >98% ee) in THF (160 mL), and the mixture was hydrogenated at 6.9 bar hydrogen pressure and 20−25 °C for 12 h. The mixture was filtered through Celite, pyridine (18.4 mL, 227.2 mmol) was added, followed by methanesulfonyl chloride (10.5 mL, 136.3 mmol), and the reaction mixture was stirred at 20 °C for 2 h, at which point HPLC analysis indicated complete conversion. Hydrochloric acid (1 M; 180 mL) was added, and after stirring for 5 min, the mixture was extracted with toluene (180 mL). The toluene solution was washed with water (2 × 90 mL) and concentrated under reduced pressure at 45 °C to 110 mL. The solution was then cooled to 20 °C, and the resulting slurry was stirred for 1 h, cooled to 10 °C, and stirred for a further 1 h. The solid was isolated by filtration, washed with toluene (2 × 10 mL), and dried at 45 °C under vacuum to give **14** as a light pink solid (38.0 g, 83%; >98% ee). Spectroscopic data were identical to those reported.[14]

Method B (from ref 14*).* Trimethyl borate (4.9 mL, 35.4 mmol) was added to a solution of (*R*)-(+)-α,α-diphenyl-2-pyrrolidinemethanol in toluene (100 mL). The cloudy mixture was stirred at 25 °C for 30 min, refluxed under Dean−Stark conditions for 1.5 h, and then cooled to 25 °C. This mixture was then added dropwise to a solution of bromoketone **16** (50 g, 125.6 mmol) in THF (1 L) while maintaining the temperature around −13 °C. Borane−methyl sulfide complex (10 M; 25 mL; 250 mmol) was then added over 30 min while maintaining the temperature around −13 °C. Once the addition was complete, methanol (100 mL) was added maintaining the temperature at around −13 °C. The reaction mixture was warmed to 25 °C and stirred for 30 min. The solution was poured into hydrochloric acid (1 M; 1 L) and extracted twice with diethyl ether (1 L, 500 mL). The combined ether solution was washed with saturated brine (500 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum to give a semisolid residue that was adsorbed onto silica gel (200 g) and purified by column chromatography eluting with EtOAc/heptane (1:1) to give bromohydrin **14** (48.3 g, 96%; 97% ee)

***N*-{2-(Benzyloxy)-5-[(1*R*)-2-bromo-1-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl]phenyl}methanesulfonamide, 1.** Bromohydrin **14** (10 g, 25.0 mmol) was dissolved in CH_2Cl_2 (20 mL). Imidazole (4.6 g, 37.5 mmol) was added, followed by TBSCl (5.3 g, 35.0 mmol), and the reaction mixture was heated to reflux for 1 h. HPLC analysis showed complete conversion, so the solution was cooled to 30 °C and diluted with isopropyl acetate (80 mL). Hydrochloric acid (2 M; 50 mL) was added, and the mixture was stirred vigorously for 10 min. The phases were separated, and the organic phase was washed with water (50 mL). The organic phase was then concentrated under reduced pressure at 45 °C to ∼25 mL and cooled to 20 °C. A suspension quickly formed and was stirred at 20 °C for 30 min. Heptane (20 mL) was then added over 10 min, and the suspension was cooled to 5 °C and stirred for 1 h. The suspension was then filtered, and the isolated solid was washed with heptane (2 × 10 mL). The resulting filter cake was dried under vacuum at 50 °C to give **1** as a white solid (11.05 g, 86% yield). Mp 122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (1H, d, J = 2.0 Hz), 7.48−7.36 (5H, m), 7.15 (1H, dd, J = 8.4, 2.0 Hz), 7.01 (1H, d, J = 8.4 Hz), 6.87 (1H, s), 5.13 (2H, s), 4.85 (1H, dd, J = 7.4, 4.7 Hz), 3.47 (2H, m), 2.93 (3H, s), 0.93 (9H, s), 0.14 (3H, s), −0.03 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.2, 135.9, 135.7, 128.9, 127.9, 126.6, 122.9, 118.6, 112.1, 74.5, 71.2, 39.5, 39.1, 25.8, 18.2, −4.7, −4.8. LCMS: found m/z 531.15/533.15 $[M + NH_4]^+$. Anal. Calcd For $C_{22}H_{32}BrNO_4SSi$: C, 51.35; H, 6.27; N, 2.72; S, 6.23. Found: C, 51.39; H, 6.25; N, 2.92; S, 6.28.

***tert*-Butyl (3-Bromobenzyl)carbamate, 18.** Triethylamine (660 mL, 4.71 mol) was added to a slurry of 3-bromobenzylamine hydrochloride **17**·HCl (1.00 kg, 4.49 mol) in ethyl acetate (4 L), and the mixture was stirred for 30 min at 20−25 °C and then cooled to 0 °C. A solution of di-*tert*-butyl dicarbonate (1.08 kg, 4.94 mol) in ethyl acetate (2 L) was then added over 30 min at such a rate as to maintain the temperature between 0 and 20 °C. The reaction mixture was then stirred at 20−25 °C for 2 h, at which point the reaction was complete. Water (3 L) was added, and the mixture was stirred vigorously for 10 min. The phases were separated, and the organic phase distilled and replaced with heptane under reduced pressure at 35−45 °C to a final volume of approximately 4 L. The solution was then cooled to 0 °C over 2 h, and the resulting suspension was stirred at 0 °C for 12 h. The product was isolated by filtration, washing with cold heptane (2 × 500 mL); the resulting filter cake was dried in a vacuum oven at 35 °C to provide **18** as a white solid (1.214 kg, 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.43 (3H, m), 7.32−7.22 (2H, m), 4.13 (2H, d, J = 6.3 Hz), 1.40 (9H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.8, 143.1, 130.4, 129.6, 129.5, 125.9, 121.5, 78.0, 42.8, 28.2. LCMS: found m/z 230.07/232.06 $[M - C_4H_8 + H]^+$.

***tert*-Butyl [(4′-Hydroxybiphenyl-3-yl)methyl]carbamate, 20.** A mixture of 4-hydroxyphenylboronic acid **19** (2.71 kg; 19.7 mol), *N*-Boc bromobenzylamine **18** (5.12 kg; 17.9 mol), and sodium carbonate (2.84 kg; 26.8 mol) in 1,4-dioxan (25.6 L) and demineralized water (25.6 L) was sparged with nitrogen for 1 h at 25 °C. $PdCl_2(dppf)\cdot CH_2Cl_2$ (14.6 g; 0.018 mol) was charged, and the mixture was sparged with nitrogen for a further 30 min. The mixture was heated to 65−70 °C and held under a nitrogen blanket for 2 h. HPLC analysis indicated 3% bromide **18** remaining, so additional $PdCl_2(dppf)\cdot CH_2Cl_2$ (14.6 g; 0.018 mol) was charged, and the mixture was held at 65−70 °C for a further 2 h. HPLC analysis indicated complete reaction, so the mixture was cooled to 20 °C, and ethyl acetate (41 L) was added.

The mixture was stirred vigorously for 10 min and then allowed to settle, and the aqueous phase was separated and discarded. The organic phase was washed with a solution of citric acid (1.90 kg) in demineralized water (19 L), followed by a solution of sodium chloride (3.15 kg) in demineralized water (19 L). Activated carbon (Darco KBB-100mesh, 5.12 kg) was added to the organic solution, and the mixture was stirred for 12 h. The mixture was filtered through a pad of Arbocel, washing with methanol (25.6 L). The combined filtrate was distilled and replaced with toluene at 40−50 °C under reduced pressure (∼100 mbar) to a final volume of approximately 15 L (two 25.6 L toluene charges were used). The solution was then cooled to 10 °C over 2 h, and the resulting suspension was stirred at 10 °C for 12 h. The solid was isolated by filtration, washed with cyclohexane (2 × 2.56 L), and dried under vacuum at 40 °C to provide the product **20** as a white solid (3.88 kg; 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50−7.30 (5H, m), 7.25 (2H, m), 6.90 (2H, d, J = 7.8 Hz), 4.95 (1H, br. s), 4.44 (2H, br. s), 1.47 (9H, s).

3′-(Aminomethyl)biphenyl-4-ol hydrochloride, 6·HCl. A solution of hydrochloric acid in 1,4-dioxane (4 M, 64.7 L; 258.8 mol) was added to a cooled solution (15 °C) of *N*-Boc biaryl amine **20** (8.09 kg; 27.0 mol) in 1,4-dioxane (12.1 L), keeping the temperature below 20 °C (∼40 min), followed by a 1,4-dioxane line wash (4 L). The mixture was held at 20−25 °C for 1 h, at which point HPLC analysis indicated complete reaction. The suspension was concentrated under vacuum at 40−45 °C to approximately 40 L and then stirred for 12 h at 20 °C. The solid was isolated by filtration, washed with 1,4-dioxane (2 × 4 L), and blown dry under nitrogen for 2 h. The resulting damp filter cake was added to acetonitrile (81 L) and heated at reflux for 2 h, then cooled to 20 °C and stirred for 1 h. The solid was isolated by filtration and washed with acetonitrile (2 × 4 L). The resulting filter cake was then dried in a vacuum oven at 40 °C to provide **6**·HCl as a white solid (3.65 kg, 58%). The combined 1,4-dioxane mother liquors and washes were charged to a vessel. The solution was heated to reflux, and water was azeotropically distilled from the mixture, maintaining the pot volume at ∼40 L by addition of fresh anhydrous 1,4-dioxane (in total 133 L was charged in four equal portions). Once the vapor temperature exceeded 100 °C, the mixture was cooled to 20 °C, and the suspension was stirred for 12 h. The solid was isolated by filtration, washing with acetonitrile (2 × 4 L), and blown dry under nitrogen for 2 h. The damp filter cake was added to acetonitrile (40 L) and heated at reflux for 2 h, then cooled to 20 °C and stirred for 1 h. The solid was isolated by filtration, washing with acetonitrile (2 × 4 L). The resulting filter cake was then dried in a vacuum oven at 40 °C to provide **6**·HCl as a light brown solid (2.36 kg, 37%). Mp 221 °C; ^{1}H NMR (400 MHz, CD_3OD) δ: 7.70 (1H, t, J = 2.0 Hz), 7.62 (1H, dt, J = 7.8, 1.6 Hz), 7.55−7.45 (3H, m), 7.38 (1H, dt, J = 7.6, 1.6 Hz), 6.90 (2H, dm, J = 8.6 Hz), 4.19 (2H, s). ^{13}C NMR (100 MHz, CD_3OD) δ: 158.7, 143.5, 134.9, 132.8, 130.6, 129.2, 128.2, 128.0, 127.9, 116.8, 44.5.

Salt Break Procedure. A suspension of **6**·HCl (1.0 g; 4.2 mmol) in aqueous sodium hydroxide (170 mg NaOH in 20 mL water) was sonicated to break up large lumps and then stirred at 25 °C for 2 h. The solid was isolated by filtration, washed with water (3 × 15 mL), and dried under vacuum at 50 °C to give the free base **6** (0.66 g; 79%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.57 (1H, s), 7.50 (2H, d, J = 8.6 Hz), 7.41 (1H, d, J = 7.4 Hz), 7.33 (1H, t, J = 7.4 Hz), 7.24 (1H, d, J = 7.4 Hz), 6.87 (2H, d, J = 8.6 Hz), 4.60 (2H, br. s), 3.78 (2H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.2, 144.5, 140.1, 131.0, 128.5, 127.9, 127.7, 125.1, 124.8, 124.4, 123.8, 115.7, 45.7. LCMS: found m/z 200.24 $[M + H]^+$. Anal. Calcd For $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.25; H, 6.53; N, 7.04.

[3-(2-{[(2*R*)-2-{4-(Benzyloxy)-3-[(methylsulfonyl)amino]-phenyl}-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-acetic Acid, 23. Ethyl [3-(2-amino-2-methylpropyl)phenyl]-acetate di(4-toluoyl)-L-tartaric acid salt **2a**·DTTA[8] (7.01 kg; 11.27 mol) was suspended in propionitrile (35 L). A solution of potassium carbonate (6.23 kg; 45.1 mol) in water (35 L) was added, and the mixture was stirred at 25 °C until all of the solids had dissolved (about 1 h). The phases were separated, and the organic phase was washed with water (17.5 L). The organic solution was concentrated under vacuum at 45−50 °C to a volume of ∼4 L, and this concentrate was used directly in the next step. A sample was concentrated to dryness, and from this the yield of free base **2a** was estimated as 92%.

A solution of amine **2a** in propionitrile (1.70 kg; approx 5.9 mol **2a**) was charged to a reactor, followed by a propionitrile line wash (1.4 L). Bromohydrin **1** (1.51 kg; 2.9 mol) was added, and the mixture was refluxed for 48 h at which point HPLC analysis indicated 4% **1** remaining. The mixture was diluted with propionitrile (6 L) and cooled to 20 °C. Hydrochloric acid (1 M; 7.55 L) was added, and the mixture was stirred for 10 min. The aqueous phase was removed and discarded, the organic phase was washed with water (3.8 kg), and triethylamine trihydrofluoride (995 mL; 5.86 mol) was added. The mixture was stirred at 25 °C for 3 h, at which point HPLC analysis showed complete conversion to alcohol **22**. Aqueous ammonia (5 M; 7.45 L) was added, and the mixture was stirred for 10 min. The aqueous phase was discarded, and the organic phase was washed with water (7.45 L). A solution of sodium hydroxide (0.7 kg; 17.5 mol) in water (7.45 L) was added, and the biphasic mixture was stirred vigorously for 21 h at 25 °C. HPLC analysis of a sample indicated complete conversion to acid **23**, so the phases were separated. The retained aqueous phase was washed with propionitrile (7.45 L) and was then diluted with 1,4-dioxane (7.45 L). Concentrated hydrochloric acid was added at such a rate as to keep the temperature below 30 °C until pH ∼6 was achieved (1.35 L was added over 2 h in this case). The resulting slurry was stirred at 20 °C for 2 h, then the solid was isolated by filtration, washing with a 1:1 mixture of 1,4-dioxane and water (2.44 L). The damp cake was suspended in water (8.1 L) and stirred at 50 °C for 15 min. The slurry was cooled to 25 °C, and the solid was isolated by filtration, washing with water (2.44 L). The filter cake was dried at 50 °C under vacuum to give **23** as a 1:1 solvate with 1,4-dioxane (1.42 kg; 80%). Mp 189 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.55 (2H, d, J = 8.0 Hz), 7.41 (2H, t, J = 7.0 Hz), 7.33 (2H, m), 7.19 (1H, dd, J = 8.6, 2.0 Hz), 7.16 (1H, d, J = 7.6 Hz), 7.10 (3H, m), 6.98 (1H, d, J = 7.4 Hz), 5.18 (2H, s), 4.66 (1H, dd, J = 8.8, 3.3 Hz), 3.58 (4H, s; 1,4-dioxane), 3.45 (2H, s), 2.91 (3H, s), 2.86 (1H, dd, J = 11.5, 3.5 Hz), 2.74 (3H, m), 1.01 (6H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 174.0, 150.7, 137.2, 136.9, 136.3, 136.1, 131.6, 128.3, 128.2, 127.8, 127.6, 127.5, 127.1, 125.5, 124.2, 124.0, 112.7, 70.4, 69.8, 66.3 (1,4-dioxane), 54.7, 49.4, 45.0, 42.6, 25.0, 24.8. LCMS: found m/z 527.20 $[M + H]^+$. Anal. Calcd For $C_{28}H_{34}N_2O_6S \cdot C_4H_8O_2$: C, 62.52; H, 6.89; N, 4.56; S, 5.22. Found: C, 62.15; H, 6.70; N, 4.89; S, 5.56.

Sodium [3-(2-{[(2*R*)-2-Hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl}ethyl]amino}-2-methylpropyl)phenyl]acetate, 24a. Sodium hydroxide (180 g; 4.38 mol) was

dissolved in water (85 L), and then acid **23** (2.5 kg; 4.38 mol) and 20 wt % $Pd(OH)_2/C$ (50% water wet; 250 g) were added and were rinsed into the vessel with water (4 L). The mixture was hydrogenated at 60 °C and 8.3 bar hydrogen pressure until hydrogen uptake ceased (90 min). The mixture was cooled to 20 °C and placed under nitrogen. Arbocel (2.5 kg) was added, followed by a water wash (10 L), and the mixture was stirred at 20 °C for 40 min. The slurry was then filtered through a Gauthier filter, washing with water (20 L). The aqueous solution was concentrated under vacuum (~100 mbar) at 50 °C to a volume of 11 L, and then a vacuum distill and replace operation was performed at 50 °C with acetonitrile until all water had been removed (maintaining ~11 L volume, around 20 L acetonitrile used). The mixture was cooled to 20 °C over 2 h and was then granulated for 16 h. The solid was isolated by filtration, washing with acetonitrile (4.6 L) and was dried at 40 °C under vacuum to give sodium salt **24a** as a light brown solid (1.38 kg; 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.14 (1H, d, J = 2.2 Hz), 7.08 (2H, m), 6.98 (1H, br. s), 6.87 (2H, m), 6.75 (1H, d, J = 8.2 Hz), 4.41 (1H, dd, J = 7.6, 4.7 Hz), 3.25 (2H, s), 2.81 (3H, s), 2.70−2.59 (2H, m), 2.55 (2H, s), 0.93 (3H, s), 0.92 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 174.5, 150.1, 138.1, 137.6, 134.7, 131.2, 127.4, 127.0, 126.8, 122.0, 114.8, 72.2, 52.6, 50.2, 46.4, 45.0, 26.7, 26.5. LCMS: found m/z 437.21 $[M + H]^+$.

***N*-[(4′-Hydroxybiphenyl-3-yl)methyl]-2-[3-(2-{[(2*R*)-2-hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl}ethyl]amino}-2-methylpropyl)phenyl]acetamide, 8.** A slurry of sodium salt **24a** (1.6 kg; 3.49 mol) and hydrochloride salt **6**·HCl (905 g; 3.84 mol) in pyridine (12.8 L) was stirred at 25 °C for 30 min, and then 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (803 g; 4.19 mol) was added in one portion. The resulting mixture was stirred at 25 °C for 12 h, at which point HPLC analysis indicated complete conversion. The mixture was distilled under reduced pressure at 40−50 °C down to a volume of 8 L. A distill and replace procedure with ethanol under reduced pressure at 40−50 °C was then used to remove the pyridine (target NMT 5% pyridine remaining), giving a final volume of 8 L. The vacuum was released, and demineralized water (17.6 L) was added at a constant rate over 1 h, maintaining the temperature at 45−50 °C. The resulting suspension was cooled to 20 °C over 2 h and was stirred at 20 °C for 12 h. The solid was isolated by filtration, washing with a 1:1 mixture of ethanol and water (2 × 3.2 L), and dried under suction for 1 h. The filter cake was dried under vacuum at 40 °C for 24 h to give crude **8** (1.73 kg, 2.8 mol, 80%).

Purification. Crude **8** (1.27 kg) was suspended in a mixture of acetone (40.7 L) and water (5.1 L), and the mixture was heated to reflux to give a solution. The hot solution was filtered through a 1.2 μm filter, washing with acetone (5 L). The filtered solution was concentrated to 20 L by distillation and then cooled to 20 °C over 4 h. The resulting slurry was granulated for 16 h, then the solid was isolated by filtration, washing twice with a mixture of filtered acetone (1.9 L) and filtered water (0.64 L). After being blown dry for 30 min, the damp cake was recharged to the vessel, and a mixture of filtered methanol (8.1 L) and filtered water (0.45 L) was added. The slurry was refluxed for 3 h, then cooled to 20 °C over 4 h, and then granulated for 16 h. The solid was isolated by filtration, washing twice with a mixture of filtered methanol (1.0 L) and filtered water (90 mL), and then tray dried at 40 °C under vacuum to give **8** (576 g; 45%) as an off-white solid. Mp 198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.53 (1H, t, J = 5.9 Hz), 7.41 (4H, m), 7.32 (1H, t, J = 7.6 Hz), 7.20 (1H, m), 7.17 (1H, d, J = 7.4 Hz), 7.13 (2H, m), 7.09 (1H, m), 7.01 (2H, ddd, J = 10.2, 8.4, 2.2 Hz), 6.83 (3H, m), 4.44 (1H, dd, J = 7.6, 4.9 Hz), 4.32 (2H, d, J = 5.9 Hz), 3.46 (3H, s), 3.45−3.20 (1H, br. s), 2.91 (1H, s), 2.65 (2H, m), 2.56 (2H, s), 0.93 (3H, s), 0.91 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.2, 157.1, 149.7, 140.2, 139.9, 138.4, 135.7, 135.4, 131.1, 130.8, 128.7, 128.4, 127.6, 127.5, 126.5, 125.2, 124.7, 124.4, 124.2, 124.0, 123.8, 115.7, 115.1, 72.0, 52.7, 50.2, 46.3, 42.5, 42.2, 26.6, 26.4. LCMS: found m/z 618.27 $[M + H]^+$. Anal. Calcd For $C_{34}H_{39}N_3O_6S$: C, 66.10; H, 6.36; N, 6.80; S, 5.19. Found: C, 65.53; H, 6.29; N, 6.54; S, 5.12.

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(13) Wilkinson, H. S.; Hett, R.; Tanoury, G. J.; Senanayake, C. H.; Wald, S. A. *Org. Process Res. Dev.* **2000**, *4*, 567.

(14) Washburn, W. N.; Girotra, R. N.; Sher, P. M.; Mikkilineni, A. B.; Poss, K. M.; Mathur, A.; Gavai, A.; Bisacchi, G. S. European Patent 659737, 1995; *Chem. Abstr.* **1995**, *124*, 8408.

(15) Rather than using 4-hydroxyphenylboronic acid **19**, some vendors chose to use an *O*-protected boronic acid (see Cladingboel, D. E. *Org. Process Res. Dev.* **2000**, *4*, 153 for a route to the THP-protected boronic acid). This had no significant impact on the product quality or impurity profile.

(16) By this time we had already started making the ethyl ester **2a** rather than methyl ester **2**.

(17) In the absence of a second equivalent of base, the reaction stalls at ~50% consumption of bromide **1**, presumably due to amine **2** forming the unreactive HBr salt.

(18) Despite our best efforts, batches of **24a** contained variable levels of inorganic impurities; however, the potency was readily determined and, if required, could be used to adjust the charges of reagents and **6**·HCl in the final step.

(19) Pilcer, G.; Amighi, K. *Int. J. Pharm.* **2010**, *392*, 1.

(20) Both normal- and reverse-phase chromatographic purification were also examined. Reverse-phase chromatography caused significant degradation of **8**. During normal-phase chromatography, **8** often precipitated from solution onto the column causing blockages; additionally, only limited purification was achieved.