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Development of a Potential Manufacturing Route to PF-00610355: A Novel Inhaled β_2-Adrenoreceptor Agonist

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ABSTRACT: The development of a practical, scalable route to PF-00610355 (**8**) is described. In this convergent approach, amine **9** is coupled to protected bromohydrin **1** to give the doubly protected intermediate **26**. TBS-Deprotection of **26** affords the benzyl protected penultimate intermediate **25** which is crystallized as the corresponding hemifumarate salt **25a**. On the basis of solubility data, the final debenzylation was conducted in aqueous THF, and the API (**8**) is isolated from acetonitrile by an unusual distillative crystallization process. The development of an efficient process to prepare amine **9** is 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 chronic obstructive pulmonary disease (COPD). As part of a program to identify an ultralong acting β_2-adrenoreceptor agonist suitable for once-daily dosing, *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 (PF-00610355, **8**), was progressed into clinical development.[1] We have recently disclosed the initial synthetic route used to prepare material for early development studies (Scheme 1).[2] While this route was ultimately successful, the final step and subsequent purification of **8** proved extremely challenging and despite considerable efforts, only provided a modest 36% yield of clinical quality material. Consequently, we initiated work on the identification of an alternative route that would be more suitable for large-scale manufacture.

RESULTS AND DISCUSSION

The initial medicinal chemistry design of **8** was based on a modular construct, comprising three components, a sulfonamide 'headgroup' **1**, an amino ester 'linker' **2**, and an amine 'tail' **7** (Scheme 2). Given the demand for material and the limited time available, as efficient processes to all three components had already been developed,[2,3] it was evident that any new process would need to utilize these or very closely related building blocks. Consequently, the key considerations during the initial analysis phase were to define the optimal route by which to combine the fragments, choice of protecting groups,[4] and critically, the final step. On the basis of our hard earned knowledge of the challenges of purifying **8**,[2] it was clear that the final step would need to be mild, high-yielding, and chemoselective. In addition, the penultimate intermediate would need to be readily prepared in high purity. This led us to two possible options, either a final step debenzylation or a final step desilylation. Both of these are highly chemoselective processes that occur under mild conditions and were unlikely to introduce additional structurally related impurities, although each presents significant processing challenges as discussed herein.

Both the medicinal chemistry[1] and our initial scale-up[2] routes had used a broadly similar strategy, wherein first the headgroup **1** and linker **2** were combined, and the tail **7** was added last. From a simple step-count analysis, this was clearly suboptimal, as **7** is prepared in 3 steps while **1** requires 6 steps. Additionally, from an evaluation of the literature, the preferred routes to prepare other β_2-agonists are those wherein the key C−N bond is formed using a fully elaborated 'linker-tail' portion (e.g., amine **9**), as depicted in the retrosynthesis of **8** in Scheme 2. In particular, salmeterol is prepared from a protected chiral ethanolamine fragment and an electrophile[5] (Scheme 2, route a) and both formoterol[6] and indacaterol[7] from the reaction between an epoxide and a fully elaborated amine (Scheme 2, route b). In the case of **8**, the former route was considered less likely to succeed due to the challenge of introducing the quaternary carbon adjacent to the secondary amine,[8] and priority was given to exploration of the latter strategy, focusing on the well-precedented epoxide or halohydrin routes shown in Scheme 2.[9]

Synthesis of Amine 9. In order to examine these alternative approaches, supplies of amine **9** were required. Since amino ester **2** was available from the previous campaign (as the di-(*p*-toluoyl)-(L)-tartaric acid (DTTA) salt, prepared in 7 steps[3]), this was converted to amine **9** as shown in Scheme 3. Boc-protection and ester hydrolysis gave protected amino acid **10** which was coupled with amine **7**·**HCl** using EDC in the presence of diisopropylethylamine and catalytic DMAP. Finally, Boc deprotection afforded the desired amine **9**. While this route successfully provided the initial supplies of **9** it was rather lengthy (10 steps) as a result of multiple protecting group interchanges, and ultimately a more efficient synthesis was required.

Since we had already developed an efficient route to chloroacetamide **13**,[3] initial studies focused on coupling **13** with amine **7**. Despite considerable effort, this was unsuccessful, largely due to the reactivity of the chloroacetamide group, resulting in the formation of numerous, unidentified byproducts under a range of amide bond-forming conditions (e.g., CDI, EDC, DCC, isobutyl

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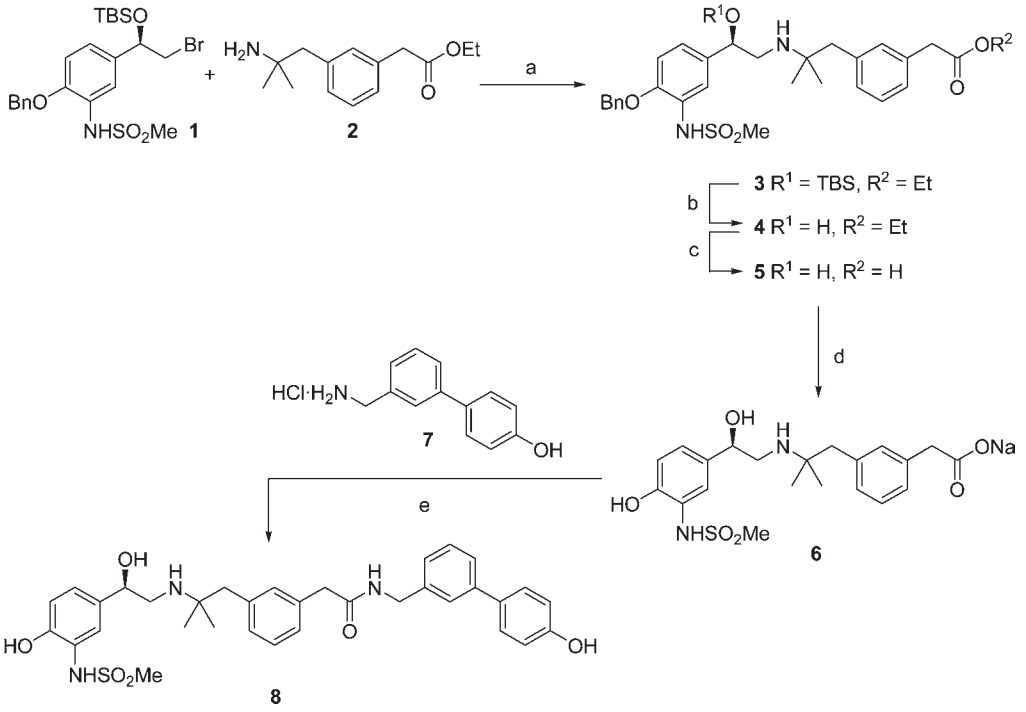
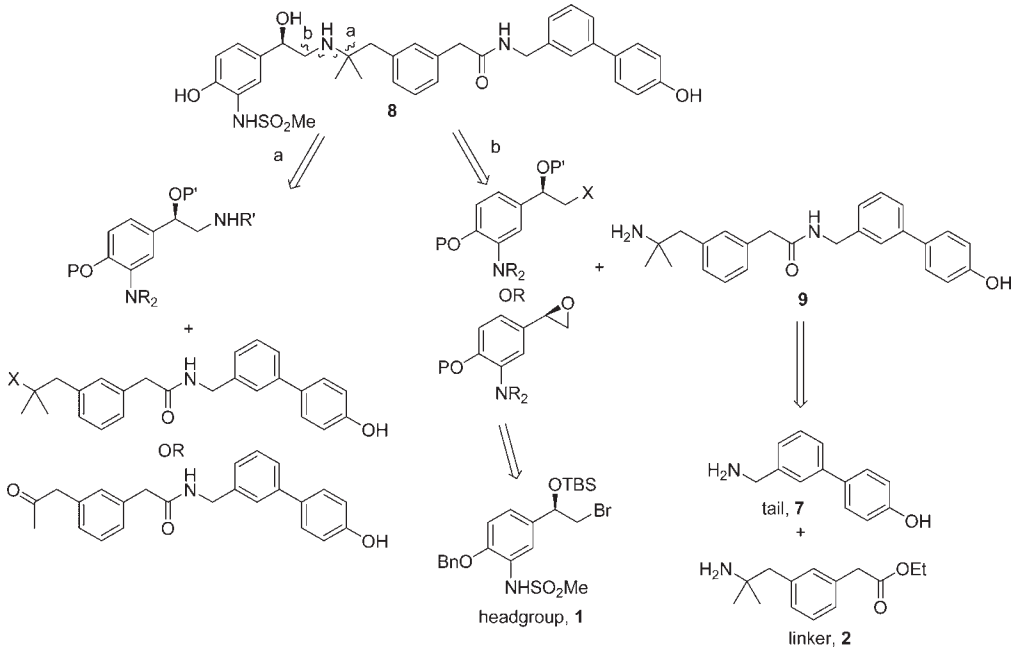
Scheme 1. Initial synthetic route to 8[a]



[a] Reagents and conditions: (a) propionitrile (EtCN), reflux; (b) $Et_3N \cdot 3HF$, EtCN; (c) (i) NaOH, EtCN/water, then HCl/1,4-dioxane; (ii) water reslurry, 80%; (d) NaOH, H_2, 20% $Pd(OH)_2/C$, water, then acetonitrile, 69%; (e) (i) EDC·HCl, pyridine, then water, 80%; (ii) acetone/water; (iii) MeOH/water reslurry, 45%.

Scheme 2. Summarized retrosynthetic analysis



chloroformate). Having established that the chloroacetamide was not a suitable protecting group, we identified a literature precedent for preparation and cleavage of a trichloroacetamide via a Ritter reaction of an alcohol with trichloroacetonitrile, followed by basic hydrolysis.[10]

The Ritter reaction between alcohol **12** (prepared in 4 steps[3]) and trichloroacetonitrile proceeded reasonably well, affording the desired trichloroacetamide **14** (83% crude yield). Subsequent coupling to amine **7** gave the desired amide **15** and basic hydrolysis afforded **9** in modest overall yield (27%, Scheme 4).[11] Upon

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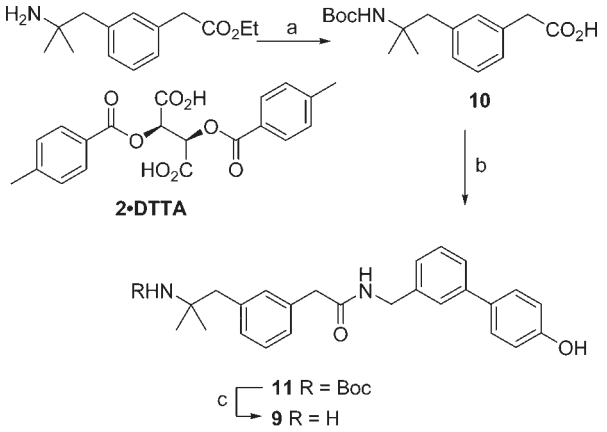
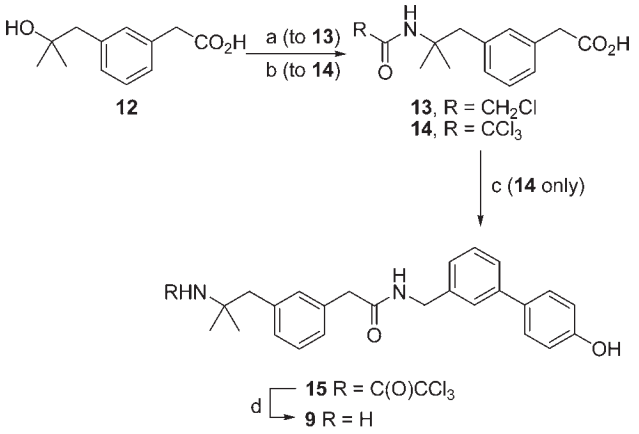
Scheme 3[a] **Initial route to amine 9**



[a] Reagents and conditions: (a) (i) Boc_2O, *i*-Pr_2NEt, EtCN; (ii) NaOH, THF/water, then HCl; (iii) toluene/heptane cryst, 90%; (b) (i) **7·HCl**, *i*-Pr_2NEt, DMAP, EDC·HCl, MeCN; (ii) water; (iii) aq citric acid, 82%; (c) (i) TFA/CH_2Cl_2, then water/aqueous ammonia; (ii) acetone cryst, 54%.

Scheme 4[a] **Alternative routes to amine 9**

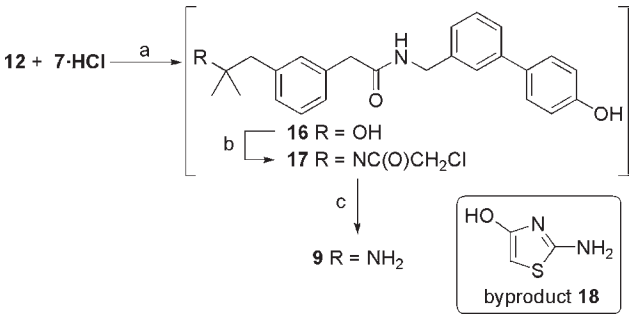


[a] Reagents and conditions: (a) chloroacetonitrile, H_2SO_4, AcOH, CH_2Cl_2; 65−70%; (b) trichloroacetonitrile, H_2SO_4, AcOH, then heptane cryst, 83%; (c) **7·HCl**, Et_3N, EDC·HCl, HOBt, EtOAc; (d) KOH, EtOH/water, then acetone cryst, 32%.

scale-up to around 100 g of alcohol **12**, the overall yield plummeted to <10%. While additional development work might have succeeded in identifying the problems and improving the yield, we had some concerns about generating chloroform in the deprotection step, and this, coupled with the successful development of an alternative route (see Scheme 5) meant that this process was not investigated further.

Recognizing that deferring installation of the amine functionality until after the amide bond formation step would avoid the issues encountered with the reactive chloroacetamide, we decided to examine the step-reordered sequence shown in Scheme 5. A range of conditions (e.g., CDI, DCC, EDC, and isobutyl chloroformate) for the coupling of amino alcohol **12** with amine **7** were examined. From this screen, EDC·HCl in the presence of HOBt and Et_3N emerged as the preferred reaction conditions.

Scheme 5[a] **Optimized route to amine 9**



[a] Reagents and conditions: (a) Et_3N, EDC·HCl, HOBt, CH_2Cl_2; (b) chloroacetonitrile, TFA, 50 °C; (c) thiourea, AcOH, reflux, then acetonitrile cryst, 64%.

Initial studies on the Ritter reaction of alcohol **16** with chloroacetonitrile using the conditions developed previously for alcohol **12** (H_2SO_4 and AcOH in dichloromethane)[3] were promising; however, as the reaction scale increased we observed increasing amounts of the intermediate olefin arising from dehydration of alcohol **16**, and were unable to convert this to the desired **17**. A literature survey identified trifluoroacetic acid (TFA)[12] as an alternative to the commonly used sulfuric acid[13] in the Ritter reaction. To our delight, when we examined the Ritter reaction of **16** with chloroacetonitrile in TFA, full conversion to the chloroacetamide **17** was observed after 2 h at 50 °C.[14]

Chemoselective deprotection of chloroacetamide **17** was accomplished by treatment with thiourea in acetic acid,[15] affording pure amine **9** after removal of the byproduct **18** and crystallization (Scheme 5). As the target amine **9** was known to be a crystalline solid and it proved challenging to crystallize the intermediate alcohol **16** and chloroacetamide **17**, we decided to develop a fully telescoped process from alcohol **12** to amine **9**.

The preferred solvent for the initial amide formation was dichloromethane, however, during the workup solubility problems were encountered (an oily phase separated out of solution during the aqueous washes); this was overcome by dilution with THF once the reaction was complete. After an aqueous workup, the solvent was readily exchanged to chloroacetonitrile (bp 124−126 °C) by distillation. Treatment with TFA at 50 °C afforded the desired chloroacetamide **17**. Unfortunately, thiourea deprotection proved unsuccessful in this TFA/chloroacetonitrile mixture; consequently dilution with dichloromethane and an aqueous workup was required to remove the TFA. Thereafter, the dichloromethane was removed by distillation and replaced with acetic acid; subsequent treatment with thiourea at reflux affected the desired deprotection. After filtration to remove byproduct **18** (Scheme 5), the acetic acid solution of amine **9** was diluted with water and back-extracted to remove residual chloroacetonitrile.[16] The workup was completed by neutralization and extraction into 2-methyltetrahydrofuran, followed by solvent exchange to acetonitrile from which **9** was isolated as a crystalline solid in an acceptable 64% yield from **12** on pilot plant scale.

Conversion of amine 9 to API (8). In parallel with the development of the route to amine **9**, both the epoxide and halohydrin routes to the active pharmaceutical ingredient (API) **8** were evaluated. While the halohydrin route offered the option of either a final step debenzylation or desilylation, the epoxide route only offered the former; however, the epoxide approach

does not require the TBS-protecting group, is potentially shorter, and has been successfully used for the synthesis of both formoterol and indacaterol.[6,7]

Bromohydrin **19** was synthesized as described,[2] and treatment with potassium carbonate in THF/MeOH afforded the anticipated epoxide **20**; however, this rapidly degraded during the workup and isolation process (Scheme 6). Attempts at generating and reacting epoxide **20** in situ were also unsuccessful. Postulating that the instability might be related to the acidic sulfonamide proton, this was protected by addition of a second methanesulfonamide group. For these initial proof-of-concept studies, epoxide **23** was prepared from TBS bromohydrin **1**,[2] as shown in Scheme 6. Addition of the second methanesulfonamide group and deprotection afforded bromohydrin **22**, and treatment with base smoothly converted **22** to the desired epoxide **23**, which was readily isolated and characterized.[17]

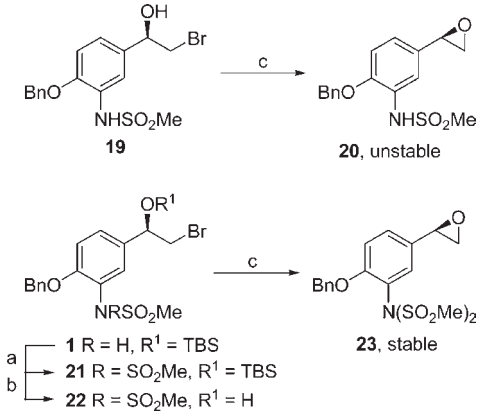
Reaction of epoxide **23** with amine **9** proceeded smoothly, although elevated temperatures were required to reach completion within 24 h (Scheme 7). After some screening, the best solvent was identified as butyronitrile (bp 118 °C); however, even under these conditions, significant byproduct formation was noted.[18] The product **24** was isolated by chromatography in 54% yield, and treatment with aqueous sodium hydroxide afforded **25** in a moderate 60% yield.

In contrast, although sluggish, the reaction between TBS bromohydrin **1** and amine **9** in refluxing propionitrile (EtCN, bp 97 °C)[2] proceeded to completion in around 54−60 h, with high selectivity and minimal byproduct generation. The reduction in byproduct levels was anticipated since, unlike epoxide **23**, bromohydrin **1** will not generate any regioisomeric impurity (formed due to epoxide opening at the benzylic position), and the presence of the TBS group as well as the bulky amine **9** should disfavor overalkylation and the formation of 'dimeric' species. The disadvantages of this approach are the slightly longer synthesis of **1**,[19] a slower coupling reaction, and the cost of the TBS protecting group.

As previously noted when conducting a similar coupling reaction,[2] some TBS-deprotection of the product **26** occurred under the reaction conditions. On the basis of our previous work,[2] this coupling reaction was initially conducted in EtCN with 2 equiv of **9**; however, switching to the higher-boiling butyronitrile (bp 118 °C) resulted in a significant increase in reaction rate (consumption of starting material within 24−36 h on small scale, rather than >48 h). Recognizing that the use of 2 equiv of **9** was inefficient and was likely to be prohibitively expensive in the long term, an extensive screen of alternative bases was conducted.[20] From this screen, addition of 5 equiv of sodium hydrogen carbonate ($NaHCO_3$) was found to completely suppress TBS-deprotection of **26**, but the reaction mixture proved challenging to stir. The best compromise was found to be 3 equiv of $NaHCO_3$ and 1 equiv of **9** in refluxing butyronitrile; under these conditions the coupling proceeded to completion in around 30 h with minimal TBS deprotection on lab scale. The bis-protected product **26** was not crystalline (and a crystalline form was not identified from an extensive salt screen) and was initially purified by chromatography, but subsequently the crude solution of **26** was simply telescoped into the next step.

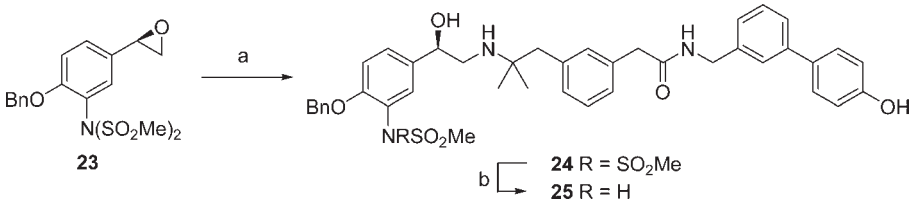
At this stage it was apparent that, while the epoxide route was potentially slightly shorter, the need for additional protection of the sulfonamide coupled with the relatively poor reaction profile, lower yields, and reduction in endgame flexibility meant that the halohydrin route was our preferred option. Having decided to utilize the halohydrin route, the use of butyronitrile for the coupling step was re-evaluated since it is not currently ICH-listed[21] and using it at the end of the synthesis would require justification. A range of alternative, ICH-listed solvents was screened, and *n*-butyl acetate (bp 126 °C) was identified as a suitable replacement. Due to the poor solubility of amine **9** in *n*-butyl acetate at ambient temperature, concentrated reaction mixtures (around 3 mL/g with respect to amine **9**) proved impossible to stir (at 20−25 °C); however, using higher dilution resulted in extremely slow reaction. This was overcome by preparing the initial reaction mixture in a relatively high volume of *n*-butyl acetate (10 mL/g with respect to amine **9**), affording a mobile slurry. Upon heating to reflux, the solubility of **9** was greatly increased, and concentration of the reaction mixture by distillation of around 7−8 mL/g of *n*-butyl acetate resulted in a significant rate increase while still keeping the reactants (**1** and **9**) in solution. A slight excess of either amine **9** or TBS bromohydrin **1** could be tolerated, but since bromohydrin **1** was easier to purge,

Scheme 6[a] Preparation of epoxides



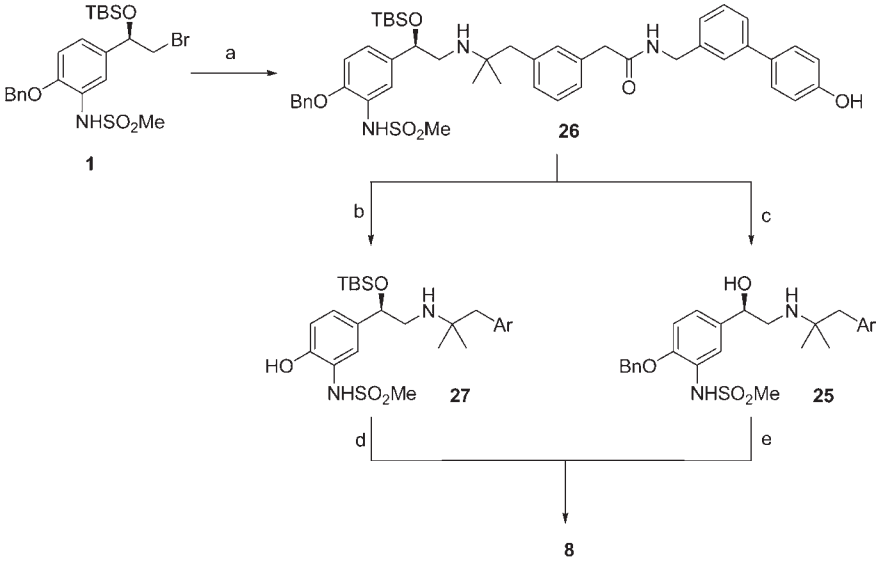
[a] Reagents and conditions: (a) MsCl, *i*-Pr_2NEt, MeCN, then water; (b) $Et_3N{\cdot}3HF$, THF/MeOH, then EtOAc, 73%; (c) K_2CO_3, THF/MeOH; dec (for **20**) or 100% (for **23**).

Scheme 7[a] Conversion of epoxide 23 to 25



[a] Reagents and conditions: (a) **9**, butyronitrile, reflux, then chromatography, 54%; (b) NaOH, EtOH/water, 60%.

Scheme 8. Coupling of amine 9 and bromide 1 and conversion to 8[a]



[a] Reagents and conditions: (a) **9**, *n*-butyl acetate, $NaHCO_3$, reflux; (b) H_2, $Pd(OH)_2/C$, *n*-butyl acetate/ethyl acetate; (c) $Et_3N \cdot 3HF$, *n*-butyl acetate/ethyl acetate/MeOH; (d) NH_4F, MeOH/water; (e) H_2, Pd/C, THF/water.

an excess (1.05 equiv) of this was used. Sodium hydrogen carbonate (3 equiv) remained the ideal HBr scavenger under these conditions.[22] On pilot-plant scale the reaction took around 40 h to reach adequate conversion (defined as <5% **9** remaining). Once the reaction was complete, the mixture was cooled to 50 °C and diluted with ethyl acetate,[23] prior to cooling to 20 °C. Initially, a series of acidic, basic, and water washes was employed to remove residual amine **9** and inorganic salts; this was simplified to a single water wash to remove the inorganic salts once adequate purge of **9** was demonstrated in the downstream steps.

In order to decide between the two potential endgame sequences (Scheme 8), two major criteria needed to be assessed. First, the final step needed to be thoroughly evaluated to ensure that suitable quality **8** could be isolated. Second, the feasibility of isolation and purification of the immediate precursors, benzyl-protected **25** or TBS-protected **27**, preferably by crystallization, needed to be established.

In order to evaluate the final step desilylation option (Scheme 8, steps b and d), the fully protected **26** was readily debenzylated by hydrogenolysis in the presence of palladium on carbon. Conveniently, the crude solution of **26** after workup (in a mixture of ethyl acetate and *n*-butyl acetate) could be used for this purpose. The product, **27**, was isolated as a foam after chromatographic purification. A large salt screen was conducted on **27** in an attempt to identify a crystalline form, however this was unsuccessful. Our medicinal chemistry colleagues had deprotected **27** using a large excess of ammonium fluoride (10 equiv) in aqueous ethanol,[1] and we were particularly attracted to the fact that this was a direct-drop process[24] that afforded acceptable quality **8** directly from the reaction mixture. Since we were concerned about the use of ammonium fluoride, which is both toxic and incompatible with glass, a selection of alternative deprotection conditions were examined (e.g., TBAF, triethylamine trihydrofluoride). While all of these reagents smoothly deprotected **27**, the product (**8**) remained in solution[25] and removing the residual reagent and byproducts proved challenging due to the low solubility (in common extraction solvents) and instability of **8**. Attempts at reducing the number of equivalents of NH_4F were also unsuccessful, as the precipitation appears to require a high ionic strength to work effectively.

Since both the coupling and deprotection steps proceeded with minimal byproduct generation, we examined the possibility of telescoping the crude debenzylation product (**27**) into the desilylation step. This proved successful, affording pure **8** in an acceptable 50% yield from amine **9** (Scheme 8).

To evaluate the final-step debenzylation option (Scheme 8, steps c and e), **26** was deprotected by treatment with $Et_3N \cdot 3HF$, affording **25** as a foam. Initial salt screening experiments identified a selection of amorphous salts of **25** that could be precipitated by addition of a solution of the salt in ethanol or a mixture of 2-butanone (methyl ethyl ketone, MEK) and *n*-butyl acetate to MTBE; the best of these was an amorphous dibenzoyl-(L)-tartaric acid salt. Given the potential challenges of developing a robust process to an amorphous salt, when further screening work led to the identification of a crystalline hemifumarate salt **25a** (Scheme 9), this was selected for development.

The final debenzylation reaction was complicated by the low solubility of **8** in most common hydrogenation solvents (e.g., MeOH), with the product precipitating from solution during the reaction, making separation from the heterogeneous hydrogenation catalyst challenging. While the reaction proceeded smoothly in solvents like DMF and NMP (in which **8** is sufficiently soluble), significant levels of Pd leaching were observed. Additionally, while **8** could be precipitated from these solvents by addition of water, the recovery was low, and the isolated **8** was not suitable for downstream processing. Alternative workup procedures were also unsuccessful due to the low solubility of **8** in water-immiscible extraction solvents.

Extensive solubility screening of **8** identified that it was reasonably soluble (~10 mL/g) in a 9:1 mixture of THF and water. Hydrogenolysis of **25** in this mixture afforded a solution of **8**; however, isolation of crystalline material with appropriate

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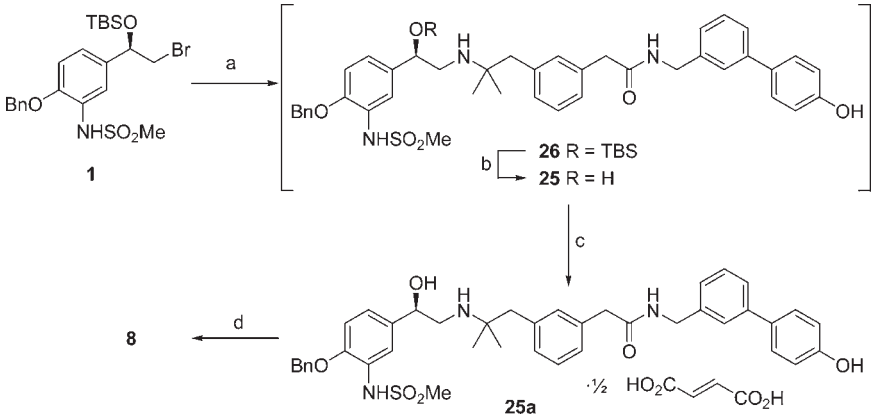
Scheme 9[a] **Optimized process to 8**



[a] Reagents and conditions: (a) **9**, *n*-butyl acetate, $NaHCO_3$, reflux, then ethyl acetate/water; (b) $Et_3N \cdot 3HF$, *n*-butyl acetate/ethyl acetate/MeOH; (c) fumaric acid, *n*-butyl acetate/MEK, 87%; (d) (i) aqueous ammonia, THF/water; (ii) carbon filtration; (iii) H_2, Pd/C, THF/water; (iv) azeotropic distillation to MeCN; (v) MeOH/water, 50 °C, 70%.

solid-form properties for an inhaled therapeutic agent[26] proved challenging. Since **8** is insoluble in both water and anhydrous THF, adjusting the solvent composition of the initial product solution by distillation to pure water or THF was examined. Unfortunately, this only afforded low yields of poor-quality product that was unsuitable for downstream processing. Dilution with excess water caused the product to oil out of solution, and addition of other antisolvents (e.g., methanol, ethanol, heptane) was equally unsuccessful.

During the development of the previous process to prepare **8**,[2] we had evaluated an extensive range of solvents and solvent−water combinations for the purification of **8**. While it had not proved useful for purification of **8**, we had noted that acetonitrile was a particularly good antisolvent; this, coupled with the knowledge that azeotropic distillation with acetonitrile would be an effective way to remove both THF and water, led us to attempt to isolate **8** from acetonitrile. As anticipated, azeotropic distillation with acetonitrile was successful in removing both THF and water and, to our delight, afforded a mobile slurry of **8**. Upon isolation, the product was found to have suitable physical properties for downstream processing, but the purity was slightly lower than required. Fortunately, a reslurry in aqueous methanol provided sufficient purity upgrade without affecting the physical properties.

Having examined both endgame options, we selected the final-step debenzylation route for further development as a crystalline penultimate intermediate (**25a**) and viable conditions for the final step had been identified. In contrast, while the final-step desilylation route had been demonstrated to provide suitable quality **8**, purification of **27** required chromatography.

As this was the only crystalline intermediate in the sequence, a telescoped process through to fumarate salt **25a** was developed (Scheme 9). The coupling reaction was conducted as described previously, affording a solution of silyl ether **26** in a mixture of *n*-butyl acetate and ethyl acetate. Treatment with $Et_3N \cdot 3HF$ removed the TBS group; however, some material was observed to oil out of solution as the reaction progressed. Fortunately, addition of a small amount of methanol to the reaction mixture solubilized this material, resolving the problem.

Once the reaction was complete, excess reagent was destroyed by addition of aqueous ammonia. The solution was concentrated to remove the volatile solvents (ethyl acetate and methanol), and the residue was dissolved in MEK. Addition of a small amount of water was essential to ensure a homogeneous solution was obtained. Upon addition of fumaric acid (0.5 equiv), an oily residue separated out of solution, but upon extended reflux (around 4 h), this slowly converted to the desired crystalline hemifumarate salt **25a**. Even in the presence of seed material, this initial oily phase could not be avoided; however, the process to convert it into a crystalline form proved robust and was successfully implemented on pilot-plant scale, affording >40 kg of **25a** in ~85% yield.

Since the hydrogenolysis had to be conducted in a 9:1 THF/water mixture to ensure the product **8** was soluble, the fact that **25** was isolated as a salt posed a concern. As THF is miscible with water, conducting a salt break step with an aqueous base could result in THF with a variable water content and pose the risk of inorganic contamination of the API. While it would have been possible to first conduct the salt break in a different solvent (e.g., dichloromethane) and then exchange this to THF for the hydrogenation step, we ideally wanted to use a single solvent. An additional concern was the possibility of deprotonating the sulfonamide; thus, only weak bases were evaluated.

After some experimentation, the best option was identified as treating a THF suspension of **25a** with aqueous ammonia of sufficient ionic strength to be immiscible with THF. The resulting THF solution of **25** was then azeotropically distilled to remove water and any residual ammonia, giving a THF solution of **25**. Subsequent dilution with water provided the appropriate solvent composition for the hydrogenolysis step.

Initially, the hydrogenolysis proceeded to completion within a few hours; however, once we started using fumarate **25a** derived from amine **9** that had been prepared using the optimized process (Scheme 5), several batches failed and required an additional charge of catalyst to reach full conversion. This suggested that a catalyst poison had been introduced, and from an inspection of the route, the most likely source was the thiourea deprotection step (Scheme 5, conversion of chloroacetamide **17** to amine **9**), with the catalyst poison tracking through the subsequent steps. Fortunately, treatment with activated carbon[27] removed the catalyst poison,[28] and the hydrogenolysis proceeded to completion with a single catalyst charge, affording **8** in 70% yield on pilot-plant scale, after isolation and purification.

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The use of palladium in the final step did pose a concern, and the palladium level in the isolated **8** was monitored to ensure that it was within safe limits. If the palladium level breached the 20 ppm limit, treatment of a THF/water solution of **8** with Quadrapure TU resin, followed by the usual isolation from acetonitrile and methanol/water reslurry, successfully purged palladium without significant degradation of **8**.[29]

In conclusion, herein we describe the development of a practical, scalable route to PF-00610355 (**8**), used to prepare >10 kg of material with the potential to form the basis of a larger-scale process to this complex molecule. In this convergent approach, a fully elaborated amine **9** is coupled to protected bromohydrin **1** to give the fully protected intermediate **26** which is not isolated and is converted to benzyl-protected penultimate intermediate **25** and crystallized as the hemifumarate salt **25a**. On the basis of solubility data, the final debenzylation is conducted in aqueous THF, and the API (**8**) is isolated from acetonitrile by an unusual distillative crystallization process. The development of an efficient process to prepare amine **9** is also described.

EXPERIMENTAL SECTION

***tert*-Butyl-{1-[3-(2-{[(4′-hydroxybiphenyl-3-yl)methyl]amino}-2-oxoethyl)phenyl]-2-methylpropan-2-yl}carbamate 11.** Diisopropylethylamine (210 mL; 1.21 mol) was added to a suspension of **2·DTTA**[3] (250 g; 0.40 mol) in propionitrile (1.0 L), giving a pale-yellow solution. A solution of di-*tert*-butyl dicarbonate (97 g; 0.44 mol) in propionitrile (250 mL) was added, and the resulting pale-yellow solution was stirred at ambient temperature for 21 h. Water (250 mL) was added, and the mixture was stirred for 30 min. The phases were separated, and the organic phase was washed successively with 10% aqueous citric acid (500 mL), water (300 mL), saturated aqueous sodium hydrogen carbonate (500 mL), and brine (500 mL). The organic phase was concentrated to a dark-orange oil and dissolved in a mixture of tetrahydrofuran (250 mL) and water (250 mL). Sodium hydroxide (80 g; 2.0 mol) was added, and the resulting mixture was stirred at ambient temperature for 91 h. Toluene (400 mL) was added, and the mixture was stirred for 30 min; then the phases were separated. The organic phase was extracted with a mixture of water (200 mL) and saturated aqueous sodium hydrogen carbonate (100 mL). The combined aqueous phase was adjusted to pH 1 with concentrated hydrochloric acid and extracted with ethyl acetate (2 × 250 mL). The combined ethyl acetate extracts were washed with water (2 × 200 mL) and then concentrated to dryness. The resulting oil was dissolved in refluxing toluene (100 mL), and heptane (~400 mL) was added. The mixture was cooled to ambient temperature and stirred for 3 h. The solid was isolated by filtration, washing with heptane (2 × 200 mL) and dried in a vacuum oven at 40 °C to give Boc amino acid **10** (111 g; 90%) as a pale-yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.23 (1H, m), 7.15 (1H, m), 7.07 (2H, m), 3.61 (2H, s), 2.96 (2H, s), 1.47 (9H, s), 1.25 (6H, s). A mixture of Boc amino acid **10** (25 g; 81.3 mmol), amine hydrochloride **7·HCl** (18.2 g; 77.3 mmol), 4-dimethylaminopyridine (100 mg; 0.81 mmol), and diisopropylethylamine (22.1 g; 170.8 mmol) in acetonitrile (125 mL) was stirred at ambient temperature under nitrogen while 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (17.15 g; 89.5 mmol) was added. The resulting mixture was stirred for 18 h at ambient temperature. Water (90 mL) was added, and the resulting suspension stirred for 1.5 h. The solid was isolated by filtration, washing with water (100 mL), and dried under suction for 20 min. The damp filter cake was slurried in 10% aqueous citric acid (100 mL) for 1 h. The solid was isolated by filtration, washed with water (100 mL), and dried at 40 °C under vacuum to give the title compound **11** (31 g; 82%) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.50 (1H, s), 8.54 (1H, t, J = 5.9 Hz), 7.44−7.39 (4H, m), 7.33 (1H, t, J = 7.6 Hz), 7.21−7.11 (3H, m), 7.06 (1H, s), 7.00 (1H, m), 6.84 (2H, d, J = 8.6 Hz), 6.25 (1H, s), 4.30 (2H, d, J = 6.1 Hz), 3.46 (2H, s), 2.88 (2H, s), 1.45 (9H, s), 1.14 (6H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.1, 157.1, 154.3, 140.2, 139.9, 138.3, 135.7, 131.2, 130.8, 128.7, 128.4, 127.6, 127.5, 126.6, 125.2, 124.7, 124.4, 115.7, 77.1, 52.1, 48.7, 42.4, 42.2, 28.4, 27.1, 26.8. LCMS: Found m/z 489.27 $[M + H]^+$.

2-[3-(2-Amino-2-methylpropyl)phenyl]-*N*-[(4′-hydroxybiphenyl-3-yl)methyl]acetamide 9. *Method A.* A suspension of Boc amine **11** (31.0 g; 63.4 mmol) in dichloromethane (150 mL) was stirred under an inert atmosphere while trifluoroacetic acid (50 mL; 649 mmol) was added. The resulting pale orange-brown solution was stirred for 1.5 h, then concentrated under reduced pressure to give a thick brown oil. The oil was treated with a mixture of water and concentrated aqueous ammonia (9:1, ~250 mL) until pH 12 was reached, and then the mixture was extracted with a mixture of ethyl acetate and methanol (9:1, 2 × 150 mL). The combined organic extracts were washed with water and concentrated under reduced pressure. The resulting foam was refluxed in acetone (500 mL) for 1 h, and the resulting slurry was cooled to ambient temperature and stirred overnight. The solid was isolated by filtration, washing with acetone, and dried at 40 °C in a vacuum oven to give the title compound **9** (13.4 g; 54%) as a white solid. Mp 123 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.59 (1H, t, J = 5.9 Hz), 7.41 (4H, m), 7.32 (1H, t, J = 7.4 Hz), 7.24−7.12 (4H, m), 7.06 (1H, br d, J = 7.2 Hz), 6.86 (2H, dm, J = 8.6 Hz), 4.34 (2H, d, J = 5.9 Hz), 3.49 (2H, s), 2.55 (2H, s), 0.97 (6H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.3, 157.3, 140.2, 139.9, 138.7, 135.8, 131.0, 130.7, 128.7, 128.4, 127.6, 127.5, 126.6, 125.2, 124.7, 124.3, 115.8, 50.4, 49.8, 42.5, 42.2, 29.9. LCMS: Found m/z 389.27 $[M + H]^+$. Anal. Calcd For $C_{25}H_{28}N_2O_2 \cdot 1/2(H_2O)$: C, 75.54; H, 7.35; N, 7.05. Found: C, 75.48; H, 7.05; N, 7.00.

Method B. Triethylamine (22.6 L; 163.2 mol) was added to a mixture of alcohol **12** (17 kg; 81.6 mol), amine hydrochloride **7·HCl** (21.1 kg, 89.5 mol), and 1-hydroxybenzotriazole hydrate (5.5 kg; 40.8 mol) in dichloromethane (155 L) at 20 °C under nitrogen, followed by a dichloromethane line wash (15 L). The mixture was stirred at 20 °C for 1 h, then 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (15.6 kg, 81.6 mol) was added, and the mixture was stirred for 5 h, at which point HPLC analysis showed complete conversion to amide **16**. THF (85 L) and water (85 L) were added, and after 10 min the phases were separated. The retained lower organic phase was washed with water (85 L), 1 M aqueous HCl (2 × 85 L), and 1 M aqueous potassium bicarbonate (2 × 85 L). The organic solution was diluted with chloroacetonitrile (61.2 L) and concentrated by distillation until a vapor temperature of 89 °C was reached (approximately 150 L of distillate was collected). The solution was cooled to 50 °C, and trifluoroacetic acid (153 L) was added over 2 h, maintaining the temperature at 50 °C. Once the addition was complete, the solution was stirred at 50 °C for a further 10 h, at which point HPLC analysis indicated complete conversion to chloroacetamide **17**. The solution was cooled to 20 °C and diluted with dichloromethane (153 L). The solution was washed with water (2 × 306 L) and 1 M aqueous potassium bicarbonate (2 × 153 L)[30] and then diluted with acetic acid (187 L). The solution was concentrated by distillation until a vapor temperature of 92 °C was reached (approximately 150 L of distillate was collected), and then cooled to 20 °C. Thiourea (26.1 kg; 342.7 mol) was added, and the mixture was heated to 70 °C and held

for 90 min. The slurry was heated to reflux and stirred for 14 h. The slurry was cooled to 20 °C and filtered to remove the byproduct **18**. The filter cake was washed with acetic acid (38 L). The acetic acid solution was diluted with water (544 L) and was extracted twice with a mixture of methanol (17 L) and dichloromethane (153 L). The retained aqueous phase was diluted with 2-methyltetrahydrofuran (170 L) and cooled to 5 °C. Concentrated aqueous ammonia (35%, 306 L) was added at such rate as to keep the temperature below 30 °C (about 1 h), followed by a 10-L water line wash. The pH of the mixture was checked (specification >9, actual pH was 10), then the mixture was diluted with 2-methyltetrahydrofuran (170 L), and the temperature was adjusted to 20 °C. The phases were separated, and the lower aqueous phase was back-extracted with 2-methyltetrahydrofuran (170 L). The combined organic extracts were washed with water (2 × 136 L) and concentrated under vacuum (around 50 mbar) at 20 °C to approximately 255 L total volume. Acetonitrile (255 L) was added, and the mixture was concentrated under vacuum (around 50 mbar) at 20 °C to approximately 255 L total volume. Acetonitrile (205 L) was added, and the mixture was concentrated under vacuum (around 50 mbar) at 20 °C to approximately 255 L total volume. The resulting slurry was diluted with acetonitrile (255 L) and aged at 20 °C for 4 h. The solid was isolated by filtration, washed with acetonitrile (2 × 68 L), and dried at 40 °C under vacuum to give the title compound **9** as a white solid (20.24 kg; 64%).

***N*-{2-(Benzyloxy)-5-[(1*R*)-2-bromo-1-hydroxyethyl]phenyl}-*N*-(methylsulfonyl)methanesulfonamide 20.** Bromide **1**[2] (20.0 g; 39.2 mmol) and diisopropylethylamine (24 mL; 138 mmol) were combined in acetonitrile (100 mL) and cooled to 5 °C. Methanesulfonyl chloride (9.0 mL; 118.8 mmol) was added over 10 min, and the resultant mixture was stirred for about 1 h at 5 °C. Water (300 mL) was added, and the resultant slurry was stirred for 15 min, filtered, and dried at 40 °C under vacuum to provide the TBS protected bis-mesylate **21** (23.3 g; 100%) as a pale-yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.53−7.47 (2H, m), 7.46−7.33 (5H, m), 7.08 (1H, d, J = 8.6 Hz), 5.16 (2H, s), 4.86 (1H, dd, J = 7.4, 4.7 Hz), 3.51−3.42 (2H, m), 3.34 (3H, s), 3.33 (3H, s), 0.93 (s, 9H), 0.15 (s, 3H), −0.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 156.2, 135.7, 135.6, 130.3, 129.6, 128.9, 128.7, 128.5, 127.8, 113.3, 74.1, 71.2, 43.7, 39.3, 25.8, 18.3, −4.7, −4.9. LCMS: Found m/z 609.12/611.12 $[M + NH_4]^+$. TBS-protected bis-mesylate **21** (19.2 g; 32.4 mmol) was suspended in a mixture of tetrahydrofuran (40 mL) and methanol (2 mL). Triethylamine trihydrofluoride (9 mL; 55.2 mmol) was added, and the resultant solution was stirred for 30 h at ambient temperature. The reaction was quenched with aqueous ammonia (35%, 20 mL), and the product was extracted into ethyl acetate (2 × 30 mL). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate and water, dried with anhydrous $MgSO_4$, filtered, and concentrated to dryness. The residue was slurried in ethyl acetate (40 mL) for 2 h, after which time the product was isolated by filtration, washing with ethyl acetate (10 mL) and *tert*-butyl methyl ether (20 mL). The solid was dried at 40 °C under vacuum for 18 h to give the title compound **22** (11.3 g, 73%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.50 (4H, m), 7.42−7.32 (3H, m), 7.21 (1H, d, J = 8.4 Hz), 5.87 (1H, d, J = 4.9 Hz), 5.23 (2H, s), 4.80 (1H, m), 3.69 (1H, dd, J = 10.2, 4.3 Hz), 3.59 (1H, dd, J = 10.2, 7.4 Hz), 3.43 (3H, s), 3.42 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.3, 136.3, 135.5, 130.4, 129.4, 128.4, 128.0, 127.5, 122.3, 113.2, 71.0, 70.1, 43.6, 40.1. LCMS: Found m/z 495.02/497.02 $[M + NH_4]^+$. Anal. Calcd For $C_{17}H_{20}BrN_2O_6S_2$: C, 42.68; H, 4.21; N, 2.93; S, 13.41. Found: C, 42.64; H, 4.17; N, 2.93; S, 13.52.

***N*-{2-(Benzyloxy)-5-[(2*R*)-oxiran-2-yl]phenyl}-*N*-(methylsulfonyl)methanesulfonamide 23.** Potassium carbonate (2.25 g; 16.3 mmol) was added to a solution of bromohydrin **22** (6.0 g; 12.5 mmol) in a mixture of methanol (30 mL) and THF (30 mL), and the resultant mixture was stirred at ambient temperature for 18 h. The reaction mixture was poured into water (60 mL) and extracted with propionitrile (2 × 60 mL). The combined propionitrile layers were washed with water (100 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated to yield the title compound **23** (4.98 g; ∼100%) as a pale-yellow solid that was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54−7.48 (2H, m), 7.44−7.40 (2H, m), 7.38−7.34 (2H, m), 7.25 (1H, d, J = 2.2 Hz), 7.08 (1H, d, J = 8.6 Hz), 5.17 (2H, s), 3.86 (1H, dd, J = 4.1, 2.5 Hz), 3.35 (3H, s), 3.33 (3H, s), 3.15 (1H, dd, J = 5.5, 4.1 Hz), 2.79 (1H, dd, J = 5.5, 2.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.4, 135.5, 131.1, 129.5, 129.1, 128.7, 128.5, 127.8, 123.3, 113.7, 71.3, 51.5, 51.3, 43.7, 43.7.

2-[3-(2-{[(2*R*)-2-{4-(Benzyloxy)-3-[(methylsulfonyl)amino]-phenyl}-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-[(4′-hydroxybiphenyl-3-yl)methyl]acetamide 25. A mixture of amine **9** (500 mg; 1.29 mmol) and epoxide **23** (670 mg; 1.69 mmol) in butyronitrile (2 mL) was heated at reflux for 20 h under an inert atmosphere. The mixture was cooled to ambient temperature, and chromatographed directly on silica gel (40 g), eluting with methanol−dichloromethane (1:19 to 1:9) to provide bis-mesylate **24** (543 mg; 54%) as a waxy oil. ^{1}H NMR (CD_3OD, 400 MHz) δ: 7.52 (2H, m), 7.46 (2H, m), 7.42−7.25 (9H, m), 7.22 (2H, m), 7.17 (1H, m), 7.13 (1H, m), 7.10 (1H, dt, J = 6.6, 1.6 Hz), 6.84 (2H, m), 5.15 (2H, s), 4.75 (1H, dd, J = 8.2, 4.7 Hz), 4.41 (2H, s), 3.56 (2H, s), 3.33 (3H, s), 3.32 (3H, s), 2.88 (2H, m), 2.74 (1H, d, J = 13.1 Hz), 2.68 (1H, d, J = 13.1 Hz), 1.07 (3H, s), 1.05 (3H, s). ^{13}C NMR (CD_3OD, 100 MHz) δ: 174.1, 158.3, 157.5, 142.7, 140.4, 138.8, 137.5, 137.4, 136.9, 133.5, 132.5, 131.4, 130.7, 130.4, 130.0, 129.7, 129.5, 129.4, 129.1, 129.1, 128.5, 126.6, 126.4, 126.3, 124.6, 116.8, 114.8, 72.3, 72.1, 56.1, 50.4, 46.8, 44.3, 44.1, 44.1, 44.0, 26.2, 25.8. LCMS: m/z 786.36 $[M + H]^+$. A solution of sodium hydroxide (500 mg; 12.5 mmol) in water (5 mL) was added to a solution of **24** (500 mg; 0.64 mmol) in ethanol (5 mL), and the resulting yellow solution was stirred at ambient temperature until reaction completion. The mixture was diluted with water (10 mL) and washed with dichloromethane (10 mL). The aqueous phase was adjusted to pH 1 with hydrochloric acid and extracted with propionitrile (2 × 20 mL). The combined propionitrile extracts were washed with water, dried with anhydrous $MgSO_4$, filtered, and concentrated to give the title compound **25** (272 mg; 60%) as a pale-yellow glassy solid. ^{1}H NMR (CD_3OD, 400 MHz) δ: 7.50−7.46 (3H, m), 7.40−7.26 (8H, m) 7.20−7.11 (5H, m), 7.05 (1H, d, J = 8.6 Hz), 7.01 (1H, m), 6.84 (2H, m), 5.18 (2H, s), 4.66 (1H, dd, J = 8.4, 4.5 Hz), 4.41 (2H, s), 3.55 (2H, s), 2.84 (3H, s), 2.82 (1H, m), 2.72 (1H, dd, J = 11.3, 4.5 Hz), 2.65 (1H, d, J = 13.1 Hz), 2.59 (1H, d, J = 13.1 Hz), 1.01 (3H, s), 0.98 (3H, s). ^{13}C NMR (CD_3OD, 100 MHz) δ: 174.1, 158.4, 151.9, 142.7, 140.4, 139.6, 138.1, 137.5, 136.7, 133.5, 132.4, 130.2, 130.0, 129.8, 129.4, 129.3, 129.1, 129.0, 128.2, 127.5, 126.6, 126.4, 126.3, 125.4, 124.1, 116.8, 114.0, 73.6, 71.8, 54.3, 50.7, 47.5, 44.3, 44.0, 40.0, 27.0, 26.6.

2-[3-(2-{[(2*R*)-2-{4-(Benzyloxy)-3-[(methylsulfonyl)amino]-phenyl}-2-hydroxyethyl]amino}-2-methylpropyl)phenyl]-*N*-[(4′-hydroxybiphenyl-3-yl)methyl]acetamide Fumaric Acid Salt 25a. Amine **9** (16.5 kg; 42.5 mol), bromide **1**[2] (22.9 kg; 44.6 mol), and sodium hydrogen carbonate (7.1 kg; 85 mol) were added to *n*-butyl acetate (165 L), and the resulting slurry was heated to reflux. After 15 min at reflux, the mixture was

concentrated by distillation to approximately 80 L reaction volume (120 L was distilled out over 2 h). The resulting slurry was refluxed for a further 37 h, at which point HPLC analysis showed no more than 5% **9** remaining, and the batch was progressed. The mixture was cooled to 50 °C, diluted with ethyl acetate (165 L), cooled to 20 °C, and washed with water (165 L). The retained organic phase was diluted with methanol (50 L), and triethylamine trihydrofluoride (6.8 kg; 42.5 mol) was added, followed by an ethyl acetate line wash (8 L). The solution was stirred at 20 °C for 3 h, at which point HPLC analysis indicated complete consumption of silyl ether **26**. A mixture of water (79 L) and concentrated aqueous ammonia (33 L) was added, followed by a water line wash (20 L), and the mixture was stirred for 20 min. The phases were separated, and the retained organic phase was washed with water (66 L) and then concentrated under vacuum at 30 °C to approximately 75 L reaction volume. The thick mixture was cooled to 20 °C and diluted with MEK (248 L). Water (3.3 L) was added, and the mixture was stirred until complete dissolution occurred (around 30 min). Fumaric acid (2.5 kg; 21.25 mol) was added; the salt was observed to oil out of solution. This oily mixture was heated to reflux for 4 h, during which time it converted into a thick, cream-colored suspension. Once crystallization had occurred, the batch was refluxed for a further 1 h, cooled to 23 °C, and aged for 4 h. The solid was isolated by filtration, washed with MEK (2 × 165 L), and dried at 40 °C under vacuum to give the product **25a** (28.27 kg; 87%) as an off-white solid. Mp 129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.61 (1H, t, J = 5.9 Hz), 7.56 (2H, dm, J = 7.0 Hz), 7.44−7.30 (9H, m), 7.26−7.19 (3H, m), 7.17−7.06 (4H, m), 6.87 (2H, dm, J = 8.8 Hz), 6.55 (1H, s), 5.19 (2H, s), 4.77 (1H, dd, J = 9.0, 2.5 Hz), 4.34 (2H, d, J = 5.9 Hz), 3.50 (2H, s), 3.02−2.96 (1H, m), 2.93 (3H, s), 2.88−2.78 (3H, m), 1.08 (3H, s), 1.07 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.2, 169.1, 157.3, 150.8, 140.2, 139.9, 136.8, 136.1, 135.8, 135.6, 131.3, 130.6, 128.7, 128.6, 128.3, 128.1, 127.8, 127.6, 127.6, 127.1, 125.6, 125.2, 124.7, 124.6, 124.3, 124.2, 124.0, 115.7, 112.8, 69.8, 56.0, 53.3, 49.1, 45.2, 44.3, 42.4, 42.2, 24.1, 24.1. LCMS: Found m/z 708.41 $[M + H]^+$. Anal. Calcd For $C_{41}H_{45}N_3O_6S \cdot 1/2(C_4H_4O_4)$: C, 67.43; H, 6.19; N, 5.49; S, 4.19. Found: C, 66.96; H, 6.18; N, 5.54; S, 4.07.

***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 suspension of fumarate **25a** (10.0 kg; 13.1 mol) in a mixture of THF (100 L) and water (20 L) was stirred at 20 °C while aqueous ammonia (35%, 10 L) was added, followed by a 10-L water line wash. The suspension was stirred until a clear solution was obtained (40 min in this case). The reactor contents were settled, and the lower aqueous phase was removed. The organic solution was washed with a solution of NaCl (3.6 kg) in water (26 L). HPLC analysis of a sample confirmed that the salt break was complete (NMT 1% fumaric acid remaining). The solution was then diluted with THF (50 L) and distilled at atmospheric pressure to approximately 90 L. Additional THF (50 L) was added, and the mixture was concentrated by distillation to 90 L. At this point the reflux temperature was >64 °C, indicating complete removal of water,[31] so the solution was cooled to 20 °C. The solution was filtered through a 16-in. Cuno carbon cartridge (Zeta carbon C16ME R54SP) at a flow rate of 10−12 L/min, followed by a THF wash (30 L) at the same flow rate. The filtered solution was transferred to a hydrogenation reactor, followed by a THF wash (60 L). Separately, a slurry of 5% Pd/C catalyst (type 87 L; 50% water wet, 1.0 kg) in water (10 L) was prepared; this was added to the THF solution, followed by a water wash (10 L). The resulting mixture was hydrogenated at 20 °C under 3.5 bar hydrogen for 5 h, at which point hydrogen uptake had ceased and HPLC analysis confirmed reaction completion. The slurry was filtered through a Gauthier filter, and the spent catalyst was washed with a mixture of THF (45 L) and water (5 L). The resulting solution was filtered through a 1.2 μm filter and concentrated by distillation to around 160 L. Acetonitrile (50 L) was added, and the mixture was distilled down to 160 L. This process was repeated until the reflux temperature exceeded 81 °C (this required eight separate 50-L acetonitrile charges), and the volume was adjusted back to 160 L. The slurry was cooled to 20 °C at a rate of 0.5 °C/min and aged for 4 h at 20 °C. The solid was isolated by filtration, washed with acetonitrile (2 × 50 L), and dried under vacuum in a tray drier at 40 °C for 20 h, to give crude **8** (6.48 kg). This crude material was suspended in a mixture of methanol (58.3 L) and water (6.5 L), and the resulting slurry was stirred at 50 °C for 2 h. The mixture was cooled to 20 °C at 1 °C/min and then aged for 18 h at 20 °C. The solid was isolated by filtration, washed with a mixture of methanol (58.3 L) and water (6.5 L), and then dried at 40 °C under vacuum in a tray drier to give **8** (5.65 kg, 70%) as a white solid. Analytical data were identical to those reported previously.[1,2]

Alternative Procedure. A mixture of bromohydrin **1**[2] (10.93 g; 21.2 mmol), amine **9** (7.50 g; 19.3 mmol) and sodium hydrogen carbonate (9.0 g; 107.1 mmol) in *n*-butyl acetate (55 mL) was refluxed under nitrogen for 53 h. The mixture was cooled to ambient temperature and diluted with water (180 mL) and ethyl acetate (180 mL). The phases were separated, and the organic phase was washed successively with aqueous (L)-tartaric acid (1 M, 55 mL), water (55 mL), a mixture of water and 35% aqueous ammonia (3:1, 60 mL), and water (55 mL). Palladium on carbon catalyst (5%, 50% water wet; 1300 mg) was added, and the resulting mixture was hydrogenated at 60 °C and 4 bar hydrogen pressure for 24 h. The reaction mixture was removed from the hydrogenation reactor, and Arbocel (13 g) was added. The resulting slurry was stirred for 30 min. The mixture was filtered through a pad of Arbocel, and the catalyst bed was washed with ethyl acetate (200 mL). The pale-yellow filtrate was concentrated under reduced pressure to remove the ethyl acetate. Then methanol (60 mL) was added, and the mixture was concentrated to dryness under reduced pressure. The resulting viscous, orange-brown oil was dissolved in methanol (100 mL) and placed in a polypropylene vessel. Ammonium fluoride (2.1 g; 56.7 mmol) was added, washing with water (20 mL) and methanol (20 mL), and the resulting solution was stirred at ambient temperature for 65 h. The precipitated solid was isolated by filtration, washed with a mixture of methanol (80 mL) and water (20 mL), and dried at 40 °C under vacuum for 4 h. The pale-brown solid was slurried in a mixture of methanol (67.5 mL) and water (7.5 mL) at 50 °C for 2 h, and at ambient temperature for 16 h. The solid was isolated by filtration, washed with methanol−water (8:2, 2 × 20 mL), and dried at 40 °C in a vacuum oven for 18 h. The resulting solid was slurried in water (80 mL) at ambient temperature for 16 h, isolated by filtration, and washed with water (50 mL) to give **8** (6.01 g; 50%) as an off-white solid.

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(4) Other protecting groups were evaluated, but the benzyl and TBS groups used in the initial synthesis were the preferred choices.

(5) Coe, D. M.; Perciaccante, R.; Procopiou, P. A. *Org. Biomol. Chem.* **2003**, *1*, 1106.

(6) Hett, R.; Fang, Q. K.; Gao, Y.; Wald, S. A.; Senanayake, C. H. *Org. Process Res. Dev.* **1998**, *2*, 96.

(7) (a) Baur, F.; Beattie, D.; Beer, D.; Bentley, D.; Bradley, M.; Bruce, I.; Charlton, S. J.; Cuenoud, B.; Ernst, R.; Fairhurst, R. A.; Faller, B.; Farr, D.; Keller, T.; Fozard, J. R.; Fullerton, J.; Garman, S.; Hatto, J.; Hayden, C.; He, H.; Howes, C.; Janus, D.; Jiang, Z.; Lewis, C.; Loeuillet-Ritzler, F.; Moser, H.; Reilly, J.; Steward, A.; Sykes, D.; Tedaldi, L.; Trifilieff, A.; Tweed, M.; Watson, S.; Wissler, E.; Wyss, D. *J. Med. Chem.* **2010**, *53*, 3675. (b) Zaborenko, N.; Bedore, M. W.; Jamison, T. F.; Jensen, K. F. *Org. Process Res. Dev.* **2011**, *15*, 131.

(8) There is precedent for construction of a *tert*-butyl amine via imine formation and addition of MeMgBr (Chung, J. Y. L.; Cvetovich, R. J.; McLaughlin, M.; Amato, J.; Tsay, F.-R.; Jensen, M.; Weissman, S.; Zewge, D. *J. Org. Chem.* **2006**, *71*, 8602). However, routes to a headgroup amine were lengthy (2−3 steps from **1**) and those to a suitable ketone (as shown in Scheme 2) were of comparable length to those for the preparation of **9**; thus, this approach was deemed lower priority and was not investigated.

(9) Several alternative strategies were examined; however, these met with little success. Examples include asymmetric reduction of an amino ketone (see Smith, P.; Brodfuehrer, P. R.; Dillon, J. L.; Vemishetti, P. *Synth. Commun.* **1995**, *25*, 1093) and asymmetric reduction of an iminoketone (see Hong, Y.; Gao, Y.; Nie, X.; Zepp, C. M. *Tetrahedron Lett.* **1994**, *35*, 5551).

(10) Brough, P.; Pecaut, J.; Rassat, A.; Rey, P. *Chem.—Eur. J.* **2006**, *12*, 5134.

(11) We did not attempt to identify any byproducts or conduct a full mass-balance analysis.

(12) Shokova, E.; Mousoulou, T.; Luzikov, Yu.; Kovalev, V. *Synthesis* **1997**, 1034.

(13) (a) Jiang, X.; Lee, G. T.; Villhauer, E. B.; Prasad, K.; Prashad, M. *Org. Process Res. Dev.* **2010**, *14*, 883. (b) Baum, J. C.; Milne, J. E.; Murry, J. A.; Thiel, O. R. *J. Org. Chem.* **2009**, *74*, 2207. (c) Chang, S.-J. *Org. Process Res. Dev.* **1999**, *3*, 232.

(14) Colleagues have recently published a similar Ritter/deprotection reaction sequence to prepare two β_3-agonists, see Bradley, P. A.; Carroll, R. J.; Lecouturier, Y. C.; Moore, R.; Noeureuil, P.; Patel, B.; Snow, J.; Wheeler, S. *Org. Process Res. Dev.* **2010**, *14*, 1326.

(15) Jirgensons, A.; Kauss, V.; Kalvinsh, I.; Gold, M. R. *Synthesis* **2000**, 1709.

(16) It is essential to remove the chloroacetonitrile before the free base (**9**) is liberated, as this reacts with chloroacetonitrile during the solvent exchange to acetonitrile, yielding the corresponding cyanomethyl adduct. In addition to reducing the yield, this impurity adversely affects the crystallization of **9**.

(17) Related epoxides with an additional protecting group on the sulfonamide are known in the patent literature, e.g. benzyl-protected, Johnson, M. R.; Hirsh, A. J.; Boucher, R. C.; Zhang, J. Pat. Appl. WO/2007/146869 A1.

(18) A 'typical' reaction HPLC trace (uncorrected) shows approximately 17% **9**, 60% **24**, 10% regioisomer, and 8% overalkylated 'dimeric' species (the regioisomer and dimers were assigned on the basis of MS data only and have not been isolated), as well as other low-level impurities. Similar regioisomeric and dimeric byproducts have been reported for the coupling of the analogous benzyl-protected epoxide, see reference 17.

(19) While we have only prepared epoxide **23** using the route described, a shorter route analogous to that used for the synthesis of the epoxide utilized in the manufacture of formoterol (five steps) should be feasible, and other, even shorter routes, can be envisaged.

(20) An initial screen of 19 bases in two solvents (DMF, NMP) was conducted, and then the two best hits from this first screen ($NaHCO_3$ and K_2HPO_4) were examined in 11 different solvents.

(21) ICH Topic Q3C: *Impurities: Guideline for Residual Solvents*, (R4); European Medicines Agency: London, issued February 2009; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002674.pdf.

(22) Only trace levels of the *N*-acyl impurity arising from reaction of amine **9** with *n*-butyl acetate were observed.

(23) The product mixture was poorly soluble in *n*-butyl acetate at ambient temperature.

(24) Chen, C. −K.; Singh, A. K. *Org. Process Res. Dev.* **2001**, *5*, 508.

(25) Solvents examined included ethanol, methanol, and THF. It appears as if the residual reagent and byproducts solubilize **8**, hampering crystallization.

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

(27) A range of carbons were evaluated from which Cuno Zeta carbon R54SP was selected.

(28) We were not able to identify the catalyst poison.

(29) Most other Pd scavengers examined caused some degradation and/or afforded poor recovery of **8**.

(30) The initial water washes are to reduce the level of TFA in order to minimize off-gassing in the subsequent potassium hydrogen carbonate washes.

(31) The THF−water azeotropic mixture distills at approximately 63 °C, while pure THF has a bp of 65−67 °C.