Organic Process Research & Development

Article

pubs.acs.org/OPRD

Identification and Development of an Efficient Route to SB-649915

Mark Armitage,[†] Guillaume Bret,[†] Bernie M. Choudary,[†] Mike Kingswood,[†] Mike Loft,[†] Steve Moore,[†] Steve Smith,[†] and Michael W. J. Urquhart*[,†]

Glaxo Group Limited, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, U.K.

Supporting Information

ABSTRACT: The discovery and development of an efficient manufacturing route to the SSRI-5-HT1A receptor antagonist 6-[(1-{2-[(2-methyl-5-quinolinyl)oxy]ethyl}-4-piperidinyl)methyl]-2*H*-1,4-benzoxazin-3(4*H*)-one (SB-649915) **1** is described. The existing route to **1** involved coupling quinoline **6** with piperidine **5** and was considered lengthy as a consequence of the nine synthetic steps required to prepare **5**. Two new routes to the key piperidine intermediate **5** are identified which deliver this compound in five and two steps respectively, from readily available materials using novel lithiation and Friedel−Crafts methodology respectively. The latter of these two routes was successfully demonstrated at 5 L scale to deliver 700 g of **5**. Development to the methanesulfonate **34**, an alternative to quinoline **6**, is also described as is the final alkylation of piperidine **5** with this methanesulfonate **34** to deliver SB-649915 **1**.

INTRODUCTION

SB-649915 is an SSRI-5-HT1A receptor antagonist in development for the treatment of depression. Herein is described the limitations of the original synthetic route to SB-649915, the identification of a new route to this entity and subsequent scale-up of this route.

RESULTS AND DISCUSSION

Initial Route to SB-649915. The original route to SB-649915A **1** has been reported[1] and involved the coupling of the piperidine **5** with the bromoethoxyquinoline **6** which proceeded in 55% yield. The chemistry to prepare the key piperidine intermediate **5** was long, comprised nine synthetic transformations from the commercially available pyridine-4-carboxaldehyde **2** and delivered **5** in an overall yield of 45%. The route to **5** is depicted in Scheme 1 and involved reaction of carboxaldehyde **2** with the Grignard formed from 4-bromoanisole to give the pyridine **3** after reductive removal of the benzylic alcohol function.[2] This represented a novel preparation of the benzyl pyridine **3** although alternative procedures are reported.[3] Subsequent acid mediated demethylation of **3**, hydrogenation, nitration, Boc protection and alkylation with methyl bromoacetate yields the ester **4**. Reduction of the nitro function in **4** using catalytic hydrogenation, followed by acid mediated removal of the carbamate protecting group, finally secures the piperidine **5**. The bromoethoxyquinoline **6** was derived from the corresponding phenol **7** by base mediated reaction with dibromoethane.[4] The phenol **7** has numerous reports available describing its manufacture.[5] The above synthesis to **1** is hampered because the synthesis of **5** requires nine steps, the alkyl bromide **6** can only be prepared in moderate yield (potential instability issues) and the final coupling to prepare SB-649915 **1** is also low yielding.[6] The convergent strategy to prepare SB-649915 **1** from the coupling of **5** with a suitable electrophile, i.e., **6**, was good; therefore a more expedient route to the piperidine **5** was key. Also important was improving the chemistry to the quinoline electrophile and maximizing the yield in the coupling reaction to SB-649915 **1**.

Identification of New Synthetic Routes to Piperidine 5. To address the aforementioned issues, we began to explore alternative approaches for the synthesis of the key benzoxazinone **5**. One key disconnection that could deliver the desired ring system more expediently would involve the direct coupling of a suitable benzoxazoline system (**11** or **10**) with either pyridine-4-carboxaldehyde **2** or isonicotinoyl chloride **13** using either a lithiation or Friedel−Crafts approach respectively (Figure 1). Such lithiation chemistry would appear to be novel, although the corresponding 6-bromobenzoxazinone **11** is known.[7,8] Friedel−Crafts reactions of both benzoxazinone **10**[9] and isonicotinoyl chloride **13**[10] are known, and they have also been reported to react together.[11] The resulting products from these reactions should secure the target piperidine **5** following an exhaustive reduction using catalytic hydrogenation.[12]

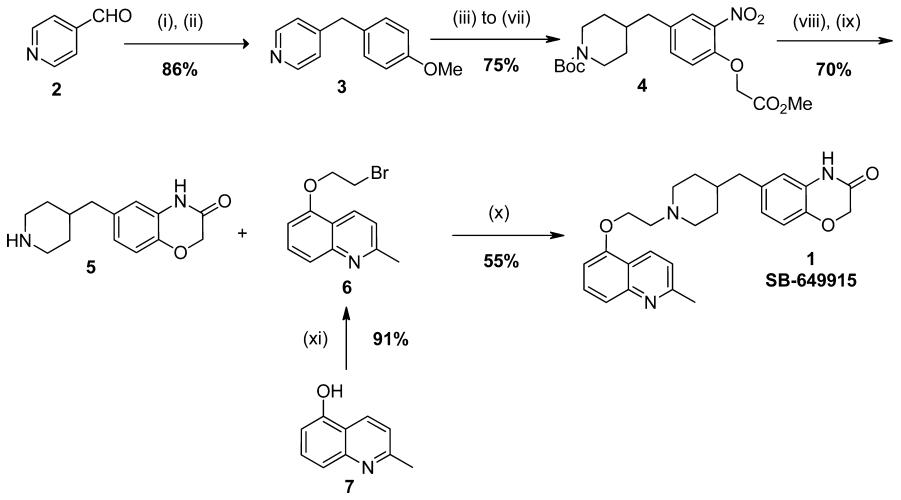
The preparation of 6-bromobenzoxazinone **11** from the parent benzoxazinone **10** has been reported,[7] but in our hands these bromination conditions only gave complex mixtures arising from nonselective bromination. Other methods to prepare **11** are known. These involve bromination of 2-nitrophenol **14**,[13] followed by alkylation of the phenol **15** with methyl chloroacetate to give ester **16** and subsequent reduction to give **11**.[10] Alternatively reduction of nitrophenol **15** to aminophenol **17** followed by acylation with chloroacetyl chloride and subsequent cyclisation[14] leads to **11** (Scheme 2).

For this work, however, an alternative approach to **11** was successfully evaluated, exploiting the cheap and readily available 2-hydroxyacetanilide **18** using a classical approach to selective bromination.[15] This approach avoided a dissolved metal reduction and therefore minimized any risk of reductive dehalogenation pathways. Phenol **18** is converted to aniline **17** via the acetamide **19** following bromination and hydrolysis,

Received: July 10, 2012
Published: August 29, 2012

dx.doi.org/10.1021/op300185s | *Org. Process Res. Dev.* 2012, 16, 1626−1634

Scheme 1. Initial Supply Route to SB-649915[a]



[a]Reagents and conditions: (i) 4-bromoanisole, Mg; (ii) Zn, HCO_2H; (iii) 48% aq HBr, Δ; (iv) H_2, PtO_2, H_2SO_4, MeOH; (v) HNO_3, AcOH; (vi) $(Boc)_2O$, NEt_3, H_2O, THF; (vii) $BrCH_2CO_2Me$, K_2CO_3, acetone, Δ; (viii) H_2, Pd/C; (ix) HCl, Et_2O, IPA, Δ; (x) DIPEA, IPA, Δ; (xi) $BrCH_2CH_2Br$, K_2CO_3, MEK, 80 °C.

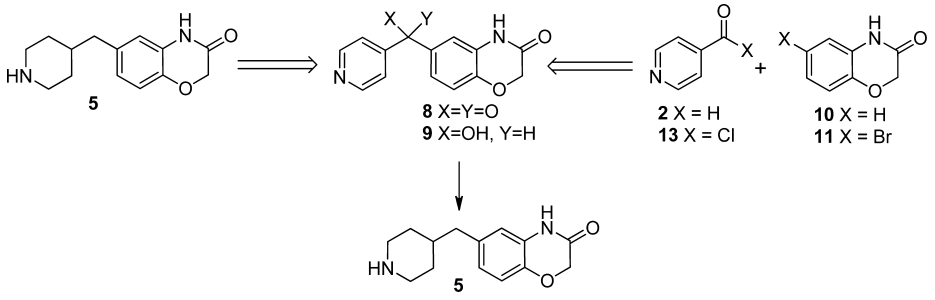
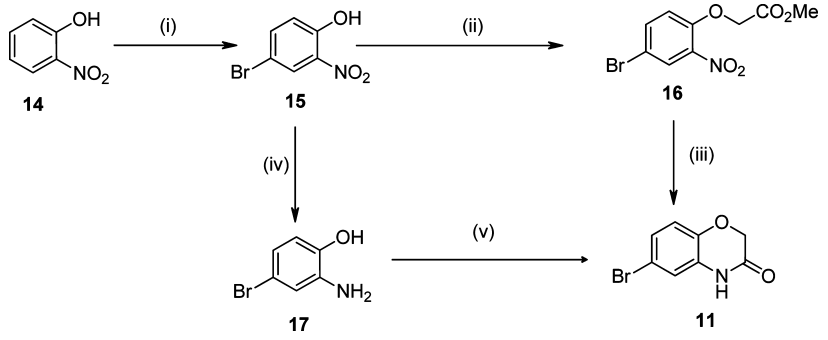


Figure 1. Retrosynthetic analysis to 6-(4-piperidinylmethyl)-2*H*-1,4-benzoxazin-3(4*H*)-one **5**.

Scheme 2. Literature Routes to 6-Bromobenzoxazinone[a]



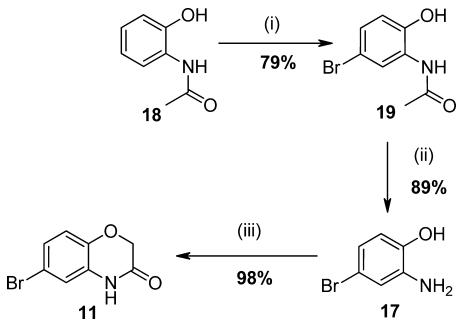
[a]Reagents and conditions: (i) bromination; (ii) $BrCH_2CO_2Me$, K_2CO_3, AcMe, Δ; (iii) Fe, AcOH; (iv) H_2, PtO_2, H^+, MeOH; (v) $ClCH_2COCl$, TEA, THF then NaH.

and subsequent acylation of **17** with chloroacetyl chloride and "in situ" cyclisation delivers benzoxazinone **11**. This chemistry proved to be remarkably facile and high yielding, and was easily scaled to deliver multiple gram quantities of the target 6-bromobenzoxazinone **11** (Scheme 3).

Initial attempts to react a mixture of pyridine-4-carboxaldehyde **2** with benzoxazinone **11** using *n*-butyllithium at low temperatures led to the 1,2-addition product **20** (Scheme 4). Following a method for the lithiation/functionalisation of bromoquinolones,[16] the dilithium anion of **11** was prepared using *n*-butyllithium, and this dianion was treated with pyridine-4-carboxaldehyde **2** to give the target product **9** in a modest yield of 45%. Inspection of the reaction by LCMS suggested that, as well as product **9** and debrominated starting material **10**, there were also several butylated products that were tentatively assigned as structures **21**, **22**, **23** and **24**. It is believed these products are derived from reaction of the dianions of **9** or **11** with the bromobutane byproduct formed within the lithium halogen exchange reaction. Further development work demonstrated that keeping this reaction cold was important for minimizing the formation of these byproducts, and a yield of 76% for product **9** was achieved for this

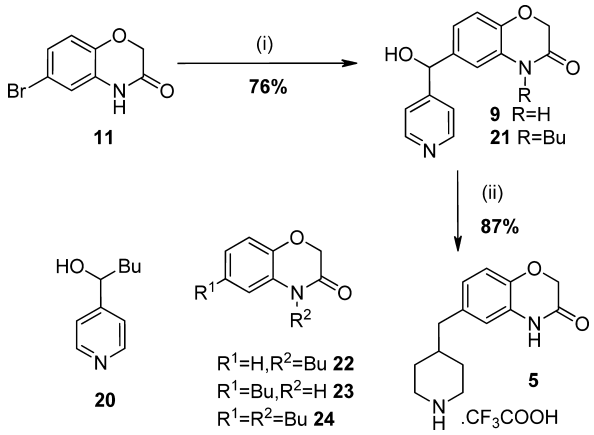
dx.doi.org/10.1021/op300185s | *Org. Process Res. Dev.* 2012, 16, 1626−1634

Scheme 3. Efficient Route to 6-Bromo-2*H*-1,4-benzoxazin-3(4*H*)-one 11[a]



[a]Reagents and conditions: (i) Br_2, AcOH; (ii) H^+, IMS, Δ; (iii) $ClCH_2COCl$, $NaHCO_3$, THF then K_2CO_3, Δ.

Scheme 4. Lithiation Route to 6-(4-Piperidinylmethyl)-2*H*-1,4-benzoxazin-3(4*H*)-one 5[a]



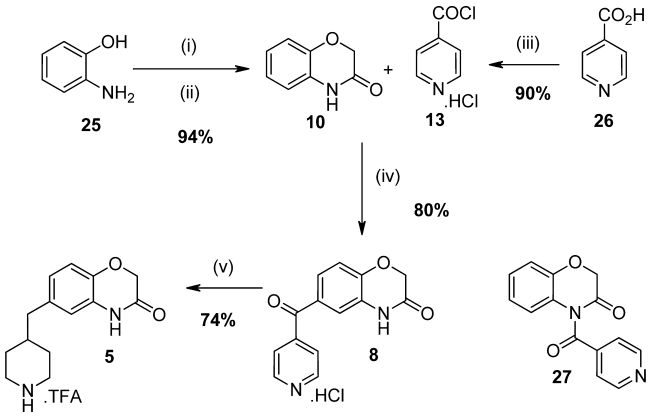
[a]Reagents and conditions: (i) *n*-BuLi, THF then 4-PyCHO **12**; (ii) H_2, Pd/C, TFA/AcOH.

reaction.[17] Another attempt to minimize alkylation side reactions involved changing the lithiation reagent from *n*- to *s*-butyllithium, as the formed *s*-butyl bromide was expected to be a less effective electrophile, but unfortunately, this modification led to a significantly more complex mixture.[18] All that now remained was the removal of the alcoholic functionality and reduction of the pyridine nucleus in **9** to afford the desired piperidine intermediate **5**. This was readily achieved in a one stage process using catalytic hydrogenation in a mixed acetic acid and trifluoroacetic acid medium to deliver piperidine **5** in excellent yield, as its trifluoroacetic acid salt. Conversion of pyridylbenzyl alcohols to the corresponding benzylpiperidines has been reported,[19] but the use of trifluoroacetic acid as the acid source appears to be novel and certainly offers significant advantages for product isolation in this instance (Scheme 4).

The above process represents a significantly more streamlined and cost-effective process to the key piperidine intermediate **5** than the existing procedure. It also demonstrates a new and highly efficient route to the bromobenzoxazinone intermediate **11**, which has proven to be a useful substrate for further homologation using lithiation chemistry and ultimately delivers piperidine **5** in an overall 44% yield from commercially available 2-acetamidophenol **18**.

As discussed above, an even more expedient route to the piperidine intermediate **5** would be from the Friedel–Crafts acylation of the parent benzoxazinone **10** with isonicotinoyl chloride **13**. Although both of these materials are commercially available, they are somewhat expensive, and hence their preparation was evaluated in-house. The synthesis of the benzoxazinone **10** is reported,[20] but we found that it can be prepared expediently in one pot from 2-aminophenol in 94% yield using similar methodology to that described above for the conversion of aminophenol **17** through to bromobenzoxazinone **11**. The improved process to **10** is conceptually similar to that reported by Dunn et al.[21] but is significantly higher yielding (94% compared to 60%), uses a more environmentally acceptable solvent (tetrahydrofuran[22] rather than chloroform) and represents a useful alternative to the reported methods. To this end, a two step one pot process was developed where aniline **25** was reacted with chloroacetyl chloride, and the intermediate chloroacetamide was smoothly converted through to the benzoxazinone **10** in excellent yield by base mediated cyclisation (Scheme 5).

Scheme 5. Friedel–Crafts Route to 6-(4-Piperidinylmethyl)-2*H*-1,4-benzoxazin-3(4*H*)-one 5[a]

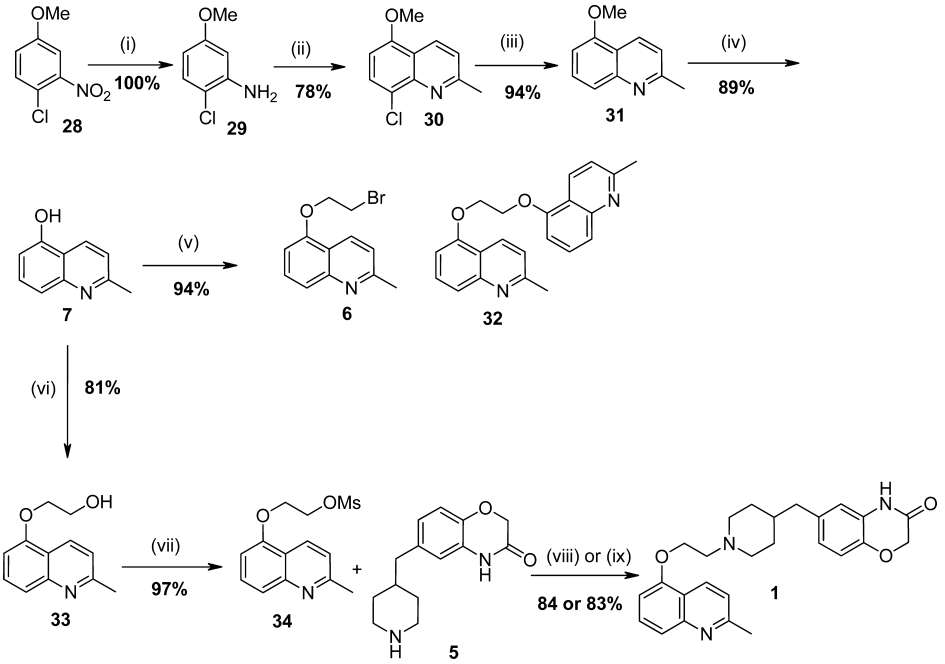


[a]Reagents and conditions: (i) $ClCH_2COCl$, $NaHCO_3$, THF; (ii) K_2CO_3, Δ; (iii) $SOCl_2$, PhMe; (iv) $AlCl_3$, DMF; (v) H_2, PdC, TFA/AcOH.

Isonicotinyl chloride hydrochloride **13** was required for the desired Friedel–Crafts investigations. It is commercially available, but its cost was considered prohibitive, hence it was decided to prepare it from isonicotinic acid **26**. This was readily achieved using thionyl chloride in toluene, and the target compound was produced in 90% yield. Evaluation of the Friedel–Crafts reaction of **13** with benzoxazinone **10** was initially disappointing as little or no reaction was observed using aluminium chloride as catalyst with numerous solvents including nitromethane, dichloromethane, dichloroethane, toluene and *N*,*N*-dimethylformamide. Interestingly some success was observed adding an equivalent of Hunig's base to the reaction where dichloromethane was used as solvent which may advocate the formation of an active complex between the base and aluminium chloride. Replacing the Lewis acid for ytterbium triflate led to no desired product **8** being formed, but low levels of the isomeric amide **27** were observed. Following on from the earlier result with Hunig's base and inspired by the report that DMF forms an active complex with aluminium chloride,[23] similar DMF conditions were tested with the benzoxazinone **10** and acid chloride **13** to deliver an excellent

dx.doi.org/10.1021/op300185s | *Org. Process Res. Dev.* 2012, 16, 1626–1634

Scheme 6. Route to 2-[(2-Methyl-5-quinolinyl)oxy]ethyl Methanesulfonate 35 and Conversion to SB649915[a]



[a]Reagents and conditions: (i) Fe, AcOH; (ii) crotonaldehyde, *p*-chloranil, HCl(aq), BuOH, Δ; (iii) H_2, PdC, MeOH; (iv) HBr, Δ; (v) $BrCH_2CH_2Br$, K_2CO_3, MeCN; (vi) ethylene carbonate, K_2CO_3, DMF; (vii) MsCl, DIPEA, THF; (viii) quinoline **34**, $NaHCO_3$, DME, Δ; (ix) quinoline **34**, diisopropylamine, MEK, Δ.

conversion to the desired product **8**. The following reduction of **8** to **5** was achieved using similar conditions to those described above for the reduction of **9**. The Friedel–Crafts reaction and subsequent reduction comprised a highly efficient route into the key piperidine **5**, and an optimized procedure was scaled up to 5 L whereby a total of 0.7 kg of **8** was prepared (Scheme 5). It was clear from this campaign, however, that further scale-up would be inadvisible as inadvertent crystallization post toluene dilution resulted in an inability to perform the dropwise quench into water, and the resulting direct quench led to significant safety concerns for further scale-up.[24]

Having developed two supply routes to the piperidine **5**, the synthesis of the quinoline **6** and its coupling with piperidine **5** to deliver the target SB-649915 **1** were needed. The synthesis of the quinoline **6** was typically derived from the corresponding phenol **7**, and although **7** is known in the literature,[25] a more efficient approach to this molecule was exploited. The aniline **29** is commercially available, but in order to try and reduce cost for the synthesis of the key quinoline fragment, methods to prepare **29** from the readily available nitrobenzene **28** were evaluated. The dissolving metal reduction conditions of iron in acetic acid proved highly efficient for this transformation and were used for delivery of early supplies, although some success was also achieved using Raney nickel hydrogenation and sodium dithionite methods, which may prove superior for future scale-up. The aniline **29** was then reacted with crotonaldehyde using chloranil as oxidant to give the quinaldine **30** in 75% yield as its hydrochloride salt. Reductive removal of the chloride in **30** was readily achieved using catalytic hydrogenation in the presence of base and delivered **31** in 94% yield. The demethylation of **31** to give the phenol **7** was achieved using hydrobromic acid under reflux, but this was a slow process and necessitated a vigorous reflux to drive the reaction to completion. The phenol **7** reacted with dibromoethane to deliver the target quinoline **6**, but the product contained significant quantities (6%) of a byproduct which was determined as the bis-quinolinyl ether **32** (Scheme 6). Aside from the hazardous nature of handling dibromoethane, this intermediate was an immediate precursor to the target API, and there were concerns with respect to controlling the formation of impurity **32** with further scale-up. It was therefore decided to prepare the methanesulfonate ester **34**, as an alternative to **6**, as it was believed this material could be made under milder conditions. The milder conditions would likely minimize side reactions as well as potentially avoiding particularly toxic and hazardous reagents. Ethylene carbonate is a nontoxic and effective reagent for the hydroxyethylation of phenols,[26] and its reaction with phenol **7** proceeded in 81% yield to give the corresponding alcohol **33**.[27] Conversion of alcohol **33** to its methanesulfonate **34**[28] was achieved in 97% yield using methanesulfonyl chloride. The key coupling reaction of the newly formed methanesulfonate **34** with the piperidine **5** was then investigated. Sodium hydrogen carbonate was selected as mild base for this transformation as alkylation on the benzoxazolinone ring nitrogen needed to be avoided, and a brief solvent screen identified 1,2-dimethoxyethane (DME) as this solvent gave a reasonable rate of reaction. Under these conditions a smooth conversion to SB-649915 **1** was achieved (Scheme 6).[29] The processes from **28** through to the methanesulfonate **34** were ultimately demonstrated on a 0.5 kg scale. Further purification of this API was accomplished by recrystallisation from either ethanol or toluene.

Given the health hazards associated with the use of DME as solvent, and that substitution is recommended wherever possible according to REACH[30] and European legislation, alternative conditions were sought for future campaigns. Hence a more comprehensive solvent base screen was conducted using principle component analysis (PCA) models where a range of

dx.doi.org/10.1021/op300185s | Org. Process Res. Dev. 2012, 16, 1626–1634

inorganic and organic bases were evaluated within a range of solvents. The output from this screen highlighted that using diisopropylamine in 3-pentanone was an excellent alternative to sodium hydrogen carbonate in DME and the resulting reaction of piperidine **5** with methanesulfonate **34** proceeded to deliver SB-649915 **1** in 83% yield with an HPLC purity of >97%.[31]

To conclude, the development of a scalable route to SB-649915 **1** is described, which offers significant advantages over the existing route to this material. Other highlights include new and highly efficient synthetic routes to the benzoxazinones **10** and **11** as well as novel streamlined processes to the complex piperidine intermediate **5**, employing novel lithiation and Friedel−Crafts methodologies. The methanesulfonate **34** was identified as a useful alternative to the existing alkyl bromide intermediate **6** as its manufacture avoided both hazardous reagents and a problematic impurity. The coupling of the piperidine **5** with methanesulfonate **34** is discussed and scaled to deliver multigram quantities of the target molecule SB-649915 **1**. Also highlighted was the development of alternative conditions that would use more sustainable conditions for the manufacture of SB-649915 **1**.

EXPERIMENTAL SECTION

General. Commercially available reagents were used without further purification. Reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen. The experimental conditions below refer to the procedures used for the preparation of multigram quantities of these materials.

4-Bromo-2-acetamidophenol (19). A solution of bromine (34.0 mL, 664 mmol) in acetic acid (160 mL) was added dropwise to a stirred solution of 2-acetamidophenol **18** (100.0 g, 662 mmol) in acetic acid (800 mL) at 20 °C over 3 h maintaining an addition temperature below 24 °C (cold water bath). The solution was quenched by the dropwise addition of water (1.5 L), and a solid was precipitated. The mixture was stirred at 20 °C for 30 min and cooled to 10 °C. Filtration, washing with water (3 × 150 mL) and drying gave the title compound **19** as a light brown solid (119.8 g, 79%). ^{1}H NMR (400 MHz, DMSO): δ 2.10 (3H, s), 6.80−6.83 (1H, m), 7.06−7.08 (1H, m), 8.07 (1H, s), 9.26 (1H, bs), 10.14 (1H, s). ^{13}C NMR (100 MHz, DMSO): δ 23.8, 109.6, 116.9, 123.8, 126.4, 128.2, 146.7 and 169.0.[32]

2-Amino-4-bromophenol (17). A stirred solution of **19** (119.8 g, 0.52 mol) in concentrated hydrochloric acid (140 mL) and industrial methylated spirit (760 mL) was heated at reflux for 4 h and then allowed to cool to ambient, solvent was removed under vacuum and the residual grey solid was carefully basified with saturated aqueous sodium hydrogen carbonate (1.5 L) as well as solid sodium hydrogen carbonate. Filtration, washing with water (2 × 200 mL) and drying gave the title compound **17** as a light brown solid (87.3 g, 89%). ^{1}H NMR (400 MHz, DMSO): δ 4.80 (2H, bs), 6.48−6.51 (1H, m), 6.55−6.57 (1H, m), 6.72 (1H, m), 9.27 (1H, bs). ^{13}C NMR (100 MHz, DMSO): δ 110.6, 115.6, 116.0, 118.1, 138.9 and 143.2.[32]

6-Bromo-2*H*-1,4-benzoxazin-3-one (11). A solution of chloroacetyl chloride (40.8 mL, 0.487 mol) in THF (110 mL) was added dropwise over 20 min to a stirred suspension of 2-amino-4-bromophenol **17** (87.3 g, 0.465 mol) and sodium hydrogen carbonate (82.1 g, 0.93 mol) in THF (1.3 L) at 6 °C (ice−water) under nitrogen. The internal temperature was maintained below 8 °C during this addition, and the suspension was then stirred cold (<5 °C) for 20 min. The mixture was treated with potassium carbonate (128.1 g, 0.93 mol), heated to reflux, stirred for 2 h, and allowed to cool to ambient and stand for 15 h. The mixture was diluted with ethyl acetate (1 L), stirred for 20 min and filtered to remove solids. The residue was washed with ethyl acetate (500 mL), and the filtrate and washings were combined. The solvent was removed under vacuum to give a pink solid, which was suspended in water (1 L) and stirred for 1 h. Filtration, washing with water (2 × 500 mL) and drying gave the title compound **11** as a pink solid (103.3 g, 98%). ^{1}H NMR (400 MHz, DMSO): δ 4.60 (2H, s), 6.91−6.93 (1H, m), 7.03 (1H, m), 7.06−7.08 (1H, m), 10.80 (1H, s). ^{13}C NMR (100 MHz, DMSO): δ 66.7, 113.3, 118.1, 125.3, 129.1, 142.6 and 164.6.[33]

6-(1-Hydroxy-1-pyridin-4-yl)methyl-4*H*-benzo[1,4]-oxazin-3-one (9). A solution of **11** (30.0 g, 131.6 mmol) in THF (570 mL) was added dropwise to a stirred 1.6 M solution of *n*-butyllithium in hexane (204 mL, 326 mmol) at −70 °C under nitrogen over 40 min maintaining an internal temperature below −60 °C. The resulting orange mixture was stirred below −70 °C for 10 min and treated with pyridine-4-carboxaldehyde **2** (21.0 mL, 0.326 mol) dropwise over 5 min, and the resulting grey suspension was stirred below −70 °C for 30 min. The mixture was stirred below −70 °C for an additional 40 min and quenched by the dropwise addition of water (450 mL), and the mixture was allowed to warm to ambient. The organic solvent was removed under vacuum, the residual biphasic mixture was diluted with ethyl acetate (300 mL) and this too was removed under vacuum with precipitation of a purple solid. The suspension was diluted with TBME (150 mL), and the suspension was allowed to stand at ambient for 15.5 h. The suspension was cooled to 5 °C (ice−water) and stirred for 1 h. Filtration, washing with TBME (3 × 50 mL) and drying gave the title compound **9** as brown crystals (25.6 g, 76%). ^{1}H NMR (400 MHz, DMSO): δ 4.58 (2H, s), 5.69 (1H, d), 6.16 (1H, d), 6.93−6.93 (3H, m), 7.38−7.40 (2H, d), 8.54−8.55 (2H, d), 10.70 (1H, s). ^{13}C NMR (100 MHz, DMSO): δ 66.7, 113.3, 118.1, 125.3, 129.1, 142.6 and 164.6.

4-[(3-Oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)-methyl]piperidinium Trifluoroacetate (5). A suspension of 10% palladium on charcoal (65% wet/wt, 3.5 g) and **9** (3.5 g, 13.66 mmol) in trifluoroacetic acid (17.5 mL) and acetic acid (35 mL) was hydrogenated at 40 psi at 70 °C for 6 h. The mixture was cooled to 20 °C, the catalyst was removed by filtration under vacuum, the residue was washed with acetic acid (30 mL) and the filtrate and washings were combined. The solvent was removed under vacuum to afford a green/grey solid, which was triturated with TBME (40 mL). Filtration and drying gave the title compound **5** as a cream solid (4.3 g, 87%). ^{1}H NMR (400 MHz, DMSO): δ 1.29 (2H, m), 1.70 (3H, m), 2.44 (2H, m), 2.80 (2H, m), 3.25 (2H, m), 4.53 (2H, s), 6.69 (1H, m), 6.72 (1H, m), 6.87 (1H, m), 8.33 (2H, bs), 8.66 (1H, bs), 10.69 (1H, s). ^{13}C NMR (100 MHz, DMSO): δ 28.1, 35.0, 40.9, 43.1, 66.8, 115.9, 116.2, 123.6, 127.1, 133.5, 141.6 and 165.0.

Preparation of 4*H*-Benzo[1,4]oxazin-3-one (10). A solution of chloroacetyl chloride (51 mL, 0.64 mol) in THF (100 mL) was added dropwise to a stirred suspension of sodium hydrogen carbonate (82.1 g, 0.93 mol) and 2-aminophenol **25** (50.8 g, 0.465 mol) in THF (700 mL) at 5 °C under nitrogen over approximately 15 min. Vigorous effervescence was observed with an exotherm to approximately

dx.doi.org/10.1021/op300185s | Org. Process Res. Dev. 2012, 16, 1626−1634

25 °C. The resulting yellow suspension was stirred at room temperature for 1.5 h. Potassium carbonate (128.1 g, 0.93 mol) was added and the mixture heated to reflux and stirred for 2 h. The mixture was allowed to cool to 40 °C and diluted with ethyl acetate (500 mL), and the inorganic solids were removed by filtration. The residue was washed with ethyl acetate (250 mL), the filtrate and washings were combined and the solvent was removed under vacuum to give a cream/purple solid. The residue was diluted with water (750 mL), and the suspension was stirred at room temperature for 90 min. Filtration, washing with water (3 × 150 mL) and drying gave the title compound **10** as an off-white solid (64.8 g, 94%). ^{1}H NMR (400 MHz, DMSO): δ 4.7 (2H, s), 7.00 (4H, m).[34]

Preparation of Isonicotinoyl Chloride Hydrochloride (13). Thionyl chloride (13 mL, 178.7 mmol, 1.1 equiv) was added to a stirred slurry of isonicotinic acid **26** (20.0 g, 162.5 mmol) in toluene (100 mL) under nitrogen, and the mixture was heated to 50 °C. The mixture was stirred for 15 min and allowed to cool to ambient and stirred for 15 h.[35] The white slurry was heated to 50 °C, stirred for 1 h and then heated further to 80 °C and stirred for 1 h. The mixture was heated to reflux and stirred for 30 min, treated with a further portion of thionyl chloride (5 mL, 68.7 mmol) and refluxed for an additional 30 min, whereby a clear yellow solution was obtained. The solution was allowed to cool to ambient and then cooled in an ice bath. The cold suspension was treated with a solution of THF saturated with HCl(g) (100 mL). Filtration under an inert atmosphere, washing with THF (2 × 30 mL) and drying at ambient under Ar gave the title compound as a white solid (26.3 g, 90%).

Preparations of 6-(1-Pyridin-4-ylmethanoyl)-4*H*-benzo[1,4]oxazine-3-one hydrochloride (8). *Method Using an Inverse Quench.* DMF (12 mL) was added dropwise to stirred aluminium chloride (53.3 g, 0.40 mol). The resulting slurry was heated to 50 °C and then treated with **10** (6.0 g, 40.0 mmol) followed by **13** (10.1 g, 60.0 mmol). The mixture was heated to 85 °C and stirred at this temperature until reaction was complete. The mixture was allowed to cool to 50 °C, and then toluene (100 mL) was added to give a dark biphasic mixture. The hot biphasic mixture was transferred dropwise via cannula into water (200 mL) at 0 °C over 20 min, and residual material was washed into the quenched mixture using 1:1 toluene:water (20 mL). The yellow slurry was stirred at 0 to 5 °C for 1.5 h. Filtration, washing with water (2 × 10 mL), THF (2 × 15 mL) and drying gave the title compound **8** as a bright yellow solid (10.8 g, 93%). ^{1}H NMR (400 MHz, DMSO): δ 4.75 (2H, s), 7.09 (1H, d), 7.35 (1H, m), 7.40 (1H, bs), 7.51 (1H, d), 8.05 (2H, d), 9.04 (2H, d), 11.03 (1H, s).

5 L Process. A 5 L jacketed vessel was charged with aluminium chloride (840 g, 6.30 mol) and the vessel stirred under nitrogen and cooled to 5 to 10 °C. DMF (168 mL) was added dropwise to the vessel maintaining an addition temperature of below 40 °C.[36] The resulting slurry was cautiously heated to 45 to 50 °C and stirred for 30 min. A combined charge of **10** (140 g, 0.93 mol) and **13** (220 g, 1.31 mol) was carefully added in portions to the stirred mixture. The mixture was heated to 80 ± 5 °C and stirred for 3 h, after which time a dark green viscous liquid was obtained, and this was cooled to 50 °C. Toluene (1.4 L) was added whereby two phases were obtained. Further cooling to 25 °C and stirring for 30 min led to the mixture becoming very thick such that the batch transfer into the quench mixture was no longer possible.[37] The reaction vessel was cooled to 5 °C, and a mixture of water and ice was added (2.8 kg) in portions over 3 h. The quenched mixture was stirred at 20 °C overnight, heated to 50 °C and stirred until deposited inorganic matter had been dissolved from the sides of the vessel. The slurry was cooled to 5 °C, stirred for 1 h and filtered, and the residue was washed with water (2 × 840 mL) and THF (2 × 840 mL) and then dried at 50 °C under vacuum to give the title compound as a bright yellow solid (217 g, 80%).

4-[(3-Oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)-methyl]piperidinium Trifluoroacetate (5). A suspension of 10% palladium on charcoal (65% wet/wt, 6.0 g) and **8** (3.0 g, 10 mmol) in trifluoroacetic acid (15 mL) and acetic acid (60 mL) was hydrogenated at 40 psi at 70 °C for 20 h. The mixture was cooled to 40−50 °C, the catalyst was removed by filtration under vacuum, the residue was washed with acetic acid (60 mL) and the filtrate and washings were combined. The solvent was removed under vacuum at 40−50 °C to afford a brown solid, which was triturated with TBME (50 mL). Filtration and drying under vacuum at 50 °C gave the title compound **5** as a cream solid (3.1 g, 83%). This product had spectroscopic properties consistent with those described above.

20 L Process. Palladium on carbon (55% wet, 1.48 kg) was added to a stirred mixture of **8** (592 g, 1.97 mol) in acetic acid (12 L). The stirred mixture was treated with trifluoroacetic acid (3 L), heated to 70 °C and hydrogenated at 40 psig/3 bar at 70 °C for 48−72 h. Once the reaction was complete, the mixture was cooled to 40 °C and filtered to remove the catalyst. The filter cake was washed with acetic acid (6 L) and methanol (6 L), under a nitrogen atmosphere. The filtrates were concentrated under vacuum at 40 °C to yield a beige coloured solid, which was triturated with TBME (6 L). The slurry was filtered, washed with TBME (300 mL) and dried to give the title compound **5** as a cream solid (541 g, 74%). This product had spectroscopic properties consistent with those described above.

Preparation of 2-Chloro-5-methoxyphenylamine (29). The nitroanisole **28** (46 g, 0.246 mol) was dissolved in acetic acid (640 mL), stirred and treated with iron powder portionwise over ∼30 min. The mixture was heated to 100 °C and stirred for 30 min. The mixture was cooled to ambient and filtered, and the residue was washed with EtOAc (500 mL). Water (500 mL), brine (200 mL) and ethyl acetate (200 mL) were added to the filtrate and the layers separated. The aqueous was extracted with ethyl acetate (300 mL), and the combined organic extracts were washed with water (200 mL) and brine (200 mL), then dried ($MgSO_4$) and filtered. The solvent was removed under vacuum to give the title compound as a dark brown oil (40.49 g, 105%). ^{1}H NMR (400 MHz, DMSO): δ 3.49 (3H, s), 5.15 (2H, bs), 5.95 (1H, m), 6.21 (1H, m), 6.85 (1H, d), 11.9 (1H, vbs).

Preparation of 8-Chloro-2-methyl-5-(methyloxy)-quinoline Hydrochloride Salt (30). The aniline **29** (38.6 g, 0.245M) and chloranil (59.3 g, 0.245M) were stirred together in 1-butanol (100 mL) and concentrated HCl (72 mL) at reflux under nitrogen. A solution of crotonaldehyde (26 mL, 20.4 g, 0.29M) in 1-butanol (30 mL) was added dropwise over ∼45 min. The reaction mixture was allowed to cool to just below reflux, and tetrahydrofuran (500 mL) was added. The mixture was stirred at 70 °C for 1 h, cooled to 5 to 10 °C and stirred for 30 min. Filtration, washing with THF (2 × 50 mL) and drying gave the title compound **30** as a yellow solid (40.9 g, 70%). ^{1}H NMR (400 MHz, DMSO): δ 2.74 (3H, s), 3.94 (3H,

dx.doi.org/10.1021/op300185s | *Org. Process Res. Dev.* 2012, 16, 1626−1634

s), 6.59 (2H, bs), 7.00 (1H, d), 7.54 (1H, d), 7.83 (1H, d), 8.55 (1H, d).

10 L Process. The aniline **29** (400 g, 2.06 mol) and chloranil (615 g, 2.06 mol) were stirred in 1-butanol (1.04 L) under nitrogen. Concentrated hydrochloric acid (760 mL) was added slowly, and the mixture was heated to reflux once the addition was completed. A solution of crotonaldehyde (174 g, 2.47 mol) was prepared in 1-butanol (320 mL), and this was added dropwise over 45 min. The mixture was stirred until the reaction was complete and cooled to just below reflux, THF (5.2 L) added slowly, to maintain the temperature, and the mixture stirred for 1 h at 70 °C. The mixture was then cooled to 5−10 °C and was stirred for 30−60 min. Filtration, washing with cooled THF (400 mL) and drying at 45 °C under vacuum gave the title compound **30** as a yellow solid (394 g, 78%). This product had spectroscopic properties consistent with those described above.

Preparation of 5-Methoxy-2-methylquinoline (31). The quinoline **30** (4.0 g, 16 mmol) was hydrogenated over 10% palladium on charcoal (2.0 g) in MeOH (22 mL) and 3 M aqueous sodium hydroxide (18 mL, 54 mmol) at 20 psi at ambient for 5 h. The catalyst was removed by filtration and the residue washed with methanol (22 mL). The filtrate was evaporated under vacuum to give an oily residue, which was partitioned between ethyl acetate (50 mL) and water (50 mL), and the layers were separated. The aqueous layer was re-extracted with ethyl acetate (50 mL). The combined organic extracts were washed with water (50 mL) and brine (30 mL) and then dried ($MgSO_4$) and filtered. The solvent was removed under vacuum to give the title compound **31** as a yellow oil, which crystallised on standing (2.3 g, 82%). ^{1}H NMR (400 MHz, DMSO): δ 2.72 (3H, s), 3.96 (3H, s), 6.78 (1H, d), 7.23 (1H, d), 7.58 (2H, m), 8.44 (1H, d).[38]

10 L Process. 10% Palladium on charcoal (250 g) was added to a solution of quinoline **30** (501 g, 2.05 mol) in methanol (2.75 L) and 3 M sodium hydroxide (2.25 L). The contents were hydrogenated at 20 psi (l.5 bar) at room temperature until the reaction was complete (20 to 48 h). The catalyst was removed by filtration and the filter cake washed with methanol (2.75 L). The filtrate was concentrated under vacuum at 40 °C to yield a pale yellow/orange coloured oil. The residue was partitioned between ethyl acetate (6 L) and water (6 L), and the layers were separated. The lower aqueous layer was extracted with ethyl acetate (6 L), the layers separated and the organic phases combined. The combined organic phases were washed with water (6 L), separated, washed with saturated brine (6.5 L), then dried ($MgSO_4$) and filtered. The solvent was removed under vacuum to give the title compound **31** as a pale yellow coloured oil (334 g, 94%). This product had spectroscopic properties consistent with those described above.

Preparation of 5-Hydroxy-2-methylquinolinium Bromide (7). The quinoline **31** (8.7 g, 50 mmol) was stirred in 48% hydrobromic acid (72 mL) at reflux under N_2 for 21.5 h. The mixture was cooled to 0 °C, stirred for 30 min and filtered. The residue was washed with acetonitrile (2 × 10 mL) and dried to give the crude title compound **7** as a light brown solid (9.5 g, 79%).[39] An analytically pure sample was generated by recrystallisation from 1-butanol (250 mL) and gave pure **7** as a beige solid (5.6 g, 47%). ^{1}H NMR (400 MHz, DMSO): δ 2.95 (3H, s), 7.23 (1H, d), 7.65 (1H, d), 7.85 (1H, d), 7.94 (1H, m), 9.06 (1H, d), 11.55 (bs).

10 L Process. The quinoline **31** (728 g, 4.20 mol) was cautiously treated with 48% aqueous hydrobromic acid (7.3 L) dropwise.[40] The reaction mixture was observed to be giving off a gas at room temperature. The reaction mixture was heated to reflux and stirred until demethylation was complete (>24 h). The mixture was cooled to 0 °C and stirred for 1 h. Filtration, washing with acetonitrile (8.7 L) and drying at 50 °C under vacuum gave the title compound **7** as a light brown solid (897 g, 89%). This product had spectroscopic properties consistent with those described above.

Preparation of 2-[(2-Methyl-5-quinolinyl)oxy]ethanol (33). A suspension of the phenol **7** (2.0 g, 8.3 mmol), ethylene carbonate (1.1 g, 12.4 mmol), tetrabutylammonium bromide (0.3 g, 0.83 mmol) and potassium carbonate (2.3 g, 16.6 mmol) was stirred in DMF (10 mL) at 110 °C under nitrogen for 1.5 h. Water (25 mL) was added and the stirred mixture allowed to cool to ambient over 2 h. The mixture was further cooled to 5−10 °C and stirred for 30 min. Filtration, washing with water (2 × 10 mL) and drying gave the title compound **33** as a brown solid (1.4 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72 (3H, s), 4.11 (2H, m), 4.27 (2H, m), 6.81 (1H, d), 7.23 (1H, d), 7.54 (1H, m), 7.62 (1H, d), 8.43 (1H, d). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8, 60.9, 69.4, 104.3, 118.4, 120.6, 120.8, 128.9, 130.3, 148.3, 153.6, 158.9.

20 L Process. Ethylene carbonate (431 g, 4.91 mol) and potassium carbonate (900 g, 6.54 mol) were added to a stirred solution of phenol **7** (785 g, 3.27 mol) in DMF (3.93 L) under a nitrogen atmosphere. The mixture was heated to 110 °C until the reaction was complete (3−6 h), and then the temperature of the reaction mixture was reduced to 95 °C. The reaction mixture was poured into water (10 L) and left to cool slowly overnight. The reaction mixture was cooled to 5−10 °C for 30−60 min. Filtration, washing with water (8 L) and drying at 50 °C under vacuum gave the title compound **33** as a brown/beige solid (537 g, 81%). This product had spectroscopic properties consistent with those described above.

Preparation of 2-[(2-Methyl-5-quinolinyl)oxy]ethyl Methanesulfonate (34). A solution of methanesulfonyl chloride (0.00636M) in THF (5 mL) was added dropwise to a stirred solution of the alcohol **33** (1.2 g, 5.9 mmol) and DIPEA (1.1 g, 1.5 mL, 8.8 mmol) in THF (12 mL) at 0−5 °C under nitrogen, keeping the temperature below 10 °C. Water (20 mL) was added to the stirred mixture followed by ethyl acetate (20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL) and then dried ($MgSO_4$) and filtered. The solvent was removed under vacuum to give the title compound **34** as a brown solid (1.5 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74 (3H, s), 3.08 (3H, s), 4.43 (2H, m), 4.71 (2H, m), 6.80 (1H, d), 7.28 (1H, d), 7.57 (1H, m), 7.66 (1H, d), 8.48 (1H, d). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 37.5, 65.8, 67.0, 104.2, 118.4, 121.0, 121.5, 128.6, 130.3, 148.4, 153.0, 159.2.

20 L Process. A solution of methanesulphonyl chloride (213 mL, 2.71 mol) in tetrahydrofuran (2 L) was added dropwise to a stirred solution of alcohol **33** (500 g, 2.46 mol) and DIPEA (348 g, 2.71 mol) in THF (5 L) at 0−5 °C under a nitrogen atmosphere maintaining the temperature of the reaction mixture below 10 °C. Once the addition was complete, the temperature was maintained at 0−5 °C for 15−30 min. Water (8 L) was added and the mixture stirred overnight. Ethyl acetate (8 L) was added, the layers were separated and the aqueous phase was extracted with ethyl acetate (2 × 4 L). The organic phases were combined, washed with water (8 L) and saturated brine solution (8 L), then dried ($MgSO_4$) and

filtered. The solvent was removed under vacuum to give the title compound **34** as a light brown solid (672 g, 97%). This product had spectroscopic properties consistent with those described above.

Preparation of SB-649915 or 6-[(1-{2-[(2-Methyl-5-quinolinyl)oxy]ethyl}-4-piperidinyl)methyl]-2*H*-1,4-benzoxazin-3(4*H*)-one (1). Sodium hydrogen carbonate (310.5 g, 3.68 mol) was added to a stirred slurry of quinoline **34** (345 g, 1.23 mol) and piperidine **5** (302 g, 0.88wt) in 1,2-dimethoxyethane (1.38 L) under a nitrogen atmosphere. Once gas evolution had ceased, the mixture was heated to 85 °C, and this was maintained until the reaction was complete (16−20 h). Water (8.6 L) was added into the vessel portionwise maintaining an internal temperature greater than 70 °C. The reaction mixture was heated to 85 °C, held for one hour and left to cool slowly overnight. The reaction mixture was further cooled in an ice/water bath to below 5 °C and was held at this temperature for a one hour. Filtration, washing with water (1.38 L) and drying under vacuum at 50 °C gave the crude title compound **1** (592 g, 98%). Further purification of this material was achieved by recrystallisation from ethanol (20 vol),[41] using a hot filtration to remove insoluble inorganic residues, and gave pure title compound **1** as a cream solid (499 g, 84%).[42] ^{1}H NMR (400 MHz, DMSO): δ 1.28 (2H, m), 1.51 (1H, m), 1.62 (2H, m), 2.39 (4H, m), 2.64 (3H, s), 3.08 (2H, s), 3.15 (2H, m), 4.34 (2H, m), 4.52 (2H, s), 6.68 (1H, s), 6.71 (1H, d), 6.85 (1H, d), 7.00 (1H, d), 7.40 (1H, d), 7.49 (1H, d), 7.61 (1H, m), 8.42 (1H, d), 10.63 (1H, s) (^{1}H NMR comparable to reported data[1]). ^{13}C NMR (100 MHz, DMSO): δ 24.8, 31.8, 37.4, 41.7, 53.7, 56.9, 66.7, 66.8, 105.1, 115.8, 116.1, 118.2, 120.3, 121.2, 123.5, 126.9, 129.6, 130.3, 134.5, 141.4, 148.2, 153.9, 158.9, 165.0.

Alternative Conditions. A mixture of piperidine **5** (1.0 g, 4.0 mmol) and quinoline **34** (1.1 g, 4.0 mmol) in 3-pentanone (11 mL) was treated with diisopropylamine (1.68 mL, 1.21 g, 11.99 mmol), heated to 85 °C and then stirred at this temperature for 36 h. The mixture was cooled to ambient, diluted with 1.0 M sodium hydrogen carbonate (aqueous) (10 mL) and stirred for 30 min. Filtration, washing with water (10 mL) and drying gave the crude title compound **1** (1.44 g, 83%) as a cream solid. ^{1}H NMR data was comparable to those described above and those reported.[1]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Michael.W.Urquhart@gsk.com.

Notes

The authors declare no competing financial interest.

[†]Formerly from Synthetic Chemistry, GlaxoSmithKline Pharmaceuticals, Old Powders Mills, Nr. Leigh, Tonbridge, Kent, TN11 9AN, U.K.

■ ACKNOWLEDGMENTS

We thank John Warren, Pritpal Slaich and Alec Simpson for spectroscopy support, David Childs for analytical support and Dave Grimshaw for process safety support throughout this project. We also thank Richard Ward from Almac (formerly CSS) for managing the scale-up of the final route.

■ REFERENCES

(1) Atkinson, P. J.; Bromidge, S. M.; Duxon, M. S.; Gaster, L. M.; Hadley, M. S.; Hammond, B.; Johnson, C. N.; Middlemiss, D. N.; North, S. E.; Price, G. W.; Rami, H. K.; Riley, G. J.; Scott, C. M.; Shaw, T. E.; Starr, K. R.; Stemp, G.; Thewlis, K. M.; Thomas, D. R.; Thompson, M.; Antonio, K. K.; Vong, A. K. K.; Watson, J. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 737−741.

(2) Efange, S. M. N.; Michelson, R. H.; Remmel, R. P.; Boudreau, R. J.; Dutta, A. K.; Freshler, A. *J. Med. Chem.* **1990**, *33*, 3133−3138.

(3) (a) Barluenga, J.; Tomas-Gamasa, M.; Aznar, F.; Valdes, C. *Nat. Chem.* **2009**, *1*, 494−499. (b) Nutaitis, C. F.; Swartz, B. D. *Org. Prep. Proc. Int.* **2005**, *37*, 507−511. (c) Lee, P. H.; Lee, K.; Shim, J. H.; Lee, S. G.; Kim, S. *Heterocycles* **2006**, *67*, 777−784.

(4) Ward, S. E.; Eddershaw, P. J.; Scott, C. M.; Gordon, L. J.; Lovell, P. J.; Moore, S. H.; Smith, P. W.; Starr, K. R.; Thewlis, K. M.; Watson, J. M. *J. Med. Chem.* **2008**, *51*, 2887−2890.

(5) (a) Ferranti, A.; Garuti, L.; Giovanninetti, G.; Gaggi, R.; Roncada, P.; Nardi, P. *Farmaco* **1987**, *42*, 237−249. (b) Choi, H. Y.; Chi, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 9202−9203. (c) Ward, S. E.; Eddershaw, P. J.; Scott, C. M.; Gordon, L. J.; Lovell, P. J.; Moore, S. H.; Smith, P. W.; Starr, K. R.; Thewlis, K. M.; Watson, J. M. *J. Med. Chem.* **2008**, *51*, 2887−2890.

(6) This original process successfully delivered 6 g of SB-649915.

(7) (a) Mazharuddin, M.; Thyagarajan, G. *Indian J. Chem.* **1969**, *7*, 658−661. (b) Hanson, J. R.; Richards, L.; Rozas, P. *J. Chem. Res., Synop.* **2003**, *11*, 681.

(8) Powell, N. A.; Ciske, F. L.; Cai, C.; Holsworth, D. D.; Mennen, K.; Van Huis, C. A.; Jalaie, M.; Day, J.; Mastronardi, M.; McConnell, P.; Mochalkin, I.; Zhang, E.; Ryan, M. J.; Bryant, J.; Collard, W.; Ferreira, S.; Gu, C.; Collins, R.; Edmunds, J. J. *Bioorg. Med. Chem.* **2007**, *15*, 5912−5949.

(9) For Friedel−Crafts reactions of benzoxazinone **10**, see: (a) Sastry, C. V. R.; Rao, K. S.; Rastogi, K.; Jain, M. L. *Indian J. Chem.* **1988**, *27B*, 871−873. (b) Kumar, T. V.; Rao, K. S.; Dubey, P. K.; Kumar, K. A.; Reddanna, P. *Ind. J. Chem., B* **2007**, *46B* (6), 1033−1037. (c) Combs, D. W.; Rampulla, M. S.; Bell, S. C.; Klaubert, D. H.; Tobia, A. J.; Falotico, R.; Haertlein, B.; Lakas-Weiss, C.; Moore, J. B *J. Med. Chem.* **1990**, *33*, 380−386.

(10) For Friedel−Crafts reactions of isonicotinoyl chloride **13**, see: (a) Qin, Z.; Mu, C.; Mao, S.; Dong, Y.; Li, N.; Zhang, S. *Faming Zhuanli Shenqing Gongkai Shuomingshu* **2005**, 9 pp. CN 1566095 A 20050119 CAN 143:422358. (b) Sartori, E.; Maillet, M.; Paugam, M. F.; Nicolai, E.; Lawrence, M. *U.S. Pat. Appl.* **2005**, 44 pp. US 2005124664 CAN 143:43883.

(11) (a) Park, C. H.; Yous, S.; Natvelle-Serpentini. C.; Seralini, G.-E.; Chang, S.-J.; Lesieur, D. *Fr. Demande* **2005**, FR 2860235 A1 20050401. (b) Park, C. H.; Yous, S.; Natvelle-Serpentini. C.; Seralini, G.-E.; Chang, S.-J.; Lesieur, D. US Patent 2007, 20070054899.

(12) The reduction of aroyl pyridines to the corresponding arylmethyl piperidines is known: Strupczewski, J. T.; Allen, R. C.; Gardner, B. A.; Schmid, B. L.; Stache, U.; Glamkowski, E. J.; Jones, M. C.; Ellis, D. B.; Huger, F. P.; Dunn, R. W. *J. Med. Chem.* **1985**, *28*, 761-769.

(13) (a) Alinezhad, H.; Tavakkoli, S. M.; Salehian, F. *Synth. Commun.* **2010**, *40*, 3226−3232. (b) Pourmousavi, S. A.; Salehi, P. *Acta Chim. Slov.* **2009**, *56*, 734−739. (c) Adibi, H.; Hajipour, A. R.; Hashemi, M. *Tetrahedron Lett.* **2007**, *48*, 1255−1259. (d) Rajagopal, R.; Jarikote, D. V.; Lahoti, R. J.; Daniel, T.; Srinivasan, K. V. *Tetrahedron Lett.* **2003**, *44*, 1815−1817. (e) Narender, N.; Srinivasu, P.; Prasad, M. R.; Kulkarni, S. J.; Raghavan, K. V. *Synth. Commun.* **2002**, *32*, 2313−2318.

(14) Buckley, G. M., Morgan, T.; Sabin, V. M. *PCT Int Appl.* WO 2008/044022 A1.

(15) Monobromination of aniline using conversion to acetanilide, bromination to 4-bromoacetanilide and subsequent hydrolysis to 4-bromoaniline: Furniss, B. S.; Hannaford, A. J.; Rogers, V.; Smith, P.

W. G.; Tatchell, A. R. *Vogel's Practical Organic Chemistry*, 4th ed.; Wiley: New York, 1978; pp 684−685.
(16) Kelly, T. R.; Bilodeau, M. T.; Bridger, G. J.; Zhao, C. *Tetrahedron Lett.* **1989**, *30*, 2485−2488.
(17) Typically conducting the lithiation and quench reaction at temperatures lower than −60 °C produced consistently good yields of product (70 to 80%) whereas running at a higher temperature (−30 to −40 °C) led to increased byproduct formation and a lower recovery of product (34%).
(18) No other lithiation reagents were evaluated for the reaction of **11** with aldehyde **2**, but other reagents may offer processing advantages, e.g., hexyllithium.
(19) Agai, B.; Proszenyak, A.; Tarkanyi, G.; Vida, L.; Faigl, F. *Eur. J. Org. Chem.* **2004**, 3623−3632.
(20) (a) Sharifi, A.; Barazandeh, M.; Saeed, A. M.; Mirzaei, M. *Tetrahedron Lett.* **2010**, *51*, 1852−1855. (b) Borate, H. B.; Maujan, S. R.; Sawargave, S. P.; Chandavarkar, M. A.; Vaiude, S. R.; Joshi, V. A.; Wakharkar, R. D.; Iyer, R.; Kelkar, R. G.; Chavan, S. P.; Kunte, S. S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 722−725. (c) Chen, D.; Shen, G.; Bao, W. *Org. Biomol. Chem.* **2009**, *7*, 4067−4073.
(21) Dunn, R.; Xie, W.; Tehim, A. *PCT Int. Appl.* 2009023844, 19 Feb **2009**.
(22) 2-Methyltetrahydrofuran would offer even greater sustainability advantages, but this solvent was not evaluated for this process.
(23) (a) Thyes, M.; Lehmann, H. D.; Gries, J.; Konig, H.; Kretzschmar, R.; Kunze, J.; Lebkucher, R.; Lenke, D. *J. Med. Chem.* **1983**, *26*, 800−807. (b) Liacha, M.; Yous, S.; Poupaert, J. H.; Depreux, P.; Aichaoui, H. *Monatsh. Chem.* **1999**, *130*, 1393−1397. (c) Aichaoui, H.; Lesieur, D.; Henichart, J. P. *J. Heterocycl. Chem.* **1992**, *29*, 171−175.
(24) Direct quench led to significant exotherms being observed with significant release of HCl gas. It is believed that adding a suitable solvent, e.g. DMF or THF, after the reaction to reduce viscosity would enable a safe inverse quench condition.
(25) (a) Choi, H. Y.; Chi, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 9202−9203. (b) Jampilek, J.; Dolezal, M.; Kunes, J.; Buchta, V.; Silva, L.; Kralova, K. *Med. Chem.* **2005**, *1*, 591−599.
(26) Dolson, M. G.; Swenton, J. S. *J. Org. Chem.* **1981**, *46*, 177−179.
(27) The mesh size for the potassium carbonate proved important for this process, and a lower mesh size was favoured, resulting in higher yields of product.
(28) (a) The methanesulfonate **34** is an alkylating agent and as such poses a potential genotoxicity risk. Future handling for this material ought to take this risk into account and appropriate safety measures instigated. (b) Risk of residual **34** being present within API was considered low based on it being consumed to low level within the coupling stage with **5**, and any residual low levels of **34** should be retained within reaction liquors because this material is highly soluble. Also the crude API **1** was then recrystallised from ethanol, giving another element of control for the removal of **34**. Final analysis of the API batches confirmed the absence of this material, proving the above chemistry argument.
(29) It was decided not to investigate alternative sulfonate esters from alcohol **33** given the ease with which methanesulfonate **34** was prepared and the success of the coupling reaction with piperidine **5**.
(30) For further information about Registration, Evaluation, Authorisation & restriction of Chemicals, see http://www.hse.gov.uk/reach/.
(31) There was no evidence for alkylation of the diisopropylamine base with the methanesulfonate **34** under these conditions. This lack of reactivity is believed a consequence of steric factors involved between the hindered base and the relatively hindered electrophile **34**.
(32) ^{1}H NMR is consistent with literature values: Nugiel, D. A.; Jacobs, K.; Cornelius, L.; Chang, C.-H.; Jadhav, P. K.; Holler, E. R.; Klabe, R. M.; Bachelor, L. T.; Cordova, B.; Garber, S.; Reid, C.; Logue, K. E.; Gorey-Feret, L. J.; Lam, G. N.; Erickson-Viitanen, S.; Seitz, S. P. *J. Med. Chem.* **1997**, *40*, 1465−1474.
(33) ^{1}H and ^{13}C NMR data is consistent with literature values: Rekowski, M.; von, W.; Pyriochou, A.; Papapetropoulos, N.; Stößel, A. *Bioorg. Med. Chem.* **2010**, *18*, 1288−1296.
(34) ^{1}H NMR data is consistent with literature values: Ramesh, C.; Raju, B. R.; Kavala, V.; Kuo, C. W.; Yao, C.-F. *Tetrahedron* **2011**, *67*, 1187−1192.
(35) Reaction monitored by HPLC by quenching aliquots of reaction mixture into methanol and monitoring the formation of methyl isoniconate.
(36) A significant exotherm was observed and a large amount of white fumes produced.
(37) It is likely that cooling the biphasic mixture to 25 °C resulted in the observed viscosity issues with respect to the desired transfer into the quench medium.
(38) ^{1}H NMR data is consistent with literature values: Choi, H. Y.; Srisook, E.; Jang, K. S.; Chi, D. Y. *J. Org. Chem.* **2005**, *70*, 1222−1226.
(39) This material was determined as being approximately 85% pure.
(40) Highly energetic addition with a 45 °C exotherm being observed.
(41) Lab work demonstrated that toluene was also a useful solvent to purify SB-649915.
(42) Purity increased from 95 to 99% following this recrystallisation.