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The Development of a New Manufacturing Route to the Novel Anticonvulsant, SB-406725A

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Abstract:

The development of an efficient manufacturing route to 3-acetyl-*N*-(5,8-dichloro-1,2,3,4-tetrahydro-7-isoquinolinyl)-4-(1-methylethoxy)-benzamide hydrochloride SB-406725A (1) is described. The synthesis begins with dichlorination of isoquinoline, followed by nitration using nitronium tetrafluoroborate in sulpholane. Nitroisoquinoline (12) was hydrogenated under pressure using Pt/C. The resultant tetrahydroisoquinoline (13) was selectively coupled with benzoate side chain (15) under base-promoted conditions using sodium hexamethyldisilazane to yield the parent molecule SB-406725 (16). SB-406725 was then converted to the HCl salt SB-406725A (1). This process has been successfully demonstrated on a pilot-plant scale to prepare ~30 kg of SB-406725A (1).

Introduction

SB-406725A **1** (Figure 1) was developed for use as a novel anticonvulsant for the treatment of neuropathic pain, migraine, and epilepsy.[1]

Initial toxicology and clinical studies were supplied via routes A and B starting from 4-nitrophenethylamine hydrochloride **2** (Scheme 1). Neither route A nor route B was suitable for use as the final route of manufacture as they did not meet our development criteria (greater than six steps) or the target for the cost of goods. In addition, there were a number of issues with routes A and B, including protection and deprotection of the trifluoroacetyl group, a low-yielding electrophilic chlorination and, in the case of route A, use of a carbonylative amidation for a quality critical coupling. We report here the identification and development of a new concise route that addresses these problems to produce the target molecule in improved yield.

Results and Discussion

Initial Supply Route to SB-406725A (1). The initial syntheses of SB-406725A **1** (Scheme 1) both proceeded through the common dichloroaniline **7**. Synthesis of dichloroaniline **7** was achieved starting from 4-nitrophenethylamine hydrochloride

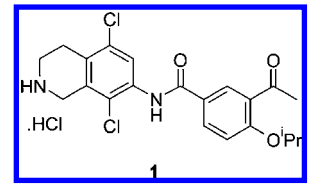

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Figure 1. **SB-406725A (1).**

2 via trifluoroacetylation, followed by in situ Pictet−Spengler cyclisation to give tetrahydroisoquinoline **3** in 81% overall yield. The trifluoroacetyl group was required to make the intermediate *N*-acyliminium species sufficiently electrophilic for attack by the electron-deficient aromatic nucleus.[2] This was followed by introduction of the chlorine in the 5-position of tetrahydroisoquinoline **3** using a two-step procedure involving selective electrophilic iodination of **3** followed by halogen metathesis from iodine to chlorine to give 5-chlorotetrahydroisoquinoline **5** in 77% overall yield.[3,4] Again, this two-step procedure was required due to the electron-deficient nature of the aromatic ring. Reduction of the nitro group in tetrahydroisoquinoline **5** was achieved in 84% yield via an iron-based dissolving metal reduction. The resultant aniline **6** was then chlorinated in 38% yield using NCS to give the required dichloroaniline fragment **7**.[5] The yield for this reaction was highly variable (between 30% and 55%), due to the generation of highly coloured polar decomposition products which inhibited crystallisation of the desired product.

For route A, dichloroaniline **7** was then carbonylatively coupled with aryl bromide **8** in DMF under 0.2 barg of carbon monoxide at ~100 °C using bis(triphenylphosphine)palladium(II) chloride as the precatalyst to give amide **9** in 75% yield.[6] This reaction was also somewhat irreproducible, possibly due to a lack of stability in the palladium carbonyl catalyst.[7] Final stage deprotection of the trifluoroacetyl group of amide **9**, followed by hydrochloride salt formation gave the product SB-406725A **1** in 85% yield (~13% overall theory yield from phenethylamine **2**).

For route B, dichloroaniline **7** was coupled with the acid chloride of benzoic acid **10** to give amide **9** in 85% yield. We

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(1) (a) Harling, J. D.; Heer, J. P.; Thompson, M. Substituted isoquinoline derivatives and their use as anticonvulsivants. U.S. Patent 6,492,378, 2002. (b) Coulton, S.; Porter, R. A. Substituted isoquinoline derivatives and their use as anticonvulsants. U.S. Patent 6,248,754, 2001. (c) Xue, C.-B.; Zheng, C.; Cao, G.; Feng, H.; Xia, M.; Anand, R.; Glenn, J.; Metcalf, B. W. 3-(4-Heteroarylcyclohexylamino)cyclopentanecarboxamides as modulators of chemokine receptors. U.S. Patent 7,307,086, 2007.

(2) Stokker, G. E. *Tetrahedron Lett.* **1996**, *37*, 5453–5456.
(3) Kraszkiewicz, L.; Sosnowski, M.; Skulski, L. *Tetrahedron* **2004**, *60*, 9113–9119.
(4) Bacon, R. G. R.; Hill, H. A. O. *J. Chem. Soc.* **1964**, 1097–1107.
(5) Neale, R. S.; Schepers, R. G.; Walsh, M. R. *J. Org. Chem.* **1964**, *29*, 3390–3393.
(6) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327–3331.
(7) For a recent review about palladium carbonyl complexes see: Stromnova, T. A.; Moiseev, I. I. *Russ. Chem. Rev.* **1998**, *67*, 485–514.

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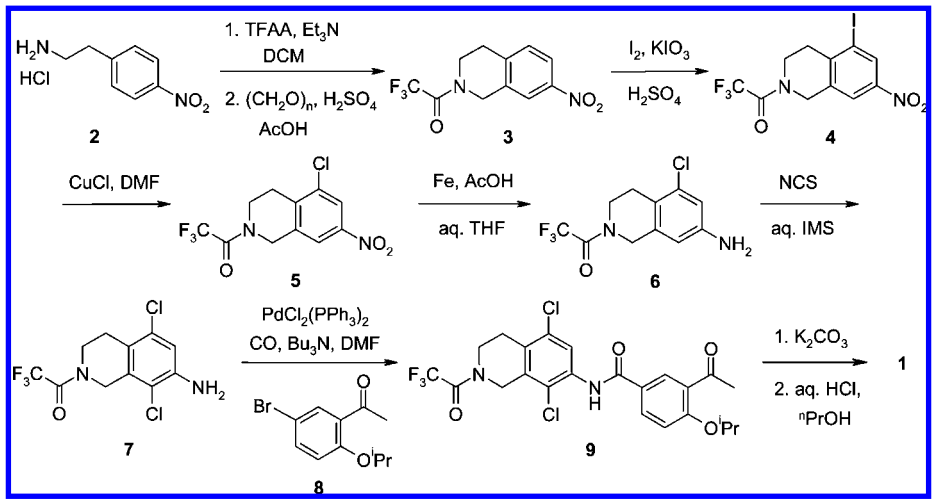
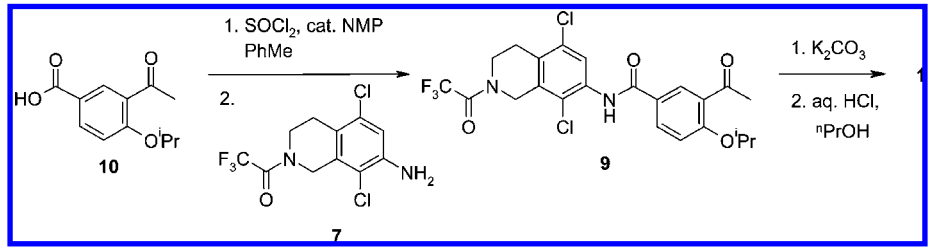
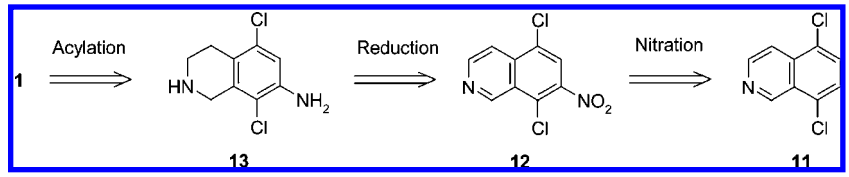
Scheme 1. **Route A to SB-406725A (1)**



Scheme 2. **Route B to SB-406725A (1)**



Scheme 3. **Alternative retrosynthetic analysis of SB-406725A (1)**



found this coupling reaction to be much more reproducible, despite some evidence of overacylation of the product in the crude reaction mixture due to the high reactivity of the intermediate acid chloride. Completion of the final stage deprotection and salt formation gave the product SB-406725A **1** in 85% yield (~12% overall yield from phenethylamine **2**).

Identification of a New Route to SB-406725A (1) via 5,8-Dichloroisoquinoline (11). In light of the difficulty experienced in carrying out the Pictet−Spengler cyclisation with these electron-deficient and sterically hindered substrates, an alternative synthetic strategy was devised that relied on the selective functionalisation of isoquinoline (Scheme 3).[8] In the forward sense, synthesis of the known isoquinoline **11** followed by nitration and reduction would yield tetrahydroisoquinoline **13** as the key coupling partner. It was then envisaged that selective acylation of this aniline **7** with a suitable benzoyl derivative (such as benzoic acid **10**) would complete the synthesis of SB-406725A **1**.

Development of the Synthesis of 5,8-Dichloroisoquinoline(11). To begin our synthesis of SB-406725A **1** a scalable method for the synthesis of 5,8-dichloroisoquinoline **11** was required. A review of the literature showed two potential routes; Pommerantz−Fritsch reaction of 2,5-dichlorobenzaldehyde and aminoacetaldehyde dimethylacetal, or dichlorination of isoquinoline using molecular chlorine and aluminium trichloride.[9,10]

Our initial attempts to synthesise 5,8-dichloroisoquinoline **11** were carried out on up to 20 g scale via the Pommerantz−Fritsch reaction. In our hands this required the intermediate imine to be preformed and added neat to 98% sulphuric acid at ~150 °C. The product was obtained in low yield (<30%) and could not be isolated sufficiently pure for further use without column chromatography. We were prompted by the report of Brown and Gouliaev on the regioselective dibromination of isoquinoline **14** to evaluate the alternative procedure using isoquinoline as the starting material and electrophilic chlorinating agents such as NCS or *N*,*N*′-dichlorodimethylhydantoin (DCDMH).[11] After screening a range of electrophilic chlorinating conditions we were pleased to be able to isolate the product

(8) Our initial strategy towards the synthesis of SB-406725 **1** was to synthesise the desired aniline **7** via a Pictet−Spengler reaction in an analogous system with both chlorines already present in the starting nitrophenethylamine. Disappointingly, exposure of 2,5-dichloro-4-nitrophenethylamine to our standard Pictet−Spengler conditions gave only recovered starting material. We attributed this lack of reactivity to the combination of steric and electronic effects further deactivating the aromatic nucleus, preventing the cyclisation onto the *N*-acyliminium ion.

(9) Bondinell, W. E.; Chapin, F. W.; Girard, G. R.; Kaiser, C.; Krog, A. J.; Pavloff, A. M.; Schwartz, M. S.; Silvestri, J. S.; Vaidya, P. D.; Lam, B. L.; Wellman, G. R.; Pendleton, R. G. *J. Med. Chem.* **1980**, *23*, 506–511.

(10) Gordon, M.; Pearson, D. E. *J. Org. Chem.* **1964**, *29*, 329–332.

(11) Brown, W. D.; Gouliaev, A. H. *Synthesis* **2002**, 83–86.

Table 1. **Classical nitration of 5,8-dichloroisoquinoline (11) using different co-acids**

entry	conditions[a]	co-acid pK_a	result
1	f. HNO_3, H_3PO_4, 18 h	2.1	recovered SM
2	f. HNO_3, TFA, 18 h	–0.3	recovered SM
3	f. HNO_3, 18 h	–1.3	recovered SM
4	f. HNO_3, MsOH, 18 h	–2.6	11% product, 86% SM[b]
5	f. HNO_3, H_2SO_4, 48 h	–3.0	29% product[c]
6	90% HNO_3, H_2SO_4, 48 h	–3.0	25% product[c]
7	69% HNO_3, H_2SO_4, 48 h	–3.0	15% product, 22% SM[c]
8	f. HNO_3, TfOH, 6d	–14.0	57% product[c]

[a] All reactions performed at RT. [b] Percentage a/a determined by HPLC. [c] Isolated yield.

in 98% yield by treating isoquinoline **14** with DCDMH in 98% sulphuric acid. We were able to use this method to prepare sufficient material for lab-scale development of the remainder of this route. We were then able to transfer production of 5,8-dichloroisoquinoline **11** via electrophilic chlorination to a third party, who supplied us with 220 kg of **11** prepared by this route.

Development of the Nitration of 5,8-Dichloroisoquinoline (11). Literature precedent for the selectivity of electrophilic substitution in 5,8-disubstituted isoquinoline systems suggested that substitution in the 7-position is favored;[10] we were therefore keen to ascertain whether this would be the case in the nitration of **11** to give the corresponding 7-nitro derivative **12**.

Initial efforts towards the nitration of 5,8-dichloroisoquinoline **11** using potassium nitrate and 98% sulphuric acid failed, giving only recovered starting material. Use of fuming nitric acid and 98% sulphuric acid gave complete consumption of the starting material after 18 h and the desired product in an isolated yield of 29%. The mass balance remained in the aqueous phase as polar aromatic decomposition products, from which pyridine-3,4-dicarboxylic acid was identified, resulting from oxidative cleavage of the starting material. An experimental design study was performed in an attempt to optimise these conditions, but unfortunately, solution yields were uniformly low (<30% yield).

We therefore decided to investigate a wider range of classical acid catalysed nitration conditions to ascertain whether nitration could be achieved in preference to oxidation (Table 1).[12]

It was interesting to note that only reactions with sulphonic acids gave significant conversions (entries 4−8), demonstrating that effective nitration depends on the ability of the co-acid to both protonate *and* dehydrate the nitric acid. The oxidising power of nitric acid is related to its concentration, so the strength of the nitric acid was varied in an effort to minimise competing oxidation (entries 5−7). However, no advantage was gained by using less concentrated nitric acid. The best isolated yield attained was 57% using triflic acid as co-acid, albeit over a prolonged reaction period.

We next turned our attention to alternative nitrating reagents, in particular, nitronium salts as a neutral source of the nitronium ion.[12] A range of nitronium salts and conditions was investigated (Table 2).

Solvent studies suggested that sulpholane was essential in order for the reaction to occur, and although dichloromethane could be used as a co-solvent, other solvents were either incompatible or led to no reaction.

Interestingly, the nature of the nitronium counterion appears to affect the selectivity observed: upon changing the counterion from tetrafluoroborate to trifluoroacetate (entries 1−4), the percentage of the 4-nitro isomer increases. This suggests a link between the nitronium counterion nucleophilicity and the regioselectivity of nitration.[14] We ultimately elected to carry out the nitration using nitronium tetrafluoroborate in sulpholane (entry 1), taking into account a combination of yield, selectivity, and the cost of trifluoromethanesulphonic acid and trifluoromethanesulphonic anhydride. We were again able to transfer production of 7-nitro-5,8-dichloroisoquinoline **12** to a third party, where the product was isolated in 76% yield on a 40 kg scale.

Development of the Reduction of 7-Nitro-5,8-dichloroisoquinoline (12). A selective reduction of both the nitro group and the isoquinoline ring in the presence of the aryl chloride in nitroisoquinoline **12** was then sought. Initial screening work demonstrated that the reduction of nitroisoquinoline **12** to amino tetrahydroisoquinoline **13** was possible with 50 psi hydrogen pressure using PtO_2 in either NMP or methanol using 98% sulphuric acid as co-catalyst. These reactions were somewhat problematic, however, due to the rate being limited by the poor solubility of intermediates generated during the reduction, in particular, that of the corresponding amino isoquinoline.[15] In addition, it was found that the isolated product from this initial method was a variable nonstoichiometric mixture of the sulphate and methylsulphate salts which was highly undesirable due to the potentially toxic nature of these counterions.

A screen of alternative solvents, catalysts, and acid co-catalysts led us to carry out the reduction using Degussa Pt/C F105 R/W as the catalyst in methanol with acetic acid as a co-catalyst with higher pK_a. This not only gave the desired **13** as a well-defined acetic acid salt but also resulted in significantly less dechlorination in solution compared to the use of 98% sulphuric acid (typically <1% a/a with acetic acid cf. ~5% a/a with sulphuric acid in solution by HPLC).

An experimental design study based on these revised reaction conditions showed that the nitro reduction and the isoquinoline reduction had differing critical parameters. For the reduction of the nitro group, catalyst loading was the major rate driver

(12) (a) Olah, G.; Kuhn, S.; Mlinkó, A. *J. Chem. Soc.* **1956**, 4257–4258. (b) Woolf, A. A.; Emeléus, H. J. *J. Chem. Soc.* **1950**, 1050–1052. (c) Goddard, D. R.; Hughes, E. D.; Ingold, C. K. *J. Chem. Soc.* **1950**, 2559–2575. (d) Olah, G. A.; Orlinkov, A.; Oxyzoglou, A. B.; Surya Prakash, G. K. *J. Org. Chem.* **1995**, *60*, 7348–7350. (e) Olah, G. A.; Rasul, G.; Aniszfeld, R.; Surya Prakash, G. K. *J. Am. Chem. Soc.* **1992**, *114*, 5608–5609.

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(14) These observations led us to speculate that the mechanism of the nitration proceeds via initial *N*-nitration to give the *N*-nitro isoquinolinium intermediate. This may then revert to starting material or react to give either the desired isoquinoline **11** or the undesired 4-nitro isomer. It is not known whether conversion of the *N*-nitro isoquinolinium intermediate to the product occurs by nitration with further NO_2^+, transfer nitration from a second *N*-nitro isoquinolinium species, or intramolecular rearrangement.

(15) Reduction was observed to occur via a poorly soluble aminoisoquinoline intermediate. Carrying out the reaction at an elevated temperature was required to prevent precipitation of this material onto the platinum catalyst, which would result in catalyst deactivation.

Table 2. **Nitration of 5,8-dichloroisoquinoline (11) using different nitronium salts**

entry	conditions[a]	product[b] (%)	4-NO_2 isomer (%)
1	2.25 equiv NO_2BF_4, sulpholane, 80 °C, 3 h	70	–
2	1.5 equiv NO_2PF_6, sulpholane, 50 °C, 18 h	60	5
3	4 equiv NO_2OTf ($^nBu_4N^+NO_3^-$ and Tf_2O), DCM/sulpholane, 40 °C, 5d[c]	75	9
4	2 equiv $NO_2^+{}_2CCF_3$ ($^nBu_4N^+NO_3^-$ and TFAA), CH_2Cl_2/ sulpholane, 40 °C, 18 h	–	38
5	1.8 equiv NO_2BF_4[d], 2 equiv TfOH, sulpholane, 80 °C, 2 h	93	–
6	1.8 equiv NO_2BF_4[d], 2 equiv MsOH, sulpholane, 80 °C, 2 h	36	–
7	1.8 equiv NO_2BF_4[d], 2 equiv $ClSO_3H$, sulpholane, 80 °C, 2 h	no reaction	–
8	2 equiv NO_2OTf ($^nBu_4N^+NO_3^-$ and Tf_2O), 2 equiv TfOH, DCM/ sulpholane, 40 °C, 24 h	83	–

[a] Reactions carried out with a 5 vol:5 vol ratio of sulpholane/DCM, where appropriate. [b] Percentage a/a determined by HPLC. [c] Reagents added portionwise over the course of the reaction. [d] 1 equiv of NO_2BF_4 after assaying the reagent and correcting for the amount of NO^+ present.[13]

followed by pressure, whereas for the isoquinoline reduction, temperature was the major rate driver followed by the stoichiometry of the acetic acid co-catalyst. In addition, reaction calorimetry showed that the reduction of the nitro group during the early phase of the reaction is strongly exothermic, accounting for the majority of the total heat evolved in the reaction. Accordingly, the process was conducted using 5% Pt/C (0.2 wt %) in methanol and acetic acid at 3.5 barg pressure starting at 20 °C. After the initial exothermic phase, the reaction was heated to 50 °C to complete the reduction of the isoquinoline functionality.

The free base of **13** was established as the preferred isolated version for the downstream chemistry. Attempts to isolate the free base directly by neutralisation, after catalyst filtration, generally gave poor-quality material and low recoveries of the desired product. Improvement in the quality of free base was achieved when the intermediate acetic acid salt was isolated as a wet cake and then neutralised prior to crystallisation from aqueous THF. A consistent level of residual platinum in the product (~100 ppm) was observed using this process, which could be tolerated in the downstream chemistry. We were able to carry out this process on a 10 kg scale, giving the product in 55% isolated yield.

Development of the Coupling of 7-Amino-5,8-dichlorotetrahydroisoquinoline (13) with a Benzoate Side Chain. Having developed a concise synthesis of amino tetrahydroisoquinoline **13** we were intrigued by the possibility of coupling this directly to a suitably functionalised side chain without protecting the secondary amine. Selective protonation of **13** with HCl and attempted amidation with benzoic acid **10** using thionyl chloride as the activating agent gave rise to a mixture of products arising from acylation of both the aniline and secondary amine centres of amino tetrahydroisoquinoline **13**, indicating that the protonation did not prevent reaction at the secondary amine centre for this substrate.[16]

At this point we were prompted by the report of Wang et al. to attempt the reaction of **13** with methyl benzoate **15** under base-promoted conditions.[17,18] We hypothesised that it would be possible to obtain chemoselectivity between the aniline and secondary amine functions by taking advantage of their relative acidities. On the basis of the reported use of sodium hexamethyldisilazane (NaHMDS) to generate aryl anilides and that NaHMDS has a pK_a of 26 (in THF), we considered it should be ideally placed to deprotonate anilines (p$K_a \approx 25-30$) in the presence of alkyl amines (p$K_a \approx 35$).[19] Our initial experiments showed that, as anticipated, the aniline group of **13** was shown to be deprotonated with NaHMDS and then to react with methyl benzoate **15** to give the required amide **16** as the free base.

Following this promising result, a range of alternative bases was screened (BuLi, KHMDS, LiHMDS, and NaOMe). The best reaction profile was achieved with NaHMDS in THF, other conditions giving either no reaction or decomposition of the starting materials. After studying the reaction parameters via an experimental design study we found that the optimum reaction conditions employed a small excess (1.1−1.3 equiv) of methyl benzoate side chain **15** and 5−6 equiv of NaHMDS at 0 °C. The process was observed to tolerate both the methyl ketone and aryl halide functionalities and was carried out on a 10 kg scale, giving the product in 83% isolated yield.[20]

We were then able to adapt the isolation from acidic aqueous propan-1-ol used in routes A and B, in order to complete the required conversion of freebase **16** to HCl salt **1**. Dissolution and clarification of the free base in THF, prior to solvent exchange into propan-1-ol and acidification with a mixture of water and 36% w/w hydrochloric acid, was shown to give the desired product with the correct form and required purity in 88% yield on an 11 kg scale (Scheme 4).

Summary

In conclusion, a robust, efficient, and scalable process has been developed suitable for the synthesis SB-406725, **1**, in 30%

(16) Oganesyan, A.; Cruz, I. A.; Amador, R. B.; Sorto, N. A.; Lozano, J.; Godinez, C. E.; Anguiano, J.; Pace, H.; Sabih, G.; Gutierrez, C. G. *Org. Lett.* **2007**, *9*, 4967–4970.

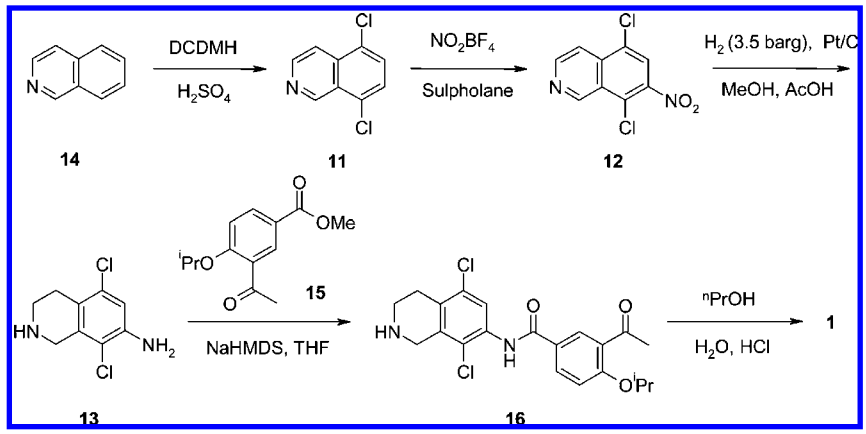
(17) Wang, J.; Rosingana, M.; Discordia, R. P.; Soundararajan, N.; Polniaszek, R. *Synlett* **2001**, *9*, 1485–1487.

(18) The production of the methyl benzoate side chain **15** was carried out externally starting from 4-hydroxybenzoic acid. *Ortho*-acylation under Fries conditions, followed by esterification with methanol and finally alkylation using isopropyl bromide provided the desired methyl benzoate side chain **15**.

(19) (a) Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232–3234. (b) In addition, NaHMDS is readily soluble in a wide range of organic solvents, is not prone to single-electron transfer side reactions, and is less pyrophoric than many other organometallic reagents, making it more suitable for use on scale.

(20) Only a trace amount (<1% a/a by HPLC) of the bis-amide species was observed in these batches which was readily removed in the subsequent hydrochloride salt formation step.

Scheme 4. **Route C synthesis of SB-406725 (1)**



overall yield.[21] This approach utilises regioselective dichlorination and nitration of isoquinoline followed by chemoselective reduction and then selective acylation of amino tetrahydroisoquinoline **13** to form the desired product **1** after salt formation. This more concise and atom-efficient route uses a readily available starting material, avoids the protection and deprotection steps required in previous routes, and also has a more robust final coupling stage.

Experimental Section

5,8-Dichloroisoquinoline (11) from Isoquinoline (14). Isoquinoline **14** (400 g, 3.09 mol) was added over 15 min to 98% sulphuric acid (2.4 L) precooled to 2 °C (the maximum temperature during the addition was 21 °C). 1,3-Dichloro-5,5-dimethylhydantoin (1200 g, 6.09 mol) was then added in portions over 30 min, while the temperature was allowed to gradually increase from 10 to 25 °C. The reaction mixture was then heated to 55 °C and stirred for 18 h. The reaction mixture was cooled to ambient temperature and quenched into water (19.2 L) at 5 °C. Thereafter, 50% w/w sodium hydroxide solution (900 g, 11.25 mol) was added over 60 min. The quenched mixture was extracted with TBME (3.2 L). The organic phase was washed with saturated aqueous sodium hydrogen carbonate (800 mL) and dried ($MgSO_4$). Evaporation gave a pale-brown solid (601 g, 98% yield): mp 116−118 °C (lit. 115−116 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.71 (d, J = 5.9 Hz, 1H), 7.97 (d, J = 5.9 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7 (CH), 145.1 (CH), 134.7 (C), 131.4 (C), 130.0 (CH), 130.0 (C), 127.3 (CH), 126.2 (C), 116.7 (CH). LRMS (ES +VE): m/z 198, 239 (M^+ + H, M^+ + MeCN).

7-Nitro-5,8-dichloroisoquinoline (12) from 5,8-Dichloroisoquinoline (11). Nitronium tetrafluoroborate (900 g, 5.35 mol) followed by 5,8-dichloroisoquinoline **11** (500 g, 2.52 mol) was added in portions to sulpholane (3.5 L) at 50 °C. The reaction mixture was then heated to 60 °C and the reaction mixture stirred for 18 h. The reaction mixture was then cooled to 20 °C and quenched by the addition of 1.5 M sodium hydroxide solution (6.6 L, 9.90 mol) over 1 h, maintaining the internal temperature below 40 °C during the quenching. The reaction mixture was then filtered and washed with water (800 mL) followed by ethanol (2 × 800 mL). The wet cake was then added to THF (6.5 L) and heated to 60 °C and then cooled to 40 °C over 40 min and then to 0 °C over 150 min. The resultant slurry was then filtered and washed with ethanol (2 × 500 mL) and dried to give a pale-brown solid (468 g, 76% yield): mp 186−188 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.83 (s, 1H), 8.98 (d, J = 5.9 Hz, 1H), 8.66 (s, 1H), 8.18 (d, J = 5.9 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 150.6 (CH), 147.7 (CH), 145.6 (C), 135.1 (C), 130.6 (C), 125.2 (CH), 125.1 (C), 123.9 (C), 116.5 (CH). MS (ES +VE): m/z 243, 284 (M^+ + H, M^+ + MeCN).

7-Amino-5,8-dichlorotetrahydroisoquinoline (13) from 7-Nitro-5,8-dichloroisoquinoline (12). A suspension of 7-nitro-5,8-dichloroisoquinoline **12** (13.0 kg, 53.5 mol) and the 5% w/w platinum on charcoal (50% wet paste) (2.6 kg) in acetic acid (19.5 L) and methanol (130 L) was hydrogenated at 20 °C and 3.5 barg for 30 min. The reaction mixture was the heated to 50 °C and then stirred for 8 h. The suspension was then treated with water (65 L), the temperature was then increased to ∼75 °C, and the mixture stirred for 10 min. The suspension was then filtered while still hot and the catalyst bed washed with methanol (13 L). The combined filtrate and wash were then allowed to cool to 20 °C, aged for 3 h, then cooled to 5 °C and aged for 16 h. The solid was then filtered, washed with methanol (13 L), and blown dry. The damp cake was then suspended in THF (130 L), heated to 50 °C, and treated with 2 M aqueous sodium hydroxide solution (26 L). The mixture was then stirred at 50 °C for 1 h to give a clear biphasic solution. The layers were then allowed to separate, and the lower aqueous layer was removed. The THF solution was then concentrated to 65 L and cooled to 0 °C over 2 h. During the cooling, after ∼1 h from the start of the cooling ramp, water (91 L) was added over 1 h. After stirring the resultant slurry at 0 °C for 16 h, the solid was filtered off, washed with water (2 × 13 L), and dried to give a cream-colored solid (6.3 kg, 55% yield): mp 198−200 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 6.78 (s, 1H), 5.35 (br s, NH_2, 2H), 3.72 (s, 2H), 2.87 (t, J = 6.0 Hz, 2H), 2.47 (t, J =

(21) Although the use of nitronium tetrafluoroborate was successfully demonstrated during the scale-up campaign, concerns about the long-term availability in commercial quantities of the reagent caused us to evaluate a further route to SB-406725A **1**. Reduction of 5,8-dichloroisoquinoline **11** to 5,8-dichlorotetrahydroisoquinoline followed by nitration using potassium nitrate and 98% sulphuric acid gave a ∼3:1 mixture of 7-nitro and 6-nitro isomers, respectively. We were able to separate these isomers by recrystallisation from methanol in 50% yield overall from 5,8-dichlorotetrahydroisoquinoline. Reduction of the nitro group of 7-nitro-5,8-dichlorotetrahydroisoquinoline could then be achieved under dissolving metal conditions to give the amino tetrahydroisoquinoline **13**, and this could then be converted into SB-406725 **1** via the NaHMDS coupling methodology as described above.

5.9 Hz, 2H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 143.2 (C), 136.2 (C), 132.0 (C), 121.3 (C), 114.1 (C), 112.4 (CH), 46.7 (CH_2), 42.5 (CH_2), 26.1 (CH_2). MS (ES +VE): *m*/*z* 217, 258 ($M^+ + H$, $M^+ +$ MeCN).

3-Acetyl-*N*-(5,8-dichloro-1,2,3,4-tetrahydro-7-isoquinolinyl)-4-(1-methylethoxy)-benzamide (16) from 7-Amino-5,8-dichlorotetrahydroisoquinoline (13). To a stirred slurry of 7-amino-5,8-dichlorotetrahydroisoquinoline **13** (9.5 kg, 43.8 mol) in THF (147 L) was added 3-acetyl-4-(1-methylethoxy)-methylbenzoate **15** (12.8 kg, 54.2 mol) and the mixture cooled to 0 °C. NaHMDS, 40% w/w in THF (119 L, 108.8 kg, 237.3 mol), was then added over ~30 min, keeping the reaction temperature below 5 °C, and the reaction was then stirred for 30 min. The reaction mixture was then treated with water (95 L), and the phases were then heated to 60 °C and mixed for 15 min before being allowed to settle for 15 min. The aqueous phase was discarded, and the organic phase was then washed with 30% w/w aqueous sodium chloride solution (95 L) at 60 °C. The yellow solution was then distilled to 170 L in volume at atmospheric pressure and then cooled back to 60 °C before being seeded with SB-406725 (9.5 g). The reaction mixture was aged at 60 °C for 30 min, cooled to 0 °C over 2 h, and then aged at 0 °C for 5 h. The resultant off-white slurry was then filtered, washed with THF at 0 °C (19 L vol), and blown dry. The wet cake was then slurried in water (95 L vol) at 50 °C for 4 h, cooled to 5 °C over 1 h, and aged at 5 °C for 1 h. The resultant off-white slurry was filtered and washed with water (19 L) at 5 °C and dried to give a cream-colored solid (15.9 kg, 83% yield): mp 170−171 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.06 (br s, 1H), 8.21 (d, J = 2.4 Hz, 1H), 8.11 (dd, J = 2.4 Hz, 8.8 Hz, 1H), 7.54 (s, 1H), 7.31 (d, J = 9.3 Hz, 1H), 4.90 (sep, J = 6.0 Hz, 1H), 3.82 (s, 2H), 2.94 (t, J = 5.9 Hz, 2H), 2.63 (t, J = 5.8 Hz, 2H), 2.56 (s, 3H), 1.37 (d, J = 6.1 Hz, 6H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 198.7 (C), 164.4 (C), 159.3 (C), 137.1 (C), 133.5 (C), 133.1 (CH), 132.9 (C), 131.5 (C), 129.7 (CH), 128.3 (C), 126.5 (C), 125.4 (CH), 125.4 (C), 113.9 (CH), 71.0 (CH), 46.8 (CH_2), 46.8 (CH_2), 31.7 (CH_3), 26.8 (CH_2), 21.6 (CH_3). MS (ES +VE): *m*/*z* 421 ($M^+ + H$).

3-Acetyl-*N*-(5,8-dichloro-1,2,3,4-tetrahydro-7-isoquinolinyl)-4-(1-methylethoxy)-benzamide hydrochloride (1) from 3-Acetyl-*N*-(5,8-dichloro-1,2,3,4-tetrahydro-7-isoquinolinyl)-4-(1-methylethoxy)-benzamide (16). A stirred slurry of SB-406725 **16** (10.5 kg, 24.9 mol) in THF (263 L) was heated to 60 °C to give a yellow solution. The solution was then clarified by filtration through a 5 μm polypropylene filter cartridge. The solution was then concentrated to ~5 vol (53 L) at atmospheric pressure. The reaction mixture was then diluted with propan-1-ol (105 L) and distilled at reduced pressure back to ~10 vol (105 L). The reaction mixture was then diluted with propan-1-ol (105 L) and distilled at reduced pressure back to ~10 vol (105 L). The reaction mixture was then diluted with propan-1-ol (105 L) and distilled at reduced pressure back to ~10 vol (105 L). The reaction mixture was then heated to 88 °C to give a yellow solution. Water (10.5 kg) and 36% w/w HCl (3.0 kg) were then added, and the reaction was kept at 88 °C. The reaction was then seeded with SB-406725A (0.01 kg). The reaction mixture was aged at 88 °C for 30 min, cooled to 0 °C over 2 h, and then aged at 0 °C for 30 min. The resultant white slurry was then filtered and washed with propan-1-ol at 0 °C (32 L). The cake was then pulled dry and oven-dried to give a white crystalline solid (10.2 kg, 88% yield): mp 241−244 °C (decomp). ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.30 (br s, 1H), 9.86 (br s, 2H), 8.24 (d, J = 2.5 Hz, 1H), 8.16 (dd, J = 2.5 Hz, 8.8 Hz, 1H), 7.72 (s, 1H), 7.35 (d, J = 9.3 Hz, 1H), 4.93 (sep, J = 6.0 Hz, 1H), 4.29 (s, 2H), 3.42 (t, J = 6.2 Hz, 2H), 3.02 (t, J = 6.1 Hz, 2H), 2.59 (s, 3H), 1.39 (d, J = 6.1 Hz, 6H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 198.7 (C), 164.4 (C), 159.4 (C), 134.8 (C), 133.2 (CH), 131.2 (C), 129.9 (C), 129.8 (C), 129.8 (CH), 128.3 (C), 127.2 (CH), 126.9 (C), 125.1 (C), 114.0 (CH), 71.0 (CH), 42.4 (CH_2), 39.4 (CH_2), 31.7 (CH_3), 23.4 (CH_2), 21.6 (CH_3). MS (ES +VE): *m*/*z* 421 ($M^+ + H$).

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Supporting Information Available

Analytical general methods and NMR, HPLC, and LC/MS data of the final product and all intermediates in the new route. This material is available free of charge via the Internet at http://pubs.acs.org.

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