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Conversion of a Benzofuran Ester to an Amide through an Enamine Lactone Pathway: Synthesis of HCV Polymerase Inhibitor GSK852A

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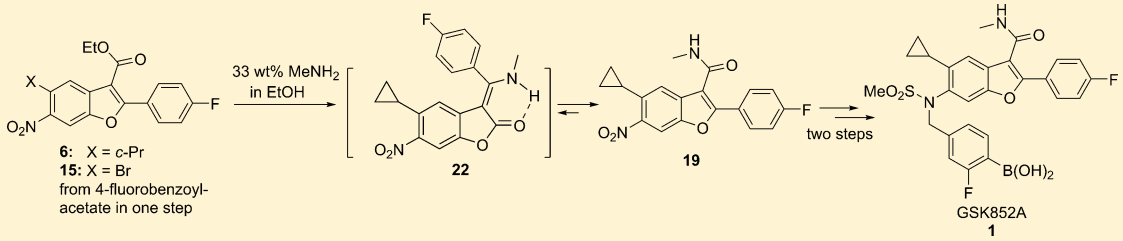
Supporting Information



ABSTRACT: HCV NS5B polymerase inhibitor GSK852A (**1**) was synthesized in only five steps from ethyl 4-fluorobenzoylacetate (**3**) in 46% overall yield. Key to the efficient route was the synthesis of the highly functionalized benzofuran core **15** from the β-keto ester in one pot and the efficient conversion of ester **6** to amide **19** via enamine lactone **22**. Serendipitous events led to identification of the isolable enamine lactone intermediate **22**. Single crystal X-ray diffraction and NMR studies supported the intramolecular hydrogen bond shown in enamine lactone **22**. The hydrogen bond was considered an enabler in the proposed pathway from ester **6** to enamine lactone **22** and its rearrangement to amide **19**. GSK852A (**1**) was obtained after reductive amination and mesylation with conditions amenable to the presence of the boronic acid moiety which was considered important for the desirable pharmacokinetics of **1**. The overall yield of 46% in five steps was a significant improvement to the previous synthesis from the same β-keto ester in 5% yield over 13 steps.

INTRODUCTION

Hepatitis C is a liver disease caused by the hepatitis C virus (HCV). According to the World Health Organization, 130–150 million people are chronically infected with HCV, and more than 350 000 people die every year from HCV related liver diseases.[1] Significant discovery efforts from the pharmaceutical industry have led to approval of drugs such as boceprevir, telaprevir, and sofosbuvir by the US Food and Drug Administration. The emergence of drug resistance is still a concern for HCV treatment: there is a need to discover and develop new therapies which have novel modes of action and resistance profiles. HCV polymerases are essential for HCV replication. The NS5B protein, an RNA-dependent RNA polymerase (RDRP) responsible for replicating the viral genome, is a clinically validated target for therapeutic intervention with many compounds in development.[2] Compound **1** shown in Figure 1 is a HCV NS5B polymerase inhibitor with 50% effective concentrations (EC_{50}) in the low nanomolar range in the genotype 1 and 2 subgenomic replicon system as well as the infectious HCV cell culture system. Its superior resistance profile suggests that it could be an attractive component of an all-oral regimen for treating HCV.[3] The boronic acid moiety in **1** is an important structural feature for the demonstrated potency.[3] The benzofuran-3-carboxamide core has been highly optimized, and its clinical relevance has led to many drug candidates from our program as well as from other research groups (e.g., HCV796 or Nesbuvir, **2**).[4] The focus of this Article is on the synthesis of GSK852A though many of the findings could also be applicable to the synthesis of

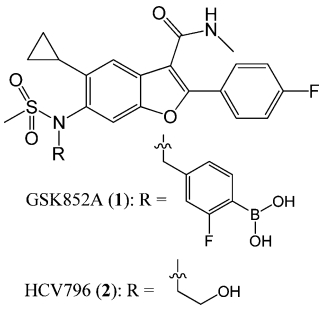


Figure 1. Structures of HCV polymerase inhibitors **1** and **2**.

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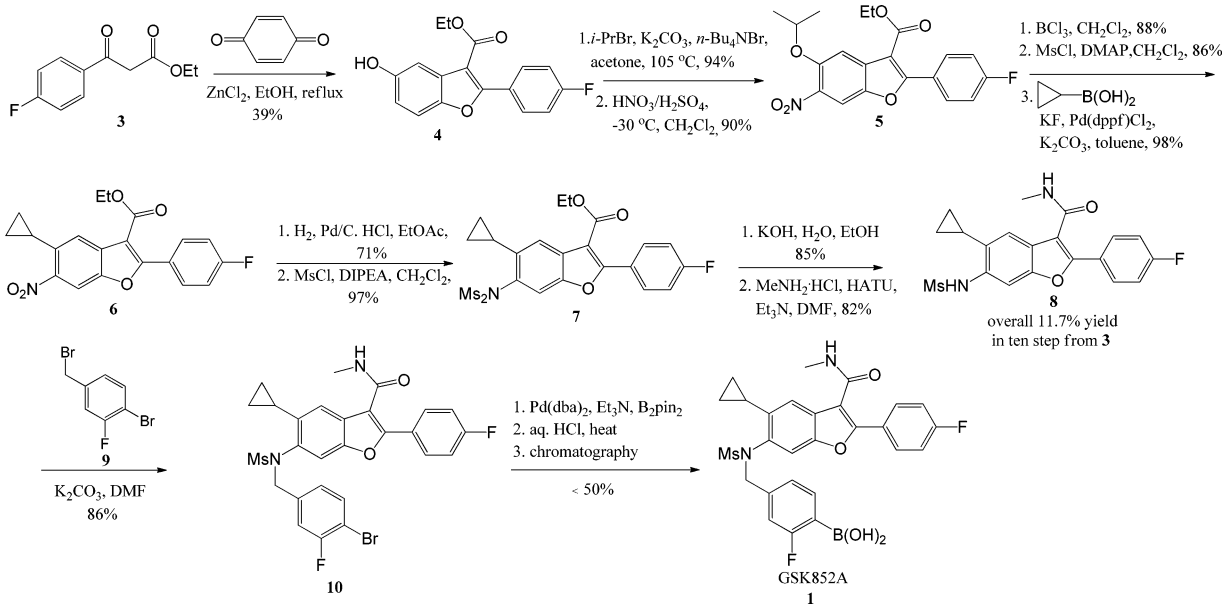
Scheme 1. Previous 13-Step Synthesis of GSK852A (1)



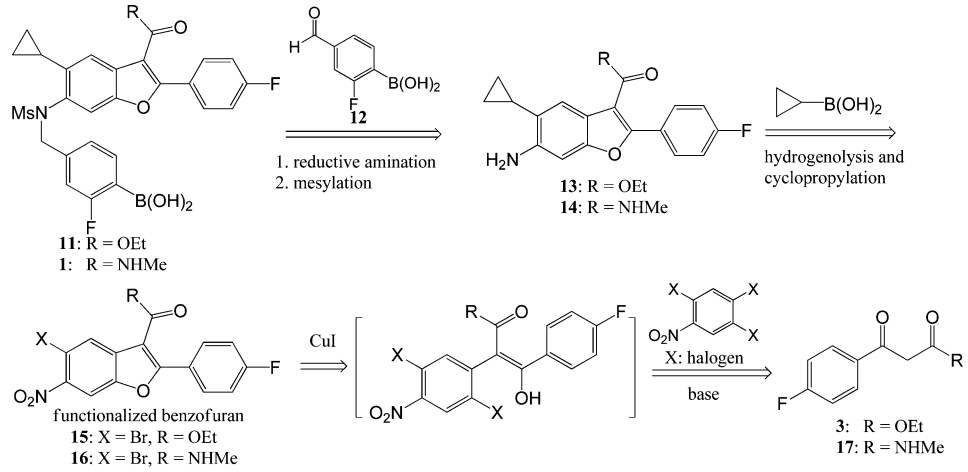


Figure 2. Plan for shorter synthesis of GSK852A from β-keto ester **3** or β-keto amide **17**.

HCV796 and other drug candidates with the benzofuran-3-carboxamide core.

The original synthesis of compound **1** is shown in Scheme 1. The synthesis started with a $ZnCl_2$ catalyzed Nenitzescu reaction between ethyl 4-fluorobenzoylacetate (**3**) and 1,4-benzoquinone to form 5-hydroxybenzofuran **4** in only 39% yield.[5] Protection of the phenol as an isopropyl ether followed by nitration led to **5**. The isopropyl protection was then removed, and the phenol was activated as a mesylate for Pd catalyzed coupling with cyclopropyl boronic acid to give **6**. Hydrogenolysis of the nitro group and mesylation led to bis-mesylate **7**. The ethyl ester was hydrolyzed with the concurrent removal of one mesyl group, which was followed by coupling with methylamine to provide the functionalized benzofuran **8**. The 10-step sequence to the benzofuran core was scaled up to 20 kg scale albeit in low overall yield of less than 12% from β-keto ester **3**. Alkylation of **8** with 1-bromo-4-(bromomethyl)-2-fluorobenzene (**9**) gave aryl bromide **10**. Borylation via $Pd(dba)_2$ catalysis, followed by harsh hydrolysis conditions with HCl, generated GSK852A (**1**) in less than 50% yield due to extensive purification required to remove large amounts of residual Pd and the des-bromo/des-boron impurities from the formation and hydrolysis of the pinacol ester. The use of the benzyl bromide was also considered an issue due to potential genotoxicity concerns and the number of steps required to prepare it from commercially available material.

The main drawbacks of the original synthesis were the large number of steps required and overall low yield of about 5% from the β-keto ester.

A new synthetic strategy, shown in Figure 2, was devised for early introduction of the benzyl fragment already containing the boronic acid moiety. Reductive amination of commercially available aldehyde **12** with aryl amines such as **13** and **14** would then provide **1** or **11**. This would not only be more efficient but would also eliminate the difficult borylation step required at the end of the synthesis. Furthermore, a one-pot synthesis of the highly functionalized benzofuran cores such as **15** and **16** was envisioned starting from a β-keto ester (**3**) or an amide (**17**) to take advantage of many commercially available trihalogenbenzenes. The synthesis of benzofurans via palladium or copper catalyzed ring closure of 2-halo aromatic ketones is known.[8,9] The 4-fluorophenyl and the ester/amide moieties were

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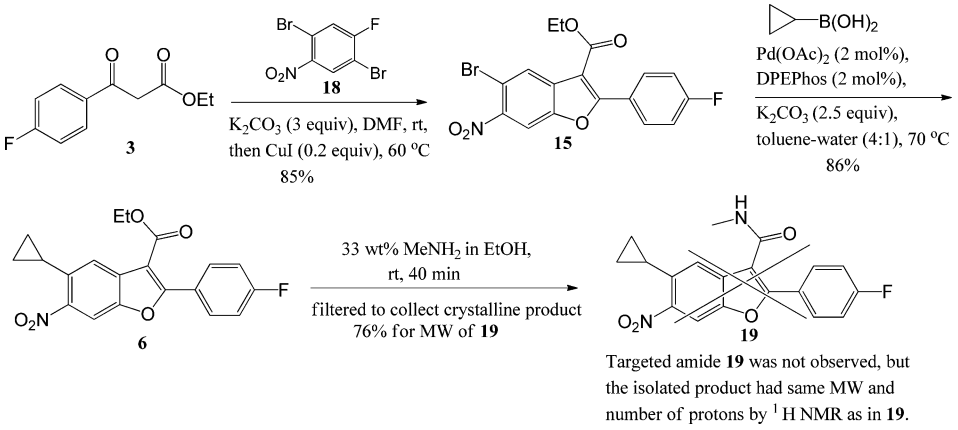
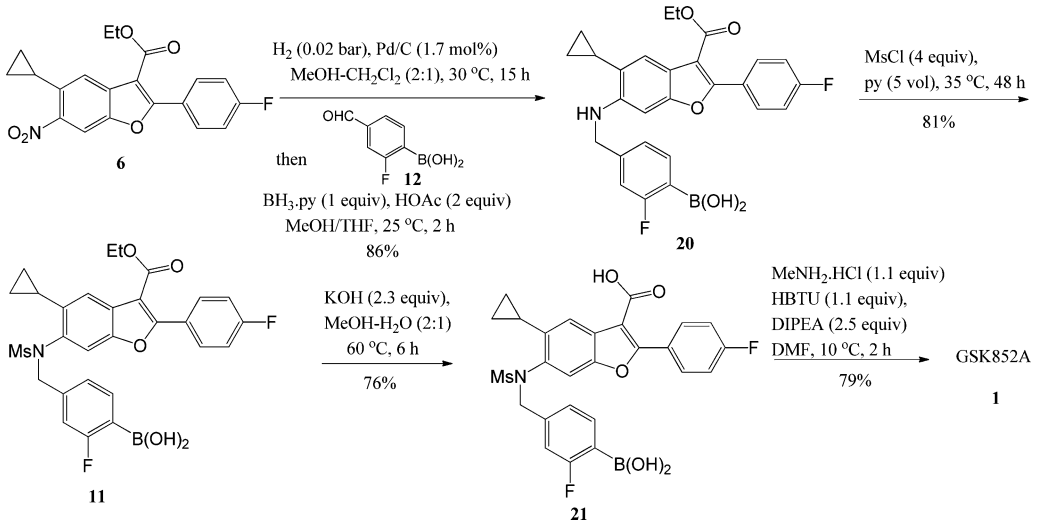
Scheme 2. Synthesis of Benzofuran Ester 6 and Attempted Conversion to Amide 19 with Methylamine



Scheme 3. Synthesis of GSK852A (1) via Intermediate 20 by Reductive Amination on an Ester Substrate



expected to contribute to a facile ring closure for a potential one-pot synthesis. This sequence would cut the number of steps significantly compared with the original synthesis starting from the same β-keto ester.

We herein report our findings in the execution of the new synthetic strategy, in particular an unexpected conversion of a benzofuran ethyl ester to an enamine lactone which rearranged to a methyl amide through a proposed reversible pathway. The unexpected amide formation along with the efficient one-pot synthesis of a highly functionalized benzofuran and the clean reductive amination and mesylation in the presence of the boronic acid moiety were all key components in a significantly improved synthesis of HCV polymerase inhibitor GSK852A (**1**).

RESULTS AND DISCUSSION

Our first attempt to synthesize a benzofuran amide is shown in Scheme 2. Coupling of ethyl 4-fluorobenzoylacetate (**3**)[6] and 1,4-dibromo-2-fluoro-5-nitrobenzene (**18**)[7] in the presence of K_2CO_3 led to a 2-phenyl-3-ketoester intermediate at room temperature. Following addition of a catalytic amount of CuI, the enol form of the coupled keto ester (see Figure 2 for the enol structure) ring closed at 60 °C to give the highly functionalized ethyl 5-bromobenzofuran-3-carboxylate core **15** in 85% of yield. The product was isolated by direct filtration upon quenching with aqueous ammonia.

The Suzuki coupling[10] with cyclopropyl boronic acid, catalyzed by palladium acetate and 1,1′-[(oxidi-2,1-phenylene)]bis[1,1-diphenylphosphine (DPEPhos), provided ethyl 5-cyclopropylbenzofuran **6** in 86% yield. The DPEPhos ligand was selected among many ligands screened because it caused the least amount of a byproduct from debromination.[11] The sequence from β-keto ester **3** to benzofuran **6** was scaled up to 6 L.[12]

Ethyl ester **6** was treated with 33 wt % $MeNH_2$ in EtOH at room temperature. This mixing led to a clear solution which, over just 40 min, gave rise to a substantial amount of crystalline solids. The purported methyl amide **19**, highly crystalline and with the expected molecular weight by LCMS and the number of protons by NMR for **19**, was isolated in 76% yield by simple filtration of the reaction mixture. The crystalline product was then carried forward for the rest of the synthesis following the planned sequence shown in Figure 2: hydrogenolysis of the nitro group, reductive amination with (2-fluoro-4-formylphenyl)boronic acid (aldehyde **12**), and mesylation with MsCl/pyridine. However, the sequence of chemistry led to a product which had slightly shorter retention time in HPLC compared to target product **1** despite the same molecular weight (MW 554.4) by LCMS as **1**.

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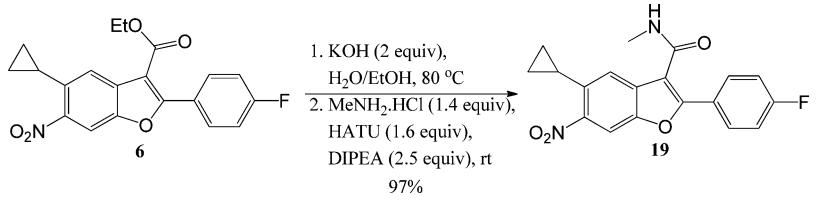
Scheme 4. Synthesis of Amide 19 from Ester 6 via Ester Hydrolysis and Coupling with Methylamine



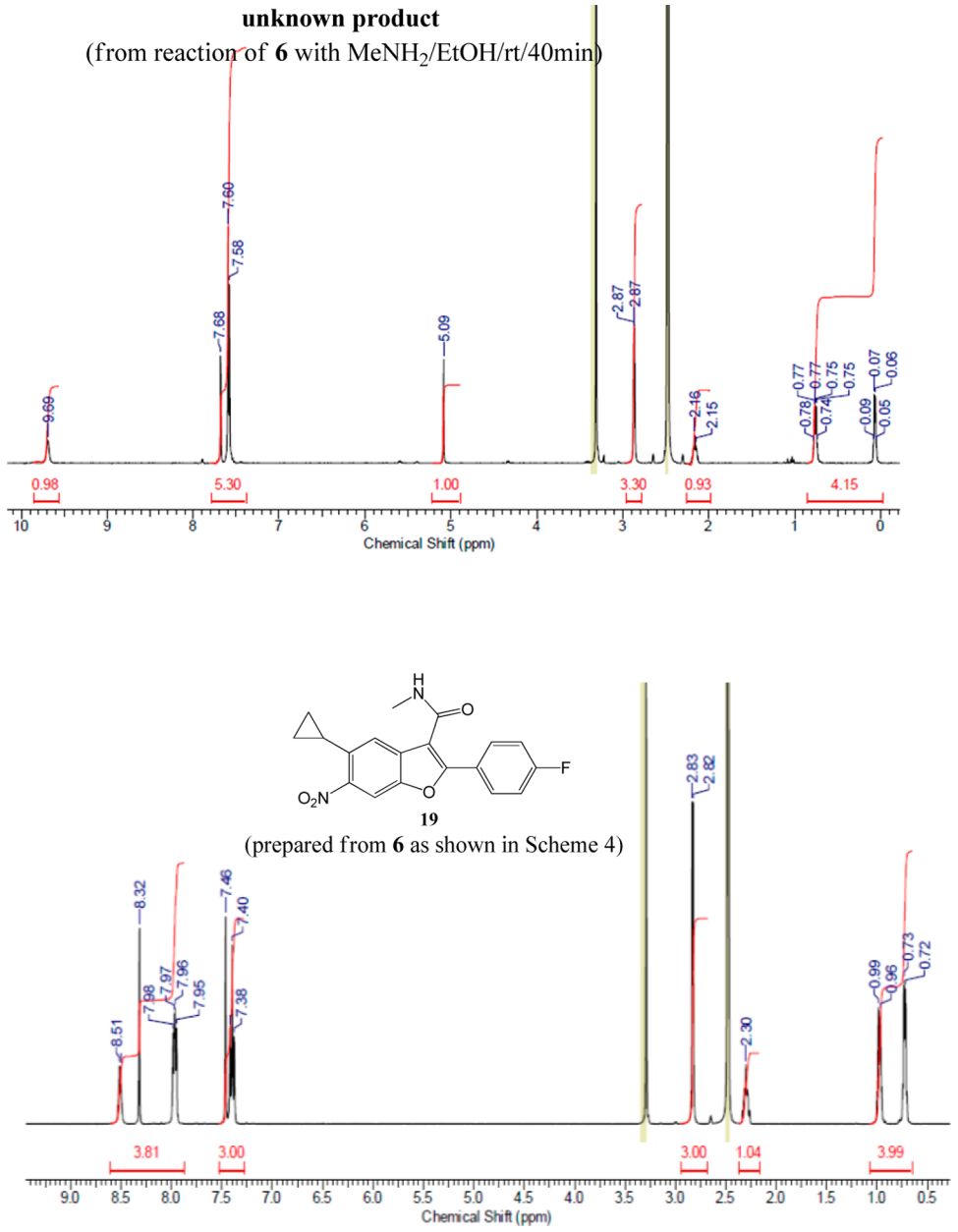


Figure 3. Comparison of the NMR spectra of the unknown and amide **19** in DMSO-d_6.

With the setback in the seemingly simple amide formation, we took a slight detour from the route originally laid out in Figure 2. Synthesis of GSK852A (**1**) was achieved in the sequence shown in Scheme 3. The nitro group of **6** underwent hydrogenolysis at 30 °C under slightly pressurized hydrogen (0.02 bar) in the presence of Pd/C.[13] Upon completion, the mixture was filtered to remove the catalyst and charcoal. The solvents were partially distilled off and replaced with MeOH for the reductive amination of intermediate 6-aminobenzofuran in the same reactor with boronic acid aldehyde **12**. Borane/pyridine[14] complex and acetic acid were superior to many other common reagents[15] for the reductive amination. The other reagents and conditions such as sodium triacetoxyborohydride failed to give good yield of **20** due to low conversion or decomposition of product with the sensitive boronic acid moiety. Amino product **20** was isolated in 86% yield by direct

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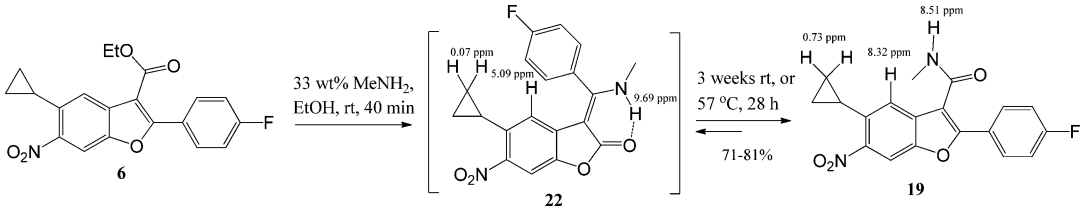
Scheme 5. Synthesis of Amide 19 from Ester 6 via Enamine Lactone 22



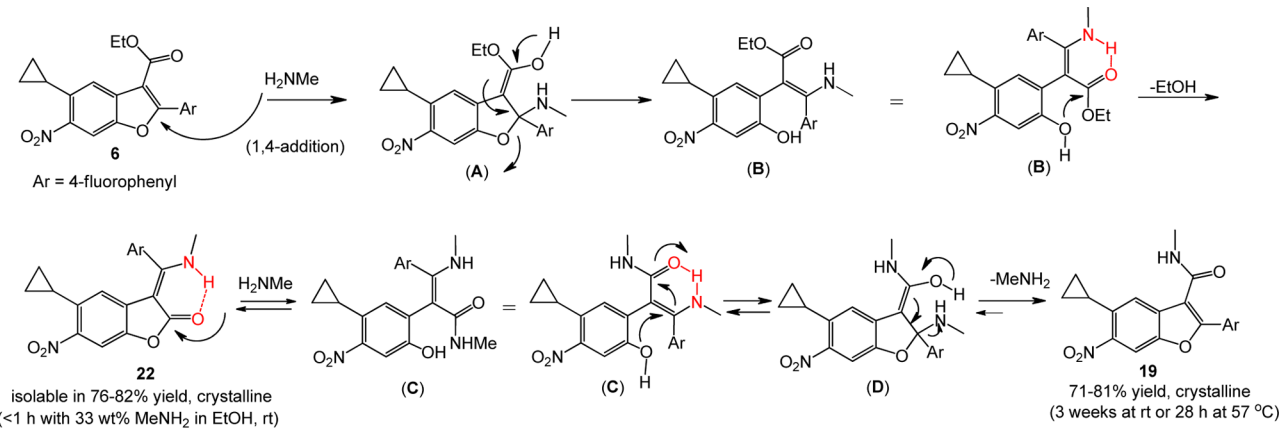


Figure 4. Proposed pathway from ethyl ester **6** to enamine lactone **22** and rearrangement of **22** to amide **19**.

filtration of the reaction mixture after quenching with aqueous HCl.

Mesylation of **20** with MsCl in pyridine was slow at 35 °C but very clean. Upon completion of the reaction after 2 days, the reaction was quenched with water and acidified with concentrated HCl. The mesylated product **21** was also isolated by direct filtration in 81% yield after quenching. The rest of the synthesis, i.e. the hydrolysis of the ethyl ester[16] and the methyl amide formation with HBTU/DIPEA,[17] went smoothly to give carboxylic acid **21** and GSK852A (**1**) in 76% and 79% yield, respectively. The overall yield of 31% from β-keto ester **3** in six steps was demonstrated in 2−6 L scale. This was a significant improvement relative to the original synthesis of overall yield of 5% in 13 steps.

While the scaleup of the chemistry shown in Scheme 3 was being carried out, further development of the chemistry continued. Ester **6** was exposed to 33% $MeNH_2$/EtOH at room temperature as before, but the reaction was allowed to continue for about 3 weeks whereupon crystals were generated as expected. To our surprise, the isolated crystals from the three-week reaction bore no resemblance to the one isolated from the previous reaction with $MeNH_2$/EtOH over 40 min when analyzed by NMR. The newly isolated product was identical to compound **19** prepared from ester **6** by a two-step chemistry shown in Scheme 4.

Inadvertent sample switching was ruled out, and another reaction with $MeNH_2$/EtOH at room temperature was set up following the exact conditions (40 min) as the first one to provide a new sample of the unknown product for further tests. The ^1H NMR spectra of the unknown and amide **19** in DMSO-d_6 were quite different as shown in Figure 3. The unknown had a more acidic proton at 9.69 ppm relative to 8.51 ppm for the NH of amide **19**. Overall, the aromatic protons for the unknown were shifted upfield. In particular there was a new peak at 5.09 ppm which appeared to be one of the aromatic protons, severely shielded to the upper field. The two methylenes for the cyclopropyl were more differentiated in the unknown with one of the methylenes shifted to 0.07 ppm, relative to 0.73 ppm in amide **19**. NMR in $CDCl_3$ showed similar pattern of shifts. It was also obvious that no ethyl group was found in the unknown.

More elaborate NMR correlation experiments on the unknown product revealed that the para-substituted aromatic ring was spatially close to the cyclopropyl moiety (NOESY) and that the carbonyl carbon was not within 3 bonds distance of any nonexchangeable protons (HMBC). On the basis of this evidence and other NMR data discussed above, an enamine lactone structure represented by **22** was tentatively assigned to the thus far unknown compound (Scheme 5). The NH proton at 9.69 ppm for **22** relative to 8.51 ppm for **19** was probably due to a potential NH hydrogen bond with the lactone carbonyl oxygen. The (*Z*)-configuration of the enamine explained the shielding effect from the 4-fluorophenyl ring on one of the benzofuran aryl protons and one of the methylenes of the cyclopropyl group.

It was clear by then that the enamine lactone **22** first formed upon treatment of ester **6** with $MeNH_2$/EtOH at room temperature. If the crystalline solid was not isolated, it substantially rearranged to amide **19** over 3 weeks at room temperature or in 1−2 days with heating. In a scale-up to 1 L, **19** was isolated as a crystalline solid in 71% yield by direct filtration of the reaction mixture after 28 h at 57 °C. In addition, the isolated amide **19**, when submitted to fresh and heated $MeNH_2$/EtOH, partially reversed to enamine lactone **22**. However, no further reversal to ester **6** was observed. The equilibrium of enamine lactone **22** and amide **19** in $MeNH_2$/EtOH was apparently biased toward the target amide **19** with the amide isolated in 71−81% yield. When the isolated enamine lactone **22** was treated with $MeNH_2$/EtOH for at 60 °C for 18 h, amide **19** was isolated in 86% yield. A reaction pathway from ester **6** to amide **19** via enamine lactone **22** was proposed as shown in Figure 4.

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We propose the 1,4-addition as the first interaction of $MeNH_2$ and the benzofuran 3-carboxylate **6** to give a ketene hemiacetal (**A**). A 1,2-addition, which would lead to amide **19** directly from **6**, would generate a tetrahedral intermediate and is expected to have much higher ΔH compared to the formation of the 1,4-addition adduct (**A**). In all the reactions we have monitored by HPLC upon addition of 33% methylamine/EtOH to ester **6** at room temperature, we observed only less than 1% of amide **19** prior to depletion of ester **6**. The ratio of enamine lactone **22** to amide **19** was typically >100:1 at the point when all ester **6** was depleted. Ring opening from the adduct (**A**) would lead to the phenolic enoate (**B**). The nucleophilic addition of the phenol OH to the ester in **B** leads to enamine lactone **22** after loss of EtOH. We believe that this ring closure is aided by the hydrogen bond shown in **B**, and this activates the ester carbonyl. Similarly, the hydrogen bond shown in **22** activates the lactone carbonyl for nucleophilic addition by methylamine to give the enamide (**C**). Intramolecular 1,4-addition from the phenol OH of **C**, aided by the hydrogen bond shown, leads to the ketene hemiaminal (**D**). Finally, rearomatization from **D** with loss of one molecule of methylamine affords the benzofuran-3-carboxamide **19**.

As discussed before, isolated amide **19** partially reversed to enamine lactone **22** when subjected to $MeNH_2$/EtOH in a heated tube. The difference in the solubility of **19** and **22** as well as the aromaticity of the benzofuran core in **19** could explain the equilibrium biased toward **19**. Experimentally, the mother liquor, after isolation of **19** from the reaction, gave rise to more crystals of **19** after standing at room temperature for a few days or being heated at 60 °C and then cooled back to room temperature. We did not observe reversibility between **22** and **6**.

More recently, we obtained the structure of **22** from an X-ray diffraction study on a single crystal (Figure 5). Although the diffraction intensities were weaker than normal owing to the small crystal size, the structure was highly informative. With the exception of a subset of the carbons in the cyclopropyl and fluorophenyl rings, the remaining non-hydrogen atoms lay essentially in a single plane. The N—H group of the amine acts as a bifurcated hydrogen bond donor (Figure 5). The (*Z*)-configuration of the exocyclic C=C double bond allows the intramolecular hydrogen bond between N14 and O26 [2.836(9) Å], while the crystal packing also generates a corresponding intermolecular interaction between the same atoms in different molecules [2.941(10) Å]. The intramolecular hydrogen bond and the (*Z*)-configuration support the observations from the NMR studies discussed previously. It also explains the reactivity for several intermediates in the proposed pathway shown in Figure 4.

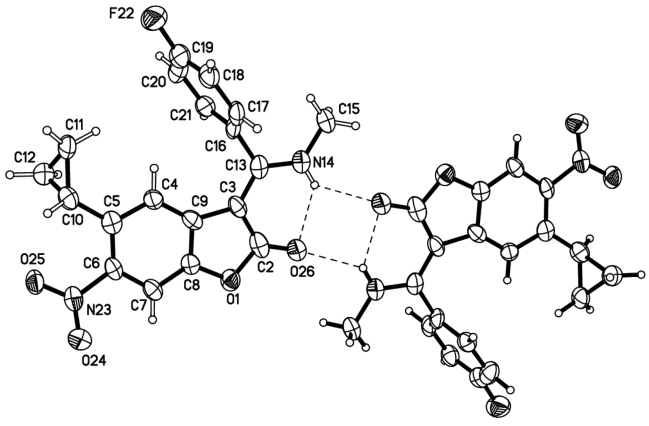

Figure 5. View of two molecules of **22** from the crystal structure, highlighting the hydrogen bonding (dashed lines) and the orientation of the 4-fluorophenyl ring, shielding a methylene of the cyclopropyl group and a methine of the fused ring system. The non-hydrogen atoms in the crystallographic asymmetric unit are numbered. Anisotropic atomic displacement ellipsoids for the non-hydrogen atoms are shown at the 50% probability level. Hydrogen atoms are displayed with an arbitrarily small radius.

The 3-(benzylidene)benzofuran-2(3*H*)-one core structure of **22** was previously known and present in marginalin isolated from the pygidial glands of the water beetle *Dytiscus marginalis* (Coleoptera).[18] The structure of marginalin is (*E*)-5-hydroxy-3-(4-hydroxybenzylidene)benzofuran-2(3*H*)-one. Barbier reported the synthesis of this natural product and determined it to be the (*E*)-configuration.[19] Subsequently, it was showed that marginalin rearranged to strongly fluorescent 5-hydroxy-2-(4′-hydroxyphenyl)-3-benzo[*b*]furan carboxylic acid or the methyl ester under basic conditions such as potassium carbonate or sodium methoxide in very low yields.[20] It was reported that the two phenolic OHs in 2-phenylbenzo[*b*]furans were important for the rearrangement.[20b] Although not mentioned in the paper, a careful examination of the structures of marginalin and the rearranged products under basic conditions revealed the involvement of oxidation in the reported rearrangement, probably through the 1.4-benzoquinone from air oxidation. This would explain the importance of the two phenolic OHs in the rearrangement. However, this was not the case for our more elaborate and nitrogen containing structure (**22**), which did not need the OH in the 5-position of the benzofuran core for the rearrangement to occur. The amino moiety of the enamine lactone (**22**) allowed nonoxidative rearrangement to the benzofuran-3-carboxamide. Aniline and bulkier alkylamines such as *i*-butylamine, however, were less efficient for the rearrangement, leading to incomplete and less clean reactions.

The final two steps of the five-step synthesis of **1** are shown in Scheme 6. Benzofuran-3-carboxamide **19**, prepared from ester **6** in one step with methylamine, was hydrogenolyzed. The amino intermediate after removal of the catalyst by filtration was subjected to the reductive amination. The boronic acid product (**23**) was isolated in 87% yield by direct filtration of the HCl quenched reaction. Mesylation of amide **23** with MsCl in pyridine was more difficult than with ester **20**, and MsCl had to be used in large excess as a cosolvent with pyridine to achieve a clean and complete reaction at 0 °C. GSK852A (**1**) was isolated in 89% yield.

The overall yield from β-keto ester **3** in five steps was 46% for this amide route. This was better than the ester route shown in Scheme 3 with 31% overall yield in six steps, and substantially better than the original synthesis shown in Scheme 1 with 5% overall yield in 13 steps. The amide route was selected for further scaleup to deliver GSK852A in the pilot plant.

■ CONCLUSIONS

GSK852A (**1**) was synthesized in only five steps from ethyl 4-fluorobenzoylacetate (**3**) in 46% overall yield, compared to the original synthesis from the same β-keto ester in 5% yield over 13 steps. The efficiency was achieved with a one-pot synthesis of the highly functionalized benzofuran core **15** from β-keto ester **3** and conversion of benzofuran-3-carboxylate **6** to benzofuran-3-carboxamide **19** via the unique rearrangement

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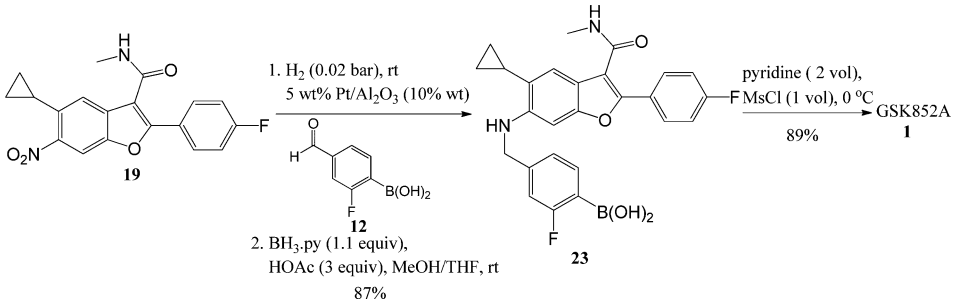
Scheme 6. Synthesis of GSK852A via Reductive Amination with a 6-Aminobenzofuran-3-carboxamide



of enamine lactone **22**. A single crystal X-ray diffraction study and NMR analysis revealed the configuration of the enamine lactone with the intramolecular hydrogen bond, which was considered an enabler for the proposed pathway from ester **6** to amide **19**. The structural cores of 6-amino-5-alkyl-2-aryl-*N*-methylbenzofuran-3-carboxamide, represented by **19**, have been highly optimized in structure−activity relationship (SAR) studies and are frequently seen in antiviral drug candidates. We have also developed the simple and clean reductive amination and mesylation in the presence of the sensitive boronic acid, which has been considered important for the biological activities of GSK852A. The methods should also be applicable to other drug candidates containing a boronic acid moiety.

EXPERIMENTAL SECTION

General Procedures. All reactions were run under nitrogen. Unless otherwise specified, concentration by rotary evaporation or distillation was carried out under house vacuum of 12−50 Torr. Melting points were not corrected. NMR spectra were recorded on a 400 MHz spectrometer. The accurate mass measurements were performed on an Orbitrap mass spectrometer. The heated electrospray ionization (HESI) source was operated in the positive ion mode under the following conditions: spray voltage, −4.0 kV; source heater temperature, 200 °C; heated capillary temperature, 250 °C; S lens RF level, 60%; sheath gas flow, 50 arbitrary units. The atmospheric pressure chemical ionization (APCI) source was operated in the positive ion mode under the following conditions: corona discharge current, 5 μA; source heater temperature, 300 °C; heated capillary temperature, 250 °C; S lens RF level, 60%; sheath gas flow, 50 arbitrary units. The single crystal X-ray diffraction data for **22** were collected with a diffractometer at 150(2) K using Cu Kα X-radiation (λ = 1.541 78 Å). Crystal data for **22** are given in the relevant section below. A description of the refinement and the full tables associated with the crystal structure are given in the Supporting Information. A crystallographic information file has been deposited with the Cambridge Crystallographic Data Centre. CCDC 1404059 contains the supplementary crystallographic data for this paper.

*Ethyl-5-bromo-2-(4-fluorophenyl)-6-nitrobenzofuran-3-carboxylate (**15**).* To a 6 L reactor were successively added 300 g (1.03 mmol) of 1,4-dibromo-2-fluoro-5-nitrobenzene, 253 g (1.20 mol) of 4-fluorobenzoylacetate (crude from evaporation of a 51% solution in EtOH), 416 g (3.01 mol) of K_2CO_3, and 2.4 L of DMF. The nearly homogeneous mixture was stirred at room temperature for 20 h. After being heated to 45 °C, the mixture was treated with 38.2 g (201 mmol) of CuI. An additional 300 mL of DMF was added as the reaction mixture became thick. The reaction was heated to 60 °C and stirred for 20 h. After being cooled to 0 °C, the reaction was quenched with 1.2 L of 28% ammonium hydroxide via an additional funnel at such a rate that the mixture was maintained below 10 °C. The mixture was further treated with 1.2 L of water and stirred for about 30 min at 0 °C. The slurry was filtered, washed with 3.0 L of water and 600 mL of MeOH, and dried in vacuo at 65 °C to give 350 g (85%) of **15** as a crystalline solid: mp 139.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1 H), 8.13 (s, 1 H), 8.13 (t, J = 8.0 Hz, 2 H), 7.25 (t, J = 8.0 Hz, 2 H), 4.48 (q, J = 8.0 Hz, 2 H), 1.47 (t, J = 8.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 164.5, 163.4, 162.5, 150.9, 146.4, 132.2 (d, J = 10.0 Hz), 128.5, 124.3, 115.7 (d, J = 21.0 Hz), 109.7, 109.5, 108.2, 81.5, 14.3. HRMS (APCI) m/z calcd for $C_{17}H_{12}BrFNO_5$ (MH^+) 407.9877, found 407.9855.

*Ethyl-5-cyclopropyl-2-(4-fluorophenyl)-6-nitrobenzofuran-3-carboxylate (**6**).* To a 6 L reactor were successively added 360 g (882 mmol) of **15**, 91.0 g (1.06 mmol) of cyclopropyl boronic acid, 3.96 g (17.6 mmol) of $Pd(OAc)_2$, 9.50 g (17.6 mmol) of DPEPhos, and 305 g (2.21 mol) of K_2CO_3 under nitrogen, followed by 2.9 L of toluene and 720 mL of water. The reaction was stirred at 70 °C for 2 h. After being cooled to 20 °C, the mixture was filtered through 360 g of Celite 545 to remove a small amount of emulsions. The Celite pad was washed with 720 mL of toluene and 1.8 L of water. The organic layer was concentrated in vacuo to give a slurry. After addition of 1.8 L of MeOH, the mixture was cooled to 0 °C and stirred overnight. The slurry was filtered, washed with 720 mL of MeOH, and dried at 65 °C in vacuo to give 279 g (86%) of **6** as a crystalline solid: mp 133.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1 H), 8.11 (t, J = 8.0 Hz, 2 H), 7.96 (s, 1 H), 7.23 (t, J = 8.0 Hz, 2 H), 4.46 (q, J = 7.8 Hz, 2 H), 2.54 (m, 1 H), 1.46 (t, J = 7.8 Hz, 3 H), 1.11 (dt, J = 6.0, 7.8 Hz, 2 H), 0.77 (dt, J = 6.0, 7.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 163.7, 163.1, 150.4, 148.4, 134.5, 132.0 (d, J = 9.0 Hz), 131.2, 124.8, 122.6, 115.7 (d, J = 22.0 Hz), 108.6, 107.9, 81.2, 14.2, 13.6, 7.5. HRMS (ESI) m/z calcd for $C_{20}H_{17}FNO_5$ (MH^+) 370.1085, found 370.1084. Anal. Calcd for $C_{20}H_{16}FNO_5$: C, 65.04; H, 4.37; N, 3.79. Found: C, 65.08; H, 4.47; N, 3.73.

*(4-(((5-Cyclopropyl-3-(ethoxycarbonyl)-2-(4-fluorophenyl)-benzofuran-6-yl)amino)methyl)-2-fluorophenyl)boronic Acid (**20**).* To a 2 L reactor were added 50.0 g (135 mmol) of **6**, 5.00 g of palladium on charcoal (10 wt %, dry basis, ∼ 50% water), 900 mL of MeOH, and 450 mL of CH_2Cl_2. After three cycles of vacuum (−0.49 bar)/nitrogen (0.01 bar) purges, the mixture was heated to 30 °C and evacuated to −0.50 bar. Hydrogen was introduced via a gas regulator to 0.02 bar. Upon completion of the hydrogenolysis over 15 h, the heterogeneous reaction mixture was purged with nitrogen and heated to 40 °C, and the intermediate hydrogenolysis product fully dissolved. The mixture was filtered through 50 g of Celite 545 and washed with 200 mL of CH_2Cl_2. The filtrate was transferred back to the reactor and concentrated in vacuo to 750 mL. After being diluted with 150 mL of MeOH, the solution was used directly for the reductive amination as follows.

To the above solution were successively added 25.0 g (149 mmol) of boronic acid aldehyde **12** and 15.5 mL (271 mmol) of acetic acid at ambient temperature. After being stirred for 15 min, the mixture was treated with 12.6 g (135 mmol) of borane pyridine complex over 5 min. Upon completion of the reaction in 1 h, the reaction was quenched with 6.80 mL (81.2 mmol) of concentrated HCl over 3 min. The mixture was stirred at 15 °C for 2 h. The yellow slurry was filtered, washed with 2 × 85 mL of MeOH, and dried at 65 °C in vacuo to give 57.5 g (86%) of **20** as a light yellow solid: mp 176.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (s, 1 H), 7.94 (m, 2 H), 7.70 (m, 1 H), 7.52 (m, 2 H), 7.30 (m, 2 H), 7.26 (m, 1 H), 7.09 (m, 1 H), 6.53 (s, 1 H), 6.31 (m, 1 H), 4.52 (m, 2 H), 4.29 (m, 2 H), 1.82 (m, 1 H), 1.31 (t, J = 6.0 Hz, 3 H), 1.02 (m, 2 H), 0.58 (m, 2 H). ^{13}C NMR

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(100 MHz, $CDCl_3$): δ 169.6, 167.1, 164.5 (d, J = 25.0 Hz), 162.1, 157.1, 154.3, 146.1, 145.4 137.1 (m), 131.2, 126.3, 124.9, 122.9, 122.2, 116.9 (d, J = 4.0 Hz), 115.1 (d, J = 21.0 Hz), 113.2 (m), 108.8, 91.9, 80.5, 50.8, 47.7, 14.3, 11.8, 5.4. HRMS (ESI) m/z calcd for $C_{27}H_{25}BF_2NO_5$ (MH^+) 492.1788, found 492.1792.

*(4-((N-(5-Cyclopropyl-3-(ethoxycarbonyl)-2-(4-fluorophenyl)-benzofuran-6-yl)methylsulfonamido)methyl)-2-fluorophenyl)-boronic Acid (**11**).* To a 2 L reactor were successively added 57.0 g (116 mmol) of **20** and 375 mL of pyridine at ambient temperature. The resultant solution was treated with 27.8 mL (360 mmol) of MsCl. The reaction was heated to 35 °C and stirred for 20 h. An additional 8.90 mL (116 mmol) of MsCl was added due to incomplete reaction overnight. After being stirred for 20 h, the reaction was cooled to 25 °C and quenched with 350 mL of water, followed by 350 mL of EtOAc. The mixture was acidified with 358 mL (4.29 mol) of concentrated HCl over 10 min. After the mixture was stirred for 15 min, an additional 150 mL of EtOAc and 150 mL of water were added, but very little further dissolution was observed. The heterogeneous mixture was then filtered, washed with 2 × 200 mL of water, and dried in vacuo at 60 °C to give 47.1 g (71%) of **11** as an off-white solid. Layers in the filtrate were separated, and the aqueous layer was back extracted with 150 mL of EtOAc. The combined organic layers were washed with 200 mL of brine and evaporated to 25.0 g. A slurry was made by addition of 20 mL of acetone, 40 mL of ethanol, and 15 mL of water to the 25.0 g of crude product. Filtration and drying at 60 °C gave 11.2 g (17%) of **11** as an off-white solid.

The two solids (47.1 + 11.2 g) were combined, treated with 60 mL of acetone and 180 mL of ethanol, and heated to 40 °C for 15 min, followed by addition of 60 mL of water. The mixture was cooled to 20 °C, stirred for 30 min, filtered, washed with 2 × 60 mL of 1:1 EtOH/water and 60 mL of EtOH, and dried at 65 °C in vacuo to give 53.2 g (81% yield for reaction, 91% recovery for recrystallization) of **11** as an off-white crystalline solid: mp 165.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (m, 2 H), 7.76 (t, J = 8.0 Hz, 1 H), 7.55 (s, 1 H), 7.31 (s, 1 H), 7.19 (t, J = 8.0 Hz, 2 H), 7.10 (dd, J = 10.0, 8.0 Hz, 2 H), 5.04 (d, J = 4.0 Hz, 2 H), 4.92 (ABq, $\Delta\delta_{AB}$ = 0.25, J_{AB} = 8.0 Hz, 2 H), 4.42 (q, J = 7.0 Hz, 2 H), 3.06 (s, 3 H), 2.24 (m, 1 H), 1.43 (t, J = 6.0 Hz, 3 H), 1.10 (m, 1 H), 0.96 (m, 2 H), 0.59 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 163.6, 162.8, 161.4, 151.2, 142.1 (d, J = 9.0 Hz), 139.8, 137.2 (d, J = 7.0 Hz), 135.0, 131.8 (d, J = 6.0 Hz), 128.1, 125.5, 117.8, 115.7 (d, J = 20.0 Hz), 115.4 (d, J = 22.0 Hz), 112.8, 108.5, 80.8, 50.1, 39.7, 14.2, 11.4, 11.0, 9.2. HRMS (ESI) m/z calcd for $C_{28}H_{27}BF_2NO_7S$ (MH^+) 570.1564, found 570.1564. Anal. Calcd for $C_{28}H_{26}BF_2NO_7S$: C, 59.06; H, 4.60; N, 2.46, S, 5.63. Found: C, 58.94; H, 4.67; N, 2.64, S, 5.73.

*6-(N-(4-Borono-3-fluorobenzyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylic Acid (**21**).* To a 2 L reactor were added 53.0 g (93.1 mmol) of **11**, 530 mL of MeOH, and 265 mL of water at ambient temperature. The white slurry was treated with 11.4 g (205 mmol) of KOH. The resultant clear solution was heated to 60 °C and stirred for 4 h. The reaction was cooled to ambient temperature and stirred overnight. An additional 3.12 g (5.56 mmol) of KOH was added due to the incompletion, and the mixture was stirred at 60 °C for 1.5 h.

The mixture was concentrated to about 400 mL by distillation in vacuo. After being cooled to ambient temperature, the mixture was treated with 500 mL of water and 500 mL of EtOAc. Layers were separated, and the aqueous layer was washed with 2 × 200 mL of EtOAc. The organic layers were discarded, and the aqueous layer was cooled to 10 °C and acidified to pH 1.0 with ~200 mL of 1 N HCl and 5.5 mL of concentrated HCl. The resultant solids seemed not suitable for filtration, so the mixture was extracted with 350 and 200 mL of EtOAc successively. The combined EtOAc extracts were washed with 200 mL of brine and concentrated in vacuo to dryness. After addition of 150 mL of EtOH, 50 mL of water, 15 mL of acetone, 2.0 mL of acetic acid, and 5 mg of seeds of **21** previous prepared in smaller scale, the solution was stirred overnight at ambient temperature for crystallization. The mixture was cooled to 0 °C, stirred for 1 h, filtered, washed with 80 and 50 mL of 1:1 EtOH/water successively, and dried at 60 °C in vacuo to give 38.3 g (76%) of **21** as an off-white crystalline solid: mp 135.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.1 (s, 1 H), 8.12 (s, 1 H), 8.05 (t, J = 8.0 Hz, 2 H), 7.84 (s, 1 H), 7.52 (m, 1 H), 7.45 (m, 1 H), 7.36 (m, 3 H), 7.02 (dd, J = 10.0, 8.0 Hz, 2 H), 4.90 (ABq, $\Delta\delta_{AB}$ = 0.14, J_{AB} = 16.0 Hz, 2 H), 3.24 (s, 3 H), 2.27 (m, 1 H), 0.98 (m, 1 H), 0.75 (m, 2 H), 0.23 (m, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.0, 164.7, 162.4, 160.4, 151.4, 140.8, 136.6, 135.9, 132.4 (d, J = 10.0 Hz), 127.6, 126.0, 124.8, 116.8, 115.9 (d, J = 22.0 Hz), 112.2, 109.4, 56.5, 54.9, 38.5, 19.0, 12.0, 11.3, 9.1. HRMS (APCI) calcd for $C_{26}H_{23}BF_2NO_7S$ (MH^+) 542.1251, found 542.1253.

*5-Cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-nitrobenzofuran-3-carboxamide (**19**). A. Amidation from **6** via Enamine Lactone **22** in Methylamine/EtOH.* To a 1 L reactor calorimetry vessel were successively added 35.0 g (94.7 mmol) of ester **6**, 245 mL of 33 wt % methylamine in ethanol, and 105 mL of absolute ethanol at ambient temperature. The well-stirred heterogeneous mixture was heated at 57 °C for 28 h. The pressure was about 0.7 bar due to the heating of the methylamine. After being cooled to 0 °C over 30 min, the mixture was stirred for 1 h, filtered, and washed with 2 × 70 mL of MeOH. The filtering cake was dried at 60 °C in vacuo to give 23.7 g (71%) of amide product **19** as a light yellow crystalline solid: mp 249.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1 H), 7.92 (t, J = 8.0 Hz, 2 H), 7.74 (s, 1 H), 7.25 (t, J = 8.0 Hz, 2 H), 5.82 (s, 1 H), 3.04 (d, J = 4.0 Hz, 3 H), 2.49 (m, 1 H), 1.09 (dt, J = 6.0, 7.8 Hz, 2 H), 0.76 (dt, J = 6.0, 7.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 163.5, 162.9, 157.7, 150.6, 148.5, 134.4, 131.5, 130.6 (d, J = 8.0 Hz), 124.7, 121.1, 116.4 (d, J = 21.0 Hz), 112.5, 108.0, 26.7, 13.6, 7.5. HRMS (ESI) calcd for $C_{19}H_{16}FN_2O_4$ (MH^+) 355.1089, found 355.1084. Anal. Calcd for $C_{19}H_{15}FN_2O_4$: C, 64.40; H, 4.27; N, 7.91. Found: C, 64.17; H, 4.27; N, 7.80.

*B. Amidation from **6** through Hydrolysis and Coupling with Methyamine Hydrochloride.* A mixture of 500 mg (1.35 mmol) of **6** and 152 mg (2.71 mmol) of KOH in 15 mL of 2:1 EtOH/water was heated to 80 °C. The solution was stirred for 20 min, cooled to room temperature, and evaporated in vacuo to remove most of the ethanol. After being treated with 5 mL of 1 N HCl, the resultant solids were filtered, washed with 2 × 5 mL water, and dried at 50 °C to give 480 mg of the carboxlic acid intermediate as a white solid. To this solid were successviely added 700 mg (1.85 mmol) of *O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU), 142 mg (2.11 mmol) of methylamine hydrochoride, and 3.5 mL of DMF. The mixture was stirred for 3 min at room temperature to form a solution, followed by addition of 0.60 mL (3.43 mmol) of *N*,*N*-diisopropylethylamine. After being stirred for 30 min, the reaction was quenched with 8 mL of water, filtered, washed with 2 × 5 mL of water, and dried at 60 °C to give 470 mg (97%) of **19** as a solid which was identical to the same product prepared from method A by ^{1}H NMR and HPLC. The compound prepared with method B was also converted to target compound **1**.

*(Z)-5-Cyclopropyl-3-((4-fluorophenyl)(methylamino)methylene)-6-nitrobenzofuran-2(3H)-one (**22**).* To a mixture of 3.00 g (8.12 mmol) of **6** and 9 mL of EtOH was added 21 mL of 33 wt % methylamine in EtOH at room temperature for 5 h. The reaction remained heterogeneous throughout the reaction. After being cooled to 0 °C, the mixture was filtered, washed with 2 × 5 mL of EtOH, and dried at 60 °C to give 2.36 g (82%) of **22** as a yellow solid. Alternatively, the reaction was run with 1.00 g (2.70 mmol) of **6** in 10 mL of 33 wt % methylamine in EtOH without additional EtOH added. The reaction was faster without the added EtOH and reached completion after 40 min. Filtering, washing with 5 mL of MeOH, and drying at 60 °C provided 734 mg (76%) of **22** isolated as a crystalline solid: mp 220.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1 H), 7.47 (s, 1 H), 7.23−7.24 (m, 4 H), 5.25 (s, 1 H), 2.82 (d, J = 4.0 Hz, 3 H), 2.12 (m, 1 H), 0.65 (dt, J = 6.0, 7.8 Hz, 2 H), 0.00 (dt, J = 6.0, 7.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 165.3, 164.7, 162.8, 146.2, 145.5, 134.2, 131.4, 129.6 (d, J = 8.0 Hz), 127.1, 117.4 (d, J = 22.0 Hz), 115.7, 106.6, 89.4, 31.5, 13.4, 7.4. HRMS (ESI) calcd for $C_{19}H_{16}FN_2O_4$ (MH^+) 355.1089, found 355.1083. Anal. Calcd for $C_{19}H_{15}FN_2O_4$: C, 64.40; H, 4.27; N, 7.91. Found: C, 64.34; H, 4.41; N, 7.77. Crystal data: $C_{19}H_{15}FN_2O_4$; M = 354.33; yellow block; crystallization from synthetic route in ethanol; 0.08 × 0.05 × 0.03

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mm^3; monoclinic; space group, $P2_1/c$ (No. 14); unit cell dimensions, a = 7.9217(15) Å, b = 20.462(6) Å, c = 9.881(2) Å, β = 100.377(18)°, V = 1575.5(6) Å^3; Z = 4; d_{calc} = 1.494 Mg m^{-3}; and μ(Cu Kα, λ = 1.541 78 Å) = 0.959 mm^{-1}.

*(4-(((5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)-benzofuran-6-yl)amino)methyl)-2-fluorophenyl)boronic Acid (**23**).* To a solution of 500 mg (1.4 mmol) of **19** in 7.5 mL of THF was added 5% Pt/alumina (0.05 g). A hydrogen filled balloon was inserted, and the mixture was stirred at room temperature for 24 h. The reaction was heated to 60 °C to ensure full dissolution of the product, and the catalyst was removed via filtration through a short pad of Celite. The Celite pad was washed with 2.5 mL of hot THF. HPLC analysis of the filtrate showed 99.5% product. That was carried into the next reaction without isolation.

A solution of crude amino intermediate from a hydrogenolysis reaction (4.58g, 14.7 mmol, assuming 100% yield from the hydrogenolysis) in THF was concentrated in vacuo to 25 mL. To the solution were successively added 2.72 g (16.2 mmol) of aldehyde **12**, 2.52 mL (44.2 mmol) of acetic acid, and 35 mL of ethanol. After reduction of the volume to 15 mL via atmospheric distillation, 35 mL of ethanol was added. The volume was again reduced to 15 mL via atmospheric distillation, followed by addition of 35 mL of ethanol. GC analysis showed 95% ethanol in the mixture. The mixture was treated with 1.57 g (16.9 mmol) of borane-pyridine complex at 70 °C. Analysis by HPLC showed the reaction mostly complete at the end of the addition. An additional 0.2 g (2.2 mmol) was added, and the reaction was stirred at 70 °C for 30 min. The reaction was quenched with 9.2 mL of water and stirred at 70 °C for 1 h, followed by addition of 20 mL of ethanol to improve the stirring. After being cooled to room temperature, the mixture was filtered, washed with 25 mL of ethanol, and dried in vacuo at 50 °C to provide 5.94 g (87%) of **23** as a white solid: mp 196.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.90 (s, 1 H), 8.27 (m, 1 H), 7.83 (m, 2 H), 7.51−7.71 (m, 1 H), 7.20−7.29 (m, 3 H), 7.15 (s, 1 H), 7.09 (dd, J = 18.0, 8.0 Hz, 2 H), 6.52 (m, 1 H), 3.58 (s, 1 H), 3.18 (s, 2 H), 2.81 (m, 3 H), 1.81 (m, 1 H), 1.00 (m, 2 H), 0.60 (m, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.1, 164.4, 163.5, 161.1, 153.9, 148.9, 146.8, 145.3, 135.8, 128.8 (d, J = 8.0 Hz), 127.0, 124.9, 122.6 (m), 119.4, 116.2 (m), 114.4, 113.7 (m), 91.8, 50.9, 49.1, 46.4, 26.0, 12.2, 6.2. HRMS (ESI) calcd for $C_{26}H_{24}BF_2N_2O_4$ (MH$^+$) 477.1792, found 477.1788.

*(4-((N-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)-benzofuran-6-yl)methylsulfonamido)methyl)-2-fluorophenyl)-boronic Acid (**1**). A. Ester Route (Scheme 3).* To a 2 L reactor were successively added 38.0 g (70.20 mmol) of **21**, 5.21 g (77.2 mmol) of methylamine hydrochloride, and 29.3 g (77.2 mmol) of *O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU), followed by 266 mL of DMF at ambient temperature. After being cooled to 10 °C, the solution was treated with 30.7 mL (175 mmol) of *N*,*N*-diisopropylethylamine (Hunig's base) over 5 min and stirred for 2 h. The reaction was quenched with 340 mL of water and 16.1 mL (281 mmol) of acetic acid, followed by addition of 380 mL of EtOAc at room temperature. Layers were separated, and the aqueous layer was back extracted with 160 and 100 mL of EtOAc successively. The combined orgnaic layers were successively washed with 160 mL of water, 160 mL of 0.5 N HCl, and 160 mL of brine, and filtered through 30 g of Celite 545.

The filtrate was returned to the reactor and concentrated in vacuo to about 100 mL. After addition of 300 mL of MeCN, the solution was further concentrated to 150 mL. After addition of 100 mL more MeCN, 50 mL of *n*-PrOH, and 45 mL of 0.25 N aqueous HCl, the mixture was heated to 35 °C to form a clear solution. About 10 mg of seeds of **1**, previously prepared in a smaller scale, was added, and this initiated crystallization immediately. The mixture was cooled to 10 °C over 30 min, stirred for 45 min, filtered, washed with 100 and 50 mL of 2:1 water/MeCN successively, and dried at 60 °C in vacuo to give 30.9 g (79%) of **1** as a white crystalline solid: mp 176.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41 (m, 1 H), 8.12 (s, 2 H), 7.93 (m, 2 H), 7.81 (s, 1 H), 7.44 (t, J = 8.0 Hz, 1 H), 7.34−7.38 (m, 2 H), 7.03 (dd, J = 18.0, 8.0 Hz, 1 H), 6.94 (s, 2 H), 4.88 (ABq, $\Delta\delta_{AB}$ = 0.12, J_{AB} = 18.0 Hz, 2 H), 3.24 (s, 3 H), 2.80 (d, J = 4.0 Hz, 3 H), 2.27 (m, 1 H), 0.96 (m, 1 H), 0.80 (m, 2 H), 0.29 (m, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.0, 164.6 (m), 163.5, 161.9, 153.6, 151.0, 140.7, 140.3, 136.4, 135.9 (d, J = 10.0 Hz), 129.8 (d, J = 8.0 Hz), 127.8, 126.1 (m), 124.8, 116.6 (d, J = 22.0 Hz), 115.9 (d, J = 10.0 Hz), 115.2, 113.9, 112.0, 54.9, 38.5, 26.6, 12.0, 11.2, 9.0. HRMS (ESI) calcd for $C_{27}H_{26}BF_2N_2O_6S$ (MH)$^+$, 555.1567, found 555.1565. Anal. Calcd for $C_{27}H_{25}BF_2N_2O_6S$: C, 58.50; H, 4.55; N, 5.05; S, 5.78. Found: C, 58.29; H, 4.66; N, 5.14; S, 5.69.

B. Amide Route (Scheme 6). To a solution of 2.00 g (4.20 mmol) of **23** in 4 mL of pyridine was added 2.00 mL (25.2 mmol) of MsCl at 0 °C. The reaction was stirred at 0 °C for 8 h. After being diluted with 8 mL of acetone, the reaction was quenched with 5 mL of water and acidified to pH < 7.0 with 2 mL of concentrated HCl. About 1 g of NaCl was added to saturate the aqueous layer. Layers were separated, and the aqueous layer was extracted with 16 mL of acetone. The combined organic layers were distilled in vacuo to 18 mL and heated to 50 °C. The solution was treated with 8 mL of water and seeded with crystals of **1** previously prepared from another route. After being stirred for 30 min, the mixture was treated with an additional 8 mL of water dropwise. The mixture was cooled to room temperature, filtered, washed with 8 mL of 1:1 acetone/water, and dried in vacuo at 50 °C to afford 2.07 g (89%) of **1** as a crystalline solid.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01598.

Crystallographic data (CIF)

NMR spectra for all new compounds, detailed NMR studies (NOESY and HMBC) for compound **22**, and full crystallographic tables (PDF)

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Notes

The authors declare no competing financial interest.

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