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Technical Note

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A Scalable Route to an Unusual 3,3-Dimethyl-2,3-dihydrobenzofuran Ring System Present in an HCV Drug Candidate

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Supporting Information

ABSTRACT: A scalable synthesis of a key intermediate used for the preparation of an HCV inhibitor containing an unusual dimethyldihydrobenzofuran ring is described. A key element for the successful completion of the synthesis was the correct ordering of a sequence of bromination, chlorination, and methylation to provide optimized selectivity and improved yield. A tin hydride-mediated ring closure was replaced with a more environmentally benign sulfuric acid-catalyzed Friedel–Crafts reaction. The overall yield for the preparation of the key intermediate was increased from less than 5 to 40%.

INTRODUCTION

Compound **12**, a potent inhibitor of hepatitis C virus (HCV) NS5B polymerase, was a potential development candidate for the treatment of HCV.[1] The conversion of aniline **11**, the final intermediate, to **12** had previously been developed and demonstrated to proceed in yields of up to 94% on a *g*-scale by our Discovery Chemistry colleagues (Scheme 1).[2] However, the existing synthesis of **11** was extremely problematic above a milligram scale.

The biggest issue in the Discovery Chemistry synthesis of **11** was the lack of regioselectivity in the nitration step, which resulted in a 1:1 mixture of **7** and isomer **8** from isomerically pure **6**. Isomer **8** presumably arises from *ipso*-substitution of **6**.[3] This mixture was chromatographically difficult to separate, and the isolated yield of **7** was only ∼30%. The lack of selectivity in the methallylation step, which gave approximately a 1:2:1 mixture of **2**, **3**, and dialkylated resorcinol, also resulted in a low yield of the desired product (40%). As a consequence, the overall yield of **12** from **1** was less than 5%. From a scale-up standpoint, the tributyltin hydride ring closure, the limited commercial availability of tribromoresorcinol, the microwave Suzuki reaction, and the four chromatographies were also undesirable.

RESULTS AND DISCUSSION

With the need for larger quantities of **12**, a new route was required as it seemed unlikely that the nitration reaction issues could be overcome. Our Discovery Chemistry colleagues had found that only the copper nitrate/acetic anhydride conditions provided any **7**, and exploration of a number of the reaction parameters had also failed to improve the selectivity. Consequently, several approaches to construct the 3,3-dimethyl-2,3-dihydrobenzofuran ring system were explored. Other than the tin hydride cyclization route, the two main alternative approaches described in the literature were a palladium-catalyzed ring closure[4] or a Friedel–Crafts alkylation with subsequent ring closure under basic conditions.[5] For the palladium route, preparation of an appropriately substituted substrate that could be elaborated into **10** was the main challenge. In the Friedel–Crafts approach, no alkylation was seen with either 1-bromo-2,4-difluoro-5-nitrobenzene (**13**) or 1-bromo-2,4-dimethoxy-5-nitrobenzene (**14**). Even elimination of the electron-withdrawing nitro group, as in **15**, failed to provide any of the desired alkylation product (Scheme 2). However, an approach based on Friedel–Crafts alkylation of the less sterically encumbered, more electron-rich, and readily available 4,6-dichlororesorcinol (**16**) was successfully developed (Scheme 3).

A mixture of **16** and methallyl chloride (5.4 equiv) were treated with sulfuric acid at 40–45 °C. This reaction was exothermic and, with no applied cooling, a slow addition of sulfuric acid was required to control the temperature. Additional methallyl chloride, added in two equal portions, followed by stirring overnight was needed for complete reaction. Likely some competing polymerization of the methallyl chloride under the strongly acidic conditions was occurring.[6] After the addition of water and cyclohexane, the organic phase was treated with 4 N potassium hydroxide and methanol to effect cyclization. Extraction with cyclohexane removed some polymeric material, and acidification followed by extraction provided crude **18** containing ∼7% of **19**. Removal of this impurity would be simplified if it could be converted to a more polar derivative. Unfortunately, preliminary attempts to derivatize the hindered alkyl chloride present in **19** were unsuccessful. Consequently, the dichloride was purified via a short plug of silica gel to provide 99% pure[7] **18** in ∼80% yield. This separation was considered very manageable on a multihundred gram scale, although a solution for pilot-plant scale would need to take advantage of the subsequent discovery that **18** was a solid. An alternative strategy for purification would be to investigate crystallization of salts of **18** and **19**.

Dechlorination of **18** using hydrogen, 10% palladium on carbon, and sodium acetate (2.5 equiv) in methanol then gave **4**. At atmospheric pressure, a loading of 22 w/w% of palladium catalyst was required to ensure complete reaction (Table 1). After removal of the catalyst by filtration, evaporation of the

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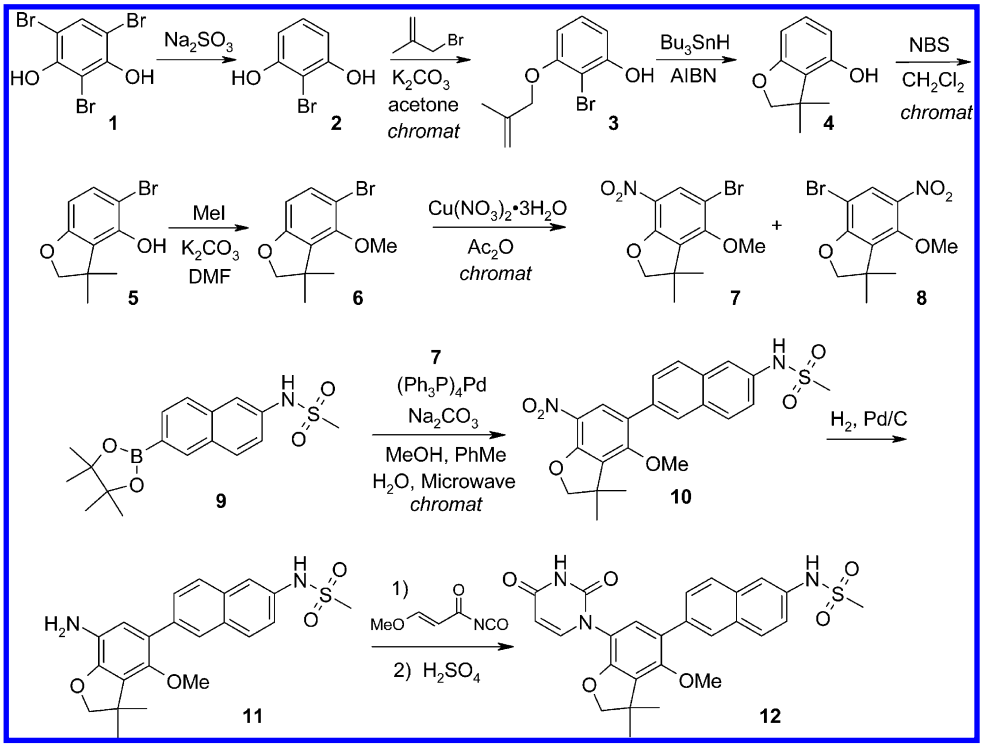
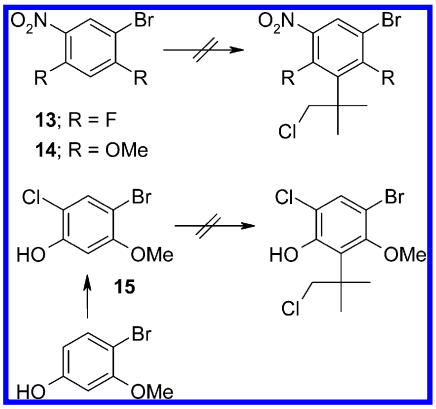
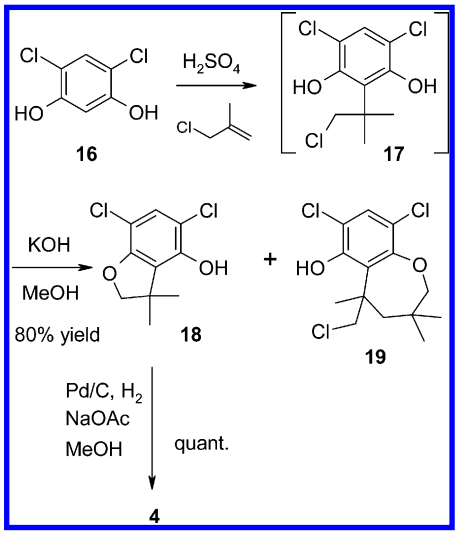
Scheme 1. Discovery chemistry route



Scheme 2. Initial Friedel-Crafts alkylation substrates



Scheme 3. 3,3-Dimethyl-2,3-dihydro-4-hydroxybenzofuran



methanol was followed by aqueous work-up with MTBE to provide **4** as an oil in quantitative yield.

Differential functionalization of the *ortho*- and *para*-positions of **4** was explored next.

Bromination of **4** was investigated in acetonitrile and dichloromethane using *N*-bromosuccinimide (NBS; 1.0 equiv). The halogenated solvent was more selective and, at 0−5 °C, provided an 89:9:2 mixture of *ortho*-, *para*-, and di-brominated products (Scheme 4, Table 2). The different partition coefficients of the potassium salts of the components of the reaction mixture permitted isolation of the desired product **5**. After partitioning the mixture in cyclohexane/methanol/potassium hydroxide, **5** was isolated in 88% yield and 94% purity; the major impurities were **20** (4%) and **21** (1.6%).

Unfortunately, as with the nitration of **6**, chlorination of **5** with *N*-chlorosuccinimide (NCS; 1.0 equiv) in dichloromethane resulted in significant scrambling (Scheme 4). Chlorination of **6**, prepared by methylation of **5**, gave a similar result.

Table 1. Dechlorination of 18

entry	scale (g)	10% Pd/C (w/w %)[a]	4 (%)[b]
1	0.2	10	70
2	1.8	22	100

[a]50% wet. [b]HPLC area % of **4**

Since the bromination−chlorination sequence was unsuccessful, chlorination−bromination of **4** was then examined (Scheme 5). Fortunately, treatment of **4** with NCS (1.0 equiv) in dichloromethane at room temperature was highly regioselective, and gave a 97:3 mixture of *ortho*- and *para*-isomers **24** and **25**. Chlorination in acetonitrile was less selective and provided a 70:16:14 ratio of **24**, **25**, and **18**. This was advantageously used to confirm the selectivity of the

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Scheme 4. Sequential bromination−chlorination of 4

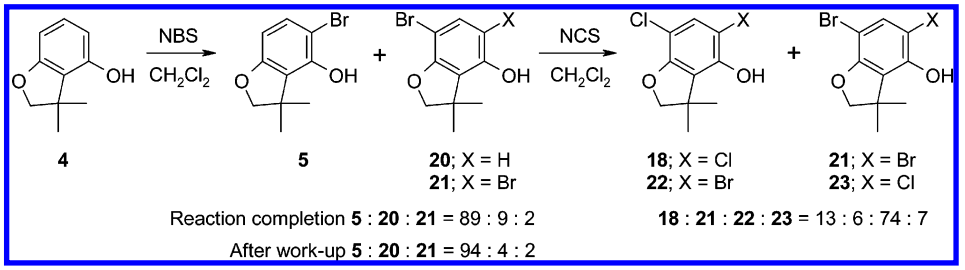


Table 2. Bromination of 4

entry	solvent	4 (%)[a]	5 (%)	20 (%)	21 (%)
1	CH_2Cl_2	0.4	89	9	1.6
2	MeCN	27	18	21	32

[a]Normalized HPLC area % of **4**, **5**, **20**, and **21**

dichloromethane chlorination since for the minor isomer an NOE was observed between the phenolic hydroxyl group and the *ortho* hydrogen.[8] Addition of NBS gave the differentially substituted phenol **23**.[9] However, none of the methylation conditions investigated subsequently provided **27**; LC/MS and ^{1}H NMR were consistent with formation of the dione **28**.[11]

Methylation, followed by bromination, was therefore explored as our next strategy. Since it precluded telescoping the halogenation reactions,[12] this approach was initially considered less attractive. Fortunately, it provided not only a successful route to **27** but also an improvement in purity due to the faster methylation of **24** over **25**.[13] During the work-up, the salt of unreacted **25** remained in the aqueous DMF phase, while product **26** was extracted into the heptane layer. After concentration, chloroanisole **26** was obtained as an oil in 99% HPLC purity. Bromination with NBS (1 equiv) in acetonitrile proceeded uneventfully to give 99% pure **27** as an oil in 90% yield from **4**. Thus, an efficient process to produce the densely substituted key intermediate **27** was achieved by the correct ordering of the chlorination, methylation, and bromination steps.

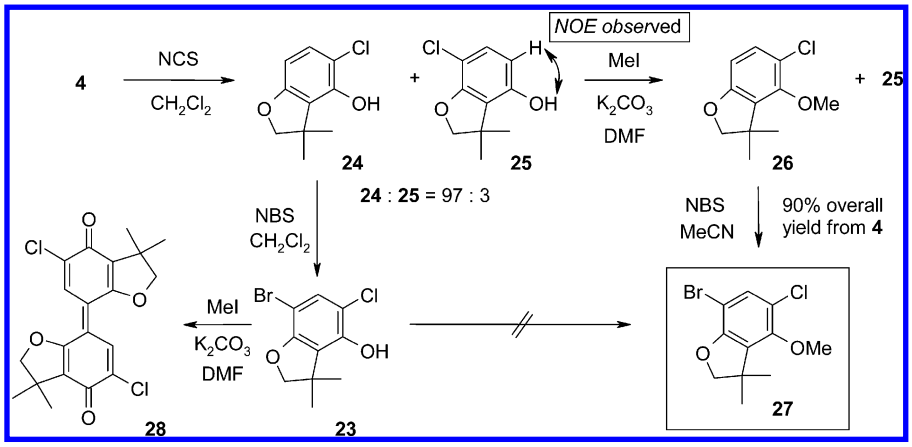
Counterintuitively, bromination of chloride **24** resulted in no halogen scrambling, in contrast to chlorination of bromide **5**.[14] One possible explanation could be the higher bond strength of C−Cl versus C−Br; a difference of ∼13 kcal/mol between the C−Br and C−Cl bond has been measured for bromo- and chloro-benzene.[15]

Elaboration of the substituted anisole **27** to the aniline **11**, the key intermediate in the Discovery Chemistry route, was achieved with sequential Buchwald−Hartwig amination followed by a Suzuki−Miyaura reaction (Scheme 6). Bromochloranisole **27** was coupled with *tert*-butyl carbamate by treatment with sodium *tert*-butoxide, $Pd_2(dba)_3$ and *t*-BuXPhos.[16] A satisfactory reaction was obtained using 5 mol % palladium in toluene for 10 min at 80 °C (Table 3), which minimized the loss of the *tert*-butyl group.[17] Extractive work-up and crystallization provided BOC protected aniline **29** in 77% yield.

Boronate **9** was next prepared by first treating 6-bromo-2-naphthylamine (**31**) with methanesulfonyl chloride and pyridine. For solubility reasons, tetrahydrofuran was the best solvent for this reaction, as compared to dichloromethane or toluene.[18] Methanesulfonamide **32** was isolated in >95% yield after drowning into water, which was preferred to adding water. The bromide was then converted to **9** by treatment with pinacol diborane, potassium acetate, XPhos, and palladium acetate in dioxane.[19] After heating to reflux for 3 h, the reaction was complete. Concentration to half volume, dilution with heptane, and filtration provided **9** in ∼80% yield.

The Suzuki−Miyaura reaction of **29** with boronate **9** using tripotassium phosphate, palladium acetate, and tricyclohexylphosphine in aqueous DMF proceeded at 80 °C to give **30**. These conditions had been used successfully in several related programs, although in this instance the reaction was more sensitive to air and thorough degassing prior to heating was critical. An excess of boronate **9** (1.3 equiv) was also required since it undergoes slow protodeboronation to **33**. Reducing the level of potassium phosphate to 1.2 equiv slowed the reaction

Scheme 5. 7-Bromo-5-chloro-4-methoxy-3,3-dimethyl-2,3-dihydrobenzofuran



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Scheme 6. Buchwald–Hartwig and Suzuki–Miyaura sequence

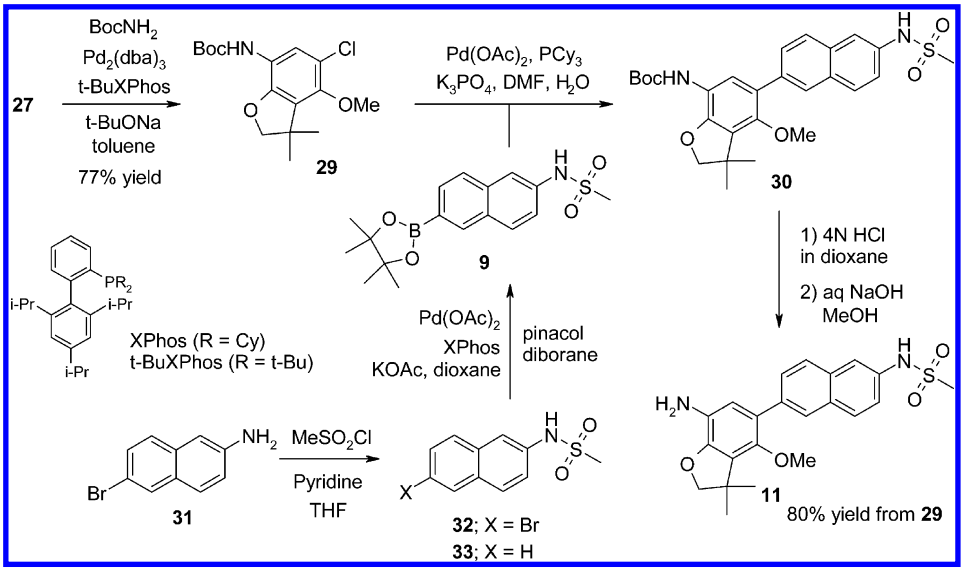

Table 3. Buchwald–Hartwig Amination

entry	scale (g)	solvent	temp. (°C)	*t*-BuXPhos (equiv)	$Pd_2(dba)_3$ (equiv)	**27** (%)[a]	**29** (%)
1	0.1	toluene	90	0.04	0.020	15	85
2	0.1	xylenes	100	0.04	0.020	30	70
3	1.0	toluene	80	0.07	0.025	10	90[b]

[a]HPLC area % normalized to **27** and **29**. [b]Isolated yield after crystallization was 77%.

and resulted in high levels of the protodeboronated side product, as well as dechlorinated **29**. In anhydrous Me-THF, protodeboronation was particularly troublesome, giving a mixture containing 90% of **33** and only 20% of product **30**. Work-up of the aqueous DMF reaction with ethyl acetate was followed with filtration of the organic phase through a plug of silica gel to remove some color. As some loss of the BOC group occurred during the coupling reaction, the deprotection step was conducted directly on the ethyl acetate solution of **30** using HCl at 50 °C. After cooling, the slurry was filtered to give the aniline hydrochloride in 96% purity. The freebase was prepared by dropwise addition of aqueous sodium bicarbonate (1.4 equiv) to a methanol solution of the aniline hydrochloride. After partial concentration of the slurry, filtration and a water wash provided pure aniline **11** in 80% yield from **29**.

CONCLUSION

Aniline **11** was prepared in 40% overall yield from cheap, commercially available dichlororesorcinol. The new route eliminated the major problem associated with the difficult chromatographic separation of **7** and **8**. Although halogen scrambling initially occurred, by first incorporating the chloro, rather than the bromo substituent, this effect was completely suppressed. The tributyltin hydride ring closure, originally used to construct the dimethyldihydrobenzofuran ring, was replaced with a more environmentally friendly sulfuric acid-promoted Friedel–Crafts alkylation. This synthetic sequence was not scaled beyond 1–10 g for most steps due to a change in the overall program direction. The remaining operations of this process do include some scale-challenged steps, such as the chromatography to remove **19**, but these should be amenable to further development, leading to a process suitable for the multikilogram scale.

EXPERIMENTAL SECTION

General Methods. Reactions were monitored by reverse phase HPLC (Zorbax Eclipse XDB C8 column, 4.6 mm × 50 mm, 1.8 μm particle size, 0.5 mL/min flow, detection at 220 nm, 5–100% acetonitrile/water containing 0.1% TFA over 10 min). HRMS was performed using an Orbitrap MSD (flow injection, 0.25 mL/min, detection at 250 nm, 80% acetonitrile/water containing 0.1% formic acid). LC/MS was performed using reverse phase HPLC with either a triple quadrupole detector (Zorbax Eclipse XDB C8 column, 3.5 mm × 50 mm, 1.8 μm particle size, 1.0 mL/min flow, detection at 220 nm with either a 5–100% or 30–100% MeCN/water containing 0.1% formic acid gradient over 10 min) or a single quadrupole detector (Zorbax Eclipse XDB C8 column, 3.5 mm × 50 mm, 1.8 μm particle size, 1.0 mL/min flow, detection at 220 nm with either a 5–100% or 30–100% MeCN/water containing 0.1% TFA gradient over 10 min).

*5,7-Dichloro-3,3-dimethyl-2,3-dihydrobenzofuran-4-ol (**18**).* To a mixture of 4,6-dichlorobenzene-1,3-diol (10 g, 55.9 mmol) and methallyl chloride (30 mL, 304 mmol) was added H_2SO_4 (5.48 g, 2.98 mL, 55.9 mmol) over 30 min at 40–45 °C. After 2 h, methallyl chloride (3 mL, 30.4 mmol) was added, followed 1 h later by additional methallyl chloride (3 mL, 30.4 mmol). The reaction mixture was stirred overnight, and diluted with cold water (50 mL) and cyclohexane (40 mL). The organic layer was separated and extracted with a mixture of 4 N KOH (30 mL) and MeOH (30 mL), which completed the cyclization of **17** to **18**. The aqueous phase was washed with cyclohexane (40 mL) and acidified with conc. HCl at 5 °C. Extraction with cyclohexane (100 mL, then 50 mL) was followed by washing the combined cyclohexane extracts with water (50 mL). Concentration gave an oil, which was purified by silica gel chromatography eluting with 0–10% EtOAc/hexanes to give **18** (10 g, 77% yield), which partially solidified upon standing: ^{1}H NMR (300 MHz, DMSO-d_6) 9.49 (br s, 1H), 7.24 (s, 1H), 4.29 (s, 2H), 1.38 (s, 6H); HRMS (ESI) *m/z* $[M - H]^-$ calcd for $C_{10}H_9O_2Cl_2$ 230.99741; Found 230.99878.

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*3,3-Dimethyl-2,3-dihydrobenzofuran-4-ol (**4**).* A mixture of **18** (1.8 g, 7.72 mmol) and NaOAc (1.58 g, 19.3 mmol) in MeOH (20 mL) was degassed with nitrogen. Then, 10% Pd/C (0.4 g, 50% wet) was added, and the mixture was stirred under an atmosphere of hydrogen for 20 h. The catalyst was removed by filtration and washed with methanol, and the combined filtrate/wash was concentrated. The residue was partitioned between water and MTBE. The organic layer was separated, washed with water, and concentrated to give **4** (1.3 g, 103% yield) as an oil: ^{1}H NMR (300 MHz, DMSO-d_6) 9.35 (s, 1H), 6.86 (apparent t, J = 7.91 Hz, 1H), 6.28 (dd, J = 8.10, 0.75 Hz, 1H), 6.19 (dd, J = 7.91, 0.75 Hz, 1H), 4.11 (s, 2H), 1.34 (s, 6H); HRMS (ESI) m/z $[M - H]^-$ calcd for $C_{10}H_{11}O_2$ 163.07536; Found 163.07664.

*5-Chloro-3,3-dimethyl-2,3-dihydrobenzofuran-4-ol (**24**).* To a solution of **4** (0.9 g, 5.48 mmol) in CH_2Cl_2 (14 mL) at rt was added NCS (732 mg, 5.48 mmol) in portions over 10 min. After stirring overnight, the mixture was concentrated, and the residue was partitioned between water (5 mL) and heptane (10 mL). The organic layer was washed with water (2 × 5 mL) and concentrated to give **24** (1.03 g, 95% yield) as a semisolid: ^{1}H NMR (300 MHz, DMSO-d_6) 9.18 (s, 1H), 7.05 (d, J = 8.48 Hz, 1H), 6.29 (d, J = 8.48 Hz, 1H), 4.18 (s, 2H), 1.37 (s, 6H); HRMS (ESI) m/z $[M - H]^-$ calcd for $C_{10}H_{10}O_2Cl$ 197.03638; Found 197.03772.

*5-Chloro-4-methoxy-3,3-dimethyl-2,3-dihydrobenzofuran (**26**).* To a slurry of **24** (1 g, 5.03 mmol) and K_2CO_3 (904 mg, 6.54 mmol) in DMF (6 mL) at rt was added CH_3I (346 μL, 5.54 mmol) dropwise. After 25 min, the mixture was partitioned between heptane (10 mL) and water (6 mL). The organic layer was separated and washed with water (2 × 6 mL) and then concentrated to give **26** (1.0 g, 93% yield) as an oil: ^{1}H NMR (300 MHz, DMSO-d_6) 7.19 (d, J = 8.55 Hz, 1H), 6.59 (d, J = 8.55 Hz, 1H), 4.21 (s, 2H), 3.85 (s, 3H), 1.38 (s, 6H); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{11}H_{14}O_2Cl$ 213.06768; Found 213.06708.

*7-Bromo-5-chloro-4-methoxy-3,3-dimethyl-2,3-dihydrobenzofuran (**27**).* To a solution of **26** (1 g, 4.7 mmol) in MeCN (10 mL) was added NBS (837 mg, 4.7 mmol). After 2 h at rt, the reaction was quenched with water and extracted with heptane (10 mL). The organic layer was separated and washed with water, then concentrated. Filtration through a silica gel plug eluting with 10% EtOAc/hexane removed some color. Concentration of the filtrate gave **27** (1.3 g, 95% yield) as a light-brown oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.50 (s, 1H), 4.32 (s, 2H), 3.86 (s, 3H), 1.39 (s, 6H).

*tert-Butyl 5-chloro-4-methoxy-3,3-dimethyl-2,3-dihydrobenzofuran-7-ylcarbamate (**29**).* A mixture of **27** (1 g, 3.43 mmol), *tert*-butyl carbamate (482 mg, 4.12 mmol) and *t*-BuONa (396 mg, 4.12 mmol) in toluene (10 mL) was degassed by evacuating and filling three times with nitrogen. $Pd_2(dba)_3$ (78.5 mg, 85.7 μmol) and 2-di-*tert*-butylphosphino-2′,4′,6′-tri-*iso*-propylbiphenyl (102 mg, 240 μmol) were added, and the mixture was heated to 80 °C over 10 min and stirred for 10 min. The reaction mixture was diluted with EtOAc and water, then filtered through a Celite pad. The organic layer was separated, washed with water, and concentrated. Filtration through a silica gel plug eluting with 6% EtOAc/hexane gave an oil, which was crystallized from heptane to give **29** (870 mg, 77% yield) as colorless crystals: ^{1}H NMR (300 MHz, DMSO-d_6) major rotamer 8.54 (s, 1H), 7.35 (br s, 1H), 4.23 (s, 2H), 3.82 (s, 3H), 1.43 (s, 9H), 1.37 (s, 6H); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{23}O_4NCl$ 328.13101; Found 328.13028.

*N-(6-Bromonaphthalen-2-yl)methanesulfonamide (**32**).*[18] To a solution of 6-bromonaphthalen-2-amine (10 g, 45.0 mmol) in THF (30 mL) was added pyridine (3.82 mL, 47.3 mmol) and, after cooling to 5 °C, methanesulfonyl chloride (3.68 mL, 47.3 mmol). The mixture was allowed to warm to rt overnight, then was poured into water (50 mL). After 2 h, the resulting solids were collected by filtration, washed with water (25 mL), and dried to give **32** (13.5 g, 100% yield): ^{1}H NMR (300 MHz, DMSO-d_6) 10.08 (s, 1H), 8.15 (d, J = 1.70 Hz, 1H), 7.89 (d, J = 8.85 Hz, 1H), 7.83 (d, J = 8.85 Hz, 1H), 7.70 (d, J = 1.88 Hz, 1H), 7.60 (dd, J = 8.85, 2.07 Hz, 1H), 7.42 (dd, J = 8.85, 2.26 Hz, 1H), 3.08 (s, 3H); HRMS (ESI) m/z $[M - H]^-$ calcd for $C_{11}H_9O_2NBrS$ 297.95319; Found 297.95441.

*N-[6-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]methanesulfonamide (**9**).* A mixture of **32** (5 g, 16.7 mmol), K_3PO_4 (9.81 g, 99.9 mmol), bis(pinacolato)-diboron (5.08 g, 20.0 mmol), 2-dicyclohexylphosphino-2′,4′,6′-tri-*iso*-propylbiphenyl (238 mg, 500 μmol), and $Pd(OAc)_2$ (74.8 mg, 333 μmol) in degassed 1,4-dioxane (30 mL) was heated in a 95 °C oil bath under a nitrogen atmosphere for 2.5 h. After cooling to rt, the slurry was diluted with 1,4-dioxane (70 mL), then filtered through a Celite pad. After washing with 1,4-dioxane (2 × 40 mL), the combined filtrate/washes were evaporated to dryness (7.4 g) then diluted with 1,4-dioxane (20 mL). After warming to dissolve the solids, heptane (30 mL) was added slowly. The addition was halted at the cloud point to initiate crystallization. After cooling slowly to 5 °C, the product was collected by filtration, washed with cold 2:1 heptane/dioxane (8 mL) and dried to give **9** (4.83 g, 84% yield): ^{1}H NMR (300 MHz, DMSO-d_6) 10.07 (s, 1H), 8.24 (s, 1H), 7.98 (d, J = 8.85 Hz, 1H), 7.80 (d, J = 8.10 Hz, 1H), 7.60−7.74 (m, 2H), 7.38 (dd, J = 8.76, 2.17 Hz, 1H), 3.08 (s, 3H), 1.33 (s, 12H); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{23}O_4NBS$ 348.14354; Found 348.14279.

*N-(6-(7-Amino-4-methoxy-3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)naphthalen-2-yl)methanesulfonamide hydrochloride (**11-HCl**).* A mixture of **29** (660 mg, 2.01 mmol), **9** (909 mg, 2.62 mmol), K_3PO_4 (855 mg, 4.03 mmol), $Pd(OAc)_2$ (18.1 mg, 80.5 μmol), and Cy_3P (45.2 mg, 161 μmol) was degassed by evacuating and filling three times with nitrogen. Degassed DMF/water (5:1 v/v, 6.6 mL) was then added, and the mixture was heated to 80 °C. After stirring for 6 h, the reaction mixture was diluted with EtOAc (5 mL) and water (6 mL) and then was filtered through a Celite pad. After the pad was washed with EtOAc (5 mL), the aqueous layer was separated, and the organic layer was washed with water. Filtration of the organic layer through a silica gel plug eluting with 50% EtOAc/heptane and concentration then gave **30** (1.03 g): LC/MS m/z $[M + H]^+$ 513. The residue was dissolved in EtOAc (10 mL) and treated with 4 N HCl in dioxane (2.5 mL, 10.0 mmol). The mixture was stirred at rt for 2 h, heated to 45 °C for 4 h, and then stirred at rt overnight. After heating for a further 3 h at 50 °C, the reaction mixture was cooled to rt, and the resulting solids were collected by filtration, washed with EtOAc, and dried by suction to give **11-HCl** (724 mg, 80% yield) as an off-white solid: ^{1}H NMR (300 MHz, DMSO-d_6) 10.45−9.45 (br, 2H), 10.06 (s, 1H), 7.86−8.04 (m, 3H), 7.72 (d, J = 1.70 Hz, 1H), 7.62 (dd, J = 8.57, 1.70 Hz, 1H), 7.42 (dd, J = 8.85, 2.07 Hz, 1H), 7.27 (s, 1H), 4.40 (s, 2H), 4.20−3.35 (br, 1H), 3.30 (s, 3H), 3.08 (s, 3H), 1.47 (s, 6H); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{25}O_4N_2S$ 413.15295; Found 413.15234.

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*N-(6-(7-Amino-4-methoxy-3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)naphthalen-2-yl)methane-sulfonamide (**11**).* Salt **11-HCl** (724 mg, 1.61 mmol) was dissolved in MeOH (10 mL), and saturated aqueous $NaHCO_3$ (2.0 mL) was added dropwise, during which time the free base crystallized out of solution. MeOH was removed partially under vacuum, and the solid was then collected by filtration, washed with water, and dried to give **11** (661 mg, 100% yield) as an off-white solid: ^{1}H NMR (300 MHz, DMSO-d_6) 9.96 (s, 1H), 7.76−8.04 (m, 3H), 7.58−7.76 (m, 2H), 7.38 (dd, J = 8.76, 2.17 Hz, 1H), 6.59 (s, 1H), 4.52 (br s, 2H), 4.21 (s, 2H), 3.21 (s, 3H), 3.06 (s, 3H), 1.42 (s, 6H); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{25}O_4N_2S$ 413.15295; Found 413.15247.[20]

■ ASSOCIATED CONTENT

Supporting Information

NOE spectra for the reaction products from the chlorination of **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(7) Purity refers to HPLC area %.

(8) See Supporting Information.

(9) Nitration of **24** or **26** was not investigated, so it is unknown if the scrambling seen in **6** would be suppressed. Developing safe nitration chemistry for large-scale use is more challenging due in part to the limited number of suitable solvents.[10] In addition, nitrated **26** produced a mutagenicity alert in an *in silico* Derek analysis.

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(12) Although this was not investigated, all the available evidence indicated that halogenation in a polar solvent like DMF would be less selective. Likewise methylation in dichloromethane was considered unlikely.

(13) The reason for the faster methylation is unclear. The hydroxyl group in **24** would appear more hindered than in **25**. Also, the pK_a of **25** is likely higher than in **24**, based on an analogy to 4- and 2-chlorophenol (9.41 and 8.56, respectively), leading to faster reaction for **25** if both **24** and **25** are fully ionized. The pK_a data were taken from Dissociation Constants of Organic Acids and Bases. In *CRC Handbook of Chemistry and Physics*, 94th ed. (Internet Version 2014) [online]: Haynes, W. M., Ed.; CRC Press/Taylor and Francis: Boca Raton, FL, 2013−2014; Chapter 5, pp 94−103. http://www.hbcpnetbase.com.

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