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Multigram Synthesis of BMS-929075, an Allosteric, Palm Site Inhibitor of HCV NS5B Replicase, Involving the Synthesis of a Highly Functionalized Benzofuran through a Telescoped Process

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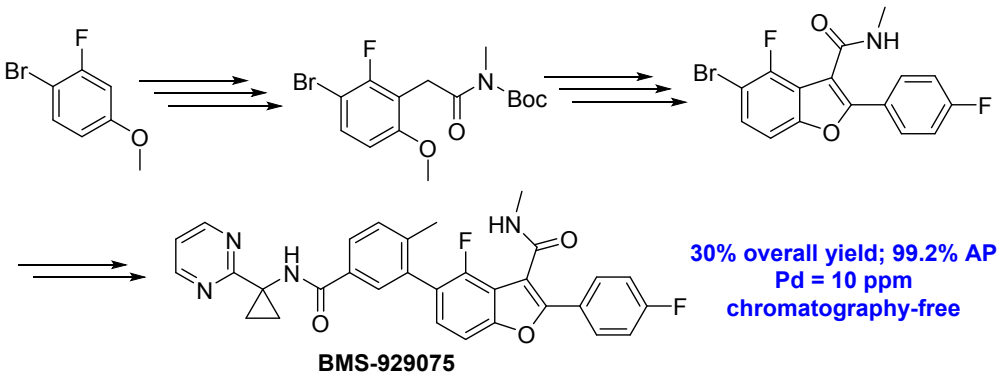
For TOC



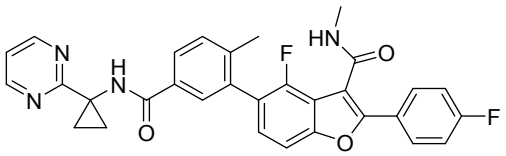
BMS-929075

ABSTRACT: An efficient scale-up synthesis of 4-fluoro-2-(4-fluorophenyl)-*N*-methyl-5-(2-methyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide (**BMS-929075**), an allosteric, palm site inhibitor of the HCV NS5B replicase is described. The highlights of the process involve: a) the copper-mediated, one-pot synthesis of 2-(3-bromo-2-fluoro-6-methoxyphenyl)acetic acid (**21**) from regio-specifically lithiated 1-bromo-2-fluoro-4-methoxybenzene (**13**) and ethyl 2-bromoacetate (**18**); b) formation of the highly functionalized benzofuran core **26** through a chromatography-free, telescoped process that proceeds *via* acylation and a subsequent concomitant demethylation and Boc deprotection using BBr_3, followed by an acid-catalyzed cyclization from Boc-protected 2-(3-bromo-2-fluoro-6-methoxyphenyl)-*N*-methylacetamide **23**. This process was applied to the preparation of 110 grams of high quality **BMS-929075** to enable preclinical toxicology studies.

KEYWORDS. HCV NS5B inhibitor, selective lithiation, benzofuran, one-pot, telescoped process

INTRODUCTION

BMS-929075 (Figure 1) is an allosteric, palm site inhibitor of the HCV NS5B replicase that was advanced into phase 1 clinical trials to assess its potential as a therapy for the treatment of hepatitis C virus (HCV) infection.[1] Preclinical studies with **BMS-929075** revealed that it exhibited high inhibitory potency in cell-based assays and demonstrated excellent oral bioavailability and pharmacokinetic properties. During the course of preclinical development of **BMS-929075**, over 100 grams of high quality API were needed to support toxicology and formulation studies.



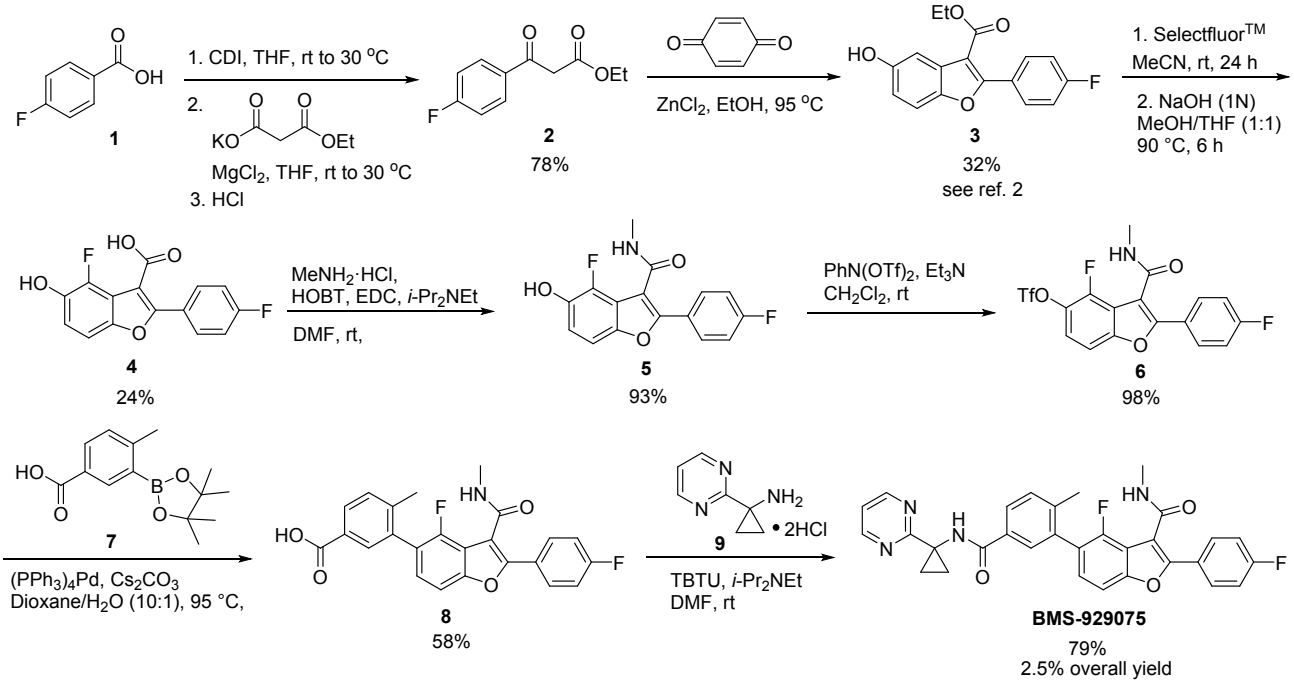
BMS-929075

Figure 1. Structure of **BMS-929075**

The medicinal chemistry approach to the preparation of BMS-929075 was straightforward and provided sufficient material for preclinical profiling that allowed its identification as a candidate for development. As

shown in Scheme 1, this route consisted of 10 steps originating from 4-fluorobenzoic acid (**1**) that involved 7 isolations and resulted in an overall yield of 2.5%. While a couple of low yielding steps were of some concern for large-scale preparation, the major challenge posed by this synthesis was the non-regiospecific fluorination of phenol intermediate **3**. The reaction of **3** with Selectfluor™ provided a mixture of the desired 4-F intermediate and the 6-F isomer in a ratio of approximately 3:1. After silica gel column chromatography to purify the crude reaction material, the inseparable mixture of the 4-F and 6-F isomers was subjected to ester hydrolysis using NaOH at 90 °C and pure **4** was isolated by preparative reversed-phase HPLC in 24% overall yield over the two steps from **3**. The tedious chromatographic purification and the low overall yield for these two steps rendered the discovery route unsuitable for scale-up to deliver the amount of high quality material required for preclinical development activities.

Scheme 1. Discovery Synthesis of BMS-929075

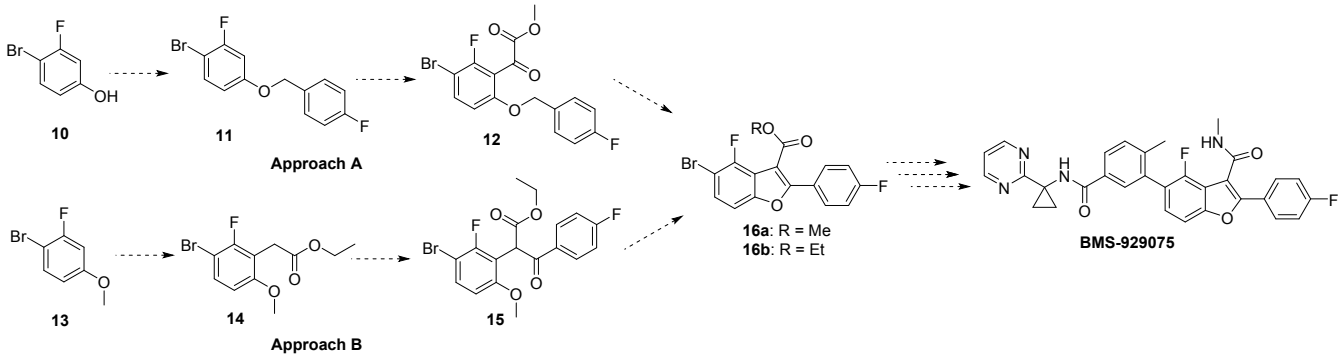


In order to deliver the required amounts of **BMS-929075** in a timely manner, the rapid development of a scalable process was required, the results of which are presented in this article.

RESULTS AND DISCUSSION

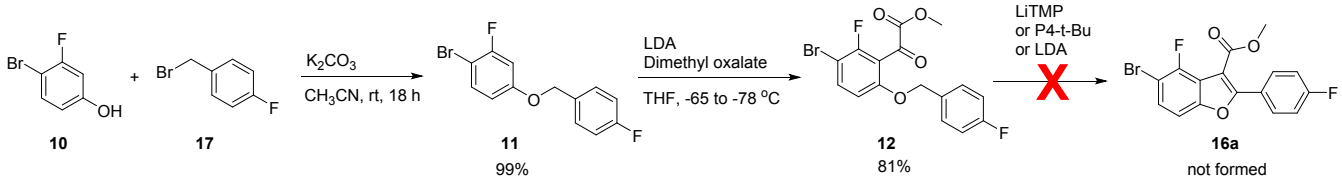
To avoid potential problems associated with the low yields and lack of regioselectivity in the fluorination of **3**, we began our new route design by searching for commercially-available fluorinated substrates, with 4-bromo-3-fluorophenol (**10**) and 4-bromo-3-fluoroanisole (**13**) particularly attractive starting materials. As illustrated in Scheme 2, two approaches to **BMS-929075** were proposed based on literature precedent that began from **10** and **13** and proceeded through the regioselective construction of the benzofurans **16a** and **16b**. Based on the results of the discovery synthesis (Scheme 1), the Suzuki coupling of triflate **6** with boronate ester **7** afforded product **8** in only a moderate 58% yield. The bromo substrates **16a** and **16b** would potentially allow for the milder reaction conditions associated with Suzuki coupling and provide higher yields. Following the original synthesis, no significant issues were anticipated for the transformation of **16a** or **16b** to **BMS-929075**. For approach A, the regioselective lithiation and acylation of **11** to **12** should be facilitated by both the fluorine and alkoxy directing groups.[3,4] Base-catalyzed cyclization of *ortho*-benzyloxybenzo ketones is a known process;[5] therefore, the formation of the bromo benzofuran **16a** from the corresponding methyl 2-(3-bromo-2-fluoro-6-((4-fluorobenzyl)oxy)phenyl)-2-oxoacetate (**12**) was anticipated to be facile. For approach B, the conversion of **13** to the aryl acetate **14** could be achieved through the selective lithiation of **13**, formation of the diorganocopper reagent (Ar_2CuLi) and then coupling with an α-halo acetate, such as ethyl bromoacetate.[6] α-Acylation of **14** with *para*-fluorobenzoyl chloride promoted by LiHMDS should afford β-keto ester **15**.[7] Finally, demethylation with BBr_3 and acid-catalyzed cyclization and dehydration would lead to the formation of the benzofuran **16b**.[8]

Scheme 2. **Initial Synthetic Approaches to BMS-929075 that Proceed through the Intermediacy of Bromo Benzofurans 16a and 16b**



The construction of the bromo benzofuran **16a** (approach A in Scheme 3) was investigated first. The alkylation of **10** with 1-(bromomethyl)-4-fluorobenzene (**17**) in the presence of K_2CO_3 in CH_3CN at rt for 18 h gave 1-bromo-2-fluoro-4-((4-fluorobenzyl)oxy)benzene (**11**) in 99% yield with 97% HPLC purity. The crude material **11**, isolated by an aqueous work-up, was used without further purification. Lithiation of **11** using LDA at -65 to -78 °C for 1 h followed by reaction with dimethyl oxalate afforded **12.** Following an aqueous work-up, pure compound **12** was obtained in 81% yield after crystallization from a mixture of EtOAc and heptane (1 : 20). No other regio-isomer was detected by LCMS. The cyclization reactions of **12** to **16a** were then examined. The cyclization of **12** to **16a** employing the literature conditions[5] proved to be problematic, with no detectable amounts of product **16a** or its corresponding acid produced when **12** was treated with LiTMP or P4-*t*-Bu or LDA as the base.[5c] Complex mixtures were observed and approach A was therefore abandoned.

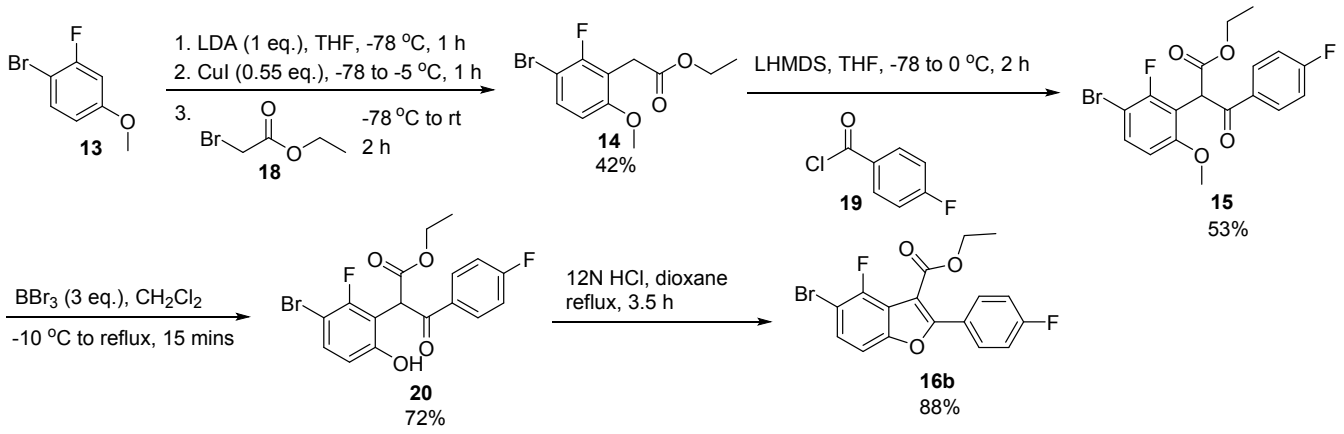
Scheme 3. Attempted Approaches A to Bromo Benzofuran 16a



Although approach A was not a viable option, we were particularly encouraged by the reaction profile associated with the regioselective lithiation and acylation of **11** to give **12**. Consequently, attention was directed toward the exploration of approach B (Scheme 4). On a 4 gram scale, deprotonation of **13** with LDA in THF at -78 °C followed by treatment with CuI (0.55 equiv) at -5 °C led to the Cu-Li intermediate as judged by the formation of a green solution. The addition of bromoacetate **18** to this solution followed by warming of the reaction mixture from -78 °C to rt afforded **14** as a colorless oil in 42% isolated yield after an extractive work-up and chromatographic purification. The addition of a solution of **14** (1 equiv) and 4-fluorobenzoyl chloride (**19**) (1.5 equiv) in THF to a 1M solution of LHMDS in THF at -78 °C afforded **15** as an oil that was a mixture of the keto and enol forms by ^{1}H NMR analysis. The product **15** was isolated in 53% yield and used for the next step without further purification. Treatment of the crude **15** with BBr_3 (3 equiv) in CH_2Cl_2 under reflux gave the product **20** in 72% isolated yield after an extractive work-up and purification by column chromatography. As expected, the

intermediate **20** was a mixture of the ketone and enol by LCMS and ^{1}H NMR in $CDCl_3$. Cyclization and dehydration of **20** to benzofuran **16b** was accomplished upon refluxing in a mixture of 12N HCl and dioxane to afford **16b**, which was isolated in 88% yield with 95% purity by a simple filtration after the reaction mixture was cooled to room temperature.

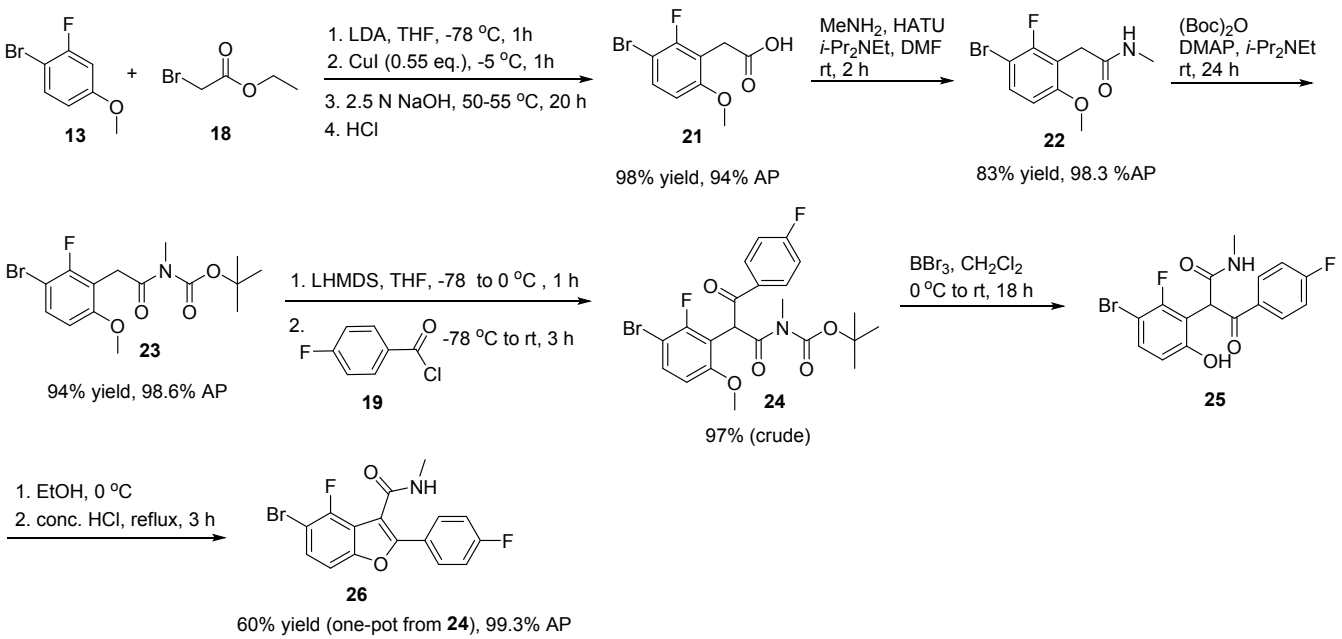
Scheme 4. Results of the Attempt to Exploit Approach B to Prepare Bromo Benzofuran 16b



While the preliminary results from exploring approach B were successful, the tedious chromatographic purification of compounds **14** and **20**, which resulted in low recovery and yields, presented a major problem for scale-up attempts. In order to surmount these scale-up issues, a modification of this route designed to avoid purification by chromatography was developed, as illustrated in Scheme 5. Based on the clean profile associated with the conversion of **13** to **14** and the oily nature of **14**, it was envisioned that a one-pot conversion of ester **14** to acid **21** might eliminate the need for chromatographic purification of **14** by taking advantage of either an acid/base extraction or crystallization. Indeed, after formation of ester **14**, treatment of the reaction mixture with a solution of 2.5N NaOH at 50-55 °C for 20 h led to the complete conversion of **14** to acid **21**. After filtration of the reaction mixture to remove the copper species, evaporation of the THF solvent, and extraction with CH_2Cl_2 to remove organic impurities, the aqueous solution was titrated with conc. HCl to precipitate **21**. Acid **21** was isolated by a simple filtration in 98% yield with 94% HPLC purity. This process was readily reproduced on multiple 100 gram scale reactions to yield more than 0.5 kg quantities of acid **21**. The subsequent procedures for the conversion of acid **21** to **22** and Boc-protection of the amide **22** to give **23** were also robust. Amide **22**

was conveniently isolated by precipitation and filtration while the Boc-protected derivative **23** was purified by crystallization, with each step allowing an upgrading of the purity of the material. The acylation of **23** with 4-fluorobenzoyl chloride (**19**) was promoted by LHMDS and cleanly gave keto amide **24** as an oil. Amide **24** existed as a mixture of the keto and enol tautomers which was confirmed by LCMS and ^{1}H NMR in $CDCl_3$. Due to the difficulties associated with purifying **24**, it was used directly as the crude material in the subsequent step. Demethylation and Boc deprotection of crude **24** proceeded smoothly with BBr_3 in CH_2Cl_2 at rt to give phenol **25** as a mixture of the ketone and its enol tautomer based on LCMS analysis of the reaction mixture. In order to avoid complications with the purification of **25**, which was a thick oil, a one-pot strategy to convert **25** to the benzofuran **26** directly without isolation was examined. After the complete conversion of **24** to **25**, as monitored by LCMS, the reaction mixture was treated with EtOH and the CH_2Cl_2 was removed. The residual mixture was treated with conc. HCl and heated at reflux for 3 hours to afford a suspension of **26** which was filtered off. The bromo benzofuran **26** was further purified by trituration from EtOH and isolated in 60% yield with 99.3% HPLC purity.

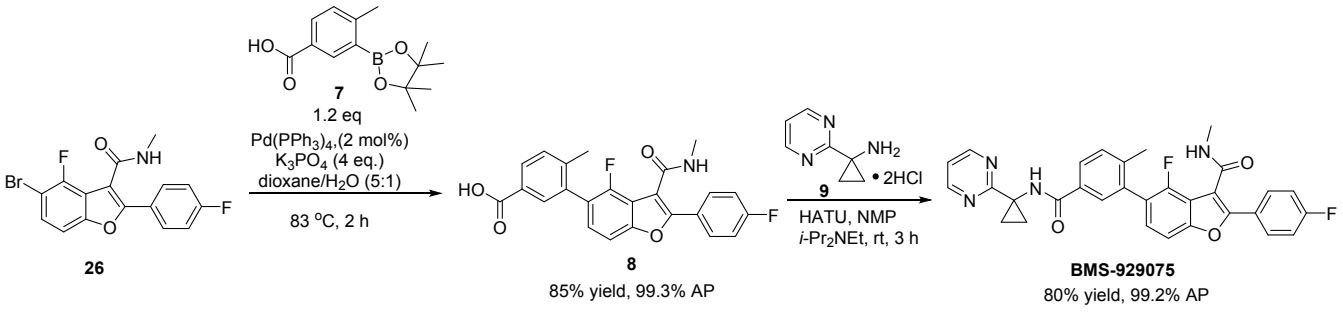
Scheme 5. Chromatography-free Preparation of Benzofuran 26



With a robust large-scale preparative procedure developed for the bromo benzofuran **26** in hand, the Suzuki coupling with 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (**7**) was investigated (Scheme 6). Using 1.2 equiv of **7** with tetrakis(triphenylphosphine)palladium(0) (2 mol%) as the catalyst and 4 equiv of K_3PO_4 as the base in a mixture of dioxane and H_2O (5:1) as solvent, the reaction proceeded at 50 °C to afford a 47% conversion in 3 h. However, at 83 °C, the reaction was complete in just two hours and afforded product **8** in 85% isolated yield. It is important to note that after precipitation of the crude product from the reaction mixture and filtration, hot trituration with EtOH followed by crystallization from EtOH was essential to improve the purity (up to 99.3%) and to reduce the Pd content to 48 ppm.

The final step in the preparation of **BMS-992075** required the installation of the amide moiety which was accomplished by coupling acid **8** with the dihydrochloride salt of 1-(pyrimidin-2-yl)cyclopropanamine (**9**) in a process promoted by HATU that proceeded cleanly both in DMF and NMP. However, precipitation of the product from reaction mixture by the addition of water gave a much better filterable slurry from NMP as the solvent compared to DMF. High quality API (99.2% HPLC, 10 ppm Pd content) was obtained by crystallization of **BMS-929075** from a mixture of EtOH and H_2O.

Scheme 6. Conversion of Benzofuran 26 to BMS-929075



Thus, the overall process to convert 1-bromo-2-fluoro-4-methoxybenzene (**13**) to **BMS-929075** required just 7 individual reaction procedures and 2 extractive work-ups and completely avoided chromatographic purification of any intermediate. Over 110 g of high quality **BMS-929075** was rapidly delivered through this route which proceeded in an overall yield of 30%.

CONCLUSION

In conclusion, an efficient, large-scale preparation of the clinical compound **BMS-929075** was developed. The synthesis was enabled by the regioselective lithiation of 1-bromo-2-fluoro-4-methoxybenzene (**13**) and copper-mediated alkylation. The formation of the benzofuran ring through an intramolecular cyclization of the keto phenol intermediate **25** was highly effective and a chromatography-free, telescoped process was developed to generate the highly functionalized key bromo benzofuran **26**. This new process provided **BMS-929075** with an overall yield of 30% which compared with the 2.5% yield achieved with the discovery synthetic route.

EXPERIMENTAL SECTION

All reagents were obtained from commercial sources and used without purification. All reactions were performed under a N_2 atmosphere and all glassware was dried and purged with N_2 before use. All reactions were monitored using a Shimadzu LCMS system using the following method: Phenomenex C18 column 10 µm 4.6 x 50 mm. Solvent: A = 10% MeOH/90% H_2O with 0.1% TFA; B = 90% MeOH/10% H_2O with 0.1% TFA. Gradient: 0-100% B over 4 min. Flow: 4 mL/min, wavelength: 220 nm. HPLC analyses were performed using a Shimadzu system (model SPD 10AV). All ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300 MHz or 500 MHz spectrometer using DMSO-d_6 or $CDCl_3$ as the solvents.

Preparation of 2-(3-bromo-2-fluoro-6-methoxyphenyl)acetic acid (21). 1-Bromo-2-fluoro-4-methoxybenzene (**13**) (103 g, 500 mmol) and anhydrous THF (500 mL) were added to a 3 L, three necked round bottom flask equipped with a mechanical stirrer. The solution was cooled to -78 ^{o}C with an IPA/dry ice bath and bubbled with N_2 for 10 minutes. A solution of lithium diisopropylamide (2M from Sigma-Aldrich Corporation, 1.05 equiv, 263 mL, 525 mmol) in THF was added dropwise over a period of 30 minutes while maintaining the temperature below -70 ^{o}C. The reaction mixture was stirred at -78 ^{o}C for 1 h and copper(I) iodide (52.4 g, 0.55 equiv, 275 mmol) was added. The reaction mixture was allowed to warm to -5 ^{o}C and stirred for 1 h to afford a dark green solution that was cooled to -78 ^{o}C before adding ethyl 2-bromoacetate (**18**) (57.0 mL, 500 mmol) dropwise over 30 minutes while maintaining the internal temperature below -70 ^{o}C. The reaction mixture was allowed to warm to rt over a period of 20 h. A solution of 2.5N NaOH (1 L) was added at rt and the reaction

mixture was heated to 50–55 °C for 20 h. After cooling to rt, the reddish suspension was filtered through a Celite pad and the pad was rinsed with a solution of 1N NaOH (100 mL). The filtrate was concentrated below 35 °C in vacuo to remove THF and the residual aqueous solution was washed with CH_2Cl_2 (2 x 500 mL). The basic aqueous layer was transferred to a 3 L, four necked round bottom flask and acidified with conc. HCl (270 mL) to adjust the pH to 1 with ice bath cooling to maintain the internal temperature below 30 °C. After the resulting suspension was cooled to 15 °C, the ice bath was removed, the mixture was stirred for 30 minutes and filtered. The filter cake was washed with H_2O (500 mL) and dried under house vacuum suction for 18 h to give 2-(3-bromo-2-fluoro-6-methoxyphenyl)acetic acid (**21**) (129.5 g, 492 mmol, 98% yield, 94% HPLC purity) as a slightly yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.46 (s, 1H), 7.56 (t, J = 8.6 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 3.80 (s, 3H), 3.58 (br s, 2H); ^{13}C NMR (75 MHz, DMSO–d_6) δ 170.36, 157.08 (d, J = 7.50 Hz), 156.12 (d, J = 240.75 Hz), 130.76 (d, J = 2.25 Hz), 112.21 (d, J = 19.50 Hz), 107.90 (d, J = 3.75 Hz), 97.78 (d, J = 22.75 Hz), 55.67, 27.83 (d, J = 3.00 Hz). LRMS m/z: $[M + Na]^+$ calcd for $C_9H_8BrFO_3$, 284.95; found, 284.96.

Preparation of 2-(3-bromo-2-fluoro-6-methoxyphenyl)-N-methylacetamide (22). A solution of 2-(3-bromo-2-fluoro-6-methoxyphenyl)acetic acid (**21**) (125 g, 475 mmol) in DMF (833 mL), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (217 g, 570 mmol) (added portionwise), *N*,*N*-di-isopropylethylamine (166 mL, 950 mmol), and a solution of methylamine (2M, 475 mL, 950 mmol) in THF were introduced into a 5 L, four necked round bottom flask with water bath cooling and overhead stirring to moderate the temperature which rose to 45 °C. The reaction mixture was stirred at rt for 2 h before slowly adding H_2O (2 L) over 30 minutes. The resulting suspension was stirred at rt for 1 h, filtered and rinsed with H_2O. The filter cake was dried by vacuum suction for 18 h to afford 2-(3-bromo-2-fluoro-6-methoxyphenyl)-*N*-methylacetamide (**22**) (108.5 g, 393 mmol, 83% yield, 98.3% HPLC purity) as a slightly yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (t, J = 8.4 Hz, 1H), 6.63 (dd, J = 9.0, 1.3 Hz, 1H), 5.49 (br s, 1H), 3.86 (s, 3H), 3.63 (d, J = 1.5 Hz, 2H), 2.78 (d, J = 4.8 Hz, 3H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 169.76, 157.78 (d, J = 7.6 Hz), 157.58 (d, J = 247.76 Hz), 131.85 (d, J = 2.28 Hz), 113.01 (d, J = 19.76 Hz), 107.60 (d, J = 3.04 Hz), 100.22 (d, J = 22.04 Hz), 56.22, 30.98 (d, J = 3.04 Hz), 26.43. LRMS m/z: $[M + H]^+$ calcd for $C_{10}H_{11}BrFNO_2$, 276.00; found, 276.01.

Preparation of tert-butyl 2-(3-bromo-2-fluoro-6-methoxyphenyl)acetyl(methyl)carbamate (23). A suspension of 2-(3-bromo-2-fluoro-6-methoxyphenyl)-*N*-methylacetamide (**22**) (106 g, 384 mmol) in CH_2Cl_2 (2 L), *N*,*N*-di-iso-propylethylamine (0.134 L, 768 mmol), 4-dimethylaminopyridine (46.9 g, 384 mmol) and di-*tert*-butyl dicarbonate (168 g, 768 mmol) were introduced into a three necked, 5 L round bottom flask equipped with a mechanical stirrer. The reaction mixture was stirred at rt for 24 h before being transferred to a 5 L separatory funnel. The reaction flask was rinsed two times with CH_2Cl_2 (100 mL) and the washings was added to the separatory funnel. The mixture was washed sequentially with 1N HCl (2 x 2 L), H_2O (2 x 2 L) and brine (2 L), dried over Na_2SO_4, filtered and concentrated in vacuo to give a yellow semi solid (~330 g) which was crystallized from heptane (500 mL) (reflux to -10 °C). The crystals were filtered and the filter cake was washed with cold heptane (-20 °C, 200 mL) to give *tert*-butyl 2-(3-bromo-2-fluoro-6-methoxyphenyl)acetyl(methyl)carbamate (**23**) (137 g, 359 mmol, 94% yield, 98.6% HPLC purity) as a slightly yellow solid after drying by vacuum suction over 3 days. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.8, 8.1 Hz, 1H), 6.56 (dd, *J* = 9.0, 1.3 Hz, 1H), 4.19 (d, *J* = 1.5 Hz, 2H), 3.76 (s, 3H), 3.13 (s, 3H), 1.54 (s, 9H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 172.31, 157.94, 157.60 (d, *J* = 245.48), 153.32, 131.28 (d, *J* = 2.28 Hz), 113.75 (d, *J* = 19.76 Hz), 107.25 (d, *J* = 3.04 Hz), 99.76 (d, *J* = 22.80 Hz), 83.13, 56.03, 33.05 (d, *J* = 3.80 Hz), 31.58, 28.00. LRMS m/z: $[M + Na]^+$ calcd for $C_{15}H_{19}BrFNO_4$, 398.04; found, 397.97.

Preparation of tert-butyl 2-(3-bromo-2-fluoro-6-methoxyphenyl)-3-(4-fluorophenyl)-3-oxopropanoyl(methyl)carbamate (24). A solution of *tert*-butyl 2-(3-bromo-2-fluoro-6-methoxyphenyl)acetyl(methyl)carbamate (**23**) (56.4 g, 150 mmol) in anhydrous THF (600 mL) in a three necked, 2 L round bottom flask was cooled to -78 °C with an IPA/dry ice bath and mechanical stirring. A solution of lithium bis(trimethylsilyl)amide (165 mL, 165 mmol) in THF was added over a period of 30 minutes while maintaining the temperature of the solution below -65 °C. The reaction mixture was warmed to 0 °C over a period of 30 minutes, stirred for 1 h at 0 °C under cooling using a wet ice bath and then cooled to -78 °C with an IPA/dry ice bath. 4-Fluorobenzoyl chloride (**19**) (26.16 g, 165 mmol) in anhydrous THF (75 mL) was added dropwise over a period of 30 minutes and the mixture was stirred at -78 °C for 1 h before being allowed to warm to rt over a period of 3 h. A saturated solution of NH_4Cl (600 mL) was added protionwise over 20 minutes

and the mixture was concentrated in vacuo to remove the majority of the THF. The residual mixture was extracted with EtOAc (2 x 450 mL). The combined organic extracts were sequentially washed with 1N HCl (450 mL), a saturated solution of $NaHCO_3$ (450 mL) and brine (450 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give crude *tert*-butyl 2-(3-bromo-2-fluoro-6-methoxyphenyl)-3-(4-fluorophenyl)-3-xopropanoyl(methyl)carbamate (**24**) (72.5 g, 145 mmol, 97% yield) as thick yellow oil which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.72 (m, 2H), 7.38 (dd, J = 8.8, 7.7 Hz, 1H), 7.05–6.91 (m, 3H), 6.55 (dd, J = 8.8, 1.5 Hz, 1H), 3.74 (s, 3H), 3.22 (s, 3H), 1.39 (s, 9H).s LRMS m/z: $[M - Boc + 1]^+$ calcd for $C_{17}H_{15}BrF_2NO_3$, 398.01; found, 398.00.

Preparation of 5-bromo-4-fluoro-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (26). A solution of *tert*-butyl 2-(3-bromo-2-fluoro-6-methoxyphenyl)-3-(4-fluorophenyl)-3-oxopropanoyl(methyl)carbamate (**24**) (74.7 g, 150 mmol) in CH_2Cl_2 (300 mL) in a four necked, 2 L round bottom flask equipped with a mechanic stirrer was cooled to 0 ^{o}C with a wet ice bath and a solution of 1M BBr_3 (450 mL, 450 mmol) in CH_2Cl_2 added dropwise over 50 minutes while maintaining the internal temperature below 10 ^{o}C. The reaction mixture was stirred while warming to rt over a period of 18 h at which point LCMS indicated the consumption of starting material and the formation of **25**. The red solution was cooled to 0 ^{o}C and 150 mL of absolute EtOH was added dropwise over 25 minutes while keeping the internal temperature below 15 ^{o}C. A solution of concentrated HCl (12N, 450 mL) was added to the reaction mixture in a fast stream via an addition funnel. A Dean-Stark apparatus and condenser were attached to the reaction flask and the reaction mixture was heated with a heating mantle to remove the CH_2Cl_2 azeotropically. After removal of the CH_2Cl_2, the Dean-Stark apparatus was removed and then the reaction mixture was refluxed for an additional 3 h before being cooled to rt. The light brown suspension was filtered and the filter cake was rinsed with H_2O (3 x 100 mL) and dried by vacuum suction for 40 minutes. The filter cake was suspended in 700 mL of EtOAc and the suspension was refluxed for 30 minutes. The resulting hot tan suspension was cooled to rt. The suspension was filtered and the filter cake was rinsed with EtOAc (100 mL), and then dried by vacuum suction for 18 h. 5-Bromo-4-fluoro-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide (**26**) (33.1 g, 90.4 mmol, 60% yield, 99.3% HPLC purity) was collected as a white solid. ^{1}H NMR (300 MHz, DMSO–d_6) δ 7.90 (br d, J = 4.4 Hz, 1H), 7.15-7.06 (m, 2H), 6.88-6.72

(m, 2H), 6.66-6.54 (m, 2H), 2.02 (d, *J* = 4.8 Hz, 3H); ^{13}C NMR (76 MHz, DMSO-d_6) δ 162.18 (d, *J* = 250.04 Hz), 161.87, 152.69 (d, *J* = 9.12 Hz), 151.19, 151.13 (d, *J* = 252.32 Hz), 128.27, 128.15, 124.13 (d, *J* = 3.04 Hz), 116.82 (d, *J* = 18.24 Hz), 115.58 (d, *J* = 22.04 Hz), 110.47, 108.78 (d, *J* = 4.56 Hz), 101.10 (d, *J* = 57.76), 25.44. LRMS m/z: $[M + H]^+$ calcd for $C_{16}H_{10}BrF_2NO_2$, 365.99; found, 365.99.

Preparation of 3-(4-fluoro-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid (8). 5-Bromo-4-fluoro-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (**26**) (60 g, 164 mmol), phosphoric acid, potassium salt (144 g, 664 mmol), dioxane (750 mL) and H_2O (145 mL) were added to a three necked, 1 L round bottom flask with mechanical stirring. The suspension was bubbled with N_2 for 5 minutes and then heated to 83 ^{o}C. 4-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (**7**) (52 g, 198 mmol) portionwise and tetrakis(triphenylphosphine)palladium(0) (3.83 g, 3.31 mmol) were added in one portion. After the reaction mixture was stirred at 83 ^{o}C for 2 h, the mixture was filtered hot through a thin layer Celite pad and the pad was rinsed with a solution of 20% H_2O in dioxane (2 x 150 mL). The filtrate was concentrated in vacuo to remove the dioxane and the resulting yellow slurry was diluted with H_2O (2 L) and acidified with conc. HCl (262 mL) with ice bath cooling. The suspension was stirred at 5 ^{o}C for 30 minutes, filtered and the filter cake was washed with H_2O (3 x 600 mL) before being dried by vacuum suction for 18 h. The dried filter cake was added to EtOH (600 mL) and the mixture was heated at reflux for 1 h. The hot solution was filtered through a Celite pad (to remove Pd content). The pad was rinsed with hot EtOH (2 x 90 mL) and the clear orange filtrate was gradually cooled to rt to afford a thick yellow suspension which was filtered. The filter cake was washed with cold EtOH (-20 ^{o}C, 2 x 75 mL) and dried under vacuum suction for 18 h to give 16.0 g of the product as the first crop. The second and third crops of product were obtained from the mother liquor by repeating the above crystallization procedure. The crops were combined to give 3-(4-fluoro-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid (**8**) (59.0 g, 140.0 mmol, 85% yield) as an off white solid. ^{1}H NMR (300 MHz, DMSO–d_6) δ 12.94 (br s, 1H), 8.73–8.65 (m, 1H), 7.97–7.88 (m, 3H), 7.78 (d, *J* = 1.5 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.51–7.31 (m, 4H), 2.79 (d, *J* = 4.4 Hz, 3H), 2.23 (s, 3H). LRMS m/z: $[M + H]^+$ calcd for $C_{24}H_{17}F_2NO_4$, 422.11; found, 422.17. Pd = 48 ppm.

Preparation of 4-fluoro-2-(4-fluorophenyl)-N-methyl-5-(2-methyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide (BMS-929075). 3-(4-Fluoro-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-5-yl)-4-methylbenzoic acid (**8**) (44 g, 104 mmol), 1-(pyrimidin-2-yl)cyclopropanamine di-HCl salt (**9**) (23.91 g, 115 mmol), NMP (300 mL) and *N*,*N*-di-iso-propylethylamine (72.7 mL, 418 mmol) were added to a four necked, 2 L round bottom flask and the mixture stirred mechanically at rt until it became a clear solution. O-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HATU) (47.6 g, 125 mmol) was added portionwise (no obvious exothermic reaction observed). The mixture was stirred at rt for 3 h and then H_2O (600 mL) was added over 10 minutes with stirring. The white suspension was stirred at rt for 1 h and filtered. The filter cake was washed with H_2O (3 x 100 mL) and dried under vacuum suction for 20 h. The filter cake was dissolved in EtOH (750 mL) under gentle reflux and the solution was filtered hot to remove a small amount of solid. H_2O (360 mL) was added to the hot filtrate over a period of 15 minutes (crystals formed at 62 ^oC). The suspension was gradually cooled to rt over a period of 2 h and then filtered. The filter cake was washed with cold EtOH (-20 ^oC, 50 mL) and dried under vacuum suction for 24 h to give 4-fluoro-2-(4-fluorophenyl)-*N*-methyl-5-(2-methyl-5-(1-(pyrimidin-2-yl)cyclopropylcarbamoyl)phenyl)benzofuran-3-carboxamide (**BMS-929075**) (45.2 g, 84 mmol, 80% yield, 99.2% HPLC purity) as a white solid. Mp 249.6 °C (by DSC). ^1H NMR (500 MHz, CD_3OD) δ 8.65 (d, *J* = 5.04 Hz, 2H), 7.96 (dd, *J* = 9.14, 5.36 Hz, 2H), 7.91 (dd, *J* = 8.04, 2.05 Hz, 1H), 7.85 (d, *J* = 1.89 Hz, 1 H), 7.54 (d, *J* = 8.51 Hz, 1H), 7.46 (d, *J* = 7.88 Hz, 1H), 7.33 (dd, *J* = 8.35, 7.09 Hz, 1H), 7.30 (t, *J* = 8.83 Hz, 2H), 7.23 (t, *J* = 4.89 Hz, 1H), 2.96 (s, 3H), 2.29 (s, 3H), 1.77 (m, 2H), 1.46 (m, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 171.48, 171.23, 167.11, 165.13 (d, *J* = 249.80 Hz), 158.38, 156.30 (d, *J* = 9.09 Hz), 154.14, 153.34 (d, *J* = 249.80 Hz), 142.48, 137.09, 133.40, 131.30, 130.92, 130.33, 130.26, 129.42 (d, *J* = 2.73 Hz), 128.42, 126.83 (d, *J* = 3.63 Hz), 124.47 (d, *J* = 15.44 Hz), 119.66, 118.01 (d, *J* = 20.90 Hz), 117.20 (d, *J* = 22.70 Hz), 112.11, 108.80 (d, *J* = 4.54 Hz), 38.24, 27.04, 20.57, 20.37; ^{19}F NMR (500 MHz, CD_3OD) δ -123.11 (s, 1F), 112.73 (s, 1F). Anal. calcd for $C_{31}H_{24}F_2N_4O_3$: C, 69.14; H, 4.49; N, 10.40. Found: C, 69.13; H, 4.56; N, 10.33. Pd = 10 ppm.

ASSOCIATED CONTENT

***Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: XX.XXX/acs.oprd.XXXXXX.

^{1}H and ^{13}C NMR spectra of compounds **21-23**, **26** and **BMS-929075**. ^{1}H NMR and LCMS of compound **24**. ^{1}H NMR of compound **8** and ^{19}F NMR of **BMS-929075**.

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) Yeung, K-S.; Beno, B. R.; Parcella, K.; Bender, J. A.; Grant-Young, K. A.; Nickel, A.; Gunaga, P.; Anjanappa, P.; Bora, R. O.; Selvakumar, K.; Rigat, K.; Wang, Y-K.; Liu, M.; Lemm, J.; Mosure, K.; Sheriff, S.; Wan, C.; Witmer, M.; Kish, K.; Hanumegowda, U.; Zhuo, X.; Shu, Y-Z.; Parker, D.; Haskell, R.; Ng, A.; Gao, Q.;

Colston, E.; Raybon, J.; Grasela, D. M.; Santone, K.; Gao, M.; Meanwell, Ni. A.; Sinz, M.; Soars, M. G.; Knipe, J. O.; Roberts, S. B.; Kadow, J. F. Discovery of a hepatitis C virus NS5B replicase palm site allosteric inhibitor (BMS-929075) advanced to phase 1 clinical studies. *J. Med. Chem.* **2017**, *60*, 4369−4385.

(2) Burns, C. J.; Del Vecchio, A. M.; Bailey, T. R.; Kulkarni, B. A.; Faitg, T. H.; Sherk, S. R.; BlackLedge, C. W.; Rys, D. J.; Lessen, T. A.; Swestock, J.; Deng, Y.; Nitz, T. J.; Reinhardt, J. A.; Feng, H.; Saha, A. K. Benzofuran compounds, compositions and methods for treatment and prophylaxis of hepatitis C viral infections and associated diseases. *World Patent Application* WO 2004/041201 A2, May 21, 2004.

(3) For alkoxy mediated ortho lithiation examples, see: (a) Mali, R. S.; Tilve, S. G. Useful synthesis of coumestans. *Synth. Commun.* **1990**, *20*, 1781-1791; (b) Hewawasam, P.; Meanwell, N. A. A general method for the synthesis of isatins: preparation of regiospecifically functionalized lsatins from anilines. *Tetrahedron Lett*. **1994**, *35*, 7303-7306; (c) Elliott, E. L.; Bushell, S. M.; Cavero, M.; Tolan, B.; Kelly, T. R. Total synthesis of nigellicine and nigeglanine hydrobromide. *Org. Lett.* **2005**, *7*, 2449-2451; (d) Marsini, M. A.; Reeves, J. T.; Desrosiers, J-N.; Herbage, M. A.; Savoie, J.; Li, Z.; Fandrick, K. R.; Sader, C. A.; McKibben, B.; Gao, D. A.; Cui, J.; Gonnella, N. C.; Lee, H.; Wei, X.; Roschangar, F.; Bruce Z. Lu, B. Z.; Senanayake, C. H. Diastereoselective synthesis of α-quaternary aziridine-2-carboxylates via aza-Corey-Chaykovsky aziridination of *N-tert*-butanesulfinyl ketimino esters. *Org. Lett*. **2015**, *17*, 5614-5617.

(4) Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, C. E. Fluorine as an ortho-directing group in aromatic metalation: generality of the reaction and the high position of fluorine in the Dir-Met potency scale. *Tetrahedron Lett*. **1992**, *33*, 7495-7498.

(5) (a) Chen, D. Y.-K.; Kang, Q.; T. Robert Wu, T. R. Modular synthesis of polyphenolic benzofurans, and application in the total synthesis of malibatol a and shoreaphenol. *Molecules* **2010**, *15*, 5909-5927; (b) Kraus, G. A; Gupta, V. A new synthetic strategy for the synthesis of bioactive stilbene dimers. A direct synthesis of amurensin H. *Tetrahedron Lett*. **2009**, *50*, 7180–7183; (c) Thasana, N.; Prachyawarakorn, V.; Tontoolarug, S.; Ruchirawat, S. Synthesis of aryl α-keto esters via the rearrangement of aryl cyanohydrin carbonate esters. *Tetrahedron Lett*. **2003**, *44*, 1019–1021.

(6) (a) Velkov, J.; Mincheva, Z.; Bary, J.; Boireau, G.; Fujier, C. A new route for the synthesis of 5-methoxychroman-3-one. *Synth. Commun.* **1997**, *27*, 375-378; (b) Oestreich, M.; Sempere-Culler, F.; Machotta, A. B. An enantioselective access to an anthracycline AB synthon by a desymmetrizing Heck cyclization. *Synlett*, **2006**, *18*, 2965–2968.

(7) For examples, see: (a) Chen, C-Y.; Dormer, P. G. Synthesis of benzo[*b*]furans via CuI-catalyzed ring closure. *J. Org. Chem*. **2005**, *70*, 6964-6967; (b) Ranatunge, R. R.; Garvey, D. S.; Janero, D. R.; Letts, L. G.; Martino, A. M.; Murty, M. G.; Richardson, S. K.; Young, D. V.; Zemetseva, I. S. Synthesis and selective cyclooxygenase-2 (COX-2) inhibitory activity of a series of novel bicyclic pyrazoles. *Bioorg. Med. Chem*. **2004**, *12*, 1357-1366; (c) Roy, O.; Riahi, A.; Henin, F.; Muzart, J. Catalysed asymmetric protonation of simple linear keto-enolic species − a route to chiral α-arylpropionic acids. *Eur. J. Org. Chem*, **2002**, *23*, 3986–3994.

(8) (a) Pahari, P.; Rohr, J. Total synthesis of psoralidin, an anticancer natural product. *J. Org. Chem*. **2009**, *74*, 2750–2754; (b) Adams, R.; Whitaker, L. Quinone imides. XXXIX. Adducts of quinone monoimides and conversion of active methylene adducts to benzofurans. *J. Am. Chem. Soc*. **1956**, *78*, 658–663.