Organic Process Research & Development

Full Paper

An Efficient Scale up Process for the Preparation of the APD334 Precursor 4-Chloromethyl-1-cyclopentyl-2-(trifluoromethyl)benzene

Dipanjan Sengupta, Tawfik Gharbaoui, Ashwin Krishnan, Daniel J. Buzard, Robert M. Jones, You-An Ma, Robert Burda, Antonio Garrido Montalban, and Graeme Semple

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.5b00038 • Publication Date (Web): 25 May 2015

Just Accepted

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

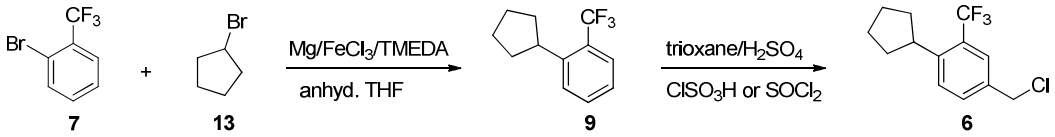
An Efficient Scale up Process for the Preparation of the APD334 Precursor 4-Chloromethyl-1-cyclopentyl-2-(trifluoromethyl)benzene

Dipanjan Sengupta, Tawfik Gharbaoui, Ashwin Krishnan, Daniel J. Buzard, Robert M. Jones, You-An Ma, Robert Burda, Antonio Garrido Montalban[*]*, Graeme Semple*

Medicinal Chemistry and Chemical Research & Development Departments, Arena Pharmaceuticals, Inc., 6154 Nancy Ridge Drive, San Diego, CA 92121, USA

[*]*Author to whom correspondence may be sent. E-mail: amontalban@arenapharm.com*

TOC Graphic


CF3
Br
7
+
Br
13
Mg/FeCl3/TMEDA
anhyd. THF
CF3
9
trioxane/H2SO4
ClSO3H or SOCl2
CF3
Cl
6

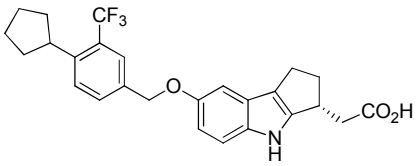
Abstract:

Synthetic studies of the APD334 precursor 4-chloromethyl-1-cyclopentyl-2-(trifluoromethyl)benzene (**6**) are described. A two-step scalable process was developed starting from commercially available and inexpensive starting materials. Iron (III) chloride catalyzed *aryl-alkyl* cross coupling reaction provided the 1-cyclopentyl-2-(trifluoromethyl)benzene intermediate **9** which was converted to the target building block **6** by a direct *regio* selective chloromethylation reaction with trioxane/thionyl chloride or chlorosulfonic acid in sulfuric acid. The process was transferred to pilot plant scale to produce >100 Kg of **6** with >98 area% HPLC purity.

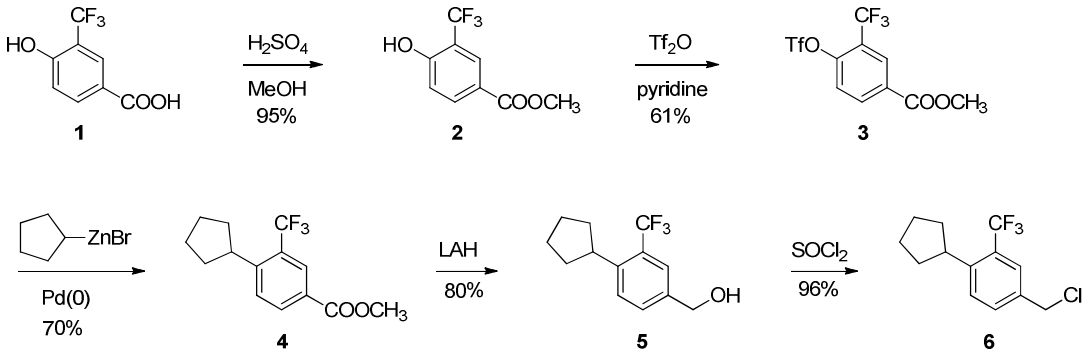
Keywords: APD334, scale-up, process, aryl-alkyl cross coupling, chloromethylation

We recently disclosed the structure of APD334 (Figure 1), our internally discovered $S1P_1$ functional antagonist currently in development for the treatment of autoimmune disease.[1] As part of the APD334 production campaign to support clinical development, we sought to identify a scalable synthetic route for the preparation of the benzyl chloride building block **6** (Scheme 1). Compound **6** was initially prepared utilizing the methods described in Scheme 1. 4-Hydroxy-3-(trifluoromethyl)benzoic acid (**1**) was converted to its methyl ester **2** which was in turn converted to the triflate **3** using triflic anhydride. Negishi coupling[2] with cyclopentyl zinc bromide in the presence of a palladium catalyst afforded the intermediate **4**. Subsequent lithium aluminium hydride reduction of the ester to the benzyl alcohol **5** and conversion to the corresponding chloromethyl group using thionyl chloride provided the desired building block **6**. While this synthesis was adequate for the small scale preparation of **6**, we had a number of concerns regarding the use of this route for larger scale batches of **6**.

Figure 1. APD334

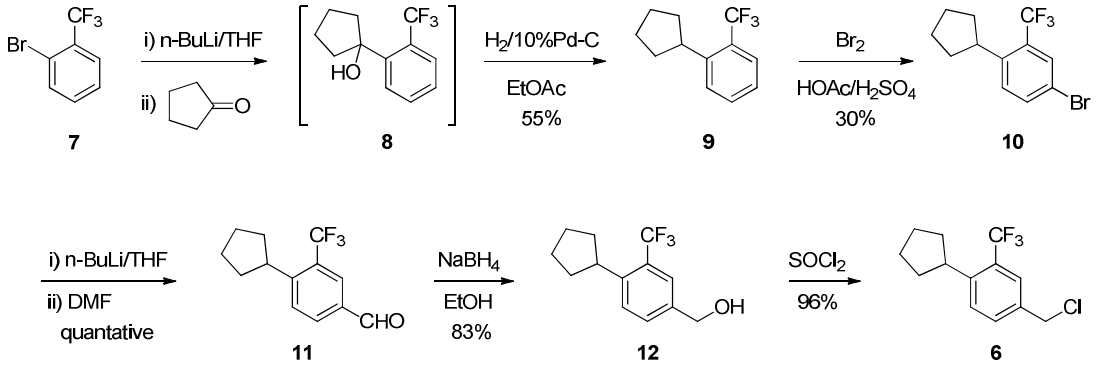


Scheme 1. Early synthesis of the building block 4-chloromethyl-1-cyclopentyl-2-(trifluoromethyl)benzene (**6**)



The starting substituted benzoic acid **1**, although commercially available, was expensive. Additionally, cyclopentyl zinc bromide and the palladium catalyst utilized in the Negishi reaction were cost prohibitive. Of further concern, the alkyl zinc reagent was obtained commercially as a 1.0M solution and would significantly impact the volume efficiency during scale up. Lastly, silica gel column chromatography was required to purify intermediate **4**. To address these issues, we investigated a second synthetic route (Scheme 2) aimed at providing multigram quantities of building block **6**.

Scheme 2. Initial approach for synthesis of the building block (4-chloromethyl-1-cyclopentyl-2-(trifluoromethyl)benzene (**6**)



This alternative synthesis started from the relatively cheaper (a recent quote from a competitive bulk supplier indicates that **1** is still 7-8 times more costly than 7) 1-bromo-2-(trifluoromethyl)benzene (**7**), which was lithiated (n-BuLi, -78 °C) and treated with cyclopentanone to afford the corresponding cyclopentyl adduct **8**. The crude adduct **8** was subjected to catalytic hydrogenation over palladium on carbon at 20 psi to obtain 1-cyclopentyl-2-(trifluoromethyl)benzene (**9**) in 55% yield (two steps).

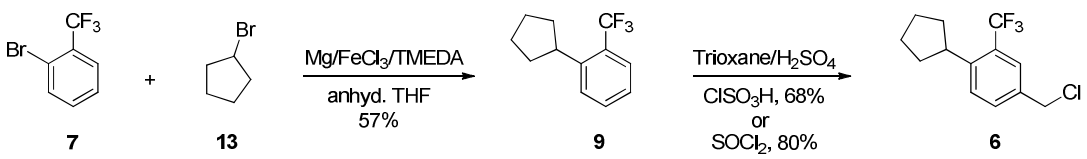
Selective aryl brominations have been reported using N-bromosuccinimide (NBS) or 1,3-dibromo-5,5-dimethylhydantoin (DBH) in either a mixture of concentrated sulfuric acid and acetic acid or trifluoroacetic acid alone.[3] Attempts to regioselectively brominate compound **9** using the reported methods did not produce acceptable results. Instead a selective, albeit modest yielding, bromination of **9** could be achieved utilizing bromine in

a mixture of acetic acid and sulfuric acid. This was carried out on a reasonable scale (190 g) and yielded the corresponding bromo benzene intermediate **10**. The aryl bromide intermediate was subsequently lithiated at -78 °C with n-BuLi/THF and treated with DMF to introduce the formyl group, thus providing compound **11** in essentially quantitative yield. Sodium borohydride reduction of the aldehyde intermediate **11** gave the corresponding benzyl alcohol **12** in 83% yield and subsequent chlorination with thionyl chloride provided the desired benzyl chloride **6** in 96% yield.

Despite having addressed some of the cost issues associated with the early synthesis, there remained considerable concerns regarding the scalability and robustness of our second route for the preparation of kilogram quantities of the building block **6**. For example, the bromination step was low yielding and the other steps entailed the use of highly reactive reagents under low temperature and high pressure conditions. While this route could potentially be adapted to scale, we sought to develop a much more robust, economical, and safe process for the manufacture of compound **6**. Toward this end, we explored the possibility of a shorter two-step process which is outlined in Scheme 3. The proposed route entailed a metal-catalyzed cross-coupling reaction to introduce the cyclopentyl moiety, followed by introduction of the chloromethyl moiety under acidic conditions in presence of trioxane and chlorosulfonic acid or sulfonyl chloride.

Direct introduction of the chloromethyl group was proposed as this has been demonstrated on biphenyls and 9, 10-dihydrophenanthrene.[4] Moreover, synthesis of 9, 10-dibromomethylanthracene was reported using trioxane in hydrobromic acid and acetic acid.[5] Our adaption of these approaches is described below to provide a 2-step synthesis of the target building block **6**.

Scheme 3. Two step synthesis of the building block 4-chloromethyl-1-cyclopentyl-2-(trifluoromethyl)benzene (**6**)



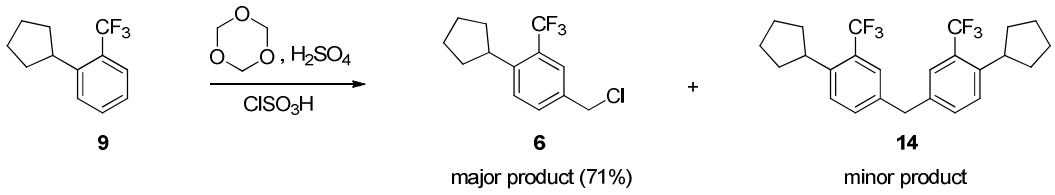
7 **13** **9** **6**

In the first step of the synthesis, 1-bromo-2-(trifluoromethyl) benzene (**7**) was coupled with bromo cyclopentane (**13**) in the presence of magnesium (20-325 mesh), Fe(III) chloride (anhydrous; Strem Chemicals) and TMEDA to obtain the intermediate **9** (Scheme 3). An effective methodology for direct cross coupling of aryl halides with alkyl halides in the presence of magnesium and Fe(III) chloride has recently been described.[6] Thus, a solution of ferric chloride in anhydrous THF was added to a slurry of magnesium in anhydrous THF and TMEDA (addition of TMEDA before or after $FeCl_3$ addition did not affect the reaction or product formation). Addition of the ferric chloride solution was moderately exothermic and the best results were obtained when the reaction temperature was maintained between 10-15 °C, followed by holding at 45 °C for 1h. Presumably, this additional heating time allows for complexation of ferric chloride, magnesium and TMEDA. Thereafter, a mixture of 1-bromo-2-(trifluoromethyl) benzene (**7**) and bromo cyclopentane (**13**) was added. Addition of these reagents was exothermic, and best results were achieved when the reaction temperature was maintained between 25-30 °C during the addition for several reasons. First, the reaction temperature limit was not allowed to exceed 30 °C due to safety considerations. The Grignard derived from **7** (Scheme 3, first step), for example, is known to violently decompose in the absence of solvent while in the presence of magnesium at temperatures as low as 40 °C.[7] Second, fast reaction kinetics were observed above 25 °C, thus, avoiding accumulation of the *in situ* generated aryl Grignard reagent that could result in a delayed and uncontrollable reaction exotherm. In our hands, no more than 20% accumulation of the aryl Grignard reagent was observed under the above conditions. Lastly, temperatures below 25 °C not only led to decrease reactivity but also to the formation of the aryl-aryl homocoupled product among other unidentified impurities, therefore, affecting the impurity profile. Qualitatively, within a temperature range of 25-30 °C, formation of the homocoupled product could be suppressed completely with the only identifiable impurities being starting material **7** and its debrominated analog (5-15 area% range by HPLC). The reaction mixture was allowed to stir overnight at 15 °C followed by quench with water then 6N HCl. After an extractive work up, the crude product was obtained as an oil and was purified by vacuum distillation to afford **9** as a near colorless oil (57%). After optimizing this process on several smaller

test batches, this cross-coupling reaction was initially employed on a 1.5 Kg scale and subsequently on a 25 Kg and 60 Kg scale.

Employing the protocols described in the literature,[4,5,8] only modest success was achieved for *regio* selective introduction of hydroxymethyl or chloromethyl motifs onto compound **9**. While no product formed from the acid catalyzed reaction of **9** with paraformaldehyde/DDQ, some success was met with trioxane/HBr or trioxane/HCl in the presence of $Sc(OTf)_3$. In both latter cases, however, the corresponding benzyl halides formed but substantial amounts of unreracted starting material **9** remained in the reaction mixtures. Notably, no method has been reported describing the direct introduction of a chloromethyl moiety onto a substituted mono-aromatic compound. We were, however, able to develop an efficient direct procedure for the synthesis of **6** from compound **9** in one step. The target building block **6** was ultimately synthesized in 71% yield by treating **9** with readily available and inexpensive sulfuric acid, trioxane, and chlorosulfonic acid at -20 to -10 °C (Scheme 4).

Scheme 4. Conversion of 1-cyclopentyl-2-(trifluoromethyl)benzene (**9**) to the building block 4-chloromethyl-1-cyclopentyl-2-(trifluoromethyl)benzene (**6**) using trioxane, H_2SO_4, and chlorosulfonic acid

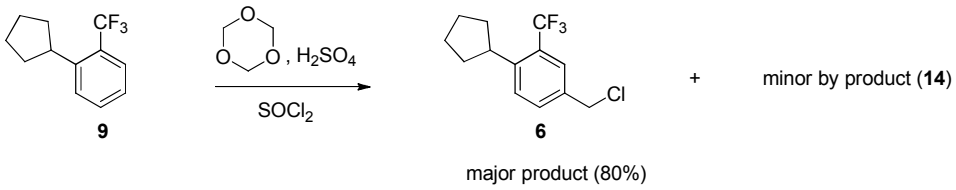


9 **6** major product (71%) **14** minor product

Chloromethylation experiments performed on 1-cyclopentyl-2-(trifluoromethyl)benzene (**9**) (200 g scale) required pre-cooling to -20 °C, followed by slow addition of sulfuric acid with efficient stirring. The moderate exotherm observed was controlled by efficient external cooling. Trioxane was then added portion wise at -20 to -19 °C. After completion of the trioxane addition, chlorosulfonic acid was charged slowly (again the addition was exothermic), while the reaction temperature was maintained between -20 to -15 °C. The reaction mixture was allowed to stir at -15 to -10 °C for a few minutes. During this time, a rapid exotherm was observed and the

temperature increased to 10 °C, and then gradually the exotherm subsided. The mixture was stirred at -5 to 0 °C for approximately 2h. LC/MS analysis showed complete consumption of **9** and formation of the desired product **6** (92.7 area%) and diarylmethane **14**[9] (7.3 area%). The diarylmethane by-product possibly arises from benzyl cation formation and rapid trapping by unreacted **9**. After aqueous quench and purification by vacuum distillation, the desired benzyl chloride **6** was isolated as an oil in 71% yield (>98 area% purity by HPLC), thus demonstrating that diarylmethane (main component of distillation residue) could be efficiently eliminated from the product mixture. Despite the successful conversion to compound **6**, major safety concerns still existed given the difficulty in controlling the exothermic events during and after the addition of chlorosulfonic acid. To address this safety concern, and to improve the overall efficiency of the process, the protocol was further modified. Thionyl chloride was substituted for chlorosulfonic acid (Scheme 5) and the order of addition was adjusted in order to minimize exothermic events.

Scheme 5. Optimized conversion of 1-cyclopentyl-2-(trifluoromethyl)benzene (**9**) to the building block 4-chloromethyl-1-cyclopentyl-2-(trifluoromethyl)benzene (**6**) using trioxane, H_2SO_4, and thionyl chloride



In the modified process, thionyl chloride was added to sulfuric acid at -5 to -3.5 °C, followed by trioxane in four equal amounts (-6.5 °C to -2 °C, portion wise addition) to mitigate the initial exotherm. Compound **9** (800 g) was then slowly added, maintaining the temperature between -5 to 0 °C. After addition, the reaction mixture was held overnight at 15 °C, and analyzed by LC/MS. Full conversion to **6** was observed with only a minor amount of the dimer by-product **14**. TLC of the reaction (5% ethyl acetate in hexane) showed only a major product spot and a minor spot corresponding to **14**, whereas

the starting compound **9** was not observed. After aqueous quench (exothermic) and MTBE extraction, the target compound **6** was obtained as an oil. The crude oil was purified by vacuum distillation to afford the desired benzyl chloride **6** in 80% yield with >98 area% purity by HPLC (*vide supra*). Again, this process was transferable to the pilot plant and successfully carried out on 24 Kg and 48 Kg of **9**, thus demonstrating it to be an effective method on scale for introduction of the requisite chloromethyl group.

Conclusion

A robust and efficient two-step process for preparation of the APD334 precursor 4-(chloromethyl)-1-cyclopentyl-2-(trifluoromethyl)benzene (**6**) has been demonstrated. An iron (III) chloride catalyzed cross coupling reaction was utilized to prepare the key 1-cyclopentyl-2-(trifluoromethyl)benzene (**9**) intermediate. A safe and direct chloromethylation procedure was developed utilizing trioxane, sulfuric acid, and thionyl chloride in order to afford the APD334 precursor **6**. This process was successfully transferred to the pilot plant and was utilized to manufacture a total of >100 Kg of **6** with >98 area% purity by HPLC.

Experimental Section

1-Cyclopentyl-2-(trifluoromethyl)benzene (9). Step 1. Under an inert atmosphere 1-bromo-2-(trifluoromethyl)benzene (**7**, 250 g, 1.11 mol) was transferred into a 5L 3-necked round bottomed (RB) flask equipped with a temperature probe, a mechanical stirrer and an addition funnel. Anhydrous THF (2 L) was transferred and stirred well. n-BuLi (2.5 M in hexanes, 487 mL, 1.218 mol) was added slowly at -65 °C (exothermic at the beginning of addition). During the n-BuLi addition the internal temperature was maintained within -64 to -65 °C. It was held at -65 °C for 45 min and sampled for LC/MS (analytical sample prepared after quenching with methanol). LC/MS analysis did not show presence of starting material, it showed the des-bromo analog of the starting material as the major peak, which indicated that lithiation was complete. A solution of cyclopentanone (112 g, 1.33 mol) in anhydrous THF (150 mL) was added dropwise (slow

addition; there was an initial exotherm) maintaining the internal temperature at -70 to -66 °C over 1h. The reaction mixture was held at -70 °C for 2h and sampled for LC/MS analysis. Product peak was observed (m/z = 213.4; M-H_2O) as the major component. The reaction temperature was raised to and maintained at 5-7 °C while the reaction mixture was slowly quenched with water (200 mL). 2N HCl (300 mL) was added slowly maintaining the internal temperature between 12 to 15 °C. The reaction was left overnight at room temperature. The pH of the reaction mixture was adjusted to 4-5 by slow addition of conc. HCl (45 mL) whereby two layers formed. The bottom aqueous layer was separated and extracted once with methylene chloride. The organic layer was concentrated under reduced pressure at 37-38 °C and 150 Torr. The residue was dissolved in methylene chloride (500 mL), combined with the previous methylene chloride layer, washed with water (2 X 300 mL), followed by brine (200 mL), dried (Na_2SO_4), filtered and the solvent removed under reduced pressure (bath temp. 37-38 °C; at 150 Torr) to afford an oil. Two more batches of compound **8** were prepared, starting from 256 g and 98 g of 1-bromo-2-(trifluoromethyl)benzene (**7**), respectively. The combined crude material was distilled under vacuum at 90-100 °C/2 Torr to give 364 g of **8**. The distillate was taken forward to the next step without further purification.

Step 2. A solution of 1-(2-(trifluoromethyl)phenyl)cyclopentanol (**8**) (364 g, 1.58 mol) in ethanol (1.4 L) was prepared. The solution was divided into two equal parts. The first portion of the solution (700 mL) was transferred into a 2L Parr pressure hydrogenation vessel and was hydrogenated for 2h at 20 psi in presence of 10% Pd-C (Degussa; 50% wet, 30 g). The second portion of the solution of **8** (700 mL) was hydrogenated as above at 20 psi for 2h. After hydrogenation, the combined reaction mixture was filtered through celite. The filtrate was poured into ice water (4L) stirred well and extracted with methylene chloride (2 X 1.4L). The combined methylene chloride layer was washed with water (1.6 L), dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to give product **9** as an oil (320 g, 55%). A sample of the product was purified by silica column for analytical data; ^{1}H NMR: (Bruker, 400 MHz, $CDCl_3$) δ 7.59 (d, J=8 Hz, 1H), 7.45-7.51 (m, 2H), 7.21-7.26 (m, 1H), 3.32-3.43 (m, 1H), 2.05-2.14 (m, 2H), 1.8-1.91 (m, 2H), 1.66-1.78 (m, 2H), 1.51-1.65 (m, 2H).

4-Bromo-1-cyclopentyl-2-(trifluoromethyl)benzene (10). 1-Cyclopentyl-2-(trifluoromethyl)benzene (**9**, 190 g, 0.887 mol) was transferred into a 5L 3-necked RB flask fitted with a mechanical stirrer, a temperature probe, an addition funnel and a base scrubber. Acetic acid (950 mL) was added and the mixture was stirred well. Bromine (320 mL, 6.21 mol) was added slowly maintaining the internal temperature below 15 °C (*exothermic*). Conc. sulfuric acid (950 mL) was added slowly (*exothermic*) *via* an addition funnel maintaining the internal temperature less than 40 °C. The reaction mixture was stirred at 45 °C for 2h. Analysis of the reaction sample by LC/MS showed a major product peak and no starting material left. The mixture was cooled to room temperature and stirred overnight. (*Note*: HBr evolution occurred during the reaction). The reaction was quenched by slowly pouring the mixture into ice water (3.5 L) with efficient stirring while maintaining the temperature below 20 °C. Excess bromine was quenched by slow and portion wise addition of sodium sulfite at 20-22 °C. The aqueous slurry was extracted with methylene chloride (2 X 800 mL). The combined methylene chloride layer was washed with water (2 X 700 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude residue was dissolved in hexane (1 L) and washed with acetonitrile (2 X 300 mL). The hexane layer was concentrated to obtain the crude product which was purified by silica plug eluting with hexane to afford 4-bromo-1-cyclopentyl-2-(trifluoromethyl)benzene (**10**, 78.3 g, 30%); ^{1}H NMR: (Bruker, 400 MHz, DMSO-d_6) δ 7.81 (dd, J=8.4 and 2.0 Hz, 1H), 7.76 (d, J=2.0 Hz, 1H), 7.57 (d, J=8.4Hz, 1H), 3.16-3.26 (m, 1H), 1.95-2.04 (m, 2H), 1.78-1.88 (m, 2H), 1.52-1.72 (m, 4H).

4-Cyclopentyl-3-(trifluoromethyl)benzaldehyde (11). 4-Bromo-1-cyclopentyl-2-(trifluoromethyl)benzene (**10**, 200 g, 0.682 mol) was transferred into a 5L reaction vessel fitted with a mechanical stirrer, thermocouple and nitrogen inlet. Anhydrous tetrahydofuran (2L) was added and stirred well. The solution was cooled to -75 °C and n-butyl lithium (1.6M in hexanes, 470 mL, 0.75 mol) was added slowly maintaining the reaction temperature below -65 °C and stirred for 1h and 40 minutes. DMF (59.8 g, 64 mL, 0.818 mol) was added slowly at -70 °C. It was gradually warmed and stirred at room temperature for 3h. The reaction mixture was cooled to -10 °C and slowly quenched with water (200 mL) followed by 6N HCl (134 mL, pH 2-3). THF was removed under reduced

pressure and the residue was extracted with ethyl acetate (2 X 200 mL). The combined organic layer was washed with water (2 X 150 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give 4-cyclopentyl-3-(trifluoromethyl)benzaldehyde (**11**, 200 g, quant.); ^{1}H NMR (Bruker, 400 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.16, (d, J=1.2 Hz, 1H), 8.12 (d, J=8 Hz, 1H), 7.86 (d, J=8 Hz, 1H), 3.29-3.37 (m, 1H), 1.95-2.09 (m, 2H), 1.79-1.94 (m, 2H), 1.55-1.7 (m, 4H).

(4-Cyclopentyl-3-(trifluoromethyl)phenyl)methanol (12). 4-Cyclopentyl-3-(trifluoromethyl)benzaldehyde (**11**, 235.2 g, 0.971 mol) was transferred into a 5L 3-necked RB flask equipped with a thermocouple, a mechanical stirrer and nitrogen inlet. Ethanol (1.88 L) was added and stirred well to obtain a light yellow solution. It was cooled to 5 °C and sodium borohydride (44.1 g, 1.16 mol) was added in small portions (*caution*: initial 25% of sodium borohydride addition was very exothermic). After addition of sodium borohydride, the mixture was stirred at room temperature for 1h and 40 minutes. Analysis of a sample of the reaction mixture by LC/MS showed the product peak as the major component, starting material was not detected. The mixture was stirred for additional 1.5 h, cooled to 5 °C and slowly quenched with water (250 mL), maintaining the temperature within 5-10 °C. The reaction was further quenched by slow addition of 6N HCl (temperature maintained below 20 °C; *exothermic and hydrogen evolution occurred*) and was acidified to pH 3. Ethanol was removed under reduced pressure and ice-water (1.5 L) was added. The aqueous slurry was extracted with methylene chloride (2 X 800 mL). The combined methylene chloride layer was washed with water, dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. The oily residue was further dried under vacuum to give the crude benzyl alcohol (**12**, 233 g). The crude product was purified by dissolving it in acetonitrile (1.5 L) and washing the acetonitrile layer with hexane (2 X 500 mL and 2 X 800 mL). The less polar impurities partitioned into the hexane layer and the pure product remained in the acetonitrile layer. The solvent was removed under reduced pressure to afford (4-cyclopentyl-3-(trifluoromethyl)phenyl)methanol (**12,** 196.7 g, 83%); ^{1}H NMR: (Bruker, 400 MHz, DMSO-d_6) δ 7.52-7.6 (m, 3H), 5.28 (t, J=5.6 Hz, 1H), 4.52 (d, J=6 Hz, 2H),

3.19-3.28 (m, 1H), 1.93-2.05 (m, 2H), 1.77-1.89 (m, 2H), 1.54-1.72 (m, 4H); LC/MS: m/z 227.3 (M-OH); 92.8 area% purity by LC/MS.

4-Chloromethyl-1-cyclopentyl-2-(trifluoromethyl)benzene (6). 4-Cyclopentyl-3-(trifluoromethyl)phenyl methanol (**12**, 110 g , 0.450 mol) was transferred into a 2 L RB flask and thionyl chloride (329 ml, 4.50 mol) was slowly added at room temperature under nitrogen. The mixture was stirred at 50 °C for 3.5 h and then cooled to room temperature and stirred for an additional 6 h. LC/MS analysis of a reaction sample showed complete conversion to the product. The reaction mixture was concentrated under reduced pressure and the residue was slowly poured into ice-water (450 ml) with efficient stirring. The aqueous slurry was extracted with methylene chloride (200 mL) and the aqueous layer was back extracted with methylene chloride (3 X 400 mL). The combined extracts were washed with saturated sodium bicarbonate (400 ml) and brine (2 X 400 ml), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 4-chloromethyl-1-cyclopentyl-2-(trifluoromethyl)benzene (**6**) as a light yellow liquid (113.3 g, 96 %); ^{1}H NMR (Bruker, 400 MHz, DMSO-d_6) δ 7.67-7.71 (m, 3H, ArH), 4.82 (s, 2H, -CH_2), 3.21-3.29 (m, 1H, -CH), 1.95-2.03 (m, 2H, -CH_2), 1.78-1.88 (m, 2H, -CH_2), 1.55-1.71 (m, 4H, -CH_2); 98.7 area% purity by LC/MS.

Iron(III) chloride catalyzed cross coupling reaction: 1-cyclopentyl-2-(trifluoromethyl)benzene (9). Kilo-lab scale. To a 30 L jacketed reactor, anhydrous THF (6 L) followed by magnesium turnings (20-320 mesh, 243 g, 10 mol, 1.5 eq.) were added under N_2. In a separate flask, $FeCl_3$ (162 g, 1.0 mol, 0.15 eq.) was dissolved (caution, exothermic) in anhydrous THF (800 mL) under N_2. This dark brown solution was cooled to ambient temperature using an ice bath and then added over 35 min to the 30 L reactor contents under N_2 at an internal temperature of 10 °C. To this yellow/green mixture, TMEDA (1.2 L, 930 g, 8 mol) was added keeping the internal temperature below 20 °C (slightly exothermic). The resulting rust brown mixture was stirred at 45 °C for 1 h under N_2. The reactor content was allowed to cool below 20 °C and a mixture of 1-bromo-2(trifluoromethyl)benzene (**7**, 1.5 kg, 6.67 mol) and bromocyclopentane (**12**, 1.19 kg, 8 mol, 1.2 eq.) added dropwise under N_2 at such a rate as to maintain the internal

temperature between 25-30 °C (caution, exothermic). After addition (3.33 h) and subsiding of the exotherm, the reaction mixture was stirred at 25 °C under N_2 overnight and allowed to cool to an internal temperature of 0 °C. The reaction was quenched with 6 N HCl (3 L) at such a rate (1.5 h) as to maintain the internal temperature below 15 °C (caution, very exothermic). After the quench, ethyl acetate (4 L) was added and the reactor content stirred at ambient temperature for 1 h. The phases were separated and the aqueous layer back extracted with ethyl acetate (2.5 L). The combined organic layers were washed with water (1 L), brine (1.5 L) and dried (Na_2SO_4). The solvent was removed under reduced pressure at 35 °C to afford the crude product as a brown oil. The crude material was purified by vacuum distillation at 65-70 °C / 0.15 Torr, to give 1-cyclopentyl-2-(trifluoromethyl)benzene (**9**) as a clear, pale yellow oil (823 g, 58%).; ^{1}H NMR (Bruker, 400 MHz, DMSO-d_6) δ 7.58-7.64 (m, 3H, ArH), 7.34-7.4 (m, 1H, ArH), 3.21-3.29 (m, 1H, -CH), 1.95-2.04 (m, 2H, -CH_2), 1.76-1.88 (m, 2H, - CH_2), 1.49-1.71 (m, 4H, -CH_2).

4-Chloromethyl-1-cyclopentyl-2-(trifluoromethyl)benzene (6). Chloromethylation with trioxane and chlorosulfonic acid. 1-Cyclopentyl-2-(trifluoromethyl)benzene (**9**, 200 g, 0.93 mol) was transferred to a 5 L 3-necked RB flask, fitted with a temperature probe, a mechanical stirrer, nitrogen inlet and cooled to -19 °C. Concentrated sulfuric acid (400 mL, 7.5 mol) was added slowly with efficient stirring (addition of sulfuric acid was exothermic). The reaction mixture was maintained at -16 °C and 1,3,5-trioxane (126 g, 1.4 mol) was added quickly in three separate portions (42 g per portion). Chlorosulfonic acid (113 mL, 1.68 mol) was added slowly *via* an addition funnel in a controlled fashion (*note*: addition that is too slow will produce more by-product **14**) and the temperature maintained below -10.4 °C during the addition. The reaction mixture was allowed to warm to -6 to -7 °C at which time an internal exotherm was observed and the temperature increased to +10.5 °C. The exotherm gradually subsided. The mixture was cooled to 5 °C and the reaction mixture was held between -2.5 to 5 °C for 2h. Analysis of the reaction by LC/MS showed a main product peak (**6**) and a minor peak corresponding to the dimer by-product **14**. In addition, no starting material was detected by TLC (5%

EtOAc in hexane). The reaction mixture was cooled to -2 to -3 °C and quenched very slowly with water (2 L) (caution: aqueous quench of the reaction mixture was very exothermic). Methylene chloride (800 mL) was added to the aqueous mixture and stirred well. The mixture was allowed to stand overnight at room temperature, filtered through celite and the organic layer was separated. The acidic aqueous layer was washed with methylene chloride (700 mL). The combined methylene chloride layer was washed with saturated aqueous $NaHCO_3$ (500 mL) and water (800 mL), and then dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure to afford an oil (248.2 g). The crude oil was distilled under vacuum at 90 °C/0.4 Torr to afford purified 4-chloromethyl-1-cyclopentyl-2-(trifluoromethyl)benzene (**6**, 173.5 g, 71%); ^{1}H NMR (Bruker, 400 MHz, DMSO-d_6) δ 7.67-7.71 (m, 3H, ArH), 4.82 (s, 2H, -CH_2), 3.21-3.29 (m, 1H, -CH), 1.95-2.03 (m, 2H, -CH_2), 1.78-1.88 (m, 2H, -CH_2), 1.55-1.71 (m, 4H, -CH_2), 98.7 area% pure by HPLC.

4-(Chloromethyl)-1-cyclopentyl-2-(trifluoromethyl)benzene (6). Chloromethylation with trioxane and thionyl chloride. To a 30 L jacketed reactor, concentrated sulfuric acid (1.61 L, 30 mol) was added and cooled to an internal temperature of -4.5 °C under N_2. Thionyl chloride (547 mL, 7.50 mol, 2 eq.) was added under stirring to the reactor content *via* an addition funnel keeping the temperature between -3.5 to -5 °C. To the resulting mixture, 1,3,5-trioxane (506 g, 5.62 mol, 1.5 eq.) was added in four portions (126.5 g each) under N_2 while maintaining the internal temperature below -1.9 °C (*note*: addition of trioxane was exothermic). 1-Cyclopentyl-2-(trifluoromethyl)benzene (**9**) (802.8 g, 3.75 mol) was then added dropwise to the reactor contents under stirring at such a rate as to maintain the temperature below -2.5 ^{o}C (addition was exothermic). After stirring at 0 °C for 2.5 h and 5 °C for 1 h, the reaction mixture was warmed to 15 °C and held at that temperature overnight. After this time, **9** could not be detected by TLC (5% EtOAc in hexanes). Analysis by LC/MS showed a major product peak (**6**), and the presence of a small amount of dimer **14**. The reaction mixture was cooled to -2 °C and quenched by the slow (caution, exothermic) addition of water (11 L) with stirring while maintaining the internal temperature below 15 °C. The aqueous slurry was extracted with MTBE (2 X 5 L). The combined MTBE layer was washed with a mixture of saturated

$NaHCO_3$ (4 L) and brine (1 L), followed by a mixture of water (2 L) and brine (2 L). The organic layer was dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure to give the crude product (**6**) as a dark brown oil (913 g). The crude product was further purified by vacuum distillation at 90-93 °C/0.15 to 0.2 Torr to yield purified 4-(chloromethyl)-1-cyclopentyl-2-(trifluoromethyl)benzene (**6**) as a clear, pale yellow oil (788.4 g, 80%); 98.4 area% by HPLC.

Acknowledgement

We would like to thank Arena Pharmaceuticals, Inc. for the generous support of our studies.

References:

(1) Buzard, D. J.; Kim, S. H.; Lopez, L.; Kawasaki, A.; Zhu, X.; Moody, J.; Thoresen, L.; Calderon, I.; Ullman, B.; Han, S.; Lehmann, J.; Gharbaoui, T.; Sengupta, D.; Calvano, L.; Garrido Montalban, A.; Ma, Y.-A.; Sage, C.; Gao, Y.; Semple, G.; Edwards, J.; Barden, J.; Morgan, M.; Chen, W.; Usmani, K.; Chen, C.; Sadeque, A.; Christopher, R. J.; Thatte, J.; Fu, L.; Soloman, M.; Mills, D.; Whelan, K.; Al-Shamma, H.; Gatlin, J.; Le, M.; Gaidarov, I.; Anthony, T.; Unett, D. J.; Blackburn, A.; Rueter, J.; Stirn, S.; Behan, D. P.; Jones, R. M. *ACS Med. Chem. Lett.* **2014**, *5*, 1313–1317.

(2) (a) Phapale, Vilas B.; Cardenas, Diego J. *Chem. Soc. Rev.* **2009**, *38,* 1598-1607. (b) Corbet, Jean-Pierre; Mignani, G. *Chem. Rev.* **2006**, *106,* 2651-2710.

(3) (a) Leazer, Jr. J.L.; Cvetovich, R.; Tsay, F-R.; Dolling, U.; Vickery, T.; Bachert, D. *J. Org. Chem*. **2003**, *68*, 3695-3698.

(b) *Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. Chem. Rev*. **2004**, *104*, 6217-6254. (c) Sherry, B. D.; Furstner, A. *Acc. Chem. Res*. **2008,** *41***,** 1500-1511.

(4) Branytska, O.; Neumann, R. *Synlett*, **2004**, *9*, 1575-1576.

(5) Kishida, T.; Yamauchi, T.; Komura, K.; Kubota, Y.; Sugi, Y. *J. Mol. Catal. A: Chem.* **2006**, *246*, 268-275.

(6) Czaplik, W. M.; Mayer, M.; von Wangelin, A. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 607-610.

(7) Tang, W.; Sarvestani, M.; Wei, X.; Nummy, L. J.; Patel, N.; Narayanan, B.; Byrne, D.; Lee, H.; Yee, N. K.; Senanayake, C. H. *Org. Proc. Res. Dev.* **2009**, *13*, 1426-1430 and references therein.

(8) Gunnlaugsson, T.; Davis, A. P.; O'Brien, J. E.; Glynn, Mark. *Org. Lett*. **2002**, *4*, 2449-2452.

(9) Sun, H.-B.; Hua, R.; Yin, Y. *Tetrahedron Lett.* **2006**, *47*, 2291-2294.