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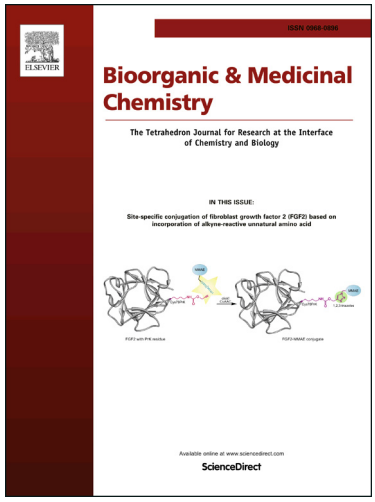

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Development of a Stereoselective and Scalable Process for the Preparation of a Methylcyclobutanol-Pyridyl Ether

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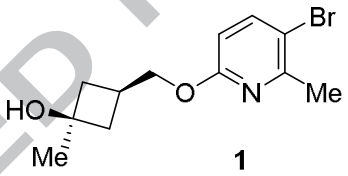
ABSTRACT : The evolution of a scalable process for the preparation of methylcyclobutanol-pyridyl ether **1** is described. Key aspects of this development including careful control of the stereochemistry, elimination of chromatography, and application to kilogram-scale synthesis are addressed.

Introduction

The ever-increasing speed with which drug candidates progress from late-stage discovery into early development requires rapid development of suitable chemistry to meet aggressive delivery timelines. Often multiple compounds varying significantly in structural design and complexity may be in contention to enter early development. Pre-investment of process chemistry resources to solve challenging synthetic chemistry issues prior to a compound entering development enables the rapid progression of these candidates into high-dose pharmacokinetic (PK) studies and early toxicological evaluation. While this only requires gram quantities for these studies, up to hundreds of grams may be required to fully profile a candidate prior to entering development. In an effort to rapidly progress drug candidates through each milestone on its way into development, the chemistry can evolve at an equally

rapid pace. In support of an accelerated drug discovery program, increasing quantities of compound **1** were required to advance a lead compound through the late stages of discovery and into development (Figure 1). The existing route used to enable SAR involved a low yielding Mitsunobu reaction between hydroxypyridine **2** and 3-hydroxymethylcyclobutanone **3** followed by addition of MeMgCl to give compound **1** (Scheme 1). The addition of the Grignard reagent was moderately selective and produced a mixture of *cis*/*trans* isomers, typically in 6:1 ratio which could only be separated by column chromatography. The introduction of the Grignard reagent in the final step was well suited for the development of structure-activity relationships (SAR) during discovery, because it provided access to an array of compounds such as **5** in a single step. However, this approach was ill-suited for the preparation of multi-gram quantities of compound **1** due to the difficulty in separating the isomers formed. In this manuscript we describe the evolution of a scalable process leading the stereoselective synthesis of multi-kilogram quantities of compound **1**.

Figure 1. Target Compound of Interest.



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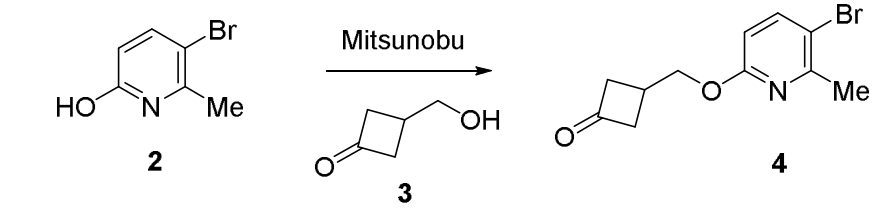
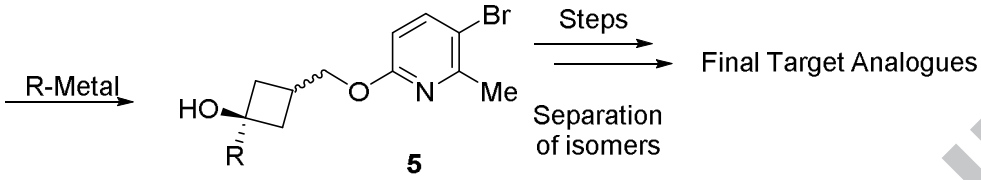
Scheme 1. SAR Synthesis and Retrosynthetic Analysis





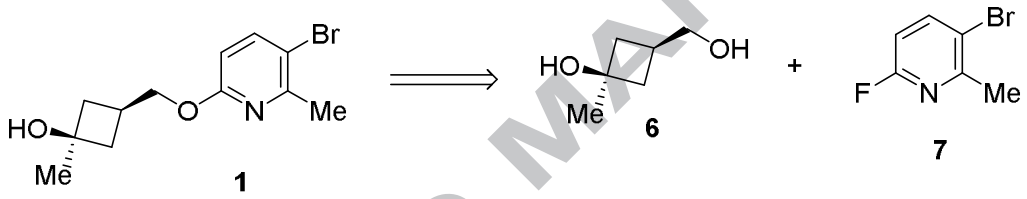
Benefits of Route

1. Concise route
2. Diversification of R
3. Acceptable yields
4. Access to both *cis* and *trans* isomers

Desired for Scale up of Single Target

1. Control of Stereochemistry
2. Improve overall yield and efficency
3. Reduce waste (e.g. eliminate chromatography and replace Mitsunobu)

RetroSynthesis of Compound **1**



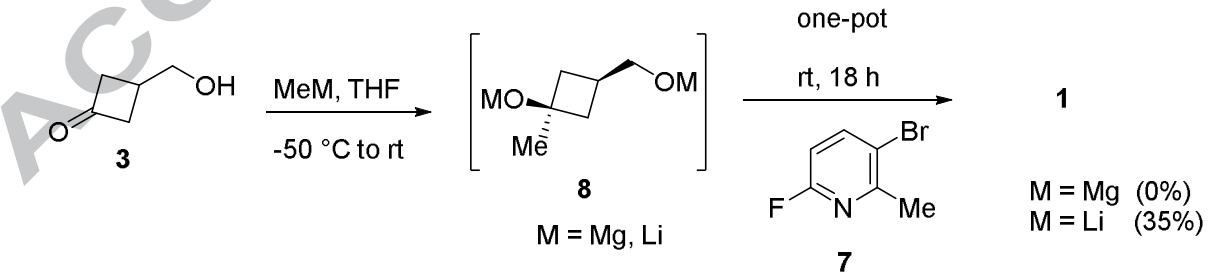
Results and Discussion

Our retrosynthetic approach to compound **1** is shown in Scheme 1 and was centered on an S_NAr displacement of readily available fluoropyridine **7** with diol **6**. In order to avoid the use of chromatographic separation of stereoisomers, it was deemed critical to control the stereoselectivity of compound **1**. While the synthesis of diol **6** had previously been reported,[1] it was not stereoselective and suffered from low yielding steps requiring the development of a new stereoselective synthesis of this intermediate. Several routes were investigated in parallel in order to advance the lead compound with an accelerated timeline.

Our initial investigations briefly focused on the one-pot *in-situ* generation of metalated diol **8** and its subsequent addition to fluoropyridine **7** (Scheme 2). For example, treatment of ketone **3** with 2

equivalents of MeMgBr at temperatures below -50 °C in 2-MeTHF followed by addition of fluoropyridine **7** did not afford any detectable desired addition product **1**. Instead, the fluoropyridine starting material was recovered unchanged. After the addition of MeMgBr, a thick slurry of the corresponding magnesium dialkoxide **8** formed. The insolubility of dialkoxide **8** may have accounted for the lack of reactivity, but the general low nucleophilicity of magnesium alkoxides may have contributed to the lack of reactivity.[2] The reaction was repeated by forming the magnesium dialkoxide at -50 °C and allowing it to warm to room temperature prior to the addition of fluoropyridine **7**; however, this also resulted in no detectable reaction to the desired product **1**. Heating the reaction to near reflux also did not afford any reaction. Since the magnesium dialkoxide of **8** proved unreactive it was reasoned that the lithium alkoxide may offer increased solubility. To this end, reaction of ketone **3** with 2 equivalents of MeLi at -50 °C in 2-MeTHF was followed by warming the reaction slurry to room temperature and the addition of fluoropyridine **7**. Stirring the reaction mixture overnight at room temperature afforded a 35% HPLC assay yield[3] of compound **1** as a disappointing 4.3:1 mixture of *cis*/*trans* isomers. The mass balance of the reaction could not be accounted for as apparent decomposition of the starting material **7** was observed. If the lithium dialkoxide was formed at higher temperatures than the initial -50 °C, further erosion in the selectivity was observed. With these results, this approach was abandoned and efforts focused on a stereoselective synthesis of diol **6**.

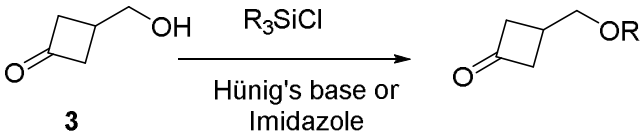
Scheme 2. Attempted One-Pot Conversion of Hydroxyketone **3** to Compound **1**



Since the addition of MeLi to ketone **3** at low temperatures did not afford a high degree of diastereoselectivity, it was reasoned that protection of the primary hydroxyl group with a bulky

protecting group may offer the opportunity for increased stereoselectivity (Scheme 3). Reaction of alcohol **3** with TBDMS-Cl in the presence of Hünig's base (DIPEA) afforded intermediate **9** in 95% yield.[4] Reaction of **9** with MeMgBr at -75 °C for 30 minutes followed by warming the reaction to -20 °C gave a ~5.3:1 mixture of *cis*- **10** and *trans*- **11** isomers as determined by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy. While this result was encouraging, higher levels of stereoselectivity were still required. Preparation of both the triisopropyl silyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) alcohols was accomplished by reaction of alcohol **3** with TIPS-Cl and TBDPS-Cl respectively in the presence of imidazole and gave good, to excellent yields, of TIPS-protected alcohol **12** (93%) and TBDPS-protected alcohol **13**[5] (80%). Compound **13** proved to be a highly crystalline solid and chromatography used in the preparation of compounds **9** and **12** was completely avoided in the isolation of intermediate **13**. The isolation of TBDPS-alcohol **13** simply involved slurring the crude reaction mixture in heptane, filtration, and drying which produced analytically pure compound **13**. Reaction of TIPS-alcohol **12** with MeMgBr at -75 °C for 30 minutes followed by warming the reaction to -20 °C afforded the same ~5.5:1 mixture of isomers **14** and **15** and did not offer any advantage. However, reaction of TBDPS-alcohol **13** under the identical reaction conditions gave a >20:1 mixture of isomers **16** and **17** in near quantitative yield. The increased steric bulk of the TBDPS protecting group of compound **13** gave the necessary level of stereoselectivity required for downstream processing and the chemistry was rapidly scaled to provide > 900 g of compound **16** to support the aggressive timelines for the preparation of multi-hundred gram quantities of intermediate **1**.

Scheme 3. Grignard Addition to Protected Hydroxy Ketones



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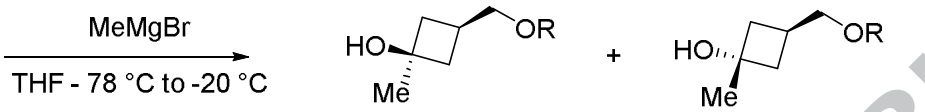
9 R = TBDMS (95%)
12 R = TIPS (93%)
13 R = TBDPS (80%)



Desired *Cis*

Ratio

Undesired *Trans*

10 R = TBDMS	5.3:1	**11** R = TBDMS
14 R = TIPS	5.5:1	**15** R = TIPS
16 R = TBDPS	>20:1	**17** R = TBDPS

With an efficient synthesis of compound **16** in hand, attention turned to its conversion to intermediate **1** (Scheme 4). Initial experiments probed the possible direct conversion of compound **16** to intermediate **1** by reaction with fluoropyridine **7** in the presence of TBAF. Treatment of compound **16** with TBAF in the presence of fluoropyridine **7** in THF did not afford any detectable formation of intermediate **1**. Evidently, the initially formed tetrabutylammonium alkoxide was not able to displace the fluorine atom on pyridine **7**. Repeating the reaction in NMP and heating at 70 °C did result in the formation of compound **1** but the reaction did not go to completion and was complicated by the formation of other unidentified by-products. Based on these experiments, it was decided to remove the TBDPS protecting group prior to reaction with fluoropyridine **7**. Removal of the TBDPS-protecting group with TBAF occurred cleanly in THF at 50 °C. The reaction was easily monitored for the disappearance of the starting material and formation of TBDPS-F. Unfortunately, all attempts to work up the reaction by quenching into any aqueous systems led to low recovery of diol **6** due to its high water solubility. Thus an aqueous workup needed to be avoided. In order to circumvent this issue, the crude reaction mixture was applied directly to a plug of silica gel and was eluted with a 3:1 mixture of ethyl acetate (EtOAc) and hexane which yielded an 82% yield of diol **6**.

Reaction of diol **6** and fluoropyridine **7** was quickly screened in the presence of a number of bases (Scheme 4). For example, reaction in the presence of 1 equivalent of NaH in DMF at room temperature afforded 50% conversion to compound **1** after 18 h. Addition of more NaH did not result in further conversion. While the safe use of NaH on scale has been demonstrated,[6] the low conversion and the desire to avoid the possible safety issues associated with NaH necessitated examining alternative bases (Table 1). Reaction in the presence of 1 equivalent of Cs_2CO_3 at room temperature in DMF did not result in any conversion to compound **1**. On the other hand, warming the mixture to 70 °C for 6 h led to the formation of desired compound **1** but only at 50% conversion. Stirring an additional 48 h at this temperature only led to 65% conversion. Additional base did not increase the conversion to compound **1**. Furthermore, it was discovered that stirring the reaction mixture with an overhead mechanical stirrer resulted in a dramatic drop in the conversion (Table 1, entry 3). This suggested that the grinding effect of a stir bar was providing increased surface area of the base to achieve higher conversions.[7] This grinding effect would not be possible on larger scale and efforts quickly turned to alternative bases. Reaction of diol **6** and fluoropyridine **7** in the presence of 1 equivalent of NaO*t*-Bu in DMF at 0 °C followed by warming to room temperature lead to 60% conversion to compound **1**. However, accompanying this was the formation of bis-alkylated by-product **18** in up to 16%.[8] Slow addition of one equivalent of KO*t*-Bu to a mixture of diol **6** and fluoropyridine **7** appeared to be the cleanest reaction giving > 90% conversion to compound **1** in < 2 h at 0-5 °C and only resulted in the formation over-alkylated by-product **18** in 3% yield (Table 1, entry 5). Interestingly, when all the reagents were added together at the same time, the formation of by-product **18** reached up to 40% in the presence of KO*t*-Bu. These results were further optimized in terms of solvent, temperature, and charge of base. The optimal conditions involved slow addition of a solution of 1.15 equivalents of KO*t*-Bu in THF to a solution of diol **6** (1.1 equivalents) and fluoropyridine **7** (1 equivalent) in a 1.7:1 ratio of DMF and THF at 0-5 °C over several hours. Under these conditions the formation of by-product **18** was minimized to <2% at near full conversion to compound **1** (Table 1, entry 6). Complete conversion to compound **1** was not observed and there still remained up to 4-5% remaining starting material **7**. The

isolation of compound **1** at this stage of development involved conversion of the free base of compound **1** to the HCl salt since a crystalline form of the free base had not been identified. Formation of the HCl salt not only provided a crystalline intermediate, but also resulted in complete removal of any trace of by-product **18**, any possible undesired trans-isomer about the cyclobutanol ring, and remaining starting material **7**. Compound **1a** was isolated as the HCl salt in 60-63% isolated yield. From initial proof-of-concept of the chemistry described in Schemes 3-4 to execution on multi-hundred gram quantities of compound **1a** took under 2 months and greatly accelerated the lead compound to move from late stage discovery to early development.

Scheme 4. Reaciton of Diol **6** with Fluoropyridine **7**

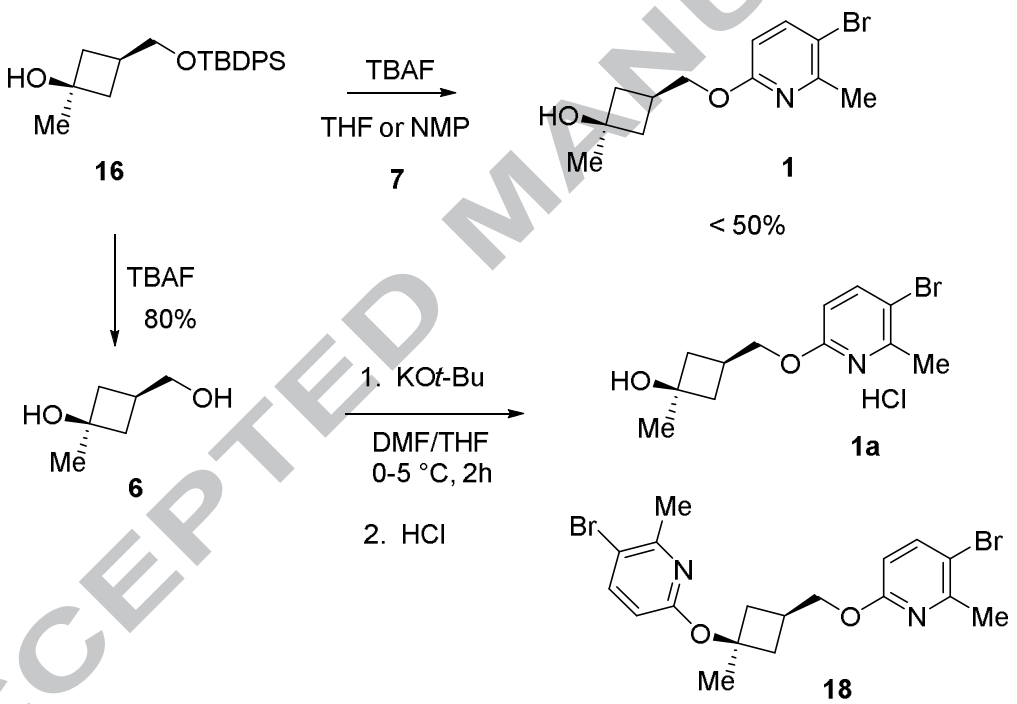


Table 1. Effect of Base

Entry	Base (equiv)	Conversion	Percent **18**
1	NaH (1)	50%	ND
2	Cs_2CO_3 (1)	65%	3%
3	Cs_2CO_3 (1)	35%[a]	3%
4	NaO*t*-Bu (1)	60%	16%
5	KO*t*-Bu (1)	90%[b]	3%
6	KO*t*-Bu (1)	94%[c]	< 2%

a. With mechanical stirring. b. Screening conditions. c. optimized conditions

Redesigned Protecting Group Free Approach

The chemistry outlined for the first generation approach to compound **1** was executed under tight timelines and enabled the lead compound to progress rapidly into development; however, the implementation of this route on larger scale required further development. Key issues that needed to be addressed included further optimization of the *cis/trans* ratio of diol **6**, elimination of chromatography of compound **6**, removal the use of a protecting group (TBDPS), and further optimization of the S_NAr displacement of fluoropyridine **7** with diol **6**.

It was recognized that further improvement in the stereoselectivity for the chemistry described in Scheme 3 would be a challenge and we elected to investigate alternative approaches to diol **6**. Efforts centered on the use of readily available ketoacid **19** as this was the precursor to hydroxymethyl ketone **3** (Scheme 5).[9] Initial experiments involved exploring the addition of MeMgCl to a solution of ketoacid **19** in THF at -70 °C. Upon complete addition of the Grignard reagent, a thick gelatinous slurry formed that was difficult to stir without the aid of a mechanical stirrer. Warming the reaction mixture at this point to room temperature resulted in slurry that was easier to stir. Quenching the mixture with 1 M H_3PO_4 and analysis of the crude NMR revealed the formation of ~7:1 ratio of desired *cis*-isomer **20** to undesired *trans*-isomer **21**. Although this result appeared to be discouraging at first, a serendipitous discovery was made that allowed for the further exploration of this chemistry. It was found that recrystallization of this initially formed mixture of isomers from methyl *tert*-butylether (MTBE) provided >99:1 stereoselectivity for the *cis*-isomer **20** with minimal loss to the mother liquors. The reaction was then fully optimized in terms of organometallic reagent, temperature, and reaction volume. For example, reaction with MeLi under the conditions described above led to the expected formation of a 7:1 mixture of isomers **20** and **21**; however, there were also a number of unidentified by-products observed and gas chromatography (GC) analysis of the crude reaction mixture only showed ~ 41% was the desired product.[10] Evaluation of MeMgBr also gave a 7:1 mixture of stereoisomers and GC showed ~70% of the crude material was the desired product. Reexamination of MeMgCl gave a GC profile that

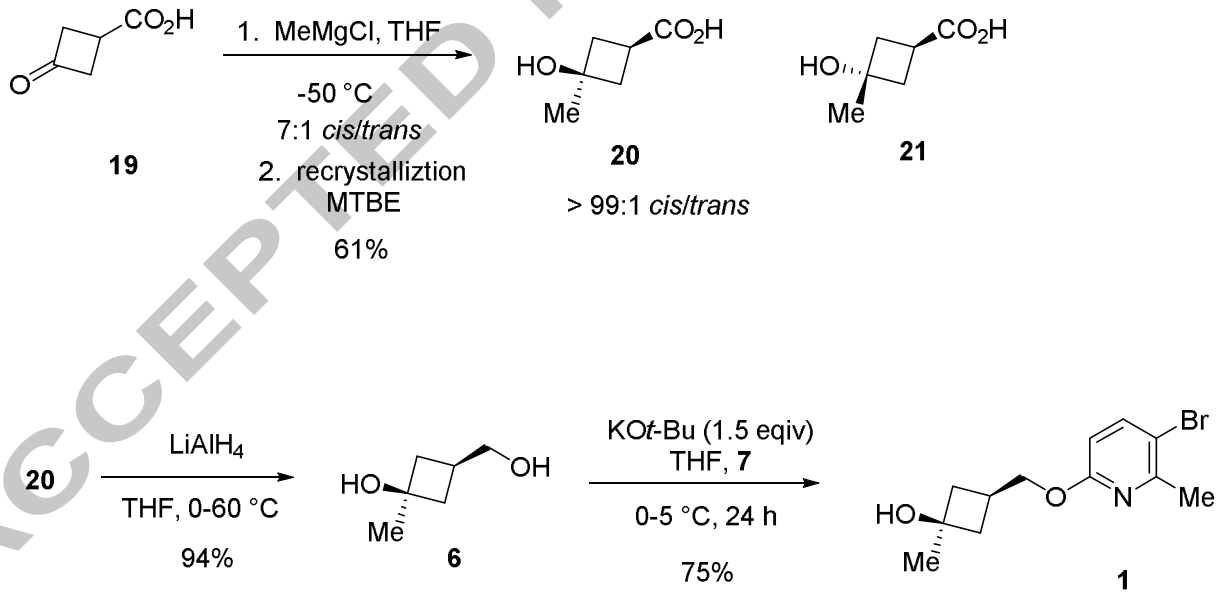
was ~ 80% of the desired product so this reagent was selected for scale-up. The effect of temperature was next examined. As noted above, at lower temperatures the reaction mixture tended to form gelatinous slurries that could be difficult to stir. Running the reaction at 0 °C saw a decrease in the stereoselectivity to ~ 4:1 and at -20 °C only increased the stereoselectity slightly to 6.3:1. While these reactions stirred well, the decrease in selectivity was unacceptable. When the reaction was performed at -50 °C, the desired 7:1 ratio was observed while maintaining good performance from a mixing perspective. Given these results this temperature was selected. The reaction volume also proved crucial to scale up. At higher dilution mixing was not problematic, but the more concentrated the reaction volume was the more difficulties were encountered. The optimal volume selected was 30 L of THF per kilogram of ketoacid **19**. The reaction was scaled to multiple kilogram scale and provided acid **20** in 61% isolated yield after recrystallization from MTBE.

The reduction of acid **20** to give diol **6** was next examined (Scheme 5). Probe experiments demonstrated that borane-THF in conjunction with a MeOH workup provided diol **6** effectively; however, the use of commercial borane on scale was not desirable due to its inherent instability.[11] While generation of borane in-situ from $NaBH_4$ and BF_3-etherate was considered, this process is generally exothermic and alternative reductions were investigated.[12] Reduction of acid **20** with $LiAlH_4$ was examined and employed in the scale up of diol **6**. Treatment of acid **6** with 2 equivalents of $LiAlH_4$ at 0 °C did not result in full conversion to diol **6**; however, if the reaction mixture was warmed to 55-60 °C full conversion to diol **6** was observed. Work up and isolation of diol **6** was next examined. Due to the fact that diol **6** was highly water soluble and extraction from water was challenging, an aqueous workup needed to be avoided. Although a Fieser work up[13] could be employed effectively, the exothermic release of hydrogen resulting from the quenching of unreacted $LiAlH_4$ at the end of the reaction needed to be controlled.[14] Therefore, at the end of the reaction of acid **20** with 2 equivalents of $LiAlH_4$, the reaction was cooled to 0 °C and the excess $LiAlH_4$ was quenched with an excess of acetone. Following a Fieser work up to remove aluminum salts, filtration and concentration gave a crude solution of diol **6**

in THF that was sufficiently pure for use as a solution in the next step without further purification. The overall yield of diol **6** was 94% for the reduction.

Finally, reexamination of the S_NAr reaction between diol **6** and fluoropyridine **7** resulted in further refinement of the chemistry and increased efficiency. For example, increasing the amount of diol **6** to 1.5 equivalents and stirring at 0-5 °C for 24 h gave an increased yield of 80% by HPLC assay with complete consumption of fluoropyridine **7**. While examining the solubility of compound **1**, it was discovered that *n*-heptane was an excellent solvent for crystallization. In addition, the solvent also was found to be effective at removing the by-product **18** which was formed in ~ 2.3%. The free base of compound **1** was obtained in 75% yield for the S_NAr reaction in >99.8% purity. The chemistry described in Scheme 5 was ultimately executed on multi-kilogram scale to provide 7.3 kg of intermediate **1**

Scheme 5



Conclusion

In summary, the evolution of a robust process for the preparation of key intermediate **1** has been described. While the first generation approach was able to provide sufficient quantities of compound **1**

under aggressive timelines for initial pharmacokinetic and toxicologlical studies, the need to provide kilogram quantities to further progress development into the clinic necessitated the investigation of an alternative approach. Features of the synthesis included the Grignard addition to ketoacid **19** followed by the upgrade in stereoselectivity of acid **20** by crystallization, LAH reduction of **20**, followed by an improved yield of compound **1**. The final process involved three synthetic transformations and proceeded in 43% overall yield from ketoacid **19**.

Experimental

All solvents and reagents were used as received from commercial sources. Analytical samples were obtained by chromatography on silica gel using an ethyl acetate-hexane mixture as the eluent unless specified otherwise. Water content (KF) was determined by Karl Fisher titration on a Metrohm 737 KF coulometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 500 spectrometer at 500 and 125 MHz, respectively, with chemical shifts give in ppm relative to TMS at δ = 0.0. Reaction mixtures and products were analyzed by reverse phase HPLC on a Agilent Technologies 1290 instrument using a 4.6 x 250 Symmetry Shield RP18 column. Solvent compositions consisted of 0.1% H_3PO_4 and acetonitrile with a flow rate of 1.5 mL/min. GC analysis was performed on a Shimadzu GC-200 using a DB-FFAP (30.0 X 0.32 µm I.D. X 1.00 µm) column from 20-240 °C.

Preparation of 3-(((*Tert*-butyldimethylsilyl)oxy)methylcyclobutan-1-one (9). To a stirred solution of 1.00 g (10 mmol) of 3-(hydroxymethyl)cyclobutan-1-one **3** in 10 mL of THF was added 1.91 mL (11.00 mmol) of Hünigs base followed by 1.58 g (10.50 mmol) of *tert*-butyldimethylsilyl chloride. The resutling solution was stirred at room temperature of 18 h, concentrated under reduced pressure, and purified by silica gel eluting 0-10% EtOAc/hexane to afford 2.03 g (95%) of 3-(((*tert*-butyldimethylsilyl)oxy)methylcyclobutan-1-one **9** as a colorless liquid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.08 (s, 6H), 0.92 (s, 9H), 2.60 (m, 1H), 2.92 (m, 2H), 3.07 (m, 2H), 3.77 (d, 2H, J = 5.50 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.4, 18.3, 25.6, 25.8, 49.0, 65.1.

Preparation of 3-(((Triisopropylsilyl)oxy)methyl)cyclobutan-1-one (12). To a stirred solution of 1.00 g (10 mmol) of 3-(hydroxymethyl)cyclobutan-1-one **3** in 10 mL of DMF was added 0.9 g (13.0 mmol) of imidazole followed by 2.54 mL (12.0 mmol) of TIPS-Cl. The resulting mixture was stirred at room temperature for 20 h, diluted with 15 mL of a 10% aqueous solution of LiCl, and extracted with 20 mL of MTBE. The organic extract was washed with 10 mL of a 10% aqueous solution of LiCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting 0-10% EtOAc/hexane to give 2.38 g (93%) of **3**-(((triisopropylsilyl)oxy)methyl)cyclobutan-1-one **12** as a colorless liquid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06-1.16 (m, 21H), 2.62 (m, 1H), 2.97-3.11 (m, 4H), 3.88 (d, 2H, *J* = 5.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.0, 17.7, 18.0, 25.9, 49.9, 65.3.

Preparation of 3-(((*Tert*-butyldiphenylsilyl)oxy)methyl)cyclobutan-1-one (13). Into a 20 L 4-necked round-bottom flask equipped with a mechanical stirrer, temperature thermocouple, and 5 L addition funnel was placed 1.10 kg (11.0 mmol) of 3-(hydroxymethyl)cyclobutan-1-one **3** in 10 L of dichloromethane (10000 mL). To this solution was added 897 g (13.2 mol) of imidazole and the mixture cooled to 0°C. To the mixture was added drop wise via the addition funnel 3.30 kg (12.0 mol) of *tert*-butyl(chloro)diphenylsilane over 30 min and the mixture was allowed to warm to room temperature and stirred an additional 30 min. The resulting solution was diluted with 5.0 L of water and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 2.70 kg (73%) of 3-[[(*tert*-butyldiphenylsilyl)oxy]methyl]cyclobutan-1-one **13** as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.09 (s, 9H), 2.62 (m, 1H), 2.97 (m, 2H), 3.09 (m, 2H), 3.82 (d, 1H, *J* = 5.6 Hz), 7.40-7.48 (m, 6H), 7.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.9, 23.8, 27.1, 38.6, 68.1, 73.3, 109.4, 112.9, 150.6, 151.2, 160.3. Anal. Calcd. For $C_{21}H_{26}O_2Si$: C, 74.51; H, 7.74. Found: C, 74.23; H, 7.90.

Preparation of 3-(((*Tert*-butyldiphenylsilyl)oxy)methyl)-1-methylcyclobutan-1-ol (16). Into a 10 L 4-necked round-bottom flask equipped with a mechanical stirrer, temperature thermocouple,

and 2 L addition funnel was added 900 g (2.66 mol) of **13** and 9.0 L of THF and the solution was cooled to -75 °C. To the mixture was then added dropwise via the addition funnel 1.15 L (3.46 mol) of a 3 M solution of CH_3MgBr at such a rate that the internal temperature did not rise above -60 °C. The mixture was stirred at this temperature for 30 minutes and then warmed to -20 °C and stirred for an additional 30 minutes and then quenched with 3.0 L of a saturated aqueous solution of NH_4Cl. The mixture was extracted with EtOAc (2 X 5.0 L) and the combined organic extract was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford 920 g (98%) of 3-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1-methylcyclobutan-1-ol **16** as yellow oil that was sufficiently pure for use in the next reaction without further purification. An analytical sample was prepared by further purification on silica gel: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.09 (s, 3H), 1.39 (s, 3H), 1.93 (m, 2H), 2.10-2.20 (m, 4H), 3.66 (d, 1H, *J* = 5.0 Hz), 7.39-7.47 (m, 6H), 7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.4, 26.9, 27.5, 40.3, 67.5, 69.7, 127.7, 129.7, 133.7, 135.8.

Preparation of 3-Hydroxy-3-methylcyclobutane-1-carboxylic acid (20). To the 1000 L reactor was charged 10 kg (88.0 mol) of 3-oxocyclobutanecarboxylic acid **19** followed by 280 kg of THF. The slurry was stirred at 25 ºC for 1h until all the solids dissolved. The solution was then cooled to -55 ºC and 65.2 kg (193.0 mol) of a 3M solution of methylmagnesium chloride was added over 2 h. Upon completion of the addition, the reaction mixtue was warmed to 22 ºC. After stirring for 7 h, the reaction mixture was cooled to 5 ºC and quenched by the addition of 210 kg of a 1M aqueous phosphoric acid solution over a period of 2.5 h. The temperature was increased to 22 ºC and the mixture was stirred for 45 min. The layers were separated and the aqueous layer was extracted with 180 kg of 2-MeTHF. The organic extracts were combined, washed with 65 kg of a 25% aqueous sodium chloride solution and concentrated under reduced pressure at 50 ºC. An azeotropic vacuum distillation was then performed by the continuous distillation with MTBE (approximately 111 kg MTBE used for the distillation) at 50 ºC until the water level reached < 1% by KF analysis. To the resulting slurry was then added 22 kg of MTBE and the slurry was heated to 52 ºC for 4h. Upon dissolving the crude solid, the mixture was then cooled to 22 ºC over the course of 5 h and held at the

same temperature for 7 h. The slurry was filtered, washed with 6.7 kg of MTBE and dried under vacuum overnight at 40 °C to afford 7.1 kg (61%) of 3-hydroxy-3-methylcyclobutanecarboxylic acid **20**. The *trans*-isomer was found to be < 1% by NMR analysis. ^{1}H NMR (500 MHz, Methanol-d_4) 2.68 (p, J = 8.9 Hz, 1H), 2.31 (td, J = 9.4, 2.4 Hz, 2H), 2.24 (td, J = 8.7, 2.5 Hz, 2H), 1.36 (s, 3H). ^{13}C NMR (126 MHz, Methanol-d_4) 177.43, 67.58, 40.40, 28.38, 25.54.

Preparation of 3-(Hydroxymethyl)-1-methylcyclobutan-1-ol (6).

Method A: In a 10 L round bottom flask containing 1.50 kg (4.23 mol) of alcohol **16** in 7 liters of THF was added 4.65 L (4.65 mol) of a 1M solution of TBAF. The resulting solution was warmed to 50 °C and stirred at this temperature for 1 h. The resulting mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford 406 g (82%) of 3-(hydroxymethyl)-1-methylcyclobutan-1-ol **6** as a light yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.41 (s, 3H), 1.79 (br m, 2H), 1.86 (m, 2H), 2.18 (m, 1H), 2.21 (m, 2H), 3.67 (d, 2H, J = 5.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.0, 27.3, 38.7, 65.6, 69.2.

Method B: To a 500 L reactor was charged with 4.2 kg (110.7 mol) of $LiAlH_4$ and 92 kg of THF and the mixture was cooled to 0 °C. To the mixture was added 7.00 kg (53.8 mol) of hydroxy acid **19** in 106 kg of THF over the course of 3 h. After the addition was complete, the reaction mixture was slowly warmed to 65 °C and stirred at this temperature of 8 h and then cooled to 0 °C. To the mixture was added 12 kg of acetone over the course of 4 h to completely quench the remaining $LiAlH_4$. To the reaction mixture was then added sequentially 4.3 L of water over 1 h, 5.0 kg of a 15% aqueous solution of NaOH over 2h, and 8 L of water over 2 h. The slurry was stirred at 0 °C for 2 h, warmed to room temperature, and filtered. The filter cake was washed with 130 kg of THF and the combined organic filtrate was dried over 32 kg of $MgSO_4$, filtered, and concentrated under reduced pressure by flushing with THF to a final volume of 15 L. This afforded 5.90 kg (94%) by HPLC assay as a 22.8 wt% solution of diol **6** in THF. An analytical sample was identical to that prepared by Method A.

Preparation of 3-(((5-Bromo-6-methylpyridin-2-yl)oxy)methyl)-1-methylcyclobutan-1-ol (1).

Method A: To a dry ice/isopropanol bath chilled solution of 3.29 g (32.9 mmol) of 3-(hydroxymethyl)cyclobutanone **3** in 75 mL of THF and 25 ml of dimethylimidazolone was added dropwise over 15 minutes 41.1 mL (65.8 mmol) of a 1.6 M solution of MeLi while maintaining the internal temperature below -50 °C. The mixture was then warmed to 30 °C, and approximately 50 mL of THF was removed by vacuum distillation. After the distillation, 3.09 mL (26.3 mmol) of 3-bromo-6-fluoro-2-methylpyridine **7** was added. The mixture was stirred at 30 ˚C for 18 h, then allowed to cool to room temperature. The reaction was quenched with 26.3 mL (13.2 mmol) of a 0.5 M aqueous citric acid solution and then diluted with 150 mL of ethyl acetate. The mixture was washed with 100 mL of water followed by 50 mL of brine, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (10:90 to 60:40 EtOAc:Hexanes) to provide 2.65 g (4.3:1 *cis*/*trans*, 35%) of 3-(((5-bromo-6-methylpyridin-2-yl)oxy)methyl)-1-methylcyclobutanol **1** as a clear oil that solidified upon standing.

Method B : In a 20 L 4 necked round bottom flask equipped with a mechanical stirrer and 5 L addition funnel was placed 594.8 g (3.13 mol) of 3-bromo-6-fluoro-2-methylpyridine **7**, 4.0 L of DMF, 2.4 L of THF, and 400 g (3.44 mmol) of 3-(hydroxymethyl)-1-methylcyclobutan-1-ol **6**. The mixture was cooled to an internal temperature of 0 °C at which point 3.63 L (3.63 mol) of a 1M solution of K*o*t-Bu was added at such a rate that the internal temperature did not exceed 5 °C. The resulting mixture was stirred at 0-5 °C for 2 h, quenched by the addition of 5.0 L of saturated solution of NH_4Cl, and extracted with EtOAc (3 X 2.0 L). The resulting organic extract was washed with a 10 wt% aqueous solution of LiCl (2 X 1.0 L) and dried over anhydrous sodium sulfate. The crude reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in 5.0 L of EtOAc and a solution of 782.5 mL of a 4 M solution of HCl in dioxane was added dropwise and the resulting slurry was stirred at room temperature for 2 h. The slurry was filtered and the wet cake was washed with EtOAc and dried under vacuum/N_2sweep to provide 610.0 g (60%) of compound **1a** as an analytically pure solid :

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.38 (s, 3H), 2.21 (m, 2H), 2.38 (m, 1H), 2.52 (m, 2H), 2.98 (s, 3H), 4.35 (d, 2H, *J* = 2.4 Hz), 7.06 (m, 1H), 8.31 (d, 1H, *J* = 8.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.9, 23.8, 27.1, 39.6, 68.1, 73.3, 109.4, 112.9, 150.7, 151.2, 160.3. Anal. Calcd. For $C_{12}H_{16}BrNO_2$: C, 50.37; H, 5.64; N, 4.89. Found: C, 50.65; H, 5.37; N, 4.93.

Method C: In a 500 L reactor was added 6.40 kg (33.7 mol) of fluoropyridine **7** , 5.90 kg (51.6 mol) of diol **6** and 51.0 kg of THF. The resulting mixture was cooled to 0 °C and 5.9 kg (52.7 mol) of KO*t*Bu in 54 kg of THF was added over the course of 4 h. The resulting mixture was stirred at 0 °C for 20 h and quenched with 19 kg of a saturated solution of NH_4Cl. The layers were separated and the aqueous layer was washed with 72 kg of heptane. The combined organic extracts were washed with 70 L of water (2X) and then concentrated under reduced pressure while solvent switching to heptane and a final volume of ~ 20 L. The resulting slurry was then warmed to 55 °C to give a homogeneous solution that was seeded with 10 grams of pure product **1**. The slurry was stirred at 55 °C for 1.5 h and then slowly cooled to 5 °C, stirred for 1 h, and then filtered. The crystalline solid was dried under vacuum/N_2 sweep at 50 °C for 20 h to afford 7.27 kg (75.4%) of compound **1** as a colorless solid and the free base: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.40 (s, 3H), 1.82 (br s, 1H), 1.94 (m, 2H), 2.16-2.33 (m, 3H), 2.52 (s, 3H), 4.24 (d, 2H, *J* = 5.8 Hz), 6.45 (d, 1H, *J* = 8.6 Hz), 7.60 (d, 1H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.4, 24.5, 27.3, 40.6, 69.2, 70.0, 109.2, 111.5, 141.8, 154.1, 162.0. Anal. Calcd. For $C_{12}H_{17}BrClNO_2$: C, 44.67; H, 5.31; N, 4.34. Found: C, 44.60; H, 5.32; N, 4.27.

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A. Supplementary data.

Supplementary data associated with this article can be found in the online version at:

These data include ^{1}H NMR and ^{13}C NMR spectra for all new compounds.

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[8] The structure of by-product **18** was determined by LCMS and NMR analysis of the crude reaction mixture. By-product **18** was not isolated.

[9] Both ketoalcohol **3** and ketoacid **19** are commercially available, for the reduction of **19** to **3**, see: Liotta DC, Mao S, Hager M. Preparation of Cyclobutyl Nucleosides for use in the treatment of infections including Retroviridae, Hepadnaviridae, or Flaviviridae in Animals and Humans. WO2006063281 A2.

[10] No attempts were made to determine the sturctures of the by-products that were formed.

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