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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.

1. 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 (Fig. 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**.

2. 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

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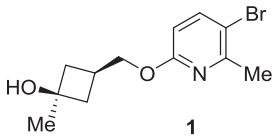
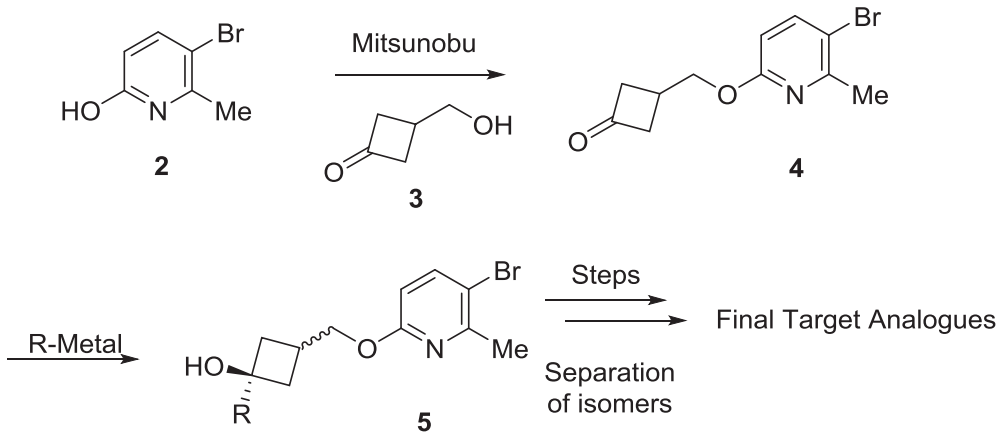


Figure 1. Target compound of interest.

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**.

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 min 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.



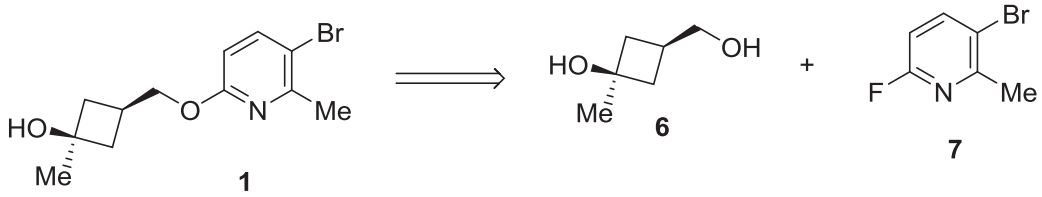
Benefits of Route

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

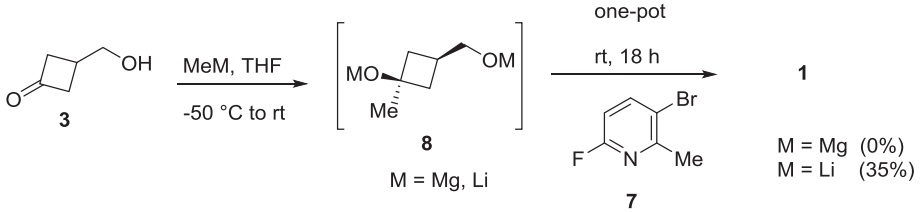
Desired for Scale up of Single Target

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

RetroSynthesis of Compound 1



Scheme 1. SAR synthesis and retrosynthetic analysis.



Scheme 2. Attempted one-pot conversion of hydroxyketone **3** to compound **1**.