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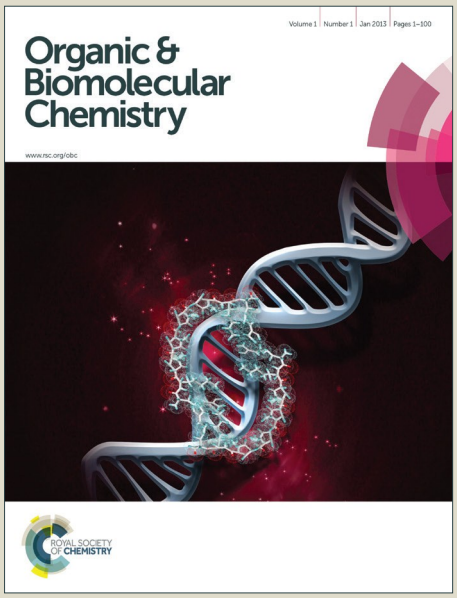




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ARTICLE

# New synthetic approaches towards analogues of bedaquiline

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Multi-drug resistant tuberculosis (MDR-TB) is of growing global concern and threatens to undermine increasing efforts to control the worldwide spread of tuberculosis (TB). Bedaquiline has recently emerged as a new drug developed to specifically treat MDR-TB. Despite being highly effective as a result of its unique mode of action, bedaquiline has been associated with significant toxicities and as such, safety concerns are limiting its clinical use. In order to access pharmaceutical agents that exhibit an improved safety profile for the treatment of MDR-TB, new synthetic pathways to facilitate the preparation bedaquiline and analogues thereof have been discovered.

## Introduction

Tuberculosis (TB) is an ancient infectious disease, caused primarily by *Mycobacterium tuberculosis* (Mtb).[1] Its impact on humanity throughout history has been devastating, claiming more lives than any other known infectious disease.[2] Despite the emergence of multiple anti-TB drugs more than half a century ago,[3] TB is still the greatest infectious killer worldwide,[4] and elimination of the disease at a global level remains elusive. Alarmingly, one-third of the world's population is estimated to be asymptomatically infected with dormant Mtb, resulting in a lifelong risk of disease reactivation.[5] Effective eradication of TB is complicated due to its ability to remain in persistent lesions, requiring extended treatment regimens involving multiple drugs. Furthermore, the emergence of multi- and extensively drug-resistant (MDR-TB and XDR-TB) strains has significantly added to the disease burden. Such cases have become increasingly difficult to manage, and as such, drug-resistant strains have led to increased morbidity and mortality.[4] Given the shortcomings of the currently available therapies, there remains a desperate need for the discovery of new anti-TB drugs that can simplify treatment regimes. Drugs that operate at novel biological targets and are effective against drug-resistant strains are deemed highly desirable.

The development of bedaquiline (**2**), the first new anti-TB drug commercialized in over 40 years promised to revolutionize the treatment of MDR-TB due to its novel mode of action against mycobacterial ATP synthase.[6] Diarylquinolines (DARQs) that were highly active against MDR-TB were discovered in 1996 at Janssen Pharmaceuticals.[6] A whole-cell screen of more than 70,000 compounds was performed against the Mtb surrogate *Mycobacterium smegmatis*, which led to the identification of the DARQ fragment **1** (Figure 1), as a promising structure warranting further optimization. Janssen's hit-to-lead effort produced a series of several hundred DARQ derivatives with *in vitro* activity against Mtb, eventually leading to the identification and development of bedaquiline (**2**) as the most effective anti-TB agent in its (*R,S*) enantiomeric form.[6,7]

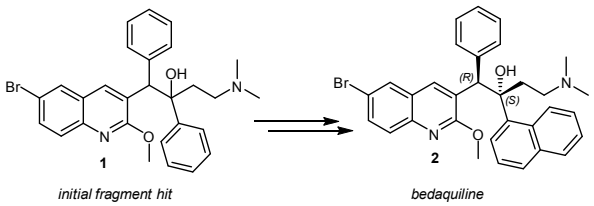


**Figure 1.** Janssen developed bedaquiline from an initial fragment screening hit.

Despite its novel mode of action and potent activity, bedaquiline's widespread use for the treatment of MDR-TB has been relatively limited as a result of the associated adverse side-effects. Of greatest concern is its ability to interfere with the heart's electrical activity, resulting in prolongation of the QT interval, which serves as a biomarker for the development of potentially fatal ventricular arrhythmias.[8] Almost all cases of drug-induced QT prolongation have been attributed to blockage of the potassium ion channel encoded by the human ether-a-go-go related gene (hERG).[9] Multiple studies aimed at probing the structural basis for hERG blockage have identified a lipophilic binding domain within the central cavity of the channel,[10-14] potentially implicating the relatively high lipophilicity of bedaquiline (ClogP 7.3) as a major source of its hERG mediated toxicity. Furthermore, the basic amine functional group present in bedaquiline, which is predominantly protonated at physiological pH (pKa 9.6),

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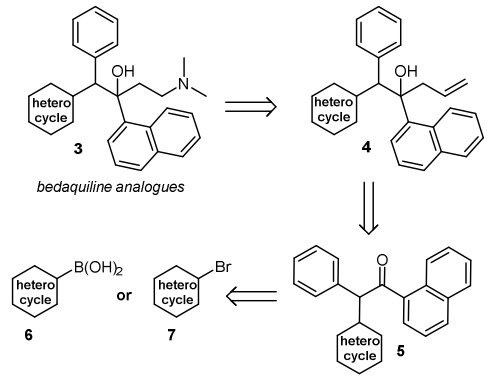
forming π-cation interactions with specific aromatic residues within this region,[15] further increasing affinity for the hERG channel. In addition to promoting hERG binding, the high lipophilicity of bedaquiline may be responsible for additional undesirable side-effects such as phospholipidosis (the accumulation of phospholipids within cells), and CYP450 (isoenzyme 3A4) mediated drug-drug interactions.[16]

In order to facilitate the effective treatment of MDR-TB, highly active bedaquiline analogues that exhibit an improved safety profile are urgently needed. One avenue considered worthy of exploration in an effort to improve the safety profile of bedaquiline involved replacing the quinoline motif with an alternative heterocyclic system. To the best of our knowledge, there appeared to be no attempt to explore variations in the heterocyclic moiety during the drug discovery program. One apparent reason for the lack of heterocyclic diversity explored in this region during the development of bedaquiline could be a result of the synthetic methods utilized during the drug discovery process which were predominantly limited to quinolines. In fact, the only report of bedaquiline analogues whereby the quinoline heterocycle was not present is a very recent publication by Li and co-workers where the nitrogen atom of the quinoline was substituted with a C-H to afford 2-methoxynaphthyl derivatives.[17]

During the drug discovery phase, Janssen prepared bedaquiline analogues by employing an LDA-mediated addition of 3-benzylquinolines to ethyl-amino substituted aryl ketones.[7] Since that time, two alternative asymmetric syntheses of bedaquiline have been reported, however, these require the initial use of substituted anilines to prepare the quinoline motif from which the remainder of the molecule is constructed.[18,19] In our hands, when attempting to replace the quinoline with alternative heterocyclic systems such as pyridines and pyrimidines, we found these methods to be inapplicable or inefficient. As such, to facilitate the discovery of pharmaceutical agents for the treatment of MDR-TB that exhibit improved safety profiles, it proved necessary that new synthetic methods to access analogues of bedaquiline were identified. To this end, we herein report the development of novel strategies towards the synthesis of bedaquiline analogues that will enable the incorporation of various carbo- and heterocyclic motifs. To validate the chemistry, 2-methoxyquinoline was utilized throughout this project, however, it is envisaged that any number of heterocyclic precursors could be applied to these synthetic pathways to readily vary the heterocyclic motif in bedaquiline analogues.

## Results and Discussion

The focus of this investigation was the discovery of alternative approaches towards the synthesis of bedaquiline analogues that would facilitate the substitution of the quinoline motif with any number of other suitable heterocycles (**3**, Scheme 1). To achieve this, α,α-disubstituted acetophenone derivatives **5** were identified as key intermediates in the synthetic pathway, providing substrates that could be further elaborated using allyl-derived organometallic reagents (such as allyl zinc bromide). To access the final bedaquiline analogues **3**, conversion of the allyl group within **4** to the requisite ethyl dimethylamine functionality could be accomplished. To render this synthetic approach useful, the main focus became the identification and development of efficient methods to access tri-aryl ketone derivatives **5**. For the synthetic routes employed to be practical for the preparation of bedaquiline analogues **3**, orthogonal pathways that facilitate the use of either an *heterocyclic boronic acid* (**6**) or a *heteroaryl halide* (**7**) are required to efficiently facilitate the inclusion of any number of heterocyclic derivatives. To this end, we herein present multiple synthetic strategies that provide access to bedaquiline analogues **3** from readily available reagents.




**Scheme 1.** Retrosynthetic analysis of the synthesis of bedaquiline analogues.

The first approach towards bedaquiline analogues was designed to facilitate the incorporation of the heterocyclic moiety from the corresponding *heteroaryl halide*. To explore this, a suitable coupling partner in 3-bromo-2-methoxyquinoline (**9**) was prepared in 4 steps from 3-bromoquinoline (refer to the supporting information). Initially, this approach was conducted in a step-wise fashion. Employing sodium *tert*-butoxide to generate the enolate from 1-acetonaphthone (**8**), a palladium-catalyzed Heck reaction between bromoquinoline **9** and the enolate took place to afford α-substituted ketone **10** in 92% yield (Scheme 2). A second Heck reaction utilizing iodobenzene as the coupling partner under similar reaction conditions was undertaken to yield the α,α-disubstituted naphthone derivative **12**. Alternatively, the Heck reaction with iodobenzene could be accomplished first to afford **11** which was subsequently coupled to the bromoquinoline **9** to furnish ketone **12**, both in good yields (Scheme 2). During optimization of this pathway, it was observed that subsequent to the second Heck reaction—if elevated temperatures and excess base were used—unwanted cyclization of the enolate onto the quinoline occurred to displace the methoxy group at the quinoline-2-position to afford furan **13** (Scheme 3). To avoid this cyclization process, the secondary Heck reaction (Scheme 2) was conducted at 40 °C by employing only 1.5 equivalents of sodium *tert*-butoxide.

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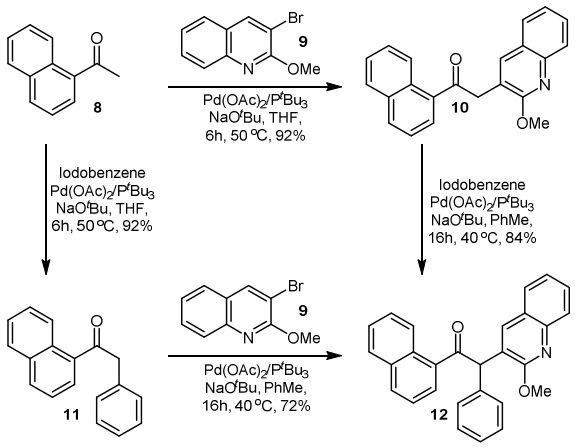
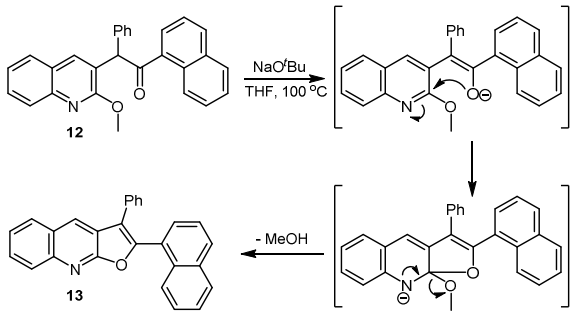
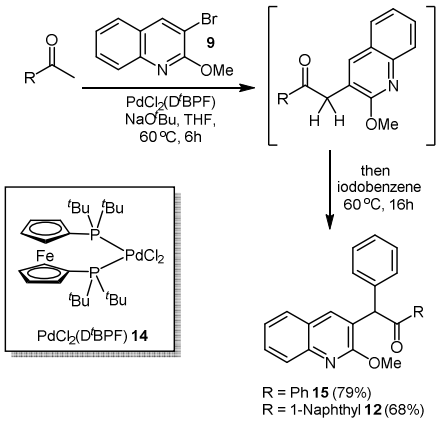



**Scheme 2.** Two alternative pathways provide access to tri-substituted ketones from 1-acetonaphthone




**Scheme 3.** At elevated temperatures, ketone **12** cyclizes to form the furan by-product **13**.

With the step-wise preparation of the α,α-disubstituted naphthone derivative **12** achieved, attention turned to determining if these two Heck reactions could be accomplished in a 'one-pot' process. Employing the stable *tert*-butyl phosphine ferrocene-derived palladium catalyst $PdCl_2(D^tBPF)$ **14**,[20] a one-pot, two-step process involving the initial Heck reaction of the bromoquinoline **9** with the enolate, followed by a second Heck reaction of the enolate with iodobenzene efficiently furnished the tri-substituted ketones containing the requisite phenyl and quinoline aromatic groups (Scheme 4).[20] This reaction was carried out with both acetophenone and 1-naphthone to afford the di-phenyl and phenyl-naphthyl derivatives **12** and **15** in good yield. Again for this reaction process, the second step was performed at moderate temperatures to avoid the formation of furan **13**.




**Scheme 4.** The one-pot palladium-catalysed di-arylation of ketones

Utilizing either the step-wise (Scheme 2) or one-pot (Scheme 4) process to access the α,α-disubstituted aryl ketones, it can be envisaged that diversely foliated triaryl ketones (that are able to be readily converted to bedaquiline analogues **3**) could be rapidly prepared from acetophenones, aryl halides and heteroaryl halides containing various substitution patterns.

A second strategy to access bedaquiline analogues from *heteroaryl halides* was then developed with the key reaction being the palladium catalysed Suzuki-Miyaura cross-coupling of bromoquinoline **9** with a di-boronate alkene derived from phenylacetylene (Scheme 5). Initially, diphenylacetylene (**16**) was reacted with bis(pinacolato)diboron in the presence of 2 mol% of $Pt(PPh_3)_4$ to afford the bis-boronate alkene **17** in 88% yield.[21] This boronic ester was then subjected to a palladium-catalysed Suzuki-Miyaura reaction with bromoquinoline **9**. Shimizu and co-workers reported that this reaction required heating at 65 °C for 48 hours to achieve full conversion,[22,23] however, in our hands it was discovered that high yields could be obtained by heating the reaction mixture at 100 °C for only 1 hour in a microwave reactor (Scheme 5). In some cases, trace amounts of the di-coupled product were observed following LCMS analysis of the crude reaction mixture, however predominantly this reaction process afforded exclusively mono-coupled alkene **18**. The vinyl boronic ester obtained was then converted to the requisite tri-substituted ketone **15** under oxidative conditions using sodium perborate in 81% yield (Scheme 5). This approach provides an alternative pathway to access similar α,α-disubstituted acetophenones to that obtained previously, however in this case they can be prepared from the corresponding disubstituted alkyne.

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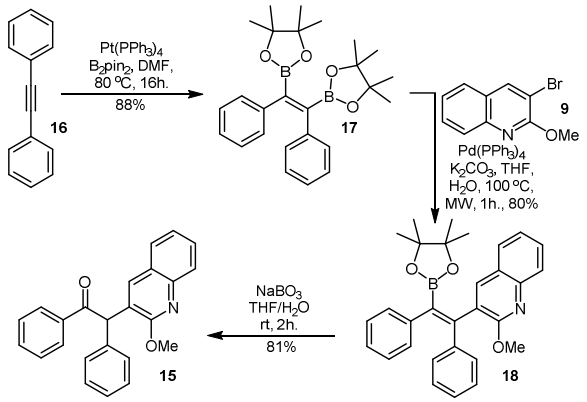
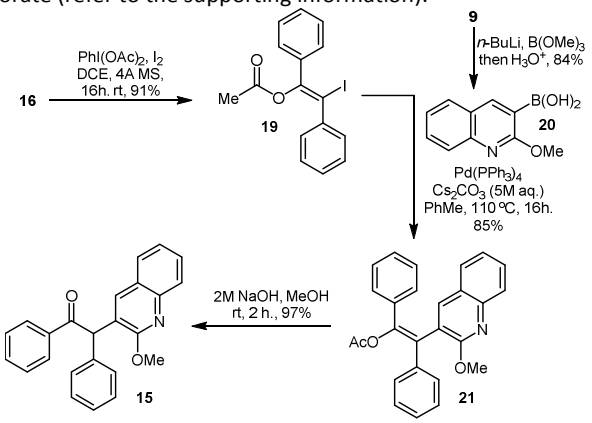



**Scheme 5.** The conversion of diphenylacetylene to a trisubstituted ketone with the key step being a Suzuki-Miyaura reaction using a heteroaryl bromide

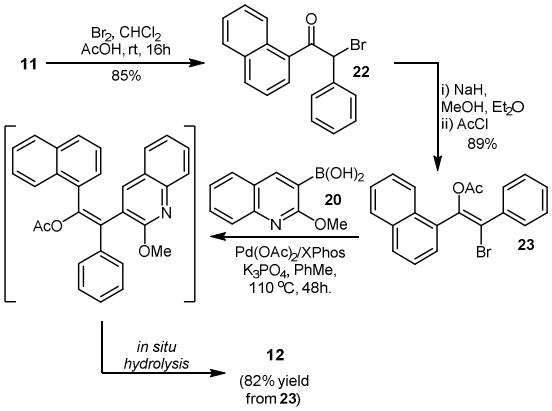
With two alternative pathways identified for the preparation of tri-substituted ketones from *heteroaryl halides* **7**, our attention then turned to an orthogonal route that would facilitate the use of *heterocyclic boronic acids* **6**. To achieve this, a Suzuki-Miyaura reaction was employed, in this case between 2-methoxyquinolinyl-3-boronic acid (**20**) and a suitable vinyl halide. Boronic acid **20** can be synthesized from 2-methoxyquinoline,[24] or 3-bromo-2-methoxy quinoline (**9**) by reaction with *n*-butyl lithium in the presence of trimethyl borate (refer to the supporting information).[25]




**Scheme 6.** The conversion of diphenylacetylene to a trisubstituted ketone with the key step being a Suzuki-Miyaura reaction using a heteroaryl boronic acid

To enable the efficient preparation of the requisite iodo-alkene **19** from diphenylacetylene (**16**), our group recently reported a new iodoacyloxylation protocol of alkynes utilizing iodobenzene diacetate and iodine.[26] This method facilitated the introduction of both a halide and acetoxy group to afford an enol ester that can readily undergo palladium cross-coupling reactions. The Suzuki-Miyaura reaction between **19** and **20** yielded tri-aryl substituted enolate **21** in 85% yield. The enolate was subsequently hydrolyzed under basic conditions to afford quinoline substituted acetophenone **15** (Scheme 6). During the Suzuki-Miyaura reaction, the formation of trace amounts of the by-product 2,2'-dimethoxy-3,3'-biquinoline was observed as a result of dimerization of the quinoline boronic acid.

The synthesis of the corresponding naphthyl derivative **12** was then conducted utilizing a similar approach. Bromo-enol acetate **23** was prepared from 1-acetonaphthone in four steps (Scheme 7).[27] The Suzuki-Miyaura cross-coupling of bromo alkene **23** with quinolyl boronic acid **20** was then performed. Initially, the conditions that were previously applied for this type of cross-coupling process (see Scheme 6) afforded only trace amounts of the desired product. Subsequent optimization identified that a catalytic system of palladium acetate and X-Phos in toluene in the presence of potassium phosphate under reflux for 48 hours was better suited to this reaction process. Under these conditions, subsequent hydrolysis of the enol acetate also occurred to afford the tri-substituted ketone **12** in 82% yield (Scheme 7). Again, it can be envisaged that by employing this approach, the rapid preparation of diversely foliated bedaquiline analogues could be achieved utilizing diphenylacetylenes, or ketones and heteroaryl boronic acids that contain varying substitution patterns.




**Scheme 7.** The synthesis of a trisubstituted ketone from 1-acetonaphthone with the key step being a Suzuki-Miyaura reaction using a heteroaryl boronic acid

With multiple methods now identified for the synthesis of α,α-disubstituted aryl ketones **12** and **15** containing the requisite heteroaryl motif, our attention turned to the elaboration of the ketone to install the dimethylethylamino tether. Although analogous transformations have been previously reported,[18,19] optimization of this pathway was still required to identify reproducible and high-yielding reaction conditions. The initial step involved the 1,2 carbonyl addition of an allyl group across ketone **12** to afford the tertiary allyl alcohol **24**. Despite numerous attempts by our group and others[19] to react various organometallic reagents with the ketone including Grignard reagents, aryl and alkyl lithiums and zinc enolates (under Reformatsky conditions), the only reaction that proved successful in this case was the use of freshly prepared allyl-ZnBr (Scheme 8).[19] It was proposed that due to the acidity of the α-proton of the ketone, basic Grignard reagents led to deprotonation and enolization of the ketone before 1,2-addition to the carbonyl group could occur. Organozincates are non-basic reagents and as such, the use of allyl zinc bromide did not promote enolization but facilitated the addition of the allyl group to the carbonyl to afford the

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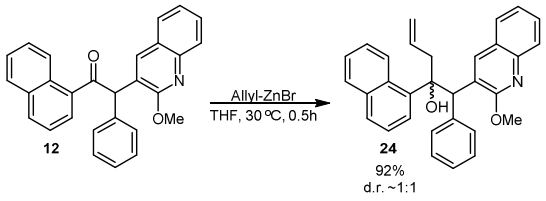
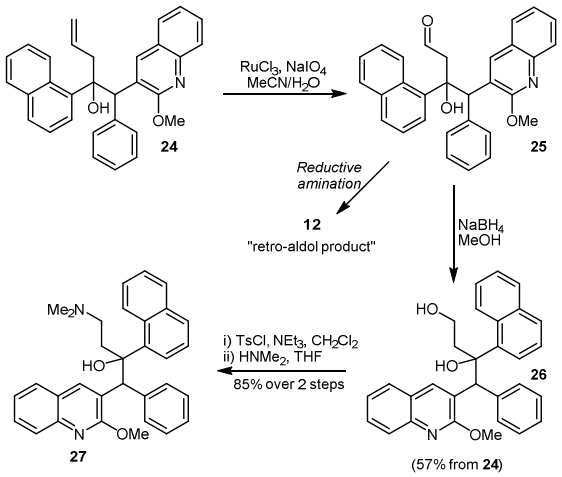
requisite tertiary alcohol **24** in excellent yield of 92% (Scheme 8).[19] An alternative approach towards enhancing the reactivity of Grignard reagents during the 1,2-addition to enolisable carbonyl compounds through the formation of $LaCl_3 \cdot 2LiCl$ complexes has been recently reported,[28, 29] however in our hands, the use of allyl-ZnBr proved satisfactory. During optimization, it was observed that if the reaction was performed at lower temperatures (for example, 0°C), the formation of the *R,R* & *S,S* diastereoisomeric pair was favored. However, typically a diastereomeric ratio of 1:1 could be achieved when the reaction was undertaken at 30 °C. If excess allyl-ZnBr (>2.0 equiv.) was employed or the reaction time prolonged (>1h), cleavage of the 2-methoxy group to afford the 2-desmethoxy version of **24** took place.




**Scheme 8.** Allylation of ketone **12** afforded the tertiary alcohol **24**

With the allyl motif installed, the next step was oxidative cleavage of the alkene to afford an aldehyde which could be subsequently reduced to the alcohol. Literature reports described the use of ozonolysis to achieve this transformation,[18] however, in our hands, ozonolysis resulted in highly variable yields and, in some cases, substrate degradation (particularly in the case of electron rich N-heterocycles). To circumvent this, a more mild ruthenium chloride catalysed oxidative cleavage protocol was employed using sodium periodate in an acetonitrile/water solvent combination (Scheme 9).[30] These reaction conditions reliably converted alkene **24** to aldehyde **25** which was subsequently reduced using $NaBH_4$ in MeOH to afford diol **26** in 57% yield over two steps. During the early stages of this investigation, reductive amination of aldehyde **25** with various amines was explored, however in each case, a retro-aldol reaction predominated to regenerate ketone **12**. To complete this pathway, tosylation of the primary alcohol, which was subsequently displaced by dimethylamine afforded the final compound **27** in an excellent yield of 85% over two steps (Scheme 9). The diastereomeric pairs (*RR* & *SS*) and (*RS & SR*) were readily separable by preparative HPLC (refer to the supporting information).




**Scheme 9.** Conversion of the allyl group to the dimethylamino tether

As demonstrated, multiple synthetic approaches have been identified to access analogues of bedaquiline **3** from either heteroaryl boronic acids **6** or heteroaryl halides **7**. These pathways facilitate access to a diverse range of bedaquiline analogues whereby the quinoline motif would be readily replaceable by any number of heterocyclic functional groups.

To further highlight the value of the synthetic approaches described herein, bedaquiline analogues were prepared whereby the 2-methoxyquinoline was replaced with either 2-methoxypyridine or 2,6-dimethoxypyridine (Scheme 10). Preparation of the 2-methoxypyridine analogue **32** involved a key palladium-catalysed Suzuki-Miyaura cross-coupling reaction between a commercially available 2-methoxypyridine-3-boronic acid (**28**) and diphenyl-iodoacetate **19** (scheme 10, left). Subsequent hydrolysis of the triaryl enol acetate **29** afforded the requisite ketone **30**. During optimization, it was observed that bromination of the 5-pyridyl position of **30** to form **31** was required prior to reaction with allyl zinc bromide to avoid allylation at this position. Allylation of **31**, followed by conversion of the allyl group to the ethyl dimethylamino tether afforded the bedaquiline analogue **32** in 49% yield over five steps. To access the 2,6-dimethoxypyridyl analogue **37**, a key palladium catalysed Suzuki-Miyaura cross-coupling reaction between bis-boronate **17** and 3-bromo-2,6-dimethoxypyridine (**33**) afforded **34** as a masked enol in 77% yield (Scheme 10, right). Oxidation of the remaining boronate group provided ketone **35** in 90% yield, which was subsequently brominated to afford 5-bromopyridine **36**, which was then able to be converted to bedaquiline analogue **37** in 38% yield over five steps using methods analogous to that described previously (Scheme 10, right).

## Conclusion

To enable the preparation of novel pharmaceutical agents for the treatment of MDR-TB that exhibit improved safety profiles, novel synthetic pathways to access bedaquiline analogues were required. To this end, multiple synthetic approaches that

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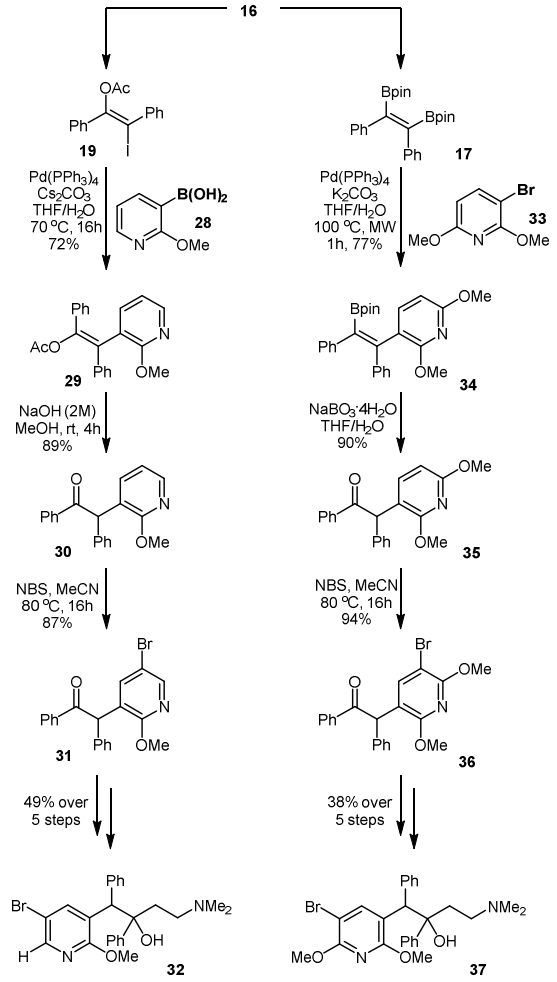
facilitate the efficient incorporation of heterocyclic motifs other than quinoline have been developed. Importantly, orthogonal approaches that allow the use of either heteroaryl halides or heteroaryl boronic acids as substrates were identified. Infact, through judicious reagent choice, the methods described herein will facilitate substitution of the quinoline, phenyl and/or naphthyl groups present in bedaquiline. Application of these synthetic pathways in a drug discovery program focused on the development of bedaquiline analogues with an improved safety profile is underway in our laboratories and these results will be reported in due course.




**Scheme 10.** Preparation of 2-methoxypyridine and 2,6-dimethoxypyridine analogues of bedaquiline from diphenylacetylene using orthogonal synthetic routes.

## Acknowledgements

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## Experimental Section

Experimental details including NMR spectra for all compounds are included in the supporting information.

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