

Improved Synthesis and Isolation of Bedaquiline

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ABSTRACT: Bedaquiline (BDQ) is the most critical pharmaceutical in the world for treating multidrug-resistant *Mycobacterium tuberculosis*. Despite it being highly effective, BDQ asymmetric synthesis remains a challenge. Herein, the influence of chiral bases, namely, bis(1-phenylethyl)amine, bisoxazoline, and sparteine on the diastereoselective lithiation reaction to obtain BDQ was investigated. The highest diastereoselective ratio (dr) emerged as 90:10 from the (+)-bis[(*R*)-1-phenylethyl] lithium amide. This is a significant improvement from the 50:50 dr achieved from the commercial synthesis. Thereafter, the desired (90:10 *RS*, *SR*) diastereomeric mixture was easily isolated via a gravity column and subjected to chiral supercritical fluid chromatography (SFC) to access the desired enantiomer (1*R*, 2*S*)-BDQ. The advantages of this procedure are enhanced diastereoselection as well as a greener, faster way to achieve excellent enantioseparation (up to 1.0 g scale).

INTRODUCTION

Tuberculosis (TB) is a global endemic cause of disability and death.¹ It is estimated that up to one-third of the world's population has been infected with TB, more commonly in areas where crowded housing, poverty, poor general health, malnutrition, HIV coinfection, and other social disruptions are present.² It is mainly caused by an infection with *Mycobacterium tuberculosis* (*M. tuberculosis*). *M. tuberculosis* has developed multidrug resistance (MDR) toward first-line TB treatment due to mutation of the pathogen upon patient discontinuation or an incorrect drug prescription.³ MDR-TB regimens are more intensive, prolonged, expensive, and often unsuccessful. Therefore, there is an urgent calling for development of new agents that may shorten the duration of therapy, have minimal interaction with antiretroviral drugs,⁴ have simple dosage schedules, improve adherence, decrease the risk of relapse while reducing mortality, and potentially control the MDR-TB epidemic.⁵

In 2005, Andries and co-workers reported the first MDR antituberculosis drug known as TMC 207⁶ at the time and now referred to as bedaquiline (BDQ) fumarate marketed under the trade name Sirturo.⁷ It was given fast approval by the Food and Drug Administration (FDA) in late 2012 under the accelerated approval program.⁸ It emerged as the first antituberculosis-specific drug in 40 years; it inhibits the proton pump for *M. tuberculosis*'s adenosine triphosphate (ATP) synthase representing a novel mechanism of action for pulmonary drug-resistant tuberculosis.⁹ BDQ has a bactericidal and sterilizing activity against *M. tuberculosis* by hindering the ATP generation whereby it targets the central region of a c

subunit of the ATP synthase enzyme. It has proven to be a significant step toward providing a shorter and more tolerable regimen for patients infected with drug-resistant tuberculosis.¹⁰ BDQ appears on the World Health Organization's List of Essential Medicines and is only commercially available in a handful of countries.¹¹ The cost of BDQ (per 6-month treatment) ranges from US\$30,000 to US\$900, from high- to low-income countries, respectively.¹²

On a molecular level, BDQ (Figure 1) contains two stereogenic centers; therefore, in the absence of an external chiral medium, its chemical synthesis will lead to four isomers, which are distributed in a mixture of two pairs of diastereoisomers, namely, (*RS*, *SR*) and (*RR*, *SS*). The (1*R*, 2*S*) stereoisomer is the most active isomer against tuberculosis and is known as BDQ. Andries et al. performed the experiments to test the activity of all four stereoisomers against multidrug-resistant strains of *M. tuberculosis*. They reported the concentration that causes 90% inhibition to bacterial growth (IC₉₀) for each isomer as well as that of the mixture of the two isomers. The (*R,S*) and (*S,R*) gave values of 0.03 and 8.8 μg/mL, respectively, and when combined, produced a value of 1.8 μg/mL, as shown in Figure 1. The (*R,R*) and (*S,S*) isomers gave IC₉₀ values of 4.4 and 8.8 μg/mL, respectively, while the mixture yielded a value of 4.4 μg/

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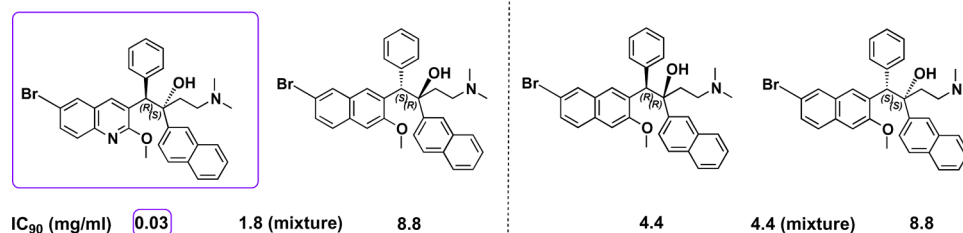


Figure 1. Four isomers of bedaquiline with the most active isomer, as depicted with its antimycobacterial activity (IC_{90}) against *M. tuberculosis*.¹³

Scheme 1. Lithiation Reaction between the Appropriate 3-Benzylquinoline (1) and 3-(Dimethylamino)phenylpropan-1-one (2) To Obtain Bedaquiline (3)

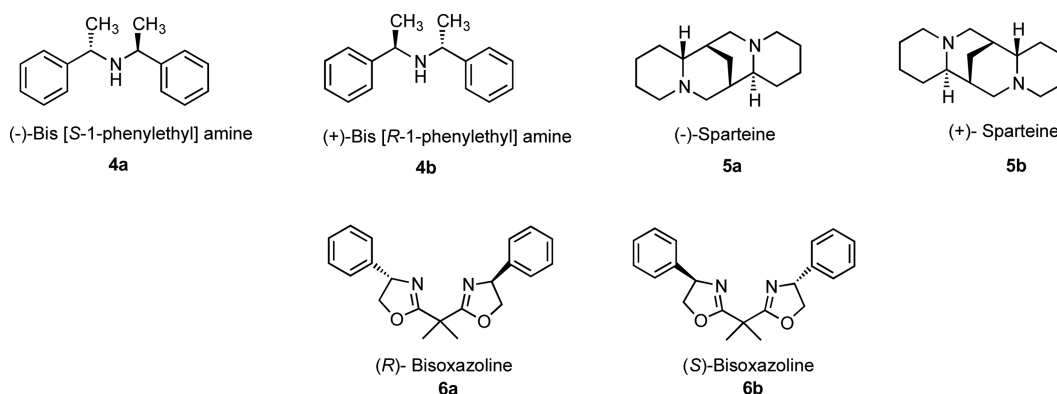
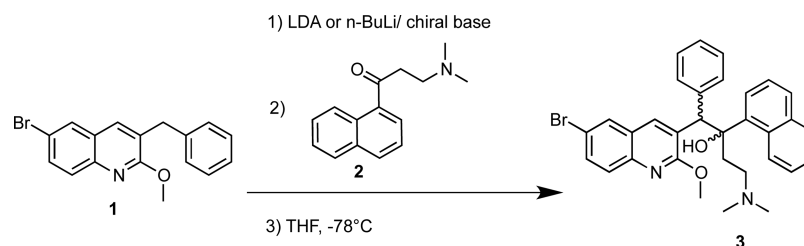


Figure 2. Chiral bases utilized in the lithiation step.

mL.¹³ These results demonstrated the need to optimally isolate the (R,S) isomer to exclusively treat *M. tuberculosis*.

The initial synthesis conducted by Johnson & Johnson reported the one-step deprotonation of the starting quinoline (1) with LDA. They accomplished the separation of the desired diastereomer from the mixture by taking advantage of the uniqueness of the diastereomer's solubility in acetic acid/THF (tetrahydrofuran). Later, they separated the mixture of two enantiomers using a chiral resolution agent. However, after separation, three-quarters of the final products were discarded, half was the undesired diastereomer, and a quarter was the undesired enantiomer.¹⁴ The overall yield obtained was merely 1%. This method resulted in low yields, poor enantioselectivity, and low efficiency, which opened the door for possible improvement. To date, there are a few synthetic routes published for the preparation of BDQ.¹⁵ The asymmetric routes include the work done by Saga et al. that developed a convergent asymmetric synthesis. Apart from the complexity of their method and the use of expensive reagents, their synthesis involved 12 linear steps from commercially available compounds with an overall yield of 5%.¹⁶ Later, Chandrasekhar and co-workers reported the asymmetric synthesis of the desired isomer. This method took the linear tactic in 10 steps with an overall yield of 12%.¹⁷ The most likely (Janssen

Pharmaceutical) industrial process relies on a one-step lithiation reaction (using LDA as the base) after which chiral resolution (with binaphthol phosphate) is being utilized to isolate the desired isomer for its large-scale production,¹⁸ however, drawbacks still include the loss of the desired diastereomer in the first step (due to the absence of chiral environment) and low overall yields. The diastereomer (RS, SR) is separated from the crude mixture of diastereomers (50:50) by recrystallization. Subsequently, the diastereomer (RS, SR) is then converted into its diastereomeric salt with a chiral resolution agent from which the desired stereoisomer (R, S) is isolated by recrystallization following neutralization of the salt to afford the free drug as a single enantiomer. The chiral resolution adds two more steps to the already low-yielding one-pot procedure.

Herein, we report the influence of replacing the nonchiral base LDA in the lithiation step to form BDQ with chiral bases, namely, bis-phenylethylamine,^{19–21} bisoxazoline,^{22,23} and sparteine^{24–26} with the intention of improving the yield of the desired diastereoisomer (RS, SR) without increasing the number of synthetic steps. Thereafter, we report the optimization and isolation of the desired enantiomer (R,S) from the mixture using chiral supercritical fluid chromatography (SFC).²⁷

Nowadays, SFC has become a widely used technique on both analytical and preparative scales due to its advantages over traditional high-performance liquid chromatography.²⁸ A remarkably faster separation speed, lower viscosity that allows higher flow rates, and high diffusivity, which result in an overall better efficiency and reduction of using organic solvents (as much as 90% less), are achieved with the use of inexpensive CO₂. These “green” aspects coupled to the ease of sample collection make SFC an attractive option to be used to assist in accessing pharmaceutically important molecules²⁷ such as BDQ, especially when the purification step could substitute some of the expensive steps within the synthetic route.

RESULTS AND DISCUSSION

First, we conducted the synthesis of BDQ using lithium diisopropylamide (LDA) as a base as per the original procedure (Scheme 1).¹⁴ This route used 5:5 equiv of *n*-BuLi/diisopropylamine in THF, the deprotonation step took place for 30 min and the reaction with the electrophile for 3 h at -78 °C.

This method formed the product mixture with a 50:50 diastereomeric ratio (dr) of (*RS*, *SR*) and (*RR*, *SS*), with approximately 10 and 17% yield, respectively, which was in keeping with the original report.¹⁴

We aimed to substitute the diisopropylamine with a chiral base, that is, **4a-b**, **5a-b**, and **6a-b** (typically reported to be used in asymmetric deprotonation lithiation) as represented in Figure 2 in hope of increasing the dr of the desired isomer.

Following the conditions from the LDA reaction, the single enantiomer **4a**¹⁹ as the chiral base was evaluated using 5:5 equiv of *n*-BuLi/**4a**. After careful examination of the results obtained during the lithiation step, we discovered that the chiral complex behaved very differently to the nonchiral LDA complex. Also, further meticulous care had to be taken to prevent the complex from being quenched with regard to the introduction of moisture from the solvent, apparatus setup, glassware used, and the concentration of the *n*-BuLi that had to be consistently checked. Although the reaction took place, there was no desired product formation; instead, the abstraction of the bromine atom took place from the commercially available quinoline **1** as well as the product **3** (refer to Scheme 1), which could have been a result of the high reactivity of the *n*-BuLi complex. After further optimization, the *n*-BuLi/**4a** concentration of 3:2 provided a 5% conversion of **1** to **3**. Further lowering the amount of the Li complex resulted in no reaction at all. (The following optimization results can be found in the Supporting Information.)

Next, we investigated the temperature of the deprotonation step (of quinoline **1**) since the literature reports this step to play a crucial role in the reactivity of certain substrates.^{20,24} The temperature was increased within the range of -60 to 0 °C to determine the optimal energy required for the chiral complex to deprotonate the substrate (**1**). The highest conversion was observed at -20 °C, which was around 15% conversion. The temperature of 0 °C resulted in a quite messy reaction indicating several undesirable reactions taking place. At this point, we considered using solvents such as toluene, diethyl ether, cumene, and hexane as they have been reported as typical solvents to conduct lithiation.^{29,30} However, the limitation was the insolubility of the reagents irrespective of concentration or temperature. Thus, THF remained as the only option to conduct further experiments.

Thereafter, the deprotonation time was optimized (from 15 to 120 min) using the same chiral base **4a** to investigate the possibility of obtaining a higher % conversion and/or a better dr. The deprotonation time of 60 min resulted in the highest % conversion of 33% even though the dr obtained was still 50:50. The dr was measured by integration of the chiral proton (H6) where 5.89 ppm (desired) and 5.73 ppm (undesired) were determined from the crude ¹H NMR spectrum.

Previous studies have indicated that the selectivity of the chiral Li complex, when using base **4a-b** for deprotonation, can be influenced by the formation of mixed aggregates between LiCl, formed by the reaction of the respective lithium complex with **1**, and **4a-b**, which is more reactive and selective than the monomer or dimer of **4a-b**.³¹ Simpkins and Bunn reported a substantial improvement in the stereochemistry of chiral base-mediated deprotonation reaction products with the presence of added LiCl.³² There are several reports that generate the **4a-b**.LiCl mixed heterodimeric Li-amide/LiCl complexes, that is, either from the direct addition of LiCl to **4a-b** or the addition of BuLi to the **4a-b** hydrochloride salt.^{21,31,33}

Thus, in the next experiment, **4a** was treated first with LiCl (2 equiv) to generate **4a**·LiCl followed by the sequential addition of **1** and **2**. In this case, the dr of the product changed to 45:55. Thereafter, the deprotonation of **1** was carried out with the in situ-generated **4a**·LiCl that was obtained by treatment of the **4a** hydrochloride salt with 3 equiv of *n*-BuLi. This reaction yielded a crude mixture with 30:70 dr in which 30% was the desired (*RS*, *SR*) and 70% was the (*RR*, *SS*) undesired diastereomer.

In the hope of reversing the dr to favor the formation of the desired diastereomer, we then conducted an experiment with the opposite enantiomer of **4a**, that is, using *n*-BuLi/**4b**. To our delight, this led to 90% of the desired (*RS*, *SR*) and 10% of the undesired (*RR*, *SS*) diastereomer. At this point, we still tried to improve the conversion with longer reaction times. However, this increased the formation of the undesired diastereomer. A possible reason could be that the mixed **4b**·LiCl complex is equilibrated toward a less active complex when the lithium alkoxide product is increasing in concentration, for example, by competing for LiCl from the Li-amide or forming less reactive mixed Li-amide/Li-alkoxide complexes.³⁴ This proved to be a limitation in the reaction from going to completion. The summary of these modifications and dr obtained are shown in Table 1.

Subsequently, we focused our attempts on using the other chiral bases, that is, sparteine and bisoxazoline using our

Table 1. Summary of Modifications Done with the Chiral Ligand **4a-b**

entry	base	dr	% conversion ^a
1	LDA	50:50	31
2	<i>n</i> -BuLi/ 4a	50:50	33
3	<i>n</i> -BuLi/ 4a ·LiCl ^b	45:55	31
4	<i>n</i> -BuLi/ 4a ·LiCl ^c	30:70	32
5	<i>n</i> -BuLi/ 4b ·LiCl	90:10	33

^a% Conversion was determined by liquid chromatography–mass spectrometry using a YMC-Triart-C18 column unless stated otherwise, and the dr was determined by crude ¹H NMR. The deprotonation step was conducted at -20 °C for 60 min; thereafter, the reaction proceeded at -78 °C. All optimization reactions were carried out on a 0.15 mmol scale unless stated otherwise. ^bAddition of LiCl to neutral **4a**. ^cAddition of *n*-BuLi to **4a**·HCl salt.

optimized conditions. With chiral complexes made from **5a** and **5b**, we again encountered the formation of 250 *m/z* during the deprotonation, which indicated abstraction of bromine taking place from **1**. Further attempts to optimize the reaction conditions were endeavored such as modifications in temperatures, chiral base equivalents, and the use of *s*-BuLi instead of *n*-BuLi as well as the reaction times. However, the optimal deprotonation still did not occur. For **6a** and **6b**, no reaction took place due to the failure of the deprotonation step to occur, as only the starting material was observed.

With the optimal conditions in hand, with *n*-BuLi/4b·LiCl (Table 1, entry 5), the reaction was carried out on a 1 g scale. The mixture of the (*RS*, *SR*) and (*RR*, *SS*) diastereomers (39% yield, 330 mg, dr of 90:10) thus obtained was then separated by a gravity column of which the desired diastereomer (86%, 285 mg, (*RS*, *SR*)) and undesired diastereomer (10%, 35 mg, (*RR*, *SS*)) were obtained. The isolated desired diastereomer was then subjected to chromatographic separation using a compact Sepiatec Prep basic SFC system fitted with a chiral analytical column for separation of the enantiomers. The simplified handling of this instrument proved to be very convenient when using the stacked injection feature. The enantiomers were successfully eluted under isocratic conditions using stacked injections to afford the desired enantiomer (1*R*, 2*S*; 130 mg) and the undesired enantiomer (1*S*, 2*R*; 142 mg). The overall reaction yield was 13% and >99 ee. The BDQ obtained from this study was further used to investigate its central nervous system penetration in an animal model.³⁵ During the preparation of this manuscript, we came across a 2017 patent written in Chinese having applied a similar concept to make BDQ. They made use of a chiral amino alcohol as the chiral inducer for the lithiation step in the presence of a mixture of both LDA and *n*-BuLi.³⁶ The obtained ratio of the diastereomers (*RS*, *SR*) and (*RR*, *SS*) was 80:20; thereafter, they made use of a chiral resolution agent to obtain the desired enantiomer in a 15% overall yield. This makes the study herein only one of the two reports that have improved the ratio of the diastereomers for the synthesis of this important drug.

CONCLUSIONS

We have achieved a highly diastereoselective synthesis of BDQ using the optimized lithiation conditions with the chiral ligand bis(1-phenylethyl)amine **4b**. The use of 3:2 equiv of *n*-BuLi/**4b** afforded the dr of 90:10 for (*RS*, *SR*) and (*RR*, *SS*) diastereomers, respectively, with 33% yield, compared to the dr of 50:50 obtained from syntheses in the absence of a chiral environment. This suggests that such a method can be utilized for the diastereoselective synthesis of BDQ. Thereafter, the desired diastereomer (*RS*, *SR*) was easily isolated via a gravity SiO₂ column and subjected to chiral SFC separation to obtain the desired (1*R*, 2*S*) enantiomer with an overall reaction yield of 13%; this is similar to other attempts reported to advance the BDQ asymmetric synthesis. To this end, the reaction turnover requires improvement without compromising the diastereoselectivity, which poses a challenge. There is also a gap for industrial chemists to further address practical isolation procedures toward the larger-scale synthesis of BDQ. Nevertheless, the advantages of this technique are improved diastereoselection and a greener and faster way to achieve excellent enantioselective separation (scalable) to obtain BDQ in the laboratory.

EXPERIMENTAL SECTION

Optimized Procedure Using 4b·HCl. The salt was made according to the reported procedure.³¹ To a solution of 4b·HCl salt (1.6 g, 2 equiv) in THF (20.0 mL), 5.61 mL of 1.6 M *n*-BuLi in hexane (9.2 mmol, 3 equiv) was added dropwise at −78 °C under the flow of argon. The solution was stirred for 10 min, warmed up to room temperature, and stirred further for 1 h. The clear yellow solution was recooled to −78 °C and again stirred for 1 h to form a pinkish solution of the chiral base complex.

Lithiation Step. A solution of **1** (1.0 g, 1 equiv) in THF (10.0 mL) was slowly added to an in situ-formed chiral base from above and stirred at −20 °C. After exactly 1 h, a solution of **2** (0.83 g, 1.2 equiv) in THF (10.0 mL) was added dropwise over 20 min via a cannula, and the resulting solution was stirred at −78 °C for 3 h. The reaction was warmed up to room temperature, quenched with aqueous NaCl (20.0 mL), and then extracted with EtOAc (5 × 10.0 mL). The organic layer was dried over anhydrous MgSO₄ and concentrated in vacuo to give a clear yellow oil. The crude product was further purified by flash column chromatography (1:1 EtOAc/hexane). The R_f values were 0.30 for the undesired (35 mg) and 0.44 for the desired (285 mg) diastereomer obtained as white solids. The (*RS*, *SR*) was then subjected to semi-preparative SFC for separation, which provided the desired enantiomer (1*R*,2*S*) (130 mg).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.9b04037>.

Further experimental details, optimization tables, and full characterization data (PDF).

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Notes

The authors declare no competing financial interest.

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