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Development of a Scalable Process for the Synthesis of DNDI-VL-2098: A Potential Preclinical Drug Candidate for the Treatment of Visceral Leishmaniasis

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ABSTRACT: A process suitable for kilogram-scale synthesis of (2*R*)-2-methyl-6-nitro-2-{[4-(trifluoromethoxy)phenoxy]-methyl}-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (DNDI-VL-2098, **2**), a preclinical drug candidate for the treatment of visceral leishmaniasis, is described. The four-step synthesis of the target compound involves the Sharpless asymmetric epoxidation of 2-methyl-2-propen-1-ol, **8**. Identification of a suitable synthetic route using retrosynthetic analysis and development of a scalable process to access several kilograms of **2** are illustrated. The process was simplified by employing in situ synthesis of some intermediates, reducing safety hazards, and eliminating the need for column chromatography. The improved reactions were carried out on the kilogram scale to produce **2** in good yield, high optical purity, and high quality.

KEYWORDS: *leishmaniasis, Sharpless asymmetric epoxidation, scalable process, safety hazards*

INTRODUCTION

Visceral leishmaniasis (VL), infamously known as kala-azar (black fever) in the Indian subcontinent, is the most lethal form of leishmaniasis and is caused by protozoan parasites.[1] This deadly disease is the second largest parasitic killer in the world, surpassed only by malaria, with a worldwide distribution in Asia, East Africa, South America, and the Mediterranean region.[2] In the search for effective treatments for visceral leishmaniasis, the Drugs for Neglected Diseases *initiative* (DND*i*) recently evaluated fexinidazole (**1**, Figure 1), a

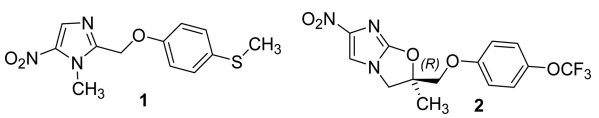

Figure 1. Structures of fexinidazole (**1**) and DNDI-VL-2098 (**2**).

nitroimidazole being developed as a treatment for Human African Trypanosomiasis. Fexinidazole **1** showed potential as a safe and effective oral drug for the treatment of visceral leishmaniasis and is now in clinical trials.[3] Earlier, through an agreement with TB Alliance and in association with the ACSRC at the University of Auckland (NZ), DND*i* screened about 70 other nitroimidazole analogues belonging to four chemical subclasses and investigated them for antileishmanial activity. Through these efforts, DNDI-VL-2098 (**2**, Figure 1) was identified as a promising drug candidate for the treatment of visceral leishmaniasis. To support preclinical studies of this nitroimidazo-oxazole based compound **2**, the process chemistry team at Advinus Therapeutics Ltd. initiated the development of a safe and scalable process to produce it on the kilogram scale. In this communication, we wish to report a robust and practical synthesis suitable for the preparation of multikilogram quantities of **2**.

ANTECEDENTS AND RESULTS

Having identified the target compound, DND*i* collaborated with Advinus Therapeutics Ltd., India for its kilogram scale synthesis. The process chemistry team at Advinus began route scouting to develop a scalable and safe process for the synthesis of **2**. The objective was to produce about 10 kg of **2** to support preclinical and pharmaceutical development studies, within a stringent time frame, utilizing the available resources, and with due regard for overall process efficiency and cost. During the initial drug discovery stage, the racemic analogue of **2** (DNDI-VL-2001) as well as the *R*- and *S*-enantiomers (DNDI-VL-2098

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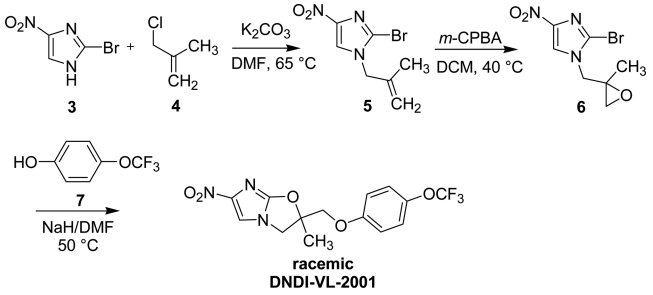
and DNDI-VL-2099, respectively) were evaluated as potential drug candidates to treat visceral leishmaniasis. The Auckland medicinal chemistry group had synthesized multigram quantities of the racemate using a route shown in Scheme 1 that had

Scheme 1. Synthesis of the Racemate DNDI-VL-2001



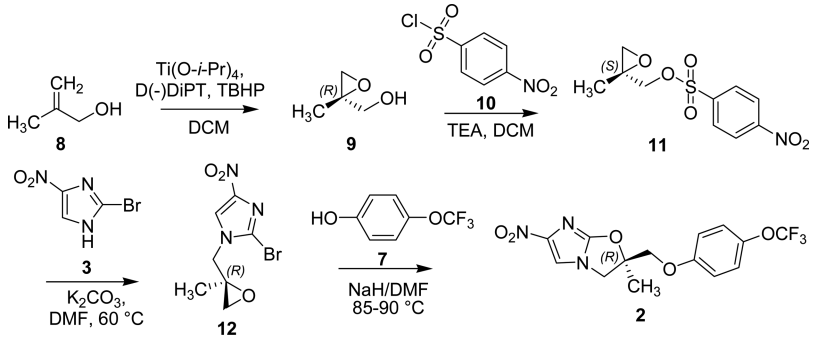
been employed in initial work at the University of Auckland.[4] Pure enantiomers needed for preliminary efficacy and pharmacokinetic evaluation were prepared at the University of Auckland using a route similar to that shown in Scheme 2 below, but using 2-chloro-4-nitroimidazole in place of 2-bromo-4-nitroimidazole in step 3. This route was based on methods published by Otsuka Pharmaceuticals[5] for the synthesis of analogues of **2**.

The process chemistry team initially considered Scheme 1 for the synthesis of DNDI-VL-2001, which could then be subjected to chiral resolution to obtain **2** in high optical purity. However, because nitroimidazoles are insufficiently basic for salt resolution processes, attention was focused on asymmetric synthetic approaches. After carrying out a detailed literature survey and careful retrosynthetic analysis, two pathways were designed for the synthesis of **2**. Both pathways (Figure 2) used 2-bromo-4-nitroimidazole **3** and 2-methyl-2-propen-1-ol **8** as key starting materials, and employed Sharpless asymmetric epoxidation of commercially available 2-methyl-2-propen-1-ol **8**. At this juncture, we also needed to ensure the availability of 2-bromo-4-nitro-1*H*-imidazole **3** in large quantities since it was identified as one of the key starting materials. Although the reported routes for the synthesis of **3** are relatively straightforward, several limitations such as poor yield, high cost, and hazardous nitration reactions prevented their use for large-scale production. Hence, the team undertook the process development of **3** in parallel to the process development of **2**. An improved, safe, and practical process suitable for the preparation of multikilogram quantities of **3** has recently been reported.[6]

In the initial Sharpless asymmetric epoxidation step, the team faced several challenges with respect to the isolation and stability of chiral epoxide **9**. Following completion of the epoxidation reaction, the usual aqueous workup resulted in substantial loss of **9** owing to its high water solubility. Nonaqueous workup involving vacuum distillation was unsuitable for scale-up due to the viscous nature of the pot residue and the tendency of epoxide **9** to undergo polymerization. The problems associated with high water solubility and stability during isolation of **9** prompted us to consider its in situ derivatization with *p*-nitrobenzenesulfonyl chloride (**10**), instead of the two-step process proposed in Scheme 2. However, the in situ reaction of **9** with *p*-nitrobenzenesulfonyl chloride (**10**) to prepare intermediate **11** was extremely tedious for several reasons. In the first step to prepare epoxide **9**, *tert*-butyl hydroperoxide (TBHP) was used as an epoxidation agent. After completion of the asymmetric epoxidation reaction, it was essential to reduce the excess TBHP by treatment with trimethyl phosphite in order to prevent its reaction with *p*-nitrobenzenesulfonyl chloride (**10**). On a larger scale, because of the violent and exothermic reaction, it was necessary to quench the excess TBHP very carefully over a long period of time under cold conditions (below −20 °C) to avoid any unsafe situation. Moreover, the necessity for high vacuum distillation to remove excess trimethyl phosphite and trimethyl phosphate, formed after reduction of TBHP, rendered scale-up even more difficult. In addition, during the sulfonylation of **9**, traces of trimethyl phosphite that remained in the reaction mixture reacted with *p*-nitrobenzenesulfonyl chloride (**10**) to form the corresponding sulfinate as an impurity, which was very difficult to separate from the reaction mixture. The multiple recrystallizations needed to obtain substantially pure intermediate **11** inevitably resulted in lower yields of **11**. In situ sulfonylation reactions carried out without quenching TBHP resulted in poor yields and purity of compound **11**; this was presumably due to the reaction of *p*-nitrobenzenesulfonyl chloride (**10**) with TBHP and alcoholic byproducts.

Difficulties in the synthesis and scale-up of **11** led us to explore the possibility of making an ester derivative using benzoyl or *p*-nitrobenzoyl chloride. Synthesis of ester derivative **14** (Scheme 3) by the reaction of the *S* enantiomer of epoxide **9** with *p*-nitrobenzoyl chloride has been reported in the literature.[7] In fact, DNDI-VL-2098 and its analogues were synthesized by Tsubouchi et al.[8] using ester **14**, as described in Scheme 3. However, this route was lengthy and unsuitable for scale-up as the purification of compounds **16**, **18**, and **2** needed column chromatography. In our hands, attempts to purify these compounds by recrystallization resulted in lower yields. In

Scheme 2. Proposed Synthetic Route for 2 Based on Retrosynthetic Pathway 1



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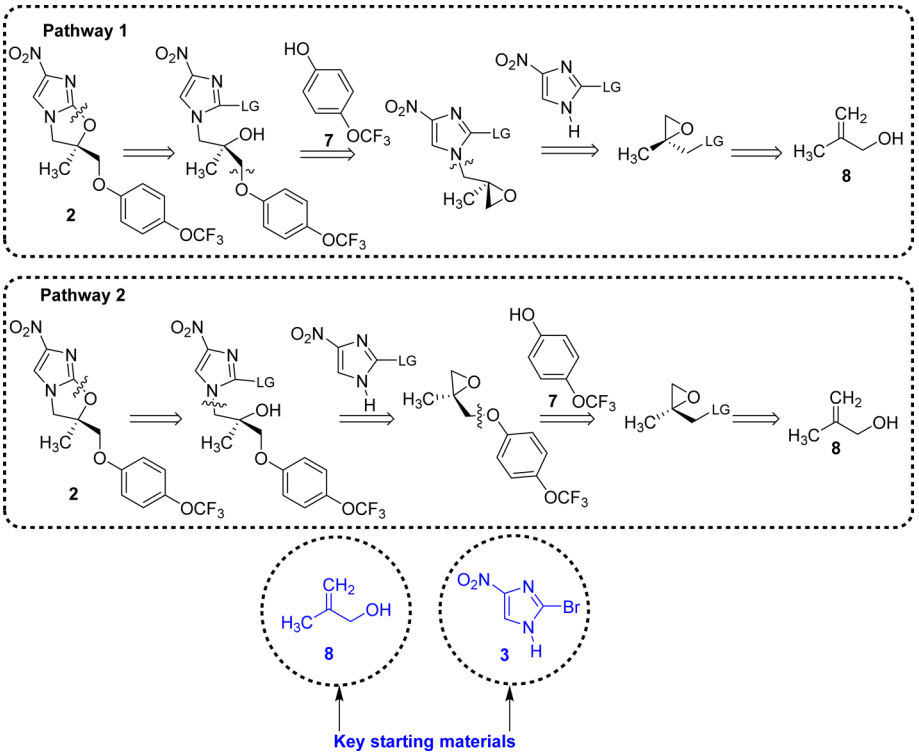
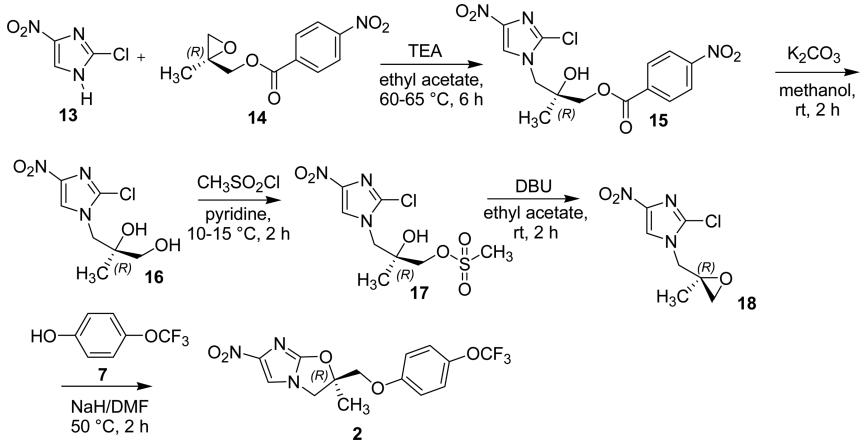


Figure 2. Retrosynthetic pathways for the synthesis of DNDI-VL-2098 (**2**).

Scheme 3. Reported Route for the Synthesis of 2



addition, the problems associated with quenching of TBHP using trimethyl phosphite, and the removal of excess trimethyl phosphite as well as trimethyl phosphate, formed after quenching, persisted even in the synthesis of (*R*)-(2-methyloxiranyl)methyl-4-nitrobenzoate (**14**).

These difficulties led us to focus our efforts on the second retrosynthetic pathway shown in Figure 2. The process team had now realized that, on a large scale, it would be difficult to make a suitable derivative of epoxide **9** in situ while keeping the epoxy ring intact and without quenching all of the TBHP. The team therefore began to explore the possibility of making a derivative of **9** in situ by opening the epoxy ring, which, after isolation, would allow for subsequent reconstruction of this ring. It occurred to us that epoxide **9** could be treated in situ with *p*-trifluoromethoxyphenol (**7**) in the presence of a base, causing nucleophilic opening of the epoxide ring to give (*R*)-2-methyl-3-(4-trifluoromethoxyphenoxy)propane-1,2-diol (**19**) directly, following aqueous workup (Scheme 4). The reaction could be carried out under mild anhydrous conditions and would not be hampered by the presence of TBHP, thus potentially eliminating the tedious low-temperature quenching step (with associated safety issues) and the need for high vacuum distillation. Furthermore, it was obvious that the sulfonylation of diol **19** with *p*-nitrobenzenesulfonyl chloride (**10**) would occur regioselectively at the terminal hydroxyl group to afford compound **20**, owing to the steric hindrance between the *p*-nitrobenzenesulfonyl group of **10** and both the 4-trifluoromethoxyphenoxy group and the 2-methyl substituent adjacent to the tertiary hydroxyl group. Nosylate **20** could then be treated with base to restore the epoxy ring, affording optically pure (*R*)-2-methyl-2-(4-trifluoromethoxyphenoxymethyl)oxirane (**21**). Oxirane **21** could subsequently be reacted with 2-bromo-4-nitroimidazole (**3**) to obtain the desired DNDI-VL-2098 (**2**).

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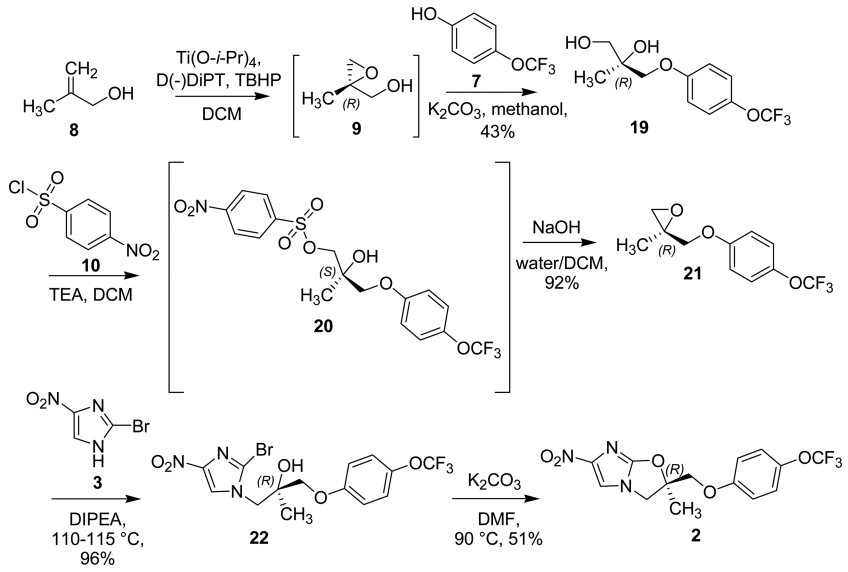
Scheme 4. An Improved Synthesis of DNDI-VL-2098 (2)



To validate the feasibility of this approach (Scheme 4), small-scale reactions (25 g) were initially performed. Fortunately, the in situ reaction of epoxide **9** with *p*-trifluoromethoxyphenol (**7**) proceeded smoothly to give the diol **19** in 45% yield. In this step, the reaction mixture obtained after Sharpless asymmetric epoxidation of **8** was added slowly to a mixture of *p*-trifluoromethoxyphenol (**7**) and anhydrous potassium carbonate in dry methanol at ambient temperature and then stirred at 60 °C for 16 h. After cooling to ambient temperature, the reaction mixture was extracted with dichloromethane, which was then thoroughly washed with water, dilute sodium hydroxide, and brine solution. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated to provide a pale yellow gummy solid, which, on the purification by column chromatography using silica gel, gave the desired diol **19** as an off-white solid in 45% yield. Next, diol **19** was subjected to sulfonylation at the terminal hydroxyl group to obtain the corresponding nosylate, **20**. The subsequent base-catalyzed ring closure proceeded smoothly to give oxirane **21** in high enantiomeric excess and >95% purity (HPLC a/a). Oxirane **21** was then treated with 2-bromo-4-nitroimidazole (**3**) and *N*,*N*-diisopropylethylamine to afford compound **22**, which was further cyclized (K_2CO_3/DMF) to provide the desired DNDI-VL-2098 (**2**) in 51% yield. In order to ascertain the exact configuration, compound **2** thus obtained was subjected to single crystal X-ray crystallographic analysis. The single crystal was obtained by slow evaporation of its saturated solution in acetone. The X-ray structure depicted in Figure 3 unambiguously established the *R*-configuration of **2**.

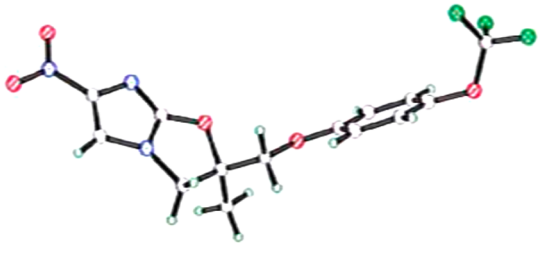


Figure 3. Single crystal X-ray structure of (*R*)-DNDI-VL-2098 (**2**).

Encouraged by these results, we decided to study the scalability of Scheme 4 to prepare DNDI-VL-2098 (**2**) in kilogram quantities. The chemistry discussed above gave rise to a putative process for the synthesis of **2**, but several issues needed to be addressed before proceeding to large-scale synthetic efforts. Especially, issues such as the preparation of anhydrous TBHP for the moisture sensitive Sharpless asymmetric epoxidation and quenching of TBHP after in situ synthesis of the diol **19** needed to be resolved. In addition, molecular sieves, used to maintain anhydrous conditions in the Sharpless asymmetric epoxidation reaction, and column chromatography, used to isolate pure **19**, had to be eliminated for convenient scale-up.

The initial Sharpless asymmetric epoxidation reaction proceeded with excellent conversion (>90% by GC); however, it was essential to maintain anhydrous conditions throughout the reaction. The main reason for this is because water destroys the titanium−tartrate complex, leading to a slow reaction rate and poor enantioselectivity of the desired epoxide.[7] In addition, the presence of water, under mildly acidic conditions, causes the epoxide ring to open, which in turn results in the formation of diol byproducts.

An even greater challenge was to prepare anhydrous TBHP on a larger scale from commercially available aqueous TBHP (~70%). Whereas TBHP in 70% aqueous solution is relative safe to handle, its anhydrous form is highly reactive, flammable, toxic, and prone to violent decomposition by adventitious catalysts and hence is exceptionally dangerous. Procedures to prepare anhydrous TBHP in dichloromethane or toluene have been reported earlier.[9,10] However, these procedures involve azeotropic distillation, which needs to be carried out behind a blast shield in a well-ventilated fume hood because of the flammable and explosive nature of TBHP.[11] The safety concerns associated with azeotropic distillation on a large scale led us to devise a simpler procedure to obtain anhydrous TBHP. The commercially available 70% aqueous TBHP solution was first stirred with dichloromethane. The organic layer was carefully separated, stirred with anhydrous sodium sulfate for 30 min, and then decanted. The procedure was repeated thrice. The solution of anhydrous TBHP in DCM was carefully collected in a clean and dry container. The strength of

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this solution of TBHP in DCM was determined by iodometric titration.[9] To the solution thus obtained were added activated molecular sieves (4 Å), and the mixture was stirred gently for 30 min. All operations were performed under a nitrogen blanket. This TBHP solution was then stored in an airtight high-density polyethylene (HDPE) container under nitrogen atmosphere at 4 °C. This method to obtain anhydrous TBHP was effective, simple, and safe, as it eliminated safety hazards associated with heating the TBHP solution during azeotropic distillation. Our team carried out this procedure many times to prepare anhydrous TBHP and used it in subsequent asymmetric epoxidation reactions to consistently obtain the desired epoxide **9** in high enantiomeric excess and excellent purity. Anhydrous TBHP in DCM is reported to be unstable at room temperature and relatively stable when stored at 4 °C.[9] At Advinus, the solution stored at 4 °C under nitrogen for more than 1 year did not show any appreciable loss in strength as determined by iodometric titration. It is not feasible to determine the moisture content of the anhydrous TBHP solution at ambient temperature because of the tendency of TBHP to react with the Karl Fisher reagent. The water content in the anhydrous TBHP solution can be measured at lower temperature (∼ −60 °C) in specialized equipment using Hydranal; however, such equipment was not available at Advinus. Hence to determine the efficacy of the anhydrous solution of TBHP in dichloromethane, the process team decided to use a performance test by trialing it in small scale (10 g) asymmetric epoxidation reactions before using it for larger scale work. Several experiments were carried out attempting to avoid molecular sieves in the asymmetric epoxidation reaction. However, as reported earlier,[9] the reactions that were performed in the absence of molecular sieves proceeded slowly, achieved lower conversion (∼40−45%), and yielded epoxide **9** in poor enantiomeric excess. Considering the high moisture sensitivity of this reaction, it was decided to perform further optimization efforts using freshly activated molecular sieves (4 Å).

Next, experiments were designed to develop the formation of epoxide **9** and its in situ reaction with phenol **7**. In these experiments, the asymmetric epoxidation reaction was carried out using molecular sieves and anhydrous TBHP, prepared as described above. All reactions were performed under a nitrogen atmosphere. In a typical reaction, (−)-diisopropyl-D-tartrate was added to the solution of 2-methyl-2-propen-1-ol (**8**) in dry dichloromethane at −30 °C. To the reaction mixture was added titanium tetraisopropoxide at −30 °C under gentle stirring. After stirring the reaction mixture at −30 °C for 1.0 h, the solution of anhydrous TBHP in dichoromethane was added over a period of 1.0 h, maintaining the temperature between −25 and −30 °C. The reaction mixture was then allowed to warm to −5 °C and stirred for 2.0 h. The progress of the reaction was monitored by GC. After the epoxidation was complete, this reaction mixture was added slowly into the mixture of *p*-trifluoromethoxyphenol (**7**) and anhydrous potassium carbonate in methanol at room temperature. The resulting reaction mixture was then stirred at 60 °C for 22 h, after distilling off dichloromethane. The progress of this reaction was monitored by HPLC. Upon completion, the reaction was quenched by adding water, and the reaction mixture was then extracted with dichloromethane. The two-phase mixture appeared translucent and did not give a clear phase separation, presumably due to the presence of molecular sieves and titanium tetraisopropoxide used in epoxidation reaction. Clear phase separation, however, was achieved after filtering the reaction mixture through Celite. The organic layer was separated and washed with water. At this stage, as revealed by GC and HPLC analysis, the organic layer contained the desired diol **19**, excess TBHP, unreacted *p*-trifluoromethoxyphenol (**7**), and tartrate ester.

It occurred to us that TBHP in the organic layer could be removed if the organic layer was washed with dilute aqueous sulfuric acid. Sulfuric acid reacts with TBHP to give peroxymonosulfuric acid, which in turn can be washed away by water. In general, for Sharpless asymmetric epoxidation reactions, the excess TBHP cannot be destroyed using dilute aqueous sulfuric acid because acid catalyzes nucleophilic attack by water on the epoxide ring, causing it to open. In our case, however, it was possible to destroy the excess TBHP using dilute aqueous sulfuric acid since epoxide **9** had been converted to diol **19** by reacting it with *p*-trifluoromethoxyphenol (**7**). Although the peroxymonosulfuric acid formed after reaction of sulfuric acid with TBHP is a strong oxidant, we considered that its solution in the aqueous layer would be too dilute to cause any harm to the product. With this rationale in mind, we decided to wash the organic layer, obtained after asymmetric epoxidation and subsequent reaction of resulting epoxide **9** with phenol **7**, with dilute aqueous sulfuric acid (15%) under cold conditions, and analyzed it by GC and HPLC. GC analysis confirmed that after one wash with dilute sulfuric acid the organic layer was free of TBHP. HPLC analysis further revealed that the organic layer was free of any unwanted byproducts, suggesting that diol **19** did not undergo oxidation or decomposition after the dilute sulfuric acid wash. The unreacted phenol **7** and tartrate ester were easily removed by washing the organic layer with 25% aqueous sodium hydroxide solution. The organic layer was then washed with 10% brine solution, dried over sodium sulfate, and concentrated to obtain a pale yellow gummy solid. The crude gummy solid so obtained was stirred in *n*-hexane to afford diol **19** as a white solid in 43% yield. HPLC analysis of **19** revealed that the compound was ∼99% pure and could be used for the next reaction without further purification. After these improvements, the team was confident of synthesizing epoxide **9** on a large scale and subsequently converting it to diol **19** without prior quenching of TBHP. We felt that, even on a large scale, this strategy of ignoring TBHP during in situ reaction of **9** with phenol **7** and later destroying it with dilute sulfuric acid would be both safe and the most convenient option.

Having developed both the epoxidation reaction to make **9** and its in situ reaction with **7**, we turned our attention to regioselective sulfonylation of diol **19** at the terminal hydroxyl group and the subsequent base-catalyzed intramolecular nucleophilic substitution reaction to reconstruct the epoxy ring. Diol **19** was treated with *p*-nitrobenzenesulfonyl chloride (**10**) in the presence of triethylamine in dichloromethane. The reaction was carried out at room temperature for 2.0 h to obtain sulfonylated compound **20**. Upon completion of this reaction, the reaction mixture was washed with aqueous hydrochloric acid (4.0 N), to remove excess triethylamine and triethylamine hydrochloride formed during reaction, followed by brine solution (10%). We envisaged that, because the *p*-nitrobenzenesulfonyl group is an excellent leaving group, its intramolecular displacement to reconstruct the epoxy ring should be possible under mildly basic biphasic conditions, which could be carried out in situ, removing the need to isolate compound **20**. The solution of **20** in dichloromethane obtained

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after sulfonylation was therefore stirred with aqueous sodium hydroxide solution at 15−20 °C, and the progress of this reaction was monitored by HPLC. HPLC analysis revealed that nosylate **20** was easily converted into the desired (*R*)-2-methyl-2-(4-trifluoromethoxyphenoxymethyl)oxirane (**21**) in 1.0 h. After the reaction was complete, the reaction mixture was worked up to obtain desired oxirane **21** in >99% enantiomeric excess, ∼95% chemical purity, and 92% yield.

While this development work was underway, our process team had also developed a robust process for the synthesis of multikilogram quantities of the required starting material, 2-bromo-4-nitroimidazole (**3**).[6] With both **3** and **21** in hand, the team proceeded to the coupling reaction. As disclosed in the Experimental Section, the reaction was performed by stirring a mixture of imidazole **3** and oxirane **21** in *N*,*N*-diisopropylethylamine at 110−115 °C. The reaction selectively produced compound **22** as a major product along with 5-nitro isomer of **22** as a minor product (∼1% a/a by HPLC). The crude solid so obtained was used for the final cyclization reaction without purification. In the final step, compound **22** was cyclized using anhydrous potassium carbonate in DMF at 90 °C to obtain DNDI-VL-2098 (**2**) having >99.5% chiral purity and >99.5% chemical purity by HPLC (area %) in 51% yield. The safer and reliable large-scale route for the synthesis of DNDI-VL-2098 (**2**) was thus established. The process chemistry team at Advinus successfully utilized this improved synthetic protocol to produce 10.2 kg of **2** in two batches of 5.6 and 4.6 kg. This compound is currently being evaluated as a potential treatment for visceral leishmaniasis.

■ CONCLUSIONS

The new process for the synthesis of DNDI-VL-2098 (**2**) has several key advantages over the reported routes, such as experimental simplicity in the conversion of epoxide **9** to key intermediate **21** by means of in situ reactions, greatly simplified isolation procedures, economy due to savings on solvents required for chromatographic purification, and easy scalability to access kilogram quantities of **2** in high chemical and chiral purities. Large-scale applicability of this method was successfully demonstrated by producing 10.2 kg of DNDI-VL-2098 API (active pharmaceutical ingredient) in good yield and excellent purity. Future work on this new process will focus on further improvements in the synthesis of hydroxyl derivative **22** and on the development of a suitable method for recrystallization of crude **2** to obtain final API having a suitable crystal form and habit as well as a particle size distribution.

■ EXPERIMENTAL SECTION

All raw materials were purchased from SD Fine Chem Ltd., India, and used without further purification. The ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a VARIAN 400 MHz NMR spectrometer. The chemical shifts are reported as δ ppm relative to tetramethylsilane. The FTIR spectra were obtained as a potassium bromide pellet using a Spectrum 100 PerkinElmer FT-IR spectrometer. Mass spectra were recorded on a Q-TOF Premier spectrometer, using electron-spray ionization. Melting points were determined on a Buchi (B-545) melting point apparatus and are uncorrected. HPLC chromatographic purities were determined on a Waters HPLC using a Cosmosil C-18 column (250 mm × 4.6 mm). Chiral purities were determined on a Waters HPLC using a CHIRALPAK AD-H column (250 mm × 4.6 mm, 5.0 μm) and CHIRALPAK IC column (250 mm × 4.6 mm, 5.0 μm) for compound **21** and compound **2**, respectively. Specific optical rotations (SORs) were recorded on a Rudolph Research Analytical AUTOPOL V automatic polarimeter.

Preparation of Anhydrous *tert*-Butyl Hydroperoxide (TBHP). In a clean and dry 20 L capacity four-neck round-bottom flask was charged TBHP (70% in water, 10.0 L) at 25−30 °C. To it was added 10% aqueous sodium chloride solution (500 mL), followed by dichloromethane (2.0 L). The biphasic mixture was stirred for 15 min and allowed to settle for 1.0 h. The organic layer was separated and charged into another clean and dry 20 L capacity four-neck round-bottom flask through a bed of anhydrous sodium sulfate. To the clear solution thus obtained was charged anhydrous sodium sulfate (750 g), and the mixture was stirred gently for 30 min. The solution of TBHP in dichloromethane was decanted, and the sodium sulfate was washed with dichloromethane (2 × 250 mL). This procedure was repeated thrice. The strength of this TBHP solution was then determined by iodometric titration.[9] Finally, activated molecular sieves (4 Å, 1.0 kg) were added into the TBHP solution. The translucent solution was stirred gently under a nitrogen blanket for 30 min and then stored in an airtight high-density polyethylene (HDPE) container at 4 °C. Before proceeding to larger scale reactions, the efficacy of anhydrous TBHP thus obtained was checked by performing a small scale (10.0 g) asymmetric epoxidation reaction using this stock solution.

*(R)-2-Methyl-3-(4-trifluoromethoxyphenoxy)propane-1,2-diol (**19**).* In a 50 L capacity AGLR (all glass-lined reactor) equipped with a temperature probe, a condenser, addition funnel, and a mechanical stirrer was charged with dichloromethane (12.0 L) and activated powdered molecular sieves (4 Å, 500 g) at room temperature under nitrogen atmosphere. 2-Methyl-2-propen-1-ol (**8**) (2.0 kg, 27.78 mol) was added, and the mixture was cooled from −25 to −30 °C. To this solution was added (−)-diisopropyl-D-tartrate (2.6 kg, 11.11 mol) and titanium(IV) isopropoxide (2.5 kg; 8.8 mol). The reaction mixture was stirred for 1.0 h at −25 to −30 °C. Anhydrous TBHP in dichloromethane (83.2 mol) was then added to the reaction mixture over a period of 1.0 h, maintaining the temperature between −25 and −30 °C. The reaction mixture was allowed to warm slowly and then stirred for 1.0 h at −5 °C. The progress of the reaction was monitored by GC. After completion of reaction, the reaction mixture was allowed to attain room temperature. It was then added into a 200 L capacity AGLR (all glass-lined reactor) containing the reaction mixture of *p*-(trifluoromethoxy)phenol (**7**) (4.45 kg, 25 mol) and anhydrous potassium carbonate (17.2 kg, 125 mol) in methanol (22 L) over a period of 2.0 h at room temperature, under a nitrogen atmosphere. During addition, no exothermicity was noticed. The reaction mixture was heated at 60 °C while simultaneously removing dichloromethane by distillation. The reaction mixture was then stirred at 60 °C for about 22 h. The progress of the reaction was monitored by HPLC and GC analysis. After completion of the reaction, water (40 L) and dichloromethane (30 L) were added to the reaction mixture. The mixture was stirred for 30 min and then filtered through Celite. The organic layer was separated, and the aqueous layer was washed with dichloromethane (10 L) and separated. The combined organic layer was then cooled to 0−5 °C and washed with aqueous sulfuric acid (15%, 30 L), aqueous sodium hydroxide (25%, 3 × 20 L), and finally with brine solution (10%, 2 × 10 L). It was dried over anhydrous sodium sulfate

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and concentrated to obtain a pale yellow crude solid, which on stirring in *n*-hexane for 30 min gave (*R*)-2-methyl-3-(4-trifluoromethoxyphenoxy)propane-1,2-diol (**19**) as a white solid (3.17 kg; 43%). Mp: 67−69 °C; HPLC: 99% (a/a); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16−7.14 (d, 2H, J = 8.0 Hz), 6.92−6.90 (d, 2H, J = 8.0 Hz), 3.96−3.89 (m, 2H), 3.74−3.71 (d, 1H, J = 12.0 Hz), 3.61−3.58 (d, 1H, J = 12.0 Hz), 2.60 (br, 1H), 2.08 (br, 1H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 143.0, 124.3−116.7 (q, J = 255 Hz, CF_3), 122.5, 115.3, 72.6, 72.2, 67.1, 21.7; IR (KBr, cm^{-1}): 3242, 2944, 1508, 1459, 1274, 1158, 918, 835; mass (m/z): 266.1 $(M)^+$.

*(R)-2-Methyl-2-(4-trifluoromethoxyphenoxymethyl)-oxirane (**21**).* In a 100 L capacity AGLR equipped with a temperature probe, a condenser, and a mechanical stirrer was charged dichloromethane (20 L) followed by diol **19** (4.0 kg, 15.04 mol) at room temperature. The solution was cooled to 0−5 °C, and triethylamine (2.73 kg, 27.07 mol) was added under stirring. To the reaction mixture was added a solution of *p*-nitrobenzenesulfonyl chloride (**10**) (5.98 kg, 27.07 mol) in dichloromethane (12 L) over a period of 1.0 h at 5−15 °C. The reaction mixture was brought to 25−30 °C and stirred for 2.0 h. The progress of the reaction was monitored by HPLC analysis. Upon completion of the reaction, hydrochloric acid (4.0 N, 6.0 L) was added to the reaction mixture, and stirring was continued for 15 min while maintaining the temperature below 30 °C. The organic layer containing compound **20** was separated, washed with brine solution (10%, 7.5 L), and cooled to 10−15 °C. A solution of sodium hydroxide (1.8 kg, 45.12 mol) in water (3.6 L) was then added to this solution of **20** in dichloromethane. The biphasic reaction mixture thus obtained was stirred for 1.0 h at 15−20 °C. The progress of the reaction was monitored by HPLC analysis. Upon completion of the reaction, the aqueous layer was separated. The organic layer was washed with water (3 × 20 L) followed by 10% brine solution (1 × 20 L), dried over anhydrous sodium sulfate, and concentrated to afford the crude product. This crude product was dissolved in *n*-heptane and stirred for 30 min. The clear solution was then filtered through Celite. Evaporation of the filtrate gave (*R*)-2-methyl-2-(4-trifluoromethoxyphenoxymethyl)oxirane (**21**) as a yellow liquid (3.43 kg, 92%). HPLC: 96.4% (a/a); HPLC (chiral): 99.3% (a/a); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13−7.15 (d, 2H, J = 8.8 Hz), 6.92−6.90 (d, 2H, J = 8.8 Hz), 4.06−4.03 (d, 1H, J = 10.4 Hz), 3.94−3.92 (d, 1H, J = 10.0 Hz), 2.86−2.85 (d, 1H, J = 4.4 Hz), 2.74−2.72 (d, 1H, J = 4.8 Hz), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 142.9, 124.3, 122.3, 116.7, 115.5, 71.8, 55.3, 51.7, 18.2; IR (KBr, cm^{-1}): 2929, 1505, 1193, 1030, 819; Mass (m/z): 248.2 $(M)^+$.

*(R)-1-(2-Bromo-4-nitroimidazol-1-yl)-2-methyl-3-(4-trifluoromethoxyphenoxy)propan-2-ol (**22**).* In a 20 L capacity AGLR equipped with a temperature probe, a condenser, and a mechanical stirrer was charged *N*,*N*-diisopropylethylamine (2.5 L), (*R*)-2-methyl-2-(4-trifluoromethoxyphenoxymethyl)oxirane (**21**) (3.5 kg, 14.11 mol), and 2-bromo-4-nitro-1*H*-imidazole[6] (**3**) (2.84 kg, 14.81 mol) at room temperature. The resulting reaction mixture was heated to 110−115 °C and stirred for 2.0 h. The progress of the reaction was monitored by HPLC analysis. Upon completion of the reaction, the reaction mixture was cooled to 25−30 °C. To the reaction mixture was added dichloromethane (12 L) under stirring. The resulting clear solution was washed with 3.0 N aqueous hydrochloric acid (2 × 14 L), 10% aqueous sodium bicarbonate solution (1 × 17.5 L), and water (1 × 17.5 L). The organic layer was dried over anhydrous sodium sulfate and concentrated to obtain **22** as a light brown gummy solid (5.93 kg, 96%). Mp: 95−97 °C; HPLC: 90% (a/a); HPLC (chiral): 99.8% (a/a); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (s, 1H), 7.32−7.30 (d, 2H, J = 8.8 Hz), 7.04−7.02 (d, 2H, J = 8.8 Hz), 5.5 (bs, 1H), 4.26−4.14 (dd, 2H, J = 14.4 Hz), 3.87−3.80 (dd, 2H, J = 9.6 Hz), 1.21 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.0, 146.0, 142.0, 125.1, 124.0, 122.5, 122.0, 121.4, 119.0, 115.8, 72.9, 70.4, 54.6, 22.5; IR (KBr, cm^{-1}): 3354, 3318, 1539, 1508, 1458, 1327, 837; mass (m/z): 440.5 $(M + 1)^+$.

*(2R)-2-Methyl-6-nitro-2-(4-trifluoromethoxyphenoxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole (**2**).* In a 100 L capacity AGLR equipped with a temperature probe, a condenser, and a mechanical stirrer was charged *N*,*N*-dimethylformamide (25 L), (*R*)-1-(2-bromo-4-nitroimidazol-1-yl)-2-methyl-3-(4-trifluoromethoxyphenoxy)propan-2-ol (**22**) (5.0 kg, 11.36 mol), and anhydrous potassium carbonate (7.8 kg, 56.8 mol) at room temperature under a nitrogen blanket. The resulting reaction mixture was heated to 85−90 °C and stirred for 6.0 h. The progress of the reaction was monitored by HPLC. After completion of the reaction, the reaction mixture was poured slowly into an ice−water mixture. The resulting mixture was then stirred for 1.0 h. The solid precipitate was filtered, washed with water (20 L), followed by *n*-heptane (5 L), and dried in an air oven at 45 °C for 8.0 h. The crude product thus obtained was dissolved in DCM (35 L) at room temperature. To the solution was added *n*-heptane (35 L) in a thin stream over a period of 45 min at room temperature. The resulting mixture was stirred for 45 min and filtered to separate the solid. This solid was washed with a mixture of DCM: *n*-heptane (1:3, 5 L) and dried in an air oven for 4.0 h to obtain compound **2** (2.08 kg, 51%). Mp: 169−171 °C; HPLC (area %): 99.52%; HPLC (chiral): 99.8% (a/a); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (s, 1H), 7.14−7.16 (d, 2H, J = 10.0 Hz), 6.83−6.86 (d, 2H, J = 7.2 Hz), 4.48−4.50 (d, 1H, J = 10.0 Hz), 4.22−4.24 (d, 1H, J = 10.0 Hz), 4.05−4.10 (t, 2H, J = 9.6 and 10.4 Hz), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 155.8, 147.1, 143.5, 122.6, 115.5, 112.6, 122.6, 121.7, and 119.1 (J_{C-F} = 255.1 Hz), 116.6, 92.9, 71.8, 51.3, 23.0; ^{19}F NMR ($CDCl_3$, 376 MHz): δ −58.4; IR (KBr, cm^{-1}): 3155, 2996, 1607, 1456, 1281, 1106, 978, 921, 834,783, 708; mass (m/z): 360.3 $(M + 1)^+$; $[\alpha]^{25}_{589}$ = (+)8.445 (c 1.00 g/100 mL, $CHCl_3$).

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Notes

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