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Development of Jacobsen Asymmetric Epoxidation and Sharpless Asymmetric Dihydroxylation Methods for the Large-Scale Preparation of a Chiral Dihydrobenzofuran Epoxide

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Abstract:

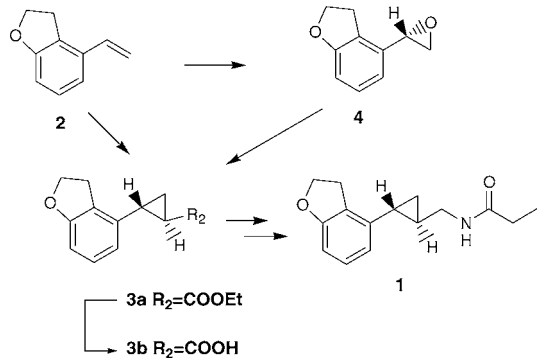
Two well-known methodologies, the Jacobsen asymmetric epoxidation (AE) and the Sharpless asymmetric dihydroxylation (AD) followed by epoxidation, were evaluated for the large-scale preparation of a chiral dihydrobenzofuran epoxide. The AE method was improved by substituting ethanol for dichloromethane for the dissolution of *meta*-chloroperbenzoic acid (*m*-CPBA). This change in solvent had a significant impact on scaleability of the AE procedure by preventing crystallization of the *m*-CPBA during addition to the cold reaction mixture. Factors affecting the enantiomeric excess and yield of the chiral epoxide resulting from AD followed by epoxidation were studied. The Sharpless AD reaction provided the intermediate chiral diol as a solid with high ee (>98.5%). The Sharpless–Kolb conversion of the chiral diol to a chiral epoxide was modified to potassium *tert*-butoxide/tetrahydrofuran to obtain the product in good yield (74–84%) and high ee (>98%). Both the AE and AD processes were scaled up to prepare large quantities of the chiral epoxide.

Introduction

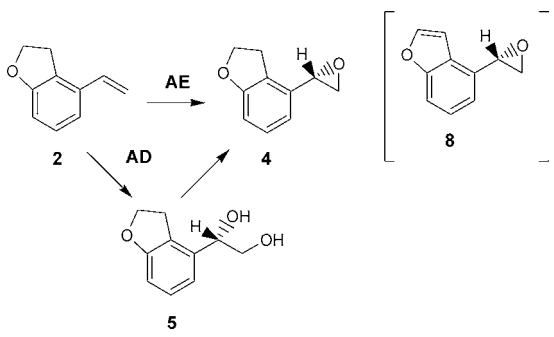
In connection with our work on a practical and commercially viable synthesis of the melatonin agonist **1**[1] (Scheme 1), olefin **2** was identified as a key intermediate[2] en route to the *trans*-cyclopropanecarboxylic ester **3a**, which was then converted to **1** in several steps. While the direct asymmetric cyclopropanation approach[3] for the preparation of ester **3a** from olefin **2** was under investigation, we needed to prepare large quantities of the drug to support the ongoing clinical and nonclinical studies. To accomplish this task expeditiously, we developed a synthetic route based on chiral epoxide **4** as a key intermediate which then was converted to the desired chiral cyclopropanecarboxylic acid **3b** in high yield and >99% enantiomeric excess.[4]

Several methods for the direct asymmetric epoxidation of olefins are known.[5] However, many of these methods are less effective in providing epoxides in high enantiomeric excess when applied to "terminal" double bonds. Furthermore, solutions to potential scale-up issues associated with these methods have not been reported. In the context of our work, we chose to evaluate asymmetric epoxidation (AE)[6a–l] and the two-step process involving asymmetric dihydroxylation (AD) followed by cyclization[7] for the large-scale preparation of epoxide **4**[8] (Scheme 2). Herein, we report our

Scheme 1. **A general strategy for the synthesis of melatonin agonist 1**



Scheme 2. **AE and AD approaches for the synthesis of chiral epoxide 4**



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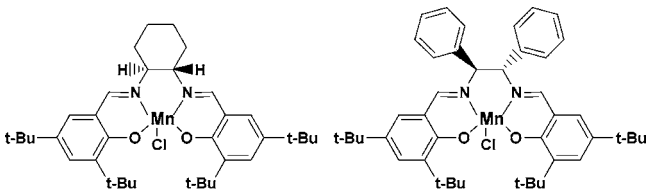

Figure 1. **Structures of the chiral catalysts 6 and 7 used in the AE investigation.**

findings that led to modifications in the reaction conditions allowing successful scale-up of both approaches.

Results and Discussion

Jacobsen Asymmetric Epoxidation Approach. The AE approach using metal−salen complexes, pioneered by Jacobsen and others, has found wide synthetic utility in the pharmaceutical industry, with substrates containing internal double bonds such as chromenes being the most ideal.[6h] One good example of the application of Jacobsen's procedure on large scale is the preparation of a chiral intermediate in the synthesis of the HIV protease inhibitor Crixivan.[6i,j] In our work, initial small-scale experiments showed that olefin **2** could be oxidized to epoxide **4** in 72−80% ee using the chiral catalysts **6**[6e] and **7**[6g] (Figure 1). In these experiments, we added a solution of *m*-CPBA in dichloromethane (DCM) to a cold (−70 °C) DCM solution containing **2**, the catalyst, and 4-methylmorpholine-*N*-oxide (NMO). On the basis of these early experiments, we selected catalyst **7** for our development work due to its ready accessibility in our laboratories.

During the initial probing experiments, we identified several issues which needed resolution prior to scale-up:

A. Enantioselectivity. Under the AE conditions, the epoxide **4** was obtained consistently in 72% ee, which necessitated a resolution step at a later step in the synthesis to obtain **1** in high enantiomeric purity.

*B. Formation of Benzofuran Impurity **8** (Scheme 2)*. Oxidation of the dihydrobenzofuran to benzofuran proved to be a troublesome side reaction, leading to **8** as an impurity. This impurity undergoes analogous transformations as dihydrobenzofuran **4** and could only be purged to acceptable levels via multiple crystallizations at the penultimate step.

C. Safety. Pure *m*-CPBA is both shock sensitive and potentially explosive in the condensed phase.[9a,b] In a differential scanning calorimetry (DSC) experiment, *m*-CPBA exhibited exothermic activity with a significant energy release (74−140 °C, 1138 J/g). The presence of *m*-chlorobenzoic acid does reduce the hazardous nature of the commercial reagent to shock and friction. Although our in-house testing of commercial *m*-CPBA (70−77% purity) to mechanical stimulus using the BAM Friction Test apparatus and Dart Drop Test apparatus resulted in no positive response test, the anhydrous reagent is still considered hazardous, and organic solutions containing the reagent must not be allowed to evaporate to dryness.[9c,d] While handling relatively large quantities (∼1 kg) of *m*-CPBA as a solution in DCM in the AE approach, we found that the reagent crystallized readily on cold surfaces of equipment such as on the tip of addition funnels and on the walls of the reaction flasks above the liquid surface. In one experiment on a 700-g scale, chunks of the crystallized *m*-CPBA dislodged and fell into the reaction mixture, causing significant off-gassing which resulted in ejection of a glass stopper from a 22-L flask. In one safety study conducted, when solid *m*-CPBA (2.3 g of 70−77% reagent) was added in one portion to a DCM solution containing a mixture of olefin **2** (6.85 mmol), catalyst **7**, and NMO cooled to −25 °C, a spontaneous temperature rise by 33 °C was observed within 29 s. In another safety study carried out at −5 °C, a rapid gas evolution (57 mL in 30 s) on 13.7 mmol scale of oelfin **2** took place with the temperature rising up to the boiling point of the solvent (∼40 °C).

Several experiments were performed to address these issues. The practical use of AE methodology has been enhanced by the use of sodium hypochlorite (household bleach) as an inexpensive and effective stoichiometric oxidant[10] and it was used successfully on scale.[6i,l] However, when applied to olefin **2**, the enantiomeric purity (40−50% ee) and yield of product were lowered significantly. A safer alternative to *m*-CPBA, magnesium monoperphthalate,[9a] was also evaluated. The reaction was not only difficult to stir but also was too slow to be practically useful (30% unreacted **2** in 24 h of reaction time) even at room temperature. Since alternatives to *m*-CPBA did not afford desired yield and quality of **4**, we turned our attention toward finding reaction conditions under which *m*-CPBA could be handled in a safe

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Table 1. **Results on asymmetric epoxidation of olefin 2 to prepare chiral epoxide 4**

entry	reactant A (equiv)	solvent for A	reactant B	solvent for B	mode of addition	temp (°C)	yield of **4** (%)	ee of **4**	unreacted **2** (%)
1	MCPBA (1.2)	none	**2**+**7**+NMO	DCM	A to B	−75	66	74	19
2	MCPBA (1.2)	none	**2**+**7**+NMO	DCM	A to B	−8	76	40	none
3	MCPBA (1.2)	none	**2**+**7**+NMO	DCM	A to B	−25	62	45	none
4	MCPBA (1.2)	none	**2**+**7**+NMO	EtOAc	A to B	−75	57	45	8
5	MCPBA (2)	EtOAc	**2**+**7**+NMO	EtOAc	B to A	−75	44	54	28
6	MCPBA (2)	EtOAc	**2**+**7**+NMO	EtOAc	B to A	−25	58	10	10
7	MCPBA (2)	DCM	**2**+**7**+NMO	DCM	B to A	−75	73	48	13
8	MCPBA (2)	DCM	**2**+**7**+NMO	DCM	B to A	−25	52	40	5
9	MCPBA (2) + NMO (0.5 equiv)	DCM	**2**+**7**+ NMO (1.5 equiv)	DCM	A to B	−75	70	72	none
10	MCPBA (1.2)	EtOAc	**2**+**7**+NMO	DCM	A to B	−75	60	76	18
11	MCPBA (1.2)	EtOAc	**2**+**7**+NMO	EtOAc	A to B	−75	62	48	8
12	MCPBA (1.6)	EtOH	**2**+**7**+NMO	DCM	A to B	−65	87	72	1 to 4

manner. Table 1 summarizes our findings. For the sake of clarity, only results from the experiments using 2 equiv of NMO, 1.2−2 equiv of *m*-CPBA (70% reagent), and 8 mol % catalyst **7** are shown.

In the first set of experiments, in which solid *m*-CPBA was charged to the reaction mixture at −75 °C, thus avoiding the safety issues in handling a solution of *m*-CPBA in DCM, the highest ee obtained was 74% (entry 1), although with incomplete reaction. At higher temperature, the reaction went to completion, but the ee was lowered substantially (entries 2 and 3). Substitution of DCM with ethyl acetate (EtOAc) improved neither ee nor yield (entry 4). A safer alternative from a scale-up perspective was to add a solution of olefin **2**, NMO and catalyst **7** either in EtOAc or DCM to a solution of *m*-CPBA in the same solvent. Unfortunately, this procedure afforded disappointing enantioselectivities and yields (entries 5−8).

We observed that 0.5 equiv of NMO increased the solubility of *m*-CPBA in DCM and prevented crystallization of this material when the solution came in contact with cold surfaces. Using these conditions, we obtained epoxide **4** in 80% yield with 70% ee (entry 9) on a small scale. However, when the reaction was scaled 10 times, an additional equivalent of *m*-CPBA was needed for reaction completion. In addition, continuous off-gassing of the NMO/MCPBA solution was observed, suggesting decomposition of *m*-CPBA.[6c]

In comparison to the solubility of *m*-CPBA in DCM (1 g in ∼9 mL), the solubility in EtOAc and ethyl alcohol (EtOH) (1 g in 1.5−2 mL) is excellent, and the reagent does not crystallize even upon cooling to −10 °C. The next set of experiments (entries 10−12) were conducted using these solvents. The best results were obtained when EtOH was used as the solvent. We used a minimal amount of EtOH to dissolve the *m*-CPBA, keeping DCM as the primary solvent for the reaction to facilitate workup.

The use of EtOH to solubilize *m*-CPBA allowed us to scale up the AE method safely.[11] Alcohols themselves are generally inert to peracids.[12] Although the use of solvents that hydrogen bond with *m*-CPBA has been reported to inhibit the epoxidation of olefins,[13] the reactions proceeded smoothly in our case. The best results were obtained at −60 to −70 °C.

Table 2. **Scale-up of asymmetric epoxidation of olefin 2 to prepare chiral epoxide 4**

entry	olefin **2**	chiral epoxide **4** (crude weight)	yield (%) (corrected)	ee (%)
1	69 g	55 g	71.8	74
2	200 g	243 g	ca. 100	70
3	850 g	1019 g	90.2	74
4	900 g	1008 g	88.6	70

The epoxidation was fast, with 90−95% consumption of **2** as soon as the addition of the *m*-CPBA solution was complete. Under the optimized conditions, 1.4−1.7 equiv of *m*-CPBA was added as a 4 M solution in EtOH to a solution of olefin **2**, NMO (2 to 2.3 equiv), and catalyst **7** (4 M%) in DCM at −65 °C to obtain epoxide **4** typically in >80% yields with 70−74% ee. An upgrade in the ee was realized at a later stage where acid **3b** was isolated as the dehydroabietylamine (DAA) salt with >99% ee. This procedure was successfully scaled up to 6 mol (900 g, Table 2) of olefin **2**, and the resulting epoxide **4** was used "as is" in the subsequent steps of the synthesis to prepare the initial supplies of the drug candidate **1** (ca. 800 g) in 22% overall yield from olefin **2**, with the low-yielding steps being the preparation of **3b** followed by its purification via the DAA salt.

Sharpless Asymmetric Dihydroxylation Approach. The use of ethanol as the cosolvent for *m*-CPBA followed by an upgrade in the ee of the acid **3b** had temporarily met our safety and ee issues with the AE process. However, formation of furan impurity **8** (up to 3%) appeared to be unavoidable. Although we do not have any experimental evidence, we speculate that the benzylic position undergoes oxidation by *m*-CPBA or by the (salen)Mn(V) oxo complex at some stage during the conversion of olefin **2** to epoxide **4**, via a benzylic radical to an hydroxy intermediate, which then undergoes dehydration to form the furan impurity. The mechanism for the formation of a benzylic radical may be similar to that

(11) Dichloromethane is often the preferred solvent for epoxidations with manganese−salen complexes. Acetonitrile as solvent for the reaction has also been described. See Gurjar, M. K.; Sarma, B. V. N. B. S.; Rama Rao, A. V. *Ind. J. Chem.* **1997**, *36B*, 213.

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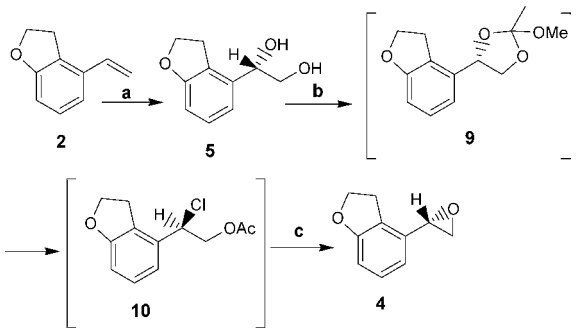
Scheme 3. **Preparation of chiral epoxide 4 using the Sharpless AD methodology**[a]



[a] (a) 0.2% $K_2OSO_4 \cdot 2H_2O$, 0.8% $(DHQ)_2PHAL$, 3 equiv K_2CO_3, 3 equiv K_3FeCN_6, 1.2:1 (water−^{t}BuOH); workup Na_2SO_3, water, ^{n}BuOAc; (b) TMOF, TMSCl, 0−5 °C; (c) K^{t}BuO, THF, 0−5 °C

proposed by Ma and co-workers for the oxidation of benzylic methylene compounds to ketones[6m] or the metal−porphyrin catalyzed hydroxylation of allylic positions[6n] with *m*-CPBA. The potential lability of protons α to the furan oxygen in the radical mechanism also may not be ruled out. In addition to the troublesome furan impurity, crude epoxide **4** was contaminated with varying levels of manganese salts. All of these factors encouraged us to explore the two-step process employing the Sharpless AD methodology (Scheme 3). A major benefit in selecting the AD route for further development was that the intermediate chiral diol **5** was found to be a solid, allowing for purification by crystallization.

A possible problem with the AD route is that the product may be contaminated with residual osmium salts. An analytical method for the determination of osmium levels would then be required. Our Analytical R & D group developed a technique using inductively coupled plasma-atomic emission spectroscopy (ICP-AES) to detect osmium at a minimum quantifiable limit of 4 ppm (we set a limit of <10 ppm of osmium as acceptable). A series of experiments were conducted on reducing the level of osmium that was present in a product-rich organic stream (∼200 ppm) before the product diol **5** was isolated. The use of metal-chelating resins (Chelex 100 and Deloxan THP II, 20 wt %) allowed for 50 and 65% reductions, respectively. Filtration through a Zetaplus pad gave a modest ∼20% reduction of osmium, also. Washing a rich organic solution of **5** with either a sodium sulfite or sodium metabisulfite solution afforded superior reduction of residual osmium in the diol. This option was selected, as this would be easy to introduce in the workup of the AD reaction. Indeed, with one sodium sulfite wash in the workup, the levels of residual osmium in the isolated diol **5** ranged from 6 ppm to not quantifiable by the ICP-AES method.

The safety issues related to the handling of toxic osmium compounds[14] and potassium ferro and ferricyanides meant that the AD reaction needed a higher level of handling controls and personal protection during processing, relative to the AE procedure. To meet a tight timeline, we made a decision to develop the AD process in our laboratories and to transfer the technology to a third-party vendor with experience in running osmium-catalyzed dihydroxylations, although we were aware that such a strategy might not be cost-effective in the long term.

Selection of Reoxidant. Both NMO and potassium ferricyanide (KFC) as reoxidants were evaluated. The use of NMO allowed for greatly reduced reaction volume, eliminated the need for filtration of inorganic salts, and was a less expensive alternative to KFC. However, the ee was about 2% less than the product made by using KFC. Furthermore, the ee in the NMO procedure was found to be dependent on the rate of addition of olefin. When a solution of olefin **2** was added quickly, an erosion of selectivity (>5%) was observed by us, corroborating Ahrgren and Sutin's observations.[15] In the case of KFC, the slow addition of olefin **2** was not critical for ee, and this proved to be a more rugged process in our hands.

The main drawbacks of KFC are that high reaction volumes are required for good agitation and the formation of a large amount of solid byproduct, which needs to be removed. Despite these drawbacks, we chose KFC for scale-up because it gave chiral diol **5** with high ee consistently, thus eliminating the need for a resolution step later in the synthesis.

The AD reaction failed completely when catalytic AD-Mix-α and excess potassium persulfate ($K_2S_2O_8$) were used.[16] For scale-up, in situ preparation of the AD-Mix-α was found to be important for achieving high enantioselectivity. The ratio of water to *tert*-butyl alcohol (*t*-BuOH) was modified to improve the solubility of olefin **2**. To overcome a problem with *t*-BuOH solutions of **2** solidifying and clogging transfer lines during addition, we used a 95:5:5 (v/v/v) mixture of *t*-BuOH/H_2O/MTBE. [If more than 5% (v/v) MTBE was present, the reaction rate was severely retarded.] After the standard workup, diol **5** was crystallized from butyl acetate (*n*-BuOAc)−heptane in 84−94% overall yield with HPLC purity of >99 area %. The ee was consistently 98−99%. Later, we found that *i*-PrOH was a suitable replacement for *t*-BuOH, affording diol **5** in a crude yield of 90% with an HPLC purity of 98% and >99% ee.

Isolation of Chiral Diol 5. Crystallization of **5** proceeded best when the water content of the rich organic solution after aqueous work up was ≤1% w/w. When the water content was >1% w/w, the crystal slurry contained numerous clumps, and a large amount of the product adhered to the reaction vessel and agitator, which made product discharge difficult.

Conversion of Chiral Diol 5 to Chiral Epoxide 4. The chiral epoxide **4** was prepared using a modified version of the Kolb and Sharpless method (Scheme 3).[7] Chiral diol **5** was treated with trimethylorthoacetate and trimethylsilyl chloride (TMSCl) in tetrahydrofuran (THF) at 0−5 °C to give ortho ester **9** initially, and then chloroacetate **10**. While epoxide **4** could be produced from **10** in excellent yield by the literature method using potassium carbonate (K_2CO_3) in MeOH, a stability issue surfaced due to formation of varying amounts of alcohol **11** (10−20% in 24 h), which resulted from MeOH attacking the product epoxide in the presence

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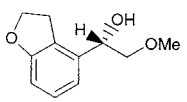
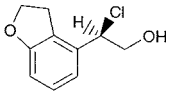
Table 3. **Conversion of chloroacetate 10 to chiral epoxide 4**

entry	base	solvent	yield (%)	purity (%)
1	K_2CO_3	2-MeTHF−MeOH	>90	>98
2	K_2CO_3	THF−MeOH	>90	>98
3	A-26 or A-27 resin	2-MeTHF−MeOH	>90	>98
4	n-Bu_4NOH	2-MeTHF	90	91
5	*n*-Bu_4NOH, NaOH	2-MeTHF	>50	91
6	KO*t*-amylate	toluene−THF	>75%	>98
7	KO*t*-Bu	THF	74−84	>98

of solubilized base.



11



12

The impurity **11** was observed whenever MeOH was present in the reaction mixture. Presumably, this would be a problem with any of the common alcoholic solvents. To circumvent formation of **11**, we looked at dilution of K_2CO_3/MeOH media with THF or 2-methyltetrahydrofuran (2-MeTHF), and the use of resins, hydroxide, and alkoxide bases. The results are provided in Table 3.

Although the use of K_2CO_3 in 2-MeTHF/MeOH or THF/MeOH mixtures reduced the formation of **11**, the problem still existed. The basic A-26 or A-27 resins worked well on small scale (up to 2 g) in 2-MeTHF/MeOH mixture, but they were not deemed practical for scale-up. The laboratory batches required approximately 5 wt equiv of resin for complete reaction, which would necessitate excessively large quantities for multikilogram batches. Tetrabutylammonium hydroxide (*n*-Bu_4NOH) or catalytic *n*-Bu_4NOH/NaOH in 2-MeTHF afforded **4**, but the yield was variable and the reactions sometimes stalled. Potassium *tert*-amylate and potassium *tert*-butoxide both worked well, and we selected the latter simply out of convenience. With KO*t*-Bu in THF (21 wt % solution), the ring-closure proceeded smoothly at 0−5 °C in about 1 h, providing chiral epoxide **4** in 74−84% yields (by HPLC quantitation) and in high purities (>98 area % by HPLC and 99% of *S*-enantiomer by chiral HPLC). Extended reaction times had no deleterious effect on the product. Thus, the entire epoxidation sequence starting from chiral diol **5** was streamlined using THF as the solvent with no intermediate workup or isolation steps. The AD process followed by the modified cyclization procedure was successfully used (Table 5) to convert olefin **2** to chiral epoxide **4** in acceptable yield and high ee. The reaction mixture containing epoxide **4** in THF was solvent exchanged into dimethoxyethane (DME) for the subsequent cyclopropanation step. Using the AD approach to prepare **4**, the drug candidate **1** was prepared in 43% overall yield starting from olefin **2**.

Conclusions

Expedient approaches are often used in process development to prepare small amounts of target molecules to fuel early drug development activities. After a candidate has been selected for full development, the methods used for intermediate synthesis undergo careful evaluation based on a host of considerations such as scaleability, safety, process ruggedness, ease of product isolation, and the ability to be used on a manufacturing scale. The selection of a method for preparation of chiral epoxide **4** is such an example.

Table 4. **Scale-up of asymmetric dihydroxylation/cyclization procedure for the conversion of olefin 2 to chiral epoxide 4**

entry	**2**	**5**	**5**, % yield (% ee)	chiral epoxide **4**	**4**, % yield (% ee)
1	20.00 g	23.30 g	94.5 (98.8)	15.1 g	84.0 (98.9)
2	1.44 kg	1.51 kg[a]	85.0 (98.9)		
3	15.38 kg	16.20 kg[a]	85.4 (99.7)		
4		8.85 kg		7.6 kg	95.4 (98.1)
5		8.86 kg		7.2 kg	90.4 (98.2)

[a] The two diol batches (entries 2 and 3) were combined and split into two batches, and each batch was then converted to the chiral epoxide (entries 4 and 5).

We evaluated the Jacobsen asymmetric epoxidation and the Sharpless asymmetric dihydroxylation/cyclization for preparation of chiral epoxide **4** on large scale. The AE chemistry was improved from a handling and safety perspective by using ethanol as an alternative to DCM. The AD method gave a crystalline diol **5** with high ee which was then converted to chiral epoxide **4** in good yield and high ee. The conversion of chiral diol **5** to chiral epoxide **4** was highly streamlined. Although preparation of chiral epoxide **4** via the AD method is more process intensive compared to the one-step AE procedure, the AD method was chosen for scale-up for obvious advantages the method offered in the present context such as the higher overall yield realized for the drug candidate **1** (43 vs 22%) and a good stereo control on the quality of epoxide **4** prepared.

Experimental Section

General. *tert*-Butyl alcohol, potassium ferricyanide, potassium osmate dihydrate, potassium carbonate, trimethyl orthoacetate, trimethylsilyl chloride, *m*-chloroperoxybenzoic acid, 4-methylmorpholine-*N*-oxide, 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde, manganese(II) acetate tetrahydrate, and lithium chloride were purchased from Aldrich Chemical Co. and were used without further purification. Potassium *tert*-butoxide (20.1 wt %) solution in THF was purchased from Callery Chemical. $(DHQ)_2PHAL$ was obtained from Rhodia Chirex. (1*S*,2*S*)-(−)-1,2-Diphenylethylenediamine was purchased from Oxford Asymmetry, and THF, DCM, and EtOH (200 proof) were purchased from EM Science. For pH measurement, a Radiometer PHM82 standard meter with an Omega pH electrode was used. The electrode was standardized using pH 4.0, 7.0, and 10.0 buffers. Moisture content was determined by coulometric titration on a Mitsubishi CA-06 moisture meter on a weight/volume basis. Proton and carbon NMR were run on a Bruker AC-300 spectrometer at 300 MHz for proton and 75 MHz for carbon. For in-process HPLC, the following conditions were employed:

For AE reactions: column: YMC ODS-A, 150 mm × 4.5 mm i.d., S-3 μm; column temperature: ambient; flow rate: 1 mL/min; detection: 225 nm; sample preparation: 50

μL of the reaction mixture was diluted to 10 mL with CH_3CN; injection volume: 10 μL; mobile phase A: water (1% H_3PO_4); mobile phase B: CH_3CN; gradient program: 0−10 min (55% A), 10−15 min (linear gradient to 90% B), 15−20 min (90% B), 20−25 min (linear gradient to 55% A), 25−30 min (55% A), run time 30 min; retention times in minutes 8.4 (**2**) and 4.3 (**4**). Chiral HPLC to determine the chiral purity of epoxide **4** (prepared from both AE and AD methods) was run under the following conditions: column: Regis Technologies, Inc. Whelk-O1 (*R*,*R*); 4.6 mm × 250 mm i.d., S-5 μm; column temperature ambient; flow rate: 1.0 mL/min.; detection: 215 nm; injection volume: 3 μL; isocratic program; mobile phase hexanes containing 1% of ethanol; sample preparation: 0.25 mg dissolved 1 mL of hexanes/*i*-PrOH (90:10, v/v); retention times in minutes 13.1 (*S* isomer of epoxide), 14.2 (*R* isomer of epoxide).

For AD reactions: column: YMC ODS-A, S-3 μm, 6 mm × 150 mm; mobile phase: 50% CH_3CN/50% 0.05M $(NH_4)H_2PO_4$ buffer (pH = 3); flow rate: 1.0 mL/min; detection: 210 nm; injection volume: 10 μL; temperature: 25 °C. Retention times (min): 3.20 (diol **5)**, 4.48, 4.70 (orthoacetate **9),** 6.00 (chloro alcohol **12**), 8.3 (**4**), 14.16 (**10)**. Chiral HPLC assay for diol **5**: sample preparation: 2−4 mg of solid was diluted to 10 mL in 10% *i*-PrOH/hexanes. HPLC method: column Chiralcel OD, 10 μm, 4.6 mm × 250 mm, mobile phase: 95% hexanes/5% EtOH; flow rate: 1 mL/min; detection: 210 nm injection volume: 5 μL; temperature: 30 °C; retention times (min): 19.5 (*R* diol), 22.9 (*S* diol).

Sample Preparation (AD reactions). For solutions, a 50 μL aliquot was diluted to 10 mL with 1:1 CH_3CN/H_2O. For solid samples, 2−5 mg was diluted to 10 mL in CH_3CN. For aqueous waste streams and distillate samples, 1 mL of solution was diluted to 10 mL with 1:1 CH_3CN/H_2O. For the dihydroxylation step, a 0.5 mL aliquot of the reaction mixture was quenched into 40−60 mg of Na_2SO_3 in H_2O, and extracted with 0.8 mL of *n*-BuOAc. A 50 μL aliquot of the *n*-BuOAc extract was diluted in 1.5 mL of mobile phase for assay.

*Preparation of Chiral Epoxide **4** (AE route).* NMO (1572 g, 13.42 mol, 2.3 equiv), catalyst **7**[6g] (170 g, 0.23 mol, 4 mol %), olefin **2** (850 g, 5.82 mol), and dichloromethane (7.7 L) were added in succession to a reactor previously inerted with nitrogen. The mixture was stirred for approximately 15 min at ambient temperature and then cooled to approximately −70 °C.

A separate reactor was charged with *m*-CPBA [70−77% reagent, 2295 g (corrected for 70% purity as determined by a titrimetric method), 9.31 mol, 1.6 equiv] to which absolute ethanol (3 L) was added and stirred until complete dissolution was observed.

The *m*-CPBA solution prepared was charged slowly over a period of approximately 3 h to the solution of olefin **2** and other reactants, while maintaining the reaction at −60 to −70 °C. A T_{zero} sample taken at the end of *m*-CPBA addition showed ∼4.3% of unreacted **2** relative to **4**. The reaction mixture was transferred to a phase splitter containing 1 M NaOH (14 L), and the mixture was agitated for ∼15 min. The organic phase was separated, and the black aqueous phase was backwashed with DCM (4 L). The combined product-rich organic phase was washed with water (2 × 9 L). The phases were separated, and the organic phase was concentrated under reduced pressure to obtain epoxide **4** as a black oil [1019 g, 90%, HPLC purity 83.5, LC/MS: 163 $(M + H)^+$, *S*-isomer by chiral HPLC, 87%]. The product was used in the subsequent step of the synthetic route without further purification.

*Preparation of Chiral Diol **5** (AD Method).* A clean, dry reactor was charged with $K_3Fe(CN)_6$ (122 kg, 370.5 mol, 3.5 equiv), $(DHQ)_2PHAL$ (0.888 kg, 1.14 mol, 0.011 equiv), $K_2OsO_4 \cdot 2H_2O$ (0.09 kg, 0.244 mol, 0.002 equiv), and K_2CO_3 (51 kg, 369.0 mol, 3.5 equiv). Deioinized water (460 L) was added, and the mixture was agitated for at least 30 min. *t*-BuOH (310 L) was added at 20−25 °C, and after stirring for at least 15 min, the resulting slurry was cooled to 0−5 °C under good agitation. A solution of olefin **2** (15.38 kg, 105.2 mol)[17] in *t*-BuOH (140 L; about 5% v/v MTBE present prevents solidification of *t*-BuOH at temperatures <30 °C) was then added at 0−5 °C at such a rate (∼400 mL/min) that the level of **2** was ≤3 area % in the HPLC trace. (If the level went above 3%, the addition was stopped until the level was below this mark.) The reaction mixture was stirred at 0−5 °C until the level of olefin **2** was ≤0.9% relative to diol **5** as determined by HPLC. When the reaction was judged complete, it was quenched with 15 wt % Na_2SO_3 solution (271 kg Na_2SO_3 in 1430 L of H_2O) and then warmed to 20 ± 5 °C. After agitating vigorously for 1 h, *n*-BuOAc (200 L),[18] was added, and stirring continued for 15−30 min.[19] The solids were filtered off and washed with *n*-BuOAc (65 L). From the filtrate the aqueous phase was separated and extracted with *n*-BuOAc (2 × 130 L). The organic layers were combined and washed first with acidic 15% Na_2SO_4 solution (100 L of Na_2SO_4 solution with 1.83 L of 50% H_2SO_4 added),[20,21] followed by basic Na_2SO_4 solution (100 L).[22] The resulting rich organic phase was polish-filtered and concentrated under reduced pressure (150−250 mbar in this case) at ≤50 °C with the addition of more *n*-BuOAc as needed to obtain a final concentration of 0.15−0.17 kg /L of the concentrate and with the water content of the batch ≤0.8% w/w. Heptane (240 L) was charged at 65−75 °C over ≥25 min. After agitation of the resulting slurry at 60−65 °C for at least 30 min, more heptane (160 L) was charged, and agitation was continued at 60−65 °C for an additional 30 min. The slurry was further cooled

(17) The olefin **2**, available as a solution in *t*-BuOH containing ∼2% of MTBE was used. If MTBE is present in greater than 10% v/v, the reaction stalls.

(18) The diol **5** is more soluble in EtOAc, but BuOAc affords a superior azeotropic removal of water during the subsequent concentration prior to crystallization. Lab experiments have demonstrated that when the water content of the rich organic was >0.8% w/w, the diol crystallized in wet clumps which badly adhered to the reactor walls and agitator shaft.

(19) As shown by HPLC analysis, the diol was stable in this mixture for up to 17 h at 20−25 °C.

(20) Prepared by dissolving 14−15 g of Na_2SO_4 in 100 mL of water containing 1% v/v concentrated H_2SO_4.

(21) The acid wash removes the chiral ligand. The acidic aqueous phase can then be basified with NaOH, and the ligand can be extracted into toluene. See ref 15.

(22) Prepared by dissolving 14−15 g of Na_2SO_4 in 100 mL of water containing 1.4 mL of 10 M NaOH. The final apparent pH should be 6.9−7.9, and it can be adjusted by addition of 10% H_2SO_4 or 5−10 M NaOH solution.

to 20−25 °C over at least 1 h and then to ∼5 °C over a minimum of 30 min. After agitation at 5 °C for 1−2 h, the slurry was filtered cold and washed with heptane/*n*-BuOAc (4:1 v/v, 2 × 75 L). The wet cake was dried at ca. 45 °C under vacuum until the loss on drying was <1% w/w to obtain 16.2 kg (90 mol, 85.5%) of chiral diol **5**, mp 91−93 °C (uncorrected), $[\alpha]_D$ +48.16° (*c* = 1, MeOH). HPLC gave a purity of 98.4 area%. Chiral HPLC showed 99.7% *S* enantiomer (99.4% ee). ^{1}H NMR (CD_3OD): δ 7.07 (t, *J* = 7.7, 15.6 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.63 (d, *J* = 7.9 Hz, 1H), 4.72 (t, *J* = 6.0, 12.3 Hz, 1H), 4.51 (dt, *J* = 1.9, 8.6, 17.3 Hz, 2H), 3.62 (d, *J* = 6.0 Hz, 2H), 3.23 (t, *J* = 8.7, 17.3 Hz, 2H); ^{13}C NMR (CD_3OD): δ 160.41, 138.92, 127.96, 125.01, 118.02, 109.99, 108.11, 73.34, 71.14, 66.47, 28.55. IR (KBr): 3221, 1558, 1480, 1460, 1332, 1239, 1198, 1116, 1076, 994, 901, and 794 cm^{-1}.

*Conversion of Chiral Diol **5** to Chiral Epoxide **4***. A clean, dry vessel was charged with chiral diol **5** (9.00 kg, 49.95 mol), THF (26.1 kg, 29.4 L), and agitated at 20−25 °C to dissolve the solids. Trimethylorthoacetate (9.6 kg, 79.9 mol) was added. After cooling the solution to 0−5 °C, TMSCl (10 L, 79.16 mol) was added, while maintaining the batch at 0−5 °C. The addition line was washed with dry THF (1 kg), and the washings were also added to the batch, and agitation was continued at 0−5 °C. After confirmation of reaction completion by HPLC (2−3 h),[23] the reaction mixture was charged with 40 kg of a 20.1 wt. % solution of KO*t*-Bu in THF (8.04 kg, 71.64 mol) at 0−5 °C and agitated at the same temperature until the reaction was complete (typically within 1 h). Water (80 kg, 80 L) was charged to the reactor to dissolve the salts formed, and the apparent pH of the mixed phases was adjusted to 7.5−8.5 with 0.5 M HCl (in this case, 6.95 kg of HCl solution was required). The organic phase was separated and washed with 25% NaCl solution (18 kg of NaCl in 54 kg of H_2O). The aqueous phases were combined and back-extracted with MTBE (2 × 50 kg; 2 × 67.5 L). The combined organic phase was concentrated under reduced pressure (ca. 500 mmHg in this case) at 65−75 °C until minimum agitation was reached or no more distillate was collected (the batch volume was 18−20 L). Dry DME (20 kg, 23.1 L) was charged to the pot, and distillation was continued under reduced pressure at 70−80 °C until the water content of the batch was <0.1% w/w (recharged with 20 kg portions of dry DME and distilled until the desired water content was reached). The DME solution of chiral epoxide **4** was stored cold until needed for the next step. The quantitated yield (by HPLC) was 7.2 kg (44.44 mol, 88.8%, 97.7 area % by HPLC). Chiral HPLC showed 98.9% of the desired *S* enantiomer (98.2% ee). For a sample concentrated to dryness in vacuo: ^{1}H NMR ($CDCl_3$): δ 7.08 (t, *J* = 7.84 Hz, 1H), 6.69 (m, 2H), 4.55 (t, *J* = 8.8 Hz, 2H), 3.81 (q, *J* = 2.6, 3.9 Hz, 1H), 3.25 (t, *J* = 8.71 Hz, 2H), 3.1 (q, *J* = 4.18, 5.15 Hz, 1H), 2.80 (q, *J* = 2.52, 5.53 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 160.03, 128.19, 125.06, 116.18, 108.62, 71.10, 50.70. 49.67, 27.81; LRMS (CI): *m*/*z* 163.0 ($[M + H]^+$), 180.2 ($[M + NH_4]^+$), 204.2 ($[M + H + CH_3CN]^+$).

(23) If the reaction stalls, additional charges of trimethylorthoacetate and TMSCl can be made.

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