Synthetic process development of (*R*)-(+)-1,2-epoxy-5-hexene: an important chiral building block

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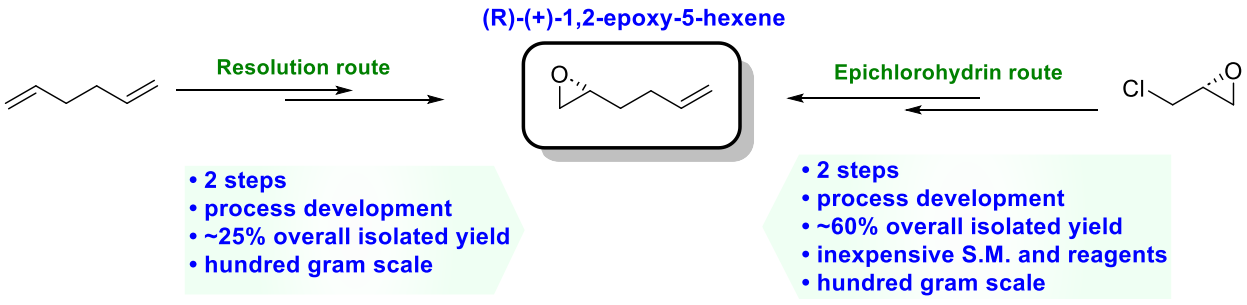


KEYWORDS: Lenacapavir, epoxide, chiral resolution, epichlorohydrin, DOE, process development, scalable.

ABSTRACT

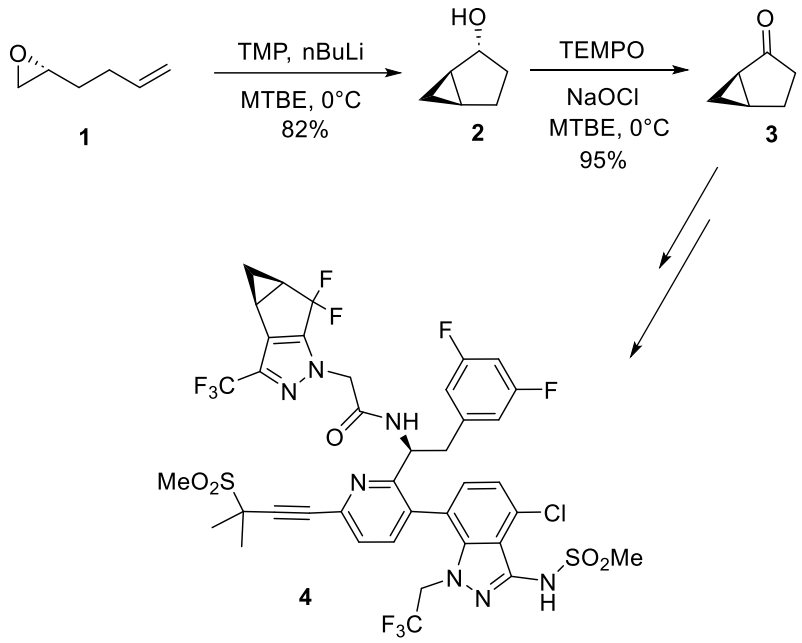
Herein, we describe two practical approaches to synthesize (*R*)-(+)-1,2-epoxy-5-hexene from inexpensive and readily available raw materials and reagents. The first approach is a two-step sequence, involving an epoxidation with meta-chloroperoxybenzoic acid (mCPBA) and a chiral resolution with (salen)Co(II), producing (*R*)-(+)-1,2-epoxy-5-hexene in 24-30% of overall yield. The second approach utilizes the readily available (*R*)-epichlorohydrin as the starting material and features an epoxide ring opening reaction with allylMgCl and the NaOH mediated ring closure reaction. Development of this two-step process affords *R*-(+)-1,2-epoxy-5-hexene in overall isolated yields of 55-60% with an exceptional purity profile. Both approaches have been successfully demonstrated on 100-200g scales.

INTRODUCTION

The epoxide, (*R*)-1,2-epoxyhex-5-ene (**1**) is an important chiral building block. It has been used in a number of asymmetric synthetic methodologies, including the syntheses of chiral isothiazolidine-1,1-dioxides,[1] benzoxathiazepine-1,1-dioxides,[2] γ-butanolides,[3] β-hydroxy morpholine amides,[4] and varied alcohols. Several natural product syntheses have also utilized compound **1**, such as in the syntheses of (+)-gigantecin and (+)-14-deoxy-9-oxygigantecin,[5] pyragonicin,[6] amphidinolides C and F,[7,8] and Sch725674 macrolactones.[9] Biologically active compounds and pharmaceutical substances have also been prepared as single enantiomers from this chiral epoxide. For example, compound **1** is used in the synthesis of the C20-C26 fragment of the anti-cancer drug − Halaven®.[10,11] A kg-scale synthesis of the bicyclic ketone, (1*R*,5*S)*-bicyclo[3.1.0]hexan-2-one (**3**), has been reported and this synthetic method begins with the chiral epoxide **1** (Scheme 1).[12] In this transformation, the chiral epoxide is reacted with catalytic lithium 2,2,6,6-tetramethylpiperidide (TMP) which allows insertion into the olefin group to provide the

bicyclic alcohol (**2**). Oxidation of the alcohol gives compound **3** as the single enantiomer. This bicyclic ketone has been used to synthesize a potent series of cannabinoid receptor modulators and active pharmaceutical ingredients.[13,14] We have successfully used compound **1** in our current synthesis of a fragment of Lenacapavir **4**, anti-HIV drug, as shown in Scheme 1.[15]

Scheme 1. A reported synthetic route for synthesis of compound **3** from epoxide **1**.



Previously, compound **1** has been prepared by enantioselective hydrolytic ring opening of the racemic mixture. In chemistry developed by the Jacobsen group, the enantioenriched epoxide is obtained by hydrolytic kinetic resolution (HKR) involving a chiral (salen)Co (III) complex (the resolution route, *Route 1*).[16,17] This method has been used by several other groups to prepare compound **1**.[7–10,18–22] The chiral epoxide **1** has been prepared from the chiral epichlorohydrin (the epichlorohydrin route, *Route 2*).[23,24] The reported routes offer initial pathways for the synthesis of (*R*)-1,2-epoxyhex-5-ene (**1**), however the methods were only done on small scale and require chromatographic purification. The racemic epoxide has been prepared by epoxidation of 1,5-hexadiene with mCPBA,[25] as well as other reagents.[26] The racemic epoxide has also been

synthesized from the chlorohydrin (itself obtained by the reaction of allyltrimethylsilane and epichlorohydrin with $TiCl_4$).[27]

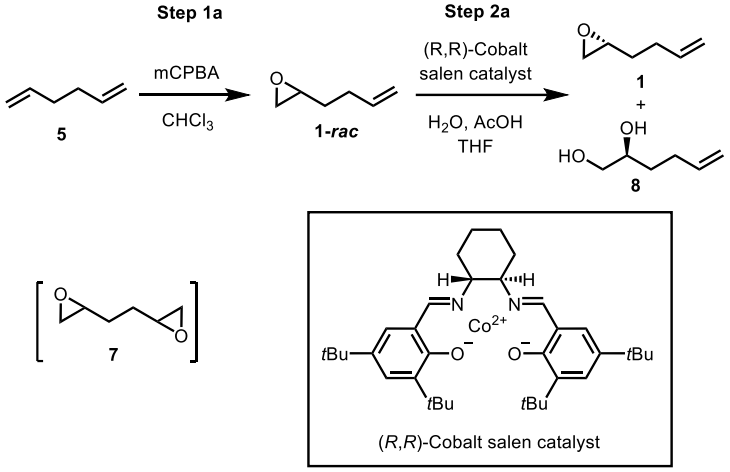
With the synthetic utility of compound **1**, we have sought to develop a process that provides a scalable and economical route to this chiral epoxide. In this study, we focus on the process development of both the resolution route and epichlorohydrin route. The results of our study are detailed in the following sections.

RESULTS AND DISCUSSION

1. Synthesis of (*R*)-(+)-1,2-epoxy-5-hexene through resolution route (*Route 1*)

1.1 Synthesis of racemic epoxide 1-*rac* through epoxidation of 1,5-hexadiene with mCPBA

Scheme 2. Resolution route for the synthesis of chiral epoxide **1**.



At the outset of our work, the chiral epoxide **1** was prepared in two steps according to the literature method: 1) epoxidation of 1,5-hexadiene **5** with mCPBA to obtain the racemic epoxide **1-*rac***;[25,28] 2) hydrolytic kinetic resolution of **1-*rac*** with Jacobsen's cobalt salen catalyst to afford the chiral epoxide **1** (Scheme 2).[16] Adding 1,5-hexadiene to mCPBA at 0°C (reverse addition), the epoxidation was conducted with a stoichiometric amount of mCPBA in $CHCl_3$ (25V) followed by

stirring the mixture for 24-30h (with warming to 25°C). This conversion is reported to give 65% isolated yield of the monoepoxide **1-*rac***.[25] Although there was no mention of the bis-epoxide **7** in the original report, we observed a significant amount of bis-epoxide **7** (~20%) using these conditions. Additionally, the isolated yield of the monoepoxide **1-*rac*** was only 41%. The over-epoxidation might be attributed to the excess amount of mCPBA during the initial charging of the 1,5-hexadiene with the reverse addition. This two-step protocol utilizes inexpensive starting materials - providing a potentially cost-effective route for the synthesis of the chiral epoxide. However the current method is not favorable for scale-up due to: 1) the formation of a significant amount of undesired bis-epoxide **7** (~20 A%); 2) the employment of chloroform (a class 2 solvent, with low permitted daily exposure (PDE) (0.6mg/day) and concentration limit (60ppm) due to its inherent toxicity).[29]

Based on the aforementioned reasons, a comprehensive optimization of this two-step process was carried out to ensure a viable approach for the synthesis of the chiral epoxide in scale. Our initial solvents optimization identified that dichloromethane (DCM) was the solvent of choice (PDE: 6.0mg/day, concentration limit: 600ppm). The reaction in DCM was completed within 3h, giving the desired epoxide **1-*rac*** in ~60 A% of yield and the bis-epoxide **7** in ~16 A%. The investigation of the addition order of the reagent showed similar results between the reverse addition (adding the 1,5-hexadiene to the mCPBA) and the regular addition (adding the mCPBA to the 1,5-hexadiene). For operational practicality, the regular addition was used for all the following investigation. It was observed that warming the reaction to room temperature might not be necessary and could be one of the reasons for the higher amount of bis-epoxide **7** formation. Therefore, the reaction in DCM was performed below 3°C, however, a similar reaction profile was observed with just a minor decrease in the formation of the bis-epoxide (see Table S1 for details).

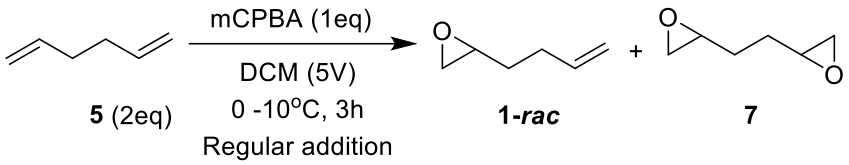
Although no significant reduction in the bis-epoxide **7** impurity was observed, this optimization informed the desired parameters for the design of experiments (DOE) analysis.

Based on the prior results, a DOE analysis was performed by varying four parameters: 1) molar ratio of mCPBA and 1,5-hexadiene (0.4 to 2.0); 2) solvent volume (5V to 25V); 3) reaction time (20min to 180min); and 4) reaction temperature (-11°C to 29°C). According to the DOE analysis, 27 experiments were designed and conducted. The detailed experimental setup and results are presented in Table S3 (see Supporting Information). Parenthetically, identical outcomes for the three center point reactions confirmed the validity of this DOE analysis. For all these reactions, the desired epoxide **1-*rac*** was monitored by GCMS. As expected, the outcome highly relied on the reaction temperature and the amount of 1,5-hexadiene. For example, at 19°C, up to 60 A% of unwanted bis-epoxide **7** was observed when the 1,5-hexadiene was the limiting reagent. In contrast, less than 10 A% of the unwanted bis-epoxide 7 was observed when performing the reaction at -1°C (under otherwise a similar reaction condition). An excess of 1,5-hexadiene is critical to minimize the formation of bis-epoxide and achieve high yield of the desired monoepoxide. For instance, at 9°C, the use of 2.0 equivalents of 1,5-hexadiene afforded the bis-epoxide **7** less than 5 A% while **1-*rac*** was up to 92 A%. However, with a molar ratio of 2:1 mCPBA to 1,5-hexadiene, **1-*rac*** is obtained in 48 A% yield while the undesired bis-epoxide **7** was up to 45 A% yield.

Based on the initial results from the DOE analysis, further optimization was designed to optimize the solvent volumes of this transformation. With 2.0 equivalents of 1,5-hexadiene, two sets of reactions with varied solvent volumes at two different temperatures (0°C and 10°C) were performed (Table S4). It was found that optimal solvent volume is 5 V and optimal reaction

temperature is about 0±5°C. Under this optimized condition, **1-*rac*** was obtained > 90 A% and the formation of bis-epoxide **7** was less than 10 A%.

Table 1. Scale-up of epoxidation of 1,5-hexadiene **5** with mCPBA.[a]



Entry	Scale (g)	Temp (°C)	In-solution yield (TIC A%)[b]			Isolated yield% (gram)[c]		***1-rac*** Purity[f] wt%
			1-*rac*	**7**	**5**	**1-*rac***	**5**	
1	150	0±5	88%	8%	94%	42% (47g)	43% (32g)[d]	85%
2	150	0±5	95%	5%	100%	71% (67g)	95% (71g)[e]	94%

[a]See experimental section for details. [b]In-solution yields were calculated based on GCMS (A%) by total ion chromatogram. [c]The corrected isolated yield was calculated based on the wt% purity. [d]Atmospheric distillation. [e]Atmospheric distillation with a N_2 flow. [f]The wt% purity was obtained from GCMS (wt%) compared to a standard of known purity.

With the optimized process in hand, two batches of reactions with 150g of 1,5-hexadiene were conducted to prepare epoxide **1-*rac*** in a 2L ChemRxnHub reactor (Table 1). In the first batch, a mixture of 1,5-hexadiene (150g) and 5 volumes of DCM was cooled to 0°C, and then 210g of mCPBA was added portion-wise over 50min. After the addition of the mCPBA, the resulting suspension was stirred at 0°C for another 3h and the mixture was quenched by an aqueous solution of NaOH (2N). Two clear layers of solution were formed, and the organic phase (in-solution) yield of **1-*rac*** was up to 88%A and the formation of bis-epoxide **7** was just 8 A%. Crude ^{1}H NMR as well as a peroxide strip test indicated the removal of peroxy materials. The mixture was then subjected to an atmospheric distillation at 50-100°C and 32g of 1,5-hexadiene was recovered as a DCM solution. The resulting crude material was further refined by distillation at 170°C and 47g of epoxide was obtained with a purity of 85 wt% by GCMS. The corrected isolated yield of epoxide was 42%. It should be noted that a drastic amount of product loss occurred during the solvent

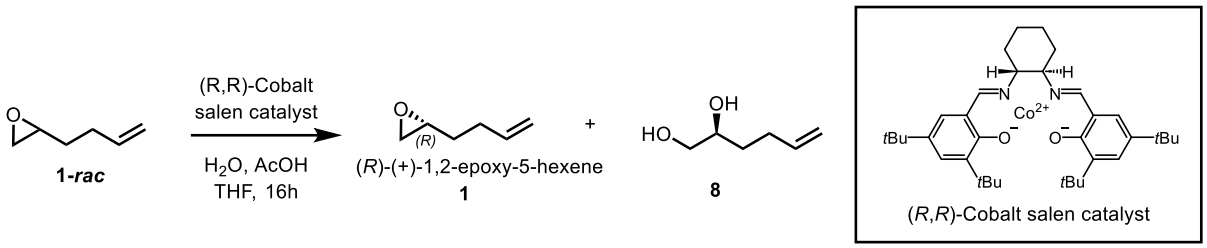
purge and distillation due to the low boiling point of the epoxide (~120°C) and 1,5-hexadiene (~60°C). To improve the recovery yield, we decreased the distillation temperature, meanwhile N_2 flow was used throughout the distillation process. This operation increased the recovery yield dramatically. As shown in the second batch, the epoxidation gave in-solution yield of **1-*rac*** up to 95%A after the aqueous workup. The resulting DCM solution was distilled at 50-80°C with N_2 flow (0.1NL/min) and 71g of 1,5-hexadiene was recovered along with DCM. The recovery yield of 1,5-hexadiene was 95%. Further distillation at 170°C with N_2 flow gave 67g of epoxide **1-*rac*** with purity of 95wt%. The isolated yield of **1-*rac*** was 71%.

1.2 Hydrolytic kinetic resolution of 1-*rac* to synthesize chiral epoxide 1

With racemic epoxide **1-*rac*** in hand, we sought to develop a scalable process for the resolution of the epoxide following Jacobsen's HKR procedure to prepare chiral epoxide **1**. Jacobsen's HKR procedure enriches one enantiomer of the epoxide by enantioselective ring opening, a process catalyzed by a chiral (salen)Co(II) catalyst. In the case of **1-*rac***, the (*R,R*)-chiral (salen)Co(II) catalyst promoted the (*S*)-epoxide to allow the ring opening reaction with water, and as a result, **1-*rac*** was resolved to obtain (*R*)-epoxide **1**.[16] The Jacobsen's HKR is well developed and finds a myriad of applications in small-scale chiral epoxide synthesis, and utilizes cost-effective reagents.[30,31] To obtain an optimal catalyst loading for scale, we screened the catalyst loading against the original 0.5 mol% catalyst loading with 1g-scale reactions. After extensive experimentation, we found that the original 0.5 mol% catalyst loading was optimal (Figure S2). As reported, the experiment with 0.5 mol% of catalyst loading was complete after 16h affording the compound **1** in up to 99.6% *ee*. Then the condition was demonstrated on 8-60g scale reactions. As shown in Table 2, the two smaller scale reactions performed well, however the 60g scale batch proceeded much slower. The reason for the slow reaction on the large scale is unknown, but it

suggests challenges of this HKR process for synthesis of epoxide **1** in scaleup. It should be noted that a significant amount of product was lost during the distillation. A higher recovery yield in distillation for a large-scale production is expected.

Table 2. Scale up of hydrolytic kinetic resolution of rac-1,2-epoxy-5-hexene **1-*rac***[a]



Entry	Scale	ee[b]	Assay yield[c]	Isolated yield (gram)[d]	Purity[e]
1	8g	95%	44%	40% (3.2g)	100%
2	20g	96%	49%	33% (6.6g)	93%
3[f]	60g	94%	49%	34% (20.4g)	99%

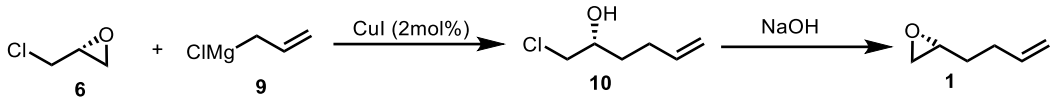
[a]All reactions were performed with (Salen)Co(II) (0.5 mol%), AcOH (2 mol%), THF (0.1 mL/g), air, water (0.55 equivalent), 0°C-rt, 16 h; [b]Monitored by chiral GC; [c]Assay yield determined by GCMS; [d]Isolated yield determined after distillation under vacuum (90°C, 90 Torr). [e]The purity was obtained by GCMS (A%); [f]The ee was achieved after 160h.

The resolution route (two-step) affords the chiral epoxide **1** from readily available 1,5-hexadiene in up to 25% overall yield in hundred gram-scale reactions. This route exhibits promise for scale-up; however, the inherent low yield (no greater than 50%) of the HKR step results in a low overall yield. To obtain a more practical and cost-effective route for the synthesis of chiral epoxide **1**, a route utilizing inexpensive and readily available (*R*)-epichlorohydrin **6** as the starting material was then investigated.

2. Synthesis of chiral epoxide 1 through the epichlorohydrin route (*Route 2*)

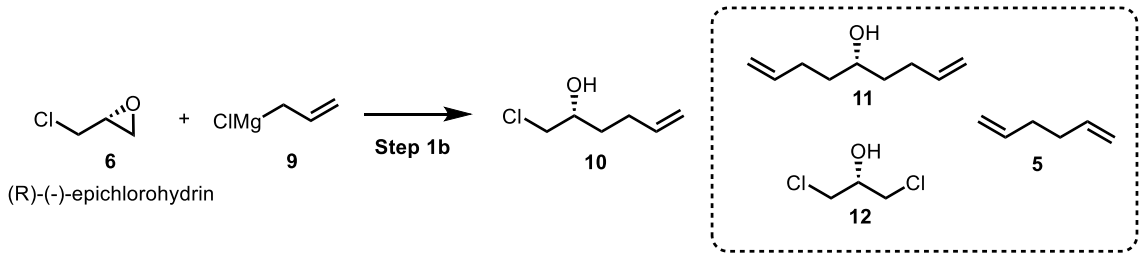
2.1 Synthesis of chlorohydrin 10 through ring opening of (*R*)-epichlorohydrin 6

Scheme 3. A reported method to synthesize chiral epoxide **1** from chiral epichlorohydrin **6**.



We initially evaluated the literature method to make epoxide **1** through the ring opening reaction of 1.0 equivalent of (*R*)-epichlorohydrin **6** with 1.2 equivalents of allylMgCl **9**, followed by NaOH treatment (Scheme 3).[23,32–34] In the presence of 2 mol% CuI, (*R*)-epichlorohydrin **6** reacted with allylMgCl **9** to afford intermediate **10** in ~60% yield after column purification. Epoxide **1** was obtained in a quantitative yield by reaction of intermediate **10** with NaOH pellets. This two-step process shows promise for the synthesis of the chiral epoxide **1** from economical starting materials. However, the low yield of the first ring opening reaction and the need for column purification impedes scale-up. The impurity profile of the crude reaction mixture of the ring-opening reaction was investigated by GCMS. It was found that the major impurities included 1,5-hexadiene **5** (up to 20%), 1,8-nonadien-5-ol **11** (up to 2%) and dichlorohydrin **12** (up to 4%). For a scalable process development of the epichlorohydrin route, we aimed to: 1) minimize the formation of 1,5-hexadiene **5** and other side products **11** and **12**, thus improving the yield of the compound **10**; 2) eliminate the need for column purification - minimizing processing costs and enabling scalability.

Table 3. Optimization of ring opening of (*R*)-epichlorohydrin **6** with allylMgCl **9**[a]



Entry	Conditions	**6** A%	**10** A%	**11** A%	**12** A%	**5** A%
1	**6:9** = 1:0.8, regular addition[b], 2 mol% CuI, rt, THF (10V)	9.6	52.7	9.6	9.4	16.8

2	**6:9** = 1:1, regular addition, 2 mol% CuI, rt, THF (10V)	4.6	58	7.3	6.8	18.5
3	**6:9** = 1:1.2, regular addition, 2 mol% CuI, rt, THF (10V)	-	60.3	1.6	3.5	21.5
4	**6:9** = 1:1.2, regular addition, 2 mol% CuI, -10°C, THF (10V), air	-	59.3	5	-	18.5
5	**6:9** = 1:1.2, regular addition, **without CuI,** -10°C, THF (10V)	-	81	-	-	1.1
6	**6:9** = 1.05:1, **reverse addition**[c], without CuI, 10°C, neat	-	93.9	6.0	0.9	-
7	**6:9** = 1.05:1, reverse addition, without CuI, 20°C, neat	-	91.2	0.4	1.4	-
8	**6:9** = 1.05:1, reverse addition, without CuI, 20°C, neat (25g)	-	73.7	-	9.1	-
9[d]	**6:9** = 1:1, **regular addition**, **without CuI**, -5°C, THF (1V)	-	94.3	-	2.2	-
10[e]	**6:9** = 1:1, regular addition, without CuI, -5°C, THF (1V)	-	86.6	-	2.1	-
11[f]	**6:9** = 1:1, regular addition, without CuI, -5°C, THF (1V)	-	81.7	-	2.1	-

[a]All reactions were carried out with **6** (1g), allylmagnesium chloride (**9**, 2M in THF) in THF under dry nitrogen at given molar ratio as shown in table, 1h, quenched with MeOH, neutralized by aq. HCl (2M), extracted with EtOAc, and analyzed on GCMS by by total ion chromatogram. [b]Regular addition: adding Grignard reagent to the solution of epichlorohydrin in THF dropwise. [c]Reverse addition: adding epichlorohydrin to Grignard reagent dropwise. [d]10g of **6** was used, quenched by aq. 2M HCl. [e]25g of **6** was used, quenched by saturated aq. NH_4Cl. [f]25g of **6** was used, quenched by aq. H_2SO_4 (1M).

As shown in Table 3, our first attempt was to screen equivalents of allylMgCl **9** in the presence of 2mol% of CuI. With the equivalents of allylMgCl **9** from 0.8 to 1.2, it was found that a significant amount of 1,5-hexadiene (up to 22 A%) always formed (Table 3, entries 1-3). The side products of 1,8-nonadien-5-ol **11** and dichlorohydrin **12** were also observed under these conditions. Specifically, both **11** and **12** were formed at a level of about 7% when a stoichiometric amount of the Grignard reagent was used (Table 3, entry 2). It is assumed that trace amounts of oxygen promote the homocoupling reaction of the Grignard reagent to form 1,5-hexadiene.[35] However, a careful removal of oxygen by purging the reaction mixture with argon gave no improvement, in contrast, the reaction proceeded similarly well under air (Table 3, entry 4). Intriguingly, the formation of 1,5-hexadiene **5** was drastically suppressed in the absence of CuI.

Without the addition of CuI, the reaction of epichlorohydrin **6** with 1.2 equivalents of allylMgCl **9** afforded the compound **10** in up to 81 A% with only 1.1 A% of 1,5-hexadiene (Table 3, entry 5). Notably, under this condition, 1,8-nonadien-5-ol **11** and dichlorohydrin **12** were not detected. Encouraged by this promising result, we further optimized the conditions - without the use of CuI by investigating addition order, the equivalents of allylMgCl **9,** and reaction temperature.

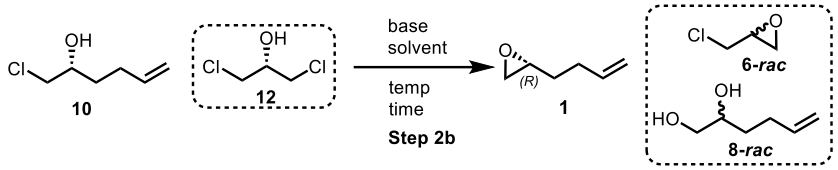
For a more convenient operation in scale, the addition of epichlorohydrin to the Grignard reagent (reverse addition) was investigated. Without the use of CuI, the reverse addition fashion showed promise on a gram scale. For instance, the reaction of 1.05 equivalent of (*R*)-epichlorohydrin **6** with 1.0 equivalent of the Grignard reagent **9** at 10°C afforded the desired product **10** in 94 A% and the formation of **11** and **12** was only 0.9 A% and 1.2 A%, respectively (Table 3, entry 6). A similar result was obtained when keeping the internal temperature at below 20°C (Table 3, entry 7). Unfortunately, when we scaled to 25g of (*R*)-epichlorohydrin **6** under these conditions, up to 9 A% of **12** was generated (Table 3, entry 8), which indicated the competition reaction of the epichlorohydrin with chloride anion at scale. As a result, the regular addition approach (adding Grignard reagent to the epichlorohydrin) was revisited. The prior results indicated that the use of excess Grignard reagent resulted in the formation of both side-product **11** and **12** while the excess (*R*)-epichlorohydrin **6** underwent ring-opening reaction with chloride anion to form the side-product **12** as well. After fine-tuning the ratio of the epichlorohydrin and Grignard reagent, it was found that the stoichiometric reaction of the epichlorohydrin and the Grignard reagent afforded the best results (Table 3, entries 9-11). Under a regular addition mode, the optimal internal temperature was identified as 0±5°C and the optimal volume of the solvent was found to be 1V. As a result, with a regular addition mode, the stoichiometric reaction between the allylMgCl **9** and (*R*)-epichlorohydrin **6** at 0±5°C in 1V of THF afforded the desired product **10** in 94 A%. The side

product of **11** was not detected and the formation of **12** was only 2.2 A%. Notably, the side product of 1,5-hexadiene **5** was also not detected under this condition (Table 3, entry 9). This process showed good repeatability as comparable results were obtained in a 25g scale reaction. It should be noted that the MeOH quench is critical before the workup.[32] A clear aqueous and organic phase separation was achieved with a MeOH quench followed by an aq. HCl (2M) neutralization. However, without the MeOH treatment, a direct acid neutralization of the reaction mixture generated a gel-like mass precluding further purification. Notably, a similar impurity profile was obtained when acidifying the reaction mixture with aq. H_2SO_4 (1M) or saturated aq. NH_4Cl (Table 3, entries 10 and 11). In all cases, the aqueous layer contained product less than 5 A% by GCMS after a one-time MTBE extraction. Attempts to separate compound **10** from the side-products **11** and **12** by distillation failed due to a similar boiling point of these compounds.

2.2 Synthesis of chiral epoxide 1 through ring closure of chlorohydrin 10

A previous report described the NaOH-promoted conversion of the chlorohydrin **10** to epoxide **1**, although this was done on a small scale. [23] To our delight, the ring closure reaction of crude **10** went smoothly in the presence of 2.0 equivalents of NaOH pellets at 60°C, and up to 94 A% yield of epoxide **1** was obtained. Impurity **12** was not detected but epichlorohydrin **6-*rac*** was observed in 1.5 A%, indicating compound **12** underwent ring closure as well (Table 4, entry 1).

Table 4. Optimization of ring closure of **10** with base.[a]



Entry	Conditions	**1** (A%)	%ee	**6-*rac*** (A%)
1	NaOH (2eq, pellets), neat, rt – 60°C, 2h	94	99.9	1.5
2	K_2CO_3 (2eq), neat, 60°C, 2h	44[b]	--	--
3	K_2CO_3 (1eq), ethylene glycol, 60°C, 4h	88[b,c]	--	--

4	DIPEA (1eq), ethylene glycol, 60°C, 4h	0[b]	--	--
5	DIPEA (1eq), diglyme, 60°C, 4h	0[b]	--	--
6	NaOH (2eq, 2M), water, rt, 12h	72.8[d]		
7	NaOH (1.2eq, 2M), MTBE (2V), rt, 12h	95	99.9	2
8	NaOH (1.2eq, 2M), MTBE (2V), 50°C, 2h	98[e]	99.9	2

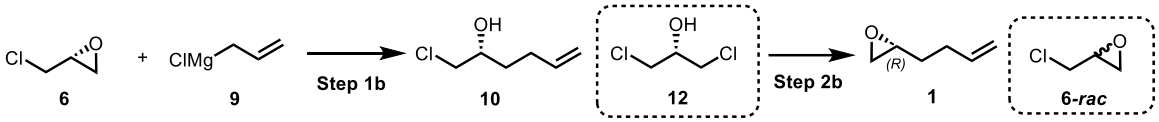
[a]All reactions were performed with **10** (1g, 1eq) and base under the conditions as indicated in table, **8-*rac*** was observed in all conditions; A% was calculated based on GCMS by total ion chromatogram. [b]Estimated by ^{1}HNMR; [c]Ring-opening with ethylene glycol was the major side-reaction; [d]20.6 A% of **10** was unreacted; [e]About 1.5 A% of **10** remained.

Although NaOH showed great promise, the use of solid NaOH is not amenable to scale-up. Additionally, it is noted that utilizing NaOH at 60ºC may cause etching of glass reactors. To develop a more practical process for the scale-up of the ring closure reaction, we screened different bases, solvents, and temperatures. As summarized in Table 4, a milder base, K_2CO_3, under a similar condition, gave a poor conversion with only 44 A% of **1** (Table 4, entry 2). In a high boiling point solvent, such as ethylene glycol, the reaction with K_2CO_3 proceeded more efficiently. For instance, the treatment of the crude **10** with K_2CO_3 in ethylene glycol afforded the epoxide in 88 A%, unfortunately, about 10 A% of adduct of the epoxide with ethylene glycol was also observed (Table 4, entry 3). The use of DIPEA gave no product either in ethylene glycol or diglyme at 60°C (Table 4, entries 4 and 5). As a result, NaOH was revisited for the epoxide formation. Initial results showed that an aqueous solution of NaOH (2N) was promising for the ring closure of compound **10**. Treating chlorohydrin **10** with 2.0 equivalents of NaOH (2N) at room temperature, the desired epoxide was obtained in 73 A% yield after 12h, and about 21 A% starting alcohol remained (Table 4, entry 6). When switching the solvent to the MTBE, 1.2 equivalents of NaOH (2N) enabled a full conversion within 12h at room temperature (Table 4, entry 7). Notably, the hex-5-ene-1,2-diol (**8-*rac***) was not detected under these conditions, which indicated the chemical inertness of epoxide **1** with NaOH. Increasing the reaction temperature to 50°C was sufficient to afford a satisfactory conversion (>98%) within 2h. For instance, the treatment of compound **10** with 1.2 equivalents of NaOH (2N) in MTBE (2V) at 50°C for 2h produced epoxide **1** in 98 A% conversion (Table 4,

entry 8). The successful epoxidation in MTBE enabled a possible direct use of the resulting MTBE solution from the prior ring-opening reaction, without the need for solvent swap. When treating the MTBE solution of the crude product **10** (from step 1b) with 1.2 equivalents of NaOH (2N) at 50°C for 2h, full conversion was obtained, the in-solution yield was up to 90 A% and the purity was up to 96 A% after water wash. It is worth mentioning that all epoxide obtained through this process was the (*R*)-enantiomer (>99.9% *ee*) as confirmed by a chiral GC analysis.

2.3 Scale up the epichlorohydrin route (*route 2*) for synthesis of chiral epoxide 1

Table 5. Two-step process for the synthesis of epoxide **1** from (R)-epichlorohydrin **6**.[a]



*Step 1b: Ring opening of epichlorohydrin to form **10***			
Entry	Scale (g)	Compound **10** (in-solution yield)[b]	Impurity **12**[c]
1	150	93%	2.5%
2	150	94%	3.9%
3	200	91%	4.0%

*Step 2b: Ring closure of **10** to yield the epoxide **1***					
Entry	Scale (g)	In-solution yield of **1**	In-solution purity[c]		Yield of **1** after distillation[d]
			Epoxide **1**	Impurity ***6-rac***	gram, yield%, A% purity, wt% purity, *ee*[e]
4[f]	--	70%	96%	1.0%	97g, 60%, 99 A%, 86wt%, 99.9%
5[g]	--	76%	96%	1.2%	91g, 56%, 98 A%, 85wt%, 99.9%
6[h]	--	77%	98%	1.5%	125g, 59%, 99 A%, 85wt%, 99.9%

[a]See experimental section for details. [b]All the in-solution yield was calculated based on GCMS (wt%). [c]The impurity percentage was obtained by GCMS (A%).[d]0.4 A% of 1,8-nonadien-5-ol **11** was also detected. [d]The area purity was obtained by GCMS (A%), wt% was obtained by GCMS (wt%), and the mass/yield was corrected data. [e]The ee was obtained by chiral column GC.[f]The distillation of compound **1** was performed under 70-80 Torr at 80°C.[g]Atmospheric distillation at 170°C with N_2 flow. [h]Atmospheric distillation at 170°C without N_2 flow.

With the optimized 2-step epichlorohydrin route for the production of **1** in hand, the scale-up of the process in a hundred-gram scale (100-200g) was demonstrated in a 5L ChemRxnHub reactor

(Table 5). This process generated the epoxide with an overall in-solution yield of 70-77 A%, a chemical purity of up to 96 A%, and an enantiomeric excess of up to 99.9%. After distillation at the second step, 56-60% of isolated yield and up to 99 A% purity were achieved. For instance, as shown in entry 1 (Table 5), at the scale of 150g of the epichlorohydrin **6**, its stoichiometric reaction with the allylMgCl **9** afforded the chlorinated alcohol **10** in 93 A% in-solution yield after workup (quenched by MeOH, neutralized with aq. HCl and extracted by MBTE (750mL)). The major impurity was dichlorohydrin **12** (2.5 A%). The crude **10** in MTBE underwent the ring closure reaction smoothly by treating with 1.2 equivalents of NaOH (2N) at 50°C for 2h. After washing the organic phase with water until the aqueous phase showed pH = 7, the resulting MTBE solution of **1** exhibited an in-solution yield of 70 wt%. As was found on the small scale, compound **12** was not observed but epichlorohydrin **6-*rac*** was detected (1 A% yield). After removal of the MTBE, the resulting crude product was purified by vacuum distillation (70-80 Torr at 80°C), affording compound **1** in 56-60% of isolated yield with excellent chemical and enantiomeric excess purities (Table 5, entries 1 and 4). It should be noted that up to 20 wt% of compound **1** was lost during the solvent purge and distillation. Other distillation approaches, such as normal pressure distillation w/o N_2 purge resulted in a similar recovery yield (Table 5, entries 5 and 6).

CONCLUSIONS

In conclusion, two scalable routes for the synthesis of *R*-(+)-1,2-epoxy-5-hexene **1** were developed from inexpensive, readily available starting materials. *Route 1* involves epoxidation and Jacobsen hydrolytic kinetic resolution. The epoxidation of 2 equivalents of 1,5-hexadiene with 1 equivalent of mCPBA afforded the assay yields of up to 95 A%. The following resolution step achieved the assay yield up to 49 A% (vs theoretical yield: 50 A%). The two-step process was

demonstrated on a hundred-gram scale, affording the chiral epoxide **1** with an overall yield of ~25% after distillation.

Route 2 employed (*R*)-epichlorohydrin as the starting material and included an epoxide ring-opening and a ring closure reaction. Development of this process successfully minimized the formation of side products thereby enabling the formation of the enantiopure epoxide **1** with an overall isolated yield of up to 56-60% and purity of up to 99 A% on a hundred-gram scale. Additionally, the excellent purity profile of the crude epoxide **1** from the epichlorohydrin route provides possible telescoping options to subsequent synthetic steps. For example, this allows implementation of the Hodgson reaction to produce **2**. Compared to the resolution route, the epichlorohydrin route provides a more efficient and scalable strategy to prepare this chiral building block, (*R*)-1,2-epoxyhex-5-ene (**1**).

We hope that these scalable approaches to the chiral epoxide **1** will inspire more applications of its use in organic synthesis routes, including further efforts to optimize the process towards cost-effective synthesis of Lenacapavir.

EXPERIMENTAL SECTION

General Information. Reagents and solvents were obtained from commercial suppliers and used as received unless otherwise indicated. (*R*)-epichlorohydrin (99%) was purchased from Oakwood Chemical and allylmagnesium chloride solution (2.0 M in THF) was purchased from Sigma-Aldrich. Reactions were conducted in oven-dried (120°C) glassware, which was assembled while hot, and cooled to ambient temperature under an inert atmosphere. All reactions were conducted under an inert atmosphere (N_2) unless otherwise noted. Reactions were monitored by TLC (precoated silica gel 60 F254 plates, EMD Chemicals), GCMS or chiral-column GC using various methods. TLC was visualized with UV light or by treatment with Phosphomolybdic acid (PMA),

ninhydrin, and/or $KMnO_4$. Flash chromatography was performed on a Teledyne ISCO Combi-Flash NEXTGEN 300+ and/or a Biotage Isolera using solvents as indicated. HRMS was recorded using Perkin Elmer Axion 2 ToF MS, ionization mode: positive with scan range: 100 - 1000 m/z, flight tube voltage: 8 kV, spray voltage: 3.5 kV, solvent: methanol. ^{1}HNMR and ^{13}CNMR spectra were routinely recorded on Bruker Avance III HD Ascend 600 MHz spectrometer. The NMR solvents used were $CDCl_3$ or CD_3CN as indicated. Tetramethylsilane (TMS) was used as an internal standard. Coupling constants J are reported in hertz (Hz). The following abbreviations were used to designate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet, p, pentet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, double of triplets; ddt, doublet of doublet of triplets; m, multiplet; br, broad. 1,3,5-trimethoxybenzene and/or triphenylmethane, were used as internal standards for quantitative ^{1}H-NMR.

Synthesis of rac-(±)-1,2-epoxy-5-hexene (1-rac) (step* 1a*, resolution route)

A 2L ChemRxnHub reactor was charged with 750 mL DCM (5V) and 1,5-hexadiene (150g, 1.83mol, 2 equiv), and the reaction solution was cooled to -5°C (internal temperature -3.8°C) with a chiller. Solid mCPBA (210.0g, 912.7mmol, 1 equiv) was added in three equal portions (3 × 70.0 g), maintaining the internal temperature < 5°C. Once the reaction cooled back down to -3°C after the final addition, the reaction was assayed for unconsumed mCPBA: ca. 10% mCPBA remained (^{1}H NMR, CD_3CN). The reaction was warmed to 5°C and stirred for 1h to complete. At which point the reaction was quenched with aq. NaOH (440mL, 2.5N, 0.6equiv), stirred briefly, separated, and the organic phase was assayed for product epoxide (86.83g, 97%). The epoxide solution was concentrated to ca. 250mL at 65°C, and further distillation of the volatiles continued at 50-80°C under gentle N_2 stream (0.4 NL/min) on a separate distillation setup with a 10" Vigreaux column, long-path condenser into a cooled (-78°C) receiving flask to recover 1,5-

hexadiene (71g, yield: 95%) as a solution in DCM. Once the volatiles were purged, atmospheric distillation continued at 170-200°C to yield *rac*-1,2-epoxy-5-hexene **1-*rac*** (67.5g, 93.8wt%, yield: 71%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.82 – 5.75 (m, 1H), 5.01 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.93 (dq, *J* = 10.2, 1.7 Hz, 1H), 2.87-2.86 (m, 1H), 2.69 – 2.68 (m, 1H), 2.42 – 2.41 (m, 1H), 2.18 – 2.11 (m, 2H), 1.62 – 1.53 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ137.6, 115.1, 51.8, 47.1, 31.8, 30.2. MS-EI (m/z) (M^+): 98.1.

Synthesis of R-(+)-1,2-epoxy-5-hexene (1) (step 2a, resolution route)

A 250 mL flask with over-head stirring was charged with (*R*,*R*)-(salen)Co(II) (1.82g, 3.01mmol, 0.005equiv). The catalyst was treated with *rac*-1,2-epoxy-5-hexene **1-*rac*** (63.1g, 93.8wt%, 602.8 mmol), AcOH (0.69mL, 12.06mmol, 0.02equiv), and 6mL of THF under aerobic conditions. The reaction flask was cooled to 0°C, and H_2O (6.0mL, 332mmol, 0.55equiv) was added in one portion. The reaction was allowed to warm to room temperature and monitored by chiral GC. After stirring for 160h, the ee was 94%, with an assay yield of 49 A%. At this time the volatile materials were distilled at 90°C under a gentle N_2 stream (0.4 NL/min), followed by vacuum transfer under 90Torr at 90°C to afford (*R*)-1,2-epoxy-5-hexene **1** (19.82g, 602.8mmol, 33.5%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.82 – 5.75 (m, 1H), 5.01 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.93 (dq, *J* = 10.2, 1.7 Hz, 1H), 2.87-2.86 (m, 1H), 2.69 – 2.68 (m, 1H), 2.42 – 2.41 (m, 1H), 2.18 – 2.11 (m, 2H), 1.62 – 1.53 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ137.6, 115.1, 51.8, 47.1, 31.8, 30.2. MS-EI (m/z) (M^+): 98.1.

Synthesis of (R)-1-chlorohex-5-en-2-ol (10) (step 1b, epichlorohydrin route)

To a 5L ChemRxnHub reactor under a nitrogen atmosphere, was added THF (200mL, 1V) followed by (*R*)-epichlorohydrin **6** (200g, 2.16mol, 1eq). This mixture was cooled at -25°C

(internal temperature was -15.5°C) using a chiller. When the internal temperature achieved -15°C, allylmagnesium chloride **9** (1.08L, 2.16mol, 1eq, 2M in THF) was added using a peristaltic pump with a flow rate of 5-10 mL/min, maintaining the internal temperature below -5.0°C. After addition, this mixture was stirred at the same temperature for an additional 1h. Then methanol (219mL, 5.4mol, 2.5eq) was added dropwise, keeping the internal temperature below 0°C, followed by addition of HCl (2.16L, 2M, 2.0eq) at 0°C. The circulating cooling system was turned off and MTBE (1L) was added. The organic layer was collected and washed with HCl (400mL, 2M) and water (400mL), respectively. This resulting organic layer (1.8L) gave an in-solution yield of 91% **10** assayed by GCMS, containing 4% of dichlorohydrin **12** and 0.4% of 1,8-nonadien-5-ol **11**. The crude of compound **10** was used for the next step without further purification. A small amount of pure compound **10** was obtained by column chromatography for analytical data.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.85 – 5.78 (m, 1H), 5.03 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.96 (dq, *J* = 10.2, 1.7 Hz, 1H), 2.92-2.89 (m, 1H), 2.73 – 2.72 (m, 1H), 2.46 – 2.45 (m, 1H), 2.24 – 2.14 (m, 2H), 1.95 (br, 1H), 1.65 – 1.56 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 137.7, 115.3, 70.8, 50.3, 33.3, 29.7. MS-EI (m/z) (M^+): 134.1.

Synthesis of R-(+)-1,2-epoxy-5-hexene (1) (step 2b, epichlorohydrin route)

A 5L ChemRxnHub reactor was charged with a solution of chlorohydrin **10** in MTBE (1.8L). To the reactor was added an aqueous solution of NaOH (1.3L, 1.2eq, 2N). The mixture was heated to 50°C and stirred for 2h. After completion, the organic layer was collected and washed with water (500mL × 4) until the aqueous measured pH = 7. The resulting organic phase gave an in-solution yield of 77 A% assayed by GCMS (TIC), containing chiral epoxide **1** of 98.6 A% and epichlorohydrin **6-*rac*** of 1.5 A%. The solution was evaporated at 90°C to remove solvents of

MTBE and THF. The resulting crude product was distilled with Vigreux column at 130-170°C to afford the desired epoxide **1** (125g, yield: 59%, purity: 99 A% by GCMS, ee: 99.9%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.82 – 5.75 (m, 1H), 5.01 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.93 (dq, *J* = 10.2, 1.7 Hz, 1H), 2.87-2.86 (m, 1H), 2.69 – 2.68 (m, 1H), 2.42 – 2.41 (m, 1H), 2.18 – 2.11 (m, 2H), 1.62 – 1.53 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ137.6, 115.1, 51.8, 47.1, 31.8, 30.2. MS-EI (m/z) (M^+): 98.1.

SUPPORTING INFORMATION

The Supporting Information is available free of charge at https://pubs.acs.org/doi/SOMEJOURNALLINK These data include additional experimental details and analytical methods.

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