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Development of a Large-Scale Process for an HIV Protease Inhibitor

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Abstract:

An efficient large-scale process to prepare the HIV protease inhibitor urea intermediate, *N*-[3(*S*)-[bis(phenylmethyl)amino-2(*R*)-hydroxy-4-phenylbutyl]-*N*′-(1,1-dimethylethyl)-*N*-(2-methylpropyl)urea was developed. The protected alcohol, *β*-(*S*)-[bis(phenylmethyl)amino]benzenepropanol, was obtained in 95% yield in one step by the benzylation of L-phenylalaninol with benzyl bromide under aqueous conditions. Oxidation of protected alcohol with sulfur trioxide pyridine complex in DMSO at 15 °C gave the corresponding aldehyde in quantitative yield. The dimethyl sulfide byproduct was easily removed by nitrogen sparging and treatment of the effluent gas stream with bleach solution. Diastereoselective reaction of the chiral amino aldehyde with (chloromethyl)lithium at −35 °C followed by warming to room temperature gave the desired epoxide stereoselectively in good yield. A DOE (statistical design of experiment) study indicated that the reaction concentration and halogen reagent were important factors for this reaction. To simplify the operations and to increase the productivity of epoxide, a continuous process was developed. Regioselective ring opening of epoxides with isobutylamine followed by reaction of the resulting amine with *tert*-butyl isocyanate in isopropyl alcohol gave the urea *N*-[3(*S*)-[bis(phenylmethyl)-amino]-2(*R*)-hydroxy-4-phenylbutyl]-*N*′-(1,1-dimethylethyl)-*N*-(2-methylpropyl)urea, in good yield. The process improvements for the crystallization of urea are also discussed.

Introduction

Inhibition of HIV protease offers an attractive target for the treatment of acquired immunodeficiency syndrome (AIDS).[2−4] Compounds incorporating hydroxyethylamine have been found to be highly potent inhibitors of HIV proteases.[5] Recently, a series of potent inhibitors containing the (*R*)-(hydroxyethylurea) isostere[6] was reported. This early work centered on the amine opening of a key intermediate epoxide **4a** (*N*,*N*,α(*S*)-tris(phenylmethyl)-2(*S*)-oxiranemethanamine). The epoxide **4a** was prepared via a six-step synthesis starting from L-phenylalanine.[5a] The use of diazomethane, the low diastereoselectivity of $NaBH_4$ reduction, and the low overall yield made the scale-up of this route impractical. Recently we reported on an alternative synthesis for the synthetic equivalent of epoxide **4a** (Scheme 1).[1] The process involved a diastereoselective methylenation of chiral amino aldehyde **3** with (chloromethyl)lithium which was generated in situ from halomethanes. In order to further scale this synthesis up to multikilogram scale, significant process development and improvements were needed. In this paper we describe our research on the optimization and further improvement of this alternative synthesis.

Results and Discussion

Step 1. The previous report[1] described two established synthetic routes to *N*,*N*-dibenzyl-L-phenylalaninol (**2**). The protected alcohol **2** could be prepared by benzylation of L-phenylalanine followed by reduction with diisobutylaluminum hydride (DIBAL-H). Alternatively, the alcohol **2** was prepared by the benzylation of L-phenylalaninol (**1**) with benzyl bromide under basic conditions in one step. To simplify the synthesis and avoid the low-temperature reduction with DIBAL-H, the route starting with L-phenylalaninol was chosen for scale-up. Potassium bromide and potassium bicarbonate were the major byproducts of this procedure. The crude product **2** containing these byproducts was washed several times with water at 10 °C until the pH was neutral. The washed solid **2** was then purified by recrystallization from a mixed solvent of ethyl acetate/heptane. To reduce the number of operations and minimize the waste, the original process was modified to use hot water extraction at 65 °C instead of a 10 °C water wash. The product was then directly crystallized from heptane to eliminate the first isolation of crude product. The modified process was scaled up to ∼40 kg scale, and the product **2** was obtained in 95% yield.

Step 2. As described previously, the aldehyde **3** was easily prepared in quantitative yield by the oxidation of *N*,*N*-dibenzylphenylalaninol (**2**) with SO_3·Py in DMSO at ∼15 °C without racemization.[1] Two alternative oxidation methods using NaOCl/Tempo[7] and P_2O_5/DMSO/Et_3N[8] were also investigated. Both methods were inferior when compared to the current method. Standard Swern oxidation using ClCOCOCl/DMSO[8] required very low temperature (−78 °C). This requirement for a special low-temperature reactor

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(1) Ng, J. S.; Przybyla, C. A.; Liu, C.; Yen, J. C.; Muellner, F. W.; Weyker, C. L. *Tetrahedron* **1995**, *51*, 6397−6410.

(2) Kohl, N. E.; Emini, E. A.; Schleif, W. A.; Davis, L. J.; Heimback, J. C.; Dixon, R. A. F.; Scolnick, E. M.; Sigal, I. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 4686−4690.

(3) Tomasselli, A. G.; Howe, W. J.; Sawyer, T. K.; Wlodawer, A.; Heinrikson, R. L. *Chim. Oggi* **1991**, May, 6−27.

(4) Debouck, C. *Hum. Retroviruses* **1992**, *8* (2), 153−164.

(5) (a) Getman, D. P.; DeCrescenzo, G. A.; Heintz, R. M.; Talley, J. J.; Bryant, M. L.; Clare, M.; Houseman, K. A.; Marr, J. J.; Mueller, R. A.; Vasquez, M. L.; Shieh, H.-S.; Stallings, W. C.; Stegeman, R. A. *J. Med. Chem.* **1993**, *36*, 288. (b) Krohn, A.; Redshaw, S.; Ritchie, J. C.; Graves, B. J.; Hatada, M. H. *J. Med. Chem.* **1991**, *34*, 3340. (c) Roberts, N. A.; Martin, J. A.; Kinnchington, D.; Broadhurst, A. V.; Craig, C.; Duncan, I. B.; Galpin, S. A.; Handa, B. K.; Kay, J.; Krohn, A.; Redshaw, S.; Ritchie, A. J.; Taylor, C. L.; Thomas, G. J.; Machlin, P. J. *Science* **1990**, *248*, 358.

(6) Getman, D. P.; DeCrescendo, G. A.; Heintz, R. M.; Reed, K. L.; Talley, J. J.; Bryant, M. L.; Clare, M.; Shieh, H.-S.; Stallings, W. C.; Stegemam, R. A. *J. Med. Chem.* **1993**, *36*, 288−291.

(7) Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029−5032.

(8) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons, Inc.: New York, 1992; pp 1193−1195.

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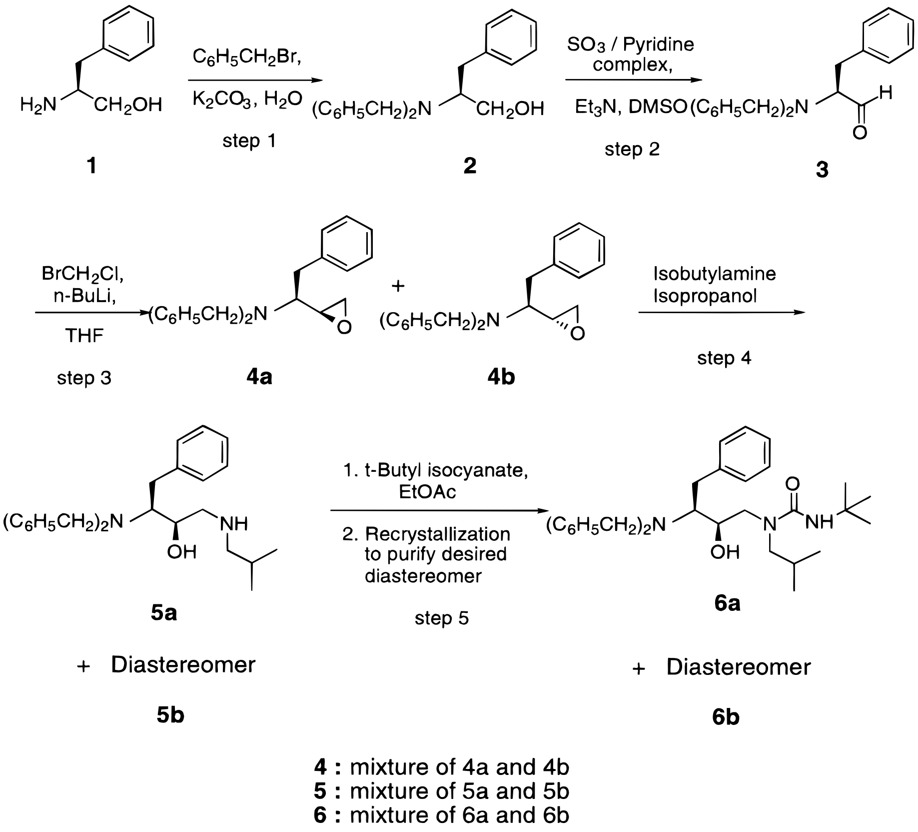
Scheme 1



would not allow rapid scale-up. The reaction with NaOCl/Tempo[7] gave impure products containing overoxidized impurities. The current method with SO_3•Py in DMSO gave product **3** cleanly without any overoxidized acid impurity. However, the highly volatile dimethyl sulfide (DMS) byproduct was produced in this reaction. The DMS emission was a potential environmental issue for this process. To control the DMS emission during the vacuum distillation of solvents and to avoid the DMS odor, the quenched reaction mixture was purged with nitrogen and the DMS off gas was scrubbed with 5% NaOCl.[9] Conversion of DMS to DMSO by NaOCl occurred very rapidly. This process was scaled up to $\sim$200 kg of alcohol **2** without any emission or odor problems. A slight excess of sulfur trioxide pyridine complex (SO_3•Py) was required to ensure the completion of the reaction. In the original report,[1] the alcohol **2** and SO_3•Py were dissolved separately in DMSO to form two solutions prior to the oxidation reaction. A large quantity of DMSO was needed, and the throughput of the reaction was poor. We discovered that one could improve the reaction throughput by using the required base triethylamine to dissolve the alcohol **2** instead of DMSO prior to the oxidation.[10] The oxidation was mildly exothermic. To avoid thermal racemization of aldehyde **3**, the reaction and solvent distillation temperature were controlled below 18 °C. The α-amino aldehyde **3** was not stable for prolonged storage, and it was normally used immediately in the next step during the pilot plant production.[11] Ethyl acetate was used to extract the product from the aqueous solution.[12] Prior to the epoxide formation reaction, THF was added and distilled from the crude aldehyde **3**. This helps to remove the residual water and ethyl acetate which would cause complications in the next reaction step.[13]

Step 3. *Selection of Halomethanes and Reaction Temperature for Plant Production.* The preparation of epoxide **4a** was the key step of this five-step synthetic route. This reaction involved three sequential reactions. The first reaction involved the metal−halogen exchange to form the (chloromethyl)lithium reagent. The second reaction was the diastereoselective addition of (chloromethyl)lithium to the aldehyde **3** to form the chlorohydrin lithium salt **8**. The third reaction was the cyclization of the chlorohydrin lithium salt **8** to give epoxides **4**. As described previously,[1] the (halomethyl)lithium reagent was generated in situ from chloroiodomethane or bromochloromethane and *n*-butyllithium at −78 to −30 °C in THF in the presence of aldehyde **3**. For a successful conversion of aldehyde **3** into the desired epoxides **4**, the rate of the metal−halogen exchange has to be faster than the addition of *n*-BuLi to the aldehyde **3**. Also, the addition rate of (chloromethyl)lithium to aldehyde **3** must be faster than the addition of *n*-BuLi to aldehyde **3** (Scheme 2).[14]

The addition of (chloromethyl)lithium to aldehyde **3** was found to be highly diastereoselective (*SR*:*SS* = 85:15). The diastereomeric ratio was determined by integration of the well-resolved ^{1}H NMR signals[1] for **4a** and **4b**. There was

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[9] Abe, K.; Machida, W. *Taiki Osen Gakkaishi* **1993**, *15* (4), 163−6.

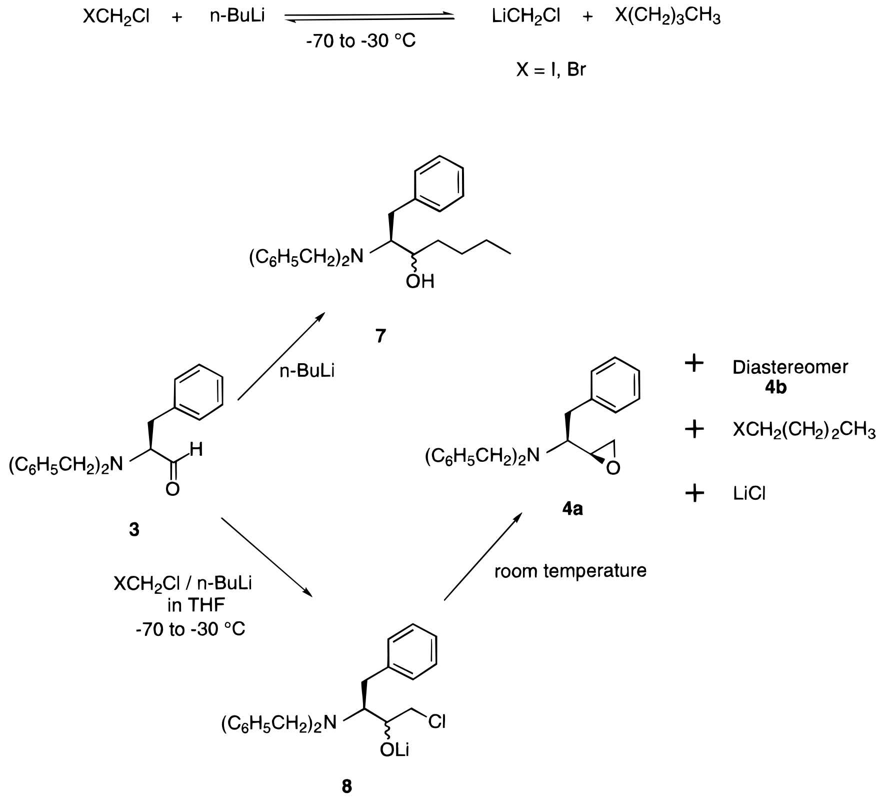
[10] Direct addition of solid sulfur trioxide pyridine complex to the alcohol/DMSO/Et_3N solution could also be used as a method to reduce the amount of DMSO used in the reaction.

[11] The crude aldehyde **3** was stored in a freezer at −78 °C for a month without appreciable degradation or racemization.

[12] Methyl *tert*-butyl ether (MTBE) could be used as an alternative solvent in the place of ethyl acetate for the extraction of aldehyde **3**.

[13] The solvent specifications for aldehyde **3** were the following: water, <0.2%; ethyl acetate, <0.5%.

Scheme 2



no significant difference in the stereoselectivity of the reaction carried out at −78 or −30 °C. Similar results were obtained when either bromochloromethane or chloroiodomethane was used as the methylenation reagent. These results were important because they allowed us to use a wider range of equipment for scale-up and also to use the less expensive and more readily available bromochloromethane for large-scale production.

In the case with chloroiodomethane, more $LiCH_2Cl$ was required at −30 °C when compared to reaction at −78 °C. Better yields were also obtained when the reactions were carried out at −78 °C. This is probably due to the fact that reagent either decomposed or reacted with $ClCH_2I$ faster at warmer temperature (−30 °C) than at lower temperature (−78 °C).[16] A reverse result was observed when $BrCH_2Cl$ was used as the reagent. Better yield and quality of the epoxide were obtained at −30 °C than at −78 °C. The reason for this observation was not clear. One suggestion for these unexpected results is given in the discussion of the results from the DOE study in the a later section of this paper. For the pilot plant production, the reaction was carried out at −30 °C, a temperature readily achieved in most low-temperature reactors. In addition, bromochloromethane was used for cost and bulk availability considerations.

The crude epoxide **4a** prepared using chloroiodomethane had a slightly better purity profile when compared to the product made from bromochloromethane (Table 4), although products from both processes were pure enough to be used directly in the next step. The major impurity of the reaction was the butyl adduct **7**. This impurity resulted from the competitive addition of *n*-butyllithium to aldehyde **3** (Scheme 2). We also observed minor (∼5%) reduction of aldehyde **3** to the alcohol **2**. The origin of this undesired reduction is not clear.

Table 1. **Solvent effect on the impurities of epoxide formation**[a]

	yield, %		
solvent type	epoxide **4a**	butyl adduct **7**	alcohol **2**
THF	59.1	7.2	5.5
DME	37	5.7	10.5
MTBE	7	20.6	0.8
DEM	7.5	35.0	19.5
THF/MTBE 75:25	50	9.3	7.3
THF/MTBE 90:10	50	6.4	8.8
THF/hexane, 75:25	53.2	9.4	5.4

[a] Reaction scale: 25 g of aldehyde **3**. *n*-BuLi addition rate: 2.5 mL/min. Agitation: 300 rpm. Temperature: −45 °C. Solvent: 10 mL/g of aldehyde **3**. $BrCH_2Cl$/*n*-BuLi, 1.3:1. Total *n*-BuLi charged: 2.2 equiv based on aldehyde **3**.

In order to further reduce production cost, we also attempted to carry out the reaction at warmer temperatures (0 to −20 °C). Unfortunately these reactions gave lower yields of the desired products and hence were not recommended for production.

Solvent Effect. The effect of a few alternate solvents in this reaction was also investigated (Table 1). Tetrahydrofuran was the best solvent for the reaction. When methyl *tert*-butyl ether (MTBE) and diethoxymethane (DEM) were used as reaction solvents, high levels of butyl adduct **7** were

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(14) Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795.

(15) (a) An attempt to prepare $ClCH_2Li$ at −105 °C by the reaction of $ClCH_2I$ with *n*-BuLi in a separate reactor was not successful. Addition of aldehyde **3** to a solution of $ClCH_2I$ with *n*-BuLi in THF prepared at −105 °C did not produce any desired epoxide **4a**. The $ClCH_2Li$ was either decomposed or polymerized. (b) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons, Inc.: New York, 1992; pp 622−626.

(16) At −70 °C, 1.6 equiv of *n*-BuLi and 2.0 equiv of $ClCH_2I$ were required to complete the reaction. At −30 °C, 2.2 equiv of *n*-BuLi and 2.9 equiv of $ClCH_2I$ were required to finish the reaction.

Table 2. **Comparison of different charging patterns**

addn no.	ratio of number of equivalents of $BrCH_2Cl$/*n*-BuLi							
1	1.3:1	1.3:1	1.3:1	1.3:1	2.7:1	2.0:1	1.3:1	1.3:1
2	0.39:0.3	0.39:0.3	0.78:0.6	1.3:1		0.45:0.3	0.345:0.3	0.3:0.3
3	0.39:0.3	0.39:0.3	0.78:0.6			0.45:0.3	0.345:0.3	0.3:0.3
4	0.20:0.15	0.39:0.3				0.23:0.15	0.345:0.3	0.3:0.3
5	0.20:0.15	0.39:0.3				0.23:0.15	0.345:0.3	0.3:0.3
6	0.20:0.15					0.23:0.15		
7	0.20:0.15					0.23:0.15		
8	0.20:0.15					0.23:0.15		
9	0.20:0.15					0.23:0.15		
unreacted aldehyde, %	<5%	<5%	>10%	>15%	>45%	>15%	<5%	<5%
yield, %	60%	60%	50%	40%			58%	55%
entry	A	B	C	D	E	F	G	H

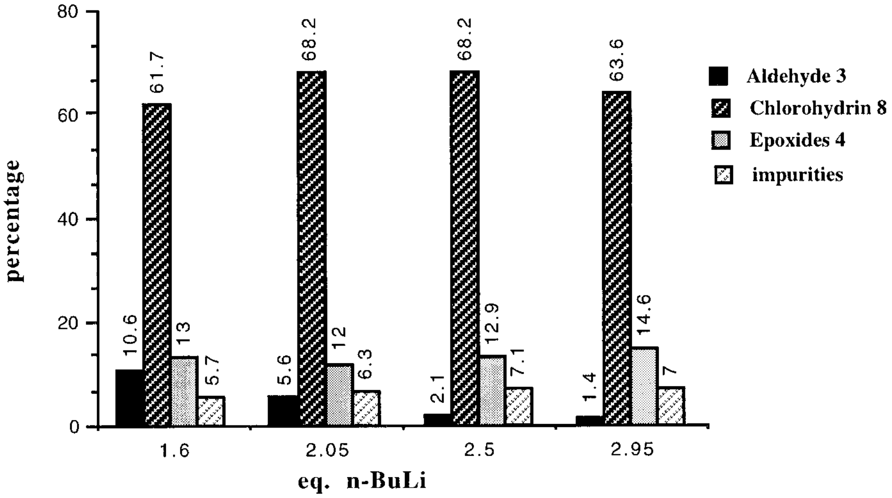

Figure 1. **Composition of reaction mixture.**

observed. It appeared that the reactions in solvents other than THF led to slower generation of (chloromethyl)lithium and more production of the side products.

The Charging Pattern of Bromochloromethane and n-Butyllithium. Because of the high reactivity of (chloromethyl)lithium and its tendency to react with bromochloromethane, we found that the best results occurred when the reagents were added in small doses. If the total quantity of $BrCH_2Cl$ was charged at once followed by the *n*-BuLi addition, more than 45% of unreacted aldehyde **3** was observed (entry E in Table 2). This was possibly due to the reaction of (chloromethyl)lithium with the large excess of $BrCH_2Cl$ present. In practice, several additions of $BrCH_2Cl$ and *n*-BuLi reagents were used to maximize the conversion of aldehyde **3** to the epoxides **4** (Table 2, entry A).[1]

The composition of the final reaction mixtures by HPLC analysis is illustrated in Figure 1. As shown in the plot, 2.05−2.5 equiv of *n*-BuLi was enough to consume >95% of aldehyde **3** and gave the optimum amount of the desired chlorohydrins and epoxides **4**. During the process development studies, the reaction was closely monitored by HPLC analysis to determine the necessity for more $BrCH_2Cl$/*n*-BuLi charge. After the initial piloting runs in the plant, we were able to simplify the operation to five additions of reagents without the continuous monitoring of the progress of the reaction.

Process development studies also indicated that the relative ratio of the number of equivalents $BrCH_2Cl$/*n*-BuLi was important to the yields of the desired products. Use of a relative ratio of greater than 1.5 resulted in more of the unreacted aldehyde **3** (entry F in Table 2). The ideal relative ratio lay between 1.25 and 1.33. It appeared that a slight excess of $BrCH_2Cl$ was necessary to obtain good yields of products with minimum impurities.[17]

Addition Rate of n-Butyllithium. Optimization of the addition rate of *n*-butyllithium could lead to a significant reduction of batch time during scale-up. The effect of *n*-BuLi addition rate was studied, and the results are shown in Table 3. The local *n*-BuLi concentration should be related to the *n*-BuLi charging rate and the speed of agitation of the reactor. A high charging rate was expected to lead to a high localized concentration of *n*-BuLi and formation of more side products such as the butyl adduct **7**. Surprisingly, the results of entries 1 and 2 were similar despite doubling the addition rate for entry 2. Another set of experiments was performed in which the charge was either split into three streams or kept as one stream. Again, similar observations were obtained (entries 3 and 4). The reason for these results was not clear. In the plant production, the addition rate of *n*-BuLi

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(17) The butyl adduct **7** level was slightly increased when the $BrCH_2Cl$:*n*-BuLi ratio decreased. The butyl adduct content for entry B was 8.2% and for entry H was 10.6%.

Table 3. **Addition rate of *n*-BuLi vs yield of epoxide 4a**[a]

entry	*n*-BuLi addn rate, g/min	yield of epoxide **4a**, %
1	0.68	61.6
2	1.70	62.5
3	4.08 through one syringe	57.7
4	total 4.08 through three syringes	58.0

[a] Reaction scale: 25 g of aldehyde **3**. *n*-BuLi addition rate: 2.5 mL/min. Agitation: 300 rpm. Temperature: −35 °C for entries 1 and 2; −45 °C for entries 3 and 4. THF: 10 mL/g of aldehyde **3**. $BrCH_2Cl$/*n*-BuLi = 1.3:1. Total *n*-BuLi charged: 2.2 equiv based on aldehyde **3**.

was adjusted to maintain the reaction temperature below −30 °C.

DOE Study. To further understand and optimize this reaction, a study using statistical design of experiment was performed.[18,19] With some foreknowledge of the relative importance of variables from preliminary experiments,[20] a 2^{4-1} fractional factorial design was employed.[21] Four variables, namely, temperature, concentration, halogen reagent, and agitation rate, were examined. The responses measured included the yield of desired epoxide **4a** (Figure 2) and percentage content of butyl adduct **7** (Figure 3). The table of experimental design (2^{4-1} factorial design) and the responses obtained under each factorial combination were provided below (Table 4).

In general, $ClCH_2I$ was a better reagent than $BrCH_2Cl$, typically resulting in higher yields of epoxide **4a** and significantly lower levels of butyl adduct **7**. With $ClCH_2I$, changing the concentration did not significantly alter the responses at the higher temperature. However, at the lower temperature (−70 °C) there was a marked concentration effect, with more favorable results being observed at lower concentration (1 g/10 mL). With $BrCH_2Cl$, the higher temperature (−20 °C) consistently resulted in a higher yield as well as lower impurity of butyl adduct **7** regardless of the concentration. Based on the literature, similar type reactions were usually carried out at very low temperature (<−70 to −130 °C).[15] For the case with $BrCH_2Cl$, it was surprising to see that the product yield and purity were better at −20 °C than at −70 °C. This result was contrary to the $ClCH_2I$ case. One possible reason could be that the metal−halogen exchange between the $BrCH_2Cl$ and *n*-BuLi was much slower at −70 °C than the exchange of $ClCH_2I$ and *n*-BuLi. Therefore, the reaction mixture contained a higher concentration of *n*-BuLi at −70 °C and the chance of *n*-BuLi reacting with aldehyde **3** was increased.

Statistical analysis of the data revealed that, among the four experimental factors, changes in agitation rate had the least effect on the responses of interest. Because the methylenation involved two very fast sequential reactions (metal−halogen exchange and addition of $ClCH_2Li$ to the aldehyde **3**) and several competitive side reactions (such as addition of *n*-BuLi to aldehyde **3** and addition of *n*-BuLi to epoxides **4**), an efficient agitation rate was still required to minimize the local concentration of reactants throughout the reaction solution. Indeed, DOE results indicated that reactions with higher agitation rate produced the epoxide **4a** in higher average yield (66.4% vs 58.1%). In summary, for best performance $ClCH_2I$ should be used and the reaction should be carried out in dilute THF solution at −70 °C with a high agitation rate. Despite these observations, the large-scale preparation was carried out with bromochloromethane at −30 °C because of the ready availability of reagent and equipment for this combination.

Development of a Continuous Process. The addition of *n*-BuLi to the $BrCH_2Cl$/aldehyde **3** solution was an extremely exothermic reaction. For a batch type reaction, the *n*-BuLi addition rate was limited by the capability of the cooling system. With stepwise addition of *n*-BuLi and $BrCH_2Cl$,[1] the operations were tedious and the process times were long. Recently, we developed a continuous system (model C, Figure 4) which gave epoxide **4a** in yields comparable to those of the batchwise process but with enhanced operational simplicity. Three different types (models A−C) of continuous addition systems were examined.

For model A, all of the 2.2 equiv of *n*-BuLi was continuously added into the reactor, which contained a well-mixed solution of 1 equiv of aldehyde **3** and 1.3 equiv of $BrCH_2Cl$. The rest of the $BrCH_2Cl$ was introduced in portions into the reactor (see Experimental Section), and the ratio among aldehyde **3**, $BrCH_2Cl$, and *n*-BuLi was kept the same as in the stepwise addition system.

For model B, the *n*-BuLi and $BrCH_2Cl$ were both continuously introduced into the reactor, which contained 1 equiv of aldehyde **3** and 1.3 equiv of $BrCH_2Cl$. After workup, the desired product was obtained in 41.8% yield.

For model C, a THF solution of aldehyde **3** and $BrCH_2Cl$ was mixed in a reactor A at room temperature. The aldehyde **3**/$BrCH_2Cl$/THF solution and *n*-BuLi were then pumped into a short static mixer which was immersed in a −35 °C cooling bath. The solution passed through the static mixer into a reactor B, where the mixture was warmed to room temperature immediately. After workup the desired product **4** was obtained in 55.5% yield, and the whole process was finished in 30 min. The advantages for this continuous process were that it (1) simplified the operations, (2) reduced the process cycle time, and (3) reduced the cost of refrigeration by eliminating the need for a large low-temperature reactor. Studies on implementing model C (Figure 4) for large-scale production are still in progress.[22]

Step 4. As described previously,[1] the nucleophilic addition of isobutylamine from the less hindered side of the epoxides **4** in 2-propanol at 75 °C for 1.5 h gave a crude diastereomeric mixture (*SR*:*SS* = 85:15) of amine **5** in almost quantitative yield.[23] No undesired regioisomer was observed.

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(18) Box, G. E. P. *The Design and Analysis of Industrial Experiments*, 4th ed.; longmans: London, 1978.

(19) Box, G. E. P.; Hunter, J. S.; Hunter, W. G. *Statistics for Experiments*; Wiley: New York, 1978.

(20) A series of screening experiments (randomized 2^{7-4} screening design) was also performed. Seven factors (agitation rate, rate of *n*-BuLi addition, reaction temperature, $ClCH_2X$:*n*-BuLi ratio, initial THF:hexane ratio, initial concentration of aldehyde **3**, $ClCH_2X$ halogen reagent) were screened. Based on results from this screening design, the reaction temperature, initial concentration of aldehyde **3**, and $ClCH_2X$ halogen reagent were found to have the most significant effect on the yield.

(21) Schwindt, M. A.; Lejon, T.; Hegedus, L. S. *Organometallics* **1990**, *9*, 2814−2819.

(22) Another continuous system in which aldehyde **3**, $BrCH_2Cl$, and *n*-BuLi are separately pumped into a static mixer through three individual pumps is still under study.

(23) In the laboratory, it was demonstrated that the epoxide-opening reaction could also be carried out in toluene. Comparing to the reaction in 2-propanol, the product was obtained in similar yield and purity.

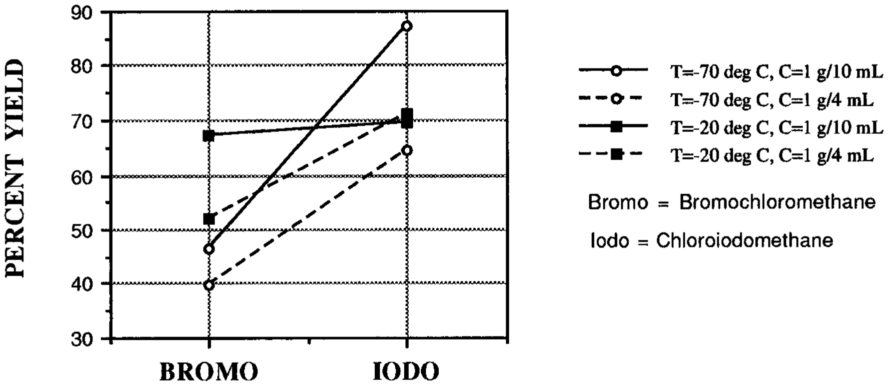

Figure 2. **Effect of halogen reagent on the yield of epoxide 4a.**

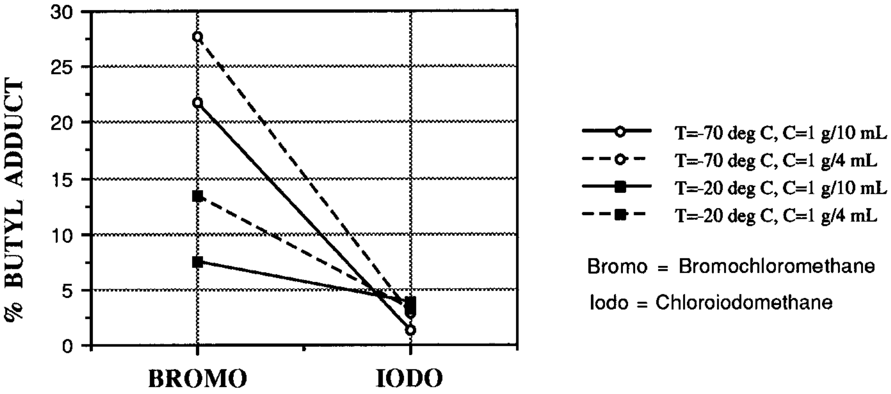

Figure 3. **Effect of halogen reagent on the impurity level of butyl adduct 7.**

Table 4. **2^{4-1} factorial design of resolution IV and response factors**[a]

					yield, %L	
factor combination	A	T	C	H	epoxide **4a**	butyl adduct **7**
1	−	−	−	−	46.3	21.8
2	+	−	−	+	87.3	1.3
3	−	+	−	+	69.6	3.8
4	+	+	−	−	67.2	7.4
5	−	−	+	+	64.4	2.9
6	+	−	+	−	39.8	27.7
7	−	+	+	−	51.9	13.3
8	+	+	+	+	71.2	3.3

exptl factors	low (−)	high (+)
A, agitation rate	50 rpm	300 rpm
T, temp	−70 °C	−20 °C
C, initial concn of aldehyde	1 g/10 mL	1 g/4 mL
H, $ClCH_2X$	X = Br	X = I

[a] Constant factors: rate of *n*-BuLi addition = 2.5 mL/min; $ClCH_2X$/*n*-BuLi ratio = 1.15.

Because of the instability of the epoxides and the lack of a practical large-scale method for the purification of crude epoxides **4**, the crude products **4** were used without purification. The residual halobutane byproducts from the crude epoxide were removed by an azeotropic distillation of the crude product with toluene before use in the epoxide-opening reaction.[24] This operation was important to prevent the potential side reaction of the halobutanes with the isobutylamine used in this step. The epoxide-opening reaction was best conducted with 5 equiv[25] of isobutylamine to prevent dimer formation. The crude amine **5** was then redissolved in ethyl acetate or toluene and concentrated to remove the excess isobutylamine before use in the next step.[26]

Step 5. Treatment of crude amine **5** with *tert*-butyl isocyanate in ethyl acetate at room temperature for 1 h provided a diastereomeric mixture (*SR*:*SS* = 85:15) of ureas **6**. It should be noted that the recrystallization of urea **6a** was the only purification step necessary for this five-step synthesis. The purification was optimized to remove all the impurities and the undesired urea isomer **6b**. The previously published process[1] utilized two crystallizations using a mixed solvent system of ethyl acetate and hexane. A simplified process was developed whereby the crude ureas **6** were purified by a crystallization from acetonitrile/H_2O[27] followed by a trituration with heptane. Using a special reactor (Cogeim),[28] the whole process could be performed without transferring the product out of the reactor/crystallizer. The desired diastereomer **6a** was obtained with better than 99% de.

In the current process, the amine **5a** and urea **6a** formation steps employed four different solvents, namely, 2-propanol, ethyl acetate, acetonitrile, and heptane. It would be beneficial to reduce this to a single solvent. As a result, we developed a process in which the epoxide opening, the urea formation,

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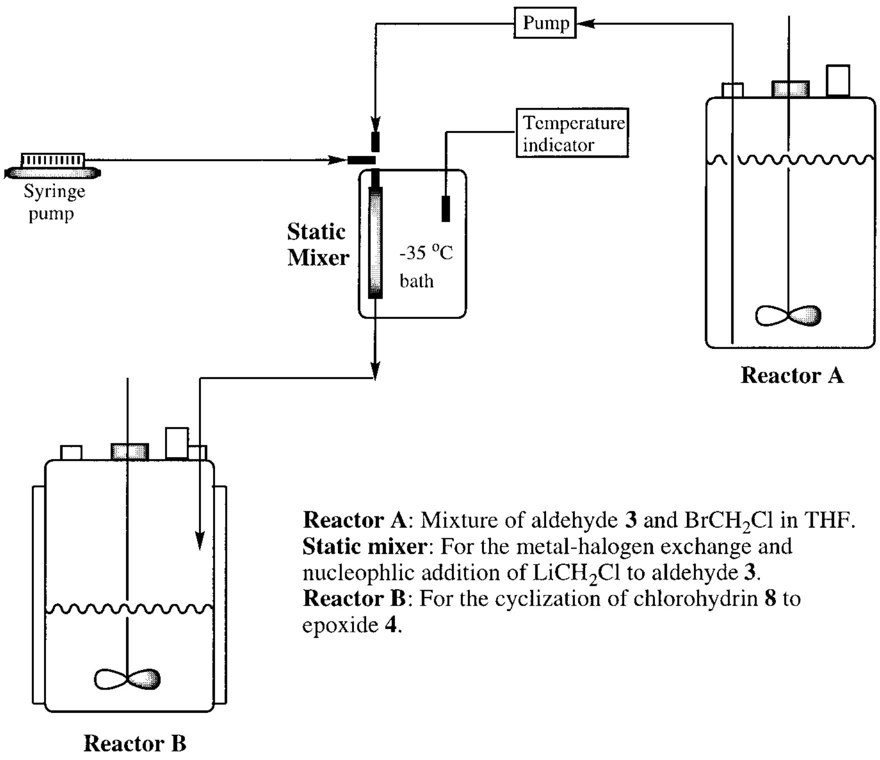
(24) In the plant production, the bromobutane level in epoxide **4** was controlled below 1%.

(25) The quantity of isobutylamine was reduced from 23 equiv to 5 equiv after the process optimization studies.[1]

(26) The isobutylamine content of the crude oil was less than 1%.

(27) Alternatively, the mixed solvent system of ethyl acetate and hexane could also be replaced by a single solvent, diisopropyl ether, for the crystallization of the desired urea **6**.

(28) Cogeim is a trade name for the jacketed reactor equipped with an internal filtration setup.



Reactor A: Mixture of aldehyde **3** and BrCH$_2$Cl in THF.
Static mixer: For the metal-halogen exchange and nucleophlic addition of LiCH$_2$Cl to aldehyde **3**.
Reactor B: For the cyclization of chlorohydrin **8** to epoxide **4**.

Figure 4. **Continuous system for epoxide 4 preparation.**

and the crystallization could all be achieved with 2-propanol. The heptane trituration was still necessary for the final purification of the urea **6a**. This laboratory process could be optimized for large-scale production of these important intermediates.

Conclusions

A detailed study of the previously reported synthesis[1] to prepare the HIV protease inhibitor urea intermediate **6a** from L-phenylalaninol (**1**) was carried out. This study has led to an improved process for the multikilogram production of these important intermediates. The extension of this technology to the preparation of HIV protease inhibitors other than the (hydroxyethyl)ureas will be reported in a separate publication.

Experimental Section

Solvents and reagents were obtained from commercial sources and were not further purified unless specified. The proton and carbon-13 NMR spectra were recorded on a GE QE-300 or a Varian VXR400 spectrometer with Me$_4$Si-d_{12} as an internal standard. Infrared (IR) spectra were recorded using a Perkin-Elmer Model 681 spectrophotometer and CHCl$_3$ solutions. Gas chromatography was performed on a Hewlett-Packard 5890 gas chromatograph equipped with a methyl silicone column (15m × 0.25 × 0.25 μm film thickness). The static mixer (FMX 8452S) was purchased from Omega Co.

Preparation of β(*S*)-[Bis(phenylmethyl)amino]benzenepropanol (2). L-Phenylalaninol (**1**)[1] (40.3 kg, 267 mol) was added to a solution of potassium carbonate (111 kg) in water (162 L). The mixture was heated to 65 °C. A solution of benzyl bromide (93.2 kg, 545 mol) in 3A ethanol (50 L) was added at such a rate as to maintain the temperature between 60−68 °C. After the biphasic solution was stirred at 65 °C for 1 h, water (126 L) and heptane (387 L) were then added into the reactor. After stirring for 15 min, the aqueous layer was separated at 65 °C. The organic layer was then washed with water (212 L), diluted with heptane (155 L), and concentrated under atmospheric pressure to remove about 190 L of distillate. The solution was filtered hot to remove the residue and then allowed to cool to 0 °C with stirring. The product was isolated by filtration and washed with heptane (155 L). The wet cake was air-dried on the filter until a loss on drying (LOD) of less than 3% was achieved to give 83.9 kg (95% yield) of **2** as a white solid. The analytical data of the compound were consistent with the published literature.[1]

HPLC analyses (column, YMC Basic (reverse phase; manufacturer, YMC); 250 mm × 4.6 mm i.d., 5 μm particle size; mobile phase, methanol/pH 3.0 triethylamine phosphate buffer, 70:30 (v/v); flow rate, 1.0 mL/min; UV detector at 210 nm; retention time of **2** = 7.0 min) indicated that the product was >98.5% pure. The optical purity of the product was determined to be >99.9% according to published literature.[1] The other analytical data such as melting points, NMR, and optical rotations were consistent with those reported in the published literature.[1]

α(*S*)-[Bis(phenylmethyl)amino]benzenepropanaldehyde (3). The alcohol **2** (190 kg, 573 mol) was dissolved in triethylamine (322 L, 2292 mol). The mixture was cooled to 12 °C, and a solution of sulfur trioxide pyridine complex (184 kg, 1156 mol) in DMSO (635 L) was added at such a rate as to maintain the temperature between 8 and 18 °C. The solution was stirred at ambient temperature for 0.75 h, at which time the reaction was complete by TLC analysis (33% ethyl acetate/hexane, silica gel). The reaction mixture was cooled to 12 °C and quenched with cold water (224 L, 10−15 °C). The mixture was then sparged with N_2 for 6 h while the temperature was maintained below 20 °C. After removal of most of the DMS, water (688 L) was added into the reactor and the resultant solution was extracted with ethyl acetate (1490 L) and washed with 5% citric acid (1777 L) and then with saturated sodium chloride solution (1376 L). The ethyl acetate was removed by vacuum distillation (100 mmHg) at 40 °C. The resulting residue was diluted with THF (287 L), and the resulting solution was distilled under vacuum (100 mmHg) at 40 °C. The highly viscous **3** was then dissolved in THF (143 L) and used directly in the next step without purification. An analytical sample of **3** was isolated as a viscous oil by concentration of a sample of the THF solution. HPLC analyses (column, Gammabond RP-1 (reverse phase; manufacturer, Astec); 250 mm × 4.6 mm i.d., 5 μm particle size; mobile phase, tetrahydrofuran/pH 9.0 ammonium phosphate buffer at 50 mM concentration, 50:50 (v/v); flow rate, 0.8 mL/min; UV detector at 230 nm; retention time of **2** = 6.5 min) indicated that the concentrated product was >95% pure. The optical purity of the product was determined to be >99.9% according to published literature.[1] The other analytical data such as NMR and optical rotations were consistent with those reported in the published literature.[1]

***N*,*N*,α(*S*)-Tris(phenylmethyl)-2(*S*)-oxiranemethanamine (4a).** A solution of the aldehyde **3** (190 kg; 576 mol) and chloroiodomethane (48.8 L; 751 mol) in tetrahydrofuran (1900 L) was cooled to −30 to −35 °C in a stainless steel reactor. A solution of *n*-butyllithium in hexane (1.6 M, 244 kg) was added at such a rate as to maintain the temperature below −30 °C. After addition, the mixture was stirred at −30 to −35 °C for 10 min. More additions of reagents were carried out in the following manner: Additional chloroiodomethane (15.2 L) was added followed by *n*-butyllithium (73.3 kg) at <−30 °C. After addition was complete, the mixture was stirred at −30 to −35 °C for 10 min. This was repeated three times. A sample was taken for in process control by HPLC analysis after each addition (HPLC conditions: column, Partisil 5 (manufacturer, Whatman); 250 mm × 4.6 mm i.d., 5 μm particle size; mobile phase, hexane/methyl *tert*-butyl ether, 95:5 (v/v); flow rate, 1.0 mL/min; UV detector at 215 nm; retention time of **2** = 6.5 min; retention time of the desired intermediate chlorohydrin = 22 min). The methylenation reaction was considered complete when the aldehyde **2** content was less than 5%. The reaction mixture was warmed to ambient temperature and stirred for at least 4 h until HPLC or TLC (silica gel, 20% ethyl acetate/hexane) indicated that the epoxide **4** formation was completed. The reaction mixture was cooled to 5 °C and quenched with 16% aqueous ammonium chloride solution (1092 L). The mixture was stirred at 25 °C for 30 min, and the layers were separated. The organic phase was washed with water (825 L) and concentrated at 60 °C under vacuum. The residue was diluted with toluene (430 L) and was then distilled under vacuum at 60 °C. This procedure was then repeated twice to give a brown oily residue **4**. The crude product weight was >100% based on theory. The composition of this crude oily product mixture was analyzed by HPLC (column, Partisil 5 (manufacturer, Whatman); 250 mm × 4.6 mm i.d., 5 μm particle size; mobile phase, hexane/methyl *tert*-butyl ether, 95:5 (v/v); flow rate, 1.0 mL/min; UV detector at 215 nm; retention time of **2** = 6.5 min; retention time of the undesired epoxide **4b** = 9.5 min; retention time of the desired epoxide **4a** = 10.5 min). The crude product usually contained approximately 55% of the desired epoxide **4a** at this point. The optical purity of the product was determined to be >99.9% according to published literature.[1] The other analytical data such as NMR were consistent with those reported in the published literature.[1] In this case, the crude product was found to contain a mixture of the two diastereomeric epoxides.

The crude product oil obtained was used in the next step without purification.

General Procedure for the DOE Study. Example for Run 4. A 1 L, three-neck Morton flask equipped with a thermocouple and a mechanical stirrer was flushed with nitrogen. Agitator speed was adjusted to 300 rpm. Aldehyde **3** (25 g, 75.9 mmol) was dissolved in THF (250 mL) and added to the flask. The solution was cooled to about −25 to −20 °C in a cooling bath (9:1 iPrOH/H_2O, dry ice). The first portion of XCH_2Cl (X = Br, 5.67 mL, 87.7 mmol) was added. The first portion of 1.6 M BuLi (47.4 mL) was then added through a syringe pump at −20 ± 3 °C at a rate of 2.5 mL/min, followed by 5 min of stirring (sequence time). This completes the first addition cycle. In each of the second through fifth addition cycles, XCH_2Cl (X = Br, 1.7 mL) was added over about 30 s, and then 1.6 M BuLi (14.2 mL) was added at −20 ± 3 °C at a rate of 2.5 mL/min followed by 5 min of stirring. The reaction mixture was then warmed to 25 °C and stirred for 3 h. It was then quenched with aqueous NH_4Cl solution (16% NH_4Cl in water, 189 mL) at about 10 °C. Stirring was continued at 10−15 °C for an additional 5 min. After settling, the aqueous (bottom) layer was separated and extracted with ether (65 mL). The organic layers were combined and dried with $MgSO_4$ (15 g). After filtration and rinsing with ether, the filtrate was evaporated under reduced pressure at 60 °C to give 31.2 g (67.2% yield after adjusting for the purity of product from HPLC assay) of a brown oil **4**.

Continuous Addition System for the Preparation of Epoxide (4a). *Model A: Stepwise Addition of $BrCH_2Cl$ and Continuous Addition of n-BuLi.* In a round-bottom flask equipped with a mechanical stirrer, a thermometer, and an addition funnel were added 760 mL of THF and 76 g (231 mmol) of aldehyde **3**. The solution was then cooled to −30 °C under nitrogen, and $BrCH_2Cl$ (39.7 g, 307 mmol) was then charged into the reaction mixture. The solution was stirred for 5 min at −35 ± 5 °C. A first portion of *n*-BuLi (144 mL) was then added into the reactor through the addition funnel. A small portion of $BrCH_2Cl$ (6 mL) was quickly introduced into the reaction mixture using a syringe without stopping the *n*-BuLi charging. After an additional 44 mL of *n*-BuLi (continuous addition) had been added into reaction mixture, another small portion of $BrCH_2Cl$ (6 mL) was transferred into the reaction mixture in the same manner. After an additional 44 mL of *n*-BuLi had been added into the reaction mixture, another small portion of $BrCH_2Cl$ (3 mL) was charged into reaction mixture and followed by 22 mL of *n*-BuLi. This addition sequence was repeated seven times without interrupting *n*-BuLi charging. The reaction mixture was then warmed to room temperature and stirred for an additional 4 h. A small aliquot was then taken and checked by TLC for the epoxide formation completion. The reaction mixture was then quenched with an aqueous NH_4Cl solution (16% NH_4Cl in water, 440 mL). After phase separation, the organic layer was concentrated at 60 °C under reduced pressure to give 82.2 g of crude oil **4**.

Model B: Continuous Addition of $BrCH_2Cl$ and n-BuLi. To a round-bottom flask equipped with a mechanical stirrer and a thermometer were added 220 mL of THF and 25 g (75.9 mmol) of aldehyde **3** under nitrogen. The solution was cooled to −35 °C, and $BrCH_2Cl$ (5.7 mL, 87.7 mmol) was charged to the reaction mixture. The solution was stirred for 5 min at −35 ± 5 °C. Simultaneous additions of $BrCH_2Cl$ (6.8 mL) and *n*-BuLi (1.6 M, 104 mL) were introduced to the reactor by syringe pumps, with addition rates of 0.16 mL/min for $BrCH_2Cl$ and 2.5 mL/min for *n*-BuLi, respectively. After the addition was complete, the reaction mixture was warmed to room temperature and stirred for 4 h. The resulting reaction mixture was quenched with 190 mL of aqueous NH_4Cl (16% NH_4Cl in water). After phase separation, the organic layer was washed with water (190 mL) and then concentrated under reduced pressure at 60 °C. An azeotrope of the residue oil with toluene (30 mL × 2) gave 27.1 g of epoxide crude oil **4**. The HPLC analysis (column, Partisil 5 (manufacturer, Whatman); 250 mm × 4.6 mm i.d., 5 μm particle size; mobile phase, hexane/methyl *tert*-butyl ether, 95:5 (v/v); flow rate, 1.0 mL/min; UV detector at 215 nm; retention time of **2** = 6.5 min; retention time of the undesired epoxide **4b** = 9.5 min; retention time of the desired epoxide **4a** = 10.5 min) indicated that the crude product contained 40.2 wt % of the desired epoxide **4a** (41.8% yield after adjusting for the purity of product from HPLC assay).

Model C: Continuous Addition of $BrCH_2Cl$ and n-BuLi. In a round-bottom flask (reactor A, Figure 4) equipped with a mechanical stirrer, a Teflon outlet line, and a thermometer were added 500 mL of THF, 10 g (30.4 mmol) of aldehyde **3**, and 5 mL (76.9 mmol) of $BrCH_2Cl$. The solution was stirred for 5 min at room temperature. The Teflon outlet of reactor A was connected to a static mixer which was immersed in a cooling bath at a temperature of around −35 °C. A separate round-bottom flask (reactor B, Figure 4) equipped with a mechanical stirrer, a Teflon inlet line, and a thermometer was connected to the outlet of the static mixer. The aldehyde **3**/$BrCH_2Cl$/THF solution in reactor A was pumped into the static mixer through the Teflon line at a speed of 21 mL/min. Simultaneously, *n*-BuLi (1.6 M) was introduced to the static mixer by a syringe pump at 1.8 mL/min. The solution coming out of the static mixer was stirred at reactor B and warmed to room temperature immediately. After the intermediate chlorohydrin **8** had been converted to the epoxide **4 in** reactor B, the reaction mixture was quenched with an aqueous NH_4Cl solution (16% NH_4Cl in water, 150 mL). The organic layer was washed with H_2O (150 mL) and concentrated. The residue was diluted with toluene (100 mL) and distilled under vacuum at 60 °C to give 11.1 g of brown crude oily **4**. HPLC analysis (column, Partisil 5 (silica gel); 250 mm × 4.6 mm i.d., 5 μm particle size; mobile phase, hexane/methyl *tert*-butyl ether, 95:5 (v/v); flow rate, 1.0 mL/min; UV detector at 215 nm; retention time of **2** = 6.5 min; retention time of the undesired epoxide **4b** = 9.5 min, retention time of the desired epoxide **4a** = 10.5 min) indicated that the crude product contained 52.3 wt % of the desired epoxide **4a** (55.5% yield after adjusting for the purity of product from HPLC assay).

***β*(*S*)-[Bis(phenylmethyl)amino]-α(*R*)-[[(2-methylpropyl)amino]methyl]benzenepropanol (5a).** *Method A.* To a solution of the crude epoxide **4** (39.6 kg, 115.3 mol) in 2-propanol (53 L) was added isobutylamine (57.3 L, 577 mol). The solution was heated to 75 °C and stirred at this temperature for 1.5 h. The solution was cooled to 40 °C and concentrated under reduced pressure at 40 °C. The brown oil residue was diluted with 47 L of ethyl acetate and distilled under vacuum at 40 °C. This operation was repeated once to give the desired amine mixture **5** as a brown oil. This mixture was redissolved in 118 L of ethyl acetate and used directly in the next step without purification. An analytical sample of this crude mixture could be prepared by concentrating a sample of the oil under vacuum (1 mmHg, 60 °C) and analyzed by HPLC (column, YMC Basic (reverse phase; manufacturer, YMC); 250 mm × 4.6 mm i.d., 5 μm particle size; mobile phase, acetonitrile/pH 7.0 triethylamine phosphate buffer with 5 mM heptanesulfonic acid, 50:50 (v/v); flow rate, 2.0 mL/min; UV detector at 210 nm; retention time of **5a** = 12.5 min; retention of **5b** = 14.0 min). ^{1}H NMR of the crude product was consistent with the published literature.[1]

Method B. To a solution of the crude epoxides **4** (4.82 g, 14.0 mmol) in 2-propanol (6.5 mL) was added isobutylamine (7.0 mL, 70.4 mmol) over 2 min. The solution was heated to 75 °C and stirred at this temperature for 1.5 h. After the reaction was complete, the warm solution was concentrated under reduced pressure at 40 °C. The brown oil residue was diluted with 2-propanol (5.6 mL) and distilled under vacuum at 70 °C. This operation was repeated once. The crude oil was redissolved in 2-propanol (25 mL) and used directly in the next step without purification. The analytical data of the compound were consistent with the published literature.[1]

***N*-[3(*S*)-[Bis(phenylmethyl)amino]-2(*R*)-hydroxy-4-phenylbutyl]-*N*′-(1,1-dimethylethyl)-*N*-(2-methylpropyl)urea (6a).** *Method A.* A solution of the crude amine **5** (126 kg, 302 mol) in ethyl acetate (310 L) was cooled to 0 °C. *tert*-Butyl isocyanate (34.1 kg, 348 mol) was added slowly to maintain the reactor temperature between 10 and 12 °C. After addition, the mixture was warmed to 25 °C. After being stirred at room temperature for 2 h, the reaction mixture was extracted twice with 5% citric acid (327 L) and twice with water (327 L) and concentrated under vacuum at 35 °C. The residue was diluted with 271 L of acetonitrile and distilled under vacuum at 50 °C to remove the residual ethyl acetate. The product was redissolved in acetonitrile (542 L) at 45 °C and then cooled to 0 °C. After stirring for 2 h at 0 °C, water (178 L) was added to the solution and the resulting mixture was further stirred at 0 °C for an additional 0.5 h. The crude solid product was collected by vacuum filtration, washed with water (716 L), and dried until the LOD was less than 15%. The crude product was triturated with heptane (417 L) at 0 °C to give 51.4 kg (32.8% overall yield from alcohol **2**) of purified product. HPLC analysis of the product **6a** (column, YMC Basic (reverse phase; manufacturer, YMC); 250 mm × 4.6 mm i.d., 5 μm particle size; mobile phase, acetonitrile/pH 3.0 triethylamine phosphate buffer with 5 mM heptanesulfonic acid, 60:40 (v/v); flow rate, 1.5 mL/min; UV detector at 210 nm; retention time of **6a** = 15.2 min, retention of **5b** = 14.0 min) indicated that the product was >98.5% pure with less than 0.5% of the undesired diastereomer **6b** and less than 0.5% of the amine **5a**. The remaining analytical data of the product such as melting points, microanalyses, optical rotation, and NMR were consistent with the published literature.[1]

Method B. A solution of the crude amine **5** in 2-propanol (25 mL) was cooled to 0 °C. *tert*-Butyl isocyanate (1.83 mL, 16.0 mol) was added to the solution of the amine over 10 min to maintain the temperature between 10 and 12 °C. The mixture was warmed to 25 °C for 4 h and then diluted with 14 mL of H_2O. The resulting solution was seeded with a small amount of urea **6a**. After stirring for 4 h at 0 °C, the solid product was collected by vacuum filtration and washed with an aqueous 2-propanol solution (2-propanol/H_2O, 2:1, 6 mL). The product was dried in a vacuum drier until the LOD was less than 5%. The crude product was triturated with heptane (40 mL) at 0 °C for 2 h. The solid was collected by vacuum filtration, washed with heptane (20 mL), and then dried under vacuum to give 3.69 g (51.0% yield) of urea **6a** with 98.4 wt % purity. The analytical data of the compound were consistent with the published literature.[1]

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