Preparation of Aminoalkyl Chlorohydrin Hydrochlorides: Key Building Blocks for Hydroxyethylamine-Based HIV Protease Inhibitors

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Enantiomerically pure *N,N*-dibenzyl-α-amino aldehydes reacted with (chloromethyl)lithium, generated *in situ* from bromochloromethane and lithium metal, to give predominantly *erythro* aminoalkyl epoxides. Treatment of the crude epoxides with aqueous hydrochloric acid gave crystalline (2*S*,3*S*)-*N,N*-dibenzylamino chlorohydrin hydrochlorides in 32−56% overall yield and high isomeric purity. These compounds are versatile synthetic intermediates for the preparation of hydroxyethylamine-based HIV protease inhibitors, either directly as such, or via conversion to the corresponding *N*-Boc-(2*S*,3*S*)-aminoalkyl epoxides. The processes described do not make use of hazardous reagents or intermediates, do not require chromatographic purifications, and are thus amenable to the preparation of large quantities of these versatile building blocks.

Introduction

The human immunodeficiency virus (HIV) has been identified as the causative agent of acquired immune deficiency syndrome (AIDS). HIV protease, an essential enzyme for viral maturation,[1] is now a well recognized target for therapeutic intervention against the deadly disease. The protease is essential for processing of the viral *gag* and *gag-pol* gene products through specific cleavages of peptide bonds (e.g. between Phe-Pro and Tyr-Pro).[2] The transition state mimic concept, as applied to the cleavage of an amide bond, has been very successful in the rational design of HIV protease inhibitors. In particular, replacement of an amide linkage by a non-scissile hydroxyethylamine (HEA) dipeptide isostere has led to potent peptidomimetic inhibitors of the enzyme and of viral replication *in vitro* (Figure 1).[3]

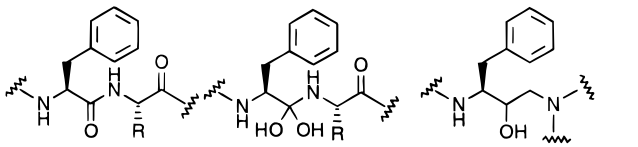

Figure 1.

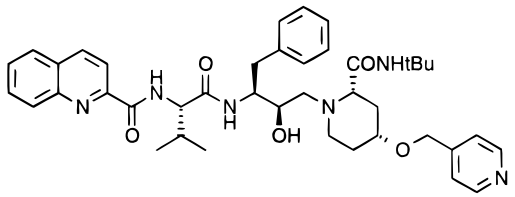

Figure 2.

Several drug candidates belonging to the HEA class of inhibitors are undergoing preclinical or clinical evaluation.[3b,d,g] We have recently introduced a new class of highly potent HIV protease inhibitors.[4] As represented by palinavir (**1**, Figure 2), these compounds contain a (*R*)-hydroxyethylamine transition state mimic and a novel 4-substituted pipecolic amide entity. Critical issues in the development of peptidomimetic anti-HIV drugs have been the complexity of structures and their limited oral bioavailability.[5] Not suprisingly, the search for simpler, nonpeptidic substances is actively being pursued.[6] To date, however, it is not uncommon to find three to five and occasionally more asymmetric centers in these molecules, each of them critical for optimal potency.[7] For this reason, extensive efforts are being invested in the search for chemical processes which allow stereocon-

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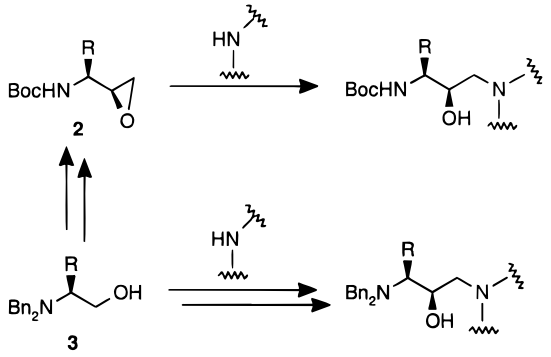
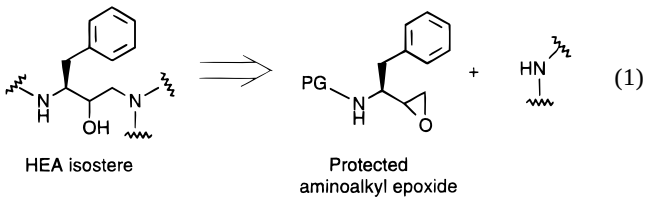
Scheme 1



trolled synthesis of these inhibitors on a large scale, in the most cost efficient fashion.

Convergent approaches to hydroxyethylamine dipeptide isosteres usually involve condensation of a protected aminoalkyl epoxide (or equivalent) with an amine nucleophile (eq 1). Recently, we reported the large scale

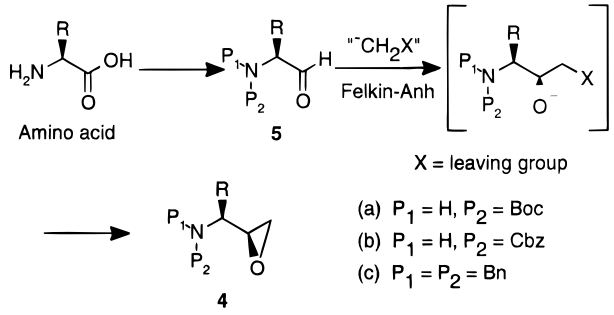


(1)

preparation of (2*S*,3*S*)-*N*-Boc-3-amino-1,2-epoxy-4-phenylbutane (**2**), a key building block for HEA-based HIV protease inhibitors, from *N*,*N*-dibenzylphenylalaninol (**3**) (Scheme 1, R = Bn).[8] The method, amenable to the preparation of kilogram quantities of this versatile building block, avoids the use of dangerous or expensive reagents, unstable intermediates, and chromatographic purifications.[9,10]

We now present this work in more detail, and its application to the preparation of **2** derived from several other amino acids. In addition, a short and novel approach to *N*,*N*-dibenzyl-protected hydroxyethylamine dipeptide isosteres from intermediates in the synthesis of **2** is also described (Scheme 1).

Scheme 2



Results and Discussion

Conceptually, the simplest approach to aminoalkyl epoxides **4**, as shown in Scheme 2, uses readily available chiral amino acids as starting materials. After conversion to a suitably protected α-amino aldehyde **5**, diastereoselective addition of methylenating reagents under nonchelating (Felkin−Anh)[11] conditions should provide epoxide **4** with the desired (2*S*,3*S*)-stereochemistry. Crucial to the success of such an approach are the direction and extent of diastereofacial selectivity that can be achieved in nucleophilic additions to **5** and its configurational stability. Both factors are highly dependent on the nature of the nitrogen protecting groups. Monoprotected aldehydes **5a** and **5b** are not useful for our purpose since they are sensitive to racemization[12a] and exhibit poor facial diastereoselectivity.[12b] *N*,*N*-Diprotected α-amino aldehydes such as **5c** on the other hand are less prone to racemization and undergo nucleophilic attack on the carbonyl according to the nonchelating model of Felkin−Anh, thus producing amino alcohols with the desired orientation of the hydroxyl group.[13]

The preparation of *N*,*N*-dibenzylamino aldehydes is depicted in Table 1. *N*,*N*-dibenzylamino alcohols **3** are easily prepared from the corresponding amino acids following the procedure reported by Reetz (method A).[13] On a large scale, however, it was found more practical to reduce amino acids to amino alcohols first[14] and then carry out the *N*,*N*-dibenzylation to **3**. This alternative sequence for the preparation of **3** (method B, Table 1) minimizes the use of benzylating agent and avoids pyrophoric reagents ($LiAlH_4$). Oxidation to amino aldehydes **6** was performed more conveniently using pyridine−sulfur trioxide complex[15] at ∼15 °C, rather than a low temperature Swern oxidation.

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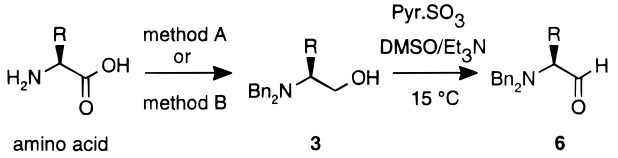
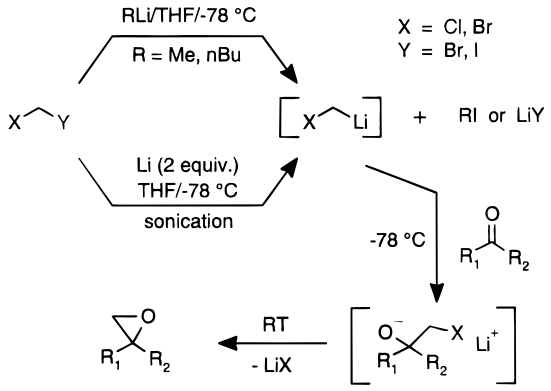
Table 1.



entry	amino acid	R	method[a]	**3** % yield[b]	**6** % yield[c]
a	Phe	Bn	*d*		99
b	Ala	Me	A	72	96
c	Val	iPr	B	65	98
d	Leu	iBu	B	89	100
e	Tyr	4-(BnO)-Bn	A[e]	74	83

[a] Method A: 3 $BnBr/K_2CO_3/EtOH$, then $LiAlH_4$. Method B: $NaBH_4/H_2SO_4$, then 2 $BnBr/K_2CO_3/EtOH$. [b] Overall yield from amino acid. [c] Yield of crude product. [d] Commercially available from the Nutrasweet Co. [e] Phenolic hydroxyl group was also benzylated.

Scheme 3

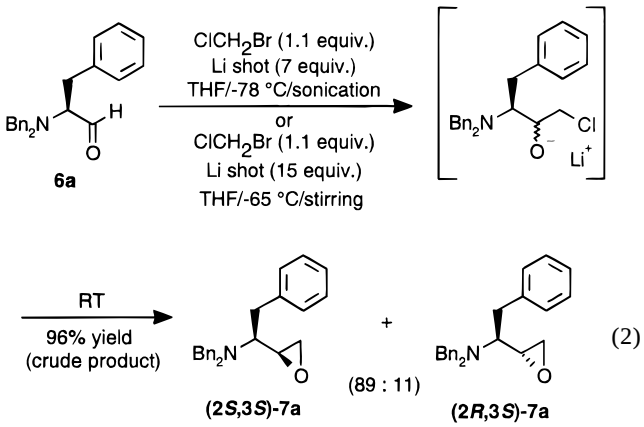


The addition of sulfur ylides to **6a** under nonchelating conditions has been reported to give epoxide **7a** in 75% yield as an 86:14 mixture of (2*S*,3*S*)- and (2*R*,3*S*)-isomers, respectively.[16] On scale up of this procedure, however, it was found that **6a** suffered substantial racemization due to the strongly basic conditions required for ylide formation,[17] and this chemistry was not pursued further.

The conversion of aldehydes and ketones into one-carbon homologated epoxides has been accomplished with *in situ*-generated (halomethyl)lithium reagents (Scheme 3).[18] (Halomethyl)lithiums are unstable at temperatures above −110 °C.[18b] When generated *in situ*, however, in the presence of electrophiles such as aldehydes or ketones, synthetically useful transformations can be achieved. Until recently, the use of these reagents in combination with sensitive racemization-prone, chiral α-amino aldehydes had not been investigated.[19]

(Halomethyl)lithiums are generally prepared by metal−halogen exchange between a *gem*-dihalide and an alkyllithium (*n*-BuLi or MeLi) at −78 °C (Scheme 3). This exchange reaction is faster than addition of RLi to carbonyl compounds[18c,19] and allows *in situ* generation of the reagent and subsequent capture. This procedure has certain drawbacks when applied to large scale preparations such as hazards associated with manipulating large quantities of pyrophoric alkyllithiums and the generation of stoichiometric amounts of a toxic alkyl iodide (iodomethane or iodobutane), which must be separated from the desired product.

The generation of (halomethyl)lithium by direct lithiation of *gem*-dihalides with lithium metal has received much less attention, despite the fact that lithium metal is much less hazardous and less expensive than RLi reagents. Furthermore, the only side product of such a reaction is an innocuous lithium halide (Scheme 3). Luche recently reported the sonication of a mixture of bromochloromethane, a carbonyl compound, and lithium metal in THF at low temperature, giving the corresponding chlorohydrin alkoxide which could be cyclized at room temperature to give an epoxide (Scheme 3, X = Cl).[18d] When aldehyde **6a** was subjected to similar treatment, crude epoxide **7a** was isolated in good yield as an 89:11 mixture of diastereomers in favor of the desired (2*S*,3*S*)-isomer (eq 2).[20] In an attempt to improve on the



diastereofacial selectivity of this reaction, we investigated the addition of bulkier, *in situ*-generated (bromomethyl)-lithium to aldehyde **6a** (eq 2, CH_2Br_2 instead of $BrCH_2Cl$). As Luche found previously,[18d] yields of **7a** went down significantly and the effect on diastereoselectivity was minimal.

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(17) (a) Enantiomeric and diastereomeric purities of epoxide **7a** were determined by normal phase HPLC analysis on chiral columns (Chiralcel OD and OD-H) as described in the Experimental Section. Authentic samples of (2*R*,3*R*)-**7a** and (2*S*,3*R*)-**7a** were prepared from D-phenylalanine. All four **7a** isomers were separable. Diastereomeric ratios were also measured by integration of well resolved ^1H NMR signals of the two isomers as assigned by Reetz.[16] (b) Racemization of **6a** upon reaction with sulfur ylides as reported by Reetz was observed by others.[19d]

(18) (a) Cainelli, G.; Tangari, N.; Ronchi, A. U. *Tetrahedron* **1972**, *28*, 3009. (b) Tarhouni, R.; Kirschleger, B.; Rambaud, M.; Villieras, J. *Tetrahedron Lett.* **1984**, *25*, 835. (c) Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795. (d) Einhorn, C.; Allavena, C.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1988**, 333.

(19) While our work was in progress, the addition of (chloromethyl)-lithium (generated *in situ* from alkyllithium and chloroiodomethane) to chiral *N*,*N*-dibenzyl-α-amino aldehydes was reported: (a) Barluenga, J.; Baragaña, B.; Alonso, A.; Concellón, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 969. (b) Barluenga, J.; Baragaña, B.; Concellón, J. M. *J. Org. Chem.* **1995**, *60*, 6696. (c) Ng, J. S.; Przybyla, C. A.; Mueller, R. A.; Vazquez, M. L.; Getman, D. P. *World Patent Appl.* no. WO 93/23388. publ. November 25, 1993. (d) Ng, J. S.; Przybyla, C. A.; Liu, C.; Yen, J. C.; Muellner, F. W.; Weyker, C. L. *Tetrahedron* **1995**, *51*, 6397. In both cases, diastereomerically pure epoxides were obtained only after careful chromatography. In addition, the use of highly pyrophoric alkyllithiums in the metal-halogen exchange reaction, high cost of chloroiodomethane, and the fact that iodoalkanes are generated as byproduct made these procedures less attractive on a large scale.

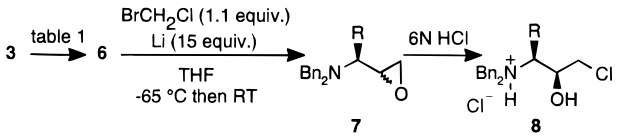
(20) (a) A high-intensity 600W ultrasonic processor equipped with a 1-in. low intensity horn (available from Ace glass or Aldrich Co.) and operating at 20−30% maximum power was used. (b) The intermediate chlorohydrin alkoxides could also be quenched at low temperature. The free base of **8a** was isolated as a mixture of diastereomers. These chlorohydrins could be purified in low yield by flash chromatography, but were found to be unstable in the free-base state.

It is unclear what role sonication plays in this Barbier-type reaction. Sound-induced cavitation is known to increase surface areas through pitting and to remove oxide layers from metal surfaces. It is also believed that tremendous localized pressures and temperatures are achieved and may assist in surmounting activation energy barriers in chemical reactions.[21] We were successful in carrying out this sonochemistry on scales up to 800 g of aldehyde **6a** in a specially designed 10 L reactor equipped with two ultrasonic probes (see supporting information for diagram of apparatus). This work illustrates that ultrasound-mediated reactions can be used for the large scale synthesis of organic compounds. In our opinion, however, further scaling up of such a process did not appear practical. Attempting to simulate the effect of sonication, the reaction was repeated under ordinary mechanical stirring conditions using a larger excess of lithium shot (15 equiv were used to provide greater reaction surface), that was bruised in a mortar prior to use to expose fresh metal surfaces. Under these conditions, we were able to reproduce the yields, purities and diastereomeric ratios obtained in sonication experiments (eq 2).[22] Again, epoxide **7a** was formed free of products derived from racemization of starting aldehyde **6a**.[17] Excess Li metal was repeatedly recovered and recycled. Yields for this reaction were found to be highly dependent on careful temperature control (if the reaction temperature was allowed to rise above ca. −55 °C, yields decreased significantly). This was especially crucial for large scale experiments, when the exothermicity of the reaction had to be controlled by portion wise addition of reagents.[8]

As previously observed by Reetz,[16] diastereomeric epoxides (2*S*,3*S*)-**7a** and (2*R*,3*S*)-**7a** could only be separated in low yield by careful, repetitive chromatography (the epoxides decomposed significantly upon silica gel flash chromatography). This represented a serious obstacle to the scale up potential of this reaction and an alternative separation/purification procedure had to be designed.[20b] When a solution of crude **7a** (89:11 mixture of isomers) in THF was added to an equal volume of 6 N aqueous HCl, a precipitate formed after standing in the cold. Recrystallization from MeOH gave >99% isomerically homogeneous (2*S*,3*S*)-*N*,*N*-dibenzyl-3-amino chlorohydrin hydrochloride **8a** in 38−45% yield from alcohol **3a** (Table 2).[23]

Similar results were obtained with aldehydes derived from other amino acids. Diastereomeric epoxides **7a-e** were formed with the (2*S*,3*S*)-isomer in excess of 86% as determined by integration of well-resolved ^{1}H NMR signals for the major and minor isomers. Crystalline (2*S*,3*S*)-*N*,*N*-dibenzyl-3-amino chlorohydrin hydrochlorides **8a-e** were isolated in 32−56% overall yield from *N*,*N*-dibenzylamino alcohols **3a-e** (Table 2). Enantiomeric purities were >97% as evaluated by HPLC analysis on chiral supports. For entries a, b, and d, the (2*R*,3*R*)-*N*,*N*-dibenzyl-3-amino chlorohydrin hydrochlorides derived from the corresponding D-amino acids were prepared as analytical standards. In the case of valine-derived **8c**, the relative (2*S*,3*S*)-stereochemistry was unambiguously verified by an X-ray crystal structure (supporting information).

Table 2.



			8	
entry	R	ratio of **7** (2*S*,3*S*):(2*R*,3*S*)[a]	% yield from **3**[b]	% isomeric purity[c]
a	Bn	89:11	38−45	>97
b	Me	96:4	51	>98
c	iPr	92:8	56	>99.5
d	iBu	86:14	56	>98
e	4-(BnO)-Bn	89:11	32	>97

[a] Diastereomeric ratios were determined by integration of well-defined ^{1}H NMR signals. [b] Yields obtained after recrystallization. [c] Determined by normal phase HPLC analysis on Chiralcel OD or OD-H columns, after conversion to free base with aqueous $NaHCO_3$, followed by extraction with hexane.

The reaction of L-phenylalanine-derived aldehyde **6a** to give **8a** was carried out on a 2.2 kg scale to illustrate the scale up potential of this methodology.[8] In this case, the reaction mixture was separated from unreacted lithium metal (recovered for recycling), and the cold chlorohydrin alkoxide solution was added directly into 6 N HCl, bypassing ring closure to epoxide **7a**. Under those conditions, **8a** was obtained in 38% yield overall (after recrystallization) from amino alcohol **3a**.

N,*N*-Dibenzyl-3-amino chlorohydrin hydrochlorides **8a-e** are versatile synthetic intermediates (Scheme 4). Hydrogenolysis under standard conditions (1 atm H_2, MeOH, 20% $Pd(OH)_2$/C) gave amino chlorohydrin hydrochlorides **9a-e** in excellent yields (Table 3). The use of the salt form is crucial to the success of this deprotection procedure. It accelerates hydrogenolysis of the benzylic C−N bonds and prevents decomposition of **8** and **9** (the free base of **9** is unstable and decomposes rapidly).

Treatment of **9a-e** with di-*tert*-butyl dicarbonate and triethylamine in THF,[24] followed by *in situ* epoxide ring closure with methanolic or ethanolic potassium hydroxide, gave crystalline *N*-Boc-aminoalkyl epoxides **2a-e** in a two step/one pot operation. Epoxides **2a-e** were obtained in good yield and high isomeric purity (Table 3).[25] Phenylalanine-derived epoxide (**2a**) was prepared in kilogram quantities and found identical in all respects to material prepared by literature procedures.[10g,12b] HPLC

(21) (a) Mason, T. J. *Practical Sonochemistry. User's Guide to Applications in Chemistry and Chemical Engineering*; Ellis Horwood Ltd.: Chichester, 1991. (b) Suslick, K. S. *Science*, **1990**, *247*, 1439 and references cited therein.

(22) In contrast to Luche[18d] who found that yields decreased substantially (by as much as 40%) under stirring conditions (i.e. no sonication), we obtained similar results for both methods, provided the Li metal was crushed prior to using. Reactions performed with sonication proceeded at faster rates then under stirring conditions, but the end result was comparable.

(23) (a) The isomeric purity of (2*S*,3*S*)-**8a** was assessed by HPLC analysis on a chiral column (Chiralcel OD-H) after neutralization to the free base using aqueous $NaHCO_3$, followed by hexane extraction (see experimental section). Under those conditions, **8a** free base was obtained almost free of contamination from the corresponding ring-closed epoxide **7a** (<2%). The (2*R*,3*R*)-isomer of **8a** was prepared from D-phenylalaninol using an analogous sequence. The (2*R*,3*S*)- and (2*S*,3*R*)-**8a** diastereomers were obtained from the corresponding (2*R*,3*S*)- and (2*S*,3*R*)-**7a** epoxides[16] by treatment with 6 N HCl. HPLC analysis gave clean separation of all four isomers and allowed detection limits <0.5%. (b) Warming of the initial reaction mixture to room temperature to allow formation of epoxide **7** is not required. Chlorohydrin hydrochlorides **8** can be isolated by direct quenching of the cold chlorohydrin alkoxides with 6 N hydrochloric acid. On a small scale however (ca. 10 g), isolation of the epoxide followed by conversion back to **8** allows removal of inorganic salts and facilitates crystallization/purification of the product.[20b]

(24) The free base of **9a-e** must be generated in the presence of the acylating agent to prevent decomposition.

Scheme 4

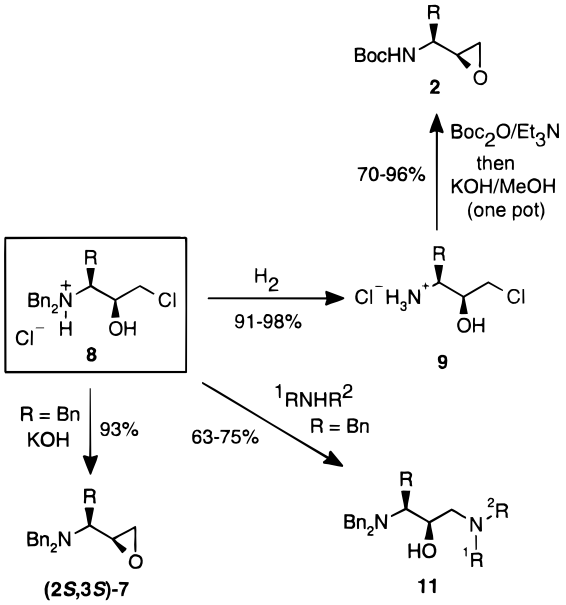
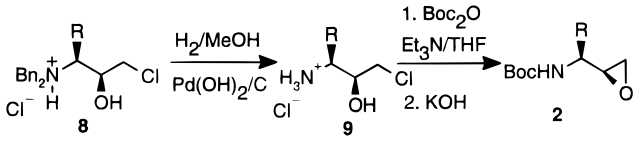


Table 3.

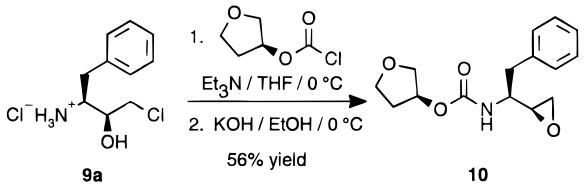


entry	R	**9** % yield	**2** % yield	**2** % purity[a]
a	Bn	97	78−96	>99.5
b	Me	93	80	>99
c	iPr	98	70	>99.5
d	iBu	91	81	>99
e	4-(BnO)-Bn	98[b]	93[b]	>99.5

[a] Isomeric purities were determined by normal phase HPLC analysis on a chiral column (Chiralcel OD), and by NMR. [b] The free hydroxyl derivative was isolated.

analysis on a chiral column and comparison to authentic samples of all four possible isomers of **2a**[25] indicated isomeric purities >99.5% (ee and de). The overall yield (four steps) of **2a** starting from commercially available *N*,*N*-dibenyl-L-phenylalaninol **3a**[26] was 28−35%.

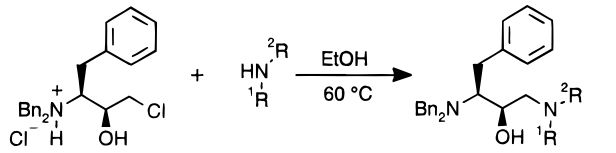
Treatment of **8a** with ethanolic potassium hydroxide gave crystalline epoxide (2*S*,3*S*)-**7a** in 93% yield (Scheme 4), identical in all respect to material reported in the literature.[16,19b] This epoxide was obtained in >99% isomeric purity (HPLC on chiral column), as shown by comparison to authentic samples of all four possible isomers,[17] without chromatographic purifications required at any stages. Reaction of **8a** with the chloroformate derived from (*S*)-3-hydroxytetrahydrofuran followed by *in situ* ring closure with ethanolic potassium hydroxide gave epoxide **10** (eq 3) as a white crystalline solid in 56% yield. This epoxide is a potentially useful intermediate in the synthesis of several HIV protease inhibitors.[3f,g]



(3)

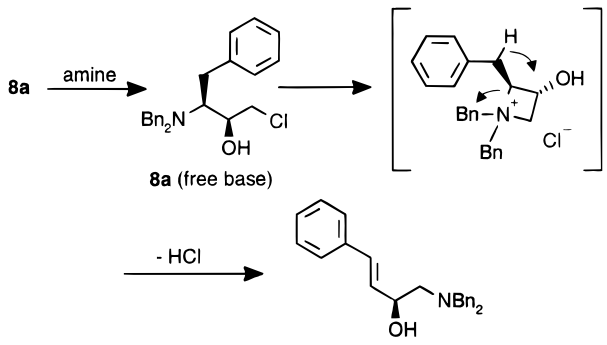
In principle, direct formation of hydroxyethylamine dipeptide isosteres (**11**, Scheme 4, Table 4) from amino chlorohydrin hydrochloride **8** should be possible without intermediate preparation of epoxide **2** or **7**. Heating ethanolic solutions of **8a** in the presence of amines gave **11f-h** in good yields as shown by selected examples in Table 4. As can be seen, **8a** reacted equally well with a primary amine, secondary amine, and aniline.[27] Protected HEA dipeptide isosteres such as **11** are potentially useful intermediates in the preparation of HIV protease inhibitors.[3c,g,h]

Table 4.



entry	^{1}R	^{2}R	% yield
f	H	iBu	65
g	H	Ph	63
h		-$(CH_2)_5$-	75

Scheme 5



In these reactions, small amounts of a side product, identified as **12** (Scheme 5) based on spectral and atomic composition data, were also isolated. This side reaction can be rationalized in terms of an internal cyclization of **8a**-free base leading to an azetidinium ion, followed by β-elimination, to give observed styrene derivative **12**. Similar internal cyclizations/β-eliminations of *N*,*N*-dibenzylamino derivatives via three-membered ring aziridinium ions have been documented.[28]

Conclusions

N-Boc-(2*S*,3*S*)-aminoalkyl epoxides can be prepared from several amino alcohols. Most notably, (2*S*,3*S*)-*N*-

(25) Enantiomeric and diastereomeric purities were determined by normal phase HPLC analysis on a chiral column (Chiralcel OD) and by ^{1}H/^{13}C NMR. In the case of **2a**, the product was compared to authentic samples of all four possible isomers derived from L- and D-phenylalanine.[9] The material had an isomeric homogeneity in excess of 99.5%. Aminoalkyl epoxides derived from alanine,[10f] valine,[10h] and leucine[10j] are known.

(26) *N*,*N*-Dibenzyl-L-phenylalaninol (**3a**) is commercially available from the Nutrasweet Co.

(27) A potentially useful application of this chemistry is the solid phase synthesis of hydroxyethylamine dipeptide isostere libraries for the rapid screening of HIV protease inhibitors (Kick, E. K.; Ellman, J. A. *J. Med. Chem.* **1995**, *38*, 1427). The functionality present in **8** should, in principle, allow attachment of the hydroxyl group to a solid support. As was demonstrated in solution phase, displacement of chlorine with nitrogen nucleophiles should generate HEA dipeptide isosteres, which could be further elaborated after hydrogenolysis of the *N*,*N*-dibenzyl protecting group.

(28) (a) Gmeiner, P.; Junge, D.; Kärtner, A. *J. Org. Chem.* **1994**, *59*, 6766. (b) Poch, M.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1991**, *32*, 6935.

Boc-3-amino-1,2-epoxy-4-phenylbutane, a key intermediate in the preparation of HIV protease inhibitors, was prepared in 28−35% yield overall from commercially available *N*,*N*-dibenzyphenylalaninol. These versatile building blocks are obtained in very high isomeric purity by a five-operation sequence, which does not involve hazardous reagents, requires no chromatographic purifications, and is amenable to the preparation of large quantities of material. The crystalline *N*,*N*-dibenzylamino chlorohydrin hydrochloride derived from L-phenylalanine, produced as an intermediate in this sequence, reacted with amines to give hydroxyethylamine dipeptide isosteres in good yield.

Experimental Section

General Experimental: Reversed-phase analyses were performed on C18 columns using 0−100% acetonitrile (containing 0.06% TFA)/0.06% aqueous TFA in 30 min gradients. Chiralcel OD-H and OD columns were obtained from Daicel Corp. Flash chromatography[29] was performed on Merck silica gel 60 (0.040−0.063 mm). Analytical thin-layer chromatography (TLC) was carried out on precoated (0.25 mm) Merck silica gel F-254 plates. Visualization was achieved by UV irradiation (254 nm) and staining with iodine or phosphomolybdic acid/cerium sulfate/sulfuric acid or 0.3% ninhydrin in 3% acetic acid/1-butanol.

All reactions requiring anhydrous conditions were conducted under a positive argon atmosphere in oven-dried glassware using standard syringe techniques. All chemicals and solvents were anhydrous, reagent grade and used as received without purification. Lithium shot was obtained from Aldrich or FMC Corporation. *N*,*N*-Dibenzyl-L-phenylalaninol (**3a**) was purchased from NSC Technologies (a division of the NutraSweet Co.).

***N*,*N*-Dibenzyl-(*S*)-2-amino-1-propanol (3b). Method A.** L-Alanine (50.0 g, 0.561 mol) and anhydrous potassium carbonate (270.0 g, 1.95 mol, 3.48 equiv) were suspended in ethanol (1 L). The mixture was stirred mechanically, and benzyl bromide (316.0 g, 220 mL, 1.85 mol, 3.29 equiv) was added dropwise over 30 min. After stirring for 5 days at room temperature, solids were separated by filtration (EtOAc was used for washings) and volatiles removed under reduced pressure. The residue was dissolved in EtOAc and the solution washed with water, aqueous $NaHCO_3$, and brine. After drying over anhydrous sodium sulfate and removal of solvent under reduced pressure, a clear oil was obtained which was dried for 4 h at 90 °C under high vacuum. Crude *N*,*N*-dibenzyl-L-alanine benzyl ester (158.3 g) was used without further purification: R_f 0.47 (9:1 hexane/EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.4−7.14 (m, 15H), 5.21 (d, J = 12.1 Hz, 1H, AB system), 5.13 (d, J = 12.4 Hz, 1H, AB system), 3.82 (d, J = 14.0 Hz, 2H, AB system), 3.62 (d, J = 14.0 Hz, 2H, AB system), 3.55 (q, J = 7.0 Hz, 1H), 1.33 (d, J = 7.0 Hz, 3H).

The crude benzyl ester from above (157.1 g, 0.45 mol) in dry THF (130 mL) was added dropwise (exothermic!) to a suspension of $LiAlH_4$ (17.1 g, 0.45 mol) in dry THF (450 mL). The mixture was refluxed overnight and cooled to room temperature, and excess hydride was quenched by dropwise addition of acetone (50 mL). After stirring for several hours, 3 N NaOH (180 mL) was slowly added, the organic supernatant was decanted, and the white solids were rinsed with EtOAc. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Distillation under high vacuum gave pure **3b** as a clear oil which solidified on standing (103.3 g, 72% from L-alanine): bp 160−174 °C (0.2 torr). R_f 0.17 (9:1 hexane/EtOAc). $[\alpha]^{25}_D$ + 89° (*c* 1, $CHCl_3$). IR (KBr) ν 3600−3100, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.4−7.2 (m, 10H), 3.82 (d, J = 13.4 Hz, 2H, AB system), 3.46 (t, J = 10.5 Hz, 1H), 3.36 (d, J = 13.4 Hz, 2H, AB system), 3.35 (m, 1H), 3.10 (broad s, 1H), 2.99 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.2, 128.8, 128.3, 127.0, 62.6, 54.1, 52.8, 8.6. MS (CI-isooctane) *m*/*z* 256 (MH^+). Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.26; N, 5.49. Found: C, 80.21; H, 8.41; N, 5.45.

***N*,*N*-Dibenzyl-(*S*)-2-amino-3-[4-(benzyloxy)phenyl]-1-propanol (3e).** Following the procedure for **3b** (method A), L-tyrosine (181.2 g, 1.0 mol) was treated with anhydrous potassium carbonate (610.0 g, 4.41 mol, 4.4 equiv) and benzyl bromide (720.0 g, 4.21 mol, 4.2 equiv) in ethanol (2 L) at room temperature for 3 days. After workup, the crude perbenzylated tyrosine derivative was obtained in quantitative yield as a yellow oil. An analytical sample was obtained after purification by flash chromatography using hexane as eluant: R_f 0.31 (9:1 hexane/EtOAc). $[\alpha]^{25}_D$ −57.0° (*c* 1.5, $CHCl_3$). IR (neat) ν 1950, 1875, 1810,1730, 1610, 1510, 1450 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.5−7.1 (m, 20H), 6.91 (m, 2H), 6.82 (m, 2H), 5.21 (d, J = 12.4 Hz, 1H, AB system), 5.11 (d, J = 12.1 Hz, 1H, AB system), 5.05 (s, 2H), 3.91 (d, J = 14.0 Hz, 2H, AB system), 3.66 (t, J = 7.6 Hz, 1H), 3.52 (d, J = 14.0 Hz, 2H, AB system), 3.07 (dd, J = 14.0, 7.6 Hz, 1H, ABX system), 2.94 (dd, J = 14.0, 7.9 Hz, 1H, ABX system). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1, 157.3, 139.2, 137.2, 135.9, 130.3, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.4, 126.8, 114.6, 70.0, 65.9, 62.5, 54.4, 34.8. MS (FAB) *m*/*z* 542 (MH^+). Anal. Calcd for $C_{37}H_{35}NO_3$: C, 82.04; H, 6.51; N, 2.59. Found: C, 82.30, H, 6.59; N, 2.60.

The crude benzyl ester from above was reduced with $LiAlH_4$ (37.95 g, 1 mol) in dry THF (1.3 L) as described for **3b**. After workup, the crude alcohol was purified by crystallization from EtOAc. Pure **3e** was obtained in two crops as a white crystalline solid (279.4 g + 45.86 g = 325.25 g, 74% yield from L-tyrosine): mp 114−116 °C. R_f 0.5 (7:3 hexane/EtOAc). $[\alpha]^{25}_D$ +56.2° (*c* 1, $CHCl_3$). IR ($CHCl_3$) ν 3450, 1955, 1885, 1810, 1610, 1510, 1455 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45−7.20 (m, 15H), 7.00 (m, 2H), 6.88 (m, 2H), 5.05 (s, 2H), 3.92 (d, J = 13.0 Hz, 2H, AB system), 3.49 (t, J = 10.5 Hz, 1H), 3.48 (d, J = 13.3 Hz, 2H, AB system), 3.34 (m, 1H), 3.30−2−95 (m, 3H), 2.39 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.3, 139.1, 137.1, 131.4, 129.9, 129.0, 128.6, 128.5, 127.9, 127.4, 127.2, 115.0, 70.0, 60.9, 60.4, 53.2, 30.8. MS (FAB) *m*/*z* 438 (MH^+). Anal. Calcd for $C_{30}H_{31}NO_2$: C, 82.35; H, 7.14; N, 3.20. Found: C, 82.73; H, 7.19; N, 3.13.

***N*,*N*-Dibenzylamino Alcohols (3). Method B.** This method was used for amino alcohols that were not water-soluble (derived from phenylalanine, valine, or leucine). The following description is representative: the amino acid was reduced to the corresponding amino alcohol using $NaBH_4$−H_2SO_4 according to the literature procedure.[14] *N*,*N*-Dibenzylation was carried out as in method A using 2.4−2.5 equiv of anhydrous potassium carbonate and 2.2 equiv of benzyl bromide in ethanol at room temperature for 3 days. The *N*,*N*-dibenzylamino alcohols were isolated in the usual way and purified by vacuum distillation (**3c**, **3d**) or crystallization (**3a**).

***N*,*N*-Dibenzyl-(*S*)-2-amino-3-phenyl-1-propanol (3a).** This material was obtained from commercial sources[26] but could be prepared from L-phenylalaninol according to method B.

***N*,*N*-Dibenzyl-(*S*)-2-amino-3-methyl-1-butanol (3c).** Obtained in 65.5% yield from L-valinol: bp 170−173 °C (0.24 torr). R_f 0.33 (8:2 hexane/EtOAc). $[\alpha]^{25}_D$ +23.5° (*c* 1, $CHCl_3$). IR (neat) ν 3450, 1950, 1880, 1810, 1750, 1603, 1490, 1450 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.5−7.1 (m, 10H), 3.85 (d, J = 13.2 Hz, 2H, AB system), 3.65 (d, J = 13.2 Hz, 2H, AB system), 3.54 (m, 1H), 3.42 (t, J = 10.0 Hz, 1H), 3.06 (broad d, J = 7.8 Hz, 1H), 2.49 (ddd, J = 9.3, 8.0, 4.7 Hz, 1H), 2.02 (m, 1H), 1.11 (d, J = 6.7 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.7, 129.1, 128.3, 127.0, 64.6, 59.1, 54.2, 27.5, 22.5, 20.0. MS (CI-isooctane) *m*/*z* 284 (MH^+). Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.26; H, 9.07; N, 4.93.

***N*,*N*-Dibenzyl-(*S*)-2-amino-4-methyl-1-pentanol (3d).** Obtained in 89% yield from L-leucinol: bp 162 °C (0.35 torr). R_f 0.19 (9:1 hexane/EtOAc). $[\alpha]^{25}_D$ +85.1° (*c* 1, $CHCl_3$). IR (neat) ν 3450, 1955, 1880, 1810, 1605, 1495, 1452 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.19 (m, 10H), 3.79 (d, J = 13.4 Hz, 2H, AB system), 3.47 (broad m, 1H), 3.40 (t, J = 10.2 Hz, 1H), 3.36 (d, J = 13.4 Hz, 2H, AB system), 3.19 (broad d, J = 6.7

(29) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Hz, 1H), 2.83 (m, 1H), 1.50 (m, 2H), 1.13 (m, 1H), 0.91 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.3, 128.8, 128.2, 126.9, 60.9, 56.6, 52.9, 34.0, 25.1, 23.7, 21.9. MS (CI-isooctane) m/z 298 (MH^+). Anal. Calcd for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71. Found: C, 80.61; H, 9.22; N, 4.64.

Preparation of *N,N*-Dibenzylamino Aldehydes (6a-e). General Procedure. The following procedure is representative. *N,N*-Dibenzyl-(*S*)-2-amino-3-phenyl-1-propanol **(3a)**[26] (500 g, 1.51 mol) and triethylamine (390 mL, 2.8 mol, 1.9 equivalent) were dissolved in reagent grade DMSO (1.5 L), and the solution was immersed in an ice bath. Pyridine−sulfur trioxide complex (400 g, 2.51 mol, 1.7 equiv) in DMSO (1.5 L) was added in small portions over 30 min (the complex can also be added as the solid). After stirring 2 h at 10−15 °C, the reaction was quenched with ice−water (3 L) and extracted with hexanes (3 × 1 L). The extracts were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The orange oil was dried further under high vacuum for 24 h. The crude aldehyde (493 g, 99% yield) was used without further purification. When stored at −10 °C under a nitrogen atmosphere, *N,N*-dibenzylamino aldehydes **6** were found to be configurationally and chemically stable for several weeks.

***N,N*-Dibenzyl-(*S*)-2-amino-3-phenylpropanal (6a):** R_f 0.55 (8:2 hexane/EtOAc). $[\alpha]^{25}_D$ −99.4° (*c* 1, $CHCl_3$), lit.[19c] $[\alpha]^{25}_D$ −92.9° (*c* 1.87, CH_2Cl_2). IR (neat) ν 1960, 1885, 1820, 1735, 1610, 1500, 1460 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.71 (s, 1H), 7.3−7.1 (m, 15H), 3.82 (d, J = 13.7 Hz, 2H, AB system), 3.68(d, J = 13.7 Hz, 2H, AB system), 3.57 (dd, J = 7.1, 6.4 Hz, 1H), 3.14 (dd, J = 14.1, 7.3 Hz, 1H, ABX system), 2.93 (dd, J = 14.0, 6.4 Hz, 1H, ABX system).[19c] ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.2, 139.3, 139.0, 129.6, 128.9, 128.5, 127.5, 126.4, 68.6, 55.0, 30.3.

***N,N*-Dibenzyl-(*S*)-2-aminopropanal (6b).** Obtained from **3b** as a yellow-orange oil (96% yield, crude): R_f 0.54 (8:2 hexane/EtOAc). $[\alpha]^{25}_D$ −44° (*c* 1.25, $CHCl_3$). IR (neat) ν 1950, 1880, 1810, 1730, 1605, 1495, 1453 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.72 (s, 1H), 7.43−7.21 (m, 10H), 3.73 (d, J = 13.7 Hz, 2H, AB system), 3.56 (d, J = 13.7 Hz, 2H, AB system), 3.32 (q, J = 7.0 Hz, 1H), 1.18 (d, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.3, 139.0, 128.7, 128.4, 127.3, 62.8, 54.9, 6.8.

***N,N*-Dibenzyl-(*S*)-2-amino-3-methylbutanal (6c).** Obtained from **3c** as an orange oil (98% yield, crude): R_f 0.56 (8:2 hexane/EtOAc). $[\alpha]^{25}_D$ −62.2° (*c* 1, $CHCl_3$). IR (neat) ν 1955, 1880, 1815, 1720, 1610, 1500, 1460 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.88 (d, J = 3.2 Hz, 1H), 7.45−7.2 (m, 10H), 4.05 (d, J = 13.7 Hz, 2H, AB system), 3.75 (d, J = 14.0 Hz, 2H, AB system), 2.77 (dd, J = 10.1, 3.2 Hz, 1H), 2.31 (m, 1H), 1.11 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.1, 139.2, 128.8, 128.4, 127.1, 71.6, 54.6, 26.1, 20.2, 19.8.

***N,N*-Dibenzyl-(*S*)-2-amino-4-methylpentanal (6d).** Obtained from **3d** as an orange oil (100% yield, crude): R_f 0.49 (9:1 hexane/EtOAc). $[\alpha]^{25}_D$ −70.4° (*c* 1, $CHCl_3$). IR (neat) ν 1975, 1900, 1830, 1740, 1615, 1510, 1470 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.75 (s, 1H), 7.5−7.2 (m, 10H), 3.81 (d, J = 13.7 Hz, 2H, AB system), 3.72 (d, J = 13.7 Hz, 2H, AB system), 3.25 (t, J = 6.5 Hz, 1H), 1.75 (m, J = 6.7 Hz, 1H), 1.63 (dt, J = 13.7, 7.0 Hz, 1H), 1.51 (dt, J = 13.7, 6.7 Hz, 1H), 0.86 (d, J = 6.7 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.0, 139.3, 128.9, 128.4, 127.2, 64.9, 54.7, 33.1, 25.2, 22.7, 22.5.

***N,N*-Dibenzyl-(*S*)-2-amino-3-[4-(benzyloxy)phenyl]propanal (6e).** Obtained from **3e** as a yellowish solid after trituration with hexane (83% yield, 3 crops): mp 76-80 °C dec. R_f 0.49 (8:2 hexane/EtOAc). $[\alpha]^{25}_D$ −50.8° (*c* 1, $CHCl_3$). IR ($CHCl_3$) ν 1730, 1610, 1510 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.72 (s, 1H), 7.45−7.2 (m, 15H), 7.05 (m, 2H), 6.87 (m, 2H), 5.05 (s, 2H), 3.82 (d, J = 13.7 Hz, 2H, AB system), 3.67 (d, J = 13.7 Hz, 2H, AB system), 3.51 (t, J = 6.7 Hz, 1H), 3.08 (dd, J = 14.0, 7.3 Hz, 1H, ABX system), 2.88 (dd, J = 14.1, 6.2 Hz, 1H, ABX system). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.2, 157.2, 138.9, 137.1, 131.2, 130.3, 128.7, 128.5, 128.3, 127.8, 127.3, 127.2, 114.8, 69.9, 68.4, 54.7, 29.2. MS (CI-isooctane) m/z 436 (MH^+). Anal. Calcd for $C_{30}H_{29}NO_2$: C, 82.73; H, 6.71; N, 3.22. Found: C, 82.62; H, 6.71; N, 3.51.

***N,N*-Dibenzylamino Epoxides 7a-e. General Procedure. (1*S*)-[1′(*S*)-(Dibenzylamino)-2-phenylethyl]oxirane (7a).**[16,19b,d] The following procedure is representative. Crude aldehyde **6a** (10.39 g, 31.5 mmol) and bromochloromethane (4.4 g, 34 mmol, 1.1 equiv) were dissolved in reagent grade anhydrous THF (150 mL), and the solution was cooled to −75 °C under an argon atmosphere. Lithium shot (Aldrich, 3.2 g, 461 mmol, 15 equiv) were bruised to expose fresh metal surfaces by crushing in a mortar and added to the cold **6a** solution. The suspension was mechanically stirred vigorously for 75 min, at which point TLC analysis indicated disappearance of starting material. The cooling bath was removed, the reaction immersed in a water bath at 20 °C and stirring continued for an additional 15−20 min. TLC analysis indicated complete conversion to desired epoxide **7a**. The suspension was filtered or suctioned to remove unreacted Li metal (the metal was washed with THF, dried under vacuum, and recycled) and the filtrate added to water (300 mL). Extraction with hexane (2 × 200 mL) followed by washing with water and brine and drying over anhydrous sodium sulfate gave, after solvent removal, crude epoxide **7a** (11.30 g, 103% yield based on mass recovery) as a yellow-orange oil. ^{1}H NMR analysis showed a 89:11 mixture of (2*S*,3*S*)- and (2*R*,3*S*)-diastereomers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.00 (m, 15H), 3.84 (major, d, J = 14.3 Hz, 1.78H, AB system), 3.73 (major, d, J = 14.0 Hz, 1.78H, AB system), 3.15 (major, m), 3.01 (m), 2.87−2.80 (m, 1H), 2.76 (m, 1H), 2.58 (minor, m, 0.11H), 2.50 (major, m, 0.89H), 2.19 (minor, m, 0.11H).[19c] R_f 0.27 (9:1 hexane/EtOAc).

This reaction was carried out on a 2.2 kg scale and is described in detail in reference 8. In this case, formation of epoxides **7a** was bypassed and the cold chlorohydrin alkoxide solution was quenched directly with 6 N aqueous HCl to give pure crystalline **8a**.

Determination of the Isomeric Purity of 7a by HPLC Analysis on a Chiral Column. In order to verify the extent of racemization that might occur during this reaction, *N,N*-dibenzyl-α-amino aldehyde **6a** derived from D-phenylalaninol was prepared and reacted with (chloromethyl)lithium as described above. Isocratic normal phase HPLC analysis on a Chiralcel OD-H column using 0.5% EtOH in hexane as eluant (flow rate: 0.5 mL/min) and UV detection at 215 nm indicated that all four possible isomers could be cleanly separated. Retention times for isomers of **7a**: (2*R*,3*R*), 19.0 min; (2*R*,3*S*), 22.7 min; (2*S*,3*S*), 24.3 min; (2*S*,3*R*), 27.2 min. In this manner, it was determined that the enantiomeric purity of **7a**, obtained after addition of (chloromethyl)lithium to aldehyde **6a**, was >99.5%.

(1*S*)-[1′(*S*)-(Dibenzylamino)ethyl]oxirane (7b).[19b] Obtained from **6b** (94% mass recovery) as a 96:4 mixture of (2*S*,3*S*)- and (2*R*,3*S*)-diastereomers: R_f 0.40 (9:1 hexane/EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.5−7.2 (m, 10H), 3.81 (major, d, J = 14.0 Hz, 1.9H, AB system), 3.61 (major, d, J = 14.0 Hz, 1.9H, AB system), 3.08 (major, m, 0.95H), 2.79 (major, dq, J = 6.7, 4.4 Hz, 0.95H), 2.73 (minor, t, J = 6.8 Hz, 0.05H), 2.67 (major, dd, J = 5.1, 4.1 Hz, 0.95H), 2.49 (minor, dd, J = 5.1, 2.9 Hz, 0.05H), 2.42 (major, dd, J = 5.1, 2.9 Hz, 0.95H), 1.04 (major, d, J = 6.7 Hz, 2.85H).

(1*S*)-[1′(*S*)-(Dibenzylamino)-2-methylpropyl]oxirane (7c).[19b] Obtained from **6c** (99% mass recovery) as a 92:8 mixture of (2*S*,3*S*)- and (2*R*,3*S*)-diastereomers: R_f 0.41 (9:1 hexane/EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.4−7.2 (m, 10H), 3.98 (major, d, J = 14.0 Hz, 1.84H, AB system), 3.63 (major, d, J = 14.0 Hz, 1.84H, AB system), 3.11 (minor, ddd, J = 6.0, 4.8, 1.3 Hz, 0.08H), 2.95 (major, ddd, J = 8.6, 4.1, 2.9 Hz, 0.92H), 2.85 (major, dd, J = 5.1, 3.8 Hz, 0.92H), 2.76 (minor, dd, J = 5.4, 3.8 Hz, 0.08H), 2.64 (major, dd, J = 5.1, 2.9 Hz, 0.92H), 2.37 (minor, dd, J = 5.4, 2.5 Hz, 0.08H), 2.10 (m, 1H), 1.85 (t, J = 8.9 Hz, 1H), 1.07 (major, d, J = 6.7 Hz, 2.76H), 1.00 (major, d, J = 7.0 Hz, 2.76H).

(1*S*)-[1′(*S*)-(Dibenzylamino)-3-methylbutyl]oxirane (7d).[19b] Obtained from **6d** (94% mass recovery) as a 87:13 mixture of (2*S*,3*S*)- and (2*R*,3*S*)-diastereomers: R_f 0.41 (9:1 hexane/EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.4−7.2 (m, 10H), 3.85 (minor, d, J = 13.4 Hz, 0.26H, AB system), 3.83 (major, d, J = 14.0 Hz, 1.74H, AB system), 3.76 (minor, d, J = 13.4 Hz, 0.26H, AB system), 3.65 (major, d, J = 14.0 Hz, 1.74H, AB system), 3.11 (minor, ddd, J = 7.6, 4.1, 2.9 Hz, 0.13H), 3.04 (major, ddd, J = 6.0, 4.1, 2.9 Hz, 0.87H), 2.79 (major, dd, J = 5.0, 4.0 Hz, 0.87H), 2.70 (minor, dd, J = 5.1, 4.5 Hz, 0.13H), 2.54 (major, dd, J = 4.8, 2.9 Hz, 0.87H), 2.47 (major, dt, J = 8.0, 6.0 Hz, 0.87H), 2.39 (minor, dd, J = 5.0, 2.5 Hz, 0.13H), 1.86 (m, 1H), 1.61 (major, ddd, J = 14.0, 8.3, 5.7 Hz, 0.87H), 1.23 (major, ddd, J = 14.0, 8.0, 6.0 Hz, 0.87H), 0.85 (major, d, J = 6.7 Hz, 2.6H), 0.81 (minor, d, J = 6.7 Hz, 0.4H), 0.67 (major, d, J = 6.7 Hz, 2.6H), 0.55 (minor, d, J = 6.4 Hz, 0.4H).

(1*S*)-[1′(*S*)-(Dibenzylamino)-2-(4-hydroxyphenyl)ethyl]-oxirane (7e). Obtained from **6e** (100% mass recovery) as a 89:11 mixture of (2*S*,3*S*)- and (2*R*,3*S*)-diastereomers: R_f 0.37 (9:1 hexane/EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.5−7.2 (m, 15H), 7.1−6.7 (m, 4H), 5.10 (s, 2H), 3.83 (major, d, J = 14.1 Hz, 1.78H, AB system), 3.72 (major, d, J = 13.7 Hz, 1.78H, AB system), 3.13 (major, m, 0.89H), 3.07 (minor, m, 0.11H), 2.95 (m, 1H), 2.78 (m, 2.7H), 2.69 (minor, m, 0.3H), 2.58 (minor, dd, J = 5.1, 4.3 Hz, 0.11H), 2.49 (major, dd, J = 5.1, 2.9 Hz, 0.89H), 2.20 (minor, dd, J = 5.1, 2.9 Hz, 0.11H).

***N,N*-Dibenzyl-(*S*)-3-amino-(*S*)-2-hydroxy-4-phenyl-1-chlorobutane Hydrochloride (8a).** Crude epoxide **7a** (10.30 g, 29.6 mmol) was dissolved in reagent grade THF (30 mL), and 6 N aqueous HCl (40 mL) was added. The solution was stirred 48 h at 5 °C. The tan-colored precipitate which was formed was collected by suction filtration and washed with water (filtrate and water washings were discarded). The crude product was crystallized from hot methanol (25−30 mL), collected, and washed with 10% MeOH in ether, to give **8a** as a white crystalline powder (5.37 g, 45% yield from **3a**, 4 crops): mp 172−174 °C. $[\alpha]^{23}_D$ −7.1° (*c* 1, MeOH). IR (KBr) ν 3270, 2540 cm^{-1}. ^{1}H NMR (MeOH-d_4, 400 MHz) δ 7.50 (broad s, 10H), 7.30−7.25 (m, 3H), 7.15−7.11 (m, 2H), 5.03 (broad d, J = 13.2 Hz, 1H), 4.71 (broad d, J = 13.6 Hz, 1H), 4.54−4.43 (m, 3H), 3.98 (m, 1H), 3.54 (dd, J = 13.6, 10.3 Hz, 1H), 3.38 (dd, J = 16.0, 4.1 Hz, 1H), 3.06 (dd, J = 10.7, 6.6 Hz, 1H), 2.70 (broad t, J = 9.6 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ136.2, 131.7, 131.4, 130.0, 129.9, 129.8, 129.5, 129.3, 129.0, 127.5, 68.0, 63.6, 56.3, 55.4, 45.6, 29.7. MS (FAB) *m*/*z* 380 (MH$^+$). Anal. Calcd for $C_{24}H_{27}Cl_2NO$: C, 69.23; H, 6.54; N, 3.36. Found: C, 68.90; H, 6.51; N, 3.33. (2*R*,3*R*)-**8a** was prepared following the same procedure starting from D-phenylalaninol: mp 172−174 °C. $[\alpha]^{23}_D$ +7.7° (*c* 1, MeOH). Anal. Calcd for $C_{24}H_{27}Cl_2NO$: C, 69.23; H, 6.54; N, 3.36. Found: C, 68.93; H, 6.52; N, 3.32. The material was used as a reference for isomeric purity determinations: samples of (2*S*,3*S*)-**8a** and (2*R*,3*R*)-**8a** were neutralized with aqueous $NaHCO_3$, extracted into hexane and analyzed by HPLC (Chiralcel OD-H column, 0.5% EtOH/hexane, isocratic, 1 mL/min): t_R (2*S*,3*S*)-**8a**, 32.3 min (>99%). t_R (2*R*,3*R*)-**8a**, 35.6 min (below detection limit).

On a large scale (2.2 kg), **8a** was prepared from **6a**, bypassing ring closure to epoxide **7a**. The product was obtained in 38% yield overall from amino alcohol **3a**.[8]

***N,N*-Dibenzyl-(*S*)-3-amino-(*S*)-2-hydroxy-4-phenyl-1-chlorobutane Hydrochloride (8a). Sonication Experiment.** Aldehyde **6a** (500 g, 1.515 mol) was dissolved in THF (10 L) and the solution cooled to −75 °C under an argon atmosphere. Lithium shot (4−16 mesh, 4 × 40 g, 23 mol total) and bromochloromethane (4 × 54 g, 1.67 mol total) were added alternatingly in four equal portions while stirring, sonicating (~100 W power using vessel described in supporting information section),[20a] and maintaining an internal temperature below −55 °C. Addition of reagents was done over 1 h, and sonication was continued for an additional 0.5 h. The solution was separated from floating lithium residues (the excess metal was recovered for future use) and transferred into 6 N HCl (2 L). Chlorohydrin hydrochloride **8a** was isolated and purified by recrystallization as described previously.[8] The material was obtained in comparable yield and found to be identical in all respect to that obtained under stirring conditions.[8]

***N,N*-Dibenzyl-(*S*)-3-amino-(*S*)-2-hydroxy-1-chlorobutane Hydrochloride (8b).** Crude epoxide **7b** (15.8 g, 59 mmol) was dissolved in THF (30 mL), and 6 N aqueous HCl (50 mL) was added. The mixture was stirred 3 days at 5 °C and the precipitated product collected by suction filtration. Washing with water and ether, followed by drying in vacuo over P_2O_5, gave **8b** as a white solid (11.35 g, 51% yield overall from **3b**). An analytical sample prepared by recrystallization from MeOH was used for characterization: mp 170−173 °C. $[\alpha]^{23}_D$ −21.3° (*c* 1, MeOH). IR (KBr) ν 3220, 1955, 1885, 1810, 1450 cm^{-1}. ^{1}H NMR (MeOH-d_4, 400 MHz) δ 7.55−7.4 (m, 10H), 5.02 (d, J = 13.2 Hz, 1H, AB system), 4.54 (d, J = 13.6 Hz, 1H, AB system), 4.48 (t, J = 6.8 Hz, 1H), 4.39 (d, J = 13.6 Hz, 1H, AB system), 4.30 (d, J = 13.2 Hz, 1H, AB system), 3.77 (q, J = 7.0 Hz, 1H), 3.55 (dd, J = 11.4, 6.3 Hz, 1H, ABX system), 3.45 (dd, J = 11.0, 8.1 Hz, 1H, ABX system), 1.52 (d, J = 7.0 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 131.5, 131.1, 130.3, 130.2, 129.1, 128.5, 128.4, 67.9, 57.7, 54.0, 53.6, 45.4. MS (FAB) *m*/*z* 304 (MH$^+$). Anal. Calcd for $C_{18}H_{23}Cl_2NO$: C, 63.53; H, 6.81; N, 4.12. Found: C, 63.61; H, 6.83; N, 4.19. A reference sample of (2*R*,3*R*)-**8b** was prepared in the same manner starting from D-alaninol and used for isomeric purity determinations: mp 171−174 °C. $[\alpha]^{23}_D$ +20.0° (*c* 1, MeOH). Anal. Calcd for $C_{18}H_{23}Cl_2NO$: C, 63.53; H, 6.81; N, 4.12. Found: C, 63.16; H, 6.79; N, 4.10. Samples of (2*S*,3*S*)-**8b** and (2*R*,3*R*)-**8b** were neutralized with aqueous $NaHCO_3$, extracted into hexane and analyzed by HPLC (Chiralcel OD column, 5% EtOH/hexane, isocratic, 0.5 mL/min): t_R (2*R*,3*R*)-**8b**, 13.4 min (0.5%). t_R (2*S*,3*S*)-**8b**, 16.0 min (99.1%).

***N,N*-Dibenzyl-(*S*)-3-amino-(*S*)-2-hydroxy-4-methyl-1-chloropentane Hydrochloride (8c).** Crude epoxide **7c** (14.2 g, 48 mmol) was dissolved in THF (50 mL), and 6 N aqueous HCl (50 mL) was added. The mixture was stirred 3 days at 5 °C and the precipitated product collected by suction filtration. Washing with water and ether and drying gave **8c** as a white powder (10.20 g, 56% yield overall from **3c**). An analytical sample prepared by recrystallization from MeOH−ether was used for characterization and X-ray crystal structure determination:[30] mp 164−165 °C. $[\alpha]^{23}_D$ −52.8° (*c* 1, MeOH). IR (KBr) ν 3200, 1960, 1900, 1825, 1495, 1450 cm^{-1}. ^{1}H NMR (MeOH-d_4, 400 MHz) δ 7.6−7.4 (m, 10H), 4.9−4.5 (broad m, 4H), 4.52 (m, 1H), 3.63 (dd, J = 8.4, 8.1 Hz, 1H, ABX system), 3.52 (dd, J = 11.8, 5.2 Hz, 1H, ABX system), 3.34 (m, 1H), 2.59 (m, J = 6.6 Hz, 1H), 1.25 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 6.6 Hz, 3H). ^{13}C NMR (MeOH-d_4, 100 MHz) δ 132.2 (broad), 131.5, 131.3, 130.8, 70.6, 58.5 (broad), 58.0 (broad), 47.3, 27.1, 21.9, 20.9. MS (FAB) *m*/*z* 332 (MH$^+$). Anal. Calcd for $C_{20}H_{27}Cl_2NO$: C, 65.22; H, 7.39; N, 3.80. Found: C, 65.08; H, 7.46; N, 3.84. HPLC (neutralization with $NaHCO_3$, hexane extraction, Chiralcel OD, 5% EtOH/hexane, isocratic, 0.5 mL/min): t_R 10.4 min (>99%).

***N,N*-Dibenzyl-(*S*)-3-amino-(*S*)-2-hydroxy-5-methyl-1-chlorohexane Hydrochloride (8d).** Crude epoxide **7d** (10.6 g, 34.2 mmol) was dissolved in THF (30 mL), and 6 N aqueous HCl (40 mL) was added. The mixture was stirred 3 days at 5 °C and the precipitated product collected by suction filtration. Washing with water and ether followed by drying, gave **8d** as a white powder (6.08 g). Mother liquors and washings were concentrated under vacuo to give a gum which was crystallized from MeOH−ether to give an additional 1.80 g of product. Total yield of **8d** was 7.88 g (56% yield overall from **3d**): mp 165−166 °C. $[\alpha]^{23}_D$ +1.5° (*c* 1, MeOH). $[\alpha]^{23}_{Hg365}$ +8.6° (*c* 1, MeOH). IR (KBr) ν 3200, 2540, 1495 cm^{-1}. ^{1}H NMR (MeOH-d_4, 400 MHz) δ 7.6−7.4 (m, 10H), 4.64 (broad d, J = 13.2 Hz, 1H, AB system), 4.55−4.43 (broad m, 3H), 4.41 (broad d, J = 13.2 Hz, 1H, AB system), 3.69 (broad m, 1H), 3.60 (dd, J = 11.1, 6.6 Hz, 1H, ABX system), 3.44 (dd, J = 11.4, 7.7 Hz, 1H, ABX system), 2.11 (broad m, 1H), 1.72 (m, 2H), 0.97 (broad d, J = 5.5 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H). ^{13}C NMR (DMSO-

(30) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

d_6, 100 MHz) δ 133.5, 133.3, 132.0, 131.2, 131.1, 71.3, 63.2, 58.2, 57.9, 47.3, 33.7, 27.4, 24.6, 22.9. MS (FAB) m/z 346 (MH^+). Anal. Calcd for $C_{21}H_{29}Cl_2NO$: C, 65.96; H, 7.64; N, 3.66. Found: C, 65.60; H, 7.69; N, 3.69. A reference sample of (2*R*,3*R*)-**8d** was prepared in the same manner starting from D-leucinol and used for isomeric purity determinations: mp 155−158 °C. $[\alpha]^{23}_D$ −1.4° (*c* 1, MeOH). Anal. Calcd for $C_{21}H_{29}Cl_2NO$: C, 65.96; H, 7.64; N, 3.66. Found: C, 65.73; H, 7.74; N, 3.62. Samples of (2*S*,3*S*)-**8d** and (2*R*,3*R*)-**8d** were neutralized with aqueous $NaHCO_3$, extracted into hexane, and analyzed by HPLC (Chiralcel OD column, 5% EtOH/hexane, isocratic, 0.5 mL/min): t_R (2*R*,3*R*)-**8d**, 10.8 min (0.06%). t_R (2*S*,3*S*)-**8d**, 11.8 min (98.1%).

***N,N*-Dibenzyl-(*S*)-3-amino-(*S*)-2-hydroxy-4-[4-(benzyloxy)phenyl]-1-chlorobutane Hydrochloride (8e).** Crude epoxide **7e** (12.32 g, 27.4 mmol) was dissolved in THF (30 mL), and 6 N aqueous HCl (50 mL) was added. After stirring overnight at 5 °C, a gummy residue was formed. The supernatant was removed by decantation and the gum was crystallized from hot MeOH. **8e** was obtained as a beige-colored solid that was collected and washed with 95:5 ether−MeOH and then ether (5.59 g, 39% yield overall from **3e**): mp 178−180 °C. $[\alpha]^{23}_D$ +12.7° (*c* 1, MeOH). $[\alpha]^{23}_{Hg365}$ +54.9° (*c* 1, MeOH). IR (KBr) ν 3250, 2560, 1610, 1510, 1450, 1290 cm^{-1}. ^1H NMR (MeOH-d_4, 400 MHz) δ 7.55−7.27 (m, 15H), 7.04 (m, 2H), 6.91 (m, 2H), 5.07 (s, 2H), 4.98 (broad d, J = 13.2 Hz, 1H, AB system), 4.70 (broad d, J = 13.6 Hz, 1H, AB system), 4.53 (broad t, J = 7.2 Hz, 1H), 4.47 (broad d, J = 13.7 Hz, 1H, AB system), 4.43 (broad d, J = 13.6 Hz, 1H, AB system), 3.92 (broad m, 1H), 3.47 (dd, J = 13.9, 10.0 Hz, 1H), 3.12 (m, 1H), 3.10 (dd, J = 11.0, 6.6 Hz, 1H), 2.78 (dd, J = 10.7, 8.1 Hz, 1H). ^{13}C NMR (157.2, 136.9, 131.8, 131.2, 130.3, 130.1, 129.3, 128.6, 128.5, 128.3, 127.7, 127.6, 114.8, 69.1, 68.6, 62.7, 54.4, 45.9, 26.6. MS (FAB) m/z 486 (MH^+). Anal. Calcd for $C_{31}H_{33}Cl_2NO_2$: C, 71.26; H, 6.37; N, 2.68. Found: C, 71.16; H, 6.36; N, 2.65. HPLC (neutralization with $NaHCO_3$, hexane extraction, Chiralcel OD, 5% EtOH/hexane, isocratic, 1 mL/min): t_R 18.7 min (>97%).

(*S*)-3-Amino Chlorohydrin Hydrochlorides 9a-e. General Procedure. The *N,N*-dibenzylamino chlorohydrin hydrochloride **8a-e** and 20% palladium hydroxide on charcoal (ca. 10% by weight) were suspended in MeOH, and the slurry was stirred under 1 atm of hydrogen gas until completion (6−48 h). The catalyst was removed by filtration using MeOH for washings, and volatiles were evaporated under reduced pressure. The residue was triturated with ether, filtered, and dried under vacuum.

(*S*)-3-Amino-(*S*)-2-hydroxy-4-phenyl-1-chlorobutane Hydrochloride (9a). Obtained in 97% yield as a white crystalline solid: mp 204−208 °C. $[\alpha]^{25}_D$ −42.5° (*c* 1, MeOH). IR (KBr) ν 3360, 1600, 1580, 1500 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.34 (broad s, 3H), 7.3−7.4 (m, 5H), 6.14 (broad d, J = 5.4 Hz, 1H), 4.00 (m, 1H), 3.63 (dd, J = 11.4, 5.4 Hz, 1H, ABX system), 3.55 (m, 1H), 3.51 (dd, J = 11.4, 7.8 Hz, 1H, ABX system), 3.02 (dd, J = 14.0, 7 Hz, 1H, ABX system), 2.92 (dd, J = 14.3, 7.2 Hz, 1H, ABX system). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 136.7, 129.3, 128.5, 126.8, 70.3, 54.3, 45.3, 32.7. MS (CI-isooctane) m/z 200 (MH^+). Anal. (analytical sample crystallized from ethanol) Calcd for $C_{10}H_{15}Cl_2NO$: C, 50.86; H, 6.40; N, 5.93. Found: C, 50.49; H, 6.43; N, 5.84.

(*S*)-3-Amino-(*S*)-2-hydroxy-1-chlorobutane Hydrochloride (9b). Obtained in 93% yield as a white crystalline solid: mp 102−105 °C. $[\alpha]^{25}_D$ −12.4° (*c* 1, MeOH). IR (KBr) ν 3350, 3260, 1585, 1510,1505 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.18 (broad s, 3H), 5.98 (d, J = 5.4 Hz, 1H), 3.93 (m, 1H), 3.64 (dd, J = 11.1, 6.0 Hz, 1H, ABX system), 3.55 (dd, J = 11.1, 6.9 Hz, 1H, ABX system), 3.33 (m, 1H), 1.13 (d, J = 6.9 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 70.1, 48.2, 45.2, 11.7. MS (FAB) m/z 124 (MH^+). Anal. Calcd for $C_4H_{11}Cl_2NO$: C, 30.02; H, 6.93; N, 8.75. Found: C, 30.09; H, 7.01; N, 8.57.

(*S*)-3-Amino-(*S*)-2-hydroxy-4-methyl-1-chloropentane Hydrochloride (9c). Obtained in 98% yield as an oil which was used without purification: $[\alpha]^{25}_D$ −10.7° (*c* 1, MeOH). ^1H NMR (DMSO-d_6, 400 MHz) δ 8.13 (broad s, 3H), 6.00 (broad s, 1H), 3.96 (broad m, 1H), 3.81 (dd, J = 11.4, 3.6 Hz, 1H, ABX system), 3.52(dd, J = 11.4, 7.8 Hz, 1H, ABX system), 2.96 (broad m, 1H), 2.01 (m, 1H), 0.99 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H). MS (FAB) m/z 152 (MH^+).

(*S*)-3-Amino-(*S*)-2-hydroxy-5-methyl-1-chlorohexane Hydrochloride (9d). Obtained in 91% yield as a white crystalline solid: mp 134−136 °C. $[\alpha]^{25}_D$ −34.6° (*c* 1, MeOH). IR (KBr) ν 3325, 1610, 1510 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.10 (broad s, 3H), 5.99 (d, J = 5.4 Hz, 1H), 3.98 (broad m, 1H), 3.65 (dd, J = 11.4, 6.0 Hz, 1H, ABX system), 3.58 (dd, J = 11.2, 7.2 Hz, 1H, ABX system), 3.26 (dt, J = 9.6, 3.3 Hz, 1H), 1.74 (m, 1H), 1.48 (ddd, J = 14.1, 10.2, 4.2 Hz, 1H), 1.32 (ddd, J = 16.2, 10.2, 3.8 Hz, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 70.5, 50.8, 45.0, 35.4, 23.4, 21.4. MS(FAB) m/z 166 (MH^+). Anal. Calcd for $C_7H_{17}Cl_2NO$: C, 41.60; H, 8.48; N, 6.93. Found: C, 41.47; H, 8.61; N, 6.90.

(*S*)-3-Amino-(*S*)-2-hydroxy-4-(4-hydroxyphenyl)-1-chlorobutane Hydrochloride (9e). Obtained in 98% yield as a white crystalline solid: mp 176−180 °C. $[\alpha]^{25}_D$ −39.9° (*c* 1, MeOH). IR (KBr) ν 3380, 1610, 1590, 1580, 1415 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.42 (s, 1H), 8.17 (broad s, 3H), 7.10 (d, J = 7.8 Hz, 2H), 6.75 (d, J = 8.1 Hz, 2H), 6.08 (d, J = 5.4 Hz, 1H), 3.95 (broad m, 1H), 3.61 (dd, J = 11.4, 4.9 Hz, 1H, ABX system), 3.48 (dd, J = 11.1, 7.8 Hz, 1H, ABX system), 3.44 (m, 1H), 2.88 (dd, J = 14.2, 6.5 Hz, 1H, ABX system), 2.56 (dd, J = 14.2, 7.4 Hz, 1H, ABX system). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 156.4, 130.3, 126.3, 115.5, 70.3, 54.6, 45.5, 31.9. MS (FAB) m/z 216 (MH^+). Anal. Calcd for $C_{10}H_{15}Cl_2NO_2$: C, 47.64; H, 6.00; N, 5.56. Found: C, 47.48; H, 6.12; N, 5.54.

(2*S*,3*S*)-*N*-Boc-3-amino-1,2-epoxy-4-phenylbutane (2a). Di-*tert*-butyl dicarbonate (1320 g, 6.05 mol) and triethylamine (1698 mL, 12.18 mol) were dissolved in reagent grade THF (10.8 L), and the solution cooled in an ice bath. Solid amino chlorohydrin hydrochloride **9a** (1418 g, 6.00 mol) was added in portions over 30 min. The cooling bath was removed and the reaction mixture stirred 3.5 h at room temperature, after which, RP-HPLC analysis indicated completion of the reaction. The white slurry was cooled again in an ice bath, and a solution of KOH (1344 g, 23.95 mol) in methanol (5.34 L) was added over 15 min. The ice bath was removed and stirring continued for an additional 75 min. TLC analysis (4:1 hexane/EtOAc) indicated complete reaction. The reaction mixture was poured into 60 L of water and the white precipitate collected by suction filtration. The material was air-dried to constant weight. **2a** was obtained as a white crystalline solid (1530 g, 96% yield): mp 124−125 °C, lit.[10a] mp 122−124.5 °C. R_f 0.49 (4:1 hexane/EtOAc). $[\alpha]^{25}_D$ +6.9° (*c* 1, $CHCl_3$), $[\alpha]^{23}_D$ −8.6° (*c* 1, MeOH), lit.[10a] $[\alpha]^{20}_D$ −8.1° (*c* 1.0%, MeOH). IR (KBr) ν 3375, 1625, 1595, 1425 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.2 (m, 5H), 4.47 (broad s, 1H), 3.70 (broad s, 1H), 2.97 (dd, J = 14.0, 5.1 Hz, 1H, ABX system), 2.91 (m, 1H), 2.85 (broad dd, J = 14.0, 7.6 Hz, 1H, ABX system), 2.79 (m, 1H), 2.75 (broad m, 1H), 1.39 (s, 9H).[10a,g] ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.3, 136.8, 129.4, 128.5, 126.7, 79.6, 53.2, 52.8, 46.8, 37.6, 28.3.[10g] MS (FAB) m/z 264 (MH^+). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.33; H, 8.08; N, 5.19.

Determination of the Isomeric Purity of 2a by HPLC Analysis on a Chiral Column. Authentic samples of all four possible isomers of **2a** were prepared by literature methods.[9] All four isomers were resolved by isocratic, normal-phase HPLC on a Chiralcel OD column using 5% EtOH in hexane as eluant. Retention times at 0.5 mL/min flow rates: (2*S*,3*R*), 11.9 min; (2*R*,3*S*), 12.5 min; (2*R*,3*R*), 13.3 min; (2*S*,3*S*), 14.1 min. The isomeric purity of **2a** was evaluated at >99.5% (detection limit <0.5%).

(2*S*,3*S*)-*N*-Boc-3-amino-1,2-epoxybutane (2b). Di-*tert*-butyl dicarbonate (2.80 g, 13 mmol) and triethylamine (3.62 g, 26 mmol) were dissolved in reagent grade THF (20 mL), and **9b** (2.00 g, 12.5 mmol) was added. The suspension was stirred 2.5 h at room temperature. KOH (2.81 g, 50 mmol) in MeOH (10 mL) was added and the mixture stirred an additional 20 min at room temperature. TLC (2:1 hexane/EtOAc) indicated complete conversion to the epoxide. The reaction mixture was concentrated to 1/4 volume under reduced pres-

sure. Water (50 mL) was added and the product extracted with EtOAc (2 × 30 mL). After washing with water, drying ($MgSO_4$), and removal of volatiles under reduced pressure, the residue was crystallized from hot hexane to give **2b** as large white crystals (1.65 g, 71% yield): mp 54−55 °C. R_f 0.45 (2:1 hexane/EtOAc). $[\alpha]^{25}_D$ −16.2° (*c* 1, $CHCl_3$). IR ($CHCl_3$) ν 3440, 1705, 1500 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 4.54 (broad s, 1H), 3.68 (broad s, 1H), 2.94 (broad m, 1H), 3.79 (t, J = 4.5 Hz, 1H), 2.73 (broad m, 1H), 1.46 (s, 9H), 1.16 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.2, 79.5, 54.6, 47.4, 46.1, 28.3, 16.3. MS (CI-isobutane) m/z 188 (MH^+). Anal. Calcd for $C_9H_{17}NO_3$: C, 57.33; H, 9.15; N, 7.48. Found: C, 57.62; H, 9.38; N, 7.45. HPLC (Chiralcel OD, 5% EtOH/hexane, isocratic, 0.65 mL/min): t_R 8.9 min (>99% homogeneity). Purification of the mother liquors by flash chromatography using 9:1 hexanes/EtOAc gave an additional 0.24 g. Total yield 1.89 g (80%).

(2*S*,3*S*)-*N*-Boc-3-amino-1,2-epoxy-4-methylpentane (2c). Crude amino chlorohydrin **9c** (8.88 g, 47 mmol) and di-*tert*-butyl dicarbonate (10.31 g, 47 mmol) were dissolved in reagent grade THF (150 mL), and triethylamine (9.55 g, 94 mmol) was added. After stirring 3 h at room temperature, KOH (10.6 g, 189 mmol) in MeOH (100 mL) was added and stirring continued for an additional 3 h. The reaction mixture was concentrated under reduced pressure, water was added, and the product was extracted into EtOAc. The extract was washed with water and dried over anhydrous Na_2SO_4. Removal of volatiles under reduced pressure gave a solid residue which was crystallized from hot hexanes to give **2c** as a white crystalline solid (7.12 g, 70% yield): mp 69−71 °C, lit.[10h] 70−72 °C. R_f 0.39 (4:1 hexane/EtOAc). $[\alpha]^{23}_D$ −6.4° (*c* 4, MeOH). $[\alpha]^{23}_{Hg365}$ −17.2° (*c* 4, MeOH). IR (KBr) ν 3450, 1710, 1500 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 4.46 (broad s, 1H), 3.20 (broad s, 1H), 2.86 (broad dt, J = 7.0, 3.4 Hz, 1H), 2.75 (t, J = 4.5 Hz, 1H), 2.72 (broad m, 1H), 1.98 (m, 1H), 1.44 (s, 9H), 1.02 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H).[10h] ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.7, 79.4, 57.3, 52.6, 45.7, 30.7, 28.3, 19.2, 17.7.[10h] MS (FAB) m/z 216 (MH^+). Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.18; H, 9.99; N, 6.50. HPLC (Chiralcel OD, 5% EtOH/hexane, isocratic, 0.65 mL/min): t_R 7.5 min (>99.5% homogeneity).

(2*S*,3*S*)-*N*-Boc-3-amino-1,2-epoxy-5-methylhexane (2d). Di-*tert*-butyl dicarbonate (3.27 g, 10.5 mmol) and triethylamine (2.8 mL, 20 mmol) were dissolved in reagent grade THF (20 mL), and **9d** (2.02 g, 10 mmol) was added. The suspension was stirred 1 h at room temperature. KOH (2.25 g, 40 mmol) in MeOH (10 mL) was added and stirring continued for an additional 1.5 h at room temperature at which point TLC (2:1 hexane/EtOAc) indicated complete conversion to epoxide **2d**. The reaction mixture was concentrated under reduced pressure to 1/2 volume, water (50 mL) was added and the product extracted with EtOAc. The extract was washed with water, dried ($MgSO_4$), and concentrated to an oil. Purification by flash chromatography (9:1 hexanes/EtOAc) gave pure **2d** as a white crystalline solid (1.85 g, 81% yield): mp 50−51 °C. R_f 0.49 (2:1 hexane/EtOAc). $[\alpha]^{25}_D$ −29.5° (*c* 1, $CHCl_3$). IR ($CHCl_3$) ν 3440, 1705, 1495 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 4.63 (broad s, 1H), 3.50 (broad s, 1H), 2.85 (broad m, 1H), 2.74 (m, 2H), 1.74 (m, J = 6.7 Hz, 1H), 1.45 (s, 9H), 1.40 (m, 2H), 0.95 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H).[10j] ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.4, 79.2, 54.4, 45.9, 40.7, 28.2, 24.3, 23.2, 21.7. MS (FAB) m/z 230 (MH^+). Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 63.03; H, 10.51; N, 6.13. HPLC (Chiralcel OD, 5% EtOH/hexane, isocratic, 0.65 mL/min): t_R 7.5 min (>99% homogeneity).

(2*S*,3*S*)-*N*-Boc-3-amino-1,2-epoxy-4-(4-hydroxyphenyl)-butane (2e). Di-*tert*-butyl dicarbonate (2.40 g, 11 mmol) and triethylamine (3.0 mL, 22 mmol) were dissolved in reagent grade THF (20 mL), and **9e** (2.52 g, 10 mmol) was added. The suspension was stirred 4 h at room temperature (complete by RP-HPLC analysis), and KOH (2.25 g, 40 mmol) in MeOH (10 mL) was added. Stirring was continued for an additional 1 h. The reaction mixture was concentrated to 1/4 volume, and 10% aqueous citric acid was added to the residue. The white precipitate was collected by suction filtration, washed with water, and dried under vacuum to give **2e** (2.61 g, 93% yield): mp 155−157 °C. R_f 0.55 (1:2 hexane/EtOAc). $[\alpha]^{25}_D$ −4.3° (*c* 1, MeOH). $[\alpha]^{25}_{Hg365}$ −11.8° (*c* 1, MeOH). IR (KBr) ν 3370, 3295, 1685, 1610, 1595, 1510 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.08 (s, 1H), 6.99 (d, J = 8.4 Hz, 2H), 6.74 (broad d, J = 8.7 Hz, 1H), 6.65 (d, J = 8.4 Hz, 2H), 3.42 (m, 1H), 2.87 (ddd, J = 6.0, 3.6, 2.7 Hz, 1H), 2.73 (dd, J = 14.1, 4.5 Hz, 1H, ABX system), 2.64 (m, 1H), 2.62 (dd, J = 5.4, 2.4 Hz, 1H, ABX system), 1.31 (s, 9H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 155.5, 155.1, 129.8, 128.2, 114.8, 77.5, 53.1, 53.0, 44.6, 36.2, 28.1. MS (FAB) m/z 280 (MH^+). Recrystallized analytical sample (EtOAc): Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.24; H, 7.67; N, 4.89. HPLC (Chiralcel OD, 5% EtOH/hexane, isocratic, 0.65 mL/min): t_R 35.9 min (>99.5% homogeneity).

(1*S*)-[1′(*S*)-(Dibenzylamino)-2-phenylethyl]oxirane (7a).[16,19b,d] *N*,*N*-Dibenzyl-3-amino chlorohydrin hydrochloride **8a** (1.45 g, 3.5 mmol) was suspended in MeOH (10 mL), and a solution of KOH (0.78 g, 14 mmol) in MeOH (10 mL) was added. After stirring 15 min at room temperature, the reaction was judged complete by TLC (4:1 hexane/EtOAc). The solvent was removed under reduced pressure, water was added, and the product was extracted with EtOAc. The extract was washed with water and dried ($MgSO_4$), and volatiles were removed under vacuum. Pure (2*S*,3*S*)-**7a** was obtained as a waxy solid (1.12 g, 93% yield): mp 54.5−55.5 °C. R_f 0.45 (4:1 hexane/EtOAc), $[\alpha]^{25}_D$ +10.9° (*c* 1, $CHCl_3$), $[\alpha]^{25}_{Hg365}$ +60.2° (*c* 1, $CHCl_3$), lit.[19b] $[\alpha]^{25}_D$ +6.5° (*c* 0.80, $CHCl_3$). IR (neat) ν 1955, 1875, 1815, 1740, 1605, 1495, 1455, 1370 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.4−7.0 (m, 15H), 3.86 (d, J = 14.0 Hz, 2H, AB system), 3.75 (d, J = 14.0 Hz, 2H, AB system), 3.17 (m, 1H), 3.03 (dd, J = 15.7, 10.0 Hz, 1H, ABX system), 2.86 (m, 2H), 2.78 (t, J = 4.5 Hz, 1H), 2.52 (dd, J = 5.9, 2.7 Hz, 1H).[20b,d] ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.7, 139.6, 129.6, 128.5, 128.3, 128.2, 127.0, 126.1, 60.4, 54.3, 52.2, 46.1, 33.9.[19b,d] MS (FAB) m/z 344 (MH^+). Anal. Calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 84.15; H, 7.30; N, 3.99. HPLC (Chiralcel OD-H, 0.5% EtOH/hexane, isocratic, 0.5 mL/min): t_R 24.0 min (2*S*,3*S*)-**7a** (99% homogeneity). t_R 22.2 min (2*R*,3*S*)-**7a** (0.05%)

***N*-[(*S*)-3-Hydroxytetrahydrofuryloxycarbonyl]-(2*S*,3*S*)-3-amino-1,2-epoxy-4-phenylbutane (10).** (*S*)-3-Hydroxytetrahydrofuran (5.00 g, 56.7 mmol) was added to a solution of phosgene in toluene (1.93 M, 50 mL, 97 mmol) and the mixture stirred 20 h at room temperature under a nitrogen atmosphere. Toluene and excess phosgene were removed under reduced pressure, and the crude chloroformate was dissolved in dry THF (250 mL). amino chlorohydrin hydrochloride **9a** (7.08 g, 30 mmol) was added and the suspension cooled in ice−water. Triethylamine (21 mL, 150 mmol) was added dropwise over 15 min and the slurry stirred for 1 h. A cooled solution of KOH (11.20 g, 200 mmol) in EtOH (75 mL) was added and the cold reaction mixture stirred for an additional 2 h. Volatiles were removed to 1/2 volume under reduced pressure, and the residue was poured in water (1.5 L) with vigorous stirring. The white precipitate was collected, washed with water, and dried. Crystallization from EtOAc/hexanes gave pure **10** as a white crystalline solid (4.70 g, 56% yield): mp 103−104 °C. R_f 0.51 (1:4 hexane/EtOAc). $[\alpha]^{25}_D$ −26.0° (*c* 1, MeOH). IR (KBr) ν 3350, 1695, 1540 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.19 (m, 5H), 5.21−5.16 (m, 1H), 4.70 (broad m, 1H), 3.92−3.69 (m, 5H), 2.99 (dd, J = 14.0, 5.1 Hz, 1H), 2.94 (m, 1H), 2.92−2.83 (m, 1H), 2.80 (t, J = 4.3 Hz, 1H), 2.75 (broad m, 1H), 2.19−2.05 (m, 1H), 1.97 (broad m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.4, 136.3, 129.3, 128.6, 126.8, 75.3, 73.2, 66.9, 53.0, 46.7, 37.5, 32.7. MS (FAB) m/z 278 (MH^+). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.94; H, 6.94; N, 5.02.

Preparation of Hydroxyethylamines 11f-h. General Procedure. *N*,*N*-Dibenzyl-3-amino chlorohydrin hydrochloride **8a** (1 equiv) was suspended in EtOH, and an amine (3 equiv) was added. The mixture was refluxed overnight under a nitrogen atmosphere. After removal of volatiles under reduced pressure, the residue was dissolved in EtOAc and the solution washed with 2 N NaOH and water. After drying ($MgSO_4$), the solvent was evaporated and the residue purified by flash chromatography.

11f: Isobutylamine was used as amine component. After purification by flash chromatography using 8:2 hexanes/EtOAc followed by 1:4 hexanes/EtOAc + 5% MeOH, **12** (29% yield) and **11f** (65% yield) were isolated as oils. Characterization of **12**, see experimental for **11h**. **11f**:[19c] R_f 0.22 (1:4 hexane/EtOAc). $[\alpha]^{25}_D$ +4.7° (*c* 1, $CHCl_3$). IR (neat) ν 3360, 1945, 1870, 1810, 1605, 1495, 1450 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.4−7.1 (m, 15H), 3.91 (ddd, J = 8.9, 5.1, 3.7 Hz, 1H), 3.74 (d, J = 13.7 Hz, 2H, AB system), 3.68 (d, J = 14.0 Hz, 2H, AB system), 3.09 (dd, J = 14.3, 8.3 Hz, 1H, ABX system), 3.01 (dd, J = 14.3, 5.1 Hz, 1H, ABX system), 2.90 (dt, J = 8.0, 5.2 Hz, 1H), 2.75 (dd, J = 12.1, 3.5 Hz, 1H, ABX system), 2.52 (dd, J = 11.8, 9.0 Hz, 1H, ABX system), 2.38 (dq, J = 11.5, 6.7 Hz, 2H), 1.67 (m, J = 6.7 Hz, 1H), 0.92 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H).[20c] ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.6, 140.0, 129.7, 128.9, 128.2, 128.1, 126.8, 125.7, 68.8, 62.3, 57.5, 54.6, 53.1, 32.7, 28.4, 20.6.[20c] MS (FAB) m/z 417 (MH^+). Anal. Calcd for $C_{28}H_{36}N_2O$: C, 80.73; H, 8.71; N, 6.72. Found: C, 80.84; H, 8.79; N, 6.69.

11g: Obtained from aniline in 63% yield after flash chromatography using 9:1 hexanes/EtOAc (oil): R_f 0.36 (8:2 hexane/EtOAc). $[\alpha]^{25}_D$ −2.2° (*c* 1, $CHCl_3$). IR (neat) ν 3400, 1950, 1875, 1815, 1610, 1515, 1510, 1455 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.4−7.2 (m, 16H), 7.20 (broad t, J = 7.6 Hz, 2H), 6.75 (broad t, J = 7.3 Hz, 1H), 6.58 (d, J = 7.6 Hz, 2H), 4.03 (m, 1H), 3.84 (d, J = 13.5 Hz, 2H, AB system), 3.67 (d, J = 13.7 Hz, 2H, AB system), 3.44 (dd, J = 12.8, 3.3 Hz, 1H, ABX system), 3.21 (dd, J = 13.3, 6.7 Hz, 1H, ABX system), 3.15−3.00 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.4, 140.9, 139.6, 129.5, 129.3, 128.9, 128.5, 128.4, 127.2, 126.1, 117.9, 113.4, 71.2, 62.0, 54.9, 48.1, 32.5. MS (FAB) m/z 437 (MH^+). Anal. Calcd for $C_{30}H_{32}N_2O$: C, 82.53; H, 7.39; N, 6.42. Found: C, 82.73; H, 7.50; N, 6.34.

11h and 12: Piperidine was used as the amine component. After flash chromatography using 9:1 hexanes/EtOAc, **12** was isolated as an oil (solidified on standing) in 17% yield. Further elution with 1:1 hexanes/EtOAc gave **11h** as an oil in 75% yield. **11h**: R_f 0.18 (1:2 hexane/EtOAc). $[\alpha]^{25}_D$ +3.2° (*c* 1, $CHCl_3$). IR (neat) ν 3390, 1955, 1875, 1815, 1605, 1495, 1455, 1270 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.1 (m, 15H), 4.04 (dt, J = 10.8, 4.0 Hz, 1H), 3.75 (d, J = 14.0 Hz, 2H, AB system), 3.64 (d, J = 14.0 Hz, 2H, AB system), 3.06 (dd, J = 14.3, 8.6 Hz, 1H, ABX system), 2.95 (dd, J = 14.3, 4.8 Hz, 1H, ABX system), 2.81 (dt, J = 8.3, 4.4 Hz, 1H), 2.59 (broad m, 2H), 2.35 (dd, J = 12.4, 3.5 Hz, 1H, ABX system), 2.24 (broad m, 2H), 2.04 (dd, J = 12.1, 6.0 Hz, 1H, ABX system), 1.56 (m, 4H), 1.45 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.7, 140.2, 129.8, 128.8, 128.1, 126.7, 125.7, 65.5, 63.2, 62.6, 54.6, 32.6, 26.2, 24.4. MS (FAB) m/z 429 (MH^+). Anal. Calcd for $C_{29}H_{36}N_2O$: C, 81.27; H, 8.47; N, 6.54. Found: C, 81.10; H, 8.52; N, 6.62.

12: R_f 0.67 (1:2 hexane/EtOAc). $[\alpha]^{22}_D$ +109.4° (*c* 1, $CHCl_3$). IR (neat) ν 3450, 1955, 1875, 1815, 1605, 1500 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.4−7.2 (m, 15H), 6.61 (d, J = 15.9 Hz, 1H), 6.06 (dd, J = 15.9, 6.4 Hz, 1H), 4.36 (m, 1H), 3.90 (d, J = 13.4 Hz, 2H, AB system), 3.51 (d, J = 13.4 Hz, 2H, AB system), 3.38 (t, J = 5.4 Hz, 1H), 2.62 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.4, 136.8, 131.1, 129.8, 129.1, 128.5, 127.6, 127.4, 126.5, 68.5, 59.7, 58.4. MS (FAB) m/z 344 (MH^+). Anal. Calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.53; H, 7.65; N, 4.28.

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Supporting Information Available: Diagram of 10 L reaction vessel used in sonication experiments and an ORTEP plot of **8c** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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