Preparation and Synthetic Applications of Enantiopure (2*S*,3*S*)- or (2*R*,3*S*)-2-Halomethyl-1,2-epoxyalkan-3-amines

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Enantiomerically pure (2*S*,3*S*)-**3** and its diastereoisomer (2*R*,3*S*)-2-halomethyl-1,2-epoxyalkan-3-amine **4** have been obtained from 1-aminoalkyl halomethyl ketones **1** and (iodomethyl)lithium or (chloromethyl)lithium, respectively. Some synthetic applications of compounds **3** are described: chiral unsaturated 1,3-aminoalcohols **8** or 2-(halomethylidene)-3-(dibenzylamino)-alkan-1-ol **11** is obtained from **3** by halogeno−lithium or by hydrogen−lithium exchange, respectively. Transformation of **8c** into its methyl ester derivative **9c** is also reported.

Introduction

Optically active epoxides with adjacent functional groups are interesting intermediates for the synthesis of natural/biologically active compounds.[1] In particular, chiral 1-chloro-2,3-epoxypropane (epichlorohydrin) is a useful building block in organic synthesis.[2] However, to the best of our knowledge, there is no direct methodology[3] for the synthesis of chiral substituted epihalohydrins. These chiral compounds, such as 2-(1-aminoalkyl)epihalohydrins **3** and **4**, are attractive starting materials for further chemical transformations, yielding products of predetermined stereo- and regiochemistry. For example, the oxirane ring can be opened by a variety of nucleophiles,[4] the halogen atom can be metalated[5] or displaced by nucleophiles,[6] and the acidic protons of **3** are susceptible to abstraction by bases.[7]

Recently, we have reported the direct preparation of chiral 1-aminoalkyl chloromethyl ketones by reaction of *N*,*N*-dibenzylated α-amino esters with in situ generated (chloromethyl)lithium.[8] We have also investigated the reduction of these dibenzylamino chloromethyl ketones and their reaction with organometallic compounds, obtaining enantiopure *threo* amino alkyl epoxides[8] and 3-azetidinols,[9] respectively. The high diastereoselectivity of these reactions prompted us to study new applications of chiral 1-aminoalkyl chloromethyl ketones in the synthesis of enantiomerically pure building blocks. In this paper, we report the preparation of enantiomerically pure (2*S*,3*S*)-**3** and its diastereoisomer (2*R*,3*S*)-2-halomethyl-1,2-epoxyalkan-3-amine **4** in an efficient synthesis starting from 1-aminoalkyl halomethyl ketones **1** and halomethyllithium. We also describe some synthetic applications of compounds **3**: chiral unsaturated 1,3-aminoalcohols **8** are obtained by halogen−lithium exchange, while hydrogen−lithium exchange leads to 2-(halomethylidene)-3-(dibenzylamino)-alkan-1-ol **11**.

Results and Discussion

Treatment of 1-aminoalkyl chloro- or bromomethyl ketones **1**[10] with in situ generated (iodomethyl)lithium at −78 °C gave the corresponding alcoholate **2**. When the reaction mixture was allowed to warm to room temperature, 2-(1-aminoalkyl)epichloro- or epibromohydrins **3** were obtained, respectively (see Scheme 1). The epoxidation of **2** proceeds with total regioselectivity, based upon the better leaving group potential of iodine over both bromine and chloride.[11]

On the basis of our earlier studies which examined the nonchelation controlled addition of organometallic com-

(1) For general reviews of the reactivity of 2,3-epoxy alcohols, see: (a) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 7. (b) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437. For other recent synthetic applications of 2,3-epoxy alcohols, see: (c) Bonini, C.; Federici, C.; Rossi, L.; Righi, G. *J. Org. Chem.* **1995**, *60*, 4803. For the reactivity of α,*β*-epoxy ketones, see: (d) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596. For synthetic applications of vinyloxiranes, see: (e) Molander, G. A.; La Belle, B. E.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 5259. For the reactivity of α,*β*-epoxy silanes, see: (f) Gorzynski, J. *Synthesis* **1984**, 629. For synthetic applications of α-amino epoxides, see: (g) Pegorier, L.; Petit, Y.; Larchevêque, M. *J. Chem. Soc., Chem. Commun.* **1994**, 633. (h) Albeck, A.; Persky, R. *Tetrahedron* **1994**, *50*, 6333. (i) Hua, D. Y.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4. (j) Luly, J. R.; Dellaraia, J. F.; Plattner, J. J. Soderquist, J. L. Yi, N. *J. Org. Chem.* **1987**, *52*, 1487. (k) Evans, E. V., Rittle, E. K.; Homnicik, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615. (l) Luly, J. R.; Plattner, J. J.; Stein, H.; Yi, N.; Cohen, J.; Tricario, K.; Dellaria, J. F. *Pharmacologist* **1985**, *27*, 260.

(2) (a) Takano, S.; Yanese, M.; Sekiguchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1987**, *28*, 1783. (b) Chong, J. M. *Tetrahedron Lett.* **1992**, *33*, 33. (c) Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron*, **1990**, *46*, 7033. (c) Polson, G.; Dittmer, D. C. *J. Org. Chem.* **1988**, *53*, 791. (d) Abrate, F.; Bravo, P.; Frigerio, M.; Viani, F.; Zanda, M. *Tetrahedron: Asymmetry* **1996**, *7*, 581.

(3) A multistep synthesis of chiral substituted epihalohydrins has been described via Sharpless epoxidation, treatment with tosyl chloride, and further displacement by chloride or bromide: Discordia, R. P.; Dittmer, D. C. *J. Org. Chem.* **1990**, *55*, 1414.

(4) (a) For general applications of epoxides in organic synthesis, see: Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1993**, *16*, 67. For other recent applications of epoxides, see: (b) Gala, D.; Dibenedetto, D. J. *Tetrahedron Lett.* **1994**, *35*, 8299. (c) Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 433. (d) Augé, J.; Leroy, F. *Tetrahedron Lett.* **1996**, *37*, 7715.

(5) Barluenga, J.; Concellón, J. M.; Llavona, L.; Bernad, P. L. *Tetrahedron* **1995**, *51*, 5573.

(6) Johnson, F.; Panella, J. P.; Carlson, A. A. *J. Org. Chem.* **1962**, *27*, 2241.

(7) Yadav, J. S.; Deshpande, P. P. K.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033.

(8) (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.

(9) Barluenga, J.; Baragaña, B.; Concellón, J. M. *J. Org. Chem.* **1997**, *62*, 5974.

(10) Barluenga, J.; Baragaña, B.; Concellón, J. M. Unpublished results.

(11) In the case of bromomethyl ketones, the reaction was slowly allowed to warm to room temperature overnight to avoid the formation of a mixture of regioisomers due to the small difference between bromine and iodide as leaving groups.

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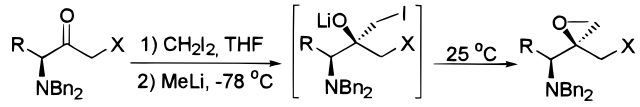
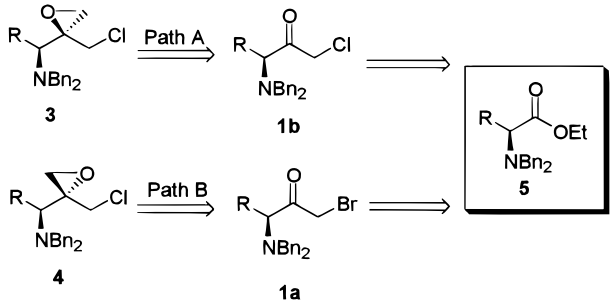
Scheme 1



Scheme 2



pounds[9] and hydride[8] to ketone **1**, the stereochemistry of **3** is believed to be *anti*. Further precedent for *anti* addition to ketone **1** is also based upon the work of Reetz and co-workers who studied the addition of organometallic compounds to dibenzylated amino aldehydes[12] and the reduction of dibenzylated α-aminoalkanones.[13] In these examples the addition of the nucleophile takes place in a nonchelation controlled fashion based on steric constraints imparted by the bulky *N*,*N*-dibenzyl protecting group, which prevents competitive chelation control. Therefore, the energetically more favored transition state has the larger substituent, dibenzylamine, and also the electronegative atom (usually O or Cl, but in this instance N) *anti* to the attack of the nucleophiles.[14] The diastereomeric excess (de) of compounds **3** (>95%) was determined by 300 MHz ^{1}H NMR analysis of the crude product.

Iodomethylation of **1** proceeds with no detectable racemization. The enantiomeric purity of compound **3c**[15] was determined by chiral HPLC analysis (Chiracel OD-H) showing an enantiomeric excess (ee) > 99%. To exclude the possibility of coelution of both enantiomers, a racemic mixture of **3c** was prepared and analyzed by HPLC.

A retrosynthetic analysis (Scheme 2) suggested that the epichlorohydrin **4** could be obtained from bromomethyl ketone **1a** and (chloromethyl)lithium, assuming that the formation of **3** or **4** comes from the sequential addition of two different nucleophiles to the ester function of **5**. Thus both diastereoisomers (2*S*,3*S*) (path **A**) and (2*R*,3*S*) (path **B**) could be prepared. In fact, treatment of bromomethyl ketone **1a** with (chloromethyl)lithium gave the corresponding alcoholate **6a** (see Scheme 3). When the reaction mixture was slowly allowed to warm to room temperature, the epichlorohydrin **4a** was isolated in 75% yield with total diastereoselectivity (de > 98%).

Scheme 3

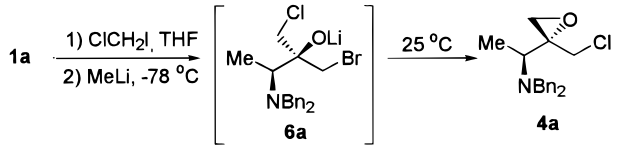


Table 1. Synthesis of Epihalohydrins 3

product	R	X	yield (%)[a]	de[b]
3a	Me	Cl	77	>95
3b	*i*-Bu	Cl	68	<95
3c	Bn	Cl	72	>95[c]
3d	Me	Br	75	>95
3e	Bn	Br	70	>95

[a] Isolated yield based on the starting ketone **1**. [b] Diastereoisomeric excess determined by 300 MHz ^{1}H NMR analysis of the crude products **3**. [c] ee > 99% HPLC (Chiracel OD-H; UV detector; 0.8 mL/min; 215 nm; 200:1 hexane/2-propanol; t_R = 13.8 min).

Scheme 4

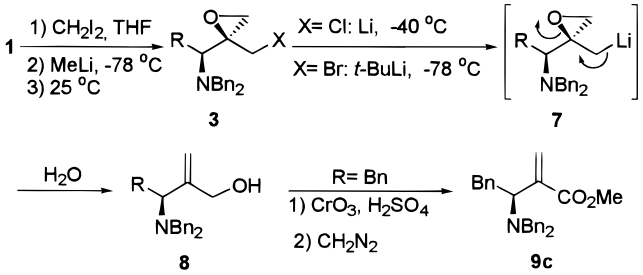


Table 2. Synthesis of Allylic Alcohols 8 and 11

product	starting ketone	R	yield (%)[a]
8a	**1b**	Me	82
8b	**1b**	*i*-Bu	76
8c	**1b**	Bn	70
8a	**1a**	Me	85
8b	**1a**	*i*-Bu	78
8c	**1a**	Bn	75
11a	**1b**	Me	81
11b	**1a**	Me	78

[a] Isolated yield based on the starting ketone **1**.

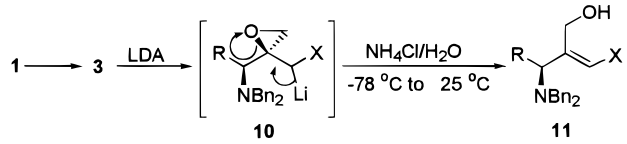
To prove the usefulness of enantiopure compounds **3** in organic synthesis, these compounds were transformed into chiral 2-methylene-3-(dibenzylamino)alkan-1-ols **8** and 2-(halomethylidene)-3-(dibenzylamino)alkan-1-ols **11**. Thus, the metalation of epichlorohydrins **3a**−**c** or epibromohydrins **3d**−**e** (see Table 1) with lithium powder or *tert*-butyllithium, respectively, led to enantiopure allyl aminoalcohols **8** (Scheme 4). The halogen−lithium exchange gave *β*-functionalized organolithium compound **7**, which undergoes a spontaneous *β*-elimination yielding compounds **8**. Chiral allyl aminoalcohols **8** were prepared in a one-pot synthesis starting from ketones **1** without isolating the epihalohydrins **3**. Successive treatment of **1** with iodomethyllithium at −78 °C, lithium powder at −40 °C or *tert*-butyllithium at −78 °C, and slow warming to room temperature gave rise to allyl aminoalcohols **8**. Yields and diastereoisomeric excesses are summarized in Table 2.

These unsaturated aminoalcohols **8** are precursors of α,*β*-unsaturated aminoesters; therefore, Jones oxidation of **8c** and esterification affords **9c** in 70% yield (Scheme 4).

Finally, 2-(halomethylidene)-3-(dibenzylamino)alkan-1-ols **11** were prepared in a one-pot synthesis starting

(12) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141.
(13) Reetz, M. T.; Lennick, K.; Schmitz, A.; Schmitz, A.; Holdgrün, X. *Tetrahedron: Asymmetry* **1990**, *1*, 375.
(14) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.
(15) The high tendency of Boc-protected aminoaldehyde derived from phenylalanine to racemize has been documented: Rittle, K. E.; Homnick, C. F.; Ponciello, G. S.; Evans, B. E. *J. Org. Chem.* **1982**, *47*, 3016.

Scheme 5



from halomethyl ketones **1** (see Scheme 5). Successive treatment of compounds **1** with (iodomethyl)lithium to obtain the epihalohydrins **3**, lithium diisopropylamide (LDA) at −78 °C, and slow warming to room temperature affords vinyl halides **11**. As depicted in Scheme 5, the proposed mechanism involves the initial formation of the *β*-functionalized organolithium compound **10** by hydrogen−lithium exchange and a further spontaneous *β*-elimination to afford the vinyl halide **11**. This reaction took place with total diastereoselectivity; NMR analysis (300 MHz) of the reaction crude showed the presence of only one diastereoisomer. The stereochemistry of compounds **11** was determined by NOESY experiments. Irradiation of the vinyl hydrogen produced positive NOE in the CHN, methyl hydrogens and benzyl hydrogens, indicating a *cis* relative configuration between the halogen and hydroxy group.

In conclusion, the results reported represent a general method for the preparation of two enantiopure diastereoisomers of substituted epihalohydrins with high yield and diastereoselectivity (de > 98%) from readily available starting materials. Moreover, we have demonstrated some synthetic applications of these substituted epihalohydrins obtaining 2-methylene-3-(dibenzylamino)-alkan-1-ols **8** and 2-(halomethylidene)-3-(dibenzylamino)-alkan-1-ols **11**.

Experimental Section

General. Analytical TLC was conducted in precoated silica gel 60 F-254 on aluminum sheets; compounds were visualized with UV light (254 nm) or iodine. ^{1}H NMR spectra were recorded at 300 or 200 MHz. ^{13}C NMR spectra were recorded at 75 or 50 MHz. Chemical shifts are reported in ppm relative to TMS in $CDCl_3$. MS and HRMS were measured at 70 eV. Only the most significant IR absorptions and the molecular ions and/or base peaks in MS are given. The enantiomeric purity was determined by chiral HPLC analysis using a Chiracel OD-H (0.46 × 25 cm, Diacel) column.

All reagents were purchased from Aldrich or Acros and were used without further purification. Halogenated ketones **1** were prepared according to literature procedures.[8] All the reactions were conducted in oven-dried glassware under dry nitrogen. All solvents were purified before use. THF was distilled from sodium benzophenone ketyl immediately prior to use.

General Procedure for the Preparation of (2*S*,3*S*)-2-Halomethyl-1,2-epoxyalkan-3-amines 3. To a −78 °C stirred solution of the corresponding ketone **1** (5 mmol) and diiodomethane (0.8 mL; 10 mmol) in dry THF (20 mL) was added methyllithium (7 mL of 1.5 M solution in diethyl ether; 10.5 mmol) dropwise over 5 min. After stirring at −78 °C for 30 min, the mixture was allowed to warm to room temperature and stirring was continued for 1 h at room temperature. In the case of bromomethyl ketones, the reaction mixture was slowly allowed to warm to room temperature overnight. The solution was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), and the solvents were removed in vacuo. The crude substituted epihalohydrins **3** were examined by ^{1}H NMR to give the diastereoisomeric excess reported in Table 1. Flash column chromatography on silica gel (20:1 hexane/ethyl acetate) provided pure 2-(1-aminoalkyl)epihalohydrins **3**.

(2*S*,3*S*)-*N*,*N*-Dibenzyl-3-Chloromethyl-3,4-epoxybutan-2-amine (3a) (77% yield): R_f 0.24 (hexane/ethyl acetate 20:1); $[\alpha]^{20}_D = +22.7$ (*c* 0.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 1.00 (d, *J* = 6.9 Hz, 3 H), 2.66−2.70 (m, 2 H), 3.36−3.40 (m, 3 H), 3.47 (q, *J* = 6.9 Hz, 1 H), 4.04 (d, *J* = 13.8 Hz, 2 H), 4.43 (d, *J* = 11.2 Hz, 1 H), 7.29−7.46 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 4.6, 45.7, 47.2, 50.2, 54.2, 60.8, 126.8, 128.1, 128.7, 139.3; IR (NaCl) 3028 cm^{-1}; MS, *m*/*e* 317 (M^+ + 2, 2), 316 (M^+ + 1, 1), 315 (M^+, 6), 224 ($M^+ - C_7H_7$, 100); HRMS calcd for $C_{19}H_{22}ClNO$ 315.1390, found 315.1385. Anal. Calcd for $C_{19}H_{22}ClNO$: C, 73.25; H, 7.02; N, 4.43. Found: C, 73.07; H, 7.08; N, 4.46.

(2*S*,3*S*)-*N*,*N*-Dibenzyl-2-chloromethyl-1,2-epoxy-5-methylhexan-3-amine (3b) (68% yield): R_f 0.54 (hexane/ethyl acetate 10:1); $[\alpha]^{20}_D = -0.5$ (*c* 0.77, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 1.04−1.14 (m, 6 H), 1.26−1.79 (m, 3 H), 2.71 (dd, *J* = 1.1, 4.1 Hz, 1 H), 2.80 (d, *J* = 4.1 Hz, 1 H), 3.28−3.52 (m, 4 H), 4.16 (d, *J* = 13.6 Hz, 2 H), 4.42 (dd, *J* = 1.1, 10.9 Hz, 1 H), 7.37−7.54 (m, 10 H); ^{13}C NMR *δ* (75 MHz, $CDCl_3$) 22.2, 23.4, 26.3, 30.4, 45.6, 48.8, 53.4, 54.7, 60.4, 126.8, 128.1, 128.9, 139.9; IR (NaCl) 3028 cm^{-1}; MS, *m*/*e* 359 (M^+ + 2, 1), 358 (M^+ + 1, < 1), 357 (M^+, 3), 266 ($M^+ - C_7H_7$, 100); HRMS calcd for $C_{22}H_{28}ClNO$ 357.1859, found 357.1855.

(2*S*,3*S*)-*N*,*N*-Dibenzyl-3-chloromethyl-3,4-epoxy-1-phenylbutan-2-amine (3c) (72% yield): R_f 0.50 (hexane/ethyl acetate 10:1); $[\alpha]^{20}_D = -6.8$ (*c* 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 2.58−2.75 (m, 3 H), 3.21 (dd, *J* = 3.4, 15.5 Hz, 1 H), 3.36 (d, *J* = 11.0 Hz, 1 H), 3.51 (d, *J* = 13.5 Hz, 2 H), 3.82 (dd, *J* = 3.4, 9.6 Hz, 1 H), 4.19 (d, *J* = 13.5 Hz, 2 H), 4.40 (d, *J* = 11.0 Hz, 1 H), 7.18−7.44 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 27.1, 46.4, 48.7, 54.7, 55.4, 60.6, 126.0, 127.0, 128.27, 128.32, 128.6, 128.9, 139.4, 140.0; IR (NaCl) 3028 cm^{-1}; MS, *m*/*e* 300 ($M^+ - C_7H_7$, $M^+ - C_3H_4ClO$, 20), 299 ($M^+ - C_3H_5ClO$, 20), 91 (100); chiral HPLC analysis ee > 99% (Chiracel OD-H, UV detector 215 nm, 0.8 mL/min, 200:1 hexane/2-propanol, t_R 13.8 min).

(2*S*,3*S*)-*N*,*N*-Dibenzyl-3-bromomethyl-3,4-epoxybutan-2-amine (3d) (75% yield): R_f 0.51 (10:1); $[\alpha]^{20}_D = +20.8$ (*c* 075, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 0.96 (d, *J* = 6.9 Hz, 3 H), 2.59 (d, *J* = 4.3 Hz, 1 H), 2.70 (dd, *J* = 1.5, 4.3 Hz, 1 H), 3.07 (d, *J* = 9.9 Hz, 1 H), 3.34 (d, *J* = 13.5 Hz, 2 H), 3.53 (q, *J* = 6.9 Hz, 1 H), 4.00 (d, *J* = 13.5 Hz, 2 H), 4.36 (d, *J* = 9.9 Hz, 1 H), 7.26−7.42 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 4.6, 45.7, 47.2, 50.2, 54.2, 60.8, 126.8, 128.1, 128.7, 139.3; IR (KBr) 3028 cm^{-1}; MS, *m*/*e* 361 (M^+ + 2, 10), 359 (M^+, 10), 255 ($M^+ - C_3H_4BrO$, 100); HRMS calcd for $C_{19}H_{22}BrNO$ 359.0885, found 359.0887. Anal. Calcd for $C_{19}H_{22}BrNO$: C, 63.34; H, 6.15; N, 3.89. Found: C, 63.19; H, 6.08; N, 3.85.

(2*S*,3*S*)-*N*,*N*-Dibenzyl-3-bromomethyl-3,4-epoxy-1-phenylbutan-2-amine (3e) (70% yield): R_f 0.51 (hexane/ethyl acetate 10:1); $[\alpha]^{20}_D = -19.1$ (*c* 0.68, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 2.47 (d, *J* = 4 Hz, 1 H), 2.56−2.68 (m, 2 H), 3.04 (d, *J* = 9.8 Hz, 1 H), 3.16 (dd, *J* = 3.2, 15.7 Hz, 1 H), 3.44 (d, *J* = 13.4 Hz, 2 H), 3.81−3.90 (m, 1 H), 4.13 (d, *J* = 13.4 Hz, 2 H), 4.29 (dd, *J* = 1.8, 9.8 Hz, 1 H), 7.17−7.38 (m, 15 H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 27.0, 35.1, 50.1, 54.8, 54.8, 60.8, 126.1, 127.0, 128.3, 128.5, 128.6, 128.8, 139.5, 140.0; IR (KBr) 3028 cm^{-1}; MS, *m*/*e* 300 ($M^+ - C_7H_7$, $M^+ - C_3H_4BrO$, 20), 299 ($M^+ - C_3H_5ClO$, 20), 91 (100). Anal. Calcd for $C_{25}H_{26}BrNO$: C, 68.81; H, 6.00; N, 3.21. Found: C, 68.73; H, 5.97; N, 3.25.

Synthesis of (2*S*,3*R*)-*N*,*N*-Dibenzyl-3-chloromethyl-3,4-epoxybutan-2-amine (4a). The procedure described for the preparation of **3d** was employed, but instead of diiodomethane, chloroiodomethane was used. **4a:** 75% yield; R_f 0.42 (hexane/ethyl acetate 10:1); $[\alpha]^{20}_D = +16.7$ (*c* 0.90, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 0.98 (d, *J* = 6.9 Hz, 3 H), 2.78 (d, *J* = 4.3 Hz, 1 H), 2.99 (d, *J* = 4.3 Hz, 1 H), 3.46 (d, *J* = 13.3 Hz, 2 H), 3.51 (q, *J* = 6.9 Hz, 1 H), 3.59 (d, *J* = 11.6 Hz, 1 H), 3.82 (d, *J* = 13.3 Hz, 2 H), 4.09 (d, *J* = 11.6 Hz, 1 H), 7.23−7.44 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 4.8, 46.9, 49.2, 50.4, 54.5, 59.3, 127.0, 128.3, 128.7, 139.1; IR (NaCl) 3028 cm^{-1}; MS, *m*/*e* 317 (M^+ + 2, 14), 316 (M^+ + 1, 10), 315 (M^+, 42), 224 ($M^+ - C_7H_7$, 100); HRMS calcd for $C_{19}H_{22}ClNO$ 315.1390, found 315.1372.

General Procedure for the Synthesis of Allylic Aminoalcohols 8. Method A. To a −78 °C stirred solution of the corresponding ketone **1b** (5 mmol) and diiodomethane (0.8 mL; 10 mmol) in dry THF (20 mL) was added methyllithium (7 mL of 1.5 M solution in diethyl ether; 10.5 mmol) dropwise over 5 min. After stirring at −78 °C for 30 min, the mixture was allowed to warm to room temperature and stirring was continued for 1 h at room temperature. Then, lithium powder (0.35 g, 50 mmol) was added at −40 °C and the reaction mixture was stirred and slowly allowed to warm to room temperature overnight. The solution was quenched with ice and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), and the solvents were removed in vacuo, yielding crude aminoalcohols **8**, which were purified by flash column chromatography (8:1 hexane/ethyl acetate).

Method B. To a −78 °C stirred solution of the corresponding ketone **1a** (5 mmol) and diiodomethane (0.8 mL; 10 mmol) in dry THF (20 mL) was added methyllithium (7 mL of 1.5 M solution in diethyl ether; 10.5 mmol) dropwise over 5 min. After stirring at −78 °C for 30 min, the reaction mixture was slowly allowed to warm to room temperature overnight. Then, *t*-BuLi (6 mL of 1.7 M solution in pentane; 10.2 mmol) was added at −78 °C, and after stirring at this temperature for 1 h, the reaction mixture was allowed to warm to room temperature. The solution was quenched with H_2O (5 mL) and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), and the solvents were removed in vacuo, yielding crude aminoalcohols **8**, which were purified by column flash chromatography (8:1 hexane/ethyl acetate).

(*S*)-3-Dibenzylamine-2-methylydenebutan-1-ol (8a) (82% yield): R_f 0.34 (hexane/ethyl acetate 5:1); $[\alpha]^{20}_D = +33.1$ (*c* 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, J = 6.7 Hz, 3 H), 3.30 (d, J = 13.1 Hz, 2 H), 3.50 (q, J = 6.7 Hz, 1 H), 3.84 (d, J = 13.1 Hz, 2 H), 4.09 (d, J = 12.8 Hz, 1 H), 5.01 (d, J = 12.8 Hz, 1 H), 5.18 (s, 2 H), 7.21−7.33 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.9, 53.2, 54.9, 67.4, 112.4, 127.1, 128.4, 128.9, 138.8, 148.9; IR (NaCl) 3393, 1651 cm^{-1}; MS, *m/e* 281 (M^+, 5), 224 ($M^+ - C_3H_5O$, 30), 91 (100); HRMS calcd for $C_{19}H_{23}NO$ 281.1780, found 281.1780. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.91; H, 8.18; N, 4.94.

(*S*)-3-Dibenzylamine-5-methyl-2-methylydenehexan-1-ol (8b) (76% yield): R_f 0.46 (hexane/ethyl acetate 5:1); $[\alpha]^{20}_D = +22.1$ (*c* 0.53, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, J = 6.2 Hz, 3 H), 0.96 (d, J = 6.2 Hz, 3 H), 1.48−1.72 (m, 3 H), 3.35 (d, J = 13.3 Hz, 2 H), 3.75 (t, J = 6.6 Hz, 1H), 3.85 (d, J = 13.3 Hz, 2 H), 4.07 (d, J = 12.5 Hz, 1 H), 4.14 (d, J = 12.5 Hz, 1 H), 5.01 (s,1 H), 5.32 (s, 1 H), 7.23−7.36 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 24.1, 25.3, 31.7, 53.1, 58.3, 68.2, 113.2, 127.1, 128.0, 129.1, 139.0, 145.9; IR (NaCl) 3399, 1560 cm^{-1}; MS, *m/e* 323 (M^+, 10), 266 ($M^+ - C_3H_5O$), 100. Anal. Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33. Found: C, 81.51; H, 9.08; N, 4.31.

(*S*)-3-Dibenzylamine-2-methylidene4-phenylbutan-1-ol (8c) (70% yield): R_f 0.55 (hexane/ethyl acetate 3:1); $[\alpha]^{20}_D = +36.1$ (*c* 0.76, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.49 (dd, J = 10.1, 14.3 Hz, 1 H), 3.34 (dd, J = 3.7, 14.3 Hz, 1 H), 3.56 (d, J = 13.3 Hz, 2 H), 3.78 (dd, J = 3.7, 10.1 Hz, 1 H), 4.03 (d, J = 13.3 Hz, 2 H), 4.12 (s, 2 H), 5.22 (s, 1 H), 5.38 (s, 1 H), 7.16−7.43 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.9, 53.4, 61.1, 67.4, 114.0, 125.8; 127.1, 128.2, 128.3, 128.8, 129.0, 138.9, 139.6, 145.7; IR (KBr) 3387, 1603 cm^{-1}; MS, *m/e* 358 ($M^+ + 2$, < 1), 357 (M^+, < 1), 356 ($M^+ - 1$, < 1), 266 ($M^+ - C_7H_7$, 100). Anal. Calcd for $C_{25}H_{27}NO$: C, 83.99; H, 7.61; N, 3.92. Found: C, 83.81; H, 7.66; N, 3.88.

Synthesis of Methyl (*S*)-3-Dibenzylamine-4-phenyl-2-methylenbutanoate (9c). To a 0 °C stirred solution of **8c** (0.54 g, 1.5 mmol) in acetone (10 mL) was added the Jones reagent (3.9 mL of 2.6 M solution of CrO_3 in H_2SO_4; 1.5 mmol); the resulting solution was stirred for 0.5 h, at the same temperature. The reaction mixture was treated with ethanol (5 mL), filtered through a pad of Celite, treated with a saturated aqueous solution of NH_4Cl (5 mL), and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), and the solvents were removed in vacuo, yielding the coreesponding crude amino acid.

Diazomethane (10 mL of a solution in ethyl ether, 3 mmol) was added to a stirred solution of crude amino acid in diethyl ether (10 mL) at 25 °C, and the mixture was stirred for 15 min. Then the reaction mixture was quenched with acetic acid, washed with H_2O, and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), and the solvents were removed in vacuo. Crude amino ester **9c**, was purified by flash column chromatography (15:1 hexane/ethyl acetate) to provide pure amino ester **9c** in 70% yield: R_f 0.57 (hexane/ethyl acetate 10:1); $[\alpha]^{20}_D = +17.5$ (*c* 0.62, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.95 (dd, J = 8.6, 14.2 Hz, 1 H), 3.27 (dd, J = 6.4, 14.2 Hz, 1 H), 3.58−3.76 (m, 7 H), 4.17−4.22 (m, 1 H), 5.62 (s, 1 H), 6.29 (s, 1 H), 7.10−7.31 (m, 15 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.0, 51.7, 54.6, 59.0, 125.8, 125.82, 126.6, 127.9, 128.0, 128.6, 129.0, 139.3, 139.4, 139.6, 168.4; IR (KBr) 1720, 1630 cm^{-1}.

General Procedure for the Synthesis of Halogenated Vinylic Amino Alcohols 11. To a −78 °C stirred solution of the corresponding ketone **1** (5 mmol) and diiodomethane (0.8 mL; 10 mmol) in dry THF (20 mL) was added methyllithium (7 mL of 1.5 M solution in diethyl ether; 10.5 mmol) dropwise over 5 min. After stirring at −78 °C for 30 min, the mixture was allowed to warm to room temperature and stirring was continued for 1 h at room temperature. Then, lithium diisopropylamide [prepared from MeLi (4 mL of 1.5 M solution in diethyl ether, 6 mmol) and diisopropylamine (0.84 mL, 6 mmol) in THF (10 mL)] was added at −78 °C, and the reaction mixture was stirred and slowly allowed to warm to room temperature overnight. The solution was quenched with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), and the solvents were removed in vacuo, yielding crude halogenated amino alcohols **11**, which were purified by flash column chromatography (15:1 hexane/ethyl acetate).

(*S*)-(*Z*)-3-Dibenzylamine-2-chloromethylidenebutan-1-ol (11a) (81% yield): R_f 0.30 (hexane/ethyl acetate 10:1); $[\alpha]^{20}_D = -1.9$ (*c* 0.79, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, J = 7.0 Hz, 3 H), 3.38 (d, J = 13.1 Hz, 2 H), 3.74 (q, J = 7.0 Hz, 1 H), 3.85 (d, J = 13.1 Hz, 2 H), 4.30 (d, J = 14.2 Hz, 1 H), 4.55 (d, J = 14.2 Hz, 1 H), 4.67 (s, 1 H), 6.01 (s, 1 H), 7.27−7.41 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.0, 53.2, 55.1, 61.6, 115.5, 127.4, 128.5, 128.9, 138.0, 142.1; IR (NaCl) 3410, 1630 cm^{-1}. Anal. Calcd for $C_{19}H_{22}ClNO$: C, 73.25; H, 7.02; N, 4.43. Found: C, 73.07; H, 7.09; N, 4.46.

(*S*)-(*Z*)- 3-Dibenzylamine-2-bromomethylidenebutan-1-ol (11b) (78% yield): R_f 0.31 (hexane/ethyl acetate 10:1); $[\alpha]^{20}_D = -6.7$ (*c* 0.30, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (d, J = 6.7 Hz, 3 H), 3.38 (d, J = 13.2 Hz, 2 H), 3.72 (q, J = 6.7 Hz, 1 H), 3.83 (d, J = 13.2 Hz, 2 H), 4.23 (d, J = 14.1 Hz, 1 H), 4.48 (d, J = 14.1 Hz, 1 H), 4.67 (s, 1 H), 6.14 (s, 1 H), 7.27−7.41 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.2, 53.4, 56.1, 64.2, 104.4, 127.5, 128.6, 129.0, 138.0, 145.0; IR (NaCl) 3418, 1620 cm^{-1}. Anal. Calcd for $C_{19}H_{22}BrNO$: C, 63.34; H, 6.15; N, 3.89. Found: C, 63.22; H, 6.10; N, 3.92.

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Supporting Information Available: Supporting Information Available: Copies of the ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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