A Synthesis of Protected Aminoalkyl Epoxides from α-Amino Acids

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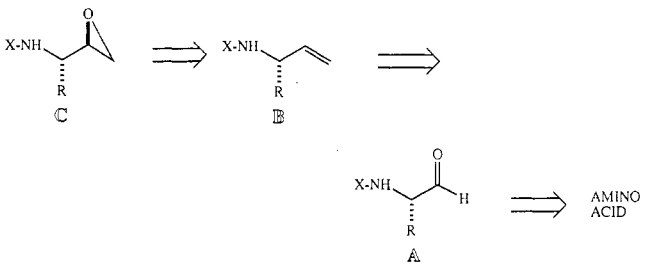
Received September 12, 1986

The synthesis of alkylamino epoxides C is presented. Key steps include the synthesis of amino aldehyde **5** by reduction (DIBAH) of ester **3** or by oxidation of N-protected amino alcohol **4**, both educts of which are derived from amino acids. A study of the olefination of aldehyde **5** with unstabilized ylides is presented, and the protected allylic amine **6**, obtained in good to excellent optical purity, is oxidized (MCPBA) to epoxide C. Threo selectivity is observed in the epoxidation reaction.

The synthesis of chiral compounds in optically pure form represents a major challenge for the organic chemist. In a program directed toward the synthesis of potent antihypertensive agents we required a versatile synthesis of aminoalkyl epoxides C (Scheme I). Retrosynthetic analysis suggested that if a ready source of the corresponding optically pure allylic amine B were available, epoxidation would provide the desired target. Perusal of the literature showed that these allylic amines could be prepared in *d,l* form by rearrangement of trichloroacetimidates derived from allylic alcohols[1] or alternatively in 78–84% enantiomeric excess by oxidative [2,3]-sigmatropic rearrangement of optically active selenides derived from ethyl lactate.[2] To maximize generality and availability of suitable precursors from the chiral pool, we sought a route that started from amino acids.[3] Conversion of a suitably protected amino acid derivative to the corresponding amino aldehyde A followed by Wittig olefination seemed to be a straightforward entry.[4]

The syntheses of α-amino aldehydes by reduction of N-protected amino esters,[5,6] *N*-methylhydroxamates,[7] acylpyrazoles,[8] acid chlorides,[9] acylimidazoles,[10] and mixed carbonic–carboxylic acid anhydrides[11] or by oxidation of N-protected amino alcohols with chromium trioxide/pyridine,[12] sulfur trioxide–pyridine complex,[13] or pyridinium dichromate[14] have been reported. Examples of the Wittig olefination of these optically sensitive[6,10,12] amino aldehydes are far fewer, and the question of racemization in this reaction has not been addressed.[15–17]

Scheme I



Scheme II

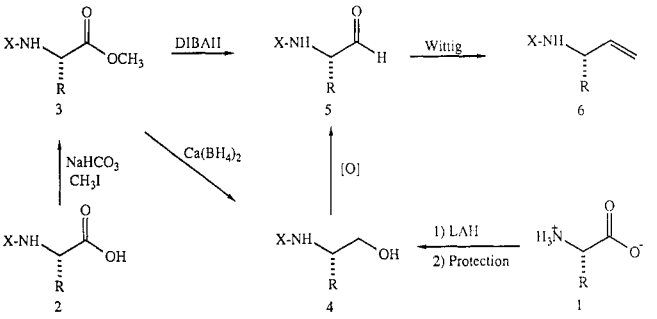


Chart I. Substituent Legend

	X	R
a	Boc	isobutyl
b	Phth	isobutyl
c	Ts	isobutyl
d	Boc	benzyl
e	Boc	cyclohexyl
f	Boc	(cyclohexyl)ethyl
g	Boc	(cyclohexyl)methyl
h	Boc	benzyloxymethyl
i	Boc	2,4,6-(trimethyl)benzyl (*d,l*)
j	Boc	benzhydryl (*d,l*)
k	Boc	(dicyclohexyl)methyl (*d,l*)
l	Cl_3CCO	(1-adamantyl)methyl (*d,l*)

For the process of synthesizing epoxides C to be useful for our immediate interests, not only must it proceed with a high degree of optical integrity but it must also give a preponderance of the 2*R*,3*S* stereochemistry. The nucleophilic C-1 opening of such epoxides yields threo amino alcohols which, when incorporated into the appropriate peptides, are potent inhibitors of the aspartic proteinase renin.[18] This amino alcohol stereochemistry is also the basis of a number of inhibitors derived from or related to the naturally occurring amino acid, statine.[19] Structure–activity work[18,19] has shown that compounds are potent

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Table I. Reaction Conditions for the Preparation of Alkenes 6

entry	product	aldehyde synthesis[a]	Wittig conditions[b]	olefin % yield[c]	optical purity (% ee)
1	**6a**	A	A	15–60	76–96
2	**6b**	B	A	41[d]	
3	**6d**	A	A	<10	
4	**6d**	A	B	65	60
5	**6d**	A	C	<10	
6	**6d**	C	B	36	91
7	**6d**	D	B	45–53	90–93
8	**6e**	C	B	65	94
9	**6f**	C	B	37–58	70–93
10	**6g**	C	B	47–64	72–92
11	**6g**	A	C	37–55	99
12	**6h**	A	C	36–49	99
13	**6a**	A	C	56	99
14	**6i**	C	B	40	
15	**6j**	C	B	51	
16	**6k**	C	B	63	

[a] A = diisobutylaluminum hydride (DIBAH) reduction of ester **3**, B = oxidation of alcohol **4** with CrO_3/Py, C = Swern oxidation of alcohol **4**, D = oxidation of alcohol **4** with SO_3/Py. [b] A = CH_3PPh_3Br + BuLi, THF, −78 to 20 °C; B = CH_3PPh_3Br + KHMDS, THF/Me_2SO, −78 to 40 °C; C = the crude DIBAH reaction mixture was added to the ylide generated by method B. [c] % yield for two steps. [d] From purified aldehyde.

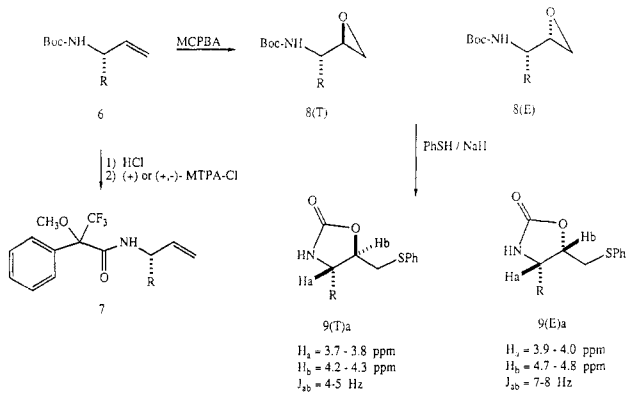
inhibitors when R is a hydrophobic group capable of binding to renin at the site that is normally occupied by the isobutyl side chain of a leucine residue. This site has also been shown to be tolerant of other hydrophobic groups.[18,19] For these reasons we set out to olefinate a series of protected amino acid aldehydes and then to briefly examine the role of protecting group on the stereochemical course of epoxidation.

Results and Discussion

Scheme II outlines the various general synthetic routes used to obtain amino aldehydes **5** with N-protecting group X and side chain R as defined in Chart I. Amino acids **1** were reduced with LAH to the corresponding amino alcohol and then N-protected with either a *tert*-butyloxycarbonyl (Boc) group to give **4d**, **4f**, **4i**, and **4j** or with a phthaloyl (Phth) group to give **4b**. Oxidation of **4** to aldehyde **5** and subsequent olefination to **6** was then performed as discussed below. Alternatively, N-protected amino esters **3** could be converted to aldehydes **5** directly by diisobutylaluminum hydride (DIBAH) reduction or sequentially by first $Ca(BH_4)_2$ reduction to the alcohols **4e** and **4g** followed by oxidation.

Since the isobutyl side chain should serve as a biological benchmark (vide supra), we began our studies with L-leucine. DIBAH reduction of Boc-Leu-OCH_3 (**3a**) and workup provided crude Boc-leucinal **5a**, which was treated directly with the ylide derived from *n*-BuLi and CH_3PPh_3Br to give the desired olefin **6a** in variable yield and optical purity[20] (Table I, entry 1). Changes in reaction time, stoichiometry, counter ion, temperature, and order

Scheme III



of addition failed to elucidate an acceptable solution, but with acceptable quantities of material in hand, we next studied the oxidation step.

As desired, epoxidation of olefin **6a** with 3-chloroperoxybenzoic acid (MCPBA, Scheme III) provided mainly the threo stereochemistry,[21] but as seen in Table II (entries 1–3), the *tert*-butyloxycarbonyl-protected material gave superior ratios compared to either the corresponding tosyl or the phthalimido compound. Definitive stereochemical assignment was carried out by epoxide opening of **8(T)** and **8(E)** mixtures with mercaptide ion followed by cyclization to the corresponding 2-oxazolidinones **9(T)** and **9(E)** as shown in Scheme III. The chemical shifts and coupling constants of the ring hydrogens are consistent with ample literature precedent.[22]

Phenylalanine represents a difficult test for our olefination methodology since the high propensity for its N-protected aldehyde to racemize has been carefully documented.[12] Under the same reaction conditions used for leucine (Table I, entry 1), the corresponding phenylalanine derivative yielded almost no detectable product (entry 3). Changing to salt-free ylide conditions (entry 4) resulted in a high chemical yield but severe loss of optical integrity. A one-pot version of this DIBAH reduction/ylide reaction was then tried (entry 5) because, as will be shown below, this method has always given fair yields and undetectable amounts of racemization in our hands.[23] Unexpectedly, this modification did not work for phenylalanine. Success was finally achieved when the Swern oxidation[24] or the Py/SO_3 oxidation[13] was employed (entries 6 and 7). Aromatic *d,l* amino acids were used to prepare olefins **6i–k** (entries 14–16) which, although were not a test for racemization, serve to broaden the scope of the sequence.

These methods could also be extended to the synthesis of aliphatic olefins **6e–g** (entries 8–10), although as entries 9 and 10 show, this process is not without variability in optical purity. However, the preparation of olefin **6g** by a one-pot DIBAH reduction of **3g** and salt-free Wittig olefination consistently provided olefin **6g** with no detectable racemization (entry 11). This method was readily

(19) For example: (a) Boger, J.; Lohr, N. S.; Ulm, E. H.; Poe, M.; Blaine, E. H.; Fanelli, G. M.; Lin, T.-Y.; Payne, L. S.; Schorn, T. W.; LaMont, B. I.; Vassil, T. C.; Stabilito, I. I.; Veber, D. F.; Rich, D. H.; Bopari, A. S. *Nature (London)* **1983**, 303, 81. (b) Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Boger, J. S.; Freidinger, R. M.; Veber, D. F. *J. Chem. Soc., Chem. Commun.* **1985**, 109. (c) Boger, J.; Payne, L. S.; Perlow, D. S.; Poe, M.; Blaine, E. H.; Ulm, E. H.; Schorn, T. W.; LaMont, B. I.; Bock, M. G.; DiPardo, R. M.; Lim, T.-Y.; Kawai, M.; Rich, D. H.; Veber, D. F. Abstracts of the Ninth American Peptide Symposium, Toronto, Ontario, Canada; June 23–28, 1985, p 112.

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(21) This threo preference has been seen in related examples: (a) CBz-Vinylglycine-OCH_3: Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515. (b) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1587. (c) Narula, A. S. *Tetrahedron Lett.* **1983**, *24*, 5421.

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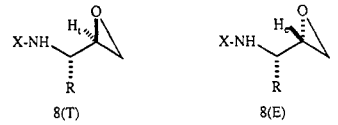
(23) Although this one-pot sequence has never been reported for the olefination of N-protected amino aldehydes or substrates prone to racemization, an example does exist in the literature: Boland, W.; Ney, P.; Jaenicki, L. *Synthesis* **1980**, 1015.

(24) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

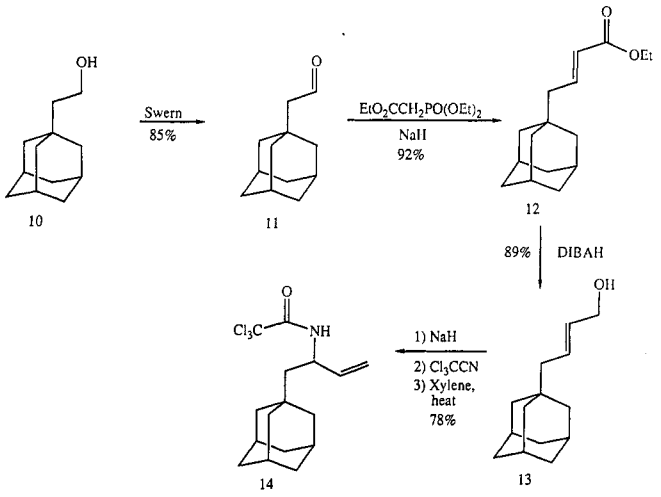
Table II. Epoxide Data



entry	epoxide	% yield	H_t (ppm)[a]	H_e (ppm)[a]	8(t):8(e)[b]
1	**8a**	62	2.99	2.84	15:1
2	**8b**	58	3.59	3.52	4:1
3	**8c**	69	2.94	2.76	3:1
4	**8d**	77–86	3.02	obscured	13:1[c]
5	**8e**	63	3.08	2.87	>10:1
6	**8f**	52	3.01	2.85	13:1
7	**8g**	60–72	2.97	2.84	15:1
8	**8l**	68	3.03	2.92	5:1

[a] Refers to center of multiplet. [b] Determined from integrated H_t:H_e from expanded 300-MHz spectra unless otherwise noted. [c] Based on relative integration of *threo*-NC*H* (4.14 ppm) and *erythro*- NC*H* (3.7 ppm).[4]

Scheme IV



extended to the preparation of **6h** ((benzyloxy)methyl side chain, entry 12) and leucine derivative **6a** (entry 13) without racemization.

In principle, one of the above amino acid based approaches could be employed to synthesize an olefin with the (1-adamantyl)methyl side chain. A multistep synthesis of the requisite (*S*)-(+)-2-amino-3-(1-adamantyl)propionic acid (**1l**) has been reported,[25] but due to its length we felt that a route directly to olefin **6l**, even in *d,l* form, should be explored. Such a synthesis was carried out in a straightforward manner as shown in Scheme IV. Commercially available 1-adamantaneethanol (**10**) was oxidized to the corresponding aldehyde **11** and then treated with sodio triethyl phosphonoacetate to give α,β-unsaturated ester **12**. DIBAH reduction to allylic alcohol **13** followed by generation and rearrangement of the corresponding trichloroacetimidate[1] provided protected allylic amine **14** in good overall yield.

Analysis of Table II reveals the strong threo stereochemical preference in the epoxidation reaction as well as the superiority of the Boc group over other types of protection (entries 2, 3, and 8). Further exploration of this chemistry and the conversion of the compounds reported here into antihypertensive renin inhibitors will be reported subsequently.

Experimental Section

Materials. All amino acids and protected amino acids were obtained from Sigma Chemical Company unless otherwise noted. (+)-2-Amino-4-phenylbutyric acid was obtained from Chemical Dynamics Corporation, South Plainfield, NJ.[26] Amino alcohol **4b**[27] and amino acids **1i** and **1j**[28] were synthesized according to literature procedures. Amino acid esters **3d** and **3g** were prepared from Boc-phenylalanine by a literature procedure[29] that was extended to the preparation of **3e** from Boc-phenylglycine. Anhydrous solvents and reagents used were dried and freshly distilled. Phosphonium salts were vacuum dried prior to use, and all reactions unless otherwise noted were run in oven-dried glassware under an atmosphere of dry nitrogen or argon.

Apparatus. Proton magnetic resonance spectra were measured on a Nicolet QE-300 (300 MHz) or Varian EM-360 (60 MHz) spectrometer. Chemical shifts are reported as δ values (parts per million) relative to Me_4Si as an internal standard and were measured at 300 MHz unless otherwise indicated. Mass spectra were obtained with Hewlett Packard HP5985 (CI, EI), Varian CH7 (EI), and Kratos MS50 (FAB, HRMS) spectrometers. Elemental analyses and the above determinations were performed by the Analytical Research Department, Abbott Laboratories. Thin-layer chromatography (TLC) was carried out by using E. Merck precoated silica gel F-254 plates (thickness, 0.25 mm). GLC analyses were carried out on a Varian Model 3700 instrument equipped with an Alltech silica gel heliflex capillary column (30 m × 0.25 mm, RSL-150). HPLC analyses were carried out with a Waters Model 680 automated gradient controller, Model 510 pumps, Model 441 absorbance detector, and C_{18} Bondapak column. Flash column chromatography[30] was carried out using Baker silica gel (40 μm).

(*S*)-2-Amino-4-cyclohexylbutyric Acid (1f) Hydrochloride. A solution of (+)-2-amino-4-phenylbutyric acid (5.0 g, 27.9 mmol) in 2 M HCl (150 mL) was hydrogenated (50 psi) over Pt black (0.25 g) for 16 h. Filtration and evaporation provided 5.2 g (84%) of **1f** hydrochloride: ^{1}H NMR (CD_3OD) δ 0.95 (m, 2 H), 1.15–1.4 (br m, 6 H), 1.6–1.8 (br m, 5 H), 1.91 (m, 2 H), 3.93 (dd, 1 H, *J* = 6, 6 Hz); mass spectrum, *m/e* $(M - Cl)^+$ 186. Anal. Calcd for $C_{10}H_{20}NO_2Cl \cdot {}^1/_3H_2O$: C, 52.7; H, 9.1; N, 6.2. Found: C, 52.7; H, 9.2; N, 6.2.

L-Boc-(Bn)Ser-OCH$_3$ (3h). To a stirred solution of Boc-(Bn)Ser-OH (2.00 g, 6.77 mmol) in dry DMF (30 mL) were added $NaHCO_3$ (1.71 g, 20.3 mmol) and CH_3I (1.06 g, 7.45 mmol) sequentially. After 5 days the mixture was filtered and concentrated in vacuo. The residue was partitioned between ethyl acetate and water, and the organic phase was then washed sequentially with 5% $Na_2S_2O_5$, 1 M $NaHCO_3$, and brine. Drying and evaporating provided 1.76 g (84%) of **3h**: ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 3.68 (dd, 1 H, *J* = 3, 10 Hz), 3.74 (s, 3 H), 3.87 (dd, 1 H, *J* = 3,

(25) Do, K. Q.; Thanei, P.; Caviezel, M.; Schwyzer, R. *Helv. Chim. Acta* **1979**, *62*, 956.

(26) The absolute stereochemistry of (+)-2-amino-4-phenylbutyric acid has been carefully determined: Weller, H. N.; Gordon, E. M. *J. Org. Chem.* **1982**, *47*, 4160.

(27) Meyers, A. I.; Poindexter, G. S.; Brich, Z. *J. Org. Chem.* **1978**, *43*, 892.

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(29) Boger, J.; Payne, L. S.; Perlow, D. S.; Lohr, N. S.; Poe, M.; Blaine, E. H.; Ulm, E. H.; Schorn, T. W.; LaMont, B. I.; Lin, T.-Y.; Kawai, M.; Rich, D. H.; Veber, D. F. *J. Med. Chem.* **1985**, *28*, 1779.

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

10 Hz), 4.43 (masked m, 1 H), 4.48 (d, 1 H, J = 13 Hz), 4.54 (d, 1 H, J = 13 Hz), 5.41 (br d, 1 H), 7.3 (m, 5 H); mass spectrum, m/e M^+ 309. Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.1; H, 7.5; N, 4.5. Found: C, 61.9; H, 7.4; N, 4.5.

Protected Amino Alcohols 4. Method A. To a stirred suspension of LAH (188 mmol) in dry THF (500 mL) was added the amino acid (or amino acid hydrochloride), at a rate that maintained a gentle reflux. After heating at reflux for 6 h, the mixture was cooled and KOH (0.96 g in 8.6 mL of H_2O) was added. Water (12 mL) was added 5 min later, and the mixture was heated to reflux, filtered through Celite, and evaporated. The Celite was extracted with several portions of dichloromethane and combined with the organic residue. Drying (Na_2SO_4), filtering, and evaporating provided the corresponding amino alcohol (74–93% yield) which was N-protected without further purification.

(1) N-*t*-Boc Protection. To a stirred solution of the amino alcohol (0.15 mol) in chloroform (225 mL) was added di-*tert*-butyl dicarbonate (0.15 mol). After 4 h the solvent was evaporated to give a residue that was redissolved in ether. The organic phase was washed sequentially with 0.5 M H_3PO_4, brine, 1 M $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and evaporated to give the N-*t*-Boc-protected amino alcohol 4 (X = *t*-Boc) in 87–94% yield.

(*S*)-2-(*t*-Boc-amino)-3-phenylpropan-1-ol (4d): ^1H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 2.84 (d, 2 H, J = 7 Hz), 3.55 (dd, 1 H, J = 5.5, 12.0 Hz), 3.67 (dd, 1 H, J = 3.5, 12.0 Hz), 3.87 (br s, 1 H), 4.75 (br d, J = 7.5 Hz, 1 H), 7.2–7.35 (m, 5 H); mass spectrum, m/e 251 (M^+), 220, 195, 178. Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.9; H, 8.4; N, 5.6. Found: C, 67.2; H, 8.5; N, 5.5.

(*S*)-2-(*t*-Boc-amino)-4-cyclohexylbutan-1-ol (4f): ^1H NMR ($CDCl_3$) δ 0.8–1.8 (several m, 15 H), 1.46 (s, 9 H), 2.5 (br, 1 H), 3.5–3.7 (br m, 4 H), 4.6 (br, 1 H); mass spectrum, m/e $(M + H)^+$ 272. Anal. Calcd for $C_{15}H_{29}NO_3$: C, 66.4; H, 10.8; N, 5.2. Found: C, 66.4; H, 10.8; N, 5.1.

(*R,S*)-2-(*t*-Boc-amino)-3-(2,4,6-trimethylphenyl)propan-1-ol (4i): ^1H NMR ($CDCl_3$) δ 1.40 (br s, 9 H), 2.24 (s, 3 H), 2.33 (s, 6 H), 2.85 (m, 2 H), 3.46 (m, 1 H), 3.66 (m, 1 H), 3.83 (m, 1 H), 4.8 (br, 1 H), 6.83 (br s, 2 H); mass spectrum, m/e M^+ 293. Anal. Calcd for $C_{12}H_{27}NO_3$: C, 69.6; H, 9.3; N, 4.8. Found: C, 69.6; H, 9.4; N, 4.7.

(*R,S*)-2-(*t*-Boc-amino)-3,3-diphenylpropan-1-ol (4j): ^1H NMR ($CDCl_3$) δ 1.34 (s, 9 H), 2.3 (br, 1 H), 3.47 (m, 1 H), 3.67 (m, 1 H), 4.17 (d, 1 H, J = 11 Hz), 4.47 (m, 1 H), 4.65 (d, 1 H, J = 9 Hz), 7.18 (m, 2 H), 7.3 (m, 8 H); mass spectrum, m/e M^+ 327, $(M - OC_4H_9)^+$ 254. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.4; H, 7.7; N, 4.3. Found: C, 73.4; H, 8.1; N, 4.1.

(2) N-Phthaloyl Protection. L-Leucinol was treated with phthalic anhydride according to a literature procedure to give **4b**.[27]

Method B. To a stirred −5 °C solution of the Boc-protected amino ester **3** (82 mmol) in ethanol (160 mL) was added a suspension of $CaCl_2$ (164 mmol) in tetrahydrofuran (100 mL) followed by $NaBH_4$ (328 mmol). After 5 h, the mixture was carefully poured into excess 1 M citric acid/ice. The mixture was extracted exhaustively with ethyl acetate, and the combined extracts were washed sequentially with saturated aqueous $NaHCO_3$ and brine. Drying, filtering, and evaporating gave the *N-t*-Boc-amino alcohol 4 in 70–94% yield.

(*S*)-2-(*t*-Boc-amino)-3-cyclohexylpropan-1-ol (4g): ^1H NMR ($CDCl_3$) δ 0.8–1.03 (m, 2 H), 1.1–1.35 (m, 5 H), 1.46 (s, 9 H), 1.6–1.85 (m, 6 H), 2.57 (br s, 1 H), 3.48 (dd, J = 11.0, 6.0 Hz, 1 H), 3.66 (br d, J = 11 Hz, 1 H), 3.75 (br s, 1 H), 4.57 (br d, J = 6 Hz, NH); mass spectrum, m/e M^+ 257. Anal. Calcd for $C_{13}H_{27}NO_3$: C, 64.2; H, 10.6; N, 5.4. Found: C, 64.6; H, 10.5; N, 5.7.

(*S*)-2-(*t*-Boc-amino)-2-cyclohexylethan-1-ol (4e): mp 76–79 °C; ^1H NMR ($CDCl_3$) δ 0.95–1.35 (br m, 5 H), 1.44 (s, 9 H), 1.6–1.8 (br m, 6 H), 2.38 (br, 1 H), 3.43 (br, 1 H), 3.56–3.75 (2 m, 2 H), 4.68 (br d, 1 H); mass spectrum, m/e M^+ 213, $(M - C_4H_9)^+$ 156, $(M - Boc)^+$ 112. Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.2; H, 10.4; N, 5.8. Found: C, 64.4; H, 10.4; N, 5.7.

(*R,S*)-2-(*t*-Boc-amino)-3,3-dicyclohexylpropan-1-ol (4k). A solution of **4j** (6.00 g, 18.3 mmol) in acetic acid (200 mL) was hydrogenated (4 atm) over Pt black (1.8 g) for 48 h. Filtration, evaporation, silica gel chromatography (97/3, dichloromethane/methanol), and recrystallization (ether/hexane) provided 5.10 g (82%) of **4k**: ^1H NMR ($CDCl_3$) δ 1.05–1.8 (several m, 23 H), 1.46 (s, 9 H), 2.48 (br, 1 H), 3.55–3.75 (m, 2 H), 3.86 (m, 1 H), 4.63 (br d, 1 H, J = 8 Hz); mass spectrum, m/e $(M + H)^+$ 340. Anal. Calcd for $C_{20}H_{37}NO_3 \cdot {}^1/_4H_2O$: C, 69.8; H, 11.0; N, 4.1. Found: C, 70.1; H, 10.8; N, 3.7.

Protected Amino Aldehydes 5. Method A. To a −78 °C stirred solution of the corresponding protected amino ester **3** (30.8 mmol) in dry toluene (85 mL) was added diisobutylaluminum hydride (43.8 g of a 25 wt % solution in toluene, 76 mmol) dropwise over 30 min. Methanol (3.3 mL) was cautiously added 30 min later, and the mixture was poured into a 0 °C stirred solution of Rochelle salt (33 mL of saturated aqueous solution diluted with 200 mL of H_2O). After being stirred for 60 min at 0 °C, the mixture was filtered through Celite, and the solids were extracted with ether (5 × 100 mL). The aqueous phase was extracted with ether (2 × 100 mL), and the combined organic phase was dried (Na_2SO_4, 0 °C), filtered, and concentrated in vacuo (T < 35 °C) to give aldehyde **5**, which was immediately used in the next step without further purification.

Method B. L-Phth-Leu-H (5b). To a mechanically stirred (0 °C, internal temperature) solution of dry pyridine (36.2 g, 0.459 mol) in dichloromethane (500 mL) was added CrO_3 (22.9 g, 0.229 mol) portionwise at a rate to keep the internal temperature below 5 °C. Celite (23 g) was then added as the temperature was lowered to −11 °C. *N*-(Phthaloyl)leucinol[27] (5.69 g, 23.0 mmol) in dichloromethane (25 mL) was added over the course of 3 min. The dichloromethane layer was carefully decanted after 30 min, and the residue was extracted with dichloromethane (2 × 60 mL). The combined organic phase was concentrated in vacuo (T < 30 °C), and the residue was extracted with ether (2 × 60 mL). Filtration through Celite and concentration in vacuo provided an oil that was chromatographed on silica gel (3/1, hexane/ether) to give 1.99 g (35%) of aldehyde **5b**, which was immediately used in the next step: ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, J = 7 Hz), 0.99 (d, 3 H, J = 7 Hz), 1.58 (m, 1 H), 1.97 (m, 1 H), 2.17 (m, 1 H), 4.78 (dd, 1 H, J = 5, 12 Hz), 7.77 (m, 2 H), 7.89 (m, 2 H), 9.68 (s, 1 H).

Method C. Ethanol-free $CHCl_3$ may be substituted for CH_2Cl_2 in the following procedure. Oxalyl chloride (7.89 g, 62.16 mmol) was dissolved in dry CH_2Cl_2 (50 mL, ~1.25 M) under N_2, flushed with N_2, and cooled to −63 °C ($CHCl_3$/dry ice, do not go below this temperature to prevent precipitation). Dry Me_2SO (6.48 g, 82.88 mmol, 2.0 equiv) was added in CH_2Cl_2 (25 mL, ~2.50 M) in a dropwise fashion over 15 min. The alcohol (41.44 mmol, 1.0 equiv) in CH_2Cl_2 (300 mL) was then added over 10 min. After stirring the resulting slightly cloudy solution for 10 min at −63 °C, Et_3N (23.1 mL, 165.8 mmol, 4.0 equiv) was added in a dropwise fashion in CH_2Cl_2 (50 mL) over 15 min. TLC after complete addition of Et_3N indicated the reaction to be ca. 90–95% complete. The reaction was quenched 15 min later by adding water (1.5 mL/mmol alcohol) to the rapidly stirred −63 °C reaction solution. The resulting slurry was immediately poured into hexanes (500 mL) and washed with 200 mL of 20% saturated aqueous $KHSO_4$ (prepared by diluting saturated aqueous $KHSO_4$ 5:1 with water). The layers were separated and the aqueous layer was back-extracted with ether (500 mL). The combined organic layers were washed (2 × 200 mL, saturated aqueous $NaHCO_3$; 3 × 200 mL, H_2O; 2 × 200 mL, brine), dried ($MgSO_4$ or Na_2SO_4), filtered, and concentrated in vacuo (bath temperature <35 °C) to provide essentially a quantitative mass recovery (100–105% unpurified). For best results the aldehyde should be used immediately without purification.

Method D. L-*t*-Boc-Phe-H (5d). A dichloromethane/dimethyl sulfoxide (1/1, v/v) solution (38 mL, anhydrous) of Py·SO_3 (2.43 g, 24 mmol) was added in a dropwise fashion to a rapidly stirred 0 °C solution of *N-t*-Boc-phenylalaninol (2.01 g, 8.0 mmol) and triethylamine (3.35 mL, 24 mmol) in the same solvent system (13 mL). The ice bath was removed after complete addition of the Py·SO_3 solution. The reaction was judged complete after 30 min and was quenched by pouring into ice/water (1/1, v/v, 250 mL). The resulting slurry was extracted with ether (3 × 300 mL), and the combined layers were washed (2 × 200 mL of citric acid, 2 × 200 mL of H_2O, 200 mL of saturated $NaHCO_3$), dried, filtered, and concentrated in vacuo (T < 35 °C) to provide aldehyde **5d** (1.49 g, 75%) as a colorless solid. The crude aldehyde is best carried on immediately without further purification.

Protected Allylic Amines 6. Wittig Olefination. Method A. To a stirred −78 °C suspension of methyltriphenyl-

phosphonium bromide (10.97 g, 30.70 mmol) in dry THF (200 mL) under argon was added *n*-BuLi (19.8 mL of a 1.55 M solution in hexane) over the course of 5 min. The mixture was warmed to room temperature for 30 min. The solution was then cooled to −78 °C and added to a stirred −78 °C solution of aldehyde **5** (15 mmol) in THF (30 mL) over the course of 30 min. The mixture was then warmed to room temperature for 3 h, quenched with water (150 mL), and extracted with hexane (4 × 100 mL). The combined organic phase was washed with brine (100 mL), dried (Na_2SO_4), filtered, evaporated, and chromatographed on silica gel (9/1 hexane/ether) to give olefin **6**.

(*S*)-3-(*t*-Boc-amino)-5-methylhex-1-ene (6a): ^{1}H NMR ($CDCl_3$) δ 0.92 (2 d, 3 H each), 1.3–1.5 (2 m, 1 H each), 1.45 (s, 9 H), 1.66 (s, 1 H), 4.13 (br, 1 H), 4.38 (br, 1 H), 5.06 (d, 1 H, *J* = 10 Hz), 5.16 (d, 1 H, *J* = 17 Hz), 5.72 (m, 1 H); mass spectrum, *m/e* $(M + H)^+$ 214. Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.6; H, 10.9; N, 6.6. Found: C, 67.8; H, 10.9; N, 6.5.

(*S*)-5-Methyl-3-(phthaloylamino)hex-1-ene (6b): ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3 H, *J* = 7 Hz), 0.95 (d, 3 H, *J* = 7 Hz), 1.5 (m, 1 H), 1.68 (m, 1 H), 2.09 (m, 1 H), 4.85 (m, 1 H), 5.17 (d, 1 H, *J* = 10 Hz), 5.23 (d, 1 H, *J* = 17 Hz), 6.20 (m, 1 H), 7.71 (m, 2 H), 7.83 (m, 1 H); mass spectrum, *m/e* M^+ 243; exact mass calcd for $C_{15}H_{17}NO_2$ M^+ 243.1259, found 243.1240; exact mass calcd for $C_{11}H_8NO_2$ $(M - C_4H_9)^{\cdot+}$, 186.0555, found 186.0540.

Method B. To a potassium hydride (35% dispersion in oil, 32.09 g) suspension in a 0 °C mixture of anhydrous THF/Me_2SO (1000 mL/200 mL) under dry N_2 was added 1,1,1,3,3,3-hexamethyldisilazane (2.09 equiv, 47.20 g, distilled) dropwise. After stirring at 0 °C for 1 h, the resulting solution was added via cannula to a 0 °C flask containing methyltriphenylphosphonium bromide (2.10 equiv). The mixture was stirred vigorously for 1 h, at which time it was cooled to −78 °C. A −78 °C THF solution of the aldehyde prepared above was then added via cannula. After being stirred at −78 °C for 15 min, the mixture was allowed to slowly warm to room temperature and then heated to 40 °C for 12 h. The mixture was then cooled to room temperature and quenched with methanol (7.66 mL), followed by aqueous Rochelle salts (100 mL of saturated solution and 500 mL of H_2O). The mixture was then extracted with ethyl acetate (2×). The combined extracts were washed with water and brine. Drying ($MgSO_4$) and evaporating provided a crude alkene, which was chromatographed on silica gel (ether/hexane) to give alkene **6**.

(*S*)-2-(*t*-Boc-amino)-1-phenylbut-3-ene (6d): ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 2.84 (br d, 2 H, *J* = 6.9 Hz), 4.42 (br s, 1 H), 5.12 (ddd, 1 H, *J* = 16.2, 0.9, 0.9 Hz), 5.17 (ddd, 1 H, *J* = 9.6, 1.0, 1.0 Hz), 5.8 (ddd, 1 H, *J* = 4.8, 9.6, 16.2 Hz), 7.15–7.33 (m, 5 H); mass spectrum, *m/e* M^+ 247. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.8; H, 8.6; N, 5.7. Found: C, 72.4; H, 8.4; N, 5.5.

(*S*)-1-(*t*-Boc-amino)-1-cyclohexylprop-2-ene (6e): ^{1}H NMR ($CDCl_3$) δ 0.85–1.8 (several m, 11 H), 1.43 (s, 9 H), 3.97 (br, 1 H), 4.52 (br, 1 H), 5.07–5.17 (2 m, 1 H each), 5.73 (m, 1 H); mass spectrum, *m/e* M^+ 239, $(M - C_4H_8)^+$ 183. Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.2; H, 10.5; N, 5.8. Found: C, 70.1; H, 10.6; N, 5.7.

(*S*)-3-(*t*-Boc-amino)-1-cyclohexylpent-4-ene (6f): ^{1}H NMR ($CDCl_3$) δ 0.8–1.75 (several m, 15 H), 1.45 (s, 9 H), 4.03 (br, 1 H), 4.42 (br, 1 H), 5.05–5.17 (2 m, 1 H each), 5.74 (m, 1 H); mass spectrum, *m/e* M^+ 267. Anal. Calcd for $C_{16}H_{29}NO_2 \cdot {}^3/_4H_2O$: C, 68.4; H, 10.9; N, 5.0. Found: C, 68.2; H, 10.8; N, 4.9.

(*S*)-2-(*t*-Boc-amino)-1-cyclohexylbut-3-ene (6g): ^{1}H NMR ($CDCl_3$) δ 0.8–1.19 (m, 13 H), 1.45 (s, 9 H), 4.18 (br s, 1 H), 4.37 (br s, 1 H), 5.07 (ddd, 1 H, *J* = 9.6, 2.1, 2.1 Hz), 5.13 (ddd, 1 H, *J* = 17.5, 1.5, 1.5 Hz), 5.73 (ddd, 1 H, *J* = 6.0, 9.6, 17.5 Hz); mass spectrum, *m/e* 254 $(M + H)^+$ 197. Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.1; H, 10.7; N, 5.5. Found: C, 70.7; H, 10.9; N, 5.4.

(*R,S*)-2-(*t*-Boc-amino)-1-(2,4,6-trimethylphenyl)but-3-ene (6i): ^{1}H NMR ($CDCl_3$) δ 1.39 (br s, 9 H), 2.24 (s, 3 H), 2.32 (s, 6 H), 2.73, 2.77 (2 d, 3:5 rotamer population, 1 H total, *J* = 8, 8 Hz), 2.9 (m, 1 H), 4.38 (br, 1 H), 4.54 (br, 1 H), 5.03 (br d, 1 H, *J* = 11 Hz), 5.1 (br d, 1 H, *J* = 17 Hz), 5.77 (m, 1 H), 6.83 (s, 2 H).

(*R,S*)-2-(*t*-Boc-amino)-1,1-diphenylbut-3-ene (6j): ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9 H), 3.97 (d, 1 H, *J* = 9 Hz), 4.4 (br, 1 H), 5.0 (br, 1 H), 5.05 (br d, 1 H, *J* = 13 Hz), 5.13 (br d, 1 H, *J* = 17 Hz), 5.77 (m, 1 H), 7.15–7.3 (m, 10 H); mass spectrum, *m/e* M^+ 323. Anal. Calcd for $C_{21}H_{25}NO_2$: C, 78.0; H, 7.8; N, 4.3. Found: C, 78.3; H, 7.8; N, 4.2.

(*R,S*)-2-(*t*-Boc-amino)-1,1-dicyclohexylbut-3-ene (6k): ^{1}H NMR ($CDCl_3$) δ 1.0–1.8 (br m, 23 H), 1.43 (s, 9 H), 4.36 (br, 1 H), 4.54 (br, 1 H), 5.06 (d, 1 H, *J* = 11 Hz), 5.13 (d, 1 H, *J* = 17 Hz), 5.78 (m, 1 H); mass spectrum, *m/e* $(M - C_4H_8)^+$ 279. Anal. Calcd for $C_{21}H_{37}NO_2$: C, 75.2; H, 11.1; N, 4.2. Found: C, 75.1; H, 11.2; N, 4.0.

Method C. To a stirred −78 °C solution of methyl ester **3** (140 mmol) in anhydrous toluene (250 mL) was added diisobutylaluminum hydride (1.30 equiv, 1.5 M solution in toluene, 121.4 mL) at a rate to keep the internal temperature below −60 °C. After being stirred for an additional 20 min at −78 °C (TLC should show no ester **3**), the aldehyde solution was used immediately as described in procedure B above.

(*R*)-1-(Benzyloxy)-2-(*t*-Boc-amino)but-3-ene (6h): ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 3.53 (m, 2 H), 4.32 (br, 1 H), 4.52 (d, 1 H, *J* = 11 Hz), 4.56 (d, 1 H, *J* = 11 Hz), 4.9 (br, 1 H), 5.18 (d, 1 H, *J* = 8.7 Hz), 5.25 (d, 1 H, *J* = 14 Hz), 5.86 (m, 1 H); mass spectrum, *m/e* $(M + H)^+$ 278; exact mass calcd for $C_{16}H_{24}NO_3$ $(M + H)^+$ 278.1756, found 278.1744.

(*S*)-2-(*t*-Boc-amino)-1-cyclohexylbut-3-ene (6g): identical with material prepared by method B above, except 99% ee.

(*S*)-3-(Toluenesulfonylamino)-5-methylhex-1-ene (6c). To a stirred solution of **6a** (2.98 g, 14.0 mmol) in methanol (10 mL) was added anhydrous 2 M HCl/methanol (90 mL). Evaporation after 18 h provided the amine hydrochloride which was partitioned between water (65 mL)/ethyl acetate (30 mL) and treated sequentially with Na_2CO_3 (9.90 g, 84.0 mmol) and tosyl chloride (3.06 g, 16.08 mmol) for 24 h. The organic phase was washed with brine, dried, and evaporated to an oil that crystallized upon addition of hexane. Filtration provided 2.71 g (72%) of **6c**: mp 76–78 °C; ^{1}H NMR ($CDCl_3$) δ 0.80 (d, 3 H, *J* = 6 Hz), 0.83 (d, 3 H, *J* = 6 Hz), 1.31 (m, 2 H), 1.61 (m, 1 H), 2.42 (s, 3 H), 3.81 (m, 1 H), 4.46 (d, 1 H, *J* = 8 Hz), 4.93 (d, 1 H, *J* = 10 Hz), 4.98 (d, 1 H, *J* = 17 Hz), 5.5 (m, 1 H), 7.28 (d, 2 H, *J* = 9 Hz), 7.74 (d, 2 H, *J* = 9 Hz); mass spectrum, *m/e* (M + 1) 268, $(M - C_4H_9)^+$ 210. Anal. Calcd for $C_{14}H_{21}NO_2S$: C, 62.9; H, 7.9; N, 5.2. Found: C, 62.9; H, 7.9; N, 4.9.

Procedure for Determining Enantiomeric Purity. Preparation and Separation of Diastereomers 7 of Allylic Amines. The Boc-protected amine **6** was treated with excess anhydrous 4 M HCl/CH_3OH (6 h) or 4 M HCl/dioxane (1 h). Evaporation provided the amine hydrochloride which was dissolved in dichloromethane and treated with triethylamine (2.50 equiv) followed by Mosher's acid chloride[20] (1.10 equiv, (+) or (−)). The organic phase was washed with 1 M H_3PO_4 and saturated $NaHCO_3$. Drying and evaporating gave the product, which was analyzed by ^{1}H NMR, HPLC, and or capillary GC and compared to a sample doped with the minor diastereomer.

Epoxides 8. To a stirred solution of the corresponding alkene **6** (1.0 mmol) in dichloromethane (10–20 mL) was added 3-chloroperoxybenzoic acid (4.0 mmol). When the reaction was complete by TLC analysis, the mixture was diluted with ether, washed sequentially with 0 °C 10% Na_2SO_3, saturated $NaHCO_3$, and brine. Drying and evaporating provided the epoxides **8**, which were examined by ^{1}H NMR to give the threo:erythro data reported in Table II.

(1*R,S*)-[1′*S*-(Boc-amino)-3-methylbutyl]oxirane (8a): mass spectrum, $(M - C_3H_7)^+$ 186, $(M - C_4H_9)$ 172; ^{1}H NMR ($CDCl_3$) analysis of mixture: threo 0.96 (d, 6 H, *J* = 6 Hz), 1.44 (s, 9 H), 1.3–1.8 (br m, 3 H), 2.6 (m, 1 H), 2.73 (dd, 1 H, *J* = 4, 4 Hz), 2.99 (m, 1 H), 3.98 (m, 1 H), 4.33 (m, 1 H). Anal. Calcd for $C_{12}H_{23}NO_3 \cdot {}^1/_3H_2O$: C, 61.2; H, 10.1; N, 6.0. Found: C, 61.0; H, 10.0; N, 5.9.

(1*R,S*)-[1′*S*-(Phthaloylamino)-3-methylbutyl]oxirane (8b). Careful chromatography on silica gel (hexane/ether, 25/15) allowed the isolation of the less polar erythro isomer (9%) as well as the threo isomer (41%, contaminated with 3% erythro). Erythro: ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 3 H, *J* = 6 Hz), 0.94 (d, 3 H, *J* = 6 Hz), 1.45 (m, 1 H), 1.86 (m, 1 H), 2.32 (m, 1 H), 2.60 (dd, 1 H, *J* = 3, 5 Hz), 2.73 (dd, 1 H, *J* = 4, 5 Hz), 3.52 (m, 1 H), 3.92 (m, 1 H), 7.73 (dd, 2 H, *J* = 3, 5 Hz), 7.84 (dd, 2 H, *J* = 3, 5 Hz). Threo: 0.92 (d, 3 H, *J* = 6 Hz), 0.94 (d, 3 H, *J* = 6 Hz), 1.45–1.65 (br m, 2 H), 2.21 (m, 1 H), 2.74 (dd, 1 H, *J* = 3, 5 Hz), 2.92 (dd, 1 H, *J* = 4.5, 4.5 Hz), 3.59 (m, 1 H), 3.98 (m, 1 H), 7.72 (dd, 2 H,

J = 3, 6 Hz), 7.84 (dd, 2 H, J = 3, 6 Hz); exact mass calcd for $C_{15}H_{17}NO_3$ M^+, 259.1209, found 259.1219.

(1*R*,*S*)-[1′*S*-(4-Toluenesulfonylamino)-3-methylbutyl]oxirane (8c): mass spectrum, m/e $(M + H)^+$ 284, $(M - C_2H_3O)^+$ 240; ^1H NMR ($CDCl_3$) analysis of mixture: threo 0.75 (d, 3 H, J = 6 Hz), 0.83 (d, 3 H, J = 6 Hz), 1.3–1.4 (m, 2 H), 1.58 (m, 1 H), 2.43 (s, 3 H), 2.6–2.7 (2 m, 1 H each), 2.94 (m, 1 H), 3.58 (m, 1 H), 4.36 (d, 1 H, J = 9 Hz), 7.31 (d, 2 H, J = 8 Hz), 7.76 (d, 2 H, J = 8 Hz). Erythro (unobscured resonances) 0.68 (d, 3 H, J = 6 Hz), 0.84 (d, 3 H, J = 6 Hz), 2.57 (dd, 1 H, J = 2, 4.5 Hz), 2.63 (partially obscured m), 2.76 (m, 1 H), 3.03 (m, 1 H), 4.52 (br d, J = 7 Hz). Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.3; H, 7.5; N, 4.9. Found: C, 59.2; H, 7.4; N, 4.9.

(1*R*,*S*)-[1′*S*-(*t*-Boc-amino)-2-phenylethyl]oxirane (8d): mass spectrum, m/e $(M + H)^+$ 264; ^1H NMR ($CDCl_3$) threo δ 1.39 (s, 9 H), 2.59 (m, 1 H), 2.70 (dd, 1 H, J = 4.5, 4.5 Hz), 2.8–3.0 (br m, 2 H), 3.02 (m, 1 H), 4.13 (br m, 1 H), 4.59 (br m, 1 H), 7.2–7.35 (m, 5 H). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.4; H, 8.0; N, 5.3. Found: C, 68.2; H, 8.0; N, 5.3.

(1*R*,*S*)-[1′*S*-(*t*-Boc-amino)-1-cyclohexylmethyl]oxirane (8e): mass spectrum, m/e M^+ 255; ^1H NMR ($CDCl_3$) threo δ 1.0–1.9 (severl m, 11 H), 1.43 (s, 9 H), 2.53 (m, 1 H), 2.70 (dd, 1 H, J = 4.5, 4.5 Hz), 3.08 (m, 1 H), 3.73 (m, 1 H), 4.48 (br d, 1 H, J = 9 Hz). Anal. Calcd for $C_{14}H_{25}NO_3$: C, 69.8; H, 9.9; N, 5.5. Found: C, 69.8; N, 10.2; N, 5.4.

(1*R*,*S*)-[1′*S*-(*t*-Boc-amino)-3-cyclohexylpropyl]oxirane (8f): mass spectrum, m/e M^+ 283; ^1H NMR ($CDCl_3$) threo δ 0.8–1.75 (several m, 15 H), 1.43 (s, 9 H), 2.59 (m, 1 H), 2.73 (dd, 1 H, J = 4.5, 4.5 Hz), 3.01 (m, 1 H), 3.83 (m, 1 H), 4.37 (m, 1 H). Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.8; H, 10.3; N, 4.9. Found: C, 67.4; H, 10.5; N, 5.3.

(1*R*,*S*)-[1′*S*-(*t*-Boc-amino)-2-cyclohexylethyl]oxirane (8g): mass spectrum, m/e $(M + H)^+$ 270; ^1H NMR ($CDCl_3$) threo δ 0.8–1.9 (several m, 13 H), 1.43 (s, 9 H), 2.60 (m, 1 H), 2.73 (dd, 1 H, J = 4.5, 4.5 Hz), 2.97 (m, 1 H), 4.02 (m, 1 H), 4.19 (m, 1 H). Anal. Calcd for $C_{15}H_{27}NO_3$: C, 65.4; H, 10.1; N, 5.0. Found: C, 65.4; H, 10.1; N, 5.1.

(1*R*,*S*)-[1′*R*,*S*-[(Trichloroacetyl)amino]-2-(1-adamantyl)ethyl]oxirane (8l). Epoxides were separated by silica gel chromatography (4/1 hexane/ether) to give the less polar threo isomer (54%) as well as the erythro isomer (12%). Threo: mass spectrum, m/e $(M + H)^+$ 366, $(M - Cl)^+$ 330; ^1H NMR ($CDCl_3$) δ 1.35–1.85 (m, 14 H), 1.73 (m, 3 H), 2.53 (dd, 1 H, J = 3, 4.5 Hz), 2.72 (dd, 1 H, J = 4.5, 4.5 Hz), 3.03 (m, 1 H), 4.33 (m, 1 H), 6.38 (br d, 1 H). Anal. Calcd for $C_{16}H_{22}NO_2Cl_3$: C, 52.4; H, 6.0; N. 3.8. Found: C, 52.3; H, 6.11; N, 3.86. Erythro: mass spectrum, m/e (M + H) 366, $(M - Cl)^+$ 330, $(M - CCl_3)^+$ 248; ^1H NMR ($CDCl_3$) δ 1.25–1.75 (m, 14 H), 1.97 (m, 3 H), 2.82 (d, 2 H, J = 3 Hz), 2.92 (m, 1 H), 3.88 (m, 1 H), 6.45 (br d, 1 H). Anal. Calcd for $C_{16}H_{22}NO_2Cl_3$: C, 52.4; H, 6.0; N, 3.8. Found: C, 52.5; H, 6.2; N, 3.6.

[(4*S*),5(*R*,*S*)]-4-(2-Methylpropyl)-5-[(phenylthio)methyl]oxazolidin-2-one (9a). Thiophenol (196 mg, 1.78 mmol) in dry dimethylformamide (1 mL) was added to a stirred suspension of NaH (80 mg of 60% NaH in oil, hexane washed 2×, 2.00 mmol) in dimethylformamide. Epoxides **8a** (370 mg, 1.62 mmol) were added. After 2 h, water was added and the mixture was extracted with ether. The combined organic phase was washed (brine), dried (Na_2SO_4), filtered, and evaporated to an oil (391 mg, 91%). Analysis of the decoupled ^1H NMR spectrum was performed on the crude mixture to assign the major isomer (threo, **9(*T*)a**) and the minor isomer (erythro, **9(*E*)a**) as shown in Scheme III.

2-(1-Adamantyl)ethanal (11). To a mechanically stirred −60 °C solution of oxalyl chloride (8.32 mL, 91.5 mmol) in anhydrous dichloromethane (200 mL) was added an anhydrous solution of dimethyl sulfoxide (14.14 mL, 183 mmol) in dichloromethane (40 mL) dropwise over the course of 3 min. After 2 min, 1-adamantaneethanol (15.00 g, 83.2 mmol, Aldrich) in dichloromethane (85 mL) was added. Triethylamine (58.2 mL, 416 mmol) was added 15 min later, and the mixture was warmed to room temperature for 1.25 h. Water (400 mL) was then added with rapid stirring, the layers were separated, and the aqueous phase was extracted with dichloromethane. The combined organic phase was washed sequentially with water (800 mL), 1 M HCl (2 × 250 mL), H_2O (250 mL), saturated $NaHCO_3$ (100 mL), and brine (150 mL). The solution was dried, filtered, and evaporated to give a residue, which was vacuum distilled to give **11** as a colorless oil (12.66 g, 85%): ^1H NMR ($CDCl_3$) δ 1.3–1.8 (m, 12 H), 1.9–2.05 (br m, 3 H), 2.13 (d, 2 H, J = 3 Hz), 9.88 (t, 1 H, J = 3 Hz). Anal. Calcd for $C_{12}H_{18}O \cdot {}^1/_3H_2O$: C, 78.2; H, 10.2. Found: C, 78.1; H, 10.2.

Ethyl 4-(1-Adamantyl)but-2(*E*)-enoate (12). To a 0 °C suspension of NaH (70.2 mmol, 1.5 equiv, hexane-washed) in anhydrous tetrahydrofuran (225 mL) was added triethyl phosphonoacetate (15.71 g, 70.1 mmol) dropwise over the course of 30 min. The mixture was then cooled to −78 °C and treated with aldehyde **11** (8.35 g, 46.8 mmol) in tetrahydrofuran (30 mL). The mixture was warmed to room temperature for 1 h and then quenched with saturated NH_4Cl (60 mL). The tetrahydrofuran was removed in vacuo, and the residue was partitioned between ethyl acetate (225 mL) and water (30 mL). The organic layer was washed with saturated K_2CO_3 (60 mL) and brine (2 × 75 mL). Drying ($MgSO_4$), filtering, and evaporating provided an oil that was chromatographed (ethyl acetate/hexane mixtures) to give 10.69 g (92%) of **12**: ^1H NMR ($CDCl_3$) δ 1.29 (t, 3 H, J = 7.5 Hz), 1.4–1.8 (m, 12 H), 1.85–2.0 (m, 5 H), 4.19 (q, 2 H, J = 7.5 Hz), 5.78 (dt, 1 H, J = 15.5, 1.3 Hz), 6.99 (dt, 1 H, J = 15.5, 8 Hz). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.4; H, 9.7. Found: C, 77.2; H, 9.8.

4-(1-Adamantyl)but-2(*E*)-en-1-ol (13). To a stirred 0 °C solution of **12** (3.36 g, 13.5 mmol) in dry toluene (50 mL) was added DIBAH (30.0 mL of a 1.5 M solution in toluene, 45.0 mmol) dropwise. After 3 h, the mixture was quenched with methanol (2 mL) and then poured into a 0 °C solution of saturated Rochelle salts (24 mL) and water (140 mL). The mixture was filtered through Celite, and the solids were extracted with several portions of ethyl acetate. The combined organic phase was washed with brine, dried, and concentrated in vacuo. Chromatography of the residue on silica gel (ethyl acetate/hexane mixtures) provided 2.48 g (89%) of **13**: ^1H NMR (60 MHz, $CDCl_3$) δ 0.8–2.2 (br m, 17 H), 4.05 (br, 2 H), 5.60 (br m, 2 H). Anal. Calcd for $C_{14}H_{22}O$: C, 81.5; H, 10.8. Found: C, 81.5; H, 11.0.

1-(1-Adamantyl)-2-[(trichloroacetyl)amino]but-3-ene (6l). To a stirred suspension of NaH (50 mg of 60% NaH dispersion in oil, hexane-washed, 1.24 mmol) in anhydrous ether (7.5 mL) was added a solution of **13** (2.55 g, 12.4 mmol) in ether (3 mL) dropwise over 5 min. When the evolution of hydrogen ceased, the mixture was stirred for another 15 min. The mixture was then cooled to −5 °C, and trichloroacetonitrile (1.79 g, 12.4 mmol) was added dropwise at a rate to maintain the internal temperature below 0 °C. The mixture was then warmed to room temperature and concentrated in vacuo. Pentane (18 mL) containing methanol (40 mg, 1.24 mmol) was added, and the mixture was shaken vigorously for 1 min. Filtration, extraction of the solid with pentane (2 × 3 mL), combination of the organic phases, and evaporation provided the corresponding crude imidate which was dissolved in xylene (40 mL) and refluxed for 12 h. Evaporation and silica gel chromatography (ethyl acetate/hexane mixtures) provided 3.39 g (78%) of alkene **14**: ^1H NMR (60 MHz, $CDCl_3$) δ 0.8–2.2 (br m, 17 H), 4.55 (br m, 1 H), 4.9–5.3 (m, 2 H), 5.5–6.2 (br m, 1 H), 6.2–6.7 (br m, 1 H). Anal. Calcd for $C_{16}H_{22}NOCl_3$: C, 54.8; H, 6.3; N, 4.0. Found: C, 54.7; H, 6.4; N, 4.0.

Acknowledgment. We thank the PPD Analytical Research Department, Abbott Laboratories, for acquiring spectral and microanalytical data. We also gratefully acknowledge the valuable technical contributions of Mr. Robert Maki.