Stereoselective Epoxidation of Phe-Gly and Phe-Phe Vinyl Isosteres

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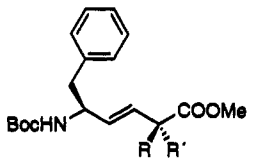
Novel Phe-Gly and Phe-Phe isosteres have been synthesized. Vinylic isosteres of Phe-Gly and Phe-Phe were prepared by facile Julia reactions, and the resulting stereoisomers were isolated and epoxidized (*m*-chloroperbenzoic acid). Observed stereoselectivities of epoxidation appear to emanate from a cooperative coordination of the incoming peracid by the carbamate group and the more weakly coordinating allylic ester function.

Introduction

As part of a current program aimed at the synthesis of dipeptidomimetics which can be used as building blocks in biologically interesting mimo-mutated peptides we design and synthesize novel bis(phenylalanine) and phenylalanyl–glycine mimetics.[1] In the present study, we have prepared the olefinic peptidomimetics **1a–1d** by a sequence



1a: R=R'=H
b: R=H; R'=CH_2Ph
c: R=CH_2Ph; R'=H
d: R=R'=CH_2Ph

involving a Julia reaction as the key step. An alternative Wittig reaction based strategy leading to **1a** proved to be inferior. Epoxidation of **1a–1d** with *m*-chloroperbenzoic acid proceeded with moderate to high stereoselectivity. A cooperative coordination of the peracid by the ester and carbamate groups of **1a–1d** appears to rationalize the observed differences in stereoselectivities, whereas the preferred π-face selectivity of the epoxidation is determined by the stereochemistry of the carbamate-bearing carbon. The stereochemically well-defined olefins and epoxides reported herein should be useful as starting materials for an array of bis-functionalized dipeptidomimetics.

Results and Discussion

Synthesis of 1a–1d. Initially,[1a] we synthesized **1a**, the vinyl isostere of Phe-Gly, by use of a previously reported strategy[2] involving a Wittig reaction to form the double bond from *tert*-butyloxycarbonyl (Boc)-protected phenylalanine aldehyde and a TMS-protected propynylphosphonium bromide (Scheme 1).[3,4] The synthesis involves several steps in which rigorous control of the reaction conditions is necessary to avoid racemization/epimerization.[5] In addition, the preparation of the Wittig reagent is difficult and unreliable. The Wittig reaction produced a mixture of the *E* and *Z* isomers in a ratio of 86:14. The isomers were separated by chromatography. The subsequent reduction/oxidation step afforded **2a** in an overall yield of 39%. In this reaction we also obtained a considerable amount (12%) of a regioisomer in which the double bond had isomerized into conjugation with the carbonyl group (Scheme 1).

Because of the problems experienced in the preparation of the starting materials and with regiocontrol in the Wittig-based procedure, we decided to use as an alternative strategy a Julia reaction, which gives an olefin from a deprotonated sulfone and an aldehyde (Scheme 2).[6,7] This synthetic route was devised by Spaltenstein *et al.*,[8] who used it to prepare four vinylic dipeptidomimetics including an epimeric mixture of **2b** and **2c** (see below).

The enantiopure sulfone **3**, which was required for the syntheses of vinyl isosteres **1a–1d** (Scheme 2), was obtained from Boc-protected L-phenylalanine.[8,9] The other reac-

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(1) (a) Li, Y.-L.; Luthman, K.; Hacksell, U. *Tetrahedron Lett.* **1992**, *33*, 4487–4490. (b) Jenmalm, A.; Luthman, K.; Lindeberg, G.; Nyberg, F.; Terenius, L.; Hacksell, U. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1693–1698. (c) Borg, S.; Luthman, K.; Nyberg, F.; Terenius, L.; Hacksell, U. *Eur. J. Med. Chem.* **1993**, *28*, 801–810.

(2) (a) Hann, M. M.; Sammes, P. G.; Kennewell, P. D.; Taylor, J. B. *J. Chem. Soc., Chem. Commun.* **1980**, 234–235. (b) Hann, M. M.; Sammes, P. G.; Kennewell, P. D.; Taylor, J. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 307–314. (c) Miles, N. J.; Sammes, P. G.; Kennewell, P. D.; Westwood, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2299–2305. (d) Kaltenbronn, J. S.; Hudspeth, J. P.; Lunney, E. A.; Michniewicz, B. M.; Nicolaides, E. D.; Repine, J. T.; Roark, W. H.; Stier, M. A.; Tinney, F. J.; Woo, P. K. W.; Essenburg, A. D. *J. Med. Chem.* **1990**, *33*, 838–845.

(3) Other synthetic procedures giving (*S*)-**5a** have been reported: (a) Cox, M. T.; Heaton, D. W.; Horbury, J. *J. Chem. Soc., Chem. Commun.* **1980**, 799–800. (b) Fujii, N.; Habashita, H.; Shigemori, N.; Otaka, A.; Ibuka, T.; Tanaka, M.; Yamamoto, Y. *Tetrahedron Lett.* **1991**, *32*, 4969–4972.

(4) Other *trans*-olefins have been used as amide bond isosteres; see, *e.g.*: (a) Cox, M. T.; Gormley, J. J.; Hayward, C. F.; Petter, N. N. *J. Chem. Soc., Chem. Commun.* **1980**, 800–802. (b) Spatola, A. F. *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*; Weinstein, B., Ed.; Marcel Dekker, Inc.: New York, 1983; Vol. 7, pp 308–315 and references cited therein. (c) Johnson, R. L. *J. Med. Chem.* **1984**, *27*, 1351–1354. (d) Shue, Y.-K.; Carrera, G. M., Jr.; Nadzan, A. M. *Tetrahedron Lett.* **1987**, *28*, 3225–3228. (e) Thompson, W. J.; Tucker, T. J.; Schwering, J. E.; Barnes, J. L. *Tetrahedron Lett.* **1990**, *31*, 6819–6822.

(5) The phenylalanine derived aldehyde has to be freshly prepared since partial (10%) racemization occurs upon storage at −22 °C overnight. Preferably, the crude aldehyde was used in the reaction since it racemizes on contact with silica gel, see: Rich, D. H.; Sun, E. T.; Boparai, A. S. *J. Org. Chem.* **1978**, *43*, 3624–3626. The temperature in the Wittig reaction has to be kept at −78 °C to avoid racemization/epimerization.

(6) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833–4836. (b) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Chem. Commun.* **1978**, 829–834.

(7) For the use of sulfones see: Trost, B. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107–124.

(8) Spaltenstein, A.; Carpino, P. A.; Miyake, F.; Hopkins, P. B. *J. Org. Chem.* **1987**, *52*, 3759–3766.

(9) Boc-protected L-phenylalanine (Boc-Phe) was prepared according to: Bolin, D. R.; Sytwu, I.-I.; Humiec, F.; Meienhofer, J. *Int. J. Peptide Protein Res.* **1989**, *33*, 353–359. In the reduction of Boc-Phe to the corresponding alcohol we used $LiBH_4$ in THF instead of $NaBH_4$ in water. The yield was 83%. The stereochemical purity of the sulfone was determined indirectly. After hydrolysis of the Boc group, the resulting amine was converted to an amide using (*S*)-Mosher acid chloride; see: Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165–7166.

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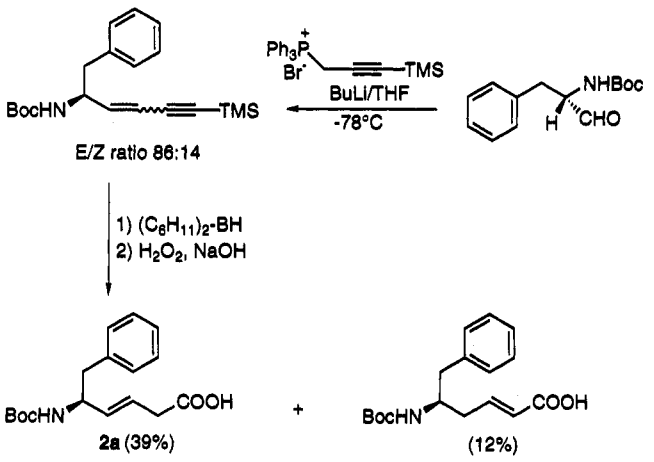
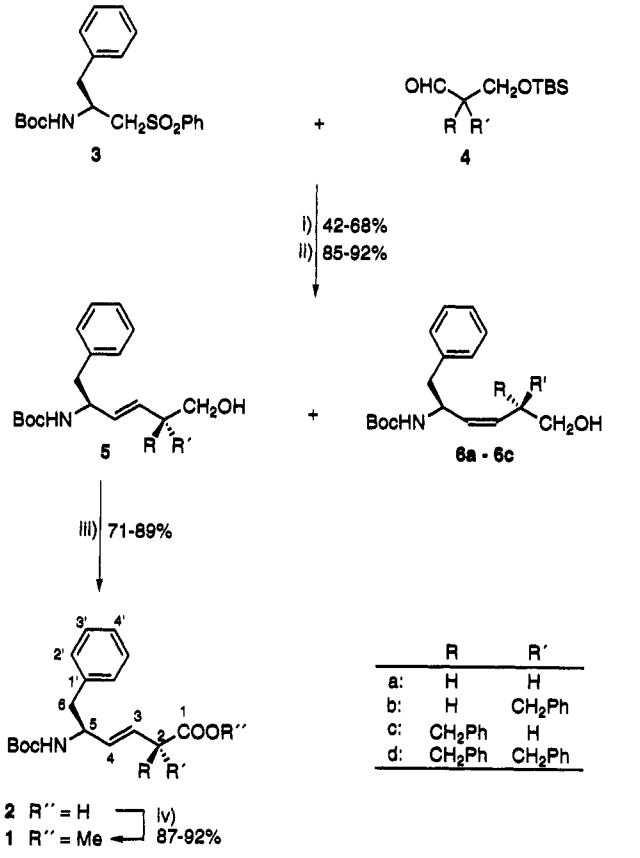
Scheme 1



Scheme 2[a]



	R	R'
a:	H	H
b:	H	CH_2Ph
c:	CH_2Ph	H
d:	CH_2Ph	CH_2Ph

[a] Key: (i) (a) THF, BuLi (2.0 equiv); (b) Na(Hg) (6%), Na_2HPO_4, MeOH; (ii) HF (2%), acetonitrile or Bu_4NF (1 M), THF; (iii) Jones' reagent (0.67 M), acetone; (iv) CH_2N_2, ether or Me_2SO_4, K_2CO_3, acetone.

tants, aldehydes **4a**, **4b**, and **4d**, were synthesized as follows: Compound **4a** was efficiently prepared from 1,3-propanediol by monosilylation (83%), which was accomplished by slow addition of *tert*-butyldimethylsilyl chloride (TBS chloride) to an excess of propanediol in CH_2Cl_2,[10] followed by a Swern oxidation (oxalyl chloride and DMSO; 75% yield).[11,12] The racemic aldehyde **4b** was synthesized from dimethyl malonate; monobenzylation using K_2CO_3 and benzyl bromide (77%)[13] followed by $LiAlH_4$ reduction (quantitative yield) produced the diol[14] which was monosilylated with TBS chloride. The free alcohol group was oxidized to the aldehyde using Swern conditions producing **4b**[15] (the yield from the diol was 68%). The dibenzylated aldehyde **4d** was synthesized from dimethyl malonate by use of a similar procedure.[16]

The Julia reaction consists of three discrete reaction steps: (i) activation of the aldehyde with DIBAL methoxide, (ii) coupling of the aldehyde–DIBAL complex with the anion of the sulfone, and (iii) an elimination–desulfonylation reaction which is performed with sodium amalgam (6%).[17] After much experimentation we established Julia reaction conditions which consistently produced moderate to good yields.[18] Throughout, the products of the Julia olefination were not isolated but directly desilylated to the corresponding alcohols.[19] Julia olefination/desilylation starting from **4a** produced an 86:14 (HPLC analysis) mixture of (*E*)-**5a** and (*Z*)-**6a** isomers in a total yield of 68%. The isomers were separated by fractional recrystallization ($CHCl_3$/hexane) or by repeated column chromatography. Application of the Julia olefination/desilylation procedure to aldehyde **4b** produced an *E*/*Z* mixture (86:14) of two *E*-isomers, **5b** and **5c** (in equal amounts), and two *Z*-isomers, **6b** and **6c** (in equal amounts), in 48% total yield. The four stereoisomers were separated by a combination of flash chromatography and semipreparative liquid chromatography.

The synthesis of the dibenzylated derivative **5d** has been briefly described elsewhere.[1b] The overall yield in the Julia reaction was 42%. In contrast to the syntheses starting with **4a** or **4b** we did not observe any formation of the *Z*-isomer when **4d** was used as starting material. However, we identified a byproduct resulting from an alternative direction of elimination/desulfonylation.[1b,20] The corresponding byproduct was also observed in the synthesis of **5b** and **5c**.[21]

The isolated *E*-homoallylic alcohols **5a–5d** were converted to the corresponding carboxylic acids **2a–2d** by a Jones' oxidation reaction.[22] In an attempt to assign the

(10) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743–4763.

(11) (a) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482. (b) Roush, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 1390–1404.

(12) For an alternative synthesis of **4a**, see: Pirrung, M. C.; Webster, N. J. G. *J. Org. Chem.* **1987**, *52*, 3603–3613.

(13) Cope, A. C.; Holmes, H. L.; House, H. O. *Org. React.* **1957**, *9*, 107–331.

(14) Mozingo, R.; Folkers, K. *J. Am. Chem. Soc.* **1948**, *70*, 227–229.

(15) Monteil, T.; Kotera, M.; Duhamel, L.; Duhamel, P.; Gros, C.; Noël, N.; Schwartz, J. C.; Lecomte, J. M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 949–954.

(16) Compound **4d** was obtained in 76% overall yield via dimethyl 2,2-dibenzylmalonate (96%; see ref 13), 2,2-dibenzyl-1,3-propanediol (100%), and **4d** (79%).

(17) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477–3478.

(18) To obtain good yields in the Julia reactions, we (a) completely dissolved the sulfone before the addition of *n*-butyllithium, (b) monitored the formation of the sulfone dianion (which has a strong yellow color), (c) avoided large excess of aldehyde (in order to simplify workup), and (d) kept the reaction temperature at −78 °C during the additon of *n*-butyllithium and the aldehyde.

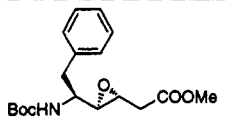
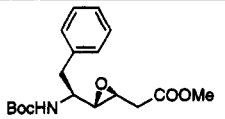
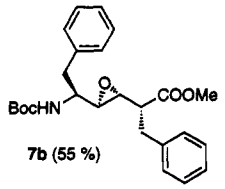
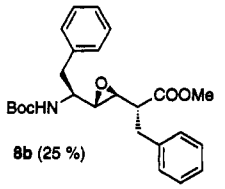
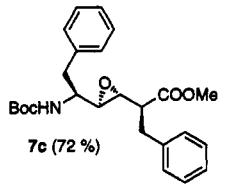
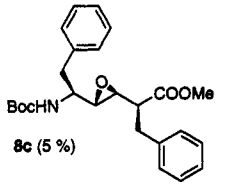
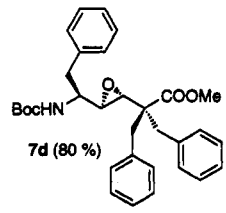
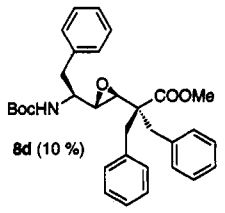
(19) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981–3982.

(20) The byproduct was formed in 12% yield (HPLC analysis), and its structure was tentatively assigned by ^{1}H-NMR spectroscopy to 2,2-dibenzyl-1-[(*tert*-butyldimethylsilyl)oxy]-6-phenyl-4-hexen-3-ol; see ref 1b.

(21) The byproduct from the synthesis of **5b** and **5c** was formed in 5% yield (HPLC analysis). Its structure was assigned by ^{1}H-NMR spectroscopy to 2-benzyl-1-[(*tert*-butyldimethylsilyl)oxy]-6-phenyl-4-hexen-3-ol. This byproduct was separable by column chromatography after desilylation.

(22) Attempts to oxidize the *Z* isomers **6a–6c** gave cyclized products which were assigned by NMR spectroscopy to 2-benzylpyridine and 2,5-dibenzylpyridine, respectively. This side reaction probably occurred after oxidation of the alcohol to the aldehyde which cyclized via an intramolecular attack by the carbamate nitrogen on the carbonyl carbon.

Table 1. Stereoselectivity in the Epoxidation of the Allylic Carbamate Esters 1a–1d with *m*-CPBA

products[a]		
 7a (75%)	19 : 1	 8a[b]
 7b (55 %)	2 : 1	 8b (25 %)
 7c (72 %)	9 : 1	 8c (5 %)
 7d (80 %)	9 : 1	 8d (10 %)

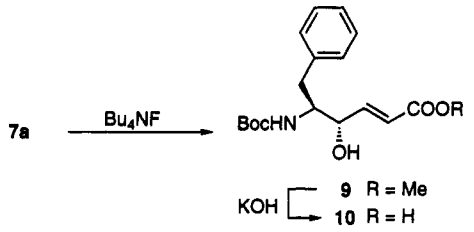
[a] Relative ratio of epoxide isomers determined by HPLC and NMR spectroscopy on the crude reaction product. Isolated yields are given in parentheses. [b] Compound 8a was not purified to homogeneity.

configuration at the stereogenic center α to the carboxylic acid group in isomers **2b** and **2c** we determined $[\alpha]_D$ values and compared them with published values.[8] However, it turned out that the reported optical rotation referred to the diastereomeric mixture of **2b** and **2c** and not to a pure stereoisomer.[23] Consequently, the literature data were of no use in the configurational assignment.

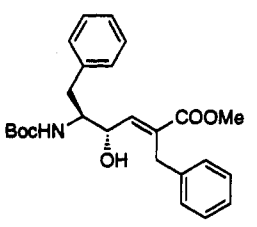
Esterification of **2a** using dimethyl sulfate/K_2CO_3 in acetone gave **1a** in 92% yield.[24] The carboxylic acids **2b** and **2c** were esterified by use of diazomethane forming **1b** and **1c** in 87% and 89% yield, respectively, since the use of dimethyl sulfate/K_2CO_3 in acetone produced more than 30% epimerization at C-2. Methyl ester **1d** was produced from **2d** by dimethyl sulfate/K_2CO_3 in acetone.

Synthesis of Epoxides 7a–7d and 8a–8d. The stereochemically pure esters **1a–1d** were treated with *m*-chloroperbenzoic acid (*m*-CPBA) to produce the corresponding epoxides **7a–7d** and **8a–8d** (Table 1). The epoxidations proceeded nicely and with high but varying stereoselectivity. The highest stereoselectivity was observed in the oxidation of the Phe-Gly vinyl isostere **1a** from which two diastereomeric epoxides[25] were formed in a 19:1 ratio (75% yield). The stereoselectivity of epoxidation of **1b** and **1c** varied with the configuration at C-2; isomer **1b** produced an isomeric product ratio of 2:1 whereas isomer **1c** gave a mixture of diastereomers in a 9:1 ratio. The yield in the epoxidations of **1b** and **1c** was 80% and 78%, respectively. The dibenzylated derivative **1d** was epoxidized with considerable stereoselectivity, giving a 9:1 mixture of diastereomeric epoxides in 90% yield. With the exception of the minor epoxide **8a**, which was not purified to homogeneity, the pure diastereomers were isolated following column chromatography.

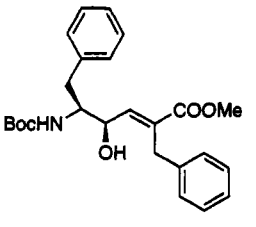
Configurational Assignments of the Epoxides. The configurational assignment of **7a** was performed by chemical conversion into the alcohol **9** formed by ring opening of the epoxide with tetrabutylammonium fluoride (TBAF) in THF,[1a,26] a reaction which should preserve the configuration at C-4. Ester hydrolysis produced carboxylic acid **10**, the melting point and optical rotation of which conformed with literature data on (4*S*,5*S*)-**10**.[26a,27] Consequently, the major epoxide **7a** was assigned the 3*R*,4*R*,5*S* configuration and the minor isomer **8a** the 3*S*,4*S*,5*S* configuration.



The stereochemistries of the diastereomers resulting from epoxidation of **1b** and **1c** were assigned on the basis of an X-ray crystallographic determination of the relative configuration of epoxide **8b** (Figure 1). Since the absolute configuration of the stereogenic centre at C-5 was known (*S*), it followed that **8b** had the 2*R*,3*S*,4*S*,5*S* configuration. This enabled us to establish the stereochemistries also of the other three isomers. A tentative assignment, which was based on the mechanistic hypothesis that the peracid would attack **1b** and **1c** with the same π-face selectivity, was unambiguously confirmed by experiments in which the major epoxide isomers **7b** and **7c** were treated with TBAF in THF to form the same unsaturated alcohol, **11**, and the minor epoxide isomers **8b** and **8c** formed **12** (Figure 2).



11



12

The configurational assignment of the diastereomeric epoxides formed from the dibenzylated derivative **1d** is

(23) The isomers **2b** and **2c** showed $[\alpha]_D$ values of −59.2° (*c* = 1.0, $CHCl_3$) and +40.2° (*c* = 1.1, $CHCl_3$), respectively (lit.[8] $[\alpha]_D$ −17° (*c* = 10, $CHCl_3$)). On the basis of our data the expected $[\alpha]_D$ value of a 1:1 mixture should be about −19°. It therefore appears that the published procedure does not produce the enantiopure product but a 1:1 mixture of isomers. In addition, the reported ^{13}C-NMR spectral data show the presence of a mixture of isomers since chemical shifts due to signals specific for each isomer were given (δ 127.1 is due to **5b** and δ 127.4 is due to **5c**).[8]

(24) An alternative method of esterification of **2a** is reported in ref 2d.

(25) Epoxidation of **1a** with *m*-CPBA has been reported (ref 2d), but the isomeric ratio of products was not determined and the resulting epoxides were not characterized.

(26) For other methods to synthesize **9**, see: (a) Hanson, G. J.; Lindberg, T. *J. Org. Chem.* **1985**, *50*, 5399–5401. (b) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370–4382.

(27) Compound **10** has also been synthesized from the epoxide; see ref 2d.

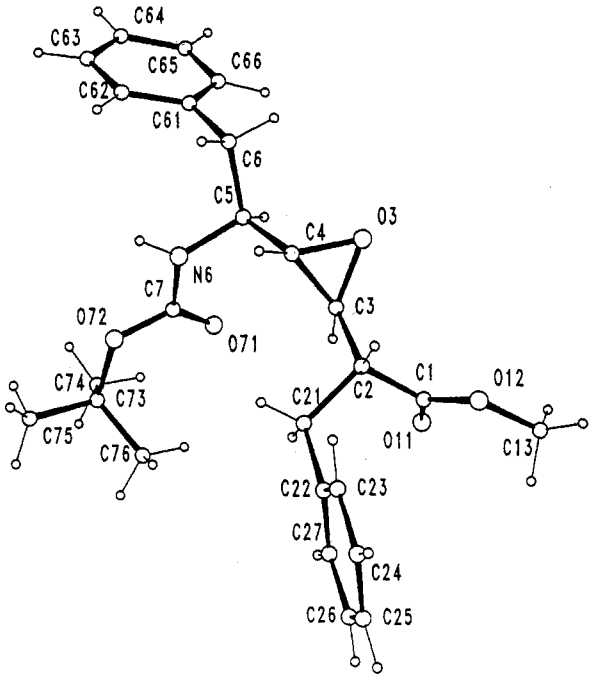


Figure 1. Perspective view of **8b** with crystallographic labelling of the atoms.

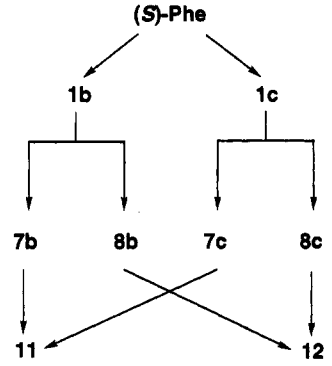


Figure 2. Determination of absolute configurations by chemical correlation. The integrity of the stereogenic centre of (*S*)-Phe is preserved throughout the reaction sequence (Scheme 2). Therefore, all compounds in the correlation scheme have the 5*S* configuration (Scheme 2). X-ray crystallographic analysis established the relative configuration of epoxide **8b**. Consequently, **8b** has the 2*R*,3*S*,4*S*,5*S* configuration, and the isomeric epoxide **7b** can be assigned the 2*R*,3*R*,4*R*,5*S* configuration. The 2*R*,5*S* configuration of the olefin **1b** follows from that of **8b**. This also allows the unambiguous assignment of the 2*S*,5*S* configuration of the epimeric olefin **1c**. Since **8b** and **8c** produce the same allylic alcohol on treatment with fluoride ion, they have the same configuration at C-4. Hence, **8c** is the 2*S*,3*S*,4*S*,5*S* isomer, and it follows that epoxide **7c**, which is also obtained from **1c**, has the 2*S*,3*R*,4*R*,5*S* configuration.

based on observed differences in ^{1}H and ^{13}C NMR spectroscopic chemical shifts between the diastereoisomeric epoxide pairs **7a** and **8a**, **7b** and **8b**, and **7c** and **8c** (Table 2); the consistent chemical shift differences between signals due to C-3, C-5, C-6, H-3, and H-5 appear to be of diagnostic value. Accordingly, following a comparison of the NMR spectroscopic chemical shift data of epoxides **7d** and **8d** with those determined for the other epoxides, the major isomer **7d** was assigned the 3*R*,4*R*,5*S* configuration and the minor isomer **8d** the 3*S*,4*S*,5*S* configuration.

Stereoselectivity in the Epoxidation Reaction. Frequently, epoxidations of olefins using *m*-CPBA proceed

Table 2. Selected ^{1}H and ^{13}C NMR Spectral Data Used for Assignments of Relative Stereochemistries of the Epoxides

	δ (ppm)				
compd	H-3	H-5	C-3	C-5	C-6
7a	3.17	4.12	51.64	50.46	39.60
8a	3.33	*a*	53.85	*a*	37.29
7b	3.04	4.05	55.80	50.58	39.26
8b	3.29	3.59	58.43	52.26	37.44
7c	3.08	3.94	55.46	50.05	39.39
8c	3.20	3.69	57.98	52.17	37.52
7d	2.98	4.02	57.65	50.01	39.36
8d	3.08	3.78	59.52	51.95	37.04

[a] Not determined.

with a pronounced stereoselectivity. The π-face selectivity of the peracid may be affected by steric effects, which disfavor an approach from the sterically hindered face, or by coordination of the incoming peracid to suitably positioned functional groups by formation of hydrogen bonds. Allylic hydroxyl, amido, and carbamate groups may act as coordinating groups in stereoselective epoxidations of acyclic olefins, consistently producing *threo*-isomers as the major products.[28] Studies of cyclic systems in which amido and hydroxyl groups occupy allylic positions have demonstrated that amides are stronger peracid directors than alcohols.[28b] Further, steric and electrostatic properties of the *N*-acyl moiety in allylic amides and carbamates affect the stereoselectivity in epoxidations using *m*-CPBA.[28b,f,i,k,l] Stereoselective epoxidations of cyclic alkenes with homoallylic amide, carbamate, and ester functionalities have indicated that the carbonyl oxygen of the homoallylic substituent directs the peracid attack by accepting a hydrogen bond.[28m,n] The weaker directing ability observed for an ester compared to the amide or the carbamate groups was suggested to be related to the weaker nucleophilicity of the ester carbonyl oxygen.[28m,n]

In a preliminary study, we speculated[1a] that the stereoselectivity in the epoxidation of **1a** was due to a coordination effect outweighing the steric effects. The formation of hydrogen bonds between the peracid and the allylic carbamate and ester groups of **1a** would direct the attack of the peracid to the β-face of the double bond.[29] Similar cooperative effects from allylic substituents in acyclic olefins have been observed previously.[28d,j]

In analogy with previous studies,[28] the four epoxidation reactions studied herein predominantly produced the *threo* isomers, but the stereoselectivity of epoxidation varied from 19:1 to 2:1 (Table 1). It was particularly informative that the epoxidation of **1b** and **1c** gave quite different

(28) (a) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958–1965. (b) Hasegawa, A.; Sable, H. Z. *J. Org. Chem.* **1966**, *31*, 4154–4161. (c) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343–4346. (d) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347–4350. (e) Narula, A. S. *Tetrahedron Lett.* **1983**, *24*, 5421–5424. (f) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1587–1590. (g) Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515–4523. (h) Hauser, F. M.; Ellenberger, S. R.; Glusker, J. P.; Smart, C. J.; Carrell, H. L. *J. Org. Chem.* **1986**, *51*, 50–57. (i) Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem.* **1987**, *52*, 5127–5136. (j) Kogen, H.; Nishi, T. *J. Chem. Soc., Chem. Commun.* **1987**, 311–312. (k) Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487–1492. (l) Kočovský, P. *Tetrahedron Lett.* **1988**, *29*, 2475–2478. (m) Mohamadi, F.; Spees, M. M. *Tetrahedron Lett.* **1989**, *30*, 1309–1310. (n) Kočovský, P.; Starý, I. *J. Org. Chem.* **1990**, *55*, 3236–3243. (o) Pettersson, H.; Gogoll, A.; Bäckvall, J.-E. *J. Org. Chem.* **1992**, *57*, 6025–6031. (p) Romeo, S.; Rich, D. H. *Tetrahedron Lett.* **1993**, *34*, 7187–7190.

(29) See legend to Figure 3 for definitions of α- and β-face.

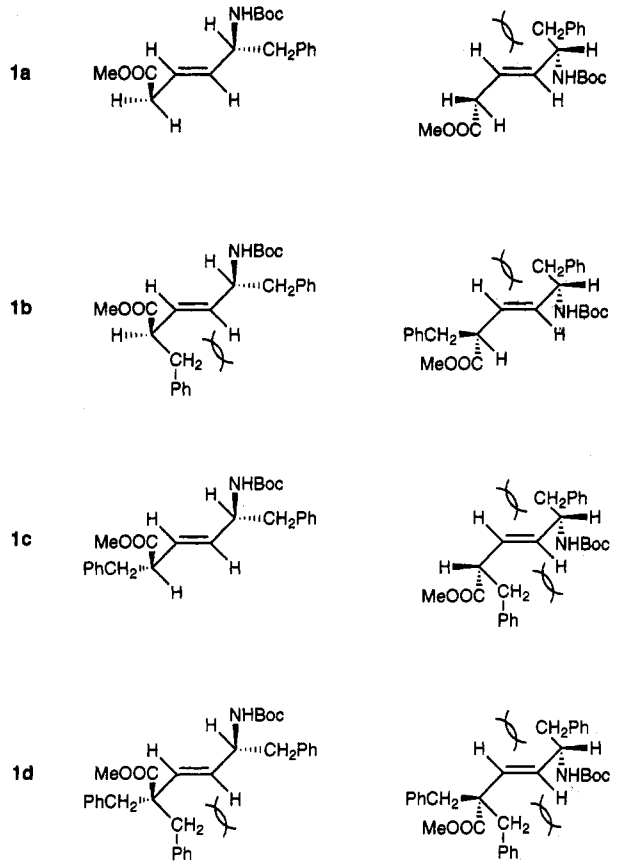
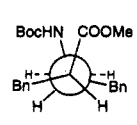


Figure 3. Conformations of **1a–1d** in which the carbamate and ester groups may direct the incoming peracid to the α-face (right) or to the β-face (left) of the alkene. Attack on the β-face results in the major isomers of epoxides **7a–7d** whereas attack on the α-face leads to the minor isomers **8a–8d**.

product ratios, although these compounds only differ in the configuration of the ester bearing carbon. A coordination of the peracid to the allylic carbamate group explains the overall *threo* selectivity but is not sufficient to explain the observed difference in stereoselectivities. However, provided that the relative stabilities of conformers which may cooperatively coordinate the peracid are taken into account, the stereochemical results obtained in the epoxidation may be rationalized in a qualitative sense. Conformations of **1a–1d**, in which a putative cooperative coordination involving both the ester and carbamate groups would direct the attack of the incoming peracid to the α- or β-face of the double bond, are shown in Figure 3 (see also ref 30). Attack of the peracid on the β-face of **1a–1d**, that is, coordination to the more stable conformers, results in the formation of the major epoxide isomers. Thus, the present analysis of a series of stereoselective epoxidations indicates that the allylic ester group may affect the stereochemistry of peracid epoxidation by cooperative coordination, thereby affecting the directing effect of the more powerfully coordinating allylic carbamate group.

(30) It is likely that the carbamate and ester functionalities are positioned as indicated by the Newman projection of compound 1c when coordinating the peracid.



1c

Concluding Remarks. The stereochemically well-characterized epoxides **7a–7d** and **8a–8d** should be excellent synthetic intermediates for a variety of Phe-Gly and Phe-Phe mimetics since the epoxide ring may be attacked by numerous nucleophiles. However, the preparation of the minor stereoisomers formed in the epoxidations is not facile. Thus, ongoing studies attempt to reverse the stereoselectivities of epoxidations reported herein.

Experimental Section

General. Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at ambient temperature. The ^1H and ^{13}C NMR spectra were obtained on a JEOL JNM-EX270 spectrometer with tetramethylsilane as internal standard. Assignments were made using ^1H–^1H and ^1H–^{13}C correlation experiments. The numbering of the atoms is given in Scheme 2. In analytical high-pressure liquid chromatography (HPLC) a Hitachi L-4000 UV detector (254 nm) and a Hitachi L-6200 Intelligent pump (flow rate 1.0–1.5 mL/min) were used with the following columns: A, Waters RCM 8 × 100 mm, 5-μm resolve silica; B, LiChroCART 4 × 250 mm, 5-μm LiChrospher Si 60. In preparative HPLC a Dynamax UV-1 UV detector (254 nm) and a Gilson 305 piston pump (flow rate 13 mL/min) were used. The separation was performed on a Dynamax 60-A 21.4 × 250 mm, 8-μm silica column. Infrared spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer. Thin-layer chromatography (TLC) was performed by using aluminum sheets precoated with silica gel 60 F_{254} (0.2 mm, E. Merck). Column chromatography was performed on silica using Kieselgel 60 (230–400 mesh, E. Merck). The elemental analyses were carried out by MikroKemi AB, Uppsala, Sweden.

Esterification of the Hexenoic Acids. Methyl (*S*)-5-[(*tert*-Butoxycarbonyl)amino]-6-phenyl-(*E*)-3-hexenoate (1a). Dimethyl sulfate (0.15 mL, 1.5 mmol) was added to a solution of **2a** (0.43 g, 1.5 mmol) and K_2CO_3 (0.51 g, 3.7 mmol) in acetone (30 mL). The reaction mixture was stirred at room temperature overnight. Insoluble material was filtered off, and the acetone was removed. Purification by flash chromatography (petroleum ether/ether (3:1)) gave 0.43 g (92%) of **1a**: HPLC (column A, 1% EtOH in hexane), 1.5 mL/min, t_R 12.5 min; mp 41–43 °C; $[\alpha]_D$ −9.1° (c = 1.0, MeOH); ^1H NMR ($CDCl_3$) δ 7.21–7.06 (m, 5H, Ph), 5.61–5.42 (m, 2H, H-3, H-4), 4.58 (br, 1H, NH), 4.30 (m, 1H, H-5), 3.56 (s, 3H, OCH_3), 2.94 (d, 2H, H-6), 2.73 (d, 2H, H-2), 1.31 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 171.93 (C-1), 155.13 (*Boc* C=O), 137.37 (C-1′), 133.99, 126.49, (C-3, C-4), 129.58 (2 C:s), 128.34 (2 C:s) (C-2′, C-3′), 122.50 (C-4′), 79.48 [$(CH_3)_3C$], 52.78 (C-5), 51.82 (OCH_3), 41.65 (C-6), 37.52 (C-2), 28.36 (3 C:s) [$(CH_3)_3C$].

Methyl (2*R*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-6-phenyl-(*E*)-3-hexenoate (1b). A solution of **2b** (226 mg, 0.572 mmol) in ether (30 mL) was treated with 10 equiv of diazomethane at room temperature overnight. Acetic acid was added, and the mixture was concentrated. Recrystallization (CH_2Cl_2/hexane) produced **1b** (205 mg, 87%) as white needles: HPLC (Column A, 0.5% EtOH in hexane), 1.5 mL/min, t_R 9.04 min; mp 73–74 °C; $[\alpha]_D$ −53.5° (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.29–7.06 (m, 10H, Ph), 5.55 (dd, 1H, J = 8.0, 15.5 Hz, H-3), 5.38 (dd, 1H, J = 5.0, 15.5 Hz, H-4), 4.36 (2H, H-5, NH), 3.60 [s, 3H, OCH_3], 3.25 (q, 1H, J = 7.7 Hz, H-2), 3.04 (dd, 1H, J = 7.6, −13.6 Hz, $PhCH_{2a}$), 2.82–2.64 (m, 3H, $PhCH_{2b}$, H-6), 1.41 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 173.64 (C-1), 154.98 (*Boc* C=O), 138.52, 137.27 (C-1′, C-1″), 133.08 (C-4), 129.52 (2 C:s), 129.04 (2 C:s), 128.29 (2 C:s), 128.25 (2 C:s) (C-2′, C-2″, C-3′, C-3″), 127.53 (C-3), 126.40 (2 C:s) (C-4′, C-4″), 79.44 [$(CH_3)_3C$], 52.72 (C-5), 51.76 (OCH_3), 50.62 (C-2), 41.70 (C-6), 38.62 ($PhCH_2$), 28.32 (3 C:s) [$(CH_3)_3C$]; IR (neat) 3360, 1730, 1700, 1160 cm^{-1}. Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.3; H, 7.6; N, 3.4. Found: C, 73.2; H, 7.6; N, 3.5.

Methyl (2*S*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-6-phenyl-(*E*)-3-hexenoate (1c). Compound 1c was synthesized from **2c** (214 mg, 0.542 mmol) using the procedure

described for the preparation of **1b**. Recrystallization (CH_2Cl_2/hexane) gave **1c** (197 mg, 89%) as white needles: HPLC (column A, 0.5% EtOH in hexane), 1.5 mL/min, t_R 9.48 min; mp 94–95 °C; $[\alpha]_D$ +44.7° (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.29–7.04 (m, 10H, Ph), 5.56 (dd, 1H, J = 8.2, 15.6 Hz, H-3), 5.41 (dd, 1H, J = 4.9, 15.6 Hz, H-4), 4.36 (br s, 2H, H-5, NH), 3.60 (s, 3H, OCH_3), 3.26 (q, 1H, $J = J$ = 7.7 Hz, H-2), 3.01 (dd, 1H, J = 7.7, −13.6 Hz, $PhCH_{2a}$), 2.79–2.71 (m, 3H, $PhCH_{2b}$, H-6), 1.40 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 173.72 (C-1), 155.00 (*Boc* C=O), 138.49, 137.12 (C-1′, C-1″), 133.12 (C-4), 129.63 (2 C:s), 129.04 (2 C:s), 128.35 (2 C:s), 128.26 (2 C:s) (C-2′, C-2″, C-3′, C-3″), 127.69 (C-3), 126.47 (2 C:s) (C-4′, C-4″), 79.42 [$(CH_3)_3C$], 52.56 (C-5), 51.80 (OCH_3), 50.71 (C-2), 41.53 (C-6), 38.67 ($PhCH_2$), 28.32 (3 C:s), [$(CH_3)_3C$]; IR (neat) 3340, 1730, 1700, 1160 cm^{-1}. Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.3; H, 7.6; N, 3.4. Found: C, 73.4; H, 7.6; N, 3.7.

Methyl (*S*)-2,2-Dibenzyl-5-[(*tert*-butoxycarbonyl)amino]-6-phenyl-(*E*)-3-hexenoate (1d). Compound **1d** was synthesized from **2d** (184 mg, 0.382 mmol), dimethyl sulfate (38 μL, 0.40 mmol), and K_2CO_3 (0.13 g, 0.96 mmol) as described above for the synthesis of **1a**. Recrystallization (CH_2Cl_2/hexane) gave **1d** (176 mg, 92%) as white needles: mp 127–128 °C; $[\alpha]_D$ −13.7° (c = 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.28–6.96 (m, 15H, Ph), 5.73 (d, 1H, J = 16.2 Hz, H-3), 5.45 (dd, 1H, J = 5.7, 16.2 Hz, H-4), 4.40–4.36 (m, 2H, NH, H-5), 3.58 (s, 3H, OCH_3), 3.16 (d, 2H, J = −13.8 Hz, $PhCH_{2a}$, $PhCH_{2a'}$), 2.97 (d, 1H, J = −13.7 Hz, $PhCH_{2b}$), 2.93 (d, 1H, J = −13.7 Hz, $PhCH_{2b'}$), 2.79–2.74 (m, 2H, H-6), 1.41 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 174.54 (C-1), 154.97 (*Boc* C=O), 137.41, 136.98, 136.93 (C-1′, C-1″, C-1‴), 131.77 (C-3), 130.94 (C-4), 130.21 (4 C:s), 129.54 (2 C:s), 128.27 (2 C:s), 127.89 (4 C:s) (C-2′, C-2″, C-2‴, C-3′, C-3″, C-3‴), 126.43 (2 C:s), 126.38 (C-4′, C-4″, C-4‴), 79.25 [$(CH_3)_3C$], 53.62 (C-2), 53.28 (C-5), 51.63 (OCH_3), 44.08, 43.92 ($PhCH_2$, $PhCH_2'$), 41.53 (C-6), 28.34 (3 C:s) [$(CH_3)_3C$]; IR (KBr) 3380, 1740, 1690, 1170 cm^{-1}. Anal. Calcd for $C_{32}H_{37}NO_4$: C, 76.9; H, 7.5; N, 2.8. Found: C, 77.1; H, 7.4; N, 2.8.

Preparation of the Hexenoic Acids. (*S*)-5-[(*tert*-Butoxycarbonyl)amino]-6-phenyl-(*E*)-3-hexenoic Acid (2a). A solution of **5a** (1.05 g, 3.6 mmol) in acetone (30 mL) was treated with Jones' reagent (0.67 M) (13 mL, 9.0 mmol) at 0 °C and stirred for 30 min. Workup by acid/base extractions afforded 1.0 g (91%) of crude **2a**, which was purified by recrystallization (ether/hexane): TLC R_f 0.34 (CH_2Cl_2/MeOH (9:1)); mp 91–93 °C; $[\alpha]_D$ −11.8° (c = 1.0, MeOH); ^1H NMR ($CDCl_3$) δ 8.42 (br s, 1H, COOH), 7.21–7.06 (m, 5H, Ph), 5.60–5.41 (m, 2H, H-3, H-4), 4.60 (br s, 1H, NH), 4.30 (m, 1H, H-5), 2.96 (d, 2H, H-6), 2.72 (d, 2H, H-2), 1.28 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 176.29 (C-1), 156.07 (*Boc* C=O), 137.38 (C-1′), 133.95, 126.38 (C-3, C-4), 129.44 (2 C:s), 128.24 (2 C:s) (C-2′, C-3′), 122.18 (C-4′), 80.00 [$(CH_3)_3C$], 52.86 (C-5), 41.67 (C-6), 37.25 (C-2), 28.17 (3 C:s) [$(CH_3)_3C$]; IR (KBr) 2980, 1720 cm^{-1}.

(2*R*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-6-phenyl-(*E*)-3-hexenoic Acid (2b). Compound **2b** was synthesized from **5b** (208 mg, 0.54 mmol) as described above for the synthesis of **2a**. The crude product (191 mg, 89% yield) was recrystallized (CH_2Cl_2/hexane) affording **2b** (160 mg, 74%): TLC R_f 0.17 ($CHCl_3$/MeOH/hexane (4:1:5)); mp 106–108 °C; $[\alpha]_D$ −59.2° (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.27–7.03 (m, 10H, Ph), 5.63–5.51 (m, 1H, H-3), 5.41 (dd, 1H, J = 5.4, 15.6 Hz, H-4), 4.46–4.17 (m, 2H, H-5, NH), 3.26 (q, 1H, J = 7.6 Hz, H-2), 3.14–3.08 (m, 1H, $PhCH_{2a}$), 2.81–2.74 (m, 3H, H-6, $PhCH_{2b}$), 1.38 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 178.29 (C-1), 155.20 (*Boc* C=O), 138.45, 137.36 (C-1′, C-1″), 133.44 (C-4), 129.52 (2 C:s), 129.16 (2 C:s), 128.35 (2 C:s), 128.28 (2 C:s) (C-2′, C-2″, C-3′, C-3″), 127.10 (C-3), 126.47, 126.41 (C-4′, C-4″), 79.57 [$(CH_3)_3C$], 52.78 (C-5), 50.40 (C-2), 41.69 (C-6), 38.35 ($PhCH_2$), 28.28 (3 C:s) [$(CH_3)_3C$]; IR (KBr) 3400–2500, 3330, 1710, 1160 cm^{-1}. Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.9; H, 7.3; N, 3.5. Found: C, 72.6; H, 7.3; N, 3.8.

(2*S*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-6-phenyl-(*E*)-3-hexenoic Acid (2c). Compound **2c** was synthesized from **5c** (238 mg, 0.623 mmol) as described above. The crude **2c** (220 mg, 89%) was recrystallized (CH_2Cl_2/hexane) to afford 156 mg (71%) of pure **2c** as white needles: TLC R_f 0.17 ($CHCl_3$/MeOH/hexane (4:1:5)); mp 64–66 °C; $[\alpha]_D$ +40.2° (c = 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.26–7.03 (m, 10H, Ph), 5.57 (dd, 1H, J = 8.3, 15.5 Hz, H-3), 5.42 (dd, 1H, J = 5.3, 15.5 Hz, H-4), 4.51–4.12 (m, 2H, H-5, NH), 3.27 (q, 1H, $J = J$ = 7.6 Hz, H-2), 3.05 (dd, 1H, J = 7.3, −13.7 Hz, $PhCH_{2a}$), 2.80–2.72 (m, 3H, H-6, $PhCH_{2b}$), 1.38 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 178.04 (C-1), 155.41 (*Boc* C=O), 138.33, 137.12 (C-1′, C-1″), 133.58 (C-4), 129.57 (2 C:s), 129.07 (2 C:s), 128.35 (2 C:s), 128.26 (2 C:s) (C-2′, C-2″, C-3′, C-3″), 127.39 (C-3), 126.47, 126.42 (C-4′, C-4″), 79.26 [$(CH_3)_3C$], 52.64 (C-5), 50.49 (C-2), 41.52 (C-6), 38.33 ($PhCH_2$), 28.26 (3 C:s) [$(CH_3)_3C$]; IR (neat) 3380, 3400–2500, 1710, 1690, 1170 cm^{-1}. Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.9; H, 7.4; N, 3.5. Found: C, 73.1; H, 7.4; N, 3.5.

(*S*)-2,2-Dibenzyl-5-[(*tert*-butoxycarbonyl)amino]-6-phenyl-(*E*)-3-hexenoic Acid (2d). Compound **2d** was synthesized from **5d** (980 mg, 2.13 mmol) as described above. However, no acid/base extraction was performed. Purification by column chromatography (CH_2Cl_2/MeOH (9:1)) gave **2d** (760 mg, 73%): TLC R_f 0.19 ($CHCl_3$/MeOH/hexane (4:1:5)); mp 174–176 °C; $[\alpha]_D$ −11.0° (c = 1.1, CH_2Cl_2); ^1H NMR (CD_3OD) δ 7.23–7.08 (m, 15H, Ph), 5.78 (d, 1H, J = 16.2 Hz, H-4), 5.55 (dd, 1H, J = 6.3, 16.2 Hz, H-3), 4.26 (app d, 1H, H-5), 3.19–2.91 (m, 4H, $PhCH_2$, $PhCH_{2'}$), 2.69 (app d, 2H, H-6), 1.37 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$/CD_3OD 1:1): δ 176.55 (C-1), 155.40 (Boc C=O), 137.39, 136.96, 136.87 (C-1′, C-1″, C-1‴), 131.55 (C-3), 130.64 (C-4), 130.06 (4 C:s), 129.20 (2 C:s), 127.98 (2 C:s), 127.53 (4 C:s) (C-2′, C-2″, C-2‴, C-3′, C-3″, C-3‴), 126.04 (3 C:s) (C-4′, C-4″, C-4‴), 79.08 [$(CH_3)_3C$], 53.01 (2 C:s) (C-2, C-5), 43.72, 43.33 ($PhCH_2$, $PhCH_{2'}$), 41.24 (C-6), 27.89 (3 C:s) [$(CH_3)_3C$]; IR (KBr) 3500–2500, 1700 cm^{-1}. Anal. Calcd for $C_{31}H_{35}NO_4 \cdot 0.5H_2O$: C, 75.3; H, 7.3; N, 2.8. Found: C, 75.3; H, 7.4; N, 2.6.

Preparation of the Propanal Derivatives. 3-[(*tert*-Butyldimethylsilyl)oxy]propanal (4a). A solution of TBS chloride (25.0 g, 166 mmol) in CH_2Cl_2 (150 mL) was added over 24 h with a syringe pump to a solution of 1,3-propanediol (50.0 g, 657 mmol) and imidazole (27.5 g, 404 mmol) in CH_2Cl_2 (50 mL) at room temperature. The solution was stirred for 4 h. The reaction mixture was diluted with CH_2Cl_2 (250 mL), washed with 1 M HCl (4 × 50 mL), saturated aqueous $NaHCO_3$ (4 × 50 mL), and H_2O (4 × 50 mL), and dried over $MgSO_4$. After filtration and evaporation of the solvent in vacuo, the residue was purified by flash chromatography (petroleum ether/ether (3:1)) to yield 26.2 g (83%) of **3-[(*tert*-butyldimethylsilyl)oxy]-1-propanol** as a colorless oil: TLC R_f 0.6 (petroleum ether/ether (2:3)); ^1H NMR ($CHCl_3$) δ 3.74 (m, 4H, H-1, H-3), 2.81 (br s, 1H, OH), 1.70 (m, 2H, H-2), 0.82 [s, 9H, $(CH_3)_3CSi$], 0.00 [s, 6H, $(CH_3)_2Si$]; ^{13}C NMR ($CDCl_3$) δ 62.64, 62.05 (C-1, C-3), 34.19 (C-2), 25.81 (3 C:s) [$(CH_3)_3CSi$], 18.12 [$(CH_3)_3CSi$], −3.65 (2 C:s) [$(CH_3)_2Si$].

A solution of DMSO (17.2 mL, 220 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of oxalyl chloride (15.7 g, 123 mmol) in CH_2Cl_2 (50 mL) at −78 °C. A solution of crude 3-[(*tert*-butyldimethylsilyl)oxy]-1-propanol (20 g, 105 mmol) from above in CH_2Cl_2 (40 mL) was added slowly at −78 °C. The reaction was stirred at −78 °C for 30 min, quenched by addition of triethylamine (46.5 g, 460 mmol), and allowed to reach room temperature. The mixture was partitioned between H_2O and CH_2Cl_2, and the organic extracts were washed with 5% aqueous HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated. The resulting colorless oil (20 g) was used in the next step without further purification. To fully characterize the compound a sample was purified by flash chromatography (petroleum ether/ether (9:1)) to yield pure **4a**: TLC R_f 0.5 (petroleum ether/ether (2:1)); ^1H NMR ($CDCl_3$) δ 9.73 (s, 1H, H-1), 3.92 (t, 2H, H-3), 2.53 (m, 2H, H-2), 0.82 [s, 9H, $(CH_3)_3CSi$], 0.00 [s, 6H, $(CH_3)_2Si$], ^{13}C NMR ($CDCl_3$) δ 201.74 (C-1), 57.25 (C-3), 46.42 (C-2), 25.66 (3 C:s) [$(CH_3)_3CSi$], 18.06 [$(CH_3)_3CSi$], 0.88 (2 C:s) [$(CH_3)_2Si$]; IR (neat) 1730 cm^{-1}.

2-Benzyl-3-[(*tert*-butyldimethylsilyl)oxy]propanal (4b). Benzyl bromide (25.0 mL, 210 mmol) and K_2CO_3 (35 g, 253 mmol) were added to a solution of dimethyl malonate (121 mL, 1.05 mol) in acetone (300 mL). The mixture was refluxed overnight. After removal of insoluble material and concentration in vacuo the remaining dimethyl malonate was distilled off. Purification by column chromatography (ether/petroleum ether (1:3)) afforded **dimethyl 2-benzylmalonate** (36.2 g, 77%) as a colorless oil. Dimethyl 2-benzylmalonate (4.41 g, 19.8 mmol) was slowly added to a slurry of $LiAlH_4$ (2.25 g, 59.3 mmol) in ether (100 mL). The reaction was stirred at room temperature overnight, cooled to 0

°C, and quenched by slow addition of H_2O (4 mL), 2 M NaOH (4 mL), and H_2O (12 mL). Insoluble material was filtered off, and the solvent was evaporated to afford **2-benzyl-1,3-propanediol** (3.30 g, 100%) as a white solid. Physical data were in agreement with those reported.[14]

A solution of 2-benzyl-1,3-propanediol (10.4 g, 62.6 mmol), triethylamine (21.8 mL, 157 mmol), and TBS chloride (9.44 g, 62.6 mmol) in dry CH_2Cl_2 (200 mL) was stirred at room temperature overnight. Aqueous 1 M HCl (100 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated to afford **2-benzyl-3-[(*tert*-butyldimethylsilyl)oxy]-1-propanol** (17.1 g) as a colorless oil. The product was used in the next step without further purification. To fully characterize the compound, a sample was purified by column chromatography (ether/petroleum ether (1:2)): TLC R_f 0.47 (ether/petroleum ether (1:1)); ^{1}H NMR ($CDCl_3$) δ 7.52–7.12 (m, 5H, Ph), 3.74–3.67 (m, 1H, H-1$_a$), 3.71 (dd, 1H, J = 4.0, –9.9 Hz, H-3$_a$), 3.62–3.54 (m, 1H, H-1$_b$), 3.57 (dd, 1H, J = 6.3, –9.9 Hz, H-3$_b$), 2.69 (s, 1H, OH), 2.57 (d, 2H, J = 7.6 Hz, PhCH_2), 2.02–1.89 (m, 1H, H-2), 0.86 [s, 9H, (CH_3)$_3$CSi], 0.02 (s, 3H, CH_3-Si), 0.01 (s, 3H, CH_3'Si); ^{13}C NMR ($CDCl_3$) δ 140.13 (C-1'), 129.00 (2 C:s) (C-2'), 128.32 (2 C:s) (C-3'), 125.98 (C-4'), 66.02 (C-1), 65.61 (C-3), 43.96 (C-2), 34.14 (PhCH_2), 25.84 (3 C:s) [(CH_3)$_3$-CSi], 18.13 [(CH$_3$)$_3$CSi], –5.62 (2 C:s) [(CH_3)$_2$Si]; IR (neat) 3380 br, 1250 cm^{-1}. Anal. Calcd for $C_{16}H_{28}O_2Si$: C, 68.5; H, 10.1. Found: C, 68.2; H, 10.2.

Compound **4b** was prepared by use of the procedure described for the synthesis of **4a** starting from DMSO (9.53 mL, 134 mmol), oxalyl chloride (5.81 mL, 67 mmol), and the crude 2-benzyl-3-[(*tert*-butyldimethylsilyl)oxy]-1-propanol (17.1 g, 61.0 mmol) from above and quenched with diisopropylethylamine (DIPEA) (50.2 mL, 305 mmol). The crude product was purified by column chromatography (ether/petroleum ether (1:9)) to afford **4b** (11.6 g, 68% from 2-benzyl-1,3-propanediol) as a colorless oil: TLC R_f 0.66 (petroleum ether/ether (1:1)); ^{1}H NMR ($CDCl_3$) δ 9.79 (s, 1H, H-1), 7.26–7.13 (m, 5H, Ph), 3.89 (dd, 1H, J = 4.3, –10.3 Hz, H-3$_a$), 3.74 (dd, 1H, J = 5.4, –10.3 Hz, H-3$_b$), 3.05 (dd, 1H, J = 6.2, –13.9 Hz, PhCH_{2a}), 2.82 (dd, 1H, J = 8.2, –13.9 Hz, PhCH_{2b}), 2.68 (dddd, 1H, H-2), 0.89 [s, 9H, (CH_3)$_3$CSi], 0.03 (s, 3H, CH_3-Si), 0.02 (s, 3H, CH_3'Si); ^{13}C NMR ($CDCl_3$) δ 203.84 (C-1), 138.82 (C-1'), 128.98 (2 C:s), 128.45 (2 C:s) (C-2', C-3'), 126.28 (C-4'), 60.63 (C-3), 55.54 (C-2), 31.13 (PhCH_2), 25.72 (3 C:s) [(CH_3)$_3$-CSi], 18.12 [(CH$_3$)$_3$CSi], –5.62, –5.65 [(CH$_3$)$_2$Si)]; IR (neat) 1730, 1100 cm^{-1}. Anal. Calcd for $C_{16}H_{28}O_2Si$: C, 69.0; H, 9.4. Found: C, 68.7; H, 9.7.

2,2-Dibenzyl-3-[(*tert*-butyldimethylsilyl)oxy]propanal (4d). Compound **4d** was prepared by use of the procedure described for the synthesis of **4b** starting from benzyl bromide (20.7 mL, 174 mmol), K_2CO_3 (24 g, 174 mmol), and dimethyl malonate (5.00 mL, 43.5 mmol) in acetone (125 mL) via **dimethyl 2,2-dibenzylmalonate,**[13] **2,2-dibenzyl-1,3-propanediol,** and **2,2-dibenzyl-3-[(*tert*-butyldimethylsilyl)oxy]-1-propanol** [TLC R_f 0.58 (petroleum ether/ether (1:2)); ^{1}H NMR ($CDCl_3$) δ 7.31–7.19 (m, 10H, Ph), 3.46–3.44 (m, 4H, H-1, H-3), 2.72 (m, 4H, PhCH_2, PhCH_2'), 2.40 (t, 1H, J = 5.4 Hz, OH), 0.95 [s, 9H, (CH_3)$_3$-CSi)], 0.07 (s, 6H, CH_3Si); ^{13}C NMR ($CDCl_3$) δ 137.87 (2 C:s) (C-1', C-1''), 130.64 (4 C:s), 127.99 (4 C:s) (C-2', C-2'', C-3', C-3''), 126.17 (2 C:s) (C-4', C-4''), 67.36 (C-1), 66.53 (C-3), 43.58 (C-2), 39.01 (2 C:s) (PhCH_2, PhCH_2'), 25.92 (3 C:s) [(CH_3)$_3$CSi], 18.17 [(CH$_3$)$_3$CSi], –5.60 (2 C:s) [(CH_3)$_2$Si]; IR (neat) 3600–3200, 1080 cm^{-1}. Anal. Calcd for $C_{23}H_{34}O_2Si$: C, 74.5; H, 9.2. Found: C, 74.2; H, 9.0]. Compound **4d** (12.2 g, 76% overall yield) was obtained as a white solid: TLC R_f 0.61 (petroleum ether/ether (1:1)); mp 52–53 °C; ^{1}H NMR ($CDCl_3$) δ 9.71 (s, 1H, H-1), 7.29–7.12 (m, 10H, Ph), 3.53 (s, 2H, H-3), 2.95 (m, 4H, PhCH_2, PhCH_2'), 0.97 [s, 9H, (CH_3)$_3$CSi], 0.04 [s, 6H, (CH$_3$)$_2$Si]; ^{13}C NMR ($CDCl_3$) δ 206.16 (C-1), 136.39 (2 C:s) (C-1', C-1''), 130.33 (4 C:s), 128.23 (4 C:s) (C-2', C-2'', C-3', C-3''), 126.65 (2 C:s) (C-4', C-4''), 61.36 (C-3), 56.17 (C-2), 37.99 (2 C:s) (PhCH_2, PhCH_2'), 25.90 (3 C:s) [(CH_3)$_3$CSi], 18.15 [(CH$_3$)$_3$CSi], –5.60 (2 C:s) [(CH_3)$_2$Si]; IR (neat) 1725, 1080 cm^{-1}. Anal. Calcd for $C_{23}H_{32}O_2Si$: C, 74.9; H, 8.8. Found: C, 75.2; H, 9.1.

Preparation of the Hexenols. (*S*)-5-[(*tert*-Butoxycarbonyl)amino]-6-phenyl-(*E*)-3-hexen-1-ol (5a) and (*S*)-5-[(*tert*-Butoxycarbonyl)amino]-6-phenyl-(*Z*)-3-hexen-1-ol (6a). A suspension of sulfone **3** (6.7 g, 18 mmol) in THF (300 mL) was refluxed until a clear solution was obtained. The solution was cooled to –78 °C, and *n*-butyllithium (1.6 M in hexane) (25 mL) was added dropwise. The solution was stirred for 30 min at –78 °C. In a separate flask, a solution of **4a** (6.7 g, 35 mmol) in THF (5 mL) was treated with DIBAL methoxide [prepared by the addition of MeOH (1.7 mL, 42 mmol) and THF (5 mL) to DIBAL (20% in toluene) (30 mL, 42 mmol) at –78 °C]. The solution of the aluminum complex was transferred via cannula to the solution of the sulfone dianion, and the mixture was stirred for 30 min at –78 °C. The reaction was quenched at –78 °C with saturated aqueous NH_4Cl and was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated. MeOH (100 mL) was added, and undissolved **3** was filtered off. The MeOH solution was cooled to 0 °C and treated with Na_2HPO_4 (14 g, 37 mmol) and 6% Na(Hg) (140 g). The mixture was stirred overnight at 0 °C, diluted with water, and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated. Flash chromatography (pentane/ether (9:1)) afforded 5.8 g of an *E*/*Z* isomeric mixture of **(*S*)-1-benzyl-*N*-(*tert*-butoxycarbonyl)-5-[(*tert*-butyldimethylsilyl)oxy]-2-pentenylamine** as a colorless oil, which was used in the next step without further purification.

The crude product (5.8 g, 14 mmol) was dissolved in acetonitrile (100 mL) containing 2% HF (5 mL of a 40% aqueous HF solution). The reaction mixture was stirred at room temperature until the deprotection was complete according to TLC, and CH_2Cl_2 and H_2O were added. The organic phase was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/$CHCl_3$/MeOH (5:4:1)) yielded 3.55 g (68% yield calculated from sulfone **3**) of a mixture of the *E* and *Z* isomers **5a** and **6a** as a colorless oil which solidified upon standing at room temperature. According to analytical HPLC the *E*/*Z* ratio was 86:14. Recrystallization twice from $CHCl_3$/hexane afforded pure **5a**. **6a** was purified by preparative HPLC (1.5% EtOH in hexane, t_R **5a** 94 min, **6a** 67 min).

5a: HPLC (column B; 50% EtOAc in hexane), 1.5 mL/min, t_R 6.97 min; mp 80–81 °C; $[\alpha]_D$ +12.7° (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.31–7.14 (m, 5H, Ph), 5.51–5.35 (m, 2H, H-3, H-4), 4.53 (br s, 1H, NH), 4.31 (m, 1H, H-5), 3.53 (q, 2H, H-1), 2.87 (dd, 1H, J = 6.5, –13.5 Hz, H-6$_a$), 2.76 (dd, 1H, J = 7.2, –13.5 Hz, H-6$_b$), 2.22 (m, 2H, H-2), 1.69 (br s, 1H, OH), 1.39 [s, 9H, (CH_3)$_3$C]; ^{13}C NMR ($CDCl_3$) δ 155.20 (*C*=O), 137.50 (C-1'), 133.08, 127.69 (C-3, C-4), 129.47 (2 C:s), 128.34 (2 C:s) (C-2', C-3') 126.49 (C-4'), 79.46 [(CH$_3$)$_3$C], 61.46 (C-1), 53.57 (C-5), 41.60 (C-6), 35.60 (C-2), 28.32 (3 C:s) [(CH_3)$_3$C]; IR (KBr) 3370, 1690, 1670, 1530 cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.1; H, 8.7; N, 4.8. Found: C, 70.0; H, 8.5; N, 4.7.

6a: HPLC (column B, 50% EtOAc in hexane), 1.5 mL/min, t_R 5.17 min; mp 92–93 °C; $[\alpha]_D$ –8.6° (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.38–7.23 (m, 5H, Ph), 5.57–5.36 (m, 2H, H-3, H-4), 4.67 (br s, 2H, H-5, NH), 3.58 (m, 1H, H-1$_a$), 3.50 (m, 1H, H-1$_b$), 2.93 (dd, 1H, H-6$_a$), 2.74 (dd, 1H, H-6$_b$), 2.49 (br s, 2H, OH, H-2$_a$), 2.06 (m, 1H, H-2$_b$), 1.47 [s, 9H, (CH_3)$_3$C]; ^{13}C NMR ($CDCl_3$) δ 155.42 (C=O), 137.22 (C-1'), 132.02, 128.66 (C-3, C-4), 129.49 (2 C:s), 128.30 (2 C:s) (C-2', C-3'), 126.49 (C-4'), 79.71 [(CH$_3$)$_3$C], 61.44 (C-1), 49.18 (C-5), 41.42 (C-6), 30.87 (C-2), 28.32 (3 C:s) [(CH_3)$_3$C]; IR (KBr) 3370, 1690, 1535 cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.1; H, 8.7; N, 4.8. Found: C, 69.9; H, 8.7; N, 4.8.

(2*R*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-6-phenyl-(*E*)-3-hexen-1-ol (5b), (2*R*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-6-phenyl-(*Z*)-3-hexen-1-ol (6b), (2*S*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-6-phenyl-(*E*)-3-hexen-1-ol (5c), and (2*S*,5*S*)-2-benzyl-5-[(*tert*-butoxycarbonyl)amino]-6-phenyl-(*Z*)-3-hexen-1-ol (6c). A mixture of **5b** (42%), **5c** (42%), **6b** (8%), and **6c** (8%) (HPLC analysis) was prepared from **3** (2.53 g, 6.45 mmol) and **4b** (2.16 g, 7.74 mmol) in 48% yield as described above for the preparation of **5a** and **6a**. The *Z*-isomer (+)-**6** (55 mg) was separated from the mixture with $CHCl_3$/MeOH/hexane (4:1:10), whereas (–)-**6** (122 mg) was separated from the *E*-isomers with ether/petroleum ether (1:1). **5b** and **5c** (809 mg) were obtained as a mixture which was separated using preparative HPLC [1% EtOH in hexane, 13 mL/min, t_R **5b** 84 min, **5c** 77 min] giving **5b** (255 mg) and **5c** (310 mg), respectively.

5b: HPLC (column A, 1.5% EtOH in hexane), 1.0 mL/min,

t_R 21.14 min; $[\alpha]_D$ −31.7° (c = 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.29–7.06 (m, 10H, Ph), 5.40–5.25 (m, 2H, H-4, H-3), 4.48 (br s, 1H, NH), 4.29–4.25 (m, 1H, H-5), 3.49 (ddd, 1H, J = 4.6, 7.8, −10.7 Hz, H-1_a), 3.30 (ddd, 1H, J = 4.1, 7.3, −10.7 Hz, H-1_b), 2.88 (dd, 1H, J = 6.1, −13.2 Hz, H-6_a), 2.71–2.60 (m, 1H, H-6_b), 2.71–2.51 (m, 2H, PhCH_2), 2.49–2.42 (m, 1H, H-2), 1.42 [s, 9H, (CH_3)$_3$C]; ^{13}C NMR ($CDCl_3$) δ 155.12 (C=O), 139.67, 137.54 (C-1′, C-1″), 132.54, 131.84 (C-3, C-4), 129.40 (2 C:s), 129.11 (2 C:s), 128.34 (2 C:s), 128.18 (2 C:s) (C-2′, C-2″, C-3′, C-3″), 126.45, 125.94 (C-4′, C-4″), 79.44 [(CH$_3$)$_3$C], 64.88 (C-1), 53.65 (C-5), 46.85 (C-2), 41.60 (C-6), 37.32 (PhCH$_2$), 28.33 (3 C:s) [(CH$_3$)$_3$C]; IR (neat) 3400, 1700, 1170 cm^{-1}. Anal. Calcd for $C_{24}H_{31}NO_3$·0.25H_2O: C, 74.7; H, 8.2; N, 3.6. Found: C, 75.0; H, 8.4; N, 3.8.

5c: HPLC (column A, 1.5% EtOH in hexane), 1.0 mL/min, t_R 19.31 min; $[\alpha]_D$ +11.0° (c = 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.29–7.04 (m, 10H, Ph), 5.35–5.33 (m, 2H, H-4, H-3), 4.49 (br s, 1H, NH), 4.31–4.22 (m, 1H, H-5), 3.52 (ddd, 1H, J = 4.4, 8.5, −10.8 Hz, H-1_a), 3.36 (ddd, 1H, J = 4.1, 7.5, −10.8 Hz, H-1_b), 2.76 (d, 2H, J = 6.5 Hz, H-6), 2.69–2.52 (m, 2H, PhCH_2), 2.54–2.45 (m, 1H, H-2), 1.40 [s, 9H, (CH_3)$_3$C]; ^{13}C NMR ($CDCl_3$) δ 155.25 (C=O), 139.62, 137.16 (C-1′, C-1″), 133.02, 132.43 (C-3, C-4), 129.50 (2 C:s), 129.14 (2 C:s), 128.41 (2 C:s), 128.26 (2 C:s) (C-2′, C-2″, C-3′, C-3″), 126.57, 126.02 (C-4′, C-4″), 79.58 [(CH$_3$)$_3$C], 64.90 (C-1), 53.82 (C-5), 47.04 (C-2), 41.38 (C-6), 37.36 (PhCH$_2$), 28.36 (3 C:s) [(CH$_3$)$_3$C]; IR (neat) 3400, 1700, 1170 cm^{-1}. Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.6; H, 8.2; N, 3.7. Found: C, 75.4; H, 8.6; N, 3.8.

(+)-6: HPLC (column A, 1.5% EtOH in hexane), 1.0 mL/min, t_R 15.15 min; mp 72–74 °C; $[\alpha]_D$ +55.6° (c = 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.30–6.98 (m, 10H, Ph), 5.31–5.21 (m, 2H, H-2, H-3), 4.52 (br d, 1H, NH), 4.35–4.24 (m, 1H, H-5), 3.78–3.71 (m, 1H, H-1_a), 3.40–3.30 (m, 2H, H-1_b, OH), 3.08–3.01 (m, 1H, H-2), 2.55 (dd, 1H, J = 5.6, −13.2 Hz, PhCH_{2a}), 2.31–2.17 (m, 3H, PhCH_{2b}, H-6), 1.35 [s, 9H, (CH_3)$_3$C]; ^{13}C NMR ($CDCl_3$) δ 155.81 (C=O), 139.80, 136.91 (C-1′, C-1″), 132.92, 132.33 (C-3, C-4), 129.40 (2 C:s), 129.22 (2 C:s), 128.43 (2 C:s), 128.21 (2 C:s) (C-2′, C-2″, C-3′, C-3″), 126.63, 126.04 (C-4′, C-4″), 80.04 [(CH$_3$)$_3$C], 66.02 (C-1), 49.17 (C-5), 43.49 (C-2), 40.36 (C-6), 38.06 (PhCH$_2$), 28.30 (3 C:s) [(CH$_3$)$_3$C]; IR (KBr) 3440, 3280, 1680, 1170 cm^{-1}. Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.6; H, 8.2; N, 3.7. Found: C, 75.3; H, 8.1; N, 3.4.

(−)-6: HPLC (column A, 1.5% EtOH in hexane), 1.0 mL/min, t_R 17.41 min; mp 66–67 °C; $[\alpha]_D$ −44.4° (c = 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.27–7.13 (m, 10H, Ph), 5.35 (dd, 1H, J = 9.1, 11.0, H-4), 5.23 (dd, 1H, J = 9.8, 11.0, H-3), 4.45–4.34 (m, 1H, H-5), 4.22 (br s, 1H, NH), 3.27 (ddd, 1H, J = 4.9, 7.3, −10.6 Hz, H-1_a), 3.11 (ddd, 1H, J = 5.3, 6.9, −10.6 Hz, H-1_b), 3.02 (dd, 1H, J = 5.0, −13.0 Hz, H-6_a), 2.78–2.71 (m, 1H, H-2), 2.71–2.46 (m, 3H, PhCH_2, H-6_b), 1.44 (s, 9H, (CH_3)$_3$C]; ^{13}C NMR ($CDCl_3$) δ 154.82 (C=O), 139.42, 137.92 (C-1′, C-1″), 133.46, 131.43 (C-3, C-4), 129.70 (2 C:s), 129.16 (2 C:s), 128.28 (2 C:s), 128.19 (2 C:s) (C-2′, C-2″, C-3′, C-3″), 126.45, 126.02 (C-4′, C-4″), 79.28 [(CH$_3$)$_3$C], 65.25 (C-1), 50.10 (C-5), 42.61 (C-2), 42.07 (C-6), 37.86 (PhCH$_2$), 28.43 (3 C:s) [(CH$_3$)$_3$C]; IR (neat) 3400, 1690, 1170 cm^{-1}. Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.6; H, 8.2; N, 3.7. Found: C, 75.6; H, 8.2; N, 3.9.

(*S*)-2,2-Dibenzyl-5-[(*tert*-butoxycarbonyl)amino]-6-phenyl-(*E*)-3-hexen-1-ol (5d). Compound **5d** was synthesized from **3** (2.36 g, 6.04 mmol) and **4d** (2.45 g, 6.64 mmol) according to the following modifications of the procedure described above. Column chromatography (ether/petroleum ether (1:9)) afforded (*S*)-1,4,4-tribenzyl-*N*-(*tert*-butoxycarbonyl)-5-[(*tert*-butyldimethylsilyl)oxy]-(*E*)-3-pentenylamine [1.60 g, 47%] containing 5% of a byproduct tentatively assigned as 2,2-dibenzyl-1-[(*tert*-butyldimethylsilyl)oxy]-6-phenyl-4-hexen-3-ol).[1b] To fully characterize the desired product a selective desilylation of the byproduct was performed by treatment of the mixture with 2% HF in aqueous acetonitrile. Column chromatography (ether/petroleum ether (1:9)) afforded pure **(*S*)-1,4,4-tribenzyl-*N*-(*tert*-butoxycarbonyl)-5-[(*tert*-butyldimethylsilyl)oxy]-(*E*)-3-pentenylamine**: $[\alpha]_D$ −15.7° (c = 1.2, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.21–6.87 (m, 15 H, Ph), 5.47 (d, 1H, J = 16.2 Hz, H-3), 4.72 (dd, 1H, J = 5.9, 16.2 Hz, H-4), 4.27–4.23 (m br, 2H, H-5, NH), 3.17 (s, 2H, H-1), 2.83–2.55 (m, 6H, H-6, PhCH_2), 1.39 [s, 9H, (CH_3)$_3$C], 0.97 [s, 9H, (CH_3)$_3$CSi], 0.03 (s, 6H, SiCH_3); ^{13}C NMR ($CDCl_3$) δ 154.90 (C=O), 138.05, 138.01, 137.48, (C-1′, C-1″, C-1‴), 135.13 (C-3), 128.37 (C-4), 130.86 (2 C:s), 130.84 (2 C:s), 129.51 (2 C:s), 128.11 (2 C:s), 127.53 (2 C:s), 127.44 (2 C:s) (C-2′, C-2″, C-2‴, C-3′, C-3″, C-3‴), 126.27, 125.98, 125.91 (C-4′, C-4″, C-4‴), 79.09 [(CH$_3$)$_3$C], 63.64 (C-1), 53.42 (C-5), 45.38 (C-2), 42.78, 42.57 (PhCH$_2$, PhCH$_2$′), 41.75 (C-6), 28.37 (3 C:s) [(CH$_3$)$_3$C], 25.99 (3 C:s) [(CH$_3$)$_3$CSi], 18.20 [(CH$_3$)$_3$CSi], −5.52, −5.55 [(CH$_3$)$_2$Si]; IR (neat) 1710, 1170 cm^{-1}. Anal. Calcd for $C_{37}H_{51}NO_3$·Si·0.5H_2O: C, 74.7; H, 8.8; N, 2.4. Found: C, 74.5; H, 8.8; N, 2.3.

A solution of the above crude product (1.37 g, 2.47 mmol) in THF (50 mL) was treated with TBAF (1 M in THF) (36 mL, 36 mmol) and stirred for 48 h at room temperature. Extraction with ether followed by column chromatography (MeOH/$CHCl_3$/hexane (1:4:5)) gave **5d** (980 mg, 86%) which was contaminated by 8% of the desilylated byproduct. To fully characterize the compound a sample was purified by repeated column chromatography (MeOH/$CHCl_3$/hexane (1:4:5)): HPLC (column A, 2.5% EtOH in hexane), 1.5 mL/min, t_R 8.84 min; $[\alpha]_D$ −16.3° (c = 2.7, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.31–7.00 (m, 15 H, Ph), 5.47 (d, 1H, J = 16.1 Hz, H-3), 5.07 (dd, 1H, J = 6.8, 16.1 Hz, H-4), 4.44 (s br, 1H, NH), 4.32–4.26 (m, 1H, H-5), 3.27 (app d, 2H, J = 6.0 Hz, H-1), 2.88–2.63 (m, 6H, H-6, PhCH_2), 1.43 [s, 9H, (CH_3)$_3$C]; ^{13}C NMR ($CDCl_3$) δ 155.13 (C=O), 137.66, 137.55, 137.39, (C-1′, C-1″, C-1‴), 136.08 (C-3), 129.68 (C-4), 130.84 (2 C:s), 130.81 (2 C:s), 129.48 (2 C:s), 128.42 (2 C:s), 127.86 (2 C:s), 127.79 (2 C:s) (C-2′, C-2″, C-2‴, C-3′, C-3″, C-3‴), 126.58, 126.19, 126.13 (C-4′, C-4″, C-4‴), 79.51 [(CH$_3$)$_3$C], 64.23 (C-1), 54.30 (C-5), 45.37 (C-2), 41.68 (C-6), 41.53, 41.42 (PhCH$_2$, PhCH$_2$′), 28.38 (3 C:s) [(CH$_3$)$_3$C]; IR (neat) 3400, 1690, 1170 cm^{-1}. Anal. Calcd for $C_{31}H_{37}NO_3$·0.5 H_2O: C, 77.5; H, 8.0; N, 2.9. Found: C, 77.5; H, 7.7; N, 2.7.

Epoxidation Reactions. Methyl (3*R*,4*R*,5*S*)-5-[(*tert*-Butoxycarbonyl)amino]-3,4-epoxy-6-phenylhexanoate (7a). *m*-CPBA (1.0 g, 5.8 mmol) was added to a solution of **1a** (0.8 g, 2.5 mmol) in CH_2Cl_2 (50 mL). After being stirred at room temperature for 40 h the reaction mixture was washed with saturated aqueous Na_2SO_3, 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The ether layer was dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (petroleum ether/ether (2:1)) gave 0.63 g (75%) of **7a**: HPLC (column A, 1% EtOH in hexane), 1.5 mL/min, t_R 20.2 min; mp 52–54 °C; $[\alpha]_D$ +7.4° (c = 1.0, MeOH); ^1H NMR ($CDCl_3$) δ 7.35–7.20 (m, 5H, Ph), 4.52 (br s, 1H, NH), 4.12 (m, 1H, H-5), 3.71 (s, 3H, OCH_3), 3.17 (ddd, 1H, J = 2.2 Hz, H-3), 2.96 (dd, 1H, J = 6.5 Hz, H-6_a), 2.84 (m, 2H, J = 8.1 Hz, H-4, H-6_b), 2.62 (dd, 1H, J = 4.1 Hz, H-2_a), 2.40 (dd, 1H, J = 7.3 Hz, H-2_b), 1.39 [s, 9H, (CH_3)$_3$C]; ^{13}C NMR ($CDCl_3$) δ 170.55 (C-1), 155.33 (Boc C=O), 137.23 (C-1′), 129.41 (2 C:s), 128.57 (2 C:s) (C-2′, C-3′), 126.68 (C-4′), 79.66 [(CH$_3$)$_3$C], 58.53 (C-4), 51.64 (C-3), 51.95 (OCH$_3$), 50.46 (C-5), 39.60 (C-6), 36.93 (C-2), 28.30 (3 C:s) [(CH$_3$)$_3$C]. Anal. Calcd for $C_{18}H_{25}NO_5$·0.25H_2O: C, 63.6; H, 7.6; N, 4.1. Found: C, 63.3; H, 7.4; N, 3.9.

Methyl (2*R*,3*R*,4*R*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-3,4-epoxy-6-phenylhexanoate (7b) and Methyl (2*R*,3*S*,4*S*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-3,4-epoxy-6-phenylhexanoate (8b). Compounds **7b** and **8b** were prepared from **1b** (170 mg, 0.42 mmol) and *m*-CPBA (153 mg, 0.62 mmol) according to the procedure described above. According to analytical HPLC and ^1H NMR spectroscopy **7b** and **8b** were formed in a ratio of 2:1. Purification by column chromatography (ether/petroleum ether (1:3)) gave **7b** (98.0 mg, 55%) and **8b** (43.5 mg, 25%).

7b: HPLC (column A, 0.5% EtOH/hexane), 1.5 mL/min, t_R 18.2 min; $[\alpha]_D$ +20.8° (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.35–7.16 (m, 10H, Ph), 4.52–4.43 (br s, 1H, NH), 4.11–3.99 (m, 1H, H-5), 3.59 (s, 3H, OCH_3), 3.07–3.01 (m, 4H, H-3, H-4, PhCH_2), 2.93–2.85 (m, 2H, H-6), 2.62–2.54 (m, 1H, H-2), 1.38 [s, 9H, (CH_3)$_3$C]; ^{13}C NMR ($CDCl_3$) δ 171.91 (C-1), 155.15 (Boc C=O), 137.93, 137.05 (C-1′, C-1″), 129.34 (2 C:s), 128.82 (2 C:s), 128.50 (2 C:s), 128.43 (2 C:s) (C-2′, C-2″, C-3′, C-3″), 126.60, 126.56 (C-4′, C-4″), 79.55 [(CH$_3$)$_3$C], 58.51 (C-4), 55.80 (C-3), 51.81 (OCH$_3$), 50.58 (C-5), 49.49 (C-2), 39.26 (C-6), 35.38 (PhCH$_2$), 28.21 (3 C:s) [(CH$_3$)$_3$C]; IR (neat) 3400, 1750, 1700, 1170 cm^{-1}. Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.6; H, 7.3; N, 3.3. Found: C, 70.6; H, 7.2; N, 3.2.

8b: HPLC (column A, 0.5% EtOH/hexane), 1.5 mL/min, t_R 23.6 min); mp 110–112 °C (CH_2Cl_2/hexane); $[\alpha]_D$ −47.8° (c = 1.0,

$CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.33–7.10 (m, 10H, Ph), 4.24 (s, 1H, NH), 3.69 (s, 3H, OCH_3), 3.63–3.55 (m, 1H, H-5), 3.29 (d, 1H, J = 7.5 Hz, H-3), 3.06 (dd, 1H, J = 7.8, −13.8 Hz, $PhCH_{2a}$), 2.90–2.68 (m, 2H, H-6), 2.82 (dd, 1H, J = 7.5, −13.7 Hz, $PhCH_{2b}$), 2.54–2.48 (m, 1H, H-4), 2.51–2.43 (m, 1H, H-2), 1.39 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 172.85 (C-1), 154.95 (Boc C=O), 137.84, 136.53 (C-1′, C-1″), 129.40 (2 C:s), 128.75 (2 C:s), 128.52 (4 C:s) (C-2′, C-2″, C-3′, C-3″), 126.72, 126.65 (C-4′, C-4″), 79.62 [$(CH_3)_3C$], 59.00 (C-4), 58.43 (C-3), 52.26 (C-5), 52.01 (OCH_3), 50.29 (C-2), 37.44 (C-6), 35.03 ($PhCH_2$), 28.25 (3 C:s) [$(CH_3)_3C$]; IR (KBr) 3410, 1735, 1700, 1180 cm^{-1}. Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.6; H, 7.3; N, 3.3. Found: C, 70.6; H, 7.6; N, 3.3.

Methyl (2*S*,3*R*,4*R*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-3,4-epoxy-6-phenylhexanoate (7c) and Methyl (2*S*,3*S*,4*S*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-3,4-epoxy-6-phenylhexanoate (8c). Compounds **7c** and **8c** were synthesized from **1c** (179 mg, 0.437 mmol) using the procedure described above. According to HPLC **7c** and **8c** were obtained in a 9:1 ratio. The mixture was purified by column chromatography (ether/petroleum ether (1:3)) giving **7c** (134 mg, 73%) and **8c** (10 mg, 5%).

7c: HPLC (column A, 0.5% EtOH/hexane), 1.5 mL/min, t_R 17.59 min; mp 123–124 °C (CH_2Cl_2/hexane); $[\alpha]_D$ +54.0° (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.30–7.11 (m, 10H, Ph), 4.41 (br d, 1H, NH), 3.98–3.90 (m, 1H, H-5), 3.71 (s, 3H, OCH_3), 3.11–3.05 (m, 1H, H-3), 3.11–3.00 (m, 1H, $PhCH_{2a}$), 2.84–2.75 (m, 2H, $PhCH_{2b}$, $H\text{-}6_a$), 2.67 (dd, 1H, J = 8.1, −13.4 Hz, $H\text{-}6_b$), 2.44–2.35 (m, 2H, H-2, H-4), 1.41 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 173.06 (C-1), 155.18 (Boc C=O), 137.68, 136.98 (C-1′, C-1″), 129.24 (2 C:s), 128.79 (2 C:s), 128.55 (2 C:s), 128.43 (2 C:s) (C-2′, C-2″, C-3′, C-3″), 126.76, 126.50 (C-4′, C-4″), 79.52 [$(CH_3)_3C$], 58.60 (C-4), 55.46 (C-3), 52.02 (OCH_3), 50.05 (C-5), 49.62 (C-2), 39.39 (C-6), 35.28 ($PhCH_2$), 28.25 (3 C:s) [$(CH_3)_3C$]; IR (KBr) 3440, 1750, 1700, 1190 cm^{-1}. Anal. Calcd for $C_{25}H_{31}NO_5 \cdot 0.25H_2O$: C, 69.8; H, 7.4; N, 3.3. Found: C, 69.8; H, 7.4; N, 3.5.

8c: HPLC (column A, 0.5% EtOH/hexane), 1.5 mL/min, t_R 20.85 min; mp 100–101 °C (CH_2Cl_2/hexane); $[\alpha]_D$ −30.7° (c = 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.34–7.16 (m, 10H, Ph), 4.41 (br s, 1H, NH), 3.75–3.64 (m, 1H, H-5), 3.59 (s, 3H, OCH_3), 3.20 (br d, 1H, J = 6.7 Hz, H-3), 3.05 (d, 2H, J = 7.2 Hz, $PhCH_2$), 2.94 (dd, 1H, J = 5.0, −14.0 Hz, $H\text{-}6_a$), 2.92–2.89 (m, 1H, H-4), 2.82 (dd, 1H, J = 7.5, −14.0 Hz, $H\text{-}6_b$), 2.65–2.56 (m, 1H, H-2), 1.38 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 171.91 (C-1), 155.09 (Boc C=O), 138.10, 136.55 (C-1′, C-1″), 129.40 (2 C:s), 128.90 (2 C:s), 128.59 (2 C:s), 128.46 (2 C:s) (C-2′, C-2″, C-3′, C-3″), 126.72, 126.60 (C-4′, C-4″), 79.64 [$(CH_3)_3C$], 58.71 (C-4), 57.98 (C-3), 52.17 (C-5), 51.81 (OCH_3), 49.94 (C-2), 37.52 (C-6), 35.49 ($PhCH_2$), 28.27 (3 C:s) [$(CH_3)_3C$]. Anal. Calcd for $C_{25}H_{31}NO_5 \cdot 0.25H_2O$: C, 69.8; H, 7.4; N, 3.3. Found: C, 69.8; H, 7.1; N, 3.0.

Methyl (3*R*,4*R*,5*S*)-2,2-Dibenzyl-5-[(*tert*-butoxycarbonyl)amino]-3,4-epoxy-6-phenylhexanoate (7d) and Methyl (3*S*,4*S*,5*S*)-2,2-Dibenzyl-5-[(*tert*-butoxycarbonyl)amino]-3,4-epoxy-6-phenylhexanoate (8d). Compounds **7d** and **8d** were synthesized from **1d** (154 mg, 0.308 mmol) using the procedure described above. According to analytical HPLC **7d** and **8d** were obtained in a 9:1 ratio. The mixture was purified by column chromatography (EtOAc/hexane (1:9)) affording **7d** (129 mg, 81%) and **8d** (14 mg, 9%).

7d: HPLC (column B, 10% EtOAc in hexane), 1.5 mL/min, t_R 17.55 min; $[\alpha]_D$ +5.95° (c = 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.29–7.10 (m, 15H, Ph), 4.38 (br d, 1H, NH), 4.05–4.00 (m, 1H, H-5), 3.62 (s, 3H, OCH_3), 3.08–3.04 (m, 1H, H-4), 3.07 (d, 1H, J = −13.9 Hz, $PhCH_{2a}$), 2.99–2.95 (m, 1H, H-3), 2.90 (d, 1H, J = −13.9 Hz, $PhCH_{2a'}$), 2.90–2.79 (m, 4H, H-6, $PhCH_{2b}$, $PhCH_{2b'}$), 1.31 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 173.23 (C-1), 155.06 (Boc C=O), 137.20, 136.49, 136.16 (C-1′, C-1″, C-1‴), 130.27 (4 C:s), 129.32 (2 C:s), 128.40 (2 C:s), 128.18 (2 C:s), 128.10 (2 C:s) (C-2′, C-2″, C-2‴, C-3′, C-3″, C-3‴), 126.73, 126.66, 126.47 (C-4′, C-4″, C-4‴), 79.26 [$(CH_3)_3C$], 57.65 (C-3), 56.34 (C-4), 51.68 (OCH_3), 51.11 (C-2), 50.01 (C-5), 40.02, 39.48 ($PhCH_2$, $PhCH_2'$), 39.36 (C-6), 28.12 (3 C:s), [$(CH_3)_3C$]; IR (neat) 3400, 1715, 1170 cm^{-1}. Anal. Calcd for $C_{32}H_{37}NO_5 \cdot 0.25H_2O$: C, 73.9; H, 7.3; N, 2.7. Found: C, 74.0; H, 7.3; N, 2.6.

8d: HPLC (column B, 10% EtOAc/hexane), 1.5 mL/min, t_R 24.70 min; $[\alpha]_D$ −16.4° (c = 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.31–7.11 (m, 15H, Ph), 4.36 (br d, 1H, NH), 3.80–3.76 (m, 1H, H-5), 3.62 (s, 3H, OCH_3), 3.12 (m, 1H, H-4), 3.08 (d, 1H, J = 2.1 Hz, H-3), 3.03 (d, 1H, J = −13.9 Hz, $PhCH_{2'}$), 3.00–2.83 (m, 2H, $PhCH_{2a}$), 2.83 (d, 1H, $PhCH_{2b}$), 2.80–2.67 (m, 2H, H-6), 1.37 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 173.25 (C-1), 155.08 (Boc C=O), 136.91, 136.58, 136.41 (C-1′, C-1″, C-1‴), 130.45 (2 C:s), 130.31 (2 C:s), 129.43 (2 C:s), 128.45 (2 C:s), 128.18 (4 C:s), (C-2′, C-2″, C-2‴, C-3′, C-3″, C-3‴), 126.80, 126.70, 126.55 (C-4′, C-4″, C-4‴), 79.49 [$(CH_3)_3C$], 59.52 (C-3), 57.04 (C-4), 51.95 (C-5), 51.75 (OCH_3), 51.29 (C-2), 40.17, 39.66 ($PhCH_2$, $PhCH_2'$), 37.03 (C-6), 28.28 (3 C:s) [$(CH_3)_3C$]; IR (neat) 3400, 1710, 1170 cm^{-1}. Anal. Calcd for $C_{32}H_{37}NO_5 \cdot H_2O$: C, 72.0; H, 7.4; N, 2.6. Found: C, 72.3; H, 7.3; N, 2.5.

Ring Opening of the Epoxides. Methyl (4*S*,5*S*)-5-[(*tert*-Butoxycarbonyl)amino]-4-hydroxy-6-phenyl-(*E*)-2-hexenoate (9). TBAF (1 M in THF) (2 mL, 1.95 mmol) was added to a solution of **7a** (0.44 g, 1.3 mmol) in THF (50 mL). The reaction was stirred at room temperature overnight. The solvent was evaporated, and the residue was purified by flash chromatography (0.5% MeOH/hexane). Recrystallization (hexane/EtOAc) gave 0.40 g (91%) of **9**: HPLC (column A, 2.5% EtOH in hexane), 1.5 mL/min, t_R 10.1 min; mp 113–114 °C; $[\alpha]_D$ −65.0° (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.34–7.21 (m, 5H, Ph), 6.96 (dd, 1H, J = 4.2, 15.6 Hz, H-3), 6.12 (dd, 1H, J = 1.4 Hz, H-2), 4.91 (d, 1H, J = 8.9 Hz, NH), 4.32 (br s, 1H, H-5), 3.85 (m, 1H, H-4), 3.73 (s, 3H, OCH_3), 3.43 (br s, 1H, OH), 2.96 (m, 2H, H-6), 1.39 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 166.84 (C-1), 156.24 (Boc C=O), 148.43, 126.59 (C-2, C-3), 137.99 (C-1′), 129.23 (2 C:s), 128.61 (2 C:s) (C-2′, C-3′), 121.17 (C-4′), 79.91 [$(CH_3)_3C$], 71.01 (C-4), 56.06 (C-5), 51.63 (OCH_3), 37.43 (C-6), 28.21 (3 C:s) [$(CH_3)_3C$]. Anal. Calcd for $C_{18}H_{25}NO_5 \cdot 0.25H_2O$: C, 63.6; H, 7.6; N, 4.1. Found: C, 63.7; H, 7.4; N, 4.0.

Methyl (4*S*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-6-phenyl-(*E*)-2-hexenoate (11). Compound **11** was synthesized from **7c** (47.9 mg, 0.113 mmol) as described above for the synthesis of **9**. Purification by column chromatography ($CHCl_3$/MeOH/hexane (4:1:15)) gave **11** (39.1 mg, 82%) as a colorless oil: HPLC (column A, 2.5% EtOH in hexane), 1.5 mL/min, t_R 12.5 min; $[\alpha]_D$ −6.1° (c = 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.32–6.97 (m, 10H, Ph), 6.86 (d, 1H, J = 9.0 Hz, H-3), 4.91 (d, 1H, J = 9.0 Hz, NH), 4.47 (d, 1H, J = 9.0 Hz, H-4), 3.73–3.64 (m, 1H, H-5), 3.70 (s, 3H, OCH_3), 3.64–3.46 (ABq, 2H, $PhCH_2$), 2.87–2.84 (m, 2H, H-6), 2.71 (br s, 1H, OH), 1.41 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 167.82 (C-1), 156.24 (Boc C=O), 141.35 (C-3), 139.14, 137.86 (C-1′, C-1″), 132.92 (C-2), 129.23 (2 C:s), 128.60 (2 C:s), 128.51 (2 C:s), 128.16 (2 C:s) (C-2′, C-2″, C-3′, C-3″), 126.58, 126.19 (C-4′, C-4″), 79.89 [$(CH_3)_3C$], 68.18 (C-4), 56.36 (C-5), 52.06 (OCH_3), 37.62 (C-6), 32.53 ($PhCH_2$), 28.27 (3 C:s) [$(CH_3)_3C$]; IR (neat) 3400 br, 1720, 1690, 1170 cm^{-1}. Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.6; H, 7.3; N, 3.3. Found: C, 70.2; H, 7.4; N, 3.0.

Methyl (4*R*,5*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-6-phenyl-(*E*)-2-hexenoate (12). Compound **12** was prepared from **8b** (22.2 mg, 0.052 mmol) as described in the synthesis of **11**. Recrystallization (CH_2Cl_2/hexane) gave **12** (18.1 mg, 82%) as white needles: HPLC (column A, 2.5% EtOH in hexane), 1.5 mL/min, t_R 12.5 min; mp 127–128 °C; $[\alpha]_D$ −53.0° (c = 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.31–7.11 (m, 10H, Ph), 6.87 (d, 1H, J = 8.8 Hz, H-3), 4.65–4.60 (m, 1H, H-4), 4.47 (br d, 1H, NH), 3.98–3.88 (m, 1H, H-5), 3.80–3.66 (m, 2H, $PhCH_2$), 3.72 (s, 3H, OCH_3), 3.26 (br s, 1H, OH), 2.87–2.72 (m, 2H, H-6), 1.36 [s, 9H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 167.80 (C-1), 156.46 (Boc C=O), 140.57 (C-3), 139.22, 137.36 (C-1′, C-1″), 133.74 (C-2), 129.20 (2 C:s), 128.55 (4 C:s), 128.25 (2 C:s) (C-2′, C-2″, C-3′, C-3″), 126.63, 126.25 (C-4′, C-4″), 80.14 [$(CH_3)_3C$], 70.73 (C-4), 56.58 (C-5), 52.08 (OCH_3), 35.76 (C-6), 32.74 ($PhCH_2$), 28.21 (3 C:s) [$(CH_3)_3C$]; IR (KBr) 3340, 1730, 1690, 1520 cm^{-1}. Anal. Calcd for $C_{25}H_{31}NO_5 \cdot 0.25H_2O$: C, 69.8; H, 7.4; N, 3.3. Found: C, 69.6; H, 7.2; N, 3.2.

Crystallography.[31] Single crystals of **8b** ($C_{25}H_{31}NO_5$, M_w = 425.52 amu) suitable for X-ray analysis were crystallized from CH_2Cl_2/hexane. The unit cell is monoclinic ($P2_1$) with a = 5.535-

(31) The authors have deposited atomic coordinates for **8b** 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.

(2) Å, b = 19.434(2) Å, c = 11.274(1) Å, β = 90.34(2)°, and V_c = 1212.7(5) Å^3 and contains two molecules [D_x = 1.165(5) gcm^{-3}, $F(000)$ = 456]. The cell dimensions are refined against θ values of 40 well-centered reflections with $10 < 2\theta < 22°$. The intensity data were collected on a STOE/AED2 diffractometer at 173 ± 1 K from a colorless single crystal with the approximate dimensions 0.4 × 0.2 × 0.1 mm, using Mo Kα radiation (λ = 0.710 69 Å, θ_{max} = 27.5°) and $\omega - 2\theta$ scan technique. Data reduction of 3175 reflections included corrections for background, Lorentz, and polarization effects, but the rather low absorption effects (μ = 0.75 cm^{-1}) were ignored.

Application of direct methods[32] yielded a preliminary model containing all non-hydrogen atoms, which was subjected to full-matrix least-squares refinement based on $|F|$.[33] Only 1261 of the totally 2638 unique reflections had $I/\sigma(I) > 1.5$, thus indicating modest scattering ability for the crystal. The hydrogen atoms were assumed in geometrically idealized positions with C–H = 1.00 Å, which were recalculated after each cycle of the refinement. The methyl groups were treated as rigid. Accordingly, refinement of the non-hydrogen atoms and their anisotropic displacement parameters together with three rotation parameters for each methyl group and a common isotropic vibrational parameter for the H positions (totally 292 variables) converged to R [= $\Sigma||\Delta F|| / \Sigma|F_o|$] = 0.056 and R_w [= $(\Sigma w|\Delta F|^2 / \Sigma w|F_o|^2)^{1/2}$] = 0.047 for 1261 observations. The weights of the structure factors were assumed as $w = 1.10/(\sigma^2(F) + 0.00070F^2)$.[31] The maximum and minimum values of the rest electron density were 0.25 and −0.25 e$^-$Å^{-3}, respectively.

Compound **8b** possesses four stereogenic centra [C-2, C-3, C-4, and C-5, *cf.* Figure 1], and the present crystals were prepared in optically pure form. The final refinement calculation was carried out for the two enantiomers, but they converged to identical crystallographic R values. Hence, only the relative configuration of the molecule could be determined directly from the X-ray diffraction data since the crystal only contains "light" atoms which do not yield observable anomalous dispersion effects with the used X-ray radiation. Nevertheless, the absolute configuration of C-5 could be deduced from chemical evidence to be *S*. Consequently, the absolute configuration of **8b** was determined to be 2*R*,3*S*,4*S*,5*S* (*cf.* Figure 1).

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