Versatile and Stereoselective Synthesis of Diamino Diol Dipeptide Isosteres, Core Units of Pseudopeptide HIV Protease Inhibitors

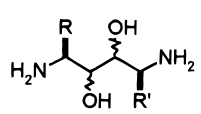
Fabio Benedetti,*,† Stanislav Miertus,‡ Stefano Norbedo,† Alessandro Tossi,§ and Pavel Zlatoidzky†

Department of Chemical Sciences and Department of Biochemistry, Biophysics and Macromolecular Sciences, University of Trieste, via Giorgieri 1, I-34127 Trieste, Italy, and Polytech, Area di Ricerca, Padriciano 99, 34012 Trieste, Italy

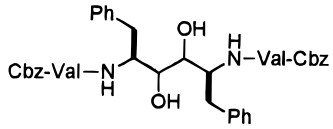
Received July 1, 1997

The human immunodeficiency virus type 1 (HIV-1), which is responsible for AIDS, encodes for three enzymes: a reverse transcriptase, a proteinase (HIV-PR), and an integrase. Each enzyme plays an essential role in the replication cycle and can thus be the target of antiretroviral therapy aimed at the selective inhibition of the virus's proliferation.[1] In the search for new drugs for the treatment of AIDS, an intense effort has been devoted to developing efficient inhibitors of the viral enzymes, in particular of the transcriptase and, more recently, of the proteinase.[2]

The HIV-1 protease is a homodimeric aspartic protease[3] responsible for the proteolytic cleavage of the $Pr55^{gag}$ and $Pr165^{gag-pol}$ polyproteins from which structural proteins and the three viral enzymes originate.[4] The presence of a C_2 axis of symmetry in the homodimer has inspired the development of a new class of protease inhibitors based on pseudopeptides of the type P_n--P_2−P_1−$P_{1'}$-$P_{2'}$--$P_{n'}$ containing a C_2-symmetric 1,4-diamino 2,3-diol **1** as the P_1−$P_{1'}$ nonscissile core unit of a short peptide chain.[2b,5] Pseudopeptides containing dibenzyl-substituted derivatives of **1**, such as, for example, the Abbott inhibitors A-75925, A-76256, and A-76214, have proved particularly effective against HIV-PR with IC_{50} values between 0.2 and 0.4 nM.[5b,6]



1



A-75925 (S,R,R,S)
A-76256 (S,S,S,S)
A-76214 (S,R,S,S)

Identically substituted dihydroxyethylene isosteres **1** (R = R′) can be obtained from C_2-symmetrical building blocks[7] or from the pinacol coupling of α-amino aldehydes.[8] Incorporation of different residues R and R′ in the diamino diol structure **1** by a convergent synthesis has been recently reported;[9] however, this methodology has only been described for benzyl substituents and is characterized by poor stereoselectivity in the crucial diol-forming step. In connection with a project on the synthesis of pseudopeptide inhibitors of HIV-1 protease,[10] we required homochiral *all-S* 1,4-diamino 2,3-diols. In this paper, we describe a practical and stereoselective synthesis that gives access to (*S*,*S*,*S*,*S*)-**1** with either identical or nonidentical R and R′ groups. In our synthetic strategy (Scheme 1), the four-carbon-atom framework is assembled first, starting from a Boc-protected L-amino acid that provides the first asymmetric center; the stereochemistry of the remaining centers is then controlled by chiral induction.

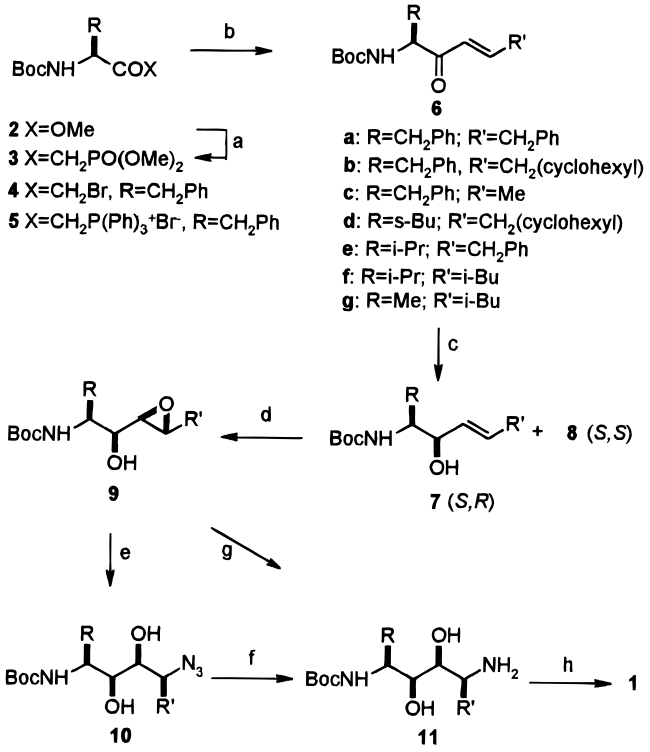
The first step consists of the synthesis of the *trans*-enones **6**. Our initial attempts to prepare **6a** by the Wittig reaction of the *β*-keto phosphonium salt **5** failed at an early stage as we could not obtain **5** from the known[11] bromide **4**. However, *β*-keto phosphonates **3** are readily prepared from amino esters **2**;[12] thus, *trans*-enones **6** were obtained in excellent yield by the Horner−Wadsworth−Emmons reaction of **3** with the appropriate aldehyde, in dry ethanol, in the presence of 1 equiv of potassium carbonate[13] (Scheme 1). Replacement of ethanol by acetonitrile and of potassium carbonate by diisopropylethylamine[14] resulted in lower yields and, in the case of **6a**, in the α,*β* to *β*,*γ* migration of the double bond.

* To whom correspondence should be addressed.
† Department of Chemical Sciences.
‡ Polytech.
§ Department of Biochemistry, Biophysics and Macromolecular Sciences.

(1) Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533.
(2) (a) Gait, M. J.; Karn, J. *Tibtech* **1995**, *13*, 430. (b) Kempf, D. J.; Sham, H. L. *Curr. Pharm. Des.* **1996**, *2*, 225. (c) Wlodawer, A.; Erickson, J. W. *Annu. Rev. Biochem.* **1993**, *62*, 543. (d) Volker, E. J. *J. Chem. Educ.* **1993**, *70*, 3.
(3) (a) Wlodawer, A.; Miller, M.; Jaskolski, M.; Sathyanarayana, B.; Baldwin, E.; Weber, I.; Selk, L.; Clawson, L.; Schneider, J.; Kent, S. *Science* **1989**, *245*, 616. (b) Navia, M. A.; Fitzgerald, P. M. D.; McKeever, B. M.; Leu, C.-T.; Heimbach, J. C.; Herber, W. K.; Sigal, I. S.; Darke, P. L.; Springer, J. P. *Nature* **1989**, *337*, 615.
(4) (a) Kramer, R. A.; Schaber, M. D.; Skalka, A. M.; Ganguly, K.; Wong-Staal, F.; Reddy, P. E. *Science* **1986**, *231*, 1580. (b) Kohl, N. E.; Emini, E. A.; Scleif, W. A.; Davis, L. J.; Heimbach, J. C.; Dixon, R. A.; Scolnik, E. M.; Sigal, I. S. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 4686.
(5) (a) Kempf, D. J.; Norbeck, D. W.; Codacovi, L.; Wang, X. C.; Kohlbrenner, W. E.; Wideburg, N. E.; Paul, D. A.; Knigge, M. F.; Vasavanonda, S.; Craig-Kennard, A.; Saldivar, A.; Rosenbrook, W. Jr.; Clement, J. J.; Plattner, J. J.; Erickson, J. *J. Med. Chem.* **1990**, *33*, 2687. (b) Kempf, D. J.; Codacovi, L.; Wang, X. C.; Kohlbrenner, W. E.; Wideburg, N. E.; Saldivar, A.; Vasavanonda, S.; Marsh, K. C.; Bryant, P.; Sham, H. L.; Green, B. E.; Betebenner, D. A.; Erickson, J.; Norbeck, D. W. *J. Med. Chem.* **1993**, *36*, 320. (c) Kempf, D. J.; Marsh, K. C.; Fino, L. C.; Bryant, P; Craig-Kennard, A.; Sham, H. L.; Zhao, C.; Vasavanonda, S.; Kohlbrenner, W. E.; Wideburg, N. E.; Saldivar, A.; Green, B. E.; Herrin, T.; Norbeck, D. W. *Bioorg. Med. Chem.* **1994**, *2*, 847. (d) Martin, J. A.; Redshaw, S.; Thomas, G. J. *Progress in Med. Chem.* **1995**, *32*, 239. (e) Budt, K. H.; Peyman, A.; Hansen, J.; Knolle, J.; Meichsner, C.; Lubkowska, L.; Silva, A. M.; Guerin, D. M. A.; Gulnik, S. V.; Yu, B.; Erickson, J. W. *Bioorg. Med. Chem.* **1996**, *4*, 1471.
(6) Hosur, M. V.; Bhat, T. N.; Kempf, D. J.; Baldwin, E. T.; Liu, B.; Gulnik, S.; Wideburg, N. E.; Norbeck, D. W.; Appelt, K.; Erickson, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 847.
(7) (a) Ghosh, A. K.; McKee, S. P.; Thompson, W. J. *Tetrahedron Lett.* **1991**, *32*, 5729. (b) Kang, S. H.; Ryu, D. H. *J. Chem. Soc., Chem. Commun.* **1996**, 355. (c) Chenera, B.; Boehm, J. C.; Dreyer, G. B. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 219.
(8) (a) Kempf, D. J.; Sowin, T. J.; Doherty, E. M.; Hannick, S. M.; Codavoci, L.; Henry, R. F.; Green, B. E.; Spanton, S. G.; Norbeck, D. W. *J. Org. Chem.* **1992**, *57*, 5692. (b) Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1992**, *57*, 29.
(9) Gurjar, M. K.; Pal, S.; Rao, A. V. R.; Pariza, R. J.; Chorgade, M. S. *Tetrahedron* **1997**, *53*, 4769.
(10) (a) Tossi, A.; Antcheva, N.; Romeo, D.; Miertus, S. *Peptide Res.* **1995**, *8*, 328. (b) Miertus, S.; Furlan, M.; Tossi, A.; Romeo, D. *Chem. Phys.* **1996**, *204*, 173.
(11) Raddatz, P.; Joncsyk, A.; Minck, K.-O.; Scmitges, C. J.; Sombroek, J. *J. Med. Chem.* **1991**, *34*, 3267.
(12) (a) Deziel, R.; Plante, R.; Caron, V.; Grenier, L.; Llinas-Brunet, M.; Duceppe, J.-S.; Malenfant, E.; Moss, N. *J. Org. Chem.* **1996**, *61*, 2901. (b) Chakravarty, P. K.; Combs, P.; Roth, A.; Greenlee, W. J. *Tetrahedron Lett.* **1987**, *28*, 611. A 1:6 ratio of amino ester to dimethyl methylphosphonate was sufficient to obtain phosphonates **3** in excellent yields and without racemization.
(13) Mikolajczyk, M.; Balczewski, P. *Synthesis* **1987**, 659.
(14) (a) Koskinen, A. M. P.; Koskinen, P. M. *Synlett* **1993**, 501. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev. (Washington, D.C.)* **1989**, *89*, 863.

S0022-3263(97)01202-4 CCC: $14.00

Scheme 1[a]



[a] Reagents and conditions: (a) 6 equiv of $LiCH_2PO(OMe)_2$, THF, −78 °C, 84−92%; (b) R′CHO, Na_2CO_3, EtOH, 25 °C, 48−90%; (c) $NaBH_4$, MeOH, 0 °C, 50−90%; (d) *m*-CPBA, CH_2Cl_2, 25 °C, 65−73%; (e) NaN_3 (5 equiv), NH_4Cl (3 equiv), MeOH/H_2O, 80 °C; (f) H_2 (1 atm), 10% Pd/C, 60−95% for two steps (e + f); (g) NH_3, EtOH, 80 °C, 36−90%; (h) 6 N HCl, 90 °C.

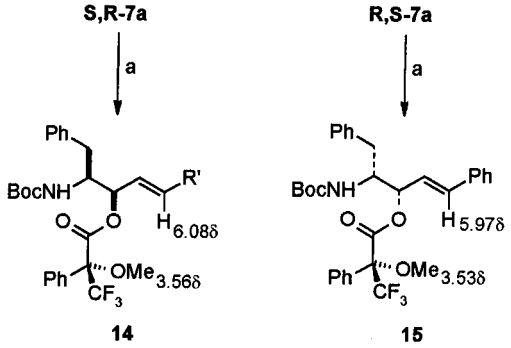
Table 1. $NaBH_4$ Reduction of Enones 6

enone	R	R′	ratio **7** (*S*,*R*):**8** (*S*,*S*)	% yield of alcohol **7**[a]
6a	CH_2Ph	CH_2Ph	3:1	73
6b	CH_2Ph	CH_2(cyclohexyl)	3:1	70
6c	CH_2Ph	CH_3	2:1	48
6d	*s*-Bu	CH_2(cyclohexyl)	16:1	90
6e	*i*-Pr	CH_2Ph	15:1	74
6f	*i*-Pr	*i*-Bu	16:1	75
6g	Me	*i*-Bu	4:1	75

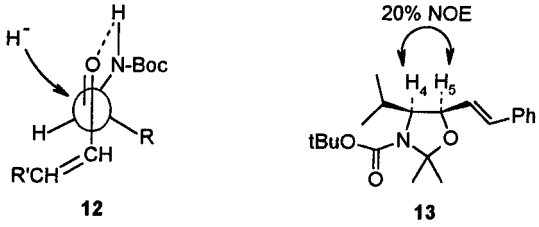
[a] Isolated yield, after purification by column chromatography and/or crystallization.

Sodium borohydride reduction of enones **6** in methanol gave mixtures of amino alcohols **7** and **8** with a diastereoselectivity level that depends on the bulkiness of the R group (Table 1). The ratio of (*S*,*R*)-**7** to the undesired *S*,*S* isomer **8** was determined by ^{1}H NMR and ranges from around 15:1 for **6d**−**f**, with a bulky isopropyl or *sec*-butyl side chain, to 2:1 for **6c**. Pure *S*,*R* diastereoisomers **7** could be easily obtained by chromatographic separation of the mixture or by crystallization. Similar results were obtained with lithium borohydride in methanol and with lithium tri-*tert*-butoxyaluminum hydride in THF, while 1,4 reduction leading to the corresponding saturated ketone is predominant when the reaction is carried out with $NaBH_4$ in isopropyl alcohol. The observed stereoselectivity and its dependence on the size of the side chain R are in agreement with previous results on the reduction of α-amino ketones[15] and can be explained with the Cram or Felkin−Anh models[16] for the addition of hydride to the free carbonyl group, NH−Boc and R being the medium and large group, respectively.[15a] Alternatively, the addition could take place with the carbonyl intramolecularly hydrogen bonded to the protected amino group, as in the cyclic-Cram model **12**. This would lead in any case to the same preference for hydride attack at the *si* face of the carbonyl and would explain the observation that the selectivity is not markedly affected by the nature of the reducing agent or by the medium.

Scheme 2[a]



[a] Reagents and conditions: (a) $Ph(CF_3)(OMe)COCl$, Py, 25 °C.



The absolute stereochemistry of the new stereocenter was confirmed by the preparation of the oxazolidine **13** by treatment of **7e** with dimethoxypropane in the presence of catalytic *p*-toluensulfonic acid. The NMR spectrum of the oxazolidine shows the presence of two rotamers, in a 1:1 ratio, with a coalescence temperature above 70 °C;[17] irradiation of either H_4 or H_5 of each rotamer induces a transfer of saturation to the corresponding proton of the other rotamer. NOE analysis, extended to both rotamers, gave a 20% enhancement between H_4 and H_5 that is consistent with a cis relationship between the two protons, also confirmed by the 5.5 Hz coupling constant.[18] The enantiomeric purity of the amino alcohols **7** was a major concern since amino ketones **3** and **6** are prone to racemize via enolization. Thus, the optical purity of the amino alcohols was determined by converting (*S*,*R*)-**7a** into the corresponding Mosher ester **14** (Scheme 2). Racemic **7a** was also synthesized by applying the same sequence to the methyl ester of D,L-phenylalanine and converted into a 1:1 mixture of diastereoisomeric esters **14** and **15**. The ^{1}H NMR spectrum of the mixture shows well-resolved

(15) (a) Albeck, A.; Persky, R. *Tetrahedron* **1994**, *21*, 6333. (b) Maugras, I.; Poncet, J.; Jouin, P. *Tetrahedron* **1990**, *46*, 2807. (c) Dufour, M.-N.; Jouin, P.; Poncet, J.; Pantaloni, A.; Castro, B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1895. (d) Tramontini, M. *Synthesis* **1982**, 605.

(16) (a) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 3210. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61. (c) Fleischer, J. M.; Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1995**, *60*, 490.

(17) See, for example: Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.

(18) A molecular mechanics conformational analysis of *cis*- and *trans*-**13** gave eight minima for the cis isomer and 11 minima for the trans isomer; H_4−H_5 coupling constants were calculated for each conformer by the Haasnot−Altona equation and are 4.6−6.0 Hz for *cis*-**13** and 1.1−4.9 Hz for *trans*-**13**. Haasnot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

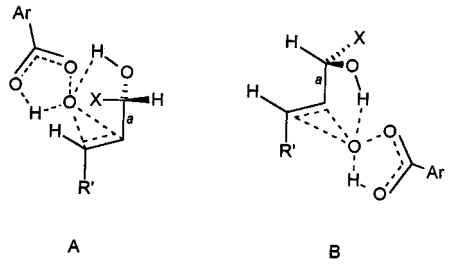


Figure 1. Transition states for the epoxidation of alkenes **7**. A leads to *S,S*-epoxide; B leads to *R,R*-epoxide **9**.

signals for a vinyl proton and for the methoxy group (Scheme 2); from the integration of these signals in the spectrum of the ester **14** obtained from optically active **7a** it was thus possible to establish an enantiomeric excess ≥(95 ± 3)% for the alcohol, corresponding to the optical purity of the starting amino ester. Epimerization at the α-carbon is thus negligible.

The next step in the synthesis is the stereoselective epoxidation of alcohols **7**. Peracid epoxidation of acyclic allylic alcohols leads preferentially to threo epoxy alcohols[19] and was thus expected to provide the epoxides with the required *R,R* stereochemistry at the new stereocenters. Indeed *m*-chloroperoxybenzoic acid epoxidation of **7** proceeds in good yields, and only one diastereoisomer (**9**) was detected in all cases by NMR and reversed-phase HPLC analysis.[20] While the preferential formation of **9** was predicted, the very high degree of stereocontrol is noteworthy, as selectivity is often poor in the epoxidation of trans-substituted allylic alcohols.[19] The highly ordered transition states for epoxidation at the diastereotopic faces of the double bond are shown in Figure 1. We suggest that the branched X = CH(NHR)Boc residue is sufficiently bulky to destabilize transition state A through allylic 1,3-strain.[21] Rotation around bond *a* relieves this interaction and directs the epoxidation on the opposite face, as in B, leading to epoxides **9**. High levels of stereoselectivity have also been observed in the amide- and urethane-directed allylic epoxidation of α-branched trans-substituted or terminal acyclic olefins.[22]

The potential of our approach was demonstrated with the synthesis of monoprotected diamino diols **11a** and **11d** (Scheme 1). Direct introduction of the second amino group can be obtained by refluxing for 1 week the corresponding epoxide **9** in ethanol saturated with ammonia; alternatively, regioselective ring opening of the epoxide by sodium azide in the presence of ammonium chloride[23] gives the azido diol **10**, which is then hydrogenated over 10% Pd on carbon. The direct ring opening with ammonia is more convenient for a large-scale synthesis, while the stepwise method provides higher yields with the rather unreactive epoxide **9a** (60% vs 30%). Amino diol **11d** can be obtained in over 90% yield by either method. For the assessment of the absolute stereochemistry of the four asymmetric centers, the *N*-Boc diol **11a** was deprotected to give the diamino diol **1a**.[8a] The NMR spectra of **1a** clearly indicate the presence of a symmetric structure. Since we start from L-phenylalanine (and no racemization occurs, as we have shown), the configuration of the first asymmetric center must necessarily be *S* and only three configurations are possible for a symmetric species, namely *S,S,R,R*, *S,R,R,S*, and *S,S,S,S*. The first configuration can be excluded because it corresponds to a meso structure, while **1a** is optically active ($[\alpha]^{25}_D = -41$), and the second configuration is not consistent with the trans geometry of epoxides **9**. Therefore, the configuration of **1a** must be necessarily *S,S,S,S*, thus confirming all the previous stereochemical assignments.

The synthesis of nonsymmetrical diol **11d**, which is obtained in overall 40% yield from isoleucine methyl ester, illustrates the versatility of our sequential approach to dipeptide isosteres with nonidentical R and R′ groups. An additional advantage of the method is that it leads directly to differentially protected diamino diols **11**. This allows the two amino groups to be coupled with different peptide chains, thus giving easy access to nonsymmetrical pseudopeptides of general structure P_n--$P_2-P_1-P_{1'}$-$P_{2'}$--$P_{n'}$.[24] Pseudopeptides with different P_n--P_2 and $P_{2'}$--$P_{n'}$ are particularly interesting as HIV-protease inhibitors because the C_2 symmetry of the central $P_1-P_{1'}$ fragment matches the symmetry of the enzyme's active site, while the inhibitor's important properties, such as binding, transport, and bioavailability, can be tuned by the amino acid sequence in the P_n--P_2 and $P_{2'}$--$P_{n'}$ fragments.[10a] Finally, via the key epoxide intermediate **9**, this route can also be extended to the synthesis of "normal" ($H_2N-P_1-P_{1'}-COOH$) rather than C_2-symmetrical ($H_2N-P_1-P_{1'}-NH_2$) dihydroxyethylene isosteres. Further work in this direction is currently in progress.

Experimental Section

Moisture-sensitive reactions were carried out in oven-dried vessels under a positive argon pressure. THF was dried over CaH_2, fractionated, and redistilled from sodium benzophenone before use. Reversed-phase HPLC chromatography was carried out on a Supelcosil C_{18} analytical column. Flash column chromatography was performed on silica gel 60 (230−400 mesh); silica gel 60_{F254} coated plastic sheets were used for TLC and developed with I_2. Melting points were determined in an open capillary apparatus and are uncorrected. Optical rotations were measured at 581 nm in methanol. IR spectra were recorded as Nujol mulls, unless otherwise noted. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100.4 MHz) were recorded for $CDCl_3$ solutions containing Me_4Si as an internal standard, unless otherwise specified. Mass spectra were obtained by electrospray ionization (es). Elemental analyses were obtained at the in-house facility of the Department of Chemical Sciences. Phosphonates **3a** ($[\alpha]^{25}_D = -52$ (*c* 0.4)), **3e** ($[\alpha]^{25}_D = -22$ (*c* 0.2)) and **3g** ($[\alpha]^{25}_D = -38$ (*c* 0.63)) were obtained as described;[12] phosphonate **3d** was also obtained with the same method.

Dimethyl [(3*S*)-3-[*N*-(*tert*-butyloxycarbonyl)amino]-4-methyl-2-oxohexyl]phosphonate (3d): 92%; colorless oil; $[\alpha]^{25}_D = -43°$ (*c* 0.2); IR (film) 3430, 3300, 1710, 1250 cm^{-1}; ^{1}H NMR δ 0.90 (t, 3H), 0.98 (d, 3H), 1.10 (m, 1H), 1.33 (m, 1H), 1.45 (s, 9H), 2.00 (m, 1H), 3.11 (dd, 1H, J = 14.2, 21.7 Hz), 3.30 (dd, 1H, J = 4.2, 22.5 Hz), 3.80 (d, 6H, J = 11.2 Hz), 4.33 (dd, 1H, J = 4.4, 9.0 Hz), 5.34 (d, NH); ^{13}C NMR δ 11.5, 15.9, 23.9, 28.2, 35.8, 38.6 (d, J = 132 Hz), 53.0 (d, J = 7.4 Hz), 64.8, 79.8, 155.7, 201.3; MS *m/z* 338 $[MH]^+$, 282 $[MH - C_4H_8]^+$, 238 $[MH - C_5H_{10}O_2]^+$.

Enones 6. Oven dried K_2CO_3 (553 mg, 4.0 mmol) was added in small portions, over 15 min, to a stirred solution of phospho-

(19) (a) Rossiter, B. A.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, *20*, 4733. (b) Narula, A. S. *Tetrahedron Lett.* **1981**, *22*, 2017. (c) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323.

(20) C_{18} Supelcosil column; MeCN/H_2O (2:8 to 7:3 gradient) + 0.05% trifluoroacetic acid.

(21) Hoffmann, R. W. *Chem. Rev. (Washington, D.C.)* **1989**, *89*, 1841.

(22) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev. (Washington, D.C.)* **1993**, *93*, 1307.

(23) (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557. (b) Guthrie, R. D.; Murphy, D. *J. Chem. Soc.* **1968**, 5288.

(24) Benedetti, F.; Norbedo, S.; Antcheva, N.; Tossi, A.; Miertus, S.; Romeo, D. Unpublished results.

nate **3** (4.0 mmol) and the appropriate aldehyde (4.0 mmol) in absolute ethanol (40 mL). After 4 h (25 min for **6a** and **6e**), the reaction mixture was filtered and the solution was neutralized with glacial acetic acid. The solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine and dried over sodium sulfate. The solvent was rotary evaporated, and the crude product was purified by flash chromatography with diethyl ether and petroleum ether (1:1) as eluant.

(5*S*)-5-[*N*-(*tert*-Butyloxycarbonyl)amino)]-1,6-diphenyl-2-hexen-4-one (6a): 50% from **3a** and phenylacetaldehyde; white crystals: mp 79−80 °C, from diisopropyl ether/petroleum ether; $[\alpha]25_D = -6.2$ (*c* 1.0); IR (Nujol) 3360, 1690, 1623 cm^{-1}; ^1H NMR δ 1.40 (s, 9H), 2.97 (dd, 1H, J = 5.9, 13.7 Hz), 3.06 (dd, 1H, J = 6.8, 13.7 Hz), 3.48 (d, 2H, J = 6.6 Hz), 4.79 (m, 1H), 5.26 (d, NH), 6.08 (d, 1H, J = 15.6 Hz), 7.03 (dt, 1H, J = 6.6, 15.6 Hz), 7.10−7.32 (m, 10H); ^{13}C NMR δ 28.3, 38.5, 38.8, 58.4, 79.7, 126.79, 126.85, 128.0, 128.4, 128.7, 128.8, 129.5, 136.1, 137.2, 147.7, 155.1, 197.4; MS *m*/*z* 366 $[MH]^+$, 310 $[MH - C_4H_8]^+$, 266 $[MH - C_5H_8O_2]^+$. Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.6; H, 7.44; N, 3.83. Found: C, 75.8; H, 7.54; N, 3.86.

(5*S*)-5-[*N*-(*tert*-Butyloxycarbonyl)amino]-1-cyclohexyl-6-phenyl-2-hexen-4-one (6b): 80% from **3a** and cyclohexylacetaldehyde; white crystals, mp 63 °C, from hexane; $[\alpha]^{25}_D = -6.5$ (*c* 0.23); IR 3450, 3350, 1715, 1690, 1630 cm^{-1}; ^1H NMR δ 0.90 (m, 2H), 1.20 (m, 2H), 1.4 (m, 1H), 1.41 (s, 9H), 1.65 (m, 6H), 2.07 (dd, 2H, J = 6.8, 7.3 Hz), 2.98 (dd, 1H, J = 13.7, 5.9 Hz), 3.10 (dd, 1H, J = 13.7, 6.3 Hz), 4.82 (m, 1H), 5.30 (d, NH), 6.09 (d, 1H, J = 16.1 Hz), 6.90 (dt, 1H, J = 7.3, 16.1 Hz), 7.11−7.27 (m, 5H); ^{13}C NMR δ 26.2, 26.3, 28.3, 33.2, 37.3, 38.6, 40.6, 58.1, 79.6, 126.8, 128.4 (two signals), 129.5, 136.2, 149.0, 155.1, 197.3; MS *m*/*z* 372 $[MH]^+$, 316 $[MH - C_4H_8]^+$, 272 $[MH - C_5H_8O_2]^+$. Anal. Calcd for $C_{23}H_{33}NO_3$: C, 74.3; H, 8.95; N, 3.79. Found: C, 74.0; H, 9.05; N, 3.77.

(5*S*)-5-[*N*-(*tert*-Butyloxycarbonyl)amino]-6-phenyl-2-hexen-4-one (6c): 83% from **3a** and acetaldehyde; white solid, mp 52 °C; $[\alpha]^{25}_D = +3.3$ (*c* 0.24); IR (CCl_4) 3430, 3352, 1714, 1696, 1633 cm^{-1}; ^1H NMR δ 1.41 (s, 9H), 1.88 (dd, 3H, J = 1.0, 6.8 Hz), 2.96 (dd, 1H, J = 5.6, 13.7 Hz), 3.11 (dd, 1H, J = 6.3, 13.7 Hz), 4.79 (m, 1H,), 5.28 (d, NH), 6.18 (dd, 1H, J = 15.6, 1.0 Hz), 6.94 (dq, 1H, J = 15.6, 6.8 Hz), 7.11−7.28 (m, 5H); ^{13}C NMR δ 18.5, 28.3, 38.3, 58.2, 79.6, 126.8, 128.4, 128.8, 129.5, 136.2, 145.1, 155.1, 197.2; MS *m*/*z* 290 $[MH]^+$, 234 $[MH - C_4H_8]^+$, 190 $[MH - C_5H_8O_2]^+$.

(5*S*,6*S*)-5-[*N*-(*tert*-Butyloxycarbonyl)amino]-1-cyclohexyl-6-methyl-2-octen-4-one (6d): 80% from **3d** and cyclohexylacetaldehyde; colorless oil; $[\alpha]^{25}_D = +3.5$ (*c* 0.87); IR (film) 3427, 3330, 1716, 1693, 1626 cm^{-1}; ^1H NMR δ 0.87 (m, 4H), 0.96 (d, 3H), 1.03−1.36 (m, 4H), 1.44 (m, 10H), 1.59−1.71 (m, 3H), 1.85 (m, 1H), 2.13 (m, 2H), 4.51 (dd, 1H, J = 5, 8.8 Hz), 5.27 (d, NH), 6.18 (d, 1H, J = 15.6 Hz), 6.96 (dt, 1H, J = 7.6, 15.6 Hz); ^{13}C NMR δ 11.6, 16.0, 24.1, 26.1, 26.2, 28.3, 33.1, 37.2, 37.8, 40.5, 61.7, 79.4, 128.8, 148.2, 155.7, 198.4; MS *m*/*z* 338 $[MH]^+$, 282 $[MH - C_4H_8]^+$, 238 $[MH - C_5H_8O_2]^+$.

(5*S*)-5-[*N*-(*tert*-butyloxycarbonyl)amino]-6-methyl-1-phenyl-2-hepten-4-one (6e): 48% from **3e** and phenylacetaldehyde; colorless oil; $[\alpha]^{25}_D = -7.0$ (*c* 0.2); IR 3400, 1720, 1700, 1630 cm^{-1}; ^1H NMR δ 0.76 (d, 3H), 0.98 (d, 3H), 1.43 (s, 9H), 2.10 (m, 1H), 3.55 (d, 2H, J = 6.4 Hz), 4.49 (dd, 1H, J = 4.4, 8.8 Hz), 5.26 (d, NH), 6.18 (d, 1H, J = 15.6 Hz), 7.09−7.33 (m, 6H); ^{13}C NMR δ 15.7, 18.8, 27.3, 29.8, 37.8, 61.1, 78.5, 125.8, 127.3, 127.7, 127.8, 136.3, 146.2, 154.9, 197.3; MS *m*/*z* 318 $[MH]^+$, 262 $[MH - C_4H_8]^+$, 218 $[MH - C_5H_8O_2]^+$.

(7*S*)-7-[*N*-(*tert*-butyloxycarbonyl)amino]-2,8-dimethyl-4-nonen-6-one (6f): 87% from **3e** and isovaleraldehyde; colorless oil; $[\alpha]^{25}_D = -3.7$ (*c* 0.51); IR (film) 3435, 3350, 1714, 1700, 1630 cm^{-1}; ^1H NMR δ 0.8 (d, 3H), 0.9 (d, 6H), 0.98 (d, 3H), 1.43 (s, 9H), 1.79 (m, 1H), 2.12 (m, 3H), 4.52 (dd, 1H, J = 4.1, 8.7 Hz), 5.30 (d, NH), 6.20 (d, 1H, J = 15.5 Hz), 6.96 (dt, 1H, J = 7.6, 15.5 Hz); ^{13}C NMR δ 16.7, 19.8, 22.38, 22.42, 27.9, 28.3, 31.0, 41.9, 61.9, 79.4, 128.7, 148.3, 155.9, 198.3; MS *m*/*z* 284 $[MH]^+$, 228 $[MH - C_4H_8]^+$, 184 $[MH - C_5H_8O_2]^+$.

(2*S*)-2-[*N*-(*tert*-butyloxycarbonyl)amino]-7-methyl-4-octen-3-one (6g): 90% from **3g** and isovaleraldehyde; colorless oil; $[\alpha]^{25}_D = -1.6$ (*c* 0.74); IR (film) 3425, 3348, 1700, 1628 cm^{-1}; ^1H NMR δ 0.93 (d, 6H), 1.34 (d, 3H, J = 6.8 Hz), 1.44 (s, 9H), 1.79 (m, 1H), 2.14 (m, 2H), 4.58 (m, 1H), 5.44 (d, NH), 6.17 (d, 1H, J = 15.6 Hz), 6.98 (dt, 1H, J = 15.6, 8 Hz); ^{13}C NMR δ 18.8, 22.3, 27.8, 28.3, 41.8, 53.1, 79.5, 127.4, 148.7, 155.1, 198.2; MS *m*/*z* 256 $[MH]^+$, 200 $[MH - C_4H_8]^+$, 156 $[MH - C_5H_8O_2]^+$.

Reduction of the Enones. NaBH4 (378 mg, 10 mmol) was added in small portions over 10 min, at 0 °C, to a stirred solution of **6** (10 mmol) in methanol. After 1 h at 0 °C the solution was neutralized with glacial acetic acid, the solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried over sodium sulfate and rotary evaporated to give the crude allyl alcohol **7**.

(4*R*,5*S*)-5-[*N*-(*tert*-Butyloxycarbonyl)amino]-4-hydroxy-1,6-diphenyl-2-hexene (7a): 78%; white crystals; mp 118 °C, from diisopropyl ether; $[\alpha]^{25}_D = -26.2$ (*c* 1.0); IR 3380, 1668 cm^{-1}; ^1H NMR δ 1.36 (s, 9H), 2.74 (m, 1H), 2.84 (dd, 1H, J = 5.5, 14.3 Hz), 3.39 (dd, 1H, J = 6.8, 21.4 Hz), 3.45 (dd, 1H, J = 6.8, 21.4 Hz), 3.95 (m, 1H), 4.20 (m, 1H), 4.56 (m, NH), 5.60 (dd, 1H, J = 6.2, 15.4 Hz), 5.91 (dt, 1H, J = 6.8, 15.4 Hz), 7.14−7.35 (m, 10H); ^{13}C NMR δ 28.3, 35.5, 37.6, 56.1, 73.1, 79.7, 126.1, 126.4, 127.3, 128.46, 128.54, 129.4, 133.3, 137.1, 138.0, 156.1; MS *m*/*z* 368 $[MH]^+$, 350 $[MH - H_2O]^+$. Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.2; H, 7.95; N, 3.81. Found: C, 74.9; H, 7.95; N, 3.70.

(4*R*,5*S*)-5-[*N*-(*tert*-Butyloxycarbonyl)amino]-1-cyclohexyl-4-hydroxy-6-phenyl-2-hexene (7b): 75%; white crystals; mp 143−145 °C, from ethyl acetate; $[\alpha]^{25}_D = -36$ (*c* 0.21); IR 3350, 1690, 1670 cm^{-1}; ^1H NMR δ 0.89 (m, 2H), 1.19 (m, 2H), 1.36 (m, 10H), 1.70 (m, 6H), 1.94 (m, 2H), 2.73 (m, 1H+OH), 2.85 (dd, 1H, J = 5.4, 14.2 Hz), 3.94 (m, 1H), 4.16 (m, 1H), 4.60 (d, NH), 5.49 (dd, 1H, J = 6.3, 15.4 Hz), 5.71 (dt, 1H, J = 7.8, 15.4 Hz), 7.18−7.30 (m, 5H); ^{13}C NMR δ 26.3, 26.5, 28.3, 33.1, 36.2, 37.8, 40.5, 56.6, 74.5, 79.7, 126.4, 128.4, 129.3, 129.4, 132.9, 138.1, 156.4; MS *m*/*z* 374 $[MH]^+$, 318 $[MH - C_4H_8]^+$. Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.9; H, 9.44; N, 3.77. Found: C, 73.4; H, 9.52; N, 3.82.

(4*R*,5*S*)-5-[*N*-(*tert*-Butyloxycarbonyl)amino]-4-hydroxy-6-phenyl-2-hexene (7c): 48%; white crystals; mp 105 °C, from diisopropyl ether; $[\alpha]^{25}_D = -40$ (*c* 0.21); IR (CCl_4) 3442, 3352, 1686 cm^{-1}; ^1H NMR δ 1.36 (s, 9H), 1.74 (d, 3H, J = 6.6 Hz), 2.73 (m, 1H), 2.84 (dd, 1H, J = 5.6, 14 Hz), 3.00 (m, OH), 3.94 (m, 1H), 4.13 (m, 1H), 4.60 (d, NH), 5.54 (dd, 1H, J = 6.6, 15.4 Hz), 5.76 (dq, 1H, J = 6.6, 15.4 Hz), 7.19−7.30 (m, 5H); ^{13}C NMR δ 17.9, 28.3, 36.2, 56.6, 74.6, 79.7, 126.4, 128.4, 129.0, 129.3, 129.7, 138.0, 156.4; MS *m*/*z* 292 $[MH]^+$, 236 $[MH - C_4H_8]^+$. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.1; H, 8.69; N, 4.83. Found: C, 69.5; H, 8.69; N, 4.85.

(4*R*,5*S*,6*S*)-5-[*N*-(*tert*-Butyloxycarbonyl)amino]-1-cyclohexyl-4-hydroxy-6-methyl-2-octene (7d): 90%; white solid; mp 69−70 °C, from hexane; $[\alpha]^{25}_D = -30.5$ (*c* 0.2); IR 3365, 3300, 1683 cm^{-1}; ^1H NMR δ 0.87−0.96 (m, 8H), 1.06−1.35 (m, 4H), 1.44 (m, 10H), 1.57 (m, 1H), 1.69 (m, 4H), 1.95 (m, 2H), 2.77 (m, OH), 3.58 (m, 1H), 4.23 (m, 1H), 4.43 (d, NH), 5.42 (dd, 1H, J = 7, 15 Hz), 5.73 (dt, 1H, J = 6, 15 Hz); ^{13}C NMR δ 11.1, 16.0, 24.9, 26.3, 26.5, 28.3, 32.9, 33.1, 35.8, 37.8, 40.4, 59.7, 73.3, 79.5, 128.9, 132.9, 157.2; MS *m*/*z* 340 $[MH]^+$, 322 $[MH - H_2O]^+$. Anal. Calcd for $C_{20}H_{37}NO_3$: C, 70.7; H, 11.0; N, 4.13. Found: C, 70.2; H, 11.1; N, 4.17.

(4*R*,5*S*)-5-[*N*-(*tert*-Butyloxycarbonyl)amino]-4-hydroxy-6-methyl-1-phenyl-2-heptene (7e): 63% after chromatography (1:1 diethyl ether and petroleum ether); white solid; mp 58−61 °C; $[\alpha]^{25}_D = -34$ (*c* 0.5); IR 3367, 1685 cm^{-1}; ^1H NMR δ 0.91 (d, 3H), 0.96 (d, 3H), 1.43 (s, 9H), 1.77 (m, 1H), 2.84 (m, OH), 3.39 (d, 2H), 3.54 (m, 1H), 4.20 (m, 1H), 4.47 (d, NH), 5.55 (dd, 1H, J = 6.83, 15.1 Hz), 5.89 (dt, 1H, J = 6.84, 15.1 Hz), 7.15−7.35 (m, 5H); ^{13}C NMR δ 17.3, 19.2, 27.3, 28.0, 37.8, 59.5, 72.4, 78.5, 125.1, 127.4, 127.5, 129.0, 131.4, 139.0, 156.1; MS *m*/*z* 320 $[MH]^+$, 246 $[MH - C_4H_8 - H_2O]^+$.

(6*R*,7*S*)-7-[*N*-(*tert*-Butyloxycarbonyl)amino]-6-hydroxy-2,8-dimethyl-4-nonene (7f): 71% after chromatography (1:1 diethyl ether and petroleum ether); white solid; mp 53 °C; $[\alpha]^{25}_D = -13$ (*c* 0.34); IR 3450, 3365, 1685 cm^{-1}; ^1H NMR δ 0.87−0.98 (m, 12H), 1.19 (m, 1H), 1.44 (s, 9H), 1.64 (m, 1H), 1.93 (m, 2H), 2.7 (m, OH), 3.55 (m, 1H), 4.19 (m, 1H), 4.45 (d, NH), 5.45 (dd, 1H J = 6.8, 15.6 Hz), 5.72 (dt, 1H, J = 7.3, 15 Hz); ^{13}C NMR δ

18.4, 20.1, 22.2, 22.3, 28.2, 28.3, 29.0, 41.7, 60.4, 73.5, 79.4, 129.4, 133.0, 157.0; MS *m/z* 332 $[MH]^+$, 276 $[MH - C_4H_8]^+$, 232 $[MH - C_5H_8O_2]^+$.

(2*S*,3*R*)-2-[*N*-(*tert*-Butyloxycarbonyl)amino]-3-hydroxy-7-methyl-4-octene (7g): 84% after chromatography (1:1 diethyl ether and petroleum ether); colorless oil; IR (CCl_4) 3442, 1693 cm^{-1}; ^1H NMR δ 0.89 (m, 6H), 1.08 (d, 3H, $J = 7.0$ Hz), 1.44 (s, 9H), 1.63 (m, 1H), 1.94 (m, 2H), 2.88 (m, OH), 3.78 (m, 1H,), 4.13 (m, 1H), 4.75 (m, NH), 5.43 (dd, 1H, $J = 6.2$, 15.4 Hz), 5.69 (dt, 1H, $J = 7$, 15.4 Hz); ^{13}C NMR δ 15.4, 22.2, 22.3, 28.2, 28.3, 41.7, 51.0, 75.6, 79.4, 129.6, 132.4, 156.2; MS *m/z* 258 $[MH]^+$.

Epoxides 9. 60% *m*-Chloroperoxybenzoic acid (3.05 g, 10.6 mmol) was added in small portions to a stirred solution of **7** (8.8 mmol) in dichloromethane. After 24 h at room temperature, the solution was washed with 10% aqueous sodium metabisulfite and saturated aqueous $NaHCO_3$ and dried over sodium sulfate. The solvent was rotary evaporated, and the crude product was purified by flash chromatography eluting with 2:1 diethyl ether and petroleum ether.

(2*R*,3*R*,4*S*,5*S*)-5-[*N*-(*tert*-Butyloxycarbonyl)amino]-2,3-epoxy-4-hydroxy-1,6-diphenylhexane (9a): 70%; white solid; mp 135−136 °C; $[\alpha]^{25}_D = -16$ (*c* 0.24); IR 3348, 1683 cm^{-1}; ^1H NMR δ 1.36 (s, 9H), 2.54 (m, OH), 2.81 (m, 1H), 2.87 (d, 2H), 2.92 (dd, 1H), 2.97 (dd, 1H, $J = 2.2$, 4.0 Hz), 3.20 (dt, 1H, $J = 2.2$, 5.5 Hz), 3.63 (m, 1H,), 3.99 (m, 1H,), 4.66 (d, NH), 7.16−7.34 (m, 10H); ^{13}C NMR δ 28.3, 36.2, 37.9, 55.2, 56.1, 58.6, 71.4, 79.7, 126.6, 126.8, 128.5, 128.7, 129.0, 129.3, 136.8, 137.5, 155.8; MS *m/z* 384 $[MH]^+$, 328 $[MH - C_4H_8]^+$, 284 $[MH - C_5H_8O_2]^+$. Anal. Calcd for $C_{23}H_{29}NO_4$: C, 71.6; H, 7.51; N, 3.48. Found: C, 71.5; H, 7.60; N, 3.54.

(2*R*,3*R*,4*S*,5*S*)-5-[*N*-(*tert*-Butyloxycarbonyl)amino]-1-cyclohexyl-2,3-epoxy-4-hydroxy-6-phenylhexane (9b): 68%; white solid; mp 153 °C; $[\alpha]^{25}_D = -16$ (*c* 0.18); IR 3351, 1684 cm^{-1}; ^1H NMR δ 0.96 (m, 2H), 1.13−1.27 (m, 3H), 1.36 (s, 9H), 1.41 (m, 3H), 1.70 (m, 5H), 2.64 (m, OH), 2.88 (m, 2H), 2.98 (m, 2H), 3.65 (m, 1H), 4.02 (m, 1H), 4.78 (d, NH), 7.21−7.31 (m, 5H); ^{13}C NMR δ 26.09, 26.12, 26.3, 28.3, 33.1, 33.5, 35.7, 36.1, 39.2, 54.8, 55.1, 59.0, 71.3, 79.5, 126.4, 128.4, 129.3, 137.6, 155.6; MS *m/z* 390 $[MH]^+$, 334 $[MH - C_4H_8]^+$, 290 $[MH - C_5H_8O_2]^+$.

(2*S*,3*S*,4*R*,5*R*)-2-[*N*-(*tert*-Butyloxycarbonyl)amino]-4,5-epoxy-3-hydroxy-1-phenylhexane (9c): 67%, white solid: mp 108 °C; $[\alpha]^{25}_D = -9.3$ (*c* 0.36); IR (CCl_4) 3440, 3365, 1685 cm^{-1}; ^1H NMR δ 1.27 (d, 3H, $J = 5.4$ Hz), 1.37 (s, 9H), 2.87 (m, 2H + OH), 3.00 (m, 2H), 3.54 (m, 1H), 4.03 (m, 1H), 4.79 (d, NH), 7.20−7.31 (m, 5H); ^{13}C NMR δ 17.0, 28.2, 36.1, 52.1, 54.7, 60.1, 71.8, 79.5, 126.4, 128.4, 129.3, 137.5, 155.6; MS *m/z* 308 $[MH]^+$, 252 $[MH - C_4H_8]^+$, 208 $[MH - C_5H_8O_2]^+$.

(2*R*,3*R*,4*S*,5*S*,6*S*)-5-[*N*-(*tert*-Butyloxycarbonyl)amino]-1-cyclohexyl-2,3-epoxy-4-hydroxy-6-methyloctane (9d): 65%; white crystals; mp 81−83 °C, from diisopropyl ether; $[\alpha]^{25}_D = +11$ (*c* 0.37); IR 3465, 3382, 3325, 1686 cm^{-1}; ^1H NMR δ 0.90−0.97 (m, 8H), 1.16 (m, 1H), 1.24 (m, 3H), 1.35 (m, 1H), 1.44 (m, 11H), 1.6 (m, 1H), 1.71 (m, 4H), 2.75 (d, OH), 2.84 (m, 1H), 3.03 (m, 1H), 3.66 (m, 2H), 4.69 (d, NH); ^{13}C NMR δ 11.5, 16.1, 24.0, 26.0, 26.1, 26.3, 28.3, 33.0, 33.5, 35.4, 35.7, 39.3, 54.8, 58.3, 59.2, 69.9, 79.3, 156.3; MS *m/z* 356 $[MH]^+$, 300 $[MH - C_4H_8]^+$, 256 $[MH - C_5H_8O_2]^+$. Anal. Calcd for $C_{20}H_{37}NO_4$: C, 67.56; H, 10.49; N, 3.96. Found: C, 67.7; H, 10.6; N, 3.99.

(2*R*,3*R*,4*S*,5*S*)-5-[*N*-(*tert*-Butyloxycarbonyl)amino]-2,3-epoxy-4-hydroxy-6-methyl-1-phenylheptane (9e): 73%; white solid; mp 80 °C; $[\alpha]^{25}_D = +11$ (*c* 0.2); IR 3367, 1685 cm^{-1}; ^1H NMR δ 0.89 (d, 3H), 0.95 (d, 3H), 1.45 (s, 9H), 2.00 (m, 1H), 2.57 (d, OH), 2.79 (dd, 1H, $J = 7$, 15 Hz), 2.95 (m, 2H), 3.55 (m, 1H), 3.62 (m, 1H), 4.61 (d, NH), 7.16−7.39 (m, 5H); ^{13}C NMR δ 17.3, 20.1, 28.4, 28.5, 37.9, 56.4, 58.5, 59.0, 70.5, 79.5, 126.7, 128.6, 129.0, 137.0, 156.4; MS *m/z* 336 $[MH]^+$, 280 $[MH - C_4H_8]^+$, 236 $[MH - C_5H_8O_2]^+$.

(2*S*,3*S*,4*S*,5*S*)-2-Azido-5-[*N*-(*tert*-Butyloxycarbonyl)amino]-3,4-dihydroxy-1,6-diphenylhexane (10a). NaN_3 (170 mg, 2.61 mmol), NH_4Cl (90 mg, 1.68 mmol), and epoxide **9a** (200 mg, 0.52 mmol) in 6 mL of 8:1 MeOH−H_2O were heated at 80 °C in a sealed tube for 48 h. The reaction mixture was cooled to room temperature and partitioned between diethyl ether and 10% aqueous $NaHCO_3$. The aqueous phase was extracted with diethyl ether, and the combined organic phases were washed with brine and dried over sodium sulfate. The solvent was rotary evaporated, and the resulting crude azide was used without further purification: $[\alpha]^{25}_D = -21$ (*c* 0.36); IR (CCl_4) 3430, 3390, 2105, 1685, 1252 cm^{-1}; ^1H NMR δ 2.85 (m, 2H), 3.22 (m, 2H), 3.35 (m, 1H), 3.5 (m, 1H), 3.79 (m, 1H), 3.88 (m, 1H), 4.48 (d, NH), 7.18−7.31 (m, 10H); ^{13}C NMR δ 28.2, 36.8, 37.2, 52.8, 63.6, 70.3, 71.8, 80.7, 126.6, 126.7, 128.3, 128.4, 128.6, 128.7, 129.2, 129.3, 137.0, 137.4, 157.4; MS *m/z* 427 $[MH]^+$, 384 $[MH - HN_3]^+$, 371 $[MH - C_4H_8]^+$.

(2*S*,3*S*,4*S*,5*S*,6*S*)-2-Azido-5-[*N*-(*tert*-butyloxycarbonyl)-amino]-1-cyclohexyl-3,4-dihydroxy-6-methyloctane (10d) was obtained with the same method (95%) from epoxide **9d**: gummy syrup; $[\alpha]^{25}_D = -13$ (*c* 0.58); IR (CCl_4) 3446, 3384, 2105, 1690, 1255 cm^{-1}; ^1H NMR δ 0.90−1.02 (m, 9H), 1.14−1.25 (m, 3H), 1.38−1.44 (m, 11H), 1.59−1.71 (m, 6H), 1.85 (m, 1H), 2.03 (m, 1H), 2.56 (m, OH), 3.32 (d, 1H, $J = 8.8$ Hz), 3.45 (m, 1H), 3.60 (m, 2H), 4.24 (m, OH), 4.58 (d, NH); ^{13}C NMR δ 12.0, 16.6, 22.6, 26.0, 26.3, 26.4, 28.2, 32.3, 33.5, 34.3, 34.4, 39.0, 57.2, 60.5, 70.1, 71.9, 80.5, 158.0; MS *m/z* 399 $[MH]^+$, 343 $[MH - C_4H_8]^+$, 299 $[MH - C_5H_8O_2]^+$.

(2*S*,3*S*,4*S*,5*S*)-5-Amino-2-[*N*-(*tert*-butyloxycarbonyl)amino]-3,4-dihydroxy-1,6-diphenylhexane (11a). Method A. The crude azide **10a** (205 mg) in 5 mL of methanol was stirred under 1 atm hydrogen for 12 h in the presence of catalytic 10% Pd/C. The solid was filtered off, and the solvent was rotary evaporated. The crude product was purified by flash chromatography with 90:10:1 CH_2Cl_2−MeOH−NEt_3 mixture as eluant (60% from the epoxide **9a**). Method B. **9a** (510 mg, 1.33 mmol) in 25 mL of ethanol saturated with NH_3 was heated at 80 °C in a sealed tube for 7 days. Solvent evaporation and flash chromatography gave the product (36%): white solid; mp 162−164 °C; $[\alpha]^{25}_D = -41$ (*c* 0.23); IR 3430, 3358, 1688 cm^{-1}; ^1H NMR δ 1.34 (s, 9H), 2.58 (dd, 1H, $J = 9.5$, 13 Hz), 2.84 (m, 1H), 2.89 (dd, 1H, $J = 4$, 13 Hz), 3.19 (dd, 1H, $J = 3$, 14 Hz), 3.43 (m, 1H), 3.53 (m, 1H), 3.62 (d, 1H, $J = 9.2$ Hz), 3.95 (m, 1H), 4.53 (d, NH), 7.17−7.31 (m, 10H); ^{13}C NMR δ 28.2, 36.4, 39.3, 52.3, 55.8, 70.5, 73.3, 80.2, 126.4, 126.6, 128.5, 128.6, 128.9, 129.1, 129.30, 129.34, 129.4, 129.6, 138.4, 157.3; MS *m/z* 401 $[MH]^+$, 345 $[MH - C_4H_8]^+$, 301 $[MH - C_5H_8O_2]^+$.

(2*S*,3*S*,4*S*,5*S*,6*S*)-2-Amino-5-[*N*-(*tert*-butyloxycarbonyl)-amino]-1-cyclohexyl-3,4-dihydroxy-6-methyloctane (11d): 100% from **10d** (Method A); 90% from **9d** (Method B); oil, $[\alpha]^{25}_D = -9.5°$ (*c* 0.56); IR (CCl_4) 3360, 1700 cm^{-1}; ^1H NMR δ 0.96 (m, 9H), 1.14−1.40 (m, 6H), 1.44 (s, 9H), 1.65 (m, 6H), 2.04 (m, OH), 3.28 (d, 1H, $J = 3.9$ Hz), 3.48 (m, 1H), 3.61−3.72 (m, 2H), 4.51 (d, NH); ^{13}C NMR δ 12.1, 16.6, 22.2, 26.1, 26.3, 26.5, 28.3, 32.6, 32.7, 34.2, 34.5, 40.5, 52.0, 56.5, 70.7, 71.5, 80.1, 157.9; MS *m/z* 373 $[MH]^+$, 317 $[MH - C_4H_8]^+$, 273 $[MH - C_5H_8O_2]^+$.

(2*S*,5*S*,3*S*,4*S*)-2,5-Diamino-3,4-dihydroxy-1,6-diphenylhexane (1a). A suspension of **11a** (60 mg, 0.15 mmol) in 6 N HCl was stirred at 90 °C for 30 min. The resulting solution was concentrated in vacuo, neutralized with 3 N aqueous NaOH, and extracted with chloroform (3 × 20 mL). The organic phases were dried over Na_2SO_4, and the solvent was removed under reduced pressure to give a white solid (45 mg, 0.15 mmol, 100%): mp 150 °C dec; $[\alpha]^{25}_D = -33°$ (*c* 0.18); ^1H NMR δ 2.63 (dd, 2H, $J = 11$, 13 Hz); 2.85 (dd, 2H, $J = 3$, 13 Hz); 3.58 (d, 2H, $J = 11$ Hz); 3.91 (m, 2H); 7.22−7.33 (m, 10H); ^{13}C NMR δ 38.6, 56.8, 72.8, 126.7, 128.8, 129.0, 138.5; MS *m/z* 301 $[MH]^+$, 284 $[MH - NH_3]^+$.

(4*S*,5*R*)-3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-5-[1-(3-phenylpropenyl)]-4-(2-propyl)-1,3-oxazolidine (13). 2 mg (0.01 mmol) of TsOH·H_2O were added to **7e** (123 mg, 0.39 mmol) in 2,2-dimethoxypropane (2 mL); the solution was refluxed for 75 min and then partitioned between diethyl ether and saturated aqueous $NaHCO_3$. The organic phase was washed with brine and dried over sodium sulfate; the solvent was evaporated in vacuo, and the crude product was purified by flash chromatography with diethyl ether and petroleum ether (7:3) as eluant to give 83 mg (60%) of oily product: ^1H NMR (C_6D_6, 70 °C) δ 0.98 (d, 3H), 1.02 (d, 3H), 1.44 (s, 9H), 1.59 (s, 3H), 1.68 (s, 3H), 1.95 (m, 1H), 3.20 (d, 2H, $J = 6.6$ Hz), 3.57 (m, 1H), 4.39 (dd, 1H, $J = 5.5$, 6 Hz), 5.48 (m, 1H, $J = 1.5$, 6.6, 15.4 Hz), 5.86 (m, 1H, $J = 1.1$, 6.6, 15.4 Hz), 7.15−7.35 (m, 5H); ^{13}C NMR (two sets of signals) δ 18.9 and 19.4, 21.5 and 21.9, 23.7 and 25.2, 26.5 and 27.1, 28.4, 28.7, 38.9, 64.98 and 65.05, 65.8 and 67.1, 77.7 and 78.1, 79.5 and 79.8, 126.1, 126.2, 128.5, 128.7, 134.3 and 134.4, 152.6; MS *m/z* 374 $[MH]^+$, 318 $[MH - C_4H_8]^+$, 274 $[MH - C_5H_8O_2]^+$.

Mosher Esters 14 and 15. (*R*)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (7.2 mg, 0.028 mmol) was added

to a solution of (−)-**7a** or (±)-**7a** (8.0 mg, 0.022 mmol) in pyridine (0.2 mL). The solution was stirred at room temperature for 18 h, diluted with 2 mL of dichloromethane, and washed with 10% aqueous citric acid. The water phase was extracted with dichloromethane (1 mL). The combined organic phases were passed through a short pad of silica gel, which was then eluted with 5 mL of dichloromethane. The solvent was rotary evaporated, obtaining 4 mg (0.007 mmol, 32%) of a white solid. **14**: ^{1}H NMR δ 1.4 (s, 9H), 2.4 (dd, 1H), 2.82 (dd, 1H), 3.4 (d, 2H), 3.56 (s, 3H), 4.1 (m, 1H), 4.2 (d, 1H), 5.55 (dd, 1H), 5.65 (m, NH), 6.08 (dt, 1H), 7−7.5 (m, 15H). **15**: ^{1}H NMR δ 1.4 (s, 9H), 2.6 (m, 1H), 2.8 (m, 1H), 3.4 (m, 2H), 3.54 (s, 3H), 4.2 (m, 1H), 4.4 (m, 1H), 5.45 (m, 1H), 5.6 (m, NH), 5.97 (dt, 1H), 7−7.5 (m, 15H).

Acknowledgment. We wish to thank the Istituto Superiore di Sanità (ISS) for financial support and the University of Trieste for a postdoctoral grant to P.Z.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **6**−**15** (51 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal and can be ordered from the ACS; see any current masthead page for ordering information.

JO971202P