Method G. Coupling with BOP. To a stirred solution of the amino acid ester component (1 mmol) in CH_2Cl_2 (10 mL) were added BOP reagent (1.1 mmol), and diprotected N-(ω-aminoalkylene)amino acids (1.1 mmol), DIEA (3 mmol) at room temperature. After 15 min the pH was checked for basicity (in cases where the pH was lower than pH = 9, more DIEA was added) and the reaction mixture left for 1 h at room temperature. The solvent was evaporated under vacuum and the crude product dissolved in EtOAc (100 mL) and washed as described in method F above (see Table IV).

Method H. Preparation of Boc-amino Acids.[20] Amino acid (0.1 mol) was dissolved in NaOH (1 N, 200 mL) and dioxane (200 mL) added. The mixture was stirred in an ice bath, and a solution of $(Boc)_2O$ (0.14 mol) in dioxane (200 mL) was added dropwise while the pH was maintained at 9. The mixture was left stirring at room temperature overnight. The dioxane was evaporated in vacuo and the water solution washed with ether (3 × 150 mL), cooled, and acidified with saturated $KHSO_4$ solution to pH 3. The precipitate was collected by filtration, washed with cold water, and dried on P_2O_5 in vacuo to constant weight. If upon acidification an oil was formed, it was extracted with EtOAc (3 × 150 mL) which was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness. After being dried over P_2O_5, the residue was crystallized from EtOAc/petroleum ether.

Method I. Preparation of Fmoc-amino Acids.[21] A solution of Fmoc-OSu (0.024 mol) in MeCN (25 mL) was added at once to a stirred aqueous solution of amino acid (0.025 mol) adjusted to pH 9 with TEA. The pH was maintained at 8.5–9 with TEA. After 15 min the pH stabilized and the reaction mixture was left another 15 min. The MeCN was evaporated in vacuo, the pH adjusted to 3 with saturated $KHSO_4$, and the precipitate collected by filtration, washed with cold water, and dried over P_2O_5 to constant weight. If upon acidification an oil formed it was treated as in method H.

Method K. Removal of the Z Protecting Group.[22] To a solution of Z-amino acid (1 g) dissolved in MeOH (5 mL) were added Pd/C (10%, 1 g) and ammonium formate (1 g) with stirring. The advance of the reaction was followed by HPLC. After completion (~2 h), the catalyst was removed by filtration and the filtrate evaporated to dryness in vacuo. The residue was dissolved in water which was lyophilized.

Method I. Preparation of Z-amino Acids.[23] Z-Amino acids were prepared according to method H, but Z-Cl was used instead of $(Boc)_2O$.

Abbreviations used are in accordance to the recommendations of IUPAC-IUB Commission on Biochemical Nomenclature in: *Eur. J. Biochem.* **1984**, *138*, 9. *J. Biol. Chem.* **1989**, *264*, 663. Other abbreviations are as follows: Bzl, benzyl; Z, benzyloxycarbonyl; Boc, (*tert*-butyloxy)carbonyl; Fmoc, (fluorenylmethoxy)carbonyl; OSu, *O*-succinimide ester; BOP-Cl, bis(2-oxo-3-oxazolidinyl)phosphinic chloride; BOP, benzotriazolyl-*N*-oxytrisdimethylaminophosphonium hexafluorophosphate; DMSO, dimethyl sulfoxide; DIEA, diisopropylethylamine; TFA, trifluoroacetic acid; TEA, triethylamine.

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Registry No. 1, 24123-14-6; 2, 90495-95-7; 3, 143192-21-6; 4, 143192-22-7; 5, 143192-23-8; 6, 143192-24-9; 7, 143192-25-0; 8, 90495-98-0; 9, 128421-96-5; 10, 143192-26-1; 11, 143192-27-2; 12, 143192-28-3; 13, 143192-29-4; 14, 143192-30-7; 15, 128421-93-2; 16, 143192-31-8; 17, 143192-32-9; 18, 143192-33-0; 19, 143192-34-1; 21, 143192-35-2; 22, 143192-36-3; 23, 143192-37-4; 24, 143192-38-5; 25, 143192-39-6; 26, 143192-40-9; 27, 143192-41-0; 28, 143192-42-1; 29, 143192-43-2; $ClCH_2COOH$, 79-11-8; $H_2NCH_2CH_2NH_2$, 107-15-3; $H_2N(CH_2)_3NH_2$, 109-76-2; $H_2N(CH_2)_6NH_2$, 124-09-4; $BocNH(CH_2)_2NH_2$, 75178-96-0; $BocNH(CH_2)_6NH_2$, 51857-17-1; Boc-Leu-OH, 13139-15-6; Boc-Phe-OH, 13734-34-4; Boc-Tip(CHO)-OH, 47355-10-2.

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Stereocontrolled Synthesis of C_2-Symmetric and Pseudo-C_2-Symmetric Diamino Alcohols and Diols for Use in HIV Protease Inhibitors

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The stereocontrolled syntheses of dibenzyldiamino alcohol 1 and dibenzyldiamino diols 2–4, core units of potent C_2-symmetric and pseudo-C_2-symmetric inhibitors of HIV protease, are described, starting from phenylalanine. Stereoselective epoxidation of trans olefin 7, produced by S_N2' displacement of an allylic mesylate, followed by regiospecific epoxide opening with lithium azide provided the azido alcohol 8 as the major product. Azide reduction and deprotection led to diamine 1. Protected diamino diols 15–17 were prepared expeditiously by intermolecular titanium- or vanadium-mediated pinacol coupling of protected phenylalaninal. Methods for the stereospecific interconversion of the major (3*R*,4*R*,5*R*,6*S*) isomer to the desired (3*S*,4*R*,5*S*,6*S*) isomer via intramolecular hydroxyl inversion are described.

The human immunodeficiency virus type 1 encodes an aspartic proteinase (HIV protease) which is responsible for proteolytic processing of the gag and gag-pol gene products. These proteolytic events are required for the production of mature, infectious progeny virions; thus, HIV protease has received considerable attention as a potential target for the chemotherapy of AIDS. The availability of detailed structural information on the retroviral proteases has inspired the design of inhibitors which exploit the unique structural aspects of these enzymes. Specifically, the recognition that HIV protease exists in its active form as a C_2-symmetric homodimer has prompted interest in

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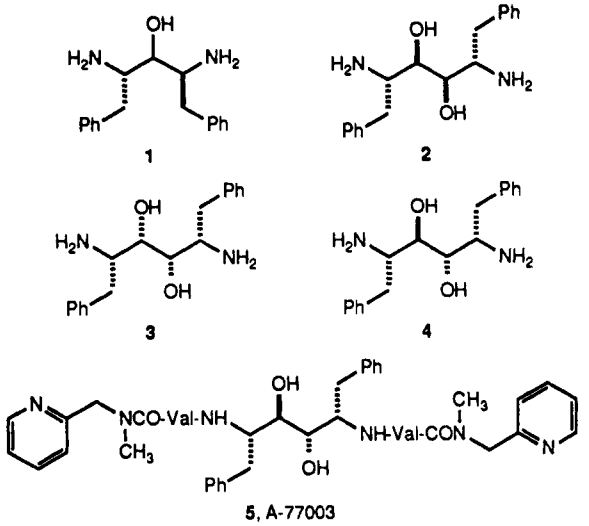
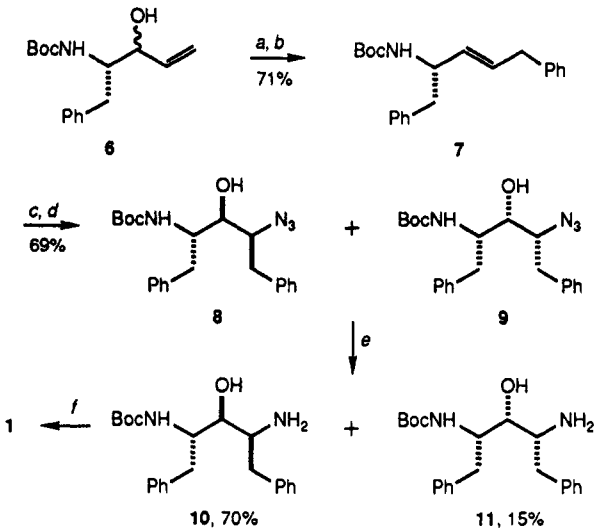
the potential utility of C_2-symmetric compounds as inhibitors. We recently described several series of C_2-symmetric and pseudo-C_2-symmetric inhibitors derived from the core diamines 1–4,[1,2] culminating in the identification of A-77003 (5), which shows promise for potential therapeutic intervention of acquired immunodeficiency syndrome.[3] During our studies, efficient syntheses of diamines 1–4 were required in order to conduct systematic structure–activity studies as well as to enable the preparation of large quantities of A-77003. Compounds with C_2-symmetry have also received much broader attention for their utility as asymmetric ligands for use in stereoselective reactions.[4] The stereocontrolled synthesis of symmetric molecules with chelating functionality is therefore of high interest.[5] We have previously reported preliminary synthetic routes to the homochiral diamines 1–4.[1] Herein we provide details of those approaches and additionally present a practical stereoselective synthesis of the diamino diols 2 and 3 beginning with L-phenylalanine.[6]



Results and Discussion

The initial target of our study was the pseudo-C_2-symmetric diamine 1.[1] By virtue of its symmetry characteristics, the central carbon (C_3) of 1 is nonstereogenic; thus, control of the stereochemistry at that center is not a requirement for stereoselective syntheses of 1. However, since we required access to derivatives of 1 with two different acylamino groups at C_2 and C_4, a synthetic approach which controlled the stereochemistry at all three central carbons was desired. Conceptually, a convergent route to

Scheme I[a]



[a] Key: (a) CH_3SO_2Cl, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, −10 °C, 10 min; (b) PhMgBr, CuCN, THF, −70 °C, 15 min; (c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 5 °C, 72 h; (d) LiN_3, NH_4Cl, DMF, H_2O, 70 °C, 32 h; (e) 10% Pd/C, $NH_4^+HCO_2^-$, CH_3OH, rt, 2.5 h; (f) HCl, dioxane, rt, 2 h.

1 from phenylalanine involves formation of the C_3–C_4 bond through use of an appropriate α-aza carbanion equivalent. Recognizing the potential difficulties for the control of stereochemistry at both C_3 and C_4 with such an approach, we instead adopted the linear pathway shown in Scheme I in which the desired diastereomer 1 was predicted to be the major product. Key to the success of this approach was the ability to produce the trans olefin 7 in good overall yield with high stereocontrol. Accordingly, allylic alcohol 6, obtained in 85% yield by sequential DIBAL reduction and in situ vinylmagnesium bromide addition[7] to Boc-L-phenylalanine methyl ester, was converted to the corresponding allylic mesylate. CuCN-catalyzed S_N2' displacement of the mesylate with phenylmagnesium bromide provided 7 in 71% yield as a ca. 10:1 mixture of *E* and *Z* isomers. An alternate approach employing a Julia olefination[8] between the sulfone derived from phenylalaninol[9] and phenylacetaldehyde resulted both in a lower yield of 7 as well as reduced stereoselectivity (4:1 *E*/*Z*). Epoxidation of 7 proceeded as expected to provide the 3*R*,4*S* epoxide as the major isomer, although the observed stereoselectivity (ca 4:1) was lower than that previously reported for the corresponding terminal alkene.[10] The mixture of epoxides was opened regiospecifically with lithium azide in the presence of aqueous ammonium chloride in order to minimize any undesired oxazolidinone formation. The mixture of azido alcohols 8 and 9 thus obtained were converted directly by transfer hydrogenation to the mixture of 10 and 11, at which point chromatographic separation on silica gel was facile. Deprotection of 10 provided diamino alcohol 1 in 89% yield. In spite of the number of steps, this route produced the diamine 1 in 26% overall yield from Boc-phenylalanine methyl ester and could be readily scaled up to produce quantities

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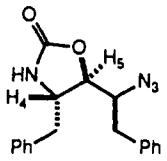
Table I. Crystal Data, Intensity Measurement, Structure Solution, and Refinement for Compounds 19, 20, 24, 27[a]

compd no.	19	20	24	27
crystal system	monoclinic	monoclinic	triclinic	monoclinic
lattice	a = 12.164 (6) Å b = 24.545 (7) Å c = 5.982 (6) Å β = 90.5°	a = 8.9407 (8) Å b = 7.792 (1) Å c = 26.269 (4) Å β = 95.52 (1)°	a = 10.590 (1) Å b = 13.728 (1) Å c = 10.089 (2) Å α = 98.86 (1)° β = 114.707 (9)° γ = 91.13 (1)°	a = 10.871 (4) Å b = 21.925 (6) Å c = 13.428 (2) Å β = 98.62 (2)°
space group	$P2_1$ (no. 4)	$P2_1$ (no. 4)	$P\bar{1}$ (no. 1)	$P2_1$ (no. 4)
Z	4	4	2	4
$2\theta_{max}$	110.0°	120.1°	120.2°	120.3°
absorption correction	trans. factors: 0.82–1.00	trans. factor: 0.88–1.00	trans. factors: 0.92–1.00	trans. factor: 0.85–1.00
secondary extinction correction	coefficient: 0.14981×10^{-6}			
no. of refl. measured	total: 2458 unique: 2330 (R_{int} = .036)	total: 3154 unique: 2943 (R_{int} = 0.42)	total: 4157 unique: 3912 (R_{int} = .058)	total: 5145 unique: 4863 (R_{int} = .064)
no. of obsvns	1547	1563	2007	1971
no. of variables	469	468	664	747
refln/parameter ratio	3.30	3.34	3.02	2.64
$R;R_w$	0.060; 0.072	0.052; 0.061	0.056; 0.060	0.057; 0.061

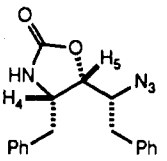
[a] Data for all compounds were collected on a Rigaku afc5 diffractometer with a rotating anode generator at ambient temperature using filtered Cu Kα radiation

of 1 in excess of 50 g. Moreover, the differentially protected intermediates 8 and 10 proved to be highly useful for the synthesis of derivatives of 1 with nonidentical acylamino groups at C_2 and C_4.

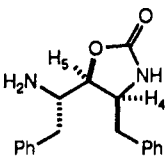
The relative stereochemistry at C_3 of 10 was confirmed by treatment of the mixture of 8 and 9 with sodium hydride in DMF to produce oxazolidinones 12 and 13. After chromatographic separation, the proton spectrum of the major isomer (51%) showed a coupling constant between H_4 and H_5 of 4.4 Hz, while the corresponding coupling in the minor product (12%) was 7.3 Hz. The major isomer was thus assigned to be the trans-disubstituted oxazolidinone 12 and the minor product to be the cis isomer 13.[11] Since 10 was derived from the trans alkene 7, the stereochemistry at C_2, bearing the unsubstituted amino group, could be inferred to be S; however, confirmation of this assignment was provided by cyclization of 10 with phosgene followed by deprotection of the C_4 Boc-amino group to provide oxazolidinone 14. The coupling constant between the ring protons of 14 (J_{4-5} = 7.7 Hz) was clearly consistent with the cis arrangement.[11]



12, J_{4-5} = 4.4 Hz



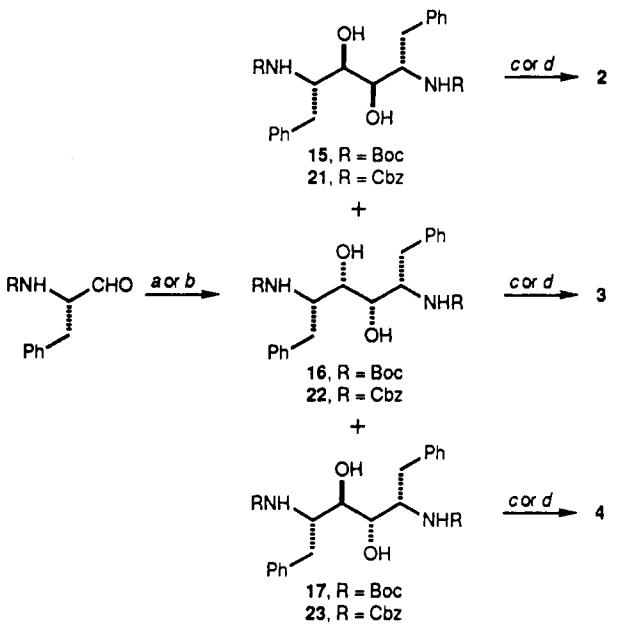
13, J_{4-5} = 7.3 Hz



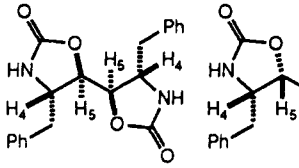
14, J_{4-5} = 7.7 Hz

Diamino diols 2–4 represent a second set of inhibitor core units, in which the axis of symmetry intersects the central carbon–carbon bond rather than a single central carbon.[1] The initial approach which we adopted for the synthesis of 2–4 utilized the intermolecular McMurry pinacol coupling[12] of Boc-L-phenylalaninal[10] (Scheme II). This convergent approach was hampered only by the low stereoselectivity of the coupling, which led to a ca. 2:1:1 mixture of 15:16:17, respectively. However, since each of the diols 2–4 was initially desired for structure–activity studies, this lack of stereoselectivity had practical advantages. Indeed, following deprotection of 15–17, peptide derivatives of all three stereoisomers showed potent inhibition of HIV protease.[1] Careful chromatography was required to separate 16 and 17; hence, a more convenient protocol entailed separation of the mixture 16/17 from 15, followed by deprotection and subsequent separation of the minor diamines 3 and 4. The stereochemistry of the hydroxyl groups of 2–4 was determined in the same manner as above by conversion to the corresponding bis(oxazolidinones) 18–20. On the basis of a 5.5-Hz coupling constant between the two sets of symmetry-related ring protons of

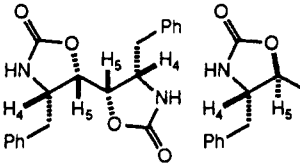
Scheme II[a]



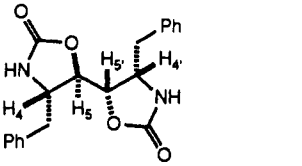
[a] Key: (a) $TiCl_3$, Zn–Cu, DME, rt, 1 h; (b) $[V_2Cl_3(THF)_6]_2[Zn_2Cl_4]$, CH_2Cl_2, rt, 16 h; (c) HCl, dioxane, rt, 2 h; (d) 10% Pd/C, $NH_4^+HCO_2^-$, DMF, 120 °C, 4 h, or $Ba(OH)_2 \cdot 8H_2O$, H_2O, dioxane, reflux, 24 h.



18, J_{4-5} = 5.5 Hz



19, J_{4-5} = 8.5 Hz



20, J_{4-5} = 4.5 Hz, $J_{4'-5'}$ = 7.5 Hz

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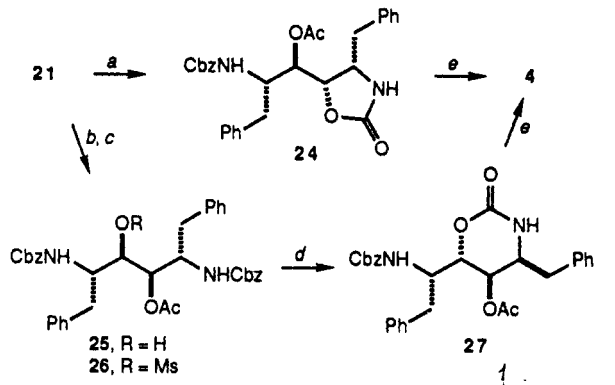
18, the major diol **15** was assigned as 2*S*,3*R*,4*R*,5*S*. Likewise, the value of J_{4-5} in the spectrum of the minor symmetric isomer **19** was 8.5 Hz, consistent with the *cis*-bis(oxazolidinone) shown. Coupling constants of 4.5 and 7.5 were observed for the trans and cis rings, respectively, of the unsymmetric isomer **20**. The cis stereochemistry of **19** was confirmed by a single-crystal X-ray determination. Crystal parameters for **19** are provided in Table I.

The low stereoselectivity and cumbersome scaleup of the McMurry coupling as well as the difficulties encountered in the chromatographic separation of protected diamines **15–17** due to lack of solubility prompted us to investigate alternate coupling methods. Preliminary reports on vanadium-assisted pinacol couplings with high stereocontrol[13] offered the possibility of the preparation of a single isomer, (3*R*,4*R*)-diol **21**. With a stereoselective synthesis of **21** in hand, inversion of one of the hydroxyl groups, followed by Cbz-removal, would provide access to diamino diol **4**, which was required for the synthesis of A-77003. Accordingly, Cbz-phenylalaninol underwent Swern oxidation[14] and homocoupling with $[V_2Cl_3(THF)_6]_2[Zn_2Cl_4]$ according to the procedure of Pedersen[5] to provide a ca. 8:1:1 mixture of **21**:**22**:**23**, respectively (Scheme II). (3*R*,4*R*)-Diol **21** was conveniently purified[15] from the mixture by acetonide formation (acetone, H_2SO_4), filtration to remove most of the insoluble acetonide of (3*S*,4*S*)-diol **22**, and selective hydrolysis of the more labile acetonide of diol **21**. The highly insoluble diol **21** was then isolated by simple filtration from the solution of acetonides in 70% overall yield from Cbz-phenylalaninol. Transfer hydrogenolysis or barium hydroxide hydrolysis of **21** provided diamino diol **2**. Additionally, acid-catalyzed hydrolysis of the acetonide of the minor product **22** followed by Cbz removal provided (3*S*,4*S*)-diamine **3**.

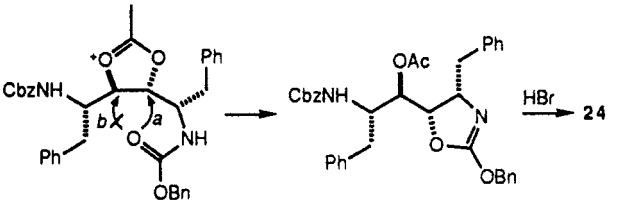
With a convenient synthesis of **21** in hand, we turned our attention to the stereochemical inversion at one of the hydroxyl groups of **21** in order to selectively prepare the (3*R*,4*S*)-isomer **4**. This presented a 2-fold challenge: differentiation of the symmetry-related hydroxyl groups of **21** and inversion at a highly hindered center (C_3 or C_4) adjacent to two electron-withdrawing groups. In view of these difficulties, we chose initially to investigate methods for diol activation, with the hope of utilizing the carbonyl oxygen of one of the Cbz groups as an internal nucleophile. Pyrolysis of the cyclic sulfate derivative of **21**[16] or treatment of the monoacetate of **21** with thionyl chloride according to the procedure of Kano et al.[17] resulted in low yields of inverted products. We next investigated methods to increase the electrophilicity of the carbon–oxygen bond via the cyclic oxonium ion **28** (vide infra). Attempted generation of **28** by protonation of the cyclic orthoacetate derived from **21** led to inconsistent results. However, direct activation of **21** by treatment with α-acetoxyisobutyryl bromide[18] in acetonitrile (Scheme III) met with much greater success, providing a 71% yield of a cyclic carbamate, tentatively assigned the structure **24** (vide infra). Hydrolysis of **24** using barium hydroxide led to unsymmetric diamino diol **4** in 57% overall yield from **21**.

Scheme III[a]



[a] Key: (a) α-acetoxyisobutyryl bromide, CH_3CN, rt, 2 h; (b) $(Et_3O)_3CH$, CH_3SO_3H, CH_3CN, rt, 45 min; (c) CH_3SO_2Cl, DMAP, Et_3N, CH_2Cl_2, 0 °C, 45 min; (d) NH_4Cl, H_2O, DMF, 122 °C, 12 h; (e) $Ba(OH)_2 \cdot 8H_2O$, H_2O, dioxane, reflux, 12 h.

Scheme IV

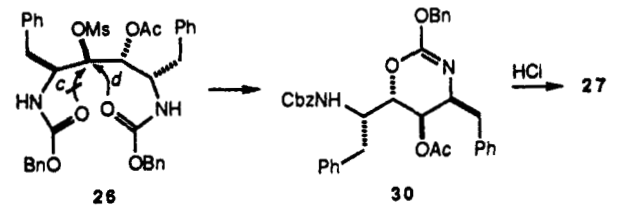


Although the above inversion protocol was straightforward on a multigram scale, the necessity for chromatographic separation of the intermediate **24** was problematic for the large-scale production of **4**, the required intermediate for the synthesis of A-77003. We thus found the slightly more circuitous route to **4** shown in Scheme III to be superior. Diol **21** was quantitatively converted to monoacetate **25** via conversion to the cyclic orthoester (triethyl orthoacetate, $MeSO_3H$), followed by aqueous hydrolysis.[19] Mesylation of the remaining hydroxyl group (methanesulfonyl chloride, DMAP, Et_3N) provided the regiochemically differentiated **26**. Pyrolysis of **26** in DMF containing aqueous ammonium chloride provided an intermediate which, unexpectedly, was not identical to **24** and was thus tentatively assigned as the six-membered carbamate **27** (vide infra). Notably, cyclization of **26** in the absence of ammonium chloride led to increased reaction times and to increased formation of byproducts. Complete hydrolysis of **27** using barium hydroxide led to **4**, which was isolated by crystallization. Therefore, this four-step inversion process was accomplished in 76% overall yield from **21**, with no intermediate purifications and no chromatographic separations. The optical purity of **4** prepared by this method was shown to be >99% ee by chiral HPLC analysis of monoacetate **25**.

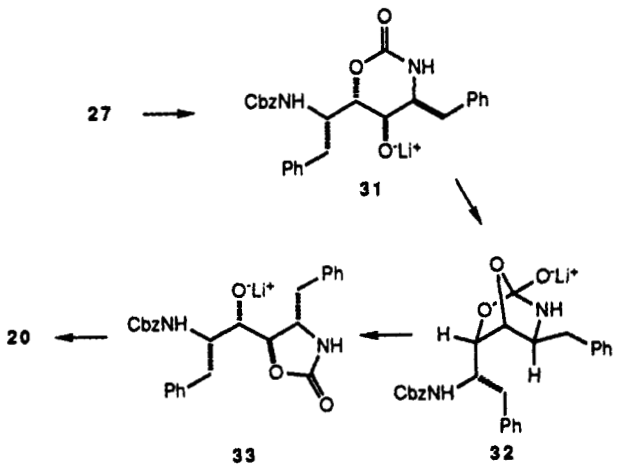
The fact that intramolecular hydroxyl inversion via the two routes described above proceeded to give different cyclic carbamates is undoubtedly reflective of a combination of geometric constraints and steric factors in the two different transition states for ring formation. Our initial assignment of **24** as the five-membered cyclic carbamate was based on consideration of oxonium ion **28**, the presumed reaction intermediate upon treatment of **21** with α-acetoxyisobutyryl bromide[18] (Scheme IV). Endocyclic displacement via pathway b to give **30** would be expected to be disfavored due to the inability of the carbonyl oxygen to adopt a suitable geometry for S_N2-like displacement.

(13) Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014.
(14) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. Derivatization of the aldehyde formed by oxidation followed by chiral HPLC analysis showed the aldehyde to be >99.5% ee (see Experimental Section).
(15) On a large scale, purification according to the published method (ref 5) resulted in low recovery of **21**.
(16) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.
(17) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1987**, *28*, 6331.
(18) Greenberg, S.; Moffatt, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4016.
(19) Reese, C. B.; Sulston, J. E. *Proc. Chem. Soc.* **1964**, 214.

Scheme V



Scheme VI



On the other hand, [5-*exo-tet*] displacement via pathway a should be facile to give, irreversibly,[20] the imino acetal **29**. Bromide-mediated dealkylation of **29** leads to the five-membered carbamate **24**. The reasons for the regioselectivity in the cyclization of monomesylate **26** are less evident. On the basis of precedent using simpler systems,[21] there is apparently no geometric constraint for either five-membered cyclization to give **29** (pathway c, Scheme V) or six-membered displacement to give **30** (pathway d). Since five-membered ring formation would be expected to occur more rapidly than six-membered, the apparent exclusive reaction of **26** through pathway d to give **30** rather than **29** suggests that steric factors play a role in destabilizing the conformation required for [5-*exo-tet*] displacement. The imino acetal **30**, formed after [6-*exo-tet*] cyclization, undergoes chloride-assisted debenzylation to give cyclic carbamate **27**.

In light of the above ambiguities, we endeavored to confirm the structures of cyclic carbamates **24** and **27** by physical methods. Selective hydrolysis of the acetate group of **24** with lithium hydroxide led, with concommitant cyclization, exclusively to the unsymmetric bis(oxazolidinone) **20**, the structure of which was authenticated by single-crystal X-ray analysis. We anticipated that, under similar conditions, **27** would lead to the corresponding fused bicyclic product. Unexpectedly, mild hydrolysis of **27** also gave the bis five-membered carbamate **20** as the major portion of an inseparable mixture of two products. The minor product, by mass spectral analysis, had a molecular weight of 477, consistent with loss of acetate from **27**. Ultimately, faced with the inability to unequivocally distinguish between **24** and **27** by chemical and spectral methods, we established the structure of each independently through X-ray analysis. Crystal parameters for **20**, **24**, and **27** are provided in Table I. The unanticipated rearrangement in the conversion of **27** to **20** apparently proceeds via the bicyclic intermediate **32**, which results from intramolecular attack of the initially formed alkoxide **31** on the cyclic carbamate (Scheme VI). Support for this mechanism over alternate possibilities is found in the crystal structure of **27**. The ORTEP plot of **27** (Figure 1) shows an axial orientation of both the C_5 acetoxy group and C_6 aminoalkyl group. Indeed, the dihedral angle between those groups through C_5 and C_6 is 174°. The interatomic distance between C_2 and the C_5 acetate oxygen is 3.0 Å; thus, little distortion is required to produce intermediate **32** following hydrolysis of the acetate of **27**. Molecular mechanics calculations on a simplified analogue of **27** indicated that the two conformers with the acetate group either axially or equatorially disposed are of similar energy.[22] Presumably, the accessibility of the axial orientation allows the alkoxide from **27** to react with the neighboring cyclic carbamate carbonyl group much more rapidly than with the remote Cbz carbonyl group. Breakdown of the tetrahedral intermediate **32** produces alkoxide **33**, which is not identical to the intermediate formed in the hydrolysis of **24**, though both lead ultimately to **20**. The minor product formed in the hydrolysis of **27** is therefore either the free alcohol corresponding to six-membered cyclic carbamate **31**, formed as a result of incomplete or reversible cyclization to **32**, or the alcohol corresponding to five-membered cyclic carbamate **33**. Cyclization of **33** under basic conditions to give the cis-oxazolidinone ring of **20** would be expected to be less facile than cyclization of the intermediate alkoxide from **24**, which forms the thermodynamically more stable *trans*-oxazolidinone ring of **20**. Spectral data on the mixture obtained from **27** do not differentiate between the above alternatives.

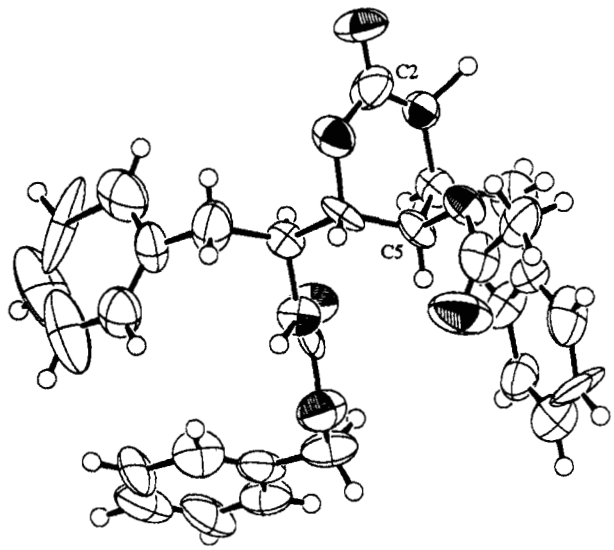


Figure 1. ORTEP view of **27**.

The transformations described above provide new methods for inversion of α-amino alcohols and diols. The activation of diols with α-acetoxyisobutyryl bromide for intramolecular displacement by the Cbz carbonyl group rather than intermolecular displacement with bromide ion[18] is, to our knowledge, unprecedented. Preliminary results indicate that the competition between these modes of reaction is highly solvent dependent. Intramolecular inversion via the ammonium chloride assisted cyclization of mesylate **26** is also of note. Fluoride-induced cyclization of *N*-(siloxycarbonyl) α-aminomesylates has been reported.[21] However, the present conversion of **26** directly to **27** obviates the need for prior replacement of the Cbz function

(20) Kobayashi, S.; Isobe, T.; Ohno, M. *Tetrahedron Lett.* **1984**, *25*, 5079.
(21) Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150.
(22) Hutchins, C., personal communication.

with the silyloxy carbamate.

The results presented here provide practical, stereoselective syntheses of the homochiral C_2-symmetric and pseudo-C_2-symmetric diamines 1–4 for use as core units in potent, structure-based inhibitors of HIV protease. Application of these synthetic approaches on large scale has provided an ample supply of intermediates for use in structure–activity studies. Moreover, the stereoselective route to diamine 4 has allowed the synthesis of large amounts of A-77003 (5), which shows high potential for clinical therapy of AIDS.[3] Results of those investigations will be reported in due course.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were measured on a GE QE-300 (300 MHz) instrument using tetramethylsilane as an internal standard. ^{1}H NMR spectra, mass spectra, and elemental analyses were performed by the Structural Chemistry Department, Abbott Laboratories. Flash column chromatography was performed on silica gel 60, 0.04–0.063 mm (E. Merck). Thin-layer chromatography was performed on precoated silica gel f-254 plates (0.25 mm; E. Merck) and was visualized with phosphomolybdic acid.

***trans*-(2*S*)-2-[[(*tert*-Butyloxy)carbonyl]amino]-1,5-diphenylpent-3-ene (7).** A solution of 15.1 g (54.5 mmol) of 4-[[(*tert*-butyloxy)carbonyl]amino]-3-hydroxy-5-phenyl-1-pentene (6)[7a] and 38 mL (220 mmol) of diisopropylethylamine in 450 mL of dry CH_2Cl_2 was cooled to −10 °C under N_2 atmosphere and treated dropwise with 8.5 mL (110 mmol) of methanesulfonyl chloride. After completion of addition, the solution was stirred for 7 min, quenched with 10% citric acid, extracted with ether, washed sequentially with water and saturated brine, dried over $MgSO_4$, and concentrated in vacuo to give the crude mesylate as an off-white solid. To a flame-dried flask equipped with an internal low-temperature thermometer was added 1.45 g (16 mmol) of anhydrous cuprous cyanide and 500 mL of anhydrous tetrahydrofuran (THF). The suspension was cooled to −78 °C under N_2 atmosphere and treated with 55 mL (165 mmol) of phenylmagnesium bromide in ether (3 M). The bath was removed, and the resulting beige suspension was warmed with stirring by use of a water bath. As the internal temperature reached −1 °C, the solution was homogeneous and was immediately recooled by placement of the flask in a dry ice/acetone bath. As the internal temperature reached −65 °C, a solution of the above crude mesylate in 75 mL of THF was added via cannula. The resulting solution was stirred at ca. −70 °C for 15 min and treated with saturated aqueous ammonium chloride, followed by ether. As the mixture warmed, 1 N NH_4OH was added, and the mixture was stirred under air atmosphere for several hours while the aqueous layer turned dark blue. The mixture was then extracted with ether, washed with saturated brine, and concentrated in vacuo without drying to give a yellow oil. The combined aqueous layers were extracted with additional ether, which was added to the above oil. The resulting solution was washed with saturated brine, dried over $MgSO_4$, and concentrated to a yellow oil. Flash chromatography using hexane/ethyl acetate mixtures provided 13.03 g (71%) of 7, mp 83–84 °C: ^{1}H NMR δ 1.40 (s, 9 H), 2.7–2.9 (m, 2 H), 3.32 (d, J = 7 Hz, 2 H), 4.4 (br, 2 H), 5.43 (dd, J = 15, 6 Hz, 1 H), 5.64 (dt, J = 15, 7 Hz, 1 H), 7.0–7.3 (m, 10 H); CIMS m/z 355 $(M + NH_4)^+$. Anal. Calcd for $C_{23}H_{27}NO_2 \cdot 0.1H_2O$: C, 78.64; H, 7.80; N, 3.99. Found: C, 78.40; H, 8.08; N, 4.15.

(2*S*,3*R*,4*S*)- and (2*R*,3*S*,4*S*)-2-Azido-4-[[(*tert*-butyloxy)carbonyl]amino]-1,5-diphenyl-3-hydroxypentane (8 and 9). A solution of 11.71 g (34.75 mmol) of 7 in 200 mL of CH_2Cl_2 was treated with 15 g (174 mmol) of $NaHCO_3$, cooled to 0 °C, and treated with 24 g (69 mmol) of *m*-chloroperbenzoic acid (50%). The resulting suspension was stirred at 5 °C for 3 days, treated with 10% sodium thiosulfate solution and ether, stirred for 2 h, and separated. The organic layer was washed sequentially with 2 M NaOH, water, and saturated brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography using ethyl acetate/hexane mixtures provided 9.36 g (76%) of a ca. 4:1 mixture of diastereomeric epoxides as an oil which solidified upon standing. A solution of 9.12 g (25.84 mmol) of this mixture, 7.0 g (140 mmol) of lithium azide, and 1.73 g (32 mmol) of ammonium chloride in 75 mL of DMF and 7.5 mL of water was heated in an oil bath at 70 °C for 32 h. After being allowed to cool, the resulting solution was partitioned between 1:1 ether/hexane and water. After extraction of the aqueous layer with additional 1:1 ether/hexane, the combined organic layers were washed sequentially with water and saturated brine, dried over $MgSO_4$, and concentrated in vacuo to a solid. Flash chromatography using ethyl acetate/hexane mixtures gave 9.26 g (91%) of a ca. 4:1 mixture of 8 and 9, respectively. 8: ^{1}H NMR ($CDCl_3$, major isomer) δ 1.42 (s, 9 H), 2.78 (m, 1 H), 2.89 (m, 1 H), 3.13 (m, 1 H), 3.29 (m, 1 H), 3.41 (m, 1 H), 3.53 (m, 1 H), 3.80 (m, 1 H), 4.06 (m, 1 H), 4.83 (m, 1 H), 7.2–7.35 (m, 10 H); ClMS m/z 397 $(M + H)^+$. Anal. Calcd for $C_{20}H_{20}N_2O_4 \cdot 0.1H_2O$: C, 66.65; H, 7.12; H, 14.13. Found: C, 66.96; H, 7.14; N, 14.02.

(2*S*,3*S*,4*S*)- and (2*R*,3*S*,4*S*)-2-Amino-4-[[(*tert*-butyloxy)carbonyl]amino]-1,5-diphenyl-3-hydroxypentane (10 and 11). A rapidly stirring suspension of 1.8 g of 10% palladium on carbon in 50 mL of CH_3OH was treated under inert atmosphere with 10 g (0.16 mol) of solid ammonium formate. After 10 min, a solution of 8.95 g (22.6 mmol) of the mixture of 8 and 9 in 80 mL of CH_3OH was added. The resulting mixture was stirred for 2.5 h and filtered through Celite, and the catalyst was washed with 1:1 CH_3OH/1 N ammonium hydroxide. The combined filtrates were concentrated in vacuo to a volume of 100 mL, treated with 1 N NaOH, and extracted with two portions of $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography using $CH_3OH/CHCl_3$/isopropylamine mixtures provided 5.85 g (70%) of 10, mp 134–135 °C, and 1.22 g (15%) of 11, mp 72–74 °C. 10: ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9 H), 2.50 (dd, J = 13, 10 Hz, 1 H), 2.8–3.1 (m, 4 H), 3.41 (br d, J = 7 Hz, 1 H), 4.11 (br q, J = 8 Hz, 1 H), 4.83 (br d, J = 9 Hz, 1 H), 7.15–7.35 (m, 10 H); CIMS m/z 371 $(M + H)^+$. Anal. Calcd for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.13; H, 8.09; N, 7.48.

11: mp 130–131 °C; ^{1}H NMR (DMSO-d_6) δ 1.03 (s, 1 H), 1.27 (s, 9 H), 2.31 (dd, J = 13, 11 Hz, 1 H), 2.51 (dd, J = 14, 11 Hz, 1 H), 2.76 (m, 1 H), 3.00 (m, 1 H), 3.11 (dd, J = 14, 3 Hz, 1 H), 3.39 (m, 1 H), 3.81 (m, 1 H), 5.09 (br, 1 H), 6.71 (d, J = 9 Hz, 1 H), 7.1–7.3 (m, 10 H); CIMS m/z 371 $(M + H)^+$. Anal. Calcd for $C_{22}H_{30}N_2O_3 \cdot 0.5H_2O$: C, 69.63; H, 8.23; N, 7.38. Found: C, 69.88; H, 7.92; N, 7.29.

(2*S*,4*S*)-2,4-Diamino-1,5-diphenyl-3-hydroxypentane (1). A solution of 4.53 g (12.2 mmol) of 10 in 60 mL of 4 M HCl in dioxane was stirred for 2 h at rt and concentrated in vacuo. The residue was taken up in water, washed twice with CH_2Cl_2, basified with NaOH, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo. The residue was recrystallized from ethyl acetate/hexane to provide 2.93 g (89%) of 1, mp 135–137 °C: ^{1}H NMR ($CDCl_3$) δ 2.51 (dd, J = 13, 10 Hz, 1 H), 2.67 (dd, J = 13, 9 Hz, 1 H), 2.85–3.0 (m, 2 H), 3.19 (m, 1 H), 3.38 (m, 2 H), 7.15–7.35 (m, 10 H); CIMS m/z 271 $(M + H)^+$. Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.71; H, 8.20; N, 10.30.

(4*S*,5*R*,1′*S*)- and (4*S*,5*S*,1′*R*)-5-(1-Azido-2-phenylethyl)-4-benzyloxazolidin-2-one (12 and 13). A solution of 44 mg (0.11 mmol) of the mixture of 8 and 9 in 0.5 mL of DMF was treated with 5 mg (0.12 mmol) of sodium hydride (60% dispersion in oil) and stirred at rt for 4 h. The resulting solution was diluted with water, extracted with two portions of ether, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography using ethyl acetate/hexane mixtures provided 17.8 mg (51%) of 12 (R_f 0.16, 3:2 hexane:ethyl acetate) and 4.2 mg (12%) of 13 (R_f 0.21).

12: ^{1}H NMR ($CDCl_3$) δ 2.72 (dd, J = 14.3, 9.1 Hz, 1 H), 2.77 (dd, J = 13.5, 8.8 Hz, 1 H), 2.9–3.0 (m, 2 H), 3.81 (ddd, J = 8.8, 6.5, 3.9 Hz, $H_{1'}$), 3.94 (m, H_4), 4.18 (dd, J = 6.5, 4.4 Hz, H_5), 7.2–7.4 (m, 10 H).

13: ^{1}H NMR ($CDCl_3$) δ 2.68 (br t, J = 12 Hz, 1 H), 2.96 (dd, J = 14.6, 8.5 Hz, 1 H), 3.09 (dd, J = 13.0, 3.1, 1 H), 3.40 (dd, J = 14.6, 3.1 Hz, 1 H), 3.94 (m, $H_{1'}$), 3.98 (m, H_4), 4.39 (dd, J = 10.4, 7.3 Hz, H_5). Irradiation at 3.98 ppm resulted in a broad doublet at 4.39 ppm (J = 10 Hz).

(4*S*,5*R*,1′*S*)-5-(1-Amino-2-phenylethyl)-4-benzyloxazolidin-2-one (14). A solution of 14.8 mg (0.04 mmol) of 10 and 60 μL of 4-methylmorpholine in 0.5 mL of CH_2Cl_2 was cooled to 0 °C and treated with 90 μL of 12.5% phosgene in toluene. The solution was stirred for 0.5 h, quenched with H_2O, partitioned

between CH_2Cl_2 and 1 N HCl, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography using ethyl acetate/$CHCl_3$ provided 5.8 mg (37%) of (4*S*,5*S*,1′*S*)-4-benzyl-5-[1-[[(*tert*-butyloxy)carbonyl]amino]-2-phenylethyl]oxazolidin-2-one, which was treated with 1 mL of 4 N HCl in dioxane. After 1 h, the solution was concentrated in vacuo, and the residue was taken up in 3 N aqueous NaOH, extracted two times with $CHCl_3$, dried over Na_2SO_4, and concentrated in vacuo to provide **14**: ^{1}H NMR ($CDCl_3$) δ 2.72 (dd, *J* = 13.4, 8.6 Hz, 1 H, benzyl), 2.92 (dd, *J* = 13.4, 5.3 Hz, 1 H, benzyl), 4.02 (ddd, *J* = 8.6, 7.7, 5.3 Hz, H_4), 4.53 (dd, *J* = 7.7, 5.9 Hz, H_5).

(2*S*,3*R*,4*R*,5*S*)-, (2*S*,3*S*,4*S*,5*S*)-, and (2*S*,3*R*,4*R*,5*S*)-2,5-Bis[[(*tert*-butyloxy)carbonyl]amino]-3,4-dihydroxy-1,6-diphenylhexane (15–17). A suspension of 27 g of $TiCl_3(DME)_2$[12] in 200 mL of anhydrous dimethoxyethane (DME) was treated in portions with 20 g of Zn–Cu couple under positive argon pressure with vigorous stirring. After the addition, stirring was continued while the mixture was heated to 85 °C for 2.5 h. The resulting mixture was cooled to 0 °C and treated via cannula with a solution of Boc-L-phenylalaninal[10] (20 mmol) in 20 mL of anhydrous DME. After 1 h, the reaction mixture was filtered through Celite, and the residue was washed with ethyl acetate. The filtrate was treated with saturated aqueous $NaHCO_3$, and air was bubbled through the suspension until it became white. The layers were separated, and the organic layer was washed with saturated brine, dried over $MgSO_4$, and concentrated to give 3.7 g of a light yellow solid. Flash chromatography using ethyl acetate/hexane mixtures provided two fractions, the more mobile (R_f 0.26, 70:30 hexane/ethyl acetate) of which contained **16** and **17** (ca. 1:1, 1.05 g, 21% yield of mixture) and the less mobile (R_f 0.10) of which contained **15** (0.9 G, 18%). Careful chromatography of a portion of the mixture **16** and **17** using ethyl acetate/$CHCl_3$ mixtures provided nearly pure samples of each. **15**: mp 200–202 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 18 H), 2.87 (dd, *J* = 13, 7 Hz, 2 H), 2.98 (dd, *J* = 13, 7 Hz, 2 H), 3.41 (m, 2 H), 3.76 (br q, *J* = 8 Hz, 2 H), 3.96 (m, 2 H), 4.77 (br d, *J* = 8 Hz, 2 H), 7.15–7.3 (m, 10 H); CIMS *m*/*z* 501 $(M + H)^+$. Anal. Calcd for $C_{28}H_{40}N_2O_6 \cdot 0.5H_2O$: C, 65.99; H, 8.11; N, 5.50. Found: C, 65.96; H, 7.96; N, 5.49.

16: mp 172–173 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 18 H), 2.97 (dd, *J* = 14, 5 Hz, 2 H), 3.20 (m, 4 H), 4.03 (m, 2 H), 4.35 (d, *J* = 5 Hz, 2 H), 4.41 (d, *J* = 9 Hz, 2 H), 7.2–7.3 (m, 10 H); CIMS *m*/*z* 501 $(M + H)^+$. Anal. Calcd for $C_{28}H_{40}N_2O_6$: C, 67.18; H, 8.05; N, 5.60. Found: C, 67.20; H, 8.09; N, 5.59.

17: ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9 H), 1.39 (s, 9 H), 2.67 (m, 1 H), 2.75–2.95 (m, 4 H), 3.46 (m, 2 H), 4.15 (m, 2 H), 4.58 (m, 1 H), 4.83 (br d, 1 H), 4.92 (br d, 1 H), 7.15–7.3 (m, 10 H); CIMS *m*/*z* 501 $(M + H)^+$. Anal. Calcd for $C_{28}H_{40}N_2O_6$: C, 67.18; H, 8.05; N, 5.60. Found: C, 67.28; H, 8.35; N, 5.68.

(2*S*,3*R*,4*R*,5*S*)-2,5-Diamino-3,4-dihydroxy-1,6-diphenylhexane (2). A suspension of 2.7 g (5.4 mmol) of **15** was treated with 200 mL of 6 N HCl and heated to 90 °C until the solid had completely dissolved (30 min). The resulting solution was cooled, concentrated in vacuo, treated with saturated brine and 3 N NaOH, extracted with $CHCl_3$, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography using CH_3OH/isopropylamine/$CHCl_3$ mixtures provided **2**, mp 86–89 °C: ^{1}H NMR ($CDCl_3$) δ 2.72 (dd, *J* = 14, 9 Hz, 2 H), 2.92 (dd, *J* = 14, 6 Hz, 2 H), 3.03 (dd, *J* = 9, 5 Hz, 2 H), 3.69 (s, 2 H), 7.15–7.35 (m, 10 H); CIMS *m*/*z* 301 $(M + H)^+$. Anal. Calcd for $C_{18}H_{24}N_2O_2 \cdot 0.25H_2O$: C, 70.91; H, 8.10; N, 9.19. Found: C, 70.52; H, 7.92; N, 8.93.

(2*S*,3*S*,4*S*,5*S*)- and (2*S*,3*S*,4*S*,5*S*)-2,5-Diamino-3,4-dihydroxy-1,6-diphenylhexane (3 and 4). Application of the above procedure to the mixture of **16** and **17** provided a mixture of diamines which was separated by flash chromatography using CH_3OH/isopropylamine/$CHCl_3$ mixtures. **3**: ^{1}H NMR ($CDCl_3$) δ 2.63 (dd, *J* = 14, 11 Hz, 2 H), 2.85 (dd, *J* = 14, 4 Hz, 2 H), 3.60 (dt, *J* = 11, 4 Hz, 2 H), 3.92 (d, *J* = 3 Hz, 2 H), 7.2–7.4 (m, 10 H); CIMS *m*/*z* 301 $(M + H)^+$.

4: ^{1}H NMR ($CDCl_3$) δ 2.46 (dd, *J* = 14, 9 Hz, 1 H), 2.61 (dd, *J* = 14, 11 Hz, 1 H), 3.02 (td, *J* = 9, 3 Hz, 1 H), 3.19 (dd, *J* = 14, 4 Hz, 1 H), 3.35–3.4 (m, 2 H), 3.51 (t, *J* = 9 Hz, 1 H), 3.76 (dd, *J* = 9, 3 Hz, 1 H), 7.2–7.4 (m, 10 H); CIMS *m*/*z* 301 $(M + H)^+$. Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.71; H, 7.96; N, 9.23.

(4*S*,5*R*,4′*S*,5′*R*)-5,5′-Bis(4-benzyloxazolidin-2-one) (18). Using a procedure analogous to the preparation of **12**, 21 mg of **15** was converted to 10 mg (68%) of **18** after flash chromatography using ethyl acetate/$CHCl_3$ mixtures: ^{1}H NMR δ 2.75 (dd, *J* = 14, 7 Hz, 2 H), 2.85 (dd, *J* = 14, 7 Hz, 2 H), 3.97 (d, *J* = 5.5 Hz, $H_{5,5'}$), 4.07 (br q, *J* = 6 Hz, $H_{4,4'}$), 5.12 (br s, 2 H), 7.09 (m, 4 H), 7.2–7.4 (m, 6 H); CIMS *m*/*z* 370 $(M + NH_4)^+$. Anal. Calcd for $C_{20}H_{20}N_2O_4 \cdot 1H_2O$: C, 64.85; H, 5.99; N, 7.56. Found: C, 65.00; H, 5.72; N, 7.95.

(4*S*,5*S*,4′*S*,5′*S*)-5,5′-Bis(4-benzyloxazolidin-2-one) (19). Using a procedure analogous to the preparation of **12**, **16** was converted to **19**, mp >270 °C: ^{1}H NMR δ 3.03 (dd, *J* = 13, 4 Hz, 2 H), 3.13 (dd, *J* = 13, 11 Hz, 2 H), 4.29 (ddd, *J* = 10, 8.5, 4 Hz, $H_{4,4'}$), 4.83 (br s, 1 H), 4.95 (d, *J* = 8.5 Hz, 1 H), 7.2–7.4 (m, 10 H). Anal. Calcd for $C_{20}H_{20}N_2O_4 \cdot 0.1H_2O$: C, 67.82; H, 5.75; N, 7.91. Found: C, 67.61; H, 5.71; N, 7.84.

(4*S*,5*R*,4′*S*,5′*S*)-5,5′-Bis(4-benzyloxazolidin-2-one) (20). Using a procedure analogous to the preparation of **12**, **17** was converted to **20**, mp 239–240 °C: ^{1}H NMR δ 2.66 (t, *J* = 13 Hz, 1 H), 2.82 (dd, *J* = 13, 10 Hz, 1 H), 3.17 (dd, *J* = 14, 4 Hz, 1 H), 3.21 (dd, *J* = 14, 3 Hz, 1 H), 4.1 (m, 2 H), 4.61 (dd, *J* = 10, 4.5 Hz, H_5), 4.73 (dd, *J* = 10, 7.5 Hz, $H_{5'}$), 4.89 (br s, 1 H), 5.02 (br s, 1 H), 7.2–7.4 (m, 10 H); CIMS *m*/*z* 370 $(M + NH_4)^+$. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.30; H, 5.75; N, 7.87.

***N*-[(Benzyloxy)carbonyl]-L-phenylalaninal.** To 870 mL of dry CH_2Cl_2 was added 24.5 mL (350 mmol, 2 equiv) of dry DMSO, and the solution was cooled to −60 °C under N_2. To this was added 131 mL (0.262 mmol, 1.5 equiv) of 2 M oxalyl chloride in CH_2Cl_2 over a 15-min period, taking care to maintain the temperature at −50 °C or lower, and the reaction was stirred at −60 °C for 15 min. Then 50.0 g (0.175 mol) of *N*-[(benzyloxy)carbonyl]-L-phenylalaninol[23] in 200 mL of CH_2Cl_2 was added over a 20-min period, taking care to maintain the temperature at −50 °C or lower, and the reaction was stirred at −60 °C for 1 h. Over a 15-min period was added 97 mL (0.700 mol, 4.0 equiv) of triethylamine, taking care to maintain the temperature at −50 °C or lower, and the reaction was stirred at −60 °C for 15 min. To the reaction vessel was then added 163 g of citric acid in 550 mL of water over a 1-min period, with the cooling bath in place. The resulting slurry was stirred vigorously for 10 min. The mixture was diluted with 1 L of water and agitated vigorously, and then the organic layer was separated and washed with 700 mL of water followed by 550 mL of water to which 150 mL of saturated sodium bicarbonate solution had been added. The organic solution was dried over magnesium sulfate, filtered, and concentrated in vacuo. The title product was obtained as light yellow crystalline mass, which was dissolved in CH_2Cl_2 and used immediately.

Determination of the Enantiomeric Purity of *N*-[(Benzyloxy)carbonyl]-L-phenylalaninal. A solution of 25–30 mg of *N*-[(benzyloxy)carbonyl]-L-phenylalaninal in 5 mL of anhydrous THF was cooled to 0 °C and treated dropwise with 0.5 mL of a 1.0 M solution of $LiAlH_4$ in THF. The resulting mixture was stirred for 10 min at 0 °C and then quenched by sequential addition of 20 μL of H_2O, 20 μL of 15% aqueous NaOH, and 60 μL of H_2O. After filtration, the solid was washed with 1 mL of THF, and the combined filtrates were concentrated in vacuo to give 20–25 mg of crude *N*-[(benzyloxy)carbonyl]-L-phenylalaninol as a clear oil which slowly crystallized. A stirred solution of the crude alcohol in 5 mL of CH_2Cl_2 was treated under N_2 with 35–40 mg of 3,5-dinitrobenzoyl chloride, 1–2 mg of DMAP (4-(dimethylamino)pyridine), and finally five drops of triethylamine. The resulting yellow solution was stirred for 15 min at rt and then quenched by addition to 4 mL of 1 N aqueous HCl. The organic layer was isolated, washed sequentially with 4 mL of aqueous $NaHCO_3$ and 4 mL of H_2O, dried over $MgSO_4$, and filtered. A 3-μL sample of the filtrate was injected onto a Pirkle D-2-naphthylalanine chiral stationary phase using 25% isopropyl alcohol in hexane as mobile phase. The elution times for the two enantiomers of *N*-[(benzyloxy)carbonyl]-L-phenylalaninol 3,5-dinitrobenzoate were approximately 18 and 24 min at 2 mL/min. Application to *N*-[(benzyloxy)carbonyl]-L-phenylalaninal prepared as above showed the sample to be >99.5% ee.

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(2S,3R,4R,5S)-2,5-Bis[[(benzyloxy)carbonyl]amino]-3,4-dihydroxy-1,6-diphenylhexane (21). A suspension of 78.5 g of $VCl_3(THF)_3$[24] and 16 g of zinc dust in 400 mL of dry CH_2Cl_2 was stirred under N_2 atmosphere for 1 h at 25 °C. A solution of 0.175 mol of Cbz-L-phenylalaninal in 200 mL of CH_2Cl_2 was then added in one portion, and the resulting mixture was stirred at rt under N_2 atmosphere for 16 h. After addition to 500 mL of 1 M aqueous HCl, the mixture was diluted with 500 mL of hot $CHCl_3$ and shaken vigorously for 2 min. The layers were separated, and the organic layer was washed with 1 M aqueous HCl and separated. Filtration of the organic phase provided a crude mixture of diols as a solid residue. The residue was slurried in 1.25 L of acetone, treated with 5 mL of concentrated H_2SO_4, and stirred for 16 h at rt. The resulting mixture was filtered, and the residue (residue A) was washed with 50 mL of acetone. The combined filtrate was concentrated to a volume of 250 mL, diluted with 1000 mL of CH_2Cl_2, washed three times with water and once with saturated brine, dried over $MgSO_4$, and concentrated to give a viscous oil. The oil was taken up in 1000 mL of 1 M HCl in CH_3OH (prepared from 71 mL of acetyl chloride and 1000 mL of CH_3OH) and stirred at rt for 2 h. The resulting precipitate was filtered, washed with CH_3OH, and air-dried on the filter to provide 26.7 g of **21** as a white solid. The filtrate was concentrated and filtered to give a second crop (8.3 g) of **21**, total yield 70%. ^1H NMR (DMSO-d_6) δ 2.59 (dd, J = 13, 5 Hz, 2 H), 2.74 (dd, J = 13, 9 Hz, 2 H), 3.26 (br, 2 H), 4.19 (m, 2 H), 4.54 (m, 2 H), 4.92 (m, 4 H), 6.82 (d, J = 9 Hz, 2 H), 7.0–7.35 (m, 20 H); CIMS m/z 569 $(M + H)^+$.

(2S,3S,4S,5S)-2,5-Bis[[(benzyloxy)carbonyl]amino]-3,4-dihydroxy-1,6-diphenylhexane (22). Residue A (above, 2.65 g) was suspended in 75 mL of THF and 75 mL of 1 M aqueous HCl and heated at reflux for 24 h. After concentration of the resulting solution in vacuo, the residue was taken up in 10% CH_3OH in $CHCl_3$, washed two times with water, dried over Na_2SO_4, and concentrated in vacuo to provide **22** as a white solid, mp 157–158 °C: ^1H NMR (DMSO-d_6) δ 2.64 (m, 2 H), 3.04 (m, 2 H), 3.49 (m, 2 H), 3.78 (m, 2 H), 4.70 (d, J = 7 Hz, 2 H), 4.93 (AA′, 4 H), 7.1–7.4 (m, 20 H); CIMS m/z 569 $(M + H)^+$. Anal. Calcd for $C_{34}H_{36}N_2O_6 \cdot 0.5H_2O$: C, 70.69; H. 6.46; N, 4.85. Found: C, 70.83; H, 6.44; N, 4.75.

Preparation of 2 from 21. A mixture of 5.0 g (9.1 mmol) of **21**, 2.85 g (45 mmol) of ammonium formate, and 2.17 g of 10% Pd/C in 50 mL of DMF was heated to 120 °C under Ar atmosphere for 4 h. The resulting mixture was allowed to cool and filtered through Celite. The filter cake was rinsed with CH_3OH, and the combined filtrates were concentrated in vacuo to a thick oil. The oil was taken up in ethyl acetate, washed sequentially with water, aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated in vacuo to an oil. The oil was taken up in ether and treated dropwise with stirring with excess 4 M HCl in dioxane. The resulting precipitate was filtered, rinsed with fresh ether, and dried in vacuo to provide pure **2**·$(HCl)_2$, mp >250 °C dec. Anal. Calcd for $C_{18}H_{26}Cl_2N_2O_2 \cdot H_2O$: C, 55.25; H, 7.21; N, 7.16. Found: C, 55.21; H, 7.10; N, 6.83. Alternately, a mixture of 14 g (25 mmol) of **21** and 15 g (50 mmol) of $Ba(OH)_2 \cdot 8H_2O$ in 200 mL of water and 400 mL of dioxane was heated at reflux for 24 h. The resulting mixture was allowed to cool, filtered, concentrated in vacuo to a volume of 200 mL, extracted with two portions of $CHCl_3$, dried over Na_2SO_4, and concentrated to give crude **2** as an oil. Pure **2**·$(HCl)_2$ was obtained in the manner described above.

Preparation of 3 from 22. A mixture of 9.65 g (17 mmol) of **22** and 16 g (51 mmol) of $Ba(OH)_2 \cdot 8H_2O$ in 200 mL of water and 300 mL of 1,4-dioxane was heated at reflux for 18 h. The resulting mixture was allowed to cool and filtered. The filtrate was concentrated in vacuo to a white solid, which was triturated with warm ethyl acetate and hexane, allowed to cool, and filtered to provide pure **3**, mp 204–205 °C. Anal. Calcd for $C_{18}H_{24}N_2O_2 \cdot 0.1H_2O$: C, 71.54; H, 8.07; N, 9.27. Found: C, 71.50; H, 7.96; N, 9.21.

(4S,5S,1′R,2′S)-5-[1-Acetoxy-2-[[(benzyloxy)carbonyl]amino]-3-phenylpropyl]-4-benzyloxazolidin-2-one (24). A suspension of 5.02 g (8.80 mmol) of **21** in 400 mL of acetonitrile was treated dropwise with 3 mL (20 mmol) of α-acetoxyisobutyryl bromide. The resulting solution was stirred under N_2 atmosphere at rt for 2 h, filtered to remove traces of solid starting material, quenched cautiously with 100 mL of aqueous $NaHCO_3$, and concentrated in vacuo to a volume of 100 mL. The resulting mixture was extracted with three portions of CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography using ethyl acetate/CH_2Cl_2 mixtures provided 3.15 g (71%) of **24** as a white foam, mp 79–81 °C: ^1H NMR ($CDCl_3$) δ 2.09 (s, 3 H), 2.53 (br t, J = 12 Hz, 1 H), 2.72 (dd, J = 13, 3 Hz, 1 H), 2.83 (dd, J = 14, 8 Hz, 1 H), 2.95 (dd, J = 14, 7 Hz, 1 H), 3.95 (m, 1 H), 4.45 (m, 1 H), 4.8 (m, 2 H), 5.0–5.1 (m, 3 H), 5.29 (dd, J = 9, 3 Hz, 1 H), 7.0–7.4 (m, 10 H); CIMS m/z 520 $(M + NH_4)^+$. Anal. Calcd for $C_{29}H_{30}N_2O_6 \cdot 0.25H_2O$: C, 68.69; H, 6.06; N, 5.52. Found: C, 68.52; H, 6.00; N, 5.42.

(2S,3R,4R,5S)-3-Acetoxy-2,5-bis[[(benzyloxy)carbonyl]amino]-4-hydroxy-1,6-diphenylhexane (25). Finely crushed diol **21** (215 g) was slurried in 6 L of CH_3CN under nitrogen atmosphere. To this stirred mixture at rt was added triethyl orthoacetate (3.0 equiv, 215 mL), followed by addition of methanesulfonic acid (15 mL) in one portion. After 15 min, the mixture became nearly homogenous. After 45 min, TLC (25% ethyl acetate/CH_2Cl_2) indicated that no starting diol **21** remained. A small amount of material that had not dissolved was removed by filtration. Water (700 mL) was added, and the solution was stirred an additional 45 min, after which TLC showed complete disappearance of the intermediate orthoester. The reaction solution was concentrated to a small volume, diluted with 2.5 L of ethyl acetate, and drained of the acidic aqueous layer. The organic layer was washed sequentially with 2.0 L of saturated aqueous $NaHCO_3$, 2.0 L of water, and 1.0 L of brine, dried over $MgSO_4$, and concentrated to give an oily solid. This residue was triturated with 800 mL of hexane, filtered, and dried under vacuum at 50 °C to give 218.2 g (98%) of **25** as an off-white powder, mp 130–131 °C: ^1H NMR ($CDCl_3$) δ 2.08 (s, 3 H), 2.66 (m, 2 H), 2.83 (m, 3 H), 3.58 (m, 1 H), 4.19 (m, 1 H), 4.47 (m, 1 H), 4.82 (d, J = 9.6 Hz, 1 H), 4.90–5.08 (m, 6 H), 7.07–7.39 (m, 20 H); CIMS m/z 628 $(M + NH_4)^+$. Anal. Calcd for $C_{36}H_{38}N_2O_7$: C, 70.80; H, 6.27; N, 4.59. Found: C, 70.58; H, 6.23; N, 4.52.

(2S,3R,4R,5S)-3-Acetoxy-2,5-bis[[(benzyloxy)carbonyl]amino]-4-[(methanesulfonyl)oxy]-1,6-diphenylhexane (26). A solution of (217.5 g) of **25** in 4.5 L of CH_2Cl_2 was cooled under N_2 atmosphere to 0 °C and treated with 7.00 g of 4-(dimethylamino)pyridine and 297 mL (6.0 equiv) of triethylamine. Finally, methanesulfonyl chloride (83.0 mL, 3.0 equiv) was added over 30 min so that the internal temperature remained below 5 °C. The resulting yellow solution was stirred for 45 min at 0 °C, after which TLC analysis (25% ethyl acetate/CH_2Cl_2) showed no starting material remaining. The reaction was quenched by the addition of 2 L of 1.0 M HCl, after which the mixture was stirred briefly and the layers were separated. The organic layer was washed sequentially with 2 L of aqueous $NaHCO_3$ and 2 L of H_2O, dried over $MgSO_4$, and concentrated to 298.7 g of a syrup that crystallized upon standing. Crude **26** thus obtained was used directly without further purification: ^1H NMR ($CDCl_3$) δ 2.13 (s, 3 H), 2.54 (dd, J = 14, 9 Hz, 1 H), 2.66 (m, 2 H), 2.74 (dd, J = 14, 6 Hz, 1 H), 3.03 (s, 3 H), 4.70 (m, 2 H), 4.85 (ABq, J = 9 Hz, 4 H), 4.99 (m, 3 H), 5.21 (d, J = 9 Hz, 1 H), 7.08–7.38 (m, 20 H); CIMS m/z 706 $(M + NH_4)^+$. Anal. Calcd for $C_{37}H_{40}N_2O_9S$: C, 64.52; H, 5.85; N, 4.07. Found: C, 64.56; H, 5.80; N, 4.02.

(4S,5R,6S,1′S)-5-Acetoxy-4-benzyl-6-[1-[[(benzyloxy)carbonyl]amino]-2-phenylethyl]-3,4,5,6-tetrahydro-2H-1,3-oxazin-2-one (27). A solution of 298 g of crude **26** and 2.5 mL of saturated aqueous NH_4Cl in 1.5 L of DMF was heated at 122 °C for 12 h. Analysis of the resulting solution by TLC (25% ethyl acetate/CH_2Cl_2) showed complete conversion of starting material. After evaporation of the solvent in vacuo, the remaining orange syrup was dissolved in 1.5 L of ethyl acetate, washed sequentially with 2 × 300 mL of water, 500 mL of aqueous $NaHCO_3$, and 300 mL of brine, dried over $MgSO_4$, and concentrated to give 193 g of crude **27** as an orange syrup that slowly crystallized upon standing. Crude **27** thus obtained was of sufficient purity for use in the next step without further purification. A pure sample of **27** was obtained by recrystallization from ethyl acetate/hexane to give **27** as off white needles, mp 140–142 °C: ^1H NMR ($CDCl_3$) δ 2.16 (s, 3 H), 2.66 (dd, J = 12, 9 Hz, 1 H), 2.86 (m, 2 H), 3.13 (dd, J = 15, 3 Hz, 1 H), 4.16 (m, 2 H), 4.34 (m, 1 H), 4.80 (m, 1 H), 5.02 (ABq, J = 12 Hz, 2 H), 5.09 (br s, 1 H), 5.15 (br s, 1 H),

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7.13–7.40 (m, 15 H); CIMS m/z 520 $(M + NH_4)^+$. Anal. Calcd for $C_{29}H_{30}N_2O_6$: C, 69.30; H, 6.02; N, 5.58. Found: C, 69.04; H, 5.97; N, 5.50.

Preparation of 4 from 27 and 24. Crude **27** (ca. 193 g, from 0.36 mol of **25**) was dissolved in 6 L of 1,4-dioxane with gentle warming. To this stirred warm solution was added 4 L of H_2O followed by 561 g (1.8 mol) of $Ba(OH)_2 \cdot 8H_2O$. The resulting mixture was heated at reflux for 11 h, after which TLC analysis (93% $CHCl_3$/5% MeOH/2% isopropylamine) showed complete conversion. The reaction mixture was allowed to cool and filtered through paper to remove solid $BaCO_3$. The filtrate was concentrated to remove the dioxane, and the resulting aqueous suspension was extracted with 4 × 500 mL of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried with anhydrous K_2CO_3 (Note: $MgSO_4$ should not be used as drying agent), and the solvent was removed to give 128 g of crude **4** as a tan solid. Recrystallization from 800 mL of ethyl acetate provided 77.7 g (65%) of pure **4** as colorless needles, mp 126.5 °C. A second crop of **4** (2.52 g) was obtained from 200 mL of ethyl acetate, and a third crop (5.1 g) was obtained from 30 mL of ethyl acetate (total yield: 85.3 g (80%). Application of the above procedure to 11.67 g of **24** provided crude **4** which was recrystallized from ethyl acetate to give 5.17 g (74%) of pure **4**. Second and third crops (0.23 g and 0.20 g) were obtained from ethyl acetate/hexane (total yield: 80%): ^1H NMR ($CDCl_3$) δ 2.46 (dd, J = 14, 9 Hz, 1 H), 2.61 (dd, J = 14, 11 Hz, 1 H), 3.02 (td, J = 9, 3 Hz, 1 H), 3.19 (dd, J = 14, 4 Hz, 1 H), 3.35–3.4 (m, 2 H), 3.51 (t, J = 9 Hz, 1 H), 3.76 (dd, J = 9, 3 Hz, 1 H), 7.2–7.4 (m, 10 H); CIMS m/z 301 $(M + H)^+$. Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.79; H, 7.99; N, 9.19.

Preparation of 20 from 24. A solution of 611 mg (1.22 mmol) of **24** in 5 mL of dioxane was treated with 5 mL of 0.5 M aqueous LiOH and stirred at rt for 18 h. After concentration of the resulting solution in vacuo, the residue was partitioned between $CHCl_3$ and water, and the organic layer was dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography using ethyl acetate/$CHCl_3$ mixtures provided 187 mg (43%) of **20**, which had spectral characteristics identical to **20** prepared above from **17**. The structure was confirmed by single-crystal X-ray analysis (Table I).

Preparation of 20 from 27. A solution of 233 mg (0.46 mmol) of **27** in 2 mL of dioxane was treated with 2 mL of 0.5 M aqueous LiOH and stirred at rt for 18 h. After concentration of the resulting solution in vacuo, the residue was partitioned between ethyl acetate and water, and the organic layer was dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography using ethyl acetate/$CHCl_3$ mixtures provided 145 mg of an inseparable mixture. NMR analysis indicated that the major portion of the mixture was identical to **20** prepared by the above methods. CIMS of the mixture showed $(M + NH_4)^+$ at 370 for **20** and 478 for the minor component (relative intensities ca. 2.5:1, respectively).

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Supplementary Material Available: Atomic coordinates for the crystal structures of **19**, **20**, **24**, and **27** (24 pages). This material is contained in many 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. Coordinates for the above structures have been deposited in the Cambridge Crystallographic Database.

Base-Promoted Reaction of O-Sulfonylated Hydroxamic Acids with Nucleophiles. A New Method for the Synthesis of α-Substituted Amides

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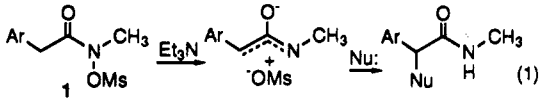
Treatment of a series of hydroxamic acids **2** with mesyl chloride in the presence of 2 equiv of triethylamine at 0 °C gives 2-chloroamides **3** in good yields. Use of a single equivalent of triethylamine gives the *N*-(mesyloxy)amides **1**, which are versatile synthetic intermediates as they can be readily converted to 2-bromoamides **4** with lithium bromide and triethylamine and to 2-hydroxyamides **5** with triethylamine in aqueous acetonitrile.

Introduction

We recently reported that O-sulfonylated N-alkyl hydroxamic acids **1** are readily converted to 2-substituted N-alkyl amides upon treatment with triethylamine and a nucleophile (eq 1).[1] A similar reaction of *N*-(sulfonyloxy)



β-lactams has also been disclosed by Miller.[2] Preliminary data implicate ion pairs, formed by α-proton removal followed by ionization of the sulfonate group from nitrogen, as key intermediates in the reaction. Capture of the ion pair by a nucleophile results in an α-substituted secondary amide (eq 1).[1] This transformation would have great synthetic potential if a wide variety of nucleophiles could be used to trap the ion pair. Herein are presented details of experiments which utilize this chemistry for the efficient preparation of 2-chloro, 2-bromo, and 2-hydroxy amides from *N*-(mesyloxy)-N-alkylamides.

Results and Discussion

The formation of 2-chloroamides was first observed during attempts to prepare O-sulfonylated hydroxamic acids **1** from readily available N-alkylhydroxamic acids **2**.[3] Using a literature procedure,[4] hydroxamic acids **2**, upon

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