54.82; H, 8.31; N, 8.97; Si, 6.75. Found: C, 54.92; H, 7.95; N, 9.15; Si, 6.73.

Acknowledgment. This work was supported in part by Grant CA39867 from the National Cancer Institute, DHHS.

Registry No. 1, 85167-76-6; 2, 85167-75-5; 3, 122924-32-7; 4, 122903-59-7; 5, 122903-60-0; 6, 122903-61-1; 7, 122903-62-2; 8 (free base), 122903-63-3; 8·TsOH, 122903-77-9; 8·TmbsOH, 122903-78-0; 9, 122903-64-4; 10, 34404-36-9; 11, 122903-65-5; 12, 122903-66-6; 13, 122903-67-7; 14, 122903-68-8; 15, 122903-69-9; 16, 122903-70-2; 17, 122903-71-3; 18, 86060-82-4; 19, 122903-72-4; 20, 122903-73-5; 21, 122903-74-6; 22, 122903-75-7; 23, 122903-76-8; BOC-Lys(Z)-OH, 2389-45-9; Fmoc-Cl, 28920-43-6; Fmoc-Lys-OH, 105047-45-8; H-Lys(Z)-OH, 1155-64-2.

Synthesis of Stereochemically Defined ψ[CH(alkyl)NH] Pseudopeptides[1]

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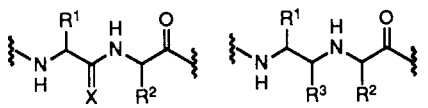
A general synthesis of ψ[CH(alkyl)NH] pseudopeptides **3**, with defined stereochemistry at the new asymmetric center, is described. Grignard reaction of amino acid derived oxazolidines **10** and **11** gave separable mixtures of benzyl-protected diamino alcohols **12–15**, the stereochemistry of which could be defined by conversion to imidazolidones **16–19**. Studies on the oxidation of these alcohols yielded a procedure for the conversion of aldehydes to acyl cyanides which is compatible with sensitive functionality. Application of this methodology to a series of monoprotected diamino alcohols (e.g. **39**) gave rise to pseudotripeptides (e.g. **41**) upon in situ coupling with (*S*)-phenylalanine methyl ester hydrochloride. This synthesis allows for variations in R^1 and R^2 of pseudopeptide **3** and permits the introduction of bulky appendages along the peptide backbone.

In recent years, considerable attention has been focused on structure–activity studies of pharmacologically interesting peptides.[2] One goal in this area deals with stabilizing a given peptide toward degradation by in vivo peptidases.[3] As a result, a variety of novel backbone-modified peptides have been synthesized in which the amide moiety of peptide **1** is replaced by groups which are inert to enzymatic hydrolysis. The synthesis of such amide bond surrogates has been reviewed[4] and includes several methods for the preparation of methyleneamino, or ψ[CH_2NH], amide bond replacements **2**. In the course of our work



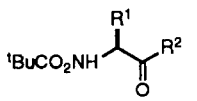
1: X = O
2: X = H_2

3

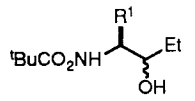
on analogues of atrial natriuretic factor, we required a general synthesis of pseudodipeptide **3** in which one of the diastereotopic protons at the original amide carbonyl carbon of **2** is replaced with an alkyl group. Pseudodipeptide **3** might therefore be designated as an alkylmethineamino amide bond replacement defined as ψ[CH(alkyl)NH] which possesses a new asymmetric carbon adjacent in most cases to another asymmetric atom (the α-carbon). Not only would amide bond replacement **3** resist proteolytic hydrolysis, but the new asymmetric center could impart unique conformational biases when incorporated into a given peptide. The synthesis of a related chiral amide bond surrogate, Glyψ[$CH(CH_3)$S], has been attempted by Spatola[5] for introduction into LH–RH derivatives; however, absent from the literature are ψ[CH(alkyl)NH] analogues with substitutions at the α-carbons on both sides of the replaced amide bond. Presented here is a general method for the synthesis of several ψ[CH(alkyl)NH] amide bond replacements of defined stereochemistry.

Results and Discussion

Methyleneamino amide bond isosteres such as **2** have been prepared efficiently by the reductive amination of protected amino aldehydes **4** with a variety of α-amino esters.[6] Our attempts to prepare pseudodipeptides **3** by reductive amination of ethyl ketone **5** (R^1 = Bn, Me) with (*S*)-valine methyl ester gave rise to a mixture of alcohols **6** under a variety of reaction conditions. This can be expected due to steric reasons, especially in cases where R^1 and R^2 effectively shield the ketone carbonyl of **5**.[7] A more general procedure which allows incorporation of bulky groups along the peptide backbone was therefore desired.



4: R^2 = H
5: R^2 = Et



6

An alternative approach is depicted in Scheme I and involves Grignard addition to amino acid derived oxazolidines, followed by oxidation of the resulting alcohols.

(1) According to IUPAC rules, the structure inside the bracket following ψ is the unit substituting for the peptide amide bond. IUPAC–IUB Joint Commission on Biochemical Nomenclature *Eur. J. Biochem.* **1984**, *138*, 9.

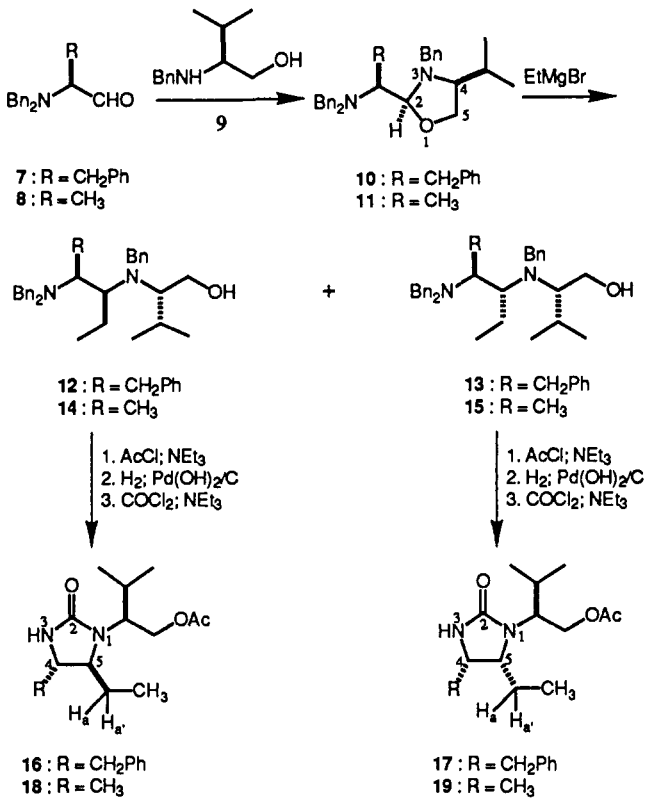
(2) (a) Moser, R.; Kluser, S.; Leist, T.; Langen, H.; Epprecht, T.; Gutte, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 719. (b) Morley, J. S. *Trends Pharm. Sci.* **1980**, 463. (c) Fauchere, J.-L. In *Advances in Drug Research*; Testa, B., Ed.; Academic: London, **1986**; Vol. 15, p 29.

(3) (a) Humphrey, M. J.; Ringrose, P. S. *Drug Metab. Rev.* **1986**, *17*, 283. (b) Heavner, G. A.; Kroon, D. J.; Audhya, T.; Goldstein, G. *Peptides* **1986**, *7*, 1015.

(4) (a) Spatola, A. F. *Chem. Biochem. Amino Acids, Pept.; Proteins* **1983**, *7*, 267. (b) Tourwe, D. *Janssen Chim. Acta* **1985**, *3*, 3. (c) Farmer, P. S. In *Drug Design*; Ariens, E. J., Ed.; Academic: New York, 1980; Vol. 10, p 119.

0022-3263/89/1954-5558$01.50/0

Scheme I



Oxazolidines **10** and **11** may be conveniently prepared by the condensation of α-amino aldehydes and α-amino alcohols of known absolute stereochemistry.[8] Thus, (*S*)-phenylalaninol was alkylated with an excess of benzyl bromide followed by Swern oxidation, which gave aldehyde **7** in 96% overall yield.[9] Condensation of crude aldehyde **7** with (*S*)-*N*-benzylvalinol (**9**) by heating in benzene with azeotropic removal of water[10a] gave oxazolidine **10**; however, we found that simple warming of **7** and **9** neat at ca. 50 °C gave the desired oxazolidine in 75% yield after recrystallization from methanol.[10b] The same process when repeated with (*S*)-alaninol gave oxazolidine **11** in 80% overall yield from aldehyde **8** after recrystallization from methanol. The stereochemical assignment of **10** and **11** was corroborated by difference NOE studies; irradiation of the C-2 methine in both **10** and **11** caused an enhancement of the signal corresponding to the C-4 methine, thus supporting a cis relationship across the oxazolidine ring.[10c] In addition, X-ray crystallographic analysis of oxazolidine **11** confirmed the stereochemical assignment at C-2.

The addition of Grignard reagents to chiral oxazolidines has been used by several researchers, including Husson[11] and Takahashi,[12] to prepare asymmetric α-substituted amines.[13] Addition of oxazolidine **10** to an ethereal solution of ethylmagnesium bromide at 0 °C gave a 2.4:1 ratio of readily separable diamino alcohols **12** and **13** in 81% yield.[14] The ratio of products was essentially the same in the case of **11**, which gave **14** and **15** in a 2.5:1 ratio (83% yield) after chromatographic separation. The choice for *N*-benzyl protection of amino aldehydes **7** and **8** is now revealed since *N*-(*tert*-butyloxycarbonyl)- and *N*-(benzyloxycarbonyl)-protected oxazolidines (formed by condensation with **9**) not only reacted sluggishly with an excess of ethylmagnesium bromide but also caused ethyl addition to the urethane function under forcing conditions. In addition, it has been shown that *N*-benzyl-protected[9c] and *N*-(9-phenylfluorenyl)-protected[9d] α-amino aldehydes are conveniently prepared and are configurationally stable at room temperature.

The relative stereochemistry of isomers **12**:**13** and **14**:**15** was established by conversion to the rigid imidazolidones **16**–**19**. This involved acetylation of the primary alcohol followed by hydrogenolysis over palladium hydroxide on carbon[15] and cyclization in the presence of phosgene. The relative stereochemistry of the ring substituents was assigned by comparison of the vicinal ring-proton coupling constants (J_{45}). The trans isomers **16** and **18** gave coupling constants of 3.4 and 4.3 Hz, respectively, while the cis isomers **17** and **19** gave corresponding values of 7.0 and 7.2 Hz, respectively. These are in good agreement with literature values.[16] In addition, NOE experiments showed that irradiation of H_a in **19** caused an enhancement of the signals corresponding to the C-4 methyl group while irradiation of H_a in **18** caused an enhancement of the signals corresponding to the C-4 proton. The same trend was observed in the phenylalaninol derived imidazolidones **16** and **17**.

The integrity of the asymmetric carbon bearing the benzyl and methyl groups in diamino alcohols **12**–**15** is supported by the isolation of only two alcohols from each oxazolidine following the Grignard reaction. This may also be assessed by the sequence of reactions shown in Scheme II, which proceeds by condensation of amino aldehyde **20** (prepared from (*R*)-phenylalaninol) with **9**, which gave an inseparable mixture of oxazolidines **21** (10:1 ratio based on ^{1}H NMR integration). The stereochemistry at C-2 of the major isomer of **21** is undetermined since irradiation of the C-2 methine gave no NOE at the C-4 methine and

(5) Spatola, A. F.; Bettag, A. L.; Agarwal, N. S.; Saneii, H.; Anwer, M. K.; Edwards, J. V.; Owen, T. J. In *Peptides: Synthesis-Structure-Function*; Rich, D. H., Gross, E., Eds.; Pierce: Rockford, Illinois, 1981; p 613.

(6) (a) Sasaki, Y.; Coy, D. *Peptides* **1987**, *8*, 119. (b) Rodriguez, M.; Bali, J.-P.; Magous, R.; Castro, B.; Martinez, J. *Int. J. Peptide Protein Res.* **1986**, *27*, 293.

(7) (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897. (b) Hutchins, R. O.; Natale, N. R. *Org. Prep. Proced. Int.* **1979**, *11*, 201. (c) Anderson, P. S.; Christy, M. E.; Colton, C. D.; Shepard, K. L. *J. Org. Chem.* **1978**, *43*, 3719. (d) Ohfune, Y.; Kurokawa, N.; Higuchi, N.; Saito, M.; Hashimoto, M.; Tanaka, T. *Chem. Lett.* **1984**, 441.

(8) For the synthesis of related thiazolidines, see: Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shioiri, T. *J. Org. Chem.* **1987**, *52*, 1252.

(9) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (b) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (c) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. (d) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236.

(10) (a) Soliman, S. A.; Abdine, H.; El-Nenaey, S. *Aust. J. Chem.* **1975**, *28*, 49. (b) Fairhurst, R. A.; Heaney, H.; Papageorgiou, G.; Wilkins, R. F.; Eyley, S. C. *Tetrahedron Lett.* **1989**, *30*, 1433. (c) Bernardi, A.; Cardani, S.; Pilati, T.; Poli, G.; Scolastico, C.; Villa, R. *J. Org. Chem.* **1988**, *53*, 1600.

(11) (a) Arseniyadis, S.; Huang, P. Q.; Husson, H.-P. *Tetrahedron Lett.* **1988**, *29*, 1391. (b) Grierson, D. S.; Royer, J.; Guerrier, L.; Husson, H.-P. *J. Org. Chem.* **1986**, *51*, 4475. (c) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754.

(12) (a) Takahashi, H.; Niwa, H.; Higashiyama, K. *Heterocycles* **1988**, *27*, 2099. (b) Takahashi, H.; Chida, Y.; Yoshi, T.; Suzuki, T.; Yanaura, S. *Chem. Pharm. Bull.* **1986**, *34*, 2071. (c) Takahashi, H.; Chida, Y.; Higashiyama, K.; Onishi, H. *Chem. Pharm. Bull.* **1985**, *33*, 4662. (d) Takahashi, H.; Chida, Y.; Suzuki, T.; Onishi, H.; Yanaura, S. *Chem. Pharm. Bull.* **1984**, *32*, 2714. (e) Takahashi, H.; Suzuki, Y.; Kametani, T. *Heterocycles* **1983**, *20*, 607.

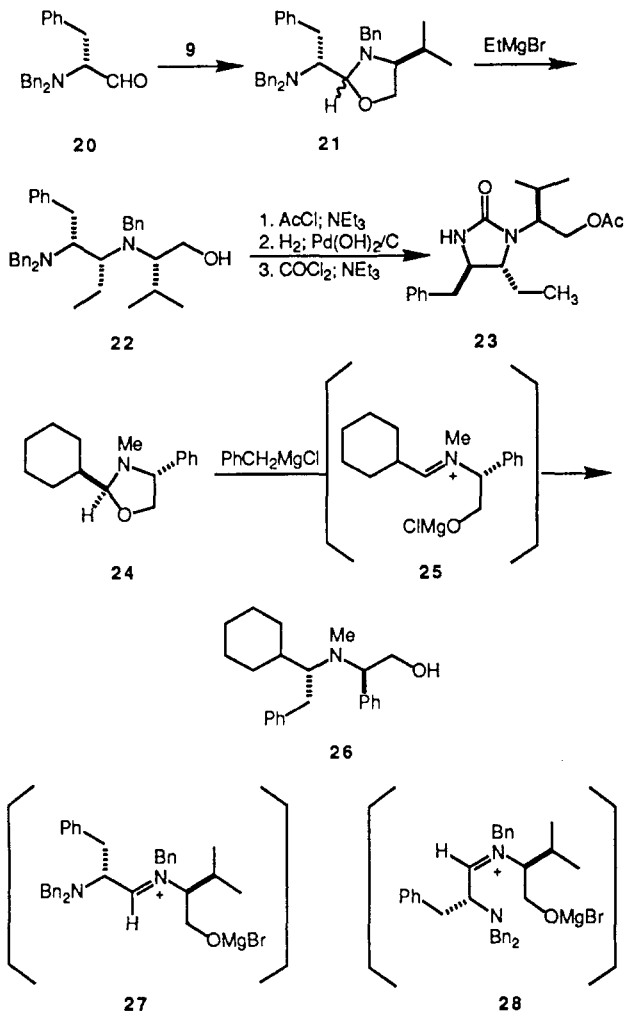
(13) (a) Goodson, L. H.; Christopher, H. *J. Am. Chem. Soc.* **1950**, *72*, 353. (b) Zeller, E.; Grierson, D. S. *Heterocycles* **1988**, *27*, 1575.

(14) Silica gel TLC of **12** and **13** eluting with hexane/ethyl acetate (9:1) gave R_f values of 0.13 and 0.12, respectively. Elution with methylene chloride/ether (95:5) reversed the order of mobility and increased the difference in R_f values (**12** = 0.42; **13** = 0.53). This trend was seen for all pairs of benzyl-protected amino alcohols.

(15) (a) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663. (b) Yoshida, K.; Nakajima, S.; Wakamatsu, T.; Ban, Y.; Shibasaki, M. *Heterocycles* **1988**, *27*, 1167.

(16) Cortes, S.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 2246.

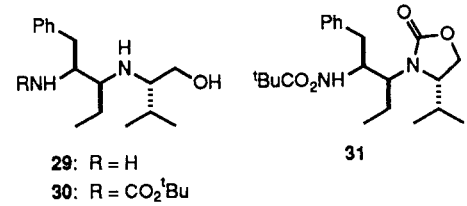
Scheme II



since other NOE experiments were inconclusive. Addition of an ethereal solution of **21** to ethylmagnesium bromide at 0 °C gave a single diamino alcohol **22** (89%), which was different from either **12** or **13** by ^{1}H NMR, ^{13}C NMR, and silica gel TLC analyses. The disparity between **22** with either **12** or **13** establishes that the asymmetric center from the original benzyl-protected amino aldehyde does not racemize during oxazolidine formation and subsequent Grignard reaction. The relative stereochemistry between the benzyl and ethyl substituents in **22** was established to be syn based on ^{1}H NMR studies of imidazolidone **23** (J_{45} = 4.0 Hz).

The exclusive production of single isomer **22** from a mixture of oxazolidines was surprising but not unprecedented. Takahashi[12b] has demonstrated that addition of Grignard reagents to a mixture of oxazolidines can lead to a single product. They have also shown that reaction of 2 equiv of benzylmagnesium chloride with oxazolidine **24** gave only one product **26** and invoke attack of the Grignard reagent from the less hindered face of trans iminium ion **25**.[12c] There is no obvious preference for addition to the α-face of iminium ions **27** or **28** so the selective addition to oxazolidine **21** (as opposed to **10** or **11**) is difficult to rationalize. It does appear, however, that the stereochemistry at C-2 in **10**, **11**, and **21** does not play an important role in Grignard reaction selectivity. Further studies in this area are warranted.

Our next objective entailed oxidation of alcohols **12–15** to the corresponding acid followed eventually by C- and N-terminal coupling to form the desired pseudopeptide. Initial attempts proved unsuccessful since direct oxidation of **12** to the acid using a wide variety of reagents gave predominantly cleavage of one or more of the *N*-benzyl groups. Hydrogenolysis of **12** over $Pd(OH)_2/C$ gave diamino alcohol **29** which also resisted oxidation after bis hydrochloride salt formation. Although **12** could be monoprotected on the primary nitrogen by hydrogenolysis in the presence of di-*tert*-butyl dicarbonate (Boc_2O), attempts to protect the secondary nitrogen of **30** without first functionalizing the primary alcohol were hampered by formation of oxazolidone **31**.

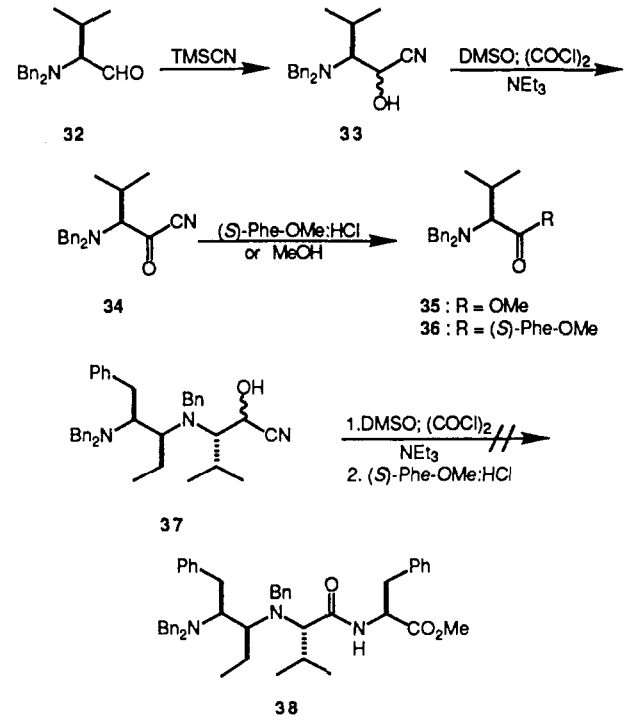


29: R = H
30: R = $CO_2{}^tBu$

Two-step oxidations of alcohols to acids (or their derivatives) through aldehydes have been well-studied and offer a viable alternative to direct methods.[17] Using the configurationally stable amino aldehyde **32**, model studies were performed to develop oxidation conditions compatible with the tertiary amino group and the α-asymmetric center (Scheme III). Again, direct oxidation of the amino aldehyde failed, prompting us to investigate the oxidation of aldehyde derivatives.[18]

Oxidation of cyanohydrins to acyl cyanides[19] has been reported by a number of researchers; however, none of these methods allow for the presence of tertiary amine

Scheme III

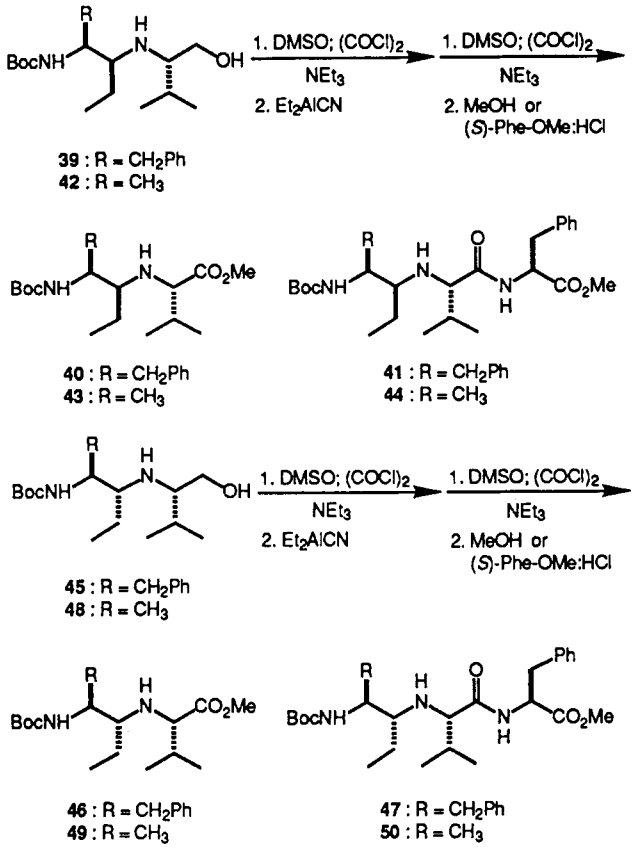


(17) For example, see: (a) Williams, D. R.; Klingler, F. D.; Allen, E. E.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1988**, *29*, 5087. (b) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537. (c) Stevens, R. V.; Chapman, K. T.; Stubbs, C. A.; Tam, W. W.; Albizati, K. F. *Tetrahedron Lett.* **1982**, *23*, 4647. (d) Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Synthesis* **1983**, 474.

(18) (a) Wuts, P. G. M.; Bergh, L. *Tetrahedron Lett.* **1986**, *27*, 3995. (b) Sugai, S.; Kodama, T.; Akaboshi, S.; Ikegami, S. *Chem. Pharm. Bull.* **1984**, *32*, 99. (c) Ellison, R. A.; Woessner, W. D.; Williams, C. C. *J. Org. Chem.* **1972**, *37*, 2759.

(19) Hunig, S.; Schaller, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 36.

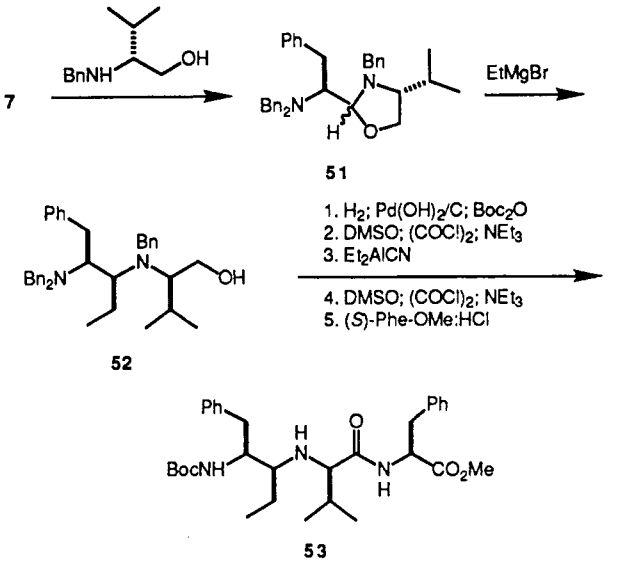
Scheme IV



groups such as **33**.[20] Following literature precedent[9c] for successful generation of aldehydes from tertiary amino alcohols via Swern oxidation, we proposed that tertiary amino cyanohydrins could also be oxidized under the same conditions to the corresponding acyl cyanides. Addition of trimethylsilyl cyanide to aldehyde **32** gave cyanohydrin **33**,[21] which was then resubjected to Swern oxidation conditions giving the unstable acyl cyanide **34** (which could be purified for characterization purposes). The in situ generated acyl cyanide **34** could be quenched with methanol to give amino ester **35** in 66% yield after column chromatography. Since the ultimate goal of these endeavors involves incorporation of the ψ[CH(alkyl)NH] amide bond replacement into a peptide, the possibility of coupling acyl cyanide **34** with an amino ester was attractive.[22] In the event, Swern oxidation of cyanohydrin **33** followed by addition of (*S*)-Phe-OMe·HCl gave dipeptide **36** in 65% yield after purification.

With the oxidation technology established for simple dibenzyl amino alcohols, we then turned to the oxidation of alcohol **12**, which could be converted to the mixture of cyanohydrins **37** by the method described by Reetz[21] or by addition of diethylaluminum cyanide[23] directly to the Swern reaction mixture. This mixture of cyanohydrins was then resubjected to Swern oxidation conditions giving the corresponding acyl cyanide;[24] however, coupling with

Scheme V



(*S*)-Phe-OMe·HCl or methanol was very slow and, although meager amounts of the methyl ester were isolated, no pseudotripeptide **38** was obtained. Prolonged reaction times failed to promote coupling as the acyl cyanide decomposed at higher temperatures.

Since it appeared that the acylating capacity of these acyl cyanides were subject to steric constraints, we converted **12** to the mono Boc-diamino alcohol **39** by hydrogenolysis in the presence of Boc_2O in 81% yield (Scheme IV). Swern oxidation followed by addition of diethylaluminum cyanide gave the crude cyanohydrins, which were again oxidized and quenched with methanol to provide pseudodipeptide **40** (represented as Boc-Pheψ[CH((*S*)-ethyl)NH]Val-OMe) in 73% yield from alcohol **39**.[25] Pseudotripeptide **41** (Boc-Pheψ[CH((*S*)-ethyl)NH]Val-Phe-OMe) was prepared in the same fashion by coupling with (*S*)-Phe-OMe·HCl in 52% yield from alcohol **39**. The same process was applied to the anti isomer **45**, which gave ester **46** and amide **47** in 65% and 48% yield, respectively, from **45**. The alanine derived Boc-amino alcohols **42** and **48** also provided esters **43** (61%) and **49** (38%) and amides **44** (51%) and **50** (37%), although the overall yields were somewhat lower presumably due to the more exposed nature of the secondary amine.

The question of racemization of the asymmetric center adjacent to the acyl cyanide during its formation and coupling was addressed by Grignard reaction with the (*R*)-*N*-benzylvalinol derived mixture of oxazolidines **51** (Scheme V).[26] Conversion of the resulting single alcohol **52** to pseudotripeptide **53** was accomplished in the same fashion as described above and **53** was clearly different from **41** by ^1H NMR and ^{13}C NMR spectroscopy.

A final example of the synthesis of stereochemically defined ψ[CH(alkyl)NH] amide bond replacements is given in Scheme VI and entails the Grignard reaction of cyclohexylmagnesium chloride to oxazolidine **11**, which gave a

(20) (a) Harle, H.; Jochims, J. C. *Chem. Ber.* **1986**, *119*, 1400. (b) Murahashi, S.; Naota, T.; Nakajima, N. *Tetrahedron Lett.* **1985**, *26*, 925. (c) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1980**, *21*, 731. (d) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

(21) Reetz, M. T.; Drewes, M. W.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, *29*, 3295.

(22) Jones, D. S.; Kenner, G. W.; Sheppard, R. C. *J. Chem. Soc.* **1965**, 4393.

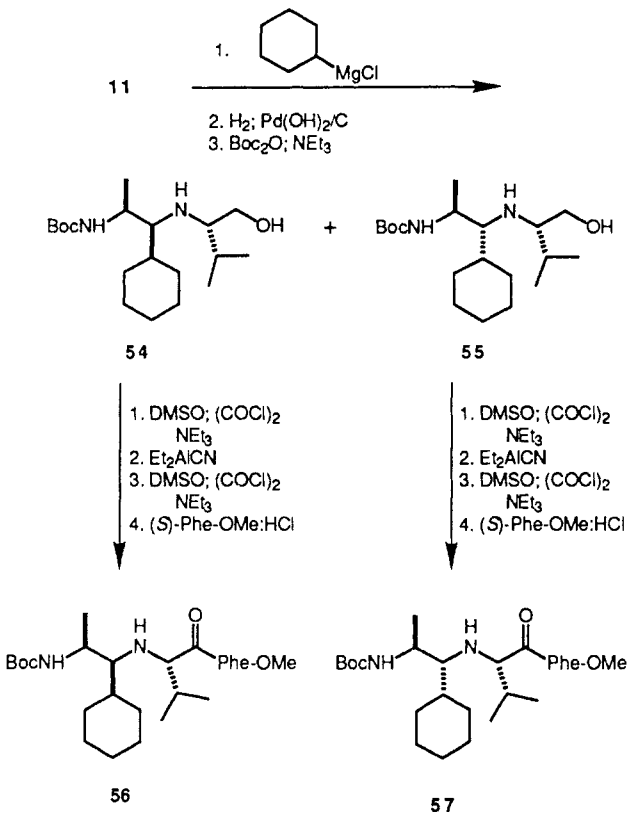
(23) (a) Nagata, W.; Yoshioka, M.; Murakami, M. *J. Am. Chem. Soc.* **1972**, *94*, 4654. (b) Nagata, W.; Yoshioka, M. *Tetrahedron Lett.* **1966**, 1913.

(24) The unstable acyl cyanide derived from **12** was isolated and gave the following spectral characteristics: IR (film) ν 2960, 2930, 2295, 1620, 1605, 1495, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.60 (d, 3 H, *J* = 6.9), 0.91 (t, 3 H, *J* = 7.8), 1.18 (d, 3 H, *J* = 6.9), 1.22–1.29 (c, 2 H), 1.42 (m, 1 H), 2.34 (m, 1 H), 2.71 (m, 1 H), 3.31–3.47 (c, 3 H), 3.48–3.63 (c, 4 H), 3.97 (d, 2 H, *J* = 12.3), 6.88 (m, 1 H), 7.01–7.47 (c, 19 H); MS (CI) $(M + H)^+$ = 558.

(25) Since the Boc-amino cyanohydrins are not stable to silica gel chromatography, these reactions were run consecutively and could be completed in 4 h.

(26) This mixture bears an enantiomeric relationship to oxazolidines **21** as is the case for alcohols **22** and **52**.

Scheme VI



1.3:1 ratio of diastereomeric alcohols **54** and **55** after hydrogenolysis and Boc protection. The relative stereochemistry at the new chiral center was again assigned by ^{1}H NMR studies of the corresponding imidazolidones. Oxidation and coupling with (*S*)-Phe-OMe·HCl gave pseudotripeptides **56** (26% from **54**) and **57** (22% from **55**), which could then be incorporated into a given peptide by solution or solid phase methods.

Conclusion

The methods presented in this paper provide access to the ψ[CH(alkyl)NH] amide bond replacements with defined stereochemistry at the new asymmetric center. Chirality at the carbons bearing R^1 and R^2 of **3** are set by the choice of starting amino alcohol while selection of the appropriate Grignard reagent defines R^3. The chirality of the newly formed asymmetric center may be established relative to the adjacent asymmetric center and provides access to both stereoisomers in some cases. Swern oxidation of cyanohydrins bearing basic amino groups has been demonstrated, and coupling of the resulting acyl cyanides gives either pseudodi- or tripeptides with defined stereochemistry.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran was distilled from sodium/benzophenone under nitrogen atmosphere immediately prior to use, and dichloromethane was dried over 4A sieves at least 24 h prior to use.

^{1}H NMR spectra were recorded on a QE-300 (300 MHz) or a GN-500 (500 MHz) spectrometer and are reported in parts per million (δ) downfield from internal tetramethylsilane (Me_4Si) with coupling constants (J) reported in hertz. Proton-decoupled ^{13}C NMR spectra were recorded on a GN-300 (300 MHz) or a GN-500 (500 MHz) spectrometer, are reported in parts per million, and include distortionless enhancement by polarization transfer (DEPT) pulse sequences (methylenes and quaternary carbons are defined as (CH_2) and (C), respectively; all other resonances are either methyls or methines). Chemical ionization mass spectra were obtained on a Hewlett-Packard 5985 or a Nermag 3010 spectrometer. Fast-atom bombardment mass spectra were obtained on a Kratos MS50 or a Finnigan MAT90 spectrometer, and high-resolution mass spectra were obtained on a Kratos MS50. Infrared spectra were recorded on a Nicolet 5XSC spectrometer as solutions in 0.1-mm NaBr cells. Elemental analyses and the above determinations were performed by the Analytical Research Department at Abbott Laboratories, Abbott Park and North Chicago, IL. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter using a continuous sodium source. Melting points were obtained on a Thomas/Hoover capillary melting point apparatus and are uncorrected.

Thin-layer chromatography (TLC) was carried out using Analtech SG-GF precoated silica gel plates (thickness = 0.25 mm). Liquid column chromatography was performed with 70–230 (gravity) mesh or 230–400 (flash, 5–10 psi of air pressure) mesh silica gel (EM Reagents). Compounds which did not absorb UV light were visualized by dipping in a phosphomolybdic acid solution (2 g of PMA/200 mL of ethanol) or a ceric sulfate solution (2 g of $Ce_2(SO_4)_3$, 5 g of $(NH_4)_2MoO_4$, 20 mL of concentrated H_2SO_4, and 180 mL of distilled H_2O) followed by heating on a hot plate. Organic phases were dried over $MgSO_4$ and concentrated using a Büchi RE111 rotary evaporator.

(*S*)-2-(Benzylamino)-3-methylbutan-1-ol (9). To a solution of (*S*)-valinol (1.03 g, 10 mmol) and benzaldehyde (1.02 mL, 10 mmol) in methanol (100 mL) at pH ~6 (adjusted by addition of glacial acetic acid) under nitrogen with stirring was added sodium cyanoborohydride (1.58 g, 25 mmol) in one portion at room temperature. This mixture was allowed to stir for 16 h at room temperature, concentrated, diluted with ether and aqueous 2 N HCl, and extracted with aqueous 2 N HCl (3 × 30 mL). The combined aqueous phases were basified with solid Na_2CO_3 to pH >9 and extracted with CH_2Cl_2 (4 × 30 mL). The organic layer was dried, filtered, and evaporated to give a yellow oil that was purified by column chromatography (gravity, 3:1–1:3 hexane/EtOAc) to give 1.53 g (79%) of **9** as a pale yellow oil: $[\alpha]_D$ +10.9° (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) ν 3420, 2950, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (d, 3 H, J = 6.8), 0.98 (d, 3 H, J = 6.8), 1.88 (m, 1 H), 2.48 (dt, 1 H, J = 4.4, 6.8), 3.48 (dd, 1 H, J = 6.8, 10.7), 3.65 (dd, 1 H, J = 4.4, 10.7), 3.77 (d, 1 H, J = 12.7), 3.85 (d, 1 H, J = 12.7), 7.23–7.36 (c, 5 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 18.4, 19.6, 28.8, 51.3 (CH_2), 60.4 (CH_2), 63.8, 127.1, 128.1, 128.4, 140.4 (C); MS (CI) $(M + H)^+$ = 194. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.25; H, 9.75; N, 7.05.

(1′*S*,2*S*,4*S*)-3-Benzyl-2-[1′-(dibenzylamino)-2′-phenylethyl]-4-(methylethyl)-1,3-oxazolidine (10). A mixture of aldehyde **7** (2.48 g, 7.5 mmol) and amino alcohol **9** (1.46 g, 7.5 mmol) was heated neat at ca. 50 °C under nitrogen without stirring for 16 h. The resulting solid was recrystallized from hot methanol (ca. 50 mL) to give 2.83 g (75%) of oxazolidine **10** as white needles: mp 84–85 °C; $[\alpha]_D$ +2.4° (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) ν 3020, 2950, 1600, 1490, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81 (d, 3 H, J = 6.9), 0.89 (d, 3 H, J = 6.9), 1.73 (m, 1 H), 2.78 (m, 1 H), 2.86 (m, 1 H), 2.96–3.06 (c, 2 H), 3.41 (d, 1 H, J = 14.4), 3.61–3.74 (c, 5 H), 3.79–3.93 (c, 2 H), 4.56 (s, 1 H), 6.72–6.76 (c, 2 H), 6.92–6.96 (c, 2 H), 7.01–7.06 (c, 4 H), 7.10–7.22 (c, 12 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 16.2, 20.0, 29.4, 30.6 (CH_2), 54.3 (CH_2), 56.4 (CH_2), 60.1, 66.9 (CH_2), 68.2, 98.2, 125.4, 126.4, 126.6, 127.8, 127.9, 128.2, 128.4, 128.8, 129.7, 139.4 (C), 140.6 (C), 141.5 (C); MS (CI) $(M + H)^+$ = 505. Anal. Calcd for $C_{35}H_{40}N_2O$: C, 83.29; H, 7.99; N, 5.55. Found: C, 83.50; H, 8.00; N, 5.37.

(1′*S*,2*S*,4*S*)-3-Benzyl-2-[1′-(dibenzylamino)ethyl]-4-(methylethyl)-1,3-oxazolidine (11). Oxazolidine **11** was prepared from aldehyde **8** via the procedure given for **10**. Recrystallization from hot methanol gave oxazolidine **11** in 80% yield as white needles: mp 89–90 °C; $[\alpha]_D$ −8.3° (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) ν 2960, 1605, 1495, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.74 (d, 3 H, J = 7.0), 0.79 (d, 3 H, J = 7.0), 1.03 (d, 3 H, J = 6.6), 1.58 (m, 1 H), 2.67 (m, 1 H), 2.78 (m, 1 H), 3.46–3.56 (c, 4 H), 3.68–3.82 (c, 2 H), 3.86 (d, 2 H, J = 14.0), 4.43 (d, 1 H, J = 1.8), 6.94–7.00 (c, 2 H), 7.12–7.29 (c, 11 H), 7.31–7.36 (c, 2 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 6.4, 16.4, 19.9, 29.4, 54.5 (CH_2), 54.8, 56.5 (CH_2), 67.1 (CH_2), 67.4, 100.3, 126.5, 126.7, 127.9, 128.0, 128.5,

128.9, 138.8 (C), 141.0 (C); MS (CI) $(M + H)^+ = 429$. Anal. Calcd for $C_{29}H_{36}N_2O$: C, 81.27; H, 8.47; N, 6.54. Found: C, 80.87; H, 8.48; N, 6.47.

(1′*S*,2*S*,3*S*)-*N*²,*N*²,*N*³-Tribenzyl-*N*³-[1′-(hydroxymethyl)-2′-methylpropyl]-1-phenyl-2,3-pentanediamine (12) and (1′*S*,2*S*,3*R*)-*N*²,*N*²,*N*³-Tribenzyl-*N*³-[1′-(hydroxymethyl)-2′-methylpropyl]-1-phenyl-2,3-pentanediamine (13). To a solution of ethylmagnesium bromide (0.47 mL, 3.0 M in ether, 1.4 mmol) in ether (10 mL) at 0 °C under nitrogen with stirring was added a solution of oxazolidine **10** (597 mg, 1.2 mmol) in ether (5.0 mL) dropwise over 3 min. This mixture was allowed to stir with warming to room temperature for 1.5 h, quenched with aqueous saturated NH_4Cl, and stirred for an additional 5 min. The layers were separated, and the aqueous phase was extracted with Et_2O (1 × 10 mL). The combined organic phases were dried, filtered, and evaporated to give a white foam that was purified by column chromatography (flash, 99:1 CH_2Cl_2/Et_2O) to give 361 mg of alcohol **12** and 148 mg of alcohol **13** (81%, 2.4:1) as colorless oils. **12**: $[\alpha]_D$ +7.1° (*c* 0.9, $CHCl_3$); IR (CCl_4) ν 3630, 2950, 1605, 1490, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.74 (d, 3 H, *J* = 7.0), 0.79 (d, 3 H, *J* = 7.0), 1.05 (t, 3 H, *J* = 7.4), 1.59–1.71 (c, 2 H), 1.89 (m, 1 H), 2.32 (m, 1 H), 2.81–2.93 (c, 2 H), 3.03 (m, 1 H), 3.12 (m, 1 H), 3.33–3.46 (c, 2 H), 3.52–3.67 (c, 6 H), 7.07–7.33 (c, 20 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 13.9, 18.9, 22.6, 22.7 (CH_2), 28.1, 32.3 (CH_2), 51.1 (CH_2), 54.4 (CH_2), 59.7 (CH_2), 62.5, 63.5, 64.2, 126.0, 126.7, 126.9, 128.1, 128.2, 128.3, 129.0, 129.4, 139.4 (C), 140.9 (C), 141.1 (C); MS (CI) $(M + H)^+ = 535$. Anal. Calcd for $C_{37}H_{46}N_2O$: C, 83.10; H, 8.67; N, 5.24. Found: C, 83.32; H, 8.64; N, 4.87. **13**: $[\alpha]_D$ −1.8° (*c* 0.9, $CHCl_3$); IR (CCl_4) ν 3630, 2950, 1600, 1490, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.63 (d, 3 H, *J* = 7.0), 0.74 (d, 3 H, *J* = 7.0), 1.00 (t, 3 H, *J* = 7.4), 1.52–1.71 (c, 2 H), 2.14 (m, 1 H), 2.29 (m, 1 H), 2.66 (m, 1 H), 2.83 (m, 1 H), 3.10–3.25 (c, 2 H), 3.38–3.43 (c, 2 H), 3.47 (d, 2 H, *J* = 14.0), 3.75 (d, 1 H, *J* = 14.3), 3.80 (d, 2 H, *J* = 14.0), 4.27 (d, 1 H, *J* = 14.3), 7.11–7.32 (c, 20 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 13.7, 18.5, 22.0 (CH_2), 22.6, 29.2, 35.3 (CH_2), 51.6 (CH_2), 54.9 (CH_2), 60.3 (CH_2), 63.2, 63.4, 66.9, 125.9, 126.6, 126.8, 128.1, 129.1, 129.2, 129.6, 137.8 (C), 141.6 (C), 142.0 (C); MS (CI) $(M + H)^+ = 535$; exact mass calcd for $C_{37}H_{47}N_2O$ 535.3688, found 535.3696.

(1′*S*,2*S*,3*S*)-*N*²,*N*²,*N*³-Tribenzyl-*N*³-[1′-(hydroxymethyl)-2′-methylpropyl]-2,3-pentanediamine (14) and (1′*S*,2*S*,3*R*)-*N*²,*N*²*N*³-Tribenzyl-*N*³-[1′-(hydroxymethyl)-2′-methylpropyl]-2,3-pentanediamine (15). Alcohols **14** and **15** were prepared from oxazolidine **11** via the procedure given for **12** and **13**. Purification by column chromatography (flash, 97.5:2.5 CH_2Cl_2/Et_2O) gave alcohols **14** and **15** (2.5:1) in 83% yield as colorless oils. **14**: $[\alpha]_D$ +22.9° (*c* 0.9, $CHCl_3$); IR (CCl_4) ν 3200, 2950, 1600, 1490, 1450 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.74 (d, 3 H, *J* = 6.6), 0.85 (d, 3 H, *J* = 6.6), 0.88 (d, 3 H, *J* = 6.6), 0.97 (t, 3 H, *J* = 7.4), 1.23 (m, 1 H), 1.47 (m, 1 H), 1.90 (m, 1 H), 2.16 (m, 1 H), 3.07 (m, 1 H), 3.10 (d, 2 H, *J* = 12.9), 3.22 (m, 1 H), 3.49 (m, 1 H), 3.52 (d, 2 H, *J* = 7.0), 3.63 (m, 1 H), 3.67 (d, 2 H, *J* = 12.9), 7.02–7.28 (c, 11 H), 7.47–7.54 (c, 4 H); ^{13}C NMR (C_6D_6, 500 MHz) δ 8.4, 13.4, 19.4, 22.8, 24.4 (CH_2), 28.5, 51.5, 54.3, 55.0 (CH_2), 58.2, 61.6 (CH_2), 64.2 (CH_2), 127.0, 127.5, 128.2, 128.6, 130.2, 130.4, 138.6 (C), 140.9 (C); MS (CI) $(M + H)^+ = 459$. Anal. Calcd for $C_{31}H_{42}N_2O$: C, 81.17; H, 9.23; N, 6.11. Found: C, 81.02; H, 8.78; N, 5.85. **15**: $[\alpha]_D$ +58.9° (*c* 0.9, $CDCl_3$); IR (CCl_4) ν 3630, 2960, 1600, 1490, 1450 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.74 (d, 3 H, *J* = 6.6), 0.78 (d, 3 H, *J* = 6.6), 1.04 (t, 3 H, *J* = 7.5), 1.13 (d, 3 H, *J* = 6.2), 1.35 (m, 1 H), 1.59 (m, 1 H), 1.80 (m, 1 H), 2.24 (m, 1 H), 2.41 (m, 1 H), 2.64 (m, 1 H), 2.75 (m, 1 H), 3.17 (d, 2 H, *J* = 13.6), 3.49 (m, 1 H), 3.60 (m, 1 H), 3.68 (d, 2 H, *J* = 13.6), 3.73 (d, 1 H, *J* = 14.3), 3.84 (d, 1 H, *J* = 14.3), 7.02–7.40 (c, 15 H); ^{13}C NMR (C_6D_6, 500 MHz) δ 10.7, 14.1, 19.0, 22.4, 22.4 (CH_2), 30.0, 52.4 (CH_2), 54.5 (CH_2), 56.5, 60.8 (CH_2), 65.1, 66.0, 126.9, 127.1, 128.4, 128.5, 129.2, 129.8, 140.5 (C), 142.0 (C); MS (CI) $(M + H)^+ = 459$. Anal. Calcd for $C_{31}H_{42}N_2O$: C, 81.17; H, 9.23; N, 6.11. Found: C, 80.88; H, 9.17; N, 6.00.

(1′*S*,4*S*,5*S*)-1-[1′-(Acetoxymethyl)-2′-methylpropyl]-4-benzyl-5-ethyl-2-imidazolidone (16). To a solution of alcohol **12** (116 mg, 0.22 mmol) in tetrahydrofuran (0.86 mL) at 0 °C under nitrogen with stirring was added triethylamine (75 μL, 0.54 mmol) followed by acetyl chloride (31 μL, 0.43 mmol). This mixture was allowed to stir with warming to room temperature for 3 h, diluted with Et_2O, and washed with H_2O (1 × 2 mL) and brine (1 × 2 mL). The organic phase was dried, filtered, and evaporated to give a pale yellow oil that was purified by column chromatography (gravity, 95:5 hexane/EtOAc) to give 102 mg (82%) of the acylated product, which was debenzylated by hydrogenation at 4 atm of hydrogen over 20% $Pd(OH)_2/C$ (100 mg, 100 wt %) in EtOAc (2.0 mL) with agitation at room temperature for 48 h. This mixture was filtered through a Celite pad, evaporated, and purified by column chromatography (gravity, 97.5:2.5:0.1 $CHCl_3$/MeOH/NH_4OH) to give 20 mg (37%) of the fully deprotected diamino alcohol that was dissolved in dichloromethane (7.4 mL). To this homogeneous solution at −20 °C under nitrogen with stirring was added triethylamine (49 μL, 0.35 mmol) followed by phosgene (91 μL, 1.93 M in toluene, 0.18 mmol). This mixture was allowed to stir for 30 min, concentrated, and diluted with EtOAc and H_2O. The layers were separated, and the organic phase was washed with aqueous 1 N H_3PO_4 (1 × 2 mL), aqueous saturated $NaHCO_3$ (1 × 2 mL), and brine (1 × 2 mL), dried, filtered, and evaporated to give a yellow oil that was purified by column chromatography (gravity, 1:1 hexane/EtOAc) to give 17 mg (78%) of imidazolidone **16** as a pale yellow oil: $[\alpha]_D$ −3.4° (*c* 0.5, $CHCl_3$); IR ($CDCl_3$) ν 3460, 2970, 1740, 1690, 1450 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.51 (t, 3 H, *J* = 7.4), 0.87 (d, 3 H, *J* = 7.0), 1.03, (d, 3 H, *J* = 7.0), 1.22–1.44 (c, 2 H), 1.76 (s, 3 H), 2.12 (m, 1 H), 2.51–2.68 (c, 2 H), 3.04 (ddd, 1 H, *J* = 3.4, 3.4, 8.3), 3.18 (ddd, 1 H, *J* = 3.4, 6.4, 6.9), 3.31 (m, 1 H), 4.46–4.55 (c, 2 H), 5.73 (b s, 1 H), 6.96–7.24 (c, 5 H); MS (CI) $(M + H)^+ = 333$.

(1′*S*,4*S*,5*R*)-1-[1′-(Acetoxymethyl)-2′-methylpropyl]-4-benzyl-5-ethyl-2-imidazolidone (17). Imidazolidone **17** was prepared from alcohol **13** via the procedure given for **16**. Purification by column chromatography (flash, 65:35 hexane/EtOAc) gave imidazolidone **17** in 19% overall yield as a colorless oil: $[\alpha]_D$ −72.5° (*c* 1.5, $CHCl_3$); IR ($CDCl_3$) ν 3440, 2970, 1740, 1695, 1430 cm^{-1}; ^1H NMR ($CDCl_3/C_6D_6$, 500 MHz) δ 0.73 (t, 3 H, *J* = 7.4), 0.77 (d, 3 H, *J* = 6.7), 0.80 (d, 3 H, *J* = 6.7), 1.38 (m, 1 H), 1.53 (m, 1 H), 1.79 (s, 3 H), 2.15 (m, 1 H), 2.31 (dd, 1 H, *J* = 11.0, 13.1), 2.51 (dd, 1 H, *J* = 3.0, 13.1), 3.12 (m, 1 H), 3.35 (ddd, 1 H, *J* = 3.0, 7.0, 11.0), 3.44 (ddd, 1 H, *J* = 3.5, 7.0, 10.8), 4.05 (b s, 1 H), 4.24–4.32 (c, 2 H), 6.91–7.13 (c, 5 H); MS (CI) $(M + H)^+ = 333$.

(1′*S*,4*S*,5*S*)-1-[1′-(Acetoxymethyl)-2′-methylpropyl]-5-ethyl-4-methyl-2-imidazolidone (18). Imidazolidone **18** was prepared from alcohol **14** via the procedure given for **16**. Purification by column chromatography (flash, 96:3:1 CH_2Cl_2/MeOH/NH_4OH) gave imidazolidone **18** in 18% overall yield as a colorless oil: $[\alpha]_D$ +18.8° (*c* 1.1, $CHCl_3$); IR ($CDCl_3$) ν 3450, 2960, 1730, 1680, 1440 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.93 (t, 3 H, *J* = 7.7), 1.00 (d, 3 H, *J* = 6.4), 1.02 (d, 3 H, *J* = 6.4), 1.22 (d, 3 H, *J* = 5.8), 1.57 (m, 1 H), 1.73 (m, 1 H), 2.05 (s, 3 H), 2.13 (m, 1 H), 3.11 (ddd, 1 H, *J* = 3.3, 4.3, 9.3), 3.30 (m, 1 H), 3.43 (dq, 1 H, *J* = 4.3, 5.8), 4.26 (b s, 1 H), 4.37–4.43 (c, 2 H); MS (CI) $(M + H)^+ = 257$.

(1′*S*,4*S*,5*R*)-1-[1′-(Acetoxymethyl)-2′-methylpropyl]-5-ethyl-4-methyl-2-imidazolidone (19). Imidazolidone **19** was prepared from alcohol **15** via the procedure given for **16**. Purification by column chromatography (gravity, 97.5:2.5 $CHCl_3$/MeOH) gave imidazolidone **19** in 18% overall yield as an yellow oil: $[\alpha]_D$ −30.7° (*c* 0.4, $CHCl_3$); IR ($CDCl_3$) ν 3440, 2970, 1740, 1695, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.94 (t, 3 H, *J* = 7.4), 0.95 (d, 3 H, *J* = 6.7), 0.99 (d, 3 H, *J* = 6.7), 1.12, (d, 3 H, *J* = 6.1), 1.52 (m, 1 H), 1.75 (m, 1 H), 2.06 (s, 3 H), 2.26 (m, 1 H), 3.24 (dt, 1 H, *J* = 7.0, 10.5), 3.62 (dq, 1 H, *J* = 6.1, 7.2), 3.67 (ddd, 1 H, *J* = 6.8, 6.8, 7.2), 4.19 (b s, 1 H), 4.39 (d, 2 H, *J* = 7.0); MS (CI) $(M + H)^+ = 257$.

(1′*R*,2*RS*,4*S*)-3-Benzyl-2-[1′-(dibenzylamino)-2′-phenylethyl]-4-(methylethyl)-1,3-oxazolidine (21). Oxazolidines **21** were prepared from aldehyde **20** via the procedure given for **10**. Purification by column chromatography (gravity, 97.5:2.5 hexane/EtOAc) gave oxazolidines **21** (10:1 by ^1H NMR) in 83% yield as a viscous yellow oil: $[\alpha]_D$ −22.1° (*c* 0.8, $CHCl_3$); IR ($CDCl_3$) ν 3020, 2950, 1600, 1490, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, major isomer) δ 0.70 (d, 3 H, *J* = 6.6), 0.83 (d, 3 H, *J* = 6.6), 1.22 (m, 1 H), 2.25 (m, 1 H), 2.63 (m, 1 H), 2.81–2.94 (c, 2 H), 3.55 (m, 1 H), 3.66–3.85 (c, 6 H), 4.02 (m, 1 H), 4.67 (d, 1 H, *J* = 8.5), 6.94–7.32 (c, 20 H); ^{13}C NMR ($CDCl_3$, 300 MHz, major isomer) δ 19.0, 20.4, 32.6, 35.0 (CH_2), 54.0 (CH_2), 60.8, 62.0 (CH_2), 67.6 (CH_2), 70.7, 99.2, 125.5, 126.4, 127.2, 127.8, 127.9, 128.2, 128.7, 129.7, 129.8, 139.0 (C), 140.3 (C), 141.2 (C); MS (FAB) $(M + H)^+$

= 505. Anal. Calcd for $C_{35}H_{40}N_2O$: C, 83.29; H, 7.99; N, 5.55. Found: C, 83.07; H, 7.95; N, 5.43.

(1′*S*,2*R*,3*R*)-*N*²,*N*²,*N*³-Tribenzyl-*N*³-[1′-(hydroxymethyl)-2′-methylpropyl]-1-phenyl-2,3-pentanediamine (22). Alcohol **22** was prepared from oxazolidines **21** via the procedure given for **12** and **13**. Purification by column chromatography (flash, 95:5 hexane/EtOAc) gave alcohol **22** in 89% yield as a colorless oil: $[\alpha]_D$ −1.2° (*c* 0.9, $CHCl_3$); IR (CCl_4) ν 3580, 2950, 1605, 1495, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.74 (d, 3 H, *J* = 6.8), 1.01 (d, 3 H, *J* = 6.8), 1.08 (t, 3 H, *J* = 7.2), 1.61–1.79 (c, 3 H), 2.38 (m, 1 H), 2.83 (m, 1 H), 2.91–2.98 (c, 2 H), 3.22–3.44 (c, 3 H), 3.51 (d, 2 H, *J* = 14.0), 3.80 (d, 2 H, *J* = 14.0), 3.83 (d, 1 H, *J* = 14.7), 3.93 (d, 1 H, *J* = 14.7), 7.03–7.11 (c, 2 H), 7.16–7.38 (c, 18 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 13.3, 19.3, 22.3, 22.3 (CH_2), 30.3, 33.8 (CH_2), 49.1 (CH_2), 53.8 (CH_2), 60.3 (CH_2), 62.2, 64.7, 67.3, 125.9, 126.6, 126.7, 128.1, 128.2, 128.5, 128.6, 129.9, 140.1 (C), 141.1 (C), 142.7 (C); MS (FAB) $(M + H)^+$ = 535; exact mass calcd for $C_{37}H_{47}N_2O$ 535.3688, found 535.3690.

(1′*S*,4*R*,5*R*)-1-[1′-(Acetoxymethyl)-2′-methylpropyl]-4-benzyl-5-ethyl-2-imidazolidone (23). Imidazolidone **23** was prepared from alcohol **22** via the procedure given for **16**. Purification by column chromatography (flash, 97:2:1 $CHCl_3$/MeOH/NH_4OH) gave imidazolidone **23** in 29% overall yield as a colorless oil: $[\alpha]_D$ +22.1° (*c* 1.3, $CHCl_3$); IR ($CDCl_3$) ν 3440, 2960, 1730, 1680, 1450 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) δ 0.72 (t, 3 H, *J* = 7.4), 0.94 (d, 3 H, *J* = 6.6), 0.99 (d, 3 H, *J* = 6.6), 1.49 (m, 1 H), 1.55 (m, 1 H), 2.03 (s, 3 H), 2.26 (m, 1 H), 2.82 (dd, 1 H, *J* = 6.6, 13.2), 2.87 (dd, 1 H, *J* = 6.6, 13.2), 3.23 (ddd, 1 H, *J* = 4.3, 8.3, 10.2), 3.38 (ddd, 1 H, *J* = 3.6, 4.0, 8.3), 3.57 (dddd, 1 H, *J* = 1.3, 4.0, 6.6, 6.6), 4.22 (dd, 1 H, *J* = 8.3, 11.2), 4.36 (dd, 1 H, *J* = 4.3, 11.2), 5.37 (b s, 1 H), 7.21–7.34 (c, 5 H); MS (FAB) $(M + H)^+$ = 333.

(2*S*)-2-(Dibenzylamino)-3-methylbutanoyl Cyanide (34). To a solution of oxalyl chloride (37 μL, 0.42 mmol) in dichloromethane (1.0 mL) at −60 °C under nitrogen with stirring was added, dropwise, dimethyl sulfoxide (60 μL, 0.85 mmol). After 10 min, a solution of cyanohydrin **33** (44 mg, 0.14 mmol) in dichloromethane (0.4 mL) was added dropwise, and this mixture was allowed to stir for 30 min at −60 °C. This homogeneous solution was quenched by addition of triethylamine (0.20 mL, 1.4 mmol) and allowed to stir with warming to −35 °C over 20 min. This yellow heterogeneous mixture was concentrated, diluted with EtOAc, filtered through a Celite pad and concentrated to give a dark brown oil which was passed through a plug of silica gel (flash, 9:1 hexane/EtOAc) to give 16.8 mg (39%) of acyl cyanide **34** as a colorless oil: IR ($CHCl_3$) ν 2295, 1630, 1600, 1490, 1450, 1360, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (d, 6 H, *J* = 6.6), 1.48 (m, 1 H), 2.84 (m, 1 H), 3.93 (s, 4 H), 7.05–7.45 (c, 10 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 21.9, 27.5, 56.0 (CH_2), 64.9, 119.1 (C), 127.8, 128.4, 128.7, 137.5 (C), 148.4 (C); MS (CI) $(M + H)^+$ = 307.

***N*,*N*-Dibenzyl-Val-OMe (35).** To a solution of oxalyl chloride (52 μL, 0.60 mmol) in dichloromethane (1.4 mL) at −60 °C under nitrogen with stirring was added, dropwise, dimethyl sulfoxide (86 μL, 1.2 mmol). After 10 min, a solution of cyanohydrin **33** (62 mg, 0.20 mmol) in dichloromethane (0.6 mL) was added dropwise, and this mixture was allowed to stir for 30 min at −60 °C. This homogeneous solution was quenched by addition of triethylamine (0.28 mL, 2.0 mmol) and allowed to stir with warming to −35 °C over 20 min. To this yellow heterogeneous mixture was added methanol (1.0 mL), and after being stirred at room temperature for 2 h, the homogeneous reaction mixture was concentrated and diluted with EtOAc and H_2O. The layers were separated, and the organic phase was washed with H_2O (1 × 5 mL) and brine (1 × 5 mL), dried, filtered, and evaporated to give a pale yellow oil that was purified by column chromatography (gravity, 9:1 hexane/EtOAc) to give 41 mg (66%) of methyl ester **35** as a colorless oil: $[\alpha]_D$ −125.9° (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) ν 2960, 1720, 1595, 1490, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (d, 3 H, *J* = 6.6), 1.02 (d, 3 H, *J* = 6.6), 2.15 (m, 1 H), 2.87 (d, 1 H, *J* = 10.7), 3.28 (d, 2 H, *J* = 14.0), 3.77, (s, 3 H), 3.99 (d, 2 H, *J* = 14.0), 7.20–7.41 (c, 10 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.5, 19.9, 27.2, 50.6, 54.6 (CH_2), 68.1, 126.9, 128.2, 128.8, 139.5 (C), 172.4 (C); MS (CI) $(M + H)^+$ = 312. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.34; H, 8.09; N, 4.51.

***N*,*N*-Dibenzyl-Val-Phe-OMe (36).** To a solution of oxalyl chloride (52 μL, 0.60 mmol) in dichloromethane (1.4 mL) at −60 °C under nitrogen with stirring was added, dropwise, dimethyl sulfoxide (86 μL, 1.2 mmol). After 10 min, a solution of cyanohydrin **33** (62 mg, 0.20 mmol) in dichloromethane (0.6 mL) was added dropwise, and this mixture was allowed to stir for 30 min at −60 °C. This homogeneous solution was quenched by addition of triethylamine (0.28 mL, 2.0 mmol) and allowed to stir with warming to −35 °C over 20 min. To this yellow heterogeneous mixture was added (*S*)-Phe-OMe·HCl (65 mg, 0.30 mmol), and after being stirred at room temperature for 16 h, the heterogeneous reaction mixture was concentrated and diluted with EtOAc and H_2O. The layers were separated, and the organic phase was washed with H_2O (1 × 5 mL) and brine (1 × 5 mL), dried, filtered, and evaporated to give a dark yellow oil that was purified by column chromatography (gravity, 3:1 hexane/EtOAc) to give 60 mg (65%) of dipeptide **36** as a pale yellow oil: $[\alpha]_D$ −42.8° (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) ν 1735, 1665, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (d, 3 H, *J* = 6.6), 1.05 (d, 3 H, *J* = 6.6), 2.21 (m, 1 H), 2.49 (d, 1 H, *J* = 8.1), 3.08 (dd, 1 H, *J* = 8.3, 14.5), 3.16 (d, 2 H, *J* = 14.3), 3.31 (dd, 1 H, *J* = 5.5, 14.5), 3.66 (s, 3 H), 3.92 (d, 2 H, *J* = 14.3), 5.03 (m, 1 H), 5.22 (b d, 1 H, *J* = 7.4), 7.17–7.51 (c, 15 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.8, 19.9, 27.2, 37.9 (CH_2), 52.4, 52.5, 54.2 (CH_2), 68.9, 126.8, 127.4, 128.3, 128.4, 128.8, 129.1, 135.9 (C), 139.7 (C), 171.1 (C), 172.3 (C); MS (CI) $(M + H)^+$ = 459. Anal. Calcd for $C_{29}H_{34}N_2O_3$: C, 75.95; H, 7.47; N, 6.11. Found: C, 75.66; H, 7.56; N, 6.07.

(1′*S*,2*S*,3*S*)-*N*²-(*tert*-Butoxycarbonyl)-*N*³-[1′-(hydroxymethyl)-2′-methylpropyl]-1-phenyl-2,3-pentanediamine (39). To a solution of alcohol **12** (556 mg, 1.0 mmol) in methanol (15 mL) at room temperature was added di-*tert*-butyl dicarbonate (250 mg, 1.1 mmol) followed by 20% $Pd(OH)_2/C$ (200 mg, 36 wt %). This mixture was hydrogenated under 4 atm of hydrogen at room temperature with agitation for 4 h, filtered through a Celite pad, and concentrated to give a pale yellow oil that was purified by column chromatography (gravity, 3:1 hexane/EtOAc) to give 307 mg (81%) of mono Boc diamino alcohol **39** as a white solid: mp 75–76 °C; $[\alpha]_D$ −3.8° (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) ν 3620, 3440, 2960, 1705, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3 H, *J* = 7.4), 0.93 (d, 3 H, *J* = 7.0), 0.98 (d, 3 H, *J* = 7.0), 1.33 (s, 9 H), 1.39–1.51 (c, 2 H), 1.79 (m, 1 H), 2.46–2.58 (c, 2 H), 2.69–2.89 (c, 2 H), 3.41 (dd, 1 H, *J* = 6.6, 10.5), 3.61 (dd, 1 H, *J* = 4.0, 10.5), 3.96 (m, 1 H), 4.71 (b d, 1 H, *J* = 9.0), 7.16–7.33 (c, 5 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 10.4, 18.0, 19.5, 24.6 (CH_2), 28.3, 29.0, 38.2 (CH_2), 53.3, 58.2, 61.0 (CH_2), 62.1, 79.0 (C), 126.1, 128.3, 129.0, 138.6 (C), 155.7 (C); MS (CI) $(M + H)^+$ = 365. Anal. Calcd for $C_{21}H_{36}N_2O_3$: C, 69.19; H, 9.95; N, 7.68. Found: C, 68.96; H, 9.86; N, 7.57.

Boc-Pheψ[CH((*S*)-ethyl)NH]Val-OMe (40). To a solution of oxalyl chloride (17 μL, 0.20 mmol) in dichloromethane (1.0 mL) at −60 °C under nitrogen with stirring was added, dropwise, dimethyl sulfoxide (28 μL, 0.40 mmol). After 10 min, a solution of mono Boc diamino alcohol **39** (48 mg, 0.13 mmol) in dichloromethane (0.3 mL) was added dropwise, and this mixture was allowed to stir for 15 min at −60 °C. This homogeneous solution was quenched by addition of triethylamine (92 μL, 0.66 mmol) and allowed to stir with warming to −30 °C over 25 min. To this white heterogeneous mixture was added diethylaluminum cyanide (0.40 mL, 1.0 M in toluene, 0.40 mmol), and after stirring for 30 min with the temperature maintained between −15 °C and −30 °C, the homogeneous reaction mixture was concentrated, diluted with EtOAc and H_2O, allowed to stir for 5 min, and filtered through a Celite pad. The layers were separated, and the organic phase was washed with H_2O (1 × 5 mL) and brine (1 × 5 mL), dried, filtered, and evaporated to give the crude cyanohydrin as a dark yellow oil that was resubjected to Swern oxidation and quenched by addition of methanol following the procedure given for **35**. Purification by column chromatography (gravity, 9:1 hexane/EtOAc) gave 38 mg (73% from **39**) of pseudodipeptide **40** as a pale yellow oil: $[\alpha]_D$ −40.5° (*c* 0.8, $CHCl_3$); IR ($CDCl_3$) ν 3680, 3430, 2960, 1730, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, 3 H, *J* = 7.5), 0.97 (d, 3 H, *J* = 6.8), 1.01 (d, 3 H, *J* = 6.8), 1.17–1.29 (c, 2 H), 1.32 (s, 9 H), 1.87 (m, 1 H), 2.45 (dt, 1 H, *J* = 1.8, 6.8), 2.71–2.88 (c, 2 H), 3.08 (d, 1 H, *J* = 6.2), 3.69 (s, 3 H), 3.87 (m, 1 H), 4.85 (b d, 1 H, *J* = 8.7), 7.12–7.31 (c, 5 H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 10.9, 18.9, 19.5, 25.8 (CH_2), 28.3,

32.3, 39.2 (CH_2), 51.4, 53.5, 60.3, 67.6, 78.8 (C), 126.0, 128.2, 129.2, 138.9 (C), 155.6 (C), 176.2 (C); MS (CI) $(M + H)^+$ = 393; exact mass calcd for $C_{22}H_{37}N_2O_4$ 393.2753, found 393.2754.

Boc-Pheψ[CH((*S*)-ethyl)NH]Val-Phe-OMe (41). To a solution of oxalyl chloride (20 μL, 0.23 mmol) in dichloromethane (1.2 mL) at −60 °C under nitrogen with stirring was added, dropwise, dimethyl sulfoxide (33 μL, 0.46 mmol). After 10 min, a solution of mono Boc diamino alcohol **39** (56 mg, 0.15 mmol) in dichloromethane (0.3 mL) was added dropwise, and this mixture was allowed to stir for 15 min at −60 °C. This homogeneous solution was quenched by addition of triethylamine (0.11 mL, 0.77 mmol) and allowed to stir with warming to −30 °C over 25 min. To this white heterogeneous mixture was added diethylaluminum cyanide (0.46 mL, 1.0 M in toluene, 0.46 mmol), and after stirring for 30 min with the temperature maintained between −15 °C and −30 °C, the homogeneous reaction mixture was concentrated, diluted with EtOAc and H_2O, allowed to stir for 5 min, and filtered through a Celite pad. The layers were separated, and the organic phase was washed with H_2O (1 × 5 mL) and brine (1 × 5 mL), dried, filtered, and evaporated to give the crude cyanohydrin as a dark yellow oil that was resubjected to Swern oxidation and quenched by addition of (*S*)-Phe-OMe·HCl via the procedure given for **36**. Purification by column chromatography (gravity, 3:1 hexane/EtOAc) gave 43 mg (52% from **39**) of pseudotripeptide **41** as a white solid: mp 137–139 °C; $[\alpha]_D$ −20.3° (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) ν 3680, 3430, 3360, 2960, 1740, 1700, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, 3 H, *J* = 7.4), 0.87 (t, 6 H, *J* = 6.8), 1.22–1.35 (c, 2 H), 1.38 (s, 9 H), 1.90 (m, 1 H), 2.33 (m, 1 H), 2.64 (m, 1 H), 2.81–2.91 (c, 2 H), 2.97–3.17 (c, 2 H), 3.70 (s, 3 H), 3.90 (m, 1 H), 4.62 (b d, 1 H, *J* = 8.4), 4.87 (m, 1 H), 6.93 (b d, 1 H, *J* = 7.5), 7.11–7.33 (c, 10 H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 10.0, 18.5, 19.5, 24.0 (CH_2), 28.3, 31.9, 37.9 (CH_2), 38.3 (CH_2), 52.1, 52.9, 53.3, 61.0, 67.5, 79.1 (C), 126.3, 127.0, 128.4, 128.6, 129.0, 129.1, 136.2 (C), 138.6 (C), 155.7 (C), 171.9 (C), 174.3 (C); MS (CI) $(M + H)^+$ = 540; exact mass calcd for $C_{31}H_{46}N_3O_5$ 540.3437, found 540.3441.

(1′*S*,2*S*,3*S*)-*N*²-(*tert*-Butoxycarbonyl)-*N*³-[1′-(hydroxymethyl)-2′-methylpropyl]-2,3-pentanediamine (42). To a solution of alcohol **14** (214 mg, 0.46 mmol) in methanol (10 mL) at room temperature was added 20% $Pd(OH)_2/C$ (99 mg, 46 wt%). This mixture was hydrogenated under 1 atm of hydrogen at room temperature with stirring for 24 h, filtered through a Celite pad, and concentrated to give a colorless oil that was resuspended in dichloromethane (5.0 mL). To this homogeneous solution at room temperature under nitrogen with stirring was added triethylamine (69 μL, 0.51 mmol) followed by di-*tert*-butyl dicarbonate (109 mg, 0.51 mmol). This mixture was allowed to stir at room temperature for 9 h, concentrated, diluted with EtOAc, and filtered through a Celite pad. The filtrate was concentrated to give a colorless oil that was purified by column chromatography (flash, 3:1 hexane/EtOAc) to give 106 mg (79%) of mono Boc diamino alcohol **42** as a colorless oil: $[\alpha]_D$ +15.5° (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) ν 3620, 3420, 2960, 1700, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (d, 3 H, *J* = 7.0), 0.95 (t, 3 H, *J* = 3.7), 0.97 (d, 3 H, *J* = 7.0), 1.13 (d, 3 H, *J* = 6.6), 1.31–1.47 (c, 2 H), 1.45 (s, 9 H), 1.81 (m, 1 H), 2.43–2.52 (c, 2 H), 3.37 (dd, 1 H, *J* = 6.6, 10.7), 3.59 (dd, 1 H, *J* = 4.0, 10.7), 3.78 (b s, 1 H), 4.60 (b s, 1 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 10.1, 17.7, 18.1, 19.5, 23.8 (CH_2), 28.4, 29.0, 47.7, 60.5, 61.0 (CH_2), 61.8, 79.2 (C), 155.7 (C); MS (CI) $(M + H)^+$ = 289. Anal. Calcd for $C_{15}H_{32}N_2O_3$: C, 62.46; H, 11.18; N, 9.71. Found: C, 62.72; H, 11.11; N, 9.52.

Boc-Alaψ[CH((*S*)-ethyl)NH]Val-OMe (43). Pseudodipeptide **43** was prepared from mono Boc diamino alcohol **42** via the procedure given for **40**. Purification by column chromatography (gravity, 9:1 hexane/EtOAc) gave pseudodipeptide **43** in 61% overall yield as a colorless oil: $[\alpha]_D$ −14.0° (*c* 1.8, $CHCl_3$); IR ($CDCl_3$) ν 3680, 3430, 2960, 1730, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, 3 H, *J* = 7.5), 0.93 (d, 3 H, *J* = 6.6), 0.97 (d, 3 H, *J* = 6.6), 1.02 (d, 3 H, *J* = 7.0), 1.28–1.43 (c, 2 H), 1.45 (s, 9 H), 1.84 (m, 1 H), 2.22 (m, 1 H), 3.05 (m, 1 H), 3.65 (m, 1 H), 3.72 (s, 3 H), 4.79 (b s, 1 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 10.9, 18.8, 19.5, 25.4 (CH_2), 28.4, 32.2, 48.0, 51.4, 62.5, 67.6, 78.8 (C), 155.6 (C), 176.3 (C); MS (CI) $(M + H)^+$ = 317; exact mass calcd for $C_{16}H_{33}N_2O_4$ 317.2440, found 317.2442.

Boc-Alaψ[CH((*S*)-ethyl)NH]Val-Phe-OMe (44). Pseudotripeptide **44** was prepared from mono Boc diamino alcohol **42** via the procedure given for **41**. Purification by column chromatography (gravity, 3:1 hexane/EtOAc) gave pseudotripeptide **44** in 51% overall yield as a white solid: mp 105–106 °C; $[\alpha]_D$ −6.5° (*c* 0.9, $CHCl_3$); IR ($CDCl_3$) ν 3680, 3430, 3350, 2960, 1740, 1700, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.74–0.83 (c, 6 H), 0.90 (d, 3 H, *J* = 7.0), 1.09 (d, 3 H, *J* = 6.6), 1.17–1.33 (c, 2 H), 1.45 (s, 9 H), 2.00 (m, 1 H), 2.27 (m, 1 H), 2.87 (d, 1 H, *J* = 5.1), 3.05 (dd, 1 H, *J* = 7.5, 13.8), 3.15 (dd, 1 H, *J* = 5.9, 13.8), 3.65–3.75 (c, 4 H), 4.54 (b d, 1 H, *J* = 8.1), 4.87 (m, 1 H), 7.12–7.34 (c, 6 H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 9.6, 17.6, 18.0, 19.5, 23.5 (CH_2), 28.4, 31.7, 38.2 (CH_2), 47.7, 52.1, 52.8, 63.3, 67.2, 79.1 (C), 127.0, 128.6 129.1, 136.2 (C), 155.6 (C), 171.9 (C), 174.4 (C); MS (CI) $(M + H)^+$ = 464; exact mass calcd for $C_{25}H_{42}N_3O_5$ 464.3124, found 464.3131.

(1′*S*,2*S*,3*R*)-*N*²-(*tert*-Butoxycarbonyl)-*N*³-[1′-(hydroxymethyl)-2′-methylpropyl]-1-phenyl-2,3-pentanediamine (45). Mono Boc diamino alcohol **45** was prepared from alcohol **13** following the procedure given for **39**. Purification by column chromatography (gravity, 3:1 hexane/EtOAc) gave mono Boc diamino alcohol **45** in 78% yield as a white solid: mp 90–91 °C; $[\alpha]_D$ −1.7° (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) ν 3680, 3440, 2960, 1700, 1505 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (d, 3 H, *J* = 6.6), 0.88 (d, 3 H, *J* = 6.6), 1.02 (t, 3 H, *J* = 7.4), 1.28 (m, 1 H), 1.33 (s, 9 H), 1.51 (m, 1 H), 1.65 (m, 1 H), 2.43–2.52 (c, 2 H), 2.64–2.79 (c, 2 H), 3.31 (m, 1 H), 3.57 (dd, 1 H, *J* = 3.5, 11.0), 4.10 (m, 1 H), 4.63 (d, 1 H, *J* = 9.6), 7.16–7.32 (c, 5 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 11.2, 17.6, 19.5, 23.5 (CH_2), 28.3, 29.2, 37.6 (CH_2), 53.4, 59.3, 61.6 (CH_2), 62.6, 79.5 (C), 126.2, 128.4, 129.0, 138.5 (C), 156.9 (C); MS (CI) $(M + H)^+$ = 365. Anal. Calcd for $C_{21}H_{36}N_2O_3$: C, 69.19; H, 9.95; N, 7.68. Found: C, 69.04; H, 9.92; N, 7.44.

Boc-Pheψ[CH((*R*)-ethyl)NH]Val-OMe (46). Pseudodipeptide **46** was prepared from mono Boc diamino alcohol **45** following the procedure given for **40**. Purification by column chromatography (gravity, 9:1 hexane/EtOAc) gave pseudodipeptide **46** in 65% overall yield as a colorless solid: mp 67–68 °C; $[\alpha]_D$ −18.2° (*c* 0.5, $CHCl_3$); IR ($CDCl_3$) ν 3680, 3430, 2960, 1725, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (d, 6 H, *J* = 7.0), 0.96 (t, 3 H, *J* =7.4), 1.34 (s, 9 H), 1.38–1.50 (c, 2 H), 1.87 (m, 1 H), 2.42 (m, 1 H), 2.66 (m, 1 H), 2.82 (dd, 1 H, *J* = 5.2, 14.0), 3.06 (d, 1 H, *J* = 5.9), 3.70 (s, 3 H), 3.92 (m, 1 H), 4.93 (b d, 1 H, *J* = 7.5), 7.15–7.31 (c, 5 H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 10.9, 18.6, 19.3, 24.5 (CH_2), 28.4, 32.0, 36.0 (CH_2), 51.5, 53.5, 61.3, 66.2, 78.8 (C), 126.1, 128.3, 129.3, 138.3 (C), 155.5 (C), 175.7 (C); MS (CI) $(M + H)^+$ = 393. Anal. Calcd for $C_{22}H_{36}N_2O_4$: C, 67.32; H, 9.24; N, 7.14. Found: C, 67.16; H, 9.17; N, 7.15.

Boc-Pheψ[CH((*R*)-ethyl)NH]Val-Phe-OMe (47). Pseudotripeptide **47** was prepared from mono Boc diamino alcohol **45** via the procedure given for **41**. Purification by column chromatography (gravity, 3:1 hexane/EtOAc) gave pseudotripeptide **47** in 48% overall yield as a white solid: mp 135–136 °C; $[\alpha]_D$ −25.3° (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) ν 3680, 3360, 2960, 1740, 1700, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.71 (d, 3 H, *J* = 6.6), 0.85 (d, 3 H, *J* = 6.6), 0.98 (t, 3 H, *J* = 7.4), 1.31 (s, 9 H), 1.40–1.54 (c, 2 H), 1.97 (m, 1 H), 2.39 (m, 1 H), 2.60 (m, 1 H), 2.81 (dd, 1 H, *J* = 4.2, 14.7), 3.01 (d, 1 H, *J* = 4.4), 3.10–3.24 (c, 2 H), 3.70 (s, 3 H), 4.01 (s, 1 H), 4.85–4.95 (c, 2 H), 7.11–7.30 (c, 10 H), 7.85 (b d, 1 H, *J* = 8.4); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 10.6, 17.8, 19.5, 24.4 (CH_2), 28.2, 31.6, 35.8 (CH_2), 37.7 (CH_2), 52.3, 52.7, 54.2, 62.3, 68.1, 78.9 (C), 126.1, 127.0, 128.2, 128.5, 129.1, 129.3, 136.4 (C), 138.7 (C), 155.7 (C), 172.4 (C), 174.0 (C); MS (FAB) $(M + H)^+$ = 540; exact mass calcd for $C_{31}H_{46}N_3O_5$ 540.3437, found 540.3435.

(1′*S*,2*S*,3*R*)-*N*²-(*tert*-Butoxycarbonyl)-*N*³-[1′-(hydroxymethyl)-2′-methylpropyl]-2,3-pentanediamine (48). Mono Boc diamino alcohol **48** was prepared from alcohol **15** via the procedure given for **42**. Purification by column chromatography (gravity, 3:1 hexane/EtOAc) gave mono Boc diamino alcohol **48** in 81% yield as a white solid: mp 86–88 °C; $[\alpha]_D$ −5.2° (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) ν 3680, 3420, 2960, 1700, 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 (d, 3 H, *J* = 6.6), 0.96 (d, 3 H, *J* = 6.6), 0.98 (t, 3 H, *J* = 7.5), 1.04 (d, 3 H, *J* = 7.0), 1.31–1.43 (c, 2 H), 1.45 (s, 9 H), 1.79 (m, 1 H), 2.44–2.53 (c, 2 H), 3.37 (dd, 1 H, *J* = 6.2, 11.0), 3.56 (dd, 1 H, *J* = 3.7, 11.0), 3.83 (m, 1 H), 4.78 (b d, 1 H, *J* = 8.7); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 11.2, 15.6, 18.0, 19.6, 24.3 (CH_2), 28.4, 29.3, 47.7, 60.6, 61.4 (CH_2), 63.0, 79.2 (C), 155.9 (C); MS (CI) $(M + H)^+$ = 289. Anal. Calcd for $C_{15}H_{32}N_2O_3$: C, 62.46; H, 11.18; N, 9.71. Found: C, 67.72; H, 11.19; N, 9.65.

Boc-Alaψ[CH((*R*)-ethyl)NH]Val-OMe (49). Pseudodipeptide **49** was prepared from mono Boc diamino alcohol **48** via the procedure given for **40**. Purification by column chromatography (gravity, 9:1 hexane/EtOAc) gave pseudodipeptide **49** in 38% overall yield as a colorless oil: $[\alpha]_D$ −23.3° (*c* 1.2, $CHCl_3$); IR ($CDCl_3$) ν 3680, 3390, 2960, 1725, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88–0.97 (c, 9 H), 1.03 (d, 3 H, J = 6.6), 1.28 (m, 1 H), 1.45 (s, 9 H), 1.48 (m, 1 H), 1.93 (m, 1 H), 2.34 (m, 1 H), 3.12 (d, 1 H, J = 5.9), 3.68 (m, 1 H), 3.74 (s, 3 H), 5.28 (b s, 1 H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 10.8, 14.4, 18.6, 19.4, 25.0 (CH_2), 28.5, 31.9, 47.8, 51.5, 61.7, 66.3, 78.6 (C), 155.5 (C), 175.8 (C); MS (CI) $(M + H)^+$ = 317; exact mass calcd for $C_{16}H_{33}N_2O_4$ 317.2440, found 317.2442.

Boc-Alaψ[CH((*R*)-ethyl)NH]Val-Phe-OMe (50). Pseudotripeptide **50** was prepared from mono Boc diamino alcohol **48** via the procedure given for **41**. Purification by column chromatography (gravity, 3:1 hexane/EtOAc) gave pseudotripeptide **50** in 37% overall yield as a pale yellow solid: mp 85–87 °C; $[\alpha]_D$ −11.4° (*c* 0.9, $CHCl_3$); IR ($CDCl_3$) ν 3680, 3430, 2960, 1740, 1700, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.70 (d, 3 H, J = 7.0), 0.84 (d, 3 H, J = 7.0), 0.92 (t, 3 H, J = 7.5), 0.95 (d, 3 H, J = 6.6), 1.21–1.35 (c, 2 H), 1.43 (s, 9 H), 1.97 (m, 1 H), 2.49 (m, 1 H), 2.96 (d, 1 H, J = 4.4), 3.11 (dd, 1 H, J = 7.5, 14.0), 3.21 (dd, 1 H, J = 5.5, 14.0), 3.73 (m, 1 H), 3.76 (s, 3 H), 4.89 (m, 1 H), 5.11 (b s, 1 H), 7.15–7.33 (c, 5 H), 7.78 (b s, 1 H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 10.6, 14.5, 17.7, 19.4, 24.4 (CH_2), 28.4, 31.6, 37.7 (CH_2), 48.4, 52.3, 52.6, 62.2, 68.0, 78.9 (C), 127.0, 128.5, 129.1, 136.3 (C), 155.5 (C), 174.0 (C); MS (CI) $(M + H)^+$ = 464; exact mass calcd for $C_{25}H_{42}N_3O_5$ 464.3124, found 464.3131.

(1′*S*,2*RS*,4*R*)-3-Benzyl-2-[1′-(dibenzylamino)-2′-phenylethyl]-4-(methylethyl)-1,3-oxazolidine (51). Oxazolidines **51** were prepared from aldehyde **7** and (*R*)-2-(benzylamino)-3-methylbutan-1-ol via the procedure given for **10**. Purification by column chromatography (gravity, 97.5:2.5 hexane/EtOAc) gave oxazolidines **51** (10:1 by ^1H NMR) in 91% yield as a viscous yellow oil: $[\alpha]_D$ +24.7° (*c* 1.1, $CHCl_3$); IR ($CDCl_3$) ν 3020, 2950, 1600, 1490, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, major isomer) δ 0.70 (d, 3 H, J = 6.6), 0.83 (d, 3 H, J = 6.6), 1.22 (m, 1 H), 2.25 (m, 1 H), 2.63 (m, 1 H), 2.81–2.94 (c, 2 H), 3.55 (m, 1 H), 3.66–3.85 (c, 6 H), 4.02 (m, 1 H), 4.67 (d, 1 H, J = 8.5), 6.94–7.32 (c, 20 H); ^{13}C NMR ($CDCl_3$, 300 MHz, major isomer) δ 19.0, 20.4, 32.6, 35.0 (CH_2), 54.0 (CH_2), 60.8, 62.0 (CH_2), 67.6 (CH_2), 70.7, 99.2, 125.5, 126.4, 127.2, 127.8, 127.9, 128.2, 128.7, 129.7, 129.8, 139.0 (C), 140.3 (C), 141.2 (C); MS (FAB) $(M + H)^+$ = 505. Anal. Calcd for $C_{35}H_{40}N_2O$: C, 83.29; H, 7.99; N, 5.55. Found: C, 83.20; H, 8.00; N, 5.45.

(1′*R*,2*S*,3*S*)-N^2,N^2,N^3-Tribenzyl-N^3-[1′-(hydroxymethyl)-2′-methylpropyl]-1-phenyl-2,3-pentanediamine (52). Alcohol **52** was prepared from oxazolidines **51** via the procedure given for **12** and **13**. Purification by column chromatography (gravity, 95:5 hexane/EtOAc) gave alcohol **52** in 87% yield as a colorless oil: $[\alpha]_D$ +0.73° (*c* 1.1, $CHCl_3$); IR (CCl_4) ν 3580, 2950, 1605, 1495, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.74 (d, 3 H, J = 6.8), 1.01 (d, 3 H, J = 6.8), 1.08 (t, 3 H, J = 7.2), 1.61–1.79 (c, 3 H), 2.38 (m, 1 H), 2.83 (m, 1 H), 2.91–2.98 (c, 2 H), 3.22–3.44 (c, 3 H), 3.51 (d, 2 H, J = 14.0), 3.80 (d, 2 H, J = 14.0), 3.83 (d, 1 H, J = 14.7), 3.93 (d, 1 H, J = 14.7), 7.03–7.11 (c, 2 H), 7.16–7.38 (c, 18 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 13.3, 19.3, 22.3, 22.3 (CH_2), 30.3, 33.8 (CH_2), 49.1 (CH_2), 53.8 (CH_2), 60.3 (CH_2), 62.2, 64.7, 67.3, 125.9, 126.6, 126.7, 128.1, 128.2, 128.5, 128.6, 129.9, 140.1 (C), 141.1 (C), 142.7 (C); MS (FAB) $(M + H)^+$ = 535; exact mass calcd for $C_{37}H_{47}N_2O$ 535.3688, found 535.3696.

Boc-Pheψ[CH((*S*)-ethyl)NH](*R*)Val-Phe-OMe (53). Pseudotripeptide **53** was prepared from alcohol **52** via the procedure given for **39** and **41**. Purification by column chromatography (gravity, 3:1 hexane/EtOAc) gave pseudotripeptide **53** in 30% overall yield as a colorless oil: $[\alpha]_D$ +25.2° (*c* 1.9, $CHCl_3$); IR ($CDCl_3$) ν 3520, 2960, 1740, 1710, 1660, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, 3 H, J = 7.4), 0.90 (d, 3 H, J = 7.0), 0.97 (d, 3 H, J = 7.0), 1.18–1.30 (c, 2 H), 1.33 (s, 9 H), 1.93–2.13 (c, 2 H), 2.22–2.43 (c, 2 H), 3.03 (d, 1 H, J = 4.0), 3.13 (dd, 1 H, J = 7.7, 14.7), 3.33 (dd, 1 H, J = 5.9, 14.7), 3.72 (s, 3 H), 3.75 (m, 1 H), 4.07 (b d, 1 H, J = 9.0), 4.95 (m, 1 H), 7.04–7.32 (c, 10 H), 7.47 (b d, 1 H, J = 7.5); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 9.2, 17.7, 19.6, 22.6 (CH_2), 28.2, 31.8, 37.0 (CH_2), 38.5 (CH_2), 52.1, 52.3, 52.7, 60.3, 65.1, 79.2 (C), 126.1, 127.1, 128.2, 128.7, 128.9, 136.3 (C), 138.5 (C), 155.9 (C), 172.1 (C), 174.2 (C); MS (FAB) $(M + H)^+$ = 540; exact mass calcd for $C_{31}H_{46}N_3O_5$ 540.3437, found 540.3435.

(1*S*,1′*S*,2*S*)-N^2-(*tert*-Butoxycarbonyl)-1-cyclohexyl-N^1-[1′-(hydroxymethyl)-2′-methylpropyl]-1,2-propanediamine (54) and (1*R*,1′*S*,2*S*)-N^2-(*tert*-Butoxycarbonyl)-1-cyclohexyl-N^1-[1′-(hydroxymethyl)-2′-methylpropyl]-1,2-propanediamine (55). To a solution of cyclohexylmagnesium chloride (3.5 mL, 2.0 M in ether, 7.0 mmol) in ether (15 mL) at 0 °C under nitrogen with stirring was added a solution of oxazolidine **11** (1.00 g, 2.3 mmol) in ether (5.0 mL) dropwise over 3 min. This mixture was allowed to stir with warming to room temperature for 2.5 h, quenched with aqueous saturated NH_4Cl, and stirred an additional 5 min. The layers were separated, and the aqueous phase was extracted with Et_2O (1 × 20 mL). The combined organic phases were dried, filtered, and evaporated to give a colorless oil that was purified by column chromatography (flash, 97.5:2.5 CH_2Cl_2/Et_2O) to give the fully protected diamino alcohols (1.3:1), which were separately converted to the mono Boc diamino alcohols **54** and **55** via the procedure given for **42**. Purification by column chromatography (flash, 3:1 hexane/EtOAc) gave mono Boc diamino alcohols **54** and **55** in 46% and 32% yield, respectively (from **11**) as colorless oils. **54**: $[\alpha]_D$ −3.9° (*c* 0.3, $CHCl_3$); IR ($CDCl_3$) ν 3620, 3440, 2920, 1700, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 (d, 3 H, J = 7.0), 0.97 (d, 3 H, J = 7.0), 1.13 (d, 3 H, J = 7.0), 1.15–1.26 (c, 3 H), 1.35 (m, 1 H), 1.45 (s, 9 H), 1.62–1.88 (c, 8 H), 2.27 (m, 1 H), 2.50 (m, 1 H), 3.45 (dd, 1 H, J = 6.2, 10.7), 3.62 (dd, 1 H, J = 4.0, 10.7), 3.78 (b s, 1 H), 4.85 (b d, 1 H, J = 7.2); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 18.0, 19.7, 20.3, 26.6 (CH_2), 26.7 (CH_2), 26.9 (CH_2), 28.5, 29.0, 29.4 (CH_2), 30.1 (CH_2), 41.2, 47.5, 61.0 (CH_2), 63.2, 63.5, 79.0 (C), 155.5 (C); MS (FAB) $(M + H)^+$ = 343. Anal. Calcd for $C_{19}H_{38}N_2O_3$: C, 66.63; H, 11.18; N, 8.18. Found: C, 66.20; H, 11.06; N, 7.98. **55**: $[\alpha]_D$ −6.5° (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) ν 3630, 3440, 2920, 1700, 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (d, 3 H, J = 7.0), 0.98 (d, 3 H, J = 6.6), 1.04 (d, 3 H, J = 6.6), 1.08–1.32 (c, 5 H), 1.45 (s, 9 H), 1.63–1.93 (c, 7 H), 2.43 (m, 1 H), 2.52 (m, 1 H), 3.43 (dd, 1 H, J = 5.3, 11.0), 3.57 (dd, 1 H, J = 3.7, 11.0), 3.86 (b s, 1 H), 5.16 (b d, 1 H, J = 8.8); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 15.4, 18.0, 20.1, 26.4 (CH_2), 26.5 (CH_2), 28.5, 29.4, 30.4 (CH_2), 30.6 (CH_2), 41.5, 47.6, 60.6 (CH_2), 63.1, 64.0, 79.0 (C), 155.6 (C); MS (FAB) $(M + H)^+$ = 343; exact mass calcd for $C_{19}H_{39}N_2O_3$ 343.2961, found 343.2965.

Boc-Alaψ[CH((*S*)-cyclohexyl)NH]Val-Phe-OMe (56). Pseudotripeptide **56** was prepared from mono Boc diamino alcohol **54** via the procedure given for **41**. Purification by column chromatography (gravity, 4:1 hexane/EtOAc) gave pseudotripeptide **56** in 26% overall yield as a colorless oil: $[\alpha]_D$ −10.0° (*c* 1.5, $CHCl_3$); IR ($CDCl_3$) ν 3680, 3430, 2920, 1735, 1695, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (d, 3 H, J = 7.4), 0.91 (d, 3 H, J = 7.4), 0.97 (m, 1 H), 1.10 (d, 3 H, J = 6.6), 1.12–1.30 (c, 4 H), 1.45 (s, 9 H), 1.52–1.73 (c, 6 H), 1.91 (m, 1 H), 2.06 (m, 1 H), 2.89 (d, 1 H, J = 5.5), 3.06 (dd, 1 H, J = 7.2, 13.8), 3.15 (dd, 1 H, J = 5.9, 13.8), 3.69 (m, 1 H), 3.72 (s, 3 H), 4.76 (b d, 1 H, J = 8.1), 4.88 (m, 1 H), 6.90 (b d, 1 H, J = 7.8), 7.13–7.17 (c, 2 H), 7.20–7.33 (c, 3 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 18.8, 19.1, 20.3, 26.4 (CH_2), 26.6 (CH_2), 26.7 (CH_2), 28.5, 28.9 (CH_2), 30.0 (CH_2), 32.1, 38.2 (CH_2), 41.2, 47.8, 52.2, 53.0, 65.9, 68.2, 79.1 (C), 127.1, 128.6, 129.1, 136.1 (C), 155.5 (C), 171.9 (C), 174.0 (C); MS (CI) $(M + H)^+$ = 518; exact mass calcd for $C_{29}H_{48}N_3O_5$ 518.3594, found 518.3599.

Boc-Alaψ[CH((*R*)-cyclohexyl)NH]Val-Phe-OMe (57). Pseudotripeptide **57** was prepared from mono Boc diamino alcohol **55** via the procedure given for **41**. Purification by column chromatography (gravity, 4:1 hexane/EtOAc) gave pseudotripeptide **57** in 22% overall yield as a colorless oil: $[\alpha]_D$ −16.6° (*c* 0.9 $CHCl_3$); IR ($CDCl_3$) ν 3680, 3360, 2920, 1735, 1695, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.82 (d, 3 H, J = 7.0), 0.84 (d, 3 H, J = 5.5), 0.95 (d, 3 H, J = 7.0), 1.03–1.32 (c, 6 H), 1.41 (s, 9 H), 1.62–1.67 (c, 2 H), 1.70–1.80 (c, 3 H), 1.95 (m, 1 H), 2.39 (b s, 1 H), 2.95 (d, 1 H, J = 4.4), 3.13 (dd, 1 H, J = 7.4, 14.0), 3.18 (dd, 1 H, J = 5.5, 14.0), 3.72 (m, 1 H), 3.76 (s, 3 H), 4.91 (m, 1 H), 5.34 (b s, 1 H), 7.13–7.17 (c, 2 H), 7.20–7.30 (c, 3 H), 7.62 (b s, 1 H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 15.2, 18.7, 19.0, 26.4 (CH_2), 26.6 (CH_2), 28.4, 29.6 (CH_2), 30.8 (CH_2), 32.0, 37.9 (CH_2), 40.7, 47.7, 52.4, 52.6, 65.8, 68.9, 78.7 (C), 127.0, 128.6, 129.1, 136.2 (C), 155.4 (C), 172.9 (C), 174.2 (C); MS (CI) $(M + H)^+$ = 518; exact

mass calcd for $C_{29}H_{48}N_3O_5$ 518.3594, found 518.3599.

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Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra for compounds characterized by high-resolution mass spectroscopy, ^1H NMR spectra for imidazolidones **16–19** and **23**, and X-ray structural data for **11** including ORTEP representation (44 pages). Ordering information is given on any current masthead page.

New Syntheses and Reactions of Some Halogenated Porphyrins

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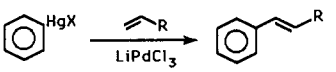
Efficient syntheses of 2,4-dibromo- and 2,4-diiododeuteroporphyrin IX have been carried out by treating zinc(II) 2,4-bis(chloromercurio)deuteroporphyrin IX dimethyl ester (**2**) with bromine or iodine. Unavoidable meso-chlorination occurs when **2** is treated with chlorine and with other free-radical chlorinating agents. Regioselective meso-chlorination and peripheral (β) bromination are shown to occur from brief treatment of copper(II) deuteroporphyrin IX or β-unsubstituted a,c-biladienes with the corresponding copper(II) halide in refluxing dimethylformamide. Protoporphyrin IX has been synthesized by vinylation of **2** via ethylene/$LiPdCl_3$ (35% yield), with vinyl bromide and Wilkinson's catalyst (63%), or from 2,4-dibromodeuteroporphyrin IX with ethenyltributylstannane/$(Ph_3P)_4Pd^0$ (85%).

Introduction

Mercurated aryl systems have been shown to undergo a myriad of transformations;[1] the most notable of these were discovered by Heck[2,3] and involve the transmetalation of an aryl mercurial with lithium chloropalladate in the presence of an olefin, efficiently generating the coupled aryl–olefin compound (Scheme I). We have recently developed a number of effective new procedures, utilizing these mercuration procedures, for the creation of new carbon–carbon bonds at the porphyrin periphery.[4,5] For example, zinc(II) deuteroporphyrin IX dimethyl ester (**1**) can be mercurated by simply warming the porphyrin in the presence of an excess of mercury(II) acetate in tetrahydrofuran. After forming the chloride salt, the mercurated deuteroporphyrin **2** is obtained in high yield. Attempts to form protoporphyrin IX dimethyl ester (**3**) by reaction of **2** with ethylene and $LiPdCl_3$ (in acetonitrile) gave ≤5% yields, but methyl acrylate added readily to the 2- and 4-positions, forming the bis-acrylate porphyrin **4** in 37% yield.[6–8] A variety of other biologically important porphyrins were also synthesized,[5] including deoxophylloerythroetioporphyrin, deoxophylloerythrin methyl ester,[9] and regioselectively deuteriated protohemes.[10]

Arylmercurials can ordinarily be halogenated with bromine and iodine in a facile manner.[11] Introduction of bromine and iodine has proven invaluable in determining the position of mercury within a new compound or for establishing the ratio of isomers of an inseparable mixture of arylmercurials. Aryl bromides and iodides are also extremely useful as synthetic intermediates leading to amines, carboxylic acids and esters, ethers, nitriles, and a host of organometallic compounds.[12] Chlorination on the other hand has received little attention and appears limited to only certain arylmercuric salts.

Scheme I



2,4-Brominated and -Iodinated Derivatives of Deuteroporphyrin IX. Using a procedure developed by Larock et al.,[13] we attempted to couple vinyl bromide with bis-mercurated deuteroporphyrin IX **2** via Wilkinson's catalyst in the hope of achieving a more efficient transformation of deuteroporphyrin IX into protoporphyrin IX. The coupling in DMSO/THF gave a very poor yield (≤10%) of protoporphyrin IX dimethyl ester (**3**), but marked improvements were observed (63%) when the more polar solvent, hexamethylphosphoramide, was used. Generalization of this coupling reaction by using 2,3-dibromopropene, surprisingly, resulted only in isolation of the dimethyl esters of 2- and 4-monobromodeuteroporphyrins (**5** and **6**, respectively), in 8% total yield, and 2,4-dibromodeuteroporphyrin (**7**) (20%). Treatment of bis-mercurated deuteroporphyrin IX **2** in tetrahydrofuran/chloroform with 2.2 equiv of bromine in chloroform gave a more acceptable 72% yield of 2,4-dibromodeuteroporphyrin IX dimethyl ester (**7**). Excess of bromine caused meso-bromination to occur (NMR).

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