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An Enantioselective Synthesis of Differentially Protected *erythro*-α,*β*-Diamino Acids and Its Application to the Synthesis of an Analogue of Rhodopeptin B5†

Timothy B. Durham and Marvin J. Miller*

Department of Chemistry and Biochemistry, 251 Nieuwland Science Hall, University of Notre Dame, Notre Dame, Indiana 46556-5670

Marvin.J.Miller.2@nd.edu

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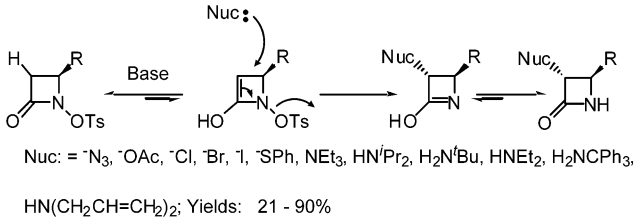
Methodology for the enantioselective synthesis of differentially protected *erythro*-α,*β*-diamino acids from *N*-tosyloxy *β*-lactams is reported. The requisite *N*-tosyloxy *β*-lactams are readily available from simple *β*-keto esters. The reported approach is flexible and compatible with a variety of functional groups. The synthetic utility of the method is demonstrated through its application to the preparation of an analogue of the antifungal cyclic peptide rhodopeptin B5.

Introduction

The stereoselective synthesis of novel amino acids is a continuing challenge for organic chemists. Finding new routes to this important class of molecules has continued to hold the attention of organic chemists not only because of their ubiquitous presence as components in biologically active natural products but also because the amino acid template holds considerable attraction in the development of new pharmacological agents due to its efficient packaging of both molecular functionality and stereochemical information. Thus, the motivation to develop methods to prepare these highly sought chemical building blocks has been quite intense and has resulted in a number of novel and efficient approaches to various types of amino acids.[1−5] Within our research program, we have offered a number of novel approaches to the synthesis of unusual amino acids, especially those found in the naturally occurring iron chelators termed siderophores.[6−10] Further, our group has also had a long-standing interest in the chemistry of *β*-lactams, which have been previously used as precursors to *β*-amino acids.[11,12] In this paper, we report the application of a unique reaction of *N*-tosyloxy *β*-lactams to the diastereoselective preparation of *erythro*-α,*β*-diamino acids. This new approach to these highly functionalized amino acids complements previously published approaches[12−14] to *threo*-α,*β*-diamino acids, allowing access to either form of these useful building blocks.

SCHEME 1



More than 20 years ago, our group reported a biomimetic synthesis of chiral *N*-hydroxy *β*-lactams from the corresponding *β*-hydroxy hydroxamates.[15] Subsequently, in the early 1990s, our group found that under basic conditions *N*-tosyloxy *β*-lactams underwent an unusual nucleophilic addition at the C3 carbon with concomitant N−O bond reduction (Scheme 1).[16−19] This powerful reaction allows the synthesis of C3-functionalized *β*-lactams in a diastereoselective fashion since the *trans* products are formed predominately with high selectivity.[17] This transformation compliments the often utilized [2 + 2] cycloaddition approaches to constructing the *β*-lactam ring system which normally give *cis* products.[20]

† Dedicated to the memory of Professor Henry Rapoport (November 15, 1918−March 6, 2002), U. C. Berkeley; a superb scientist, teacher, mentor, and friend.

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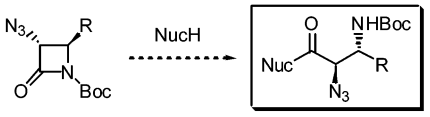
While a number of different types of nucleophiles including halides and carboxylic acids have been shown to be effective in this reaction,[17] this approach was found to be especially efficient for the introduction of nitrogen functionality at the C3 position by the use of either sterically encumbered amines[18] or azide as the nucleophile[16,17,21] (Scheme 1). Recently, we reported a methodology to convert the *trans*-3-azido-*β*-lactams produced through this unusual reaction to optically enriched α-amino acids.[22] During the course of this previous work, we recognized the incredible potential of these species to allow the synthesis of differentially protected *erythro*-α,*β*-diamino acids and their corresponding peptides by exploiting our approach to *trans*-substituted *β*-lactams.

The use of *N1*-urethane-protected *β*-lactams as precursors to *β*-amino acids has been previously demonstrated by several groups.[11,12,23,24] In particular, Palomo and coworkers have reported the direct use of such systems in coupling reactions using *trans*-acylation catalysts such as potassium cyanide and sodium azide.[14,25,26] Application of similar reaction conditions to α-azido-*β*-lactam systems should, therefore, provide access to the corresponding *erythro*-α,*β*-diamino acids (eq 1). The power of such a



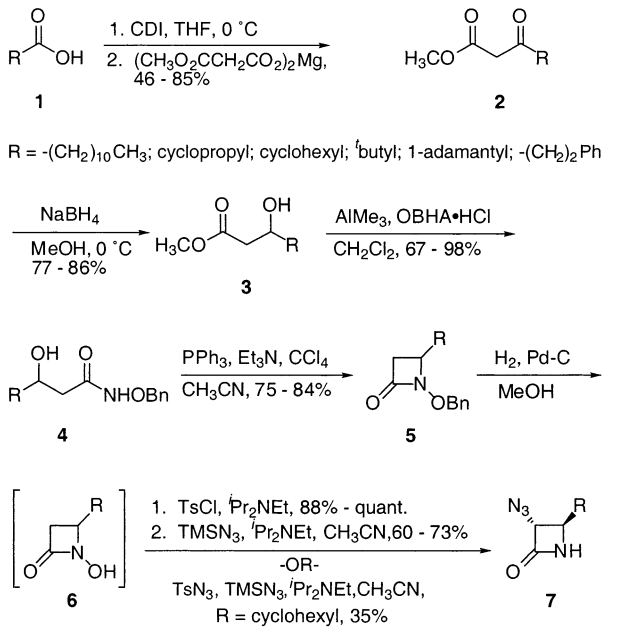
(1)

method would be immense since not only could the *N1*-urethane-protected α-azido-*β*-lactam be used directly for coupling with the selected nucleophile, but also, depending on the protecting group choice, the resulting ring-opened product would contain orthogonally protected amino groups, allowing easy differentiation in subsequent elaboration steps. The use of such an approach in total synthesis or drug design could be highly advantageous.

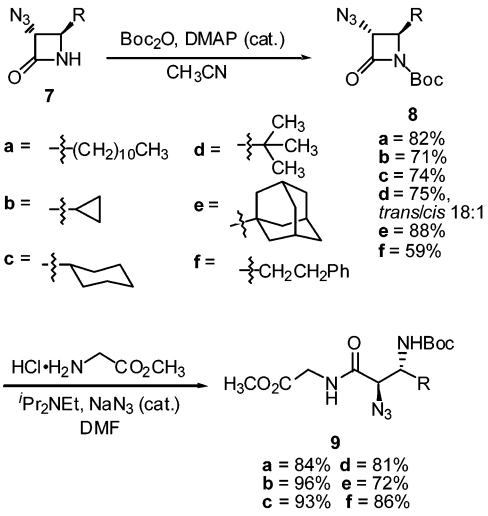
Results and Discussion

Our studies began with the synthesis of a small library of *trans*-3-azido-*β*-lactams using our unique nucleophilic addition/N−O bond reduction reaction (Scheme 2).[22] The corresponding carboxylic acid precursors **1** were converted to *β*-keto esters **2** using the Masamune−Brooks reaction.[27] Subsequent sodium borohydride reduction provided the *β*-hydroxy esters **3**, which were converted in a single step to the hydroxamates **4** using trimethylaluminum and *O*-benzylhydroxylamine hydrochloride (OBHA·HCl).[28] Subjection of these hydroxamates to

SCHEME 2



SCHEME 3



activated triphenylphosphine under basic conditions provided the cyclized dehydration products, *β*-lactams **5**. Hydrogenolysis of the benzyl moieties set the stage for the preparation of the targeted *trans*-3-azido-*β*-lactams **7** through either a two-step sequence of tosylation followed by treatment of the isolated tosylate with $TMSN_3$ in the presence of Hunig's base[17] or treatment with tosyl azide to generate the tosylate in situ followed by addition of excess azide.[21]

With the preparation of the requisite *trans*-3-azido-*β*-lactams, our attention was focused on carbamate protection of N1. We were gratified to find that the *N1*-Boc-α-azido-*β*-lactams **8a**−**f** could be prepared directly using standard conditions (Scheme 3).[14,29] Finally, exposure of our *N1*-Boc-α-azido-*β*-lactams to the in situ generated free base of glycine methyl ester in the presence of a catalytic amount of sodium azide provided the desired

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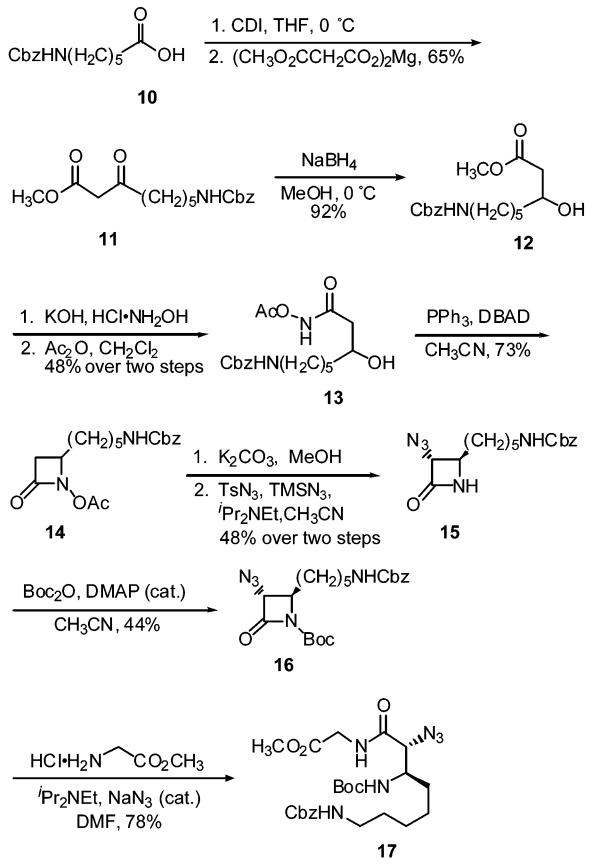
SCHEME 4



dipeptides **9a**−**f** in good to excellent yields. Spectroscopic analysis of the reaction products showed no detectable epimerization at the α-position. It is interesting to note that increased steric demands in the *β*-lactam partner do not appear to significantly depress the efficiency of this coupling reaction, highlighting the robustness of this approach to differentially protected dipeptides.

Emboldened by our initial success with simple C4-alkyl-substituted systems, we targeted a more functionalized diamino acid to demonstrate the flexibility of our chemistry. Toward this end, dipeptide **17** bearing three fully differentiated amino moieties was targeted for synthesis (Scheme 4). While the use of benzyl protecting groups had previously been effective in our simple alkyl systems, it was recognized that this protecting group was incompatible with easily reducible functionalities such as alkenes and alkynes or benzyl carbamate protecting groups. Therefore, a different oxygen protecting group was required. In this regard, our group has previously shown that the acetyl group can be used effectively in our *β*-lactam chemistries.[21] Our synthesis of dipeptide **17** began with *N*-Cbz-6-aminocaproic acid (**10**). Carbon chain extension and reduction of the resultant ketone, as before, provided ester **12**, which was converted to the *O*-acetyl-protected hydroxamate **13** by formation of the hydroxamic acid potassium salt and subsequent acetylation. Exposure of hydroxamate **13** to Mitsunobu reaction conditions provided *β*-lactam **14** in good yield. Removal of the acetyl group under basic transesterification conditions provided the requisite hydroxamic acid, which was then treated with TsN_3 to provide *trans*-3-azido-*β*-lactam **15**. *N1*-Boc protection of the *β*-lactam

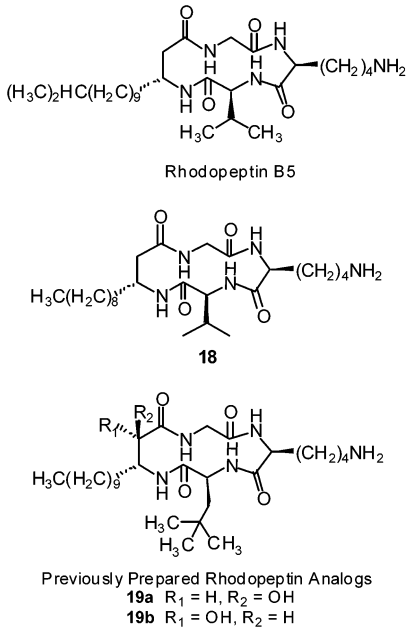


FIGURE 1. Naturally occurring antifungal agent rhodopeptin B5 and some of its reported synthetic analogues.

using the previous conditions was successful but resulted in a lower overall yield probably due to unwanted polymerization reactions. In any event, coupling of the urethane-protected *β*-lactam **16** with the methyl ester of glycine provided the fully differentiated dipeptide **17**.

With the demonstration of the feasibility and generality of the proposed method, a suitable application was sought to demonstrate its utility. We recognized that the dipeptide **9a** derived from lauric acid derivative **8a** bore close resemblance to the western portion of the family of cyclic peptides known as the rhodopeptins which had been recently isolated from the *Rhodococus* species Mer-N1033 (Figure 1).[30] These cyclic peptides have shown antifungal activities similar in magnitude to those of amphotericin B against *Candida albicans* and *Cryptococcus neoformans* but have been reported to have poor solubility in water, limiting their viability as potential antifungal therapeutic agents.[30] Construction of a rhodopeptin analogue utilizing dipeptide **9** could allow the incorporation of amino functionality at the α-position of the hydrophobic amino acid moiety. Such an analogue might have increased water solubility relative to the parent compound, making it a more attractive medicinal candidate. This general approach has already been shown to be successful by Ohta and co-workers in their synthesis of analogues such as **19a** and **19b**[31a] (Figure 1) and others.[31b,c] These analogues retained the antifungal activity of the parent molecules and displayed increased water solubility.[31] We therefore set out to prepare rhodopeptin B5 analogue **20** in an enantioselective fashion using our newly designed methodology (Scheme 5).

Retrosynthetically, we envisioned that peptide **20** could arise from the fully protected macrolactam **21** in which

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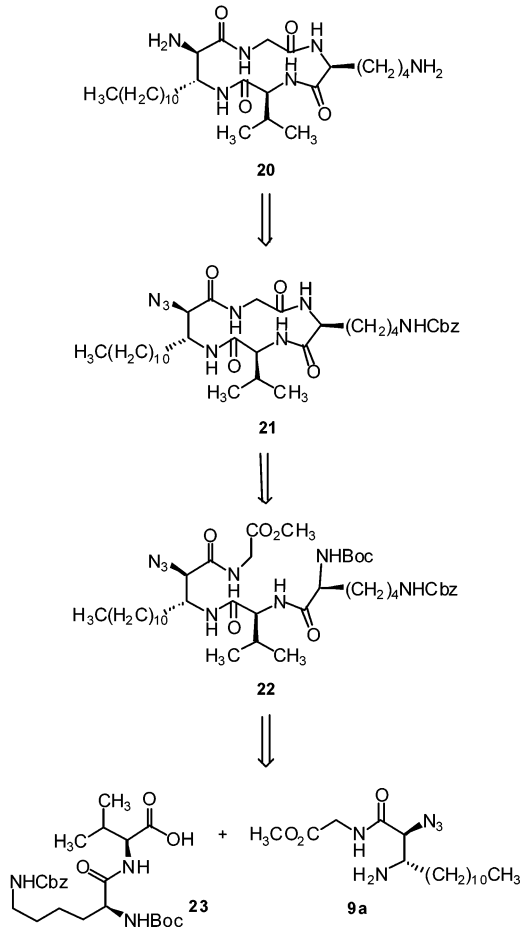
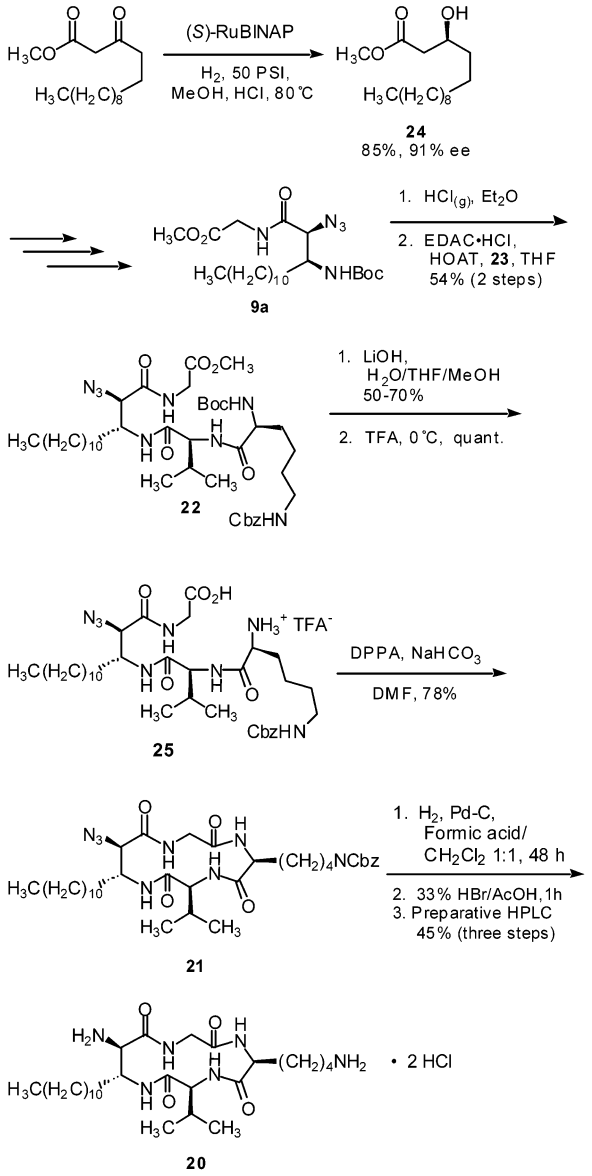
SCHEME 5



SCHEME 6



the azide functionality would represent a masked form of the α-amino group of the *β*-amino acid (Scheme 5). Scission of the glycine−lysine peptide bond revealed linear tetrapeptide **22**, which was further bisected to the lysine−valine fragment **23** and dipeptide **9a**. Thus, key to the success of our approach would be the preparation of optically enriched dipeptide **9a**.

Toward this end, dipeptide **9a** was prepared beginning with enantiomerically enriched *β*-hydroxy ester **24**[22] prepared from the corresponding *β*-keto ester using a Noyori−Taber reduction (Scheme 6).[32] The synthetic sequence was then carried out as before (see Schemes 2 and 3) to give the dipeptide **9a** in enantiomerically enriched form. Deprotection of **9a** allowed coupling with dipeptide **23** to give tetrapeptide **22**, which was easily separated from its minor diastereomer, arising from reaction with trace amounts of *ent*-**9a**, by chromatography. Peptide **22** was then transformed to the trifluoroacetic acid salt **25**. Using the previously reported method, the tetrapeptide **25** was cyclized to fully protected analogue **21**.[31a,33,34]

We originally envisioned a global deprotection under simple hydrogenation conditions would allow access to the desired product **20**. However, while extended hydrogenation in acidic media was efficient in the reduction of the azide moiety, in some instances it was unable to fully remove the terminal benzyl carbamate. Similar difficulties in removal of this protecting group appear to have been encountered by Chiba and co-workers.[33] This reticence would, most likely, seem to be due to the unusual physiochemical properties of this class of peptides and their salts. While the exact cause of this mitigated reactivity to catalytic hydrogenation is unknown, these compounds have been observed by both ourselves and others to have a number of unusual features including poor solubility[33] (especially in the case of compound **21**), detergent-like behavior, and unusual internal hydrogen bonding.[31b] On the basis of a series of experiments using our reaction conditions, we subsequently found that the outcome of the reaction is quite sensitive and can give different results on the basis of the experimental conditions used. In particular, it appears at higher substrate concentrations and lower catalyst loadings incomplete removal of the carbamate

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TABLE 1. MIC Values of Rhodopeptin B5 and Its Analogues (μg/mL)[a]

compd	*Candida albicans*	*Crytococcus neoformans*	*Aspergillus fumigatus*	*Candida parapsilosis*
rhodopeptin B5[b]	1.25−2.0	0.63	>80	N/A[f]
18[c]	1.6−3.2[d]/10	10	>50	N/A
20[a]	20	10	40	20
19a[e]	32	8	32	N/A
19b[e]	16	4	32	N/A
amphotericin B[a]	0.078	0.078	0.156	0.156

[a] Assays performed using a microtiter broth dilution assay (based upon National Committee for Clinical Laboratory Standards (NCCLS) guidelines) in 96-well plates. The compounds were solubulized in DMSO and tested in RPMI and MOPS, pH 7.0. Strains used: *C. albicans* A26, *C. neoformans* M1-106, *A. fumigatus* WM1, and *C. parapsilosis* CP18. [b] Strains used: *C. albicans* IFM4009 and ATCC10231, *C. neoformans* TIMM0354, and *A.* fumigatus TIMM0063, IFM 4942, and IFM41088.[30] [c] Strains used: *C.* albicans ATCC24433, C. *neoformans* IAM12253, and *A. fumigatus* ATCC36607.[31b] [d] Strains used: *C.* albicans ATCC10231 and ATCC24433.[33] [e] Strains used: *C. albicans* ATCC24433, C. *neoformans* IFO 1420, *A. fumigatus* TIMM0063.[31a] [f] N/A = data not available.

can be observed, but at more dilute concentrations complete deprotection is achieved. These observations offer the tantalizing possibility of selective deprotection of the azide moiety under simple hydrogenation conditions. Currently, we are trying to develop an optimized set of conditions to effect this result with the hope that we can subsequently use this technology to enable the selective synthesis of a siderophore drug conjugate of our analogue.[9]

In any event, to ensure the reaction had gone to completion, and therefore simplify our purification sequence, we opted to treat the hydrogenated material with HBr/AcOH to remove any carbamate which might still remain. This approach was successful and provided the targeted analogue **20**.

Compound **20** was tested for antifungal activity against *C. albicans* (ATCC 48130). The cyclic peptide showed concentration-dependent growth inhibitory activity against *C. albicans* in a kinetic growth assay in which the optical densities of Luria broth cultures of the fungus which had been treated with various concentration ranges of compound **20** were measured every 30 min over a 24 h period at 37 °C. Encouraged by this initial result, we submitted **20** for MIC determination against four fungal strains. The results of these studies along with the literature values reported for the parent compound and its analogues **18**,[33,31b] **19a**,[31a] and **19b**[31a] are shown in Table 1. Although a truly direct comparison across assays is not possible due to the use of different fungal strains in each assay, from these data it appears that the antifungal activity of analogue **20** is comparable in magnitude to those of α-hydroxy-β-amino acid analogues **19a** and **19b** and the simplified analogue **18**. From a medicinal chemistry standpoint, this result is very intriguing. Although the incorporation of a hydroxy functionality at the α-position of the lipophilic β-amino acid had been shown to be tolerated within this template, the incorporation of a primary amino group (which under physiological conditions should exist in its protonated form) at this position, to give an analogue which still shows comparable antifungal activity, is truly impressive. This result might be unexpected since the parent molecule rhodopeptin B5 can be viewed as a lipid-like molecule containing a polar head portion (the lysine moiety) and a hydrophobic tail (the β-amino acid moiety). However, analogue **20**, along with compounds **19a** and **19b**, demonstrates that additional highly polar and even positively charged functional groups in the normally hydrophobic portion of the parent system can be tolerated effectively. This exciting result further raises questions as to the mode of action of these unusual cyclic peptides and their biological target within the fungal pathogens for which they display activity. It also opens the possibility for the synthesis of whole new classes of rhodopeptin analogues with various nitrogen functionalities at the α-position of the lipophilic β-amino acid. Subjection of compound **20** to broad screen antifungal testing to further study its biological activity profile is currently under way.

In conclusion, a general and facile method for accessing *erythro*-α,β-diamino acids from *N*-tosyloxy β-lactams in a stereoselective fashion has been developed. Further, this method allows easy differentiation of the two amino moieties. This method was successfully applied to the preparation of rhodopeptin B5 analogue **20** in a diastereoselective fashion. Analogue **20** has been shown to retain antifungal activity at least as well as previous analogues **19a,b**, and displayed good water solubility, allowing access to a whole new class of rhodopeptin analogues. We anticipate that the synthetic technology described in this paper will be quite useful in the preparation of other highly functionalized amino acids and other rhodopeptin analogues.

Experimental Section

General Methods. Tosyl azide,[35] monomethyl malonate,[36] and compounds **2**−**7** and **24** were prepared according to the reported procedures.[22] All solvents were distilled prior to use. Triethylamine was distilled from calcium hydride under argon. Carbon tetrachloride was stored over molecular sieves. All other reagents were used as received. During the course of this work, gram scale quantities of 3-azido β-lactams were prepared. Although we have noted no explosive tendencies from any of the compounds reported, *caution* in handling is advised. The 3-azido β-lactams showed little to no decomposition after storage for several months at −4 °C. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured at 300 and 75 MHz, respectively, unless otherwise noted. All chemical shifts (δ) are relative to that of either tetramethylsilane or residual solvent. Silica gel flash chromatography was carried out using silica gel 60 (30−70 mm irregular particles).

General Procedure for the Synthesis of *N*1-Boc-3-azido-β-lactams. The β-lactam and DMAP (10 mol %) were dissolved in dry acetonitrile. To the resulting solution was added Boc_2O (1.2 equiv) as a solution in dry acetonitrile. After 20 min, the solvent was evaporated by rotary evaporator, and the residue was chromatographed to provide the title compounds.

(±)-*trans*-3-Azido-1-(*tert*-butoxycarbonyl)-4-undecyl-2-azetidinone (8a). Flash chromatography (10:1 hexanes/EtOAc) provided the title compound as a yellow oil (82%): ^{1}H NMR ($CDCl_3$) δ 4.23 (d, J = 3.00 Hz, 1H), 3.76 (m, 1H), 2.16 (m, 1H), 1.53 (s, 12H), 1.35 (m, 6H), 1.27 (m, 16H), 0.88 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 161.80, 147.95, 84.27, 68.31, 60.32, 32.08, 31.17, 29.77, 29.64, 29.58, 29.51, 29.42, 28.19, 25.06,

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22.87, 14.29; IR (neat) 2111, 1817, 1731 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{19}H_{35}N_4O_3$ (M − H$^+$) 367.2709 found 337.2699.

(±)-*trans*-3-Azido-1-(*tert*-butoxycarbonyl)-4-cyclopropyl-2-azetidinone (8b). Filtration through a plug of silica (10:1 hexanes/EtOAc) provided the title compound as a clear oil (71%): ^{1}H NMR ($CDCl_3$) δ 4.37 (d, J = 2.70 Hz, 1H), 3.26 (dd, J_1 = 8.70 Hz, J_2 = 2.40 Hz, 1H), 1.54 (s, 9H), 1.07 (m, 1H), 0.81 (m, 1H), 0.62 (m, 2H), 0.38 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 162.19, 147.82, 84.09, 68.18, 64.81, 28.12, 12.24, 5.83, 1.74; IR (neat) 2111, 1816, 1728 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{11}H_{17}N_4O_3$ (M − H$^+$) 253.1301, found 253.1320.

(±)-*trans*-3-Azido-1-(*tert*-butoxycarbonyl)-4-cyclohexyl-2-azetidinone (8c). Filtration through a plug of silica (10:1 hexanes/EtOAc) provided the title compound as a clear oil (74%): ^{1}H NMR ($CDCl_3$) δ 4.39 (d, J = 3.00 Hz, 1H), 3.74 (dd, J_1 = 5.40 Hz, J_2 = 3.00 Hz, 1H), 2.01 (m, 1H), 1.73 (m, 5H), 1.53 (s, 9H), 1.26 (m, 3H), 1.01 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 162.08, 148.25, 84.20, 65.02, 64.43, 37.64, 29.25, 28.18, 26.51, 26.31, 25.94, 25.70; IR (neat) 2110, 1815, 1728 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{14}H_{23}N_4O_3$ (M − H$^+$) 295.1770, found 295.1783.

(±)-*trans*-3-Azido-1-(*tert*-butoxycarbonyl)-4-(*tert*-butyl)-2-azetidinone (8d). Flash chromatography (10:1 hexanes/EtOAc) produced the title compound as a clear oil as an inseparable mixture (18:1 *trans*/*cis*) of isomers (75%): ^{1}H NMR ($CDCl_3$) δ 4.45 (d, J = 2.70 Hz, 1H, *cis* isomer), 4.34 (d, J = 3.00 Hz, 1H, *trans* isomer), 3.84 (d, J = 2.70 Hz, 1H, *cis* isomer), 3.64 (d, J = 3.00 Hz, 1H, *trans* isomer), 1.51 (s, 9H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$) δ (*trans* isomer) 162.78, 148.63, 84.30, 69.16, 64.99, 32.86, 28.08, 26.44; (*cis* isomer) 72.59, 59.42, 33.62, 26.34; IR (neat) 2112, 1814, 1734 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{12}H_{21}N_4O_3$ (M − H$^+$) 269.1614, found 269.1613.

(±)-*trans*-3-Azido-1-(*tert*-butoxycarbonyl)-4-(1-adamantyl)-2-azetidinone (8e). Filtration through a plug of silica (10:1 hexanes/EtOAc) provided the title compound as a clear oil (88%): ^{1}H NMR ($CDCl_3$) δ 4.50 (d, J = 2.40 Hz, 1H), 3.51 (d, J = 2.70 Hz, 1H), 2.05 (br s, 3H), 1.67 (m, 12H), 1.54 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.88, 148.93, 84.30, 69.45, 63.39, 38.69, 36.76, 34.50, 28.17, 27.99; IR (neat) 2110, 1811, 1733 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{18}H_{26}N_4O_3$ (M − H$^+$) 347.2083, found 347.2104.

(±)-*trans*-3-Azido-1-(*tert*-butoxycarbonyl)-4-(2-phenyl-1-ethyl)-2-azetidinone (8f). Filtration through a plug of silica (10:1 hexanes/EtOAc) provided the title compound as a clear oil (59%): ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 2H), 7.22 (m, 3H), 4.12 (d, J = 2.70 Hz, 1H), 3.77 (dt, J_1 = 9.80 Hz, J_2 = 2.92 Hz, 1H), 2.74 (m, 2H), 2.55 (m, 1H), 1.92 (dd, J_1 = 13.80 Hz, J_2 = 7.20 Hz, 1H), 1.87 (dd, J_1 = 13.95 Hz, J_2 = 7.35 Hz, 1H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 161.76, 147.83, 140.02, 128.89, 128.48, 126.73, 84.38, 68.31, 59.82, 32.85, 31.54, 28.14; IR (neat) 2111, 1814, 1727 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{16}H_{21}N_4O_3$ (M − H$^+$) 317.1614, found 317.1588.

General Procedure for the Synthesis of Differentiated Dipeptides. To the *N1*-Boc-β-lactam and glycine methyl ester hydrochloride (2.5 equiv) suspended in dry DMF under Ar was added diisopropylethylamine (2.5 equiv) followed by sodium azide (10−15 mol %). The reaction was stirred at room temperature until judged complete by TLC and then diluted with EtOAc (40 mL). The solution was then washed with water (3×) and brine, dried over Na_2SO_4, filtered, and evaporated. The residue was then filtered through a plug of silica to give the title compounds.

(±)-(*R,R*)-Methylglycine-2-azido-3-N-(*tert*-butoxycarbonyl)tetradecamide (9a). Filtration through a plug of silica (4:1 hexanes/EtOAc) gave the title compound as a white solid (84%). An analytical sample was obtained by recrystallization from diethyl ether/hexanes: mp 75.5−77.0 °C; ^{1}H NMR ($CDCl_3$) δ 6.85 (m, 1H), 4.78 (d, J = 8.40 Hz, 1H), 4.38 (s, 1H), 4.13 (dd, J_1 = 18.00 Hz, J_2 = 5.70 Hz, 2H), 3.99 (dd, J_1 = 18.15 Hz, J_2 = 4.65 Hz, 1H), 3.77 (s, 2H) 1.46 (br s, 12H), 1.25 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 170.04, 167.87, 155.58, 80.09, 66.74, 53.56, 52.70, 41.22, 32.11, 30.20, 29.82, 29.74, 29.68, 29.53, 29.46, 28.53, 26.27, 22.88, 14.31; IR (KBr) 3331, 2107, 1752, 1690, 1658 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{22}H_{42}N_5O_5$ (M − H$^+$) 456.3186 found 456.3200.

(±)-(*R,R*)-Methylglycine-2-azido-3-N-(*tert*-butoxycarbonyl)-3-cyclopropylpropamide (9b). Filtration through a plug of silica (2:1 hexanes/EtOAc) provided the title compound as a white solid (96%): mp 108−109 °C; ^{1}H NMR ($CDCl_3$) δ 6.99 (br s, 1H), 5.07 (m, 1H), 4.55 (br s, 1H), 4.08 (m, 2H), 3.78 (s, 3H), 3.39 (m, 1H), 1.46 (s, 9H), 1.01 (m, 1H), 0.51 (m, 2H), 0.34 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.08, 167.73, 155.31, 80.15, 66.14, 58.50, 52.65, 41.19, 11.59, 4.68, 2.88; IR (film) 3332, 2112, 1754, 1694, 1673 cm^{-1}; FAB−HRMS *m/z* calcd for $C_{14}H_{25}N_5O_5$ (M − H$^+$) 342.1777 found 342.1769.

(±)-(*R,R*)-Methylglycine-2-azido-3-*N*-(*tert*-butoxycarbonyl)-3-(cyclohexyl)propamide (9c). Filtration through a plug of silica (2:1 hexanes/EtOAc) provided the title compound as a glass (93%): ^{1}H NMR ($CDCl_3$) δ 6.90 (br s, 1H), 5.10 (d, J = 9.90 Hz, 1H), 4.28 (m, 1H), 4.14 (dd, J_1 = 18.30 Hz, J_2 = 5.70 Hz, 1H), 3.99 (dd, J_1 = 18.30 Hz, J_2 = 5.40 Hz, 1H), 3.87 (m, 1H), 3.78 (s, 3H), 1.70 (m, 5H), 1.49 (m, 10H), 1.16 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 170.05, 168.38, 156.10, 79.82, 64.35, 57.79, 52.72, 41.25, 30.70, 28.97, 28.53, 28.14, 26.31, 26.05; IR (KBr) 3325, 2106, 1757, 1694, 1661 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{17}H_{30}N_5O_5$ (M − H$^+$) 384.2247, found 384.2233.

(±)-(*R,R*)-Methylglycine-2-azido-3-*N*-(*tert*-butoxycarbonyl)-4,4-dimethylpentamide (9d). Flash chromatography (gradient 7:1 to 4:1 hexanes/EtOAc) produced the title compound as a white solid (81%): mp 105−106 °C; ^{1}H NMR ($CDCl_3$) δ 7.02 (s, 1H), 5.58 (d, J = 9.60 Hz, 1H), 4.05 (m, 2H), 3.84 (m, 1H), 3.77 (s, 3H), 1.43 (s, 9H), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.86, 169.07, 156.20, 79.74, 62.77, 61.62, 52.70, 41.27, 35.16, 28.51, 26.97; IR (KBr) 2102, 1756, 1715 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{15}H_{28}N_5O_5$ (M − H$^+$) 358.2090, found 358.2085.

(±)-(*R,R*)-Methylglycine-2-azido-3-(1-adamantyl)-3-*N*-(*tert*-butoxycarbonyl)propamide (9e). Filtration through a plug of silica (2:1 hexanes/EtOAc) provided the title compound as a white solid (72%): mp 139−140 °C; ^{1}H NMR ($CDCl_3$) δ 6.82 (m, 1H), 5.45 (d, J = 10.50 Hz, 1H), 4.11 (dd, J_1 = 18.00 Hz, J_2 = 5.70 Hz, 1H), 4.11 (dd, J_1 = 19.05 Hz, J_2 = 4.65 Hz, 1H), 3.78 (s, 3H), 3.70 (dd, J_1 = 10.50 Hz, J_2 = 3.00 Hz, 1H), 2.00 (as, 3H), 1.63 (m, 12H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.82, 169.04, 156.29, 79.72, 77.43, 62.42, 61.20, 52.76, 41.31, 38.94, 36.87, 28.57, 28.41; IR (KBr) 3360, 3294, 2112, 1756, 1684, 1657 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{21}H_{33}N_5O_5$ (M − H$^+$) 436.2560, found 436.2555.

(±)-(*R,R*)-Methylglycine-2-azido-3-*N*-(*tert*-butoxycarbonyl)-5-phenylpentamide (9f). Filtration through a plug of silica (1:1 hexanes/EtOAc) provided the title compound as a white solid (86%): mp 111−112 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 2H), 7.18 (m, 3H), 6.82 (m, 1H), 4.90 (d, J = 8.40 Hz, 1H), 4.33 (as, 1H), 4.18 (m, 1H), 4.00 (dd, J_1 = 18.15 Hz, J_2 = 5.25 Hz, 1H), 3.96 (dd, J_1 = 18.60 Hz, J_2 = 4.50 Hz, 1H), 3.74 (s, 3H), 2.72 (m, 1H), 2.00 (m, 1H), 1.78 (m, 2H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.98, 167.76, 155.54, 141.24, 128.68, 128.60, 126.31, 80.21, 66.66, 53.32, 52.71, 41.24, 32.62, 32.15, 28.53; IR (neat) 3373, 3279, 2095, 1751, 1687, 1665 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{19}H_{28}N_5O_5$ (M − H$^+$) 406.2090, found 406.2077.

8-(*N*-Benzyloxycarbonyl)-3-oxomethyloctanoate (11). To carboxylic acid **10** (7.917 g, 29.8 mmol) dissolved in dry THF cooled to 0 °C with an ice bath under an argon atmosphere was added CDI (5.83 g, 36.0 mmol) in several portions over 10 min. The resulting solution was stirred at 0 °C for 1 h. In a separate flask, monomethyl malonate (3.892 g, 32.9 mmol) was dissolved in dry THF under argon and cooled to −78 °C. To this solution was added slowly a heptane solution of Bu_2Mg (16.6 mL, 1.0M, 33.2 mmol). After several minutes the −78 °C bath was removed and the resulting slurry stirred at room temperature for 1 h. After this time, the acyl imidazole solution was added via cannula to the magnesium salt and the resulting mixture stirred at room temperature for 23 h.

The reaction was concentrated and the residue dissolved in EtOAc (100 mL), washed with 1.2 M HCl (4 × 25 mL) and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by using a Biotage Flash 40 system (32−63 μm silica cartridge, gradient 10:1 to 1:1 hexanes/EtOAc) to give the title compound as a clear oil (6.626 g, 65%). Spectral data for this material have been reported previously.[37]

8-(*N*-Benzyloxycarbonyl)-3-hydroxymethyloctanoate (12). To an ice-cooled solution of **11** (6.299 g, 19.6 mmol) in dry methanol (190 mL), under argon, was added $NaBH_4$ (488 mg, 13.2 mmol) in two portions over 1 h. Upon complete consumption of the starting material, as determined by TLC analysis, the reaction was quenched by the addition of acetone. After several minutes, the solvent was evaporated on the rotary evaporator and the residue redissolved in EtOAc (125 mL). The resulting solution was washed with saturated $NaHCO_3$ (3 × 25 mL) and brine, dried over $MgSO_4$, filtered, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (2:1 hexanes/EtOAc) to give the title compound as a white solid (6.048 g, 95%): mp 41.5−43.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5H), 5.46 (br s, 1H), 5.05 (m, 2H), 3.97 (br s, 1H), 3.64 (s, 3H), 3.51 (s, 1H), 3.12 (m, 2H), 2.41 (m, 2H), 1.34 (br m, 8H); ^{13}C NMR ($CDCl_3$) δ 172.94, 156.43, 136.56, 128.22, 127.75, 67.59, 66.18, 51.42, 41.32, 40.66, 36.32, 29.60, 26.30, 24.87; IR (KBr) 3311, 1718, 1690 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{17}H_{26}NO_5$ (M − H$^+$) 324.1811, found 324.1817.

***N*-Acetoxy-4-(1-(5-*N*-benzyloxycarbonyl)pentyl)-2-azetidinone (14).** To alcohol **12** (3.48 g, 10.8 mmol) and KOH (0.606 g, 10.8 mmol) in dry MeOH (25 mL) was added by gravity filtration a solution of NH_2OH in MeOH (generated by combining 3.8 g of NH_2OH·HCl and 1.5 g of KOH in 25 mL of dry MeOH at 0 °C and stirring for 30 min). This addition was repeated two more times over a period of 3 days. When the reaction was judged complete by TLC analysis, the solution was concentrated, the resulting white solid was suspended in CH_2Cl_2 (25 mL), and acetic anhydride (2.1 mL, 22.3 mmol) was added. After 19 h, the reaction was judged complete when it no longer showed a color change with $FeCl_3$ solution. The reaction mixture was then poured into a separatory funnel containing EtOAc (200 mL) and 5% Na_2CO_3 solution (200 mL). The layers were separated, and the organic phase was extracted with 10% Na_2CO_3 solution (5 × 100 mL). All of the aqueous extracts were then combined, acidified to pH 6.5−7.5 with HCl solution, and then extracted with EtOAc (5 × 100 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a white solid (3.041 g). The white solid was then recrystallized from Et_2O/hexanes to give hydroxamate **13** as white crystals (1.905 g, 48% from **12**). This material was then used for the next reaction.

To an ice-bath-cooled solution of hydroxamate **13** (0.992 g, 2.71 mmol) and PPh_3 (0.888 g, 3.39 mmol) in dry acetonitrile (24 mL) under Ar was added a solution of DBAD (0.753 g, 3.27 mmol) in acetonitrile (4 mL) via syringe over 5 min. After 40 min, the reaction was warmed to room temperature. After 3 h and 20 min, the reaction was concentrated and the residue purified by flash chromatography (2:1 hexanes/EtOAc) to give the title compound as a light yellow oil (607 mg, 73%): ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5H), 5.09 (s, 2H), 4.89 (br s, 1H), 4.01 (m, 1H), 3.18 (m, 2H), 2.98 (dd, J_1 = 13.95 Hz, J_2 = 5.55 Hz, 1H), 2.49 (dd, J_1 = 13.80 Hz, J_2 = 2.40 Hz, 1H), 2.15 (s, 3H), 1.80 (m, 1H), 1.56 (m, 3H), 1.36 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 168.09, 164.45, 156.56, 136.75, 128.63, 128.22, 66.70, 59.33, 40.93, 38.29, 32.67, 29.92, 26.55, 25.37, 18.13; IR (neat) 3339, 1806, 1770, 1715 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{18}H_{25}N_2O_5$ (M − H$^+$) 349.1764, found 349.1799.s

(±)-*trans*-3-Azido-4-(1-(5-*N*-benzyloxycarbonyl)pentyl)-2-azetidinone (15). To an ice-bath-cooled solution of β-lactam **14** (687 mg, 1.972 mmol) dissolved in dry MeOH (20 mL) was added K_2CO_3 (330 mg, 2.39 mmol). After 10 min, the reaction was poured into a separatory funnel (100 mL), and 0.10 M HCl was added until the aqueous layer tested acidic by litmus test. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The organic solutions were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to a yellow oil. The oil was then dissolved in dry acetonitrile (18 mL) under argon. The resulting solution was cooled to 0 °C, and TsN_3 (360 μL, 2.35 mmol) was added followed by Hunig's base (1.5 mL, 8.59 mmol). After 30 min, $TMSN_3$ (540 μL, 4.03 mmol) was added and the ice bath removed. After 3.5 days, the reaction mixture was concentrated and the residue purified by flash chromatography (gradient 2:1 to 1:1 hexanes/EtOAc) to give the title compound as an orange oil (48%): ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 5H), 5.32 (m, 1H), 5.06 (s, 1H), 4.09 (as, 1H), 3.41 (m, 1H), 3.15 (m, 2H), 1.57 (m, 2H), 1.48 (m, 2H), 1.31 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 164.83, 156.71, 136.69, 128.63, 128.23, 128.15, 69.62, 66.74, 56.86, 40.70, 33.37, 29.87, 26.15, 25.57; IR (neat) 3306, 2108, 1770, 1694 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{16}H_{22}N_5O_3$ (M − H$^+$) 332.1723, found 332.1708.

(±)-*trans*-3-Azido-1-(*tert*-butoxycarbonyl)-4-(1-(5-*N*-benzyloxycarbonyl)pentyl)-2-azetidinone (16). Compound **16** was prepared according to the same general procedure as compounds **8a**−**f**. Flash chromatography (gradient 7:1 to 2:1 hexanes/EtOAc) produced the title compound as a clear oil (44%): ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5H), 5.09 (s, 2H), 4.86 (m, 1H), 4.22 (m, 1H), 3.74 (m, 1H), 3.20 (m, 2H), 2.15 (m, 1H), 1.52 (m, 12H), 1.38 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 161.69, 156.58, 147.91, 136.77, 128.67, 128.26, 84.32, 68.18, 66.77, 60.04, 40.86, 31.11, 29.95, 28.14, 26.43, 24.72; IR (neat) 3379, 2110, 1812, 1720 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{21}H_{30}N_5O_5$ (M − H$^+$) 432.2247, found 432.2227.

(±)-(*R,R*)-Methylglycine-2-azido-8-*N*-(benzyloxycarbonyl)-3-*N*-(*tert*-butoxycarbonyl)octamide (17). Compound **17** was prepared according to the same general procedure as compounds **9a**−**f**. Flash chromatography (gradient 2:1 to 1:1 hexanes/EtOAc) produced the title compound as a white solid (78%): mp 97−98 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H), 7.03 (m, 1H), 5.08 (m, 2H), 4.96 (m, 2H), 4.32 (s, 1H), 4.10 (m, 2H), 3.97 (dd, J_1 = 18.45 Hz, J_2 = 5.25 Hz, 1H), 3.74 (s, 3H), 3.16 (m, 2H), 1.45 (m, 14H), 1.30 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 170.05, 167.97, 156.62, 155.61, 136.83, 128.63, 128.19, 80.06, 66.69, 66.32, 53.18, 52.62, 41.13, 40.87, 29.98, 29.70, 28.47, 26.22, 25.53; IR (neat) 3333, 2110, 1749, 1694 cm^{-1}; FAB-HRMS *m/z* calcd for $C_{24}H_{37}N_4O_3$ (M − H$^+$) 521.2723, found 521.2739.

***N*$^\epsilon$-(Benzyloxycarbonyl)-*N*$^\alpha$-(*tert*-butoxycarbonyl)-L-lysyl-L-valyl(2-azido-3-decyl-β-alanyl)glycine Methyl Ester (22).** Optically enriched dipeptide **9a** (189 mg, 0.415 mmol) was dissolved in Et_2O (5 mL), and HCl gas was bubbled through the resulting solution for 30 min. The desired HCl salt was observed as a white precipitate during this addition. To the resulting suspension were added CH_2Cl_2 (30 mL) and saturated $NaHCO_3$ (20 mL). The layers were separated, and the aqueous solution extracted with CH_2Cl_2 (2 × 25 mL). All of the organics were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated, and the free amine product was dried under vacuum. The free amine was then dissolved in dry THF (8 mL) under argon, and this solution was added via cannula to a round-bottom flask containing HOAT (166 mg, 1.22 mmol), EDAC·HCl (214 mg, 1.22 mmol), and dipeptide **23** (503 mg, 1.05 mmol) under argon. The resulting mixture was stirred at room temperature for 54 h and then concentrated. The residue was dissolved in CH_2Cl_2 (30 mL), washed with 10% citric acid solution (2 × 10 mL), saturated $NaHCO_3$ (2 × 10 mL), and brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (gradient 40:1 to 20:1 CH_2Cl_2/^{i}PrOH) to give the title compound as a white solid (180 mg, 54%): mp 152−154 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (m, 1H), 7.30 (m, 5H), 6.72 (m, 1H), 5.67 (m, 1H), 5.26

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(m, 1H), 5.14 (m, 1H), 5.04 (m, 1H), 4.37 (m, 2H), 4.16 (m, 1H), 3.79 (m, 2H), 3.77 (s, 3H), 3.27 (m, 1H), 3.16 (m, 1H), 2.06 (m, 1H), 1.63 (m, 2H), 1.4 (m, 15H), 1.24 (m, 18H), 0.96 (m, 6H), 0.89 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 173.04, 172.09, 171.81, 168.15, 156.92, 155.69, 136.99, 128.68, 128.39, 128.26, 80.21, 76.81, 67.71, 66.74, 60.83, 54.30, 52.83, 51.15, 41.47, 40.35, 32.46, 32.07, 30.90, 29.79 (br), 29.68, 29.63, 29.56, 29.49, 29.32, 28.49, 26.58, 22.84, 22.06, 19.51, 19.04, 14.26; IR (KBr) 3283, 2117, 1750, 1692, 1647 cm^{-1}; FAB-HRMS *m*/*z* calcd for $C_{41}H_{69}N_8O_9$ (M − H$^+$) 817.5188, found 817.5201.

***N*$^\epsilon$-(Benzyloxycarbonyl)-L-lysyl-L-valyl(2-azido-3-decyl-*β*-alanyl)glycine Trifluroracetyl Salt (25).** To ester **22** (180 mg, 0.220 mmol) dissolved in an ice-cooled solvent system composed of 2 mL of THF, 3 mL of MeOH, and 0.4 mL of water was added LiOH (9 mg, 0.376 mmol), and the resulting mixture was stirred for 30 min, after which time the ice bath was removed. After 3 h, the reaction was diluted with EtOAc and water. The aqueous layer was acidified with 10% citric acid solution to pH ≈ 2.5, and then the layers were separated. The aqueous phase was extracted with EtOAc (4×). All of the EtOAc fractions were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated, and the residue was purified by flash chromatography (10:1 $CHCl_3$/MeOH + 1% AcOH) to give the carboxylic acid as a white solid (217 mg, 82%). This material was placed in a dry round-bottom flask and the vessel purged with argon. To the solid was added, via cannula, TFA which had been precooled to 0 °C. The resulting solution was stirred at 0 °C for 30 min, then diluted with toluene, and concentrated under reduced pressure to a white solid. This material was purified by flash chromatography (gradient 10:1 to 5:1$CHCl_3$/MeOH) to provide the title compound as a white solid (169 mg, 94%): ^{1}H NMR (CD_3OD) δ 7.31 (m, 5H), 5.09 (m, 2H), 4.32 (m, 1H), 4.12 (m, 2H), 3.91 (m, 2H), 3.73 (m, 1H), 3.16 (m, 2H), 2.06 (m, 1H), 1.84 (m, 2H), 1.51 (m, 6H), 1.27 (s, 18H), 1.00 (d, J = 6.6 Hz, 6H), 0.89 (m, 3H); ^{13}C NMR (CD_3OD) δ 177.68, 173.53, 171.56, 170.08, 163.37 (q, J = 34.74 Hz), 159.06, 138.46, 129.59, 129.10, 128.91, 118.17 (q, J = 292.13 Hz), 68.35, 67.60, 61.47, 54.55, 52.54, 44.78, 41.33, 33.11, 32.94, 31.47, 31.04, 30.78, 30.71, 30.58, 30.47, 30.28, 27.37, 23.77, 23.04, 19.95, 19.18, 14.51; IR (film) 2111, 1648 (br) cm^{-1}.

***cyclo*-*N*$^\epsilon$-(Benzyloxycarbonyl)-L-lysyl-L-valyl(2-azido-3-decyl-*β*-alanyl)glycine Tetrapeptide (21).** To an ice-cooled slurry of salt **25** (185 mg, 0.226 mmol) and $NaHCO_3$ (172 mg, 2.05 mmol) in dry DMF (23 mL) under argon was added DPPA (74 μL, 0.343 mmol). After 1 h, the flask was transferred to a 5 °C cooler, and the mixture was stirred for 47 h. During this period, a white precipitate formed. The reaction mixture was warmed to room temperature, stirred for 5 h, and then recooled to 0 °C. The reaction was then diluted with water to roughly twice its original volume and allowed to stand for several minutes. The precipitate was then collected by vacuum filtration and dried under vacuum to give the title compound as an off-white solid (131 mg, 85%), which was used as received for the next reaction.

***cyclo*-L-Lysyl-L-valyl(2-amino-3-decyl-*β*-alanyl)glycine Tetrapeptide Dihydrochloride (20).** Cyclic peptide **21** (131 mg, 0191 mmol) was dissolved in a 1:1 mixture of CH_2Cl_2/formic acid (4 mL), and 10 wt % Pd−C was added (230 mg). The flask was charged with hydrogen (1 atm) and the heterogeneous mixture stirred for 60 h. The mixture was then filtered through a cotton plug with acetic acid to remove the catalyst. The filtrate was concentrated and purified by reversed-phase flash chromatography (C_{18} column, gradient 1:1 to 4:1 CH_3CN/0.1% HCl_{aq}). All of the ninhydrin positive fractions were collected, and the acetonitrile was removed at low temperature on the rotary evaporator (the use of low temperature was required to avoid foaming). The remaining aqueous solution was then lyophilized to give 97 mg of a white solid which was a mixture of the fully deprotected and Cbz-protected material. This solid was then suspended in CH_2Cl_2 (25 mL) and cooled to 0 °C. To this cooled suspension was added 33% HBr/AcOH (25 mL, 90% technical grade, Acros), and the solution became homogeneous. The ice bath was removed and the orange solution stirred at room temperature for 1 h, then diluted with chloroform, and concentrated on the rotary evaporator to give an orange solid. This solid was loaded onto a reversed-phase flash chromatography C_{18} column and washed with several column volumes of water to remove some colored impurities. The column was then washed with a 1:1 CH_3CN/0.1% HCl_{aq} solution until the fractions collected were no longer ninhydrin positive. All of the ninhydrin positive fractions were then collected, the acetontrile was removed at low temperature, and the resulting aqueous solution was lyophilized to give 93 mg of a white solid. This material was dissolved in water (14 mL), and individual aliquots (2.0 mL) were purified by preparative HPLC using a Prep LC 25 mm module loaded with one Prepak cartridge packed with Prep Nova-Pak HR C18 silica (6 μm, 60 Å, 25 × 100 mm) with a flow rate of 3.0 mL/min. Absorbance was measured at 210 nm. Fractions which tested ninhydrin positive and which had retention times between 10 and 20 min were pooled together. Acetonitrile was removed by rotary evaporator and the remaining aqueous solution lyophilized to provide the desired salt **20** as a flocculent white solid (52 mg, 45%). Heteroatom protons were determined by addition of one drop of D_2O to a DMSO-d_6 solution of the HCl salt and observance of the disappearance of those peaks over several hours by ^{1}H NMR: ^{1}H NMR (CD_3SOCD_3, 500 MHz) δ 9.37 (d, J = 4.50 Hz, NH, 1H), 9.27 (m, NH, 1H), 8.10 (br s, NH, 3H), 7.89 (m, NH, 3H), 6.69 (d, J = 9.50 Hz, NH, 1H), 6.24 (d, J = 9.00 Hz, NH, 1H), 4.22 (dd, J = 9.25, 4.75 Hz, 1H), 4.16 (m, 2H), 3.85 (m, 1H), 3.82 (as, 1H), 3.55 (dd, J = 14.25, 5.75 Hz, 1H), 2.76 (as, 2H), 2.23 (m, 1H), 1.68 (m, 4H), 1.59 (m, 2H), 1.43 (m, 2H), 1.23 (s, 18H), 0.83 (m, 9H); ^{13}C NMR (CD_3SOCD_3, 125 MHz) δ 172.68, 172.27, 171.52, 167.97, 57.36, 56.60, 55.34, 51.37, 42.96, 38.35, 31.30, 31.12, 29.61, 29.04, 29.02, 28.86, 28.72, 28.40, 26.36, 25.82, 22.70, 22.09, 19.96, 17.20, 13.96; IR (KBr) 3436, 1653 cm^{-1}; FAB-HRMS *m*/*z* calcd for $C_{27}H_{52}N_6O_4$ (M − H$^+$) 525.4128, found 525.4153.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **7**−**9**, **12**, **14**−**17**, **20**, **22**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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