Acylnitrene Route to Vicinal Amino Alcohols. Application to the Synthesis of (−)-Bestatin and Analogues

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Bestatin, valinoctin A, and microginin are naturally occurring small peptides containing a nonproteinogenic α-hydroxy-*β*-amino acid at the N-terminus of the peptide chain. We report here our development of a general method for the synthesis of α-hydroxy-*β*-amino acids and exemplify this with a synthesis of (−)-bestatin and analogues. Our synthesis utilizes an intramolecular acylnitrene-mediated aziridination to generate a key bicyclic aziridine in excellent yield and stereoselectivity. This bicyclic aziridine can be opened with a number of organometallic reagents to provide a series of substituted oxazolidinones. The oxazolidinones are readily converted to bestatin and a series of bestatin analogues. As part of this approach, we have developed a new method for the synthesis of azidoformates. We have also demonstrated that oxazolidinones can be selectively hydrolyzed in the presence of peptide bonds. This acylnitrene route to bestatin should prove useful for the synthesis of a variety of analogues of bestatin as well as other α-hydroxy-*β*-amino acids and their corresponding peptides.

Introduction

Bestatin,[1] valinoctin A,[2] and microginin[3] are naturally occurring small peptides containing a nonproteinogenic α-hydroxy-*β*-amino acid at the N-terminus of the peptide chain. The compounds are representative of a class of compounds which numbers over 30 different peptides with widely varying biological activities. Bestatin, for example, is an aminopeptidase inhibitor that exhibits immunostimulatory activity as well as cytotoxic activity.[4] Bestatin is used clinically as an anticancer agent. Valinoctin A is a potent inhibitor of farnesyl transferase and may be promising as an anticancer agent.[2] Microginin is an ACE inhibitor and could be useful as an antihypertensive agent.[5]

While the peptides have some structural differences, a core structure of all of these compounds can be drawn as compound **4** (Figure 1). In this core structure, R is a variety of aliphatic or aryl groups and aa can be a single amino acid residue or a small peptide chain. Given the wide variations in biological activity and the corresponding variations in the carbon chain of the N-terminal α-hydroxy-*β*-amino acid, a general synthetic route to α-hydroxy-*β*-amino acids is desirable. A synthesis of α-hydroxy-*β*-amino acids that both installs R and forms the peptide bond late in the synthesis will be a general route to any and all of these compounds.

Our acylnitrene aziridination/aziridine opening method is a versatile method for the synthesis of this group of molecules.[6] As shown in Scheme 1, an allylic alcohol is converted to an azidoformate (**6**) and thermally cyclized to a bicyclic aziridine (**7**). This step transfers the stereochemical information of the allylic alcohol to the aziridine. The aziridine can then be readily opened with both carbon and heteroatom nucleophiles to provide oxazolidinone **8**. The oxazolidinone can be hydrolyzed by a number of methods to produce the amino alcohol **9**. We report here our development of a general method for the synthesis of these nonproteogenic peptides and exemplify this with a synthesis of (−)-bestatin and analogues.

Results and Discussion

A retrosynthesis of the dipeptides is shown in Scheme 2. The core structure (**4**) should be readily obtained from the corresponding α-hydroxy-*β*-amino acid **10**. Compound **10** can be prepared from bicyclic aziridine **11** through aziridine opening and oxazolidinone hydrolysis. The

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† Telephone: 614-292-5499. E-mail: bergmeier.1@osu.edu.

(1) Isolation and structure determination of bestatin: (a) Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1976**, *29*, 97. (b) Nakamura, H.; Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 102. For some recent syntheses of bestatin, see: (c) De, A.; Basak, P.; Iqbal, J. *Tetrahedron Lett.* **1997**, *38*, 8383 and references therein. (d) Fuji, K.; Kawabata, T.; Diryu, Y.; Sugiura, Y. *Heterocycles* **1996**, *42*, 701. (e) Koseki, K.; Ebata, T.; Matsushita, H. *Biosci. Biotechnol. Biochem.* **1996**, *60*, 534. (f) Palomo, C.; Aizpurua, J. M.; Cuevas, C. *J. Chem. Soc., Chem. Commun.* **1994**, 1957. (g) Herranz, R.; Castro-Pichel, J.; Garcia-Lopez, M. T.; Gomez-Monterrey, I.; Perez, C.; Vinulesa, S. *Arch. Pharm. (Weinheim, Ger.)* **1993**, *326*, 395. (h) Matsuda, F.; Matsumoto, T.; Ohsaki, M.; Ito, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 360. (i) Norman, B. H.; Morris, M. L. *Tetrahedron Lett.* **1992**, *33*, 6803. (j) Matsuda, F.; Matsumoto, T.; Ohsaki, M.; Ito, Y.; Terashima, S. *Chem. Lett.* **1990**, 723. (k) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **1989**, *54*, 4235.

(2) Sekizawa, R.; Iinuma, H.; Muraoka, Y.; Naganawa, H.; Kinoshita, N.; Nakamura, H.; Hamada, M.; Takeuchi, T.; Umezawa, K. *J. Nat. Prod.* **1996**, *59*, 232. (b) Tsuda, M.; Muraoka, Y.; Takeuchi, T. *J. Antibiot.* **1996**, *49*, 1031.

(3) Isolation of microginin: (a) Okino, T.; Matsuda, H.; Murakami, M.; Yamaguchi, K. *Tetrahedron Lett.* **1993**, *34*, 501. For some syntheses of microginin, see: (b) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1994**, *5*, 203. (c) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, *50*, 11303. (d) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1995**, *6*, 165. (e) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1995**, *51*, 12193. (f) Jefford, C. W.; McNulty, J.; Lu, Z. H.; Wang, J. B. *Helv. Chim. Acta* **1996**, *79*, 1203. (g) Tuch, A.; Saniere, M.; Le Merrer, Y.; Depexay, J.-C. *Tetrahedron: Asymmetry* **1996**, *7*, 2901.

(4) Umezawa, H.; Ishizuka, M.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1976**, *29*, 857. (b) Ino, K.; Goto, S.; Nomura, S.; Isobe, K.-I.; Nawa, A.; Okamoto, T.; Tomoda, Y. *Anticancer Res.* **1995**, *15*, 2081.

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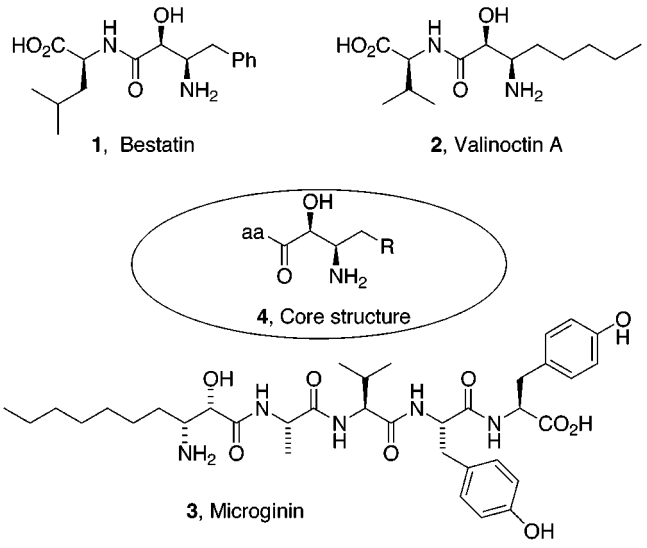
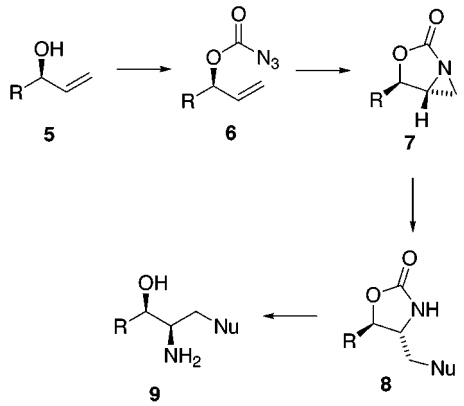
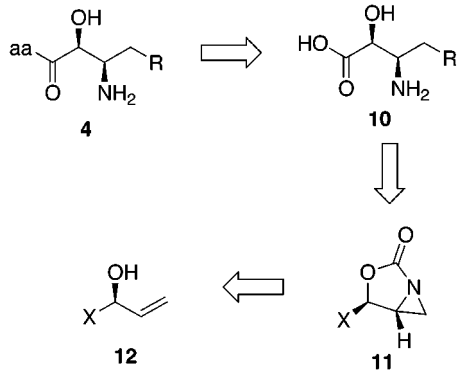


Figure 1.

Scheme 1

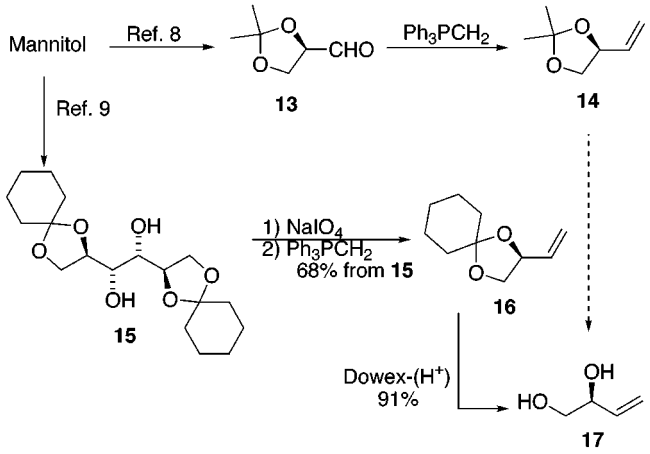


Scheme 2

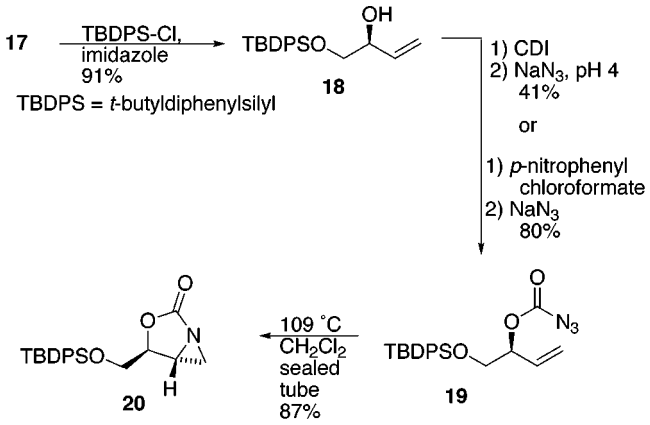


group X will need to be either a carboxylic acid or a CH_2OH group. If X is COOH, then our chiral starting material would be (*R*)- or (*S*)-vinyl glycolic acid. While this is a known compound, its resolution is difficult and it is not easily prepared on a large scale.[7] When X is CH_2OH, compound **12** could be readily derived in optically pure form from glyceraldehyde, a well-known and easily prepared chiral starting material.[8]

Scheme 3



Scheme 4



On the basis of these considerations, glyceraldehyde was used as the source of chirality for this synthesis. We converted mannitol to (*R*)-glyceraldehyde acetonide.[8] As shown in Scheme 3, our plan was to prepare olefin **14** and hydrolyze the acetonide to provide diol **17**. Unfortunately, the olefin **14** was inseparable from the reaction mixture. Attempts to distill this volatile olefin led to mixtures of **14**, THF, and hexane. Attempts to use other solvents for the Wittig reaction or to use the crude olefin in the next reaction were not successful. We then turned to the cyclohexanone ketal **15**.[9] This compound was readily converted to the olefin **16**. Olefin **16** was not as volatile as **14** and could be chromatographically purified. The ketal was readily hydrolyzed with Dowex-(H^+) resin to provide the nonracemic diol **17** in excellent yield.

As shown in Scheme 4, diol **17** could be selectively monosilylated with *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) (**18**) in good yield. We initially attempted to convert allylic alcohol **18** to the corresponding azidoformate **19** using the procedure of Yuan et al.[10] This procedure uses CDI to make an initial imidazolide which, upon treatment with NaN_3 at pH 4, produces azidoformates in generally excellent yields.[6] The use of **18** under these reaction conditions gave only a 41% yield of azidoformate **19**. We suspect that the neighboring azidoformate (or imidazolide) assists in the acid-catalyzed deprotection of the normally robust silyl ether. We were

(7) Li, R.; Powers, V. M.; Kozarich, J. W.; Kenyon, G. L. *J. Org. Chem.* **1995**, *60*, 3347.

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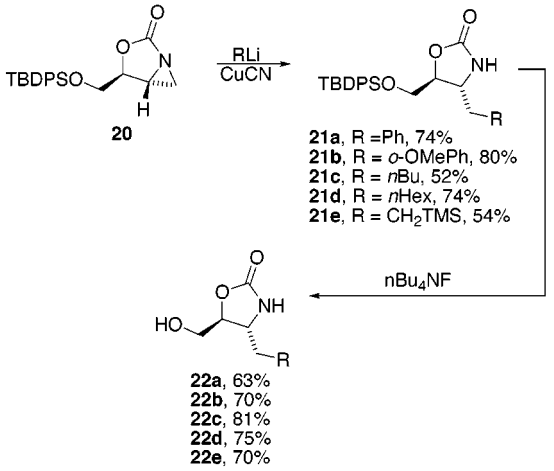
(9) Sugiyama, T.; Sugawara, H.; Watanabe, M.; Yamashita, K. *Agric. Biol. Chem.* **1984**, *48*, 1841.

(10) Yuan, P.; Plourde, R.; Shoemaker, M. R.; Moore, C. L.; Hansen, D. E. *J. Org. Chem.* **1995**, *60*, 5360.

Scheme 5



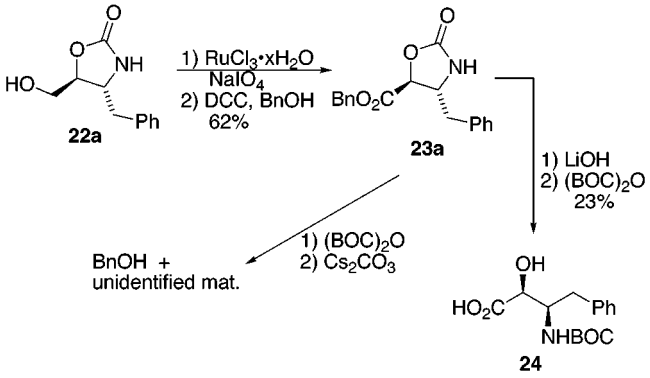
thus forced to develop a new method of azidoformate formation that proceeded under neutral or basic conditions. Treatment of alcohol **18** with *p*-nitrophenyl chloroformate gave the intermediate carbonate in almost quantitative yield. The carbonate could not be purified via chromatography but was simply treated with NaN_3 in DMF to provide excellent yields of azidoformate **19**.

Following our standard protocol, the azidoformate **19** was heated in a sealed tube at 109 °C for 13 h to provide the bicyclic aziridine **20** in good yield. The use of CH_2Cl_2 in a sealed tube has continued to be the optimal method for this transformation. Using other solvents (e.g., toluene, tetrachloroethane) produces products arising from the reaction of the acylnitrene with the solvent.[6,11] ^1H NMR showed the presence of a single bicyclic aziridine. As we have noted previously, these bicyclic aziridines cannot be chromatographically purified but are moderately stable to storage.[12]

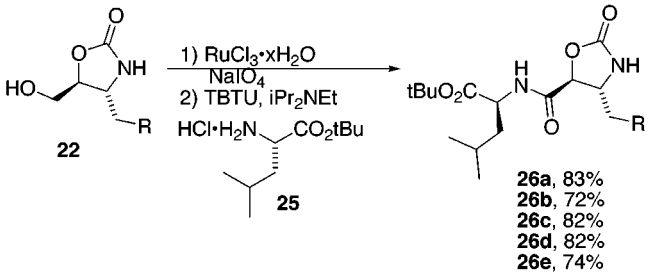
To prepare bestatin, we needed only to open the aziridine with a phenyl anion. To demonstrate the utility of the method for the preparation of analogues, a variety of other organometallic reagents were used as well. As we have previously reported, neither Grignard nor organolithium reagents effectively opened the aziridine ring.[6] Optimum yields are obtained with an organocuprate reagent derived from the organolithium reagent and CuCN. We have used several commercially available organolithium reagents (Scheme 5). These include *n*BuLi, *n*HexLi, Me_3SiCH_2Li, and PhLi. We have also prepared *o*-MeO-PhLi through the ortholithiation[13] of anisole. These organocuprate reagents provided the aziridine opened products **21a**−**21e** in generally good yields. The organolithium reagent $Ph(CH_2)_3Li$ was also prepared[14] and used, but the yield of the aziridine-opened product was very low (15−20%).

With the aziridine ring opened using the desired organocuprate reagent, all that remained was to convert the protected alcohol to a carboxyl group and couple with the appropriate amino acid. The alcohol was deprotected with nBu_4NF to provide alcohols **22a**−**22f** in good yield. Of particular note is alcohol **22e** in which the side chain contains a trimethylsilyl group. This compound gave an excellent yield of **22e** from **21e**.

Scheme 6



Scheme 7



As shown in Scheme 6, oxidation of **22a** directly to the carboxylic acid was accomplished with $RuCl_3{\cdot}xH_2O/NaIO_4$ although in very poor isolated yield (~20%).[15] The coupling of the crude acid with benzyl alcohol using DCC gave an improved yield of the ester **23a**. At this stage we were faced with several options on the conversion of acid **23a** to the dipeptide. Our initial strategy was to directly convert oxazolidinone **23a** to the *N*-BOC-protected α-hydroxy-*β*-amino acid **24**. Our first attempt at this transformation involved an initial hydrolysis of the oxazolidinone followed by in situ protection of the amine with a BOC group. This reaction sequence gave a very low yield of **24**. Believing that milder conditions should improve the yields in this transformation, we next sought to convert **23a** to the *N*-BOC-oxazolidinone and hydrolyze this to **24** using Cs_2CO_3.[16] This hydrolysis only resulted in the cleavage of the *N*-BOC from the oxazolidinone. Use of other reaction conditions (base, temperature, solvent) gave no significant improvement in the yield of **24**. This is not too surprising considering the recent observation that the Cs_2CO_3-mediated hydrolysis of *N*-BOC-oxazolidinone only works well when a carboxyl group is adjacent to the nitrogen of the oxazolidinone ring.[16b]

Faced with these results, we decided to couple the acid to the C-terminal amino acid and then attempt oxazolidinone hydrolysis (Scheme 7). In an attempt to improve the yield, the acid was not purified but was directly coupled to *O*-*t*-BuLeu (**25**) using 2-(1*H*-benzotriazol-1-yl)-

(11) Bergmeier, S. C.; Stanchina, D. M. *Tetrahedron Lett.* **1995**, *36*, 4533.

(12) The stability of the bicyclic aziridines is dependent upon their purity and the identity of the aziridine. Aziridine **20** for example begins to decompose after 5−7 days in the freezer. However, a related bicyclic aziridine in which the TBDPS group is replaced with a trityl group is stable at room temperature for several weeks.

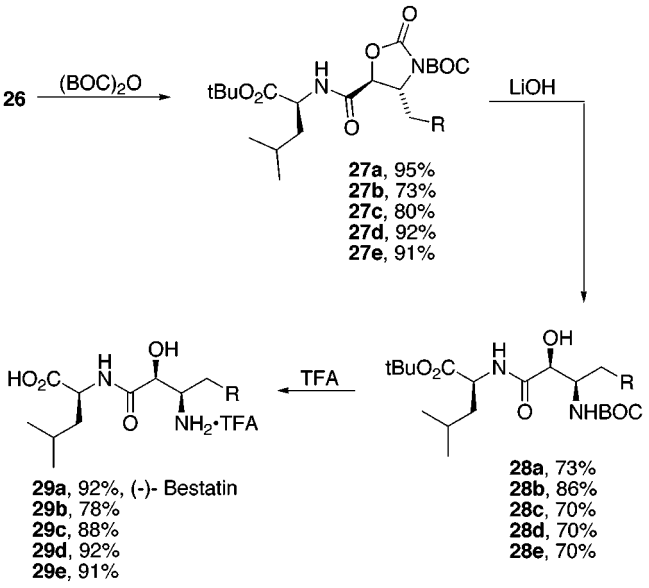
(13) (a) Finnegan, R. A.; Altshuld, J. W.; *J. Organomet. Chem.* **1967**, *9*, 193. (b) Shirley, D. A.; Johnson, J. R., Jr.; Hendrix, J. P. *J. Organomet. Chem.* **1968**, *11*, 209.

(14) (a) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404. (b) Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406.

(15) Carlsen, P. J.; Katsuki, T.; Marin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(16) (a) Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *36*, 4185. (b) DiGiovanni, M. C.; Misiti, D.; Villani, C.; Zappia, G. *Tetrahedron: Asymmetry* **1996**, *8*, 2277.

Scheme 8



1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) as the coupling agent.[17] This procedure led to dramatically improved yields of the dipeptide from the alcohol (72−84% over two steps). Apparently our previous attempts at purifying the acid led to lower yields, possibly through loss of the product on the column. Several other coupling agents including DCC and carbonyldiimidazole were examined, but the yields of **26** were significantly lower than with TBTU.

Once the peptide bond had been formed, all that remained was to hydrolyze the oxazolidinone ring to provide the free amino alcohol. We were quite concerned about this step as we were attempting to selectively hydrolyze a carbamate (oxazolidinone ring) in the presence of another carbamate (BOC) and an amide bond. We chose to first activate the oxazolidinone ring by putting a *tert*-butoxycarbonyl group on the nitrogen.[18] This was accomplished by treating **26a**−**26e** with 1.2 equiv of $(BOC)_2O$ to provide **27a**−**27e** in 73−95% yield (Scheme 8) . Again, hydrolysis of **27** with Cs_2CO_3 only yielded the deprotected oxazolidinone **26**. The examination of a variety of bases showed that a selective hydrolysis of the oxazolidinone ring could be accomplished in good yield with LiOH at 0 °C.[19]

With the oxazolidinone ring hydrolyzed, we had in hand a diprotected version of our target dipeptides. The BOC and *t*Bu ester were concurrently removed by treatment with TFA to provide the TFA salt. This provided (−)-bestatin as well as a series of aryl and alkyl analogues.

In conclusion we have developed and applied a novel method for the synthesis of α-hydroxy-*β*-amino acids to the synthesis of (−)-bestatin and analogues. This new method installs a variety of alkyl and aryl groups on the carbon chain of bestatin. As part of this approach, we have developed a new method for the synthesis of azidoformates. We have also demonstrated that oxazolidinones can be selectively hydrolyzed in the presence of peptide bonds. This acylnitrene route to bestatin should prove useful for the synthesis of a variety of analogues of bestatin as well as other α-hydroxy-*β*-amino acids and their corresponding peptides.

(17) We substituted HBTU used in this procedure with TBTU. This was the only modification made to the reported procedure: Dourtoglow, V.; Gross, B. *Synthesis* **1984**, 572.

(18) Burk, M. J.; Allen, J. G. *J. Org. Chem.* **1997**, *62*, 7054.

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Experimental Section[20]

2,3-*O*-Cyclohexylidene-D-glyceraldehyde. To a solution of 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol[9] (27.39 g, 80.0 mmol) in 60% aqueous CH_3CN (120 mL) cooled to 5 °C was added $NaIO_4$ (34.56 g, 160 mmol) in small portions at room temperature over 40 min. After the addition was complete, the solution stirred at room temperature for 1 h and filtered. The filtrate was mixed with water and extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL) and brine (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting syrup was distilled under vacuum and used immediately in the next reaction. Analytical data matched that reported for the known compound.[9]

(2*S*)-1,2-*O*-Cyclohexylidenebut-3-ene-1,2-diol (16). To a suspension of methyltriphenylphosphonium iodide (38.80 g, 96.0 mmol) in THF (296 mL) at 0 °C was added *n*BuLi (42.0 mL of a 2.3 M solution in hexanes, 96.0 mmol). The reaction mixture was stirred for 15 min at 0 °C and was then warmed to room temperature where stirring continued for 45 min. The solution was then recooled to −78 °C, and a solution of 2,3-*O*-cyclohexylidene-D-glyceraldehyde (13.61 g, 80.0 mmol) in THF (99 mL) was added. The reaction mixture was stirred at −78 °C for 1 h and was then warmed to room temperature where stirring continued for 16 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl, extracted with EtOAc (3 × 100 mL), washed with brine (2 × 100 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed (hexanes) to give 9.12 g of **16** (68%) from **15** as a colorless oil: $[\alpha]_D$ + 4.0° (*c* 1.7, EtOAc); ^{1}H NMR δ 5.75 (m, 1H), 5.28 (d, 1H, J = 21.0 Hz), 5.15 (d, 1H, J = 10.2 Hz), 4.45 (q, 1H, J = 5.1 Hz), 4.05 (dd, 1H, J = 5.1, 7.8 Hz), 3.55 (t, 1H, J = 7.6 Hz), 1.70−1.20 (m, 10H); ^{13}C NMR δ 136.4, 117.3, 109.9, 76.9, 68.9, 36.2, 35.4, 25.1, 23.9, 23.8; IR (neat) 3084, 1647, 1440 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.00; H, 9.95.

(2*S*)-3-Butene-1,2-diol (17). To a solution of **16** (4.50 g, 26.74 mmol) in MeOH (60 mL) was added Dowex 50X8-200 acidic ion-exchange resin (30.0 g) at room temperature. The reaction mixture stirred for 23 h at room temperature and was then filtered and washed with MeOH. The filtrate was concentrated and chromatographed (70% EtOAc/hexanes) to afford 1.91 g of **17** (91% taking into account 500 mg of recovered **18**) as a colorless oil: $[\alpha]_D$ −28.4° (*c* 5.0, EtOAc); ^{1}H NMR δ 5.80 (m, 1H), 5.30 (d, 1H, J = 21.0 Hz), 5.18 (d, 1H, J = 10.0 Hz), 4.20 (m, 1H), 3.60 (m, 1H), 3.40 (m, 1H); ^{13}C NMR

(20) General Methods. Thin-layer chromatography (TLC) was performed on Whatman precoated silica gel F_{254} aluminum foils. Visualization was accomplished with UV light and/or phosphomolybdic acid solution followed by heating. Purification of the reaction products was carried out by flash column chromatography using glass column dry packed with silica gel (230−400 mesh ASTM) according to the method of Still.[21] ^{1}H NMR spectra referenced to TMS were recorded using a Bruker AF 250 or Bruker AF 270 model spectrometer. Data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quarte,t and m = multiplet), integration, coupling constant (Hz). Unless otherwise noted all spectra were recorded in $CDCl_3$. All reactions were carried out under an atmosphere of nitrogen unless specified otherwise. Glassware was flame dried under a flow of nitrogen. Tetrahydrofuran and diethyl ether were distilled over sodium/benzophenone ketyl immediately prior to use. Dichloromethane was distilled over CaH_2 prior to use. Organolithium reagents used for the reactions were purchased from Aldrich Chemical Co. or prepared via the method of Negishi.[14b] **CAUTION: Azides are potentially explosive, especially upon heating. While we have observed no problems with stability or formation of the azidoformates, care should be exercised.**

(21) Still, C. W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *50*, 2923.

δ 136.8, 116.5, 73.3, 66.2; IR (neat) 3355, 1647, 1426 cm^{-1}. Anal. Calcd for $C_4H_8O_2$: C, 54.53; H, 9.15. Found: C, 54.21; H, 9.47.

(2*S*)-1-*O*-(*tert*-Butyldiphenylsilyl)-3-butene-1,2-diol (18). To a solution of **17** (920 mg, 10.44 mmol) and imidazole (1.56 g, 22.92 mmol) in DMF (10.4 mL) at 0 °C was added a solution TBDPSCl (3.15 g, 11.46 mmol) in DMF (2.5 mL). The reaction mixture was warmed to room temperature where stirring was continued for 22 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc (3 × 30 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed (2% EtOAc/hexanes) to afford 3.12 g of **18** (91%) as a colorless oil: $[\alpha]_D$ −18.4° (*c* 2.6, EtOAc); ^{1}H NMR δ 7.75 (m, 4H), 7.45 (m, 6H), 5.85 (m, 1H), 5.38 (d, 1H, J = 22.0 Hz), 5.22 (d, 1H, J = 10.0 Hz), 4.30 (m, 1H), 3.75 (m, 1H), 3.65 (m, 1H), 2.80 (d, 1H, J = 4.2 Hz), 1.15 (s, 9H); ^{13}C NMR δ 136.8, 135.5, 135.4, 134.8, 133.1, 133.0, 129.8, 129.4, 127.7, 127.6, 116.2, 72.9, 67.7, 26.8, 19.2; IR (neat) 3430, 1890, 1590, 1472 cm^{-1}. Anal. Calcd for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03. Found: C, 73.39; H, 8.03.

(2*S*)-1-*O*-(*tert*-Butyldiphenylsilyl)-2-[(azidocarbonyl)-oxy]-3-butene (19). CAUTION: Azides are potentially explosive, especially upon heating. While we have observed no problems with stability or formation of the azidoformates, care should be exercised. To a solution of **18** (7.50 g, 22.97 mmol) in benzene (73 mL) and pyridine (5.46 g, 69.03 mmol) at room temperature was added *p*-nitrophenyl chloroformate (9.26 g, 45.94 mmol). After stirring for 2.5 h at room temperature, the reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ (2 × 70 mL) and brine (2 × 70 mL), dried ($MgSO_4$), filtered, and concentrated to give a yellow solid. This crude material was dissolved in DMF (106 mL), and NaN_3 (14.93 g, 229.7 mmol) was added at room temperature. The reaction mixture was then warmed to 35 °C where stirring continued for 19 h. The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl, washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed (hexanes) to give 7.26 g of **19** (80%) as a colorless oil: $[\alpha]_D$ −20.8° (*c* 1.7, EtOAc); ^{1}H NMR δ 7.75 (m, 4H), 7.45 (m, 6H), 5.85 (m, 1H), 5.35 (m, 3H), 3.80 (d, 2H, J = 6.1 Hz), 1.15 (s, 9H); ^{13}C NMR δ 156.8, 135.6, 135.5, 133.1, 133.0, 131.9, 129.8, 129.7, 127.7, 119.3, 79.7, 65.0, 26.9, 19.2; IR (neat) 2133, 1733 cm^{-1}. Anal. Calcd for $C_{21}H_{25}N_3O_3Si$: C, 63.77; H, 6.37; N, 10.62. Found: C, 63.85; H, 6.42; N, 10.34.

(4*R*,5*S*)-5-(*tert*-Butyldiphenylsilyloxymethyl)-1-oxa-3-azabicyclo[3.1.0]hexan-2-one (20). A solution of **19** (400 mg, 1.91 mmol) and BHT (42 mg, 0.19 mmol) in CH_2Cl_2 (30 mL) was placed in an ACE Glass Model 8648B 100 mL capacity pressure tube. **CAUTION: Reactions conducted in pressure tubes are potentially explosive and should be carried out behind a protective shield. While we have observed no problems, care should be excercised.** The reaction vessel was cooled to −78 °C, evacuated, and sealed. The reaction mixture was then warmed to 109 °C in an oil bath for 13 h. It was then cooled to room temperature and concentrated to afford 300 mg (87%) of **20**. An ^{1}H NMR analysis of the crude material using the signal for the aromatic protons (6.85 ppm) of BHT as an internal standard was used to determine the yield of the reaction. This material was used directly in the following organocuprate reactions without any further purification:[6] ^{1}H NMR δ 7.65 (m, 4 H), 7.35 (m, 6H), 4.60 (m, 1H), 3.80 (m, 2H), 3.10 (t, 1H, J = 3.8 Hz), 2.50 (d, 1H, J = 4.6 Hz), 2.15 (d, 1H, J = 4.6 Hz), 1.10 (s, 9H); ^{13}C NMR δ 166.8, 135.6, 135.5, 132.7, 130.0, 130.0, 129.6, 127.9, 78.0, 64.3, 39.7, 26.7, 19.2; IR (neat) 1793 cm^{-1}.

(4*R*,5*S*)-5-Benzyl-4-(*tert*-butyldiphenylsilyloxymethyl)-1,3-oxazolidin-2-one (21a). To a suspension of copper(I) cyanide (170 mg, 1.91 mmol) in THF (6.7 mL) cooled to −78 °C was added PhLi (2.20 mL of a 1.8 M solution in cyclohexane/Et_2O, 3.82 mmol). The reaction mixture was warmed to −40 °C and stirred for 40 min. The solution was then cooled to −78 °C, and **20** (700 mg, 1.91 mmol) in THF (2.6 mL) was added and stirring continued at −78 °C for 20 min. The reaction mixture was slowly warmed to room temperature by removing the ice bath. After 5 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl, extracted with EtOAc (3 × 40 mL), washed with brine (2 × 40 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed (22% EtOAc/hexanes) to afford 630 mg of **21a** (74%) as a yellow oil: $[\alpha]_D$ +58.6° (*c* 0.7, EtOAc); ^{1}H NMR δ 7.60 (m, 6H), 7.40 (m, 9H), 4.40 (m, 1H), 4.05 (m, 1H), 3.80 (m, 2H), 3.55 (d, 2H, J = 7.5 Hz), 2.85 (m, 2H), 1.05 (s, 9H); ^{13}C NMR δ 158.5, 135.6, 135.5, 132.7, 130.0, 129.6, 127.9, 114.6, 79.5, 64.1, 55.2, 45.9, 26.7, 19.2; HRMS calcd for $C_{27}H_{31}NO_3Si$ 445.6255, found 445.6258.

(4*R*,5*S*)-5-[(2-Methoxyphenyl)methyl]-4-(*tert*-butyldiphenylsilyloxymethyl)-1,3-oxazolidin-2-one (21b). Anisole (1.76 g, 16.24 mmol) in Et_2O (19.3 mL) was heated to reflux, and *n*BuLi (6.81 mL of a 2.5 M solution in hexane, 17.02 mmol) was added dropwise over 15 min. Refluxing continued for 22.5 h. The reaction mixture was then cooled to room temperature for use in the next reaction. To a suspension of CuCN (470 mg, 5.28 mmol) in Et_2O (18.2 mL) cooled to −78 °C was added the previously prepared organolithium reagent. The reaction mixture was then warmed to −40 °C and stirred for 45 min. The solution was recooled to −78 °C, and **20** (1.94 g, 5.28 mmol) in Et_2O (8.6 mL) was added and stirring continued at −78 °C for 20 min. The reaction was warmed to room temperature by removing the ice bath, and stirring was continued for 4 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (2 × 30 mL). The organic layer was washed with brine (2 × 30 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed (25% EtOAc/hexanes) to afford 1.99 g of **21b** (80%): $[\alpha]_D$ +17.2° (*c* 0.4, EtOAc); ^{1}H NMR δ 7.65 (m, 5H), 7.40 (m, 5H), 7.20 (m, 2H), 7.05 (m, 1H), 6.90 (m, 2H), 4.35 (m, 1H), 4.15 (m, 1H), 3.75 (m, 5H), 3.55 (dd, 1H, J = 2.7, 8.1 Hz), 2.90 (m, 2H), 1.05 (s, 9H); ^{13}C NMR δ 157.3, 135.6, 135.5, 135.4, 131.1, 129.8, 128.5, 127.8, 127.7, 124.3, 120.7, 110.5, 107.0, 81.4, 63.7, 55.1, 53.7, 36.6, 26.7, 19.1; HRMS calcd for $C_{28}H_{32}NO_4Si$ 474.6500, found 474.6497.

(4*R*,5*S*)-5-Pentyl-4-(*tert*-butyldiphenylsilyloxymethyl)-1,3-oxazolidin-2-one (21c). To a suspension of copper(I) cyanide (570 mg, 6.39 mmol) in THF (22.5 mL) cooled to −78 °C was added *n*-BuLi (5.12 mL of a 2.5 M solution in hexanes, 12.79 mmol). The reaction mixture was warmed to −40 °C and stirred for 40 min. The solution was then cooled to −78 °C, and **20** (2.35 g, 6.39 mmol) in THF (10 mL) was added and stirring continued at −78 °C for 20 min. The reaction mixture was slowly warmed to room temperature by removing the ice bath. After 5 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl, extracted with EtOAc (3 × 40 mL), washed with brine (2 × 40 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed (20% EtOAc/hexanes) to afford 1.41 of **21c** (52%) as a yellow oil: $[\alpha]_D$ +7.4° (*c* 0.4, EtOAc); ^{1}H NMR δ 7.65 (m, 5H), 7.40 (m, 5H), 4.20 (m, 1H), 3.75 (m, 3 H), 1.50 (m, 2H), 1.30 (m, 6H), 1.05 (s, 9H), 0.85 (t, 3H, J = 5.3 Hz); ^{13}C δ 159.3, 135.6, 135.5, 132.8, 129.7, 127.8, 81.8, 64.3, 54.5, 35.6, 31.4, 26.7, 24.7, 22.3, 19.2, 13.8; HRMS calcd for $C_{25}H_{35}NO_3Si$ 425.2388, found 425.2396.

(4*R*,5*S*)-5-Heptyl-4-(*tert*-butyldiphenylsilyloxymethyl)-1,3-oxazolidin-2-one (21d). To a suspension of CuCN (180 mg, 2.03 mmol) in THF (7.1 mL) cooled to −78 °C was added *n*-hexyllithium (2.03 mL of a 2.0 M solution in hexane, 4.06 mmol). The reaction mixture was then warmed to −40 °C and stirred for 45 min. After the solution was cooled to −78 °C, **20** (746 mg, 2.03 mmol) in THF (3.1 mL) was added and stirring continued at −78 °C for 20 min. The reaction was warmed to room temperature by removing the ice bath, and stirring was continued for 5 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (2 × 30 mL). The organic layer was washed with brine (2 × 30 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed (15% EtOAc/hexanes) to afford 680 mg of **21d** (74%) as a pale yellow oil: $[\alpha]_D$ + 13.7° (*c* 0.7, EtOAc); ^{1}H NMR δ 7.65 (m, 4H), 7.40 (m, 6H), 4.20 (m, 1H), 3.75 (m, 3H), 1.55 (m, 2H), 1.30 (s, 13H), 1.05 (s, 9H); ^{13}C NMR δ 159.3, 135.6, 135.5, 133.0, 132.9, 132.8, 129.9, 127.8, 81.8, 64.3, 54.5, 35.6, 31.6, 29.2, 28.9, 26.7, 25.1, 22.5, 19.2, 14.0, 13.9; HRMS calcd for $C_{27}H_{39}NO_3Si$ 453.2701, found 453.2698.

(4*R*,5*S*)-5-(2-(Trimethylsilyl)ethyl)-4-(*tert*-butyldiphenylsilyloxymethyl)-1,3-oxazolidin-2-one (21e). To a suspension of CuCN (340 mg, 3.78 mmol) in THF (13.8 mL) cooled to −78 °C was added methyltrimethylsilyllithium (7.56 mL of a 1.0 M solution in pentane, 7.56 mmol). The reaction mixture was then warmed to −40 °C and stirred for 45 min. After the solution was cooled to −78 °C, **20** (1.39 g, 3.78 mmol) in THF (4.8 mL) was added and stirring continued at −78 °C for 20 min. The reaction was warmed to room temperature by removing the ice bath, and stirring was continued for 5 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (2 × 30 mL). The organic layer was washed with brine (2 × 30 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed (20% EtOAc/hexanes) to afford 930 mg of **21e** (54%) as a yellow oil: $[\alpha]_D$ +8.6° (*c* 0.5, EtOAc); ^{1}H NMR δ 7.65 (m, 5H), 7.40 (m, 5H), 4.20 (m, 1H), 3.70 (m, 4H), 1.50 (m, 2H), 1.05 (s, 9H), 0.00 (s, 9H); ^{13}C NMR δ 158.6, 135.6, 135.5, 133.1, 132.8, 129.9, 127.8, 81.4, 64.5, 56.7, 30.8, 26.6, 19.3, 11.6, −1.9. Anal. Calcd for $C_{25}H_{37}NO_3Si_2$: C, 65.89; H, 8.18; N, 3.07. Found: C, 65.62; H, 7.91; N, 2.96.

(4*R*,5*S*)-5-Benzyl-4-(hydroxymethyl)-1,3-oxazolidin-2-one (22a). To a solution of **21a** (1.75 g, 3.93 mmol) in THF (7.6 mL) at 0 °C was added nBu$_4$NF (4.34 mL of a 1.0 M solution in THF, 4.34 mmol) dropwise over 5 min. The reaction mixture stirred at 0 °C for 3 h. It was then diluted with EtOAc, washed with water (3 × 40 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed (75% EtOAc/hexanes) to give 660 mg of **22a** (81%): $[\alpha]_D$ +71.6° (*c* 1.1, EtOAc); ^{1}H NMR δ 7.20 (m, 5H), 5.92 (bs, 1H), 4.30 (m, 1H), 3.95 (m, 1H), 3.70 (dd, 1H, J = 3.1, 11.7 Hz), 3.40 (dd, 1H, J = 4.7, 11.7 Hz), 2.85 (m, 2H); ^{13}C NMR δ 158.7, 135.8, 129.1, 128.9, 127.2, 81.9, 62.7, 54.9, 41.5; IR (neat) 3580, 1754 cm^{-1}; HRMS calcd for $C_{11}H_{13}NO_3$ 207.2247, found 207.2237.

(4*R*,5*S*)-5-(2-Methoxyphenyl)-4-(hydroxymethyl)-1,3-oxazolidin-2-one (22b). The alcohol **22b** was prepared from **21b** (5 mmol) by the same method used for **22a** which after chromatography (75% EtOAc/hexanes) gave 0.83 g of **22b** (70%) as a yellow oil: $[\alpha]_D$ +7.4° (*c* 0.7, EtOAc); ^{1}H NMR δ 7.25 (m, 2H), 7.10 (m, 1H), 6.85 (m, 2H), 4.35 (m, 1H), 3.95 (m, 1H), 3.85 (s, 3H), 3.70 (m, 1H), 3.50 (m, 1H), 2.90 (m, 2H); ^{13}C NMR δ 157.4, 131.0, 128.7, 124.1, 120.8, 110.6, 109.7, 105.3, 82.0, 62.9, 55.3, 53.4, 36.3; IR (CCl_4) 3415, 1753, 1216 cm^{-1}; HRMS calcd for $C_{12}H_{15}NO_4$ 237.1001, found 237.0986.

(4*R*,5*S*)-5-Pentyl-4-(hydroxymethyl)-1,3-oxazolidin-2-one (22c). The alcohol **22c** was prepared from **21c** (3.3 mmol) by the same method used for **22a** which after chromatography (65% EtOAc/hexanes) gave 0.50 g of **22c** (81%) as a yellow oil: $[\alpha]_D$ +104.8° (*c* 0.1, EtOAc); ^{1}H NMR δ 4.20 (m, 1H), 3.70 (m, 4H), 1.50 (m, 2H), 1.30 (s, 6H), 0.80 (t, 3H, J = 5.3 Hz); ^{13}C NMR δ 159.5, 82.7, 62.8, 53.8, 35.3, 31.4, 24.6, 22.3; IR (neat) 3460, 1752, 1215 cm^{-1}. Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.49; H, 9.06; N, 7.33.

(4*R*,5*S*)-5-Heptyl-4-(hydroxymethyl)-1,3-oxazolidin-2-one (22d). The alcohol **22d** was prepared from **21d** (3.3 mmol) by the same method used for **22a** which after chromatography (65% EtOAc/hexanes) gave 0.53 g of **22d** (75%) as a colorless solid, mp 65−67 °C: $[\alpha]_D$ +50.1° (*c* 1.1, EtOAc); ^{1}H NMR δ 4.20 (m, 1H), 3.70 (m, 4H), 1.50 (m, 2H), 1.20 (m, 8H), 0.80 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 159.5, 82.7, 62.8, 53.6, 35.3, 31.6, 29.2, 28.2, 25.0, 22.5, 13.6; IR (neat) 3290, 1752, 1215 cm^{-1}. Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.52; H, 9.85; N, 6.44.

(4*R*,5*S*)-5-(2-(Trimethylsilyl)ethyl)-4-(hydroxymethyl)-1,3-oxazolidin-2-one (22e). The alcohol **22e** was prepared from **21e** (1.7 mmol) by the same method used for **22a** which after chromatography (65% EtOAc/hexanes) gave 0.26 g of **22e** (70%) as a colorless solid, mp 116−118 °C: $[\alpha]_D$ +5.1° (*c* 0.5, EtOAc); ^{1}H NMR δ 4.20 (m, 1H), 3.80 (m, 1H), 3.60 (m, 2H), 3.30 (t, 1H, J = 6.1 Hz), 1.50 (m, 1H), 0.45 (m, 2H), 0.00 (s, 9H); ^{13}C NMR δ 159.2, 82.2, 63.3, 56.2, 29.7, 11.4, −1.9; IR (CCl_4) 3460, 1755, 1422, 1215 cm^{-1}. Anal. Calcd for $C_9H_{19}NO_3$-Si: C, 49.74; H, 8.81; N, 6.44. Found: C, 50.00; H, 8.48; N, 6.26.

Phenyl Oxazolidinone Dipeptide 26a. To a solution of **22a** (77 mg, 0.37 mmol) in CCl_4 (1 mL), CH_3CN (1 mL), and water (1.5 mL) was added $NaIO_4$ (235 mg, 1.1 mmol) followed by $RuCl_3 \cdot xH_2O$ (1.7 mg, 0.008 mmol). The reaction mixture was stirred vigorously for 15.5 h. The upper aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting crude material was diluted with EtOAc (30 mL), and a saturated aqueous solution of K_2CO_3 was added. This solution was extracted with EtOAc (2 × 30 mL). The aqueous layer was acidified with 6 M HCl to pH 1 and extracted with EtOAc (4 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford 70 mg of the acid (85%) as a colorless oil. The acid was not subjected to further purification and was used immediately in the next reaction: ^{1}H NMR δ 9.40 (bs, 1H), 7.20 (m, 5H), 4.65 (d, 1H, J = 4.6 Hz), 4.15 (m, 1H), 3.00 (dd, 1H, J = 13.7, 25.1 Hz), 2.90 (dd, 1H, J = 13.7, 25.1 Hz); ^{13}C NMR δ 171.3, 158.9, 135.0, 129.3, 129.0, 127.4, 60.5, 57.2, 41.2, 14.1; IR (neat) 3030, 1755, 1417 cm^{-1}. To a solution of H-Leu-OtBu·HCl (71 mg, 0.32 mmol) in CH_3CN (2.35 mL) at 0 °C was added iPr$_2$NEt (82 mg, 0.63 mmol). The resulting mixture was added to a solution of the acid (70 mg, 0.32 mmol) and TBTU (100 mg, 0.32 mmol) in CH_3CN (0.77 mL). The reaction mixture stirred at room temperature for 21.5 h, concentrated, and chromatographed (15% EtOAc/hexanes) to afford 100 mg of **26a** (71% from **22a**) as a colorless solid, mp 128−130 °C: $[\alpha]_D$ +31.6° (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 7.25 (m, 5H), 4.60 (d, 1H, J = 5.0 Hz), 4.45 (m, 1H), 4.25 (m, 1H), 3.20 (dd, 1H, J = 3.9, 13.5 Hz), 2.80 (dd, 1H, J = 9.4, 8.0 Hz), 1.60 (m, 3H), 1.40 (s, 9H), 0.90 (m, 6H); ^{13}C NMR δ 171.0, 168.2, 156.0, 136.8, 135.7, 129.2, 129.1, 127.5, 82.3, 78.3, 57.3, 51.4, 42.2, 41.5, 28.0, 25.0, 22.7, 22.0; IR (CCl_4) 1770, 1731, 1682, 1216 cm^{-1}. Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.60; H, 7.74; N, 7.17. Found: C, 64.86; H, 7.42; N, 6.95.

Methoxyphenyl Oxazolidinone Dipeptide 26b. The dipeptide **26b** was prepared by the same method used to prepare **26a**. The carboxylic acid, which was used immediately in the next reaction, was prepared on a 0.97 mmol scale in 82% crude yield from **22b**: ^{1}H NMR δ 10.10 (s, 1H), 7.25 (m, 2H), 7.10 (m, 1H), 6.85 (m, 2H), 4.70 (d, 1H, J = 4.4 Hz), 4.20 (m, 1H), 3.70 (s, 3H), 2.90 (m, 2H); ^{13}C NMR δ 171.5, 158.9, 131.2, 128.9, 123.5, 120.8, 110.8, 77.5, 56.3, 55.3, 36.1; IR (CCl_4) 3305, 1755, 1752, 1246 cm^{-1}. The coupling reaction was done on a 0.80 mmol scale which after chromatography (25% EtOAc/hexanes) gave 241 mg of **26b** (59% from **22b**) as a yellow oil: $[\alpha]_D$ +32.2° (*c* 0.3, EtOAc); ^{1}H NMR δ 7.25 (m, 2H), 7.15 (m, 1H), 6.85 (m, 2H), 4.70 (m, 1H), 4.50 (m, 1H), 4.25 (m, 1H), 3.85 (m, 5H), 3.20 (dd, 1H, J = 12.5, 25.0 Hz), 2.90 (m, 1H), 1.60 (m, 12H), 0.90 (m, 6H); ^{13}C NMR δ 174.3, 171.0, 168.4, 157.6, 131.3, 128.9, 124.0, 121.0, 110.9, 82.1, 78.5, 56.3, 55.5, 51.3, 41.5, 36.5, 28.1, 25.0, 22.7, 22.0; HRMS-FAB (M + NH_4^+) calcd for $C_{22}H_{32}N_2O_6 - NH_4$ 438.2606, found 438.2610.

Butyl Oxazolidinone Dipeptide 26c. The dipeptide **26c** was prepared by the same method used to prepare **26a**. The carboxylic acid, which was used immediately in the next reaction, was prepared on a 0.37 mmol scale in 81% crude yield from **22c**: ^{1}H NMR δ 10.20 (s, 1H), 4.60 (d, 1H, J = 4.7 Hz), 3.90 (m, 1H), 1.70 (m, 2H), 1.30 (m, 6H), 0.85 (t, 3H, J = 5.0 Hz); ^{13}C NMR δ 176.6, 158.5, 56.5, 35.7, 31.2, 24.4, 22.3, 20.6, 13.8; IR (CCl_4) 3278, 1759, 1216, 1418 cm^{-1}. The coupling reaction was done on a 0.30 mmol scale which after chromatography (20% EtOAc/hexanes) gave 91 mg of **26c** (66% from **22c**) as a colorless oil: $[\alpha]_D$ +37.2° (*c* 0.2, EtOAc); ^{1}H NMR δ 4.45 (m, 2H), 3.85 (m, 1H), 1.70−0.09 (m, 14H); ^{13}C NMR δ 171.0, 168.6, 157.4, 82.1, 79.0, 56.3, 51.4, 41.4, 36.1, 31.3, 27.9, 25.0, 24.6, 22.7, 22.3, 22.0, 13.8. Anal. Calcd for $C_{19}H_{34}N_2O_5$: C, 61.59; H, 9.25; N, 7.56. Found: C, 61.56; H, 8.99; N, 7.32.

Hexyl Oxazolidinone Dipeptide 26d. The dipeptide **26d** was prepared by the same method used to prepare **26a**. The carboxylic acid, which was used immediately in the next reaction, was prepared on a 0.46 mmol scale in 100% crude yield from **22d**: ^{1}H NMR δ 10.70 (s, 1H), 4.60 (d, 1H, J = 4.9 Hz), 4.10 (m, 1H), 3.90 (m, 1H), 1.60 (m, 2H), 1.25 (9H), 0.80 (m, 3H); ^{13}C NMR δ 171.6, 159.5, 77.8, 60.5, 56.5, 35.6, 31.6, 29.0, 28.9, 24.7, 22.5, 20.9, 14.0, 13.9; IR (CCl_4) 3300, 1759, 1418, 1230 cm^{-1}. The coupling reaction was done on a 0.46

mmol scale which after chromatography (25% EtOAc/hexanes) gave 150 mg of **26d** (82% from **22d**) as a colorless oil: $[\alpha]_D$ +31.4° (*c* 0.4, EtOAc); ^{1}H NMR δ 4.45 (m, 2H), 3.85 (m, 1H), 1.80−1.15 (m, 12H), 0.90 (m, 9H); ^{13}C NMR δ 171.0, 168.6, 157.3, 79.0, 77.5, 56.3, 51.4, 41.4, 36.1, 31.6, 29.1, 28.9, 27.9, 25.0, 22.7, 22.5, 22.0, 13.9; IR (neat) 1768, 1765, 1751, 1215 cm^{-1}. Anal. Calcd for $C_{21}H_{38}N_2O_5$: C, 63.29; H, 9.61; N, 7.03. Found: C, 63.23; H, 9.32; N, 6.90.

Trimethylsilylmethyl Oxazolidinone Dipeptide 26e. The dipeptide **26e** was prepared by the same method used to prepare **26a**. The carboxylic acid, which was used immediately in the next reaction, was prepared on a 0.97 mmol scale in 82% crude yield from **22e**: ^{1}H NMR δ 11.40 (s, 1H), 4.60 (d, 1H, J = 4.2 Hz), 3.85 (m, 1H), 1.60 (m, 2H), 0.50 (m, 2H), 0.00 (s, 9H); ^{13}C NMR δ 171.9, 159.6, 77.5, 60.6, 58.7, 30.1, 20.9, 14.0, 10.9, −1.98; IR (CCl_4) 3023, 1755, 1418, 1250 cm^{-1}. The coupling reaction was done on a 0.79 mmol scale which after chromatography (15% EtOAc/hexanes) gave 237 mg of **26e** (61% from **22e**) as a colorless oil: $[\alpha]_D$ +4.5° (*c* 0.5, EtOAc); ^{1}H NMR δ 4.45 (m, 2H), 3.80 (m, 1H), 1.50 (m, 12H), 0.85 (m, 6H), 0.50 (m, 2H), −0.05 (s, 9H); ^{13}C NMR δ 171.1, 168.7, 157.6, 82.1, 78.5, 58.6, 51.2, 41.3, 30.6, 27.9, 24.9, 22.7, 21.9, 11.2, −1.9; HRMS-FAB (M + NH_4^+) calcd for $C_{19}H_{36}N_2O_5Si$ − NH_4 418.2739, found 418.2727.

Boc Phenyl Dipeptide 27a. To a solution of **26a** (60 mg, 0.15 mmol) and DMAP (13 mg, 0.11 mmol) in THF (0.85 mL) at 0 °C was added Boc_2O (36 mg, 0.165 mmol). The reaction mixture was warmed to room temperature by removing the ice bath. Stirring continued at room temperature for 21.5 h. The reaction mixture was diluted with EtOAc (25 mL), washed with brine (3 × 25 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed (15% EtOAc/hexanes) to afford 70 mg of **27a** (95%) as a colorless solid, mp 133−135 °C: $[\alpha]_D$ −7.7° (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 7.25 (m, 5H), 4.75 (m, 1H), 4.50 (d, 1H, J = 2.2 Hz), 4.40 (m, 1H), 3.20 (dd, 1H, J = 13.9 25.0 Hz), 3.05 (m, 1H), 1.60 (m, 3H), 1.55 (s, 9H), 1.40 (s, 9H), 0.90 (m, 6H); ^{13}C NMR δ 170.8, 167.6, 150.1, 134.2, 129.5, 129.0, 127.6, 84.5, 82.3, 73.8, 58.8, 51.6, 41.3, 38.6, 27.9, 25.0, 22.6, 22.1; IR (CCl_4) 1823, 1731, 1686, 1524, 1370, 1216 cm^{-1}. Anal. Calcd for $C_{26}H_{38}N_2O_7$: C, 63.65; H, 7.81; N, 5.71. Found: C, 63.49; H, 7.85; N, 5.51.

Boc Methoxyphenyl Dipeptide 27b. The dipeptide **27b** was prepared from **26b** (0.66 mmol) by the same method used to prepare **27a** which after chromatography (15% EtOAc/hexanes) gave 251 mg of **27b** (73%) as a yellow solid, mp 95−97 °C: $[\alpha]_D$ +12.5° (*c* 0.1, EtOAc); ^{1}H NMR δ 7.25 (m, 2H), 7.10 (m, 1H), 6.85 (m, 2H), 4.80 (m, 1H), 4.60 (d, 1H, J = 2.1 Hz), 4.40 (m, 1H), 3.80 (s, 3H), 3.15 (m, 2H), 1.60−1.25 (m, 22H), 0.85 (m, 6H); ^{13}C NMR δ 176.5, 170.9, 168.0, 157.9, 150.4, 148.6, 131.6, 129.0, 122.9, 120.9, 110.9, 84.0, 82.2, 74.2, 58.5, 55.4, 51.6, 41.4, 33.4, 27.9, 25.1, 22.6, 22.1. Anal. Calcd for $C_{27}H_{40}N_2O_8$: C, 62.29; H, 7.74; N, 5.38. Found: C, 62.24; H, 7.73; N, 5.15.

Boc Butyl Dipeptide 27c. The dipeptide **27c** was prepared from **26c** (1.0 mmol) by the same method used to prepare **27a** which after chromatography (10% EtOAc/hexanes) gave 377 mg of **27c** (80%) as a colorless solid, mp 133−135 °C: $[\alpha]_D$ +13.3° (*c* 0.1, EtOAc); ^{1}H NMR δ 4.45 (m, 3H), 1.80−1.55 (m, 13 H), 1.40 (s, 9 H), 1.35 (s, 9 H), 1.25 (m, 2 H), 0.85 (m, 6H); ^{13}C NMR δ 170.9, 168.0, 150.4, 148.6, 84.3, 82.3, 77.5, 77.0, 58.6, 51.7, 41.4, 33.3, 31.3, 28.0, 25.1, 23.4, 22.6, 22.1 13.8. Anal. Calcd for $C_{24}H_{42}N_2O_7$: C, 61.25; H, 8.99; N, 5.95. Found: C, 61.45; H, 8.92; N, 5.84.

Boc Hexyl Dipeptide 27d. The dipeptide **27d** was prepared from **26d** (0.25 mmol) by the same method used to prepare **27a** which after chromatography (10% EtOAc/hexanes) gave 115 mg of **27d** (92%) as colorless plates, mp 135−137 °C: $[\alpha]_D$ −14.4° (*c* 0.1, EtOAc); ^{1}H NMR δ 4.40 (m, 4H), 1.90−1.70 (m, 4 H), 1.70−1.05 (m, 26H), 0.85 (m, 6H); ^{13}C NMR δ 170.9, 168.0, 150.1, 148.6, 84.3, 82.3, 75.1, 58.6, 51.6, 41.4, 33.3, 31.6, 29.1, 29.0, 28.0, 27.9, 25.1, 23.7, 22.6, 22.1, 13.9. Anal. Calcd for $C_{26}H_{46}N_2O_7$: C, 61.63; H, 9.29; N, 5.62. Found: C, 62.81; H, 9.19; N, 5.45.

Boc Trimethylsilylmethyl Dipeptide 27e. The dipeptide **27e** was prepared from **26e** (0.45 mmol) by the same method used to prepare **27a** which after chromatography (5% EtOAc/hexanes) gave 205 mg of **27e** (91%) as a colorless oil: $[\alpha]_D$ +12.5° (*c* 0.3, EtOAc); ^{1}H NMR δ 4.40 (m, 4H), 1.80 (m, 3H), 1.70−1.55 (m, 6 H), 1.55−1.40 (m, 24 H), 0.85 (m, 6H), 0.45 (m, 2H), 0.00 (s, 9H); ^{13}C NMR δ 170.9, 168.1, 150.6, 148.6, 84.2, 82.3, 74.5, 60.3, 51.6, 41.4, 28.0, 27.6, 25.1, 22.6, 22.1, 9.5, −1.9. Anal. Calcd for $C_{24}H_{44}N_2O_7Si$: C, 57.57; H, 8.85; N, 5.59. Found: C, 57.41; H, 8.64; N, 5.20.

Boc Phenyl Amino Alcohol 28a. To a 0.05 M solution of **27a** (80 mg, 0.16 mmol) in 3:1 THF/H_2O (3.29 mL) at 0 °C was added $LiOH\cdot H_2O$ (14 mg, 0.33 mmol). The solution was slowly warmed to room temperature where stirring continued for 21 h. The reaction mixture was extracted with EtOAc (3 × 25 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed (15% → 25% EtOAc/hexanes) to afford 55 mg of **28a** (73%): $[\alpha]_D$ +3.9° (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 7.25 (m, 5H), 4.50 (m, 1H), 4.15 (m, 1H), 3.95 (m, 1H), 3.05 (m, 2H), 1.60 (m, 2H), 1.30 (s, 9H), 1.40 (s, 9H), 0.85 (m, 6H); ^{13}C NMR δ 172.3, 168.2, 158.2, 138.2, 129.3, 128.5, 126.6, 81.9, 80.2, 56.8, 51.2, 41.9, 28.2, 28.0, 24.9, 22.9, 21.9. HRMS-FAB (M + H) calcd for $C_{25}H_{40}N_2O_6$ 465.2966, found 465.2955.

Boc Methoxyphenyl Amino Alcohol 28b. The amino alcohol **28b** was prepared from **27b** (0.19 mmol) by the same method used for the preparation of **28a** which after chromatography (25% EtOAc/hexanes) gave 81 mg of **28b** (86%) as a colorless oil: $[\alpha]_D$ +13.6° (*c* 0.1, EtOAc); ^{1}H NMR δ 7.20 (m, 2H), 6.85 (m, 2H), 5.30 (m, 1H), 5.00 (m, 1H), 4.50 (m, 1H), 4.05 (m, 2H), 3.80 (s, 3H), 3.05 (m, 2H) 1.45 (s, 9H), 1.40 (s, 9H), 0.85 (m, 6H); ^{13}C NMR δ 173.6, 171.9, 157.6, 131.6, 128.0, 126.3, 121.0, 110.5, 81.7, 79.9, 55.5, 51.0, 42.0, 28.2, 28.0, 25.0, 22.9, 21.9; HRMS-FAB (M + H) calcd for $C_{26}H_{42}N_2O_7$ 495.2994, found 495.2974.

Boc Butyl Amino Alcohol 28c. The amino alcohol **28c** was prepared from **27c** (0.74 mmol) by the same method used for the preparation of **28a** which after chromatography (15% EtOAc/hexanes) gave 230 mg of **28c** (70%) as a colorless solid, mp 114−116 °C: $[\alpha]_{546}$ +11.7° (*c* 0.1, EtOAc); ^{1}H NMR δ 5.25 (m, 2H), 4.45 (m, 1H), 4.10 (m, 1H), 3.70 (m, 1H), 1.70−1.50 (m, 6 H), 1.50−1.15 (m, 23 H), 0.85 (m, 9H); ^{13}C NMR δ 171.0, 168.5, 163.4, 82.2, 79.0, 56.7, 54.2, 51.4, 41.8, 36.1, 31.5, 28.3, 28.0, 26.0, 24.9, 22.3, 21.9, 13.9. Anal. Calcd for $C_{23}H_{44}N_2O_6$: C, 62.13; H, 9.97; N, 6.30. Found: C, 62.33; H, 9.81; N, 6.23.

Boc Hexyl Amino Alcohol 28d. The amino alcohol **28d** was prepared from **27d** (0.20 mmol) by the same method used for the preparation of **28a** which after chromatography (15% EtOAc/hexanes) gave 66 mg of **28d** (70%) as a clear oil: $[\alpha]_{546}$ +15.0° (*c* 1.5, EtOAc); ^{1}H NMR δ 5.30 (m, 2H), 4.45 (m, 1H), 4.10 (m, 1H), 3.70 (m, 1H), 1.70−1.50 (m, 9 H), 1.45−1.40 (m, 18 H), 1.40−1.15 (m, 6 H), 0.85 (m, 9H); ^{13}C NMR δ 171.7, 168.5, 157.2, 82.2, 77.4, 56.2, 54.2, 51.3, 41.9, 31.8, 29.3, 29.0, 28.2, 28.0, 26.3, 25.0, 22.8, 22.5, 22.0, 14.0. Anal. Calcd for $C_{25}H_{48}N_2O_6$: C, 63.52; H, 10.23; N, 5.93. Found: C, 63.50; H, 10.14; N, 5.77.

Boc Trimethylsilylmethyl Amino Alcohol 28e. The amino alcohol **28e** was prepared from **27e** (0.36 mmol) by the same method used for the preparation of **28a** which after chromatography (15% EtOAc/hexanes) gave 119 mg of **28e** (70%) as a clear oil: $[\alpha]_D$ +34.2° (*c* 0.3, EtOAc); ^{1}H NMR δ 5.25 (m, 2H), 4.50 (m, 1H), 4.15 (m, 1H), 3.60 (m, 1H), 1.60 (m, 6H), 1.45 (s, 9H), 1.40 (s, 9H), 0.85 (m, 6H), 0.50 (m, 2H), 0.00 (s, 9H); ^{13}C NMR δ 172.5, 171.8, 157.3, 81.9, 79.9, 74.1, 57.1, 51.0, 41.8, 28.3, 28.0, 24.8, 22.9, 21.9, 13.3, −1.8. Anal. Calcd for $C_{23}H_{46}N_2O_6Si$: C, 58.19; H, 9.77; N, 5.90. Found: C, 58.19; H, 9.57; N, 5.67.

(−)-Bestatin (TFA Salt) 29a. A solution of **28a** (30 mg, 0.065 mmol) in TFA (65 μL) was stirred at 0 °C for 10 min. The reaction mixture was then warmed to room temperature where stirring continued for 5.5 h. The reaction was concentrated. The crude solid was then purified by filtering and rinsing with Et_2O to afford 25 mg of **29a** (92%) as a colorless solid, mp 150−152 °C: $[\alpha]_D$ −14.0° (*c* 0.5, 1 N HCl) [lit.[1k] $[\alpha]_D$ −14.3° (*c* 0.5, 1 N HCl)]; ^{1}H and ^{13}C NMR data matched that reported for the known compound.[1k]

Anisole Analogue 29b. The salt **29b** was prepared from **28b** (49 mg, 0.10 mmol) by the same procedure used for the

preparation of **29a** to yield 26 mg of **29b** (78%) as a colorless solid, mp 134−136 °C: $[\alpha]_D$ +88.3° (*c* 0.1, EtOAc); ^{1}H NMR (d_6-DMSO) δ 7.25 (m, 2H), 7.05 (m, 1H), 6.90 (m, 1H), 4.20 (m, 1H), 3.95 (m, 1H), 3.75 (s, 3H), 3.35 (m, 3H), 2.85 (m, 2H), 1.50 (m, 3H), 0.85 (m, 6H); ^{13}C NMR (d_6-DMSO) δ 170.9, 167.8, 157.4, 130.8, 128.4, 123.8, 120.3, 110.9, 94.1, 68.1, 55.2, 50.8, 24.2, 22.5, 21.4; HRMS-FAB (M + H) calcd for $C_{17}H_{26}N_2O_5$ 339.1921, found 339.1919.

Butyl Analogue 29c. The salt **29c** was prepared from **28c** (15 mg, 0.034 mmol) by the same procedure used for the preparation of **29a** to yield 8 mg of **29c** (88%) as a colorless solid, mp 158−160 °C: $[\alpha]_D$ +68.0° (*c* 0.1, $CHCl_3$); ^{1}H NMR (d_6-DMSO) δ 4.25 (m, 1H), 4.05 (m, 1H), 1.70−1.00 (m, 8H), 0.85 (m, 9H); ^{13}C NMR (d_6-DMSO) δ 175.4, 170.9, 69.6, 53.2, 50.2, 30.8, 28.3, 24.2, 22.6, 21.5, 21.3, 13.6; HRMS-FAB (M + H) calcd for $C_{14}H_{28}N_2O_4$ 289.2128, found 289.2112.

Hexyl Analogue 29d. The salt **29d** was prepared from **28d** (127 mg, 0.27 mmol) by the same procedure used for the preparation of **29a** to yield 79 mg of **29d** (92%) as a colorless solid, mp 78−80 °C: $[\alpha]_D$ +25.2° (*c* 0.1, EtOAc); ^{1}H NMR (d_6-DMSO) δ 4.25 (m, 1H), 4.10 (m, 1H), 3.35 (m, 2H), 3.15 (m, 1H), 1.70−1.30 (m, 7 H), 1.30−1.15 (m, 13 H), 1.05 (t, 3H, J = 6.4 Hz), 0.85 (m, 6H); ^{13}C NMR (d_6-DMSO) δ 173.5, 171.1, 94.3, 69.7, 53.4, 50.2, 31.0, 28.7, 28.5, 28.3, 24.7, 24.3, 22.6, 21.9, 21.3, 14.9, 13.6. HRMS-FAB (M+ H) calcd for $C_{16}H_{33}N_2O_4$ 318.4522, found 318.4509.

Trimethylsilylmethyl Analogue 29e. The salt **29e** was prepared from **28e** (66 mg, 0.14 mmol) by the same procedure used for the preparation of **29a** to yield 41 mg of **29e** (91%) as colorless needles, mp 106−108 °C: $[\alpha]_D$ +50.0° (*c* 0.2, EtOAc); ^{1}H NMR (d_6-DMSO) δ 4.25 (m, 1H), 4.10 (m, 1H), 1.50 (m, 6H), 0.85 (m, 6H), 0.60 (m, 1H), 0.55 (m, 1H), 0.00 (s, 9H); ^{13}C NMR (d_6-DMSO) δ 173.6, 171.1, 69.5, 55.9, 50.0, 24.3, 22.8, 22.7, 21.3, 11.6, −1.9; HRMS-FAB (M + H) calcd for $C_{14}H_{30}N_2O_4$-Si 319.2054, found 319.2051.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **16**, **17**, **18**, **19**, **20**, **21a**, **21b**, **21c**, **21d**, **22a**, **22b**, **26b**, **26e**, **28a**, **28b**, **29b**, **29c**, **29d**, and **29e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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