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Short Stereoselective Synthesis of α-Substituted γ-Lactams

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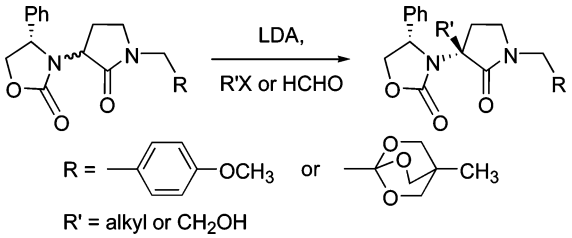
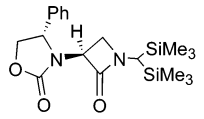


A concise, stereoselective synthesis of α-substituted γ-lactams is reported. γ-Lactam scaffolds **2** and **3**, possessing an Evans' chiral auxiliary and two types of N substituents, were successfully alkylated with different electrophiles to give α-substituted γ-lactams with reasonable diastereoselectivities. The use of a masked carboxymethyl function off the lactam nitrogen provided a convergent means to α-substituted γ-lactam dipeptide isosteres.

γ-Lactams, with their ψ angle constrained, are important constituents of β-turn peptidomimetics. Our ongoing research on the synthesis of unsubstituted[1,2] and substituted[3] γ-lactam peptide isosteres as Pro−Leu−Gly−NH_2 mimics led us to reinvestigate the existing synthetic methodologies to this scaffold. Over the years, several approaches have been used for the synthesis of peptidomimetics containing lactam scaffolds. One method of obtaining the lactam is through a route established by Freidinger et al.,[4] involving the formation of a sulfonium salt followed by a subsequent intramolecular cyclization. Other widely used approaches are reductive amination followed by thermal cyclization[5] and an intramolecular Mitsunobu reaction.[6] For α-substituted γ-lactams, the stereoselective synthesis of α,α-dialkyl amino acids has to be achieved prior to their incorporation into the lactam by the above methods.[5,7,8] In short, the current methods for the synthesis of α-substituted γ-lactams are linear in their approach. Thus, there is a need for a more efficient and versatile approach for such syntheses.



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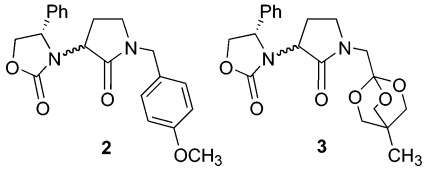

2 **3**

Recently, Palomo et al.[9] constructed α-substituted β-lactams in a stereoselective manner with template **1**. We felt that such an approach could be adapted to the more commonly used γ-lactam scaffold, thereby providing a method for the stereoselective synthesis of the highly desirable α-substituted γ-lactams. Such a method would greatly enhance the utility of the γ-lactam scaffold in peptidomimetic design. Because the synthetic approach used for template **1** was not deemed applicable for the γ-lactam system, compounds **2** and **3** were designed to serve as potential templates for the stereoselective synthesis of α-alkylated γ-lactams.

In **2**, the 4-methoxy-benzyl moiety was incorporated as the lactam N substituent in our initial studies because of its ready availability and its ease of removal. We recognized, however, that template **2** suffered from the same drawback as template **1** in that for both lactam templates to serve as useful synthetic dipeptide isosteres, the lactam N substituent first needed to be removed before the lactam could be N alkylated with a suitable carboxymethyl derivative. We felt that the versatility of a template like **2** could be enhanced if the N substituent was a masked carboxymethyl moiety that when unmasked would provide a dipeptide isostere. The use of the 4-methyl-2,6,7-trioxabicyclo[2.2.2]-oct-1-yl (OBO) ester[10] in the synthetic approach would fulfill this requirement and thus provide template **3**. The advantages of this functionality were viewed to be (1) an ease of formation and cleavage, (2) a stability to strong nucleophilic and basic conditions, and (3) an ability to decrease the acidity of the α proton of the amino acid, making it resistant to deprotonation, thus providing regioselectivity during alkylation.

The synthesis of template **2** and its α-alkylation reaction is outlined in Scheme 1. The starting material, 2,4-dibromobutyryl chloride (**4**), was synthesized from γ-butyrolactone by a slight modification of a reported procedure.[11] This was then condensed with 4-methoxy-benzylamine in the presence of NaOH and tetrabutylammonium hydrogen sulfate as a phase-transfer catalyst to give lactam **5**.[12] The bromolactam, after purification by

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SCHEME 1. Synthesis of γ-Lactam Template 2 and Its α-Alkylated Derivatives

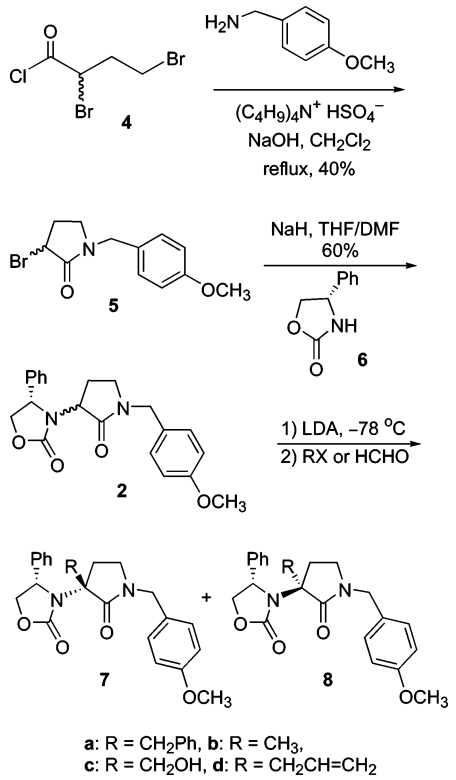

TABLE 1. Yields and Diastereomeric Ratios Obtained upon the Alkylation of Template 2 with Different Electrophiles

electrophile	yield (%)	ratio
$PhCH_2Br$	60	**7a**:**8a** = 6:1
CH_3I	80	**7b**:**8b** = 6:1
paraformaldehyde	33	**7c** only
HCHO	75	**7c**:**8c** = 5:1
allyl bromide	80	**7d**:**8d** = 6:1
$PhCH_2Br$ (HMPA, 1 equiv)	60	**7a**:**8a** = 3:2
allyl bromide (LiCl, 10 equiv)	80	**7d**:**8d** = 6:1

column chromatography, was coupled to Evans' chiral auxiliary (*S*)-4-phenyl-2-oxazolidinone (**6**)[13−15] using NaH to give template **2** as a mixture of diastereoisomers.

The lithium enolate of **2** in THF was subjected to alkylation with different electrophiles to give α-alkylated γ lactams **7a**−**d** and **8a**−**d**. The yields and diastereomeric ratios for these alkylations are reported in Table 1. In most cases, both of the diastereomers were isolated, with isomer **7** always predominating. The relative stereochemistry of **7** and **8** was predicted on the basis of the known directing effects of the (*S*)-4-phenyl-2-oxazolidinone chiral auxiliary.[9,16,17] This was verified in the case where benzyl bromide was used as the electrophile. The major diastereomer of the benzyl alkylated product, **7a**, was crystallized with CH_2Cl_2/MeOH/EtOAc. The stereochemistry of the isomer was determined by X-ray crystallography to have the predicted *R* stereochemistry about the α carbon of the γ lactam (Figure 1 in Supporting Information).

In the alkylation of **2** with formaldehyde, it could be argued that the alkylation might occur in a different stereochemical fashion by virtue of a lithium−oxygen coordination. The results of the NOESY and ROESY studies were inconclusive in ascertaining the stereochemistry at the γ-lactam α carbon of **7c**. The relative stereochemistry of this center was assigned as *R* on the basis of (1) our belief that the formation of a six-membered transition state comprised of formaldehyde, lithium, and the carbonyl oxygen of the enolate would more likely form on the *si* face, away from the steric bulk of the phenyl group on the *re* face, (2) the X-ray structure of the benzyl derivative **7a** , and (3) a previous report of the stereodirecting effects of Evans' auxiliary with the formaldehyde alkylation of enolates.[18]

HMPA and LiCl were added to several trials to determine their effects on the alkylation diastereoselectivity. The presence of HMPA in the trial with benzyl bromide as the electrophile led to a reduction in the diastereomeric ratio of **7a** and **8a** to 3:2. When LiCl was used in the alkylation reaction with allyl bromide, no change in the diastereomeric ratio of **7d** and **8d** was seen.

On the basis of the alkylation results with template **2**, we decided to explore template **3**. The synthesis of template **3** is outlined in Scheme 2. This approach required the synthesis of the OBO ortho ester derivative of glycine: compound **13**. This was accomplished by adapting literature procedures to Cbz-glycine (**9**). Cbz-glycine was coupled to 3-methyl-3-oxetane methanol (**10**) with DCC and catalytic amounts of 4-DMAP to give the oxetane ester **11**.[19] The order of addition of the reagents, that is, addition of small portions of acid **9** to the reaction mixture containing DCC, 4-DMAP, and Cbz-glycine, was important to minimize the formation of an imide between the carbamate nitrogen and the acid function of another molecule of glycine. The oxetane ester (**11**) was then treated with $BF_3 \cdot Et_2O$ to give the compound **12**.[10] Hydrogenolysis of **12** yielded the glycine OBO ester **13**. The reaction of the amino ortho ester **13** with 2,4-dibromobutyryl chloride (**4**) yielded α-bromolactam **14**. Initially, we used the same conditions that were used for 4-methoxy-benzylamine. However, the OBO group was cleaved under these conditions, indicating the need for increased equivalents of a base that was soluble in the reaction solvent. The use of DBU and 4-DMAP led to the desired α-bromolactam **14**, but over time or on standing, a S_N2 attack was observed at the α position. The nonnucleophilic, nonquaternizable base, pentamethyl piperidine,[20] was found to be much more suitable for the reaction. After bromolactam **14** was purified on a Florisil column, it was coupled with Evans' auxiliary **6** to give **3** as a mixture of diastereoisomers.

The alkylation of **3** was carried out in a manner similar to that used with **2**. The results of the alkylation are shown in Table 2. Although the yields of alkylation with benzyl bromide were lower as compared to those of the alkylation of **2**, the diastereoselectivity was much greater. As in the alkylation of **2**, the relative stereochemistries of **15** and **16** were predicted

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SCHEME 2. Synthesis of γ-Lactam Template 3 and Its α-Alkylated Derivatives

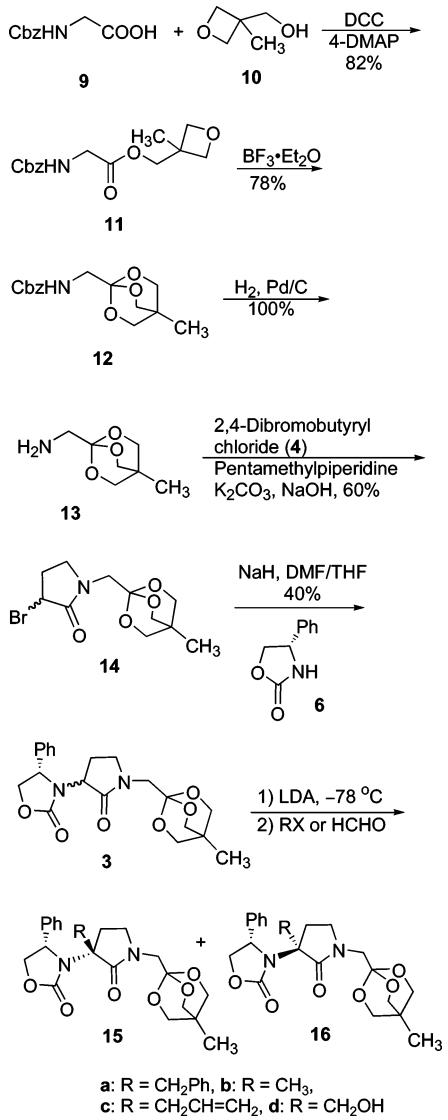


TABLE 2. Yields and Diastereomeric Ratios Obtained upon the Alkylation of Template 3 with Different Electrophiles

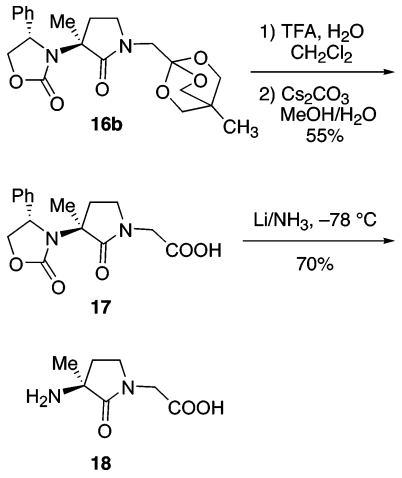
electrophile	yield (%)	ratio
$PhCH_2Br$[a]	45	**15a**:**16a** = 19:1
CH_3I[b]	80	**15b**:**16b** = 3:1
CH_3I (10 equiv LiCl)[b]	80	**15b**:**16b** = 3:1
allyl bromide	80	**15c**:**16c** = 4:1[b]; 7:1[a]
HCHO[b]	50	**15d**:**16d** = 1:1

[a] Addition of a solution of **3** to a LDA solution at −78 °C. [b] Addition of **3** as a solid to a LDA solution at −78 °C, stirring at −40 °C for 20 min and then at −78 °C for 30 min before the addition of the electrophile.

on the basis of the known directing effects of Evans' chiral auxiliary. The predicted stereochemistry of the major isomer formed with benzyl bromide as the electrophile; compound **15a**, was confirmed by X-ray crystallography to be the *R* configuration about the α carbon of the γ lactam (Figure 2 in Supporting Information).

A lower ratio of diastereoselectivity was seen with methyl iodide and formaldehyde. The decrease in diastereoselectivity with methyl iodide was comparable to that reported by Palomo et al.[9] The reason for this could be the smaller size of the

SCHEME 3. Conversion of 16b to the γ-Lactam Dipeptide Isostere 18



electrophile. The use of LiCl in the reaction did not improve the ratio significantly. When allyl bromide was used as the electrophile, it was observed that the temperature at which the enolate was formed played an important role in the diastereoselectivity. In comparison with the results seen with **2**, the size of the electrophile also seemed to be a determinant in the diastereoselectivity seen with **3**. A possible reason for the generally consistent results seen in the alkylation of **2** could be intramolecular stacking interactions between the phenyl groups, thereby providing even greater steric hindrance to attack from the bottom face.

To convert **15** and **16** to their dipeptide isosteres, which are amenable to functionalization, the chiral auxiliary and the OBO ortho ester have to be cleaved. In the present study, the OBO ortho ester was readily converted to the desired carboxylic acid, as illustrated by the treatment of **16b** with TFA/CH_2Cl_2, followed by exposure to 10% Cs_2CO_3 solution to obtain acid **17** (Scheme 3).[21] The cleavage of Evans' auxiliary from acid **17** was achieved by Li/NH_3[9] to give the α-methyl-γ-lactam dipeptide isostere **18**.

In summary, we have devised a versatile and concise stereoselective synthetic route to α-substituted γ lactams with both the N- and the C-terminal ends of the lactam open to a variety of modifications capable of providing lactam-based peptidomimetics. Furthermore, this method potentially can be extended to the six-membered lactams by the use of the higher homologue of **4**.

Experimental Section

Bromo-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-ylmethyl)-pyrrolidin-2-one (14). The glycine OBO ester (**13**, 4.5 g, 28.3 mmol) was dissolved in 200 mL of dry CH_2Cl_2 under nitrogen. To this solution was added NaOH (4.5 g, 113.2 mmol), K_2CO_3 (7 g, 50 mmol), and pentamethyl piperidine (15 mL, 84.9 mmol). A solution of **4** (7.9 g, 28.3 mmol) in 20 mL of CH_2Cl_2 was added dropwise to the reaction with vigorous stirring over a period of 10 min. The reaction mixture started refluxing slightly. The reaction was then refluxed overnight. The next day, ice was added to the reaction, and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over Na_2SO_4 and then concentrated under vacuum to

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give a reddish brown residue. The residue was then adsorbed onto Florisil, which was then loaded on a Florisil column and eluted with EtOAc/hexanes (1:1), followed by EtOAc/hexanes (2:1) to give the product in a 60% yield as a white solid, which also had some contamination with pentamethylpiperidine. TLC R_f 0.32 (EtOAc/hexanes, 2:1); ^{1}H NMR ($CDCl_3$, COSY assignment) δ 0.75 (s, 3H), 2.17−2.26 (m, 1H), 2.46−2.58 (m, 1H), 3.37 (d, 1H, J = 14.1 Hz), 3.55−3.62 (m, 2H), 3.55 (d, 1H, J = 14.7 Hz), 3.83 (s, 6H), 4.36 (dd, 1H, J = 2.85, 7.35 Hz); ^{13}C NMR ($CDCl_3$, HMQC assignment) δ 14.8, 30.8, 30.9, 44.6, 46.7, 47.6, 72.8, 107.5, 171.3; ESI HRMS (*m*/*z*) 328.0157 and 330.0140 $[M + Na]^+$; $C_{11}H_{16}NO_4$-Br + Na^+ requires 328.0160 and 330.0140.

General Procedure for Templates 2 and 3. 3-[1-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-ylmethyl)-2-oxo-pyrrolidin-3(*R*,*S*)-yl]-4(*S*)-phenyl-oxazolidin-2-one (3). To a solution of **6** (3.19 g, 19.6 mmol) in THF at 0 °C under argon was added NaH (60% dispersion in mineral oil, 784 mg, 19.6 mmol). A white precipitate formed with the evolution of hydrogen. After vigorous stirring for 30 min, a solution of **14** (5 g, 16.3 mmol) in DMF (dried over molecular sieves) was added dropwise. The reaction color changed from orange to brown and then to gray overnight. The disappearance of **14** was monitored by TLC. The next day, saturated NH_4Cl solution (20 mL) was added, and the solution color turned dark brown. The reaction mixture was concentrated under vacuum, and the residue partitioned between brine and CH_2Cl_2 (150 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 100 mL). The organic layers were combined and dried over Na_2SO_4. After the removal of the solvent under vacuum, an orange residue was obtained that contained two diastereoisomers in the ratio 1:1. Xylenes were used to azeotrope the DMF present in the residue. The diastereoisomers were purified by column chromatography with EtOAc/hexanes (1:1, 2:1, and 4:1) on a silica gel column (8 × 5 cm) that had been pretreated with Et_3N. The final elution was with CH_2Cl_2/MeOH (20:1). The diastereoisomers were separable under chromatographic conditions, and they were crystallized from CH_2Cl_2/ether. The separated diastereoisomers were analyzed by NMR, but in each case, a trace amount of the other diastereoisomer was observed by TLC. The reaction went in a 40% yield (2.3 g of product). In subsequent alkylation studies, the oxazolidinone was used as a mixture of diastereoisomers. **Diastereoisomer A**: TLC R_f 0.30 (EtOAc/hexanes, 4:1); ^{1}H NMR ($CDCl_3$, COSY assignment) δ 0.80 (s, 3H), 1.32−1.46 (m, 1H), 2.03−2.13 (m, 1H), 2.96 (dt, 1H, J = 2.5, 9.6 Hz), 3.20 (d, 1H, J = 13.8 Hz), 3.23−3.32 (m, 1H), 3.61 (d, 1H, J = 14.1 Hz), 3.86 (s, 6H), 4.17−4.22 (m, 1H), 4.56 (t, 1H, J = 9.45 Hz), 4.67 (t, 1H, J = 9 Hz), 5.20 (dd, 1H, J = 6.15, 9.15 Hz), 7.37−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, HMQC assignment) δ 14.8, 24.6, 30.9, 45.4, 47.6, 54.9, 58.3, 70.9, 72.8, 107.4, 127.7, 129.2, 129.3, 139.6, 158.6, 170.2; ESI HRMS (*m*/*z*) 411.1526 $[M + Na]^+$; $C_{20}H_{24}N_2O_6$ + Na^+ requires 411.1532. **Diastereoisomer B**: TLC R_f 0.22 (EtOAC/hexanes, 4:1); ^{1}H NMR ($CDCl_3$, COSY assignment) δ 0.75 (s, 3H), 1.96−2.07 (m, 1H), 2.55−2.69 (m, 1H), 3.00 (d, 1H, J = 14.4 Hz), 3.34−3.52 (m, 2H), 3.65 (t, 1H, J = 9.6 Hz), 3.82 (s, 6H), 3.92 (d, 1H, J = 14.7 Hz), 4.04 (t, 1H, J = 8.7 Hz), 4.63 (t, 1H, J = 8.85 Hz), 5.20 (t, 1H, J = 9 Hz), 7.34−7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, HMQC assignment) δ 14.8, 22.9, 30.9, 45.8, 47.6, 54.5, 63, 70.6, 72.8, 107.4, 127.6, 129.3, 129.4, 137.7, 157.7, 171.2; ESI HRMS (*m*/*z*) 389.1710 $[M + H]^+$; $C_{20}H_{24}N_2O_6$ + H^+ requires 389.1713.

General Procedure for the Alkylation of Templates 2 and 3. 3-[3(*R*,*S*)-Allyl-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl-methyl)-2-oxo-pyrrolidin-3-yl]-4(*S*)-phenyl-oxazolidin-2-one (15c and 16c). To a solution of diisopropylamine (0.13 mL, 1.07 mmol) in 2 mL of THF under argon at −78 °C was added *n*-BuLi (2.56 M solution in hexanes, 0.32 mL, 0.79 mmol). The reaction was stirred for 5 min at −78 °C and then warmed to 0 °C. After 15 min, the reaction mixture was cooled back to −78 °C. γ-Lactam **3** (200 mg, 0.5 mmol) was dissolved in 3 mL of THF, and this solution was cooled to −78 °C and then added dropwise to the solution containing LDA. The enolate formed had a yellow color. The reaction was stirred at −78 °C for 30 min before the addition of the allyl bromide (0.17 mL, 2 mmol). The next day, 5 mL of saturated NH_4Cl solution was added, and the mixture was extracted with CH_2Cl_2 (2 × 25 mL). The organic layers were combined, dried over $MgSO_4$, and then concentrated under vacuum to give an oily residue. The diastereoisomers were isolated by loading on a silica gel column (2 × 4.6 cm) that had been pretreated with Et_3N and then eluting with EtOAc/hexanes (2:1), followed by CH_2Cl_2/MeOH (20:1). The alkylation occurred with around 80% yield, and the diastereoisomeric ratio was around 6:1. The diastereoisomers were crystallized using CH_2Cl_2/ether. When the starting material was added in one portion to LDA, the reaction was stirred for 15 min. The reaction was warmed to −40 °C, and the color of the reaction turned to bright yellow over a period of 30 min. After stirring at −78 °C for an additional 20 min, allyl bromide was added. The workup was the same as mentioned above. In this case, the diastereoselectivity was more like 4:1. **15c** (major isomer, 3*R* configuration): TLC R_f 0.32 (EtOAc/hexanes, 4:1); $[\alpha]_D$ +39.4 (*c* 0.8, CH_3OH); mp 131−133 °C; ^{1}H NMR (CD_3OD, COSY assignment) δ 0.78 (s, 3H), 1.68 (ddd, J = 2.4, 8.4, 13.2 Hz, 1H), 2.25 (dd, 1H, J = 9, 12.9 Hz), 2.38−2.48 (m, 1H, β-CH_2), 2.63 (dd, 1H, J = 5.7, 13.2 Hz), 3.0 (d, 1H, J = 14.1 Hz), 3.26−3.33 (m, 1H), 3.39−3.48 (m, 1H), 3.85−3.89 (m, 7H), 4.10 (dd, 1H, J = 3, 8.7 Hz), 4.71 (t, 1H, J = 8.7 Hz), 4.97−5.09 (m, 2H), 5.17 (dd, 1H, J = 3, 9 Hz), 5.72−5.86 (m, 1H), 7.34−7.44 (m, 5H); ^{13}C NMR (CD_3OD, HMQC assignment) δ 13.2, 29.9, 30.5, 40.3, 45.7, 47.5, 59.2, 63.8, 71.3, 72.4, 107.3, 119.0, 126.2, 128.7, 129.2, 131.4, 141.5, 157.9, 173.4; ESI HRMS (*m*/*z*) 429.2020 $[M + H]^+$; $C_2H_{28}N_2O_6$ + H^+ requires 429.2026. **16c** (minor isomer, 3*S* configuration): TLC R_f = 0.49 (EtOAc/hexanes, 4:1); $[\alpha]_D$ +140 (*c* 0.93, CH_3OH); mp 158−160 °C; ^{1}H NMR (CD_3OD, COSY assignment) δ 0.75 (s, 3H), 2.16−2.25 (m, 1H), 2.27 (d, 1H, J = 14.1 Hz), 2.31−2.41 (m, 1H), 2.65−2.74 (m, 3H), 3.29−3.46 (m, 1H), 3.44 (d, 1H, J = 14.1 Hz), 3.80 (s, 6H), 4.08 (dd, 1H, J = 3.15, 8.7 Hz), 4.63 (t, 1H, J = 9 Hz), 5.08−5.19 (m, 3H), 5.73−5.87 (m, 1H), 7.29−7.40 (m, 5H); ^{13}C NMR (CD_3OD, HMQC assignment) δ 13.2, 29.2, 30.4, 39.9, 45.0, 46.9, 59.1, 63.6, 71.2, 72.4, 107.0, 118.8, 126.8, 128.5, 128.7, 132.6, 141.0, 158.4, 171.7; ESI HRMS (*m*/*z*) 451.1850 $[M + Na]^+$; $C_{23}H_{28}N_2O_6$ + Na^+ requires 451.1845.

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Supporting Information Available: Experimental procedures and spectral data for **2**, **5**, **7**, **8**, **11**−**13**, and **15**−**18**. X-ray structure data (ORTEP diagrams and CIF files) for **7a** and **15a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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