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Short Stereoselective Synthesis of α -Substituted γ -Lactams

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Abstract

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 substituted³ γ -lactam peptide isosteres as Pro-Leu-Gly-NH₂ (PLG) 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 al⁴, involving the formation of a sulfonium salt followed by subsequent intramolecular cyclization. Other widely used approaches are reductive amination followed by thermal cyclization⁵ 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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SUPPORTING INFORMATION. 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>.

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 highly desirable α -substituted γ -lactams. Such a method would greatly enhance the utility of the γ -lactam scaffold in peptidomimetic design. Since 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 in order for both lactam templates to serve as useful synthetic dipeptide isosteres, the lactam N-substituent first needed to be removed and the lactam then 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) ester¹⁰ 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) stability to strong nucleophilic and basic conditions, and (3) 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-methoxybenzylamine in the presence of NaOH and tetrabutyl ammonium hydrogen sulfate as a phase transfer catalyst to give lactam **5**.¹² The bromolactam, after purification by 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 the diastereomers were isolated with isomer **7**

always predominating. The relative stereochemistry of **7** and **8** was predicted based upon 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 CH₂Cl₂/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 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 comprising 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 formaldehyde alkylation of enolates.¹⁸

HMPA and LiCl were added to several trials to determine their effects on 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.

Based on 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 orthoester 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 reagents, i.e. addition of small portions of acid **9** to the reaction mixture containing DCC, 4-DMAP and Cbzglycine, was important in order 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 BF₃·Et₂O to give the compound **12**.¹⁰ Hydrogenolysis of **12** yielded the glycine OBO ester **13**. The reaction of amino ortho ester **13** with 2,4-dibromobutyl 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 non-nucleophilic, non-quaternizable base, pentamethyl piperidine (PMP),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.

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 the alkylation of **2**, the diastereoselectivity was much greater. As in the alkylation of **2**, the relative stereochemistry of **15** and **16** was predicted based upon 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 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 is formed plays 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.

In order to convert **15** and **16** to their dipeptide isosteres that are amenable to functionalization, the chiral auxiliary and the OBO ortho ester have to be cleaved. In the present study, the OBO orthoester was readily converted to the desired carboxylic acid as illustrated by the treatment of **16b** with TFA/CH₂Cl₂ followed by exposure to 10% Cs₂CO₃ solution to obtain acid **17** (Scheme 3).²¹ The cleavage of Evans' auxiliary from acid **17** was achieved by Li/NH₃⁹ 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 N- and 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 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**)

Glycine OBO ester (**13**, 4.5 g, 28.3 mmol) was dissolved in 200 mL dry CH₂Cl₂ under nitrogen. To this solution was added NaOH (4.5 g, 113.2 mmol), K₂CO₃ (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 CH₂Cl₂ 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 separated. The aqueous layer was washed with CH₂Cl₂ (2 $\times$ 100 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under vacuum to give a reddish brown residue. The residue was then adsorbed onto Florisil, which was then loaded on 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. For the synthesis of **2**, the procedure was similar to the general synthetic route reported for α -bromolactams.¹² TLC *R*_f 0.32 (EtOAc/hexanes, 2:1); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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]⁺, (C₁₁H₁₆N₁O₄Br + 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(*RS*)-yl]-4(*S*)-phenyl-oxazolidin-2-one (**3**)

To a solution of **6** (3.19g, 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** (5g, 16.3 mmol) in DMF (dried over molecular sieves) was added dropwise. The reaction color changed from orange to brown and then to grey overnight. The disappearance of **14** was monitored by TLC. The next day saturated NH₄Cl 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 CH₂Cl₂ (150 mL). The aqueous layer was washed with CH₂Cl₂ (2 × 100 mL). The organic layers were combined and dried over Na₂SO₄. After removal of solvent under vacuum, an orange residue was obtained which contained two diastereoisomers in the ratio 1:1. Xylenes was used to azeotrope the DMF present in the residue. The diastereoisomers were purified by column chromatography with EtOAc/hexanes (1:1, 2:1, 4:1) on a silica gel column (8 × 5 cm) that had been pretreated with Et₃N. The final elution was with CH₂Cl₂/MeOH (20:1). The diastereoisomers were separable under chromatographic conditions and they were crystallized from CH₂Cl₂/ether. The separated diastereoisomers were analyzed by NMR, but in each case, trace of the other diastereoisomer was observed by TLC. The reaction went in a 36 % 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); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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]⁺, (C₂₀H₂₄N₂O₆ + Na⁺) requires 411.1532. **Diastereoisomer B**: TLC *R_f* 0.22 (EtOAc/hexanes, 4:1); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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]⁺, (C₂₀H₂₄N₂O₆ + H⁺) requires 389.1713.

General procedure for alkylation of template 2 and 3. 3-[3(*RS*)-Allyl-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-ylmethyl)-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 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 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 allyl bromide (0.17 mL, 2 mmol). The next day 5 mL of saturated NH₄Cl solution was added and the mixture extracted with CH₂Cl₂ (2 × 25 mL). The organic layers were combined, dried over MgSO₄ 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 Et₃N and then eluting with EtOAc/hexanes (2:1) followed by CH₂Cl₂/MeOH (20:1). The alkylation went in around 80 % yield and the diastereoisomeric ratio was around 6:1. The diastereoisomers were crystallized using CH₂Cl₂/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 a further 20 min, allyl bromide was added. The workup was 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); [α]_D +39.4 (c 0.8, CH₃OH); mp 131–133 °C; ¹H NMR (CD₃OD, 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 -CH₂), 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); ¹³C NMR (CD₃OD, 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]⁺ (C₂₈H₂₈N₂O₆ + 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, CH₃OH); mp 158–160 °C; ¹H NMR (CD₃OD, 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); ¹³C NMR (CD₃OD, 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]⁺, (C₂₃H₂₈N₂O₆ + Na⁺) requires 451.1845.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Synthesis of γ -lactam template **2** and its α -alkylated derivatives

Scheme 2. Synthesis of γ -lactam template **3** and its α -alkylated derivatives

Scheme 3.
Conversion of **16b** to the γ -lactam dipeptide isostere **18**.

Table 1Yields and diastereomeric ratios obtained upon the alkylation of template **2** with different electrophiles

Electrophile	Yield	Ratio
PhCH ₂ Br	60%	7a:8a = 6:1
CH ₃ I	80%	7b:8b = 6:1
paraformaldehyde	33%	7c only
HCHO	75%	7c:8c = 5:1
Allyl bromide	80%	7d:8d = 6:1
PhCH ₂ Br	60%	7a:8a = 3:2
(HMPA 1 equiv)		
Allyl bromide	80%	7d:8d = 6:1
(LiCl 10 equiv)		

Table 2Yields and diastereomeric ratios obtained upon the alkylation of template **3** with different electrophiles

Electrophile	Yield	Ratio
PhCH ₂ Br ^a	45%	15a:16a = 19:1
CH ₃ I ^b	80%	15b:16b = 3:1
CH ₃ I (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 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 addition of the electrophile.