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Stereoselective Alkylation of *N*-Boc-protected-5-substituted δ-Lactams: Synthesis of α,δ-Disubstituted δ-Amino Acids

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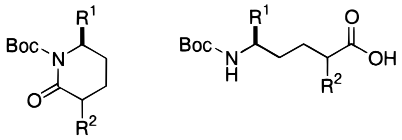
ABSTRACT



***N*-Boc-protected-5-substituted δ-lactams were readily prepared from the corresponding β^3-amino acids. Alkylation reactions of their Na enolates with various electrophiles proceeded in high yields with high facial selectivity. The structure of the alkylation products was confirmed by single-crystal X-ray analysis. This method provides a fast access to optically active α,δ-disubstituted δ-amino acids.**

The interest in ω-amino acids and ω-amino acid-containing peptides[1] has increased enormously with the finding that short chain peptides consisting exclusively of optically active β- or γ-amino acids can form stable folded structures in solution and in the solid state.[2,3] Recently, a few reports have highlighted the potential of higher ω-amino acids, including δ-amino acids, for studying peptide folding[4] and for the construction of novel oligomers.[5] Optically active δ-amino acids with various substitution patterns and diverse side chain functionalities, e.g., α,δ-disubstitued δ-amino acids, are thus of interest for further studies in this area. Additionally, α,δ-disubstituted δ-amino acids can serve as dipeptide mimetics in which the amide bond has been replaced by the nonhydrolyzable ethylene unit $\psi[CH_2CH_2]$.[6]

Although there are a few reports on the synthesis of "carba" $\psi[CH_2CH_2]$ dipeptide units in the literature,[6] no general stereoselective synthetic route has been described so far.[7] In an effort to develop a general method for the

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(1) Banerjee, A.; Balaram, P. *Curr. Sci.* **1997**, *73*, 1067.

(2) For reviews on β-peptides, see: (a) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173.

(3) For leading references on γ-peptides, see: (a) Hintermann, T.; Gademann, K.; Jaun, B.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 983. (b) Hanessian, S.; Luo, X.; Schaum, R.; Michnick, S. *J. Am. Chem. Soc.* **1998**, *120*, 8569. (c) Hanessian, S.; Luo, X.; Schaum, R. *Tetrahedron Lett.* **1999**, *40*, 4925.

(4) (a) Banerjee, A.; Pramanik, A.; Bhattacharrjya, S.; Balaram, P. *Biopolymers* **1996**, *39*, 769. (b) Shankaramma, S. C.; Singh, S. K.; Sathyamurthy, A.; Balaram, P. *J. Am. Chem. Soc.* **1999**, *121*, 5360.

(5) Szabo, L.; Smith, B. L.; McReynolds, K. D.; Parrill, A. B.; Morris, E. R.; Gervay, J. *J. Org. Chem.* **1998**, *63*, 1074.

(6) (a) Rodriguez, M.; Heitz, A.; Martinez, J. *Tetrahedron Lett.* **1990**, *31*, 7319. (b) Attwood, M. R.; Conway, E. A.; Dunsdon, R. M.; Greening, J. R.; Handa, B. K.; Jones, P. S.; Jordan, S. C.; Keech, E.; Wilson, F. X. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 429.

(7) For an enantioselective synthesis of a Gly$\psi[CH_2CH_2]$Ala dipeptide unit using Evans methodology, see ref 6c.

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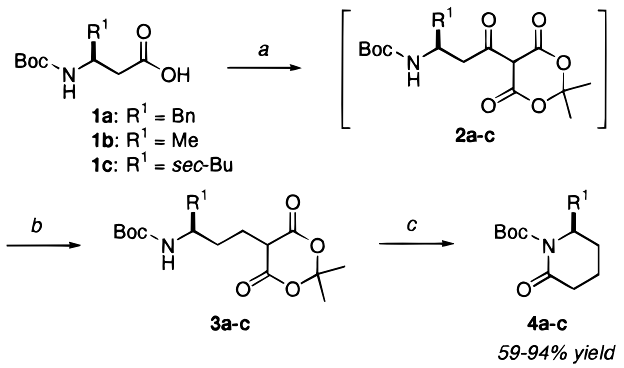
preparation of optically active α,δ-disubstituted δ-amino acids which would be amenable to the synthesis of all four possible diastereomers and which would allow the introduction of various natural and unnatural side chains at the α-position, we investigated the synthesis and the alkylation of *N*-Boc-protected-5-substituted δ-lactams **4**.[8]

Prior to alkylation studies, we required a convenient method for preparing *N*-Boc-protected lactams **4**. We found that the method described by Smreina et al.[9] for the synthesis of γ-substituted γ-amino acids was very efficient for the conversion of *N*-Boc-protected β^3-amino acids **1a**−**c** (with side chains of Ala, Phe, and Ile) into the corresponding 5-substituted δ-lactams **4a**−**c** (Scheme 1).

Scheme 1



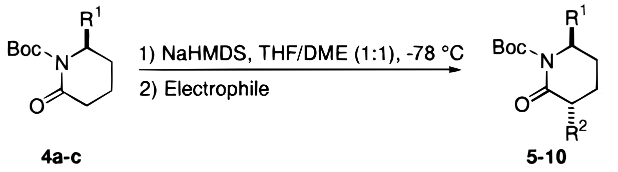
^{a} Meldrum's acid, EDC, DMAP, CH_2Cl_2, rt, 2 h. ^{b} $NaBH_4$, CH_2Cl_2/AcOH (10:1), 0 °C, 12 h. ^{c} Toluene, 110 °C, 4 h.

The condensation of **1** with Meldrum's acid in the presence of EDC (1.5 equiv) and DMAP (1.5 equiv) afforded the corresponding β-aminoacyl Meldrum's acid **2** in good yield and purity. As expected, reduction of the keto functionality of crude **2** with $NaBH_4$ yielded **3** which was easily purified by crystallization in all cases. Decarboxylative ring closure of **3** in toluene at 110 °C afforded lactam **4** in high yield after flash chromatography. The overall yields for this three-step reaction sequence from **1** ranged between 59% and 94%.

By analogy with previous studies on *N*-acyl piperidines[10] and *N*-acyl morpholinones,[11,12] we anticipated that the ring substituent in the C-5 position of lactam **4** would preferentially adopt an axial conformation as a consequence of pseudoallylic A(1,3) strain, thus providing stereocontrol during alkylation of the enolate anion generated from **4**.

Table 1 shows the results of alkylation of enolates of **4a**−**c** with various electrophiles. The results are reported for Na enolates generated with NaHMDS (1.0 equiv) in THF/DME (1:1) solution (0.2−0.25 mM) for 2 h 30 min at −78 °C.

Table 1. Alkylation of *N*-Boc-protected Lactams **4**



compd **4**	R^1	electrophile	product	yield^a (%)	dr^b
4a	Bn	BnBr	**5**	82	>99:1
4a	Bn	MeI	**6**	94	98:2
4a	Bn	$CH_2{=}CHCH_2Br$	**7**	57	>99:1
4b	Me	BnBr	**8**	65	>99:1
4b	Me	MeI	**9**	99	>99:1
4c	*sec*-Bu	$CH_2{=}C(Me)CH_2Br$	**10**	81	99:1
4c	*sec*-Bu	$(CH_3)_2CHCH_2Br$	**11**	0	

^{a} Yield after flash chromatography. ^{b} Ratio determined by analytical C_{18} RP-HPLC of the crude product.

Under these optimized conditions, high levels of 1,4-asymmetric induction were achieved with each of the three lactams (anti:syn >98:2), thus demonstrating that the selectivity is independent of the bulk of the R^1 side chain.[13]

As shown by alkylation studies on **4a**, the stereochemical outcome of the reaction was not affected by the size of the electrophile. Yields of alkylation were good to excellent except with isobutyl bromide. In this case, no reaction occurred under our standard reaction conditions. Since the reactivity of the enolate is sensitive both to solvent and counterion effects, additional studies are needed to determine the optimum conditions for alkylation by isobutyl bromide and other primary halides.

The relative configuration at the newly formed stereogenic center in compounds **6** and **10** was unambiguously assigned by X-ray crystal structure analysis (one example is given in Figure 1). The configuration of the other alkylation products was assigned by analogy.

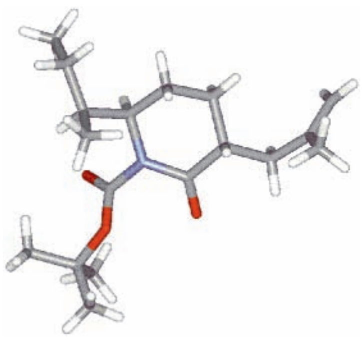


Figure 1. Structure of lactam **10** (X-ray).

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(8) For previously reported alkylations of *N*-Boc-protected δ-lactams, see: (a) Murray, P. J.; Starkey, I. D. *Tetrahedron Lett.* **1996**, *37*, 1875. (b) Hanessian, S.; Reinhold U.; Gentile, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1881. (c) Battistini, L.; Rassu, G.; Pinna, L.; Zanardi, F.; Casiraghi, G. *Tetrahedron: Asymmetry* **1999**, *10*, 765.

(9) Smreina, M.; Majer, P.; Tatiana, E. M.; Guerassina, T. A.; Eissenstat, M. A. *Tetrahedron* **1997**, *53*, 12867.

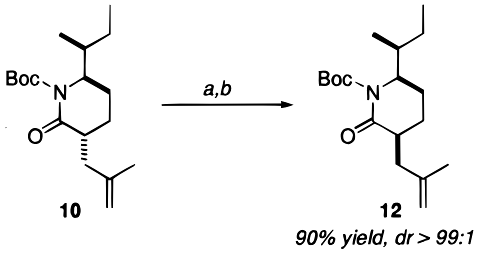
(10) Sugg, E. E.; Griffin, J. F.; Portoghese, P. S. *J. Org. Chem.* **1985**, *50*, 5032.

(11) Williams, R. M.; Im, M.-N. *Tetrahedron Lett.* **1988**, *29*, 6075. (b) Dellaria, J. F.; Santarsiero, B. D. *Tetrahedron Lett.* **1988**, *29*, 6079.

(12) Anthony, N. J.; Gomez, R. P.; Holtz, W. J. Murphy, J. S. Ball, R. G.; Lee, T.-J. *Tetrahedron Lett.* **1995**, *36*, 3821. Norman, B. H.; Kroin, J. S. *Tetrahedron Lett.* **1995**, *36*, 4151.

Interestingly, deprotonation/kinetic protonation of adduct **10** afforded lactam **12** with inverted configuration at C-2 in excellent yield and with high stereoselectivity (90% yield, dr > 99:1 as determined by analytical C_{18} RP-HPLC) (Scheme 2).

Scheme 2

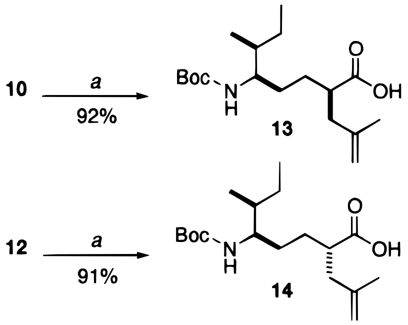


[a] NaHMDS, THF/DME (1:1), 4 h, −78 °C. [b] Saturated NH_4Cl.

Finally, conversion of lactams **10** and **12** to the corresponding *N*-Boc-protected-α,δ-disubstituted δ-amino acids was performed smoothly and in good yield, by treatment with LiOOH in THF/H_2O. No significant epimerization (<5%) occurred at the α-position as evidenced by RP-HPLC analysis of peptides incorporating δ-amino acids **13** and **14** (Scheme 3).

This method provides a general entry into this class of compounds by making accessible all four possible diastereomers, depending on the configuration of the starting β-amino acid. Additional studies to broaden the scope of these lactam enolate alkylations and utilization of α,δ-substituted δ-amino acids for the construction of novel δ-oligomers are in progress in our laboratories.

Scheme 3



[a] LiOH, H_2O_2, THF/H_2O (4:1).

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Supporting Information Available: Full characterization of compounds **4a−c** and **5−14**. X-ray data for compound **10** (. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) While this work was in progress, Battistini et al. (ref 8c) also reported complete diastereoselectivity in the addition of benzyl bromide to the lithium enolate of a 4,5-disubstitued *N*-Boc δ-lactam.