α-Alkyl-α-Amino-β-Lactam Peptides: Design, Synthesis, and Conformational Features**

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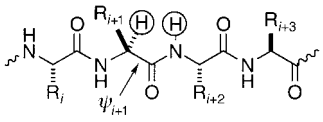
The concept of linking two neighboring α-amino acids in peptide **1** (Figure 1) to stabilize a single conformation was established by Freidinger et al. in the early 1980s.[1] Since then,



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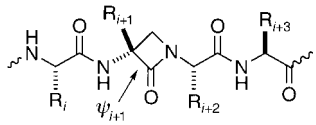

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Figure 1. The approach for the introduction of conformational constraints into peptides by the $C\alpha_{i+1}$–N_{i+2} linkage. A methylene bridge generates the constraint in **2**, and the R_{i+1} group mimics the original residue in the parent peptides **1**.

several lactam peptides of various ring sizes and β-turn mimetics have been prepared either to control the conformation of peptides and/or as potential pharmaceuticals.[2] However, despite considerable success to date,[3] it is not always easy to confidently predict the optimal structure which will generate a desired type of conformational restriction.[4] There are various reasons to consider β-lactam peptides of type **2** (Figure 1) as potential candidates for β-turn mimetics and/or as promising leads for pharmaceutical drug discovery:

1) They possess the rigid azetidin-2-one ring[5] and therefore the same ψ_{i+1} torsion angle (120°) as ideal type II and type VI β-turns.[6]
2) They show minimum structural divergence with respect to the parent peptides **1**, retaining the R_{i+1} substituent of the original residue and thus facilitating recognition by receptors or enzymes.[7]
3) Owing to the presence of the α,α-disubstitution pattern, they are expected to exhibit enhanced resistance to chemical and enzymatic hydrolysis by proteases.[8]

However, access to this kind of lactam peptide is hampered by the difficulty in forming β-unsubstituted β-lactams with quaternary stereogenic centers at the Cα position.[9] In particular, the asymmetric α-alkylation of a 4-unsubstituted 3-aminoazetidin-2-one, which would be the most straightforward method for creating a quaternary center, has remained elusive until now.[10] The main reason is probably the lack of efficient methodology to generate an appropriate chiral building block.[11] Recently we reported the synthesis of the β-lactam **3**[12] (see Scheme 1), which has a removable chiral tether whose stereogenic center is close to the Cα position of the β-lactam ring. We now report that this synthetic building block acts as a new and very useful β-amino alaninate equivalent, which makes possible the preparation and study of β-lactam peptides of type **2** for the first time.

Upon deprotonation with a base at the C3 methine, **3** should probably generate an enolate with W-type geometry (Scheme 1). If so, the reaction of the latter with alkyl halides should take place from the enolate side opposite to that occupied by the phenyl group, and a certain degree of diastereoselectivity should be observed. The reaction of representative alkyl halides with the lithium enolate of **3** proceeded as expected to give products **4**/**5** with good to excellent diastereoselectivities. According to the data collected in Table 1, the diastereomeric ratios attained depend upon the nature of the alkyl halide used, but allyl and benzyl halides lead to the formation of **4** essentially as the sole diastereomer. The stereochemical course of these reactions was assumed to be uniform, as established by hydrogenation of the double bond in **4d** to give **4b**, which was identical to that produced by the direct route. The *R* configuration at the Cα position for the major products **4** was assigned by single-crystal X-ray analysis of **4b** and **4f**. Finally, deprotection of the carbamate and azetidinone nitrogen atoms according to our procedure[12] led to the desired α-alkyl-β-aminoalanine equivalents **6**–**8** in good overall yields.

With these compounds in hand, a variety of α,α-disubstituted β-lactam-derived peptides became accessible, and provided insight into the conformational preferences of these compounds. For instance, *N*-alkylation of **8** with benzyl bromoacetate gave, after hydrogenolytic cleavage of the benzyl ester group, the Boc-Phe-Gly dipeptide analogue **9** (Scheme 2). Coupling of **9** with α-amino isobutyric acid

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Table 1. Asymmetric alkylation of **3**.[a]

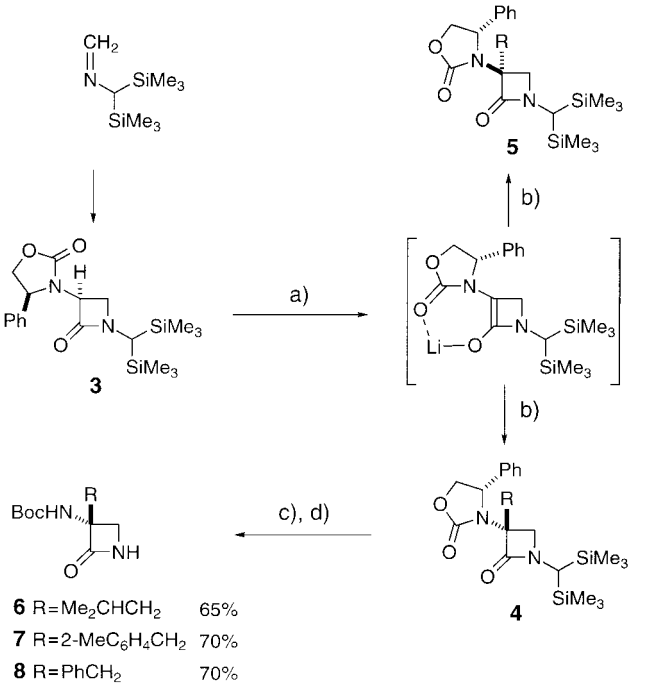
R–X	**4**:**5**[b]	Yield of **4** [%]	M.p. [°C]	$[\alpha]_D^{25}$
CH_3-I	70:30	–[c] (**4a**)	oil	–
$CH_3CH_2CH_2$-Br	80:20	40 (**4b**)	oil	+82.1[d]
$(CH_3)_2CHCH_2$-Br	91:9	62 (**4c**)	99–100	−26.8[d]
CH_2=$CHCH_2$-Br	>98:2	70 (**4d**)	111–112	−16.8
2-$MeC_6H_4CH_2$-Br	>98:2	80 (**4e**)	152–153	+32.1
$PhCH_2$-Br	>98:2	90 (**4f**)	168–169	+21.5

[a] Reactions were carried out in THF with 4×10^{-3} mol of β-lactam using a LDA:**3**:RX ratio of 1.5:1:5.0. [b] Determined by ^{1}H NMR spectroscopy (300 MHz) of the crude reaction mixture. [c] Not isolated. The yield of the mixture of isomers **4**/**5** was 65%. [d] Measured on analytically pure samples separated by preparative HPLC.

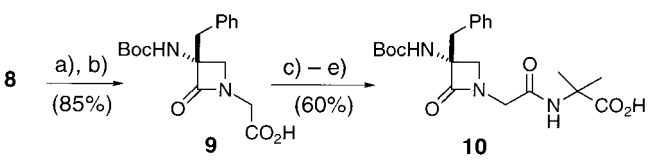
Table 2. Solid-state (X-ray), solution (NMR), and theoretical structure data (RHF/3–21G) for compound **10**.

	(ϕ_1, ψ_1); (ϕ_2, ψ_2) [°]	C=O···HN [Å]	=O···N [Å]	=O···H–N [°]
ideal type II β-turn	(−60.0,120.0); (80.0,00.0)	1.8–2.5	–	≈160
X-ray[a]	(−40.9,122.5); (100.5, −2.1)	2.32	3.05	164
X-ray[a]	(−47.1,122.5); (104.5, −13.7)	2.37	3.12	167
NMR[b]	(−41.7,114.6); (132.9, −59.5)	1.81	2.68	136
RHF/3–21G[c]	(−46.2,122.0); (116.2, −31.1)	2.04	2.98	155

[a] Two symmetry-independent structures in the cell unit. [b] Measured in $CDCl_3$ (10^{-3} mol L^{-1}).[16] [c] The relative energy difference between the β-turn and the γ-turn conformers of **10** was estimated at 9.91 kcal mol^{-1} (the extended conformation could not be characterized as a proper energy minimum). This value was calculated by a Monte Carlo random variational search using the Amber force field and the solution model GB/SA, followed by a RHF/3–21G full optimization of the relative energies and structural parameters. The Amber force field was used as implemented in Macromodel, version 5.5.[17]



Scheme 1. Asymmetric synthesis of 4-unsubstituted 3-alkyl-3-amino-azetidin-2-ones **6**–**8**. a) Lithium diisopropylamide (LDA), THF, −78 °C; b) R–X (5 equiv, see Table 1), −78 °C→room temperature, overnight; c) Li, NH_3, THF, then $(Boc)_2O$; d) $(NH_4)_2Ce(NO_3)_6$, then $NaHCO_3$. Boc = *tert*-butyloxycarbonyl. See reference [12] for the synthesis of **3**.



Scheme 2. Synthesis of Boc-tripeptide **10**. a) $BrCH_2CO_2Bn$, Cs_2CO_3; b) H_2, Pd/C; c) cyanuric fluoride, pyridine; d) $H_2NCMe_2CO_2Bn$, *N*-methylpyrrolidine; e) H_2, Pd. Bn = benzyl.

benzyl ester (AibOBn) according to the procedure of Carpino et al.[13] and subsequent O-debenzylation provided the tripeptide **10** (m.p. 183–185 °C, $[\alpha]_D^{25} = +89.7$ (CH_2Cl_2, $c = 0.24$)).

The X-ray analysis of a single crystal of **10**[14] showed two symmetry-independent molecules in the asymmetric unit having quite similar conformations (Table 2, Figure 2a) which displayed a S(10) graph set[15] for intermolecular hydrogen

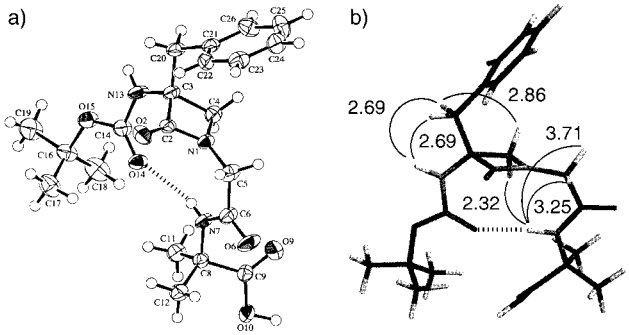


Figure 2. The type II β-turn conformation of **10**. a) Ortep plot of the solid-state X-ray structure (only one of the two symmetry-independent structures in the cell unit is represented). b) Conformation derived from ^{1}H NMR spectroscopy[16] in $CDCl_3$ (10^{-3} mol L^{-1}, 20 °C). Representative measured interprotonic distances [Å] are shown.

bonds. Most remarkably, each conformer of **10** presented intramolecular N–H···O hydrogen bonds forming a β-turn motif which fitted reasonably well with the structural parameters of a slightly deformed type II β-turn. Finally, high-resolution structural analysis of **10** by ^{1}H NMR spectroscopy (500 MHz, $CDCl_3$, NOESY, ROESY)[16] and molecular modeling[17] confirmed the presence of a very stable type II β-turn conformation at 20 °C (Table 2, Figure 2b).

In conclusion, we have found a new family of molecular scaffolds that can open the way to new dual-action peptido-

mimetics combining the biological activity of β-lactams and the countless bioactive properties of conformationally restricted oligopeptides.

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Double Insertion of Coordinated Phosphanylalkyne Ligands into a Pt–C_6F_5 Bond**

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Carbon – carbon bond forming reactions promoted by transition metals are among the basic goals of organometallic chemistry and play an important role in the design of efficient and selective processes.[1] The intramolecular coupling of alkyne and related C_2 ligands (alkynyl, vinyl, vinylidene) is particularly interesting because it constitutes an effective method for the synthesis of useful organic products.[2] The facile migratory insertion of C≡C units into M–H and M–C bonds seems to be decisive not only for these reactions but also for many catalytic processes.[1, 2] Usually bonds between a metal and a perfluorocarbon atom are quite inert towards insertion reactions, and there is currently little or no knowledge on the insertion of acetylene fragments into the robust M–R_F bonds.[3]

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