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## A New Peptide Bond Surrogate : 2-Isoxazoline in Pseudodipeptide Chemistry

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Abstract : The 2-isoxazoline ring has been incorporated as a new peptide bond surrogate into pseudodipeptide. An easy and versatile general method for the preparation of pseudodipeptides is described.

The use of peptide bond surrogate is an established approach to overcoming the poor stability, lack of oral absorption, and marginal ability to cross the blood-brain barrier in the use of peptides as therapeutic agents. These shortcomings have been attributed to the rapid degradation of peptides by peptidase.<sup>1</sup> More than dozen peptide bond replacements<sup>2</sup> have been studied to circumvent some of the therapeutic limitations of peptides. Among them, the use of 2-imidazoline moiety as an amide bond isostere has paved the way for the utility of heterocycles as peptide bond isosteres.<sup>2</sup> Recognizing the relationship among the amide (A) functional group, ketomethylene isostere<sup>2a,f,g</sup> (B), and imine (C) functional group, and as an extention of our



involvement with 2-isoxazolines<sup>3</sup>, we have developed the 2-isoxazoline moiety (**D**) as an amide bond replacement.

Synthesis of the psudodipeptides possessing 2-isoxazoline isosteres is envisioned in Fig. 1. The key feature in the reterosynthetic analysis is the asymmetric dipolar cycloadditions with  $\alpha$ -amino nitrile oxides derived from various natural  $\alpha$ -amino acids. This strategy has several merits in the efficiency and versatility of the product formation, and the good control of the stereochemistry in the pseudodipeptides.



As precursors of the chiral dipoles,  $\alpha$ -amino nitrile oxides, optically active N-protected  $\alpha$ -amino aldehydes<sup>4</sup> were needed. Various N-protected  $\alpha$ -amino esters 1-6 were prepared by standard methods<sup>5</sup> in

good yield [1:3 steps (46% overall) from L-Ser, 2:3 steps (40% overall) from L-Ser, 3:3 steps (48% overall) from L-Thr, 4:3 steps (46% overall) from L-Thr, 5:2-steps (87% overall) from L-Leu, 6:2 steps (74% overall) from L-Phe]. The  $\alpha$ -amino esters 1-6 were converted to the corresponding  $\alpha$ -amino aldehydes by DIBAL reduction under the condition a [DIBAL(1.5 eq.), toluene, -78 °C, 1 h] or condition b [DIBAL(2.3 eq.), toluene, -78 °C, 5min]. Due to relative unstability of  $\alpha$ -amino aldehydes,<sup>4</sup> these compounds were directly transformed to the corresponding amino oximes 7-12 (Eq. 1). Experimental results for the amino oxime<sup>6</sup> formation are listed in Table 1.



				reduction	amino	overall yield	
х	R <sub>1</sub> R <sub>2</sub>		R <sub>3</sub>	condition	oxime	(%)	
Boc	-CH	(t-Bu)O-	Н	a	7	52	
Cbz	-C(0	CH3)2O-	Н	b	8	53	
Boc	-C(0	CH3)2O-	CH3	b	9	61	
Boc	Н	-OTBDMS	CH <sub>3</sub>	b	10	<b>54</b>	
Boc	Н	-CH(CH <sub>3</sub> ) <sub>2</sub>	Н	b	11	60	
Boc	Н	-C,H,	н	b	12	47	
	X Boc Cbz Boc Boc Boc Boc	X R <sub>1</sub> Boc -CH Cbz -C(0 Boc -C(0 Boc H Boc H Boc H	X $R_1$ $R_2$ Boc-CH(t-Bu)O-Cbz-C(CH_3)_2O-Boc-C(CH_3)_2O-BocH-OTBDMSBocH-CH(CH_3)_2BocH-CqH_5	X $R_1$ $R_2$ $R_3$ Boc       -CH(*-Bu)O-       H         Cbz       -C(CH_3)_2O-       H         Boc       -C(CH_3)_2O-       CH_3         Boc       H       -OTBDMS       CH_3         Boc       H       -CH(CH_3)_2       H         Boc       H       -CH(CH_3)_2       H         Boc       H       -CCH(CH_3)_2       H         Boc       H       -CgH_5       H	reductionX $R_1$ $R_2$ $R_3$ conditionBoc-CH(t-Bu)O-HaCbz-C(CH_3)_2O-HbBoc-C(CH_3)_2O-CH_3bBocH-OTBDMSCH_3bBocH-CH(CH_3)_2HbBocH-CH(CH_3)_2Hb	reduction         amino           X $R_1$ $R_2$ $R_3$ condition         oxime           Boc         -CH(t-Bu)O-         H         a         7           Cbz         -C(CH_3)_2O-         H         b         8           Boc         -C(CH_3)_2O-         CH_3         b         9           Boc         -C(CH_3)_2O-         CH_3         b         10           Boc         H         -CH(CH_3)_2         H         b         11           Boc         H         -C_6H_5         H         b         12	

Table 1. Preparation of N-protected amino oximes

a: DIBAL (1.5 eq.), toluene, -78 °C, 1h, b: DIBAL (2.3 eq.), toluene, -78 °C, 5 min.

Asymmetric dipolar cycloaddition of the nitrile oxides prepared in situ from the amino oximes 7-12 with N - acryloyl (2R)-bornane-10,2-sultam or N -acryloyl (2S)-bornane-10,2-sultam provided diastereometric mixtures of 2-isoxazoline cycloadducts (Eq. 2).



Table 2. Asymmetric dipolar cycloadditions of  $\alpha$ -amino nitrile oxides

entry	amino oxime	x	<b>R</b> <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Xc	major cycloadduct	ratio (major:minor)	yield (%)	
1	7	Boc	-CH(t-H	Bu)O-	Н	2 <b>R</b>	13	-	57	
2	7	Boc	-CH(t-I	Bu)O-	Н	2S	14	<b>92 : 8</b>	48	
3	8	Cbz	-C(CH	( <sub>3</sub> ) <sub>2</sub> O-	н	2 <b>R</b>	15	-	66	
4	9	Boc	-C(CH	[ <sub>3</sub> ) <sub>2</sub> O-	СН,	2R	16	-	76	
5	10	Boc	н -01	BDMS	CH <sub>3</sub>	2R	17	91 : 9	44	
6	11	Boc	H -CH	H(CH <sub>3</sub> ) <sub>2</sub>	Н	2R	18	89:11	61	
7	12	Boc	н -С	C₀H₅	Н	2R	19	90:10	69	

Table 2 summarizes some of experimental results. Diastereometric ratios (ca. 90:10) were determined by  ${}^{1}$ H NMR and/or HPLC method, and the major cycloadducts 13-19<sup>7</sup> were isolated by the flash chromatography for further reactions. The absolute stereochemistry of the newly generated C12 streogenic center of major cycloadduct 15 was rigorously determined as R by X-ray crystallography (Fig.2).<sup>4</sup> The stereochemistry of C15 carbon was retained as the same sense as that of starting L-Ser. The stereochemistry of other major cycloadducts were tentatively assigned by analogy.



Fig.2. X-ray crystal structure of cycloadduct 15

The N-protected pseudodipeptides 20-24 (Fig.3) were prepared from the corresponding cycloadducts in two steps [ 20 : 78% yield from 13, 21 : 83% yield from 14, 22 : 47% yield from 16, 23 : 76% yield from 18, 24 : 69% yield from 19]. The first step involves the removal of chiral auxiliary using LiOH in aq. THF<sup>2</sup> and next step is a simple esterification of the resulting carboxylic acid.



In summary, we have developed a general synthetic method for the pseudodipeptide possessing 2-isoxazoline isosteres. This kind of a novel peptide bond surrogate will find various applications to the synthesis of enzyme inhibitors.

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## **References and Notes**

<sup>†</sup>To whom inquiries regarding the X-ray crystallographic analysis should be directed.

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- 6. 7 :  $[\alpha]_{D}^{28} = -12.2$  (c 1.00, CHCl<sub>3</sub>), 8 :  $[\alpha]_{D}^{24} = -23.3$  (c 1.84, CHCl<sub>3</sub>), 9 :  $[\alpha]_{D}^{24} = -25.4$  (c 4.50, CHCl<sub>3</sub>), 10 :  $[\alpha]_{D}^{24} = +8.3$  (c 4.01, CHCl<sub>3</sub>), 11 :  $[\alpha]_{D}^{24} = -27.4$  (c 1.05, CHCl<sub>3</sub>), 12 :  $[\alpha]_{D}^{24} = -6.2$  (c 1.85, CHCl<sub>3</sub>) Oximation gave two isomers and major oxime products, 7-12 were isolated.
- 7. **13** :  $[\alpha]_D^{25}$  =-185.0 (c 1.00, CHCl<sub>3</sub>), **14** :  $[\alpha]_D^{24}$  =+188.6 (c 1.00 CHCl<sub>3</sub>), **15** :  $[\alpha]_D^{25}$  =-234.3 (c 2.71, CHCl<sub>3</sub>), **16** :  $[\alpha]_D^{24}$  =-232.9 (c 2.22, CHCl<sub>3</sub>), **17** :  $[\alpha]_D^{24}$  =-148.8 (c 2.56, CHCl<sub>3</sub>), **18** :  $[\alpha]_D^{30}$  =-160.7 (c 2.10, CHCl<sub>3</sub>), **19** :  $[\alpha]_D^{30}$  =-150.2 (c 1.52, CHCl<sub>3</sub>) 8. Crystallographic details: C<sub>27</sub>H<sub>35</sub>N<sub>3</sub>O<sub>7</sub>S, M<sub>r</sub> = 545.65, monoclinic, C2, a =23.581 (5), b =9.098(1),
- 8. Crystallographic details:  $C_{27}H_{35}N_3O_7S$ ,  $M_r = 545.65$ , monoclinic, C2, a = 23.581 (5), b = 9.098(1), c = 14.188 (2) Å,  $\beta = 116.628$  (7)°, V = 2720.9 (8) Å<sup>3</sup>,  $D_x = 1.332$  gcm<sup>-3</sup>, Z = 4,  $\mu = 1.603$  cm<sup>-1</sup>. Intensities were measured on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Mo K $\alpha$  radiation ( $\lambda$ (Mo K $\alpha_1$ ) = 0.70929 Å). The structure was solved by direct methods using SHELXS-86 and refined by full matrix least-squares methods. All non-H atoms were refined anisotropically. The hydrogen atom positions at C(12) and C(15) were calculated and added as fixed contribution to the structure factors. The positional and thermal parameters for all the other hydrogen atoms were refined. The refinement converged to R = 0.037, R<sub>w</sub> = 0.040 where  $\omega = 4(F_{\omega})^2/[\sigma(F_{\omega})^2]^2$  for 3614 observations (I>3  $\sigma(I)$ ) and 458 variables. GOF = 1.31: The largest (shift/esd.) was 0.35. All calculations except for the structure-solving were performed with Enraf-Nonius MolEN program package. The lists of final coordinates are deposited at the Cambridge Crystallographic Data Center.
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