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Synthesis and Derivatization of a Versatile α-Substituted Lactam Dipeptide Isostere

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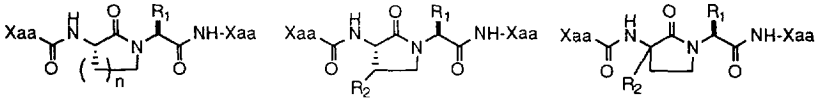
Abstract: The diastereoselective synthesis of a versatile lactam constrained dipeptide isostere is described. The facile derivatization of this intermediate is demonstrated.

The design of peptide isosteres is an important art for the medicinal chemist. Isosteres often provide improved potency, selectivity, and stability to pharmacologically active peptides. In the course of our work on MHC Class II blockade, we sought to employ an α-substituted D-γ-lactam as a constrained dipeptide isostere for a key region of a peptide lead.[1] Lactam constrained peptide isosteres are well known and may be classified as simple sidechain to backbone of various ring sizes (**A**)[2], substituted sidechain to backbone (**B**)[3], and backbone to backbone (**C**)[4-6] types.

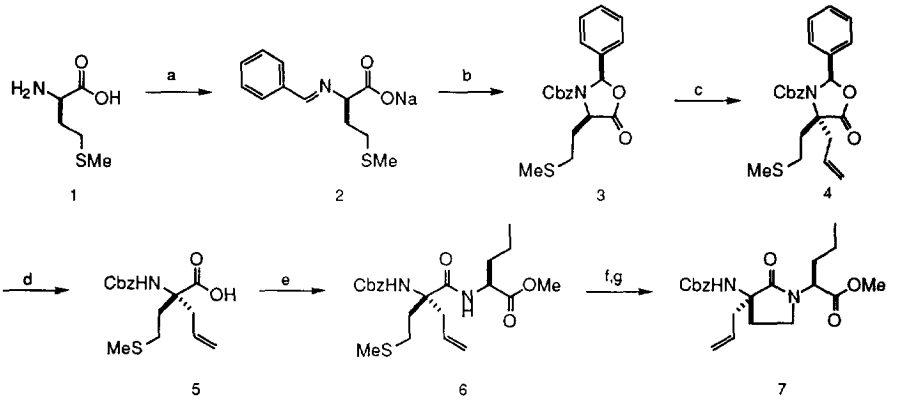


A n=1-3 **B** **C**

Syntheses of each type of lactam constraint have been described.[2-6] We desired an enantioselective route to the α-substituted-γ-lactam isostere (type C) that would allow access to a variety of side chain variants from a single lactam preparation. None of the reported constructions bore these features.[4-6] We sought to employ the Friedinger ring closure strategy[2] in the context of an enantioselectively allylated methionine precursor. The sulfonium salt mediated closure has been applied to type C systems.[5] Stereorandom allylation in a similar though not applicable context has been reported,[4] while appropriate enantioselective alkylations are known.[7] Consequently we were able to meet our goal by fusing elements of each of these syntheses.

Our initial task, then, was to prepare the methionine derived oxazolidinone **3**. In order to access the (R) lactam through the oxazolidinone (predicted to be cis based on literature precedent)[7,8] we needed to start with D-methionine (**1**). The Schiff's base **2** was prepared by condensation with benzaldehyde in 98% yield. Stirring Schiff's base **2** in CH_2Cl_2 at -20°C with benzyl chloroformate produced the oxazolidinone **3** in 88/12 cis/trans ratio. Purification to >98% cis was only possible by preparative RP-HPLC. The cis configuration was confirmed by NOE difference spectroscopy.[9]

Alkylation of **3** with allyl iodide ($KN(SiMe_3)_2$, THF, -78°C) gave the allyl oxazolidinone **4** as a single diastereomer in yields typically around 50%.[10] The α-substituted amino acid equivalent was then hydrolyzed (NaOH, THF/water) to α-(R)-allyl methionine (**5**) in 99% yield. Acylation of **5** with L-norvaline methyl ester provided dipeptide **6** in 93% yield. Conversion of **6** to the methylsulfonium iodide salt (CH_3I, ≥24 hours), followed by treatment with $KN(SiMe_3)_2$ and quenching with ethyl acetate and ammonium chloride gave the lactam dipeptide isostere **7** as a single diastereomer in yields ranging between 57% and 68%.[11,12]

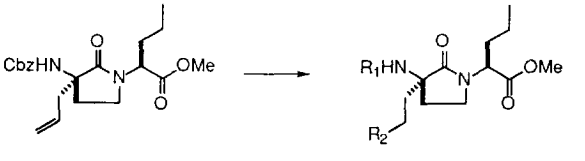


1 2 3 4

5 6 7

a) NaOH, EtOH/H_2O; PhCHO, CH_2Cl_2/pentane, Δ, Dean-Stark b) Cbz-Cl, CH_2Cl_2 -20°C , N_2 c) $KN(SiMe_3)_2$, allyl iodide, THF, -78°C , N_2 d) NaOH, THF/H_2O e) Nva-OMe·HCl, EDC, HOBT, DIEA, CH_2Cl_2, N_2 f) CH_3I g) $KN(SiMe_3)_2$, THF, 0°C, N_2

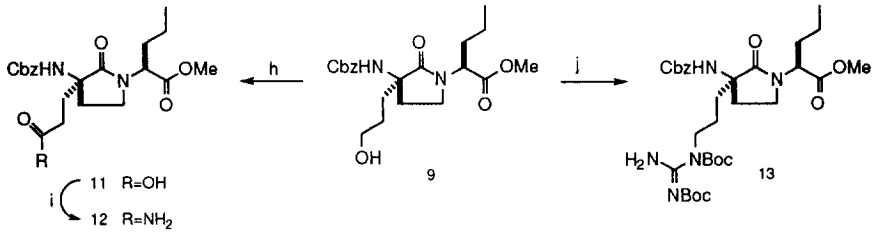
The preparation of a number of natural and unnatural amino acid derivatives by simple one and two step sequences serves to demonstrate the utility of this intermediate. Hydrogenolysis of **7** gave the norvaline analog as the free amine **8** in 85% yield.[13] The 3-hydroxypropyl analog **9** was recovered in 67% yield after hydroboration of **7** with 9-BBN followed by treatment with aqueous NaOH and 30% H_2O_2.[14] Ozonolysis of **7** followed by a $NaBH_4$ quench provided the homoserine derivative **10** in 55% yield.



7 8-10

#	R_1	R_2	Conditions
8	H	CH_3	H_2, 10% Pd-C, MeOH
9	Cbz	CH_2OH	1) 9-BBN, THF 2) NaOH, H_2O_2
10	Cbz	OH	1) O_3, MeOH 2) $NaBH_4$

The 3-hydroxypropyl analog **9** is a useful synthetic intermediate (as is the 2-hydroxyethyl analog), as it can be used to prepare a number of other side chain analogs. The glutamic acid derivative can be prepared by oxidizing **9** ($RuCl_3$, $NaIO_4$, $CH_2Cl_2/CH_3CN/H_2O$) directly to **11** in 56% yield.[15] Compound **11** can then be treated with EDC and HOBT followed by NH_3 to give the glutamine derivative **12**. Finally, using **9** in a Mitsunobu reaction with N,N'-bis(*tert*-butyloxycarbonyl)guanidine provides the Boc protected arginine derivative **13** in 53% yield.[16,17]



h) $RuCl_3$, $NaIO_4$, CH_2Cl_2, CH_3CN, H_2O i) EDC, HOBT, NH_3, CH_2Cl_2 j) N,N'-bis(tert-butyloxycarbonyl)guanidine, PPh_3, DIAD, toluene, 0°C to r.t., N_2, 16 hrs.

In summary, we have developed a diastereoselective synthesis that generates a convenient and synthetically versatile lactam constrained dipeptide isostere. Side chain functionalization can be carried out at the dipeptide stage (as we have shown), or after further extension if more convenient.[1] A variety of side chains can be constructed, as demonstrated. We believe the scheme should provide a useful general procedure.

Acknowledgements

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References and Notes

1. This work will be described in future reports.
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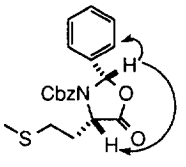
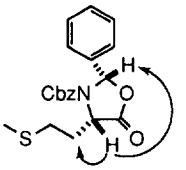
8. It is, of course, important to correctly set the relative stereochemistry of the oxazolidinone product and to choose the correct configuration of amino acid, because the alkylation of the oxazolidinone will take place on the face opposite the 2-phenyl function. See ref. 7 ; also Seebach, D. and Fadel, A., *Helv.Chim.Acta*, **1985**, 68, 1243; Fadel, A. and Salaün, J., *Tetrahedron Lett.*, **1987**, 28, 2243.
9. As shown schematically below on the oxazolidinone made from L-methionine, irradiation of H-2 and H-4 indicate that the major isomer is the cis oxazolidinone.



H-2 irrad.



H-4 irrad.

10. Our yields were lower than those of Karady (ref. 7). We explored different bases, such as LDA (lithium diisopropylamide) and LDEA (lithium diethylamide) *cf.* Seebach (ref. 8), changes in temperature, base equivalents, and addition order. The best conditions we found were to add 1.2 eq. of allyl iodide to a -78°C solution of 1.0 eq. of the oxazolidinone in distilled THF, followed by 1.5 eq. of $KN(SiMe_3)_2$. Larger excesses of allyl iodide were avoided because of the possibility of S-alkylation.
11. Freidinger et. al. (ref. 2) observed 12-15% epimerization of phenylalanine when using NaH as the base for cyclization. The other amino acids in their study were not epimerized, while all were hydrolyzed to the acids to a substantial degree. We observed 25-35% epimerization of norvaline using their acetic acid quench procedure. Alternate bases did not by themselves solve the problem. Only when an ethyl acetate quenching protocol (*cf.* Freidinger) was used with the $KN(SiMe_3)_2$ cyclization reaction did we observe the product as a single diastereomer. No ester hydrolysis was noted. Freidinger also reports an LDA mediated sulfonium salt cyclization to the lactam, while Thaisvirongs (ref. 5) uses lithium N-methylacetamide.
12. NMR (500 MHz, CD_3OD);Compound **7**: δ 7.36 (m, Ph, 5H), 5.84 (m, $CH_2\underline{CH}{=}CH_2$, 1H), 5.16 (d & dd, $CH_2CH{=}\underline{CH_2}$, 2H), 5.03 (s, $Ph\underline{CH_2}O$, 2H), 4.71 (dd, Nva-α, 1H), 3.71 (s, $COO\underline{CH_3}$, 3H), 3.41 (m, Lac-γ, 1H), 3.32 (m, Lac-γ, 1H), 2.42 (m, Lac-β & $\underline{CH_2}CH{=}CH_2$, 3H), 2.21 (m, Lac-β, 1H), 1.89 (m, Nva-β, 1H), 1.79 (m, Nva-β, 1H), 1.48-1.26 (m, $CH_2\underline{CH_2}CH_3$, 2H), 0.96 (t, Nva-CH_3, 3H). MS: found: 388.1987; calculated 388.1998 [HRMS].
13. NMR (500 MHz, CD_3OD);Compound **8**: δ 4.64 (dd, Nva-α, 1H), 3.70 (s, $COO\underline{CH_3}$, 3H), 3.35 (m, Lac-γ, 2H), 2.18 (m, Lac-β, 1H), 1.92 (m, Lac-β, 1H), 1.89 (m, Nva-β, 1H), 1.79 (m, Nva-β, 1H), 1.55 (m, α-$\underline{CH_2}CH_2CH_3$, 2H), 1.48-1.26 (m, both $CH_2\underline{CH_2}CH_3$'s, 4H), 0.96 (t, Nva-CH_3, 3H), 0.93 (t, α-$CH_2CH_2\underline{CH_3}$, 3H). MS: found: 256.1809; calculated 256.1787 [HRMS].
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17. NMR (500 MHz, CD_3OD);Compound **14**: δ 7.31 (m, Ph, 5H), 5.03 (s, $Ph\underline{CH_2}O$, 2H), 4.72 (dd, Nva-α,1H), 3.86 & 3.77 (m, $CH_2CH_2\underline{CH_2}N(Boc)C(=NBoc)NH_2$, 1H each), 3.67 (s, $COO\underline{CH_3}$, 3H), 3.38 (m, Lac-γ, 2H), 2.48(m, Lac-β, 1H), 2.16(m, Lac-β, 1H), 1.89 (m, Nva-β, 1H), 1.79 (m, Nva-β, 1H), 1.69 (br, $CH_2\underline{CH_2}CH_2N(Boc)C(=NBoc)NH_2$, 2H), 1.52 (s, $CH_2CH_2CH_2N(\underline{Boc})C(=NBoc)NH_2$, 9H), 1.46 (s, $CH_2CH_2CH_2N(Boc)C(=N\underline{Boc})NH_2$, 9H), 1.48-1.26 (m, $CH_2\underline{CH_2}CH_3$, 2H), 1.25 (d, $\underline{CH_2}CH_2CH_2N(Boc)C(=NBoc)NH_2$, 2H), 0.96 (t, Nva-$CH_3$, 3H). MS: 648.6 (M+1) [ESI].

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