Bioorganic & Medicinal Chemistry Letters, Vol.3, No.2, pp. 231-234, 1993
Printed in Great Britain

0960-894X/93 \$6.00 + .00

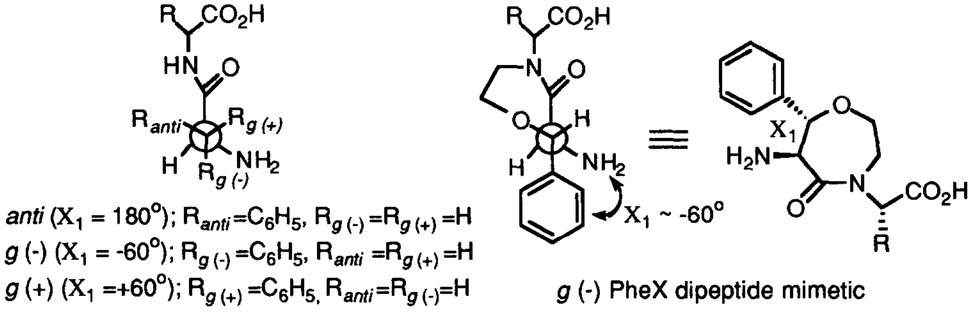
THE SYNTHESIS OF 6-AMINO-5-OXO-7-PHENYL-1,4-OXAZEPINES AS CONFORMATIONALLY CONSTRAINED *GAUCHE* (-) DIPEPTIDE MIMETICS

Timothy P. Burkholder*, Edward W. Huber, and Gary A. Flynn
Marion Merrell Dow Research Institute, 2110 E. Galbraith Road, Cincinnati, Ohio 45215

(*Received in USA* 9 *October* 1992)

Abstract: 6-Amino-5-oxo-7-phenyl-1,4-oxazepines were synthesized from β-phenylserine by a versatile route to provide *gauche* (-) phenylalanyl-X dipeptide mimetics(1a-h). NMR was utilized to elucidate the solution conformation of the protected mimetics. The seven membered ring was found to be in a chair conformation with the phthalimide moiety and the phenyl ring pseudo-equatorial, consistent with the *gauche* (-) conformation (dihedral angle X_1=-60°). Dipeptide mimetic 2 was synthesized from 1a to probe the effect of the *gauche* (-) conformation on the inhibition of metalloproteinases These *gauche* (-) dipeptide mimetics may be useful tools for the investigation of conformational preferences of enzyme substrates and receptor ligands.

Conformationally restricted molecules that mimic energetically favored and hence highly populated orientations of amino acid side chains are useful in probing the binding conformations of enzyme substrates and receptor ligands.[1] Three staggered conformations of phenylalanyl containing dipeptides with respect to the dihedral angle X_1 are *anti* (X_1=180°), *gauche* (-) (*g* (-), X_1=-60°), and *gauche* (+) (*g* (+), X_1=60°) (Figure 1). The *anti* and *g* (-) conformations have a single *gauche* interaction between the β-phenyl ring and a substituent at the α-carbon. In the *g* (+) conformation, the β-phenyl ring has *gauche* interactions with both substituents at the α-carbon and therefore, it is predicted to be higher in energy and less populated.[2] We have been interested in mimicking low energy conformations of dipeptides and previously we described the synthesis of benzazepinones as mimics of *anti* conformations of phenylalanine containing dipeptides.[3] We felt that 6-amino-5-oxo-7-phenyl-1,4-oxazepine *g* (-) dipeptide mimetics would be complementary to the benzazepinone *anti* mimetics because each ring system would mimic a specific conformation with respect to X_1 while maintaining similar Ψ and ω angles. These tools may aid the investigation of conformational preferences for enzyme substrates and receptor ligands.

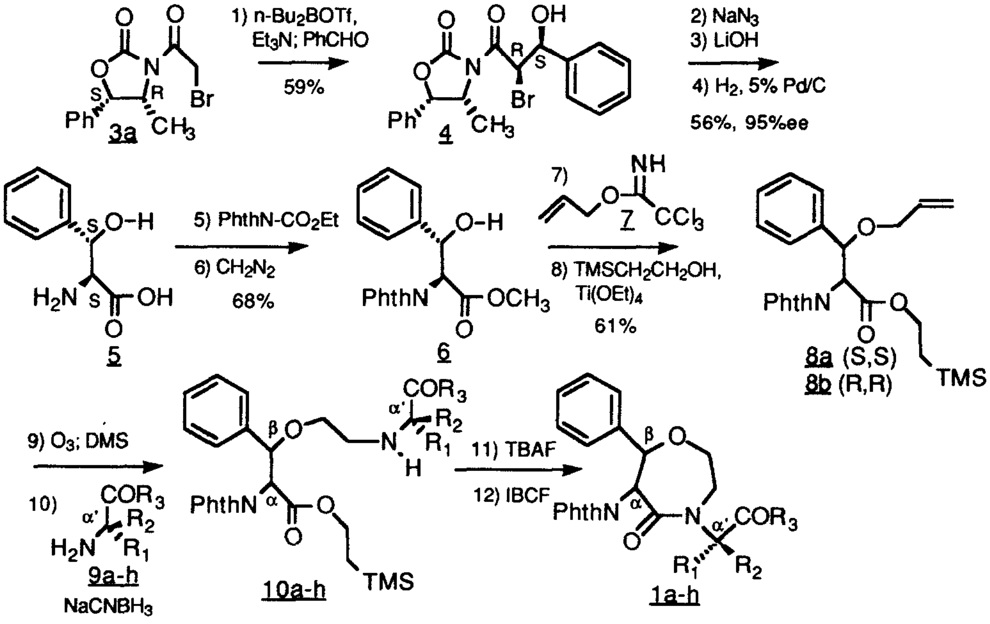


anti (X_1 = 180°); $R_{anti}=C_6H_5$, $R_{g(-)}=R_{g(+)}=H$
g (-) (X_1 = -60°); $R_{g(-)}=C_6H_5$, $R_{anti}=R_{g(+)}=H$
g (+) (X_1 =+60°); $R_{g(+)}=C_6H_5$, $R_{anti}=R_{g(-)}=H$

g (-) PheX dipeptide mimetic

Figure 1 Staggered conformations of PheX and *g* (-) PheX mimetic.

We report a versatile synthesis of 6-amino-5-oxo-7-phenyl-1,4-oxazepines as conformationally constrained *g* (-) PheX dipeptide mimetics. (S,S)-*Erythro*-β-phenylserine (5) was synthesized by the method of Evans[4] (33% overall yield from 3a, $[\alpha]_D$ =+79.4° (c=1, 6N HCl), 95% ee,[5] Scheme 1). The amine 5 was protected with N-carbethoxyphthalimide (Na_2CO_3, H_2O, 20°C) to give the corresponding phthalimido-carboxylic acid which was esterified with diazomethane to afford methylester 6 in 68% yield ($[\alpha]_D$ =-149°, c=1, $CHCl_3$). The alcohol was allowed to react with allylimidate 7 in the presence of trifluoromethanesulfonic acid in methylene chloride/cyclohexane to afford the corresponding allyl ether in 70% yield.[6] Transesterification[7] ($Ti(OEt)_4$, $TMSCH_2CH_2OH$, THF, Δ) afforded the β-trimethylsilylethyl ester 8a in 87% yield (Scheme 1). Allyl ether 8b was synthesized by an analogous method starting with (4S,5R)-(-)-4-methyl-5-phenyl-2-oxazolidinone.[8] Allyl ethers 8a and 8b were treated with ozone in methylene chloride/methanol at -78°C followed by methylsulfide to afford the corresponding aldehydes in 67-80% yield (Scheme 1). Reductive amination of amino acid derivatives 9a-h[9] and the aldehyde derived from 8a or 8b afforded the esters 10a-h in 41-83% yield. Deprotection of the β-trimethylsilylethyl ester (TBAF, THF, 20°C) and intramolecular cyclization (isobutylchloroformate, N-methylmorpholine, THF, 0°C) afforded the substituted oxazepines 1a-h in 46-81% yield (Scheme 1, Table 1).



Scheme 1

Table 1.

				Yield		Stereochemistry		
1	R_1	R_2	R_3	step 10	steps 11 & 12	α	β	α'
a	*i*-Bu	H	O-Bn	73%	78%	S	S	S
b	H	C_6H_5	O-CH_2CH_3	69%	75%	S	S	R
c	C_6H_5	H	NH-*i*-Bu	68%	65%	S	S	S
d	$CH_2CH_2SCH_3$	H	NH-*i*-Bu	83%	78%	S	S	S
e	$CH_2CH_2SCH_3$	H	O-CH_3	76%	46%	S	S	S
f	*i*-Bu	H	O-*tert*-Bu	60%	78%	S	S	S
g	*i*-Bu	H	O-*tert*-Bu	56%	81%	R	R	S
h	*i*-Bu	H	O-Bn	41%	63%	R	R	S

NMR was utilized to determine the solution conformation of the protected mimetics. For 1a the observed coupling constant between the α and β protons (J_{H_6,H_7}= 8.9 Hz) and the transannular NOEs observed for H_3-H_6 and H_2-H_7 are consistent with the seven membered ring adopting a chair conformation with the phthalimide moiety and the phenyl ring pseudo-equatorial (Figure 2). This conformation of the seven membered ring constrains the phenyl ring and the phthalimide moiety in the *g* (-) conformation where the dihedral angle X_1 is approximately -60°. The observed coupling constants ($J_{H_\alpha,H_{\beta S}}$=10.3Hz, $J_{H_\alpha,H_{\beta R}}$=5.0Hz) indicate conformational rigidity of the leucine side chain. Two low energy conformations from molecular modeling studies of the *g* (-) PheLeu mimetic 1a which are consistent with the observed NMR results are shown in Figure 2.

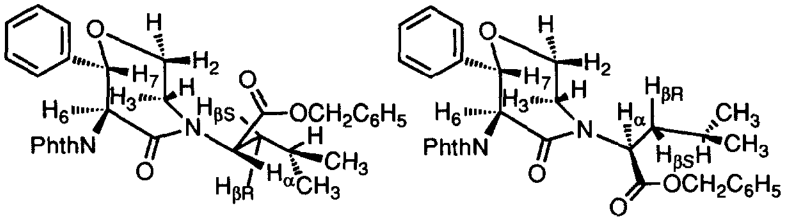
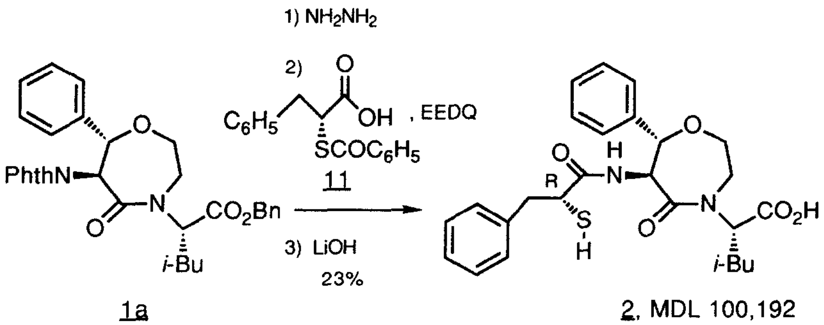


Figure 2

Incorporation of the (R)-2-benzoylthio-3-phenyl-propionic acid side chain on the *g* (-) PheLeu constrained mimetic 1a, allowed us to investigate the effect of the *g* (-) conformation of phenylalanyl-leucine on the inhibition of metalloproteinases. Deprotection of 1a (NH_2NH_2, CH_3OH, Δ) afforded the amino-methyl ester.[10] Coupling with (R)-2-benzoylthio-3-phenyl-propionic acid (11),[11] and saponification (LiOH, THF/CH_3OH, 0°C) afforded 2 (MDL100,192, Scheme 2). MDL 100,192 was found to be a poor inhibitor of atriopeptidase (neutral endopeptidase 24.11, NEP) and angiotensin converting enzyme (ACE). A detailed comparison of the effect of the *g* (-) and *anti* conformations of phenylalanyl-leucine with inhibitors on NEP and ACE will be described in a full paper. The K_i for MDL 100,192 for NEP was 330nM and the K_i for ACE was 50μM.



Scheme 2

ACKNOWLEDGMENTS

We would like to thank Douglas W. Beight for providing a sample of 11 and Dr. F. Mark Laskovics for synthesizing additional quantities of (S,S)- and (R,R)-*erythro*-β-phenylserine. The biochemical evaluation of 2 was performed by Jack R. Koehl and Drs. Eugene L. Giroux and Shujaath Mehdi.

---

[1] For a review of conformationally restricted receptor-selective peptide ligands see Hruby V.J., Al-Obeidi F., Kazmierski W.M. *Biochem. J.*, **1990**, *268*, 249.

[2] For a recent example of conformationally restricting aromatic amino acid side-chains into gauche (-) and gauche (+) conformations using 1,2,3,4-tetrahydroisoquinolinecarboxylic acid see Kazmierski W.M.,Yamamura H.I., Hruby V.J., *J. Am. Chem. Soc.*, **1991**, *113*, 2275.

[3] a) Flynn, G.A.; Giroux, E.L.; Dage, R.C. *J. Am. Chem. Soc.*, **1987**, *109*, 7914.
b) Flynn, G.A.; Burkholder, T.P.; Huber, E.W.; Bey, P. *Bioorganic and Medicinal Chemistry Letters*, **1991**, *1*, 309.

[4] Evans, D.A.; Sjogren, E.B.; Weber, A.E.; Conn, R.E. *Tetrahedron Lett.*, **1987**, *28*, 39.

[5] Based on literature rotation for (S,S)-*Erythro*-β-phenylserine of $[\alpha]_D = +82.6^o$, (c=1, 6NHCl), Arold Von H., Feist H. *J.Prakt.Chem.*, **1970**, *312*, 1145.

[6] Burkholder, T.P.; Le, T.-B.; Giroux, E.L.; Flynn, G.A. *Bioorganic and Medicinal Chemistry Letters*, **1992**, *2*, 579.

[7] a) Seebach D., Hungerbuhler E., Naef R., Schnurrenberger P., Weidmann B., Zuger M. *Synthesis* **1982**, 140.
b) Rehwinkel, H. Steglich W. *Synthesis*, **1982**, 826.

[8] (R,R)-*Erythro*-N-phthalimido-β-phenylserine methyl ester had a rotation of $[\alpha]_D = +149^o$ (c=1.01, $CHCl_3$)

[9] 9a,b,e,f,g,h were obtained from Sigma Chemical Company. 9c and 9d were prepared from (S)-phenylglycine and (S)-methionine. The amine was protected as the *tert*-butyl carbamate and the carboxylic acid was converted to the N-*i*-butyl carboxamide with *i*-butylamine under mixed anhydride conditions. The boc group was removed with etheral · HCl to afford the HCl salts, 9c and 9d respectively, which were used without further purification.

[10] The benzyl ester was converted to the methyl ester during the removal of the phthalimide protecting group.

[11] Strijtveen B., Kellogg R.M. *J. Org. Chem.* **1986**, *51*, 3664.