Synthesis of β-Lactam Scaffolds for Ditopic Peptidomimetics

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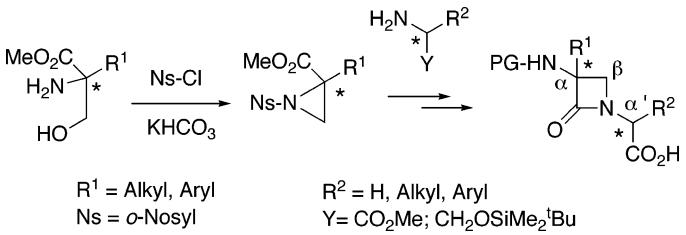
ABSTRACT



Ring opening of α-substituted- α-methoxycarbonyl-N-nosylaziridines provides a practical access to enantiopure α,α'- disubstituted β-lactam scaffolds, novel types of ditopic reverse turn surrogates. The procedure is general, short, and high yielding and starts from handy a-substituted serinates and α-amino acid derivatives.

Since their introduction by Freidinger,[1] externally scaffolded lactam peptides **1** (Figure 1) are among the most efficient

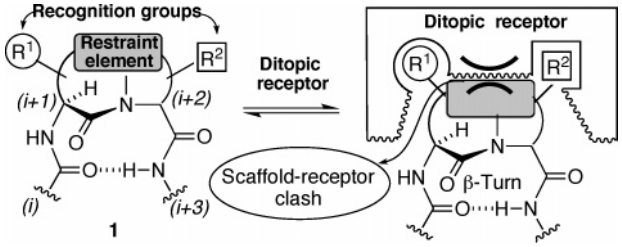


Figure 1. Scaffold/ditopic receptor interaction in *β*-turn lactam peptidomimetics: a bulky restraint element may preclude efficient recognition of R^1 and R^2 groups.

and popular β-turn mimics.[2] They present two major advantages over cyclic peptides or internally scaffolded peptidomimetics: (a) recognition by receptors can be tuned owing to the flexibility of the C=O···HN hydrogen bond, and (b) incorporation of the *β*-turn surrogate (i + 1) - (i + *2)* segment into the peptide chain is not compromised by macrocyclization reactions.

The design of lactam peptidomimetics presents, however, an important limitation. As the restraint element (cycle) and recognition groups (R1, R2) are usually crammed in the scaffold, it is very difficult to devise lactam structures free from undesired interactions with the receptor, especially for ditopic[3] ones.

Most of the lactam peptidomimetics used routinely as β-turn surrogates (Figure 2) require one or two cycles to correctly overlay the dihedral angles of the *β*-genic (i + 1)–(*i* + *2*) residues to a particular *β*-turn type (e.g., Nagai's bicyclic lactams **2** or Freidinger's lactams **3**). Hence, the

(1) (a) Freidinger, R. M.; Veber, D. F.; Perlow, D. S.; Brookas, J. R.; Saperstein, R. *Science* **1980**, *210*, 656–658. (b) Freidinger, R. M. *J. Med. Chem.* **2003**, *46*, 5553–5566.

(2) For reviews, see: (a) Souers, A. J.; Ellman, J. A. *Tetrahedron* **2001**, *57*, 7431–7448. (b) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854. (c) Kahn, M.; Eguchi, M. Synthesis of Peptides Incorporating *β*-Turn Inducers and Mimetics. In *Houben-Weyl, Methods of Organic Chemistry*; Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; Thieme: Stuttgart, New York, 2003; Vol. E22c, pp 695–740 and references therein.

(3) *Comprehensive Supramolecular Chemistry*; Lehn, J.-M., Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, 1996.

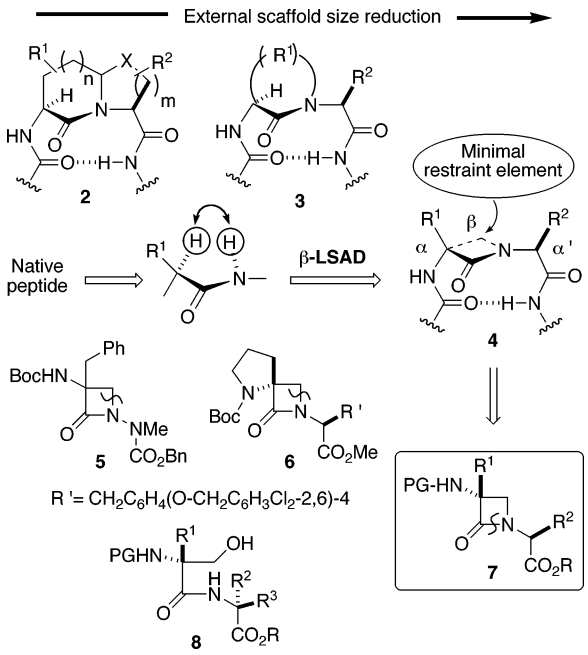


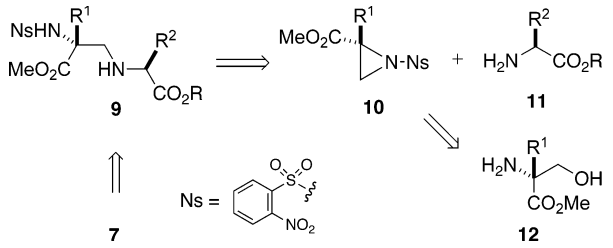
Figure 2. β-Lactam scaffold-assisted design (β-LSAD): formal insertion in the native peptide of a carbon atom (Cα-*H* + *H*−N -> *CH*$_2$) provides the minimal pseudopeptide **4** required to accommodate a β-turn conformation. PG: protecting group.

design of "minimal" lactam peptidomimetics incorporating restraint elements as small as possible becomes highly attractive. Within this endeavor, we have undertaken the development of pseudopeptides **4** by applying a "β-lactam scaffold-assisted design" (β-LSAD). Mimetics resulting from such an approach differ only in one single carbon atom from the native peptides and are characterized by (a) an (*i* + *1*) residue consisting of an R-alkyl-R-amino β-lactam ring unsubstituted at position β and (b) a linear disposition of the Cα, N, and Cα' atoms.[4]

Although the synthesis of scaffolds for *monotopic* β-lactam pseudopeptides **4** (R^2 =H) is known,[4,5] no general method exists to prepare the *ditopic* β-lactam counterparts required for the full development of β-LSAD.[6] Only the syntheses of the racemic azapeptidomimetic β-lactam **5**[7] and the proline-derived β-lactam scaffold **6**[8] have been reported. In both instances, a Mitsunobu-type N1−C4 cyclization was the key step to form the 2-azetidinone ring from R-substituted serine dipeptides **8**. Unfortunately, the general applicability of such intermediates to the synthesis of β-lactam scaffolds **7** is drastically limited by the low acidity of the amide moiety and the steric hindrance of substituents nearby.[9]

Herein, we report a general preparation of enantiopure ditopic β-lactam scaffolds **7** by means of an alternative N1−C2 ester−amine cyclization strategy (Scheme 1). Our

Scheme 1



synthetic plan employed β-*N*-peptidyl-azaserinates **9** as β-lactam ring precursors and involved the reaction of R-amino esters **11**[10] with *N*-(*o*-nosyl)-aziridines **10**,[11] which acted as N-protected, O-activated equivalents of R-substituted serinates **12**.[12]

Nosylation of methyl α-benzylserinate **15** under standard conditions (*o*-Ns-Cl, Et_3N, DMAP catalyst) proved surprisingly troublesome (Scheme 2), yielding the expected N- monoprotected product in less than 25% yield. Changing to inorganic bases (K_2CO_3) also led to the formation of the same product along with the unexpected oxazolidin-2-one **16**, incorporating a carbamate carbonyl group from potassium carbonate. Gratifyingly, we found that R-substituted methyl serinates (**15** and **17**) or their peptides (**18**) were cleanly

(4) Palomo, C.; Aizpurua, J. M.; Benito, A.; Miranda, J. I.; Fratila, R. M.; Matute, C.; Domercq, M.; Gago, F.; Martin-Santamaria, S.; Linden, A. *J. Am. Chem. Soc.* **2003**, *125*, 16243−16260.

(5) (a) Macias, A.; Ramallal, A. M.; Alonso, E.; Del Pozo, C.; Gonzalez, J. *J. Org. Chem.* **2006**, *71*, 7721−7730. (b) Palomo, C.; Aizpurua, J. M.; Benito, A.; Galarza, R.; Khamrai, U. K.; Vazquez, J.; DePascual-Teresa, B.; Nieto, P. M.; Linden, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3056−3058. (c) Wu, Z.; Georg, G. I.; Cathers, B. E.; Schloss, J. V. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 983−986.

(6) Freidinger-type β-lactam scaffolds (R^1H): (a) Turner, J. J.; Sikkema, F. D.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. *Synlett* **2001**, 1727−1730. (b) Sreenivasan, U.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1993**, *36*, 256−263. For related β-substituted β-lactam scaffolds, see: (c) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Benito, A.; Cuerdo, L.; Fratila, R. M.; Jimenez, A.; Loinaz, I.; Miranda, J. I.; Pytlewska, K. R.; Micle, A.; Linden, A. *Org. Lett.* **2004**, *6*, 4443−4446. (d) Alonso, E.; López-Ortiz, F.; Del Pozo, C.; Peralta, E.; Macías, A.; González, J. *J. Org. Chem.* **2001**, *66*, 6333−6338. (e) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383−389. (f) Maier, T. C.; Frey, W. U.; Podlech, J. *Eur. J. Org. Chem.* **2002**, 2686−2689.

(7) Broadrup, R. L.; Wang, B.; Malachowski, W. P. *Tetrahedron* **2005**, *61*, 10277−10284.

(8) (a) Bittermann, H.; Gmeiner, P. *J. Org. Chem.* **2006**, *71*, 97−102. (b) Bittermann, H.; Böckler, F.; Einsiedel, J.; Gmeiner, P. *Chem.−Eur. J.* **2006**, *12*, 6315−6322.

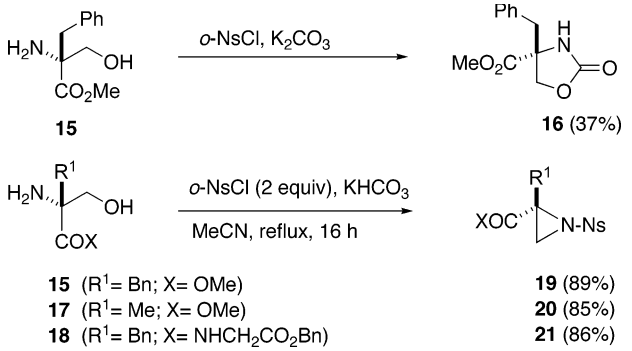
(9) For instance, in our hands, dipeptide CHO-(D)-Ser(αBn)-GlyOBn failed repeatedly to cyclize to the corresponding β-lactam **7** (PG = CHO; R^1 = Bn; R^2 = H, R = Bn) under several Mitsunobu conditions, including those reported in refs 7 and 8.

(10) Alternative access to β-*N*-peptidyl-azaserinates **9** was also explored from R-amino esters (including unhindered benzyl glycinate) and R-substituted serines with the hydroxy group activated as *O*-mesylate **13** and lactone **14**, but all attempts to prepare the desired α,β-diamino esters met with failure.

(11) Monographs on the reactivity of aziridines: (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599−619. (b) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Pergamon: New York, 1996; Vol. 1A, p 1−60. (c) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519−1559. (d) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693−1715.

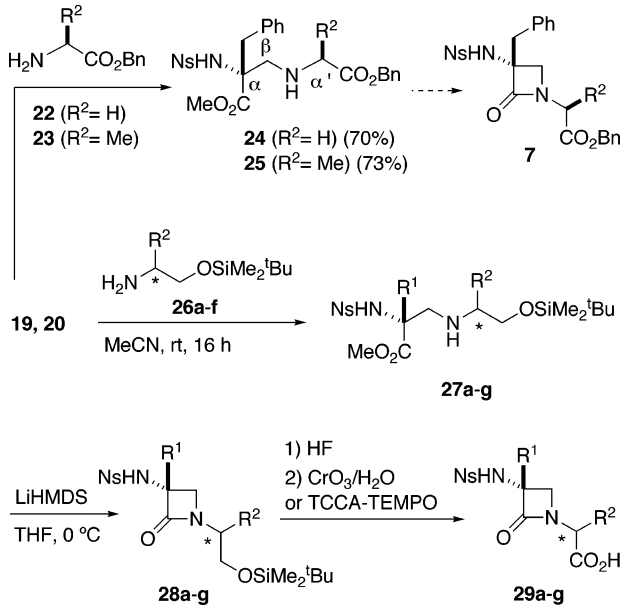
(12) Available from (D)-serine. See: Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194−1216.

Scheme 2



transformed into the corresponding *N*-nosyl aziridines by treatment with 2 equiv of *o*-Ns-Cl and excess $KHCO_3$ in acetonitrile at reflux. This reaction avoids cumbersome N- or O-monoprotections required for conventional stepwise transformation of α,β-aminoalcohols into *N*-sulfonylaziridines[13] and enables further in situ ring-opening reactions of the products, *vide infra*. Reaction of benzyl glycinate **22** and benzyl alaninate **23** with N-nosylaziridine **19** (Scheme 3) led to a clean and

Scheme 3



completely *β*-regioselective ring-opening reaction to form the R-substituted *β*-*N*-peptidyl-azaserines **24** and **25** in good yields.[14] These compounds might be converted into **7** after previous hydrolysis to the corresponding *β*-amino acids, followed by cyclodehydration.[15] However, all attempts to hydrolyze the methoxycarbonyl group were thwarted by previous debenzylation or decomposition. Alternative intramolecular base-promoted direct ester-amine condensation of **24** and **25** to **7** also proved impractical.[16] These behaviors were attributed primarily to the sterical shielding around the CO^2Me group and also to the latent acidity of the α'proton. To cancel this later effect, b-aminoalcohol silyl ethers **26**[17] were investigated as nonenolizable surrogates of R-amino esters **22** and **23**.

As shown in Table 1, aziridines **19** and **20** give a smooth ring-opening reaction with amines **26** to the corresponding

Table 1. Synthesis of *β*-Lactam Scaffolds **29** from Aziridines **19** and **20**

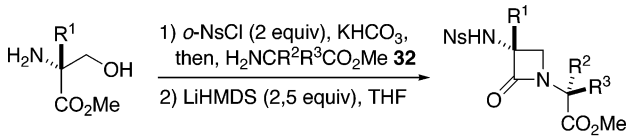
entry	R^1	R^2	product	yield (%)[a]	product	yield (%)[c]
1	CH_2Ph	H	**27a**	72 (75)[b]	**29a**	62 (81)[d]
2	CH_2Ph	Me, (*S*)*	**27b**	56 (67)[b]	**29b**	82
3	CH_2Ph	Me, (*R*)*	**27c**	56 (65)[b]	**29c**	81
4	CH_2Ph	Ph, (*S*)*	**27d**	52	**29d**	60
5	CH_2Ph	Ph, (*R*)*	**27e**	56	**29e**	50
6	Me	H	**27f**	-- (66)[b]	**29f**	-- (74)[d]
7	Me	^{i}Pr, (*R*)*	**27g**	53	**29g**	78

[a] Yield of pure isolated products. [b]Overall yields of **27** from α-alkyl serinates **15** and **17** by in situ ring opening of intermediate aziridines **19** and **20** with *β*-aminoalcohol silyl ethers **26**. [c]Overall yields of the pure products for transformation **27——29**. [d]Oxidation step conducted using the TCCA/TEMPO reagent.

α,β-diamino esters **27**, but in contrast to their enolizable counterparts **24** and **25**, cyclization of **27–28** was now conducted in virtually quantitative yields (90–98%) upon treatment with LiHMDS.[18] Finally, the C-terminal carboxylic group was restored after desilylation by oxidation with Jones' reagent or the trichloroisocyanuric acid/2,2,6,6-tetramethyl-1-piperidinyloxyl system (TCCA/TEMPO).[19] The method was applicable both to ditopic and to monotopic *β*-lactam scaffolds (see entries 1 and 6 in Table 1). Furthermore, isolation of aziridines was not necessary to prepare *β*-N-substituted azaserines **27**. Indeed, slightly higher overall yields were attained when *N*-nosyl aziridines obtained from methyl serinates **15** and **17** were immediately opened in situ with *β*-aminoalcohol silyl ethers (entries 1–3 and 6).

Importantly, the method could also be extended to the synthesis of α,α',α'-trisubstituted *β*-lactam scaffolds (Scheme 4, Table 2). We found that ring-opening reaction of *N*-*o*-nosylaziridines generated in situ from R-substituted methyl

Scheme 4



(13) For a related one-pot tosylation/aziridination of α,β-aminoalcohols, see: Bieber, L. W.; de Araújo, M. C. F. *Molecules* **2002**, *7*, 902–906.

(14) To the best of our knowledge, these examples represent the first general preparation of α-substituted β-*N*-peptidyl-azaserines in enantiopure form. For stereocontrolled synthesis of α-substituted β-*N*-alkyl-azaserines, see: (a) Pfammatter, E.; Seebach, D. *Liebigs Ann. Chem.* **1991**, 1323–1336. (b) Burgaud, B. G. M.; Horwell, D. C.; Padova, A.; Pritchard, M. C. *Tetrahedron* **1996**, *52*, 13035–13050.

Table 2. Synthesis of β-Lactam Scaffolds **33** from α-Substituted Serines **15**, **17**, **30**, and **31**

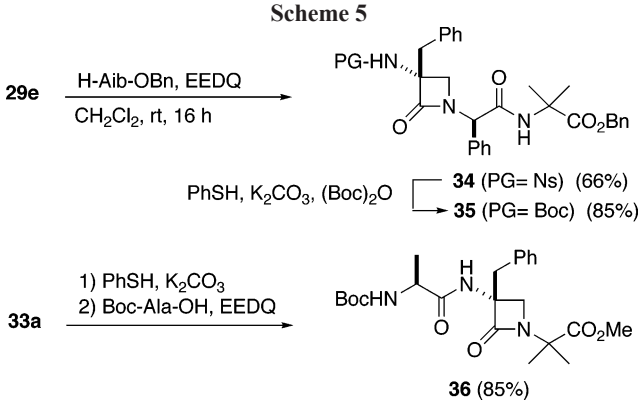
entry	serine	R^1	product	R^2	R^3	yield (%)[a]
1	**15**	CH_2Ph	**33a**	Me	Me	70
2	**15**	CH_2Ph	**33b**	$-(CH_2)_4-$		51
3	**17**	Me	**33c**	$-(CH_2)_4-$		59
4	**30**	^{i}Bu	**33d**	Me	Me	45
5	**31**	$CH_2C_6F_5$	**33e**	Me	Me	40

[a] Overall nonoptimized yields of pure isolated products **33** from α-alkyl serinates. One equivalent of R-amino ester was used in all examples.

serinates **15**, **17**, **30**, and **31** with the α,α-disubstituted amino esters[20] **32** afforded the corresponding α,β -diamino esters in a one-pot operation. Treatment of these intermediates with LiHMDS resulted in clean cyclization to provide the corresponding β-lactams **33** in fair to good overall yields. These results confirm the striking effect of the lack of α' acidic protons on the reaction and represent one of the shortest and more efficient routes to prepare highly hindered β-lactam peptidomimetics.

Finally, coupling reactions involving orthogonal depro tection reactions at the N- and C-termini of the β-lactam dipeptides **29e** and **33a** were performed to illustrate the easy incorporation of the β-lactam scaffolds prepared into pseudopeptides (Scheme 5). After screening, *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ)[21] was found to be the dehydration reagent of choice to couple the carboxylic function of **29e** to sterically demanding α-amino esters (e.g., H−Aib−OBn) without significant epimerization at the phenylglycine residue.[22] On the other hand, standard N-denosylation with thiophenol and simultaneous reprotection with the Boc group was achieved in high yield.[23] Conversely, inversion of the nosyl cleavage/peptide coupling sequence in **33a** permitted an efficient and epimerization- free elaboration of the highly hindered α-amino-β-lactam group (e.g., with Boc−Ala−H), providing the pseudopeptide **36** in high yield.

Scheme 5



In conclusion, a short, practical, and epimerization-free procedure to obtain mono- and ditopic β-lactam scaffolds has been developed, paving the way for the full application of the β-LSAD concept. Several families of β-lactam pseudopeptides resulting from this approach have been prepared in our laboratory, and evaluation of their conformational and biological behavior is underway.

Acknowledgment. We thank the Ministerio de Educación y Ciencia (MEC, Spain) (Project: CTQ2006-13891/BQU), UPV/EHU, and Gobierno Vasco (ETORTEK-BiomaGUNE IE-05/143) for financial support and SGIker UPV/EHU for NMR facilities. Grants from MEC to J.O. and from the European Commission (Marie Curie HMPT-CT-2000-00173) to E.B. are acknowledged.

Supporting Information Available: Preparation procedures and physical and spectroscopic data for compounds **13**−**36**. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) For a related carboxylic acid−amine cyclization on α-unsubstituted β-*N*-peptidyl azaserines, see ref 6a.

(16) A survey of procedures to obtain 2-azetidinones by cyclization of β-amino esters: Backes, J. In *Houben-Weyl, Methoden der Organischen Chemie, Band E16b*; Müller, E., Bayer, O., Eds.; Thieme: Stuttgart, 1991; pp 97−101.

(17) β-Aminoalcohol *tert*-butyldimethylsilyl ethers **26** were prepared in 75−95% overall yields from the corresponding α-amino acids. See Supporting Information for details.

(18) Gennari, C.; Venturini, I.; Gilson, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227−230.

(19) De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999−5001.

(20) For some reviews on the preparation of α,α-disubstituted amino esters, see: (a) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127−5143. (b) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517−3599.

(21) (a) Kiso, Y.; Yajima, H. *J. Chem. Soc., Chem. Commun.* **1972**, 942−943. (b) Kiso, Y.; Kai, Y.; Yajima, H. *Chem. Pharm. Bull.* **1973**, *21*, 2570−2510.

(22) Phenylglycine derivatives are prone to loss of configurational integrity under basic conditions. When transformation **29e** → **34** was tried with EDC/HOBT/Et_3N ("water-soluble carbodiimide method"), complete epimerization was observed at the α' position.

(23) Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253−5256.