Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 5983–5986
Tetrahedron Letters

# Diastereoselective synthesis of homologous bicyclic lactams—potential building blocks for peptide mimics ☆

Bernhard Westermann,* Nicole Diedrichs, Ralf Krelaus, Armin Walter and Ina Gedrath

*Leibniz-Institute of Plant Biochemistry, Department of Bioorganic Chemistry, Weinberg 3, 06120 Halle (Saale), Germany*

Received 27 April 2004; revised 27 May 2004; accepted 11 June 2004

**Abstract**—Bicyclic lactams serve as building blocks for the synthesis of conformationally restricted peptides. A route to these building blocks is described. They can serve as *cis*- and *trans*-peptide bond surrogates. Due to the de novo synthesis, both enantiomeric forms of these products can be produced. Key steps are a lipase-catalyzed saponification of oximes and a highly diastereoselective cyclization utilizing phenylselenyl bromide. In addition, attachment to a solid support has been achieved.


The synthesis of conformationally restricted amino acids and their utilization in the synthesis of peptide conformation mimics such as β-turn mimics has been of considerable interest.[2–4] Therefore, efforts have been directed towards the synthesis of bicyclic lactams **1**, which are effective in resembling peptidic secondary structures.[5–8] In addition, these heterocyclic products are of particular relevance, because they mimic a Xaa-Pro dipeptide either in the *cis*- or the *trans*-configuration (Fig. 1).[9]

Although derivatives have been made that mimic *cis*-amide bonds or *trans*-amide bonds, the structure of **1** offers the incorporation of both of these structural elements into a peptide utilizing the same building block.[10,11]

Despite a large variety of methods successfully carried out for the synthesis of derivatives of **1**, strategies leading to homologous [*x*,*y*,0]-bicyclic β-turn mimetics are rare.[5] One reason for these limitations is that most syntheses start from products provided by the *chiral pool*.[12] This limits access to homologous starting materials and to the natural stereoisomer. In this communication we present the de novo synthesis of homologous bicyclic lactams and their utilization for the synthesis of tetrapeptides.

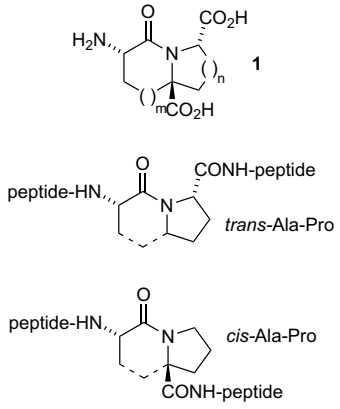


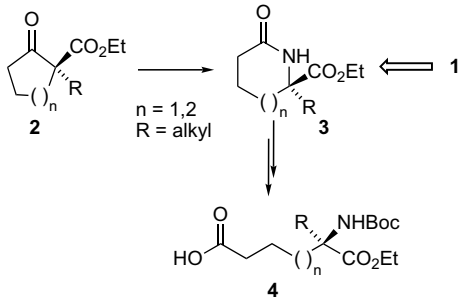

**Figure 1.**

We recently developed a short synthetic pathway to α,α′-disubstituted α-amino acids **4** in enantiomerically pure form (Scheme 1).[13] In addition, the intermediate lactam **3** can be envisioned as a suitable precursor leading to bicyclic lactams **1**.

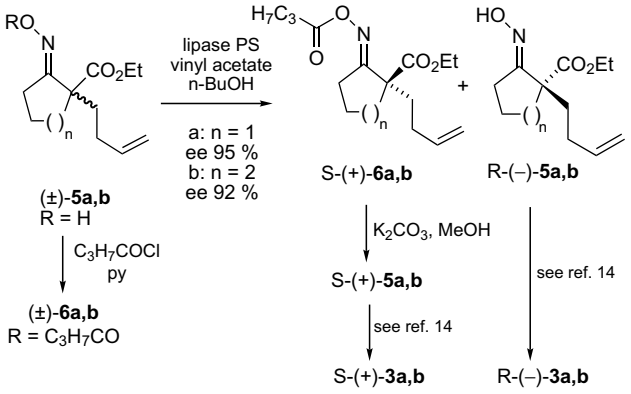
The synthesis of enantiomerically pure lactams **3** can be initiated by lipase-catalyzed transesterification of racemic *E*-oximes **5**. These can be easily obtained by addition of hydroxyl amine to racemic β-ketoesters **2** under kinetic conditions.[14] The oxime is formed in pyridine/

*Keywords*: Peptide mimics; Lipase; Beckmann rearrangement; Seleno annelation.
☆ See Ref. 1.
* Corresponding author. Tel.: +49-345-5582-1340; fax: +49-345-5582-1309; e-mail: bwesterm@ipb-halle.de

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.06.051



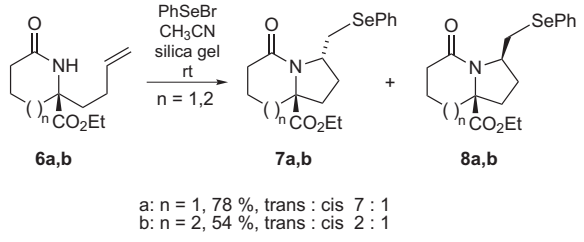

**Scheme 1.**




**Scheme 2.**

methanol at 0 °C, which affords the *E*-oxime **5** almost exclusively (50:1, GLC). For the lipase-catalyzed separation of racemate **5**, the corresponding butyrate **6** has been proven to be a good substrate. After obtaining the highly enantiomerically enriched oximes, the Beckmann rearrangement towards lactams **3** is carried out under conditions described previously (Scheme 2).[13]

For the synthesis of bicyclic lactams we envisioned a seleno-mediated ring closure (Scheme 3).[15] Employing PhSeBr in the presence of silica gel affords lactams **7** and **8** in 78% and 54% yield, respectively. Furthermore, this reaction turns out to be highly regio- and diastereoselective. Regioselective ring closure occurs by a 5 *exo tet* process. No product from a 6 *endo tet* process is formed. The diastereomeric ratio for the 6,5-bicyclized product is 7:1. For the 7,5-bicyclized product it is 2:1 as shown in Scheme 3.[16]




**Scheme 3.**

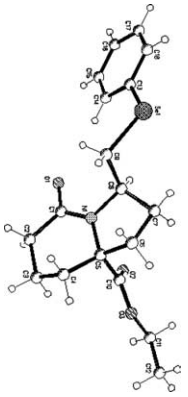


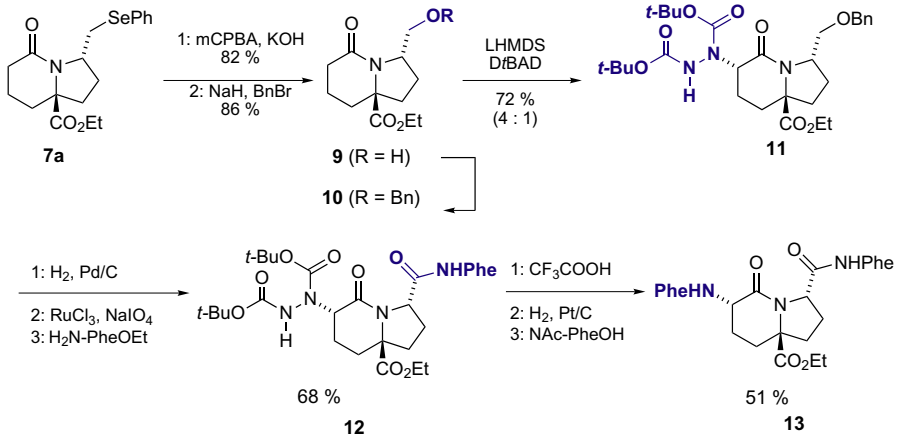
**Figure 2.** ORTEP plot of **7a**.

The stereochemical outcome of this cyclization is controlled by the carboxylate moiety at the quaternary carbon center. Attempts to cyclize decarboxylated lactams under identical conditions lead to a 1:1 mixture of diastereomers. However, in the presence of this carboxylate group the thermodynamically most stable cyclized product formed is the 5,8-*trans*-configurated lactam. The configuration has been determined by NMR and X-ray crystallography (Fig. 2). To improve the diastereoselectivity further, the Nicolaou reagent has been employed, but no increase can be observed.[17] Furthermore, the yield decreases (27% for **6a**).

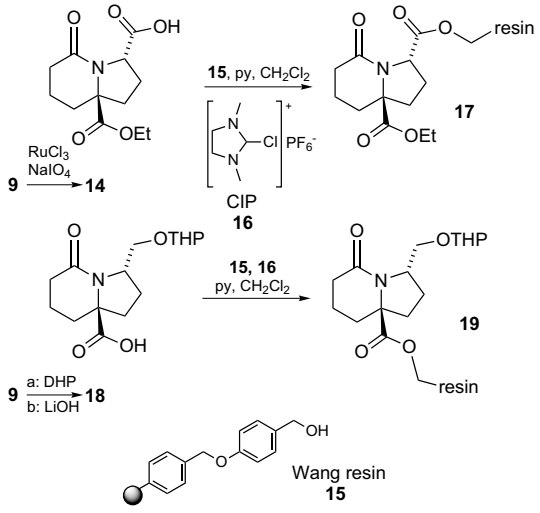
The phenylselenyl substituent offers widespread opportunities for modification (Scheme 4). By oxidation with *m*-chloro perbenzoic acid in the presence of KOH (10 equiv), the seleno moiety can be oxidized and substituted by a hydroxyl group. This leads to the hydroxylated lactam **9** in 82% yield.[18] Protection of the hydroxyl moiety with benzyl bromide affords **10** in 86% yield. To introduce the amide side chain, deprotonation with lithium hexamethylsiliazide is carried out, followed by addition of *tert*-butyl diazodicarboxylate to give **11** in 72% yield.[19]

In this amination reaction, two diastereomers are formed in the ratio of 4:1. These can be separated by chromatography. Debenzylation, oxidation to the carboxylic acid under slightly acidic conditions and attachment of C-protected phenylalanine gives **12** in 68% yield (over three steps). Cleavage of *tert*-butyl esters and hydrogenation gives an amine derivative, which is coupled to N-protected phenylalanine. The tetrapeptide **13** is formed in 51% yield (over three steps).

For peptide synthesis, it is useful to have one amino acid attached to a solid support. Due to the high degree of functionalization, lactam **9** is an ideal candidate to be used for this purpose. Bicyclic **9** is oxidized to acid **14** in the presence of $RuCl_3/NaIO_4$ in 85% yield. As the resin we choose the Wang-resin **15**. Attachment can be achieved by simple agitation of the resin with lactam **14** in pyridine and dichloromethane. We have found that the coupling reagent CIP **16** is superior to others.[20] After the reaction a loading percentage of 60% can be obtained (Scheme 5).




**Scheme 4.**




**Scheme 5.**

Whereas attachment of **14** to the resin allows for the incorporation of *cis*-configured dipeptides, attachment of the resin to the carboxyl moiety of the bicyclic heterocycle **18** allows for the incorporation of a *trans*-peptide. To apply the same methodology, the hydroxyl group of **9** is protected as the THP ether and the ester is saponified with LiOH. Subsequently, the corresponding acid **18** is coupled to the Wang-resin (Scheme 5).

In summary, we have developed a synthesis of highly substituted bicyclic lactams that can mimic either a *trans*- or a *cis*-peptide bond. Both heterocycles can be attached easily to a solid support, allowing for peptide synthesis from the C- or the N-terminus.

## Acknowledgements

This work has been supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie (grants to N.D. and I.K.)

## References and notes

1. This work has been carried out mainly at the University of Paderborn, Germany.
2. Gante, J. *Angew. Chem.* **1994**, *106*, 1780–1802; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699–1720.
3. Giannis, A.; Kolter, T. *Angew. Chem.* **1993**, *105*, 1303–1326; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244–1267.
4. Hruby, V. *Biopolymers* **1997**, *43*, 219–266.
5. Hanessian, S.; McNaughton-Smith, G.; Lombart, H. G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854, and references cited therein.
6. Belvisi, L.; Bernardi, A.; Manzoni, L.; Potenzy, D.; Scolastico, C. *Eur. J. Org. Chem.* **2000**, 12789–12854.
7. Sun, H.; Moeller, K. D. *Org. Lett.* **2001**, *4*, 1547–1550.
8. Maison, W.; Küntzer, D.; Grohs, D. *Synlett* **2002**, 1795–1798.
9. Wüthrich, K. *Nature Struct. Biol.* **2001**, *8*, 923–925.
10. Kim, K.; Dumas, J. P.; Germanas, J. P. *J. Org. Chem.* **1996**, *61*, 3138–3144.
11. Curran, T. P.; McEnaney, P. M. *Tetrahedron Lett.* **1995**, *36*, 191–194.
12. Sato, K.; Nagai, U. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1231–1234 (an early and prominent example).
13. Westermann, B.; Gedrath, I. *Synlett* **1996**, 665–666.
14. Diedrichs, N.; Krelaus, R.; Gedrath, I.; Westermann, B. *Can. J. Chem.* **2002**, *80*, 686–691.
15. Tiecco, M. Electrophilic Selenium, Selenocyclizations. In: *Topics Curr. Chem.*; Springer: Berlin, 2000; Vol. 208, and references cited therein.
16. Procedure for the synthesis of (3*S*,8a*S*)-**7a**: Lactam **6a** (279 mg, 1.2 mmol) was dissolved in acetonitrile (10 mL) and stirred with silica gel (0.8 g). A solution of PhSeBr (293 mg, 1.2 mmol) in acetonitrile (10 mL) was added dropwise over the period of 1.5 h. Stirring was continued for 1 d, upon which the solution was filtered, extracted with dichloromethane and washed with sat. aqueous sodium bicarbonate. Extracting of the aqueous phase with dichloromethane, combining the organic phases, drying over sodium sulfate, evaporating of the solvent and column chromatography on silica gel (petroleum/ethyl acetate 1:1) led to crystalline **7a** (320 mg, 68%). $[\alpha]_D$ −19.9 (*c* 1.25 in chloroform). $^1$H NMR ($CDCl_3$): $\delta = 1.24$ (t, 3H), 1.49–2.44 (m, 10H), 3.13 (dd, $J = 8.4$ Hz, $J = 12.6$ Hz, 1H), 3.57 (dd, $J = 2.6$ Hz, $J = 12.6$ Hz, 1H), 4.18 (q, 2H), 4.37–4.45 (m, 1H), 7.15–7.31 (m, 3H), 7.56–7.60 (m, 2H). $^{13}$C NMR ($CDCl_3$): $\delta = 14.6$, 19.1, 27.3, 29.7, 30.8, 32.2, 36.0, 57.5, 62.3, 71.5, 126.8, 129.5,

130.5, 131.7, 170.8, 174.1. $C_{18}H_{23}NO_3Se$ (cal./found): C 56.80/56.87, H 6.10/6.22, N 3.68/3.59.

Procedure for the synthesis of (3*S*,8a*S*)-**9**: To lactam **7a** (100 mg, 0.26 mmol), dissolved in THF (15 mL), freshly powdered KOH (97 mg, 1.7 mmol) was added. The reaction mixture was heated to reflux, upon which *m*CPBA (227 mg, 1.3 mmol) in THF (10 mL) was added. After 8 h under reflux conditions, the slurry was stirred for additional 12 h at room temperature. Ethyl acetate was added and the mixture was washed with water, HCl (5%), water, sat. $NaHCO_3$ and water. Drying of the organic phase and evaporating of the solvent under reduced pressure led to a white solid, which was purified by chromatography on silica gel ($CH_2Cl_2$/MeOH 9:1) to afford oily **9** (54 mg, 85%). $[\alpha]_D$ −29.0 (*c* 0.31 in $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta = 1.26$ (t, 3H), 1.43–2.10 (m, 6H), 2.24–2.53 (m, 4H), 3.68 (d, $J = 5.3$ Hz, 2H), 4.19 (q, 2H), 4.23–4.34 (m, 1H), 4.78 (s, 1H). $^{13}C$ NMR ($CDCl_3$): $\delta = 14.6$, 18.7, 25.9, 30.7, 32.3, 36.3, 61.5, 62.4, 67.1, 72.0, 172.8, 173.8. $C_{12}H_{19}NO_4$ (cal./found): C 59.74/60.01, H 7.94/7.86, N 5.83/6.01.

17. Webb, R. R.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 1357–1360.
18. Krief, A.; Dumont, W.; Denis, J. N. *J. Chem. Soc., Chem. Commun.* **1985**, 571–572.
19. Gramberg, D.; Robinson, J. A. *Tetrahedron Lett.* **1994**, *35*, 861–864.
20. Katritzky, A. R.; Suzuki, K.; Singh, S. K. *Arkivoc* **2004**, 12–35.