Pergamon

Tetrahedron Letters 42 (2001) 4943–4945

TETRAHEDRON LETTERS

A convenient and versatile synthesis of 6,5- and 7,5-fused bicyclic lactams as peptidomimetics

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Received 1 April 2001; accepted 22 May 2001

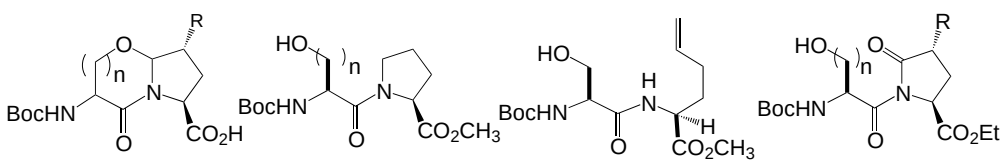
Abstract—Chemo-selective reduction of the pyroglutamate ring carbonyl in a serine-pyroglutamate or homoserine to pyroglutamate dipeptide gave a hemiaminal. Treatment of the hemiaminal with a catalytic amount of TFA in CH_2Cl_2 generated an *N*-acyliminium ion that was intramolecularly trapped by the side-chain hydroxyl to give a 6,5 or 7,5-bicyclic lactam.

Design and synthesis of novel bicyclic lactams as peptidomimetics is currently an area of intensive research in the field of peptide and medicinal chemistry.[1–3] The backbone structure of these scaffolds maintains important conformational information derived from a parent peptide lead. They can effectively mimic the peptide binding conformation and incorporate critical hydrogen-bond donors and acceptors such as an amide NH and carbonyl groups. One example of such scaffolds is bicyclic lactam **A**, based on proline (Fig. 1), which has been studied as both reverse turn and extended conformation inducer.[4,5]

Although both the 6,5 and 7,5-systems of lactam **A** have been prepared previously, a more versatile approach is still highly desired due to certain limitations of previous methods. Marshall, et al reported an electrooxidation–cyclization sequence to produce both 6,5- and 7,5- systems from an Xaa-Pro dipeptide **B**.[6,7] This simple sequence gave a good yield for the 7,5-system, but low yields for the 6,5-system. Baldwin et al. reported an alternative approach to the 6,5-system involving ozonolysis of a dipeptide **C**, followed by cyclization of the *N*-acyliminium intermediate.[8] This approach, however, required a chiral synthesis of homoallyl glycine, an unnatural amino acid. Both approaches also lack easy methods to attach additional functional groups off the proline ring.

We report here a more versatile synthetic sequence to **A** involving a chemo-selective reduction of the pyroglutamate ring carbonyl in dipeptide **D**, followed by an intramolecular trapping of the *N*-acylimminium ion generated in situ from the hemiaminal. The advantage of this approach is it allows easy introduction of substituents off the proline ring by alkylation of the pyroglutamate, a reaction well documented in the literature.[9–11]

To prepare (3*S*,6*S*,9*S*)-6,5-bicyclic lactam **4**, the sodium salt of (*S*)-ethyl pyroglutamate was reacted with commercially available Boc-(L)-ser(Bzl)-ONp in toluene to



A (n = 1, 2) **B** (n= 1, 2) **C** **D** (n = 1, 2)

Figure 1. Bicyclic lactam **A** and precursors.

Keywords: 6,5- and 7,5-fused bicyclic lactams; peptidomimetics; *N*-acyliminium ion.

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0040-4039/01/$ - see front matter
PII: S0040-4039(01)00909-1

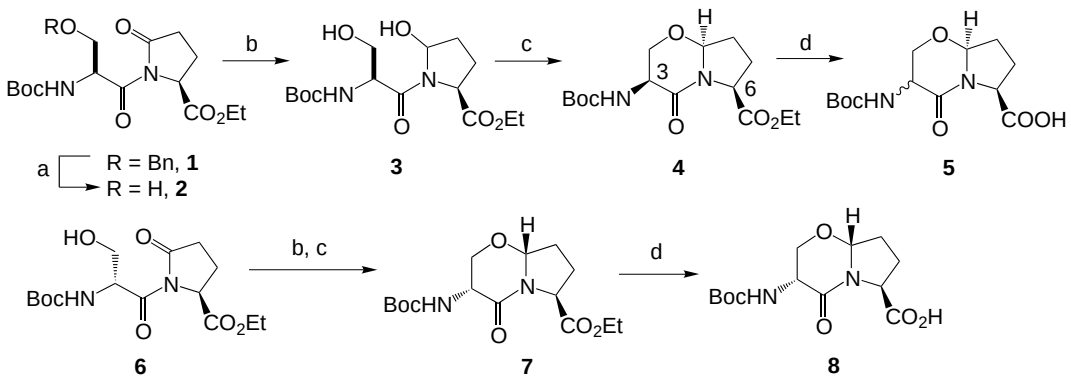
give a dipeptide **1** (Scheme 1).[12] Deprotection of the benzyl group of **1** and reduction of **2** with $LiBEt_3H$ in THF at −78°C gave hemiaminal **3**. Preferential reduction of the ring carbonyl was anticipated based on its reactivity towards nucleophiles.[13,14] Attempts to purify **3** by silica-gel column resulted in its decompostion. ^1H NMR of **3** is complicated by the presence of two diastereomers and the equilibrium between the aminal and the aldehyde form. Its structure was thus, proved by the following chemical transformation: cyclization in CH_2Cl_2 in the presence of TFA (25% mol) gave the 6,5-bicyclic lactam **4** in good yield. Similarly, diastereomer (3*R*,6*S*,9*R*)-**7** was prepared in 50% isolated yield from **6** using Boc-(D)-Ser(Bzl)-OH as starting material. Isolation of bicyclic lactams **4** and **7** suggests intermediacy of an *N*-acyliminium ion and its trapping by the side chain hydroxyl group.[15]

Compounds **4** and **7** were fully characterized by ^1H, ^{13}C, DEPT and HRMS. The stereo configuration at the ring-fused carbon was established by NOE experiments, and by comparison with literature data.[5,7] Isolation of the 9*S* conformer for **4** and the 9*R* for **7** is consistent with the previous observation that the cyclization is not influenced by the chirality of proline, rather dictated by the chirality of serine.[6] During the hydrolysis of the ester **4**, epimerization at the serine α-carbon occurred, giving a 1:1 mixture of the acids **5**.[7] However, hydrolysis of **7** gave clean formation of the acid **8**, with no epimerization detected by ^1H NMR.

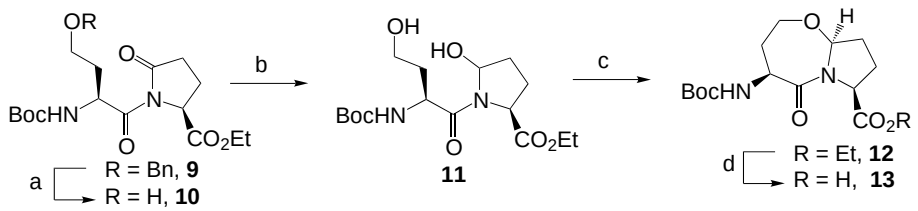
Starting from Boc-(L)-homoser(Bzl)-OH, the 7,5-system was also conveniently prepared. Compound **12** was isolated in 35% yield from **9** in three steps (Scheme 2). As in the case of **4**, the stereo configuration at the ring-fused carbon was identified to be 10*S* by NOE experiments.

Attaching functional groups to the proline ring to pick up additional binding with a target enzyme or receptor in these bicyclic systems can be important. This can be achieved by a stereoselective alkylation of the pyroglutamate precursor with a wide variety of electrophiles.[9] For example (Scheme 3), the lithium enolate of *N*-Boc-(*S*)-ethyl pyroglutamate **14** was alkylated with cinnamyl bromide to give compound **15**.[9] Removal of the Boc group and amide formation of **16** with Boc-(D)-ser(Bzl)-OSu gave dipeptide **17**. Following the same chemistry described above, removal of the benzyl protection in **17**, selective reduction of the pyroglutamate ring carbonyl in **18**, and cyclization of hemiaminal **19** afforded 6,5-system **20** carrying a phenylpropyl group off the proline. Again, the stereo configuration at the ring-fused carbon was established as 9*R* by NOE experiments, similar to that obtained in compound **7**. The stereochemistry of the phenpropyl off the proline ring was retained based on NOE studies. The ethyl ester **20** was cleanly hydrolyzed to its acid **21**, which could be readily incorporated into other peptides.

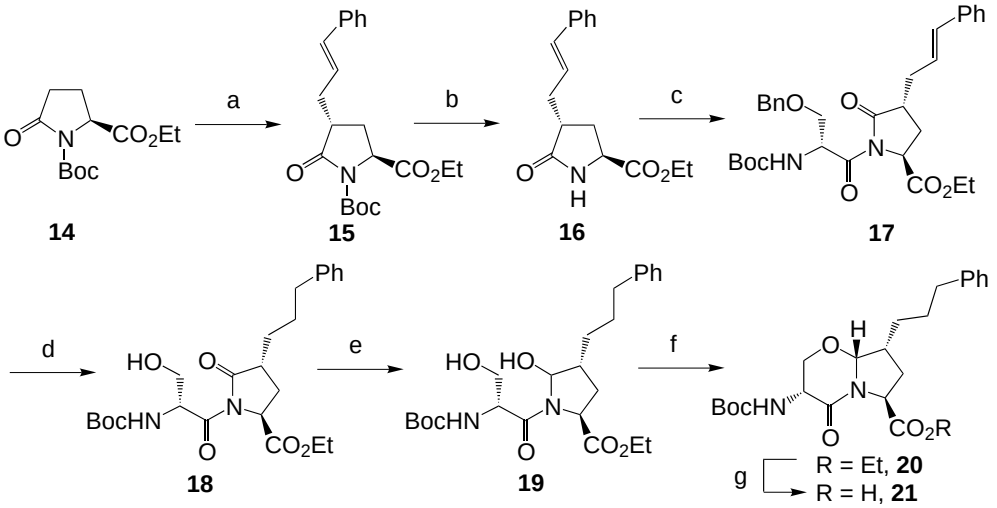
In summary, we have developed a versatile procedure to prepare both 6,5- and 7,5-bicyclic lactam peptidomimetics based on a chemo-selective reduction of the pyroglutamate ring carbonyl, followed by an intramolecular trapping of an *N*-acyliminium ion by side-chain hydroxyl groups. Furthermore, due to the ready availability of starting materials and the ability to incorporate additional functionality on the proline ring, we consider this to be a valuable addition to previous methodologies.



Scheme 1. Synthesis of 6,5-bicyclic lactams. (a) H_2, Pd/C, MeOH; (b) $LiBEt_3H$, THF, −78°C; (c) TFA (cat.), CH_2Cl_2, 50°C, 50%; (d) LiOH, H_2O/THF, 100%.



Scheme 2. Synthesis of 7,5-bicyclic lactam. (a) H_2, Pd/C, MeOH; (b) $LiBEt_3H$, THF, −78°C; (c) TFA (cat.), CH_2Cl_2, 50°C, 35%; (d) LiOH, H_2O/THF, 100%.



Scheme 3. Synthesis of 6,5-bicyclic lactam carrying functional group off the proline ring. (a) LHMDS, THF, cinnamyl bromide, −78°C, 60%; (b) TFA, CH_2Cl_2; (c) 1. LHMDS, THF, −30°C, 2. Boc-(D)-Ser(Bzl)-OSu, 85% for two steps; (d) H_2, Pd/C, MeOH; (e) $LiBEt_3H$, THF, −78°C; (f) TFA (cat.), CH_2Cl_2, 50°C, 35% for three steps; (g) LiOH, H_2O/THF, 100%.

Acknowledgements

We thank Dr. Carl Decicco for his support of this work, Dr. David Nugiel for his critical reading of the manuscript and Dr. Laurie Galya for all the ^1H NOE experiments.

References

1. Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699–1720.
2. Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244–1267.
3. Robl, J. A. *Tetrahedron Lett.* **1994**, *35*, 393–396.
4. Chalmers, D. K.; Marshall, G. R. *J. Am. Chem. Soc.* **1995**, *117*, 5927–5937.
5. Claridge, T. D. W.; Hulme, C.; Kelly, R. J.; Lee, V.; Nash, I. A.; Schofield, C. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 485–490.
6. Cornille, F.; Slomczynska, U.; Smythe, M. L.; Beusen, D. D.; Moeller, K. D.; Marshall, G. R. *J. Am. Chem. Soc.* **1995**, *117*, 909–917.
7. Slomczynska, U.; Chalmers, D. K.; Cornille, F.; Smythe, M. L.; Beusen, D. D.; Moeller, K. D.; Marshall, G. R. *J. Org. Chem.* **1996**, *61*, 1198–1204.
8. Baldwin, J. E.; Hulme, C.; Schofield, C. J.; Edwards, A. J. *J. Chem. Soc., Chem. Commun.* **1993**, 935–936.
9. Ezquerra, J.; Pedregal, C.; Rubio, A.; Yruretagoyena, B.; Escribano, A.; Ferrando, S. S. *Tetrahedron* **1993**, *49*, 8665–8678.
10. Ezquerra, J.; Pedregal, C.; Rubio, A. *J. Org. Chem.* **1994**, *59*, 4327–4331.
11. Najera, C.; Miguel, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 2245–2303.
12. Johnson, A. L.; Price, W. A.; Wong, P. C.; Vavala, R. F.; Stump, J. M. *J. Med. Chem.* **1985**, *28*, 1596–1602.
13. Ohta, T.; Shiokawa, S.; Iwashita, E.; Sato, N.; Sakurai, K.; Ineyama, T.; Izawa, H.; Izawa, K.; Nozoe, S. *Heterocycles* **1992**, *33*, 143–146.
14. Ezquerra, J.; Pedregal, C.; Rubio, A.; Valenciano, J.; Navio, J. L. G.; Alvarez–Builla, J.; Vaquero, J. J. *Tetrahedron Lett.* **1993**, *34*, 6317–6320.
15. Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856.