Bioorganic & Medicinal Chemistry Letters, Vol.3, No.12, pp. 2537-2540, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

Synthesis of Aminoazalactams as Cyclic Mimetics of Basic Alkyl Amino Acids

Roger E. Markwell, Shahzad S. Rahman*, Robert W. Ward

SmithKline Beecham Pharmaceuticals, Department of Medicinal Chemistry,

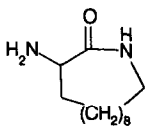
Coldharbour Road, The Pinnacles, Harlow, Essex, CM19 5AD, UK

(*Received in Belgium* 21 *June* 1993)

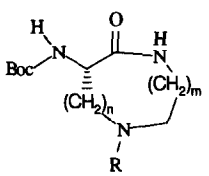
Abstract: Novel medium ring conformationally constrained amino acid derivatives **2** for incorporation into collagenase inhibitors were prepared, utilising natural amino acids as starting materials, *via* a reductive intramolecular imine cyclisation.

Inhibitors of matrix metalloproteinases (MMPs)[1], and in particular collagenase (MMP-1)[2], are important targets for drug-discovery as they are believed to be responsible for cartilage destruction in diseases such as rheumatoid arthritis and osteoarthritis[3].

Several series of di- and tri-peptide collagenase inhibitors have been described[4]. Our interest in collagenase inhibitors led us to investigate the synthesis of novel medium ring conformationally constrained cyclic mimics of the basic amino acids lysine and ornithine. These analogues are an extension of earlier work on medium ring lactam **1** designed to mimic the C-terminus P_2' residue[5]. A potential advantage of these cyclic structures over the corresponding natural amino acids is stabilization towards proteolytic enzymes leading to enhanced bioavailability. Additionally, restriction in the number of available conformers may increase binding affinity. Indeed, conformationally restricted analogues are now emerging as useful tools in developing peptide-derived pharmaceutical agents[6].



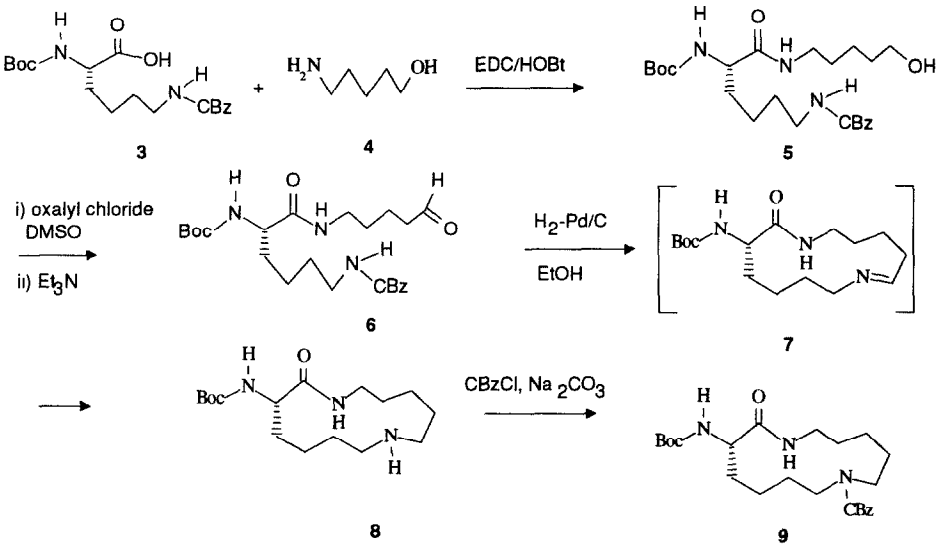
1



2 n=3,4; m=2,4,5
R=CBz, Me, H

In this paper we discuss our approaches to the synthesis of aminoazalactams of ring size 11, 13, and 14 with the general structure **2**. Unlike the previously reported cyclic lactam **1**, these aminoazalactams **2** are derived from a natural chiral pool and therefore require no resolution. In our hands, the highly lipophilic lactam **1** introduces low aqueous solubility when incorporated into collagenase inhibitors. This problem is overcome in the basic aminoazalactams **2** by virtue of the amine group present in the molecule, which will be protonated at physiological pH.

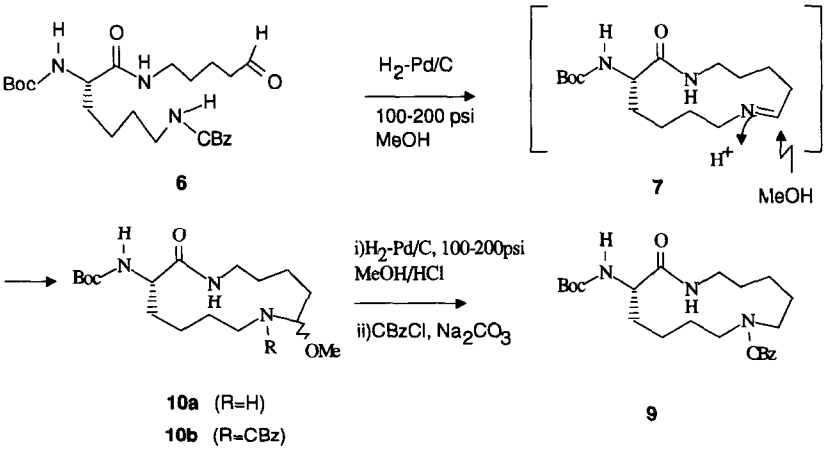
Our general approach is exemplified by the synthesis of aminoazalactam **9** (Scheme 1). The route relies on reductive intramolecular iminium cyclisation of the (S)-aminoaldehyde **6** to the aminoazalactam **8**.



Scheme 1.

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) / 1-hydroxybenzotriazole (HOBT) mediated coupling of lysine derivative **3** with amino alcohol **4** gave the alcohol **5** (83%). Oxidation of **5** using a modified Swern[7] procedure (1.5 equiv. oxalyl chloride, 3 equiv. DMSO, -60 to -30 °C) and subsequent purification by flash chromatography afforded the aldehyde **6**, (78%). Our initial attempt at the key transformation, intramolecular reductive amination of the aldehyde **6**, gave the requisite aminoazalactam **9** in 11% yield. The protocol involved removal of the N^{ε}–benzyloxycarbonyl (N^{ε}-CBz) group (H_2-Pd/C, EtOH) at atmospheric pressure and concomitant intramolecular cyclisation to afford the imine **7**. Continued hydrogenation with fresh catalyst completed the reduction of the imine **7**. The product, crude amine **8**, was protected (CBz)[8] and purified by silica gel chromatography to give the aminoazalactam **9**.

The efficiency of the reductive ring closure reaction was significantly improved by modifying the original conditions. Hydrogenation of the aldehyde **6** at high pressure (100-200 psi) in methanol over Pd/C afforded an intermediate, presumed to be amino-ether **10a**. This could be purified following N-protection (CBz) to give the carbamate **10b**. Hydrogenation of **10a** under mild acidic conditions (H_2-Pd/C, 100-200 psi; MeOH/HCl, pH=3-4) resulted in hydrogenolysis of the methoxy group to afford amine **8**. By this procedure **9** was isolated, optically pure[9], in excess of 30% yield from the aldehyde **6**.



Scheme 2.

The aminoazalactams **11**, **12**, and **14** were prepared in 11-40% (Table 1) following similar procedures with one exception; the best reducing agent for the cyclization leading to **11** proved to be $NaBH_3CN$[10]. The low yield observed in some cases may be due to the degree of transannular ring strain[11] associated with rings of this size. The aminoazalactam **13** was prepared by reductive alkylation of the amine **8** (generated *in situ* from **9**) using formaldehyde.

Table1. Synthesis of aminoazalactams of general structure **2** by intramolecular reductive cyclisation

Aminoazalactam	Ring size	n	m	R	Yields(%)	Conditions
9	13	4	4	CBz	31	A
11	14	4	5	CBz	40	B
12	13	3	5	CBz	12	A
13	13	4	4	CH_3	30	C
14	11	4	2	CBz	11	A

Conditions: (A) H_2-Pd/C, 100-200 psi then H_2-Pd/C 100 psi, MeOH/HCl; (B) H_2-Pd/C, 100-200 psi then $NaBH_3CN$, pH = 3-4, (HCl); (C) **9**, 100 psi H_2-Pd/C, MeOH/40% aq. formaldehyde.

These novel amino acid derivatives have obvious potential for incorporation into other biologically active peptides or pseudo-peptides. We are now incorporating these aminoazalactams as C-terminus residues in novel inhibitors of collagenase. Preliminary data show that these water soluble compounds retain high inhibitory potency. Full details of biological studies and SAR will be published elsewhere.

Acknowledgement. We wish to thank the Analytical Sciences Department at SmithKline Beecham for spectroscopic determinations.

References and Notes:

1. Docherty, A.J.P.; Murphy, G. *Ann. Rheum. Dis.* **1990**, *49*, 469-479.
2. Stricklin, G.P.; Bauer, E.A.; Jeffrey, J.J.; Eisen, A.Z. *Biochemistry* **1977**, *16*, 1607-1615.
3. Henderson, B.; Docherty, A.J.P.; Beeley, N.R.A. *Drugs of the Future* **1990**, *15*, 495-508.
4. For a recent review see: Schwartz, M. A.; Van Wart, H.E. *Progress in MedicinalChemistry* **1992**, *29*, 271-334.
5. Broadhurst, M.A.; Handa, B.K.; Johnson, W.H.; Lawton, G.; Machin, P.J. *European Patent* 0 276 436 **1988**; Borkakoti, N.; Broadhurst, M.J.; Brown, P.A.; Handa, B.K.; Johnson, W.H.; Lawton, G.; Machin, P.J.; Roberts, N.A. 'Design and synthesis of phosphinic acid collagenase inhibitors.' Poster presented at 'Peptides as target for drug research' University of York, **1988.**
6. Hruby, V.J.; Al-Obeidi, F.; Kazmierski, W. *Biochem. J.* **1990**, *268*, 249-262.
7. Mancuso, A.J.; Swern, D. *Synthesis* **1981**, 165.
8. Bergmann, M.; Zervas, L. *Ber.* **1932**, *65*, 1192.
9. The aminoazalactams **9**, **11**, **12**, **13**, and **14** gave single diastereoisomers when coupled to optically pure amino acid derivatives in the synthesis of collagenase inhibitors.
10. Borch, R.F.; Bernstein, M.D.; Durst, H.D. *J. Amer. Chem. Soc.* **1971**, *93*, 2897-2904.
11. Eliel, E.L. *Stereochemistry of Carbon Compounds*; McGraw-Hill Book Company, Inc.: New York, 1962; pp 252-269.
12. Spectroscopic data for compounds **9-14** follows
    9. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.3-1.8(21H, m), 3.05(1H, m), 3.1-3.4(4H, m), 3.55(1H, brs), 4.0(1H, m), 5.05(1H, brs), 5.1(2H, s), 5.7(1H, brs), 7.4(5H,m); MS (EI): 447 (M^+); $[\alpha]^{22}_D$= -23(c=1.2 MeOH); R_f 0.47(5%MeOH/EtOAc); ν_{max} (neat) 3334m, 3304m, 1702s, 1678s and 1652s cm^{-1}.
    10b. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.3-1.7(21H, m), 3.2(4H, m) 3.3(3H, s), 4.0(1H, m), 4.35(1H, t), 4.9(1H, m), 5.1(2H, s), 6.15(1H, m), 7.3-7.4(H, m); MS (EI): 477 (M^+).
    11. ^{1}H NMR (250 MHz, $CDCl_3$): δ 51.25-1.4(6H, m), 1.45(9H, s), 1.5-1.7(6H, m), 1.85(2H, m), 2(3H,m), 3.45(2H, m), 3.65(1H, m), 4.05(1H, m), 5.1(2H, s), 5.25(1H, brs), 6.05(1H, brs), 7.35(5H, m); MS (EI): 461 (M^+); $[\alpha]^{22}_D$= -17(c=2 MeOH); R_f 0.48(5%MeOH/EtOAc); ν_{max} (neat) 3334m, 1692s, and 1650s cm^{-1}
    12. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.2-1.8(21H, m), 3.0-3.5(6H, m), 3.9(1H, m), 5.05(1H, m), 5.1(2H, s), 5.8(1H, brs), 7.3-7.4(5H, m); MS (EI): 447 (M^+); $[\alpha]^{22}_D$= -35(c=0.64 MeOH); R_f 0.42(5%MeOH/EtOAc); ν_{max} (neat) 3334m, 1703s, and 1644s cm^{-1}.
    13. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.4-1.7(20H, m), 1.75(1H, m), 2.45(3H, brs), 2.6-2.75(4H, m), 3.05(1H, dd), 3.55(1H, m), 4.05(1H, m); MS (EI): 327 (M^+); $[\alpha]^{22}_D$= -29(c=1 MeOH); R_f 0.1(20%MeOH/$CHCl_3$); ν_{max} (neat) 3337m, 1684s and 1654s cm^{-1}.
    14. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.2-2.0(17H, m), 2.9-3.3(6H, m), 4.0(1H, brs), 5.1(2H, s), 5.3(1H, brs), 6.7(1H, brs), 7.3(5H, m); MS (CI): 419 (M^+); $[\alpha]^{22}_D$= -14(c=0.8 MeOH); R_f 0.39(5% MeOH/ EtOAc); ν_{max} (neat) 3342m, 1701s, 1683s and 1656s cm^{-1}.