Bioorganic & Medicinal Chemistry Letters, Vol.2, No.9, pp. 925-928, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

A DIVERGENT ROUTE TOWARD LACTAM-BASED DIPEPTIDYL BUILDING BLOCKS

Jeffrey Aubé* and Michael S. Wolfe

Department of Medicinal Chemistry
University of Kansas
Lawrence, Kansas 66045-2506

(*Received* 13 *May* 1992)

Key Words: lactams, oxaziridines, peptide analogues, conformational restriction.

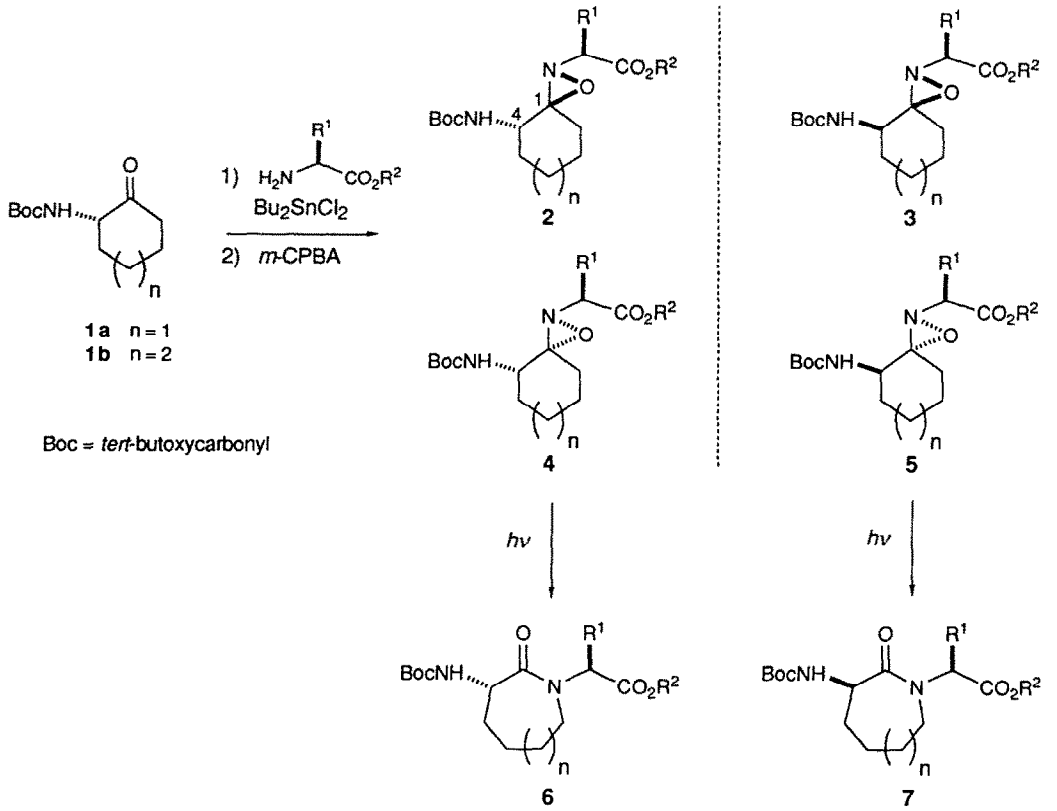
Abstract: *A series of chiral lactams which represent conformationally restricted peptidomimetic building blocks have been synthesized from enantiopure* tert-*butoxycarbonyl (Boc)-protected 2-aminocycloalkanones by (1) imine formation utilizing* L-*α-amino esters, (2) oxidation to oxaziridines, and (3) photorearrangement.*

Conformational restriction is a well-established strategy for improving the potency, selectivity, and metabolic stability of peptide neurotransmitters and hormones.[1] Lactams which maintain a given dipeptidyl unit in the trans amide conformer and bias neighboring ψ and φ angles,[2] moieties pioneered by Freidinger,[3] have proven particularly useful in a number of applications (e.g., the development of inhibitors of the renin-angiotensin system[4] and agonists of human growth hormone[5]).

Despite the demonstrated utility of such dipeptidyl lactams, a general synthetic route toward these moieties which allow obtention of various ring sizes in enantiomerically pure form has not been realized. An "ideal" method would (1) be applicable to lactams of various sizes, (2) allow the installation of potentially expensive and/or scarce amino acid moieties late in the scheme, permitting divergence to a number of amino acid substitutions, (3) incorporate protection schemes consonant with standard peptide chemistry, and (4) allow control over relative and absolute stereochemistry. Previous reports from this laboratory described the stereoselective synthesis of chiral lactams from cyclic ketones via spirocyclic oxaziridines.[6] We felt this synthetic strategy could potentially address all of the above criteria. Herein, we communicate the synthesis of enantio- and diastereomerically pure dipeptoid lactams using oxaziridines as key intermediates.

Our strategy (scheme) involved the condensation of enantiopure *tert*-butoxycarbonyl (Boc)-protected 2-aminocycloalkanones **1**[7,8] with commercially available α-amino esters, oxidation of the imines with *m*-CPBA to form oxaziridines, and photorearrangement of these oxaziridines to lactams. Condensation of ketone **1a** with L-phenylalanine methyl ester (L-Phe-OMe) in the presence of dibutyltin dichloride[9] followed by oxidation with *m*-CPBA[10,11] resulted in oxaziridine **2** in 78% yield (entry 1). However, when the oxaziridine formation was carried out with the antipode of ketone **1a** (*ent*-**1a**; entry 2), a 76% yield of a mixture of diastereomeric oxaziridines **2**, **3** and **5** (17: 48: 11) resulted, indicating that the integrity of the C-4 stereocenter had been compromised.

These diastereomeric L-Phe-OMe-derived oxaziridines were readily separable by flash chromatography, and their photochemical rearrangement[12] resulted in diastereomeric lactams **6** (from **2**) and **7** (from **3** and **5**). Oxaziridines are known to rearrange to lactams under these conditions with stereoelectronic control: the carbon atom anti to the nitrogen lone pair of electrons migrates.[6b,c] Hence, all three of the isolated oxaziridines must



Entry	ketone	R^1	R^2	oxaziridines yield(%)	oxaziridines ratio(2+4/3+5)[a]	lactams yield 6(%)[b]	lactams yield 7(%)[b]
1	**1a**	CH_2Ph	Me	78	<99:1	69	63
2	***ent*-1a**	CH_2Ph	Me	76	77:23[c]	69	63
3	**1a**	*i*-Bu	Me	72	88:12[c]	65	69
4	**1a**	*s*-Bu	Me	81	75:25	60	54
5	**1a**	*i*-Pr	CH_2Ph	73	88:12	58	45
6	**1a**	CH_2CO_2Me	Me	71	75:25[d]	56	---
7	**1a**	$(CH_2)_2CO_2Me$	Me	65	56:44[c,d]	61	48
8	**1a**	CH_2OCH_2Ph	CH_2Ph	81	*c,d*	35[e]	---
9	**1b**	CH_2Ph	Me	35	85:15	50	---

[a]Only **2** and **3** were isolated, except where indicated. [b]From single purified diastereomeric oxaziridine. [c]Both **3** and **5** formed. [d]Both **2** and **4** formed. [e]Inseparable oxaziridines gave diastereomeric lactams.

have the ester moiety oriented trans to the carbamate substituted carbon. This conclusion is corroborated by ^{13}C-NMR analysis (the C-4 peaks for these compounds have similar chemical shift values).[6c] The preponderance of **2** over **3** and **5** in the reaction of **1a** with L-Phe-OMe (and vice versa with *ent*-**1a**) indicates that the stereocenter adjacent to the ketone carbonyl did not epimerize en route to the major products.

The enantiomeric purity of lactam **6** (>95%) was determined via ^{1}H-NMR chiral shift studies utilizing Eu(hfc)$_3$;[13] hence, the stereocenter derived from the α-amino ester remained intact throughout the synthetic sequence. On the other hand, employment of standard conditions in our laboratory for the synthesis of oxaziridines (refluxing toluene, Dean-Stark trap), resulted in significant loss of optical activity. Therefore, the mild conditions employed (ambient temperature, Bu_2SnCl_2 catalyst) are necessary for the obtention of enantiopure products.

In contrast to the results with L-Phe-OMe, oxaziridine formation between **1a** and other amino esters resulted in variable amounts of C-4 epimers; however, in almost all cases, the diastereomers can be separated by flash chromatography, and photorearrangement leads to diastereomerically pure lactams. It is not surprising that some of these amino esters would show different stereochemical preferences with respect to oxidation compared with L-Phe-OMe; hence, C-1 diastereomers of **2** (i.e., **4**) are formed upon employment of L-Asp(OMe)-OMe, L-Glu(OMe)-OMe, and L-Ser(OBzl)-OBzl (entries 6, 7, and 8, respectively). Despite the appearance of several diastereomers in some cases, photorearrangement of oxaziridines **2** and **4** converge on lactam **6**, and oxaziridines **3** and **5** likewise form lactam **7**. In many cases, racemic ketone may be utilized, and the diastereomeric oxaziridines can then be separated and photorearranged to stereochemically defined lactams.

The effect of a larger ring size for the cycloalkanone was explored using L-Phe-OMe. Cycloheptanone **1b** (entry 9) reacted sluggishly: imine formation with larger amounts of tin catalyst (50 mol %) over 2 days resulted in 35% yield of the desired oxaziridine, although the ketone could be recovered. Photorearrangement resulted in the corresponding eight-membered ring lactam in 50% yield. Lactams of this size are difficult to obtain by other methods.[4c,d]

In conclusion, we have developed a general, divergent, synthetic route to stereochemically-defined lactam-based dipeptide building blocks suitable for incorporation into appropriate peptides by standard chemistry. This methodology offers the advantage of utilizing commercially available α-amino esters and allows the installation of a stereocenter adjacent to nitrogen in the product lactams. We are continuing to search for conditions which eliminate the epimerization at C-4. Concurrently, we are applying this chemistry to the synthesis of peptide analogues designed to interact with biologically relevent targets.

Acknowledgement. This work was supported by the National Institutes of Health. The American Heart Association-Kansas Affiliate is thanked for providing a postdoctoral research fellowship to M. S. W. J. A. acknowledges an Eli Lilly Granteeship (1989-1991).

References and Notes

1. For a general review, see Hruby, V. J.; Kazmierski, W.; Kawasaki, A. M.; Matsunaga, T. O. In *Peptide Pharmaceuticals*; D. Ward, Ed.; Open University Press: Milton Keynes, U. K., 1991; Chapter 5.

2. (a) Paul, P. K. C.; Burney, P. A.; Campbell, M. M.; Osguthorpe, D. J. *J. Comput.-Aided Mol. Des* **1990**, *4*, 239-253. (b) Toniolo, C. *Int. J. Peptide Protein Res.* **1990**, *35*, 287-300.

3. (a) Freidinger, R. M.; Perlow, D. S.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104-109. (b) Freidinger, R. M.; Veber, D. F.; Perlow, D. S.; Brooks, J. R.; Saperstein, R. *Science* **1980**, *210*, 656-658.

4. (a) Williams, P. D.; Perlow, D. S.; Payne, L. S.; Holloway, M. K.; Siegl, P. K. S.; Schorn, T. W.; Lynch, R. J.; Doyle, J. J.; Strouse, J. F.; Vlasuk, G. P.; Hoogsteen, K.; Springer, J. P.; Bush, B. L.; Halgren, T. A.; Richards, A. D.; Kay, J.; Veber, D. F. *J. Med. Chem.* **1991**, *34*, 887-900. (b) Thorsett, E. D.; Harris, E. E.; Aster, S. D.; Peterson, E. R.; Tristram, E. W.; Snyder, J. P.; Springer, J. P.; Patchett, A. A. In *Peptides: Structure and Function* ; V. J. Hruby and D. H. Rich, Eds.; Pierce Chemical Co.: Rockford, Illinois, 1983; pp. 555-558. (c) Thorsett, E. D.; Harris, E. E.; Aster, S. D.; Peterson, E. R.; Snyder, J. P.; Springer, J. P.; Hirshfield, J.; Tristram, E. W.; Patchett, A. A.; Ulm, E. H.; Vassil, T. C. *J. Med. Chem.* **1986**, *29*, 251-260. (d) Yanagisawa, H.; Ishihara, S.; Ando, A.; Kanazaki, T.; Miyamoto, S.; Koike, H.; Iijima, Y, Oizumi, K.; Matsushita, Y.; Hata, T. *J. Med. Chem.* **1988**, *31*, 422-428.

5. Ede, N. J.; Rae, I. D.; Hearn, M. T. W. *Tetrahedron Lett.* **1990**, *31*, 6071-6074.

6. (a) Aubé, J.; Burgett, P. M.; Wang, Y. *Tetrahedron Lett.* **1988**, *29*, 151-154. (b) Aubé, J.; Wang, Y.; Hammond, M.; Tanol, M.; Takusagawa, F.; Vander Velde, D. *J. Am. Chem. Soc.* **1990**, *112*, 4879-4891. (c) Aubé, J.; Hammond, M.; Gherardini, E.; Takusagawa, F. *J. Org. Chem.* **1991**, *56*, 499-508. (d) Aubé, J.; Wang, Y.; Ghosh, S.; Langhans, K. L. *Synth. Commun.* **1991**, *21*, 693-701.

7. Ketones **1a** and **1b** were obtained from their respective enantiopure *trans*-2-aminocycloalkanols[8] through subsequent reactions with di-*tert*-butyl dicarbonate and pyridinium chlorochromate. Aubé, J.; Wolfe, M. S.; Yantiss, R. K.; Cook, S. M. *Synth. Commun.*, paper submitted.

8. Overman, L. E.; Sugai, S. *J. Org. Chem.* **1985**, *50*, 4154-4155

9. Stetin, C.; de Jeso, B.; Pommier, J. C. *Synth. Commun.* **1982**, *12*, 495-499.

10. General procedure for oxaziridine formation: To a 0.78 M solution of ketone **1** in toluene (stored over 5Å molecular sieves) was added 2 equiv of $NaHCO_3$, crushed 5Å molecular sieves (250 mg/100 mg ketone), 4.2 equiv of amino ester, and 20 mol % of Bu_2SnCl_2. The suspension was sealed over N_2, stirred for 20-25 h at 4 °C,[11] and then transferred via wide bore cannula to a -78 °C suspension of 1.5 equiv of *m*-CPBA in toluene (73 mM). After 30 min, the suspension was allowed to warm to ambient temperature, whereupon it was quenched with 10% aq $Na_2S_2O_3$ solution, diluted with Et_2O, washed with copious amounts of sat'd $NaHCO_3$ solution, and, ultimately, sat'd NaCl solution. After drying over Na_2SO_4, filtration, and concentration, the oil was passed through flash silica gel with hexane/EtOAc (usually 5:1 to 3:1) as eluent.

11. In the case of L-Phe-OMe, the oxaziridines were formed with 5 mol % Bu_2SnCl_2 at ambient temperature for 3h.

12. All photochemical rearrangements were performed at 254 nM in benzene (10-30 mM; degassed with N_2 for 20 min). Required reaction time varied (2-12 h) with the nature of the amino ester moiety.

13. Eu(hfc)$_3$ = Tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato], europium (III) derivative.