Pergamon

Tetrahedron Letters 39 (1998) 9309–9312

TETRAHEDRON LETTERS

A novel method for the formation of 2-azocanones by lactone-to-lactam ring contraction of 2-oxonanones

Sam Derrer,* Neil Feeder, Simon J. Teat,[a] John E. Davies and Andrew B. Holmes*

Cambridge Centre for Molecular Recognition, University Chemical Laboratory, Lensfield Road, CAMBRIDGE CB2 1EW, UNITED KINGDOM

[a]CLRC Daresbury Laboratory, Daresbury, WARRINGTON WA4 4AD, UNITED KINGDOM

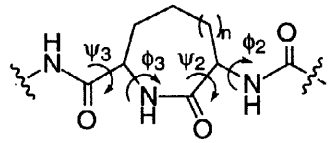
Received 16 September 1998; accepted 1 October 1998

Abstract

As part of a project evaluating medium-ring lactams as constrained peptidomimetics, a novel method for the formation of multisubstituted eight-membered lactams has been developed. *N*-Protected 7-amino-8-hydroxy-octenoic acids were cyclised to give 8-amino-5,6-dehydro-2-oxocanones which underwent clean intramolecular *O*-to-*N*-acyl (lactone-to-lactam) ring contraction to yield 8-hydroxymethyl-6,7-dehydro-2-azocanones, suitable for elaboration to eight-membered lactam dipeptides.

Keywords: Lactamisation; Medium-ring heterocycles; Lactones; Ring transformations

The design and synthesis of conformationally constrained peptidomimetics is an important tool in today's drug discovery process [1-4]. The most prominent approach to restricted peptides is through the incorporation of substituted five- to seven-membered lactams into peptide chains [5]. Larger ring sizes have been neglected owing to difficulties with ring closure reactions. However, the recognition of the medium-ring conformational bias (restricting up to four torsion angles, **Figure 1**) has recently led to a wider application in medicinal chemistry [6-8]. As part of an ongoing project evaluating a family of medium-ring lactams **1** as peptide conformational constraints [9-11], we have investigated the formation of substituted eight-membered lactams.



1, n = 1, 2, 3, 4

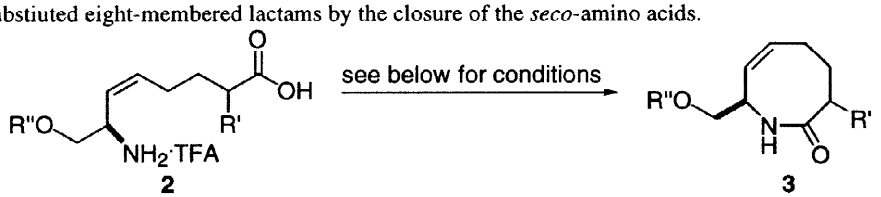
Figure 1. Medium ring lactams as constrained dipeptide surrogates

A possible strategy for the construction of eight-membered lactams is the closure of *seco*-amino acids, and we chose such methods as starting points for the preparation of functionalised 6,7-dehydro-2-azocanones (**Table**). Firstly, we employed the *n*-Bu_2SnO-mediated [9,12] cyclisation of *seco*-amino acid **2a**, which afforded the lactam **3a** in moderate

0040-4039/98/$ - see front matter
PII: S0040-4039(98)02093-0

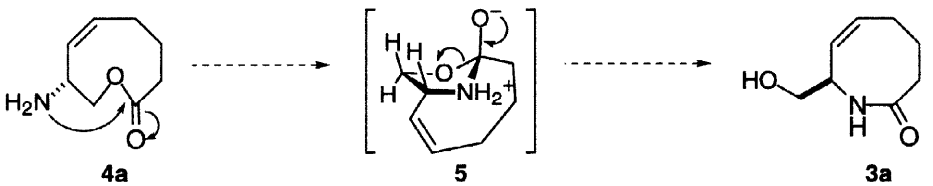
yield (46%).[1] However, owing to the harsh reaction conditions (refluxing xylene) the α-azido-lactam **3b** could not be prepared in this way. Alternatively, a method reported by Nakagawa *et al.* [13] using the activation of the amino acid with diphenylphosphoryl azide (DPPA) gave rise to α-azido-lactam **3b** in 40% yield.[2] This yield was greatly improved by protecting the hydroxymethyl substituent. Thus, the amino acid **2c** was converted into lactam **3c** in 86% yield and, accordingly, amino acids **2d** and **2e** into the corresponding lactams **3d** and **3e** in 73% and 67% yields, respectively.

Table
Formation of substiuted eight-membered lactams by the closure of the *seco*-amino acids.



2 **3**

amino acid	R' (config.)	R"	conditions	lactam	yield
2a	H	H	*n*-Bu_2SnO (0.5 eq.), xylene, reflux, 15 h	**3a**	46%
2b	N_3 (R)	H	*n*-Bu_2SnO (0.5 eq.), xylene, reflux, 15 h	**3b**	0%
2b	N_3 (R)	H	DPPA (5 eq.), Et_3N (6 eq.), DMF, 20 °C, 18 h	**3b**	40%
2c	H	TBDPS	DPPA (5 eq.), Et_3N (6 eq.), THF, 20 °C, 48 h	**3c**	86%
2d	N_3 (R)	TBDPS	DPPA (5 eq.), Et_3N (6 eq.), THF, 30 °C, 48 h	**3d**	73%
2e	N_3 (S)	TBDPS	DPPA (5 eq.), Et_3N (6 eq.), THF, 30 °C, 40 h	**3e**	67%



4a **5** **3a**

Scheme 1: Lactone-to-lactam ring contraction of a nine-membered 6-amino-lactone

It then occurred to us that it might be possible to effect the rearrangement of the amino-lactone **4a** by ring contraction to the hydroxymethyl-lactam **3a** *via* bicyclic intermediate **5** (**Scheme 1**). In order to test this hypothesis, compound **4a** was synthesised. This was convienently achieved from hydroxy acid **6a**[3] using Mulzer's procedure [14] based on the Yamaguchi lactonisation method [15].[4] The lactone **7a** was isolated in 89% yield. After BOC-deprotection with TFA, the lactone-to-lactam ring contraction of the TFA salt **9** was first carried out with DBU (2 equiv.) in refluxing xylene [16]. However, Et_3N in toluene at 20-40 °C proved to be equally effective (quantitative yield), albeit slightly slower (**Scheme 2**). It was also found that the carbon-carbon double bond constraint was not a prerequisite

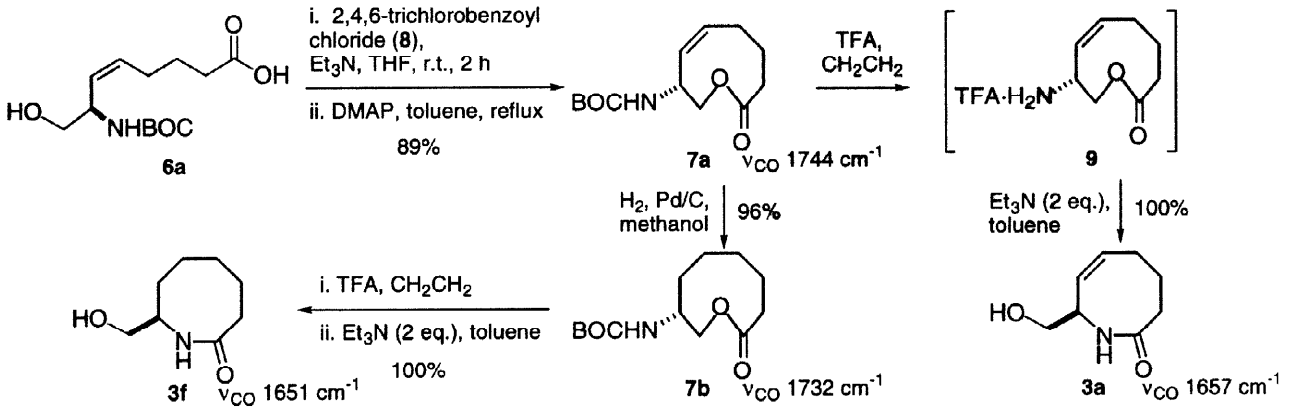
[1] All compounds reported herein were fully characterised by ^1H and ^{13}C NMR, IR, specific rotation, elemental analysis and/or HRMS.

[2] A full paper giving experimental detail for some of the described chemistry is in preparation.

[3] Compound **6a** was obtained from the L-serine-derived octenoic acid described in ref. 13, by acetonide deprotection with HOAc-H_2O.

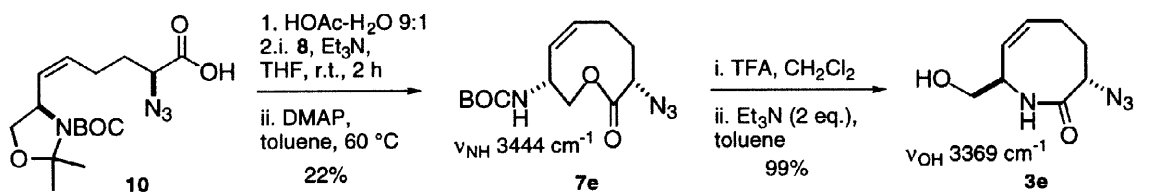
[4] Hydroxy acid **6a** was converted into the mixed anhydride with 2,4,6-trichlorobenzoyl chloride (**8**), and Et_3N in THF at room temperature, followed by dilution with toluene and the slow addition to a refluxing solution of *N,N*-dimethylaminopyridine in toluene.

for the ring contraction step, and conversion of saturated lactone **7b**, obtained by catalytic hydrogenation of **7a**, into lactam **3f** proceeded with ease.



Scheme 2

Because of the instability of the azido-acid **10** (crystal structure shown in **Figure 2a**) under conditions of lactonisation (>100 °C), the azido-lactone **7e** (crystal structure shown in **Figure 2b**) was obtained in only 12% yield (**Scheme 3**). This yield could be slightly improved (22%, along with 57% of cyclic and linear dimers) by performing the cyclisation at 60 °C. The free amino-lactone derived by deprotection of **7e** then underwent ring contraction to the lactam **3e** in quantitative yield.



Scheme 3

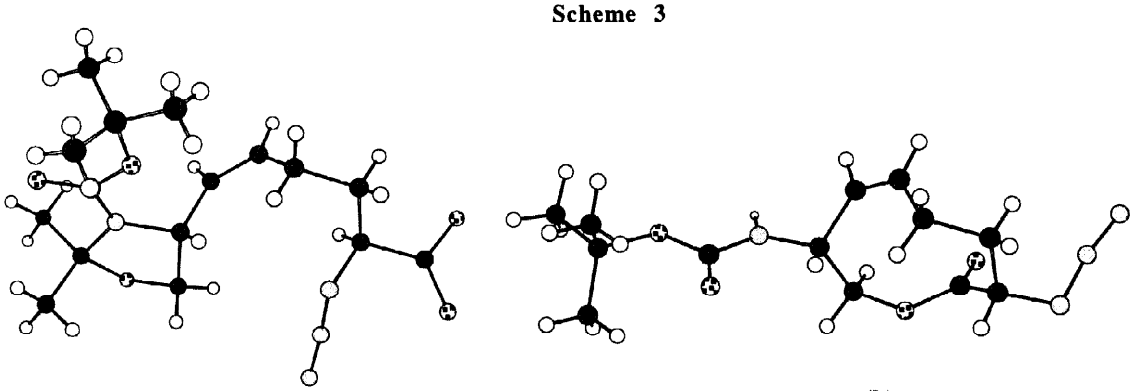
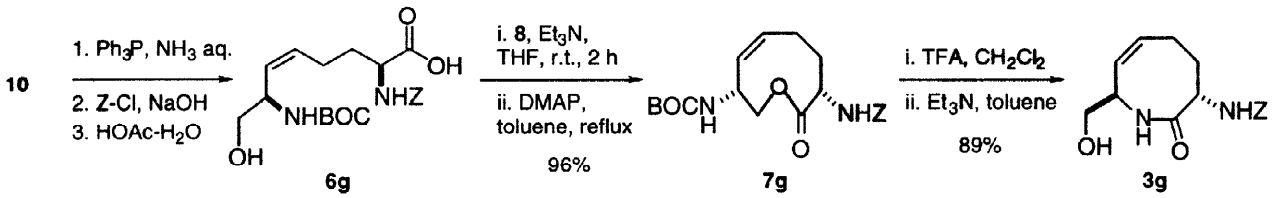


Figure 2. Chem3D representations of *X*-ray single crystal structures of (**a**) the *seco*-acid **10**[5] and of (**b**) the nine-membered azido-lactone **7e**.[6]

[5]Crystal data for **10**: orthorhombic; $P2_12_12_1$; a = 12.233(3) Å, b = 15.107(5) Å, c = 10.673(5) Å, α = 90°, β = 90°, γ = 90°; Z = 4; goodness-of-fit on F^2 1.058; final R indices [$I > 2\sigma(I)$] R1= 0.0569, wR2 = 0.1449; R indices (all data) R1 = 0.0898, wR2 = 0.1757.

[6]Crystal data for **7a**: monoclinic; $P2_1$; a = 5.15070(10) Å, b = 10.09460(10) Å, c = 14.9056(2) Å, α = 90°, β = 93.8330(10)°, γ = 90°; Z = 2; goodness-of-fit on F^2 1.058; final R indices [$I > 2\sigma(I)$] R1= 0.0439, wR2 = 0.1077; R indices (all data) R1 = 0.0488, wR2 = 0.1177. Diffraction data acquired using the Daresbury Synchrotron Station 9.8.

To overcome the problems with the thermal lability of the azido group, compound **10** was converted into a carbamate prior to cyclisation using standard procedures (**Scheme 4**). The cyclisation of *seco*-acid **6g** gave rise to lactone **7g** in excellent yield and the subsequent deprotection and lactone-to-lactam ring contraction gave the *trans*-disubstituted eight-membered lactam **3g** ready for elaboration to the β-turn mimetic **1** (n = 2) [11].



Scheme 4

In summary, we have demonstrated that the lactone-to-lactam ring contraction of 5,6-dehydro-2-oxocanones provides a novel access to multisubstituted eight-membered lactams. This sequence takes advantage of the fact that nine-membered lactones are more easily formed by ring closure than eight-membered lactams[17]. Similarly, the lactone-to-lactam ring expansion of δ-(2-aminoethyl)-δ-lactones to 2-azocanones is currently under investigation.

Acknowledgements: We thank the Engineering and Physical Sciences Research Council, UK, for financial support and provision of the Swansea Mass Spectrometry Service and the Daresbury Synchrotron Station. We thank Clare College for the award of a Research Fellowship (SD), Pfizer Central Research for financial support and Senn Chemicals AG (Switzerland) for a generous donation of chemicals.

References

[1] Giannis A. Angew. Chem. Int. Ed. Engl. 1993;32:1244-1267.
[2] Adang AEP, Hermkens PHH, Linders JTM, Ottenheijm HCJ, van Staveren CJ. Recl. Trav. Chim. Pays-Bas 1994;113:63-78.
[3] Gante J. Angew. Chem. Int. Ed. Engl. 1994;33:1699-1720.
[4] Liskamp RMJ. Recl. Trav. Chim. Pays-Bas 1994;113:1-19.
[5] Freidinger RM, Perlow DS, Veber DF, Brooks JR, Saperstein R. Science 1980;210:656-658.
[6] Thorsett ED, Harris EE, Aster SD, Peterson ER, Snyder JP, Springer JP, Hirshfield J, Tristram EW, Patchett AA, Ulm EH, Vassil TC. J. Med. Chem. 1986;29:251-260.
[7] Brouillette WJ, Jestkov VP, Brown ML, Akhtar MS, DeLorey TM, Brown GB. J. Med. Chem. 1994;37:3289-3293.
[8] Mazurov AA, Andronati SA, Korotenko TI, Sokolenko NI, Dyadenko AI, Shapiro YE, Gorbatyuk VY, Voronina TA, Bioorg. Med. Chem. Lett. 1997;5:2029-2040.
[9] Nadin A, Derrer S, McGeary RP, Goodman JM, Raithby PR, Holmes AB. J. Am. Chem. Soc. 1995;117:9768-9769.
[10] Nadin A, Derrer S, McGeary RP, Goodman JM, Holmes AB, Raithby PR. Mater. Sci. & Eng. C 1996;4:59-62.
[11] Derrer S, Davies JE, Holmes AB. submitted for publication.
[12] Steliou K, Poupart MA. J. Am. Chem. Soc. 1983;105:7130-7138.
[13] Torisawa Y, Motohashi Y, Ma JA, Hino T, Nakagawa M. Tetrahedron Lett. 1995;36:5579-5580.
[14] Mulzer J, Kirstein HM, Buschmann J, Lehmann C, Luger P. J. Am. Chem. Soc. 1991;113:910-923.
[15] Inanaga J, Hirata K, Hiroko S, Katsuki T, Yamaguchi M. Bull. Chem. Soc. Jpn. 1979;52:1989-1993.
[16] Rassu G, Casiraghi G, Pinna L, Spanu P, Ulgheri F. Tetrahedron 1993;49:6627-6636.
[17] Iluminati G, Mandolini L. Acc. Chem. Res. 1981;14:95-102.