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

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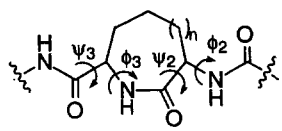
Abstract

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

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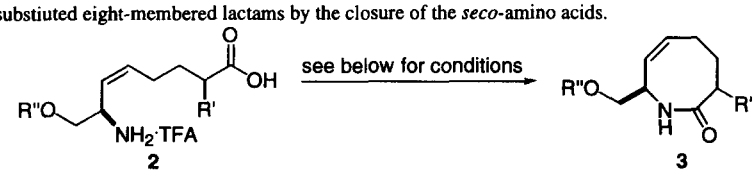
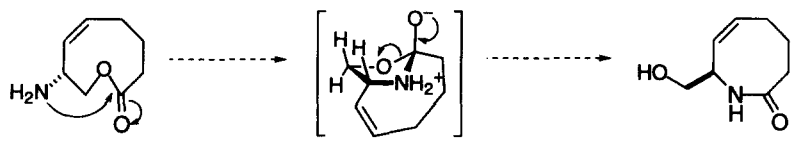
yield (46%).[1] However, owing to the harsh reaction conditions (refluxing xylene) the α-azido-lactam **3b** could not be prepared in this way. Alternatively, a method reported by Nakagawa *et al.* [13] using the activation of the amino acid with diphenylphosphoryl azide (DPPA) gave rise to α-azido-lactam **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

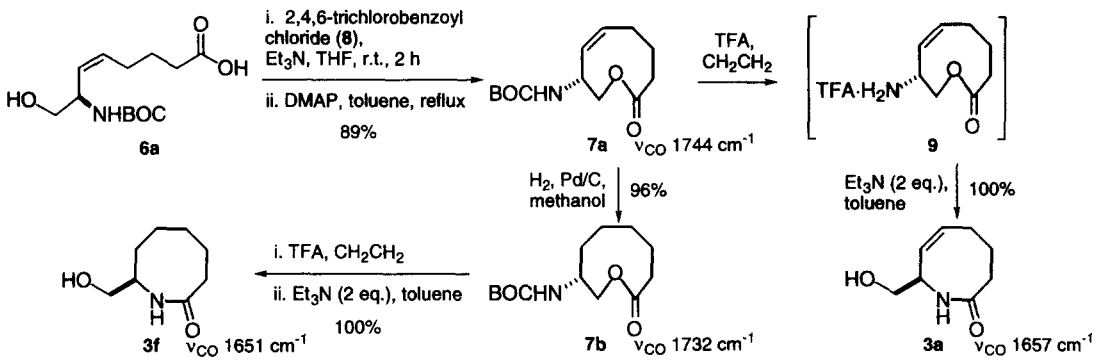
[1] All compounds reported herein were fully characterised by ^1H and ^{13}C NMR, IR, specific rotation, elemental analysis and/or HRMS.

[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.

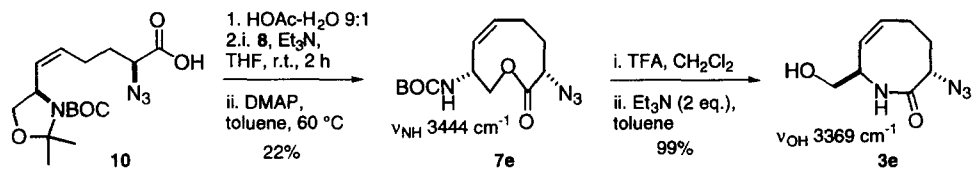
[4] Hydroxy acid **6a** was converted into the mixed anhydride with 2,4,6-trichlorobenzoyl chloride (**8**), and Et_3N in THF at room temperature, followed by dilution with toluene and the slow addition to a refluxing solution of *N,N*-dimethylaminopyridine in toluene.

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

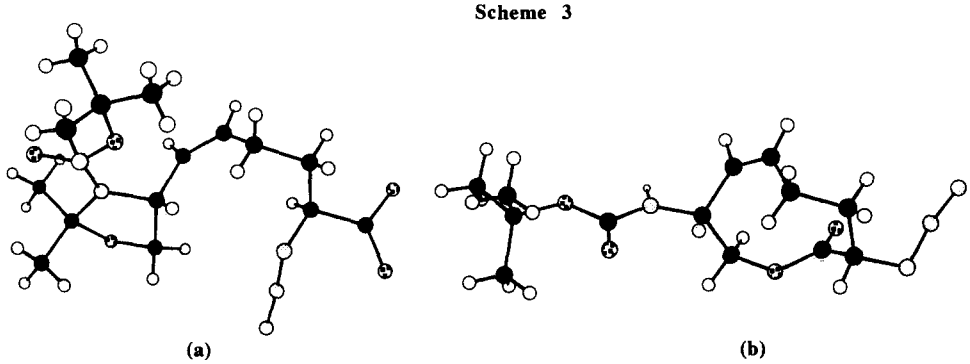


Figure 2. Chem3D representations of *X*-ray single crystal structures of (**a**) the *seco*-acid **10**[5] and of (**b**) the nine-membered azido-lactone **7e**.[6]

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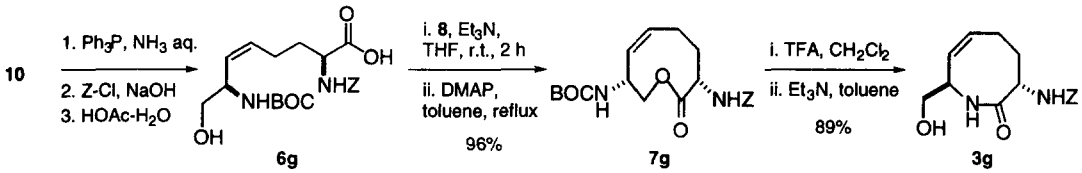
[5]Crystal data for **10**: orthorhombic; $P2_12_12_1$; a = 12.233(3) Å, b = 15.107(5) Å, c = 10.673(5) Å, α = 90°, β = 90°, γ = 90°; Z = 4; goodness-of-fit on F^2 1.058; final R indices [$I > 2\sigma(I)$] R1= 0.0569, wR2 = 0.1449; R indices (all data) R1 = 0.0898, wR2 = 0.1757.

[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.

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