

“Synthesis of a bicyclic oxo- γ -lactam from a simple caprolactam derivative”

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Electronic Supplementary Information (ESI) available: CCDC 1528320 and 1522636. For synthetic procedures, crystallographic and spectroscopic data see DOI: 10.1039/x0xx00000x

Abstract

The synthesis of the 6-azabicyclo[3.2.1]octane ring system, *via* Dieckmann cyclization, is described. Ring closure involves reaction of a caprolactam enolate with a C-6 ester, the reactive axial conformation of which is promoted by the presence of an *N-tert*-butyloxycarbonyl group on the lactam nitrogen. The results will enable the synthesis of new bridged caprolactams for testing as antibacterials and nucleophilic enzyme inhibitors.

The β -lactams remain the most important antibacterials; they work by reaction with a nucleophile serine residue in penicillin binding proteins (PBPs), which catalyse essential transpeptidase reactions during bacterial cell-wall peptidoglycan biosynthesis. A common mechanism of resistance to the β -lactam antibacterials, involves β -lactamases, which catalyse β -lactam hydrolysis. All clinically used PBP inhibitors are β -lactams and until recently this has been the case for β -lactamase inhibitors.¹ Following on from synthetic γ -lactam analogues of the β -lactams and the discovery of the natural product lactivicin, the cyclic urea avibactam has recently been introduced as a broad spectrum serine β -lactamase inhibitor.² However, while the β -lactam based inhibitors react irreversibly with the nucleophile serine of the PBPs and β -lactamases, avibactam reacts reversibly with its target serine β -lactamases.³ The discovery of avibactam has stimulated interest in non β -lactam inhibitors of the serine β -lactamases and PBPs. We have been interested in bridged lactams as inhibitors of nucleophilic serine / threonine / cysteine enzymes; however, for ring sizes > 6 there are only limited reports on their synthesis. Here we describe the synthesis of the 6-azabicyclo[3.2.1]octane bridged ring system, starting from a readily available caprolactam precursor (Fig. 1).

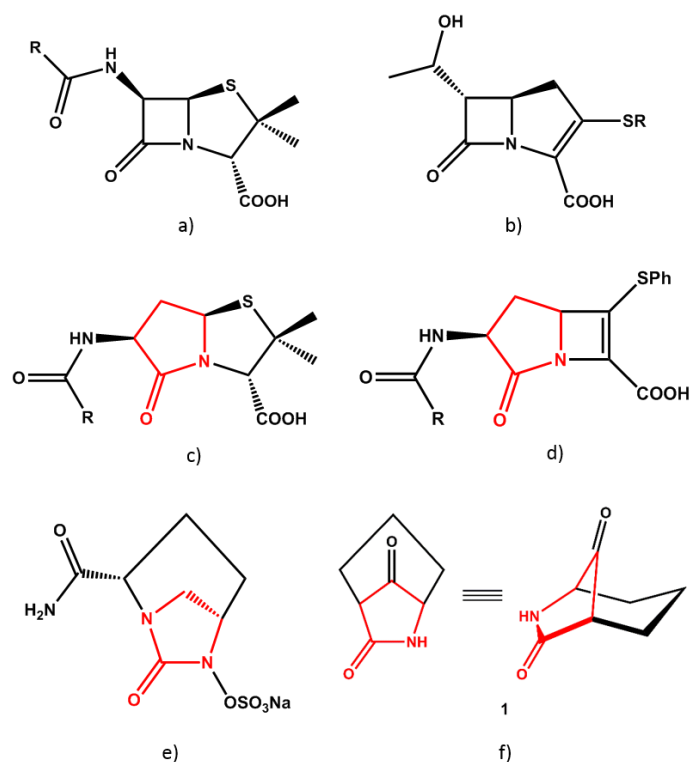


Fig. 1 Examples of β -lactam antibacterials, β -lactam inhibitors and non- β -lactam analogues: a) penicillins, b) carbapenems, c) an inactive γ -lactam analogue, d) an active γ -lactam analogue, e) avibactam and f) the target of the current work (1) which has a 6-azabicyclo[3.2.1]octane core ring system.

The 6-azabicyclo[3.2.1]octane ring system is present in a wide range of biologically active compounds and is isomeric with the tropane nucleus present in alkaloids, including cocaine and atropine.⁴ Preparation of respective 6-azabicyclo[3.2.1]octane derivatives and related compounds is restricted to the intramolecular ring closure of γ -lactam derivatives,⁵ amide formation in substituted cyclohexanes⁶ and Diels-Alder reaction of appropriately unsaturated γ -lactams with acrylic acid.⁷ There is only one reported route to a 7,8-dioxo-6-

azabicyclo[3.2.1]octane derivative of (**1**), which employs semipinacol rearrangement of a β -lactam precursor.⁸ We envisaged bicycle **1** could be succinctly prepared from of a simple caprolactam *via* Dieckmann cyclization. We anticipated that then Dieckmann cyclization may only proceed efficiently, when the ester group adopts an axial position (Fig. 2a/b/c).

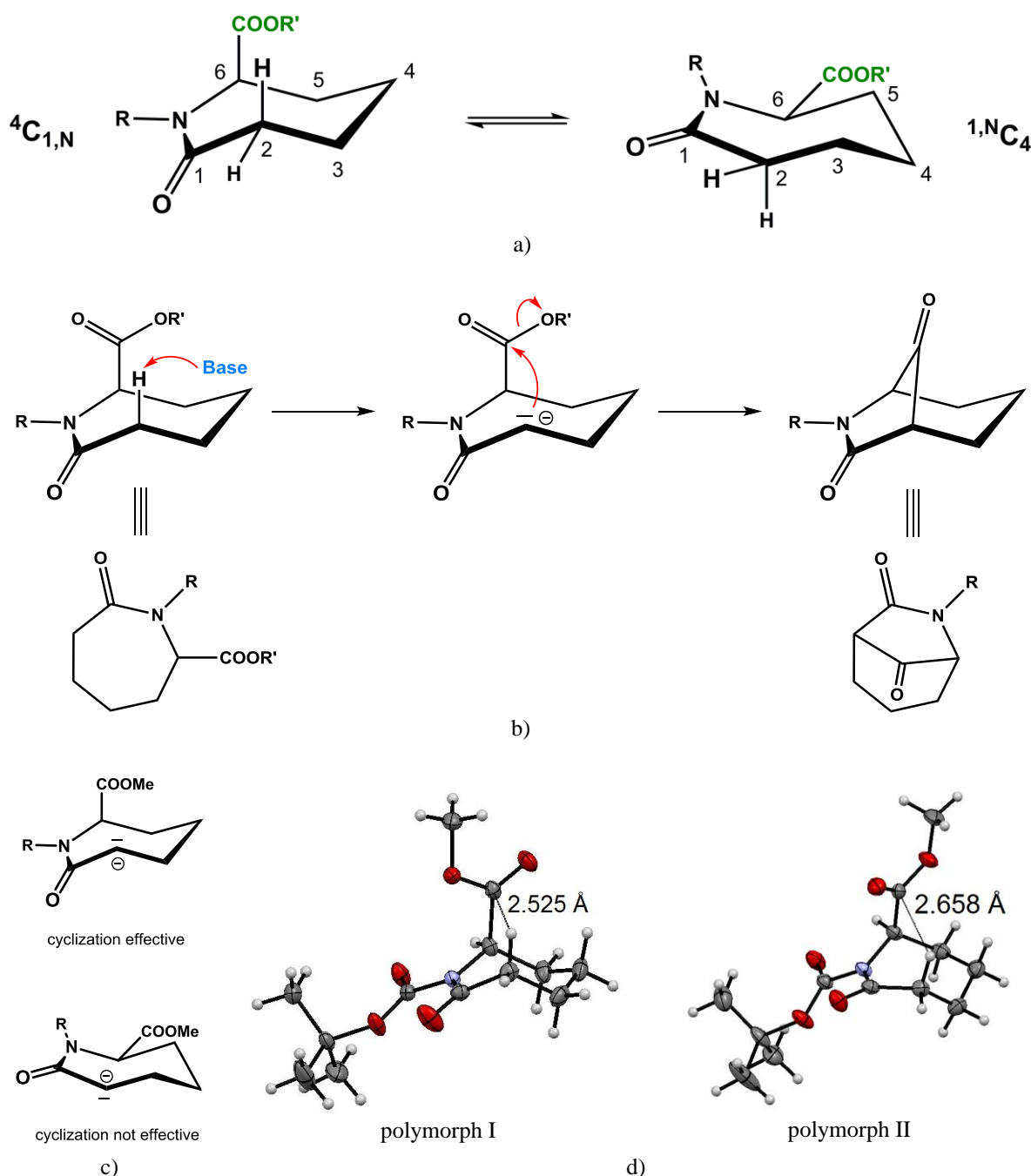


Fig. 2 Proposed Dieckmann cyclisation to give the 6-azabicyclo[3.2.1]octane ring system. a) The two energetically favoured ‘pseudo chair’ conformations of an *N*-substituted caprolactam methylester. b) Synthesis of **1** *via* Dieckmann cyclization. c) Only the axially positioned ester group can react *via* the desired Dieckmann cyclization. d) View from a crystal structure of **3** showing that the –COOMe group adopts an axial conformation, as observed for both polymorphs. In solution an equilibrium between the ‘axial’ and ‘equatorial’ conformers (70 % : 30 %) is observed.¹²

Caprolactams can adopt (pseudo) chair, boat or transition (twist boat) forms.⁹ In the ‘chair’ form, two energetically favoured conformations are manifested ($^1N C_4$ and $^4C_{1,N}$) assuming an planar amide.¹⁰ Similar to cyclohexane chair conformations, caprolactams feature axial and

equatorial positions of ring hydrogens and respective substituents. The axial substituents are higher in energy than equatorial ones as shown for C-2/C-6 monosubstituted caprolactams.¹¹ In a previous study,¹² we investigated the influence of a second substituent on the conformation of the C-6 caprolactam methylester (**2**) (Fig. 3). Especially promising for our purposes proved to be the introduction of a *tert*-butyloxycarbonyl (Boc) group which delivers **3**. After substitution of the amide proton with the bulky Boc, the -COOMe and the -COOC(CH₃)₃ on the nitrogen atom are in the *trans* position to each other. This can be explained by the steric demand of both groups, with the Boc carbonyl being coplanar to the amide segment forcing the former equatorial ester pendant of **2** into the normally energetically disfavoured axial position. Note the short distance of 2.53 Å (polymorph I)¹² and 2.66 Å (polymorph II, Tabs. S1 and S2, Scheme S1, ESI), respectively, between the C-6 ester carbonyl and the axial C-2 hydrogen as observed by X-ray crystallography (Fig. 2d), which seems to be necessary for a transannular reaction. Indeed, treatment of **3** with LiHDMS (lithium bis(trimethylsilyl)amide) produced the desired bicyclic lactam in its protected form (**1a**) in low (8 %) yield (Fig. 3). In order to optimise the reaction, several attempts to improve the yield of the cyclization by the use of different solvents (increase to 11 % yield for toluene) and the variation of temperature (higher temperatures prevent the cyclization). Furthermore, we varied the amount of base (increase to 12 % yield for 2.1 equivalents) (Table 1).

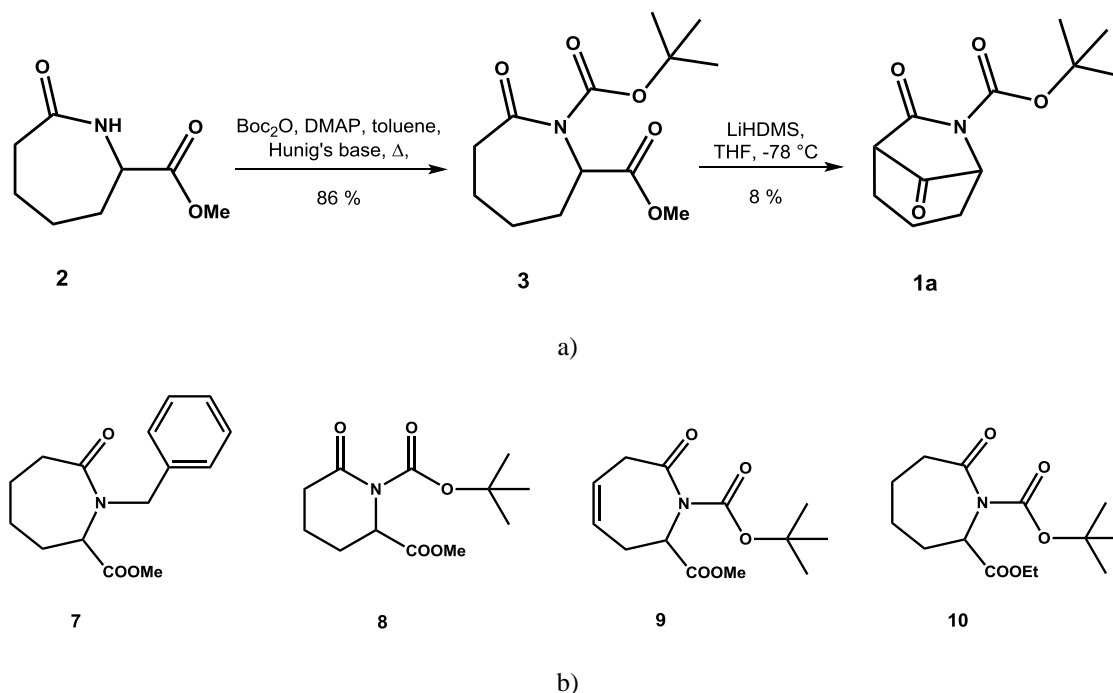


Fig. 3 a) Synthetic pathway to bicycle **1a**. b) Alternative substrates subjected to the here described cyclization conditions.

It had been shown that the introduction of a Boc group at the lactam nitrogen activates the C-2 position for an electrophilic attack.¹³ However, other studies have proven that the lithium ion of LiHDMS can prevent related reactions by forming a complex with the amide carbonyl and the Boc group of the substrate.¹⁴ To test this theory for our system we used the related bases NaHDMS and KHDMS featuring larger cations than LiHDMS. The yield of **1a** did only increase slightly when higher amounts of base were used as observed above, ruling out that complexformation with the respective alkali ion is the reason for the low yield.

Furthermore, we suspected, the formation of the smallest possible ketone, *i.e.* the five membered ring could compete with the formation of the dimer, *i.e.* the 10-membered ring, as well as oligomers. Inspired by high dilution conditions known from macroketone syntheses,¹⁵

we varied the concentration of the educt with the outcome being displayed in Tab. S3 (ESI). Interestingly, the concentration did not seem to influence the yield significantly.

Table 1 Conditions for the optimization of the here presented Dieckmann cyclization

Expt. No.	substrate	Cyclization conditions					Isolated yields of bicycle (%)
		base	protecting group	solvent	equivalents of base (eq)	temperature (°C)	
1	3	LiHDMS	Boc	THF	1.1	-78	8
2	3	LiHDMS	Boc	<i>n</i> -hexane	1.3	-85	8
3	3	LiHDMS	Boc	toluene	1.3	-85	11
4	3	LiHDMS	Boc	THF	1.1	rt	0
5	3	LiHDMS	Boc	THF	1.1	0	0
6	3	LiHDMS	Boc	THF	1.3	-85	8
7	3	LiHDMS	Boc	THF	1.3	-100	7
8	3	LiHMDS	Boc	THF	2.1	-85	12
9	3	KHMDS	Boc	THF	1.3	-85	8
10	3	KHMDS	Boc	THF	2.1	-85	13
11	3	NaHDMS	Boc	THF	1.3	-85	7
12	3	NaHDMS	Boc	THF	2.1	-85	11
13	7	LiHDMS	Bn	THF	1.3	-85	0
14	7	KHMDS	Bn	THF	1.3	-85	0
15	7	KHMDS	Bn	THF	2.1	-85	0
16	8	LiHDMS	Boc	THF	1.3	-85	0
17	9	LiHDMS	Boc	THF	1.1	-85	0
18	10	LiHDMS	Boc	THF	1.1	-85	15

In order to study the influence of the amide protecting group, the ring size and the flexibility of the caprolactam rings on the here described Dieckmann cyclization, we prepared the related lactams **7-9** (Fig. 3b). Although, when applying the standard cyclization conditions on this substrates, no cyclization was observed. This leads to the interesting observation, that the benzyl group on **7** seems to prevent an electrophilic attack in C-2 position as already shown for the respective butyrolactam.¹³ Moreover, smaller rings and less flexible caprolactams do not undergo the Dieckmann cyclization when applying above reaction conditions.

Caprolactam **3** features two C-H acidic position (C-2 and C-6) and a competing deprotonation may be another reason for the low yield of the bicyclic lactam **1a** in the cyclisation step. To investigate the proposal of competing C-6 deprotonation, Boc-protected ethylester **10** (Fig. 3) was prepared. Thus, caprolactam methylester **2** was saponified to yield the free acid, which was esterified with EtOH and, subsequently, treated with Boc anhydride. When **10** was subjected the Dieckmann cyclization, a higher yield of **1a** (15 %) was achieved, likely due to reduced C-6 deprotonation relative to **3** due to the higher steric demand of the ethyl ester.

¹H and ¹³C NMR (Fig. S1, ESI) as well as COSY analyses (Fig. S2, ESI) support the assigned structure of **1a**. Of note, the ¹H spectrum exhibits a ‘doublet of doublets of doublets’ (ddd) coupling for *H2* and *H6*. The third coupling likely results from ⁴*J*_{H,H} long-range ‘W’

coupling^{16,17} of *H*2 with *H*6 over the keto bridge. For the bicyclic lactam **1a**, *H*2 and *H*6 couple with 4J values of 4.89 and $^4J=4.88$ Hz respectively; the analogous value for cyclobutanone is 4.8 Hz.¹⁸ By contrast the 3J -couplings are rather low, both for the coupling of *H*2 with *H*3/*H*3' ($^3J=2.50/1.95$ Hz) and of *H*2 with *H*6 ($^3J=1.88/1.33$ Hz) (Fig. 4; Fig. S3, ESI).

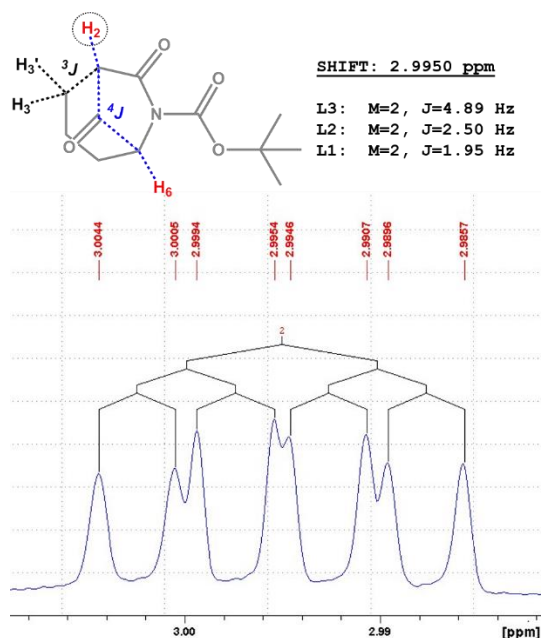


Fig. 4 Close up view from the ^1H NMR (125 MHz) spectrum of **1a**; the *H*2 signal with the respective ddd coupling pattern and the respective $^3J_{\text{H,H}}$ and $^4J_{\text{H,H}}$ values is shown.

Bicycle **1a** crystallized from ethyl acetate and cyclohexane as its corresponding hydrate **1b** (Fig. 5a), a phenomenon which was already observed with a related compound.⁴ The plate like twinned crystals are in space group *P*-1 with molecules featuring (*R,R*) and (*S,S*) stereochemistry. As expected, the five-membered ring of **1b** adopts an envelope conformation, while the caprolactam adopts the rarer boat conformation (Fig. 5b). A comprehensive comparison of bond lengths and angles with related compounds can be found in the Supplementary Material (Tab. S4, ESI). The molecules of **1b** arrange in hydrogen bonded ribbons running in the direction of the crystallographic *a* axis. In the ribbons two diols face each other making an $R_2^2(8)$ motif and these dimers then bond into C6 chains *via* the ring carbonyl groups (Fig. 5c; Tab. S5, ESI). The ribbons stack up on each other with only weak C-H \cdots O(-H) hydrogen bonds in the direction of the crystallographic *b* axis. The *tert*-butyl groups point outward from the sheet assembled *via* these interactions and stacking errors of these sheets cause the crystals to be twinned.

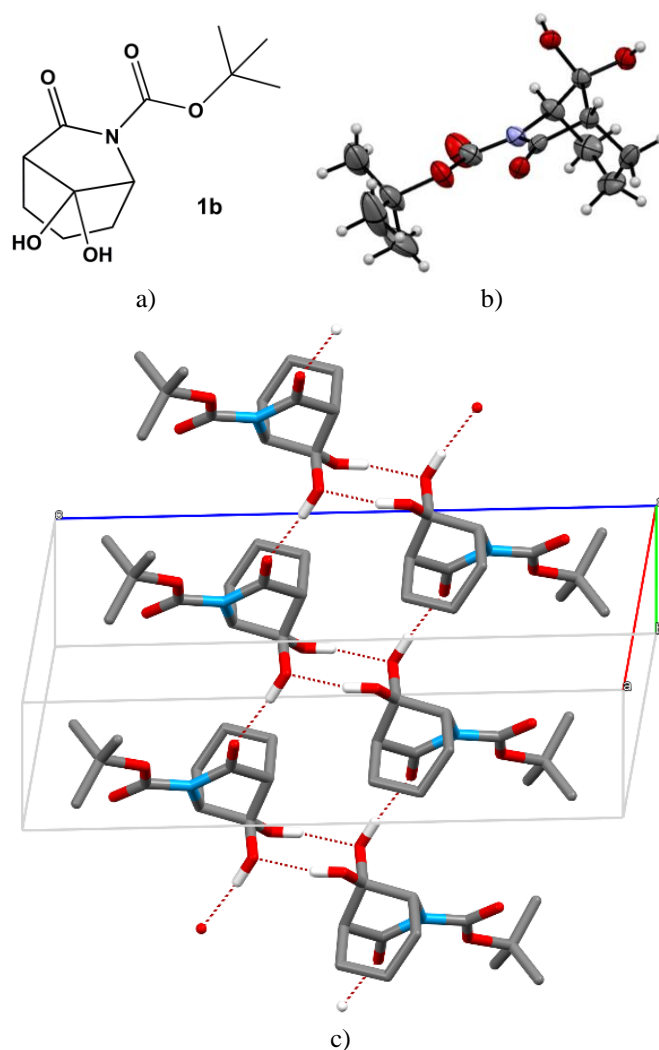


Fig. 5 a) Molecular formula of the hydrate of **1a**, *i.e.* **1b**.
 b) Ortep plot at 50 % probability of crystal structure of **1b**.
 c) Hydrogen bonded ribbons of **1b** running along the crystallographic *a* axis.

Conclusions

Overall, we have described the concise synthesis of a bridged caprolactam ring system, *via* Dieckmann cyclization. This route builds upon work that has defined the transformations of readily accessible caprolactam derivatives. Closure to give the 6-azabicyclo[3.2.1]octane ring system involves the reaction of a caprolactam enolate with an C-6 ester in an axial conformation. The presence of the reactive axial conformation is promoted by an *N*-butyloxycarbonyl group on the caprolactam nitrogen. The yield is increased slightly by the use of non-polar solvents, higher amounts of base and an ethyl, rather than a methyl, ester, likely due to diminished C-6 deprotonation with the ethyl ester. Future work will focus on a deeper understanding of the mechanism and minimising side reactions. The results will enable the synthesis of 6-azabicyclo[3.2.1]octane ring derivatives for testing as antibacterials and nucleophilic enzyme inhibitors.

Experimental

Here we present the cyclization procedure for the optimization experiment delivering the highest yield.

***tert*-Butyl 7,8-dioxo-6-azabicyclo[3.2.1]octane-6-carboxylate (1a).** To a stirred solution of the appropriate Boc-protected lactam ethylester **10** (172 mg, 0.60 mmol) in dry THF (30 ml) at -78 °C was added a 1M solution of lithium hexamethyldisilazide (LiHDMS) in ethylbenzene/THF (660 µl, 0.66 mmol, 1.1 eq.). The reaction mixture was then stirred at -78 °C for 3 h. Subsequently, the reaction was quenched with sat. aqueous ammonium chloride solution (30 ml) at -78 °C and extracted with ethyl acetate (3x30 ml). The combined organic phases were dried (Na₂SO₄), then filtered. Evaporation of the solvent yielded a dark, oily residue which was separated by flash column chromatography (SiO₂; *n*-hexane/ethyl acetate = 1:1 → ethyl acetate) to yield 15 % (22 mg, 0.092 mmol) of a white solid. Mp. 93-94 °C. R_f = 0.30 (SiO₂; *n*-hexane/ethyl acetate = 1:1). ¹³C NMR (125 MHz, CDCl₃): δ = 207.3 (CO), 168.9 (CONCOO^tBu), 148.4 (NCOO^tBu), 84.1 (CH₃)₃, 64.9 (COCHCO), 55.0 (NCHCO), 33.2 (CH₂), 32.7 (CH₂), 28.0 (CH₃)₃, 17.1 (CH₂). ¹H NMR (500 MHz, CDCl₃): δ = 4.39 (m, 1H, NHCH), 2.99 (m, 1H, COCHCO), 2.44-2.31 (m, 2H, CH₂), 2.05-1.96 (m, 1H, CH₂), 1.95-1.88 (m, 1H, CH₂), 1.84-1.75 (m, 2H, CH₂), 1.54 (s, 9H, C(CH₃)₃). IR: 3391, 2992, 2932, 2874, 1769, 1752, 1713, 1448, 1393, 1365, 1326, 1305, 1249, 1220, 1154, 1089, 1068, 1052, 1014, 993, 975, 953, 888, 865, 712. m/z = 238.11 [M-H⁺], calc. 238.12.

X-ray crystallography

Bicycle **1a** was crystallized from ethyl acetate and cyclohexane using the vapor diffusion approach resulting in hydrate **1b**. Crystals suitable for single crystal X-ray diffraction studies of polymorph II of compound **3** were obtained by crystallization from ethyl acetate/*n*-hexane (1:2) and have a melting point of 69-71 °C; this is about 20 K higher than observed for polymorph I¹² (CSD refcode: BOLHOB).

Single crystal X-ray diffraction was performed at 173K with a Bruker D8 Venture diffractometer using a Cu-K_α source. Structure solution was carried out with shelxt¹⁹ and structure refinement with shelxl²⁰ was finished using ShelXle²¹ software. The twin matrix for **1b** was acquired from twinrotmat in Platon.²² For crystal data and refinement parameters see ESI. CCDC numbers 1528320 (**1b**) and 1522636 (**3**).

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

FO thanks the ‘Verein der Freunde und Förderer der TU Bergakademie Freiberg’ for a travel scholarship. CW and TG gratefully acknowledge financial support from the Institute of Organic Chemistry, University of Freiberg and the School of Pharmacy, University of Lincoln. Furthermore, the authors are indebted to Dr Erica Brendler, Institute of Analytical Chemistry, University of Freiberg, for recording the 2D NMR spectra and for her helpful advice. CJS thanks the Medical research Council for support.

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