

**ELECTRONIC SUPPLEMENTARY MATERIAL (ESI) FOR
NEW JOURNAL OF CHEMISTRY**

Supporting Information

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

Christian Weck,^{a,b} Franziska Obst,^a Elisa Nauha,^c Christopher J. Schofield,^d and
Tobias Gruber,^{a,b*}

^a *Institute of Organic Chemistry, Technische Universität Bergakademie Freiberg, Leipziger
Straße 29, Freiberg/Sachsen, Germany*

^b *School of Pharmacy, University of Lincoln, Joseph Banks Laboratories, Green Lane,
Lincoln LN6 7DL, United Kingdom. E-mail: tgruber@lincoln.ac.uk; Tel: +44 152 283 7396*

^c *School of Chemistry, University of Lincoln, Joseph Banks Laboratories, Green Lane,
Lincoln LN6 7DL, United Kingdom.*

^d *University of Oxford, Department of Chemistry, Chemistry Research Laboratory, 12
Mansfield Road, Oxford OX1 3TA, United Kingdom.*

SYNTHETIC PROCEDURES

Ethyl 7-oxoazepane-2-carboxylate (5)

Ethanol (10 ml) was cooled to -10 °C, then thionylchloride (923 μ l, 12.72 mmol) was added dropwise with stirring. Subsequently, 7-oxoazepane-2-carboxylic acid¹ (**3**) (1.0 g, 6.36 mmol) was added; the reaction mixture was then allowed to warm to room temperature and stirred overnight. The solvents were removed in vacuo and the residue purified by flash chromatography (SiO₂; eluent: ethyl acetate) to yield 79 % (929 mg, 5.02 mmol) of a colourless oil. R_f = 0.40 (SiO₂; ethyl acetate). ¹³C NMR (100 MHz, CDCl₃): δ = 176.2 (COOCH₂), 171.4 (CONH), 62.2 (OCH₂CH₃), 55.9 (NHCH), 37.1 (CH₂), 33.8 (CH₂), 29.7 (CH₂), 22.9 (CH₂), 14.1 (OCH₂CH₃). ¹H NMR (400 MHz, CDCl₃): δ = 6.43 (br s, 1H), 4.23 (q, ³J = 7.0 Hz, 2H, OCH₂CH₃), 4.09-4.05 (m, 1H, NHCH), 2.56-2.48 (m, 1H, CH₂), 2.46-2.38 (m, 1H, CH₂), 2.29-2.21 (m, 1H, CH₂), 2.11-2.06 (m, 1H, CH₂), 1.91-1.85 (m, 1H, CH₂), 1.63-1.47 (m, 3H, CH₂), 1.30 (t, ³J = 7.0 Hz, 3H, OCH₂CH₃). IR: 3411, 2974, 2937, 2872, 1770, 1716, 1459, 1394, 1366, 1302, 1255, 1213, 1151, 1113, 1081, 1055, 995, 953, 926, 906, 875, 842, 782, 763, 741. m/z = 186.15 [M+H⁺], calc. 186.11.

Alternatively, the synthesis of **5** was conducted similarly to that of the respective methylester¹ (**2**): Ethanol (10 ml) was cooled to -10 °C, then thionylchloride (2.0 ml, 27.57 mmol) was added dropwise with stirring. Subsequently, 2-aminopimelic acid (1.0 g, 5.71 mmol) was added; the reaction mixture was allowed to warm to room temperature, then stirred overnight. The solvents were removed in vacuo, to yield the hydrochloride of the amino acid, which was used without purification. It was neutralized by addition of a small amount of aqueous sodium bicarbonate (1 eq.), before extraction with ethyl acetate. The organic phase was dried (MgSO₄), filtered and concentrated to afford the free base. After addition of *p*-cymene (60 ml), the mixture was stirred at reflux for 72 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO₂; eluent: ethyl acetate) to give the product as a pale-yellow oil. Yield: 25 % (267 mg, 1.44 mmol).

1-tert-Butyl 2-ethyl 7-oxoazepane-1,2-dicarboxylate (6)

Under a nitrogen atmosphere lactam **5** (155 mg, 0.84 mmol) was dissolved in dry toluene (20 ml). Subsequently, Hunig's base (286 μ l, 1.68 mmol) and 4-(*N,N*-dimethylamino)pyridine (21 mg, 0.17 mmol) were added at room temperature. After that, a solution of di(*tert*-butyl)dicarbonate (915 mg, 4.2 mmol) in dry toluene (5 ml) was added. The resultant mixture was stirred overnight under reflux. After cooling, water (5 ml) was added and the mixture stirred at room temperature for 30 min, before more water (20 ml) was added. The organic layer was then separated and dried over Na₂SO₄. Evaporation of the solvent and column chromatography yielded the crude product, which was purified by column chromatography (SiO₂; ethyl acetate). Yield: 72 % (172 mg, 0.60 mmol) of a colourless oil. R_f = 0.90 (SiO₂; ethyl acetate). ¹³C NMR (100 MHz, CDCl₃): δ = 175.5 (COOCH₂), 170.4 (CONH), 153.4 (NCOO^tBu), 83.2 (C(CH₃)₃), 61.6 (OCH₂CH₃), 56.6 (NHCH), 39.6 (CH₂), 29.8 (CH₂), 27.8 (C(CH₃)₃), 25.6 (CH₂), 22.7 (CH₂), 14.2 (OCH₂CH₃). ¹H NMR (400 MHz, CDCl₃): δ = 5.20-5.16 (m, 1H, NHCH), 4.26-4.19 (m, 2H, OCH₂CH₃), 2.71-2.61 (m, 1H, CH₂), 2.52-2.43 (m, 1H, CH₂), 2.45-2.34 (m, 1H, CH₂), 1.82-1.70 (m, 3H, CH₂), 1.58-1.48 (m, 2H, CH₂), 1.44 (s, 9H, C(CH₃)₃), 1.25 (t, 3H, ³J = 12.5 Hz, OCH₂CH₃). IR: 2980, 2935, 2866, 1771, 1711, 1449, 1385, 1367, 1292, 1249, 1192, 1151, 1083, 1045, 1022, 963, 912, 851, 815, 779, 746, 719. m/z = 286.20 [M+H⁺], calc. 286.16.

¹ T. Gruber, A. L. Thompson, B. Odell, P. Bombicz and C. J. Schofield, *New J. Chem.*, 2014, **38**, 5905-5917.

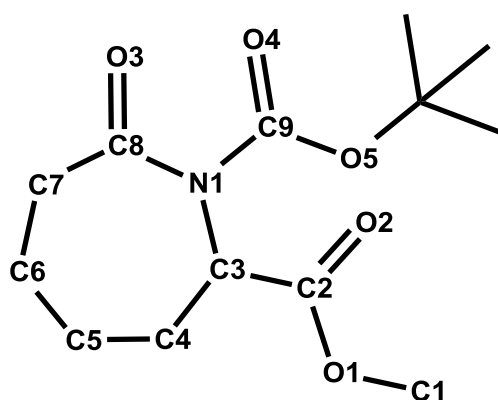
CRYSTALLOGRAPHIC AND SPECTROSCOPIC DETAILS

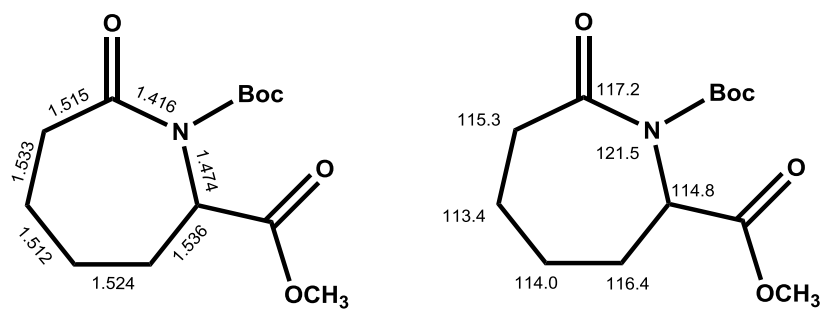
Table S1 Crystal data and selected details of the data collection and refinement calculations for **1b** and **3**

Compound	1b	3 (Polymorph II)
Empirical formula	C ₁₂ H ₁₉ NO ₅	C ₁₃ H ₂₁ NO ₅
Formula weight	257.28	271.31
Temperature	173(2) K	173(2) K
Wavelength	1.54178 Å	1.54178 Å
Crystal system	triclinic	orthorhombic
Space group	<i>P</i> -1	<i>Pbca</i>
Unit cell dimensions	a = 6.1511(6) Å b = 6.3794(7) Å c = 17.5260(18) Å α = 88.877(5)° β = 80.145(5)° γ = 82.187(5)°	a = 10.8289(3) Å b = 12.9518(4) Å c = 20.3412(6) Å α = 90° β = 90° γ = 90°
Volume	671.28(12) Å ³	2852.93(15) Å ³
Z	2	8
Density (calculated)	1.273 Mg/m ³	1.263 Mg/m ³
Absorption coefficient	0.830 mm ⁻¹	0.806 mm ⁻¹
F(000)	276	1168
Crystal size	0.370 x 0.208 x 0.048 mm ³	0.341 x 0.211 x 0.209 mm ³
Theta range for data collection	2.559 to 74.382°	4.347 to 72.471°
Index ranges ± <i>h</i> , ± <i>k</i> , ± <i>l</i>	-7/7, -7/7, -21/21	-13/11, -15/16, -25/25
Reflections collected	7972	51777
Independent reflections	2624 [R(int) = 0.0503]	2819 [R(int) = 0.0345]
Completeness to theta = 67.679°	99.7 %	100.00%
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	0.7536 and 0.6019	0.7536 and 0.6615
Refinement method	Full-matrix least-squares on <i>F</i> ²	Full-matrix least-squares on <i>F</i> ²
Data / restraints / parameters	2624 / 0 / 173	2819 / 0 / 177
Goodness-of-fit on <i>F</i> ²	1.061	1.046
Final R indices [I > 2σ(I)]	R ₁ = 0.0677, wR ₂ = 0.1764	R ₁ = 0.0369, wR ₂ = 0.0956
R indices (all data)	R ₁ = 0.0738, wR ₂ = 0.1859	R ₁ = 0.0395, wR ₂ = 0.0979
Extinction coefficient	n/a	0.00186(16)
Largest diff. peak and hole	0.274 and -0.317 e.Å ⁻³	0.352 and -0.261 e.Å ⁻³

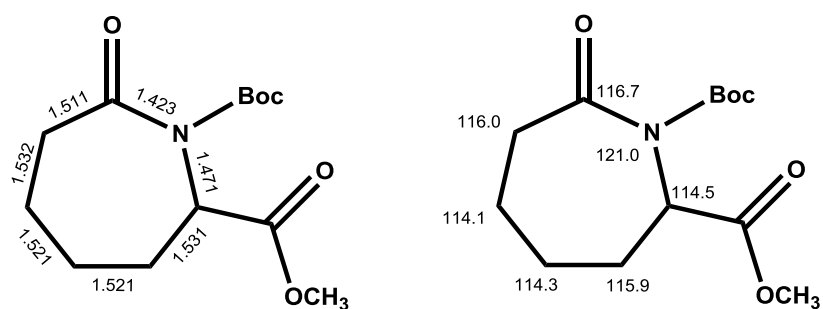
Table S2Torsion angles (°) for ring atoms in the two polymorphs of **3**

Atoms	Polymorph I ¹	Polymorph II
C1-C2-C3-C4	84.34	85.07(14)
C2-C3-C4-C5	-60.79	-68.90(14)
C3-C4-C5-C6	60.03	54.37(15)
C4-C5-C6-N1	-79.65	-70.47(13)
C1-N1-C6-C5	65.01	82.29(13)
C6-N1-C1-C2	-0.49	-32.44(15)
N1-C1-C2-C3	-67.95	-43.03(15)
N1-C6-C7-O2	14.50	-6.67(16)
C8-N1-C9-O5	8.38	-15.48(16)

General numbering scheme for compound **3**:



polymorph I



polymorph II

Scheme S1

Bond lengths (Å) and angles (°) for the two polymorphs of **3**.

Table S3

Results of the investigation of the concentration of the educt **3** on the yield of **1a**

batch	n(educt) [mmol]	V(solvent) [ml]	c(educt) [mmol/l]	Yield [%]
1	3.35	100	33.5	7.0
2	1.29	40	32.3	5.5
3	7.63	250	30.5	6.3
4	2.95	100	29.5	5.7
5	2.76	250	11.0	7.6
6	1.73	250	6.9	7.5

The $-\text{COOCH}_3$ signal (3.79 ppm) of **3** is not present in the spectrum of **1a**, supporting reaction via the proposed intramolecular ring closure. The signals for H_2 and H_6 (5.26 ppm and 2.68 ppm, respectively) are shifted significantly on conversion of **3** to **1a**.

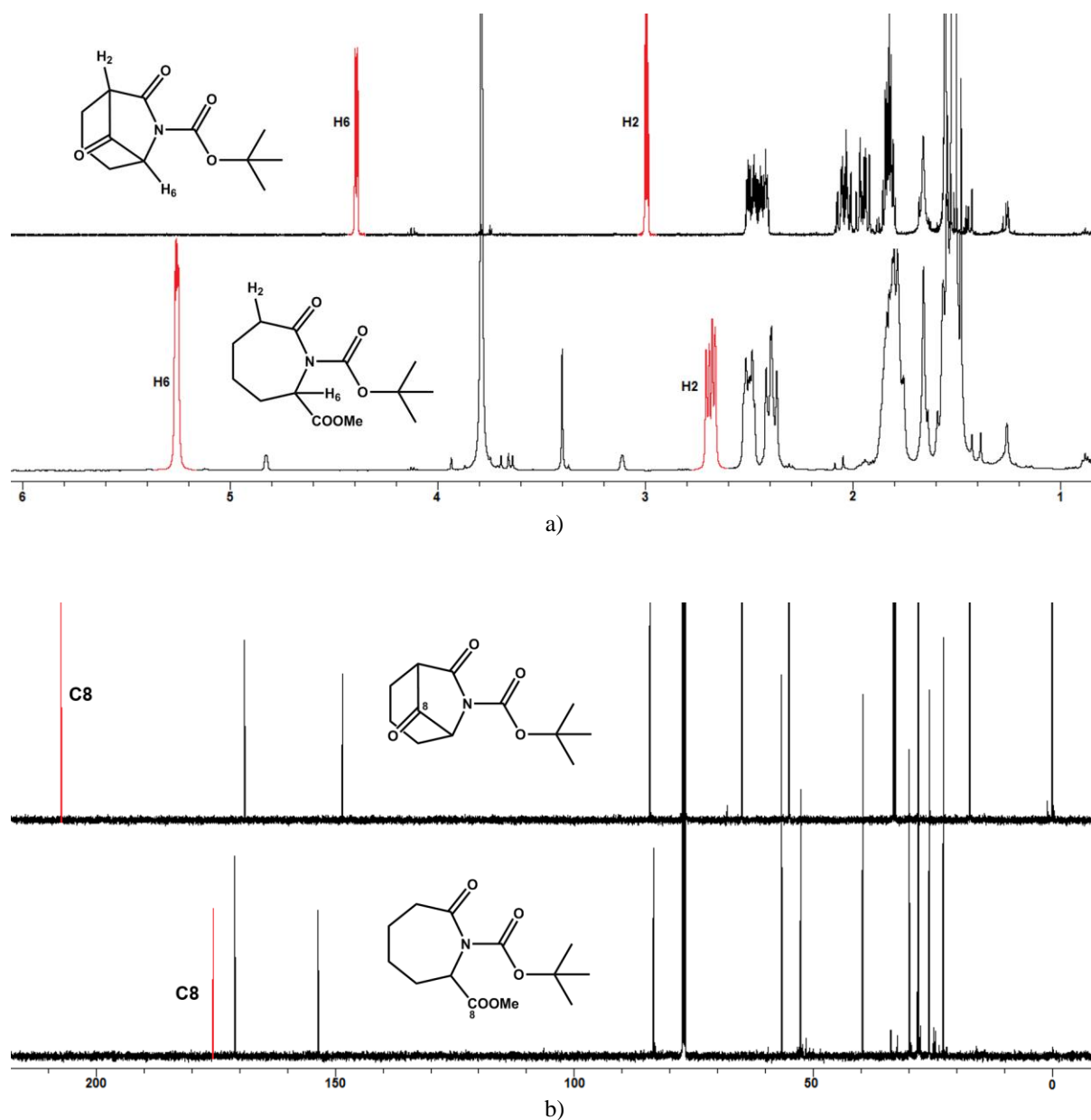


Fig. S1 a) ^1H NMR (125 MHz) spectrum of bicyclic lactam **1a** and the respective starting material (**3**). Note that shifts in the signals for H_2 and H_6 are apparent. b) ^{13}C NMR spectrum (500 MHz) of the assigned bicyclic lactam **1a** and the respective material. The loss of the ester carbonyl carbon (175.8 ppm) in **3** and the appearance of a keto carbon signal in **1** are highlighted, supporting the assigned product structure.

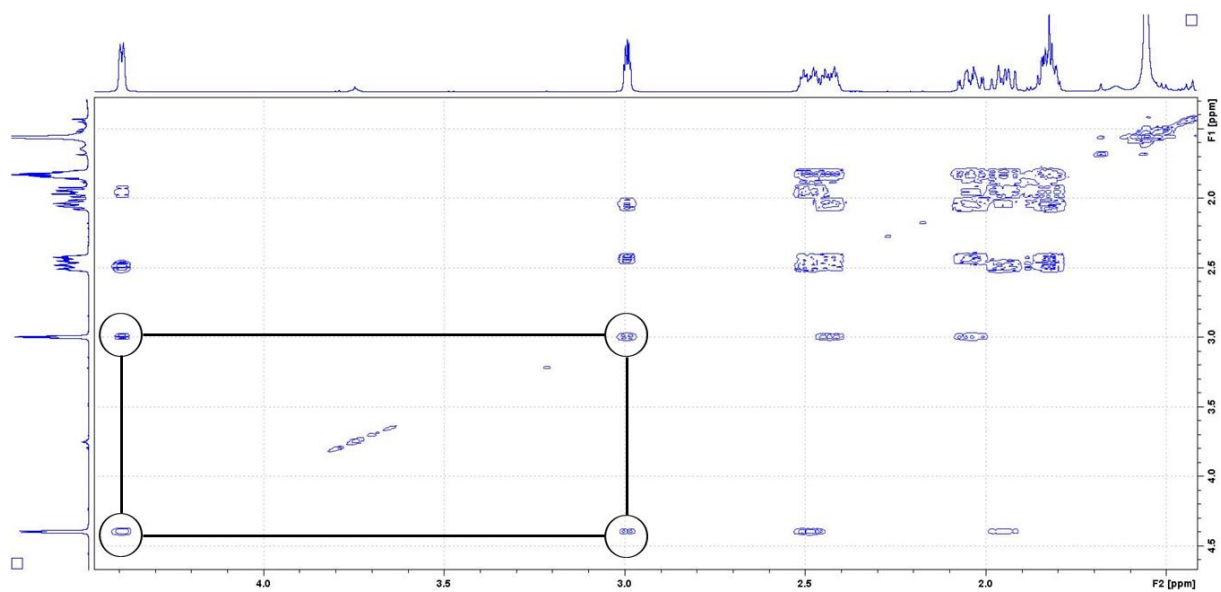


Fig. S2 Close up view from a COSY-spectrum of bicyclic lactam **1a**. Cross-correlation between *H2* and *H6* is apparent; this is likely due to 4J -coupling from *H2* to *H6*, *i.e.* over the carbonyl bridge, supporting the assigned structure.

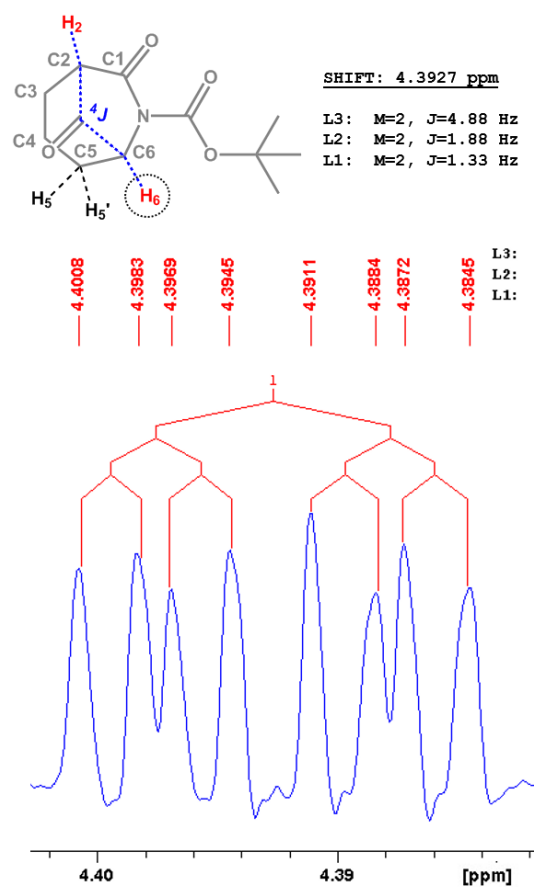
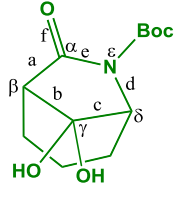
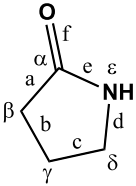
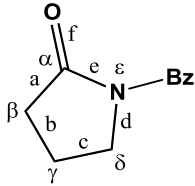
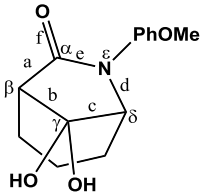
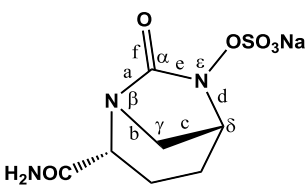
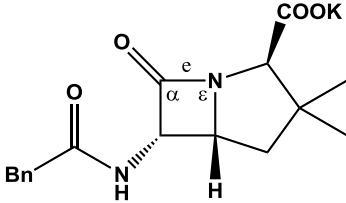


Fig. S3 Close up view from the ^1H NMR (125 MHz) spectrum of bicyclic lactam **1a**; the *H6* signal with the respective ddd coupling pattern and the respective $^3J_{\text{H,H}}$ and $^4J_{\text{H,H}}$ values is shown.

Table S4

Angles and distances in the structure of **1b** in comparison to related compounds. For avibactam we used an energy-minimized structure (MacroModel, MCM, OPLS2005, 2,500 steps, without solvent)

			
	1b	I^a	II^a
	Angles (°)		
α	106.5	108.5	107.4
β	101.5	104.4	106.1
γ	100.4	104.3	107.6
δ	99.9	103.1	103.9
ϵ	110.2	114.1	111.8
	Bond lengths (Å)		
a	1.518	1.518	1.504
b	1.528	1.526	1.480
c	1.521	1.534	1.499
d	1.486	1.460	1.472
e	1.394	1.335	1.402
f	1.211	1.238	1.209

			
	III^a	IV^a	V^a
	Angles (°)		
α	107.2	104.8	92.4
β	101.5	107.4	-
γ	99.3	96.9	-
δ	99.4	98.2	-
ϵ	111.7	111.9	94.1
	Bond lengths (Å)		
a	1.509	1.343	-
b	1.525	1.461	-
c	1.543	1.518	-
d	1.496	1.459	-
e	1.339	1.340	1.384
f	1.242	1.231	-

^a **I**: 2-pyrrolidone²; **II**: *N*-Benzoyl-2-pyrrolidone³; **III**: (1*R*,5*S*)-8,8-Dihydroxy-6-(4-methoxyphenyl)-6-azabicyclo[3.2.1]octan-7-one⁴; **IV**: NXL-104 (avibactam); **V**: penicillin G⁵

² R. Goddard, O. Heinemann, C. Krüger, I. Magdó, F. Mark and K. Schaffner, *Acta Crystallogr., Sect. C*, 1998, **54**, 501-504.

³ T. Yamane, Y. Ito, T. Ashida, K. Hashimoto and H. Sumitomo, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 886-891.

⁴ M. Betou, L. Male, J. W. Steed and R. S. Grainger, *Chem. Eur. J.*, 2014, **20**, 6505-6517.

⁵ D. D. Dexter and J. M. van der Veen, *J. Chem. Soc. Perkin Trans. 1*, 1978, 185-190.

Table S5 Hydrogen bonds for **1b**

atoms	symmetry	distances (Å)			angle (°)
		D–H	D···A	H···A	
1b					
O(2)-H(2O)···O(1)	$x-1, y, z$	0.91(5)	2.779(3)	1.87(5)	177(4)
O(3)-H(3O)···O(2)	$-x+1, -y+1, -z+1$	0.84(5)	2.789(4)	1.95(5)	174(5)