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

SYNTHETIC PROCEDURES

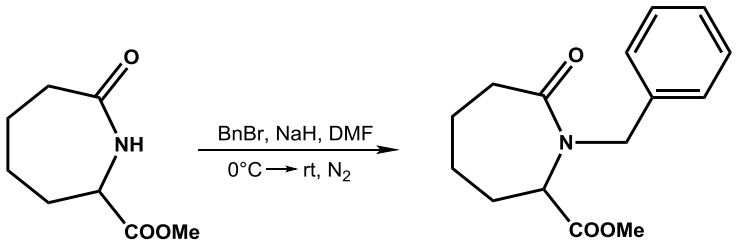
Materials and Methods

Melting points were determined using a microscope heating stage PHMK Rapido (VEB Dresden Analytik). IR spectra were measured using a Bruker Tensor 27 ATR-FT-IR with the ATR method. NMR spectra were recorded using a Bruker Avance DRX 500 spectrometer at 500.13 MHz (^{1}H NMR) and 125.77 MHz (^{13}C NMR), respectively. Chemical shifts δ are reported in parts per million (ppm) relative to the internal reference TMS. Multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet) and m (multiplet). Mass spectra were measured on a Varian 320 MS. The GC/MS data were collected on a HP Series II 5890 (Column 30.0 m x 250 µm, ms5).

All reactions involving moisture sensitive reagents were carried out under a nitrogen atmosphere. Cooling was performed in ice-water baths (0 °C) or dry ice-acetone baths (-78 °C). Anhydrous solvents were used as supplied. Thin layer chromatography (TLC) was performed on Merck DC-Kieselgel 60 F 254 0.2 mm precoated plates with fluorescence indicator. Visualization of spots was achieved using UV light (254 nm) and by developing in a basic solution of $KMnO_4$ followed by heating.

The syntheses of the starting caprolactam **2**, the Boc-protected lactam **3** and the free caprolactam acid have been described previously.[1] The six-membered methylester **8**[2] and the hydrochloride of methyl aminopentenoic acid[3] were prepared according to literature procedures.

1-Benzyl 2-methyl 7-oxoazepane-2-dicarboxylate (7)



2 **7**

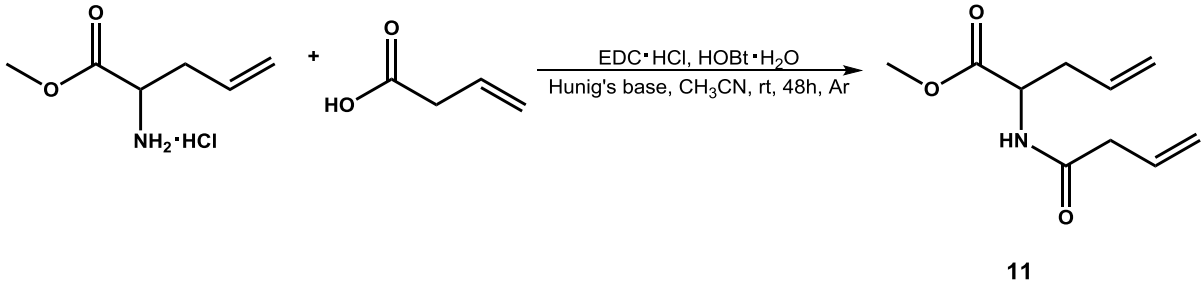
NaH (60 % suspension in mineral oil) (130.6 mg, 3.2 mmol, 1.1 eq) and lactam ester **2** (504.4 mg, 2.9 mmol, 1.0 eq) were suspended in dry DMF (25 ml) under argon. The mixture was cooled to 0 °C, then stirred for 30 mins before benzyl bromide (0.382 ml, 3.2 mmol, 1.1 eq) was added *via* syringe. The mixture was allowed to warm to room temperature and stirred overnight. Saturated, aqueous NH_4Cl solution (10 ml) was added and the mixture stirred for another 30 mins. After adding water (20 ml) the mixture is extracted with ethyl acetate (5 x 50 ml). The combined organic phases were dried over $MgSO_4$, the solvent was removed in vacuo and the resulting residue is purified by column chromatography (SiO_2; ethyl acetate/*n*-hexane = 1:1), which yielded 413 mg (66 %) of a viscous, yellow oil. R_f = 0.35 (SiO_2; ethyl acetate/*n*-hexane = 1:1). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.1 (*C*ONH), 171.2 (*C*OOCH$_3$), 137.2 (Ar*C*), 128.6 (Ar*C*), 127.6 (Ar*C*), 59.9 (COO*C*H$_3$), 52.5 (N*C*H$_2$Ar), 52.0 (N*C*H), 38.0 (*C*H$_2$), 30.7 (*C*H$_2$), 25.9 (*C*H$_2$), 22.7 (*C*H$_2$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (m, 5H

[1] T. Gruber, A. L. Thompson, B. Odell, P. Bombicz and C. J. Schofield, *New J. Chem.*, 2014, **38**, 5905-5917.
[2] A. Sadiq and N. Sewald, *J. Amino Acids*, 2013, Article ID 252813, 8 pages.
[3] C. Joannesse, C. P. Johnston, C. Concellon, C. Simal, D. Philp and A. D. Smith, *Angew. Chem., Int. Ed.*, 2009, **48**, 8914-8918.

Ar*H*), 5.22, 4.09 (each d, ^{2}J=14.8 Hz, 2H, NCH_2Ar), 4.07 (m, 1H, NC*H*), 2.72 (m, 1H, CH_2), 2.36 (m, 1H, CH_2), 2.29 (m, 1H, CH_2), 1.79 (m, 2H, CH_2), 1.48 (m, 3H, CH_2). IR: 2934, 2859, 1740, 1637, 1495, 1467, 1432, 1359, 1288, 1264, 1222, 1104, 1078, 992, 969, 933, 864, 844, 792, 699, 633, 578, 511, 476, 455. m/z = 262.14 [M+H$^+$]; calc. 262.13.

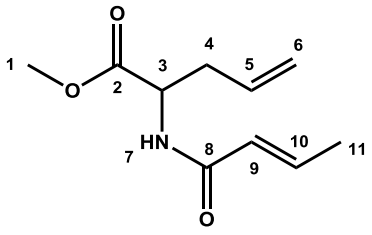
Synthesis of the desaturated caprolactam 9

Methyl 2-(but-3-enamido)-pent-4-enoate (11)



11

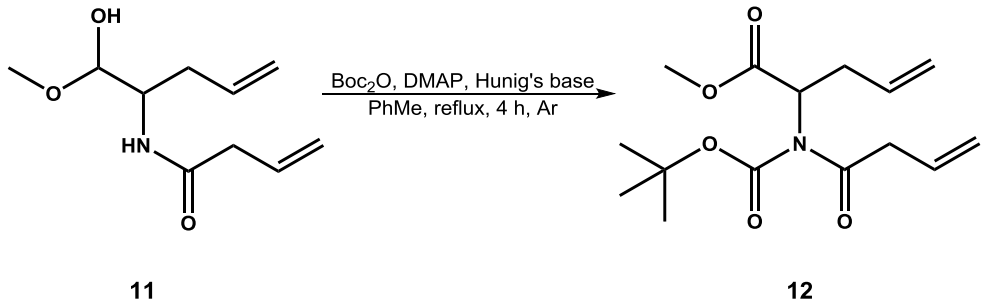
In a three-necked flask, equipped with a thermometer, a reflux condenser and a septum, EDC·HCl (1.63 g, 8.5 mmol) and HOBt·H_2O (1.29 g, 8.4 mmol) were provided under an argon atmosphere. Dry acetonitrile (60 ml) was added, which dissolved the solids within 60 min. The resulting solution was cooled to below -10 °C; 3-butenoic acid (0.85 ml, 10.0 mmol) was then added dropwise. The reaction mixture was stirred for 10 min followed by dropwise addition of Hunig's base (DIPEA) (1.4 ml, 8.24 mmol). The temperature of the reaction mixture did not exceed -10 °C at any point during the addition. Subsequently, methyl aminopentenoic acid, as its hydrochloride form, (1.00 g, 6.0 mmol) suspended in dry acetonitrile (15 ml), was added dropwise over 60 min. The reaction mixture was stirred for another 60 min at below -10 °C, then allowed to warm to room temperature after which it was stirred for 48 h. Subsequently, saturated, aqueous NH_4Cl solution (50 ml) was added slowly. A white, slightly yellow, fluffy solid precipitated and the mixture was stirred for another 60 min. Saturated, aqueous NaCl solution (50 ml) and ethyl acetate (150 ml) were then added to enable phase seperation. The aqueous phase was extracted with ethyl acetate (3x50 ml); the combined organic phases were washed with brine (25 ml), dried over $MgSO_4$, and the organic solvent was then removed in vacuo. The resulting yellow oil was flash column chromatographed (SiO_2; ethyl acetate/*n*-hexane = 1:1) to give 0.88 g (74 %) a colorless liquid. The results of characterization revealed that additionally to **11** (66 %), ist regioisomer **11a** = methyl 2-(but-2-enamido)-pent-4-enoate (33 %) was also formed in the reaction. Several attempts to purify the desired product **11** *via* flash column chromatography (different solvent mixtures, different solid phases) were unsuccesful.



11a

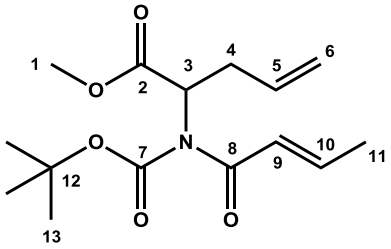
R_f (mixture of isomers): 0.35 (SiO_2; ethyl acetate/*n*-hexane = 1:1). **11**: ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2 (*C2*), 170.4 (*C8*), 132.1 (*C5*), 130.9 (*C10*), 120.0 (*C11*), 119.3 (*C6*), 57.4 (*C1*), 41.3 (*C9*), 36.5 (*C4*). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.17 (br s, 1H, *H7*), 5.93 (ddt, J_t=7.1 Hz, J_{dt}=10.5 Hz, J_{ddt}=16.8 Hz, 1H, *H10*), 5.66 (ddt, J_t=7.1 Hz, J_{dt}=10.1 Hz, J_{ddt}=17.0 Hz, 1H, *H5*), 5.27-5.22 (m, 1H, *H11*), 5.14-5.09 (m, 1H, *H6*), 4.71-4.66 (m, 1H, *H3*), 3.75 (s, 3H, *H1*), 3.04 (dt, ^3J_t=1.3 Hz, ^3J_d=7.2 Hz, 2H, *H9*), 2.66-2.48 (m, 2H, *H4*). **11a**: ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2 (*C2*), 170.2 (*C8*), 140.9 (*C10*), 130.9 (*C5*), 124.5 (*C9*), 119.3 (*C6*), 52.4 (*C1*), 51.5 (*C3*), 36.7 (*C4*), 18.2 (*C11*). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.87 (dq, J_q=6.9 Hz, J_d=15.2 Hz, 1H, *H10*), 6.01 (br s, 1H, *H7*), 5.85 (dq, ^4J_q=1.7 Hz, $^3J_{d,trans}$=15.2 Hz, 1H, *H9*), 5.66 (ddt, J_t=7.1 Hz, J_{dt}=10.1 Hz, J_{ddt}=17.0 Hz, 1H, *H5*), 5.14-5.09 (m, 1H, *H6*), 4.79-4.74 (m, 1H, *H3*), 3.75 (s, 3H, *H1*), 2.66-2.48 (m, 2H, *H4*), 1.86 (dd, ^3J_d=1.8 Hz, $^3J_{dd}$=6.8 Hz, 3H, *H11*). IR (mixture of isomers): 3292, 3079, 2953, 2852, 1742, 1650, 1536, 1436, 1361, 1271, 1199, 1147, 992, 917, 748, 674, 602, 514, 460. GC/MS: R_t = 9.38 min, 9.96 min (60 °C, 3 min, 20 °C · min^{-1}), m/z = 197 [M^+], calc. 197.

Methyl 2-(*tert*-butyl-1-carboxy-but-3-enamido)pent-4-enoate (12)



11 **12**

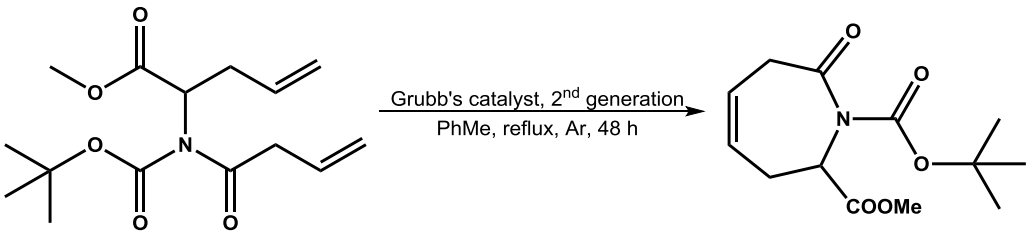
The mixture of isomers **11** and **11a**, obtained from the previous reaction (0.30 g, 1.5 mmol) was placed in a three-necked round flask under an argon atmosphere. 4-(*N*,*N*-Dimethyl)-amino pyridine (DMAP) (53 mg, 0.43 mmol) was then added, followed by dry toluene (40 ml) and di-*tert*-butyl dicarbonate (Boc_2O) (1.0 ml, 4.67 mmol), which was added dropwise. The colour of the mixture turned from a slight yellow to an intense red. Subsequently, Hunig's base (DIPEA) (0.35 ml, 2.06 mmol) was added dropwise and the reaction mixture was refluxed for 4 h. After the mixture was cooled to room temperature, water (30 ml) was added and the mixture was stirred for another 90 min. The intense red organic phase was separated, the colorless aqueous phase was extracted with toluene (3x30 ml) and the combined organic phases were dried over $MgSO_4$. The solvent was removed in vacuo and the residue was coloumn chromatographed (SiO_2; ethyl acetate/*n*-hexane = 1:1) to give an intense yellow liquid product (0.35 g, 79 %). The analytical results revealed the product mixture contains of **12** (66 %) and the respective regioisomer **12a** = methyl 2-(*tert*-butyl-1-carboxy-but-2-enamido)pent-4-enoate (33 %). Several attempts to separate **12** and **12a** by flash chromatography were unsuccesful.



12a

R_f (mixture of isomers): 0.90 (SiO_2; ethyl acetate/*n*-hexane = 1:1). **12**: ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.9 (*C8*), 170.7 (*C2*), 151.9 (*C7*), 133.9 (*C5*), 131.2 (*C10*), 118.1 (*C6*, *C11*), 84.1 (*C12*), 55.0 (*C3*), 52.2 (*C1*), 42.7 (*C9*), 34.4 (*C4*), 27.9 (*C13*). ^1H NMR (500 MHz, $CDCl_3$): δ = 6.01-5.93 (m, 1H, *H10*), 5.76-5.66 (m, 1H, *H5*), 5.36 (dd, ^3J_d=5.1 Hz, $^3J_{dd}$=10.2 Hz, 1H, *H3*) 5.18- 5.13 (m, 1H, *H11*), 5.08-5.02 (m, 2H, *H6*), 3.71 (s, 3H, *H1*), 3.69-3.66 (m, 1H, *H9*), 2.68-2.58 (m, 1H, *H4*), 1.50 (s, 9H, *H13*). **12a**: ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.7 (*C2*), 168.3 (*C8*), 152.3 (*C7*), 143.6 (*C10*), 125.4 (*C9*), 118.1 (*C6*), 83.9 (*C12*), 55.5 (*C3*), 52.2 (*C1*), 34.4 (*C4*), 27.9 (*C13*), 18.3 (*C11*). ^1H NMR (500 MHz, $CDCl_3$): δ = 6.97 (dq, ^3J_q=6.9 Hz, $^3J_{dq,trans}$=15.0 Hz, 1H, *H10*), 6.78 (dq, ^4J_q=1.6 Hz, $^3J_{dq,trans}$=15.2 Hz, 1H, *H9*), 5.76-5.66 (m, 1H, *H5*), 5.31 (dd, ^3J_d=5.2 Hz, $^3J_{dd}$=10.1 Hz, 1H, *H3*), 5.08-5.02 (m, 2H, *H6*), 3.71 (s, 3H, *H1*), 2.68-2.58 (m, 2H, *H4*), 1.92 (dd, J_d=1.6 Hz, J_d=6.9 Hz, 3H, *H11*), 1.50 (s, 9H, *H13*). IR (mixture of isomers): 2980, 2933, 1806, 1736, 1697, 1642, 1477, 1368, 1287, 1254, 1208, 1143, 1117, 1068, 1032, 993, 916, 846, 777, 720, 648, 491, 462. GC-MS: R_t = 11.01 min, 11.39 min (60 °C, 3 min, 20 °C · min^{-1}), m/z = 297 [M^+], calc. 297.

1-*tert*-Butyl 2-methyl 7-oxo-2,3,6,7-tetrahydro-1*H*-azepine-1,2-dicarboxylate (9)

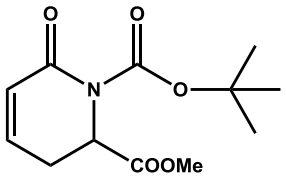


12 **9**

Under an argon atmosphere, the 2nd generation Grubb's catalyst, (28.4 mg, 0.033 mmol) was placed in a three-necked round flask and dissolved in dry toluene (120 ml). A mixture of isomers **12** and **12a** (400 mg; 0.896 mmol of **12**, 0.447 mmol of **12a**) was dissolved in dry toluene (3 ml), added to the catalyst solution and the resulting mixture was refluxed for 48 h. After TLC indicated completion of reaction, the mixture was allowed to cool to room temperature; the solvent was then removed in vacuo and the residue purified by flash chromatography (SiO_2, ethyl acetate/*n*-hexane = 1:2). The starting mixture consisting of **12** and **12a** yielded the respective desaturated caprolactam **9** (85 mg, 35 % referred to **12**) and valerolactam **9a** (67 mg, 60 % referred to **12a**) as two dark brown, highly viscous oils each.

*1-tert-Butyl 2-methyl 7-oxo-2,3,6,7-tetrahydro-1H-azepine-1,2-dicarboxylate (**9**).* R_f: 0.50 (SiO_2; ethyl acetate/*n*-hexane = 1:1). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.4 (*C*$OOCH_3$), 170.3 (*C*$ONCOO^tBu$), 152.2 (N*C*OO^tBu), 127.8 ($COCH_2$*C*HCH), 119.5 ($COCH_2CHCH$), 84.0 (*C*$(CH_3)_3$), 55.7 (N*C*H), 52.7 ($COOCH_3$), 38.7 ($NCHCH_2$), 30.2 ($COCH_2CHCH$), 28.0

($C(CH_3)_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.74-5.69 (m, 1H, $COCH_2CHCH$), 5.57-5.52 (m, 1H, $COCH_2CHCH$), 5.16 (dd, ^3J_d=4.0 Hz, $^3J_{dd}$=7.0 Hz, 1H, NC*H*), 3.78 (s, 3H, $COOCH_3$), 3.35 (dtd, J_d=1.5 Hz, J_{dt}=2.2 Hz, J_{dtd}=6.3 Hz, 0.35H, $COCH^a{}_2CHCH$, configuration 2), 3.32 (dtd, J_d=1.5 Hz, J_{dt}=2.2 Hz, J_{dtd}=6.3 Hz, 0.63H, $COCH^a{}_2CHCH$, configuration 1), 3.22 (m, 0.65H, $COCH^b{}_2CHCH$, configuration 1), 3.19 (m, 0.38H, $COCH^b{}_2CHCH$, configuration 2), 2.97-2.94 (m, 0.42H, $NCHCH^a{}_2$, configuration 2), 2.94-2.90 (m, 0.61H, $NCHCH^a{}_2$, configuration 1), 2.74-2.72 (m, 0.61H, $NCHCH^b{}_2$, configuration 1), 2.71-2.69 (m, 0.47H, $NCHCH^b{}_2$, configuration 2), 1.52 (s, 9H, $C(CH_3)_3$). IR: 3012, 2979, 1737, 1699, 1624, 1454, 1434, 1421, 1384, 1364, 1337, 1296, 1240, 1219, 1208, 1153, 1128, 1084, 1049, 998, 980, 967, 925, 894, 850, 838, 823, 813, 777, 757, 730, 660, 599, 558, 470, 441. m/z = 292.1 [M+Na$^+$], calc. 292.1.



9a

*1-tert-Butyl 2-methyl 3,6-dihydro-6-oxo-1,2(2*H*)-pyridinedicarboxylate (**9a**).*[4] R_f: 0.37 (SiO_2; ethyl acetate/*n*-hexane = 1:1). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.2 ($COOCH_3$), 162.3 ($CONCOO^tBu$), 152.4 ($NCOO^tBu$), 139.8 ($COCH_2CHCH$), 126.7 ($COCH_2CHCH$), 83.7 ($C(CH_3)_3$), 55.6 (NCH), 52.9 ($COOCH_3$), 28.0 ($C(CH_3)_3$), 27.2 ($NCHCH_2$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.63-6.59 (m, 1H, $COCHCH$), 5.97 (ddd, J_d=0.8 Hz, J_{dd}=3.0 Hz, J_{ddd}=9.9 Hz, 1H, $COCHCH$), 5.07 (ddd, J_d=1.1 Hz, J_{dd}=2.0 Hz, J_{ddd}=7.8 Hz, 1H, NC*H*), 3.74 (s, 3H, $COOCH_3$), 2.91 (ddd, J_d=0.8 Hz, J_{dd}=2.0 Hz, J_{ddd}=6.1 Hz, 0.29H, $NCHCH^a{}_2$, configuration 2), 2.87 (ddd, J_d=0.8 Hz, J_{dd}=2.0 Hz, J_{ddd}=6.0 Hz, 0.70H, $NCHCH^a{}_2$, configuration 1), 2.82 (ddd, J_d=2.4 Hz, J_{dd}=2.9 Hz, J_{ddd}=6.8 Hz, 0.71H, $NCHCH^b{}_2$, configuration 1), 2.78 (ddd, J_d=2.4 Hz, J_{dd}=2.9 Hz, J_{ddd}=6.8 Hz, 0.30H, $NCHCH^b{}_2$, configuration 2), 1.55 (s, 9H, $C(CH_3)_3$). IR: 2979, 1774, 1742, 1709, 1437, 1392, 1368, 1292, 1252, 1221, 1141, 1082, 1044, 1015, 920, 888, 848, 809, 776, 752, 709, 666, 592, 567, 462. m/z = 278.1 [M+Na$^+$], calc. 278.1.

Synthesis of the caprolactam ethylester 10

Ethyl 7-oxoazepane-2-carboxylate (13)

13

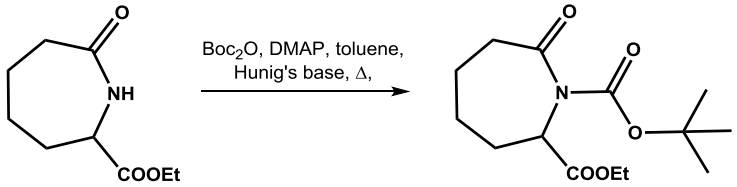
Ethanol (10 ml) was cooled to -10 °C; thionylchloride (923 µl, 12.72 mmol) was then added dropwise with stirring. Subsequently, 7-oxoazepane-2-carboxylic acid[1] (1.0 g, 6.36 mmol) was added; the reaction mixture was then allowed to warm to room temperature and stirred

[4] M. Muller, A. Schoenfelder, B. Didier, A. Mann, C.-G. Wermuth, *Chem. Commun.*, 1999, **8**, 683-684.

overnight. The solvents were removed in vacuo and the residue purified by flash chromatography (SiO_2; eluent: ethyl acetate) to yield 79 % (929 mg, 5.02 mmol) of a colourless oil. R_f = 0.40 (SiO_2; ethyl acetate). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.2 (*C*OOCH$_2$), 171.4 (*C*ONH), 62.2 (O*C*H$_2$CH$_3$), 55.9 (NH*C*H), 37.1 (*C*H$_2$), 33.8 (*C*H$_2$), 29.7 (*C*H$_2$), 22.9 (*C*H$_2$), 14.1 (OCH$_2$*C*H$_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.43 (br s, 1H, N*H*), 4.23 (q, ^3J = 7.0 Hz, 2H, OC*H*$_2$CH$_3$), 4.09-4.05 (m, 1H, NHC*H*), 2.56-2.48 (m, 1H, C*H*$_2$), 2.46-2.38 (m, 1H, C*H*$_2$), 2.29-2.21 (m, 1H, C*H*$_2$), 2.11-2.06 (m, 1H, C*H*$_2$), 1.91-1.85 (m, 1H, C*H*$_2$), 1.63-1.47 (m, 3H, C*H*$_2$), 1.30 (t, ^3J = 7.0 Hz, 3H, OCH$_2$C*H*$_3$). 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 **13** was conducted similarly to that of its respective methyl-ester[1] (**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 ($MgSO_4$), 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 (SiO_2; eluent: ethyl acetate) to give the product as a colourless oil. Yield: 25 % (267 mg, 1.44 mmol).

1-*tert*-Butyl 2-ethyl 7-oxoazepane-1,2-dicarboxylate (10)



13 **10**

Under a nitrogen atmosphere lactam **13** (155 mg, 0.84 mmol) was dissolved in dry toluene (20 ml). Subsequently, Hunig's base (286 µl, 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 Na_2SO_4. Evaporation of the solvent and column chromatography yielded the crude product, which was purified by column chromatography (SiO_2; ethyl acetate). Yield: 72 % (172 mg, 0.60 mmol) of a colourless oil. R_f = 0.90 (SiO_2; ethyl acetate). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5 (*C*OOCH$_2$), 170.4 (*C*ONH), 153.4 (N*C*OO^{t}Bu), 83.2 (*C*(CH$_3$)$_3$), 61.6 (O*C*H$_2$CH$_3$), 56.6 (NH*C*H), 39.6 (*C*H$_2$), 29.8 (*C*H$_2$), 27.8 (C(*C*H$_3$)$_3$), 25.6 (*C*H$_2$), 22.7 (*C*H$_2$), 14.2 (OCH$_2$*C*H$_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.20-5.16 (m, 1H, NHC*H*), 4.26-4.19 (m, 2H, OC*H*$_2$CH$_3$), 2.71-2.61 (m, 1H, C*H*$_2$), 2.52-2.43 (m, 1H, C*H*$_2$), 2.45-2.34 (m, 1H, C*H*$_2$), 1.82-1.70 (m, 3H, C*H*$_2$), 1.58-1.48 (m, 2H, C*H*$_2$), 1.44 (s, 9H, C(C*H*$_3$)$_3$), 1.25 (t, 3H, ^3J = 12.5 Hz, OCH$_2$C*H*$_3$). 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.

CRYSTALLOGRAPHIC AND SPECTROSCOPIC DETAILS

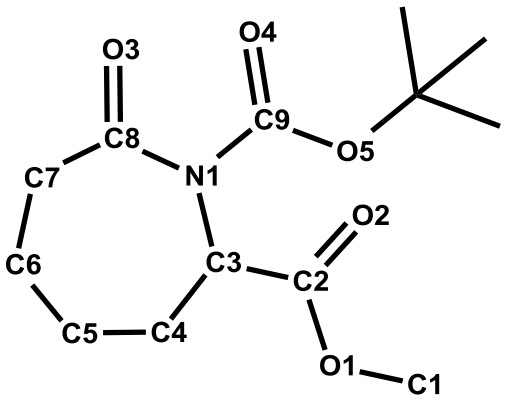
Table S1 Crystal data and selected details of the data collection and refinement calculations for **1b** and **3**

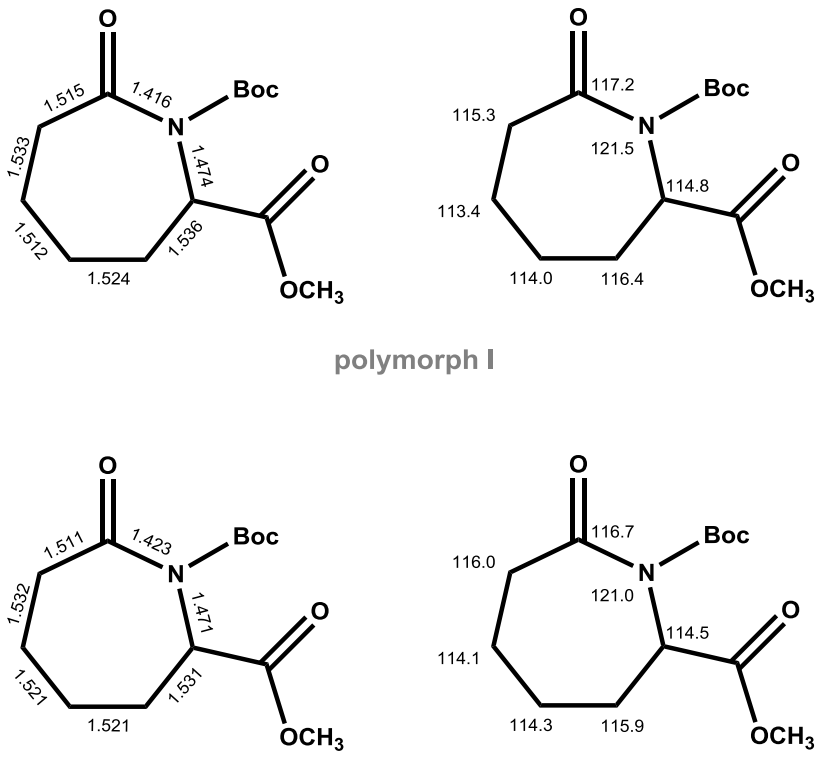
Compound	**1b**	**3** (Polymorph II)
Empirical formula	$C_{12}H_{19}NO_5$	$C_{13}H_{21}NO_5$
Formula weight	257.28	271.31
Temperature	173(2) K	173(2) K
Wavelength	1.54178 Å	1.54178 Å
Crystal system	triclinic	orthorhombic
Space group	*P*-1	*Pbca*
Unit cell dimensions	a = 6.1511(6) Å	a = 10.8289(3) Å
	b = 6.3794(7) Å	b = 12.9518(4) Å
	c = 17.5260(18) Å	c = 20.3412(6) Å
	α= 88.877(5)°	α= 90°
	β= 80.145(5)°	β= 90°
	γ = 82.187(5)°	γ = 90°
Volume	671.28(12) $Å^3$	2852.93(15) Å3
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 ±*h*, ±*k*, ±*l*	-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 F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	2624 / 0 / 173	2819 / 0 / 177
Goodness-of-fit on F^2	1.061	1.046
Final R indices [I>2sigma(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 S2
Torsion 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**:



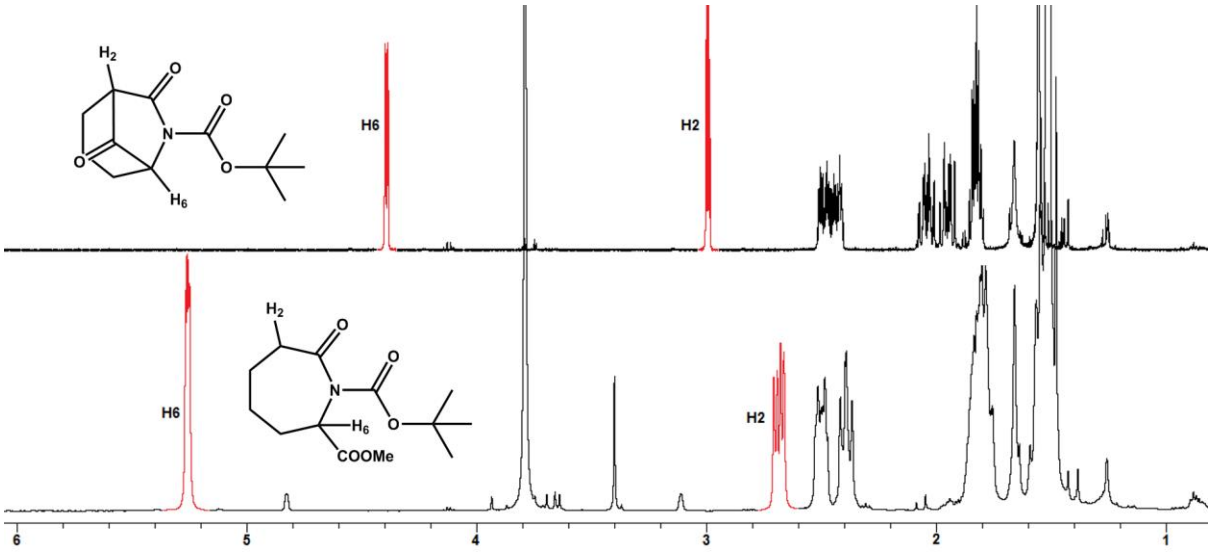


Scheme S1
Bond lengths (Å) and angles (°) for the two polymorphs of **3**.

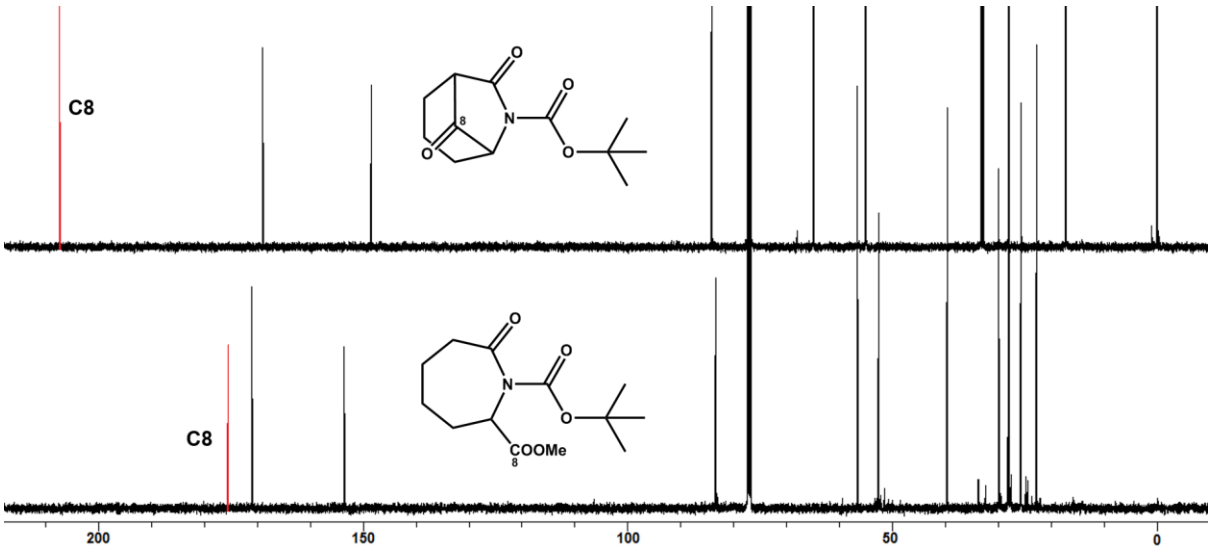
Table S3
Results of the investigation of the concentration of the educt **3** on the yield of **1a**

batch	n(educt) [mmol]	V(solvent) [ml]	c(educt) [mmol/l]	Yield [%]
1	3.35	100	33.5	7
2	1.29	40	32.3	6
3	7.63	250	30.5	7
4	2.95	100	29.5	6
5	2.76	250	11.0	8
6	1.73	250	6.9	8

The –COO*CH*$_3$ 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 *H2* and *H6* (5.26 ppm and 2.68 ppm, respectively) are shifted significantly on conversion of **3** to **1a**.



a)



b)

Fig. S1 a) ^{1}H NMR (125 MHz) spectrum of bicyclic lactam **1a** and the respective starting material (**3**). Note that shifts in the signals for *H2* and *H6* 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.

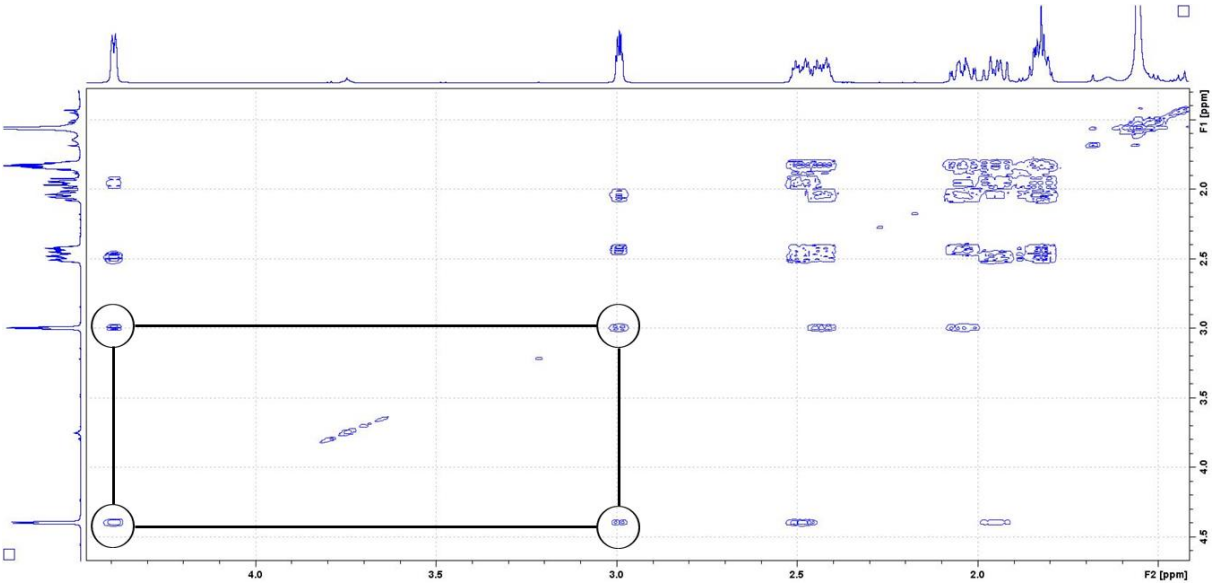


Fig. S2 Close up view from a COSY-spectrum of bicyclic lactam **1a**. Cross-correlation between *H2* and *H6* is apparent; this is likely due to ^{4}J-coupling from *H2* to *H6*, *i.e.* over the carbonyl bridge, supporting the assigned structure.

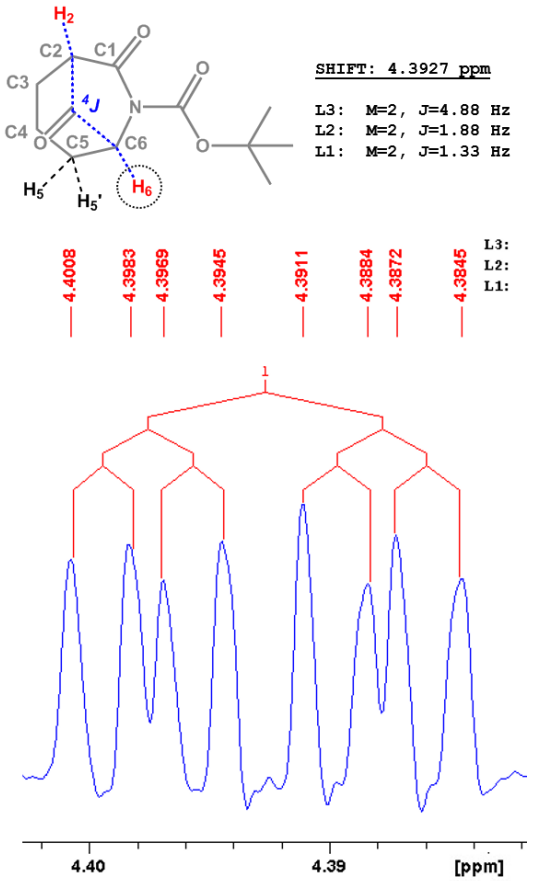
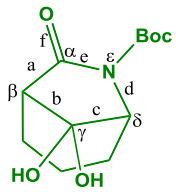
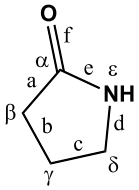
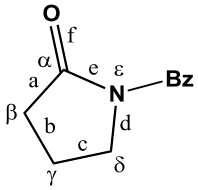
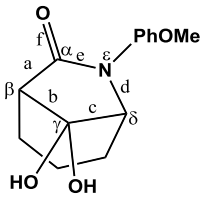
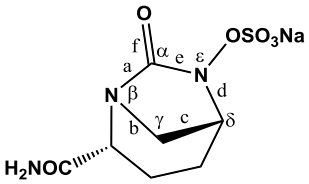
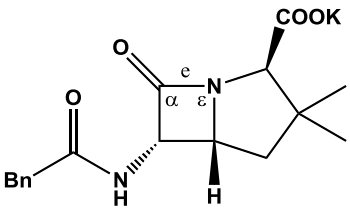


Fig. S3 Close up view from the ^{1}H NMR (125 MHz) spectrum of bicyclic lactam **1a**; the *H6* signal with the respective ddd coupling pattern and the respective $^{3}J_{H,H}$ and $^{4}J_{H,H}$ values is shown.

Table S4
Angles and distances in the structure of **1b** in comparison to related compounds. For avibactam we used an energy-minimized structure (MacroModel, MCMM, 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-pyrrolidone[5]; **II**: *N*-Benzoyl-2-pyrrolidone[6]; **III**: (1*R*,5*S*)-8,8-Dihydroxy-6-(4-methoxyphenyl)-6-azabicyclo[3.2.1]octan-7-one[7]; **IV**: NXL-104 (avibactam); **V**: pencillin G[8]

[5] R. Goddard, O. Heinemann, C. Krüger, I. Magdó, F. Mark and K. Schaffner, *Acta Crystallogr., Sect. C*, 1998, **54**, 501-504.
[6] T. Yamane, Y. Ito, T. Ashida, K. Hashimoto and H. Sumitomo, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 886-891.
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Table S5 Hydrogen bonds for **1b**

atoms	symmetry	distances (Å)			angle (°)
		D–H	D···A	H···A	D–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)