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The Synthesis of 4-Acetoxy-azetidin-2-ones as Key Intermediates for β-Lactams

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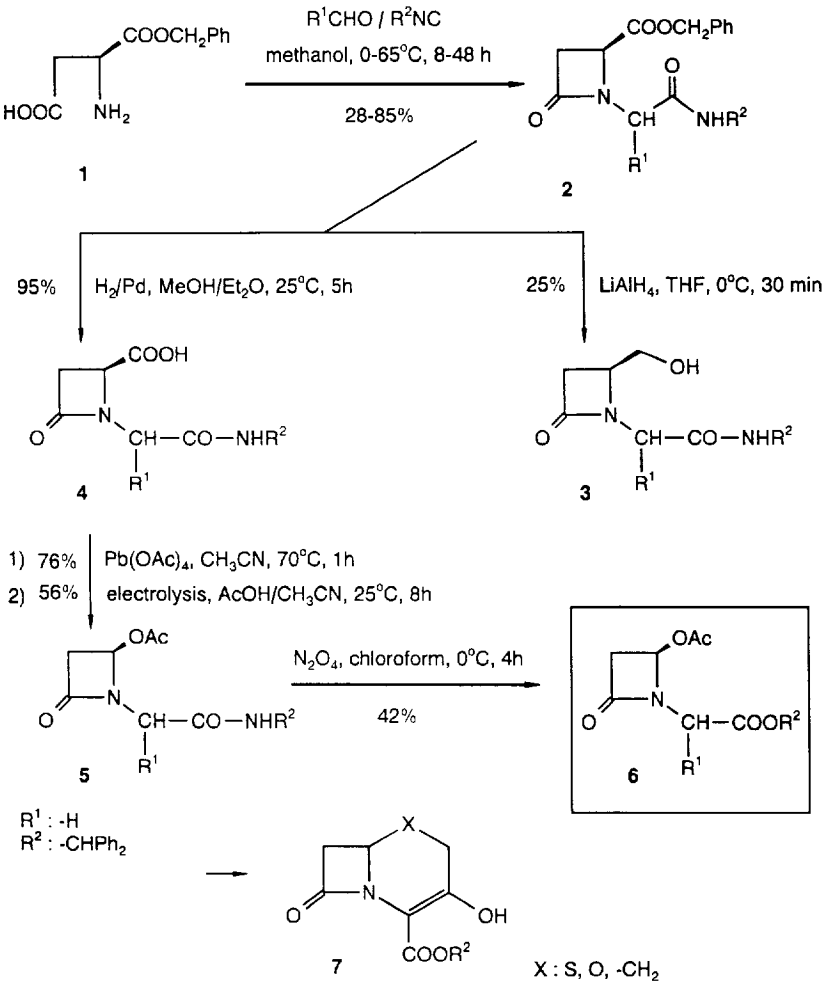
Abstract: A short synthesis of a chiral precursor of a cephem derivative is described. Starting material is the inexpensive chiral-pool chemical aspartic acid. The central step in forming the β-lactam moiety is an Ugi reaction.

Antibiotics of the β-lactam type are still being produced by biotechnological methods with subsequent synthetic modifications. In recent years, however, more and more β-lactam drugs have been made by total chemical synthesis.[1] Hereby, the formation of the β-lactam system itself proves to be a crucial step. It is generally performed via 2+2 cycloadditions.[2] An alternative is employing the four component reaction of Ugi (U-4CR) featuring a rather simple one pot procedure.[3] The first synthesis of β-lactams has already been performed in the early 1960's;[4-6] penicillin analogues and derivatives could be made shortly after. The extraordinary efficiency of these multi-component reactions has been demonstrated recently.[7]

In 1979, very effective syntheses of cephem derivates via the Ugi-reaction were described.[8,9]

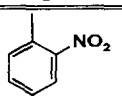
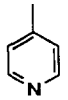
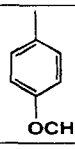
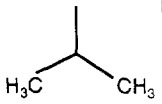
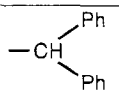
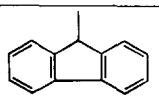
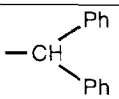
In 1983, a Japanese group found that the α-benzyl ester of L-aspartic acid can be converted to β-lactam derivatives, which are ideal starting materials for the preparation of antibiotics. We investigated the reactions of **1** leading to many useful products **2** (Table 1) and the further modification of these into versatile β-lactams **3-6** (Scheme 1).



Scheme 1: Reaction path leading to 4-acetoxy-azetidin-2-ones 6.

Cephem 7 represents the target structure of the Scheme. Key step of any β-lactam antibiotic synthesis is the formation of the four-membered ring. The four component reaction is generally suited for this purpose. This synthesis is performed as a one pot reaction involving four different components: an aldehyde or ketone, an isocyanide and a β-amino acid, the latter representing two components combined in one molecule.

Table 1 Formation of 4-CR products 2a-2h from α-Benzyl L-Aspartate, Aldehydes and Isocyanides.

β-Lactam 2	Aldehyde R^1	Isocyanide R^2	Reaction time [h]	mp [°C]	Temperature [°C]	Molecular formula[a]	Yield [%]
2a		$-C(CH_3)_3$	12	oil	0	$C_{23}H_{25}N_3O_6$ (439.46)	85
2b		$-C(CH_3)_3$	12	oil	0	$C_{22}H_{25}N_3O_4$ (395.46)	31
2c		$-C(CH_3)_3$	12	oil	0	$C_{24}H_{28}N_2O_5$ (424.49)	80
2d		$-CH_2-CH=CH_2$	8	oil	0	$C_{19}H_{24}N_2O_4$ (344.41)	28
2e		$-C(CH_3)_3$	12	amorphous foam 58	0	$C_{24}H_{26}N_2O_5$ (422.48)	58
2f	-H		12	51	0	$C_{26}H_{24}N_2O_4$ (428.5)	83
2g		$-C(CH_3)_3$	24	56	0	$C_{20}H_{23}N_2Cl_3O_4$ (461.77)	72
2h			48h	amorphous foam	65	$C_{39}H_{32}N_2O_4$ (592.69)	33

[a] All compounds 2a-2h gave satisfactory microanalytical data: C ± 0.70, H ± 0.33, N ± 0.41.

Corresponding to the work of Sato et al.[10] α-benzyl L-aspartate (**1**) is choosen as the β-amino acid. Its preparation involves a two step procedure starting from L-aspartic acid via the dibenzyl L-aspartate toluene p-sulfonate[11,12] and selective hydrolysis of the β-esters by hydriodic acid.[13] The α-ester **1** is condensed with formaldehyde and diphenylmethyl isocyanide[14] to azetidin-2-one **2f**. Reduction at the C_4-position of 4-benzyloxycarbonyl-1-[(N-diphenylmethyl carbamoyl)methyl]azetidin-2-one (**2f**) with lithium aluminum hydride at 0°C to the hydroxy moiety **3** shows a remarkable chemoselectivity (differentiation of β-lactam

amide, amide and ester) and a reaction time of only 30 min.[15] Alternatively, azetidin-2-one **2f** may be deprotected to the free carboxylic acid **4** through hydrogenolysis. This conversion into **4** is finished after 5 hours of treatment in methanol. The carboxy group at C_4-position of azetidin-2-one **4** is converted into an acetoxy group by oxidative decarboxylation, which is a useable leaving group in further modifications. Two different oxidative methods were used for acetylation leading to the 4-acetoxy derivative **5**: the first one employing lead tetraacetate in acetonitrile, yielding 76% of product;[16] the second involving electrochemical oxidation in acetic acid/acetonitrile, yielding 56% of **5**.[17] The conversion of amide **5** into ester **6** is accomplished by dinitrogen tetraoxide[18] in acetate buffer-solution. The reaction involves formation of the corresponding N-nitrosoamide, which gives ester **6** by way of nitrogen extrusion.[19] Compound **6** should be an important building block for future syntheses of β-lactam antibiotics **7** (Scheme 1).

Starting from α-benzyl L-aspartate **1**, eight additional β-lactams have been synthesized. Methanol was used as the general solvent. All products **2a-2h** were obtained as diastereomeric mixtures, diastereomeric excess values ranging from 0% to 70% d.e. Combined yields of the diastereomers heavily depend on the choosen aldehyde, respectively isocyanide. All reactions except entry **2h** were performed at 0°C. The longer reaction times of **2h** are due to the tautomeric character of fluorene-9-carbaldehyde, prefering the enol structure, which greatly reduces its carbonyl activity.

EXPERIMENTAL

General procedure for the preparation of 2a-h

A solution of L-aspartic acid α-benzyl ester (**1**) (2.23 g, 10 mmol) in methanol (80 ml) is cooled to -10°C. To this solution aldehyde (10 mmol) and isocyanide (10 mmol) are added under vigorous stirring. After 1h, the mixture is allowed to warm to room temperature and stirring is continued until the starting material has completely disappeared (TLC control). The colourless solution is evaporated and the residue taken up in methylene chloride (50 ml). This solution is extracted with 5% phosphoric acid (30 ml) and water (50 ml), respectively. The solvent is removed in vacuo giving an amorphous foam.

4-Benzyloxycarbonyl-1-[(N-tert.-butyl carbamoyl) (2-nitrophenyl) methyl]azetidin-2-one (2a)

R_f (EE,H, 1:1, v:v)=0.46; ^{1}H NMR ($CDCl_3$, 360 MHz): 1.33 (s, 9H, -C(CH_3)$_3$); 2.98 (dd, 1H, ^{2}J=15.13 Hz, ^{3}J=2.73 Hz, -CH_2-CO-N-); 3.33 (dd, 1H, ^{2}J=15.13 Hz, ^{3}J=5.92 Hz, -CH_2-CO-N-); 4.51 (dd, 1H, ^{3}J=2.73 Hz, ^{3}J=5.92 Hz, -CH-COO-); 5.15 (s, 2H, -CH_2Ph); 5.57 (s, 1H, -N-CH-CO); 6.9 (s, 1H, -NH-); 7.2-8.1 (m, 9H, Ar). ^{13}C NMR ($CDCl_3$, 360 MHz): 28.47 (3x -CH_3); 42.26 (-CH_2-CO-N-); 51.88 (-CH-COO-); 52.11 (-C); 58.31 (-N-CH-CO-); 67.31 (-CH_2Ph); 124-135 (Ar-C); 140 (Ar-CH); 165.21 (-CO-NH-); 167.26 (-CO-N-); 171.98 (-COO-). MS (70eV), m/z (%) : 439 (M^+, 98). IR ν(cm^{-1}): 1726.

4-Benzyloxycarbonyl-1-[(N-tert.-butyl carbamoyl) (4-pyridinyl) methyl]azetidin-2-one (2b)

R_f (EE,H, 1:2, v:v)=0.48; ^{1}H NMR ($CDCl_3$, 360 MHz): 1.28 (s, 9H, -C(CH_3)$_3$); 2.9 (dd, 1H, ^{2}J=14.91 Hz, ^{3}J=2.8 Hz, -CH_2-CO-N-); 3.29 (dd, 1H, ^{2}J=14.91 Hz, ^{3}J=5.92 Hz, -CH_2-CO-N-); 4.49 (dd, 1H, ^{3}J=2.8 Hz, ^{3}J=5.92 Hz, -CH-COO-); 4.9 (m, 1H, -N-CH-CO-); 5.2 (s, 2H, -CH_2Ph); 6.8 (s, 1H, -NH-); 7.05-7.3 (m, 5H,

Ar); 8.31-8.36 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$, 360 MHz): 28.35 (3x-CH_3); 41.77 (-CH_2-CO-N-); 51.6 (-C); 51.96 (-CH-COO-); 60.96 (-N-CH-CO-); 67.77 (-CH_2Ph); 122.06-151.12 (Ar); 166 (-CO-NH-); 166.2 (-CO-N-); 171.33 (-COO-). MS (70eV), m/z (%) : 395 (M^+, 16). IR ν(cm^{-1}): 1731.

4-Benzyloxycarbonyl-1-[(N-tert.butyl carbamoyl) (4-methoxyphenyl) methyl]azetidin-2-one (2c)

Mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 360 MHz): 1.18 (s, 9H, -C(CH_3)$_3$); 1.37 (s, 9H, -C(CH_3)); 2.79 (dd, 1H, -CH_2-CO-N-); 2.86 (dd, 1H, ^{2}J= 14.7 Hz, -CH_2-CO-N-); 3.08 (dd, 1H, -CH_2-CO-N-); 3.16 (dd, 1H, ^{2}J= 14.7 Hz, ^{3}J= 6.14 Hz, -CH_2-CO-N-); 3.27 (s, 3H, -OCH_3); 3.66 (s, 3H, -OCH_3); 3.82 (dd, 1H, -CH-COO-); 4.48 (dd, 1H, ^{3}J=6.14 Hz, ^{3}J=2.74 Hz, -CH-COO-); 4.77 (m, 1H, -N-CH-CO-); 5.02 (m, 1H, -N-CH-CO-); 5.26 (m, 2H, -CH_2Ph); 6.55-7.2 (m, 9H, Ar). ^{13}C NMR ($CDCl_3$, 360 MHz): 28.41 (-C(CH_3)$_3$); 41.1 (-CH_2-CO-N-); 51.46 (-C); 53.6 (-OCH_3); 55.12 (-CH-COO); 59.6 (-N-CH-CO); 66.46 (-CH_2Ph); 126.2-129.3 (Ar); 165.8 (-C=O); 168.4 (-C=O); 169.9 (-C=O); 171.3 (-C=O). MS (70eV), m/z (%): 425 (M^+, 2). IR ν(cm^{-1}): 1716.

4-Benzyloxycarbonyl-1-[(N-allyl carbamoyl) (isopropyl) methyl]azetidin-2-one (2d)

R_f (EE,H, 1:1, v:v)=0.49; ^{1}H NMR ($CDCl_3$, 360 MHz): 0.93 (m, 6H, -CH-(CH_3)$_2$); 1.99 (m, 1H, -CH-(CH_3)$_2$); 2.93 (dd, 1H, ^{2}J= 14.86 Hz, ^{3}J= 3.0 Hz, -CH_2-CO-N-); 3.25 (dd, 1H, ^{2}J= 14.86 Hz, ^{3}J= 5.97 Hz, (-CH_2-CO-N-); 3.6 (m, 1H, -N-CH-CO-); 3.87 (t, 2H, ^{3}J= 6.56 Hz, -CH_2-CH=); 4.35 (dd, 1H, ^{3}J= 3.0 Hz, ^{3}J= 5.97 Hz, -CH-COO-); 5.1 (m, 2H, =CH_2); 5.21 (s, 2H, -CH_2Ph); 5.8 (m, 1H, -CH=); 6.72 (t, 1H, ^{3}J= 5.72 Hz, -NH-); 7.4 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 360 MHz): 18.51 (-CH_3); 19.11 (-CH_3); 29.92 (-CH-(CH_3)$_2$); 41.19 (-CH_2-CH=); 41.8 (-CH_2-CO-N-); 51.24 (-N-CH-CO-); 52.39 (-CH-COO-); 67.41 (-CH_2Ph); 116.55 (-CH_2=); 128.46 (Ar); 133.83 (-CH=); 166.79 (-CO-NH-); 168.5 (-CON-); 172.95 (-COO-). MS (70eV), m/z (%) : 343 (M^+-1, 42). IR ν(cm^{-1}): 1736.

4-Benzyloxycarbonyl-1-[(N-tert.-butyl carbamoyl) (benzoyl) methyl]azetidin-2-one (2e)

R_f (EE,H, 1:1, v/v)=0.62, 0.37; ^{1}H NMR ($CDCl_3$, 360 MHz): 1.27 (s, 9H, -C(CH_3)$_3$); 2.89 (dd, 1H, ^{2}J= 14.81 Hz, ^{3}J= 2.69 Hz, -CH_2-CO-N-); 3.18 (dd, 1H, ^{2}J= 14.81 Hz, ^{3}J= 5.84 Hz, -CH_2-CO-N-); 4.51 (dd, 1H, ^{3}J=5.84 Hz, ^{3}J= 2.69 Hz, -CHCOO); 5.16 (s, 2H, -CH_2Ph); 5.92 (s, 1H, -N-CH-CO); 7.1-7.4 (m, 10H, Ar); 15.3 (s, 1H, -NH). ^{13}C NMR ($CDCl_3$, 360 MHz): 28.58 (-C(CH_3)$_3$); 42.14 (-CH_2-CO-N-); 51.82 (-C); 52.9 (-CH-COO-); 62.38 (-N-CH-CO); 68.01 (-CH_2Ph); 126.91-129.45 (Ar-CH); 134.25 (Ar-C); 163.41 (-CO); 166.75 (-CO); 169.81 (-CO); 172.91 (-CO). MS (70 eV), m/z (%): 423 (M^++1, 4). IR (KBr), ν(cm^{-1}): 3250, 1750, 1675.

4-Benzyloxycarbonyl-1-[(N-diphenylmethyl carbamoyl)methyl]azetidin-2-one (2f)

^{1}H NMR ($CDCl_3$, 360 MHz): 2.95 (dd, 1H, ^{2}J= 14.5 Hz, ^{3}J= 2.6 Hz, -CH_2-CO-N); 3.22 (dd, 1H, ^{2}J= 14.5 Hz, ^{3}J= 6.0 Hz, -CH_2-CO-N); 3.91(d, 1H, ^{2}J= 17.1 Hz, -N-CH_2-CO-NH); 4.0 (d, 1H, ^{2}J= 17.1 Hz, -N-CH_2-CO-NH); 4.36 (dd, 1H, ^{3}J= 2.6 Hz, ^{3}J= 6.0 Hz, -CH-COO); 5.15 (s, 2H, -CH_2Ph); 6.2 (d, 1H, ^{3}J= 7.2 Hz, -CH-Ph_2); 7.0-7.5 (m, 15H Ar); 7.7 (d, 1H,^{3}J= 7.2 Hz, -NH). ^{13}C NMR ($CDCl_3$, 360 MHz): 42.7 (-CH_2-CO-N); 45.8 (-N-CH_2-CO-); 52.2 (-CH-COO-); 57.14 (-CH-Ph_2); 67.70 (-CH_2Ph); 127.2-128.8 (Ar-CH); 134.6, 141.0, 141.8 (Ar-C); 166.2 (-CO-NH-); 166.5 (-CO-N-); 170.9 (-COO-). MS (70eV), (m/z): 428 (M^+, 1.5%). IR(KBr), ν(cm^{-1}): 1740, 1660.

4-Benzyloxycarbonyl-1-[(N-tert.-butyl carbamoyl) (3,3,3,trichloro-1-propenyl) methyl]azetidin-2-one (2g)

R_f (EE,H, 1:2, v/v)=0.5; ^{1}H NMR ($CDCl_3$, 360 MHz): 1.34 (s, 9H, -C(CH_3)$_3$); 3.11 (dd, 1H, ^{2}J= 15.32 Hz, ^{3}J= 2.93 Hz, -CH_2-CO-N-); 3.40 (dd, 1H, ^{2}J= 15.32 Hz, ^{3}J= 6.19 Hz, -CH_2-CO-N-); 3.77 (m, 1H, -N-CH-CO); 4.74 (dd, 1H, ^{3}J= 6.19 Hz, ^{3}J= 2.93 Hz, -CH-COO-); 5.18 (m, 2H, -CH_2Ph); 6.14 (s, 1H, -NH-); 6.59 (d, 1H, ^{3}J= 11.12 Hz, -CH=); 6.75 (d, 1H, ^{3}J= 11.12 Hz, =CH-Cl_3); 7.25-7.4 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 360 MHz): 28.42 (-C(CH_3)$_3$); 42.03 (-CH_2-CO-N-); 50.66 (-N-CH-CO); 51.56 (-C); 51.99 (-CH-COO-);

67.75 (-CH_2Ph); 94.83 (-CCl_3); 120.5 (-CH=); 123.97 (=$CHCCl_3$); 128.42-128.8 (Ar-C); 164.18 (-CONH-); 167.27 (-CO-N-); 170.32 (-COO-). MS (70eV), m/z (%): 424 (M^+-HCl, 100). IR (KBr), ν(cm^{-1}): 3300, 1750, 1665.

4-Benzyloxycarbonyl-1-[(N-diphenylmethyl carbamoyl) (9-fluorenyl) methyl]azetidin-2-one (2h)

R_f (EE,H, 1:3, v/v)=0.42; ^{1}H NMR ($CDCl_3$, 360 MHz): 2.53 (d, 1H, ^{3}J= 4.3 Hz, -CH-Fluorenyl); 2.71 (dd, 1H, ^{2}J= 14.8 Hz, ^{3}J= 2.7 Hz, -CH_2-CO-N); 2.95 (dd, 1H, ^{2}J= 14.8 Hz, ^{3}J= 5.84 Hz, -CH_2-CO-N); 4.11 (dd, 1H, ^{3}J= 2.7 Hz, ^{3}J= 5.84 Hz, -CH-COO); 5.15 (s, 2H, -CH_2Ph); 5.29 (d, 1H, ^{3}J= 4.3 Hz, -N-CH-CO); 6.82 (d, 1H, ^{3}J= 7.9 Hz, -CH-Ph_2); 6.9-7.98 (m, Ar); 8.1 (d, 1H,^{3}J= 7.9 Hz, -NH). ^{13}C NMR ($CDCl_3$, 360 MHz): 28.33 (-CH-fluorenyl); 41.9 (-CH_2-CO-N); 52.6 (-CH-COO); 57.16 (-CH-Ph_2); 67.32 (CH_2Ph); 74.2 (-N-CH-CO); 119.8-144.1 (Ar); 166.1, 166.6, 173.5 (C=O). MS (70eV), m/z (%): 592 (M^+, 19). IR (KBr), ν(cm^{-1}): 1754.

4-Hydroxymethyl-1-[(N-diphenylmethyl carbamoyl)methyl]azetidin-2-one (3)

A solution of 4-benzyloxycarbonyl-1-[(N-diphenylmethyl carbamoyl)methyl]azetidin-2-one (**2f**) (4.28 g, 10 mmol) in THF (20 ml) is added dropwise at 0°C and under a nitrogen atmosphere to a solution of lithium aluminum hydride (0.19 g, 5 mmol) in THF (10 ml). The reaction mixture is then stirred at room temperature. The reaction is completed after 30 min (TLC control). To this mixture are added water (100 ml) and 5% phosphoric acid (50 ml). The resulting solution is extracted with methylene chloride (3 x 50 ml), and the combined organic phases are dried over magnesium sulfate. Removal of the solvent in vacuo gives a yellow oil.
$C_{19}H_{20}N_2O_3$ = 324.36g/mol; Yield: 0.8g(25%) yellow oil; ^{1}H NMR ($CDCl_3$, 360 MHz): 2.61 (dd, 1H, ^{2}J= 17.06 Hz, ^{3}J= 8.08 Hz, -CH_2-CO-N); 2.78 (dd, 1H, ^{2}J= 17.06 Hz, ^{3}J= 6.28 Hz, -CH_2-CO-N); 3.62 (m, 1H, -CH-CH_2OH); 3.76 (d, 1H, ^{2}J= 17.5 Hz, -N-CH_2-CO-NH); 3.92 (d, 1H, ^{2}J= 17.5 Hz, -N-CH_2-CO-NH); 4.11 (m, 2H, -CH_2OH); 6.25 (d, 1H, ^{3}J= 8.08 Hz, -CH-Ph_2); 7.12-7.6 (m, 10H, Ar); 8.15 (d, 1H, ^{3}J= 8.08 Hz, -NH). ^{13}C NMR ($CDCl_3$, 360 MHz): 42.19 (-CH_2-CO-N); 46.3 (N-CH_2-CO); 51.9 (-CH-CH_2OH); 57.1 (-CH-Ph_2); 65.17 (-CH_2OH); 128-141.9 (Ar); 166.9 (-CO-NH); 167.1 (-CO-N). MS (70eV), (m/z): 324 (M^+, 3%). IR ν (cm^{-1}): 1721. Elemental analysis: calc.: C, 70.35%; H, 6.21%; N, 8.64%; found.: C, 71.22%; H, 6.12%; N, 8.43%.

4-Carboxy-1-[(N-diphenylmethyl carbamoyl)methyl]azetidin-2-one (4)

A solution of 4-benzyloxycarbonyl-1-[(N-diphenylmethyl carbamoyl)-methyl]azetidin-2-one (**2f**) (4.4 g, 10.27 mmol) in methanol (100 ml) is mixed with diethyl ether (40 ml) containing 10% palladium on charcoal (0.55 g, 5.2 mmol). After hydrogenation at ambient pressure for 5h no more hydrogen uptake is observed and the catalyst is filtered off. Removal of the solvent under reduced pressure results in a colourless solid.
$C_{19}H_{18}N_2O_4$ = 338.36g/mol; Yield: 3.3g (95%) colourless crystals; mp: 78°C; ^{1}H NMR (DMSO, 360 MHz): 2.85 (dd, 1H, ^{2}J= 14.4 Hz, ^{3}J= 2.5 Hz, -CH_2-CO-N); 3.25 (dd, 1H, ^{2}J= 14.4 Hz, ^{3}J= 6.0 Hz, -CH_2-CO-N); 3.80 (d, 1H, ^{2}J= 17.0 Hz, -N-CH_2-CO-NH); 3.93 (d, 1H, ^{2}J= 17.0 Hz, -N-CH_2-CO-NH); (4.15 (dd, 1H, ^{3}J= 2.5 Hz, ^{3}J= 6.0 Hz, -CH-COOH); 6.10 (d, 1H, ^{3}J= 7.6 Hz, -CH-Ph_2); 7.0-7.35 (m, 11H Ar); 7.7 (d, 1H,^{3}J= 7.6 Hz, -NH); 9.20 (s, 1H, -COOH). ^{13}C NMR (DMSO, 360 MHz): 41.8 (-CH_2-CO-N); 43.8 (-N-CH_2-CO-); 51.3 (-CH-COOH); 56.0 (-CH-Ph_2); 125.8-128.7 (Ar-CH), 142.04, 142.08 (Ar-C); 166.1 (-CO-NH-); 166.4 (-CO-N-); 172.5 (-COOH). MS (70eV), (m/z): 338 (M^+, 0.8%). IR (KBr), ν (cm^{-1}): 1730, 1640.
Elemental analysis: calc. C, 67.44%, H, 5.36%; N, 8.28%; found: C, 67.29%, H, 5.41%; N, 8.29%.

4-Acetoxy-1-[(N-diphenylmethyl carbamoyl)methyl]azetidin-2-one (5)

Procedure 1: oxidative decarboxylation with lead tetraacetate.
Lead tetraacetate (55 g, 0.124 mol) is added in small amounts under a nitrogen atmosphere to a solution of 4-carboxy-1-[(N-diphenylmethyl carbamoyl)methyl]azetidin-2-one (**4**) (2 g, 6 mmol) in acetonitrile (300 ml). The mixture is stirred at 70°C for 1h. The solution is then poured into water (300 ml) and the mixture is

extracted with diethylether (3 x 150 ml). Drying with magnesium sulfate and removal of the solvent gives a dark yellow oil.
$C_{20}H_{20}N_2O_4$ = 352g/mol Yield: 1.6g (76%) dark yellow oil.

Procedure 2: Electrochemical oxidation.
A solution of 4-carboxy-1-[(N-diphenylmethyl carbamoyl)methyl]azetidin-2-one (**4**) (0.8 g, 2.37 mmol) in acetic acid (20 ml) and acetonitrile (80 ml) is subjected to a galvanostatic electrolysis in a three-electrode cell. The electrodes are composed of a mercuric chloride standard electrode, anode and cathode consisting of platinum. Sodium acetate is used as electrolyte. After stirring for 8h in a nitrogen atmosphere the reaction is complete. The solvent is removed and the resulting pale yellow crystals are dissolved in chloroform (80 ml) and extracted with water (3x50ml). Evaporation of the solvent after drying the organic phase over magnesium sulfate gives a yellow oil.
$C_{20}H_{20}N_2O_4$ = 352g/mol; Yield: 0.47g (56%) yellow oil, ^{1}H NMR ($CDCl_3$, 360 MHz): 1.90 (s, 3H, $-CH_3$); 2.90 (dd, 1H, ^{2}J= 15.3 Hz, ^{3}J= 2.3 Hz, $-CH_2$-CO-N); 3.20 (dd, 1H, ^{2}J= 15.3 Hz, ^{3}J= 4.1 Hz, $-CH_2$-CO-N); 3.97 (d, 1H, ^{2}J= 12.0 Hz, -N-CH_2-CO-NH); 4.02 (d, 1H, ^{2}J= 12.0 Hz, -N-CH_2-CO-NH) 5.9 (dd, 1H, ^{3}J= 2.3 Hz, ^{3}J= 4.1 Hz, -CH-OAc); 6.20 (d, 1H, ^{3}J= 8.0 Hz, -CH-Ph_2); 7.2-7.34 (m, 10H Ar); 7.9 (d, 1H,^{3}J= 8.0 Hz, -NH). ^{13}C NMR ($CDCl_3$, 360 MHz): 20.4 ($-CH_3$) 44.7 ($-CH_2$-CO-N); 45.3 (-N-CH_2-CO-); 57.2 (-CH-Ph_2); 77.0 (-CH-OAc); 126.9-132.4 (Ar-CH), 140.9, 141.2 (Ar-C); 166.1 (-CO-NH-); 166.4 (-CO-N-); 171.0 (-OAc). MS (70eV), (m/z): 292 (M^+-AcOH, 4%). IR ν (cm^{-1}): 1700. Elemental analysis: calc.: C, 68.17%; H, 5.72%; N, 7.95%; found: C, 68.42%, H, 5.69%; N, 7.93%.

4-Acetoxy-1-[(N-diphenylmethyl oxycarbonyl)methyl]azetidin-2-one (6)

Unter a nitrogen blanket a solution of dinitrogen tetraoxide (0.7 ml, 11 mmol) in chloroform (10 ml) is added at 0°C over a period of 15 min to a stirred mixture of sodium acetate (1.2 g, 14.8 mmol) and chloroform (18 ml). After completion, a solution of amide **5** (1.3 g, 3.7 mmol) in dry chloroform (16 ml) is added dropwise in the course of 15 min. After 1h the reaction mixture is allowed to warm to room temperature and stirring is continued for three more hours. Quenching is performed by dropwise addition of sodium hydrogen carbonate (1.25 g) in water (15 ml), followed by stirring for one additional hour. The organic solvent is evaporated and the remaining mixture is extracted with ethyl acetate (2 x 15 ml), the extract washed with water and dried over magnesium sulfate. After removal of the solvent, a brownish-yellow oil results.
$C_{20}H_{19}NO_5$ = 353.37g/mol Yield: 0.55g (42%) yellow oil, ^{1}H NMR ($CDCl_3$, 360 MHz): 1.95 (s, 3H, $-CH_3$); 3.0 (dd, 1H, ^{2}J= 15.1 Hz, ^{3}J= 3.7 Hz, $-CH_2$-CO-N), 3.3 (dd, 1H, ^{2}J= 15.1 Hz, ^{3}J= 4.1 Hz, $-CH_2$-CO-N); 4.05 (d, 1H, ^{2}J= 17.9 Hz, -N-CH_2-CO-NH); 4.20 (d, 1H, ^{2}J= 17.9 Hz, -N-CH_2-CO-NH) 5.9 (dd, 1H, ^{3}J= 4.1 Hz, ^{3}J= 3.7 Hz, -CH-OAc), 6.87 (s, 1H, -CH-Ph_2), 7.22-7.35 (m, 10H Ar). ^{13}C NMR ($CDCl_3$, 360 MHz): 21.2 ($-CH_3$) 41.9 ($-CH_2$-CO-N); 44.4 (-N-CH_2-CO-); 77.1 (-CH-OAc); 78.4 (-CH-Ph_2) 127.0-132.4 (Ar-CH); 140.9, 141.1 (Ar-C); 171.0 (-OAc) 171.4 (-COOCH-) MS (70eV), (m/z): 311 (11%). IR ν (cm^{-1}): 1750. Elemental analysis calc.: C, 67.98%; H, 5.42%; N, 3.96%; found: C, 67.88%; H, 5.51%; N, 3.98%.

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