Electrooxidation Based Strategy Towards the Core 3-Amino-6-Hydroxy-azepan-2-one

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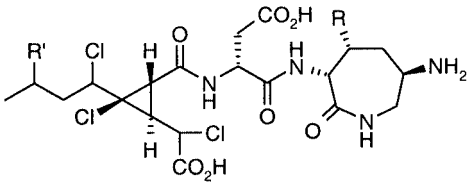
Abstract: We describe a practical synthesis of protected (3*S*,6*R*)-6-hydroxy-cyclolysine derivatives starting from cyclic L-lysine. Evaluation of the electrochemical oxidation of various protected amino-caprolactams allowed a regioselective electromethoxylation at the α-position to the lactam nitrogen. Formation of the corresponding enamide by elimination of methanol followed by a diastereoselective dihydroxylation, diacetylation and subsequent regioselective reduction afford the orthogonally protected (3*S*,6*R*)-3-amino-6-hydroxy-azepan-2-one.

Key words: bengamides, diastereoselectivity, dihydroxylation, electrooxidation, osmium

The 6-substituted 3-amino caprolactam is a common core skeleton of various naturally occurring products (Figure 1). Among them are Peritoxins A and B, isolated from the soil-borne fungus *Periconia circinata*, which are involved in the milo disease syndrome.[1] Twenty-four structurally related cyclolysine derivatives, bengamides, were isolated from sponges of the genus *Jaspus* (family Jaspidae).[2] Some of these secondary metabolites, principally bengamides bearing myristate group at C-6 of the caprolactam core, were evaluated *in vitro* in the NCI 60 cell line screening and found to have a unique profile compared to that of standard antitumor agents. Bengamide B and its analogues proved to have impressive *in vitro* and *in vivo* antitumor activities against MDA-MB-435 human breast carcinoma.[2f,g,3]

Among bengamides and analogues those belonging to the hydroxylysine derived category are considered the most promising clinical candidates. One of this analogues developed by Novartis entered phase I trials in 2000.[3c–d] Methionine aminopeptidases were very recently identified as (unanticipated) intracellular molecular target of bengamides.[4]

All reported syntheses[3,5] of bengamides and analogues rely on the coupling of the polyol side chain and the 6-O-acylated 3-amino-6-hydroxy caprolactam subunit (Scheme 1). Kinder et al.[5e] reported on the shortest synthesis of this heterocyclic core in three steps starting from (5*R*)-hydroxy-L-lysine. Recently, Boeckman et al.[5g,h] described an elegant approach to (3*S*,6*S*)-3-amino-6-hydroxycaprolactam in eight steps from D-aspartic acid



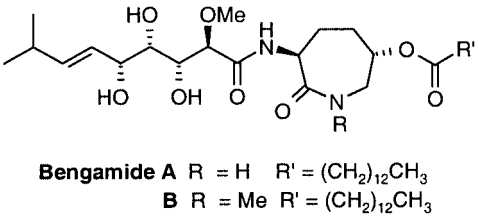
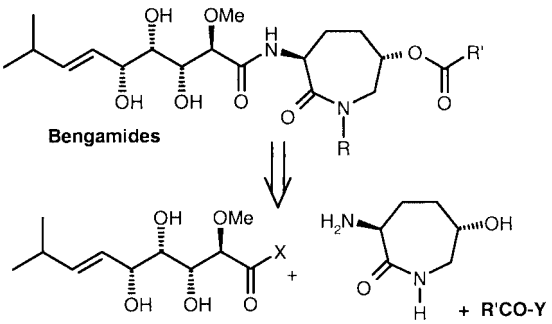


Figure 1 3-Amino-hydroxycaprolactam containing compounds

based on an enantioselective C-alkylation of an iminoglycine ester in the presence of a chiral phase-transfer catalyst.

In this letter we report on the synthesis of protected (3*S*,6*R*)-3-amino-6-hydroxy-azepan-2-ones **1**, starting from (*S*)-3-amino-azepan-2-one hydrochloride. As outlined in Scheme 2, our strategy relies on two key steps; a diastereoselective dihydroxylation of enamides **2** derived from aminoethers **3** which, in turn, were obtained by a regioselective electrochemical oxidation of a judiciously protected cyclic L-lysine.

The oxidation of amides leading to the corresponding α-oxy-compounds is one of the most developed electrochemical methods in organic synthesis. While this reac-



Scheme 1

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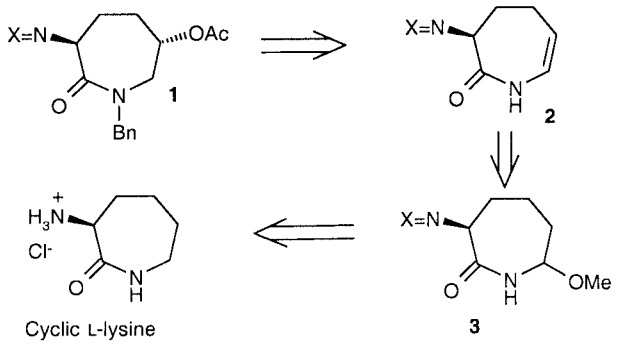
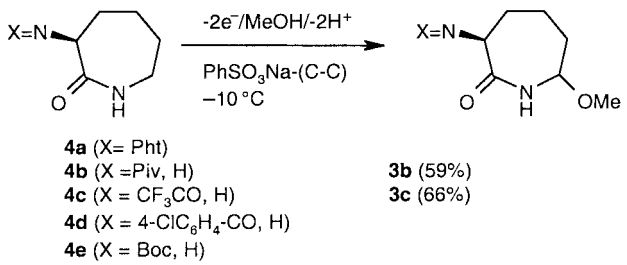


Scheme 2

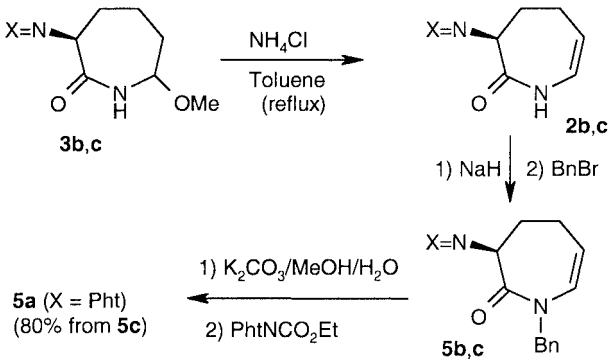
tion was extensively studied in the case of carbamates,[6] particularly by Shono's group, amides and lactams were less examined. A few examples of direct (anodic) or indirect (anode-NaCl as catalyst) regioselective oxidation of dipeptides were reported by Steckhan[7] and Moeller.[8] To be successful, our strategy would require the previously undemonstrated regioselective endocyclic electromethoxylation of *exo* N-acylated 3-aminocaprolactams.[9] To differentiate the two N-acyl groups during a direct α-electromethoxylation, we envisioned modulating the availability of the exocyclic nitrogen lone pair by means of an appropriate electron withdrawing group to both protect and deactivate the 3-amino substituent of the caprolactam. To this end, five 3-N-acylated amino caprolactams **4a-e** (Scheme 3) were prepared from L-lysine by conventional methods.[10] Preliminary experiments, performed in an undivided cell with graphite electrodes, revealed that only the pivaloyl and trifluoroacetyl derivatives **4b** and **4c** gave the expected α-methoxylated compounds **3b**,**c**. Because of the very low solubility in methanol, oxidation of substrates **4a** and **4d** could not be examined, whereas, electrochemical oxidation of carbamate **4e** gives a complex mixture. Therefore, only substrates **4b**,**c** were involved in further screening experiments where various electrolysis conditions were examined (electrolyte, temperature and concentration of electrolyte and substrates).



Scheme 3

The best results were obtained when the electrolysis was performed at –10 °C with sodium benzene sulfonate (0.05 $mol \cdot L^{-1}$) as supporting electrolyte[11] using a substrate concentration of ca 0.3 $mol \cdot L^{-1}$ (Scheme 3). Electrolysis of solutions with lower concentrations of substrates resulted in decreased chemical and electrical yields, probably due to the competition between lactam and solvent oxidation. Similar effect of yield improvement with electromethoxylations utilizing higher concentration of substrate was reported by Steckhan.[12] A possible explanation, as suggested by Steckhan,[12] would involve either a replacement of solvent molecules by substrate within the Helmholtz-layer, or an electron hopping mechanism between substrate radical-cations inside the Helmholtz-layer with the substrate outside this layer.

After screening various repported conditions,[13] we prepared the expected enamides **2b**,**c** in acceptable and reproducible yields (67 and 68% respectively) by refluxing the corresponding methoxylated caprolactams **3** in toluene in the presence of ca. ten equivalents of ammonium chloride (Scheme 4).



Scheme 4

Previous reports showed that β-hydroxylation of enamides could be achieved by oxidative hydroboration.[14] Unfortunately, treatment of enamides **2** with various boranes [BH_3·THF, BH_3·SMe_2, 9-BBN, $HBCl_2$·SMe_2, $HBBr_2$·SMe_2 (free from BBr_3)] affords either starting material or, when excess borane is utilized, reduction of the amide functionality. Next, we performed a regioselective N-benzylation of the endocyclic amides **5** and submitted the resulting N-benzyl derivatives **5b**,**c** to the same oxidative hydroboration procedures. No conversion of these substrates was observed, except the formation (51%) of the unexpected bridged aminal **6b** (Figure 2) when enamide **5b** was treated with $HBBr_2$·SMe_2.

To avoid this intramolecular participation of the exocyclic amide, **5c** was converted in two steps to the phthalimido analogue **5a** (Scheme 4) which was submitted to the same hydroboration/oxidation conditions. Regrettably, no hydroxylated compound could be obtained. Use of excess $HBBr_2$·SMe_2 in methylene chloride, followed by an oxidative treatment (H_2O_2/NaOH) resulted in the reduced compound **6a**[15] (31%) (Figure 2).

After these disappointing attempts, we explored less straightforward oxidative methods. First, we examined the conditions described by Correia and coworkers[16] who performed the hydroxymethoxylation of endocyclic encarbamates using *m*-CPBA in methanol. Unfortunately,

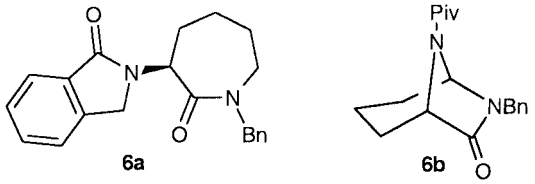


Figure 2

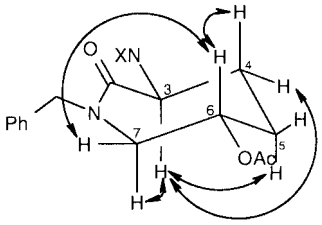
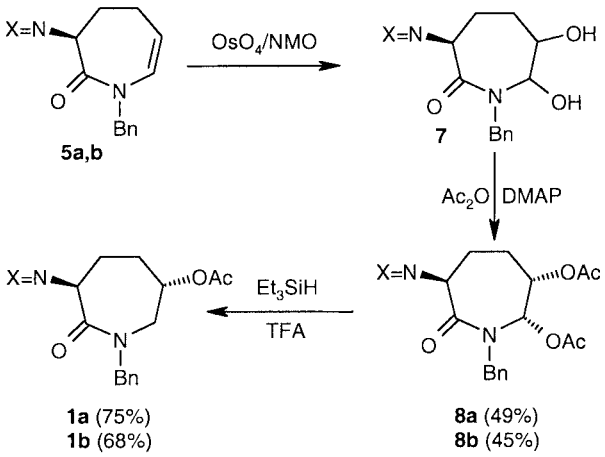


Figure 3 The most significant observed nOe

under these conditions (with or without bicarbonate) **5** did not react. The same absence of reactivity was observed with other known conditions for epoxidation (H_2O_2/Cl_3CCN,[17] H_2O_2/urea/TFAA[18]). Finally, enamide **5a** was oxidized using osmylation[19] leading to 6,7-dihydroxylated caprolactam **7a**, which was isolated in 30% yield. However, when the crude diol **7a** was acetylated prior to purification, the corresponding diacetate **8a** was isolated in 49% overall yield (Scheme 5). The same sequence (dihydroxylation/acetylation) applied to enamide **5b** afforded the corresponding diacetate **8b** in 45% overall yield.[20] According to NMR data, both **8a** and **8b** are obtained as single stereoisomers with a *cis* relative configuration of both acetate substituents, indicating the absence of epimerization of the hemiaminal carbon of diols **7**.



Scheme 5

In order to reach the key caprolactam **1**, we submitted derivatives **8** to various conditions for the reduction of the O-acetylated hemiaminal carbon (Scheme 5). The best yields were obtained using triethylsilane as the reducing agent with trifluoroacetic acid as the solvent and catalyst for the generation of the transient iminium ion.[21a] Use of Lewis acids ($BF_3{\cdot}OEt_2$, $TiCl_4$) or TFA in methylene chloride as solvent resulted in poor conversions.[21b]

The relative *trans* stereochemistry of lactams **1a**,**b** was established by NOESY experiments (see Figure 3). The coupling constants and the observed nuclear Overhauser effect (nOe) are consistent with a chair-like conformation,[22] where the amide carbon-nitrogen bond corresponds to the 'flat' end with both substituents being in equatorial orientations (Figure 3).

The total diastereoselective dihydroxylation observed in the case of **5a**,**b** came as a pleasant surprise. Indeed, owing to the enamide moiety, the ring of enamides **5** was assumed to be flattened (six atoms in the same plane C5-C6-C7-N-C2-C3), and hence low or no diastereoselectivities were expected to arise from addition reactions with enamides **5**. The observed diastereoselectivities suggest a non fully conjugated C=C bond with the endocyclic amide moiety[23]. Based on ^1H and ^{13}C NMR spectra, enamide rings of **5a-c** exist in a single conformation. Among the possible conformations[22b] only the twisted-boat conformation shown in Figure 4 is consistent with the observed ^3J coupling constants values of H-3 and H-6. In this conformation (Figure 4) the pseudoaxial proton of C4 position blocks the β-face of the carbon-carbon double bond while the α-face seems more accessible to the dihydroxylation reagent.

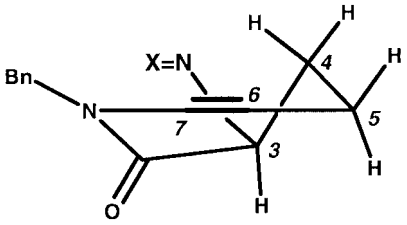


Figure 4

The results obtained herein represent a novel and efficient electrochemical based procedure to the orthogonally protected (3*S*,6*S*)-3-amino-6-hydroxy caprolactam, the azaheterocyclic subunit of bengamides. The synthetic applications of this methodology are under investigation.

Typical Experimental Procedures

(*S*)-3-Trifluoroacetamido-7-methoxy-azepan-2-one (3c)

An undivided beaker type cell with cooling mantle (-10 °C) equipped with graphite electrodes plates (15 cm^2) and charged with 4 g (17.9 mmol) of trifluoroacetimido caprolactam **4c**, 540 mg (3.0 mmol) of sodium benzene sulfonate and 60 mL of MeOH. After 28500 Coulombs (16.5 F/mol, at 12 V) passed the reaction mixture was concentrated under vacuum and chromatographied on silica gel (1:1 EtOAc/cyclohexane) to afford 3.0 g (66%) of the desired methoxylated compound **3c** as a yellow solid: mp 109-111 °C; $[\alpha]^{16}_D$ = – 87.3 (*c* 1.00, MeOH); ^1H NMR (250 MHz, $CDCl_3$): δ 7.77 (bs, NH), 7.00 (bs, NH), 4.75-4.55 (m, 1H), 4.45-4.30 (m, 1H), 3.34 (s, 3H), 2.20-2.12 (m, 3H); 1.81-1.70 (m, 1H); 1.60-1.23 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 174.5, 156.0 (q, *J* = 37 Hz), 115.7 (q, *J* = 286 Hz), 83.1, 55.5, 53.4, 32.9, 30.1, 20.8; IR (neat): 3235, 2928, 1725, 1666, 1163 cm^{-1}; HRMS: *m/z* calcd. for $C_9H_{14}F_3N_2O_3$ (M+1): 255.0956. Found: 255.0952.

(*S*)-3-Trifluoroacetamido-1,3,4,5-tetrahydro-azepin-2-one (2c)
A round bottom flask equipped with a condenser was charged with 3.3 g (13.0 mmol) of methoxy trifluoroacetimido caprolactam **3c**, 8 g (149.53 mmol) of ammonium chloride and 80 mL of toluene. After being refluxed for 64 h the mixture was concentrated under reduced pressure and the solid residue triturated with DCM. Filtration, evaporation of the volatiles and column chromatography on silica gel (1:1 EtOAc/cyclohexane) of the residue afforded 1.97 g (68%) of the enamide **2c** as a white solid: mp 111-113 °C; $[\alpha]^{16}_D$ = - 155.3 (*c* 1.07, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.72 (bs, NH), 6.72 (bs, NH), 5.82 (apparent tdd, J_t = 2, J_d = 4.9, J_d = 9.6 Hz, 1H), 5.25 (apparent qt, J = 4.6 Hz, 1H), 4.44 (ddd, J_1 = 2.5, J_2 = 5, J_3 = 10.6 Hz, 1H), 2.57-2.30 (m, 3H), 2.04-1.86 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 171.6, 156.4 (q, J = 37 Hz), 121.6, 115.8, 115.6 (q, J = 285 Hz), 53.2, 30.2, 26.2; IR (neat): 3230, 2923, 1730, 1662, 1176, 1151, 722 cm^{-1}; HRMS: *m/z* calcd. for $C_8H_{10}F_3N_2O_2$ (M+1): 223.0694. Found: 223.0696.

(*S*)-1-Benzyl-3-trifluoroacetamido-1,3,4,5-tetrahydro-azepin-2-one (5c)
To a suspension of 1.08 g of sodium hydride (45.00 mmol, 60% dispersion in oil) in 35 mL of THF was added dropwise at 0 °C a solution of 1.97 g (8.87 mmol) of trifluoroacetamido enamide **2c** in 25 mL of THF. After 15 min 1.05 mL (8.78 mmol) of benzyl bromide were added dropwise. The ice bath was removed 15 min later and stirring continued overnight at room temperature. The reaction mixture was then washed with a saturated aqueous NH_4Cl solution and the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography on silica gel (1:1 EtOAc/cyclohexane) afforded 2.48 g (90%) of the expected compound as a colorless oil : $[\alpha]^{20}_D$ = - 393.7 (*c* 1.04, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.86 (bs, 1H), 7.40-7.10 (m, 5H), 5.92 (td, J_t = 1.3, J_d = 8.7 Hz, 1H), 5.53 (td, J_t = 5.8, J_d = 8.6 Hz, 1H), 4.88 and 4.42 (q_{AB}, J = 14.6 Hz, 2H, Ph-CH_2), 4.71-4.62 (m, 1H), 2.52-2.45 (m, 1H), 2.25-2.16 (m, 2H), 1.98-1.88 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 169.8, 156.1 (q, J = 37 Hz), 136.4, 128.7, 128.5, 127.9, 127.8, 120.1, 115.7, (q, J = 286 Hz), 52.2, 51.0, 34.2, 23.7; IR (neat): 3285, 2938, 1721, 1645, 1208, 1149, 725, 699 cm^{-1}; HRMS: *m/z* calcd. for $C_{15}H_{16}F_3N_2O_2$ (M+1): 313.1164. Found: 313.1159.

(*S*)-1-Benzyl-3-Phtalimido-1,3,4,5-tetrahydro-azepin-2-one (5a)
To a solution of 1.49 g (4.78 mmol) of benzylated trifluoroacetimido enamide **5c** in 200 mL of MeOH at 0 °C was added dropwise a solution of 3.33 g (24.10 mmol) of potassium carbonate in 200 mL of water. After 30 min the ice bath was removed and stirring continued overnight at room temperature. The reaction mixture was then concentrated under vacuum, the residue dissolved in Et_2O and potassium carbonate was added. After 1 h of stirring the solid was filtered off and rinsed with Et_2O. Evaporation afforded 1.03 g (100%) of the desired amine as a white liquid which was used in the next step without further purification: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.29-7.21 (m, 5H), 5.90 (dd, J_1 = 1.9 Hz, J_2 = 8.3 Hz, 1H), 5.60-5.40 (m, 1H), 4.88 and 4.39 (q_{AB}, J = 14.6 Hz, 2H, Ph-CH_2), 3.92 (bs, 2H, NH_2), 3.74 (apparent q, J = 5.3 Hz, 1H), 2.40-1.80 (m, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 175.3, 137.2, 129.2, 128.6, 128.0, 127.5, 119.8, 53.4, 50.8, 37.9, 23.7; IR (neat): 3365, 2951, 1641, 1237, 1222, 749, 702 cm^{-1}. To a solution of the amine thus obtained (1.03 g, 4.77 mmol) in 30 mL of DMF was added 1.05 g (4.79 mmol) of *N*-carbethoxyphtalimide. After being stirred overnight the solvent was evaporated off and the residue filtered through a plug of silica gel (7:3 EtOAc/cyclohexane). After evaporation 25 mL of water and 25 mL of abs EtOH were added to the residue and the solvents were evaporated under reduced pressure. abs EtOH was added and the mixture concentrated under vacuum. This procedure was repeated at least three times in order to eliminate urethane via a ternary system. This method afford 1.33 g (80% over 2 steps) of the desired phtalimide **5a** as a white solid: mp 42-44 °C; $[\alpha]^{16}_D$ = – 226.3 (*c* 1.02, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.85 (dd, J_m = 3.1, J_o = 5.4 Hz, 2H), 7.70 (dd, J_m = 3.1, J_o = 5.4 Hz, 2H), 7.35-7.15 (m, 5H), 5.94 (dd, J_1 = 1.7 Hz, J_2 = 9.2 Hz, 1H), 5.39 (td, J_t = 5.5, J_d = 9 Hz, 1H), 5.08 (dd, J_1 = 3.6 Hz, J_2 = 11.1 Hz, 1H), 4.81 and 4.53 (q_{AB}, J = 14.8 Hz, 2H, Ph-CH_2), 3.20-2.95 (m, 1H), 2.55-2.15 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 168.9, 168.3, 136.9, 134.0, 132.1, 128.9, 128.7, 128.0, 127.6, 123.5, 117.2, 53.6, 51.4, 30.5, 25.6; IR (neat): 3386, 2931, 1773, 1710, 1659, 1386, 716, 699 cm^{-1}; HRMS: *m/z* calcd. for $C_{21}H_{19}N_2O_3$ (M+1): 347.1396. Found: 347.1391.

(*S*)-1-Benzyl-6,7-diacetoxy-3-phtalimido-azepan-2-one (8a)
To a stirred solution of 490 mg (1.42 mmol) of phtalimidobenzyle **5a** in 4 mL of a 1:1 mixture of acetone and acetonitrile were added successively 2 mL of water, 380 mg (2.81 mmol) of NMO and dropwise 1.8 mL of a 1 wt.% aqueous solution of osmium tetroxide (5 mol%). After being stirred at room temperature overnight the reaction mixture was diluted with EtOAc, solid $Na_2S_2O_3$ (2 g) was added and stirring continued for 30 min. Filtration and evaporation under reduced pressure afforded the desired diol **7a** as a white liquid which was used in the next step without further purification: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.83 (dd, J_m = 3, J_o = 5.4 Hz, 2H), 7.69 (dd, J_m = 3, J_o = 5.4 Hz, 2H), 7.32-75.25 (m, 5H), 5.45 (bd, J = 11.7 Hz, 1H), 4.94 (bs, 1H), 4.71 and 4.51 (ABq, J = 14.8 Hz, 2H, Ph-CH_2), 3.93 (bs, 1H), 3.60-3.40 (m, 1H), 2.85-2.60 (m, 1H), 2.45-2.20 (m, 1H), 2.20-1.90 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 171.0, 168.6, 137.3, 134.1, 132.1, 129.0, 128.4, 127.9, 123.5, 85.2, 72.1, 54.6, 52.1, 30.4, 27.3. To a solution of the previous diol in 8 mL of DCM were added successively 1.04 g (8.51 mmol) of DMAP and 800 µL (8.55 mmol) of acetic anhydride at room temperature and stirring is continued overnight. The reaction mixture was washed with a saturated aqueous NH_4Cl solution, the aqueous phase is then extracted with DCM and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography on silica gel (3:2 EtOAc/cyclohexane) afforded 320 mg (49% over 2 steps) of the expected compound **8a** as a white solid: mp 64-66 °C; $[\alpha]^{16}_D$ = - 48.4 (*c* 1.10, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.83 (bd, J = 3 Hz, 2H), 7.01 (dd,, J_m = 3, J_o = 5.4 Hz, 2H), 7.40-7.15 (m, 5H), 6.03 (d, J = 1.7 Hz, 1H), 5.37 (bd, J = 11.3 Hz, 1H), 5.00 and 4.46 (ABq, J = 14.6 Hz, 2H, Ph-CH_2), 4.67 (ddd, J_1 = 1.9 Hz, J_2 = 4.7 Hz, J_3 = 11.2 Hz, 1H), 2.95-2.70 (m, 1H), 2.30-1.85 (m including 2s at 2.19 and 1.96, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 170.3, 169.6, 169.1, 168.2, 136.5, 134.1, 132.0, 128.8, 128.6, 127.9, 123.5, 81.1, 72.6, 54.3, 52.8, 27.6, 26.5, 20.8, 20.7; IR (neat): 2938, 1752, 1713, 1673, 1212, 718 cm^{-1}; HRMS: *m/z* calcd. for $C_{25}H_{24}N_2O_7$ (M+1): 465.1662. Found: 465.1657.

(*S*)-1-Benzyl-6-acetoxy-3-phtalimido-azepan-2-one (1a)
To 222 mg (0.48 mmol) of diacetate **8a** were added 550 µL (3.41 mmol) of triethylsilane and 2.8 mL of TFA. The mixture is stirred for 75 min then diluted with DCM. A saturated $NaHCO_3$ aqueous solution and solid $NaHCO_3$ were added. After evolution of CO_2 has ceased the organic phase was washed, separated and the aqueous phase was reextracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography on silica gel (1:1 EtOAc/cyclohexane) afforded 145 mg (75%) of the expected monoacetate **1a** as a colorless liquid: $[\alpha]^{18}_D$ = +95.6 (*c* 1.02, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.84 (dd, J_m = 3, J_o = 5.4 Hz, 2H), 7.70 (dd, J_m = 3, J_o = 5.4 Hz, 2H), 7.40-7.22 (m, 5H), 5.13 (dd, J_1 = 2.3 Hz, J_2 = 11.2 Hz, 1H, PhtN-CH), 5.03 and 4.23 (ABq, J = 14.6 Hz, 2H, Ph-CH_2), 4.62 (tt, J_1 = 3.5, J_2 = 9.9 Hz, 1H, AcO-CH), 3.49 (dd, J_1 = 9.9 Hz, J_2 = 15.0 Hz, 1H), 3.33 (bd, J = 15 Hz, 1H), 2.82 (apparent dq, J_d = 2.4 Hz, J_q = 11.4 Hz, 1H), 2.27-2.20 (m, 1H), 2.20-2.13 (m,

1H), 2.02 (s, 3H), 1.83 (apparent dq, J_d = 2.9 Hz, J_q = 13.0 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 170.0 (2C), 168.2, 136.6, 134.1, 132.1, 128.8, 128.5, 127.8, 123.5, 70.1, 53.6, 52.0, 50.7, 33.4, 26.6, 21.1; IR (neat): 2963, 1777, 1710, 1664, 1387, 1087, 1030, 798, 717 cm^{-1}; HRMS: *m/z* calcd. for $C_{23}H_{23}N_2O_5$ (M^++1): 407.1607, found: 407.1604.

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