Diastereoselective Cationic Tandem-Cyclizations to *N*-heterocyclic Scaffolds: Total Synthesis of (–)-Dysibetaine PP

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Supporting Information

General information: Unless noted otherwise, materials were purchased from commercial suppliers and used without purification. Dichloromethane and acetonitrile were freshly distilled from calcium hydride. All air and moisture sensitive reactions were carried out under an inert atmosphere of dry argon. Column chromatography was performed using Acros silica gel (0.035-0.070 mm). TLC was performed using precoated silica gel (60 F254) plates and compounds were detected with UV light and/or with potassium permanganate. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. ¹H NMR and ¹³C NMR spectra were measured in the indicated solvent on a Bruker DMX300 (300 and 75 MHz, respectively) or a Varian Inova 400 (400 and 100 MHz, respectively) and are reported in units of ppm on the δ scale. X-ray data are collected on a Nonius KappaCCD with area detector f and w scan. Infrared spectra were recorded on an ATI Mattson Genesis FTIR spectrometer. Mass spectra were measured using a JEOL JMS SX/SX102A four-sector mass spectrometer, coupled to a JEOL MS-MP7000 data system. Melting points are uncorrected. Preparative HPLC separations were performed on a Zorbax Extend-C18 PrepHT column (21.2 $\times$ 150 mm, 5 μ m) using indicated mixtures of 10 mM aqueous NH₄OH and acetonitrile as eluent. The BOP reagent used in the peptide coupling reactions refers to (benzotriazol-1-ylxy)tris(dimethylamino)phosphonium hexafluorophosphate.

General procedure I: Synthesis of dipeptides 7a-i

A suspension of *N*-Cbz-protected L-allysine ethylene acetal methyl ester and 10% Pd/C (10 mol% Pd) in EtOAc (0.1M) was stirred under hydrogen pressure (balloon). After stirring for 4 h at room temperature the reaction mixture was filtered over Celite and the solvent was evaporated under pressure yielding **5**, which was used without further purification. The amino acids **6a-i** were *N*-Cbz-protected and coupled with **5** according to the following protocol. A suspension of the amino acid **6** in dioxane (2M) was cooled to 0 °C. A solution of NaOH (1 equiv. of a 10% aqueous sol.) was added, followed by NaHCO₃ (1 equiv.) and Cbz-OSu (1 equiv.). After stirring overnight the solvent was removed under reduced pressure, and a solution of 2.5% aqueous NaHCO₃ was added. The aqueous solution was extracted with Et₂O (3 $\times$), acidified by dropwise addition of 6M aqueous HCl to pH = 3 and extracted with EtOAc (3 $\times$). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The obtained Cbz-AA-OH (**6a-i**) (1 equiv.) was added without further purification to a mixture of **5** (1 equiv.) in CH₂Cl₂ (0.1 M) along with BOP (1.2 equiv.) and DIPEA (1.5 equiv.) at 0 °C. After stirring the mixture for 3 h the reaction was quenched with saturated aqueous NaHCO₃. The aqueous layer was separated and extracted with CH₂Cl₂. The combined organic layers were washed with brine and dried over Na₂SO₄ before concentrating *in vacuo*.

(S)-Methyl 2-(2-(benzyloxycarbonylamino)acetamido)-5-(1,3-dioxolan-2-yl)pentanoate (7a)

L-Allysine ethylene acetal methyl ester **5** (1.70 mmol) was coupled with Cbz-Gly-OH **6a** (356 mg, 1.70 mmol) according to general procedure **I**. The crude product was purified by column chromatography (EtOAc:heptane = 3:1) yielding dipeptide **7a** (468 mg, 1.19 mmol, 70%) as a colorless oil. R_f = 0.20. $[\alpha]_D^{20}$ +14.0 (c 0.66, CH_2Cl_2). ^1H NMR (CDCl_3 , 300 MHz) δ 7.32-7.24 (m, 5H), 7.19 (d, J = 7.6 Hz, 1H), 6.09 (t, J = 5.5 Hz, 1H), 5.08 (br s, 2H), 4.78 (t, J = 4.5 Hz, 1H), 4.52 (dt, J = 7.9, 5.3 Hz, 1H), 3.93-3.74 (m, 6H), 3.67 (s, 3H), 1.89-1.78 (m, 1H), 1.75-1.56 (m, 3H), 1.46-1.34 (m, 2H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.4, 169.1, 156.5, 135.9, 128.2, 127.9, 127.7, 103.4, 67.0, 64.7, 53.6, 52.4, 52.3, 44.3, 33.2, 31.8, 20.0. IR ν 3322, 2952, 2357, 1719, 1663, 1525, 1232, 1138, 840, 694, 556. HRMS (FAB^+): calcd for $\text{C}_{19}\text{H}_{27}\text{N}_2\text{O}_7$ ($M+\text{H}^+$): 395.1818, found: 395.1810.

(S)-Methyl 2-((S)-2-(benzyloxycarbonylamino)propanamido)-5-(1,3-dioxolan-2-yl)pentanoate (7b)

L-Allysine ethylene acetal methyl ester **5** (1.70 mmol) was coupled with Cbz-L-Ala-OH **6b** (379 mg, 1.70 mmol) according to general procedure **I**. The crude product was purified by column chromatography (EtOAc:heptane = 2:1) yielding dipeptide **7b** (502 mg, 1.22 mmol, 72%) as a white solid. R_f = 0.27. M.p. 132 °C. $[\alpha]_D^{20}$ +2.1 (c 0.43, CH_2Cl_2). ^1H NMR (CDCl_3 , 300 MHz) δ 7.36-7.26 (m, 5H), 6.58 (d, J = 6.1 Hz, 1H), 5.40 (d, J = 5.3 Hz, 1H), 5.10 (s, 2H), 4.80 (t, J = 4.6 Hz, 1H), 4.58-4.51 (m, 1H), 4.31-4.26 (m, 1H), 3.94-3.81 (m, 2H), 3.82-3.77 (m, 2H), 3.72 (s, 3H), 1.94-1.82 (m, 1H), 1.77-1.62 (m, 3H), 1.51-1.37 (m, 5H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.5, 171.9, 155.9, 136.3, 128.7, 128.3, 128.2, 104.3, 67.4, 65.2, 52.8, 52.6, 50.9, 33.6, 32.5, 20.3, 19.1. IR ν 3300, 3058, 2954, 2859, 1740, 1688, 1645, 1528, 1204, 1122, 1044, 694. HRMS (FAB^+): calcd for $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_7$ ($M+\text{H}^+$): 409.1975, found: 409.1976.

(S)-Methyl 2-((R)-2-(benzyloxycarbonylamino)propanamido)-5-(1,3-dioxolan-2-yl)pentanoate (7c)

L-Allysine ethylene acetal methyl ester **5** (1.70 mmol) was coupled with Cbz-D-Ala-OH **6c** (376 mg, 1.68 mmol) according to general procedure **I**. The crude product was purified by column chromatography (EtOAc:heptane = 2:1) yielding dipeptide **7c** (515 mg, 1.26 mmol, 75%) as a white solid. R_f = 0.27.

M.p. 79.9 °C. $[\alpha]_D^{20} +28.7$ (*c* 0.96, CH₂Cl₂). ¹H NMR (CDCl₃, 300 MHz) δ 7.36-7.26 (m, 5H), 6.75 (d, *J* = 6.3 Hz, 1H), 5.48 (d, *J* = 7.0 Hz, 1H), 5.10 (s, 2H), 4.80 (t, *J* = 4.6 Hz, 1H), 4.58-4.51 (m, 1H), 4.31-4.26 (m, 1H), 3.94-3.81 (m, 2H), 3.82-3.77 (m, 2H), 3.72 (s, 3H), 1.94-1.82 (m, 2H), 1.77-1.62 (m, 2H), 1.51-1.37 (m, 5H). ¹³C NMR (CDCl₃, 75 MHz) δ 172.6, 172.2, 156.0, 136.3, 128.6, 128.3, 128.1, 104.3, 67.4, 65.2, 52.8, 52.5, 50.9, 33.6, 32.4, 20.3, 19.2. IR ν 3663, 3309, 2964, 2896, 2353, 1711, 1659, 1388, 1241, 1052, 888, 690. HRMS (FAB⁺): calcd for C₂₀H₂₉N₂O₇ (*M*+H⁺): 409.1975, found: 409.1990.

(S)-Methyl 2-((S)-2-(benzyloxycarbonylamino)-3-methylbutanamido)-5-(1,3-dioxolan-2-yl)pentanoate (7d)

L-Allysine ethylene acetal methyl ester **5** (1.70 mmol) was coupled with Cbz-L-Val-OH **6d** (428 mg, 1.70 mmol) according to general procedure **I**. The crude product was purified by column chromatography (EtOAc:heptane = 3:2) yielding the dipeptide **7d** (527 mg, 1.20 mmol, 69%) as a white solid. *R_f* = 0.34. M.p. 145.0 °C. $[\alpha]_D^{20} +0.6$ (*c* 0.80, CH₂Cl₂). ¹H NMR (CDCl₃, 300 MHz) δ 7.34-7.28 (m, 5H), 6.28 (d, *J* = 7.8 Hz, 1H), 5.32 (d, *J* = 8.8 Hz, 1H), 5.10 (s, 2H), 4.81 (t, *J* = 4.6 Hz, 1H), 4.56 (dt, *J* = 7.6, 5.3 Hz, 1H), 4.03-3.98 (m, 1H), 3.95-3.90 (m, 2H), 3.83-3.78 (m, 2H), 3.73 (s, 3H), 2.18-2.08 (m, 1H), 1.93-1.83 (m, 1H), 1.81-1.63 (m, 3H), 1.50-1.40 (m, 2H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ 172.5, 170.9, 156.4, 136.4, 128.7, 128.3, 128.1, 104.3, 67.4, 65.2, 60.6, 52.8, 52.6, 33.6, 32.4, 31.8, 20.3, 19.6, 18.2. IR ν 3296, 3032, 2954, 2876, 1735, 1692, 1640, 1528, 1242, 1143, 1044, 698. HRMS (FAB⁺): calcd for C₂₂H₃₃N₂O₇ (*M*+H⁺): 437.2288, found: 437.2271.

(S)-Methyl 2-((R)-2-(benzyloxycarbonylamino)-3-methylbutanamido)-5-(1,3-dioxolan-2-yl)pentanoate (7e)

L-Allysine ethylene acetal methyl ester **5** (1.70 mmol) was coupled with Cbz-D-Val-OH **6e** (430 mg, 1.71 mmol) according to general procedure **I**. The crude product was purified by column chromatography (EtOAc:heptane = 3:2) yielding dipeptide **7e** (537 mg, 1.20 mmol, 72%) as a white solid. *R_f* = 0.34. M.p. 143.8 °C. $[\alpha]_D^{20} +9.1$ (*c* 1.02, CH₂Cl₂). ¹H NMR (CDCl₃, 300 MHz) δ 7.34-7.28 (m, 5H), 6.39 (d, *J* = 8.0 Hz, 1H), 5.30 (d, *J* = 8.8 Hz, 1H), 5.10 (s, 2H), 4.80 (t, *J* = 4.5 Hz, 1H), 4.57 (dt, *J* = 7.5, 5.5 Hz, 1H), 4.07-4.02 (m, 1H), 3.95-3.87 (m, 2H), 3.86-3.78 (m, 2H), 3.72 (s, 3H), 2.21-2.11 (m, 1H), 1.94-1.83 (m, 1H), 1.78-1.62 (m, 3H), 1.51-1.37 (m, 2H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ 172.5, 171.1, 156.4, 136.3, 128.6, 128.2, 128.1, 104.2, 67.3, 65.1, 60.5, 52.7, 52.5, 33.6, 32.4, 31.6, 20.3, 19.7, 18.1. IR ν 3300, 3067, 2950, 2863, 1735, 1692, 1645, 1532, 1243, 1139, 1040, 698. HRMS (FAB⁺): calcd for C₂₂H₃₃N₂O₇ (*M*+H⁺): 437.2288, found: 437.2291.

(S)-Methyl 2-((S)-2-(benzyloxycarbonylamino)-3-phenylpropanamido)-5-(1,3-dioxolan-2-yl)pentanoate (7f)

L-Allysine ethylene acetal methyl ester **5** (1.22 mmol) was coupled with Cbz-L-Phe-OH **6f** (360 mg, 1.20 mmol) according to general procedure **I**. The crude product was purified by column chromatography (EtOAc:heptane = 3:2) yielding dipeptide **7f** (461 mg, 0.95 mmol, 79%) as a white solid. R_f = 0.35. M.p. 119.6 °C. $[\alpha]_D^{20}$ +5.8 (c 0.38, CH₂Cl₂). ¹H NMR (CDCl₃, 400 MHz) δ 7.35-7.15 (m, 10H), 6.23 (d, J = 7.2 Hz, 1H), 5.26 (br s, 1H), 5.08 (s, 2H), 4.77 (t, J = 4.6 Hz, 1H), 4.50 (dt, J = 7.3, 5.7 Hz, 1H), 4.45-4.38 (m, 1H), 3.96-3.77 (m, 4H), 3.69 (s, 3H), 3.15-3.00 (m, 2H), 1.88-1.76 (m, 1H), 1.72-1.57 (m, 3H), 1.40-1.25 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz) δ 171.7, 170.2, 155.5, 136.0, 135.9, 129.1, 128.3, 128.2, 127.9, 127.7, 126.7, 103.6, 67.0, 64.7, 56.0, 52.3, 52.3, 38.5, 33.2, 32.1, 29.8, 19.8. IR ν 3278, 3092, 2954, 1735, 1688, 1643, 1528, 1276, 1242, 1036, 841, 746. HRMS (FAB⁺): calcd for C₂₆H₃₃N₂O₇ (M +H⁺): 485.2288, found: 485.2276.

(S)-Methyl 2-((R)-2-(benzyloxycarbonylamino)-3-phenylpropanamido)-5-(1,3-dioxolan-2-yl)pentanoate (7g)

L-Allysine ethylene acetal methyl ester **5** (1.22 mmol) was coupled with Cbz-D-Phe-OH **6g** (359 mg, 1.20 mmol) according to general procedure **I**. The crude product was purified by column chromatography (EtOAc:heptane = 1:1) yielding dipeptide **7g** (454 mg, 0.94 mmol, 78%) as a white solid. R_f = 0.25. M.p. 110.1 °C. $[\alpha]_D^{20}$ +1.8 (c 0.27, CH₂Cl₂). ¹H NMR (CDCl₃, 300 MHz) δ 7.36-7.16 (m, 10H), 6.16 (d, J = 7.9 Hz, 1H), 5.29 (br s, 1H), 5.07 (s, 2H), 4.76 (t, J = 4.7 Hz, 1H), 4.48 (dt, J = 7.3, 5.7 Hz, 1H), 4.46-4.36 (m, 1H), 3.95-3.79 (m, 4H), 3.68 (s, 3H), 3.13-2.99 (m, 2H), 1.76-1.64 (m, 1H), 1.62-1.50 (m, 3H), 1.30-1.20 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz) δ 171.9, 170.0, 129.1, 128.6, 128.3, 128.0, 127.9, 126.9, 104.0, 96.6, 95.3, 67.1, 64.9, 52.5, 52.2, 38.9, 33.3, 32.2, 19.9. IR ν 3296, 3058, 2954, 2859, 1740, 1692, 1640, 1532, 1234, 1126, 1031, 694. HRMS (FAB⁺): calcd for C₂₆H₃₃N₂O₇ (M +H⁺): 485.2288, found: 485.2279.

(S)-Methyl 2-((S)-2-(benzyloxycarbonylamino)pent-4-enamido)-5-(1,3-dioxolan-2-yl)pentanoate (7h)

L-Allysine ethylene acetal methyl ester **5** (1.70 mmol) was coupled with Cbz-L-Alg-OH **6h** (424 mg, 1.70 mmol) according to general procedure **I**. The crude product was purified by column chromatography (EtOAc:heptane = 3:2) yielding dipeptide **7h** (532 mg, 1.22 mmol, 72%) as a white solid. R_f = 0.34. M.p. 132.5 °C. $[\alpha]_D^{20}$ 0 (c 0.49, CH₂Cl₂). ¹H NMR (CDCl₃, 300 MHz) δ 7.34-7.26 (m, 5H), 6.50 (d, J = 7.6 Hz, 1H), 5.80-5.67 (m, 1H), 5.17-5.14 (m, 1H), 5.11 (s, 3H), 4.80 (t, J = 4.6 Hz, 1H), 4.55 (dt, J = 7.6, 5.4 Hz, 1H), 4.27-4.20 (m, 1H), 3.95-3.87 (m, 2H), 3.86-3.78 (m, 2H), 3.72 (s, 3H), 2.54-2.50 (m, 2H), 1.95-1.83 (m, 1H), 1.78-1.70 (m, 1H), 1.69-1.62 (m, 3H), 1.53-1.36 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz) δ 172.2, 170.5, 155.8, 136.0, 132.6, 128.4, 128.1, 128.0, 119.3, 104.1, 67.3, 65.0, 54.3, 52.6, 52.4, 37.2, 33.4, 32.3, 20.0. IR ν 3296, 3057, 2949, 2880, 1740, 1692, 1640, 1537, 1428, 1385, 1255, 1208, 1039, 690. HRMS (FAB⁺): calcd for C₂₂H₃₁N₂O₇ ($M+H^+$): 435.2131, found: 435.2128.

(S)-Methyl 2-((R)-2-(benzyloxycarbonylamino)pent-4-enamido)-5-(1,3-dioxolan-2-yl)pentanoate (7i)

L-Allysine ethylene acetal methyl ester **5** (1.70 mmol) was coupled with Cbz-D-Alg-OH **6i** (424 mg, 1.70 mmol) according to general procedure **I**. The crude product was purified by column chromatography (EtOAc:heptane = 3:2) yielding dipeptide **7i** (561 mg, 1.29 mmol, 76%) as a white solid. R_f = 0.34. M.p. 100.0 °C. $[\alpha]_D^{20}$ +15.9 (c 0.78, CH₂Cl₂). ¹H NMR (CDCl₃, 300 MHz) δ 7.33-7.28 (m, 5H), 6.55 (br s, 1H), 5.80-5.66 (m, 1H), 5.30 (br s, 1H), 5.16-5.15 (m, 1H), 5.10 (s, 3H), 4.80 (t, J = 4.5 Hz, 1H), 4.55 (dt, J = 7.6, 5.4 Hz, 1H), 4.30-4.23 (m, 1H), 3.95-3.87 (m, 2H), 3.86-3.78 (m, 2H), 3.71 (s, 3H), 2.58-2.48 (m, 2H), 1.93-1.81 (m, 1H), 1.76-1.62 (m, 3H), 1.53-1.36 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz) δ 172.5, 170.7, 156.0, 136.1, 132.6, 128.5, 128.2, 128.0, 119.3, 104.0, 67.1, 64.8, 54.1, 52.4, 52.1, 36.9, 33.1, 31.9, 19.7. IR ν 3291, 3067, 2950, 1731, 1688, 1645, 1532, 1230, 1048, 694. HRMS (FAB⁺): calcd for C₂₂H₃₁N₂O₇ ($M+H^+$): 435.2131, found: 435.2134.

General procedure II: Tandem-cyclizations catalyzed by TsOH.

A solution of the cyclization precursor and TsOH (10 mol%) in toluene (0.1 M) was stirred at reflux temperature for 1 h. After cooling to room temperature the solution was washed with saturated aqueous NaHCO₃ and dried over Na₂SO₄. The solvent was evaporated *in vacuo* yielding the crude product as a mixture of diastereomers, which was analyzed by HPLC to determine the diastereomeric ratio.

General procedure III: Cbz-deprotections with HBr.

The *trans/cis* mixtures of *N*-Cbz-protected cyclic dipeptides were dissolved in a solution of HBr (33 wt%) in glacial acetic acid (0.1 M). After stirring for 1 h at room temperature the reaction mixture was concentrated *in vacuo*. The crude product was dissolved in water and washed twice with diethyl ether. Removal of the water under pressure yielded the HBr salt of the product, as an unchanged mixture of *trans/cis*-isomers.

(5*S*)-Methyl 3-oxooctahydroimidazo[1,2-*a*]pyridine-5-carboxylate hydrobromide (9a**)**

According to general procedure **II** dipeptide **7a** (110 mg, 0.28 mmol) afforded **8a** (76 mg, 0.23 mmol, 82%) after purification by flash column chromatography (R_f = 0.40, EtOAc/heptane 1:1) as a colorless oil with a d.r. of 5:1 (*trans*-**8a**:*cis*-**8a**). According to general procedure **III** the mixture of diastereomers **8a** (36 mg, 0.11 mmol) was deprotected yielding the corresponding *trans/cis* mixture of **9a** (31 mg, 0.11 mmol, 99%) as a light yellow oil. *trans*-**9a**: ^1H NMR (D_2O , 300 MHz) δ 5.12 (dd, J = 11.3, 4.0 Hz, 1H), 4.93 (d, J = 5.5 Hz, 1H), 4.07 (d, J = 15.8 Hz, 1H), 3.94 (d, J = 15.8 Hz, 1H), 3.72 (s, 3H), 2.29-2.16 (m, 2H), 1.97-1.86 (m, 1H), 1.76-1.56 (m, 2H), 1.49-1.33 (m, 1H).

(2*S*,5*S*,8*aR*)-1-Benzyl 5-methyl 2-methyl-3-oxohexahydroimidazo[1,2-*a*]pyridine-1,5(*5H*)-dicarboxylate (*trans*-8b**) and (2*S*,5*S*,8*aS*)-1-Benzyl 5-methyl 2-methyl-3-oxohexahydroimidazo[1,2-*a*]pyridine-1,5(*5H*)-dicarboxylate (*cis*-**8b**)**

According to general procedure **II** dipeptide **7b** (139 mg, 0.34 mmol) afforded **8b** (92 mg, 0.27 mmol, 79%) after purification by flash column chromatography (R_f = 0.39, EtOAc:heptane = 1:1) as a colorless oil with a d.r. of 15:1 (*trans*-**8b**:*cis*-**8b**). The two diastereomers were separated by preparative HPLC (eluent: 45% acetonitrile; flow: 20 mL/min, t_R = 6.43 (*cis*-**8b**), 7.11 (*trans*-**8b**)).

trans-**8b**: $[\alpha]_D^{20}$ -4.6 (c 0.33, CH_2Cl_2). ^1H NMR (CDCl_3 , 400 MHz) δ 7.40-7.31 (m, 5H), 5.25-5.11 (m, 3H), 5.04 (d, J = 5.8 Hz, 1H), 4.27 (br s, 1H), 3.75 (s, 3H), 2.59-2.31 (m, 1H), 2.27-2.16 (m, 1H), 1.87-1.74 (m, 1H), 1.66-1.57 (m, 1H), 1.49 (br s, 4H), 1.18-1.10 (m, 1H). ^{13}C NMR (CD_3CN , 75 MHz) δ 171.5, 169.9, 155.1, 137.8, 129.7, 129.5, 129.4, 129.2, 128.9, 70.5, 68.2, 66.7, 55.9, 55.7, 53.6, 52.5, 34.3, 27.5, 27.3, 20.5, 16.2. IR ν 3027, 2941, 2353, 1753, 1701, 1398, 1355, 1277, 1203, 1117, 1027, 689. HRMS (FAB^+): calcd for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_5$ ($M+\text{H}^+$): 347.1607, found: 347.1606.

cis-**8b**: R_f = 0.39. $[\alpha]_D^{20}$ -24.7 (c 0.1, CH_2Cl_2). ^1H NMR (CD_3CN , 300 MHz) δ 7.37-7.31 (m, 5H), 5.19-5.08 (m, 2H), 4.98-4.87 (m, 1H), 4.05 (dq, J = 6.6, 1.7 Hz, 1H), 3.89-3.78 (m, 1H), 3.68 (s, 3H), 2.66-2.56 (m, 0.5H, rotamer), 2.43-2.36 (m, 0.5H, rotamer), 1.90-1.78 (m, 2H), 1.67-1.50 (m, 2H), 1.45-1.33 (m, 3H), 1.27 (br s, 1H). IR ν 2993, 2941, 2855, 2358, 1748, 1709, 1407, 1359, 1303, 1203, 1126, 1026, 694. HRMS (FAB^+): calcd for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_5$ ($M+\text{H}^+$): 347.1607, found: 347.1604.

A ^1H NMR NOESY experiment on *cis*-**8b** showed a strong spatial relationship between protons H^5 and H^{8a} , which was not observed with *trans*-**8b**.

(2*R*,5*S*,8*aR*)-1-Benzyl 5-methyl 2-methyl-3-oxohexahydroimidazo[1,2-*a*]pyridine-1,5(5*H*)-dicarboxylate (*trans*-8c**) and (2*R*,5*S*,8*aS*)-1-Benzyl 5-methyl 2-methyl-3-oxohexahydroimidazo[1,2-*a*]pyridine-1,5(5*H*)-dicarboxylate (*cis*-**8c**)**

According to general procedure **II** dipeptide **7c** (139 mg, 0.34 mmol) afforded **8c** (90 mg, 0.26 mmol, 76%) after purification by flash column chromatography (R_f = 0.39 and 0.33, EtOAc:heptane = 1:1) as a colorless oil with a d.r. of 2:1 (*trans*-**8c**:*cis*-**8c**). The two diastereomers were separated by preparative HPLC (eluent: 40% acetonitrile; flow: 20 mL/min, t_R = 9.78 (*cis*-**8c**), 10.87 (*trans*-**8c**)).

trans-**8c**: $[\alpha]_D^{20}$ -66.3 (c 0.61, CH_2Cl_2). ^1H NMR (CD_3CN , 300 MHz) δ 7.38-7.29 (m, 5H), 5.20-5.08 (m, 2H), 5.08-5.03 (m, 1H), 4.94-4.83 (m, 1H), 4.12 (dq, J = 6.6, 2.0 Hz, 1H), 3.70 (s, 3H), 2.70-2.55 (m, 0.5H, rotamer), 2.48-2.37 (m, 0.5H, rotamer), 2.19-2.06 (m, 1H), 1.82-1.70 (m, 1H), 1.66-1.36 (m, 5H), 1.28-1.09 (m, 1H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 170.0, 169.3, 169.1, 153.1, 135.7, 128.4, 128.1, 128.0, 127.9, 69.1, 68.8, 67.4, 67.3, 54.7, 54.6, 52.7, 51.0, 32.1, 31.1, 26.3, 26.2, 19.5, 17.7, 17.6, 16.5. IR ν 3464, 2924, 2358, 2336, 1701, 1398, 1204, 1130, 1018, 698. HRMS (FAB^+): calcd for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_5$ ($M+\text{H}^+$): 347.1607, found: 347.1609.

cis-**8c**: ^1H NMR (CD_3CN , 400 MHz) δ 7.39-7.33 (m, 5H), 5.12 (br s, 2H), 4.93 (dd, J = 7.5, 3.2 Hz, 1H), 4.11 (dq, J = 6.8, 0.7 Hz, 1H), 3.88-3.86 (m, 1H), 3.69 (s, 3H), 2.36-2.29 (m, 1H), 1.89-1.79 (m, 2H), 1.69-1.54 (m, 2H), 1.37 (d, J = 6.8 Hz, 3H), 1.32-1.23 (m, 1H). ^{13}C NMR (CD_3CN , 75 MHz) δ 170.2, 169.3, 154.9, 137.7, 129.5, 129.0, 128.7, 72.4, 68.0, 67.9, 56.7, 56.0, 52.9, 33.8, 33.7, 27.6, 21.4, 20.4. IR ν 3477, 2950, 2357, 1701, 1407, 1295, 1200, 1121, 1035, 754, 694. HRMS (FAB^+): calcd for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_5$ ($M+\text{H}^+$): 347.1607, found: 347.1608.

A ^1H NMR NOESY experiment on *cis*-**8c** showed a strong spatial relationship between protons H^5 and H^{8a} , which was not observed with *trans*-**8c**.

(2*S*,5*S*)-Methyl-2-isopropyl-3-oxooctahydroimidazo[1,2-*a*]pyridine-5-carboxylate hydrobromide (9d**)**

According to general procedure **II** dipeptide **7d** (178 mg, 0.41 mmol) afforded **8d** (117 mg, 0.31 mmol, 76%) after purification by flash column chromatography (R_f = 0.26, EtOAc:heptane = 1:2) as a colorless oil with a d.r. of 9:1 (*trans*-**8d**:*cis*-**8d**). According to general procedure **III** the mixture of diastereomers **8d** (34 mg, 0.09 mmol) was deprotected yielding the corresponding *trans/cis* mixture of **9d** (28 mg, 0.08 mmol, 97%) as a light yellow oil. *trans*-**9d**: ^1H NMR (D_2O , 300 MHz) δ 4.99 (dd, J = 11.3, 3.8 Hz, 1H), 4.90 (d, J = 5.9 Hz, 1H), 4.16 (d, J = 6.0 Hz, 1H), 3.71 (s, 3H), 2.36-2.18 (m, 3H), 1.98-1.86 (m, 1H), 1.78-1.56 (m, 2H), 1.47-1.29 (m, 1H), 1.10 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H).

(2*R*,5*S*)-Methyl-2-isopropyl-3-oxooctahydroimidazo[1,2-*a*]pyridine-5-carboxylate hydrobromide (7e**)**

According to general procedure **II** dipeptide **7e** (153 mg, 0.35 mmol) afforded **8e** (104 mg, 0.28 mmol, 80%) after purification by flash column chromatography (R_f = 0.26 and 0.21, EtOAc:heptane = 1:2) as a colorless oil with a d.r. of 4:1 (*trans*-**8e**:*cis*-**8e**). According to general procedure **III** the mixture of diastereomers **8e** (51 mg, 0.14 mmol) was deprotected yielding the corresponding *trans/cis* mixture of **9e** (42 mg, 0.13 mmol, 98%) as a light yellow oil. *trans*-**9e**: ^1H NMR (CD_3OD , 300 MHz) δ 5.12 (dd, J = 11.2, 3.7 Hz, 1H), 4.95 (d, J = 6.2 Hz, 1H), 4.07 (dd, J = 4.2, 0.5 Hz, 1H), 3.79 (s, 3H), 2.51-2.35 (m, 1H), 2.33-2.21 (m, 2H), 2.06-1.95 (m, 1H), 1.85-1.64 (m, 2H), 1.60-1.43 (m, 1H), 1.24 (m, 6H).

(2*S*,5*S*)-Methyl 2-benzyl-3-oxooctahydroimidazo[1,2-*a*]pyridine-5-carboxylate hydrobromide (7f**)**

According to general procedure **II** dipeptide **7f** (143 mg, 0.30 mmol) afforded **8f** (110 mg, 0.16 mmol, 87%) after purification by flash column chromatography (R_f = 0.22, EtOAc:heptane = 1:2) with a d.r. of 13:1 (*trans*-**8f**:*cis*-**8f**) as a colorless oil. To a solution of the mixture of diastereomers **8f** (157 mg, 0.37 mmol) in EtOAc (25 mL) was added 10% Pd/C (10 mol%). The suspension was allowed to stir overnight at room temperature under an atmosphere of hydrogen. The suspension was filtered over Celite and concentrated *in vacuo* to yield the corresponding *trans/cis* mixture of **9f** (101 mg, 0.35 mmol, 95%) as a colorless oil. *trans*-**9f**: ^1H NMR (CDCl_3 , 300 MHz) δ 7.30-7.18 (m, 5H), 4.77 (d, J = 5.7 Hz, 1H), 4.49 (dd, J = 10.6, 3.5 Hz, 1H), 3.82-3.78 (m, 1H), 3.72 (s, 3H), 3.19 (dd, J = 14.1, 4.2 Hz (AB), 1H), 2.94 (dd, J = 14.1, 7.2 Hz (AB), 1H), 2.19-2.14 (m, 1H), 2.00-1.91 (m, 1H), 1.74-1.67 (m, 2H), 1.56-1.44 (m, 1H), 1.41-1.27 (m, 1H), 0.83-0.70 (m, 1H).

(2*R*,5*S*)-Methyl 2-benzyl-3-oxooctahydroimidazo[1,2-*a*]pyridine-5-carboxylate hydrobromide (9g**)**

According to general procedure **II** dipeptide **7g** (210 mg, 0.43 mmol) afforded **8g** (161 mg, 0.38 mmol, 88%) after purification by flash column chromatography (R_f = 0.26, EtOAc:heptane = 1:2) as a colorless oil with a d.r. of 1:1 (*trans*-**8g**:*cis*-**8g**). According to general procedure **III** the mixture of diastereomers **8g** (51 mg, 0.12 mmol) was deprotected yielding the corresponding *trans/cis* mixture of **9g** (42 mg, 0.11 mmol, 95%) as a white solid. ^1H NMR (D_2O , 300 MHz, both diastereomers) δ 7.37-7.22 (m, 10H), 4.99 (dd, J = 7.2, 3.9 Hz, 1H), 4.87 (d, J = 5.7 Hz, 1H), 4.77-4.70 (m, 1H), 4.50-4.40 (m, 2H), 4.06-4.01 (m, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.49-3.36 (m, 1H), 3.27 (s, 1H), 3.24 (s, 1H), 3.06-2.97 (m, 1H), 2.16-2.11 (m, 3H), 2.06-1.83 (m, 3H), 1.72-1.51 (m, 4H), 1.49-1.29 (m, 2H).

(2*S*,5*S*)-Methyl 2-allyl-3-oxooctahydroimidazo[1,2-*a*]pyridine-5-carboxylate hydrobromide (9h**)**

According to general procedure **II** dipeptide **7h** (172 mg, 0.40 mmol) afforded **8h** (114 mg, 0.31 mmol, 78%) after purification by flash column chromatography (R_f = 0.43, EtOAc:heptane = 1:1) as a colorless oil with a d.r. of 15:1 (*trans*-**8h**:*cis*-**8h**). According to general procedure **III** the mixture of diastereomers **8h** (59 mg, 0.16 mmol) was deprotected yielding the corresponding *trans/cis* mixture of **9h** (31 mg, 0.13 mmol, 82%) as a light yellow oil. *trans*-**9h**: ^1H NMR (D_2O , 300 MHz) δ 5.83-5.70 (m, 1H), 5.29-5.21 (m, 2H), 5.01 (dd, J = 7.4, 3.9 Hz, 1H), 4.89 (d, J = 6.3 Hz, 1H), 4.39 (dd, J = 5.5, 4.2 Hz, 1H), 3.71 (s, 3H), 2.87-2.78 (m, 1H), 2.57-2.46 (m, 1H), 2.27-2.12 (m, 2H), 1.92-1.85 (m, 1H), 1.77-1.57 (m, 2H), 1.45-1.31 (m, 1H).

(2*R*,5*S*)-Methyl 2-allyl-3-oxooctahydroimidazo[1,2-*a*]pyridine-5-carboxylate hydrobromide (9i)

According to general procedure **II** dipeptide **7i** (174 mg, 0.40 mmol) afforded **8i** (104 mg, 0.28 mmol, 70%) after purification by flash column chromatography (R_f = 0.43 and 0.37, EtOAc:heptane = 1:1) as a colorless oil with a d.r. of 1:1 (*trans*-**8i**:*cis*-**8i**). According to general procedure **III** the mixture of diastereomers **8i** (61 mg, 0.16 mmol) was deprotected yielding the corresponding *trans/cis* mixture of **9i** (32 mg, 0.13 mmol, 83%) as a light yellow oil. ^1H NMR (CD_3OD , 300 MHz, both diastereomers) δ 5.94-5.70 (m, 2H), 5.35-5.21 (m, 4H), 5.09-4.97 (m, 2H), 4.77-4.70 (m, 2H), 4.06-4.01 (m, 2H), 3.72 (s, 3H), 3.69 (s, 3H), 2.92-2.75 (m, 2H), 2.58-2.43 (m, 2H), 2.28-2.14 (m, 4H), 1.92-1.84 (m, 2H), 1.79-1.58 (m, 4H), 1.48-1.32 (m, 2H).

(*S*)-Methyl 2-((*S*)-3-(benzyloxycarbonylamino)-3-phenylpropanamido)-5-(1,3-dioxolan-2-yl)pentanoate (10a)

L-Allysine ethylene acetal methyl ester **5** (1.10 mmol) was coupled with Cbz-3-(*S*)- β -Phe-OH (306 mg, 1.02 mmol) according to general procedure **I**. The crude product was purified by column chromatography (R_f = 0.27, EtOAc:heptane = 2:1) yielding dipeptide **10a** (431 mg, 0.89 mmol, 89%) as a white solid. M.p. 109.2 °C. $[\alpha]_D^{20}$ -6.5 (c 0.62, CH_2Cl_2). ^1H NMR (CDCl_3 , 300 MHz) δ 7.45-7.19 (m, 10H), 6.62 (br s, 1H), 6.03 (d, J = 7.4 Hz, 1H), 5.18-5.05 (m, 3H), 4.72 (t, J = 4.8 Hz, 1H), 4.47 (dt, J = 5.2, 7.1 Hz, 1H), 3.98-3.88 (m, 2H), 3.86-3.78 (m, 2H), 3.71 (s, 3H), 2.83-2.69 (m, 2H), 1.77-1.59 (m, 1H), 1.58-1.44 (m, 3H), 1.31-1.09 (m, 2H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 170.9, 166.8, 154.3, 141.8, 135.9, 128.6, 128.5, 128.3, 127.9, 127.5, 126.1, 104.1, 66.7, 64.8, 52.5, 52.4, 52.0, 38.3, 33.1, 31.8, 19.6. IR ν 3334, 3058, 2946, 1739, 1709, 1670, 1528, 1333, 1199, 1022, 741, 702. HRMS (ESI $^+$): calcd for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_7\text{Na}$ ($M+\text{Na}^+$): 507.2107, found: 507.2095.

(*S*)-Methyl 2-((*R*)-3-(benzyloxycarbonylamino)-3-phenylpropanamido)-5-(1,3-dioxolan-2-yl)pentanoate (10b)

L-Allysine ethylene acetal methyl ester **5** (1.70 mmol) was coupled with Cbz-3-(*R*)- β -Phe-OH (509 mg, 1.70 mmol) according to general procedure **I**. The crude product was purified by column chromatography (R_f = 0.25, EtOAc:heptane = 2:1) yielding dipeptide **10b** (610 mg, 1.26 mmol, 74%) as a white solid. M.p. 116.0 °C. $[\alpha]_D^{20}$ +17.3 (c 0.15, CH_2Cl_2). ^1H NMR (CDCl_3 , 300 MHz) δ 7.37-7.22 (m, 10H), 6.24 (br s, 1H), 6.07 (d, J = 7.7 Hz, 1H), 5.14-5.03 (m, 3H), 4.78 (t, J = 4.6 Hz, 1H), 4.48 (dt, J = 5.4, 7.5 Hz, 1H), 3.95-3.87 (m, 2H), 3.86-3.78 (m, 2H), 3.67 (s, 3H), 2.77-2.74 (m, 2H), 1.84-1.72 (m, 1H), 1.68-1.55 (m, 3H), 1.37-1.24 (m, 2H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.5, 169.9, 155.8, 141.1, 136.4, 128.6, 128.5, 128.3, 127.9, 127.4, 126.1, 104.0, 66.7, 64.8, 52.4, 52.3, 52.0, 42.3, 42.4, 33.1, 31.8, 19.6. IR ν 3304, 3058, 2946, 1731, 1684, 1640, 1532, 1260, 1139, 1027, 836, 694. HRMS (FAB $^+$): calcd for $\text{C}_{26}\text{H}_{33}\text{N}_2\text{O}_7$ ($M+\text{H}^+$): 485.2288, found: 485.2276.

(2*S*,6*S*)-1-Benzyl 6-methyl 4-oxo-2-phenylhexahydro-1*H*-pyrido[1,2-*a*]pyrimidine-1,6(2*H*,6*H*)-dicarboxylate (11a)

According to general procedure **II** dipeptide **10a** (210 mg, 0.43 mmol) afforded **11a** (153 mg, 0.36 mmol, 84%) after purification by flash column chromatography (R_f = 0.33, EtOAc:heptane = 1:1) as a colorless oil with a d.r. of 19:1 (*trans*-11a:*cis*-11a). *trans*-11a: ^1H NMR (CDCl_3 , 300 MHz) δ 7.39-7.24 (m, 5H), 7.23-7.15 (m, 5H), 6.96-6.94 (m, 2H), 5.62-5.60 (m, 1H), 5.41-5.32 (m, 2H), 5.09-4.94 (m, 2H), 3.80 (s, 3H), 2.96 (dd, J = 16.3, 6.3 Hz, (AB), 1H), 2.76 (dd, J = 16.3, 2.5 Hz, (AB), 1H), 2.45-2.40 (m, 1H), 2.22-2.17 (m, 1H), 1.88-1.77 (m, 1H), 1.76-1.52 (m, 3H), 1.48-1.33 (m, 1H).

(2*R*,6*S*,9*aR*)-1-Benzyl 6-methyl 4-oxo-2-phenylhexahydro-1*H*-pyrido[1,2-*a*]pyrimidine-1,6(2*H*,6*H*)-dicarboxylate (11b)

According to general procedure **II** dipeptide **10b** (146 mg, 0.30 mmol) afforded **11b** (107 mg, 0.25 mmol, 84%) after purification by flash column chromatography (R_f = 0.33, EtOAc/heptane = 1:1) as a colorless oil as a single diastereomer. $[\alpha]_D^{20}$ -28.5 (c 0.49, CH_2Cl_2). ^1H NMR (CDCl_3 , 300 MHz) δ 7.39-7.34 (m, 5H), 7.32-7.25 (m, 5H), 5.86 (d, J = 5.8 Hz, 1H), 5.63 (d, J = 3.7 Hz, 1H), 5.44 (dd, J = 11.5, 2.8 Hz, 1H), 5.32-5.23 (m, 2H), 3.72 (s, 3H), 3.09 (dd, J = 17.3, 1.8 Hz, (AB), 1H), 2.95 (dd, J = 17.3, 6.5 Hz, (AB), 1H), 2.17-2.06 (m, 1H), 1.66-1.57 (m, 1H), 1.50-1.42 (m, 1H), 1.36-1.23 (m, 3H). HRMS (FAB^+): calcd for $\text{C}_{24}\text{H}_{27}\text{N}_2\text{O}_5$ ($M+\text{H}^+$): 423.1920, found: 423.1928.

(*S*)-Methyl 2-(2-aminobenzamido)-5-(1,3-dioxolan-2-yl)pentanoate (13)

A suspension of Cbz-protected L-allysine ethylene acetal methyl ester (674 mg, 2.0 mmol) and 10% Pd/C (10 mol% Pd) in EtOAc (20 mL) was stirred under an atmosphere of hydrogen for 4 h at room temperature. The reaction mixture was filtered over Celite and the solvent was evaporated *in vacuo*. The liberated amine (**5**) was dissolved in CH_2Cl_2 (20 mL) and anthranilic acid (270 mg, 1.97 mmol) was added after cooling to 0 °C along with BOP (955 mg, 2.20 mmol) and DIPEA (450 μL , 2.60 mmol). After stirring the solution for 4 h at room temperature the reaction was quenched with saturated aqueous NH_4Cl solution (15 mL). The solution was extracted with CH_2Cl_2 (3 $\times$ 15 mL) and the organic layers were washed with saturated aqueous NaCl and dried over Na_2SO_4 . After filtration the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (R_f = 0.42, EtOAc:heptane = 2:1) yielding **13** (615 mg, 1.90 mmol, 95%) as a light yellow oil. $[\alpha]_D^{20}$ -3.2 (c 0.47, CH_2Cl_2). ^1H NMR (CDCl_3 , 300 MHz) δ 7.44-7.37 (m, 1H), 7.24-7.19 (m, 1H), 6.68-6.64 (m, 3H), 4.85 (t, J = 4.6 Hz, 1H), 4.76, (dt, J = 7.5, 5.3 Hz,

1H), 4.42 (br s, 2H), 3.99-3.81 (m, 4H), 3.78 (s, 3H), 2.04-1.95 (m, 1H), 1.89-1.79 (m, 1H), 1.74-1.68 (m, 2H), 1.58-1.46 (m, 2H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 173.0, 168.8, 148.7, 132.4, 127.4, 117.1, 116.3, 115.1, 103.9, 64.6, 53.3, 52.3, 52.1, 33.0, 32.0, 19.8, 14.0. IR ν 3456, 3352, 2945, 2353, 1731, 1627, 1515, 1269, 1208, 1143, 1027, 746, 525. HRMS (FAB^+): calcd for $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_5$ ($M+\text{H}^+$): 323.1607, found: 323.1602.

(5a*S*,9*S*)-Methyl 11-oxo-5a,6,7,8,9,11-hexahydro-5*H*-pyrido[2,1-*b*]quinazoline-9-carboxylate (*trans*-14**) and (5a*R*,9*S*)-methyl 11-oxo-5a,6,7,8,9,11-hexahydro-5*H*-pyrido[2,1-*b*]quinazoline-9-carboxylate (*cis*-**14**)**

A solution of dipeptide **13** (121 mg, 0.38 mmol) in acetonitrile (5 mL) was cooled to $-40\text{ }^\circ\text{C}$ under an argon atmosphere before slowly adding $\text{BF}_3\cdot\text{Et}_2\text{O}$ (165 μL , 0.62 mmol). The reaction mixture was stirred overnight during which the temperature was allowed to rise to $0\text{ }^\circ\text{C}$. The reaction was quenched with saturated aqueous NaHCO_3 (5 mL). The aqueous phase was extracted with EtOAc ($3 \times 50\text{ mL}$). The combined organic layers were washed with brine and dried over Na_2SO_4 . After filtration the solvent was removed *in vacuo* and after purification by flash column chromatography ($R_f = 0.51$, EtOAc:heptane = 2:1) **14** (78 mg, 0.30 mmol, 79%) was isolated as a colorless oil with a d.r. of 4:1 (*trans*-**14**:*cis*-**14**). The two diastereomers were separated by preparative HPLC (eluent: 40% acetonitrile; flow: 20 mL/min, $t_R = 3.04$ (*cis*-**14**), 3.93 (*trans*-**14**)).

trans-**14**: $[\alpha]_D^{20} +318.6$ (c 0.63, CH_2Cl_2). ^1H NMR (CD_3CN , 300 MHz) δ 7.71-7.68 (m, 1H), 7.31-7.25 (m, 1H), 6.77-6.67 (m, 2H), 5.23 (s, 1H), 5.08-5.03 (m, 2H), 3.68 (s, 3H), 2.22-2.13 (m, 2H), 2.07-1.99 (m, 1H), 1.78-1.67 (m, 2H), 1.65-1.55 (m, 1H), 1.40-1.25 (m, 1H). ^{13}C NMR (CD_3CN , 75 MHz) δ 172.7, 165.9, 148.4, 134.2, 128.6, 118.8, 115.6, 114.7, 66.7, 53.7, 52.6, 32.2, 26.8, 18.8. IR ν 3299, 2945, 2859, 1731, 1631, 1610, 1506, 1411, 1307, 1199, 1000, 750, 512. HRMS (FAB^+): calcd for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_3$ ($M+\text{H}^+$): 261.1239, found: 261.1234.

cis-**14**: $R_f = 0.36$. $[\alpha]_D^{20} -178.4$ (c 0.19, CH_2Cl_2). ^1H NMR (CD_3CN , 300 MHz) δ 7.71-7.69 (m, 1H), 7.32-7.26 (m, 1H), 6.79-6.70 (m, 2H), 5.38 (br s, 1H), 4.70-4.65 (m, 1H), 3.90 (dd, $J = 11.2, 4.3\text{ Hz}$, 1H), 3.64 (s, 3H), 2.24-2.15 (m, 2H), 2.06-1.98 (m, 1H), 1.78-1.67 (m, 2H), 1.65-1.55 (m, 1H), 1.40-1.25 (m, 1H). IR ν 3299, 2945, 2859, 1731, 1631, 1610, 1506, 1411, 1307, 1199, 1000, 750, 512. HRMS (FAB^+): calcd for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_3$ ($M+\text{H}^+$): 261.1239, found: 261.1237.

A ^1H NMR NOESY experiment on *cis*-**14** showed a strong spatial relationship between protons H^{5a} and H^9 , which was not observed with *trans*-**14**.

(S)-Benzyl 3-(2-(5-(1,3-dioxolan-2-yl)-1-methoxy-1-oxopentan-2-ylamino)-2-oxoethyl)-1H-indole-1-carboxylate (17)

A suspension of the Cbz-protected L-allysine ethylene acetal methyl ester (607 mg, 1.80 mmol) and 10% Pd/C (10 mol% Pd) in EtOAc (20 mL) was stirred under an atmosphere of hydrogen for 4 h at room temperature. Subsequently, the reaction mixture was filtered over Celite and the solvent was evaporated *in vacuo*. The amine (**5**) was dissolved in 20 mL CH₂Cl₂ and Cbz-protected indolylacetic acid **16** (548 mg, 1.80 mmol) was added after cooling to 0 °C along with BOP (882 mg, 2.00 mmol) and DIPEA (700 µL, 4.00 mmol). After stirring the solution for 3 h at room temperature the reaction was quenched with saturated aqueous NaHCO₃ (15 mL). The solution was extracted with CH₂Cl₂ (3 × 15 mL) and the organic layers were washed with brine and dried over Na₂SO₄. After filtration the solvent was evaporated *in vacuo*. Purification by flash column chromatography (*R_f* = 0.40, EtOAc:heptane = 2:1) yielded **17** (650 mg, 1.31 mmol, 73%) as a white solid. M.p. 99.5 °C. [α]_D²⁰ -0.9 (*c* 0.44, CH₂Cl₂). ¹H NMR (CDCl₃, 300 MHz) δ 8.16 (d, *J* = 7.8 Hz, 1H), 7.60 (s, 1H), 7.60-7.45 (m, 3H), 7.44-7.21 (m, 5H), 6.08 (d, *J* = 7.9 Hz, 1H), 5.43 (s, 2H), 4.68 (t, *J* = 4.6 Hz, 1H), 4.57 (dt, *J* = 5.3, 7.7 Hz, 1H), 3.89-3.73 (m, 4H), 3.66 (s, 2H), 3.64 (s, 3H), 1.86-1.75 (m, 1H), 1.65-1.52 (m, 3H), 1.35-1.23 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz) δ 172.2, 169.3, 150.3, 135.4, 134.7, 129.6, 128.6, 128.3, 125.0, 124.2, 123.0, 119.0, 115.2, 114.4, 103.9, 68.8, 64.8, 52.4, 52.3, 33.3, 33.1, 32.0, 19.9. IR ν 3304, 3062, 2958, 2876, 2358, 1744, 1632, 1541, 1455, 1389, 1243, 1079, 1014, 741, 694. HRMS (FAB⁺): calcd for C₂₇H₃₁N₂O₇ (*M*+H⁺): 495.2131, found: 495.2117.

(4S)-12-Benzyl 4-methyl 6-oxo-1,2,3,4,6,7-hexahydroindolo[2,3-a]quinolizine-4,12(12bH)-dicarboxylate (18)

Dipeptide **17** (122 mg, 0.25 mmol) was dissolved in TFA (2 mL) and stirred for 2 h at room temperature. The solution was diluted with EtOAc (2 mL) and washed with saturated aqueous NaHCO₃ (2 mL). The organic layer was dried over Na₂SO₄. Filtration and concentration *in vacuo*, followed by purification by flash column chromatography (*R_f* = 0.35, EtOAc:heptane = 1:1) yielded **18** (66 mg, 0.15 mmol, 61%) as an off-white solid with a d.r. of 80:1 (*cis*-**18**:*trans*-**18**). *cis*-**18**: ¹H NMR (CDCl₃, 300 MHz) δ 8.08 (d, *J* = 7.8 Hz, 1H), 7.48-7.21 (m, 8H), 5.48-5.38 (m, 2H), 5.05 (d, *J* = 10.6 Hz, 1H), 3.73 (s, 3H), 3.71-3.44 (m, 3H), 2.26 (d, *J* = 11.4 Hz, 1H), 2.05-2.01 (m, 1H), 1.91-1.79 (m, 2H), 1.51-1.23 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz) δ 169.2, 167.5, 150.6, 135.8, 134.1, 131.6, 128.9, 128.8, 128.7, 127.4, 125.0, 124.9, 123.3, 118.1, 115.8, 112.4, 61.3, 59.5, 52.1, 35.0, 28.9, 25.6, 23.7. IR ν 3447, 3054, 2941, 2863, 2353, 1735, 1653, 1454, 1286, 1208, 1139, 1022, 750, 694.

A ¹H NMR NOESY experiment on *cis*-**18** showed a strong spatial relationship between protons H^{12b} and H⁴.

(S)-Methyl 2-((R)-2-(benzyloxycarbonylamino)hex-5-enamido)-5-(1,3-dioxolan-2-yl)pentanoate (20)

L-Allysine ethylene acetal methyl ester **5** (14.5 mmol) was coupled with (*S*)-*N*-Cbz-2-amino-5-hexenoic acid **21** (3.8 g, 14.5 mmol) according to general procedure **I**. The crude product was purified by column chromatography (R_f = 0.35, EtOAc:heptane = 2:1) yielding dipeptide **20** (4.0 g, 9.0 mmol, 62%) as a white solid. M.p. 127.2 °C. $[\alpha]_D^{20}$ +3.2 (*c* 0.69, CH₂Cl₂). ¹H NMR (CDCl₃, 400 MHz) δ 7.36-7.29 (m, 5H), 6.56 (d, *J* = 7.5 Hz, 1H), 5.84-5.74 (m, 1H), 5.44 (d, *J* = 5.0 Hz, 1H), 5.14-5.08 (m, 2H), 5.04-4.99 (m, 1H), 4.81 (t, *J* = 4.6 Hz, 1H), 4.57 (dt, *J* = 5.4, 7.7 Hz, 1H), 4.25-4.19 (m, 1H), 3.94-3.88 (m, 2H), 3.85-3.78 (m, 2H), 3.73 (s, 3H), 2.16-2.11 (m, 2H), 1.98-1.84 (m, 2H), 1.78-1.70 (m, 2H), 1.68-1.63 (m, 3H), 1.50-1.38 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz) δ 172.4, 171.3, 155.5, 137.1, 136.2, 128.5, 128.5, 128.1, 127.9, 127.0, 115.8, 104.1, 104.0, 67.0, 64.8, 54.3, 52.6, 52.3, 52.2, 33.0, 31.9, 31.8, 29.4, 19.7. IR ν 3301, 2935, 2866, 1733, 1689, 1642, 1530, 1241, 1043, 694. HRMS (FAB⁺): calcd for C₂₃H₃₃N₂O₇ (*M*+H⁺): 449.2288, found: 449.2280.

(2S,5S,8aR)-1-Benzyl 5-methyl 3-oxo-2-(3-oxopropyl)hexahydroimidazo[1,2-a]pyridine-1,5(5H)-dicarboxylate (21)

According to general procedure **II** dipeptide **20** (2.0 g, 4.57 mmol) afforded **19** (1.6 g, 4.22 mmol, 92%) after purification by flash column chromatography (R_f = 0.28, EtOAc:heptane = 1:2) as a colorless oil with a d.r. of 10:1 (*trans*-**19**:*cis*-**19**). Subsequently, a solution of **19** (768 mg, 1.99 mmol) in CH₂Cl₂ (100 mL) was cooled to -78 °C. Ozone was bubbled through for 10 min. after which the solution became blue. Next, oxygen was bubbled through until the solution became colorless again. Triphenylphosphine was added (765 mg, 2.92 mmol) and the mixture was allowed to warm to room temperature and stirred for 16 h. Evaporation of the solvent and purification by flash column chromatography (R_f = 0.23, EtOAc:heptane = 1:1) afforded **21** (777 mg, 1.99 mmol, 99%) as a colorless oil. **21**: ¹H NMR (CDCl₃, 400 MHz) δ 9.68 (bs, 1H), 7.41-7.32 (m, 5H), 5.23-5.11 (m, 3H), 5.00 (d, *J* = 5.8 Hz, 1H), 4.32 (br s, 1H), 3.75 (s, 3H), 2.69-2.40 (m, 2H), 2.38-2.16 (m, 2H), 1.87-1.80 (m, 1H), 1.68 (br s, 1H), 1.69-1.56 (m, 1H), 1.54-1.43 (m, 1H), 1.29-1.14 (m, 2H).

Tricyclic intermediate 22

To a solution of **21** (540 mg, 1.39 mmol) in EtOAc (20 mL) was added 10% Pd/C (150 mg, 10 mol%). The suspension was allowed to stir for 16 h room temperature under an atmosphere of hydrogen. Next, the suspension was filtered over Celite and concentrated *in vacuo*. The residue was dissolved in EtOAc (5 mL)

and saturated aqueous NaHCO_3 (5 mL). This mixture was stirred for an additional 2 h at room temperature. The layers were separated and the aqueous phase was extracted with EtOAc (2×5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield **22** (306 mg, 1.28 mmol, 92%) as a colorless oil, which was used in the next reaction without further purification. ^1H NMR (CDCl_3 , 400 MHz) δ 4.67 (dd, $J = 11.6, 3.8$ Hz, 1H), 4.60 (d, $J = 6.1$ Hz, 1H), 3.75-3.72 (m, 1H), 3.67 (s, 3H), 2.83-2.79 (m, 1H), 2.56-2.45 (m, 1H), 2.20-2.05 (m, 2H), 1.97-1.87 (m, 2H), 1.83-1.71 (m, 3H), 1.61-1.52 (m, 1H), 1.49-1.39 (m, 1H), 1.36-1.27 (m, 1H).

(-)-Dysibetaine PP

Compound **22** (306 mg, 1.28 mmol) was dissolved in CH_2Cl_2 (10 mL) after which MeI (240 μL , 3.9 mmol) was added. The reaction mixture was stirred for 16 h at room temperature in the dark. Subsequently, the mixture was concentrated *in vacuo* and the residue was dissolved in a mixture of THF/MeOH (10 mL, 1:1) before adding a 0.15M LiOH solution (12.3 mL, 1.92 mmol). After stirring for 1 h at room temperature the mixture was neutralized by the addition of 1M HCl after which the solvents were removed *in vacuo*. Purification by ion exchange chromatography over Dowex 50 $\times$ 4 and lyophilization afforded (-)-dysibetaine PP as a white solid (272 mg, 1.14 mmol, 89%). $[\alpha]_{\text{D}}^{20} -80.3$ (c 0.58, H_2O) {lit.¹ $[\alpha]_{\text{D}}^{18} -70.3$ (c 0.24, H_2O)}. Spectral data identical to the data reported in literature.¹

¹ Sakai, R.; Suzuki K.; Shimamoto, K.; Kamiya, H. *J. Org. Chem.* **2004**, 69, 1180.

^1H NMR spectra of compounds *trans*-**8b**, *cis*-**8b**, *trans*-**8c**, *cis*-**8c** and (–)-dysibetaine PP.