Synthesis of L-2-Amino-8-oxodecanoic Acid: An Amino Acid Component of Apicidins

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Abstract: The synthesis of L-2-amino-8-oxodecanoic acid (Aoda) is described. This is a rare amino acid component of apicidins, a family of new cyclic tetrapeptides, inhibitors of histone deacetylase. Aoda was synthesised in seven steps from L-glutamic acid, along with some derivatives.

Key words: amino acid, Aoda, apicidins, histone deacetylase, inhibitors

Apicidins **1a–d** are a new family of natural cyclic tetrapeptides that have been recently identified as antiprotozoal agents inhibiting parasite histone deacetylase (HDAC) in vitro. HDACs are nuclear isozymes that regulate gene transcription via the dynamic acetylation/deacetylation at specific residues in histones.[3] Four analogues, apicidin (**1a**), apicidin A (**1b**), apicidin B (**1c**) and apicidin C (**1d**) have been recently isolated from the fermentation broth of *Fusarium pallidoserum* (ATCC 74289) (Figure 1).[4,5] They are structurally related to other naturally occurring cyclic tetrapeptides described in the literature as, for instance, HC-toxin, trapoxin A, WF-3161, Cly-2, and chlamydocin, which display potent antineoplastic or antiprotozoal activity.[6–10] Also, **1a** has shown in vivo efficacy against *Plasmodium berghei* malaria. The potential use of **1a** for the treatment of cancer has been suggested.[11] Thus, four patents have been reported claiming apicidins and derivatives as therapeutic agents against protozoal infections or as components of anti-tumour compositions.[12] Additional potent inhibitors of HDAC are largely restricted to hydroxamic acid containing molecules such as the natural product trichostatin A and derivatives.[13–15]

The four apicidins are structurally related by the presence of (2*S*)-amino-8-oxodecanoic acid (Aoda; **2**) and Trp moieties (Figure 1). The ethyl ketone side-chain in **2** is unique to apicidins and is not present in related HDAC cyclic tetrapeptide inhibitors. The C-8 keto group of the **2** moiety mimics the C-8 keto group of the acetylated lysine residue of histones **3** (Figure 1). Although chemical modification of **2**[16–18] and Trp[19–21] residues in **1a** produced some transition-state analogues, it only led to a limited SAR. The presence of a C-8 oxo group in the side-chain in **2** has been shown of significance for the activity of analogues of **1a**.

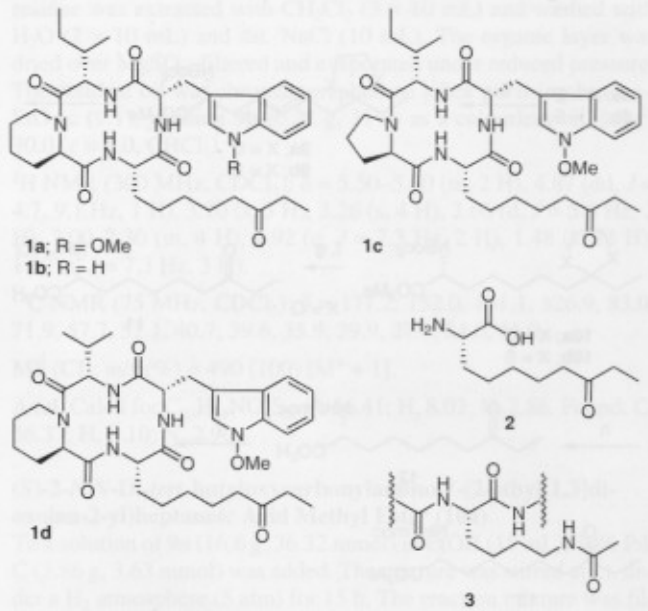

Figure 1 The family of apicidins **1a–d**, Aoda (**2**) and acylated lysine **3** in histones.

Recently, three syntheses of apicidins have been reported. First, **1a** was synthesised using a precursor of **2** bearing a silyl ether group in the C-8 position. In this synthesis **2** was not synthesised but its 8-*tert*-butyldiphenylsilyloxy derivative (23.8% from L-Ser) that was transformed to the 8-keto group once the cyclic tetrapeptide core was built. After cyclisation, silyl ether was deprotected and the resulting secondary alcohol oxidised to give **1a**.[22] The first synthesis of **2** as its 2-benzyloxycarbonyl methyl ester derivative was performed from L-glutamic acid in six steps (23% yield) and was used to prepare **1b**.[23] The key step was a Michael addition on ethyl vinyl ketone under photolytic conditions in the presence of tri-*n*-butyltin hydride. Finally, **2** was also synthesised as its *N*-Boc-derivative from Garner's aldehyde in six steps (33.6% yield) to prepare a tetrapeptoid analogue of **1c** and apicidin A (**1a**) through solution- and solid-phase synthesis, respectively.[24]

In this article we report a synthesis of **2** and derivatives which can be suitable for developing apidicin analogues by modification at any amino acid residue in **1a–d** (Scheme 1). Starting from commercially available **4**, the

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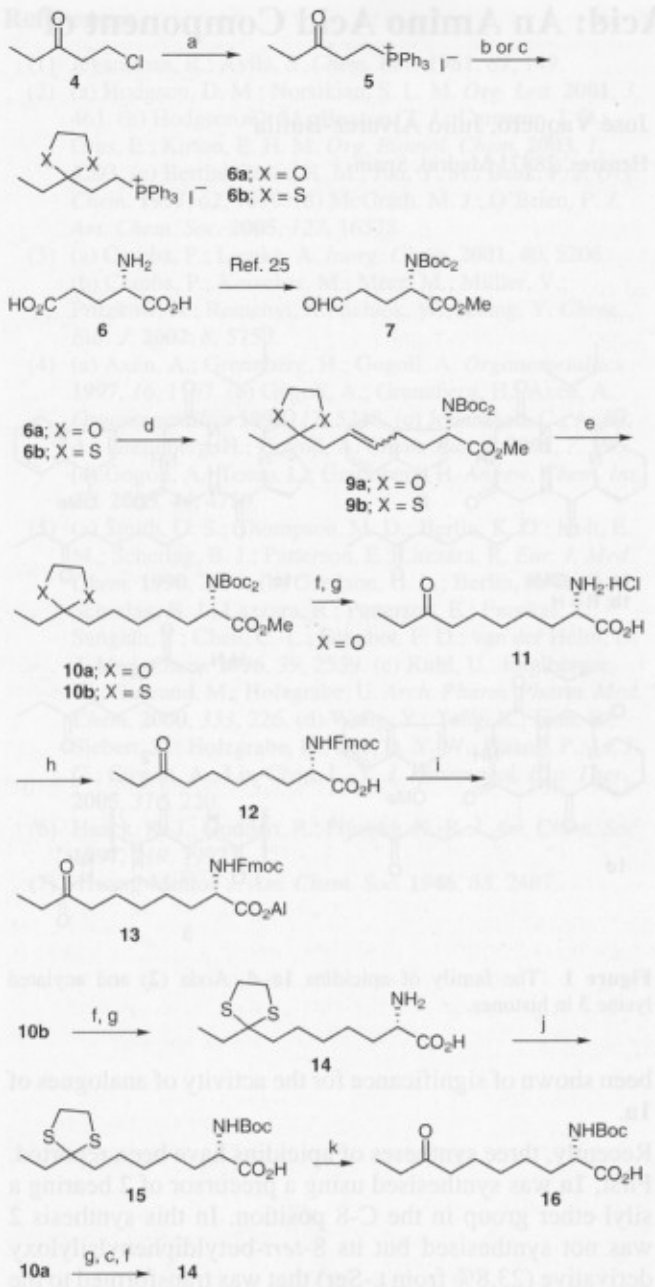

Scheme 1 Synthesis of Aoda and derivatives. *Reagents and conditions*: (a) PPh_3, NaI, EtOAc, reflux, 22 h; (b) ethanediol, PPTS, toluene, reflux, 14 h; (c) Ethanedithiol, BF_3-Et_2O, THF, r.t., 20 h. (d) i. LiHMDS, THF, –78 °C, 1 h (X = O) or 5 h (X = S); ii. **7**, THF, –78 °C; 2 h (X = O) or 5 h (X = S); (e) H_2 (5 atm), 10% Pd/C, EtOAc, r.t. (X = O) or 35 °C (X = S), 15 h; (f) i. 1 N NaOH, MeOH, r.t., 19 h (X = O) or 3 h (X = S); (g) 6 N HCl, THF, r.t., 20 h (X = O) or 6 h (X = S); (h) FmocCl, 10% K_2CO_3, dioxane, 0 °C–r.t., 4 h; (i) allyl bromide, DIPEA, r.t., 6 h; (j) Boc_2O, MeOH, Et_3N, 60 °C, 1 h then r.t., 3 h; (k) clayfen, CH_2Cl_2, r.t., 2 h.

reaction with triphenylphosphine in ethyl acetate, in the presence of sodium iodide gave quantitatively the insoluble phosphonium salt **5** (99%). The oxo group was then protected as 1,3-dioxolane or 1,3-dithiolane to give **6a** (85%) and **6b** (83%) respectively. Wittig reaction between **6a**,**b** and **7** led to a satisfactory yield of **9a** (72%; *cis*/*trans* = 93:7) but only a low yield of **9b** (31%; *cis*-isomer). Aldehyde **7** was obtained from L-glutamic acid (**8**) in two steps in an improved yield to that reported (91%).[25] This approach to long-chain amino acids has been previously described for the synthesis of an inhibitor of pancreatic lipase.[26] Both **6a** and **7** were synthesised on 200 g scale in our pilot plant facilities.[27] Compounds **9a**,**b** were subsequently hydrogenated on Pd/C to quantitatively yield **10a** (98%) and **10b** (93%). Compound **10a** was sequentially hydrolysed under basic and acidic conditions to give Aoda (**2**; 79%; 47% overall yield from **4**) as its hydrochloride **11**.[20] Further treatment of **11** with FmocCl in the presence of 10% potassium carbonate led to **12** (85%). Finally, allyl ester formation was carried out using allyl bromide and *N*,*N*-diisopropylethylamine to give **13** (95%; 39% overall yield from **4**). Sequential hydrolysis of **10b** under basic and acidic conditions gave **14** (98%). Further treatment with di-*tert*-butyl dicarbonate and triethylamine yielded **15** (78%; 18.1% overall yield from **4**). Further treatment with clayfen gave Boc-Aoda (**16**; 88%). In the order to improve the low yield for **9b**, **10a** was hydrolysed by acid and then treated with ethanedithiol before final basic hydrolysis to give **14** (76%). After protection of amine group **16** was obtained in an improved yield (78%; 35.2% overall yield from **4**).

In summary, a synthesis of **2** has been developed with an improved overall yield, in comparison to previously reported syntheses, from readily accessible precursors, and can be easily scaled up in initial steps.

Solvents and reagents were purchased from Aldrich Co. and were not further purified. Clayfen was prepared as previously reported.[28] Solvents were dried by standard methods. Reactions under anhydrous conditions were performed under argon using deoxygenated and anhydrous solvents. ^{1}H NMR spectra were recorded on Varian Unity 300 or Varian Unity 500 (300 MHz and 500 MHz, respectively) spectrometers. ^{13}C NMR spectra were recorded on a Varian Unity 300 (75 MHz) spectrometer. Mass spectra were obtained on a Hewlett–Packard 5988A instrument (EI or CI, 70 eV) by direct inlet or electrospray. Microanalyses were performed on a Heraeus CHN Rapid instrument. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. Melting points were measured with an Electrothermal IA 6304 instrument.

3-Oxopentyltriphenylphosphonium Iodide (5)

To a solution of **4** (25 g, 0.207 mol) in EtOAc (210 mL), Ph_3P (54.38 g, 0.207 mol) and NaI (31.03 g, 0.207 mol) were added. The reaction mixture was stirred at reflux temperature for 22 h. The precipitated NaCl was filtered off and the remaining mixture was washed with EtOAc. The solvent was evaporated under reduced pressure and the residue was treated with Et_2O. The precipitated solid was filtered and dried, yielding **5** (97.14 g, 99%) as a white solid; mp 214–215 °C (hexane–EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.80 (m, 15 H), 3.86 (p, *J* = 6.8 Hz, 2 H), 3.10–3.20 (m, 2 H), 2.43 (q, *J* = 7.2 Hz, 2 H), 0.87 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 229.7, 134.9, 134.9, 133.4, 133.3, 130.4, 130.3, 130.2, 118.3, 117.1, 36.1, 35.2, 17.6, 16.9, 7.7.

MS (EI): *m*/*z* (%) = 262 (82), 183 (100), 128 (92), 108 (68).

Anal. Calcd for $C_{23}H_{24}IOP$: C, 58.22; H, 5.10. Found: C, 58.40; H, 5.30.

{2-(2-Ethyl[1,3]dioxolan-2-yl)ethyl}triphenylphosphonium Iodide (6a)

To a slurry of **5** (46 g, 96.84 mmol) in toluene (500 mL), PPTS (2.47 g, 9.68 mmol) and ethylene glycol (13.53 mL, 242.1 mmol) were added. H_2O was removed using a Dean–Stark trap, heating at reflux temperature for 14 h. The solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with H_2O and sat. NaCl soln. The organic layer was dried over $MgSO_4$, filtered and evaporated. The residual oil was treated with THF, yielding **6a** (41.13 g, 82%) as a white solid; mp 137–137 °C (hexane–EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.80 (m, 15 H), 4.04 (t, *J* = 6.8 Hz, 2 H), 3.91 (t, *J* = 6.8 Hz, 2 H), 3.40–3.50 (m, 2 H), 1.80–2.10 (m, 1 H), 1.63 (q, *J* = 7.6 Hz, 2 H), 0.78 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.0, 133.3, 133.1, 130.5, 130.3, 117.9, 116.8, 109.9, 109.7, 62.2, 30.5, 29.6, 28.7, 17.7, 16.9, 7.7.

MS (EI): *m/z* (%) = 262 (77), 183 (100), 128 (18), 108 (69).

Anal. Calcd for $C_{25}H_{28}IO_2P$: C, 59.17; H, 5.76. Found: C, 59.01; H, 5.65.

{2-(2-Ethyl[1,3]dithiolan-2-yl)-ethyl}triphenylphosphonium Iodide (6b)

To a solution of **5** (40.8 g, 86.0 mmol) in CH_2Cl_2 (330 mL), 1,2-ethanedithiol (21.6 mL, 258 mmol) and BF_3·Et_2O (4.3 mL, 34 mmol) were added. The reaction mixture was stirred at r.t. for 20 h under an argon atmosphere. The solvent was removed under reduced pressure. Residual oil was triturated with hexane, yielding **6b** (41.20 g, 87%) as a white solid; mp 124–125 °C (hexane–EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.80 (m, 15 H), 3.60–3.70 (m, 2 H), 3.20–3.30 (m, 4 H), 2.00–2.10 (m, 2 H), 2.00 (q, *J* = 7.0 Hz, 2 H), 1.00 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.1, 133.3, 133.2, 130.6, 130.4, 117.9, 116.8, 72.3, 72.1, 40.9, 36.7, 35.2, 28.8, 21.1, 11.2.

MS (EI): *m/z* (%) = 262 (83), 183 (100), 128 (33), 77 (70).

Anal. Calcd for $C_{25}H_{28}IS_2P$: C, 54.14; H, 5.13. Found: C, 54.57; H, 5.18.

(*S*)-2-*N*,*N*-Di-*tert*-butyloxycarbonylamino-7-(2-ethyl[1,3]dioxolan-2-yl)hept-5-enoic Acid Methyl Ester (9a)

To a slurry of **6a** (46.75 g, 90.25 mmol) in THF (1.1 L), 1 M LiHMDS in THF (65.99 mL, 65.99 mmol) was added dropwise at –78 °C for 30 min. The reaction mixture was stirred at this temperature for 1 h. Then, a solution of **7** (18.86 g, 54.66 mmol) in THF was added. The reaction mixture was stirred at –78 °C for 2 h. H_2O (100 mL) was added and the mixture was stirred for 30 min at r.t. The solvent was removed under reduced pressure and the aqueous residue was extracted with CH_2Cl_2 (3 × 300 mL). The organic layer was washed with H_2O (2 × 200 mL), sat. NaCl (100 mL) and dried over $MgSO_4$. After removal of solid and solvent, the residue was chromatographed on silica gel using hexane–EtOAc (9:1) yielding **9a** (18 g, 72%) as a colourless oil; $[\alpha]_D^{25}$ –33.1 (*c* = 1.14, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$; selected signals): δ = 5.52 (dt, *J* = 2.5, 11.0 Hz, 1 H, *cis*), 5.47 (dt, *J* = 1.7, 11.0 Hz, 1 H, *cis*), 4.84 (dd, *J* = 4.9, 8.8 Hz, 1 H), 3.85 (m, 4 H), 3.69 (s, 3 H, *trans*), 3.68 (s, 3 H, *cis*), 2.35 (d, *J* = 5.5, 14.2 Hz, 1 H, *cis*), 2.10–2.20 (m, 3 H), 1.85 (m, 1 H), 1.61 (q, *J* = 7.5 Hz, 2 H, *cis*), 1.53 (d, *J* = 14.2 Hz, 1 H, *cis*), 1.47 (s, 18 H), 0.88 (t, *J* = 7.5 Hz, 3 H, *trans*), 0.87 (t, *J* = 7.5 Hz, 3 H, *cis*).

^{13}C NMR (75 MHz, $CDCl_3$, *cis*-isomer): δ = 171.2, 152.0, 130.9, 125.1, 111.7, 82.9, 65.1, 57.7, 52.1, 34.8, 30.1, 29.9, 27.9, 24.3, 7.8.

MS (EI): *m/z* (%) = 458 (56) [M$^+$ + 1], 258 (100), 240 (16), 142 (14), 101 (48).

Anal. Calcd for $C_{23}H_{39}NO_8$: C, 60.35; H, 8.59; N, 3.06. Found: C, 60.21; H, 8.52; N, 3.05.

(*S*)-*cis*-2-*N*,*N*-Di-*tert*-butyloxycarbonylamino-7-(2-ethyl[1,3]dithiolan-2-yl)hept-5-enoic Acid Methyl Ester (9b)

To a slurry of **6b** (1.18 g, 2.11 mmol) in THF (30 mL), a 1 M solution of *n*-BuLi in hexane (1.25 mL, 2.01 mmol) was added dropwise at –78 °C. The reaction mixture was stirred at –78 °C for 5 h. Then, a solution of **7** (0.5 g, 1.44 mmol) in THF (10 mL) was added. The reaction mixture was stirred at –78 °C for 3 h. H_2O (5 mL) was added and the mixture was stirred at r.t. for 30 min. The organic solvents were removed under reduced pressure and the aqueous residue was extracted with CH_2Cl_2 (3 × 10 mL) and washed with H_2O (2 × 10 mL) and sat. NaCl (10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residual oil was chromatographed on silica gel using hexane–EtOAc (9:1), yielding **9b** (0.22 g, 31%) as a colourless oil; $[\alpha]_D^{25}$ 30.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.50–5.60 (m, 2 H), 4.87 (dd, *J* = 4.7, 9.1 Hz, 1 H), 3.70 (s, 3 H), 3.26 (s, 4 H), 2.66 (d, *J* = 5.5 Hz, 2 H), 2.00–2.30 (m, 4 H), 1.92 (q, *J* = 7.3 Hz, 2 H), 1.48 (s, 18 H), 1.02 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 152.0, 131.1, 126.9, 83.0, 71.9, 57.7, 52.1, 40.7, 39.6, 35.9, 29.9, 27.9, 24.6, 11.0.

MS (CI): *m/z* (%) = 490 (100) [M$^+$ + 1].

Anal. Calcd for $C_{23}H_{39}NO_6S_2$: C, 56.41; H, 8.03; N, 2.86. Found: C, 56.37; H, 8.10; N, 2.90.

(*S*)-2-*N*,*N*-Di-*tert*-butyloxycarbonylamino-7-(2-ethyl[1,3]dioxolan-2-yl)heptanoic Acid Methyl Ester (10a)

To a solution of **9a** (16.6 g, 36.32 mmol) in EtOH (15 mL), 10% Pd/C (3.86 g, 3.63 mmol) was added. The mixture was stirred at r.t. under a H_2 atmosphere (5 atm) for 15 h. The reaction mixture was filtered through Celite and washed with EtOH. The solvent was evaporated under reduced pressure, yielding **10a** (16.33 g, 98%) as a colourless oil; $[\alpha]_D^{25}$ –20.6 (*c* = 0.33, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.81 (dd, *J* = 5.1, 9.5 Hz, 1 H), 3.88 (s, 4 H), 3.87 (s, 3 H), 2.30–2.40 (m, 1 H), 2.00–2.10 (m, 2 H), 1.80–1.90 (m, 2 H), 1.50–1.70 (m, 3 H), 1.46 (s, 18 H), 1.20–1.40 (m, 4 H), 0.86 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 151.7, 130.9, 111.7, 82.8, 64.9, 58.1, 52.1, 36.7, 29.9, 29.7, 28.2, 26.3, 23.8, 8.3.

MS (EI): *m/z* (%) = 460 (42) [M$^+$ + 1], 430 (15), 101 (87), 57 (100).

Anal. Calcd for $C_{23}H_{41}NO_8$: C, 60.11; H, 8.99; N, 3.05. Found: C, 60.11; H, 9.10; N, 3.10.

(*S*)-2-*N*,*N*-Di-*tert*-butyloxycarbonylamino-7-(2-ethyl[1,3]dithiolan-2-yl)heptanoic Acid Methyl Ester (10b)

To a solution of **9b** (1.4 g, 2.86 mmol) in EtOAc (10 mL), 10% Pd/C (0.30 g, 0.28 mmol) was added. The reaction mixture was stirred at 35 °C under H_2 (5 atm) for 18 h. After filtering through Celite and washing with EtOAc, the filtrate was evaporated under reduced pressure yielding **10b** (1.3 g, 93%) as a colourless oil; $[\alpha]_D^{25}$ 20.3 (*c* = 1.03, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.84 (dd, *J* = 5.1, 9.5 Hz, 1 H), 3.70 (s, 3 H), 3.24 (s, 4 H), 2.00–2.10 (m, 1 H), 1.90–2.00 (m, 4 H), 1.48 (s, 18 H), 1.30–1.40 (m, 7 H), 1.02 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 151.7, 82.9, 72.3, 58.1, 52.2, 42.9, 39.6, 36.3, 30.0, 29.8, 29.6, 28.1, 26.9, 26.3, 11.5.

MS (CI): *m/z* (%) = 492 (100) [M$^+$ + 1].

Anal. Calcd for $C_{23}H_{41}NO_6S_2$: C, 56.18; H, 8.40; N, 2.85. Found: C, 56.78; H, 8.90; N, 2.83.

(*S*)-2-Amino-8-oxodecanoic Acid Hydrochloride (11)

To a solution of **10a** (11 g, 23.96 mmol) in MeOH (156 mL), 1 M NaOH (72 mL) was added at 0 °C and the mixture was stirred at r.t. for 12 h. The solvent was removed under reduced pressure and the aqueous basic solution was extracted with Et_2O (2 × 20 mL). The aqueous layer was treated with 3.5% HCl until pH = 4–5 and then extracted with Et_2O (3 × 50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was dissolved in THF (35 mL), cooled at 0 °C and treated with 1 N HCl (34.5 mL). The mixture was stirred at r.t. for 8 h. The solvent was removed under reduced pressure. The residual oil was dissolved in EtOAc and treated with Et_2O, yielding **11** (9.99 g, 92%) as a white solid; mp 207–208 °C (Et_2O–EtOH); $[\alpha]_D^{25}$ 4.4 (*c* = 1.06, MeOH).

^{1}H NMR (300 MHz, CD_3OD): δ = 3.94 (t, *J* = 6.0 Hz, 1 H), 2.46 (q, *J* = 7.2 Hz, 4 H), 1.8–2.0 (m, 2 H), 1.5–1.6 (m, 6 H), 1.00 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 214.3, 171.9, 42.7, 36.6, 31.3, 29.6, 25.7, 24.4, 8.1.

MS (ES$^+$): *m*/*z* (%) = 202 (100) [M + 1].

MS (ES$^-$): *m*/*z* (%) = 201 (100) [M – 1].

Anal. Calcd for $C_{10}H_{20}ClNO_3$: C, 50.60; H, 8.50; N, 5.90. Found: C, 50.46; H, 8.76; N, 5.55.

(*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-8-oxodecanoic Acid (12)

To a slurry of **11** (6.2 g, 26.08 mmol) in 10% Na_2CO_3 (68.2 mL), FmocCl (6.96 g, 26.08 mmol) in dioxane (62 mL) was added at 0 °C and the mixture was stirred at r.t. for 3 h. Then, H_2O (200 mL) was added and the reaction mixture was extracted with Et_2O (2 × 20 mL). The aqueous layer was acidified with 3.5% HCl and then extracted with EtOAc (4 × 100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to yield **12** (7.48 g, 68%) as a yellowish solid; mp 108–109 °C; $[\alpha]_D^{25}$ 6.27 (*c* = 1.04, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.3 Hz, 2 H), 7.59 (d, *J* = 5.8 Hz, 2 H), 7.39 (t, *J* = 7.3 Hz, 2 H), 7.30 (t, *J* = 7.3 Hz, 2 H), 5.33 (d, *J* = 8.0 Hz, 1 H), 4.30–4.40 (m, 3 H), 4.22 (t, *J* = 6.7 Hz, 1 H), 2.39 (q, *J* = 7.3 Hz, 4 H), 1.80–2.00 (m, 1 H), 1.50–1.80 (m, 3 H), 1.20–1.50 (m, 4 H), 1.04 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.2, 176.3, 156.1, 143.6, 141.2, 127.6, 127.0, 125.0, 119.9, 66.9, 53.6, 47.0, 42.0, 35.8, 32.1, 28.6, 24.9, 23.4, 7.7.

MS (ES$^+$): *m*/*z* (%) = 446 (100) [M$^+$ + Na].

MS (ES$^-$): *m*/*z* (%) = 201 (100) [M$^+$ – 1].

Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.88; H, 6.90; N, 3.30. Found: C, 70.85; H, 7.06; N, 3.40.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-8-oxodecanoic Acid Allyl Ester (13)

To a solution of **12** (12.77 g, 30.15 mmol) in anhyd MeCN (230 mL), allyl bromide (117.4 mL, 1.35 mmoL) and DIPEA (5.25 mL, 30.15 mmol) were added and the mixture was stirred at r.t. for 6 h. Then, EtOAc (200 mL) was added and the reaction mixture was washed with 10% Na_2CO_3 (2 × 25 mL) and sat. NaCl. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel using hexane–EtOAc (8:2), yielding **13** (9.8 g, 70%) as a white solid; mp 64–65 °C; $[\alpha]_D^{25}$ 1.8 (*c* = 1.04, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.2 Hz, 2 H), 7.60 (d, *J* = 5.8 Hz, 2 H), 7.40 (t, *J* = 7.2 Hz, 2 H), 7.31 (t, *J* = 7.2 Hz, 2 H), 5.80–6.00 (m, 1 H), 5.20–5.40 (m, 3 H), 4.62 (d, *J* = 5.6 Hz, 2 H), 4.39 (d, *J* = 6.4 Hz, 2 H), 4.22 (t, *J* = 7.0 Hz, 1 H), 2.30–2.40 (m, 4 H), 1.80–1.90 (m, 1 H), 1.50–1.70 (m, 3 H), 1.20–1.40 (m, 4 H), 1.04 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.5, 172.2, 155.8, 143.8, 143.7, 141.3, 131.5, 127.6, 127.0, 125.0, 119.9, 118.9, 66.9, 65.9, 53.8, 47.1, 42.1, 35.8, 32.5, 28.7, 24.9, 23.4, 7.8.

MS (ES$^+$): *m*/*z* (%) = 464 [M$^+$ + H], 486 [M$^+$ + Na].

Anal. Calcd for $C_{28}H_{33}NO_5$: C, 72.53; H, 7.17; N, 3.02. Found: C, 72.83; H, 7.26; N, 3.08.

(*S*)-2-Amino-7-(2-ethyl[1,3]dithiolan-2-yl)heptanoic Acid (14)

To a solution of **10a** (2.47 g, 5.39 mmol) in EtOAc (7.6 mL), 4 M HCl (7.6 mL, 30.4 mmol) was added at 0 °C and the mixture was stirred at r.t. for 8 h. The solvents were removed under reduced pressure and the residue was treated with EtOAc, filtered and washed (EtOAc and Et_2O). The solid was suspended in anhyd CH_2Cl_2 (50 mL) and 1,2-ethanediol (0.66 mL, 8.08 mmol) and $BF_3{\cdot}Et_2O$ (0.54 mmol) were added under an argon atmosphere. The mixture was stirred at r.t. for 20 h. The solvent was removed to dryness and the residue was dissolved in H_2O (50 mL) and extracted with Et_2O (2 × 25 mL). The aqueous layer was evaporated to dryness, dissolved in MeOH (30 mL) and treated with 1 N NaOH (27 mL, 27 mmol) at r.t. for 12 h. MeOH was evaporated under reduced pressure and the aqueous residue was neutralised with 3.5% HCl yielding **14** (1.46 g, 98%) as a white solid; mp 222–223 °C; $[\alpha]_D^{25}$ 2.0 (*c* = 1.0, MeOH).

^{1}H NMR (300 MHz, CD_3OD): δ = 3.51 (t, *J* = 5.3 Hz, 1 H), 3.24 (s, 4 H), 1.80–1.90 (m, 4 H), 1.70–1.80 (m, 2 H), 1.40–1.50 (m, 7 H), 1.03 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 174.0, 73.0, 56.1, 44.1, 40.4, 37.4, 32.4, 30.7, 27.8, 26.3, 11.6.

MS (ES$^-$): *m*/*z* (%) = 276 (100) [M$^+$ – 1].

MS (ES$^+$): *m*/*z* (%) = 278 (100) [M$^+$ + 1].

Anal. Calcd for $C_{12}H_{23}NO_2S_2$: C, 51.96; H, 8.36; N, 5.05; S, 23.07. Found: C, 56.68; H, 8.20; N, 4.83; S, 22.96.

(*S*)-2-*tert*-Butoxycarbonylamino-7-(2-ethyl[1,3]dithiolan-2-yl)heptanoic Acid (15)

To a solution of **14** (1.46 g, 5.39 mmol) in MeOH (36 mL), di-*tert*-butyl dicarbonate (1.8 g, 8.6 mmol) and Et_3N (4.13 mL, 29.67 mmol) were added. The reaction mixture was heated at 60 °C for 1 h, and then left at r.t. for 2 h. The solvent was concentrated to dryness and treated with 3.5% HCl to pH 4–5. The mixture was extracted with EtOAc (3 × 25 mL) and the organic layer was washed with sat. NaCl, dried over $MgSO_4$, filtered and evaporated under reduced pressure to yield **15** (1.58 g, 78%) as a brownish oil; $[\alpha]_D^{25}$ 7.4 (*c* = 1.06, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.20 (br s, 1 H), 5.01 (d, *J* = 8.2 Hz, 1 H), 4.11 (d, *J* = 7.1 Hz, 1 H), 3.25 (s, 4 H), 1.80–2.00 (m, 4 H), 1.60–1.70 (m, 1 H), 1.44 (s, 9 H), 1.30–1.40 (m, 7 H), 1.02 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.3, 155.5, 80.1, 72.3, 53.4, 42.8, 39.5, 36.2, 32.4, 29.3, 28.3, 26.6, 25.2, 11.2.

MS (ES$^+$): *m*/*z* (%) = 278 [M$^+$ – 100], 400 (100) [M$^+$ + Na].

Anal. Calcd for $C_{17}H_{31}NO_4S_2$: C, 54.08; H, 8.28; N, 3.71; S, 16.95. Found: C, 53.47; H, 8.20; N, 3.80; S, 16.88.

(*S*)-2-*tert*-Butoxycarbonylamino-8-oxodecanoic Acid (16)

To a solution of **15** (0.1 g, 0.26 mmol) in CH_2Cl_2 (10 mL), clayfen (0.27 g, 0.29 mmol) was added and the mixture was stirred at r.t. for 2 h. After filtering through Celite, the filtrate was evaporated to dryness to yield **16** (70.2 mg, 88%) as a colourless oil; $[\alpha]_D^{25}$ –2.5 (*c* = 0.51, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.10 (d, *J* = 7.9 Hz, 1 H), 4.20–4.30 (m, 1 H), 2.49–2.50 (m, 4 H), 1.70–1.80 (m, 1 H), 1.50–1.70 (m, 4 H), 1.45 (s, 9 H), 1.30–1.40 (m, 4 H), 1.05 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.0, 176.8, 155.6, 80.1, 53.2, 42.1, 35.8, 32.2, 28.6, 28.2, 24.9, 23.5, 7.7.

HRMS (ES^+): *m/z* calcd for $C_{15}H_{26}NO_5$: 300.1802; found: 300.1811.

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