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Pyranocyclopropanyl sugar amino acids, a new class of constrained (di)peptide isosteres

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On the occasion of the 65th birthday of Professor George Fleet

ABSTRACT

The design, synthesis and application of oxabicyclo[4.1.0]heptane amino acids as conformationally restricted sugar amino acid dipeptide isosteres are reported.

1. Introduction

Sugar amino acids (SAAs) are hybrid structures with elements from both carbohydrates and amino acids embedded in their structure.[1] They are used to construct both peptidomimetics and glycomimetics and the resulting oligomers[2] are subjected to conformational analysis, biological activity assays or both.[3] Peptidomimetics can be obtained by incorporation of a specific SAA in an oligopeptide sequence at a predesigned position whereas glycomimetics are accessed by the assembly of oligomers composed of SAA monomers exclusively. Carbohydrates constitute a highly diverse class of compounds with numerous structural and configurational variations. They are often relatively inexpensive and offer ample synthetic potential to create carbohydrate-derived compounds with desirable functionalities. These combined properties are the basis of the extensive literature on the synthesis and application of SAAs in carbohydrate and peptide chemistries.[4] An attractive feature of carbohydrates as a starting point in amino acid design is the potential to adapt the functional groups inherent to the parent saccharide and that remain after installment of the amine and carboxylate groups. Alkylation of SAA hydroxy groups[1,4] may tune solubility and conformational behavior or bring desirable pharmacophores to a predetermined site in oligomers assembled from them. In a specific class of SAAs and the subject of this paper, the functional diversity of monosaccharides is utilized to introduce added conformational constraint through the annulation of an extra ring.

2. Results and discussion

We[5] and others[6] have reported on the design of dioxabicyclo[3.3.0]octane SAAs, dioxabicyclo[3.2.0]heptane SAAs, dioxabicyclo[3.2.1]heptane SAAs, dioxabicyclo[4.4.0]decane SAAs as well as *spiro*-furanofuran SAAs. A logical extension of these series is the oxabicyclo[4.1.0]heptane SAAs and oxabicyclo[3.1.0]hexane SAAs, especially when taking into account the literature precedent[7] on the efficient and often asymmetric cyclopropanations one can perform on glycals derived from furanoses and pyranoses. Several groups have reported on the rhodium(II)-catalyzed cyclopropanation of protected D-glucal with ethyl diazoacetate and we considered this reaction as a good starting point in the generation of oxabicyclo[4.1.0]heptane SAAs as a new class of carbohydrate-derived δ amino acids. Both benzyl and silyl protective groups are reportedly compatible with these conditions. Indeed, when we treated 1,2-anhydro-3,4-tri-*O*-benzyl-6-*O*-(*tert*)butyldimethylsilyl-D-glucose **1**[8] with ethyl diazoacetate and Rh_2OAc_4 (5 mol %, Scheme 1) in methylene chloride we obtained alpha-*exo* ester **2** as an inseparable mixture of two diastereoisomers. The configuration of these could not be established at this stage, but proton NMR indicated the presence of a major isomer in a ratio of about 10:1. Fluoride-mediated removal of the silyl protective group proceeded uneventfully and at this stage the mixture of diastereomers was readily separated by silica gel chromatography. The major stereomer (58% over the two steps) was determined by NMR spectroscopy as the alpha-*exo* derivative **3**, the expected stereoisomer considering the literature data on the rhodium(II)-catalyzed cyclopropanation of perbenzylated or persilylated glucal with ethyl diazoacetate.[9] Mitsunobu reaction of **3** with hydrazoic acid (triphenylphosphine, diethylazodicarboxylate, toluene, 85% yield) followed by saponification of the ester (LiOH, dioxane, 82% yield) gave azido-acid **6** in four steps with an overall yield of 40% based on glucal **1**.

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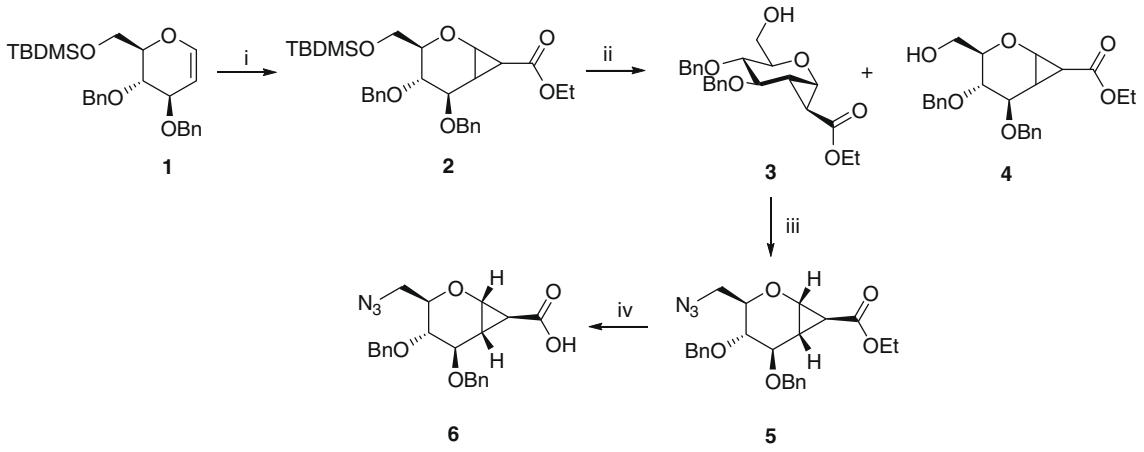
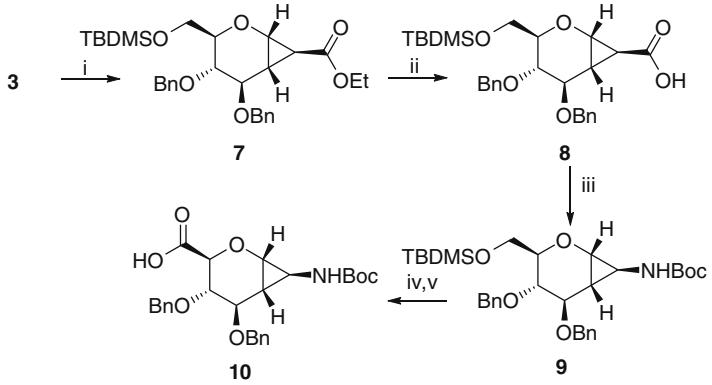


Scheme 1. Reagents and conditions: (i) Ethyl diazoacetate, Rh_2OAc_4 (5 mol %), CH_2Cl_2; (ii) TBAF, THF (**3** 58%, **4** 8%, two steps); (iii) HN_3, PPh_3, DEAD, toluene (85%); (iv) LiOH, dioxane (82%).



Scheme 2. Reagents and conditions: (i) TBDMSCl, imidazole, DMF (95%); (ii) LiOH, dioxane (79%); iii) DPPA, Et_3N, *t*BuOH Δ (72%); (iv) TBAF, THF (95%); (v) 2 equiv H_2CrO_4 (1 M), acetone (86%).

In an alternative strategy, resilylation of the enantiopure oxabicyclo[4.1.0]heptane **3** (TBDMSCl, imidazole, dioxane, 95%, Scheme 2) opened the way to the synthesis of the inversed (relative to **6**) SAA **10** featuring a Curtius rearrangement as the key step. Saponification of fully protected compound **7** (LiOH, dioxane) gave carboxylate **8** in 79% yield. Treatment of **8** with diphenylphosphoryl azide and triethylamine in *tert*-butyl alcohol at reflux gave with retention of configuration, secondary amine **9** in 72% yield. Elaboration of the primary alcohol in **9** (TBAF-mediated desilylation followed by Jones oxidation) gave a second oxabicyclo[4.1.0]heptane SAA **10** in 80% yield over the last two steps.

Both bicyclo-SAA entities were next subjected to a sequence of homo-oligomerization reactions to arrive at two tetrameric glycomimetics **13** (Scheme 3) and **17** (Scheme 4). Selective reduction of azide in **5** (Lindlar's catalyst, ethanol) followed by condensation (HATU, DiPEA, DMF) with carboxylate **6** gave fully protected dimer **11** (74%, two steps, Scheme 3). Lindlar reduction of the azide in **11** gave amine **12a** whereas saponification of the ester in **11** gave carboxylate **12b**, both in good yield. Condensation of **12a** and **12b** finally gave tetramer **13,** which was purified to homogeneity by HPLC (13% yield).

For the construction of tetramer **17**, a sample of acid **10** was esterified (TMS–diazomethane, methanol, toluene, 99%) to give the fully protected oxabicyclo[4.1.0]heptane **14**. Removal of the *tert*-butyloxycarbonyl group in **14** (trifluoroacetic acid, methylene chloride) and subsequent condensation of the resulting TFA–amine salt with **10** (HATU, DiPEA, DCM, DMF) gave dimer **15** in 68% yield over the two steps based on **10**. Removal of the Boc-protective group in one portion of **10** to give **16a** (TFA, DCM) and removal of the ester group in another portion of **10** gave **16b** employing trimethyltin hydroxide as the base in ethylene chloride (as this reagent gave the best yield, 95%).[10] Compounds **16a** and **16b** were condensed to give tetrasaccharide mimic **17** in 18% yield after HPLC purification.

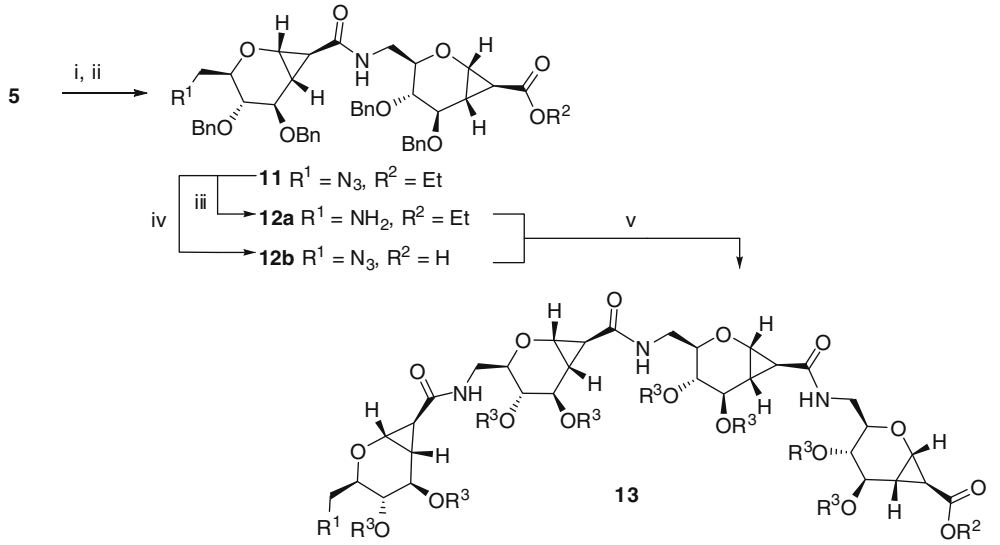
3. Conclusion

The NMR analysis of the purified tetramers revealed the presence of a single product in both examples and we can conclude that both oxabicyclo[4.1.0]heptanes SAAs **6** and **10** can be subjected to condensation reactions inherent to peptide chemistry without unexpected complications. Our strategy should be readily transposable to glycals derived from other pyranoses and likely also furanoses, thus bringing a whole panel of oxabicyclo[4.1.0]heptane SAAs and oxabicyclo[3.1.0]hexane SAAs for installment in both peptidomimetics and glycomimetics within reach.

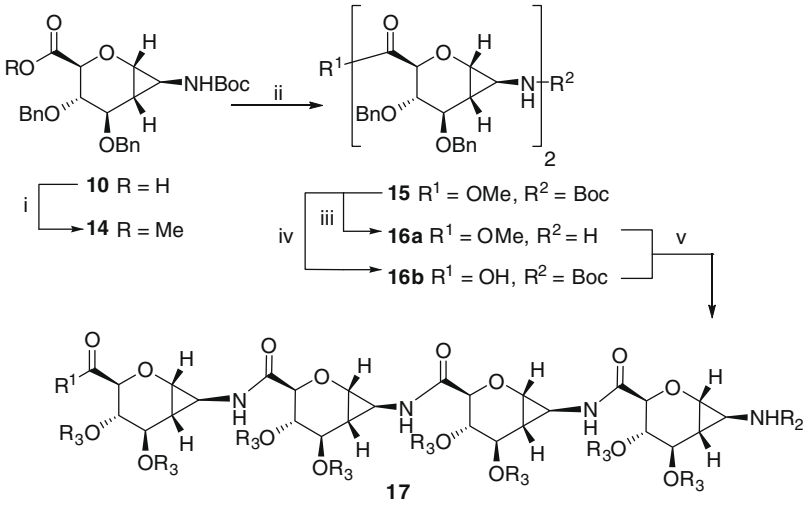
4. Experimental

4.1. General

Solvents and reagents were used as provided. Analysis of linear-protected tetramers was performed on a Jasco HPLC-system



Scheme 3. Reagents and conditions: (i) H_2, Lindlar's cat. EtOH; (ii) **6**, HATU, DIPEA, DMF (74%, two steps); (iii) H_2, Lindlar's cat. EtOH; (iv) LiOH, dioxane (76%); (v) HATU, DIPEA, DMF (13%, two steps). $R^1 = N_3$, $R^2 = Et$, $R^3 = Bn$.



Scheme 4. Reagents and conditions: (i) TMS–diazomethane, methanol, toluene (quant.); (ii) first TFA/DCM (1:1 v/v) then **10**, HATU, DIPEA DCM, DMF (68%); (iii) TFA/DCM (1:1 v/v); (iv) Me_3SnOH $ClCH_2CH_2Cl$ (95%); (v) HATU, DIPEA DCM, DMF $R^1 = OMe$, $R^2 = Boc$, $R^3 = Bn$ (19%).

(detection simultaneously at 214 nm) coupled to a Perkin Elmer Sciex API 165 mass instrument with a custom-made Electronspray Interface (ESI). An analytical Alltima CN column (Alltech, 150 × 4.6 mm, 5 μm) was used in combination with buffers A: H_2O, B: MeCN, and C: 1.0% TFA in H_2O.

NMR spectra were recorded on a Bruker DMX600 using deuterated solvents. All carbon spectra are proton-decoupled. CD_3OH was used as provided. Chemical shifts (δ) are given in ppm, relative to the solvent peak of CD_3OH; 3.31 ppm in ^1H spectra, 49.0 ppm in ^{13}C spectra. Coupling constants are given in hertz.

IR spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR Spectrometer.

High resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile; 50/50; v/v, and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electro spray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution $R = 60{,}000$ at m/z 400 (mass range $m/z = 150$–2000) and dioctylphthalate ($m/z = 391.28428$) as a 'lock mass'. The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan).

4.1.1. (1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-Ethyl 4,5-bis(benzyloxy)-3-hydroxymethyl)-2-oxabicyclo[4.1.0]heptane-7-carboxylate 3

Compound **1**[7] (9.7 g, 22.0 mmol) was coevaporated with toluene (2 × 50 mL), taken up in CH_2Cl_2 (250 mL) and Rh_2OAc_4 (200 mg, 0.45 mmol) was added. The solution was placed under an argon atmosphere. Under vigorous stirring ethyl diazoacetate (7.0 mL, 7.5 g, 66 mmol) was added slowly over 6 h. Stirring was continued for an hour after which the mixture was filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (0→15% EtOAc in light petroleum). This yielded product **2** contaminated with a minor stereoisomer and considerable amounts of diethyl fumarate. This mixture was taken up in THF (250 mL) and tetrabutylammonium fluoride (22 mL, 1 M in THF) was added after which the mixture was stirred for 2 h. The reaction mixture was diluted with ethyl acetate (400 mL) and washed with water

(3 × 300 mL) and saturated aqueous NaCl. The organic layer was dried on Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel chromatography (0→30% EtOAc in light petroleum) yielded the product **3** as an oil (5.28 g, 12.8 mmol, 58% two steps) and minor amounts (0.363 g, 0.88 mmol, 4%) of a stereoisomer of undetermined configuration. ^{1}H NMR ($CDCl_3$): δ 1.23 (t, 3H, J = 10.8 Hz), 1.80 (m, 1H), 2.00 (m, 1H), 2.59 (b, 1H), 3.49 (m, 1H), 3.65 (m, 1H), 3.78 (m, 2H), 3.95 (dd, 1H, J = 2.4 Hz, J = 7.6 Hz), 4.09 (q, 2H, J = 7.2 Hz), 4.54–4.73 (m, 4H), 7.20–7.31 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 13.95, 23.32, 23.86, 57.64, 60.49, 61.66, 71.26, 73.21, 74.36, 75.12, 76.25, 127.53, 127.58, 127.63, 128.15, 128.22, 137.43, 137.77, 171.43. Exact mass calculated for ($C_{24}H_{28}O_6$ + H)$^+$ = 413.19587, mass found: 413.19583. $[\alpha]_D$ = +20 (*c* 1.0, $CHCl_3$). IR = cm^{-1} 3500 (wb), 2870 (w), 1718 (vs), 1180 (m), 1090 (s), 530 (vs).

4.1.2. (1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-Ethyl 3-(azidomethyl)-4,5 bis(benzyloxy)-2-oxabicyclo[4.1.0]heptane-7-carboxylate 5

Hydrazoic acid solution (*Caution*: HN_3 is volatile, highly toxic, and explosive!): Sodium azide (4.0 g, 61.5 mmol) was dissolved in water (10 mL). Toluene (50 mL) was added and the resulting biphasic system was cooled on ice to 0 °C. Under vigorous stirring, concentrated sulfuric acid (8 mL) was added dropwise. After 30 min of stirring, the organic layer was separated and stored on anhydrous Na_2SO_4.

Compound **3** (2.4 g, 5.8 mmol) was coevaporated with toluene (2 × 20 mL) and taken up in toluene (60 mL). To the reaction mixture were added triphenylphosphine (3.0 g, 11.6 mmol), diethylazodicarboxylate (5.3 mL 40% in toluene, 11.6 mmol), and 5 mL of the freshly prepared hydrazoic acid stock solution. Stirring was continued for 1 h during which the appearance of the reaction mixture shifted from clear and bright yellow to turbid and colorless. The mixture was concentrated in vacuo and the residue was purified by silica gel chromatography (0→15% EtOAc in light petroleum). This provided the product **5** (2.04 g, 4.9 mmol, 85%) as an oil. ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H, J = 7.2 Hz), 1.83 (m, 1H), 2.01 (dd, 1H, J = 2 Hz, J = 5.6 Hz), 3.28 (dd, 1H, J = 3.6 Hz, J = 13.2 Hz), 3.45 (t, 1H, J = 6.0 Hz), 3.52 (m, 1H), 3.62 (m, 1H), 3.80 (dd, 1H, J = 5.2 Hz), 3.94 (dd, 1H, J = 1.6 Hz, J = 7.2 Hz), 4.12 (m, 2H), 4.56 (d, 2H, J = 11.6 Hz), 4.71 (dd, 2H, J = 2.4 Hz, J = 11.2 Hz), 7.20–7.36 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 14.07, 23.70, 23.86, 51.13, 57.04, 60.65, 71.36, 73.17, 73.24, 75.09, 75.32, 127.64, 127.77, 128.32, 128.37, 137.38, 137.56, 171.30. Exact mass calculated for ($C_{24}H_{27}N_3O_6$ + H)$^+$ = 438.20235, mass found: 438.20226. $[\alpha]_D$ = +43.4 (*c* 1.0, $CHCl_3$). IR = cm^{-1} 2870 (w), 2095 (vs), 1720 (vs), 1280 (bm), 1180 (m), 1090 (s), 530 (vs).

4.1.3. (1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-3-(Azidomethyl)-4,5-bis(benzyloxy) 2-oxabicyclo[4.1.0]heptane-7-carboxylic acid 6

Compound **5** (1.81 g, 4.14 mmol) in THF (50 mL) was treated with aqueous LiOH (4.0 mL, 4.0 M). Stirring was continued for 16 h. The mixture was neutralized by the addition of amberlite IR-120 (H^+ form) resin. The resin was removed by filtration and the filtrate was diluted with ethyl acetate (100 mL). The solution was washed with 1 M HCl (2 × 50 mL) and saturated aqueous NaCl (50 mL). The organic layers were dried on Na_2SO_4 and concentrated in vacuo. Chromatography on silica gel (0→ 100% [1% HOAc in EtOAc] in light petroleum) yielded the product **6** (1.39 g, 3.40 mmol, 82%) as a colorless syrup. ^{1}H NMR ($CDCl_3$): δ 1.87 (m, 1H), 2.02 (m, 1H), 3.28 (dd, 1H, J = 3.6 Hz, J = 13.2 Hz), 3.44–3.53 (m, 2H), 3.61 (m, 1H), 3.80 (dd, 1H, J = 1.2 Hz, J = 6 Hz), 4.00 (dd, 1H, J = 2.0 Hz, J = 7.2 Hz), 4.53–4.71 (m, 4H), 7.16–7.42 (m, 10 H), 11.05 (b, 1H). ^{13}C NMR ($CDCl_3$): δ 23.62, 24.84, 51.03, 57.74, 71.42, 73.20, 73.23, 74.87, 75.03, 76.69, 127.70, 127.79, 127.84, 127.87, 128.36, 128.42, 137.24, 137.45, 171.62. Exact mass calculated for ($C_{22}H_{23}N_3O_6$ + Na)$^+$ = 432.15299, mass found: 432.15294. $[\alpha]_D$ = +54.8 (*c* 1.0, $CHCl_3$). IR = cm^{-1} 2870 (w), 2360 (w), 2095 (vs), 1685 (vs), 1455 (m), 1280 (bm), 1090 (s), 525 (vs).

4.1.4. (1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-Ethyl 4,5-bis(benzyloxy)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[4.1.0]heptane-7-carboxylate 7

Compound **3** (2.1 g, 5.1 mmol) was coevaporated with toluene (2 × 20 mL) and taken up in DMF (50 mL). To the solution were added imidazole (0.48 g, 7.0 mmol) and *tert*-butylchlorodimethylsilane (0.845 g, 5.6 mmol) and the mixture was stirred under an argon atmosphere for 1 h. The reaction mixture was diluted with diethyl ether (200 mL) and washed with water (3 × 100 mL) and saturated aqueous NaCl (100 mL). The organic layer was dried on Na_2SO_4 and concentrated in vacuo. Chromatography of the residue (0→15% EtOAc in light petroleum) yielded the product **7** (2.55 g, 4.85 mmol, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.08 (2 × s, 6H), 0.93 (s, 9H), 1.27 (t, 3H, J = 7.2 Hz), 1.80 (m, 1H), 1.95 (m, 1H), 3.56 (m, 1H), 3.69 (t, 1H, J = 6.8 Hz), 3.77 (m, 2H), 3.86 (dd, 1H, J = 4.4 Hz, J = 10.8 Hz), 4.14 (m, 2H), 4.63–4.82 (m, 4H), 7.29–7.38 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ −5.47, −5.33, 14.18, 18.21, 24.91, 25.03, 25.84, 57.81, 60.58, 62.57, 71.44, 73.54, 75.07, 76.51, 77.17, 127.65, 127.71, 127.85, 128.33, 128.38, 137.83, 138.27, 171.60. Exact mass calculated for ($C_{30}H_{43}O_6Si$ + H)$^+$ = 527.28234, mass found: 527.28226. $[\alpha]_D$ = +25.4 (*c* 1.0 in $CHCl_3$). IR = cm^{-1} 2930 (w), 2855 (w), 2360 (w), 2340 (w), 1718 (vs), 1120 (s), 1090 (s), 835 (vs), 530 (vs).

4.1.5. (1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-4,5-Bis(benzyloxy)-3-((*tert*-butyl dimethylsilyloxy)methyl)-2-oxabicyclo[4.1.0]heptane-7-carboxylic acid 8

Compound **7** (2.3 g, 4.4 mmol) in THF (50 mL) was treated with aqueous LiOH (4.5 mL, 4 M). Stirring was continued for 16 h. The mixture was neutralized by the addition of amberlite IR-120 (H^+ form) resin. The resin was removed by filtration and the filtrate was diluted with ethyl acetate (100 mL). The solution was washed with 10% aqueous citric acid (2 × 50 mL) and saturated aqueous NaCl (50 mL). The organic layers were dried on Na_2SO_4 and concentrated in vacuo. Chromatography on silica gel (0→ 100% [1% HOAc in EtOAc] in light petroleum) yielded the product **8** (1.74 g, 3.48 mmol, 79%) as a colorless syrup. ^{1}H NMR ($CDCl_3$): δ 0.12 (2 × s, 6H), 0.98 (s, 9H), 1.89 (m, 1H), 1.99 (m, 1H), 3.61 (m, 1H), 3.73 (t, 1H, J = 6.8 Hz), 3.80 (m, 2H), 3.89 (dd, 1H, J = 4.4 Hz, J = 11.2 Hz), 4.07 (dd, 1H, J = 1.4 Hz, J = 7.2 Hz), 4.66–4.84 (m, 4H), 7.32–7.43 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ −5.46, −5.33, 18.21, 24.86, 25.84, 58.44, 62.57, 71.51, 73.53, 74.88, 76.41, 76.81, 127.68, 127.74, 127.78, 127.85, 128.08, 128.33, 128.40, 137.69, 138.16, 177.81. Exact mass calculated for ($C_{28}H_{38}O_6Si$ + H)$^+$ = 499.25104, mass found: 499.25104. $[\alpha]_D$ = +21.8 (*c* 1.0, $CHCl_3$). IR = cm^{-1} 2930 (w), 2855 (w), 1690 (vs), 1455 (s), 1255 (m), 1090 (vs), 835 (vs).

4.1.6. *tert*-Butyl(1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-4,5-bis(benzyloxy)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[4.1.0]heptane-7-ylcarbamate 9

Compound **8** (1.55 g, 3.11 mmol) was coevaporated with toluene (2 × 20 mL) and taken up in *tert*-butanol (60 mL). To this solution were added freshly activated molecular sieves (rods, 4 Å), diphenylphosphoryl azide (0.94 g, 3.42 mmol), and triethylamine (0.346 g, 3.42 mmol). Stirring was continued, while gentle heating at reflux and under an argon atmosphere for 20 h. The reaction mixture was filtered, concentrated in vacuo, and taken up in ethyl acetate (150 mL). This solution was washed with 1 M HCl (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The organic layer was dried on Na_2SO_4 and concentrated in vacuo. Chromatography of the residue on silica gel (0→25% EtOAc in light petroleum) yielded the product **9** (1.28 g, 2.24 mmol, 72%) as a colorless syrup. ^{1}H

NMR ($CDCl_3$): δ 0.05 (2 × s, 6H), 0.89 (s, 9H), 1,21 (m, 1H), 1.44 (s, 9H), 2.61 (m, 1H), 3.53 (dd, 1H, J = 1.2, J = 7.6 Hz), 3.57–3.80 (m, 5H), 4.60–4.89 (m, 5H), 7.21–7.41 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −5.45, −5.36, 18.22, 25.47, 25.89, 28.34, 34.57, 56.13, 63.41, 71.24, 73.41, 75.77, 76.68, 78.79, 79.58, 127.44, 127.76, 127.89, 128.21, 128.25, 138.63, 138.74, 155.87. Exact mass calculated for $(C_{32}H_{47}NO_6Si + NH_4)^+$ = 588.35445, mass found: 588.35407. $[\alpha]_D$ = +39.0 (c 1.0, $CHCl_3$). IR = cm^{-1} 2930 (w), 2365 (w), 1720 (vs), 1455 (m), 1365 (m), 1255 (m), 1095 (s), 835 (s), 525 (vs).

4.1.7. (1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-4,5-Bis(benzyloxy)-7-((*tert*-butyloxycarbonylamino)-2-oxabicyclo[4.1.0]heptane-3-carboxylic acid 10

Chromic acid stock solution (1.0 M) (*Caution*: Chromic acid is corrosive, toxic, and carcinogenic!): Concentrated sulfuric acid (9 mL, 162 mmol) is taken up in water (50 mL). To this solution CrO_3 (10 g, 100 mmol) is added and the bright red solution is stirred until all solids are completely dissolved. The solution is diluted with water to a total volume of 100 mL.

Compound **8** (1.11 g, 1.95 mmol) in THF (20 mL) was treated with tetrabutylammonium fluoride (2.2 mL, 1 M in THF) and stirring is continued for 2 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water (2 × 50 mL). The organic fraction is dried on Na_2SO_4 and concentrated in vacuo. Chromatography on silica gel (0→60% ethylacetate in light petroleum) yielded the product (0.483 g, 1.85 mmol, 95%) as a white foam. The obtained alcohol (0.512 g, 1.12 mmol) was taken up in acetone (20 mL). The solution was cooled on ice and a freshly prepared chromic acid stock solution (2.3 mL, 2.3 mmol) added. Stirring was continued for 16 h during which the color of the reaction mixture shifted from bright orange to green. The reaction mixture was diluted with ethyl acetate (60 mL) and washed with 1 M HCl (2 × 30 mL) and saturated aqueous NaCl (30 mL). The organic layer was dried on Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (0→100% [1% HOAc in EtOAc] in light petroleum) yielding product **10** (0.451 g, 0.96 mmol, 86%) as a white foam. ^{1}H NMR ($CDCl_3$): δ 1.28 (m, 1H),1.43 (s, 9H), 2.89 (m, 1H), 3.85–3.87 (m, 2H), 3.94–3.96 (m, 1H), 4.30 (d, 1H, J = 3.2 Hz), 4.59–4.64 (m, 4H), 7.21–7.32 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 24.71, 28.35, 33.49, 56.05, 71.24, 72.20, 76.07, 127.54, 127.59, 127.76, 128.29, 128.38, 129.84, 137.72, 138.02, 175.01. Exact mass calculated for $(C_{26}H_{31}NO_7 + Na)^+$ = 492.19927, mass found: 492.19929. $[\alpha]_D$ = +43.0 (c 1.0, $CHCl_3$). IR = cm^{-1} 2980 (w), 2350 (w), 1720 (vs), 1455 (m), 1395 (m), 1255 (w), 1075 (s), 750 (s), 525 (vs).

4.1.8. (1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-Ethyl 3-(((1S,3R,4S,5R,6S,7S)-3-(azidomethyl)-4,5-bis(benzyloxy)-2-oxabicyclo[4.1.0]heptane-7-carboxamido)methyl)-4,5-bis(benzyloxy)-2-oxabicyclo[4.1.0]heptane-7-carboxylate 11

Compound **5** (183 mg, 0.42 mmol) in ethanol (10 mL) was treated with Lindlar's catalyst (30 mg). The reaction mixture was stirred vigorously and hydrogen gas was bubbled through for 5 h. The dark grey catalyst was removed by filtration and the filtrate concentrated in vacuo.

In a separate vessel, compound **6** (207 mg, 0.51 mmol) in DMF (5 mL) was treated with HATU (175 mg, 0.46 mmol) and DIPEA (260 μL, 1.50 mmol). After stirring for 5 min, the reaction mixture was added to the crude amine in the other vessel. The resulting mixture was stirred for 16 h after which the solution was diluted with ethyl acetate (50 mL), washed with 10% aqueous citric acid (2 × 25 mL) and saturated aqueous NaCl (25 mL). The organic fraction was dried on Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by gel filtration (LH-20, MeOH) giving the product (249 mg, 0.31 mmol, 74%) as an off-white foam. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 3H, J = 4.0 Hz), 1.70 (dd, 1H, J = 2.0 Hz, 6.0 Hz), 1.84 (m, 1H), 1.92 (m, 1H), 2.03 (dd, 1H, J = 2.4 Hz, J = 5.6 Hz), 3.25 (dd, 1H, J = 3.6 Hz, J = 12.8 Hz), 3.36 (t, 1H, J = 5.5 Hz), 3.44 (t, 1H, J = 5.2 Hz), 3.46–3.61 (m, 5H), 3.78 (m, 1H), 3.82 (m, 1H), 3.86 (dd, 1H, J = 1.6 Hz, J = 7.2 Hz), 3.91 (dd, 1H, J = 2.0 Hz, J = 7.2 Hz), 4.11 (q, 2H, J = 7.2 Hz), 4.51–4.72 (m, 8H), 5.97 (m, 1H), 7.22–7.35 (m, 20H). ^{13}C NMR ($CDCl_3$): δ 14.10, 22.48, 23.40, 23.69, 25.70, 40.12, 51.10, 55.84, 57.06, 60.69, 71.13, 71.44, 72.37, 72.85, 73.06, 73.46, 74.19, 75.29, 75.37, 75.54, 127.61, 127.67, 127.72, 127.81, 127.85, 127.96, 128.36, 128.42, 137.41, 137.49, 137.55, 169.92, 171.42. Exact mass calculated for $(C_{46}H_{50}N_4O_9 + H)^+$ = 803.36506, mass found: 803.36552. $[\alpha]_D$ = +18 (c 1.0, $CHCl_3$). IR = cm^{-1} 2870 (w), 2350 (w), 2100 (s), 1720 (bs), 1455 (m), 1295 (w), 1180 (w), 1075 (s), 750 (s), 525 (vs).

4.1.9. (1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-3-(((1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-3-(Azidomethyl)-4,5-bis(benzyloxy)-2-oxabicyclo[4.1.0]heptane-7-carboxamido)methyl)-4,5-bis(benzyloxy)-2-oxabicyclo[4.1.0]heptane-7-carboxylic acid 12b

Compound **11** (145 mg, 0.18 mmol) in dioxane/MeOH (2.5 mL, 4:1 v/v) was treated with aqueous LiOH (500 μL, 4 M). After stirring for 16 h the reaction mixture was neutralized by the addition of amberlite IR-120 (H^+ form) resin. The resin was filtered off and the filtrate was diluted with ethyl acetate (20 mL). The solution was washed with 10% aqueous citric acid (2 × 10 mL) and saturated aqueous NaCl (10 mL). The organic layers were dried on Na_2SO_4 and concentrated in vacuo. The residue was purified by gel filtration (LH-20, MeOH) giving the product **12b** (109 mg, 0.14 mmol, 76%) as an off white foam. ^{1}H NMR ($CDCl_3$): δ 1.71–2.31 (m, 4H), 3.23–4.22 (m, 10H), 4.50–4.72 (m, 8H), 6.02 (m, 1H), 7.10–7.51 (m, 20H). ^{13}C NMR ($CDCl_3$): δ 22.54, 23.38, 24.43, 25.74, 29.59, 40.18, 51.11, 55.90, 57.56, 71.20, 71.48, 72.45, 72.90, 73.11, 73.50, 74.08, 75.13, 75.28, 75.44, 127.68, 127.74, 127.80, 127.89, 128.03, 128.44, 128.50, 130.0, 137.34, 137.50, 170.28, 176.40. Exact mass calculated for $(C_{44}H_{47}N_4O_9 + H)^+$ = 775.33376, mass found: 775.33423. $[\alpha]_D$ = +41 (c 2.0, $CHCl_3$). IR = cm^{-1} 2870 (w), 2095 (s), 2100 (s), 1650 (m), 1455 (m), 1280 (bm), 1195 (b), 1075 (s), 735 (s), 695 (s).

4.1.10. (1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-Ethyl 3-(((1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-3-(((1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-3-(((1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-3-(azidomethyl)-4,5-bis(benzyloxy)-2-oxabicyclo[4.1.0]heptane-7-carboxamido)methyl)-4,5-bis(benzyloxy)-2-oxabicyclo[4.1.0]heptane-7-carboxamido)methyl)-4,5-bis(benzyloxy)-2-oxabicyclo[4.1.0]heptane-7-carboxamido)methyl)-4,5-bis(benzyloxy)-2-oxabicyclo[4.1.0]heptane-7-carboxylate 13

Compound **11** (97 mg, 0.12 mmol) in ethanol (3 mL) was treated with Lindlar's catalyst (10 mg). The reaction mixture was stirred vigorously and hydrogen gas was bubbled through for 5 h. The dark grey catalyst was removed by filtration and the filtrate concentrated in vacuo.

In a separate vessel, compound **12b** (101 mg, 0.13 mmol) in DMF (5 mL) was treated with HATU (46 mg, 0.12 mmol) and DIPEA (63 μL, 0.36 mmol). After stirring for 5 min, the reaction mixture was added to the crude amine in the other vessel. The reaction mixture was stirred for 16 h after which the solution was diluted with ethyl acetate (20 mL), washed with 10% aqueous citric acid (2 × 10 mL) and saturated aqueous NaCl (10 mL). The organic fraction was dried on Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by RP-HPLC using a gradient of acetonitrile in water containing 1% TFA, providing the tetramer **13** (24 mg, 15.6 μmol, 13%) as a white foam. ^{1}H NMR ($CDCl_3$): δ 1.21–1.30 (m, 3H), 1.68–2.06 (m, 8H), 3.27–4.16 (m, 26H), 4.50–4.77 (m, 16H), 5.95 (m, 3H), 7.28–7.35 (m, 40H). ^{13}C NMR ($CDCl_3$): δ 14.24, 22.60, 22.81, 23.71, 23.91, 25.59, 26.07, 40.40, 40.51, 44.92, 51.50, 56.15, 56.20, 57.24, 60.28, 60.80, 65.50, 71.44, 71.52, 71.75, 72.58, 72.67, 72.80, 73.01, 73.15, 73.35, 73.54, 73.86, 74.74, 74.79, 74.93, 75.67, 75.89, 76.04, 76.11, 76.68,

76.99, 77.32, 80.47, 81.80, 102.50, 110.07, 127.72, 127.82, 127.87, 127.96, 128.13, 128.30, 128.52, 128.56, 128.57, 137.64, 137.74, 137.83, 170.03, 170.13, 171.43. Exact mass calculated for $(C_{90}H_{96}N_6O_{17} + H)^+$ = 1533.69047, mass found: 1533.69190. $[\alpha]_D$ = +36 (*c* 0.1, $CHCl_3$). IR = cm^{-1} 3285 (w), 2920 (w), 2880 (w), 2100 (w), 1722 (w), 1635 (s), 1565 (s), 1560 (s), 1495 (w), 1455 (m), 1360 (w), 1075 (bs), 1025 (m), 875 (w), 735 (s), 695 (s).

4.1.11. (1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-Methyl 4,5-bis(benzyloxy)-7-((*tert*-butyloxycarbonylamino)-2-oxabicyclo[4.1.0]heptane-3-carboxylate 14

Compound **10** (0.217 g, 0.462 mmol) was taken up in a mixture of toluene (3 mL) and methanol (1 mL). To this mixture was added trimethylsilyldiazomethane (1.5 mL, 2 M in hexanes, 3.0 mmol) and stirring was continued for 1 h. The reaction mixture was concentrated in vacuo and used without further purification. The methyl ester **14** (0.225 g, 0.462 mmol, quantitative) was obtained as a pale yellow foam. ^{1}H NMR ($CDCl_3$): δ 1.35 (m, 1H), 1.41 (s, 9H), 2.89 (m, 1H), 3.57 (s, 3H), 3.86–3.90 (m, 3H), 4.29 (t, 1H, *J* = 1.6), 4.54–4.62 (m, 5H),7.24–7.33 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 24.74, 28.35, 33.37, 51.75, 56.22, 71.33, 72.01, 72.13, 73.66, 76.15, 79.58, 127.61, 127.76, 128.27, 128.37, 137.76, 138.06, 155.84, 170.91. Exact mass calculated for $(C_{27}H_{33}NO_7 + NH_4)^+$ = 501.25953, mass found: 501.25944. $[\alpha]_D$ = +73.4 (*c* 1.0, $CHCl_3$). IR = cm^{-1} 2980 (w), 2350 (w), 1752 (m), 1720 (vs), 1455 (m), 1365 (m), 1250 (w), 1141 (vs), 1075 (s), 735 (s), 695 (vs).

4.1.12. (1*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-Methyl 4,5-bis(benzyloxy)-7-((1*S*,3*R*,-4*S*,5*R*,6*S*,7*S*)-4,5-bis(benzyloxy)-7-(*tert*-butoxy-carbonylamino)-2-oxabicyclo[4.1.0]heptane-3-carboxamido)-2-oxabicyclo-[4.1.0]heptane-7-carboxylate 15

Compound **14** (203 mg, 0.42 mmol), was taken up in TFA/CH_2Cl_2 (10 mL, 1:1, v/v), and allowed to stand for 30 min. The solution was concentrated and the residue was coevaporated once with toluene (10 mL).

In a separate vessel, compound **10** (221 mg, 0.47 mmol) was taken up in DMF/CH_2Cl_2 (5 mL, 1:1, v/v). To this solution were added HATU (171 mg, 0.45 mmol) and DIPEA (235 μL, 1.35 mmol). After stirring for 5 min the reaction mixture was added to the crude amine in the other vessel. The resulting mixture was stirred for 16 h after which the solution was diluted with ethyl acetate (20 mL), washed with 10% aqueous citric acid (2 × 10 mL) and saturated aqueous NaCl (10 mL). The organic fraction was dried on Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by gel filtration (LH-20, MeOH) giving the product **15** (242 mg, 0.29 mmol, 68%) as an off white foam. ^{1}H NMR ($CDCl_3$): δ 1.20–1.42 (m, 11H), 2.76–2.99 (m, 3H), 3.62–4.74 (m, 15H), 6.62 (m, 1H), 7.23–7.47 (m, 20H). ^{13}C NMR ($CDCl_3$): δ 24.32, 24.99, 25.60, 28.26, 29.52, 32.44, 33.66, 35.62, 38.46, 51.68, 55.70, 55.78, 56.53, 71.09, 71.23, 71.90, 72.11, 72.72, 73.80, 74.03, 74.11, 75.65, 76.08, 77.50, 78.43, 79.65, 127.09, 127.44, 127.56, 127.66, 127.71, 127.76, 127.81, 128.02, 128.12, 128.23, 128.28, 129.72, 137.65, 137.96, 138.08, 138.22, 138.71, 155.70, 170.85, 171.16. Exact mass calculated for $(C_{48}H_{54}N_2O_{11} + H)^+$ = 835.38004, mass found: 835.38077. $[\alpha]_D$ = +36 (*c* 1.0, $CHCl_3$). IR = cm^{-1} 2870 (w), 2365 (s), 1680 (s), 1455 (m), 1250 (bw), 1070 (s), 735 (s), 695 (s).

4.1.13. (1*S*,3*S*,4*S*,5*R*,6*S*,7*S*)-4,5-Bis(benzyloxy)-7 ((1*S*,3*S*,4*S*,5*R*,6*S*,7*S*)-4,5-bis(benzyloxy)-7-(*tert*-butoxy-carbonylamino)-2-oxabicyclo[4.1.0]heptane-3-carbox-amido)-2-oxabicyclo[4.1.0] heptane-3-carboxylic acid 16b

Compound **15** (132 mg, 0.16 mmol) in $ClCH_2CH_2Cl$ (15 mL) was treated with Me_3SnOH (290 mg, 1.6 mmol) and the solution was heated at 85 °C for 16 h. The reaction mixture was concentrated in vacuo and coevaporated with toluene. The product **16b** (125 mg, 0.15 mmol, 95%) obtained as a white foam is used without further purification. ^{1}H NMR ($CDCl_3$): δ 1.20–1.35 (m, 11H), 1.42 (s, 9H), 3.0 (m, 1H), 3.50 (m, 1H), 3.60 (m, 1H), 3.80 (m, 1H), 3.95 (m, 1H), 4.10–4.20 (m, 3H), 4.35 (m, 1H), 4.50–4.80 (m, 9H), 7.20–7.40 (m, 20H). ^{13}C NMR ($CDCl_3$): δ 24.96, 28.36, 33.49, 55.45, 70.98, 71.80, 72.72, 73.48, 75.50, 76.75, 76.79, 77.00, 77.21, 127.44, 127.63, 127.68, 127.84, 127.88, 127.92, 128.26, 128.33, 128.35, 128.40, 128.50, 138.03, 138.30, 171.48. Mass found for $((C_{47}H_{52}N_2O_{11} + H)^+$ = 821.1. $[\alpha]_D$ = +46 (*c* 0.1, $CHCl_3$). IR = cm^{-1} 3300 (w), 2925 (w), 1705 (m), 1700 (m), 1680 (m), 1650 (m), 1495 (w), 1455 (w), 1365 (w), 1250 (w), 1070 (bs), 1025 (s), 730 (s), 695 (s).

4.1.14. (1*S*,3*S*,4*S*,5*R*,6*S*,7*S*)-Methyl 4,5-bis(benzyloxy)-7-(1*S*,3*S*,4*S*,5*R*,6*S*,7*S*)-4,5-bis(benzyloxy)-7-((1*S*,3*S*,4*S*,5*R*,6*S*,7*S*)-4,5-bis(benzyloxy)-7-((1*S*,3*S*,4*S*,5*R*,6*S*,7*S*)-4,5-bis(benzyloxy)-7-(*tert*-butoxy-carbonylamino)-2-oxabicyclo[4.1.0]heptane-3-carbox-amido)-2-oxabicyclo[4.1.0]heptane-3-carboxamido)-2-oxabicyclo[4.1.0]heptane-3-carboxamido)-2-oxabicyclo[4.1.0]heptane-3-carboxylate 17

Compound **15** (102 mg, 0.12 mmol) was treated with TFA/CH_2Cl_2 (1:1, v/v). Stirring was continued for 30 min, the reaction mixture concentrated and the residue coevaporated with toluene (10 mL). The obtained crude product **16a** was condensed with pre-activated compound **16b** (110 mg, 0.13 mmol) using HATU (46 mg, 0.12 mmol) and DIPEA (65 μL, 0.37 mmol) in DMF/CH_2Cl_2 (5 mL, 1:1, v/v). The reaction mixture was stirred for 16 h after which the solution was diluted with ethyl acetate (20 mL), washed with 10% aqueous citric acid (2 × 10 mL) and saturated aqueous NaCl (10 mL). The organic fraction was dried on Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by RP-HPLC using a gradient of acetonitrile in water containing 1% TFA, to give the tetramer (32 mg, 0.021 mmol, 18%) as a white foam. ^{1}H NMR ($CDCl_3$): δ 1.21–1.35 (m, 4H), 1.42 (s, 9H), 2.85–2.98 (m, 4H), 3.55 (s, 3H), 3.57–3.72 (m, 6H), 3.87–3.91 (m, 3H), 4.05–4.13 (m, 6H), 4.31 (d, *J* = 3 Hz, 1H), 4.51–4.72 (m, 17H), 6.32–6.38 (m, 3H), 7.15–7.31 (m, 40H). ^{13}C NMR ($CDCl_3$): δ 22.64, 24.42, 24.86, 24.89, 25.10, 28.36, 29.32, 29.63, 29.67, 32.46, 32.81, 32.87, 33.64, 51.86, 55.41, 55.44, 55.84, 55.86, 71.21, 71.24, 71.31, 71.52, 71.83, 72.23, 72.88, 73.00, 73.61, 73.71, 75.61, 75.67, 76.07, 76.79, 77.00, 77.22, 77.26, 79.97, 125.10, 125.30, 127.57, 127.61, 127.65, 127.70, 127.75, 127.78, 127.81, 127.83, 127.85, 127.93, 127.96, 128.01, 128.03, 128.22, 128.27, 128.34, 128.36, 128.40, 128.43, 129.03, 137.71, 138.00, 138.06, 138.07, 138.10, 138.19, 138.24, 170.99, 171.35, 171.39. Mass found for $((C_{90}H_{96}N_4O_{19}–Boc) + H)^+$ = 1438.9. $[\alpha]_D$ = +24 (*c* 0.1, $CHCl_3$). IR = cm^{-1} 3305 (w), 2920 (w), 2800 (w), 1680 (s), 1660 (s), 1650 (s), 1520 (m), 1455 (m), 1360 (w), 1090 (s), 850 (w), 730 (s), 695 (s).

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9. Based on LC/MS and NMR data compound **4** was identified as an isomer. We did not determine the stereochemistry of this minor isomer **4** (formed in 8% over the two steps) since we felt that the limited accessibility of this isomer following this particular route made it less useful in the generation of SAAs.
10. The use of LiOH to hydrolyse the ester in the dimer stage gave partial epimerization at the α–H next to the COOH group.