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Synthesis of functionalized heterocycles via a tandem Staudinger/aza-Wittig/Ugi multicomponent reaction

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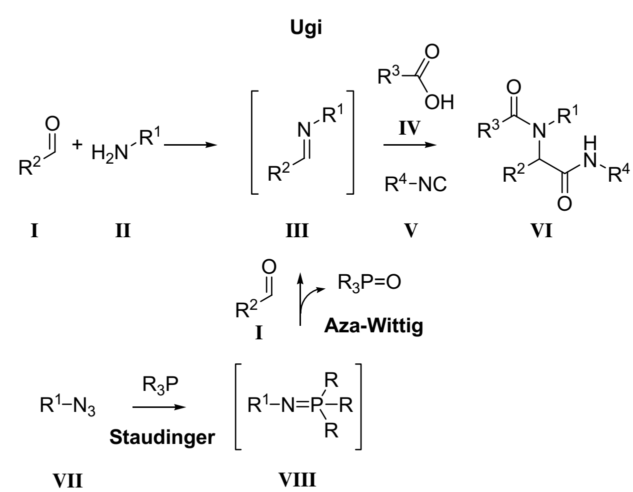
With deep sadness the authors inform the reader that our colleague, Jacques van Boom, died on July 31st, at the age of 67

Abstract—By combining a Staudinger/aza-Wittig and an Ugi three-component reaction in a one-pot process (SAWU-3CR), a new and efficient multicomponent reaction was developed. The application of this reaction on readily available azido-aldehydes gave easy access to highly functionalized, enantiomerically pure pipecolic acid amides and bridged morpholine amide derivatives. The versatility of this methodology is demonstrated by the construction of a molecular library.

1. Introduction

Multicomponent reactions (MCRs), processes in which three or more reactants are combined in one reaction vessel resulting in the formation of products featuring characteristics of all reactants, have found wide application in the synthesis of many structurally diverse molecules.[1] In 1959, Ugi et al. reported[2] the one-pot condensation of an aldehyde **I**, an amine **II**, a carboxylic acid **IV** and an isocyanide **V** (Scheme 1). This reaction, now referred to as the Ugi 4-component reaction (Ugi-4CR), provides an efficient entry to the construction of functionalized acylamidoacetamides **VI**. In the first step of the Ugi-4CR, aldehyde **I** is condensed with amine **II** to produce an intermediate imine **III** that further reacts with the isocyanide and carboxylic acid entities to the bisamide end product.

It occurred to us that the generation of the bis-substituted imine **III**, which plays a pivotal role in the Ugi-4CR process, could be accomplished by executing a tandem Staudinger/aza-Wittig event.[3] Thus, reaction of the azide **VII** with trialkyl(aryl)phosphine would lead to the formation of the intermediate phosphazene **VIII**



Scheme 1. Ugi four component and Staudinger/aza-Wittig reactions.

which, in turn, undergoes an aza-Wittig reaction with the aldehyde **I** to produce the imine **III** and the inert trialkyl(aryl)phosphine oxide. An attractive and important aspect of performing a tandem Staudinger/aza-Wittig sequence is depicted in Scheme 2. It can be seen that a substrate containing both an azide and an aldehyde, as well as functional groups (R) will give access to a substituted cyclic imine, thus opening the way to the

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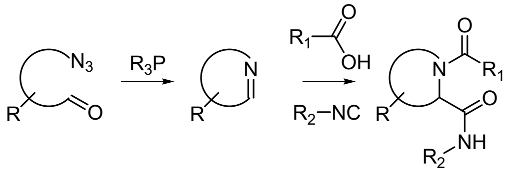


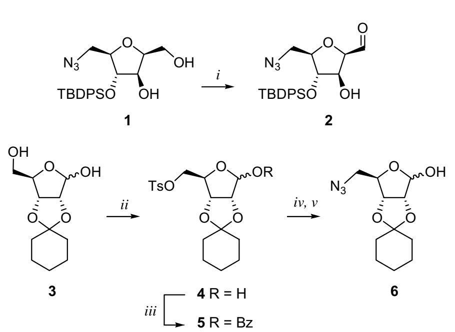
Scheme 2. Tandem Staudinger/aza-Wittig/Ugi (SAWU-3CR).

construction of cyclic dipeptides via an overall one-pot Staudinger/aza-Wittig/Ugi (SAWU-3CR) process.

Herein we report the development of a tandem one-pot SAWU-3CR process for the synthesis of highly functionalized chiral piperidines and morpholines, starting from orthogonally protected carbohydrate-derived azido-aldehydes. In addition it will be shown that the chiral information embedded in the starting carbohydrate templates provides control over the stereochemical outcome of the overall transformations, resulting in the exclusive formation of a single diastereomer in each case.

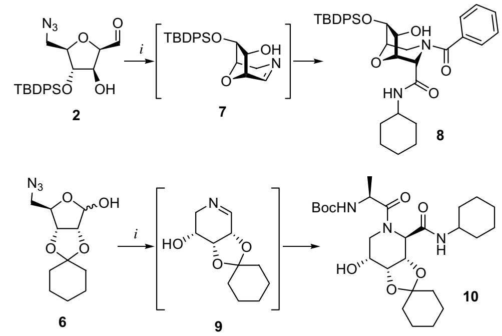
2. Results

As starting carbohydrate-derived azido-aldehydes we selected the partially protected 6-azido-2,5-anhydro-D-glucofuranoside **2** and 5-azido-D-ribofuranoside **6**, which were prepared by the following sequence of events (Scheme 3). Selective oxidation of the primary hydroxyl[4] in the known anhydroglucoside **1**[5] employing the Dess–Martin periodinane[6] afforded the target azido-aldehyde **2** in 85% yield. Selective tosylation[7] of the primary hydroxyl in 2,3-*O*-cyclohexylidene-D-ribose **3**[8] and benzoylation of the anomeric hydroxyl in the resulting tosylate **4** gave the fully protected ribofuranoside **5**. Treatment of **5** with sodium azide in DMF at elevated temperature and subsequent anomeric debenzoylation using a catalytic amount of sodium methoxide in methanol afforded the target azido hemi-acetal **6** in good overall yield.[9]



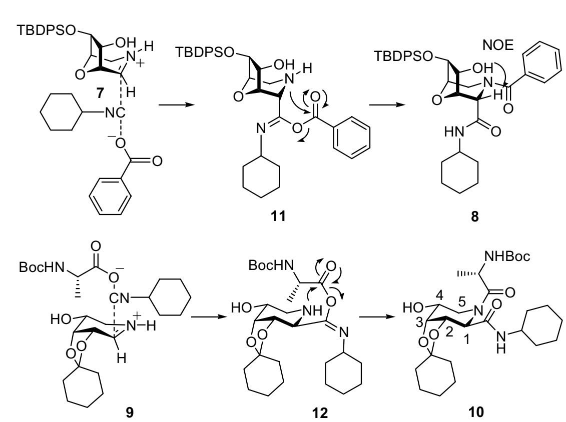
Scheme 3. Synthesis of SAWU substrates **2** and **6**. Reagents and conditions: (i) Dess–Martin periodinane, DCM, 0 °C, 2 h, 85%; (ii) TsCl (1.1 equiv), py, −5 °C→rt, 16 h; (iii) BzCl (2.5 equiv), pyridine, 1.5 h; (iv) NaN_3, DMF, 120 °C, 16 h; (v) NaOMe (cat.), MeOH, 2 h, 51% over four steps; Ts = *p*-toluenesulfonyl, Bz = benzoyl, TBDPS = *t*-butyl-diphenyl-silanyl.

With both azido-aldehydes in hand, we set out to establish their potential as precursors in the SAWU-3CR construction of morpholine-based (from **2**) and piperidine-based (from **6**) bisamides. To this end, compound **2** was subjected to trimethylphosphine in methanol at 0 °C for 15 min until evolution of nitrogen gas ceased (Scheme 4). At this stage, the intermediate imine **7** was brought to −78 °C upon which benzoic acid and cyclohexyl isocyanide were added. After stirring for 2 h at room temperature, removal of the solvent and purification by silica gel column chromatography afforded the homogeneous SAWU-3CR product **8** as a single diastereoisomer in 36% yield.[10] In a similar fashion, the intermediate imine **9**, formed upon subjection of the azido-aldehyde **6** to the Staudinger–aza-Wittig conditions, was condensed with Boc–Ala–OH and cyclohexyl isocyanide to give the pipecolic amide **10** (34%), also as a single diastereoisomer.



Scheme 4. SAWU-3CR. Reagents and conditions: (i) Me_3P, MeOH, 0 °C, 15 min, then Ph–COOH or Boc–Ala–OH, cyclohexyl–NC, −78 °C, 2 h (**8**: 36%, **10**: 34%).

Complete diastereoselectivity was observed in the formation of SAWU-3CR products **8** and **10**. The absolute configuration of the newly formed stereocentre in **8** was readily determined by NOE NMR experiments. Long range NOE interaction between the hydroxyl proton and H-1 of the morpholine ring (see Scheme 5) confirmed the axial orientation of the newly introduced *N*-(cyclohexyl) carboxamide functionality. In contrast, the assignment of the absolute configuration of the new stereocentre in **10** by NMR proved to be more complicated. No long range NOEs were detected, and the observed coupling constant between H-1 and H-2 could



Scheme 5. Mode of diastereoselective formation of **8** and **10**.

indicate either a *cis* or a *trans* relationship between the two substituents at C-1 and C-2, depending on the conformation of the piperidine ring. Fortunately, analysis of the X-ray diffraction data of compound **10** (Fig. 1), readily crystallized from chloroform/*n*-heptane, unambiguously established the *trans* relationship at C-1 and C-2, with the piperidine ring adopting a pseudo-boat conformation.

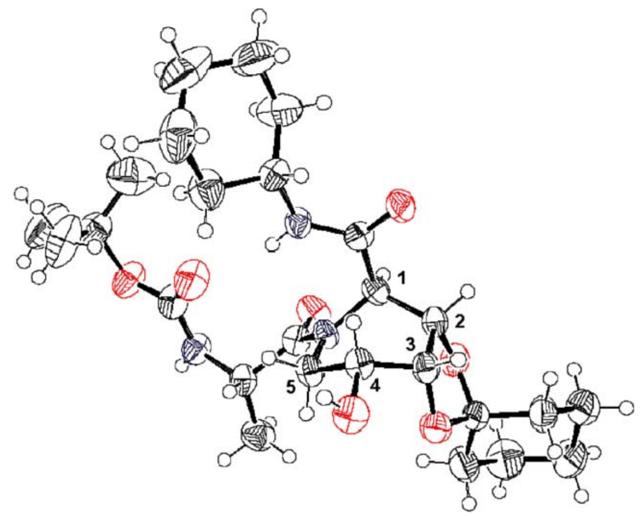


Figure 1. ORTEP representation of the X-ray crystal structure of **10**.

The stereochemical outcome of both transformations can be explained (Scheme 5) by assuming the approach of the isocyanide and acid components from the less hindered convex side of the intermediate cyclic imines **7** and **9**. Rearrangement of the resulting intermediate anhydrides **11** and **12** then leads to the *exo*-products **8** and **10**, respectively. The general applicability of the SAWU-3CR is demonstrated in the synthesis of a small library of two sets of compounds (see Fig. 2): that is six bridged morpholines (starting from **2**) and 12 piperidines (starting from **6**). The stereochemical outcome of the SAWU-3CRs was in both series highly diastereoselective. Comparison of the NMR data with those of the corresponding analogues revealed that the stereochemistry of the newly introduced stereogenic centres is the same as those of **8** (morpholines) and **10** (piperidines). The results clearly demonstrate that a variety of carboxylic acids and isocyanides can participate in a SAWU-3CR, with yields ranging from 22% **28** to a maximum of 78% **18**. Interestingly, the nature of the isocyanide has a considerable influence on the overall yield of the process, which is reflected in the decrease in yield going from *t*-butyl isocyanide to cyclohexyl isocyanide to *n*-butyl isocyanide (see e.g., **18**, **22** and **25**).

3. Conclusion

In summary, a new and efficient multicomponent reaction by combining the Staudinger–aza-Wittig mediated synthesis of imines with the Ugi-3CR mediated synthesis of functionalized bisamides has been developed. The versatility of the SAWU-3CR process is demonstrated in the preparation of a small library of diverse, chiral and enantiomerically pure functionalized piperidines and morpholines. We believe that the piperidine and morpholine scaffolds will be of great value in the field of combinatorial chemistry. The nature of the carboxylic acid- and isocyanide components can be altered, whereas the orthogonality of the hydroxyl functionalities inherent to the parent sugars opens the way to further selective derivatization. Moreover, the pipecolinic acid scaffold (e.g., **10**) holds great promise in the construction of pharmacologically active agents. Finally,

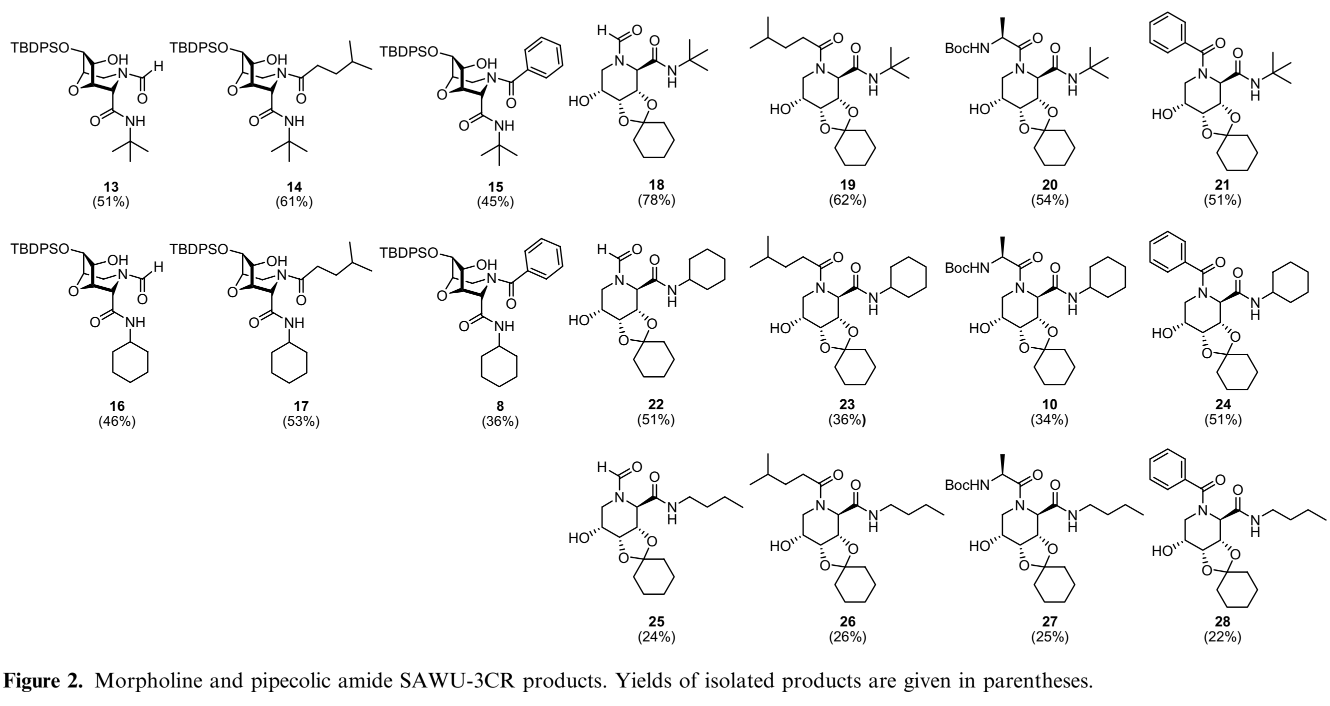


Figure 2. Morpholine and pipecolic amide SAWU-3CR products. Yields of isolated products are given in parentheses.

the transformation of carbohydrates, rich in structural and functional variation, into other azido-aldehyde derivatives opens the way to the one-pot synthesis of analogous, highly functionalized heterocyclic scaffolds.

4. Experimental

4.1. 2,5-Anhydro-6-azido-4-*O*-(*t*-butyl-diphenyl-silanyl)-6-deoxy-D-glucose 2

Dess–Martin periodinane (1.1 equiv, 4.68 g, 11 mmol) was added to a stirred, dry solution of diol **1** (4.27 g, 10 mmol) in DCM (50 mL), under an argon atmosphere, at 0 °C. After stirring for 30 min, a mixture of satd aq NaS_2O_3 and satd aq $NaHCO_3$ (50 mL, 7/3, v/v) was added. After stirring for an additional 15 min, the organic layer was separated, washed with H_2O and brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (toluene→ethyl acetate/toluene, 1/4, v/v) yielding the title compound as a colourless oil (3.61 g, 8.5 mmol, 85%): IR (thin film) 3429, 3065, 2932, 2897, 2858, 2098, 1736, 1427, 1252, 1103, 1065, 997, 821, 741, 702 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.69 (d, $J_{1,2}$ = 1.1 Hz, 1H, C(O)H), 7.70–7.58 (m, 4H, CHPh), 7.43–7.38 (m, 6H, CHPh), 4.23–3.83 (m, 4H, H-2, H-3, H-4 and H-5), 3.04–2.88 (m, 2H, H-6), 1.08 (s, 9H, *t*Bu); ^{13}C NMR (50.1 MHz, $CDCl_3$): δ 201.0 (C(O)H), 135.5 (CHPh), 132.6, 132.4 (CPh), 129.9, 127.7 (CHPh), 86.4, 81.1, 80.0, 79.0 (C-2, C-3, C-4, C-5), 51.7 (C-6), 29.7 (C*t*Bu), 26.8 (CH_3*t*Bu), ESI-MS (*m*/*e*): 426.2 $[M+H]^+$, 448.2 $[M+Na]^+$.

4.2. 5-Azido-2,3-*O*-cyclohexylidene-5-deoxy-α/β-D-ribofuranose 6

p-Toluenesulfonyl chloride (9.45 g, 49.5 mmol) was added to a cooled (0 °C) and stirred solution of 2,3-*O*-cyclohexylidene-D-ribofuranose **3** (11.5 g, 50 mmol) in dry pyridine (250 mL). The mixture was allowed to warm to room temperature and stirring was continued for 16 h. Benzoyl chloride (14.5 mL, 125 mmol, 2.5 equiv) was added and after stirring for an additional 90 min the mixture was concentrated, taken up in ethyl acetate and subsequently washed with saturated aqueous $NaHCO_3$ (2×), saturated aqueous NH_4Cl and brine (2×). The organic layer was dried ($MgSO_4$) and concentrated to obtain a yellow oil, which was coevaporated with toluene and dissolved in 250 mL dry DMF. Sodium azide (16.25 g, 250 mmol, 5 equiv) was added and the resulting suspension was stirred for 12 h at 120 °C. The mixture was concentrated, taken up in ethyl acetate and washed with saturated aqueous $NaHCO_3$ (2×) and brine (2×). The organic layer was dried ($MgSO_4$) and concentrated. The residue was dissolved in methanol (300 mL), brought to pH 9 with sodium methanolate and stirred for 14 h. After neutralization of the solution with amberlyte H^+, the mixture was filtered and concentrated in vacuo yielding a yellow oil. The residue was taken up in ethyl acetate and washed with brine (3×), dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (light petroleum ether → ethyl acetate/light petroleum ether, 1/4, v/v) yielded compound **6** (α/β, 6/1) as a pale yellow oil (6.51 g, 25.5 mmol, 51%) as well as a minor fraction of the starting material 2,3-*O*-cyclohexylidene-D-ribofuranose **3** (2.26 g, 4,9 mmol, 9.8%). $[\alpha]_D^{20} = +40$ (*c* = 0.1, MeCN); IR (thin film) 3422, 2936, 2838, 2098, 1450, 1369, 1269, 1231, 1161, 1096, 1057, 999, 968, 937 cm^{-1}; α-anomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.47 (d, $J_{1,OH}$ = 4.8 Hz, 1H, H-1), 4.66 (dd, $J_{2,3}$ = 5.9 Hz, $J_{3,4}$ = 1.1 Hz, 1H, H-3), 4.62 (d, 1H, H-2), 4.35 (ddd, $J_{4,5a}$ = 6.8 Hz, $J_{4,5b}$ = 5.5 Hz, 1H, H-4), 3.58 (dd, $J_{5a,5b}$ = 12.5 Hz, 1H, H-5a), 3.41 (dd, 1H, H-5b), 3.04 (br d, 1H, OH), 1.76–1.38 (m, 10H, CH_2–Cy); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 112.5, 102.4, 84.7, 81.1, 53.1, 35.4, 33.6, 24.2, 23.2, 22.9; ESI-MS (*m*/*e*): 278.2 $[M+Na]^+$, 533.1 $[2M+Na]^+$.

4.3. General procedure for the SAWU-3CR

Azido-aldehyde **2** (0.16 mmol) or **4** (0.25 mmol) was coevaporated with toluene and dissolved in MeOH (0.5 mL) under an argon atmosphere at 0 °C. After dropwise addition of a solution of trimethylphosphine (0.5 mmol, 0.50 mL, 1 M in toluene), stirring was continued until nitrogen evolution ceased. The mixture was cooled to −78 °C, carboxylic acid (0.5 mmol) and isocyanide (0.5 mmol) were added and stirring was continued for 12 h at rt. The mixture was concentrated and the SAWU-3CR product was isolated by flash column chromatography (toluene ethyl→acetate/toluene, 1/4, v/v).

4.4. (1*S*,2*S*,5*R*,6*S*,7*R*)-3-Benzoyl-6-(*t*-butyl-diphenyl-silanyloxy)-7-hydroxy-8-oxa-3-aza-bicyclo[3.2.1]octane-2-carboxylic acid cyclohexylamide 8

(36 mg, 58 μmol, 36%, 1.2:1 ratio of rotamers[11]): $[\alpha]_D^{20} = -3.8$ (*c* 0.25, $CDCl_3$); IR (thin film) 3394, 3304, 3071, 2930, 2856, 1651, 1624, 1539, 1448, 1427, 1391, 1362, 1252, 1192, 1151, 1103, 1060, 1028, 1005, 966, 906, 860, 843, 822, 779, 729, 700 cm^{-1}; Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.07 (m, 15H, CHPh), 6.12 (d, $J_{NH,CH}$ = 8.4 Hz, 1H, NH), 4.71 (d, $J_{1,7}$ = 6.7 Hz, 1H, H-1), 4.26 (br d, 1H, H-7), 4.13 (d, $J_{6,7}$ = 1.3 Hz, 1H, H-6), 4.12 (br s, 1H, H-5), 4.09 (s, 1H, H-2), 4.08 (d, $^2J_{4ax,4eq}$ = 13.0 Hz, 1H, H-4eq), 3.79 (m, 1H, CHCy), 3.08 (dd, $J_{4ax,5}$ = 2.7 Hz, 1H, H-4ax), 1.97–1.11 (m, 10H, Cy), 1.11 (s, 9H, *t*Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 172.5 (PhC(O)), 168.0 (C(O)NCy), 135.8, 135.7 (CHPh), 134.8, 133.7, 132.8 (CPh), 130.2, 130.1, 130.0, 128.7, 128.1, 127.9, 126.7 (CHPh), 82.6 (C-6), 81.5 (C-5), 80.6 (C-7), 77.8 (C-1), 58.7 (C-2), 48.7 (CH Cy), 43.2 (C-4), 32.9, 32.8 (CH_2Cy), 29.7 (C*t*Bu), 26.9 (CH_3*t*Bu), 25.4, 24.9, 24.7 (CH_2Cy); Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.07 (m, 15H, CHPh), 6.23 (d, $J_{NH,CH}$ = 7.7 Hz, 1H, NH), 5.12 (s, 1H, H-2), 4.82 (d, $J_{1,7}$ = 6.5 Hz, 1H, H-1), 4.45 (br dd, $J_{6,7}$ = 1.5 Hz, 1H, H-7), 3.92 (d, $J_{6,7}$ = 1.9 Hz, 1H, H-6), 3.79 (m, 1H, CHCy), 3.63 (br s, 1H, H-5), 3.41 (dd, $^2J_{4ax,4eq}$ = 12.7 Hz, $J_{4ax,5}$ = 1.6 Hz, 1H, H-4ax), 2.71 (d, 1H, H-4eq), 1.97–1.11 (m, 10H, Cy), 1.05 (s, 9H, *t*Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 173.2 (PhC(O)), 167.8 (C(O)NCy), 135.7, 135.5 (CHPh), 134.5, 133.3, 132.9 (C Ph), 130.25, 130.15, 130.07, 128.4, 128.1, 127.8, 126.9 (CHPh), 82.5

(C-6), 81.0 (C-5), 80.9 (C-7), 78.6 (C-1), 52.2 (C-2), 49.4 (C-4), 48.4 (CHCy), 33.1, 33.0 (CH_2Cy), 29.7 (C*t*Bu), 26.8 (CH_3*t*Bu), 25.5, 24.8, 24.6 (CH_2Cy); ESI-MS (*m*/*z*): 613.5 $[M+H]^+$, 635.6 $[M+Na]^+$; HRMS *m*/*z* calcd for $C_{36}H_{44}N_2O_5Si$: 613.3092, obsd: 613.3068.

4.5. (2*S*,3*S*,4*R*,5*R*)-1-(*N*-Benzyloxycarbonyl-L-alanyl)-3,4-*O*-cyclohexylidene-3,4,5-trihydroxy-pipecolic acid cyclohexylamide 10

(43 mg, 85 μmol, 34%): $[\alpha]_D^{20} = +140$ (*c* 0.1, $CDCl_3$); IR (thin film) 3294, 2924, 2844, 1676.0, 1655, 1626, 1537, 1524, 1452, 1427, 1369, 1273, 1252, 1159, 1115, 1092, 1069, 1051, 1020, 945 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.83 (d, $J_{NH,CH(Cy)} = 7.5$ Hz, 1H, NH–Cy), 5.17 (d, $J_{NH,\alpha} = 6.9$ Hz, 1H, BocNH), 5.15 (d, $J_{1,2} = 2.0$ Hz, 1H, H-1), 5.02 (d, $J_{2,3} = 7.5$ Hz, 1H, H-2), 4.58 (dd, $J_{3,4} = 3.4$ Hz, 1H, H-3), 4.51 (app p, $J_{\alpha,\beta} = 6.9$ Hz, 1H, H-α), 3.99 (ddd, $J_{4,5ax} = 10.6$ Hz, $J_{4,5eq} = 4.8$ Hz, 1H, H-4), 3.82–3.77 (dd, $J_{5ax,5eq} = 10.7$ Hz, 1H, H-5_{eq}), 3.68–3.64 (m, 1H, CHN–Cy), 3.28 (dd, 1H, H-5_{ax}), 2.29 (s, 1H, OH), 1.95–1.12 (m, 20H, CH_2–Cy), 1.45 (s, 9H, *t*Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.3, 168.2, 109.5, 72.6, 71.7, 64.4, 54.5, 48.4, 46.8, 43.8, 35.9, 33.5, 32.6, 32.5, 28.3, 25.4, 25.1, 24.7, 23.9, 23.4, 17.1; ESI-MS (*m*/*z*): 510.4 $[M+H]^+$; HRMS *m*/*z* calcd for $C_{26}H_{44}N_3O_7$: 510.3179, obsd: 510.3181.

4.6. (1*S*,2*S*,5*R*,6*S*,7*R*)-6-(*t*-Butyl-diphenyl-silanyloxy)-3-formyl-7-hydroxy-8-oxa-3-aza-bicyclo[3.2.1]octane-2-carboxylic acid *t*-butylamide 13

(43 mg, 82 μmol, 51%, 2:1 ratio of rotamers): $[\alpha]_D^{20} = -5.8$ (*c* 0.25, $CDCl_3$); IR (thin film) 3392, 3333, 3065, 2957, 2930, 2856, 1663, 1541, 1450, 1427, 1393, 1364, 1223, 1186, 1113, 1063, 1030, 997, 964, 822, 741, 702 cm^{-1}; Major rotamer: ^1H NMR (400 MHz, $CDCl_3$): 7.86 (s, 1H, C(O)H), 7.72–7.61 (m, 4H, CHPh), 7.50–7.37 (m, 6H, CHPh), 5.83 (s, 1H, NH), 4.86 (d, $J_{1,7} = 6.8$ Hz, 1H, H-1), 4.29 (br d, 1H, H-7), 4.03 (br s, 1H, H-5), 3.98 (s, 1H, H-2), 3.92 (d, $J_{6,7} = 1.6$ Hz, 1H, H-6), 3.81 (d, $^2J_{4ax,4eq} = 13.5$ Hz, 1H, H-4eq), 2.89 (dd, $J_{4ax,5} = 3.0$ Hz, 1H, H-4ax), 1.33 (s, 9H, *t*BuN), 1.07 (s, 9H, *t*BuTBDPS); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 167.6 (C(O)N*t*Bu), 164.1 (HC(O)), 135.6 (CHPh), 133.5, 133.0 (CPh), 130.3, 128.1 (CHPh), 82.9 (C-6), 81.3 (C-5), 80.4 (C-7), 77.2 (C-1), 56.7 (C-2), 51.8 (CN*t*Bu), 41.6 (C-4), 29.7 (CTBDPS), 28.7 (CH_3*t*BuN), 26.8 (CH_3TBDPS); Minor rotamer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H, C(O)H), 7.72–7.61 (m, 4H, CHPh), 7.50–7.37 (m, 6H, CHPh), 5.92 (s, 1H, NH), 4.71 (d, $J_{1,7} = 6.8$ Hz, 1H, H-1), 4.63 (s, 1H, H-2), 4.37 (br dd, $J_{6,7} = 1.7$ Hz, 1H, H-7), 3.97 (br s, 1H, H-5), 3.92 (d, 1H, H-6), 3.44 (dd, $^2J_{4ax,4eq} = 12.5$ Hz, $J_{4ax,5} = 2.6$ Hz, 1H, H-4ax), 2.65 (d, 1H, H-4eq), 1.31 (s, 9H, *t*BuN), 1.08 (s, 9H, *t*BuTBDPS); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 167.4 (C(O)N*t*Bu), 162.7 (HC(O)), 135.5 (CHPh), 133.3, 133.2 (CPh), 130.2, 128.0 (CHPh), 82.9 (C-6), 81.1 (C-5), 80.3 (C-7), 77.9 (C-1), 51.6 (C-2), 51.5 (CN*t*Bu), 46.8 (C-4), 29.7 (CTBDPS), 28.7 (CH_3*t*BuN), 26.8 (CH_3TBDPS); ESI-MS (*m*/*z*): 511.5 $[M+H]^+$, 533.2 $[M+Na]^+$.

4.7. (1*S*,2*S*,5*R*,6*S*,7*R*)-6-(*t*-Butyl-diphenyl-silanyloxy)-7-hydroxy-3-(4-methyl-pentanoyl)-8-oxa-3-aza-bicyclo-3.2.1]octane-2-carboxylic acid *t*-butylamide 14

(58 mg, 98 μmol, 61%, 4:3 ratio of rotamers): $[\alpha]_D^{20} = -5.1$ (*c* 0.25, $CDCl_3$); IR (thin film) 3385, 3298, 3064, 2957, 2930, 2858, 1663, 1630, 1558, 1456, 1427, 1393, 1364, 1286, 1223, 1196, 1111, 1063, 962, 908, 822, 735, 702 cm^{-1}; Minor rotamer: ^1H NMR (400 MHz, $CDCl_3$): 7.73–7.60 (m, 4H, CHPh), 7.50–7.37 (m, 6H, CHPh), 5.92 (s, 1H, NH), 4.75 (s, 1H, H-2), 4.71 (d, $J_{1,7} = 6.7$ Hz, 1H, H-1), 4.41 (br dd, $J_{6,7} = 2.2$ Hz, 1H, H-7), 3.93 (br s, 1H, H-5), 3.87 (d, 1H, H-6), 3.39 (dd, $^2J_{4ax,4eq} = 12.5$ Hz, $J_{4ax,5} = 2.5$ Hz, 1H, H-4ax), 2.76 (d, 1H, H-4eq), 2.20 (dt, $J_{H\text{-}\alpha a,H\text{-}\alpha b} = 16.0$ Hz, $J_{H\text{-}\alpha a,H\text{-}\beta} = 7.6$ Hz, 1H, H-αa), 2.09 (dt, $J_{H\text{-}\alpha b,H\text{-}\beta} = 7.6$ Hz, 1H, H-αb), 1.93 (dhept, $J_{H\text{-},H\text{-}\gamma} = J_{H\text{-}\gamma,H\text{-}\delta} = 7.6$ Hz, 1H, H-γ), 1.40 (m, 2H, H-β), 1.29 (s, 9H, *t*BuN), 1.08 (s, 9H, *t*BuTBDPS), 0.82 (d, 6H, H-δ); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.0 (CH_2C(O)N), 167.1 (C(O)N*t*Bu), 135.7 (CHPh), 133.5, 133.1 (CPh), 130.2, 128.0 (CHPh), 82.7 (C-6), 81.0 (C-5), 80.5 (C-7), 78.2 (C-1), 52.2 (C-2), 51.5 (CN*t*Bu), 46.7 (C-4), 33.3 (CH_2-β), 31.3 (CH_2-α), 29.7 (CTBDPS), 28.7 (CH_3*t*BuN), 27.8 (CH_2-γ), 26.8 (CH_3TBDPS), 22.4 (CH_2-δ); Minor rotamer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.73–7.60 (m, 4H, CHPh), 7.50–7.37 (m, 6H, CHPh), 5.72 (s, 1H, NH), 4.79 (d, $J_{1,7} = 6.7$ Hz, 1H, H-1), 4.23 (br d, 1H, H-7), 4.17 (s, 1H, H-2), 4.06 (br s, 1H, H-5), 4.03 (d, $^2J_{4ax,4eq} = 13.6$ Hz, 1H, H-4eq), 3.89 (d, $J_{6,7} = 1.6$ Hz, 1H, H-6), 2.84 (dd, $J_{4ax,5} = 2.6$ Hz, 1H, H-4ax), 2.20 (dt, $J_{H\text{-}\alpha a,H\text{-}\alpha b} = 16.0$, Hz, $J_{H\text{-}\alpha a,H\text{-}\beta} = 7.6$ Hz, 1H, H-αa), 2.09 (dt, $J_{H\text{-}\alpha b,H\text{-}\beta} = 7.6$ Hz, 1H, H-αb), 1.93 (dhept, $J_{H\text{-}\beta,H\text{-}\gamma} = J_{H\text{-}\gamma,H\text{-}\delta} = 7.6$ Hz, 1H, H-γ), 1.40 (m, 2H, H-β), 1.32 (s, 9H, *t*BuN), 1.08 (s, 9H, *t*BuTBDPS), 0.82 (d, 6H, H-δ); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.3 (CH_2C(O)N), 168.3 (C(O)N*t*Bu), 135.7 (CHPh), 133.7, 133.2 (CPh), 130.2, 128.0 (CHPh), 83.0 (C-6), 81.7 (C-5), 80.2 (C-7), 76.7 (C-1), 56.5 (C-2), 51.7 (CN*t*Bu), 42.3 (C-4), 33.4 (CH_2-β), 30.4 (CH_2-α), 29.7 (CTBDPS), 28.7 (CH_3*t*BuN), 27.6 (CH_2-γ), 26.8 (CH_3TBDPS), 22.3 (CH_2-δ); ESI-MS (*m*/*z*): 581.4 $[M+H]^+$, 603.5 $[M+Na]^+$; HRMS *m*/*z* calcd for $C_{33}H_{48}N_2O_5Si$: 581.3405, obsd: 581.3383.

4.8. (1*S*,2*S*,5*R*,6*S*,7*R*)-3-Benzoyl-6-(*t*-butyl-diphenyl-silanyloxy)-7-hydroxy-8-oxa-3-aza-bicyclo[3.2.1]octane-2-carboxylic acid *t*-butylamide 15

(43 mg, 72 μmol, 45%, 1.1:1 ratio of rotamers): $[\alpha]_D^{20} = -2.7$ (*c* 0.25, $CDCl_3$); IR (thin film) 3395, 3308, 3065, 2957, 2930, 2858, 1663, 1622, 1558, 1427, 1393, 1364, 1286, 1223, 1111, 1059, 1030, 1005, 964, 822, 739, 702 cm^{-1}; Major rotamer: ^1H NMR (400 MHz, $CDCl_3$): 7.78–7.06 (m, 15H, CHPh), 5.88 (s, 1H, NH), 5.04 (s, 1H, H-2), 4.84 (d, $J_{1,7} = 6.7$ Hz, 1H, H-1), 4.44 (br s, 1H, H-7), 3.90 (d, $J_{6,7} = 2.4$ Hz, 1H, H-6), 3.64 (br s, 1H, H-5), 3.39 (dd, $^2J_{4ax,4eq} = 13.0$ Hz, $J_{4ax,5} = 2.3$ Hz, 1H, H-4ax), 2.76 (d, 1H, H-4eq), 1.35 (s, 9H, *t*BuN), 1.05 (s, 9H, *t*BuTBDPS); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 172.4 (PhC(O)), 167.7 (C(O)N*t*Bu), 135.7, 135.5 (CHPh), 135.0, 133.3, 132.8 (CPh), 130.0, 129.9, 128.7, 128.1, 127.9 (CHPh), 82.5

(C-6), 81.0 (C-5), 80.9 (C-7), 78.5 (C-1), 52.4 (C-2), 51.5 (CN*t*Bu), 49.3 (C-4), 29.7 (CTBDPS), 28.8 (CH_3*t*BuN), 26.8 (CH_3TBDPS); Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78–7.06 (m, 15H, CHPh), 5.65 (s, 1H, NH), 4.65 (d, $J_{1,7}$ = 6.7 Hz, 1H, H-1), 4.21 (br d, 1H, H-7), 4.18 (d, $^2J_{4ax,4eq}$ = 13.0 Hz, 1H, H-4eq), 4.15 (d, $J_{6,7}$ = 1.7 Hz, 1H, H-6), 4.12 (br s, 1H, H-5), 4.01 (s, 1H, H-2), 3.14 (dd, $J_{4ax,5}$ = 3.0 Hz, 1H, H-4ax), 1.34 (s, 9H, *t*BuN), 1.10 (s, 9H, *t*BuTBDPS); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 173.1 (PhC(O)), 168.2 (C(O)N*t*Bu), 135.7, 135.6 (CHPh), 134.4, 133.7, 133.2 (CPh), 130.22, 130.16, 128.2, 128.1, 126.7 (CHPh), 82.6 (C-6), 81.6 (C-5), 80.6 (C-7), 77.8 (C-1), 58.8 (C-2), 51.8 (CN*t*Bu), 43.1 (C-4), 29.7 (CTBDPS), 28.7 (CH_3*t*BuN), 26.9 (CH_3TBDPS); ESI-MS (*m/z*): 587.6 $[M+H]^+$, 609.4 $[M+Na]^+$; HRMS *m/z* calcd for $C_{34}H_{42}N_2O_5Si$: 587.2936, obsd: 587.2910.

4.9. (1*S*,2*S*,5*R*,6*S*,7*R*)-6-(*t*-Butyl-diphenyl-silanyloxy)-3-formyl-7-hydroxy-8-oxa-3-aza-bicyclo[3.2.1]octane-2-carboxylic acid cyclohexylamide 16

(41 mg, 74 µmol, 46%, 2:1 ratio of rotamers): $[\alpha]_D^{20} = -3.9$ (*c* 0.25, $CDCl_3$); IR (thin film) 3285, 3065, 2930, 2855, 1655, 1539, 1450, 1427, 1387, 1250, 1113, 1063, 1030, 999, 964, 822, 741, 704 cm^{-1}; Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H, C(O)H), 7.72–7.62 (m, 4H, CHPh), 7.50–7.38 (m, 6H, CHPh), 5.96 (d, $J_{NH,CH}$ = 8.1 Hz, 1H, NH), 4.90 (d, $J_{1,7}$ = 6.9 Hz, 1H, H-1), 4.71 (s, 1H, H-2), 4.31 (br d, 1H, H-7), 4.07 (br s, 1H, H-5), 4.03 (s, 1H, H-2), 3.94 (d, 1H, H-6), 3.88 (m, 1H, CHCy), 3.81 (d, $^2J_{4ax,4eq}$ = 13.5 Hz, 1H, H-4eq), 2.90 (dd, $J_{4ax,5}$ = 2.8 Hz, 1H, H-4ax), 1.98–1.10 (m, 10H, CH_2Cy), 1.09 (s, 9H, *t*Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 167.4 (C(O)NCy), 164.1 (HC(O)), 135.6 (CHPh), 133.5, 133.0 (CPh), 130.2, 128.1 (CHPh), 82.9 (C-6), 81.3 (C-5), 80.4 (C-7), 77.2 (C-1), 56.3 (C-2), 47.1 (CHCy), 41.6 (C-4), 32.9, 32.8 (CH_2Cy), 29.7 (C*t*Bu), 26.8 (CH_3*t*Bu), 25.4, 24.7 (CH_2Cy); Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H, C(O)H), 7.72–7.62 (m, 4H, CHPh), 7.50–7.38 (m, 6H, CHPh), 5.90 (d, $J_{NH,CH}$ = 7.8 Hz, 1H, NH), 4.85 (d, $J_{1,7}$ = 6.8 Hz, 1H, H-1), 4.71 (s, 1H, H-2), 4.40 (br d, 1H, H-7), 3.96 (br s, 1H, H-5), 3.94 (s, 1H, H-6), 3.88 (m, 1H, CHCy), 3.39 (dd, $^2J_{4ax,4eq}$ = 12.7 Hz, $J_{4ax,5}$ = 2.5 Hz, 1H, H-4ax), 2.66 (d, 1H, H-4eq), 1.98–1.10 (m, 10H, CH_2Cy), 1.09 (s, 9H, *t*Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 167.1 (C(O)NCy), 163.5 (HC(O)), 135.5 (CHPh), 133.5, 133.2 (CPh), 130.2, 128.0 (CHPh), 82.9 (C-6), 81.1 (C-5), 80.3 (C-7), 77.9 (C-1), 51.4 (C-2), 48.6 (CHCy), 46.8 (C-4), 33.0, 32.9 (CH_2Cy), 29.7 (C*t*Bu), 26.8 (CH_3*t*Bu), 25.4, 24.7 (CH_2Cy); ESI-MS (*m/z*): 537.2 $[M+H]^+$, 559.4 $[M+Na]^+$; HRMS *m/z* calcd for C_{30} $H_{40}N_2$ O_5 Si: 537.2779, obsd: 537.2763.

4.10. (1*S*,2*S*,5*R*,6*S*,7*R*)-6-(*t*-Butyl-diphenyl-silanyloxy)-7-hydroxy-3-(4-methyl-pentanoyl)-8-oxa-3-aza-bicyclo-[3.2.1]octane-2-carboxylic acid cyclohexylamide 17

(53 mg, 85 µmol, 53%, 2:1 ratio of rotamers): $[\alpha]_D^{20} = -3.5$ (*c* 0.25, $CDCl_3$); IR (thin film) 3391, 3304, 3064, 2930, 2856, 1636, 1539, 1448, 1427, 1387, 1362, 1250, 1192, 1106, 1063, 1030, 968, 907, 845, 822, 733, 702 cm^{-1}; Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.71–7.61 (m, 4H, CHPh), 7.49–7.39 (m, 6H, CHPh), 5.82 (d, $J_{NH,CH}$ = 8.3 Hz, 1H, NH), 4.82 (d, $J_{1,7}$ = 4.2 Hz, 1H, H-1), 4.25 (s, 1H, H-2), 4.22 (br d, 1H, H-7), 4.07 (br s, 1H, H-5), 4.04 (d, $^2J_{4ax,4eq}$ = 12.7 Hz, 1H, H-4eq), 3.89 (d, $J_{6,7}$ = 1.5 Hz, 1H, H-6), 3.80 (m, 1H, CHCy), 2.84 (dd, $J_{4ax,5}$ = 2.9 Hz, 1H, H-4ax), 2.20–1.10 (m, 15H, Cy and *i*-pentyl), 1.08 (s, 9H, *t*Bu), 0.82 (d, $J_{\gamma,\delta}$ = 6.5 Hz, 6H, H-δ); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.4 (CH_2C(O)N), 168.0 (C(O)N*t*Bu), 135.7 (CHPh), 133.7, 133.1 (CPh), 130.3, 128.2 (CH Ph), 82.8 (C-6), 81.7 (C-5), 80.6 (C-7), 78.1 (C-1), 56.2 (C-2), 48.5 (CHCy), 42.5 (C-4), 33.3 (CH_2-β), 32.9, 32.8 (CH_2Cy), 31.3 (CH_2-α), 29.7 (C*t*Bu), 27.6 (CH_2-γ), 26.8 (CH_3*t*Bu), 25.4, 24.8, 24.7 (CH_2Cy), 22.3 (CH_2-δ); Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71–7.61 (m, 4H, CHPh), 7.49–7.39 (m, 6H, CHPh), 5.88 (d, $J_{NH,CH}$ = 7.8 Hz, 1H, NH), 4.84 (s, 1H, H-2), 4.75 (d, $J_{1,7}$ = 6.7 Hz, 1H, H-1), 4.40 (br dd, $J_{6,7}$ = 1.7 Hz, 1H, H-7), 3.94 (br s, 1H, H-5), 3.88 (d, 1H, H-6), 3.72 (m, 1H, CHCy), 3.38 (dd, $^2J_{4ax,4eq}$ = 12.6 Hz, $J_{4ax,5}$ = 2.3 Hz, 1H, H-4ax), 2.80 (d, 1H, H-4eq), 2.20–1.10 (m, 15H, Cy and *i*-pentyl), 1.09 (s, 9H, *t*Bu), 0.82 (d, $J_{\gamma,\delta}$ = 6.5 Hz, 6H, H-δ); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.0 (CH_2C(O)N), 167.8 (C(O)N*t*Bu), 135.6 (CHPh), 133.7, 133.1 (CPh), 130.2, 128.0 (CH Ph), 83.0 (C-6), 81.7 (C-5), 80.6 (C-7), 78.1 (C-1), 51.9 (C-2), 48.2 (CHCy), 46.1 (C-4), 33.3 (CH_2-β), 33.1, 33.0 (CH_2Cy), 30.4 (CH_2-α), 29.7 (C*t*Bu), 27.6 (CH_2-γ), 26.8 (CH_3*t*Bu), 25.5, 24.8, 24.7 (CH_2Cy), 22.4 (CH_2-δ); ESI-MS (*m/z*): 607.5 $[M+H]^+$, 629.5 $[M+Na]^+$; HRMS *m/z* calcd for C_{35} $H_{50}N_2$ O_5 Si: 607.3562, obsd: 607.3542.

4.11. (2*S*,3S,4*R*,5*R*)-3,4-*O*-Cyclohexylidene-1-formyl-3,4,5-trihydroxy-pipecolic acid *t*-butylamide 18

(66 mg, 195 µmol, 78%): $[\alpha]_D^{20} = +120$ (*c* 0.7, $CDCl_3$); IR (thin film) 3304, 2924, 1682, 1643, 1551, 1450, 1416, 1367, 1286, 1165, 1097, 1086, 1042, 988, 949 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): Major rotamer: δ 8.21 (s, 1H, C(O)H), 6.82 (s, 1H, NH), 4.95 (d, $J_{1,2}$ = 2.1 Hz, 1H, H-1), 4.81 (dd, $J_{2,3}$ = 7.2 Hz, 1H, H-2), 4.67 (dd, $J_{3,4}$ = 4.2 Hz, 1H, H-3), 4.04 (dddd, $J_{4,5eq}$ = 4.2 Hz, $J_{4,5ax}$ = 10.4 Hz, $J_{4,OH}$ = 9.2 Hz, 1H, H-4), 3.47 (dd, $J_{5ax,5eq}$ = 11.1 Hz, 1H, H-5_{eq}), 3.38 (dd, 1H, H-5_{ax}), 2.45 (d, 1H, OH), 1.74–1.38 (m, 10H, CH_2–Cy), 1.34 (s, 9H, *t*Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$): Major rotamer: δ 168.2, 164.3, 109.4, 72.4, 72.0, 64.5, 53.4, 43.9, 35.8, 33.4, 28.5, 25.0, 23.9, 23.5; ESI-MS (*m/z*): 341.1 $[M+H]^+$; HRMS *m/z* calcd for C_{17} $H_{29}N_2$ O_5: 341.2076, obsd: 341.2078.

4.12. (2*S*,3*S*,4*R*,5*R*)-3,4-*O*-Cyclohexylidene-3,4,5-trihydroxy-1-(4-methyl-pentanoyl)-pipecolic acid *t*-butylamide 19

(64 mg, 155 µmol, 62%): $[\alpha]_D^{20} = +153$ (*c* 0.6, $CDCl_3$); IR (thin film) 3317, 2934, 1670, 1630, 1541, 1449, 1416, 1366, 1225, 1163, 1094, 1045, 949 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (s, 1H, NH), 5.06 (d, $J_{1,2}$ = 2.5 Hz, 1H, H-1), 4.80 (ddd, $J_{2,3}$ = 7.5 Hz,

$^4J_{3,5eq}$ = 1.1 Hz, 1H, H-2), 4.64 (dd, $J_{3,4}$ = 3.9 Hz, 1H, H-3), 4.04 (app dt, $J_{4,5eq}$ = 4.6 Hz, $J_{4,5ax}$ = 11.0 Hz, 1H, H-4), 3.47 (ddd, $J_{5ax,5eq}$ = 10.6 Hz, 1H, H-5$_{eq}$), 3.26 (app t, 1H, H-5$_{ax}$), 2.38–2.31 (m, 3H, OH and CH$_2$-α), 1.65–1.24 (m, 13H, CH$_2$-β, CH-γ and CH$_2$–Cy), 1.28 (s, 9H, *t*Bu), 0.93 (d, *J* = 6.4 Hz, 3H, CH$_3$-δ), 0.91 (d, *J* = 6.4 Hz, 3H, CH$_3$-δ); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ 175.7, 169.5, 109.2, 72.4, 71.5, 64.8, 54.9, 51.0, 44.3, 35.8, 33.7, 33.3, 31.6, 28.5, 27.8, 25.0, 23.9, 23.4, 22.3, 22.2; ESI-MS (*m*/*e*): 411.2 [M+H]$^+$; HRMS *m*/*z* calcd for $C_{22}H_{39}N_2O_5$: 411.2859, obsd: 411.2950.

4.13. (2*S*,3*S*,4*R*,5*R*)-1-(*N*-Benzyloxycarbonyl-L-alanyl)-3,4-*O*-cyclohexylidene-3,4,5-trihydroxy-pipecolic acid *t*-butylamide 20

(65 mg, 135 μmol, 54%): $[\alpha]_D^{20}$ = +119 (*c* 0.2, CDCl$_3$); IR (thin film) 3333.7, 2937, 1695, 1643, 1514, 1448, 1433, 1366, 1165, 1102, 1093, 1049, 947, 908 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.74 (s, 1H, NH), 5.10 (d, $J_{NH,\alpha}$ = 7.1 Hz, 1H, BocNH), 5.04 (s, 1H, H-1), 4.90 (d, $J_{2,3}$ = 6.8 Hz, 1H, H-2), 4.57 (dd, $J_{3,4}$ = 3.4 Hz, 1H, H-3), 4.51 (app p, $J_{\alpha,\beta}$ = 7.1 Hz, 1H, H-α), 4.05–4.01 (m, 1H, H-4), 3.77–3.73 (m, 1H, H-5$_{eq}$), 3.24 (app t, $J_{4,5ax}$ = 10.8 Hz, 1H, H-5$_{ax}$), 2.29 (d, $J_{4,OH}$ = 8.0 Hz, 1H, OH), 1.95–1.12 (m, 10H, CH$_2$–Cy), 1.41 (s, 9H, O*t*Bu), 1.26 (s, 9H, N*t*Bu); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ 175.5, 168.7, 109.4, 72.4, 71.6, 64.5, 55.2, 51.3, 46.9, 43.8, 35.9, 33.4, 28.5, 28.3, 25.1, 23.8, 23.4, 17.3; ESI-MS (*m*/*z*): 484.5 [M+H]$^+$; HRMS *m*/*z* calcd for $C_{24}H_{42}N_3O_7$: 484.3023, obsd: 484.3011.

4.14. (2*S*,3*S*,4*R*,5*R*)-1-Benzoyl-3,4-*O*-cyclohexylidene-3,4,5-trihydroxy-pipecolic acid *t*-butylamid 21

(52 mg, 125 μmol, 51%): $[\alpha]_D^{20}$ = +105 (*c* 0.7, CDCl$_3$); IR (thin film) 2924, 2852, 1689, 1674, 1628, 1541, 1448, 1418, 1366, 1226, 1163, 1102, 1093, 1045, 991, 947 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.59–7.43 (m, 5H, CH$_{arom}$), 6.05 (br s, 1H, NH), 5.21 (d, $J_{1,2}$ = 1.8 Hz, 1H, H-1), 4.88 (dd, $J_{2,3}$ = 7.1 Hz, 1H, H-2), 4.65 (dd, $J_{3,4}$ = 4.0 Hz, 1H, H-3), 3.96 (app dt, $J_{4,5ax}$ = 4.0 Hz, $J_{4,5eq}$ = 10.6 Hz, 1H, H-4), 3.37 (app t, $J_{3,4}$ = 11.2 Hz, 1H, H-5$_{ax}$), 3.24 (dd, 1H, H-5$_{ax}$), 1.73–1.26 (m, 10H, CH$_2$–Cy), 1.35 (s, 9H, *t*Bu); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ 173.3, 166.8, 135.2, 133.4, 130.2, 130.1, 128.6, 128.4, 126.9, 109.4, 72.5, 71.9, 64.7, 55.8, 46.6, 35.9, 33.5, 29.7, 28.6, 25.1, 24.0, 23.5; ESI-MS (*m*/*z*): 417.4 [M+H]$^+$; HRMS *m*/*z* calcd for $C_{23}H_{33}N_2O_5$: 417.2389, obsd: 417.2433.

4.15. (2*S*,3*S*,4*R*,5*R*)-3,4-*O*-Cyclohexylidene-1-formyl-3,4,5-trihydroxy-pipecolic acid cyclohexylamide 22

(47 mg, 128 μmol, 51%): $[\alpha]_D^{20}$ = +119 (*c* 0.2, CDCl$_3$); IR (thin film) 3306, 2932, 2855, 1665, 1645, 1539, 1408, 1369, 1163, 1093, 1086, 1043, 988, 949 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): Major rotamer: δ 8.18 (s, 1H, C(O)H), 6.79 (d, $J_{NH,CHN}$ = 7.6 Hz, 1H, NH), 4.95 (d, $J_{1,2}$ = 2.1 Hz, 1H, H-1), 4.79 (dd, $J_{2,3}$ = 7.2 Hz, 1H, H-2), 4.63 (dd, $J_{3,4}$ = 4.2 Hz, 1H, H-3), 4.18–4.16 (m, 1H, H-4), 3.68–3.64 (m, 1H, CHN–Cy), 3.44 (dd, $J_{4,5eq}$ = 4.2, $J_{5ax,5eq}$ = 11.3 Hz, 1H, H-5$_{eq}$), 3.35 (dd, $J_{4,5ax}$ = 10.9 Hz, 1H, H-5$_{ax}$), 2.47 (d, $J_{4,OH}$ = 7.8 Hz, 1H, OH), 1.89–1.14 (m, 20H, CH$_2$–Cy); ^{13}C NMR (100.6 MHz, CDCl$_3$): Major rotamer: δ 173.3, 164.3, 109.4, 72.4, 72.1, 64.5, 53.8, 48.3, 43.9, 35.8, 33.4, 32.5, 25.4, 23.9, 23.5; ESI-MS (*m*/*z*): 367.4 [M+H]$^+$; HRMS *m*/*z* calcd for $C_{19}H_{31}N_2O_5$: 367.2233, obsd: 367.2202.

4.16. (2*S*,3*S*,4*R*,5*R*)-3,4-*O*-Cyclohexylidene-3,4,5-trihydroxy-1-(4-methyl-pentanoyl)-pipecolic acid cyclohexylamide 23

(40 mg, 91 μmol, 36%): $[\alpha]_D^{20}$ = +138 (*c* 0.3, CDCl$_3$); IR (thin film) 3306, 2932, 2853, 1732, 1634, 1533, 1448, 1416, 1366, 1163, 1092, 1045, 947 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.10 (d, $J_{NH,CH}$ = 7.9 Hz, 1H, NH), 5.09 (d, $J_{1,2}$ = 2.4 Hz, 1H, H-1), 4.82 (dd, $J_{2,3}$ = 7.4 Hz, 1H, H-2), 4.64 (dd, $J_{3,4}$ = 3.8 Hz, 1H, H-3), 4.05–4.01 (m, 1H, H-4), 3.69–3.57 (m, 1H, C*H*N), 3.45 (dd, $J_{4,5eq}$ = 4.7 Hz, $J_{5ax,5eq}$ = 10.5 Hz, 1H, H-5$_{eq}$), 3.25 (app t, $J_{5ax,4}$ = 11.0 Hz, 1H, H-5$_{ax}$), 2.41–2.36 (m, 3H, OH and CH$_2$-α), 1.95–1.12 (m, 23H, CH$_2$-β, CH-γ and CH$_2$–Cy), 0.93 (d, *J* = 6.4 Hz, 3H, CH$_3$-δ), 0.91 (d, *J* = 6.4 Hz, 3H, CH$_3$-δ′); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ 175.7, 169.2, 109.3, 72.4, 71.5, 64.8, 54.3, 47.9, 44.4, 35.8, 33.7, 33.4, 32.5, 31.6, 27.8, 25.5, 25.1, 24.4, 23.9, 23.5, 22.4, 22.3; ESI-MS (*m*/*z*): 437.3 [M+H]$^+$; HRMS *m*/*z* calcd for $C_{24}H_{41}N_2O_5$: 437.3015, obsd: 437.2949.

4.17. (2*S*,3*S*,4*R*,5*R*)-1-Benzoyl-3,4-*O*-cyclohexylidene-3,4,5-trihydroxy-pipecolic acid cyclohexylamide 24

(56 mg, 128 μmol, 51%): $[\alpha]_D^{20}$ = +119 (*c* 1.0, CDCl$_3$); IR (thin film) 3317, 2924, 2862, 1736, 1626, 1531, 1447, 1412, 1371, 1244, 1163, 1102, 1093, 1045, 949 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.48–7.37 (m, 6H, CH$_{arom}$ and NH), 5.24 (d, $J_{1,2}$ = 1.8 Hz, 1H, H-1), 4.88 (dd, $J_{2,3}$ = 7.0 Hz, 1H, H-2), 4.64 (dd, $J_{3,4}$ = 3.9 Hz, 1H, H-3), 4.02–3.92 (m, 1H, H-4), 3.84–3.61 (m, 1H, CHN–Cy), 3.36 (app t, $J_{5ax,4}$ = $J_{5ax,5eq}$ = 11.1 Hz, 1H, H-5$_{ax}$), 3.22 (dd, $J_{4,5eq}$ = 3.9 Hz, 1H, H-5$_{eq}$), 2.44 (d, $J_{4,OH}$ = 9.3 Hz, 1H, OH), 1.87–1.12 (m, 20H, CH$_2$–Cy); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ 173.3, 168.8, 135.1, 130.2, 128.6, 126.9, 109.4, 72.5, 71.9, 64.7, 55.1, 48.0, 46.6, 43.4, 35.9, 33.5, 32.6, 32.5, 29.6, 25.5, 25.1, 24.4, 24.0, 23.5; ESI-MS (*m*/*z*): 443.2 [M+H]$^+$, 465.2 [M+Na]$^+$, 885.5 [2M+H]$^+$, 907.5 [2M+Na]$^+$; HRMS *m*/*z* calcd for $C_{25}H_{35}N_2O_5$: 443.2546, obsd: 443.2539.

4.18. (2*S*,3*S*,4*R*,5*R*)-3,4-*O*-Cyclohexylidene-1-formyl-3,4,5-trihydroxy-pipecolic acid *n*-butylamide 25

(20 mg, 60 μmol, 24%): $[\alpha]_D^{20}$ = +95 (*c* 0.3, CDCl$_3$); IR (thin film) 3305, 2932, 2834, 1647, 1537, 1416, 1369, 1286, 1163, 1092, 1043, 988, 947 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): Major rotamer: δ 8.18 (s, 1H, C(O)H), 6.90 (s, 1H, NH), 4.96 (d, $J_{1,2}$ = 2.0 Hz, 1H, H-1), 4.79 (dd, $J_{2,3}$ = 7.2 Hz, 1H, H-2), 4.6 (dd, $J_{3,4}$ = 4.2 Hz, 1H, H-3), 4.04–4.00 (m, 1H, H-4), 3.49–3.16 (m, 2H, H-5$_{eq}$ and H-5$_{ax}$), 2.45 (d, $J_{4,OH}$ = 9.2 Hz, 1H, OH), 1.74–1.25 (m, 14H, CH$_2$–Cy and CH$_2$–Bu), 0.91 (t, *J* = 7.5 Hz, 3H, CH$_3$); ^{13}C NMR

(100.6 MHz, $CDCl_3$): Major rotamer: 168.8, 164.3, 109.4, 72.4, 72.0, 64.4, 53.6, 43.9, 39.2, 35.8, 33.4, 31.3, 25.0, 23.9, 23.5, 20.0, 13.6; ESI-MS (*m/z*): 341.1 $[M+H]^+$; HRMS *m/z* calcd for $C_{17}H_{29}N_2O_5$: 341.2076, obsd: 341.2081.

4.19. (2*S*,3*S*,4*R*,5*R*)-3,4-*O*-cyclohexylidene-3,4,5-trihydroxy-1-(4-methyl-pentanoyl)-pipecolic acid *n*-butylamide 26

(27 mg, 65 μmol, 26%): $[\alpha]_D^{20} = +132$ (*c* 0.4, $CDCl_3$); IR (thin film) 3317, 2934, 2862, 1735, 1634, 1533, 1416, 1367, 1271, 1232, 1163, 1094, 1045, 949 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (t, $J_{NH} = 5.9$ Hz, 1H, CH_2NH), 5.14 (d, $J_{1,2} = 2.5$ Hz, 1H, H-1), 4.85 (dd, $J_{2,3} = 7.5$ Hz, 1H, H-2), 4.64 (dd, $J_{3,4} = 3.9$ Hz, 1H, H-3), 4.07 (m, 1H, H-4), 3.49 (dd, $J_{5ax,5eq} = 10.6$ Hz, $J_{4,5eq} = 11.5$ Hz, 1H, H-5_{eq}), 3.29 (dd, $J_{4,5ax} = 4.9$ Hz, 1H, H-5_{ax}), 3.19 (dt, $J = 6.8$ Hz, 2H, CH_2CH_2NH), 2.40–2.35 (m, 3H, OH and CH_2-α), 1.72–1.27 (m, 17H, CH_2-β, CH-γ, 2 × CH_2*n*-Bu and CH_2–Cy), 0.961 (d, $J_{\gamma,\delta} = 6.4$ Hz, 3H, CH_3-δ), 0.959 (d, $J_{\gamma,\delta'} = 6.4$ Hz, 3H, CH_3-δ'), 0.93 (t, $J = 7.3$ Hz, 3H, CH_3*n*-Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.7, 170.1, 109.3, 72.4, 71.5, 64.7, 54.2, 44.3, 38.9, 35.8, 33.6, 33.4, 31.6, 31.4, 27.8, 25.1, 23.9, 23.5, 22.4, 22.2, 20.0, 13.7; ESI-MS (*m/e*): 411.2 $[M+H]^+$; HRMS *m/z* calcd for $C_{22}H_{39}N_2O_5$: 411.2859, obsd: 411.2932.

4.20. (2*S*,3*S*,4*R*,5*R*)-1-(*N*-Benzyloxycarbonyl-L-alanyl)-3,4-*O*-cyclohexylidene-3,4,5-trihydroxy-pipecolic acid *n*-butylamide 27

(30 mg, 63 μmol, 25%): $[\alpha]_D^{20} = +94$ (*c* 0.1, $CDCl_3$); IR (thin film) 3304, 2928, 2855, 1715, 1674, 1639, 1524, 1454, 1367, 1252, 1163, 1069, 1020, 947 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.05 (s, 1H, NH), 5.36 (d, $J_{NH,\alpha} = 6.2$ Hz, 1H, BocNH), 5.18 (s, 1H, H-1), 5.07 (d, $J_{2,3} = 7.5$ Hz, 1H, H-2), 4.57 (dd, $J_{3,4} = 3.1$ Hz, 1H, H-3), 4.51 (app p, $J_{\alpha,\beta} = 6.8$ Hz, 1H, H-α), 3.99–3.95 (m, 1H, H-4), 3.86–3.82 (m, 1H, H-5eq), 3.31 (app t, $J_{4,5ax} = 10.4$ Hz, 1H, H-5ax), 3.25 (m, 2H, CH_2N and OH), 3.12 (m, 1H, CH_2N), 1.66–1.24 (m, 14H, CH_2–Cy and CH_2–Bu), 0.90 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, CDCl3): δ 175.3, 168.5, 109.6, 80.1, 72.6, 66.0, 54.4, 44.9, 43.8 39.3, 35.9, 33.4, 33.1 32.9, 31.4, 29.7, 25.5, 25.0, 23.8, 23.4, 22.5, 20.2 20.1 20.0; ESI-MS (*m/z*): 484.3 $[M+H]^+$, 506.4 $[M+Na]^+$; HRMS *m/z* calcd for $C_{24}H_{42}N_3O_7$: 484.3023, obsd: 484.3032.

4.21. (2*S*,3*S*,4*R*,5*R*)-1-Benzoyl-3,4-*O*-cyclohexylidene-3,4,5-trihydroxy-pipecolic acid *n*-butylamide 28

(23 mg, 55 μmol, 22%): $[\alpha]_D^{20} = +123$ (*c* 0.2, $CDCl_3$); IR (thin film) 3317, 2934, 2842, 1722, 1624, 1533, 1412, 1369, 1271, 1232, 1163, 1102, 1093, 1074, 1045, 989, 949 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55–7.37 (m, 6H, CH_{arom} and NH), 5.24 (d, $J_{1,2} = 2.0$ Hz, 1H, H-1), 4.88 (dd, $J_{2,3} = 7.2$ Hz, 1H, H-2), 4.66 (dd, $J_{3,4} = 3.9$ Hz, 1H, H-3), 4.02–3.98 (m, 1H, H-4), 3.37 (app t, $J_{4,5ax} = J_{5ax,5eq} = 11.1$ Hz, 1H, H-5_{ax}), 3.33–3.15 (m, 3H, H-5_{ax} and CH_2N), 2.37 (d, $J_{4,OH} = 8.7$ Hz, 1H, OH), 1.74–1.25 (m, 14H, CH_2–Cy and CH_2–Bu), 0.94 (t, $J = 7.3$ Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 173.3, 166.8, 135.1, 130.3, 128.6, 127.0, 109.4, 72.5, 71.9, 64.7, 55.0, 46.7, 39.1, 36.0, 33.5, 31.4, 25.1, 24.0, 23.5, 20.0, 13.7; ESI-MS (*m/z*): 417.2 $[M+H]^+$; HRMS *m/z* calcd for $C_{23}H_{33}N_2O_5$: 417.2389, obsd: 417.2431.

4.22. X-ray crystallographic data for 10

$C_{52}H_{88}N_6O_{15}$, $M_r = 1037.28$, monoclinic, space group *C2*, $a = 31.9170(14)$, $b = 56.5430(3)$, $c = 13.6200(7)$ (Å), α = 90, β = 92.491(2), γ = 90°, $V = 2841.6(2)$ (Å) 3, $Z = 2$, $\rho_{calcd} = 1.212$ g cm^{-1}, $T = 293(2)$, μ (Mo Kα) = 0.089 mm^{-1}, 5763 measured reflections, 3165 independent, 346 parameters, $R1 = 0.0597$ ($I > 2\sigma(I)$), $wR2 = 0.1385$ (all data). The intensity data were collected on a Bruker Kappa CCD diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ (Å)). The structures were solved by the direct method and refined by fullmatrix least squares on F2 using SHELXL 97 (G. M. Sheldrick, University of Göttingen, 1997). The non-hydrogen atoms were refined anisotropically. Three hydrogen atoms were refined isotropically, the remaining hydrogen atoms were idealized by using the riding models. CCDC 227314 contains the supplementary crystallographic data. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK, fax: (+44)1223-336-033 or deposit@ccdc.cam.ac.uk).

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10. In initial studies aimed at optimizing the reaction conditions, we found that methanol proved to be superior to other solvents (dichloromethane, tetrahydrofuran) in the tandem process. Application of triphenylphosphine for the initial Staudinger step proved to be equally effective as trimethylphosphine. We elected to use the latter because the formed trimethylphosphine oxide can be easier removed from the reaction mixture than the corresponding triphenylphosphine oxide.
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