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# Sugar $\gamma$ -amino acids as building blocks for the synthesis of cyclic neoglycopeptides

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**Abstract:** Cyclopeptides have interesting biological properties or find potential applications as templates for anchoring of a wide range of biomolecules or detection dyes. Anomeric sugar  $\gamma$ -amino acids efficiently obtained by nucleophilic addition of nitronate anion on sugar olefins are usefull building blocks for the preparation of new cyclic glycopeptides. We report here the synthesis of two types of cyclic systems containing  $\gamma$ -glyco amino acid and  $\alpha$ -amino acid units. A first example was prepared to demonstrate the feasibility of the cyclization of these original structures. To explore these systems as template for multivalency,  $\alpha$ -amino acid and sugar amino-acid moieties bearing additional functions were choosen as building blocks for the second macrocyle. Furthermore, we describe and explain some unexpected results obtained during deprotection of these new cyclic glycopeptides.

Cyclic peptides are naturally occurring substances exhibiting improved properties compared to the linear ones. Indeed, linear peptides usually show low metabolic stability limiting their use as drugs and display conformational flexibility reducing the strength of the ligand-target binding.<sup>1–6</sup> Therefore, the development of original cyclopeptide-based therapeutics is currently a growing interest. Some of them like the well-known vancomycin and its derivatives,<sup>6,7</sup> gramicidin,<sup>8,9</sup> colistin,<sup>10</sup> octreotide,<sup>11</sup> and RGD derivatives<sup>12,13</sup> exhibit useful biological properties as antibiotics, anticancer and integrin inhibitors. Cyclic peptides also proved to be useful for the design of functional nanotubes from self-assembly.<sup>14,15</sup> Cyclic peptides or peptidomimetics can be useful in drug design<sup>16–21</sup> and serve as templates for attaching and assembling a wide variety of ligands.<sup>5,22,23</sup> Such templates allow the facile and versatile attachment of multiple ligands (multivalency) by suitable functions.<sup>5,23–25</sup> One noteworthy example are the Regioselectively Addressable Functionalized Templates (RAFT) developed by Dumy *et al.*<sup>26–28</sup> which have found powerful applications in biology and imaging.<sup>27,29,30</sup> A wide range of multivalent (glyco)cyclopeptides and synthetic glycoclusters based on cyclic peptides have been described for their related applications in glycobiology.<sup>5,25,31–34</sup>

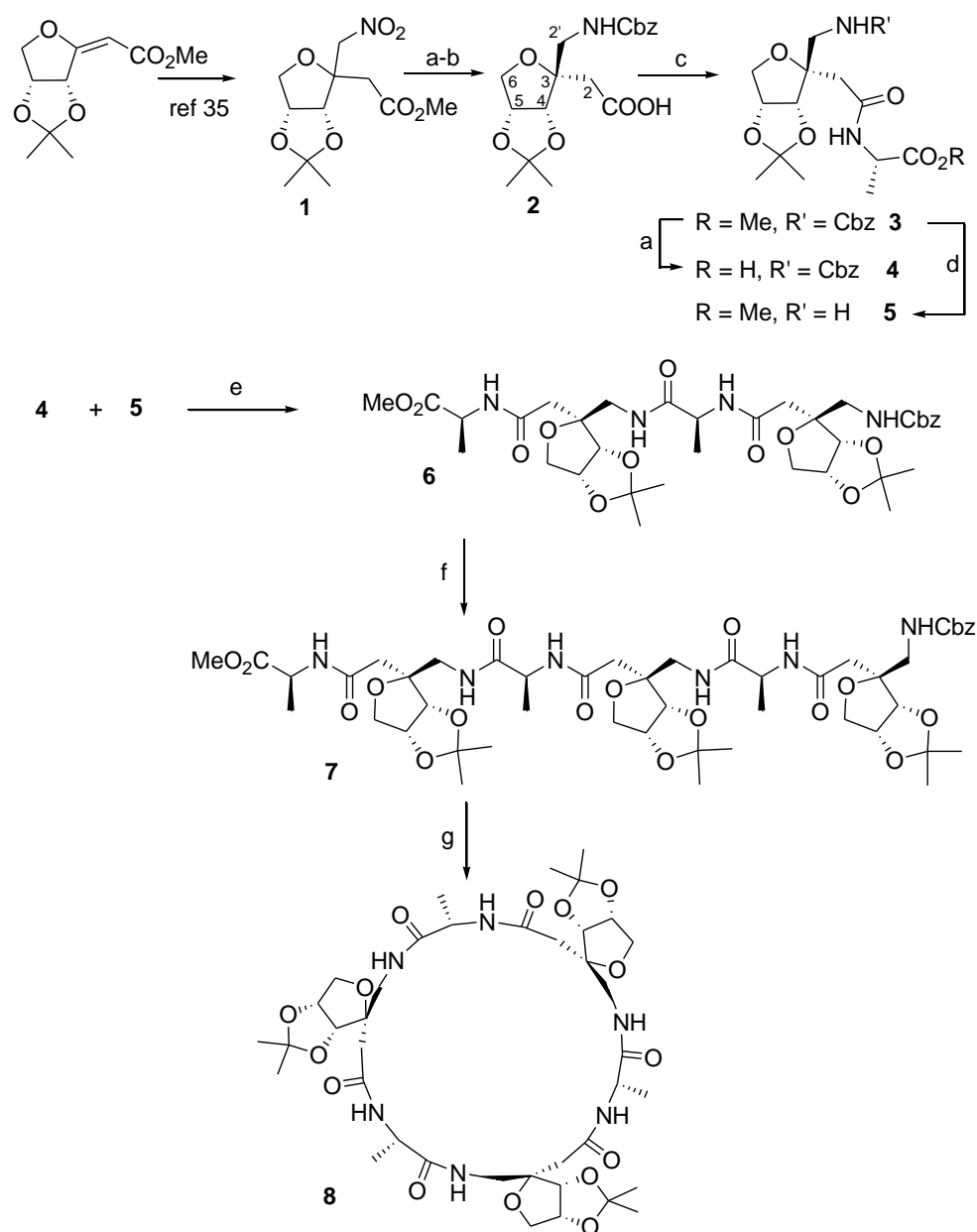
Designing and synthesizing new types of biocompatible and functionalizable molecular scaffolds for multivalent presentation are great challenges for synthetic chemists. As unusual amino acids with multiple functionalization points, sugar amino acids are good candidates and can be incorporated into peptidic structures. A few years ago, we developed anomeric sugar  $\beta$ - and  $\gamma$ -amino acids<sup>35–37</sup> and we integrated them into small mixed peptides,<sup>38,39</sup> and cyclic glycopeptides.<sup>38,40</sup>

In connection with our research on new carbohydrates-containing peptides, we proposed the construction of original hybrid macrocyclic structures built with sugar  $\gamma$ -amino acids and  $\alpha$ -amino acids. Furthermore, to explore the scope of these structures as templates for multivalency, both amino-acid moieties were carefully chosen to provide additional anchoring points. We give in this paper a full account of the synthesis of these original cyclic hybrid glycopeptides.

## Results and discussion

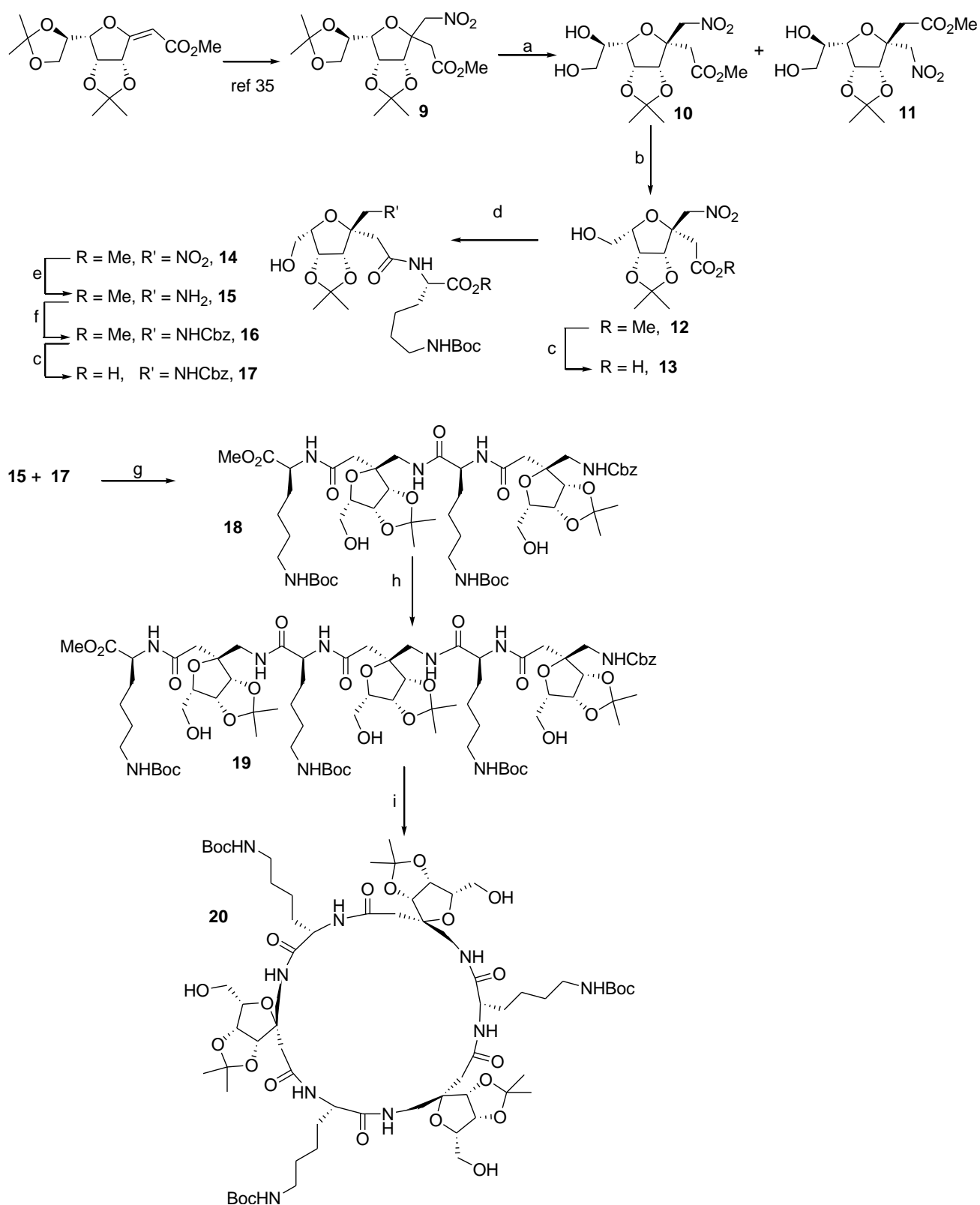
The nucleophilic addition of a nitronate anion on push-pull anomeric sugar olefins has been previously studied in our group (Scheme 1).<sup>35</sup> Michael adducts **1** were obtained in excellent yield as a mixture of inseparable nitro esters starting from the corresponding *erythro*-glycosylidene (14/86: $\alpha/\beta$  ratio), the major anomer bearing the nitro group on the less hindered face of the sugar. We have previously demonstrated that both anomers are in equilibrium, likely as a result of opening and closure of the sugar ring. The configuration of the major anomer (methyl carboxylate and isopropylidene on the same face) was established on the basis of <sup>1</sup>H NMR spectroscopic data by NOESY experiments on  $\alpha/\beta$  mixture and X-ray crystallographic analysis.<sup>35</sup> Anomeric mixture of nitro esters **1** was treated with lithium hydroxide in THF/H<sub>2</sub>O to give the corresponding carboxylic acid in very good yield. At this stage, the separation of both anomers could be performed by chromatography and the subsequent steps were carried out on the major isomer. Reduction of the nitro group required medium hydrogen pressure (40 psi) to give the expected amine subsequently protected with a benzyloxycarbonyl group under standard conditions. The NH-Cbz protected compound **2** thusly prepared was coupled with H-L-ala-OMe giving **3** in 85% yield. At this point, either amine or acid terminal functions of **3** were deprotected by hydrogenolysis (H<sub>2</sub>, Pd/C, MeOH) or by saponification (LiOH, THF/H<sub>2</sub>O) respectively. Building blocks **5** and **4** were then coupled using HATU (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) as activating agent and led to the tetrapeptide **6** in 78% yield. Compound **7** was obtained in 79% yield by hydrogenolysis of *N*-benzyloxycarbonyl protecting group and subsequent coupling with **4**. Having achieved the synthesis of the linear hexapeptide **7**, we next envisioned the cyclization step using classical peptide chemistry. First, saponification of the ester function of **7** with LiOH in THF/MeOH mixture led to the crude carboxylic acid. The *N*-benzyloxycarbonyl group was then removed by catalytic hydrogenolysis using Pd/C in MeOH. Without purification, the fully deprotected glycopeptide was treated with HATU as coupling agent in CH<sub>2</sub>Cl<sub>2</sub>/DMF mixture for 3 days under high dilution conditions (*c* = 0.1 mmol/L) to promote macrocyclization over poly(oligo)merization.<sup>41</sup> After purification, the cyclic glycopeptide **8** was obtained in 42% yield. The use of other coupling agent (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, PyBop) did not significantly improve the yield of **8**. As expected by the symmetric structure of **8**, <sup>1</sup>H and <sup>13</sup>C NMR spectra revealed only one set of signals corresponding to a sugar/alanine unit. Nevertheless, mass spectrometry unambiguously

confirmed the formation of expected cyclic structure (see SI, Figure S1, see scheme 1 for atom numbering).



Scheme 1. a: LiOH, THF/H<sub>2</sub>O (3/1), **4**: quantitative yield; b: 1) H<sub>2</sub>, Pd/C (10%), MeOH, 3 bars, 80%; 2) TMSCl (2 eq.), DCM, 3) DIEA, CbzCl, 65% three steps; c: H-L-Ala-OMe, DIEA, HATU, DMF, 85%; d) H<sub>2</sub>, Pd/C, MeOH, 99%; e) DIEA, HATU, DMF, 78%; f) i. H<sub>2</sub>, Pd/C, MeOH, ii. **4**, DIEA, HATU, DMF, 79%; g) i. LiOH, THF/H<sub>2</sub>O, ii. H<sub>2</sub>, Pd/C, MeOH, iii. DIEA, HATU, DMF/CH<sub>2</sub>Cl<sub>2</sub>, 42%.

After the validation of this proof of concept, *i.e.* the successful synthesis of **8** and the confirmation of the cyclization of these structures, we continued our work with the synthesis of a more functionalized cyclic peptide. This second example is built with  $\gamma$ -glycoamino acid and  $\alpha$ -amino acid bearing additional reactive groups (Scheme 2). For this purpose, L-lysine with a *tert*-butoxycarbonyl as side chain protecting group was selected as  $\alpha$ -amino acid partner. Derivative **9** was chosen as  $\gamma$ -glycoamino acid partner and modified in order to display a hydroxymethyl arm. As explained above, the nitro ester **9** was obtained as a mixture of anomers (15/85  $\alpha/\beta$  ratio) by addition of the nitromethane carbanion on the corresponding *exo*-glycal. The selective removal of the 7,8-*O*-isopropylidene protecting group was achieved by treatment with 1N HCl in MeOH. The corresponding diol was obtained as a mixture of anomers and separated by column chromatography.<sup>35</sup> We decided to go ahead with the major isomer **10** and oxidative cleavage of the diol followed by reduction of the aldehyde intermediate led to compound **12** bearing a hydroxymethyl arm. The nitro function acting as an amino protecting group was maintained for the first coupling with H-L-Lysine(Boc)-OMe and the compound **14** was obtained in 90% yield. We first planned to protect the hydroxyl group as a silyl ether derivative but this protection step appeared unnecessary since the unprotected hydroxyl was not affecting the peptidic coupling. The nitro group was next hydrogenated and the resulting amine **15** was protected with a benzyloxycarbonyl group. Methyl ester of **16** could be selectively removed by saponification leading to acid **17** in quantitative yield. Coupling of compounds **15** and **17** using HATU in DMF led to glycopeptides **18** and then **19** in 69% and 47% yields respectively. Cyclic derivative **20** was obtained after amine and acid deprotection followed by activation with HATU and intramolecular coupling in CH<sub>2</sub>Cl<sub>2</sub>/DMF mixture under high dilution conditions (*c* = 0.1 mmol/L). Retrieval of compound **20** in the crude was tedious and purification inefficient although the expected molecular pic was detected by mass spectrometry ( $[M+Na]^+ = 1436.7626$ , calculated for C<sub>66</sub>H<sub>111</sub>N<sub>9</sub>O<sub>24</sub>Na: 1436.7634). We next turned to PyBop as activating agent in the same high dilution conditions. In this case, the recovery of **20** was easier but also required two purifications by column chromatography on silica gel explaining the low yield of **20** (22%). Even though the cyclization step was tedious, we were pleased to obtain a macrocycle bearing two different reactive groups.



Scheme 2. a) 1N HCl, MeOH, 0°C, 68%; b) i. NaIO<sub>4</sub>, MeOH; ii. NaBH<sub>4</sub>, MeOH, 0°C, 98%; c) LiOH, THF/H<sub>2</sub>O, **13** 98%, **17** 99%; d) HCl.H-L-Lys(Boc)-OMe, DIEA, HATU, DMF, 0°C, 90%; e) H<sub>2</sub>, Pd/C, MeOH, 99%; f) DIEA, CbzCl, DCM, 0°C, 70%; g) HATU, DIEA, DMF,

0°C, 69%; h) i. H<sub>2</sub>, Pd/C, MeOH, ii. **17**, HATU, DIEA, DMF, 0°C, 47%; i) i. LiOH, THF/H<sub>2</sub>O, ii. H<sub>2</sub>, Pd/C, MeOH, , iii. HATU, DIEA, DMF/CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 22%.

To go further with these macrocyclic structures, we envisaged to modulate their hydrosolubility by removing the sugar hydroxyl protecting groups, namely 4,5-isopropylidene. Moreover, these hydroxyls could also be considered as additional functionalization points. The cycloglycopeptide **8** was treated by a mixture of TFA/H<sub>2</sub>O (1/1) at 0°C, commonly used for isopropylidene removal (Scheme 3). Unexpectedly, we only observed the formation of C-glycosyl lactone **21** in quantitative yield, as a result of several concomitant intramolecular amide-to-ester conversions of **8**. We postulated that compound **21** results from TFA promoted acetal removal followed by nucleophilic attack of O4 on carboxamide function. Few intramolecular lactonizations of C-glycosyl ester derivatives have already been described in the literature and led to the formation of C-glycosyl bicyclic lactones where the lactone ring is annulated to a furanoid<sup>42</sup> or a pyranoid<sup>43</sup> system. However, to the best of our knowledge, no lactonization of amide derivatives in such saccharidic systems has been described. This prompted us to study this reaction on less elaborate precursors in order to find experimental conditions enabling deprotection while preventing lactonization (Scheme 4). We first envisioned the 4,5-isopropylidene removal on β-nitro ester **10** (major isomer with methyl carboxylate and isopropylidene on the same face). As expected, the lactone **22** was obtained by treating **10** with a TFA/H<sub>2</sub>O mixture at 0°C, and no traces of nitro ester **23** were detected. The same reaction performed on α-nitro ester **11** (minor anomer) gave the nitro ester **24** in quantitative yield without lactonization reaction since the methyl carboxylate and O4 are not on the same face. Taking into account the formation of lactone **21** resulting from intramolecular esterification of amide functions of **8**, we planned to investigate the 4,5-isopropylidene removal on a simple amide like **25**, obtained from **10** after saponification of methyl ester and coupling with H-L-ala-OMe (Scheme 4). To find efficient experimental conditions for 4,5-isopropylidene removal leading to compound **26** without concomitant lactonization, the nature of the acid, the solvent, the temperature and the reaction time were studied (Table 1). Treatment of **25** by a 1/1 TFA/H<sub>2</sub>O mixture led to C-glycosyl lactone **22** in quantitative yield (entry 1) although no reaction was observed while maintaining the temperature at 0°C (entry 2). Similarly, compound **26** was not formed when AcOH (entry 3), acidic resin (Amberlite IR 120, entry 4)<sup>44</sup> or FeCl<sub>3</sub><sup>45</sup> (entry 5) were used. In these conditions, 30 to 50% of starting amide **25** were recovered and lactonization occurred up to 10 %. Moreover, prolonged reaction time led to the degradation of the starting compound **25**.

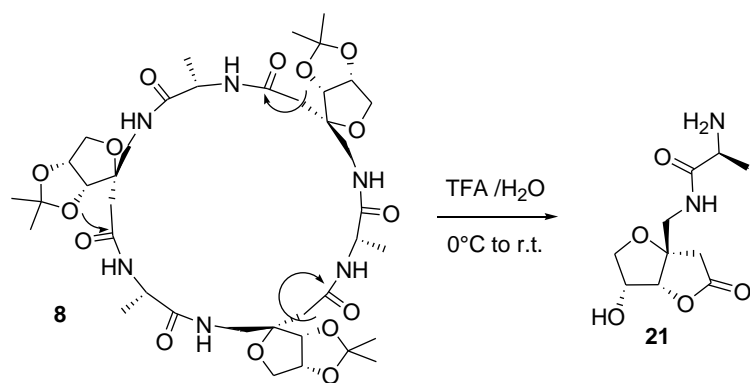


We eventually investigated the use of HCl in MeOH. When performed at 50°C, the reaction only gave the lactone **22** in 82% yield in 2 hours (entry 6). TLC monitoring showed that maintaining the temperature at -5° C could led to the expected 4,5-diol **26** without lactonization (compound **26** is more polar than lactone **22** on TLC) but this nitro ester was immediately converted into lactone **22** during evaporation of the solvent, even though the reaction mixture was neutralized with NaHCO<sub>3</sub>. Despite investigating various experimental conditions, it clearly appeared that lactonization of amide **25** during removal of the 4,5-isopropylidene moiety could not be prevented. Consequently, removal of the isopropylidene group for hydrosolubility modulation or for additional functionalization was not an option in this context.

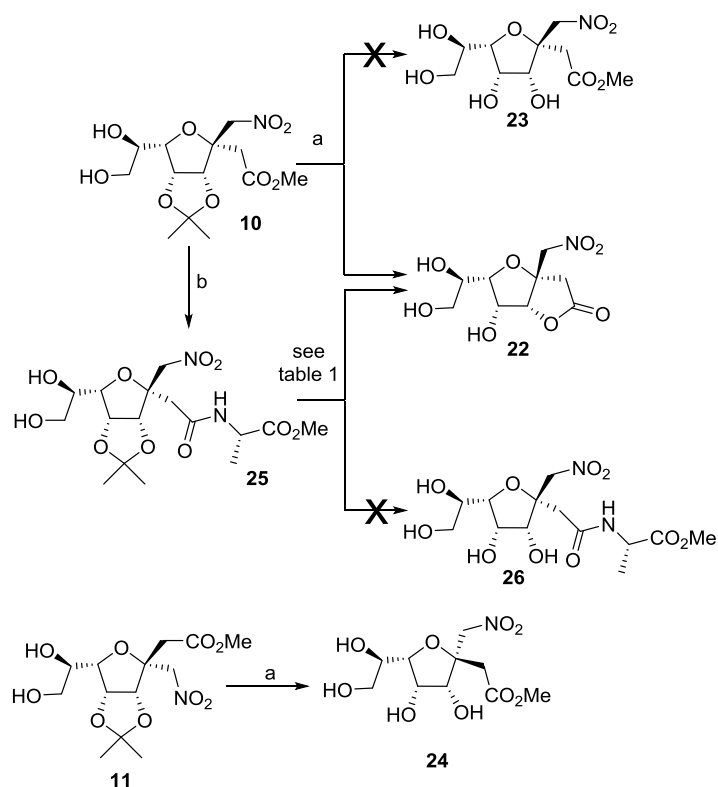
Table 1. 4,5-isopropylidene removal of **25**

entry	solvent	acid	temperature	reaction time (h)	yield of <b>22</b> (%)	recovery of <b>25</b> (%)
1	H <sub>2</sub> O	TFA	0°C then rt	7	99	0
2	H <sub>2</sub> O	TFA	0°C	7	0	99
3	H <sub>2</sub> O	AcOH	50°C	48	<10	50
4	CHCl <sub>3</sub> /MeOH	acidic resin	40°C	48	<10	30
5	CH <sub>2</sub> Cl <sub>2</sub>	FeCl <sub>3</sub> .H <sub>2</sub> O	40°C	48	<10	30
6	MeOH	HCl	50°C	2	82	0
7	MeOH	HCl	0°C then rt	7	80	20
8	MeOH	HCl	-5°C	12	80*	20

\* The reaction mixture was maintained at -5°C during 12h and then neutralized with NaHCO<sub>3</sub>. The formation of the lactone was observed during evaporation of the solvent.



Scheme 3. Deprotection of cyclopeptide **8**



Scheme 4. a: TFA/H<sub>2</sub>O, (1/1), 0°C; quantitative yield; b) i. LiOH, THF/H<sub>2</sub>O, 74%, ii. H-L-ala-OMe, DIEA, HATU, DMF, 40%; c) HCl/MeOH, 0°C, 82%.

These results unambiguously suggested that the minor  $\alpha$ -anomer **11** displaying the methyl carboxylate on one side of the sugar ring and the isopropylidene on the other side could be a valuable unit for cyclic hybrid glycopeptides synthesis and efficient isopropylidene deprotection. A similar pathway was thus investigated starting from **11** (see SI, scheme S1). However, it is important to note that compound **11** was obtained in 15% yield after addition of nitromethane anion (minor anomer). Furthermore, after preliminary intramolecular coupling experiments, the cyclic product could not be isolated. The nature and structure of the linear precursor clearly affected the macrocyclization process. In particular, the anomeric configuration did not seem to induce a favorable folding of this linear precursor or provide the required spatial arrangement between amino and carboxylic acid moieties. Moreover, the steric hindrance around the anomeric aminomethyl moiety (on the same face of isopropylidene and hydroxymethyl chain) could prevent the cyclization reaction.

## Conclusion

To sum up this work, we have synthesized new and original cyclic glycopeptides containing two types of amino acids, a  $\gamma$ -glycoamino acid and an  $\alpha$ -amino acid. The construction of the linear precursors based on two building blocks was achieved by a multistep sequence. A first macrocycle was obtained as a proof of concept to validate the cyclization capabilities of these glycopeptides. The second structure is more elaborate and has proved challenging to synthesize and purify. Nevertheless, this later presents an extended number of chemical functionalities, with the idea of exploring their scope as template for multivalency. During acid catalyzed removal of isopropylidene of these new cyclic glycopeptides, a C-glycosyl lactone in which the lactone ring is annulated to a furanoid system was unexpectedly and spontaneously formed. Intense investigations are now devoted to functionalization of these cyclopeptides via coupling of the amino or hydroxymethyl moieties to relevant biomolecules and/or dyes for biological applications.

## **Experimental part**

### **Reagents and general methods**

DMF was dried by distillation from calcium hydride. Other solvents and reagents were purchased from commercial sources and used without further purification. TLC analyses were performed using standard procedures on Kieselgel 60 F254 plates (Merck). Compounds were visualized using UV light (254 nm) and 30% methanolic H<sub>2</sub>SO<sub>4</sub>/heat as developing agent. Column chromatography was performed on silica gel SI 60 (63-200  $\mu$ m) or Lichroprep RP-18 (40-63 $\mu$ m) (Merck). FTIR spectra were recorded on a Perkin-Elmer spectrum 1000 on NaCl windows (film) or KBr pellets (cm<sup>-1</sup>). Melting points were determined with a Tottoli apparatus and are uncorrected. Optical rotations were measured on an Anton Paar MC300 polarimeter. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker spectrometer DPX250 (250 MHz and 62.9 MHz, respectively) and DRX400 (400 MHz and 100.6 MHz, respectively). For complete assignment of <sup>1</sup>H and <sup>13</sup>C signals, two-dimensional <sup>1</sup>H,<sup>1</sup>H COSY and <sup>1</sup>H,<sup>13</sup>C correlation spectra were recorded. Mass spectra (MS) were recorded on an ESI/QqTOF Bruker spectrometer. Ethyl acetate = EA, Cyclohexane = cyH. Compounds **1**, **2**, **9**, **10**, **11** were prepared in accordance with literature procedures.<sup>35</sup>

### **Procedure A: General procedure for peptidic coupling with HATU**

To a solution of amine (1.1 mmol, 1.1 eq.) and carboxylic acid (1 mmol, 1 eq.) in DMF (10 mL) were added HATU (570 mg, 1.5 mmol, 1.5 eq.) and DIEA (363  $\mu$ L, 2.1 mmol, 2.1 eq.) at 0°C under argon atmosphere. After stirring at room temperature for 24h, the solvent was evaporated. The residue was dissolved in ethyl acetate (20 mL), washed with HCl 1N (5 mL), a saturated aqueous solution of NaHCO<sub>3</sub> (5 mL) and brine (5 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated. The product was purified by column chromatography (silica gel, cyH/EA).

### Procedure B: General procedure for saponification with LiOH

To a solution of methyl ester (2 mmol) in THF (15 mL) and water (5 mL) was added LiOH (144 mg, 6 mmol, 3 eq.) and the mixture was stirred until completion of the reaction. THF was removed under reduced pressure, ethyl acetate (20 mL) was added and the pH was adjusted to 2-3 with aqueous 1N HCl. The organic layer was washed with brine and dried over MgSO<sub>4</sub>, filtered and concentrated. When necessary, the crude residue was purified by column chromatography (silica gel, cyH/EA).

### Procedure C: General procedure for nitro reduction or Cbz hydrogenolysis

To a solution of protected compound (10 mmol) in MeOH (20 mL) was added Pd/C(10%) (40%w/w). The mixture was hydrogenated under H<sub>2</sub> atmosphere (40 psi) for 24 h. The reaction mixture was then filtered through a pad of celite and concentrated to give the desired product. The crude product was used without further purification.

### Compound 3

The above described procedure A was applied to **2** (580 mg, 1.59 mmol) and alanine methyl ester hydrochloride to provide **3** (608 mg, 85% yield). Colorless gum.  $R_f$  = 0.58 (EA),  $[\alpha]_D = -30.9$  (c 0.5 in CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 1.33 (s, 3H, CH<sub>3</sub>), 1.38 (d, 3H,  $J$  = 7.0 Hz, CH<sub>3</sub> alanine), 1.52 (s, 3H, CH<sub>3</sub>), 2.61 (d, 1H,  $J_{gem}$  = 14.0 Hz,  $H$ -2), 2.67 (d, 1H,  $H$ -2), 3.20 (dd, 1H,  $J_{gem}$  = 14.5,  $J_{2',NH}$  = 5.5 Hz,  $H$ -2'), 3.37 (dd, 1H,  $J_{2',NH}$  = 7.5 Hz,  $H$ -2'), 3.72 (s, 3H, OMe), 3.92 (dd, 1H,  $J_{gem}$  = 11.0,  $J_{5,6}$  = 3.5 Hz,  $H$ -6), 4.01 (d, 1H,  $H$ -6), 4.46-4.57 (m, 2H,  $H$ - $\alpha$ ,  $H$ -4), 4.90 (dd, 1H,  $J_{4,5}$  = 6.0 Hz,  $H$ -5), 5.06 (d, 1H,  $J_{gem}$  = 12.0 Hz, CH<sub>2</sub>-Ph), 5.12 (d, 1H, CH<sub>2</sub>-Ph), 5.66 (t, 1H, N- $H$ ), 6.80 (d, 1H,  $J_{\alpha,NH}$  = 6.5 Hz, N- $H$ ), 7.29-7.40 (m, 5H,  $H$ -Ar). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 62.9 MHz):  $\delta$  = 17.9 (CH<sub>3</sub> alanine), 24.6, 26.1 (2 C(CH<sub>3</sub>)<sub>2</sub>), 40.3 (C-2), 42.1 (C-2'), 48.1 (C- $\alpha$ ), 52.4 (OCH<sub>3</sub>), 66.8 (CH<sub>2</sub>-Ph), 71.4 (C-6), 81.4, 83.0 (C-4, C-5), 85.6 (C-3), 112.6 (C(CH<sub>3</sub>)<sub>2</sub>), 128.0 (2 C-Ar), 128.5 (3 C-Ar), 136.4 (C-Ar), 156.8 (C=O Cbz),

170.4 (C=O), 173.2 (C=O). ESI-HRMS  $[M+Na]^+$   $m/z$  = found 473.1902 (calculated for  $C_{22}H_{30}N_2O_8Na$ : 473.1894). IR (NaCl)  $\nu_{max}/cm^{-1}$  3341, 1725, 1662

### Compound 6

The above described procedure B was applied to **3** and acid **4** was obtained in quantitative yield. The amine **5** was obtained from **3** in 99 % yield *via* procedure C. Acid **4** (392 mg, 0.9 mmol, 1 eq.) and amine **5** (313 mg, 0.99 mmol, 1.1 eq.) were coupled according to procedure A to provide **6** (411 mg, 78% yield). Colorless gum.  $R_f$  = 0.29 (EA).  $[\alpha]_D = -33.3^\circ$  (c 1 in  $CHCl_3$ ).  $^1H$  NMR ( $CDCl_3$ , 400 MHz):  $\delta$  = 1.32, 1.34 (s, 6H,  $C(CH_3)_2$ ), 1.37 (d, 6H,  $J$  = 7.0 Hz,  $CH_3$  alanine), 1.49, 1.52 (s, 6H,  $C(CH_3)_2$ ), 2.64 (s, 2H,  $H_{A-2}$ ), 2.65 (d, 1H,  $J_{gem}$  = 14.5 Hz,  $H_{B-2}$ ), 2.70 (d, 1H,  $H_{B-2}$ ), 3.19 (dd, 1H,  $J_{gem}$  = 14.5,  $J$  = 6.0 Hz,  $H_{B-2'}$ ), 3.26 (dd, 1H,  $J_{gem}$  = 14.5,  $J$  = 6.0 Hz,  $H_{A-2'}$ ), 3.38 (dd, 1H,  $J$  = 7.0 Hz,  $H_{B-2'}$ ), 3.42 (dd, 1H,  $J$  = 7.0 Hz,  $H_{A-2'}$ ), 3.74 (s, 3H,  $OCH_3$ ), 3.90-4.01 (m, 4H,  $H-6$ ), 4.41-4.54 (m, 3H, 2  $H-\alpha$ ,  $H-4$ ), 4.57 (d, 1H,  $J_{4,5}$  = 6.0 Hz,  $H-4$ ), 4.88-4.91 (m, 2H,  $H-5$ ), 5.10 (s, 2H,  $CH_2$ -Ph), 6.03 (t, 1H,  $J$  = 6.5 Hz,  $NHCbz$ ), 6.71 (d, 1H,  $J$  = 7.0 Hz,  $N_3H$ ), 6.86 (d, 1H,  $J$  = 7.0 Hz,  $N_1H$ ), 7.19 (t, 1H,  $N_2H$ ), 7.27-7.37 (m, 5H,  $H$ -Ar).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz):  $\delta$  = 17.6, 17.7 (2  $CH_3$  alanine), 24.6, 26.1 (4  $CH_3$ ), 39.5 ( $C_{B-2}$ ), 39.9 ( $C_{A-2}$ ), 40.2 ( $C_{A-2'}$ ), 42.2 ( $C_{B-2'}$ ), 48.2 (C- $\alpha$ ), 49.2 (C- $\alpha$ ), 52.5 ( $OCH_3$ ), 66.8 ( $CH_2$ -Ph), 71.4, 71.5 ( $C_{A-6}$ ,  $C_{B-6}$ ), 81.3, 81.4 ( $C_{B-5}$ ,  $C_{A-5}$ ), 83.1, 83.4 ( $C_{B-4}$ ,  $C_{A-4}$ ), 85.5, 85.8 ( $C_{B-3}$ ,  $C_{A-3}$ ), 112.5 (2  $C(CH_3)_2$ ), 128.0 (3 C-Ar), 128.5 (2 C-Ar), 136.5 (C-Ar), 157.1 (C=O Cbz), 170.6 ( $C_4=O$ ), 170.8 ( $C_2=O$ ), 172.6 ( $C_3=O$ ), 173.5 ( $C_1=O$ ). ESI-HRMS  $[M+Na]^+$   $m/z$  = found 757.3257 (calculated for  $C_{35}H_{50}N_4O_{13}Na$ : 757.3267). IR (NaCl)  $\nu_{max}/cm^{-1}$  3322, 2985, 2938, 1721, 1659, 1532

### Compound 7

Compound **6** was deprotected using general procedure C and the corresponding amine (396 mg, 0.66 mmol, 1.1 eq.) was coupled with acid **4** (262 mg, 0.6 mmol, 1 eq.) following procedure A to provide **7** (482 mg, 79% yield). Colorless gum  $R_f$  = 0.17 (EA).  $[\alpha]_D = -35.2^\circ$  (c 0.6 in  $CHCl_3$ ).  $^1H$  NMR ( $CDCl_3$ , 400 MHz):  $\delta$  = 1.30-1.35 (m, 12H, 4  $CH_3$ ), 1.37 (d, 3H,  $J$  = 7.5 Hz,  $CH_3$  alanine), 1.42 (d, 3H,  $J$  = 7.5 Hz,  $CH_3$  alanine), 1.48 (s, 3H,  $CH_3$ ), 1.51 (s, 6H, 2  $CH_3$ ), 2.59-2.75 (m, 6H, 6  $H-2$ ), 3.12 (dd, 1H,  $J_{gem}$  = 14.5,  $J$  = 5.0 Hz,  $H-2'$ ), 3.23 (dd, 1H,  $J_{gem}$  = 14.5,  $J$  = 6.0 Hz,  $H-2'$ ), 3.30 (dd, 1H,  $J_{gem}$  = 14.5,  $J$  = 5.5 Hz,  $H-2'$ ), 3.39 (dd, 1H,  $J$  = 6.5 Hz,  $H-2'$ ), 3.43 (dd, 1H,  $J$  = 6.5 Hz,  $H-2'$ ), 3.51 (dd, 1H,  $J$  = 7.0 Hz,  $H-2'$ ), 3.75 (s, 3H,  $OCH_3$ ), 3.90 (dd, 1H,  $J_{gem}$  = 11.0,  $J$  = 4.0 Hz,  $H-6$ ), 3.93-3.99 (m, 5H, 5  $H-6$ ), 4.39 (m, 1H,  $H-\alpha$ ), 4.44-4.55 (m, 4H, 2  $H-\alpha$ , 2  $H-4$ ), 4.57 (d, 1H,  $J_{4,5}$  = 6.0 Hz,  $H-4$ ), 4.87-4.92 (m, 3H, 3  $H-$

5), 5.08 (d, 1H,  $J_{\text{gem}} = 12.5$  Hz,  $\text{CH}_2\text{-Ph}$ ), 5.12 (d, 1H,  $\text{CH}_2\text{-Ph}$ ), 6.06 (t, 1H,  $J = 6.0$  Hz,  $\text{NHCbz}$ ), 6.74 (d, 1H,  $J = 7.0$  Hz,  $\text{NH}$ ), 6.88 (d, 1H,  $J = 7.0$  Hz,  $\text{NH}$ ), 7.07 (d, 1H,  $J = 7.0$  Hz,  $\text{NH}$ ), 7.25 (m, 1H,  $\text{NH}$ ), 7.30-7.39 (m, 5H, 5  $H\text{-Ar}$ ), 7.46 (t, 1H,  $J = 6.0$  Hz,  $\text{NH}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta = 17.5$ , 17.7, 18.0 (3  $\text{CH}_3$  alanine), 24.6 (3  $\text{CH}_3$ ), 26.1 (3  $\text{CH}_3$ ), 39.2, 39.7, 39.8, 40.1, 40.7, 41.9 (3  $C\text{-2}$ , 3  $C\text{-2'}$ ), 48.2, 49.2, 49.4 (3  $C\text{-}\alpha$ ), 52.5 ( $\text{OCH}_3$ ), 66.8 ( $\text{CH}_2\text{-Ph}$ ), 71.2, 71.4, 71.6 (3  $C\text{-6}$ ), 81.2, 81.3, 81.4 (3  $C\text{-5}$ ), 83.1, 83.3, 83.4 (3  $C\text{-4}$ ), 85.5, 85.7, 85.8 (3  $C\text{-3}$ ), 112.4, 112.5 (3  $\text{C}(\text{CH}_3)_2$ ), 128.0 (3  $C\text{-Ar}$ ), 128.5 (2  $C\text{-Ar}$ ), 136.6 ( $C\text{-Ar}$ ), 157.1 ( $\text{C=O Cbz}$ ), 170.5, 170.7, 171.2, 172.9, 173.5 (6  $\text{C=O}$ ). ESI-HRMS  $[\text{M}+\text{Na}]^+$   $m/z$  = found 1041.4649 (calculated for  $\text{C}_{48}\text{H}_{70}\text{N}_6\text{O}_{18}\text{Na}$ : 1041.4639). IR (NaCl)  $\nu_{\text{max}}/\text{cm}^{-1}$  3327, 2985, 2938, 1718, 1657, 1529

### Cyclopeptide 8

Compound **7** was deprotected using general procedures B and C. To a solution of the deprotected glyco-amino acid (348 mg, 0.4 mmol, 1 eq.) in  $\text{CH}_2\text{Cl}_2/\text{DMF}$  (4/1) at  $0^\circ\text{C}$  under argon, were added DIEA (346  $\mu\text{L}$ , 2.0 mmol, 5.0 eq.) and HATU (182 mg, 0.48 mmol, 1.2 eq.). After stirring at room temperature for 3 days, the solvents were evaporated and the residue was taken up in ethyl acetate (30 mL). The solution was washed with brine (10 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated. The product was purified by column chromatography (silica gel,  $\text{AcOEt}/\text{MeOH}$ ) to provide **8** (143 mg, 42% yield). White solid.  $\text{Mp} = 180^\circ\text{C}$ .  $\text{Rf} = 0.33$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ : 9/1).  $[\alpha]_{\text{D}} = -50.5^\circ$  (c 0.5 in  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz):  $\delta = 1.36$  (s, 3H,  $\text{CH}_3$ ), 1.42 (d, 3H,  $J = 7.0$  Hz,  $\text{CH}_3$  alanine), 1.53 (s, 3H,  $\text{CH}_3$ ), 2.64 (d, 1H,  $J_{\text{gem}} = 14.5$  Hz,  $H\text{-2}$ ), 2.79 (d, 1H,  $H\text{-2}$ ), 3.32 (dd, 1H,  $J_{\text{gem}} = 14.5$ ,  $J_{2',\text{NH}} = 6.0$  Hz,  $H\text{-2'}$ ), 3.47 (dd, 1H,  $J_{2',\text{NH}} = 6.0$  Hz,  $H\text{-2'}$ ), 3.98 (d, 1H,  $J_{\text{gem}} = 11.5$  Hz,  $H\text{-6}$ ), 4.05 (dd, 1H,  $J_{5,6} = 3.5$  Hz,  $H\text{-6'}$ ), 4.48 (m, 1H,  $H\text{-}\alpha$ ), 4.51 (d, 1H,  $J_{4,5} = 6.0$  Hz,  $H\text{-4}$ ), 4.94 (dd, 1H,  $H\text{-5}$ ), 6.72 (d, 1H,  $J = 6.0$  Hz,  $\text{NH ala}$ ), 7.40 (t, 1H,  $\text{NH erythro}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 62.9 MHz):  $\delta = 17.8$  ( $\text{CH}_3$  alanine), 24.8 ( $\text{CH}_3$ ), 26.3 ( $\text{CH}_3$ ), 40.7, 41.0 ( $C\text{-2}$ ,  $C\text{-2'}$ ), 49.6 ( $C\text{-}\alpha$ ), 71.7 ( $C\text{-6}$ ), 81.6 ( $C\text{-5}$ ), 83.4 ( $C\text{-4}$ ), 85.9 ( $C\text{-3}$ ), 112.8 ( $\text{C}(\text{CH}_3)_2$ ), 171.5, 173.2 (2  $\text{C=O}$ ). ESI-HRMS  $[\text{M}+\text{Na}]^+$   $m/z$  = found 875.4012 (calculated for  $\text{C}_{39}\text{H}_{60}\text{N}_6\text{O}_{15}\text{Na}$ : 875.4009). IR (NaCl)  $\nu_{\text{max}}/\text{cm}^{-1}$  3312, 3056, 2981, 2933, 2857, 1737, 1657, 1529

### Compound 12

To a stirred solution of **10** (5.42 g, 16.2 mmol, 1 eq.) in methanol (340 mL) was added  $\text{NaIO}_4$  (6.93 g, 32.4 mmol, 2 eq.) under argon. After stirring at room temperature until completion of the reaction, the solvent was removed by half *in vacuo*. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$

(300 mL). The organic layer was washed with water (3 x 100 mL), dried over  $\text{MgSO}_4$ , filtered and the solvent was removed under reduced pressure. The crude product was solubilized in MeOH (130 mL) and  $\text{NaBH}_4$  (622 mg, 1.51 mmol, 1 eq.) was added at  $0^\circ\text{C}$ . After 1 h at room temperature, the solvent was removed under reduced pressure. The residue was diluted in  $\text{CH}_2\text{Cl}_2$  (200 mL) and the organic layer was washed with a solution of 1N HCl (70 mL) and with water until pH = 7. The organic layer was dried over  $\text{MgSO}_4$ , filtered and evaporated under reduced pressure. The crude product **12** (5.10 g, 98% yield) was used without further purification. Colorless oil.  $R_f$  = 0.50 (cH/EA: 1/2).  $[\alpha]_D = -10.4^\circ$  (c 0.4 in  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz):  $\delta$  = 1.31 (s, 3H,  $\text{CH}_3$ ), 1.48 (s, 3H,  $\text{CH}_3$ ), 2.09 (br s, 1H, OH), 2.90 (d, 1H,  $J_{\text{gem}} = 18.0$  Hz,  $H-2$ ), 3.09 (d, 1H,  $H-2$ ), 3.73 (s, 3H,  $\text{OCH}_3$ ), 3.83-3.90 (m, 2H,  $H-7$ ,  $H-7'$ ), 4.11 (m, 1H,  $H-6$ ), 4.59 (d, 1H,  $J_{\text{gem}} = 11.5$  Hz,  $H-2'$ ), 4.67 (d, 1H,  $J_{4,5} = 6.0$  Hz,  $H-4$ ), 4.90 (dd, 1H,  $J_{5,6} = 4.0$  Hz,  $H-5$ ), 5.06 (d, 1H,  $H-2'$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 62.9 MHz):  $\delta$  = 24.5 ( $\text{CH}_3$ ), 25.8 ( $\text{CH}_3$ ), 36.3 ( $C-2$ ), 52.0 ( $\text{OCH}_3$ ), 61.0 ( $C-7$ ), 76.0 ( $C-2'$ ), 79.7, 81.4, 83.7 ( $C-4$ ,  $C-5$ ,  $C-6$ ), 83.3 ( $C-3$ ), 113.6 ( $\text{C}(\text{CH}_3)_2$ ), 171.1 ( $\text{C}=\text{O}$ ). ESI-HRMS  $[\text{M}+\text{Na}]^+$   $m/z$  = found 328.1014 (calculated for  $\text{C}_{12}\text{H}_{19}\text{NO}_8\text{Na}$ : 328.1003). IR (NaCl)  $\nu_{\text{max}}/\text{cm}^{-1}$  3507, 2985, 2943, 1735, 1553

#### Compound 14

Compound **12** (5.10 g, 15.9 mmol) was saponified by LiOH (general procedure B) to provide **13** (4.78 g, 98% yield). Compound **13** (4.78 g, 15.6 mmol) was coupled with H-L-Lys(Boc)-OMe following procedure A to provide **14** (7.72 g, 90 %). Colorless oil.  $R_f$  = 0.21 (cH/EA: 3/7).  $[\alpha]_D = -22.0^\circ$  (c 0.4 in  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz):  $\delta$  = 1.25-1.54 (m, 4H, 2  $\text{CH}_2$  lys), 1.32 (s, 3H,  $\text{CH}_3$ ), 1.43 (s, 9H,  $\text{C}(\text{CH}_3)_3$  boc), 1.51 (s, 3H,  $\text{CH}_3$ ), 1.66-1.90 (m, 2H,  $\text{CH}_2$  lys), 2.77 (d, 1H,  $J_{\text{gem}} = 16.0$  Hz,  $H-2$ ), 2.99-3.12 (m, 3H,  $H-2$ ,  $\text{CH}_2$  lys), 3.75 (s, 3H,  $\text{OCH}_3$ ), 3.80-3.92 (m, 2H, 2  $H-7$ ), 4.13 (m, 1H,  $H-6$ ), 4.51-4.64 (m, 3H,  $H-2'$ ,  $H-\alpha$ ,  $\text{NHBoc}$ ), 4.79 (d, 1H,  $J_{4,5} = 6.0$  Hz,  $H-4$ ), 4.92 (dd, 1H,  $J_{5,6} = 4.0$  Hz,  $H-5$ ), 5.09 (d, 1H,  $J_{\text{gem}} = 12.0$  Hz,  $H-2'$ ), 6.49 (d, 1H,  $J = 8.0$  Hz, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 62.9 MHz):  $\delta$  = 22.4 ( $\text{CH}_2$  lys), 24.3 ( $\text{CH}_3$ ), 25.8 ( $\text{CH}_3$ ), 28.4 ( $\text{C}(\text{CH}_3)_3$  boc), 29.5 ( $\text{CH}_2$  lys), 31.9 ( $\text{CH}_2$  lys), 38.5 ( $C-2$ ), 40.4 ( $\text{CH}_2$  lys), 52.0, 52.5 ( $C-\alpha$ ,  $\text{OCH}_3$ ), 61.2 ( $C-7$ ), 76.7 ( $C-2'$ ), 79.9, 81.5 ( $\text{C}(\text{CH}_3)_3$  boc,  $C-5$ ,  $C-6$ ), 83.4 ( $C-3$ ), 83.9 ( $C-4$ ), 113.3 ( $\text{C}(\text{CH}_3)_2$ ), 156.2 ( $\text{C}=\text{O}$  boc), 169.4 ( $\text{C}=\text{O}$ ), 172.7 ( $\text{C}=\text{O}$  lys). ESI-HRMS  $[\text{M}+\text{Na}]^+$   $m/z$  = found 556.2485 (calculated for  $\text{C}_{23}\text{H}_{39}\text{N}_3\text{O}_{11}\text{Na}$ : 556.2477). IR (NaCl)  $\nu_{\text{max}}/\text{cm}^{-1}$  3364, 2981, 2933, 2867, 1742, 1690, 1666, 1551, 1529

#### Compound 16

Compound **14** (3.85 g, 7 mmol) was deprotected according to general procedure C to provide amine **15** (3.52 g, 7 mmol, 99%) which was then protected with a benzyloxycarbonyl group. The crude was suspended in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and DIEA (2.18 mL, 12.6 mmol, 1.8 eq.) followed by Cbz-Cl (1.5 mL, 10.5 mmol, 1.5 eq.) were added at 0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. Solvent was removed under vacuum and the residue was dissolved in ethyl acetate (40 mL), washed with 0.5M HCl (20 mL) and brine (20 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified by column chromatography (silica gel, cyH/EA) to provide **16** (3.12 g, 70%). Colorless oil. *R*<sub>f</sub> = 0.08 (cH/EA: 1/1). [ $\alpha$ ]<sub>D</sub> = -1.8° (c 0.5 in CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 1.28-1.58 (m, 4H, 2 CH<sub>2</sub> lys), 1.34 (s, 3H, CH<sub>3</sub>), 1.47 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub> boc), 1.54 (s, 3H, CH<sub>3</sub>), 1.66-1.92 (m, 2H, CH<sub>2</sub> lys), 2.38 (br s, 1H, OH), 2.63 (d, 1H, *J*<sub>gem</sub> = 14.0 Hz, *H*-2), 2.72 (d, 1H, *H*-2), 3.08-3.15 (m, 2H, CH<sub>2</sub> lys), 3.22 (dd, 1H, *J*<sub>gem</sub> = 15.0, *J*<sub>2',NH</sub> = 6.5 Hz, *H*-2'), 3.46 (dd, 1H, *J*<sub>2',NH</sub> = 7.5 Hz, *H*-2'), 3.74 (s, 3H, OCH<sub>3</sub>), 3.84-3.96 (m, 2H, 2 *H*-7), 4.15 (m, 1H, *H*-6), 4.54 (m, 1H, *H*- $\alpha$ ), 4.63 (d, 1H, *J*<sub>4,5</sub> = 5.5 Hz, *H*-4), 4.70 (t, 1H, *J* = 5.0 Hz, *NH* Boc), 4.89 (dd, 1H, *J*<sub>5,6</sub> = 4.5 Hz, *H*-5), 5.08 (d, 1H, *J*<sub>gem</sub> = 13.0 Hz, *CH*-Ph), 5.15 (d, 1H, *CH*-Ph), 5.78 (m, 1H, *NH* Cbz), 6.98 (d, 1H, *J* = 7.5 Hz, *NH*), 7.33-7.41 (m, 5H, 5 *H*-Ar). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 62.9 MHz):  $\delta$  = 22.5 (CH<sub>2</sub> lys), 24.3 (CH<sub>3</sub>), 25.8 (CH<sub>3</sub>), 28.4 (C(CH<sub>3</sub>)<sub>3</sub> boc), 29.5 (CH<sub>2</sub> lys), 31.8 (CH<sub>2</sub> lys), 40.1, 40.4 (*C*-2, CH<sub>2</sub> lys), 42.9 (*C*-2'), 52.2, 52.5 (*C*- $\alpha$ , OCH<sub>3</sub>), 61.5 (*C*-7), 66.9 (CH<sub>2</sub>-Ph), 79.4, 81.7 (C(CH<sub>3</sub>)<sub>3</sub> boc, *C*-5, *C*-6), 83.7, 84.9 (*C*-3, *C*-4), 113.0 (C(CH<sub>3</sub>)<sub>2</sub>), 128.0 (2 *C*-Ar), 128.1 (*C*-Ar), 128.5 (2 *C*-Ar), 136.4 (*C*-Ar), 156.3, 156.9 (C=O Boc, C=O Cbz), 170.9 (C=O), 172.9 (C=O lys). ESI-HRMS [M+Na]<sup>+</sup> *m/z* = found 660.3112 (calculated for C<sub>31</sub>H<sub>47</sub>N<sub>3</sub>O<sub>11</sub>Na: 660.3103). IR (NaCl)  $\nu_{\text{max}}$ /cm<sup>-1</sup> 3345, 2976, 2933, 2867, 1709, 1662, 1525

### Compound 18

Compound **14** was converted to amine **15** by catalytic hydrogenolysis (procedure C) and acid **17** was obtained by saponification of compound **16** (procedure B). Amine **15** (1.14 g, 2.2 mmol, 1.1 eq.) and acid **17** (1.28 g, 2 mmol, 1 eq.) were coupled according to procedure A to provide **18** (1.53 g, 69%). White foam. *R*<sub>f</sub> = 0.6 (EA/MeOH: 9/1). [ $\alpha$ ]<sub>D</sub> = +1.6° (c 0.2 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 1.30-1.54 (m, 8H, 4 CH<sub>2</sub> lys), 1.31 (s, 6H, 2 CH<sub>3</sub>), 1.45 (s, 18H, 2 C(CH<sub>3</sub>)<sub>3</sub> boc), 1.48 (s, 3H, CH<sub>3</sub>), 1.51 (s, 3H, CH<sub>3</sub>), 1.63-1.86 (m, 4H, 2 CH<sub>2</sub> lys), 2.50-2.77 (m, 6H, 2 OH, 4 *H*-2), 3.03-3.18 (m, 5H, 2 CH<sub>2</sub> lys, *H*-2'), 3.25 (dd, 1H, *J*<sub>gem</sub> = 15.0, *J*<sub>2',NH</sub> = 5.5 Hz, *H*-2'), 3.51 (dd, 1H, *J*<sub>gem</sub> = 15.0, *J*<sub>2',NH</sub> = 8.0 Hz, *H*-2'), 3.58 (dd, 1H, *J*<sub>gem</sub> = 14.5, *J*<sub>2',NH</sub> = 7.0 Hz, *H*-2'), 3.75 (s, 3H, OCH<sub>3</sub>), 3.82-3.88 (m, 4H, 4 *H*-7), 4.13-4.18



(m, 2H, 2 *H*-6), 4.31 (m, 1H, *H*- $\alpha$ ), 4.41-4.48 (m, 2H, *H*- $\alpha$ , *H*-4), 4.69 (d, 1H,  $J_{4,5}$  = 5.5 Hz, *H*-4), 4.79-4.88 (m, 4H, 2 *H*-5, 2 *NH* Boc), 5.07 (d, 1H,  $J_{\text{gem}}$  = 13.0 Hz, *CH*-Ph), 5.16 (d, 1H, *CH*-Ph), 6.43 (m, 1H, *NH* sucre), 7.15 (m, 1H, *NH* lys), 7.24 (m, 1H, *NH* lys), 7.31-7.41 (m, 6H, 5 *H*-Ar, *NH* sucre).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  = 22.7, 22.9 (2  $\text{CH}_2$  lys), 24.2, 24.3 (2  $\text{CH}_3$ ), 25.8 (2  $\text{CH}_3$ ), 28.4 (2  $\text{C}(\text{CH}_3)_3$ ), 29.5, 29.6 (2  $\text{CH}_2$  lys), 30.8, 31.5 (2  $\text{CH}_2$  lys), 39.6, 40.1, 40.7 (2 *C*-2, *C*-2', 2  $\text{CH}_2$  lys), 42.9 (*C*-2'), 52.7 (*C*- $\alpha$ ,  $\text{OCH}_3$ ), 53.8 (*C*- $\alpha$ ), 61.4, 61.7 (2 *C*-7), 66.8 ( $\text{CH}_2$ -Ph), 79.2, 79.3 (2  $\text{C}(\text{CH}_3)_3$ ), 79.9 (2 *C*-6), 81.2, 81.5 (2 *C*-5), 83.6, 84.0 (2 *C*-4), 85.0 (2 *C*-3), 112.9 (2  $\text{C}(\text{CH}_3)_2$ ), 128.0 (2 *C*-Ar), 128.1 (*C*-Ar), 128.5 (2 *C*-Ar), 136.5 (*C*-Ar), 156.2 (2 *C*=O Boc), 157.3 (*C*=O Cbz), 171.0, 171.6, 172.9, 173.9 (4 *C*=O). ESI-HRMS  $[\text{M}+\text{Na}]^+$   $m/z$  = found 1131.5654 (calculated for  $\text{C}_{53}\text{H}_{84}\text{N}_6\text{O}_{19}\text{Na}$ : 1131.5683). IR (NaCl)  $\nu_{\text{max}}/\text{cm}^{-1}$  3336, 2976, 2933, 2862, 1692, 1655, 1525

### Compound 19

Compound **18** was deprotected by catalytic hydrogenation (procedure C) and the corresponding amine (1.32 mg, 1.35 mmol, 1.1 eq.) was coupled with acid **17** (787 mg, 1.23 mmol, 1 eq.) according to procedure A to provide **19** (914 mg, 47% yield). White solid. Mp = 117 °C.  $R_f$  = 0.39 (EA/MeOH: 9/1).  $[\alpha]_D = +1.2^\circ$  (c 0.4 in  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  = 1.23-1.53 (m, 12H, 6  $\text{CH}_2$  lys), 1.28 (s, 3H,  $\text{CH}_3$ ), 1.31 (s, 6H, 2  $\text{CH}_3$ ), 1.45 (s, 27H, 3  $\text{C}(\text{CH}_3)_3$  boc), 1.50 (s, 9H, 3  $\text{CH}_3$ ), 1.60-1.89 (m, 6H, 3  $\text{CH}_2$  lys), 2.42-2.60 (m, 3H, 3 *H*-2), 2.75-2.87 (m, 3H, 3 *H*-2), 3.03-3.19 (m, 7H, 3  $\text{CH}_2$  lys, *H*-2'), 3.26 (dd, 1H,  $J_{\text{gem}}$  = 14.0,  $J_{2',\text{NH}}$  = 4.0 Hz, *H*-2'), 3.35 (dd, 1H,  $J_{\text{gem}}$  = 14.0,  $J_{2',\text{NH}}$  = 4.0 Hz, *H*-2'), 3.46-3.56 (m, 2H, 2 *H*-2'), 3.65 (m, 1H, *H*-2'), 3.76 (s, 3H,  $\text{OCH}_3$ ), 3.80-3.90 (m, 6H, 6 *H*-7), 4.13-4.21 (m, 4H, 3 *H*-6, *H*- $\alpha$ ), 4.39-4.55 (m, 5H, 2 *H*- $\alpha$ , 2 *H*-4, *NH* Boc), 4.67 (d, 1H,  $J_{4,5}$  = 6.0 Hz, *H*-4), 4.81-4.96 (m, 5H, 3 *H*-5, 2 *NH* Boc), 5.07 (d, 1H,  $J_{\text{gem}}$  = 12.0 Hz, *CH*-Ph), 5.15 (d, 1H, *CH*-Ph), 6.47 (m, 1H, *NH*), 7.12 (m, 1H, *NH*), 7.31-7.43 (m, 8H, 5 *H*-Ar, 3 *NH*), 7.93 (m, 1H, *NH*).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  = 22.7, 22.8 (3  $\text{CH}_2$  lys), 24.3, 24.4 (3  $\text{CH}_3$ ), 25.8, 25.9 (3  $\text{CH}_3$ ), 28.5 (3  $\text{C}(\text{CH}_3)_3$ ), 29.4, 29.6, 29.7 (3  $\text{CH}_2$  lys), 30.9, 31.2, 31.7 (3  $\text{CH}_2$  lys), 39.6, 40.2, 40.3, 41.0, 42.7 (3 *C*-2, 3 *C*-2', 3  $\text{CH}_2$  lys), 52.5, 52.7 (*C*- $\alpha$ ,  $\text{OCH}_3$ ), 53.3 (*C*- $\alpha$ ), 54.3 (*C*- $\alpha$ ), 61.4, 61.7 (3 *C*-7), 66.8 ( $\text{CH}_2$ -Ph), 79.1 (3  $\text{C}(\text{CH}_3)_3$ ), 79.7, 80.0, 80.3 (3 *C*-6), 81.3, 81.4, 81.6 (3 *C*-5), 83.7, 84.0, 84.2, 84.3, 84.9 (3 *C*-3, 3 *C*-4), 112.8 (2  $\text{C}(\text{CH}_3)_2$ ), 112.9 ( $\text{C}(\text{CH}_3)_2$ ), 128.1 (2 *C*-Ar), 128.5 (3 *C*-Ar), 136.6 (*C*-Ar), 156.2 (3 *C*=O Boc), 157.2 (*C*=O Cbz), 170.8, 171.4, 171.6, 172.9, 173.2, 173.9 (6 *C*=O). ESI-HRMS  $[\text{M}+\text{H}]^+$   $m/z$  = found 1580.8481 (calculated for  $\text{C}_{75}\text{H}_{122}\text{N}_9\text{O}_{27}$ : 1580.8445). IR (NaCl)  $\nu_{\text{max}}/\text{cm}^{-1}$  3331, 2981, 2933, 2867, 1692, 1655, 1525

## Compound 20

Compound **19** was saponified (procedure B) and deprotected by catalytic hydrolysis (procedure C). To a solution of deprotected glyco-amino acid (573 mg, 0.4 mmol, 1 eq.) in CH<sub>2</sub>Cl<sub>2</sub>/DMF (4/1) at 0°C under argon, were added DIEA (346 µL, 2.0 mmol, 5.0 eq.) and HATU (182 mg, 0.48 mmol, 1.2 eq.). After stirring at room temperature for 3 days, the solvents were evaporated and the residue was taken up in ethyl acetate (30 mL). The solution was washed with brine (10 mL), dried over MgSO<sub>4</sub>, filtered and concentrated. The product was purified by column chromatography (silica gel, AcOEt/MeOH) to provide **20** (123 mg, 22% yield). White foam. *R*<sub>f</sub> = 0.24 (EtOAc/MeOH : 95/5). [ $\alpha$ ]<sub>D</sub> = -20.7° (c 0.2 in CHCl<sub>3</sub>). <sup>1</sup>H (MeOH-d<sub>4</sub>, 250 MHz): 1.27-1.50 (m, 4H, 2 CH<sub>2</sub> lys), 1.30 (s, 3H, CH<sub>3</sub>), 1.44 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub> boc), 1.46 (s, 3H, CH<sub>3</sub>), 1.66 (m, 1H, CH<sub>2</sub> lys), 1.81 (m, 1H, CH<sub>2</sub> lys), 2.63 (d, 1H, *J*<sub>gem</sub> = 14.0 Hz, *H*-2), 2.69 (d, 1H, *H*-2), 3.00-3.07 (m, 2H, CH<sub>2</sub> lys), 3.29 (m, 1H, *H*-2'), 3.66-3.76 (m, 2H, *H*-2', *H*-7), 3.82 (m, 1H, *J*<sub>gem</sub> = 11.0, *J*<sub>6,7'</sub> = 4.5 Hz, *H*-7'), 4.08 (m, 1H, *H*-6), 4.26 (m, 1H, *H*-α), 4.60 (d, 1H, *J*<sub>4,5</sub> = 6.0 Hz, *H*-4), 4.87 (m, 1H, *H*-5). <sup>13</sup>C (MeOH-d<sub>4</sub>, 62.9 MHz): 24.3, 24.7 (CH<sub>2</sub> lys, CH<sub>3</sub>), 26.3 (CH<sub>3</sub>), 28.9 (C(CH<sub>3</sub>)<sub>3</sub>), 30.6 (CH<sub>2</sub> lys), 32.6 (CH<sub>2</sub> lys), 39.6 (*C*-2), 41.1, 41.2 (CH<sub>2</sub> lys, *C*-2'), 55.2 (*C*-α), 61.6 (*C*-7), 79.9 (*C*-6), 80.6 (C(CH<sub>3</sub>)<sub>3</sub>), 82.3 (*C*-5), 85.2 (*C*-4), 85.9 (*C*-3), 113.4 (C(CH<sub>3</sub>)<sub>2</sub>), 158.5 (C=O boc), 173.0, 175.1 (2 C=O). ESI-HRMS [M+Na]<sup>+</sup> *m/z* = found 1436.7626 (calculated for C<sub>66</sub>H<sub>111</sub>N<sub>9</sub>O<sub>24</sub>Na: 1436.7634). IR (NaCl)  $\nu_{\text{max}}$ /cm<sup>-1</sup> 3345, 2976, 2928, 2862, 1685, 1657, 1522, 1454

## Compound 21

To a stirred solution of **8** (42 mg, 0.049 mmol) in H<sub>2</sub>O (0.50 ml) at 0°C was added trifluoroacetic acid (0.50 ml). After completion of the reaction (TLC monitoring), the solvents were removed under reduced pressure and coevaporated with Et<sub>2</sub>O (3x5 mL). The residue was purified by column chromatography (RP-18 silica gel, H<sub>2</sub>O/MeOH) and lyophilized to provide **21** (35.6 mg, 99% yield).

White foam. *R*<sub>f</sub> = 0.80 (H<sub>2</sub>O/MeOH: 1/1). [ $\alpha$ ]<sub>D</sub> = +14.5° (c 0.4 in H<sub>2</sub>O). <sup>1</sup>H (D<sub>2</sub>O, 250 MHz):  $\delta$  = 1.57 (d, 3H, *J* = 7.0 Hz, CH<sub>3</sub> alanine), 2.88 (d, 1H, *J*<sub>gem</sub> = 19.0 Hz, *H*-2), 3.04 (d, 1H, *H*-2), 3.67 (s, 2H, 2 *H*-2'), 3.79 (dd, 1H, *J*<sub>gem</sub> = 9.5, *J*<sub>5,6</sub> = 5.0 Hz, *H*-6), 4.13 (q, 1H, *H*-α), 4.17 (dd, 1H, *J*<sub>5,6'</sub> = 6.0 Hz, *H*-6'), 4.54 (m, 1H, *H*-5), 4.96 (d, 1H, *J*<sub>4,5</sub> = 5.0 Hz, *H*-4). <sup>13</sup>C (D<sub>2</sub>O, 62.9 MHz):  $\delta$  = 16.6 (CH<sub>3</sub> alanine), 39.0, 43.2 (*C*-2, *C*-2'), 49.1 (*C*-α), 70.3, 70.4 (*C*-6, *C*-5), 84.6 (*C*-4), 87.2 (*C*-3), 114.0, 118.7 (TFA), 162.6, 163.2 (TFA), 171.4, 178.0 (2 C=O). ESI-HRMS [M+H]<sup>+</sup> *m/z* = found 245.1165 (calculated for C<sub>10</sub>H<sub>17</sub>N<sub>2</sub>O<sub>5</sub>: 245.1132). IR (pellets)  $\nu_{\text{max}}$ /cm<sup>-1</sup> 3383, 3255, 3094, 2995, 2938, 1782, 1678

## Compound 22

To a stirred solution of **25** (488 mg, 1.2 mmol) in methanol (8 mL) was added HCl (0.8 mL) dropwise. After stirring at 50°C until completion of the reaction (2 h), the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, EA/MeOH) to provide **22** (259 mg, 82% yield). White solide.  $R_f = 0.45$  (EA). mp 140°C (from diethyl ether).  $[\alpha]_D = -25.1^\circ$  (c 0.1 in CH<sub>3</sub>OH). <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz):  $\delta = 2.93$  (d, 1H,  $J_{gem} = 19.0$  Hz, *H*-2), 3.00 (d, 1H, *H*-2), 3.59 (dd, 1H,  $J_{gem} = 11.5$  Hz,  $J_{8a-7} = 6.0$  Hz, *H*-8), 3.65 (dd, 1H,  $J_{8b-7} = 5.0$  Hz, *H*-8), 3.96 (app td, 1H,  $J_{7-6} = J_{7-8b} = 5.0$  Hz,  $J_{7-8a} = 6.0$  Hz, *H*-7), 4.07 (dd, 1H,  $J_{6-5} = 4.0$  Hz, *H*-6), 4.49 (dd, 1H,  $J_{5-4} = 5.0$  Hz, *H*-5), 4.88 (d, 1H,  $J_{gem} = 14.0$  Hz, *H*-2'), 4.92 (d, 1H, *H*-2'), 5.14 (d, 1H, *H*-4). <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100.6 MHz):  $\delta = 41.30$  (*C*-2), 64.0 (*C*-8), 72.0 (*C*-7), 72.4 (*C*-5), 78.9 (*C*-2'), 83.9 (*C*-6), 84.7 (*C*-3), 85.8 (*C*-4), 176.7 (*C*=O). ESI-HRMS  $[M+Na]^+$   $m/z$  = found 286.0463 (calculated for C<sub>9</sub>H<sub>13</sub>NNaO<sub>8</sub>: 286.0539). IR (NaCl)  $\nu_{max}/cm^{-1}$  3343, 2949, 1730, 1647, 11548, 1436, 1375, 1207

## Compound 24

To a stirred solution of **11** (503 mg, 1.5 mmol) in H<sub>2</sub>O (3 mL) was added TFA (3 mL) dropwise at 0°C. After stirring at rt until completion of the reaction (6h), the solvent was removed under reduced pressure. The residue was co-evaporated with diethyl ether to provide **24** (438.4 mg, 99% yield). Colourless gum.  $R_f = 0.40$  (MeOH/EA: 1/9).  $[\alpha]_D = +14.9^\circ$  (c 0.1 in CH<sub>3</sub>OH). <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz):  $\delta = 2.93$  (d, 1H,  $J_{gem} = 16.0$  Hz, *H*-2), 2.98 (d, 1H, *H*-2), 3.60 (dd, 1H,  $J = 11.0$  Hz,  $J = 5.5$  Hz, *H*-8), 3.66 (dd, 1H,  $J = 11.0$  Hz,  $J = 5.0$  Hz, *H*-8), 3.69 (s, 3H, *OCH*<sub>3</sub>), 3.91 (app td, 1H,  $J_{7-8a} = J_{7-6} = 5.5$  Hz,  $J_{7-8b} = 5.0$  Hz, *H*-7), 4.04 (dd, 1H,  $J_{6-7} = 5.5$  Hz;  $J_{6-5} = 4.5$  Hz, *H*-6), 4.34 (app t, 1H,  $J_{5-4} = J_{5-6} = 4.5$  Hz, *H*-5), 4.49 (d, 1H, *H*-4), 4.75 (d, 1H,  $J_{gem} = 12.0$  Hz, *H*-2'), 5.10 (d, 1H, *H*-2'). <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100.6 MHz)  $\delta = 40.6$  (*C*-2), 52.2 (CH<sub>3</sub>), 64.0 (*C*-8), 72.3 (*C*-7), 73.2 (*C*-5), 78.1 (*C*-4), 79.4 (*C*-2'), 81.8 (*C*-3), 82.1 (*C*-6), 172.3 (*C*=O). IR (NaCl)  $\nu_{max}/cm^{-1}$  3304, 2928, 1722, 1674, 1549, 1437, 1381, 1202.

## Compound 25

Compound **10** was deprotected using general procedure B and the corresponding acide (1.30 g, 4.05 mmol, 1 eq.) was coupled with alanine methyl ester hydrochloride (905 mg, 1.6 eq, 6.48 mmol) following procedure A to provide **25** (658 mg, 40% yield). Yellow solide.  $R_f = 0.55$  (EA). mp 70°C (from diethyl ether).  $[\alpha]_D = -58.5^\circ$  (c 0.1 in CH<sub>3</sub>OH). <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz):  $\delta = 1.31$  (s, 3H, *CH*<sub>3</sub>), 1.38 (d, 3H,  $J_{CH_3ala-CHala} = 7.5$  Hz, *CH*<sub>3</sub> *ala*), 1.47 (s, 3H,

$CH_3$ ), 2.82 (d, 1H,  $J_{gem} = 16.0$  Hz,  $H-2$ ), 3.02 (d, 1H,  $H-2$ ), 3.64 (dd, 1H,  $J_{gem} = 11.5$  Hz,  $J_{8a-7} = 5.5$  Hz,  $H-8$ ), 3.72 (s, 3H,  $OCH_3$ ), 3.73 (dd, 1H,  $J_{8b-7} = 3.0$  Hz,  $H-8$ ), 3.91 (ddd, 1H,  $J_{7-6} = 7.5$  Hz,  $H-7$ ), 4.01 (dd, 1H,  $J_{6-5} = 3.5$  Hz,  $H-6$ ), 4.43 (q, 1H,  $J_{Hala-CH3ala} = 7.5$  Hz,  $H-ala$ ), 4.68 (d, 1H,  $J_{4-5} = 6.0$  Hz,  $H-4$ ), 4.77 (d, 1H,  $J_{gem} = 12.0$  Hz,  $H-2'$ ), 4.89 (dd, 1H,  $H-5$ ), 5.08 (d, 1H,  $H-2'$ ).  $^{13}C$  NMR (62.9 MHz, DMSO- $D_6$ ):  $\delta = 17.1$  ( $CH_3$  ala), 24.6 ( $CH_3$ ), 25.9 ( $CH_3$ ), 36.6 (C-2), 47.5 (C- $\alpha$ ), 50.1 ( $OCH_3$ ), 63.1 (C-8), 70.8 (C-7), 75.8 (C-2'), 80.1 (C-6), 80.7 (C-5), 82.8 (C-3), 83.5 (C-4), 111.5 ( $C(CH_3)_2$ ), 169.3, 173.4 (2 C=O). ESI-HRMS  $[M+Na]^+$   $m/z$  = found 429.1502 (calculated for  $C_{16}H_{26}N_2NaO_{10}$ : 429.1485). IR (NaCl)  $\nu_{max}/cm^{-1}$  3395, 2916, 1798, 1556, 1360, 1161.

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## Electronic supplementary information

Copies of  $^1H$  and  $^{13}C$  NMR spectra, experimental procedures and characterizations of intermediates obtained from minor anomer **11**.

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