# Ring Closing Methatesis mediated synthesis of D-galactose derived β-amino acids

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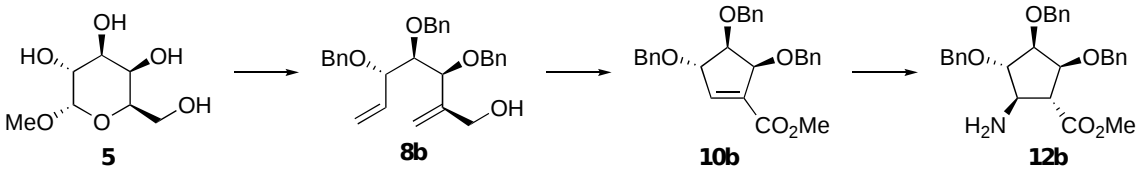



The first example of a new stereocontrolled synthesis of polyhydroxylated 2-aminocyclopetanecarboxylic acids from hexoses is reported. It consists of the transformation of D-galactose derivative **5** into polysubstituted cyclopentane β-amino acid derivative **12b** by means of a sequence that involves a Ring Closing Metathesis of the corresponding polysubstituted 2-methylenehept-6-ene **8b**, followed by a stereocontrolled aza-Michael functionalization of the first reported polysubstituted cyclopent-1-ene-1-carboxylic acid ester **10b**. Preliminary studies on peptides incorporating these alicyclic α-amino acids are also reported. The incorporation of β-amino acid derivative **12b** into peptides is also reported.

## Introduction

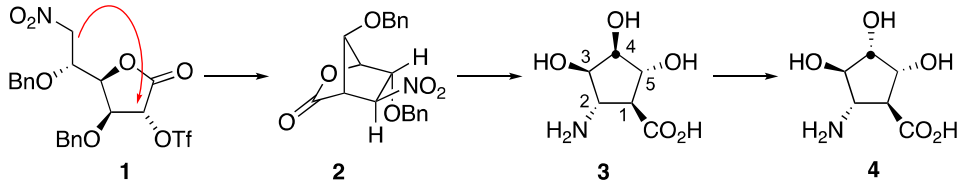
The enantioselective synthesis of β-amino acids has received great attention in recent times,[1,2] because they are used as chiral auxiliaries and catalysts in organic synthesis and as suitable building blocks for the preparation of diverse compounds of chemical and biological interest, mainly peptidomimetics that may overcome the pharmacological limitations of natural peptides.[3,4–7,8,9,10] These systems are more resistant than α-peptides to microorganisms and to protease and peptidase degradation and their conformational properties and stability facilitate their interaction with receptors and enzymes, and this usually results in improved activity.[11,12,13]

Among the many β-amino acids that have been studied, cyclopentane based β-amino acids are particularly attractive building blocks, because their β-peptides exhibit specific folding properties and their homo-oligomers show a high tendency to fold in very rigid secondary structures in short peptide sequences, a structural property that often gives them enhanced biostability and activity.[14,15] Thus, oligomers that contain at least four units of *trans*-2-aminocyclopentanecarboxylic acids adopt a stable 12-helix with topological dimensions similar to those of the α-helix in α-peptides.[16,17] On the other hand, *cis*-2-aminocyclopentanecarboxylic acids can satisfactorily replace prolines as inducers of β-turns in α-peptides,[18,19] and their *cis*-homo-oligomers adopt β-sheet secondary structures.[20] Accordingly,

cyclopentane β-amino acids proved to be ideal candidates for the stabilization of conformations in peptides.[21]

The development of methodologies for the stereo- and regioselective synthesis of polysubstituted cyclopentane rings continues to be a challenge in synthetic chemistry.[22–24,25] An specific goal of this significant area of research is to increase substantially the limited number of known polyhydroxylated cyclopetane β-amino acids and thus to enable access to a large variety of hydro- or liposoluble cyclopentane-based β-peptides.[26,27] This latter goal can be achieved by protection or deprotection of the hydroxy substituents present on the cyclopentane rings. In addition, it is feasible that these substituents on the cyclopentane rings could provide access to novel folding properties in β-peptides, a matter of evident interest in materials chemistry.

**Scheme 1.** First synthesis of polyhydroxylated cyclopentane β-amino acids.



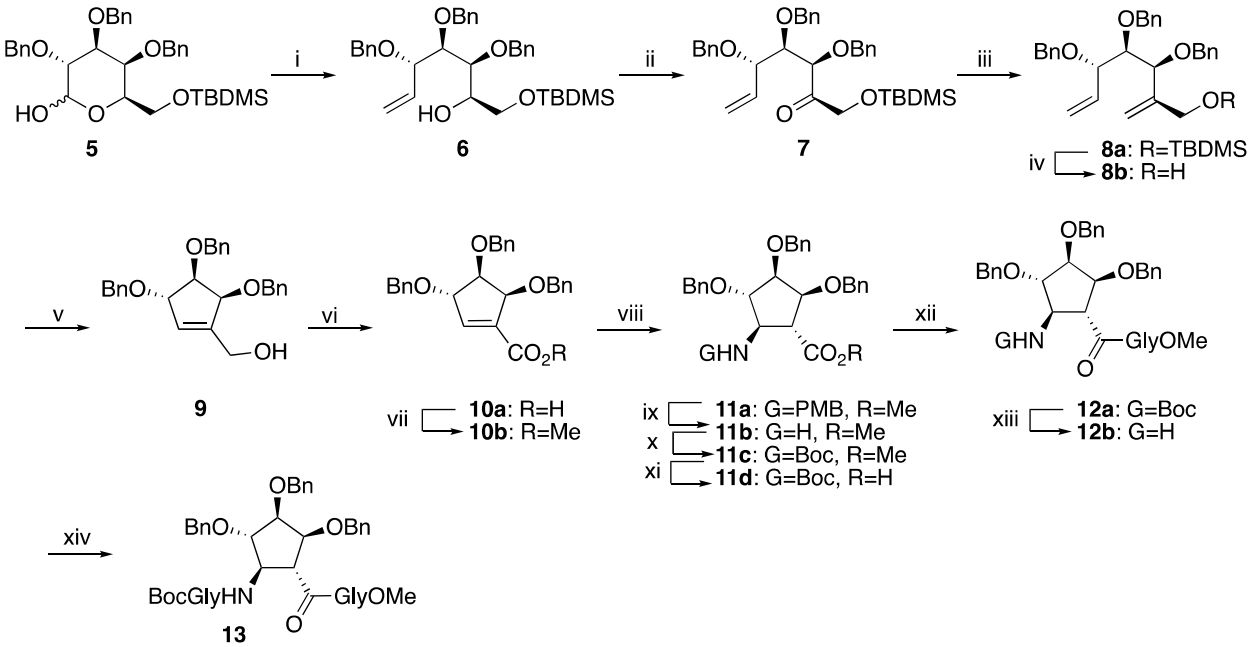

The first reported polyhydroxylated cyclopentane β-amino acid, the *trans*-2-aminocyclopentanecarboxylic acid derivative **3**, was obtained by a novel approach involving the key stereocontrolled cyclization of nitronate of D-glucose nitro sugar derivative **1** to bicyclolactone **2** (Scheme 1).[28,29] Application of this approach to L-idose provided the first polyhydroxylated *cis*-2-aminocyclopentanecarboxylic acid.[29] Nevertheless, this promising synthetic strategy is of limited scope, because it can only provide direct access to eight 2-polyhydroxylated cyclopentane β-amino acids, i.e. only those arising from the eight hexoses that meet the stereochemical requirements for the key intramolecular alkylation leading bicyclic lactones **2** (D-glucose, D-idose, D-allose, D-talose, L-glucose, L-idose, L-allose and L-talose).[30] Other polyhydroxylated 2-aminocyclopentanecarboxylic acids include cyclopentane β-amino acid **4**, which was prepared from β–amino acid **3** by an sequence involving the inversion of the configuration at its stereogenic center at C-4.[31,27] We report here a stereocontrolled synthesis of derivatives **11a-g** of enantiomer of polyhydroxylated cyclopentane β-amino acid **4** from D-galactose, that overcomes this limitation (Scheme 2). It combines a Ring Closing Metathesis mediated synthesis of richly functionalized cyclopentenes **10b** (Scheme 2) and **10d** (Scheme 4), the two first reported 3,4,5-trihydroxycyclopent-1-ene-1-carboxylic acid derivatives, and amination of their α,β-unsaturated carboxylic acid ester moieties.

**Results and discussion**

We first studied the preparation of 3,4,5-tribenzyloxycyclopent-1-ene-1-carboxylic acid derivative **10a** from the orthogonally protected diene **8a**, which was obtained from the known D-galactose derivative **5a**[33] via compounds **6a** and **7a** (Scheme 2).[34,35,36] Removal of the silyl ether group at C-1 of **8a** by treatment with TBAF gave the desired key diolefin **8b**. According to our synthetic plan, when this compound was subjected to standard RCM reaction conditions, the expected cyclopentenol **9a**

was formed in 89% yield.[35] Oxidation of this compound under the conditions stated in Scheme 2 gave cyclopentenecarboxylic acid **10a** through the spontaneous oxidation of the corresponding aldehyde. Reaction of **10a** with $NaHCO_3$ and MeI furnished its methyl ester derivative **10b** in 97% yield for the three last steps.

**Scheme 2.** Synthesis of polyhydroxylated cyclopentane β-amino acid derivative **11a** and its incorporation into tripeptide **13**.

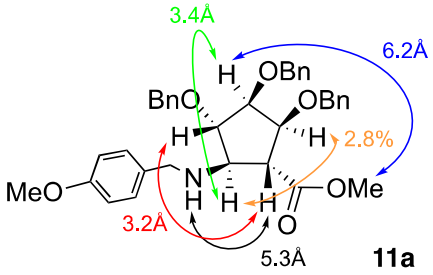



*Conditions.-* i) *n*-BuLi, $Ph_3PCH_3Br$, THF, -78 ºC to rt, 12 h, 80%. ii) Dess-Martin, $CH_2Cl_2$, rt, 2 h, 82%. iii) *n*-BuLi, $Ph_3PCH_3Br$, THF, -78 ºC to rt, 12 h, 85%. iv) TBAF, THF, rt, 1 h, 87%, v) Grubbs 2nd, toluene, ref., 24 h, 89%. vi) a. TEMPO, BAIB, $NBu_4I$, $CH_2Cl_2/H_2O$, rt, 2 h. b. $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene. vii) $NaHCO_3$, MeI, DMF, rt, 12 h, 97%. (from **9a**). viii) $NH_2PMB$, DMF, rt, 24 h, 80%. ix) CAN, $CH_3CN/H_2O$, 0 ˚C->rt, 6 h, x) $(Boc)_2O$, $NaHCO_3$, rt, 18 h, 75% xi) $Ba(OH)_2{\cdot}8\ H_2O$, $THF/H_2O$, rt, 1 h. xii) HCl-Gly-OMe, HATU, DIEA, $CH_2Cl_2$, rt, 14 h 60% (from **11c**). xiii) TFA, THF, rt, 1 h. xiv) Boc-Gly-OH, HATU, DIEA $CH_2Cl_2$, rt, 10 h, 55% (from **12a**)

Following the generation of the cyclopentene ring of compound **10b**, the programed functionalization of its α,β-unsaturated ester subunit was attempted, selecting *p*-methoxybenzylamine as the nucleophile, in order to obtain cyclopentane β-amino acid derivative **11a**, with its nitrogen atom and its hydroxy groups orthogonally protected. Accordingly, treatment of **10b** with *p*-methoxybenzylamine resulted in a stereoselective aza-Michael addition of this bulky amine to its α,β-unsaturated carboxylic acid ester moiety,[37] that provided compound **11a** in 80% yield. Finally, chemoselective *N*-debenzylation of **11a** with CAN gave the free amine intermediate **11b**,[38] which was directly reacted with $(Boc)_2O$ to furnish the orthogonally protected β-amino acid ester **11c** (CPCA-11c) in 75% yield. According to our plan, next, glycine subunits were linked to both the *N*- and the *C*-terminal positions of amino acid derivative **11c**, in order to test the ability of its incorporation into peptides.[39] As shown in Scheme 2, hydrolysis of the methoxycarbonyl moiety of compound **11c** under basic conditions was followed by treatment of the resulting carboxylic acid **11d** with HATU as an activating reagent

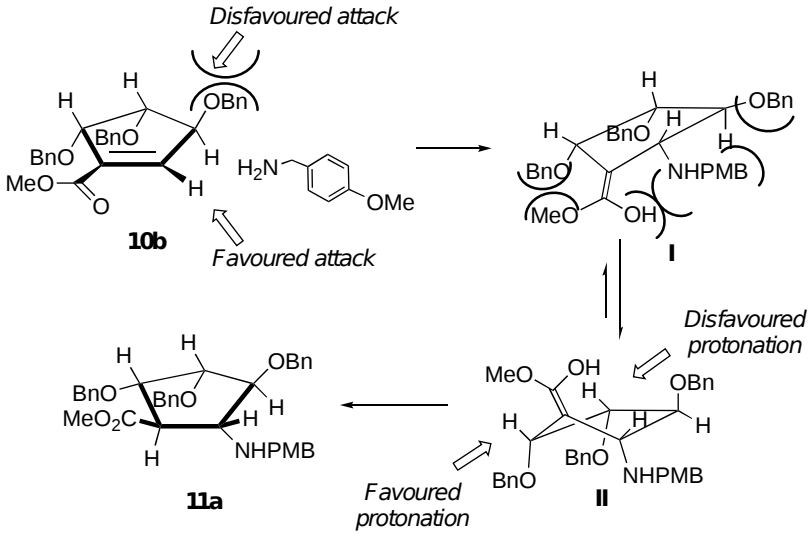
and then with glycine hydrochloride. Thus, dipeptide **12a** was isolated in 60% yield. The Boc group of this compound was easily cleaved with TFA and the resulting amine **12b** was reacted with Boc-Gly-OH, upon activation with HATU. This reaction furnished tripeptide **13** in 55% yield for the last two steps.
This new approach to polyhydrylated cyclopentane β-amino acids **11** resulted to be shorter and more efficient than the previous nitro sugar based synthesis of this targets.[28,29]

**Figure 1.** Selected nOe enhancements observed for compound **17**.




The relative configurations at the C-1 and C-5 stereogenic centers of **11a** were assigned from $^{1}$H-NMR NOE experiments (Figure 1). A 6.2% enhancement from –$CO_2$Me to C(3)–H indicates a *cis* relationship between these groups. In addition, the 2.8% and 3.4% enhancements observed from C(5)–H to C(2)–H and to C(3)–H, respectively, is consistent with the configuration proposed for C-5. Finally, a 5.3% nOe enhancement observed between PMBN–H and C(1)–H allowed us to establish the *trans* disposition of this group at C-5 and the carbomethoxy group at C-1.

**Scheme 3.** Proposed model to explain the selectivity observed in the Michael addition of $PMBNH_2$ on cyclopentenecarboxylic acid ester **10b**.




A tentative explanation for the stereochemistry observed for the transformation of cyclopentene carboxylic acid derivative **10b** into cyclopentane β-amino acid derivative **11a** is shown in Scheme 3. The outcome of this reaction is related to complete diastereofacial control by the substituent at position C-3 of **10b**, that favours an *anti* nucleophilic attack of PMB on the C-2 position. [40,41] The preferential

*anti* Michael addition results in the formation of enol **I**, which can exist as an equilibrium mixture of conformers **I** and **II**. The thermodynamically preferred conformer **II** favours an *anti* protonation, which leads to compound **11a**.

## Conclusion

In conclusion, we have developed a promising new strategy for the transformation of sugars into polyhydroxylated cyclopentane ⌊ⲭ-amino acids. This approach allowed us to prepare derivatives **17**, **18**, **19** and **20** of the third reported polyhydroxylated cyclopentane ⌊ⲭ-amino acid [(1*R*,2*R*,3*S*,4*S*,5*S*)-2-amino-3,4,5-trihydroxycyclopentanecar-boxylic acid]. Orthogonally protected derivative **20** allowed the incorporation of this novel ⌊ⲭ-amino acid into tripeptide **23**.

This promising new approach to the synthesis of highly complex polyhydroxylated cyclopentane β–amino acids is clearly an improvement on the previous approach to these targets from nitro sugars. The present method has greater scope because it could be extended to the pool of hexoses. Moreover, as this route proved to be shorter and more efficient, it allowed compound **19** to be prepared on a multigram scale, as required for the preparation and structural studies of homo- and heteropeptides based on polyhydroxylated cyclopentane β-amino acid.

Future work in this field will include the extension of this synthetic methodology to hexoses other than d-galactose in order to establish the scope of this novel, promising approach to polyhydroxylated cyclopentane β–amino acids and their peptides

## Experimental Section

General Experimental Information. All non-aqueous reactions were carried out under a positive atmosphere of argon in flame-dried glassware unless otherwise stated. Air- and moisture-sensitive liquid reagents were added by dry syringe or cannula. Anhydrous tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under argon and all other solvents and reagents were used as obtained from commercial sources without further purification unless stated. Flash chromatography was performed using 60 Merck 230–400 mesh (flash, 0.04–0.063) silica. Thin layer chromatography (t.l.c.) was carried out on aluminum backed sheets coated with 60 GF254 silica. Plates were developed using a spray of 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid, or in 5% w/v ninhydrin in methanol. $^{1}$H and $^{13}$C NMR spectra were recorded on Bruker DPX 250 (250 MHz for $^{1}$H and 62.5 MHz for $^{13}$C), Varian Mercury 300 (300 MHz for 1H and 75 MHz for 13C), Varian Inova 400 (400 MHz for 1H and 100 MHz for 13C) and Bruker AMX 500 (500 MHz for $^{1}$H and 125 MHz for $^{13}$C) spectrometers at room temperature unless otherwise stated. All chemical shifts are quoted on the δ scale using residual solvent as internal standard; s, d, t, q, m, and br designate singlet, doublet, triplet, quadruplet, multiplet, and broad, respectively. Coupling constants (J) are measured in Hz. Low resolution mass spectra were recorded on a Micromass Autospec spectrometer [by chemical ionisation (NH3, Cl) as stated]. Infrared spectra were recorded on a FT-IR Mattson Cygnus-100 spectrometer. Only the characteristic peaks are quoted (in units of cm$^{-1}$); st, m, and br designate strong,

medium, and broad, respectively. All the spectra were measured in KBr. Optical rotations were measured on a Jasco DIP-370 polarimeter with a path length of 0.5 dm and Na (589 nm) lamp. Concentrations are given in g/100 mL. Elemental analyses were carried out on a Carlo Erba EA 1108 analyser. Compound **5** was prepared according to known procedures.

**(2*R*,3*S*,4*R*,5*S*)-3,4,5-Tris(benzyloxy)-1-(*tert*-butyldimethylsilyloxy)-hept-6-ene-2-ol (6).-** A suspension of $Ph_3PCH_3Br$ (7.99 g, 22.36 mmol) in dry THF (37.3 mL) was cooled to –78 ºC under argon and *n*-BuLi (14 mL, 22.36 mmol, 1.6 M solution in hexane) was added dropwise. The mixture was stirred at –78 ºC for 30 min and at 0 ºC for 30 min. A solution of **5** (4.21 g, 7.45 mmol) in THF (37.3 mL) was added dropwise to the resulting ylide at –78 ºC and the new reaction mixture was allowed to warm up to room temperature and then was heated under reflux for 12 h. The mixture was quenched with saturated aq. $NH_4Cl$ (50 mL) and extracted with $Et_2O$ (100 mL). The organic layer was dried (anhydrous $Na_2SO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc/hexane 1:9) to afford compound **6** (3.36 g, 5.96 mmol, 80% yield) as a yellowish oil. $[\alpha]_D^{20}$ –2.1º (*c* 1.7, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$, ppm): 0.02 (s, 6 H), 0.88 (s, 9 H); 3.06 (d, 1 H, *J* = 4.9 Hz), 3.56–3.62 (m, 2 H), 3.79–3.97 (m, 3 H), 4.08 (dd, 1 H, *J* = 7.9 Hz, *J* = 4.9 Hz), 4.35 (d, 1 H, *J* = 11.8 Hz); 4.43 (d, 1 H, *J* = 11.5 Hz); 4.50 (d, 1 H, *J* = 11.5 Hz); 4.65 (d, 1 H, *J* = 11.8 Hz), 4.76 (br, 2 H), 5.30 (dd, 1 H, *J* = 17.5, 1.6 Hz), 5.35 (dd, 1H, *J* = 10.5, 1.6 Hz), 5.84 (ddd, 1 H, *J* = 17.6, 10.4, 7.9 Hz), 7.22–7.38 (m, 15 H). $^{13}$C NMR (62.5 MHz, $CDCl_3$, ppm): –5.5, –5.4, 18.1, 25.8, 63.3, 70.2, 71.2, 73.2, 75.2, 75.7, 80.9, 82.3, 119.1, 127.4, 127.5, 127.6, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 135.5, 138.1, 138.2, 138.3. MS (CI, *m*/*z*, %): 564 (18, $[M + H]^+$); 456 (23, $[M – OCH_2Ph]^+$); 91 (100, $[CH_2Ph]^+$). IR (NaCl, $\nu_{máx}$, $cm^{-1}$): 3492 (br, OH), 1104 (st, Si-O-C). Anal. calculated for $C_{34}H_{46}O_5Si$: C 72.56; H 8.24; found: C 72.49; H 8.49.

**(3*R*,4*R*,5*S*)-3,4,5-Tris(benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)-hept-6-en-2-one (7).-** A solution of compound **6** (1.87 g, 3.31 mmol) in $CH_2Cl_2$ (16.6 mL) was stirred with Dess–Martin periodinane (1.62 g, 3.81 mmol) for 2 h at room temperature. The mixture was quenched with saturated aq. $Na_2S_2O_3$ (30 mL) and extracted with $Et_2O$ (50 mL). The organic layer was dried (anhydrous $Na_2SO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc/hexane 1:15) to afford compound **7** (1.52 g, 2.72 mmol, 82% yield) as a yellowish oil. $[\alpha]_D^{21}$ +20.7º (*c* 1.9, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$, ppm): –0.03 (s, 3H), 0.00 (s, 3H), 0.87 (s, 9H), 3.87 (dd, 1H, *J* = 6.3, 4.4 Hz), 4.12 (dd, 1H, *J* = 7.1, 6.3 Hz), 4.22 (d, 1H, *J* = 4.4 Hz), 4.38 (d, 1H, *J* = 11.8 Hz), 4.45 (d, 2H, *J* = 10.2 Hz), 4.46 (br, 2H), 4.60 (d, 1H, *J* = 11.0 Hz), 4.62 (d, 1H, *J* = 11.8 Hz), 4.75 (d, 1H, *J* = 11.0 Hz), 5.35 (dd, 1H, *J* = 17.3, 1.7 Hz), 5.40 (dd, 1H, *J* = 10.5, 1.7 Hz), 5.84 (ddd, 1H, *J* = 17.3, 10.5, 7.1 Hz), 7.21–7.38 (m, 15H). $^{13}$C NMR (62.5 MHz, $CDCl_3$, ppm): –5.8, –5.6, 18.1, 25.6, 68.9, 70.4, 72.2, 74.7, 80.5, 81.4, 82.6, 119.2, 127.2, 127.3, 127.5, 127.6, 127.8, 127.9, 128.0, 128.1, 134.9, 136.9, 137.8, 138.0, 208.0. MS (CI, *m*/*z*, %): 562 (85, $[M + H]^+$); 454 (100, $[M – OCH_2Ph]^+$), 91 (90, $[CH_2Ph]^+$). IR (NaCl, $\nu_{máx}$, $cm^{-1}$): 1735 (st, C=O), 1091 (st, Si-O-C). Anal. calculated for $C_{34}H_{44}O_5Si$: C 72.82; H 7.91; found: C 72.66; H 8.03.

**(3*S*,4*R*,5*S*)-3,4,5-Tris(benzyloxy)-1-(*tert*-butyldimethylsilyloxy)-2-methylen-hept-6-ene (8a).-** A suspension of $Ph_3PCH_3Br$ (4.01 g, 11.23 mmol) in dry THF (11.2 mL) was cooled to –78 ºC under argon and *n*-BuLi (6.8 mL, 10.86

mmol, 1.6 M solution in hexane) was added dropwise. The mixture was stirred at –78 ºC for 30 min and at 0 ºC for 30 min. A solution of compound **7** (2.10 g, 3.75 mmol) in THF (11.2 mL) was added dropwise to the ylide, at –78 ºC. The reaction mixture was allowed to warm up to room temperature and was stirred for 2 h. The mixture was quenched with saturated aq. $NH_4Cl$ (50 mL) and extracted with $Et_2O$ (100 mL). The organic layer was dried with anhydrous $Na_2SO_4$ and concentrated *in vacuo*. Flash column chromatography of the crude product (EtOAc/hexane 1:19) afforded compound **8a** (1.78 g, 3.18 mmol, 85% yield) as a yellowish oil. $[\alpha]_D^{20}$ +19.3º (*c* 1.4, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$, ppm): 0.02 (s, 3H), 0.03 (s, 3H), 0.91 (s, 9H), 3.59 (dd, 1H, *J* = 7.6, 3.8 Hz), 4.10 (d, 1H, *J* = 11.0 Hz), 4.12 (dd, 1H, *J* = 7.8, 7.6 Hz), 4.13 (d, 1H, *J* = 12.1 Hz), 4.25 (br, 2H), 4.32 (d, 1H, *J* = 12.1 Hz), 4.45 (d, 1H, *J* = 11.3 Hz), 4.57 (d, 1H, *J* = 11.0 Hz), 4.60 (d, 1H, *J* = 3.8 Hz), 4.63 (d, 1H, *J* = 11.3 Hz), 5.25 (dd, 1H, *J* = 17.6, 1.9 Hz), 5.28 (dd, 1H, *J* = 1.9 Hz), 5.32 (dd, 1H, *J* = 10.4, 1.9 Hz), 5.48 (d, 1H, *J* = 1.9 Hz), 5.89 (ddd, 1H, *J* = 17.6, 10.4, 7.7 Hz), 7.16–7.36 (m, 15H). $^{13}$C NMR (62.5 MHz, $CDCl_3$, ppm): –5.5, 18.2, 25.9, 63.4, 70.0, 70.4, 74.9, 79.2, 80.1, 83.7, 113.4, 118.2, 127.3, 127.4, 127.6, 127.9, 128.0, 128.1, 136.1, 138.2, 138.3, 138.4, 146.4. MS (CI, *m/z*, %): 559 (15, $[M+H]^+$); 468 (66, $[M - CH_2Ph]^+$); 91 (100, $[CH_2Ph)]^+$). IR (NaCl, $\nu_{máx}$, $cm^{-1}$): 1099 (st, Si-O-C). Anal. calculated for $C_{35}H_{46}O_4Si$: C 75.23; H 8.30; found: C 75.37; H 8.20.

**(3*S*,4*R*,5*S*)-3,4,5-Tris(benzyloxy)-2-methylen-hept-6-ene-1-ol (8b).-** Compound **8a** (1.78 g, 3.18 mmol) was dissolved in THF (15.9 mL) and stirred with TBAF (3.8 mL, 3.8 mmol, 1 M solution in THF) at room temperature for 1 h. The reaction mixture was treated with saturated aq. $NH_4Cl$ (25 mL) and extracted with $Et_2O$ (25 mL). The organic layer was dried (anhydrous $Na_2SO_4$) and concentrated to dryness. The crude product was subjected to flash column chromatography (EtOAc/hexane 1:4) to afford compound **8b** (1.23 g, 2.77 mmol, 87% yield) as a yellowish oil. $[\alpha]_D^{19}$ +26.8º (*c* 1.3, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$, ppm): 2.85 (dd, 1H, *J* = 7.4, 5.2 Hz), 2.72 (t, 1H, *J* = 5.8 Hz), 4.04 (dd, 1H, *J* = 7.9, 7.4 Hz), 4.10–4.22 (m, 3H), 4.15 (d, 1H, *J* = 11.5 Hz), 4.34 (d, 1H, *J* = 12.1 Hz), 4.45 (d, 1H, *J* = 11.5 Hz), 4.62 (d, 1H, *J* = 12.1 Hz), 4.69 (d, 1H, *J* = 11.0 Hz), 4.76 (d, 1H, *J* = 11.0 Hz), 5.22 (dd, 1H, *J* = 17.3, 1.9 Hz), 5.29 (dd, 1H, *J* = 1.9 Hz), 5.35 (dd, 1H, *J* = 10.4, 1.9 Hz), 5.38 (dd, 1H, *J* = 1.9 Hz), 5.84 (ddd, 1H, *J* = 17.3, 10.4, 7.9 Hz), 7.20–7.34 (m, 15H). $^{13}$C NMR (62.5 MHz, $CDCl_3$, ppm): 62.6, 69.7, 70.2, 75.1, 79.9, 80.3, 83.4, 116.4, 118.5, 127.1, 127.3, 127.6, 127.8, 127.9, 128.0, 135.3, 137.7, 137.8, 138.0, 145.4. MS (CI, *m/z*, %): 446 (54, $[M + H]^+$); 231 (64, $[M – (2 \times OCH_2Ph]^+$); 91 (100, $[CH_2Ph]^+$). IR (NaCl, $\nu_{máx}$, $cm^{-1}$): 3450 (br, OH). Anal. calculated for $C_{29}H_{32}O_4$: C 78.35; H 7.26; found: C 78.53; H 7.50.

**(3*S*,4*R*,5*S*)-1-Hydroxymethyl-3,4,5-tris(benzyloxy)-cyclopent-1-ene (9).-** Grubbs' second generation catalyst (0.12 g, 0.14 mmol) was added to a deoxygenated solution of compound **8b** (1.23 g, 2.77 mmol) in toluene (83 mL) and the mixture was refluxed under argon for 24 h. The reaction mixture was concentrated to dryness under vaccuum. The crude product was purified by flash column chromatography (EtOAc/hexane 1:2) to provide compound **9a** (1.03 g, 2.46 mmol, 89% yield) as a yellow oil. $[\alpha]_D^{19}$ +19.5º (*c* 1.7, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$, ppm): 1.70 (br, 1H); 4.03 (dd, 1H, *J* = 5.8, 4.1 Hz), 4.16 (d, 1H, *J* = 14.5 Hz), 4.25 (d, 1H, *J* = 14.5 Hz), 4.53 (d, 1H, *J* = 11.3 Hz), 4.63 (d, 1H, *J* = 11.3 Hz), 4.64 (d, 1H, *J* = 10.4 Hz), 4.67 (d, 1H, *J* = 11.8 Hz), 4.68 (d, 1H, *J* = 10.4 Hz), 4.71 (d, 1H, *J* = 5.8 Hz), 4.74 (d, 1H, *J* = 11.8 Hz), 4.77 (dd, 1H, *J* = 4.1, 1.4 Hz), 5.94 (d, 1H,

*J* = 1.4 Hz), 7.28–7.40 (m, 15H). $^{13}$C NMR (62.5 MHz, $CDCl_3$, ppm): 59.7, 71.0, 71.4, 71.9, 78.7, 83.8, 86.0, 125.1, 127.4, 127.5, 127.6, 127.8, 128.0, 128.1, 137.8, 137.9, 138.1, 146.7. MS (CI, *m*/*z*, %): 418 (4, $[M + H]^+$); 400 (63, $[M – OH]^+$); 91 (100, $[CH_2Ph]^+$). IR (NaCl, $\nu_{máx}$, $cm^{-1}$): 3301 (br, NH), 1757 (st, C=O). Anal. calculated for $C_{27}H_{28}O_4$: C 77.86; H 6.78; found: C 77.70; H 6.92.

**Methyl (3*S*,4*R*,5*S*)-3,4,5-tris(benzyloxy)cyclopent-1-enecarboxylate (10b).-** To a solution of compound **9a** (1.03 g, 2.46 mmol) in $CH_2Cl_2$/$H_2O$ (17.3 mL, 3:1) $NBu_4I$ (0.05 g, 0.12 mmol), TEMPO (0.08 g, 0.49 mmol) and DAIB (1.98 g, 6.15 mmol) were added. The mixture was stirred at room temperature for 2 h and then was quenched with saturated aq. $Na_2S_2O_3$ (30 mL) and extracted with EtOAc (30 mL). The organic layer was dried (anhydrous $Na_2SO_4$) and concentrated *in vacuo*. The crude product was dissolved in $^t$BuOH (12.3 mL) and 2-methyl-2-butene (1.8 mL, 17.23 mmol), and a solution containing $NaClO_2$ (0.36 g, 3.20 mmol, 80%) and $NaH_2PO_4·H_2O$ (0.50 g (3.20 mmol) in water (12.3 mL) was added. The mixture was stirred at room temperature for 1 h and then was quenched with 10% aq. HCl (20 mL) and extracted with EtOAc (20 mL). The organic layer was dried (anhydrous $Na_2SO_4$) and concentrated *in vacuo*. To a solution of the resulting carboxylic acid in dry DMF (12.3 mL) $NaHCO_3$ (0.39 g, 4.68 mmol) and MeI (0.38 mL, 6.15 mmol) were added. The mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with $NH_4Cl$ (20 mL) and extracted with EtOAc (20 mL). The organic layer was dried (anhydrous $Na_2SO_4$) and concentrated *in vacuo*. Flash column chromatography of the crude (EtOAc/hexane 1:6) furnished compound **10b** (1.06 g, 2.39 mmol, 97% yield) as a colorless oil. $[\alpha]_D^{20}$ +17.3º (*c* 1.2, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$, ppm): 3.72 (s, 3H), 3.98 (dd, 1H, *J* = 5.8, 4.3 Hz), 4.56 (d, 1H, *J* = 11.8 Hz), 4.64–4.80 (m, 6H), 4.98 (d, 1H, *J* = 5.8 Hz), 7.02 (d, 1H, *J* = 1.4 Hz), 7.28–7.40 (m, 15H). $^{13}$C NMR (62.5 MHz, $CDCl_3$, ppm): 57.5, 71.9, 72.1, 72.3, 76.5, 84.9, 85.3, 127.4, 127.5, 127.6, 128.0, 128.1, 128.2, 128.3, 135.8, 137.6, 138.1, 147.5, 168.5. MS (CI, *m*/*z*, %): 446 (17, $[M + H]^+$); 430 (76, $[M – CH_3]^+$); 91 (100, $[CH_2Ph]^+$). IR (NaCl, $\nu_{máx}$, $cm^{-1}$): 1733 (st, C=O). Anal. calculated for $C_{28}H_{28}O_5$: C 75.65; H 6.35; found: C 75.45; H 6.32.

**Methyl (1*R*,2*S*,3*S*,4*S*,5*R*)- 2,3,4-tris(benzyloxy)-5-((*p*-methoxy(benzyl)amino)-cyclopentane-1-carboxylate (11a).-** Compound **10b** (1.03 g, 2.39 mmol) was dissolved in dry DMF (7.2 mL) and stirred with $PMBNH_2$ (0.37 mL, 2.86 mmol) at room temperature under argon for 24 h. The reaction mixture was diluted with $NH_4Cl$ (10 mL) and extracted with EtOAc (10 mL). The organic layer was dried (anhydrous $Na_2SO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc/hexane 1:4) to afford compound **11a** (1.11 g, 1.91 mmol, 80% yield) as a yellowish oil. $[\alpha]_D^{22}$ +27.5º (*c* 1.8, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$, ppm): 1.87 (bs, 1H), 2.87 (dd, 1H, *J* = 5.5, 3.3 Hz), 3.32 (dd, 1H, *J* = 9.0, 7.3 Hz), 3.41 (s, 3H), 3.43 (dd, 1H, *J* = 9.0, 7.1 Hz), 3.55 (dd, 1H, *J* = 7.3, 5.5 Hz), 3.66 (dd, 1H, *J* = 7.1, 3.3 Hz), 3.72 (s, 3H), 3.76 (d, 1H, *J* = 13.0 Hz), 3.78 (d, 1H, *J* = 13.0 Hz), 4.03–4.26 (m, 6H), 6.85–6.90 (m, 2H), 7.20–7.36 (m, 17H). $^{13}$C NMR (62.5 MHz, $CDCl_3$, ppm): 51.6, 51.9, 53.9, 57.5, 63.6, 72.1, 72.3, 73.3, 80.0, 80.9, 85.9, 113.0, 126.3, 126.5, 126.6, 126.9, 127.0, 127.1, 127.2, 130.4, 131.8, 137.4, 137.7, 138.3, 146.6, 173.7. MS (CI, *m*/*z*, %): 583 (42, $[M + H]^+$); 551 (27, $[M – OCH_3]^+$); 91 (100, $[CH_2Ph]^+$). IR (NaCl, $\nu_{máx}$, $cm^{-1}$): 3351 (br, NH), 1751 (st, C=O). Anal. calculated for $C_{36}H_{39}NO_6$: C 74.33; H 6.76; N 2.41; found: C 74.12; H 6.52; N 2.21.

**Methyl (1*R*,2*S*,3*S*,4*S*,5*R*) -2,3,4-tris-(benzyloxy)-5-*tert*-((butoxycarbonyl)amino)cyclo-pentane-1-carboxylate (11c).-** CAN (4.19 g, 7.64 mmol) was added to a solution of compound **11a** (1.11 g, 1.91 mmol) in $CH_3CN/H_2O$ (95.5 mL, 4:1) at 0 ºC. The mixture was allowed to warm up to room temperature and stirred for 6 h. Analysis by t.l.c. (EtOAc/hexane 1:5) revealed the complete transformation of the starting material. The mixture was quenched with saturated aq. $Na_2S_2O_3$ (a few drops) and concentrated *in vacuo*. The crude product was dissolved in dioxane (38.2 mL) and treated with $(Boc)_2O$ (2.08 g, 9.55 mmol) and saturated aq. $NaHCO_3$ until basic pH. The mixture was stirred at room temperature for 18 h and t.l.c. ($CH_2Cl_2$/MeOH 9:1) revealed that the starting material had been consumed. The mixture was diluted with 10% aq. HCl (50 mL) and extracted with EtOAc (100 mL). The organic layer was dried (anhydrous $Na_2SO_4$) and concentrated to dryness under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/hexane 1:4) to give compound **11c** (0.80 g, 1.43 mmol, 75% yield) as a yellowish oil. $[\alpha]_D^{23}$ +37.0º (*c* 1.6, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$, ppm): 1.41 (s, 9H), 3.16 (dd, 1H, *J* = 6.0, 4.1 Hz), 3.28 (dd, 1H, *J* = 7.8, 5.6 Hz), 3.72 (s, 3H), 3.80 (dd, 1H, *J* = 7.8, 7.1 Hz), 3.98 (dd, 1H, *J* = 5.6, 4.1 Hz), 4.18 (dd, 1H, *J* = 7.1, 6.0 Hz), 4.30–4.60 (m, 6H), 5.44 (br, 1H), 7.28–7.38 (m, 15H). $^{13}$C NMR (62.5 MHz, $CDCl_3$, ppm): 29.0, 52.4, 54.2, 54.7, 72.0, 72.4, 72.7, 74.7, 80.0, 83.3, 84.8, 127.1, 127.2, 127.3, 127.4, 128.1, 128.2, 128.3, 137.0, 137.2, 138.7, 155.3, 174.2. MS (CI, *m/z*, %): 563 (12, $[M + H]^+$); 505 (49, $[M - CO_2{}^tBu]^+$); 91 (100, $[CH_2Ph]^+$). IR (NaCl, $\nu_{máx}$, $cm^{-1}$): 3348 (br, NH), 1751 (st, C=O). Anal. calculated for $C_{33}H_{39}NO_7$: C 70.57; H 7.00; N 2.49; found: C 70.37; H 6.92; N 2.62.

**BocHN-(CPCA-11c)-Gly-OMe (12a).-** $Ba(OH)_2.8H_2O$ (1.34 g, 4.26 mmol) was added to a solution of compound **11c** (0.80 g, 1.42 mmol) in a 1:2 THF/$H_2O$ mixture (15 mL). The reulting mixture was stirred at rt for 1 h and then neutralized with 50WX4-50 DOWEX resin, which was then filtered off and washed with MeOH. The solvent was removed under vacuum on a rotary evaporator. A solution of the resulting solid residue, HATU (0.57 g, 1.70 mmol) and DIEA (0.72 mL, 4.26 mmol) in $CH_2Cl_2$ (10 mL) was stirred at rt for 15 min. HCl-Gly-OMe (0.20 g, 1.56 mmol) was then added and the stirring was continued for 14 h. $CH_2Cl_2$ (15 mL) was added, the mixture was washed with 10% aq. HCl, and the organic layer was dried (anhydrous $Na_2SO_4$) and concentrated to dryness under vacuum. Column chromatography of the solid residue (1:1 AcOEt/hexane) led to the isolation of dipeptide **12a** (0.33g, 0.53 mmol, 60% overall yield from compound **11c**) as a colorless oil. $[\alpha]_D^{21}$ +68.2º (*c* 1.5, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$, ppm): 1.37 (s, 9H), 3.18 (dd, 1H, *J* = 5.8, 4.0 Hz), 3.27 (dd, 1H, $J_3$ = 7.8, 5.6 Hz), 3.61 (s, 3H), 3.77–3.96 (m, 2H), 4.03 (s, 2H), 4.13 (dd, 1H, *J* = 7.0, 5.8 Hz), 4.28–4.48 (m, 6H), 5.67 (bs, 1H), 6.91 (bs, 1H), 7.28–7.41 (m, 15H). $^{13}$C NMR (62.5 MHz, $CDCl_3$, ppm): 29.3, 39.7, 52.6, 54.2, 55.0, 72.2, 72.5, 73.6, 74.7, 80.7, 83.4, 85.4, 127.4, 128.3, 128.5, 128.6, 137.4, 137.7, 138.7, 157.3, 169.3, 172.5. MS (CI, *m/z*, %): 620 (56, $[M + H]^+$); 588 (64, $[M - OCH_3]^+$); 91 (100, $[CH_2Ph]^+$). Anal. calculated for $C_{35}H_{42}N_2O_8$: C 67.94; H 6.84; N 4.53; found: C 68.12; H 7.01; N 4.29.

**BocHN-Gly-(CPCA-11c)-Gly-OMe (13).-** TFA (2 mL) in THF (5 mL) was added to a solution of compound **12a** (0.33 g, 0.53 mmol) and the mixture was stirred at rt for 1 h. The solvent was coevaporated with toluene (3x2 mL) under vacuum in a rotary evaporator. HATU (0.21 g, 0.64 mmol) and DIEA (0.27 mL, 1.59 mmol) were

added to a solution of Boc-Gly-OH (0.10 g, 0.58 mmol) in dry $CH_2Cl_2$ (5 mL) and the mixture was stirred at rt for 15 m. A solution of the crude amine from the previous transformation in $CH_2Cl_2$ (10 mL) was added and the resulting mixture was stirred at rt for 10 h. The crude reaction mixture was washed with 10% aq HCl (20 mL) and the organic layer was dried (anhydrous $Na_2SO_4$), filtered and concentrated to dryness under vacuum. Column chromatography of the solid residue (AcOEt) provided pure tripeptide **13** (0.20 g, 0.30 mmol, 55% overall yield from compound **12a**) as a colorless oil. $[\alpha]_D^{18}$ +21.7º (*c* 1.1, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$, ppm): 1.37 (s, 9H), 3.12–3.14 (m, 1H), 3.20 (dd, 1H, *J* = 7.4, 5.1 Hz), 3.66 (s, 3H), 3.79–3.91 (m, 2H), 4.03–4.09 (m, 4H), 4.31–4.43 (m, 6H), 4.55 (bs, 1H), 5.55 (bs, 1H), 6.93 (bs, 1H), 6.96 (bs, 1H), 7.27–7.39 (m, 15H). $^{13}$C NMR (62.5 MHz, $CDCl_3$, ppm): 29.0, 40.0, 42.5, 52.8, 55.3, 56.3, 72.0, 72.2, 72.6, 75.0, 81.1, 84.7, 85.3, 127.9, 128.5, 128.7, 128.9, 138.3, 138.6, 139.0, 156.9, 166.0, 169.8, 172.2. MS (CI, *m/z*, %): 677 (18, $[M + H]^+$); 569 (64, $[M – OBn]^+$); 91 (100, $[CH_2Ph]^+$). Anal. calculated for $C_{37}H_{45}N_3O_9$: C 65.76; H 6.71; N 6.22; found: C 65.59; H 6.49; N 5.98.

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