Polyhydroxylated Cyclopentane β -Amino Acids Derived from D-Mannose and D-Galactose: Synthesis and Protocol for Incorporation into Peptides

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ABSTRACT: A stereoselective synthesis of polyhydroxylated cyclopentane β -amino acids from hexoses is reported. The reaction sequence comprises, as key steps, ring-closing metathesis of a polysubstituted diene intermediate followed by the stereoselective aza-Michael functionalization of the resulting cyclopent-1-ene-1-carboxylic acid ester. Examples of synthesis of polysubstituted 2-aminocyclopentanecarboxylic acid derivatives starting from protected D-mannose and D-galactose are presented. A general protocol for the incorporation of these highly functionalized alicyclic β -amino acids into peptides is also reported.

INTRODUCTION

The enantioselective synthesis of β -amino acids has received great attention in recent times,^{1–5} mainly because peptidomimetics⁶ based on these amino acids may overcome the pharmacological limitations of natural peptides.^{7–10} They are more resistant than α -peptides to protease and peptidase degradation,^{11–13} and their conformational properties and stability facilitate their interaction with receptors and enzymes, which usually results in improved activity and no side effects.¹⁴ More recently, α,β -peptides have evidenced promising applications in material sciences, mainly as nanomaterials.¹⁵

Among the many β -amino acids that have been studied, cyclopentane-based β -amino acids are particularly attractive building blocks because their peptides exhibit specific folding properties. For instance, their homo-oligomers show a high propensity to fold in well-defined secondary structures in short peptide sequences, a structural property that often gives them enhanced biostability and activity.^{16,17} Thus, oligomers that contain at least four units of *trans*-2-aminocyclopentanecarboxylic acids (*trans*-ACPC) adopt a stable 12-helix with topological dimensions similar to those of the α -helix in α -peptides,^{18–20} while their *cis*-homo-oligomers adopt β -sheet secondary structures.²¹ Homo-oligomers with alternating heterochiral *cis*-ACPC sequences form a 10/12 helix, while those with alternating heterochiral *trans*-ACPC tend to attain a polar-strand secondary structure in solution.²² In contrast with their homo-oligomers, we demonstrated that short peptides based on alternating *trans*-ACPC and *trans*-2-aminocyclohexane adopt a 14-helix fold in aqueous SDS solution but not in organic solvents.²³ Moreover, *cis*-ACPC can satisfactorily replace prolines as inducers of β -turns in α -peptides.^{24,25} Controlled self-assembly of helical homo-oligomers of *trans*-

ACPC in the presence of surfactant gives rise to 3D nanostructures of different shapes.^{26,27} Accordingly, cyclopentane β -amino acids proved to be ideal candidates for the stabilization of conformations in peptides.

The development of methodologies for the stereo- and regioselective synthesis of polysubstituted cyclopentane rings continues to be a challenge in synthetic chemistry.^{28–31} A specific goal of this significant area of research is to increase the limited number of known polyhydroxylated cyclopentane β -amino acids^{3,32,33} that would enable access to a larger variety of hydro- or liposoluble cyclopentane-based β -peptides. This latter goal can be achieved by protection or deprotection of the hydroxyl substituents in polyhydroxylated cyclopentane rings. In addition, it is feasible that these substituents on the cyclopentane rings could result in novel folding properties in β -peptides, which is a matter of evident interest in materials chemistry. Furthermore, polyhydroxylated cyclopentane β -amino acids have potential as clinical drugs^{33,34} and biological tools.^{14,35} Also, other molecules containing the polyhydroxylated cyclopentane ring, like some 4-amino-5-(hydroxymethyl)-1,2,3-cyclopentanetriols, have been described as potent glycosidase inhibitors.^{36–38}

The first reported polyhydroxylated cyclopentane β -amino acid was the *trans*-2-aminocyclopentanecarboxylic acid deriv-

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Scheme 1. First Syntheses of Polyhydroxylated Cyclopentane β -Amino Acids Scheme 2. Outline of the Synthesis of Functionalized Cyclopentane β -Amino Acids from Hexoses^a ^aP: protecting group.Scheme 3. Synthesis of Polyhydroxylated Cyclopentane β -Amino acid Derivative 12^a

^aConditions: (i) TBDPSCl, imidazole, CH_2Cl_2 , rt, 15 min, 98%. (ii) Dess–Martin, CH_2Cl_2 , rt, 2 h, 88%. (iii) *n*-BuLi, $\text{Ph}_3\text{PCH}_2\text{Br}$, THF, -78°C to rt, 2 h, 83%. (iv) NaH, MeI, THF, 0°C to rt, 4 h, 95%. (v) TBAF, THF, rt, 2 h, 85%. (vi) Grubbs 1st, CH_2Cl_2 , rt, 24 h, 90%. (vii) a: TEMPO, BAIB, NBu_4I , $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, rt, 2 h. b: NaClO_2 , $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$, 2-methyl-2-butene, $^t\text{BuOH}/\text{H}_2\text{O}$, rt, 1 h. (viii) NaHCO_3 , MeI, DMF, rt, 12 h, 85% (from 10). (ix) NH_2Bn , DMF, rt, 48 h, 91%.

ative 3a, which was obtained in our laboratory by a novel approach involving the key stereocontrolled cyclization of D-glucose nitrosugar derivative 1 to bicyclic lactones like 2 or 5 (i.e., D-glucose, D-idose, D-allose, D-talose, L-glucose, L-idose, L-allose and L-talose).⁴²

Here, we report a more general and efficient method for the stereocontrolled synthesis of polyhydroxylated cyclopentane β -amino acids from hexoses. This approach is, in principle, of general application to all hexoses and, in consequence, should give access to a larger variety of relative configurations of these β -amino acids. Starting from a conveniently protected hexose, the strategy involves the ring-closing metathesis (RCM)⁴³ reaction of a richly functionalized diene intermediate A leading to cyclopentenol B (Scheme 2), which is then transformed into cyclopentene carboxylic acid derivative C, followed by an aza-

meet the stereochemical requirements for the key intramolecular alkylation leading to bicyclic lactones like 2 or 5 (i.e., D-glucose, D-idose, D-allose, D-talose, L-glucose, L-idose, L-allose and L-talose).⁴²

meets the stereochemical requirements for the key intramolecular alkylation leading to bicyclic lactones like 2 or 5 (i.e., D-glucose, D-idose, D-allose, D-talose, L-glucose, L-idose, L-allose and L-talose).⁴²

Scheme 4. Synthesis of Polyhydroxylated Cyclopentane β -Amino Acid Derivative 19a^a

^aConditions: (i) *n*-BuLi, Ph₃PCH₃Br, THF, −78 °C to rt, 12 h, 80%. (ii) Dess–Martin, CH₂Cl₂, rt, 2 h, 82%. (iii) *n*-BuLi, Ph₃PCH₃Br, THF, −78 °C to rt, 12 h, 85%. (iv) TBAF, THF, rt, 1 h, 87%. (v) Grubbs 2nd, toluene, reflux, 24 h, 89%. (vi) a: TEMPO, BAIB, NBU₄I, CH₂Cl₂/H₂O, rt, 2 h. b: NaClO₂, NaH₂PO₄·2H₂O, 2-methyl-2-butene. (vii) NaHCO₃, MeI, DMF, rt, 12 h, 97% (from 17a). (viii) PMBNH₂, DMF, rt, 24 h, 80%.

Scheme 5. Synthesis of Polyhydroxylated Cyclopentane β -Amino Acid Derivative 19b^a

^aConditions: (i) NaH, MeI, THF, 0 °C to rt, 4 h, 93%. (ii) NH₄HCO₂, Pd/C, MeOH, rt, 12 h, 86%. (iii) *n*-BuLi, Ph₃PCH₃Br, THF, −78 °C to rt, 12 h, 80%. (iv) Dess–Martin, CH₂Cl₂, rt, 24 h, 81%. (v) *n*-BuLi, Ph₃PCH₃Br, THF, −78 °C to rt, 2 h, 93%. (vi) TBAF, THF, rt, 1 h, 82%. (vii) Grubbs 1st, CH₂Cl₂, rt, 24 h, 92%. (viii) a: TEMPO, BAIB, NBU₄I, CH₂Cl₂/H₂O, rt, 2 h. b: NaClO₂, NaH₂PO₄·2H₂O, 2-methyl-2-butene. (ix) NaHCO₃, MeI, DMF, rt, 12 h, 82% (from 18c). (x) NH₂Bn, DMF, rt, 24 h, 80%.

Michael amination⁴⁴ of the α,β -unsaturated carboxylic moiety to give the target highly functionalized β -amino acid **D**.

In order to demonstrate the generality of the method, we synthesized protected polyhydroxylated cyclopentane β -amino acids starting from two hexoses (D-mannose and D-galactose) that cannot give access to them using the previous strategy via nitrosugars. Specifically, starting from D-galactose, we synthesized the derived cyclopentane β -amino acid with two alternative protecting group schemes suitable for the incorporation into peptides. In one case, we observed an unwanted elimination reaction when trying to couple these β -amino acids into peptides as already described in a previous work.⁴⁰ Finally, we devised an alternative and more general procedure for the successful incorporation of this type of amino acids into peptides.⁴⁵

RESULTS AND DISCUSSION

Synthesis of Polyhydroxylated Cyclopentane β -Amino Acid Derivative 12. In order to demonstrate the feasibility of this strategy with hexoses other than those suitable for the already described intramolecular nitronate cyclization strategy, we synthesized polyhydroxylated cyclopentane β -amino acid derivative **12** from D-mannose (Scheme 3). Selective protection of the primary hydroxyl group of D-mannose derivative **7a**⁴⁶ with TBDPS and oxidation of its C5 free hydroxyl group with Dess–Martin reagent gave ketone **8**.

When **8** was submitted to Wittig reaction conditions, a double olefination occurs, one at the ketone group and the other one at the anomeric position, which spontaneously deacetylated in the basic medium of the reaction to give the expected diolefin **9a**. Its free hydroxyl group was methylated, and then its silyl ether was deprotected to give diolefin **9c**, which is suitably protected for the RCM reaction.

Cyclopentenol **10** was formed in 90% yield from **9c** under standard RCM reaction conditions using the first-generation Grubbs catalyst. Then, oxidation of the primary hydroxyl group of **10** gave cyclopentenecarboxylic acid **11a**. Reaction of **11a** with NaHCO₃ and MeI furnished its methyl ester derivative **11b** in 85% yield for the last three steps. Finally, treatment of **11b** with benzylamine resulted in the expected stereoselective aza-Michael addition on the conjugated double bond, which provided compound **12** in 91% yield. The total yield for the transformation of **7a** to **12** was 40% (nine steps). This yield is much higher than that of the similar β -amino acid derivative **3b** synthesized from D-glucose by the nitrosugar strategy (8% yield, nine steps).⁴⁰

Synthesis of Polyhydroxylated Cyclopentane β -Amino Acid Derivative 19a. The satisfactory results of our strategy for the transformation of D-mannose into β -amino acid **12** prompted us to apply it to other hexoses, like the transformation of D-galactose into β -amino acid **19a** (Scheme 4). The key reaction to build the cyclopentane ring of **19a** was

the RCM reaction of diolefin **16b**, which was prepared from the known D-galactose derivative **13a**.⁴⁷ Olefination of the hemiacetal of **13a** followed by the oxidation of the hydroxyl group of **14a** gave ketone **15a**, which was subjected to a second olefination step to give diolefin **16a** (Scheme 4). Removal of the silyl ether group at the C1 of **16a** by treatment with TBAF gave the desired key diolefin **16b**. According to our synthetic plan, standard RCM reaction conditions, using the second-generation Grubbs catalyst, gave the expected cyclopentenol **17a** in 89% yield. Oxidation of this compound with TEMPO gave cyclopentenecarboxylic acid **18a** through the spontaneous oxidation of the intermediate aldehyde. Reaction of acid **18a** with NaHCO₃ and MeI furnished its methyl ester derivative **18b** in 97% yield for the three last steps. The stereoselective aza-Michael addition to the double bond of **18a** was performed with *p*-methoxybenzylamine (PMBNH₂), instead of benzylamine (Scheme 3), to enable the selective deprotection of the amino group of **19a** in the presence of the OBn substituents. The total yield of the transformation of **13a** into **19a** was 34% for the eight steps.

Synthesis of Polyhydroxylated Cyclopentane β -Amino Acid Derivative **19b.** Next, we devised a different protection pattern for the same hexose that led to the β -amino acid derivative **19b** (Scheme 5), which has its *cis* hydroxy substituents protected with an isopropylidene substituent. This alternative protecting scheme would open the possibility of selective deprotection of chosen hydroxyl groups. Furthermore, this substitution pattern allows us to compare the efficacy of this synthetic strategy with the one previously reported by us, which had led to the enantiomer (except for the protection of the N atom, Bn or Cbz) of **19b** through a modification of the intramolecular nitronate cyclization strategy.⁴⁸

Accordingly, reaction of D-galactose derivative **13b**⁴⁹ with methyl iodide gave its O-methylated derivative **13c**, which was then converted into the anomeric mixture **13d** and then into the key diene **16d**, via compounds **14b**, **15b**, and **16c** (Scheme 5), following the protocol leading to its analog **16b** (Scheme 4). Next, diene **16d** was subjected to standard RCM reaction conditions to yield the desired cyclopentenol **17b** in 92% yield. In contrast to cyclization of diene **16b**, this reaction was effective using the first-generation Grubbs catalyst, probably because the steric hindrance is now lower. Compound **17b** was next converted into cyclopentene carboxylic acid **18c** and then into its ester **18d**. The stereoselective aza-Michael addition of BnNH₂ led to the cyclopentane β -amino acid derivative **19b**. This synthesis is noticeably more efficient (24% yield from **13b** to **19b**, 10 steps) than the previously described synthesis of the enantiomer (except for the protection of the N atom, Bn or Cbz) of **19b** from its nitrosugar precursor **1** (8% yield, nine steps).⁴⁸

It is worth comparing the yields of the two critical steps (ring-closing metathesis and aza-Michael addition) in the above-described synthetic sequences (Schemes 3 to 5). Although all these yields are reasonably high (80–92%), an attempt to justify the differences can be done. Regarding the RCM reaction, the more reactive second-generation Grubbs catalyst was needed for the transformation **16b** $\rightarrow$ **17a** (Scheme 4), i.e., with the galactose derivative with its hydroxyls protected with benzyl groups. The reason cannot be the configuration of the starting hexose as the mannose **9c** (Scheme 3) and galactose **16d** (Scheme 5) derivatives, which have less bulky protecting groups, reacted equally well with the

less reactive first-generation Grubbs catalyst. It is unclear if the ultimate reason is the steric hindrance of the relatively bulky benzyl groups of **16b** or if it is a consequence of the restrained conformational flexibility of intermediates **9c** and **16d** due to the protection of their *cis*-diols as cyclic acetonides; perhaps this might place the double bonds in a position more favorable for the reaction with the less reactive first-generation Grubbs catalyst.

Regarding the aza-Michael step, the yields are similar for the transformations of the galactose derivatives **18b** $\rightarrow$ **19a** (80%; Scheme 4) and **18d** $\rightarrow$ **19b** (80%; Scheme 5), while the yield of the mannose derivatives **11b** $\rightarrow$ **12** reaches 91% (Scheme 3). The amine approximates the double bond from the side opposite to the C3 –OR substituent in all cases. That face of the double bond is more hindered in the galactose derivatives (Schemes 4 and 5) than in the mannose derivative (Scheme 3), and this could explain the difference in yield.

Synthesis of Tripeptide **21.** Next, to demonstrate the usefulness of the orthogonally protected polyhydroxylated cyclopentane β -amino acids synthesized, we studied the feasibility of their incorporation into short peptide chains by peptide coupling reactions (Schemes 6 and 7). With this

Scheme 6. Incorporation of Polysubstituted Cyclopentane β -Amino Acid **19a** into Peptide **21**^a

^aConditions: (i) CAN, CH₃CN/H₂O, 0 °C to rt, 6 h, (ii) (Boc)₂O, NaHCO₃, rt, 18 h, 75% (from **19a**), (iii) Ba(OH)₂·8 H₂O, THF/H₂O, rt, 1 h. (iv) HCl-HGly-OMe, HATU, DIEA, CH₂Cl₂, rt, 14 h 60% (from **19d**). (v) TFA, THF, rt, 1 h. (vi) Boc-Gly-OH, HATU, DIEA CH₂Cl₂, rt, 10 h, 55% (from **20a**).

purpose, removal of the PMB-protecting group of **19a** with CAN gave the free amine intermediate **19c**, which was directly reacted with (Boc)₂O to furnish the orthogonally protected β -amino acid ester **19d** in 75% yield in the two steps (Scheme 6). Hydrolysis of the methoxycarbonyl group of compound **19d** under mild basic conditions was followed by treatment of the resulting carboxylic acid **19e** with HATU as activating reagent and then with glycine hydrochloride. Dipeptide **20a** was isolated in 60% yield (two steps). The N-Boc group was easily cleaved with TFA, and the resulting amine **20b** was reacted with Boc-Gly-OH upon activation with HATU. This furnished tripeptide **21** in 25% yield from **19a** (six steps).

Synthesis of Pentapeptide **24.** Incorporation of **19b** into peptides is more problematic, as hydrolysis of its methyl ester in basic conditions is usually accompanied by the beta elimination of the –OR substituent contiguous to the carboxymethyl alpha position as we previously reported for two analogs of the enantiomer of **19b**.⁴⁰ The solution we devised here involves protecting the carboxylic acid group as trimethylsilyl ester (**18e**; Scheme 7) instead of the methyl ester **18d** shown in Scheme 5. This choice of protecting group is made on intermediate **18c** prior to the aza-Michael addition. So, starting from carboxylic acid **18c**, esterification with trimethylsilyl ethanol provided the expected cyclopentenecarboxylic acid ester **18e**,⁵⁰ which furnished β -amino acid

Scheme 7. Protocol for the Incorporation of Polysubstituted Cyclopentane β -Amino Acid **19b** into Peptide **24**^a

^aConditions: (i) $\text{HO}(\text{CH}_2)_2\text{SiMe}_3$, DMAP, DCC, CH_2Cl_2 , rt, 12 h, 77%. (ii) BnNH_2 , DMF, rt, 60 h, 69%. (iii) TBAF, THF, rt, 24 h. (iv) **22a**, PyBOP, HOBT, DIEA, DMF, 43% (two steps). (v) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$ 20%, MeOH, overnight. (vi) **22b**, PyBOP, HOBT, DIEA, DMF, 59% (two steps).

derivative **19f** when subjected to the aza-Michael addition using benzylamine as the nucleophile. Hydrolysis of this ester **19f** under mild basic conditions with TBAF resulted in carboxylic acid **19g**, which was efficiently transformed into tripeptide **23a** by direct coupling with dipeptide **22a**.⁵¹ Removal of the *N*-benzyl-protecting group of **23a**, by catalytic hydrogenation, provided its free amino derivative **23b**, which gave pentapeptide **24** when reacted with dipeptide **22b** under the stated coupling conditions. The overall yield from **18c** was 14% (six steps).

In conclusion, we present here a promising approach to the stereocontrolled synthesis of highly complex cyclopentane β -amino acids. This method is more general and efficient than the previously reported alternative from nitrosugars as it could be extended, in principle, to the pool of hexoses. To demonstrate the generality of the method, we applied it to two different hexoses (D-mannose and D-galactose) and with two alternative protecting patterns in the case of D-galactose. This allowed us to synthesize, in the gram scale, three new β -amino acids (**12**, **19a**, and **19b**), which are orthogonally protected for their incorporation into peptides. This method opens up opportunities for a new access to 4-amino-5-(hydroxymethyl)-1,2,3-cyclopentanetriols (potent glycosidase inhibitors) by reduction of the methoxycarbonyl group to hydroxymethyl. Furthermore, we have demonstrated how to incorporate these β -amino acids into peptide chains using classical procedures. In the case of those amino acids that present problems by classical methods, we have also developed an alternative procedure for their incorporation into peptides. The availability of more richly functionalized cyclopentane β -amino acids, like the ones shown here, would expand the opportunities of designing a larger variety of hydro- or liposoluble β -peptides. We continue working in the synthesis of monomers and peptides containing hydroxylated groups as well as studying their potential applications in biological chemistry, new materials, and catalysis. As preliminary studies, our immediate plans are directed toward the synthesis of amphiphilic β -peptides of this nature as potential ice

recrystallization inhibitors and gelling agents, which are two issues of great present interest.

EXPERIMENTAL SECTION

General Information. All nonaqueous 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 (tlc) was carried out on aluminium-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. ¹H and ¹³C NMR spectra were recorded on Bruker DPX 250 (250 MHz for ¹H and 62.5 MHz for ¹³C) and Varian Mercury 300 (300 MHz for ¹H and 75 MHz for ¹³C) 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. Mass spectra were recorded on a Micromass VG-Autospec spectrometer [by chemical ionization (NH_3 , CI) or electrospray techniques, 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 unless stated. Optical rotations were measured on a Jasco DIP-370 polarimeter with a path length of 0.5 dm and in a Na (589 nm) lamp. Concentrations are given in g/100 mL. Elemental analyses were carried out on a Carlo Erba EA 1108 analyzer.

Synthesis of Polyhydroxylated Cyclopentane β -Amino Acid Derivative **12.** (3*aS*,4*R*,6*R*,6*aS*)-6-((*R*)-2-((*tert*-Butyldiphenylsilyl)oxy)-1-hydroxyethyl)-2,2-

dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl Acetate (7b). A solution of imidazole (7.04 g, 103.33 mmol), TBDPSCl (12.7 mL, 49.6 mmol), and compound 7a (10.84 g, 41.33 mmol) in CH₂Cl₂ (83 mL) was stirred at rt. for 15 min and then washed with water (100 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated to dryness under reduced pressure. Solid residue was purified by flash column chromatography (EtOAc/hexane 1:3) and provided 7b (20.28 g, 40.51 mmol, 98% yield) as a white solid. Mp 88–89 °C (CH₂Cl₂/hexane). $[\alpha]_D^{22} = +19.1$ (c 1.9, CHCl₃). ¹H NMR (250 MHz, CDCl₃, ppm): δ 1.06 (s, 9H), 1.35 (s, 3H), 1.46 (s, 3H), 2.02 (s, 3H), 2.78 (br, 1H), 3.85–3.89 (m, 2H), 4.00–4.10 (m, 1H), 4.19 (dd, 1H, $J_{4,5} = 8.2$, $J_{4,3} = 3.3$ Hz), 4.70 (d, 1H, $J_{2,3} = 5.8$ Hz), 4.94 (dd, 1H, $J_{3,2} = 5.8$ Hz, $J_{3,4} = 3.3$ Hz), 6.17 (s, 1H), 7.35–7.47 (m, 6H), 7.63–7.70 (m, 4H). ¹³C{¹H} NMR (62.5 MHz, CDCl₃, ppm): δ 18.8, 20.4, 24.4, 25.6, 26.3, 64.7, 68.8, 79.3, 80.2, 84.3, 100.1, 112.4, 127.3, 129.3, 132.4, 132.6, 135.0, 168.8. IR (NaCl, cm⁻¹): ν 3593 (br, OH), 1746 (st, C=O), 1111 (st, Si-O-C). MS (CI, m/z , %): 501 (8, [M + H]⁺), 484 (60), 444 (100). Anal. calc. for C₂₇H₃₆O₇Si: C, 64.77; H, 7.25. Found: C, 64.67; H, 7.33.

(3aS,4R,6S,6aR)-6-(2-((tert-Butyldiphenylsilyloxy)acetyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl Acetate (8). A solution of compound 7b (11.27 g, 22.51 mmol) in CH₂Cl₂ (106 mL) was stirred with Dess–Martin periodinane (12.41 g, 29.26 mmol) for 2 h at room temperature. The mixture was quenched with saturated aq. Na₂S₂O₃ (50 mL) and extracted with Et₂O (50 mL). The organic layer was dried (anhydrous Na₂SO₄) and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/hexane 1:4) and provided compound 8 (9.88 g, 19.81 mmol, 88%) as a white solid. Mp 55–56 °C (CH₂Cl₂/hexane). $[\alpha]_D^{21} = -3.5$ (c 1.6, CHCl₃). ¹H NMR (250 MHz, CDCl₃, ppm): δ 1.10 (s, 9H), 1.25 (s, 3H), 1.27 (s, 3H), 2.06 (s, 3H), 4.47 (s, 2H), 4.68 (d, 1H, $J_{2,3} = 5.8$ Hz), 4.85 (d, 1H, $J_{4,3} = 4.1$ Hz), 5.20 (dd, 1H, $J_{3,2} = 5.8$ Hz, $J_{3,4} = 4.1$ Hz), 6.22 (s, 1H), 7.34–7.44 (m, 6H), 7.65–7.70 (m, 4H). ¹³C{¹H} NMR (62.5 MHz, CDCl₃, ppm): δ 18.9, 20.5, 24.2, 25.3, 26.4, 68.6, 80.0, 83.8, 85.5, 100.0, 113.1, 127.4, 127.5, 129.5, 129.6, 132.1, 132.2, 135.1, 135.2, 168, 202.0. IR (NaCl, cm⁻¹): ν 1745 (st, C=O), 1113 (st, Si-O-C). MS (CI, m/z , %): 499 (15, [M + H]⁺), 484 (27), 440 (100). Anal. calc. for C₂₇H₃₄O₇Si: C, 65.04; H, 6.87. Found: C, 65.21; H, 7.08.

(R)-2-(((tert-Butyldiphenylsilyloxy)methyl)-1-((4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (9a). A suspension of Ph₃PCH₃Br (1.48 g, 4.15 mmol) in dry THF (5 mL) was cooled to –78 °C under argon, *n*-BuLi (1.5 mL, 3.82 mmol, 2.5 M solution in hexane) was added dropwise, and the mixture was stirred at –78 °C for 30 min and at 0 °C for 30 min. A solution of 8 (0.76 g, 1.66 mmol) in THF (5 mL) was added dropwise to the resulting ylide at –78 °C, and the new reaction mixture was allowed to warm up to room temperature and then heated under reflux for 12 h. The mixture was quenched with saturated aq. NH₄Cl (10 mL) and extracted with Et₂O (20 mL). The organic layer was dried (anhydrous Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/hexane 1:12) to afford compound 9a (0.64 g, 1.42 mmol, 85%) as a yellowish oil. $[\alpha]_D^{20} = -16.1$ (c 1.5, CHCl₃). ¹H NMR (250 MHz, CDCl₃, ppm): δ 1.05 (s, 9H), 1.37 (s, 3H), 1.52 (s, 3H), 2.52 (d, 1H, $J_{OH,3} = 6.6$ Hz), 4.17 (dd, 1H, $J_{3,OH} = 6.6$ Hz, $J_{3,4} = 4.4$ Hz), 4.27 (br, 2H), 4.31 (dd, 1H, $J_{4,5} = 6.9$ Hz, $J_{4,3} = 4.4$ Hz), 4.57 (dd, 1H, $J_{5,6} = 7.7$

Hz, $J_{5,4} = 6.9$ Hz), 5.21 (dd, 1H, $J_{7a,6} = 10.1$ Hz, $J_{7a,7b} = 1.4$ Hz), 5.24 (d, 1H, $J_{1a,1b} = 1.7$ Hz), 5.28 (dd, 1H, $J_{7b,6} = 17.3$ Hz, $J_{7b,7a} = 1.4$ Hz), 5.31 (d, 1H, $J_{1b,1a} = 1.7$ Hz), 6.00 (ddd, 1H, $J_{6,7b} = 17.3$ Hz, $J_{6,7a} = 10.1$ Hz, $J_{6,5} = 7.7$ Hz), 7.36–7.44 (m, 6H), 7.65–7.70 (m, 4H). ¹³C{¹H} NMR (62.5 MHz, CDCl₃, ppm): δ 19.0, 24.7, 26.6, 27.0, 64.7, 70.4, 78.7, 78.9, 108.4, 112.7, 118.9, 127.5, 129.6, 133.0, 133.9, 135.3, 146.5. IR (NaCl, cm⁻¹): ν 3514 (br, OH), 1112 (st, Si-O-C). MS (CI, m/z , %): 453 (5, [M + H]⁺), 379 (20), 198 (100). Anal. calc. for C₂₇H₃₆O₄Si: C, 71.64; H, 8.02. Found: C, 71.29; H, 8.14.

tert-Butyl((2-((R)-((4R,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)(methoxy)methyl)allyloxy)-diphenylsilane (9b). Sodium hydride (0.36 g, 9.05 mmol, 60%) was added in small portions over a 0 °C cooled solution of 9a (2.73 g, 6.03 mmol) in 24 mL of dry THF. Once the hydrogen bubbles ceased, methyl iodide (0.71 mL, 11.46 mmol) was added, and the reaction was stirred at room temperature for 4 h. Water (20 mL) was then added, and the mixture was extracted with EtOAc (20 mL). The organic layer was dried (anhydrous Na₂SO₄), filtered, and evaporated in vacuo to give compound 9b (2.67 g, 5.73 mmol, 95%) as a pure colorless oil. $[\alpha]_D^{20} = -18.6$ (c 1.1, CHCl₃). ¹H NMR (250 MHz, CDCl₃, ppm): δ 1.00 (s, 9H), 1.31 (s, 3H), 1.47 (s, 3H), 3.30 (s, 3H), 3.83 (d, 1H, $J_{3,4} = 4.3$ Hz), 4.28–4.30 (m, 2H), 4.35 (dd, 1H, $J_{4,5} = 6.0$ Hz, $J_{4,3} = 4.3$ Hz), 4.63 (dd, 1H, $J_{5,6} = 7.7$ Hz, $J_{5,4} = 6.0$ Hz), 5.18 (dd, 1H, $J_{7a,6} = 10.5$ Hz, $J_{7a,7b} = 1.6$ Hz), 5.22 (d, 1H, $J_{1a,1b} = 1.4$ Hz), 5.26 (dd, 1H, $J_{7b,6} = 17.1$ Hz, $J_{7b,7a} = 1.6$ Hz), 5.32 (d, 1H, $J_{1b,1a} = 1.4$ Hz), 5.97 (ddd, 1H, $J_{6,7b} = 17.1$ Hz, $J_{6,7a} = 10.5$ Hz, $J_{6,5} = 7.2$ Hz), 7.37–7.46 (m, 6H), 7.59–7.63 (m, 4H). ¹³C{¹H} NMR (62.5 MHz, CDCl₃, ppm): δ 19.2, 25.0, 26.5, 27.4, 54.7, 65.1, 70.0, 79.0, 80.4, 108.1, 112.4, 119.7, 127.9, 129.3, 132.5, 133.3, 134.7, 146.7. IR (NaCl, cm⁻¹): ν 1115 (st, Si-O-C). MS (CI, m/z , %): 467 (25, [M + H]⁺), 436 (88), 410 (100). Anal. calc. for C₂₈H₃₈O₄Si: C, 72.06; H, 8.21. Found: C, 71.96; H, 8.15.

2-((R)-((4R,5R)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-(methoxy)-methyl)prop-2-en-1-ol (9c). Compound 9b (1.66 g, 3.56 mmol) was dissolved in THF (10.7 mL) and stirred with TBAF (4.3 mL, 4.3 mmol, 1 M solution in THF) at room temperature for 2 h. The reaction mixture was treated with saturated aq. NH₄Cl (25 mL) and extracted with Et₂O (25 mL). The organic layer was dried (anhydrous Na₂SO₄) and concentrated to dryness. The crude product was subjected to flash column chromatography (EtOAc/hexane 1:4) to afford compound 9c (0.69 g, 3.02 mmol, 85%) as a yellowish oil. $[\alpha]_D^{19} = -27.3$ (c 1.4, CHCl₃). ¹H NMR (250 MHz, CDCl₃, ppm): δ 1.40 (s, 3H), 1.56 (s, 3H), 2.85 (br, 1H), 3.24 (s, 3H), 3.64 (d, 1H, $J_{3,4} = 4.1$ Hz), 4.08 (d, 1H, $J_{1a,1b} = 13.0$ Hz), 4.20 (d, 1H, $J_{1b,1a} = 13.0$ Hz), 4.27 (dd, 1H, $J_{4,5} = 6.8$ Hz, $J_{4,3} = 4.1$ Hz), 4.60 (dd, 1H, $J_{5,6} = 8.2$ Hz, $J_{5,4} = 6.8$ Hz), 5.13 (d, 1H, $J_{2a,2b} = 1.4$ Hz), 5.29 (dd, 1H, $J_{7b,6} = 17.3$ Hz, $J_{7b,7a} = 1.7$ Hz), 5.34 (dd, 1H, $J_{7a,6} = 10.2$ Hz, $J_{7a,7b} = 1.7$ Hz), 5.36 (d, 1H, $J_{2b,2a} = 1.4$ Hz), 5.96 (ddd, 1H, $J_{6,7b} = 17.3$ Hz, $J_{6,7a} = 10.2$ Hz, $J_{6,5} = 8.2$ Hz). ¹³C{¹H} NMR (62.5 MHz, CDCl₃, ppm): δ 24.6, 26.3, 54.8, 60.8, 78.2, 78.7, 81.1, 107.9, 115.1, 117.9, 133.5, 143.9. IR (NaCl, cm⁻¹): ν 3462 (br, OH). MS (CI, m/z , %): 229 (13, [M + H]⁺), 171 (12), 166 (100). Anal. calc. for C₁₂H₂₀O₄: C, 63.14; H, 8.83. Found: C, 62.85; H, 8.67.

((3aR,4R,6aR)-4-Methoxy-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxol-5-yl)methanol (10). Grubbs first-generation catalyst (0.12 g, 0.15 mmol) was added to a deoxygenated solution of compound 9c (0.69 g, 3.02 mmol) in Cl₂CH₂ (91 mL), and the mixture was refluxed under argon for

24 h. Then, the mixture was concentrated to dryness under reduced pressure, and the crude product was purified by flash column chromatography (EtOAc/hexane 1:1) to provide compound **10** (0.55 g, 2.72 mmol, 90%) as a yellow oil. $[\alpha]_D^{18} = +31.7$ (c 1.5, CHCl₃). ¹H NMR (250 MHz, CDCl₃, ppm): δ 1.38 (s, 3H), 1.43 (s, 3H), 2.15 (br, 1H), 3.50 (s, 3H), 4.36 (d, 1H, $J_{1'a,1'b} = 13.7$ Hz), 4.38 (d, 1H, $J_{1'b,1'a} = 13.7$ Hz), 4.39 (s, 1H), 4.61 (d, 1H, $J_{4,3} = 5.8$ Hz), 5.20 (d, 1H, $J_{3,4} = 5.8$ Hz), 5.91 (s, 1H). ¹³C{¹H} NMR (62.5 MHz, CDCl₃, ppm): δ 24.8, 26.5, 56.5, 58.7, 82.4, 82.6, 89.0, 110.9, 127.3, 146.4. IR (NaCl, cm⁻¹): ν 3448 (br, OH). MS (CI, m/z , %): 201 (12, [M + H]⁺), 158 (15), 127 (100). Anal. calc. for C₁₀H₁₆O₄: C, 59.98; H, 8.05. Found: C, 59.73; H, 8.21.

Methyl (3aR,4R,6aR)-4-methoxy-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxole-5-carboxylate (11b). To a solution of compound **10** (0.55 g, 2.72 mmol) in CH₂Cl₂/H₂O (19 mL, 3:1), NBu₄I (0.05 g, 0.14 mmol), TEMPO (0.09 g, 0.54 mmol), and DAIB (2.19 g, 6.81 mmol) were added. The mixture was stirred at room temperature for 2 h, quenched with saturated aq. Na₂S₂O₃ (35 mL), and extracted with EtOAc (30 mL). The organic layer was dried (anhydrous Na₂SO₄) and concentrated in vacuo. The crude product was dissolved in ^tBuOH (13.6 mL) and 2-methyl-2-butene (2.02 mL, 19.05 mmol), and a solution containing NaClO₂ (0.40 g, 3.54 mmol, 80%) and NaH₂PO₄·H₂O (0.55 g, 3.54 mmol) in water (13.6 mL) was added. The mixture was stirred at room temperature for 1 h, quenched with 10% aq. HCl (20 mL), and extracted with EtOAc (20 mL). The organic layer was dried (anhydrous Na₂SO₄) and concentrated in vacuo. To a solution of the resulting carboxylic acid in dry DMF (13.6 mL), NaHCO₃ (0.43 g, 5.17 mmol) and MeI (0.42 mL, 6.81 mmol) were added. The mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with NH₄Cl (20 mL) and extracted with EtOAc (20 mL). The organic layer was dried (anhydrous Na₂SO₄) and concentrated in vacuo. Flash column chromatography of the crude (EtOAc/hexane 1:4) furnished compound **11b** (0.53 g, 2.31 mmol, 85% yield from **10**) as a colorless oil. $[\alpha]_D^{18} = -16.1$ (c 1.5, CHCl₃). ¹H NMR (250 MHz, CDCl₃, ppm): δ 1.36 (s, 3H), 1.38 (s, 3H), 3.51 (s, 3H), 3.80 (s, 3H), 4.54 (d, 1H, $J_{5,4} = 1.6$ Hz), 4.61 (d, 1H, $J_{3,4} = 5.2$ Hz), 5.43 (dd, 1H, $J_{4,3} = 5.2$ Hz, $J_4 = 1.6$ Hz), 6.80 (s, 1H). ¹³C{¹H} NMR (62.5 MHz, CDCl₃, ppm): δ 25.1, 26.7, 51.2, 57.4, 81.9, 82.8, 86.9, 111.2, 136.4, 144.0, 163.0. IR (NaCl, cm⁻¹): ν 1726 (st, C=O). MS (CI, m/z , %): 229 (7, [M + H]⁺), 197 (8), 186 (100). Anal. calc. for C₁₁H₁₆O₅: C, 57.89; H, 7.07. Found: C, 57.73; H, 7.01.

Methyl (3aR,4S,5S,6R,6aS)-4-(benzylamino)-6-methoxy-2,2-dimethyltetrahydro-4H-cyclopenta[d][1,3]dioxole-5-carboxylate (12). Benzylamine (0.72 mL, 6.60 mmol) was added over a solution of compound **11b** (1.26 g, 5.50 mmol) in dry DMF (16.5 mL), and the resulting solution was stirred at room temperature for 48 h. The reaction mixture was then poured into a saturated aqueous solution of NH₄Cl (20 mL) and extracted with EtOAc (20 mL). The organic layer was dried (anhydrous Na₂SO₄), filtered, and evaporated in vacuo. The resulting residue was submitted to flash column chromatography (EtOAc/hexane 1:3), to give compound **12** (1.67 g, 4.98 mmol, 91% yield) as a pale yellow oil. $[\alpha]_D^{17} = -56.8$ (c 1.8, CHCl₃). ¹H NMR (250 MHz, CDCl₃, ppm): δ 1.31 (s, 3H), 1.47 (s, 3H), 1.92 (br, 1H), 2.86 (dd, 1H, $J_{1,2} = 8.8$ Hz, $J_{1,5} = 7.9$ Hz), 3.41 (s, 3H), 3.43 (dd, 1H, $J_{2,1} = 8.8$ Hz, $J_{2,3} = 2.7$ Hz), 3.72 (s, 3H), 3.77 (d, 1H, $J_{H,H'} = 13.0$ Hz), 3.91 (d, 1H, $J_{H,H'} = 13.0$ Hz), 4.06 (dd, 1H, $J_{5,1} = 7.9$ Hz, $J_{5,4} = 2.5$ Hz),

4.47–4.55 (m, 2H), 7.24–7.35 (m, 5H). ¹³C{¹H} NMR (62.5 MHz, CDCl₃, ppm): δ 24.5, 26.3, 51.2, 51.6, 54.3, 57.1, 64.3, 83.2, 84.4, 86.1, 112.4, 126.5, 127.7, 127.9, 139.5, 171.8. IR (NaCl, cm⁻¹): ν 3325 (br, NH), 1737 (st, C=O). MS (CI, m/z , %): 336 (100, [M + H]⁺), 304 (22), 262 (27). Anal. calc. for C₁₈H₂₅NO₅: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.17; H, 7.53; N, 4.04.

Synthesis of Polyhydroxylated Cyclopentane β-Amino Acid Derivative 19a. (2R,3S,4R,5S)-3,4,5-Tris(benzyloxy)-1-(tert-butyltrimethylsilyloxy)hept-6-ene-2-ol (14a). A suspension of Ph₃PCH₃Br (7.99 g, 22.36 mmol) in dry THF (37.3 mL) was cooled to −78 °C 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 °C for 30 min and at 0 °C for 30 min. A solution of **13a** (4.21 g, 7.45 mmol) in THF (37.3 mL) was added dropwise to the resulting ylide at −78 °C, and the new reaction mixture was allowed to warm up to room temperature and then heated under reflux for 12 h. The mixture was quenched with saturated aq. NH₄Cl (50 mL) and extracted with Et₂O (100 mL). The organic layer was dried (anhydrous Na₂SO₄) and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/hexane 1:9) to afford compound **14a** (3.36 g, 5.96 mmol, 80% yield) as a yellowish oil. $[\alpha]_D^{20} = -2.1$ (c 1.7, CHCl₃). ¹H NMR (250 MHz, CDCl₃, ppm): δ 0.02 (s, 6H), 0.88 (s, 9H); 3.06 (d, 1H, $J = 4.9$ Hz), 3.56–3.62 (m, 2H), 3.79–3.97 (m, 3H), 4.08 (dd, 1H, $J = 7.9$ Hz, $J = 4.9$ Hz), 4.35 (d, 1H, $J = 11.8$ Hz); 4.43 (d, 1H, $J = 11.5$ Hz); 4.50 (d, 1H, $J = 11.5$ Hz); 4.65 (d, 1H, $J = 11.8$ Hz), 4.76 (br, 2H), 5.30 (dd, 1H, $J = 17.5$, 1.6 Hz), 5.35 (dd, 1H, $J = 10.5$, 1.6 Hz), 5.84 (ddd, 1H, $J = 17.6$, 10.4, 7.9 Hz), 7.22–7.38 (m, 15H). ¹³C{¹H} NMR (62.5 MHz, CDCl₃, ppm): δ −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 , %): 563 (18, [M + H]⁺); 456 (23); 91 (100). IR (NaCl, cm⁻¹): ν 3492 (br, OH), 1104 (st, Si-O-C). Anal. Calc. for C₃₄H₄₆O₅Si: C 72.56; H 8.24. Found: C 72.49; H 8.49.

(3R,4R,5S)-3,4,5-Tris(benzyloxy)-1-((tert-butyltrimethylsilyloxy)hept-6-en-2-one (15a). After compound **14a** (1.86 g, 3.31 mmol) was subjected to the procedure for the preparation of **8**, flash column chromatography of the crude reaction product (EtOAc/hexane 1:15) provided compound **15a** (1.52 g, 2.72 mmol, 82% yield) as a yellowish oil. $[\alpha]_D^{21} = +20.7$ (c 1.9, CHCl₃). ¹H NMR (250 MHz, CDCl₃, ppm): δ −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, $J = 11.8$ sHz), 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). ¹³C{¹H} NMR (62.5 MHz, CDCl₃, ppm): δ −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 , %): 561 (85, [M + H]⁺); 454 (100), 91 (90). IR (NaCl, cm⁻¹): ν 1735 (st, C=O), 1091 (st, Si-O-C). Anal. Calc. for C₃₄H₄₄O₅Si: C 72.82; H 7.91. Found: C 72.66; H 8.03.

(3S,4R,5S)-3,4,5-Tris(benzyloxy)-1-(tert-butyltrimethylsilyloxy)-2-methylenhept-6-ene (16a). A suspension of Ph₃PCH₃Br (4.01 g, 11.23 mmol) in dry THF (11.2 mL) was cooled to −78 °C 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°C for 30 min and at 0°C for 30 min. A solution of compound **15a** (2.10 g, 3.75 mmol) in THF (11.2 mL) was added dropwise to the ylide at -78°C . 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 (25 mL) and extracted with Et_2O (50 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography of the crude product ($\text{EtOAc}/\text{hexane}$ 1:19) afforded compound **16a** (1.78 g, 3.18 mmol, 85% yield) as a yellowish oil. $[\alpha]_{\text{D}}^{20} = +19.3$ (c 1.4, CHCl_3). ^1H NMR (250 MHz, CDCl_3 , ppm): δ 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 (d, 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (62.5 MHz, CDCl_3 , ppm): δ 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, $[\text{M} + \text{H}]^+$); 468 (66); 91 (100). IR (NaCl, cm^{-1}): ν 1099 (st, Si–O–C). Anal. calc. for $\text{C}_{35}\text{H}_{46}\text{O}_4\text{Si}$: C 75.23; H 8.30. Found: C 75.37; H 8.20.

(3S,4R,5S)-3,4,5-Tris(benzyloxy)-2-methylenhept-6-ene-1-ol (16b). Compound **16a** (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 ($\text{EtOAc}/\text{hexane}$ 1:4) to afford compound **16b** (1.23 g, 2.77 mmol, 87% yield) as a yellowish oil. $[\alpha]_{\text{D}}^{19} = +26.8$ (c 1.3, CHCl_3). ^1H NMR (250 MHz, CDCl_3 , ppm): δ 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 (d, 1H, $J = 1.9$ Hz), 5.35 (dd, 1H, $J = 10.4$, 1.9 Hz), 5.38 (d, 1H, $J = 1.9$ Hz), 5.84 (ddd, 1H, $J = 17.3$, 10.4, 7.9 Hz), 7.20–7.34 (m, 15H). $^{13}\text{C}\{^1\text{H}\}$ NMR (62.5 MHz, CDCl_3 , ppm): δ 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 , %): 445 (54, $[\text{M} + \text{H}]^+$); 231 (64); 91 (100). IR (NaCl, cm^{-1}): ν 3450 (br, OH). Anal. calc. for $\text{C}_{29}\text{H}_{32}\text{O}_4$: C 78.35; H 7.26. Found: C 78.53; H 7.50.

(3S,4R,5S)-1-Hydroxymethyl-3,4,5-tris(benzyloxy)-cyclopent-1-ene (17a). Grubbs second-generation catalyst (0.12 g, 0.14 mmol) was added to a deoxygenated solution of compound **16b** (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 a vacuum. The crude product was purified by flash column chromatography ($\text{EtOAc}/\text{hexane}$ 1:2) to provide compound **17a** (1.03 g, 2.46 mmol, 89% yield) as a yellow oil. $[\alpha]_{\text{D}}^{19} = +19.5$ (c 1.7, CHCl_3). ^1H NMR (250 MHz, CDCl_3 , ppm): δ 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (62.5 MHz, CDCl_3 , ppm): δ 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 , %): 417 (4, $[\text{M} + \text{H}]^+$); 400 (63); 91 (100). IR (NaCl, cm^{-1}): ν 3301 (br, NH), 1757 (st, C=O). Anal. calc. for $\text{C}_{27}\text{H}_{28}\text{O}_4$: C 77.86; H 6.78. Found: C 77.70; H 6.92.

Methyl (3S,4R,5S)-3,4,5-tris(benzyloxy)cyclopent-1-ene-1-carboxylate (18b). Compound **17a** (1.03 g, 2.46 mmol) was subjected to the procedure for the preparation of compound **11b**. Compound **18b** (1.06 g, 2.39 mmol, 97% yield from **17a**, two steps) was obtained as a colorless oil after flash column chromatography ($\text{EtOAc}/\text{hexane}$ 1:6). $[\alpha]_{\text{D}}^{20} = +17.3$ (c 1.2, CHCl_3). ^1H NMR (250 MHz, CDCl_3 , ppm): δ 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (62.5 MHz, CDCl_3 , ppm): δ 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 , %): 445 (17, $[\text{M} + \text{H}]^+$); 430 (76); 91 (100). IR (NaCl, cm^{-1}): ν 1733 (st, C=O). Anal. calc. for $\text{C}_{28}\text{H}_{28}\text{O}_5$: C 75.66; H 6.35. Found: C 75.45; H 6.32.

Methyl (1R,2S,3S,4S,5R)-2,3,4-tris(benzyloxy)-5-((4-methoxybenzyl)amino)cyclopentane-1-carboxylate (19a). Compound **18b** (1.06 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 ($\text{EtOAc}/\text{hexane}$ 1:4) to afford compound **19a** (1.11 g, 1.91 mmol, 80% yield) as a yellowish oil. $[\alpha]_{\text{D}}^{22} = +27.5$ (c 1.8, CHCl_3). ^1H NMR (250 MHz, CDCl_3 , ppm): δ 1.87 (br, 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (62.5 MHz, CDCl_3 , ppm): δ 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 , %): 582 (42, $[\text{M} + \text{H}]^+$); 551 (27); 91 (100). IR (NaCl, cm^{-1}): ν 3351 (br, NH), 1751 (st, C=O). Anal. calc. for $\text{C}_{36}\text{H}_{39}\text{NO}_6$: C 74.33; H 6.76; N 2.41; found: C 74.12; H 6.52; N 2.21.

Synthesis of Polyhydroxylated Cyclopentane β -Amino Acid Derivative 19b. (((3aS,4R,6R,7R,7aS)-6-(Benzyloxy)-7-methoxy-2,2-dimethyltetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-4-yl)methoxy)(tert-butyl)dimethylsilane (**13c**). After compound **13b** (2.10 g, 4.93 mmol) was subjected to the procedure for the preparation of **9b**, compound **13c** (2.01 g, 4.59 mmol, 93%) was obtained as a pure colorless oil. $[\alpha]_{\text{D}}^{20} = -14.5$ (c 1.7, CHCl_3). ^1H NMR (250 MHz, CDCl_3 , ppm): δ 0.10 (s, 6H), 0.91 (s, 9H), 1.34 (s, 3H), 1.54 (s, 3H), 3.24 (dd, 1H, $J = 8.0$, 7.1 Hz), 3.60 (s, 3H), 3.74 (ddd, 1H, $J = 7.1$, 5.5, 1.9 Hz), 3.87 (dd, 1H, $J = 10.1$, 5.5 Hz), 3.93 (dd, 1H, $J = 10.1$, 7.1 Hz), 4.03 (dd, 1H, $J = 7.1$, 5.4 Hz), 4.17 (dd, 1H, $J = 5.4$, 1.9 Hz), 4.28 (d, 1H, $J = 8.0$ Hz), 4.65 (d, 1H, $J = 11.8$ Hz), 4.92 (d, 1H, $J = 11.8$ Hz), 7.29–7.39 (m, 5H). $^{13}\text{C}\{^1\text{H}\}$ NMR (62.5 MHz, CDCl_3 , ppm): δ 5.7, 5.5, 18.0, 25.6,

26.0, 27.9, 60.0, 61.9, 70.0, 73.0, 73.2, 78.8, 82.3, 101.0, 109.4, 127.5, 127.7, 128.1, 137.0. MS (CI, m/z , %): 439 (11, $[M + H]^+$); 332 (24); 91 (100). IR (NaCl, cm^{-1}): ν 1101 (st, Si-O-C). Anal. calc. for $\text{C}_{23}\text{H}_{38}\text{O}_6\text{Si}$: C, 62.98; H, 8.73. Found: C, 62.77; H, 8.55.

(3a*S*,4*R*,6*R*,7*R*,7*aS*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-7-methoxy-2,2-dimethyltetrahydro-4*H*-[1,3]-dioxolo[4,5-*c*]pyran-6-ol and (3a*S*,4*R*,6*S*,7*R*,7*aS*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-methoxy-2,2-dimethyltetrahydro-4*H*-[1,3]-dioxolo[4,5-*c*]pyran-6-ol (**13d**). Pd/C (0.64 g, 10%) and NH_4HCO_2 (4.58 g, 72.54 mmol) were added sequentially over a deoxygenated solution of **13c** (3.18 g, 7.25 mmol) in MeOH (51 mL), and the resulting suspension was refluxed for 12 h. The reaction was then filtered through Celite and washed with MeOH, and the solution was concentrated to dryness under a vacuum. The residue was dissolved in EtOAc (50 mL) and washed with water (50 mL); the organic layer was dried (anhydrous Na_2SO_4) and filtered, and the solvent was removed under a vacuum. The obtained residue was submitted to flash column chromatography (EtOAc/hexane 1:2) to give compounds **13d** (2.17 g, 6.24 mmol, 86%) as a yellow oil. Proportion 2:1 (d.e. 33%). ^1H NMR (250 MHz, CDCl_3 , ppm): δ 0.08 (s, 12H), 0.89 (s, 9H), 0.90 (s, 9H), 1.35 (s, 6H), 1.51 (s, 3H), 1.54 (s, 3H), 3.19–3.24 (m, 1H), 3.36–3.43 (m, 2H), 3.54 (s, 3H), 3.58 (s, 3H), 3.75–3.87 (m, 5H), 4.11–4.28 (m, 5H), 4.33–4.39 (m, 1H), 4.65–4.69 (m, 1H), 5.25–5.29 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (62.5 MHz, CDCl_3 , ppm): δ – 6.0, –5.9, –5.8, 17.8, 17.9, 25.4, 25.5, 25.6, 25.7, 27.5, 27.6, 58.0, 59.3, 61.5, 61.8, 67.2, 72.3, 72.5, 72.6, 74.6, 78.2, 79.1, 82.9, 89.9, 95.7, 108.4, 109.1. MS (CI, m/z , %): 349 (36, $[M + H]^+$); 332 (63); 275 (100). IR (NaCl, cm^{-1}): ν 3421 (br, OH); 1105 (st, Si-O-C). Anal. Calc. for $\text{C}_{16}\text{H}_{32}\text{O}_6\text{Si}$: C, 55.14; H, 9.26. Found: C, 55.27; H, 9.33.

(*R*)-2-(((*tert*-Butyldimethylsilyl)oxy)-1-((4*S*,5*R*)-5-((*S*)-1-methoxyallyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethan-1-ol (**14b**). Starting from the mixture **13d** (2.16 g, 6.24 mmol) and following the same procedure as per compound **14a**, compound **14b** was obtained (1.73 g, 4.99 mmol, 80%) as a pale yellow oil after flash column chromatography (EtOAc/hexane 1:7). $[\alpha]_{\text{D}}^{20} = -8.6$ (c 1.2, CHCl_3). ^1H NMR (250 MHz, CDCl_3 , ppm): δ 0.07 (s, 6H), 0.89 (s, 9H), 1.38 (s, 3H), 1.55 (s, 3H), 3.22 (d, 1H, $J = 4.1$ Hz), 3.34 (s, 3H), 3.60–3.75 (m, 3H), 3.93 (dd, 1H, $J = 8.5$, 3.6 Hz), 4.19 (d, 1H, $J = 10.4$ Hz), 4.23 (d, 1H, $J = 10.4$ Hz), 5.39 (dd, 1H, $J = 16.7$, 1.6 Hz), 5.41 (dd, 1H, $J = 11.3$, 1.6 Hz), 5.83 (ddd, 1H, $J = 16.7$, 11.3, 8.5 Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (62.5 MHz, CDCl_3 , ppm): δ – 5.8, –5.7, 17.9, 24.7, 25.5, 25.9, 55.5, 63.5, 69.3, 75.1, 78.8, 80.4, 107.9, 119.9, 134.3. MS (CI, m/z , %): 347 (96, $[M + H]^+$); 316 (87); 259 (100). IR (NaCl, cm^{-1}): ν 3480 (br, OH); 1119 (st, Si-O-C). Anal. calc. for $\text{C}_{17}\text{H}_{34}\text{O}_5\text{Si}$: C, 58.92; H, 9.89. Found: C, 59.08; H, 10.18.

2-(((*tert*-Butyldimethylsilyl)oxy)-1-((4*R*,5*R*)-5-((*S*)-1-methoxyallyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethan-1-one (**15b**). After compound **14b** (1.73 g, 4.99 mmol) was subjected to the procedure for the preparation of **15a**, flash column chromatography of the crude reaction product (EtOAc/hexane 1:9) provided compound **15b** (1.39 g, 4.04 mmol, 81%) as a pale yellow oil. $[\alpha]_{\text{D}}^{20} = +91.4$ (c 1.1, CHCl_3). ^1H NMR (250 MHz, CDCl_3 , ppm): δ 0.08 (s, 3H), 0.11 (s, 3H), 0.93 (s, 9H), 1.33 (s, 3H), 1.58 (s, 3H), 3.06 (s, 3H), 3.58 (dd, 1H, $J = 8.5$, 1.6 Hz), 4.42 (dd, 1H, $J = 8.2$, 1.6 Hz), 4.45 (d, 1H, $J = 18.7$ Hz), 4.52 (d, 1H, $J = 8.2$ Hz), 4.76 (d, 1H, $J = 18.7$ Hz), 5.28 (dd, 1H, $J = 17.3$, 1.6 Hz), 5.33 (dd, 1H, $J = 10.4$, 1.6 Hz),

5.85 (ddd, 1H, $J = 17.3$, 10.4, 8.5 Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (62.5 MHz, CDCl_3 , ppm): δ – 5.7, –5.4, 18.2, 23.9, 25.7, 26.0, 55.7, 67.9, 78.9, 79.5, 81.7, 109.9, 119.2, 134.2, 206.8. MS (CI, m/z , %): 345 (6, $[M + H]^+$); 314 (27); 288 (100). IR (NaCl, cm^{-1}): ν 1750 (st, C=O); 1100 (st, Si-O-C). Anal. calc. for $\text{C}_{17}\text{H}_{32}\text{O}_5\text{Si}$: C, 59.27; H, 9.36. Found: C, 59.10; H, 9.47.

tert-Butyl((2-((4*S*,5*R*)-5-((*S*)-1-methoxyallyl)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)oxy)dimethylsilane (**16c**). When the procedure for the preparation of compound **16a** was applied to compound **15b** (1.39 g, 4.04 mmol) and the solid residue from the reaction mixture was subjected to flash column chromatography (EtOAc/hexane 1:19), compound **16c** was isolated (1.29 g, 3.77 mmol, 93%) as a pale yellow oil. $[\alpha]_{\text{D}}^{20} = +32.6$ (c 1.6, CHCl_3). ^1H NMR (250 MHz, CDCl_3 , ppm): δ 0.08 (s, 6H); 0.92 (s, 9H), 1.38 (s, 3H), 1.54 (s, 3H), 3.23 (s, 3H), 3.56 (dd, 1H, $J = 7.4$, 6.0 Hz), 4.16 (dd, 1H, $J = 6.6$, 6.0 Hz), 4.20 (m, 2H), 4.63 (d, 1H, $J = 6.6$ Hz), 5.24 (dd, 1H, $J = 17.3$, 1.9 Hz), 5.26 (d, 1H, $J = 1.6$ Hz), 5.30 (dd, 1H, $J = 10.7$, 1.9 Hz), 5.31 (d, 1H, $J = 1.6$ Hz), 5.69 (ddd, 1H, $J = 17.3$, 10.7, 7.4 Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (62.5 MHz, CDCl_3 , ppm): δ – 5.8, –5.7, 18.0, 24.8, 25.6, 26.1, 55.7, 63.9, 77.9, 80.2, 80.5, 107.9, 111.9, 118.7, 134.6, 144.2. MS (CI, m/z , %): 343 (11, $[M + H]^+$); 312 (49); 255 (100). IR (NaCl, cm^{-1}): ν 1252 (st, Si-O-C). Anal. calc. for $\text{C}_{18}\text{H}_{34}\text{O}_4\text{Si}$: C, 63.11; H, 10.00. Found: C, 62.90; H, 10.05.

2-((4*S*,5*R*)-5-((*S*)-1-Methoxyallyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (**16d**). Starting from compound **16c** (1.29 g, 3.77 mmol) and following the same procedure as per compound **16b**, compound **16d** was obtained (0.71 g, 3.09 mmol, 82%) as a pale yellow oil after flash column chromatography (EtOAc/hexane 1:4). $[\alpha]_{\text{D}}^{20} = +66.6$ (c 1.6, CHCl_3). ^1H NMR (250 MHz, CDCl_3 , ppm): δ 1.39 (s, 3H), 1.57 (s, 3H), 2.65 (br, 1H), 3.23 (s, 3H), 3.60 (dd, 1H, $J = 7.9$, 5.2 Hz), 4.19 (br, 2H), 4.29 (dd, 1H, $J = 6.9$, 5.2 Hz), 4.76 (d, 1H, $J = 6.9$ Hz), 5.21 (dd, 1H, $J = 17.3$, 1.9 Hz), 5.24 (d, 1H, $J = 1.6$ Hz), 5.33 (dd, 1H, $J = 10.4$, 1.9 Hz), 5.36 (d, 1H, $J_{2'b,2'a} = 1.6$ Hz, $H_{2'b}$), 5.79 (ddd, 1H, $J_{6,7b} = 17.3$ Hz, $J_{6,7a} = 10.4$ Hz, $J = 7.9$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (62.5 MHz, CDCl_3 , ppm): δ 24.3, 25.8, 55.4, 63.2, 77.7, 79.6, 80.4, 107.8, 112.6, 119.1, 133.9, 144.7. MS (CI, m/z , %): 229 (6, $[M + H]^+$); 186 (19); 166 (100). IR (NaCl, cm^{-1}): ν 3400 (br, OH). Anal. calc. for $\text{C}_{12}\text{H}_{20}\text{O}_4$: C, 63.14; H, 8.83. Found: C, 63.29; H, 9.05.

((3a*R*,4*S*,6a*S*)-4-Methoxy-2,2-dimethyl-3a,6a-dihydro-4*H*-cyclopenta[*d*][1,3]dioxol-6-yl)methanol (**17b**). When compound **16d** (2.37 g, 10.37 mmol) was submitted to the same procedure as per compound **10**, compound **17b** (1.91 g, 9.54 mmol, 92%) was obtained after flash column chromatography (EtOAc/hexane 1:1) as a yellow oil. $[\alpha]_{\text{D}}^{20} = +31.7$ (c 1.5, CHCl_3). ^1H NMR (250 MHz, CDCl_3 , ppm): δ 1.36 (s, 3H), 1.41 (s, 3H), 2.16 (br, 1H), 3.43 (s, 3H), 4.25–4.40 (m, 3H), 4.58 (d, 1H, $J = 6.0$ Hz), 5.18 (dd, 1H, $J = 6.0$, 0.8 Hz), 5.78 (d, 1H, $J = 1.4$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (62.5 MHz, CDCl_3 , ppm): δ 24.9, 26.4, 56.0, 58.5, 82.4, 82.6, 88.4, 111.1, 124.3, 148.8. MS (CI, m/z , %): 201 (20, $[M + H]^+$); 158 (18); 127 (100). IR (NaCl, cm^{-1}): ν 3448 (br, OH). Anal. calc. for $\text{C}_{10}\text{H}_{16}\text{O}_4$: C, 59.98; H, 8.05. Found: C, 59.93; H, 7.85.

Methyl (3a*R*,4*S*,6a*S*)-4-methoxy-2,2-dimethyl-3a,6a-dihydro-4*H*-cyclopenta[*d*][1,3]dioxole-6-carboxylate (**18d**). When compound **17b** (1.91 g, 9.54 mmol) was subjected to the procedure for the preparation of compound **11b**, compound **18d** (1.79 g, 7.83 mmol, 82%) was obtained as a colorless oil after flash column chromatography (EtOAc/hexane 1:4). $[\alpha]_{\text{D}}^{20} = +26.7$ (c 1.2, CHCl_3). ^1H NMR (250

MHz, CDCl₃, ppm): δ 1.39 (s, 3H), 1.43 (s, 3H), 3.46 (s, 3H), 3.82 (s, 3H), 4.40–4.43 (m, 1H), 4.63 (d, 1H, J = 6.0 Hz), 5.43 (dd, 1H, J = 6.0, 1.6 Hz), 6.77 (d, 1H, J = 1.4 Hz). ¹³C{¹H} NMR (62.5 MHz, CDCl₃, ppm): δ 24.4, 26.2, 51.0, 56.3, 81.6, 82.6, 88.4, 111.5, 138.3, 141.3, 163.1. MS (CI, m/z , %): 229 (6, [M + H]⁺); 197 (100); 186 (9). IR (NaCl, cm^{−1}): ν 1728 (st, C=O). Anal. calc. for C₁₁H₁₆O₅: C, 57.89; H, 7.07. Found: C, 57.78; H, 7.19.

Methyl (3a*S*,4*R*,5*R*,6*S*,6a*S*)-5-(benzylamino)-6-methoxy-2,2-dimethyltetrahydro-4*H*-cyclopenta[*d*][1,3]dioxole-4-carboxylate (19b). Starting from compound 18d (1.79 g, 7.86 mmol) and following the same procedure as for the preparation of compound 12, compound 19b (2.10 g, 6.26 mmol, 80% yield) was obtained as a yellowish oil after flash column chromatography (EtOAc/hexane 1:3). [α]_D²⁰ = +44.6 (c 1.5, CHCl₃). ¹H NMR (250 MHz, CDCl₃, ppm): δ 1.31 (s, 3H), 1.49 (s, 3H), 2.58 (d, 1H, J = 3.6 Hz), 2.92 (dd, 1H, J = 9.3, 5.5 Hz), 3.41 (s, 3H), 3.44 (ddd, 1H, J = 9.3, 7.4, 3.6 Hz), 3.66 (dd, 1H, J = 7.4, 3.3 Hz), 3.71 (s, 3H), 3.78 (d, 1H, J = 13.2 Hz), 3.84 (d, 1H, J = 13.2 Hz), 4.43 (dd, 1H, J = 7.1, 3.3 Hz), 4.83 (dd, 1H, J = 7.1, 5.5 Hz), 7.24–7.34 (m, 5H). ¹³C{¹H} NMR (62.5 MHz, CDCl₃, ppm): δ 24.0, 26.4, 50.8, 51.5, 53.1, 56.9, 64.2, 79.0, 82.4, 89.2, 111.7, 126.4, 127.6, 127.8, 139.5, 172.3. MS (CI, m/z , %): 336 (83, [M + H]⁺); 304 (12); 262 (100). IR (NaCl, cm^{−1}): ν 3339 (br, NH); 1733 (st, C=O). Anal. calc. for C₁₈H₂₅NO₅: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.18; H, 7.39; N, 4.00.

Synthesis of Tripeptide 21. Methyl (1*R*,2*S*,3*S*,4*S*,5*R*)-2,3,4-*Tris*-(benzyloxy)-5-*tert*-(butoxycarbonyl)amino)-cyclopentane-1-carboxylate (19d). CAN (4.19 g, 7.64 mmol) was added to a solution of compound 19a (1.11 g, 1.91 mmol) in CH₃CN/H₂O (95.5 mL, 4:1) at 0 °C. The mixture was allowed to warm up to room temperature and stirred for 6 h. The mixture was quenched with saturated aq. Na₂S₂O₃ (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. NaHCO₃ until basic pH was reached. The mixture was stirred at room temperature for 18 h, diluted with 10% aq. HCl (50 mL), and extracted with EtOAc (100 mL). The organic layer was dried (anhydrous Na₂SO₄) and concentrated to dryness under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/hexane 1:4) to give compound 19d (0.80 g, 1.43 mmol, 75% yield) as a yellowish oil. [α]_D²³ = +37.0 (c 1.6, CHCl₃). ¹H NMR (250 MHz, CDCl₃, ppm): δ 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). ¹³C{¹H} NMR (62.5 MHz, CDCl₃, ppm): δ 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 , %): 562 (12, [M + H]⁺); 505 (49); 91 (100). IR (NaCl, cm^{−1}): ν 3348 (br, NH), 1751 (st, C=O). Anal. calc. for C₃₃H₃₉NO₇: C, 70.57; H, 7.00; N, 2.49. Found: C, 70.37; H, 6.92; N, 2.62.

Dipeptide 20a. Ba(OH)₂·8H₂O (1.34 g, 4.26 mmol) was added to a solution of compound 19d (0.80 g, 1.42 mmol) in a 1:2 THF/H₂O mixture (15 mL). The reaction 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 dry CH₂Cl₂ (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. CH₂Cl₂ (15 mL) was added, the mixture was washed with 10% aq. HCl (15 mL), and the organic layer was dried (anhydrous Na₂SO₄) and concentrated to dryness under a vacuum. Column chromatography of the solid residue (EtOAc/hexane 1:1) led to the isolation of dipeptide 20a (0.33 g, 0.53 mmol, 60% overall yield from compound 19d) as a colorless oil. [α]_D²¹ = +68.2 (c 1.5, CHCl₃). ¹H NMR (250 MHz, CDCl₃, ppm): δ 1.37 (s, 9H), 3.18 (dd, 1H, J = 5.8, 4.0 Hz), 3.27 (dd, 1H, J = 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 (br, 1H), 6.91 (br, 1H), 7.28–7.41 (m, 15H). ¹³C{¹H} NMR (62.5 MHz, CDCl₃, ppm): δ 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 , %): 619 (56, [M + H]⁺); 588 (64); 91 (100). Anal. calc. for C₃₅H₄₂N₂O₈: C, 67.94; H, 6.84; N, 4.53. Found: C, 68.12; H, 7.01; N, 4.29.

Tripeptide 21. TFA (2 mL) in THF (5 mL) was added to a solution of compound 20a (0.33 g, 0.53 mmol), and the mixture was stirred at rt. for 1 h. The solvent was then coevaporated with toluene (3 × 2 mL) under a 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 CH₂Cl₂ (5 mL), and the mixture was stirred at rt. for 15 min. A solution of the crude amine from the previous transformation in CH₂Cl₂ (10 mL) was added, and the resulting mixture was stirred at rt. for 10 h. The reaction mixture was washed with 10% aq. HCl (20 mL), and the organic layer was dried (anhydrous Na₂SO₄), filtered, and concentrated to dryness under a vacuum. Column chromatography of the solid residue (EtOAc) provided pure tripeptide 21 (0.20 g, 0.30 mmol, 55% overall yield from compound 20a) as a colorless oil. [α]_D¹⁸ = +21.7 (c 1.1, CHCl₃). ¹H NMR (250 MHz, CDCl₃, ppm): δ 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 (br, 1H), 5.55 (br, 1H), 6.93 (br, 1H), 6.96 (br, 1H), 7.27–7.39 (m, 15H). ¹³C{¹H} NMR (62.5 MHz, CDCl₃, ppm): δ 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 , %): 676 (18); 569 (64); 91 (100). Anal. Calc. for C₃₇H₄₅N₃O₉: C, 65.76; H, 6.71; N, 6.22. Found: C, 65.59; H, 6.49; N, 5.98.

Synthesis of Pentapeptide 24. 2-(Trimethylsilyl)ethyl (3a*R*,4*S*,6a*S*)-4-methoxy-2,2-dimethyl-3a,6a-dihydro-4*H*-cyclopenta[*d*][1,3]dioxole-6-carboxylate (18e). A solution of DCC (0.12 g, 0.56 mmol) in CH₂Cl₂ (2.2 mL) was added to a solution of carboxylic acid 18c (0.11 g, 0.51 mmol), 2-(trimethylsilyl)ethanol (15 μ L, 1.02 mmol), and DMAP (6 mg, 0.05 mmol) in CH₂Cl₂ (2.2 mL), and the mixture was stirred at rt. for 12 h. Water (10 mL) was then added, and the resulting mixture was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with aq. saturated solution of NaHCO₃ (20 mL) and brine (20 mL), dried (anhydrous Na₂SO₄), filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane 1:7) to obtain ester 18e (0.13 g, 77%) as a clear oil. [α]_D²² = +34.5 (c 0.5, CHCl₃). ¹H NMR (CDCl₃, 300 MHz, ppm): δ 0.05 (s, 9H, 3 × CH₃), 0.88–1.19 (m, 2H, CH₂Si), 1.37 (s, 3H, CH₃), 1.41 (s, 3H, CH₃), 3.45 (s, 3H, OMe), 4.21–4.38 (m, 2H, CH₂O), 4.40

(td, 1H, $J = 2.1, 1.0$ Hz, H-4), 4.61 (dt, 1H, $J = 6.0, 1.0$ Hz, H-3a), 5.42 (dd, 1H, $J = 6.0, 1.8$ Hz, H-6a), 6.71 (dd, 1H, $J = 2.1, 0.8$ Hz, H-5). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz, ppm): δ -1.4, 17.4, 25.4, 27.2, 57.5, 63.4, 82.6, 83.4, 89.3, 112.6, 141.4, 145.7, 163.9. IR (NaCl, cm^{-1}): ν 1720 (st, C=O). HRMS (ESI⁺): calc. for $\text{C}_{15}\text{H}_{26}\text{O}_5\text{Si}$ ($\text{M} + \text{Na}$)⁺ 337.1442, found 337.1447.

2-(Trimethylsilyl)ethyl (3a*S*,4*R*,5*R*,6*S*,6a*S*)-5-(benzylamino)-6-methoxy-2,2-dimethyltetrahydro-4*H*-cyclopenta[*d*]-[1,3]dioxole-4-carboxylate (19f). Benzylamine (18 μL , 0.16 mmol) was added to a solution of ester **18e** (42 mg, 0.134 mmol) in DMF (0.4 mL), and the resulting mixture was stirred at rt. for 60 h when the solvents were removed under reduced pressure. The resulting residue was taken up in EtOAc (10 mL), washed with water (3×5 mL), dried (anhydrous Na_2SO_4), and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane 1:3), to obtain compound **19f** (39 mg, 69%) as a clear oil. $[\alpha]_{\text{D}}^{22} = -5.4$ (c 3.4, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz, ppm): δ 0.04 (s, 9H, $3 \times \text{CH}_3$), 0.99 (ddd, 2H, $J = 9.1, 7.1, 1.0$ Hz, $\text{CH}_2\text{-Si}$), 1.30 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.92 (s, 1H, NH), 2.88 (dd, 1H, $J = 9.1, 5.3$ Hz, H-4), 3.37–3.47 (m, 4H, OMe + H-5), 3.65 (dd, 1H, $J = 7.2, 3.3$ Hz, H-6), 3.82 (d, 2H, $J = 2.5$ Hz, CH_2Bn), 4.19 (ddd, 2H, $J = 9.2, 7.1, 1.0$ Hz, $\text{CH}_2\text{-O}$), 4.42 (dd, 1H, $J = 7.3, 3.3$ Hz, H-6a), 4.84 (dd, 1H, $J = 7.3, 5.3$ Hz, H-3a), 7.18–7.37 (m, 5H, $5 \times \text{H-Ar}$). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz, ppm): δ -1.4, 17.5, 24.8, 27.1, 51.7, 54.1, 57.7, 63.6, 65.1, 79.8, 83.2, 90.1, 112.5, 127.1, 128.3, 128.5, 140.2, 172.9. IR (NaCl, cm^{-1}): ν 3350 (br, NH); 1726 (st, C=O). HRMS (ESI⁺) m/z ($\text{M} + \text{H}$)⁺ calc. for $\text{C}_{22}\text{H}_{36}\text{O}_5\text{Si}$ 422.2357. Found 422.2360.

Tripeptide 23a. A 1 M solution of TBAF in THF (0.17 mL) was added to a solution of amino acid ester **19f** (65 mg, 0.154 mmol) in THF (3 mL), and the resulting mixture was stirred at rt. for 24 h. The reaction mixture was diluted with aq. saturated solution of NH_4Cl (5 mL) and extracted with ethyl acetate (3×5 mL). The combined organic layers were dried (anhydrous Na_2SO_4) and filtered, and the solvent was evaporated under reduced pressure. The resulting crude of **19g** was dissolved in dry DMF (4 mL), and then PyBOP (104 mg, 0.200 mmol) and $\text{HOBt} \cdot \text{H}_2\text{O}$ (31 mg, 0.200 mmol) were added. After 10 min at rt., ACPC dimer **22a** (54 mg, 0.185 mmol) and DIEA (110 μL , 0.616 mmol) were added, and the reaction mixture was stirred overnight at rt. The reaction was then diluted with CH_2Cl_2 (20 mL) and washed with 1 M HCl (20 mL), aq. saturated solution of NaHCO_3 (20 mL), and brine (20 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (EtOAc) to yield compound **23a** (37 mg, 43%) as a white solid. $[\alpha]_{\text{D}}^{22} = +29.1$ (c 2.0, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz, ppm): δ 1.22–1.45 (m, 4H, $\text{CH}_3 + \text{CH}_2$), 1.51 (s, 3H, CH_3), 1.53–1.79 (m, 5H, $2 \times \text{CH}_2 + \text{CH}_2$), 1.83–2.27 (m, 7H, $3 \times \text{CH}_2 + \text{NH}$), 2.47 (dd, 1H, $J = 8.4, 4.5$ Hz, CH-CO), 2.56–2.68 (m, 2H, $2 \times \text{CH-CO}$), 3.22 (dd, 1H, $J = 11.9, 8.6$ Hz, CH-N), 3.47 (s, 3H, OMe), 3.59–3.71 (m, 4H, OMe + CH-N), 3.83 (d, 1H, $J = 13.9$ Hz, CH_2Bn), 3.96 (d, $J = 12.9$ Hz, 1H, CH_2Bn), 4.11 (t, $J = 6.3$ Hz, 1H, CH-N), 4.30–4.41 (m, 2H, $2 \times \text{CH-O}$), 4.79 (t, 1H, $J = 7.1$ Hz, CH-O), 7.30 (td, 5H, $J = 9.6, 8.6, 3.6$ Hz, $5 \times \text{H-Ar}$), 7.65 (d, 1H, $J = 6.3$ Hz, NH), 7.92 (d, 1H, $J = 7.1$ Hz, NH). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz, ppm): δ 23.1, 24.8, 24.9, 27.2, 27.3, 28.4, 32.8, 33.3, 50.4, 50.7, 52.0, 52.4, 53.2, 54.9, 56.1, 57.8, 63.8, 77.4, 82.0, 90.4 (CH), 113.1, 127.6, 128.3, 128.7, 139.3, 172.5, 173.3, 175.6. IR (NaCl, cm^{-1}): ν

3287 (br, NH); 1732, 1643 (st, C=O). HRMS (ESI⁺) m/z ($\text{M} + \text{H}$)⁺ calc. for $\text{C}_{30}\text{H}_{44}\text{N}_3\text{O}_7$ 558.3174. Found 558.3174.

Pentapeptide 24. 20% $\text{Pd}(\text{OH})_2/\text{C}$ (12 mg) was added over a deoxygenated solution of compound **23a** (23 mg, 0.041 mmol) in methanol (4 mL), and the resulting suspension was deoxygenated again and stirred overnight under a hydrogen atmosphere ($P = 1$ atm). The reaction was filtered through Celite and washed with methanol, and the filtrate was evaporated to dryness under a vacuum to give chromatographically pure **23b**. PyBOP (28 mg, 0.054 mmol), HOBt (8 mg, 0.054 mmol), and DIEA (0.28 mL, 1.59 mmol) were added over a solution of ACPC dimer **22b** (20 mg, 0.054 mmol) in dry DMF (1 mL). After 5 min stirring, a solution of the crude of **23b** in dry DMF (1 mL) was added to the other solution, and the reaction mixture was stirred at rt. overnight. Then, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1 M HCl (10 mL), aq. saturated solution of NaHCO_3 (10 mL), and brine (10 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (EtOAc/hexane 4:1) to obtain pentamer **24** (20 mg, 59%) as a white solid. $[\alpha]_{\text{D}}^{22} = +47.7$ (c 1.0, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz, ppm): δ 1.27 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.55–1.81 (m, 12H, CH_2), 1.90–2.17 (m, 13H, $\text{CH}_2 + \text{CH-CO}$), 2.38–2.49 (m, 1H, CH-CO), 2.62 (dd, $J = 9.5, 4.1$ Hz, 2H, CH-CO), 2.89–3.04 (m, 1H, CH-CO), 3.45 (s, 3H, OMe), 3.66 (s, 3H, OMe), 3.85 (dd, $J = 9.8, 5.4$ Hz, 1H, CH-N), 4.08–4.22 (m, 3H, $\text{CH-N} + \text{CH-O}$), 4.33 (q, $J = 9.1, 8.6$ Hz, 2H, CH-N), 4.41–4.51 (m, 2H, CH-O), 5.00 (dd, $J = 7.2, 4.3$ Hz, 1H, CH-O), 5.12 (dd, $J = 12.3, 16.7$ Hz, 2H, $\text{CH}_2\text{-Ar}$), 5.89 (d, $J = 7.9$ Hz, 1H, NH), 6.47 (d, $J = 8.4$ Hz, 1H, NH), 7.36 (s, 5H, $\text{CH}_2\text{-Ar}$), 7.69 (d, $J = 8.1$ Hz, 1H, NH), 8.13–8.48 (m, 2H, NH). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz, ppm): δ 23.6, 24.1, 24.4, 25.4, 25.5, 27.6, 28.3, 28.9, 29.0, 29.8, 32.5, 33.6, 33.9, 50.2, 51.8, 51.9, 53.1, 53.5, 54.7, 55.0, 55.6, 55.7, 57.7, 57.9, 58.0, 67.0, 78.9, 82.5, 89.4, 112.5, 127.9, 128.4, 128.8, 136.4, 156.8, 171.2, 174.3, 174.6, 175.1, 176.6. IR (ATR, cm^{-1}): ν 3289 (NH), 3037 (NH), 1699 (C=O), 1645 (C=O), 1555 (C=O). HRMS (ESI⁺) m/z ($\text{M} + \text{Na}$)⁺ calc. for $\text{C}_{43}\text{H}_{61}\text{N}_5\text{NaO}_{11}$ 846.4260. Found 846.4262.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.1c05468>.

Copies of ^1H , $^{13}\text{C}\{^1\text{H}\}$, and DEPT-135 NMR spectra for compounds **7b**, **8**, **9a**, **9b**, **9c**, **10**, **11b**, **12**, **13c**, **13d**, **14a**, **14b**, **15a**, **15b**, **16a**, **16b**, **16c**, **16d**, **17a**, **17b**, **18b**, **18d**, **18e**, **19a**, **19b**, **19d**, **19f**, **20a**, **21**, **23a**, and **24** (PDF)

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Notes

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