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 stereoselectiveaza-Michael functionalization of the resulting cyclopent-1-ene-1-carboxylic acid ester. Examples of synthesis of polysubstituted 2-amino-cyclopentanecarboxylic 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,1–3 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-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-amino-cyclopentanecarboxylic 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-amino-cyclohexane 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

The first reported polyhydroxylated cyclopentane β-amino acid was the trans-2-amino-cyclopentanecarboxylic acid deriv-
ative 3a, which was obtained in our laboratory by a novel approach involving the key stereocontrolled cyclization of D-glucose nitrosugar derivative 1 to bicyclolactone 2 (Scheme 1). Amino acid 3a was converted into its derivative 3b, which is suitably functionalized for incorporation into peptides. Applications of this approach to L-idose nitrosugar derivative 4 provided the first polyhydroxylated cis-2-amino-cyclopentanecarboxylic acid 6 (Scheme 1). Nevertheless, this strategy turned out unsuitable for preparing peptides based on these β-amino acids due to the low global yields achieved for 3a (12% yield, seven steps), 3b (8% yield, 10 steps), and 6 (15% yield, seven steps). Furthermore, the scope of this synthetic strategy is relatively limited because it can provide direct access to only eight 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 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).

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) 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-
Michael amination\(^{44}\) of the \(\alpha,\beta\)-unsaturated carboxylic moiety to give the target highly functionalized \(\beta\)-amino acid \(\text{D}\).

In order to demonstrate the generality of the method, we synthesized protected polyhydroxylated cyclopentane \(\beta\)-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 \(\beta\)-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 \(\beta\)-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 \(\beta\)-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 \(\beta\)-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 reactive 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 silylether 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 cyclopentencarboxylic acid \(11a\). Reaction of \(11a\) with \(\text{NaHCO}_3\) and \(\text{MeI}\) furnished its methyl ester derivative \(11b\) in 85% yield for the last three steps. Finally, treatment of \(11b\) with benzylamine resulted in the expected stereoselectiveaza-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 \(\beta\)-amino acid derivative \(3b\) synthesized from D-glucose by the nitrosugar strategy (8% yield, nine steps).\(^{40}\)

### Synthesis of Polyhydroxylated Cyclopentane \(\beta\)-Amino Acid Derivative 19a.

The satisfactory results of our strategy for the transformation of D-mannose into \(\beta\)-amino acid 12 prompted us to apply it to other hexoses, like the transformation of D-galactose into \(\beta\)-amino acid 19a (Scheme 4). The key reaction to build the cyclopentane ring of 19a was...
the RCM reaction of diolenin 16b, which was prepared from the known δ-galactose derivative 13a. 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 diolenin 16a (Scheme 4). Removal of the silyl ether group at the C1 of 16a by treatment with TBAF gave the desired key diolenin 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 cyclopentencarboxylic 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 azamichael 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 hydroxyl 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 19b, see Scheme 4.

Accordingly, reaction of δ-galactose derivative 13b with methyl iodide gave its O-methylated derivative 13c, which was then converted into the anomic 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 azamichael 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 orCbz) of 19b from its nitrosugar precursor 1 (8% yield, nine steps).

It is worth comparing the yields of the two critical steps (ring-closing metathesis and azamichael 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 → 17a (Scheme 4), i.e. with the galactose derivative with its hydroxyls protected with benzylic 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 benzylic 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 acetones; 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 azamichael step, the yields are similar for the transformations of the galactose derivatives 18b → 19a (80%; Scheme 4) and 18d → 19b (80%; Scheme 5), while the yield of the mannoside derivatives 11b → 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 mannoside 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 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. Dipetide 20a was isolated in 60% yield (TFA), 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. 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 azamichael addition. So, starting from carboxylic acid 18c, esterification with trimethylsilylchloromethane provided the expected cyclopentencarboxylic acid ester 18e, which furnished β-amino acid...
Our immediate plans are directed toward the synthesis of chemistry, new materials, and catalysis. As preliminary studies, as well as studying their potential applications in biological of monomers and peptides containing hydroxylated groups as amino acids (\(\text{R}^{1}\)). This allowed us to synthesize, in the gram scale, three new liposoluble amino acids, like the ones shown here, would expand the availability of more richly functionalized cyclopentane an alternative procedure for their incorporation into peptides. In the case of those amino acids that incorporate these hydroxymethyl. Furthermore, we have demonstrated how to inhibit (glycosidase inhibitors) by reduction of the methoxycarbonyl group to (hydroxymethyl)-1,2,3-cyclopentanetriols (potent glycosidase opens up opportunities for a new access to 4-amino-5-protected for their incorporation into peptides. This method is more general and can be extended, in principle, to the pool of hexoses. To demonstrate the generality of the method, we applied it to the previously reported alternative from nitrosugars as it could different hexoses (D-mannose and D-galactose) and with different protecting patterns in the case of D-galactose. In conclusion, we present here a promising approach to the stereocontrolled synthesis of highly complex cyclopentane \(\beta\)-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 four 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 \(\beta\)-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 \(\beta\)-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 \(\beta\)-amino acids, like the ones shown here, would expand the opportunities of designing a larger variety of hydro- or liposoluble \(\beta\)-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 \(\beta\)-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. \(^1\)H and \(^13\)C NMR spectra were recorded on Bruker DPX 250 (250 MHz for \(^1\)H and 62.5 MHz for \(^13\)C) and Varian Mercury 300 (300 MHz for \(^1\)H and 75 MHz for \(^13\)C) spectrometers at room temperature unless otherwise stated. All chemical shifts are quoted on the \(\delta\) scale using residual solvent as internal standard; \(s, d, t, q, m, and br\) designate singlet, doublet, triplet, quartuplet, 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\(_3,\) Cl) 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\(^{-1}\)]; \(s, m, and br\) 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 Polysubstituted Cyclopentane \(\beta\)-Amino Acid Derivative 12. \((3aS,4R,6R,6aS)-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 (CHCl₃/hexane).

δ(1H, J=1H) 7.13 (s, 1H), 6.75 (d, 1H, J=1H = 14.7 Hz), 5.97 (ddd, 1H, J=6Hz = 8.2 Hz, J=7b6 = 14.7 Hz), 5.52 (dd, 1H, J=1a1b = 1.7 Hz, J=1a2b = 13.7 Hz), 5.31 (d, 1H, J=1a1b = 1.8 Hz), 4.72 (dd, 1H, J=1b1a = 1.8 Hz, J=1b2b = 13.9 Hz), 4.37 (dd, 1H, J=1b2b = 1.8 Hz, J=1b2a = 13.9 Hz), 4.27 (br, 2H), 3.41 (dd, 1H, J=1b2a = 1.8 Hz, J=1b2a = 13.9 Hz), 2.85 (br, 1H), 3.24 (s, 3H), 1.40 (s, 3H), 1.56 (s, 3H), 2.85 (br, 1H), 3.24 (s, 3H), 1.40 (s, 3H), 1.56 (s, 3H).

J(C1) 25.6, 26.3, 64.7, 68.8, 79.3, 80.2, 84.3, 127.9, 129.3, 132.4, 132.6, 135.0, 168.8. IR (NaCl, cm⁻¹): 3593 (br, OH), 3191 (C=O), 1744 (C=O), 1656 (C=O), 1638 (C=O). 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=6Hz = 8.2 Hz, J=7b6 = 14.7 Hz), 4.70 (d, 1H, J=6Hz = 8.2 Hz, J=7b6 = 14.7 Hz), 4.94 (dd, 1H, J=1a1b = 1.7 Hz), 5.18 (dd, 1H, J=1b2b = 1.8 Hz, J=1b2a = 13.9 Hz), 5.32 (dd, 1H, J=1b2b = 1.8 Hz, J=1b2a = 13.9 Hz), 5.50 (d, 1H, J=1b1a = 1.7 Hz, J=1b2b = 1.8 Hz), 5.54 (d, 1H, J=1b1a = 1.8 Hz, J=1b2b = 1.8 Hz), 6.03 (d, 1H, J=1b2b = 1.8 Hz, J=1b2a = 13.9 Hz), 6.17 (s, 1H), 7.35–7.47 (m, 4H), 6.73–7.67 (m, 4H).

13C{1H} NMR (62.5 MHz, CDCl₃, ppm): δ 18.8, 20.4, 24.4, 25.6, 26.3, 64.7, 78.8, 79.3, 80.2, 84.3, 100.1, 112.4, 127.3, 129.3, 129.3, 129.4, 127.9, 127.9, 127.9, 132.5, 133.3, 134.7, 146.7. IR (NaCl, cm⁻¹): 3593 (br, OH), 1746 (st, C=O), 1111 (st, Si-O-C). MS (CI, m/z, %): 501 (8, [M + H]⁺).
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. $\delta_{1}^{1}H$ NMR (250 MHz, CDCl$_{3}$, ppm): $\delta$ 1.36 (s, 3H), 1.38 (s, 3H), 2.45 (d, 1H, $J_{1H} = 7.5$ Hz), 4.36 (d, 1H, $J_{1H} = 7.9$ Hz), 4.44 (d, 2H, $J_{1H} = 7.9$ Hz), 4.59 (d, 1H, $J_{1H} = 7.9$ Hz), 4.60 (t, 1H, $J_{1H} = 7.5$ Hz), 5.26 (s, 1H), 7.07 (s, 5H). $\delta_{13}^{1}C$ NMR (62.5 MHz, CDCl$_{3}$, ppm): 123.3, 123.5, 126.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 134.9, 136.9, 137.8, 139.5, 171.8. IR (NaCl, cm$^{-1}$): $\nu$ 3325 (br, NH), 1737 (s, C=O). MS (CI, m/ z %): 366 (100, [M + H$^+$]), 304 (22), 262 (27). Anal. calc. for C$_{34}$H$_{34}$O$_{5}$Si: C, 72.56; H, 7.91. Found: C 72.46; H, 7.53; N, 4.04.

**Synthesis of Polyhydroxylated Cyclopentane β-Amino Acid Derivative 19a.**

A suspension of Ph$_{3}$PCH$_{2}$Br (7.99 g, 22.36 mmol) in dry THF (37.3 mL) was cooled to $-78^\circ$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 $-78^\circ$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 $-78^\circ$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. NaNH$_{2}$Cl (50 mL) and extracted with EtO$_{2}$ (100 mL). The organic layer was dried (anhydrous Na$_{2}$SO$_{4}$) 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 yellow oil. $\delta_{1}^{1}H$ NMR (250 MHz, CDCl$_{3}$, ppm): $\delta$ 0.02 (s, 6H), 0.88 (s, 9H); 3.06 (d, 1H, $J = 4.9$ Hz), 3.56–3.62 (m, 2H, $J = 4.2$ Hz), 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, $J = 11.8$ Hz), 4.65 (d, 1H, $J = 11.8$ Hz), 4.76 (br, 2H, $J = 4.2$ Hz), 5.30 (dd, 1H, $J = 17.5$, 1.6 Hz), 5.35 (dd, 1H, $J = 10.5$, 1.6 Hz), 5.84 (dd, 1H, $J = 17.6$, 10.4 Hz), 7.22–7.38 (m, 15H). $\delta_{13}^{1}C$ NMR (62.5 MHz, CDCl$_{3}$, ppm): $\delta$ –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$^{-1}$): $\nu$ 3492 (br, OH), 1104 (st, Si-O-C). Anal. Calc. for C$_{36}$H$_{40}$O$_{5}$Si: C 72.56; H, 7.84. Found: C 72.49; H, 8.49.

**3,4,5-Tris(benzylxy) -1-((tert-butyldimethylsilyloxy)hept-6-ene-2-ol (15a).** After purification by flash column chromatography (EtOAc/hexane 1:4), a furnished compound 11b (0.53 g, 2.31 mmol, 85% yield from 10) as a colorless oil. $\delta_{1}^{1}H$ NMR (250 MHz, CDCl$_{3}$, ppm): $\delta$ 1.36 (s, 3H), 1.38 (s, 3H), 3.80 (s, 3H), 4.54 (d, 1H, $J = 16.6$ Hz), 4.61 (d, 1H, $J = 16.6$ Hz), 5.24 (d, 1H, $J = 16.6$ Hz), 7.07 (s, 5H), 7.10 (s, 5H). $\delta_{13}^{1}C$ NMR (62.5 MHz, CDCl$_{3}$, ppm): $\delta$ 25.1, 26.7, 51.2, 51.9, 52.4, 68.9, 70.4, 72.2, 74.7, 80.5, 81.4, 82.6, 82.8, 86.9, 111.2, 136.4, 140.0, 163.0. IR (NaCl, cm$^{-1}$): $\nu$ 3430 (st, Si-O-C). Anal. Calc. for C$_{34}$H$_{44}$O$_{5}$Si: C 72.56; H 7.84. Found: C 72.49; H, 8.49.

**3,4,5-Tris(benzylxy) -1-((tert-butyldimethylsilyloxy)hept-6-ene-2-ol (15a).** After purification by flash column chromatography (EtOAc/hexane 1:4), a furnished compound 11b (0.53 g, 2.31 mmol, 85% yield from 10) as a colorless oil. $\delta_{1}^{1}H$ NMR (250 MHz, CDCl$_{3}$, ppm): $\delta$ 1.36 (s, 3H), 1.38 (s, 3H), 3.80 (s, 3H), 4.54 (d, 1H, $J = 16.6$ Hz), 4.61 (d, 1H, $J = 16.6$ Hz), 5.24 (d, 1H, $J = 16.6$ Hz), 7.07 (s, 5H), 7.10 (s, 5H). $\delta_{13}^{1}C$ NMR (62.5 MHz, CDCl$_{3}$, ppm): $\delta$ 25.1, 26.7, 51.2, 51.9, 52.4, 68.9, 70.4, 72.2, 74.7, 80.5, 81.4, 82.6, 82.8, 86.9, 111.2, 136.4, 140.0, 163.0. IR (NaCl, cm$^{-1}$): $\nu$ 3430 (st, Si-O-C). Anal. Calc. for C$_{34}$H$_{44}$O$_{5}$Si: C 72.56; H 7.84. Found: C 72.49; H, 8.49.
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. NaHCl (25 mL) and extracted with EtO (50 mL). The organic layer was dried with anhydrous Na₂SO₄ and concentrated in vacuo. Flash column chromatography of the crude product (EtOAc/hexane 1:19) afforded compound 16a (1.78 g, 3.18 mmol, 85% yield) as a yellowish oil. [α]₀^20 = +19.3 (c 1.4, CHCl₃). ¹H NMR (250 MHz, CDCl₃ 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 (dd, 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 (dd, 1H, J = 17.6, 10.4, 7.7 Hz), 7.16−7.36 (m, 15H). ¹³C{¹H} NMR (62.5 MHz, CDCl₃ 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, 128.0, 128.1, 136.1, 138.2, 138.3, 144.6. MS (Cl, m/z %): 591 (15, [M + H]⁺); 468 (66); 91 (100). IR (NaCl, cm⁻¹): ν 1099 (st, Si-O-C). Anal. calc. for C₁₃H₂₄O₄Si: C 75.23; H 8.30. Found: C 75.37; H 8.20.

(3S,4R,5S)-3,4,5-Tris(benzylxoy)-2-methylhex-6-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 (EtOAc/hexane 1:6). [α]₀^20 = +17.3 (c 1.2, CHCl₃). ¹H NMR (250 MHz, CDCl₃ ppm): δ 3.72 (s, 3H), 3.98 (dd, 1H, J = 8.0, 7.1 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). ¹³C{¹H} NMR (62.5 MHz, CDCl₃ ppm): δ 57.5, 71.9, 72.1, 72.3, 76.5, 84.9, 85.3, 124.7, 127.5, 127.6, 128.0, 128.1, 128.3, 135.8, 137.6, 138.1, 147.5, 168.5. MS (Cl, m/z %): 445 (17, [M + H]⁺); 430 (76); 91 (100). IR (NaCl, cm⁻¹): ν 1733 (st, C=O). Anal. calc. for C₂₇H₃₂O₄C: C 75.66; H 6.35. Found: C 75.45; H 6.32.

Methyl (1R,2S,5,5,SR)-2,3,4-tris(benzylxoy)-5-(4-(methoxybenzyl)amino)cyclopentan-1-carboxylate (19a). Compound 18b (1.06 g, 2.39 mmol) was dissolved in dry DMF (7.2 mL) and stirred with PBMNH₂ (0.37 mL, 2.86 mmol) at room temperature under argon for 24 h. The reaction mixture was diluted with NH₄Cl (10 mL) and extracted with EtOAc (10 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) to afford compound 19a (1.11 g, 1.91 mmol, 80% yield) as a yellowish oil. [α]₀^20 = +27.5 (c 1.8, CHCl₃). ¹H NMR (250 MHz, CDCl₃ 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 = 13.3 Hz), 4.03−4.26 (m, 6H), 6.85−6.90 (m, 2H), 7.20−7.36 (m, 17H). ¹³C{¹H} NMR (62.5 MHz, CDCl₃ 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, 127.0, 127.1, 127.2, 130.4, 131.8, 137.4, 137.7, 138.3, 146.6, 173.7. MS (Cl, m/z %): 582 (42, [M + H]⁺); 551 (27); 91 (100). IR (NaCl, cm⁻¹): ν 3351 (br, NH), 1751 (st, C=O). Anal. calc. for C₃₉H₄₇NO₄C: 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. ((3S,4R,6R,7S,5S)-6-Benzylxoy-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 13b, compound 13c (2.01 g, 4.59 mmol, 93%) was obtained as a pure colorless oil. [α]₀^20 = −14.5 (c 1.7, CHCl₃). ¹H NMR (250 MHz, CDCl₃ 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 (dd, 1H, J = 7.1, 5.5, 19.3 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, 19.3 Hz), 4.28 (d, 1H, J = 8.0, 4.65 d, 1H, J = 11.8 Hz), 4.92 (d, 1H, J = 11.8 Hz), 7.29−7.39 (m, 5H). ¹³C{¹H} NMR (62.5 MHz, CDCl₃ ppm): δ −5.7, −5.5, 18.0, 25.6.
g, 10%) and NH4HCO2 (4.58 g, 72.54 mmol) were added to the reaction mixture. The reaction mixture was submitted to 13C{1H} NMR (62.5 MHz, CDCl3, ppm): δ 8.5 Hz). 13C{1H} NMR (62.5 MHz, CDCl3, ppm): δ = −8.5, −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 (Cl, 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 C19H24O3Si: C, 59.27; H, 9.36. Found: C, 59.10; H, 9.47.

1-{[(Butyldimethylsiloxy)oxy]-methyl}-7-methoxy-2,2-dimethyltetrahydro-4H-[1,3]-dioxolo[4,5-c]pyran-6-ol (14c). 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 compound 15b was isolated (1.29 g, 3.77 mmol, 93%) as a pale yellow oil. [α]D20 = +32.6 (c 1.6, CHCl3). 1H NMR (250 MHz, CDCl3, ppm): δ 0.08 (s, 6H); 0.92 (s, 9H); 1.34 (s, 3H); 1.54 (s, 3H); 2.32 (m, 1H), 3.56 (dd, 1H, J = 6.6, 6.0 Hz), 4.16 (dd, 1H, J = 10.7, 7.4 Hz), 2.0 (m, 2H), 4.63 (dd, 1H, J = 6.6 Hz), 5.24 (dd, 1H, J = 17.3, 1.9 Hz), 5.26 (dd, 1H, J = 1.6 Hz), 5.30 (dd, 1H, J = 17.3, 1.9 Hz), 5.31 (dd, 1H, J = 1.6 Hz), 5.69 (dd, 1H, J = 17.3, 10.7, 7.4 Hz). 13C{1H} NMR (62.5 MHz, CDCl3, 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 (Cl, m/z, %): 343 (11, [M + H]+); 312 (49); 255 (100). IR (NaCl, cm−1): ν = 1252 (st, Si-O-C). Anal. calc. for C19H24O3Si: C, 63.11; H, 10.00. Found: C, 62.90; H, 10.05.

2-((4S,5R)-5-(5-(1-Methoxyallyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (16d). Starting from the procedure for preparation of 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). [α]D20 = +66.6 (c 1.6, CHCl3). 1H NMR (250 MHz, CDCl3, 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 (dd, 1H, J = 16.2 Hz, H-2b), 5.79 (dd, 1H, J = 17.3 Hz, JH2c = 10.4 Hz), J = 7.9 Hz). 13C{1H} NMR (62.5 MHz, CDCl3, 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 (Cl, m/z, %): 229 (6, [M + H]+); 186 (19); 166 (100). IR (NaCl, cm−1): ν = 3400 (br, OH). Anal. calc. for C19H24O3Si: C, 63.14; H, 8.83. Found: C, 63.29; H, 9.05.

[(3aR,5aS)-4-Methoxy-2,2-dimethyl-3a,6a-dihydro-4-cyclopenta[d][1,3]dioxole-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. [α]D20 = +31.7 (c 1.5, CHCl3). 1H NMR (250 MHz, CDCl3, 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 (dd, 1H, J = 1.4 Hz). 13C{1H} NMR (62.5 MHz, CDCl3, ppm): δ 24.9, 26.4, 56.0, 58.5, 82.4, 82.6, 88.4, 111.1, 124.3, 148.8. MS (Cl, m/z, %): 201 (20, [M + H]+); 158 (18); 127 (100). IR (NaCl, cm−1): ν = 3448 (br, OH). Anal. calc. for C19H24O3Si: C, 59.98; H, 8.05. Found: C, 59.93; H, 7.85.

Methyl (3aR,5aS)-4-methoxy-2,2-dimethyl-3a,6a-dihydro-4H-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). [α]D20 = +26.7 (c 1.2, CHCl3). 1H NMR (250 MHz, CDCl3, ppm):
5.6, 4.1 Hz), 4.18 (dd, 1H, J = 7.4, 5.1 Hz), 3.66 (s, 3H), 3.79 (m, 2H), 4.30–4.40 (m, 6H), 4.54 (br, 1H), 7.28–7.38 (m, 15H). 13C{1H} NMR (62.5 MHz, CDCl3, ppm): δ 29.0, 54.2, 54.2, 54.7, 70.2, 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, 132.8, 137.7, 155.3, 174.2. MS (Cl, 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 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 evaporated to give tripeptide 21 as a colorless oil. [α]D20 = +44.6 (c 1.0, 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, 157.3, 169.3, 172.5. MS (Cl, m/z, %): 619 (56, [M + H]+); 588 (64); 91 (100). Anal. calc. for C35H39N2O8: C, 70.00; H, 6.14; N, 4.53.

**Synthesis of Pentapeptide 24.** 2-(Trimethylsilyl)ethyl (3R,4S,5R,6S,6aS,-5-(benzylamino)-6-methoxy-2,2-dimethyltetrahydro-4H-cyclopent[a][1,3]dioxole-4-carboxylate (18e). A solution of DCC (0.12 g, 0.56 mmol) in CH2Cl2 (2.2 mL) was added to a solution of compound 20a (0.33 g, 0.56 mmol) in CH2Cl2 (2.2 mL) over a period of 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, and 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 pentapeptide 24 (0.33 g, 0.53 mmol, 60% overall yield from compound 19d) as a colorless oil. [α]D20 = +86.0 (c 0.5, 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 29.0, 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, 150.9, 156.9, 166.0, 169.8, 172.2. MS (Cl, m/z, %): 676 (18); 569 (64); 91 (100). Anal. calc. for C35H43N2O8: C, 65.76; H, 6.71; N, 4.62. Found: C, 65.59; H, 6.49; N, 5.98.

**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 50%W xo-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, and 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]D20 = +86.0 (c 0.5, 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 29.0, 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, 150.9, 156.9, 166.0, 169.8, 172.2. MS (Cl, m/z, %): 676 (18); 569 (64); 91 (100). Anal. calc. for C35H43N2O8: C, 65.76; H, 6.71; N, 4.62. Found: C, 65.59; H, 6.49; N, 5.98.
(tid, 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). 13C{1H} NMR (CDCl3, 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 C18H18O6Si (M + Na)+ 337.1442, found 337.1447.

2-(Trimethylsilyl)ethyl (3aS,4R,5S,6aS)-5-(benzylamino)-6-methoxy-2,2-dimethyltetrahydro-4H-cyclopenta[d]-[1,3]dioxole-4-carboxylate (19f). Benzyamine (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 Na2SO4), 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. [α]D22 = −5.4 (c 3.4, CHCl3).

1H NMR (CDCl3, 300 MHz, ppm): δ = 0.04 (s, 9H, 3CH2), 0.99 (ddd, 2H, J = 9.1, 7.1, 1.0 Hz, CH2-Si), 1.30 (s, 3H, CH3), 1.48 (s, 3H, CH3), 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-O), 3.65 (ddd, 1H, J = 7.2, 3.3 Hz, H-6), 3.82 (dd, 2H, J = 2.5 Hz, CH2-Br), 4.19 (ddd, 2H, J = 9.2, 7.1, 1.0 Hz, CH2-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×H-Ar). 13C{1H} NMR (CDCl3, 75 MHz, ppm): δ = 3.4, CHCl3). 1H NMR (CDCl3, 300 MHz, ppm): δ = 8.0–8.1 (m, 13H, CH3 + CH2-CH3-CO), 3.05–3.19 (m, 1H, CH2-CO), 2.62 (dd, J = 9.5, 4.1 Hz, 2H, CH2-CO), 1.90–2.17 (m, 13H, CH3 + CH2-CH3-CO), 2.38–2.49 (m, 1H, CH2-CO), 2.62 (dd, J = 9.5, 4.1 Hz, 2H, CH2-CO), 2.89–3.04 (m, 1H, CH2-CO), 3.45 (s, 3H, OMe), 3.66 (s, 3H, OMe), 3.85 (dd, d, J = 9.8, 5.4 Hz, 1H, CH-N), 3.98–4.02 (m, 1H, CH-N), 4.08–4.22 (m, 1H, CH2-N + CH2-CO), 4.33 (q, J = 9.1, 8.6 Hz, 2H, CH2-N), 4.41—4.51 (m, 2H, CH2-CO), 5.00 (dd, d, J = 7.2, 4.3 Hz, 1H, CH-O), 5.12 (dd, d, J = 12.3, 16.7 Hz, 2H, CH2-Ar), 5.89 (d, J = 7.9 Hz, 1H, NH), 6.47 (d, J = 8.4 Hz, 1H, NH), 7.36 (s, 5H, CH2-Ar), 7.69 (d, J = 8.1 Hz, 1H, NH), 8.13–8.48 (m, 2H, CH2), 1H NMR (CDCl3, 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, 59.7, 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), 3073 (CH2), 1699 (C=O), 1645 (C=O), 1555 (C=O). HRMS (ESI+): m/z (M + Na)+ calc. for C30H45N3NaO11 546.3462. Found 546.3462.

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, 13C{1H}, 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
The authors declare no competing financial interest.

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