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5-Amino-5-deoxyshikimic Acid as a Versatile γ-Amino Acid for Peptidomimetic Synthesis

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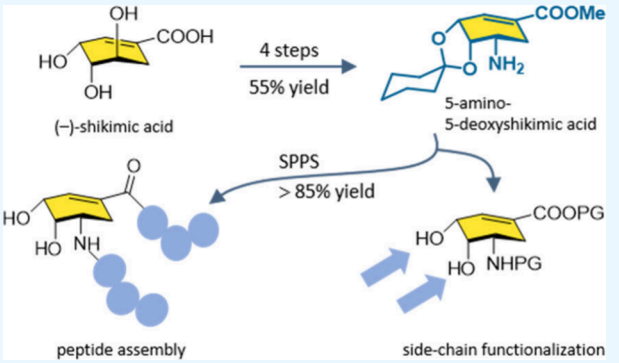
ABSTRACT: An efficient and scalable four-step synthesis of the 5-amino-5-deoxyshikimic acid derivative is described. This cyclic, unsaturated γ-amino acid was employed in both solution- and solid-phase peptide syntheses to afford products of high purity and yield. Furthermore, functionalization of the secondary hydroxyl groups was demonstrated, enabling systematic structural diversification and optimization of aminocarbasugar derivatives for potential applications in foldamer design, catalysis, and drug discovery.



INTRODUCTION

Among the diverse array of naturally occurring compounds, carbasugars occupy a unique position. These carbohydrate analogues feature the substitution of the endocyclic oxygen atom with a methylene group, a seemingly subtle modification that affords highly oxygenated cyclohexane or cyclopentane scaffolds, and their unsaturated counterparts, with enhanced resistance to enzymatic degradation.[1] Carbasugars are frequently encountered as structural subunits in diverse natural products, particularly those derived from bacterial sources. Representative examples include the α-amylase inhibitor acarbose and the α-glucosidase inhibitor voglibose, both clinically employed in the management of insulin-independent type II diabetes (Figure 1A).[2] The carbasugar (+)-pericosine A, a metabolite of *Periconia byssoides* OUPS-N133,[3] exhibits potent *in vivo* antitumor activity as an epidermal growth factor receptor (EGFR) inhibitor.[4] Inositol trisphosphate, an essential intracellular signaling molecule, also belongs to this class, whereas oseltamivir phosphate (Tamiflu), an anti-influenza agent, represents the most widely recognized carbasugar in current therapeutic use (Figure 1A). As nonhydrolyzable carbohydrate analogues, carbasugars are predominantly regarded as glycosidase inhibitors and have attracted considerable attention due to their therapeutic potential in cancer, viral infections, neurodegenerative disorders and autoimmune diseases. Artola et al. reported 1,6-epi-cyclophellitol cyclosulfamidate as a new class of reversible α-glucosidase inhibitors, offering a promising alternative to existing therapies for Pompe disease (Figure 1B).[5] Sollogoub et al. designed 1,3-glycosyl carbasugars that interact with GH99 endo-α-mannosidases through precise shape and charge mimicry of their natural substrates.[6] However, there are other areas of use for carbasugars, as yet only partially explored. Thus, screening for chiral ligands in asymmetric catalysis identified carbafructopyranosyl-1,2-diamine-derived salen ligands as highly effective for the hydrolytic kinetic resolution of 3-phenylpropylene oxide.[7] Berkowitz et al. demonstrated that the chiral environment of such ligands can be tuned by suppressing the anomeric effect and replacing carbohydrate frameworks with carbasugars, thereby enhancing chiral bias and catalytic performance (Figure 1B).

The transformation of stereochemically rich, enzymatically stable, and highly functionalizable carbasugar scaffolds into amino acid building blocks presents new opportunities for application in medicinal chemistry and catalyst development. However, synthetic methodologies for the preparation of polyhydroxylated cyclopentane and cyclohexane amino acids remain underdeveloped, and only a limited number of studies describe carbasugar-derived amino acids. González et al. reported the synthesis of polyhydroxylated 2-aminomethylcyclohexane carboxylic acids from shikimic acid (Figure 1C), together with a protocol for incorporating these γ-amino acids into tripeptides.[8] However, optimization of conventional peptide coupling protocols was required due to β-elimination associated with methyl ester deprotection under basic

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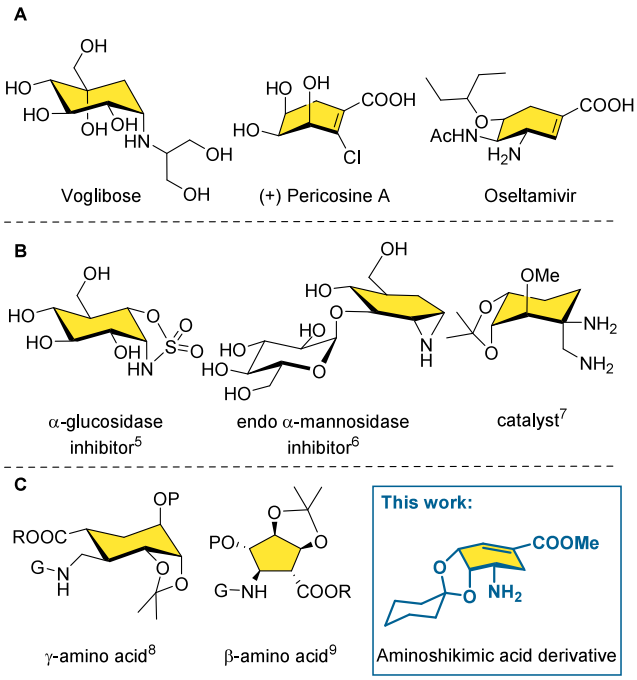


Figure 1. (A) Selective examples of carbasugar therapeutics. (B) Selective examples of carbasugars reported as glycosidase inhibitors and catalysts. (C) Carbasugar-derived amino acids.

conditions. More recently, Fernandez et al. prepared polyhydroxylated cyclopentane *β*-amino acids from D-mannose and D-galactose and evaluated their incorporation into short peptides.[9]

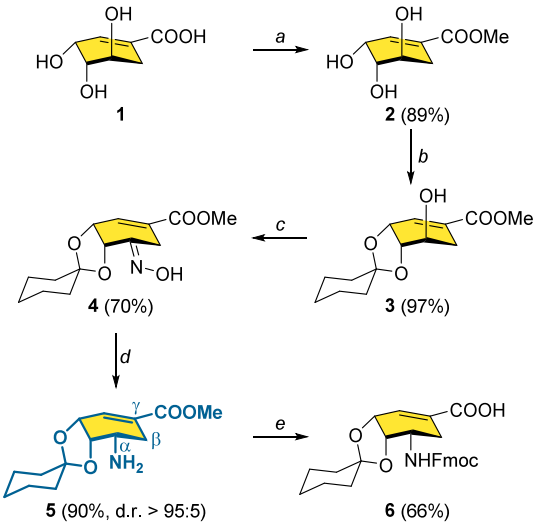
The growing demand for accessible and affordable non-proteinogenic amino acids has motivated us to focus on the synthesis of carbasugar-derived amino acids and peptides. The structural diversity and stereochemical complexity of carbasugars, when incorporated into amino acid frameworks, can promote a rich network of noncovalent interactions that underpin molecular recognition and binding, features highly sought after in both biological and catalytic systems. Furthermore, the presence of multiple hydroxyl functionalities provides versatile sites for derivatization, thereby enhancing the three-dimensional structural diversity and functional tunability of the resulting peptides.

In this study, we describe an efficient and scalable synthesis of an aminoshikimic acid (5-amino-5-deoxyshikimic acid, ASA) derivative suitable for peptide synthesis (Figure 1C). Aminoshikimic acid is an intermediate in the shikimate pathway,[10,11] an essential metabolic route by which microorganisms and plants produce the aromatic amino acids and a variety of other metabolites with diverse biological activities. ASA has been employed as an intermediate in the synthesis of aminocarbasugars[12] and serves as a promising alternative to shikimic acid as a starting material for the industrial production of Tamiflu.[13] Despite its importance, this *γ*-amino acid has been largely overlooked as a valuable building block in peptide chemistry. To promote its broader application, we report a concise, high-yielding four-step synthesis of an ASA derivative and demonstrate its successful incorporation into peptide frameworks using both solution-phase and solid-phase synthesis.

RESULTS AND DISCUSSION

Synthetic strategies for the synthesis of carbasugars can be broadly classified into two groups: the use of carbohydrates as precursors and synthesis from noncarbohydrate starting materials.[14,15] Moreover, polyhydroxylated natural compounds are also suitable precursors for carbasugar derivatives. Thus, we used commercially available (−)-shikimic acid (**1**) for the synthesis of its amino-derivative (Scheme 1). Initial

Scheme 1. Aminoshikimic Acid (ASA) Synthesis[a]



[a]Reagents and conditions: (*a*) Amberlite H^+, MeOH, 65 °C, 24 h; (*b*) cyclohexanone (5 equiv), *p*-TSA·H_2O (0.1 equiv), toluene, 115 °C, 4 h; (*c*) Dess-Martin periodinane (2 equiv), DCM, rt, 2 h, then NH_2−OH·HCl (5 equiv), pyridine, rt, 2 h; (*d*) MoO_3 (1.5 equiv), $NaBH_4$ (10 equiv), MeOH, 0 °C, 1 h; (*e*) 1 M NaOH (2 equiv), MeOH, 65 °C, 1 h, then Fmoc-OSu (1.1 eq), MeCN, rt, 2 h.

esterification with methanol under acidic conditions gave methyl ester **2** in 89% yield. Ester **2** has previously been prepared by esterification with methanol in the presence of $SOCl_2$,[16] and using oxone as a catalyst,[17] but here we chose an acidic ion-exchange resin, which can be easily removed from the reaction by filtration. Ketal protection of the diol functionality with cyclohexanone in the presence of *p*-toluenesulfonic acid monohydrate (*p*-TSA·H_2O) afforded protected intermediate **3** in 97% yield. Compound **3** has been previously utilized in the synthesis of (−)-pericosine E, a metabolite of the *Periconia byssoides* OUPS-N133 isolated from the sea hare *Aplysia kurodai*.[18] Oxidation of the secondary alcohol with Dess−Martin periodinane gave the corresponding ketone, which was smoothly converted *in situ* into the oxime **4** under mild conditions (70%). A similar transformation of secondary alcohols has been reported in the synthesis of Tamiflu from D-mannose.[12] Reduction of the oxime **4** with sodium borohydride in the presence of MoO_3[12] furnished the key derivative **5** with an installed C-5 amino group in excellent yield (90%) and diastereoselectivity (d.r. > 95:5). The overall yield of these four steps was 55%, and the protocol could be scaled up to 5 mmol without any loss of efficiency. Deprotection of the ester group with sodium hydroxide, followed by Fmoc protection of the amine group, afforded derivative **6** suitable for solid-phase peptide synthesis (SPPS) in 66% yield.

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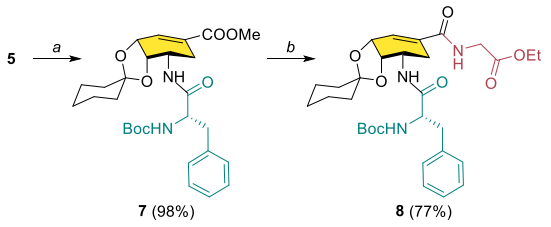
To evaluate the potential of ASA as a γ-amino acid scaffold in peptide synthesis, compound **5** was coupled with Boc-protected phenylalanine under BOP/HOBt conditions to afford dipeptide methyl ester **7** in excellent yield (98%). Subsequent saponification of the ester furnished carboxylic acid, which was then elongated with glycine ethyl ester to provide tripeptide **8** in a 77% yield. These two steps demonstrate the full compatibility of ASA with standard peptide coupling protocols (Scheme 2).

Scheme 2. Incorporation of Aminoshikimic Acid Derivative into Peptide Framework[a]



[a]Reagents and conditions: (*a*) Boc-Phe-COOH (1 equiv), BOP (1.2 equiv), HOBt (1.2 equiv), NMM (1.5 equiv), DCM, rt, 24 h; (*b*) 1 M NaOH (2 equiv), MeOH, 65 °C, 1 h; (*c*) HCl·NH_2-Gly-OEt (1.5 equiv), BOP (1.2 equiv), HOBt (1.2 equiv), NMM (1.5 equiv), DCM, rt, 24 h.

Backbone-expanded amino acids have been widely utilized in foldamers to access diverse helical architectures.[19] In contrast to β-amino acid–based systems, γ-amino acid incorporation remains less explored, representing only ∼7% of oligomers in the FoldamerDB database,[20] likely due to challenges in obtaining stereochemically pure building blocks.[21] Stereochemically defined and accessible ASA derivatives therefore offer a valuable potential for oligomer synthesis. To assess ASA's utility, we performed a solid-phase synthesis of two model heptapeptides containing ASA either at the N-terminus or at the fourth position of a leucine oligomer (Figure 2). Peptides were assembled on Wang–Leu–Fmoc resin using standard Fmoc-SPPS protocols. Cleavage with trifluoroacetic acid removed all protecting groups, affording peptides **9** and **10** in high crude yields (93% and 96%) and purities (87% and 89%), indicating efficient incorporation with minimal formation of side products. The crude peptides were purified by crystallization from methanol/diisopropyl ether.

NMR analysis confirmed efficient ASA incorporation. In peptide **10**, backbone expansion caused distinct perturbation of neighboring leucine proton shifts, with well-resolved amide NH signals enabling full backbone assignment. In contrast, N-terminal ASA incorporation resulted in a much smaller differentiation of the amide proton signals (Figure 3). Circular dichroism spectra of both peptides exhibited similar line shapes below 240 nm but differed in intensity (Figure 3), consistent with local conformational variations induced by ASA incorporation.

The polyhydroxylated scaffold of carbasugars and carbasugar-derived amino acids offers multiple sites for additional chemical modification. Functionalization of these hydroxyl groups with diverse substituents provides a versatile platform for generating structurally varied conjugates. To demonstrate this potential, the cyclohexyl protecting group in derivative **5** was removed under acidic conditions, followed by Boc protection of the amine to afford derivative **11** in 70% yield,

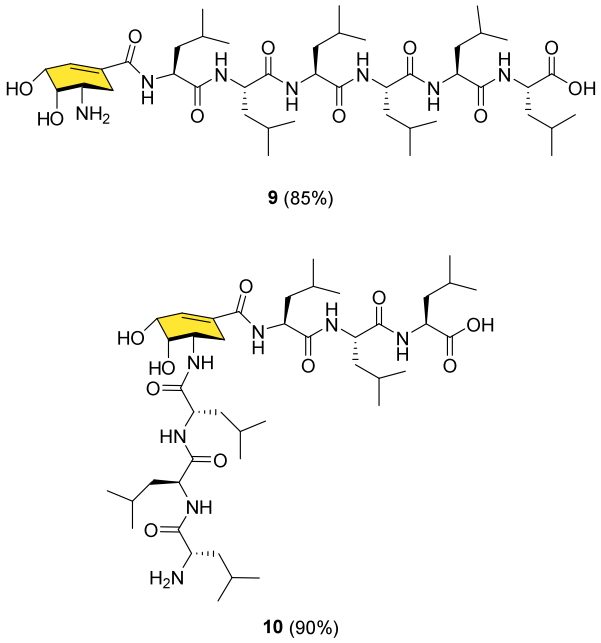


Figure 2. ASA-incorporated heptapeptides obtained by SPPS.

suitable for further derivatization at secondary hydroxyl sites. ASA derivative **11** was subsequently coupled with Cbz–Gly–COOH under BOP/HOBt activation in dichloromethane at room temperature, furnishing compound **12** in 64% yield. Reaction with 8-hydroxyoctanoic acid under similar conditions afforded compound **13** in a 13% yield (Scheme 3).

These "side-chain" modifications expand the chemical space of aminocarbasugars and enable the generation of structurally diverse molecular libraries for drug discovery. Furthermore, variation in hydroxyl substituents allows fine-tuning of key physicochemical properties, including solubility, charge distribution, and hydrogen-bonding capacity, thereby influencing pharmacokinetic and bioavailability profiles. The orthogonal protecting group patterns in compounds **12** and **13** also offer broad opportunities for subsequent site-selective functionalization in multiple directions.

CONCLUSIONS

In summary, we have established a highly efficient and scalable four-step synthesis of the 5-amino-5-deoxyshikimic acid (ASA) derivative. This cyclic, unsaturated γ-amino acid serves as a versatile and synthetically accessible building block for both solution- and solid-phase peptide synthesis, delivering products in high yields and purities. Moreover, the secondary hydroxyl groups provide a valuable handle for further functionalization, enabling structural diversification and fine-tuning of aminocarbasugar properties for applications in foldamer design, catalysis, and drug discovery.

EXPERIMENTAL SECTION

General Methods

Unless otherwise indicated, solvents were used as supplied (analytical or HPLC grade) without further purification. "Petrol ether" (PE) refers to the fraction of petroleum ether boiling in the range of 40–60 °C. Where mixtures of solvents are specified, the stated ratios are volume:volume. Unless otherwise indicated, all aqueous solutions used were saturated. Reagents were used directly as supplied by major chemical suppliers. Reactions were magnetically stirred and

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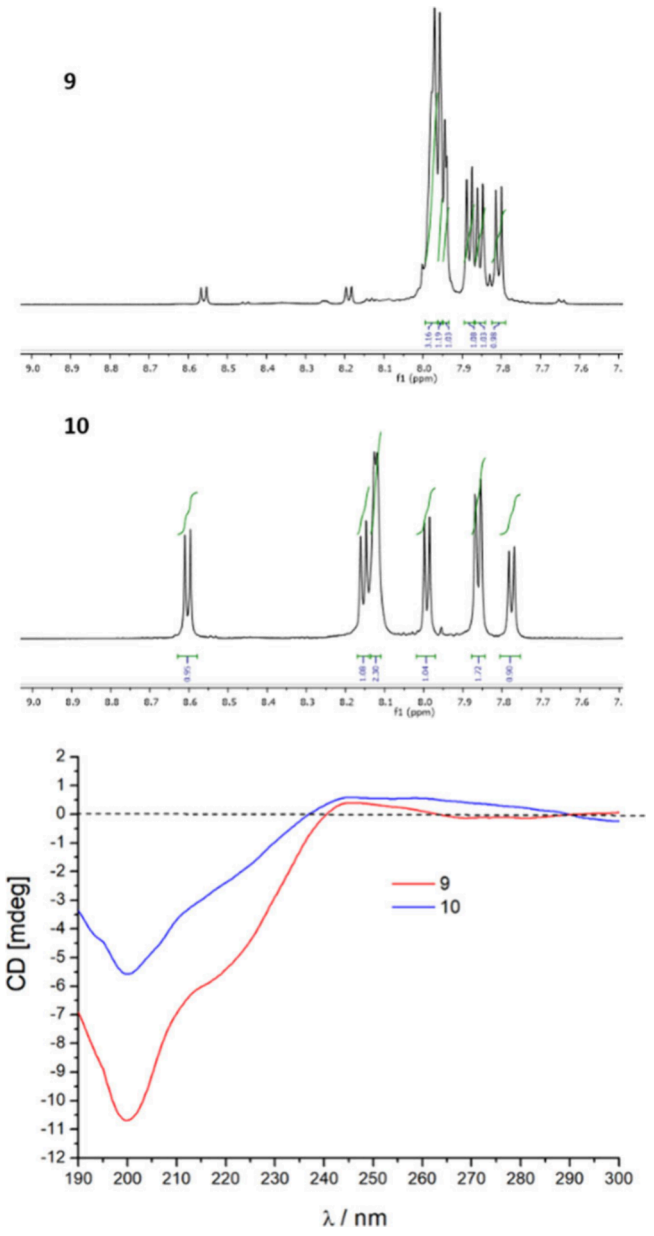
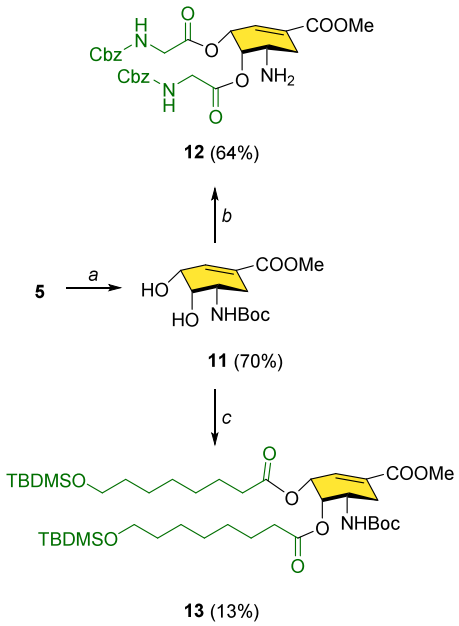


Figure 3. Amide part of the ^{1}H NMR spectra of peptides **9** and **10**, and their CD spectra.

monitored by analytical thin layer chromatography (TLC) performed on Merck Kieselgel 60 F254 0.25 mm precoated aluminum plates. After elution, the plate was visualized under UV illumination at 254 nm for UV active materials. Further visualization was achieved by staining with ceric ammonium molybdate (CAM) and charring on a hot plate. Compounds possessing free amino groups were detected by dipping them in a solution of ninhydrin. Flash column chromatography was performed on silica gel (Merck, 40−63 μm particle size) by standard techniques eluting with solvents as indicated. Melting points were determined on a Tottoli (Büchi) apparatus and are uncorrected. Optical rotations were measured at 25 °C using an Optical Activity LTD automatic AA-10 polarimeter.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 600 MHz spectrometer equipped with a room-temperature (RT) 5 mm PABBO probehead and a z-gradient accessory and on a Bruker Avance 300 MHz spectrometer equipped with a RT 5 mm BBO probehead and a z-gradient accessory. Chemical shifts are reported in parts per million and referenced to the solvent signal. Coupling constants (J) are given in Hz. HPLC-MS analysis was performed on a

Scheme 3. Hydroxyl Group Functionalization[a]



[a]Reagents and conditions: (*a*) 90% TFA in H_2O, rt, 1 h, then Boc_2O (1.5 equiv), TEA (2 equiv), DCM, rt, 24 h; (*b*) Cbz-Gly-COOH (4 equiv), BOP (2 equiv), HOBt (2 equiv), NMM (1.5 equiv), DCM, rt, 24 h; (*c*) TBDMSO-$(CH_2)_7$COOH (4 equiv), BOP (2 equiv), HOBt (2 equiv), NMM (1.5 equiv), DCM, rt, 48 h.

Shimadzu HPLC system Nexera XR coupled with a diode array detector (SPD-M40) and a single quadrupole mass spectrometer (LCMS-2020) operating in positive electrospray ionization (ESI) mode. High-resolution mass spectrometry (HRMS) was performed using a Shimadzu LCMS-9030. The method involved direct sample injection at a concentration of 10 pmol/μL, with dilution carried out using Optima LC/MS grade methanol (Fisher Chemicals). The mass spectrometry scan range was set from 250 to 1200 Da. The mobile phase consisted of Optima LC/MS grade methanol (Fisher Chemicals), with 0.1% formic acid (Fisher Chemicals) added.

CD spectra were recorded on a JASCO J815 spectrophotometer at room temperature using 0.01 cm path sandwich-type quartz cuvettes in the wavelength range 190−300 nm. The solvent background was subtracted from each spectrum. CD spectra were recorded from a 7×10^{-3} M solution in hexafluoro-isopropanol (HFIP, 1,1,1,3,3,3-hexafluoro-2-propanol).

Where given, systematic compound names are those generated by ChemBioDraw Ultra 12.0, following IUPAC conventions.

(3R,4S,5R)-Methyl 3,4,5-Trihydroxycyclohex-1-enecarboxylate (2). (−)-Shikimic acid (1 g, 5.74 mmol) was dissolved in a suspension of MeOH (20 mL) and Amberlite 120 H^+ (1.6 g). Reaction was stirred at 65 °C for 24 h. After all starting material has been consumed, the Amberlite was filtered off and filtrate was evaporated. Final compound was recrystallized from MeOH/Et_2O. Analytical data agree with those published in refs 16 and 17. Yield: 89% (0.964 g); white solid; mp 113 °C; R_f = 0.85 (EtOAc:EtOH:AcOH:H_2O = 7:1:1:1). ^{1}H NMR (300 MHz, MeOD) δ 6.80 (s, 1H), 4.39 (s, 1H), 4.01 (dd, J = 12.0, 5.2 Hz, 1H), 3.76 (s, 3H), 3.70 (dd, J = 7.0, 4.2 Hz, 1H), 2.78−2.65 (m, 1H), 2.22 (dd, J = 18.2, 5.1 Hz, 1H). ^{13}C NMR (151 MHz, MeOD): δ 167.9, 137.7, 128.8, 71.2, 66.9, 65.8, 50.9, 30.1.

(3aS,4R,7aR)-Methyl 4-Hydroxy-3a,4,5,7a-tetrahydrospiro-[benzo[d][1,3]dioxole-2,1′-cyclohexane]-6-carboxylate (3).[16] Compound **2** (1 g; 5.31 mmol), cyclohexanone (2.8 mL; 26.6 mmol; 5 equiv) and p-TSA (0.101 g; 0.53 mmol; 0.1 equiv) were dissolved in toluene (20 mL). Reaction was stirred at 115 °C for 4 h with a Dean−Stark apparatus for water extraction. After all starting material was consumed, the reaction was diluted with 10% aq.

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$NaHCO_3$ solution. Aqueous layer was extracted with DCM, dried over Na_2SO_4, filtered, and evaporated. Crude compound was purified by flash column chromatography with eluent PE:EtOAc = 1:1. Yield: 97% (1.37 g); yellow oil; R_f = 0.6 (PE: EtOAc = 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.94 (s, 1H), 4.75−4.71 (m, 1H), 4.09−4.05 (m, 1H), 3.93−3.88 (m, 1H), 3.77 (s, 3H), 2.79 (dd, J = 17.4, 4.6 Hz, 1H), 2.25 (d, J = 8.3 Hz, 1H), 2.22 (dd, J = 6.2, 1.6 Hz, 1H), 1.69−1.62 (m, 3H), 1.61−1.54 (m, 4H), 1.45−1.29 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 166.9, 134.5, 130.9, 110.8, 77.9, 72.2, 69.4, 58.8, 52.5, 38.2, 35.5, 29.7, 25.4, 24.4, 24.1, 18.8.

(3aS,7aR,E)-Methyl 4-(Hydroxyimino)-3a,4,5,7a-tetrahydrospiro[benzo[d][1,3]dioxole-2,1′-cyclohexane]-6-carboxylate (4). To a solution of compound **3** (0.5 g; 1.86 mmol) in dry DCM (20 mL) was added Dess-Martin periodinane (1.6 g; 3.73 mmol; 2 equiv) at rt for 2 h. The reaction was quenched by adding a saturated $Na_2S_2O_3$ solution followed by saturated $NaHCO_3$. The organic layer is extracted using DCM, and the combined fractions are collected and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude ketone was used in the following step without purification. To the crude ketone in EtOH (4 mL) was added hydroxylamine hydrochloride (0.646 g; 9.3 mmol; 5 equiv) followed by pyridine (2 mL). The reaction mixture was stirred at rt for 2 h. The solution was poured into water and extracted with DCM. The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude oxime was purified by PE:EtOAc = 9:1 to give the final product. Yield: 70% (361 mg); yellow oil; R_f = 0.75 (PE:EtOAc = 2:1); $[\alpha]_D$= +5.5° (c = 0.85, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.80−6.78 (m, 1H), 4.81 (td, J = 4.8, 2.3 Hz, 1H), 4.64 (d, J = 5.1 Hz, 1H), 3.81−3.78 (m, 3.5H), 3.76 (t, J = 1.6 Hz, 0.5H), 3.02 (dt, J = 21.7, 2.4 Hz, 1H), 1.65−1.55 (m, 9H), 1.41−1.33 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 166.5, 152.9, 136.1, 126.6, 111.2, 73.4, 73.1, 52.2, 37.7, 35.9, 24.9, 23.9, 23.8, 21.1. HRMS (ESI-TOF) m/z $[M + H]^+$: calcd for $C_{14}H_{20}NO_5$ 282.1341, found 282.1349.

(3aS,4R,7aR)-Methyl 4-Amino-3a,4,5,7a-tetrahydrospiro-[benzo[d][1,3]dioxole-2,1′-cyclohexane]-6-carboxylate (5). To a mixture of oxime **4** (0.361 g; 1.28 mmol) and MoO_3 (0.276 g; 1.92 mmol; 1.5 equiv) in MeOH (10 mL) at 0 °C was added $NaBH_4$ (0.485 g; 12.8 mmol; 10 equiv) portionwise. An exothermic reaction occurred with a vigorous gas evolution. The reaction mixture was stirred at room temperature for 1 h. To the reaction mixture was added brine, and the precipitate was filtered off over Celite. The filtrate was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give amine **5**. Yield: 90% (0.309 g); R_f = 0.8 (DCM:MeOH = 9:1); $[\alpha]_D$= +4.5° (c = 0.5, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.94 (s, 1H), 4.69−4.65 (m, 1H), 3.92 (dd, J = 7.8, 6.3 Hz, 1H), 3.76 (s, 3H), 3.04 (td, J = 8.4, 4.6 Hz, 1H), 2.71 (dd, J = 17.4, 4.4 Hz, 1H), 2.05 (dd, J = 17.4, 8.8 Hz, 1H), 1.66−1.52 (m, 9H), 1.46−1.33 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 167.1, 135.4, 130.0, 110.1, 76.1, 72.9, 52.0, 48.8, 37.4, 35.8, 28.8, 25.0, 24.1, 23.9. HRMS (ESI-TOF) m/z $[M + H]^+$: calcd for $C_{14}H_{22}NO_4$ 268.1549, found 268.1553.

(3aS,4R,7aR)-4-((((9H-fluoren-9-yl)methoxy)carbonyl)-amino)-3a,4,5,7a-tetrahydrospiro[benzo[d][1,3]dioxole-2,1′-cyclohexane]-6-carboxylic Acid (6). To a solution of compound **5** (0.324 g; 1.21 mmol) in MeOH (4 mL) was added 1 M NaOH (2.4 mL; 2.42 mmol; 2 equiv). The reaction mixture was stirred at solvent reflux (65 °C) until full consumption of starting material (1h). Reaction mixture was evaporated under reduced pressure. Final product was dissolved in H_2O (15 mL). pH was adjusted to 9 by adding 1 M HCl (initial pH was 12). Solution of Fmoc-OSu (0.450 g; 1.33 mmol; 1.1 equiv) in MeCN (5 mL) was added dropwise. Reaction mixture was stirred at room temperature for 2h with constant pH adjustment by addition of 1 M NaOH. After full consumption of starting material, pH was adjusted to 2 by adding 10% aqueous citric acid solution and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude compound was purified by flash column chromatography with eluent DCM:MeOH = 10:1. Yield: 66% (0.378 g); R_f = 0.52 (DCM:MeOH = 10:1); $[\alpha]_D$= +6.0° (c = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.78 (d, J = 7.5 Hz, 2H), 7.61 (d, J = 7.4 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.33 (t, J = 7.4 Hz, 2H), 6.87 (br s, 1H), 5.24 (d, J = 9.4 Hz, 1H), 4.76 (s, 1H), 4.50−4.41 (m, 2H), 4.35 (d, J = 3.8 Hz, 1H), 4.23 (t, J = 6.8 Hz, 1H), 4.04 (dd, J = 12.7, 7.8 Hz, 1H), 2.70 (dd, J = 16.6, 5.0 Hz, 1H), 2.29−2.21 (m, 1H), 1.63−1.54 (m, 6H), 1.52−1.46 (m, 2H), 1.39 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 165.3, 150.5, 138.5, 136.0, 132.0, 123.7, 122.4, 121.8, 119.7, 114.7, 105.4, 68.6, 67.3, 61.6, 42.9, 41.9, 32.0, 30.6, 19.8, 19.6, 18.7, 18.5. HRMS (ESI-TOF) m/z $[M + H]^+$: calcd for $C_{28}H_{29}NO_6$ 476.1995, found 476.2017.

(3aS,4R,7aR)-Methyl 4-((R)-2-((*tert*-Butoxycarbonyl)amino)-3-phenylpropanamido)-3a,4,5,7a tetrahydrospiro[benzo[d]-[1,3]dioxole-2,1′-cyclohexane]-6-carboxylate (7). Boc-Phe-COOH (0.04 g; 0.15 mmol) was dissolved in dry DCM (250 μL)) together with BOP (0.08 g; 0.18 mmol; 1.2 equiv), HOBt (0.024 g; 0.18 mmol; 1.2 equiv), and NMM (25 μL; 0.23 mmol; 1.5 equiv). Reaction was stirred for 15 min at room temperature when solution of compound **5** in dry DCM (250 μL) and NMM (25 μL; 0.23 mmol; 1.5 equiv) was added dropwise. Reaction mixture was stirred at room temperature for 24 h. Solvent was evaporated under reduced pressure, and crude compound was purified by flash column chromatography with eluent PE:EtOAc = 1:1. Yield: 98% (75 mg); R_f = 0.80 (PE: EtOAc = 1:1); $[\alpha]_D$= +2.5° (c = 0.78, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (t, J = 7.2 Hz, 2H), 7.27 (s, 1H), 7.22 (t, J = 10.7 Hz, 2H), 6.77 (s, 1H), 5.72 (d, J = 7.9 Hz, 1H), 5.08 (s, 1H), 4.31 (s, 1H), 4.23 (d, J = 6.8 Hz, 2H), 3.95 (t, J = 5.8 Hz, 1H), 3.75 (s, 3H), 3.07 (dd, J = 13.7, 6.2 Hz, 1H), 2.99 (dd, J = 13.7, 8.0 Hz, 1H), 2.70 (d, J = 17.2 Hz, 1H), 2.17 (d, J = 16.6 Hz, 1H), 1.65 (br s, 2H), 1.57−1.48 (m, 6H), 1.41 (s, 9H), 1.36 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 171.0, 166.5, 135.1, 129.3, 128.7, 127.1, 110.5, 73.3, 70.5, 60.4, 56.0, 52.1, 46.9, 38.7, 37.7, 35.5, 28.3, 24.9, 24.0, 23.8, 14.2. HRMS (ESI-TOF) m/z $[M + H]^+$: calcd for $C_{28}H_{39}N_2O_7$ 515.2757, found 515.2768.

Ethyl 2-((3aS,4R,7aR)-4-((R)-2-((*tert*-Butoxycarbonyl)amino)-3-phenylpropanamido)-3a,4,5,7a-tetrahydrospiro[benzo[d]-[1,3]dioxole-2,1′-cyclohexan]-6-ylcarboxamido) Acetate (8). To a solution of 7 (0.075 g; 0.15 mmol) in MeOH (4 mL) was added 1 M NaOH (300 μL; 0.3 mmol; 2 equiv). The reaction mixture was stirred at 65 °C until full consumption of starting material (1 h). Reaction solvent was evaporated under reduced pressure. Crude product (50 mg) was dissolved in dry DCM (250 μL) together with BOP (0.053 g; 0.12 mmol; 1.2 equiv), HOBt (0.016 g; 0.12 mmol; 1.2 equiv), and NMM (17 μL; 0.15 mmol; 1.5 equiv). Reaction was stirred for 15 min at room temperature, and then solution of HCl·NH_2-Gly-OEt (0.014 g; 0.1 mmol) in dry DCM (250 μL) and NMM (17 μL; 0.15 mmol; 1.5 equiv) was added dropwise. Reaction mixture was stirred at room temperature for 24 h. Solvent was evaporated under reduced pressure, and crude compound was purified by flash column chromatography with eluent EtOAc:PE = 3:1. Yield: 77% (45 mg); R_f = 0.65 (EtOAc:PE = 3:1); $[\alpha]_D$= +2.5° (c = 0.75, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (dd, J = 16.7, 9.3 Hz, 3H), 7.23 (t, J = 7.7 Hz, 2H), 6.46 (s, 1H), 6.41 (s, 1H), 6.08 (s, 1H), 5.25 (s, 1H), 4.32 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 4.14−4.10 (m, 1H), 4.06 (d, J = 5.1 Hz, 2H), 3.94 (t, J = 5.6 Hz, 1H), 3.06 (dd, J = 13.6, 6.4 Hz, 1H), 2.97 (dd, J = 13.5, 8.1 Hz, 1H), 2.66 (d, J = 16.1 Hz, 1H), 2.17 (dd, J = 17.1, 4.4 Hz, 1H), 1.72 (s, 3H), 1.54 (d, J = 13.2 Hz, 5H), 1.40 (s, 9H), 1.37 (br s, 2H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 171.3, 169.9, 167.0, 136.7, 129.9, 129.4, 128.7, 127.1, 110.4, 73.2, 70.4, 61.7, 60.4, 55.7, 41.6, 39.1, 37.7, 35.6, 28.3, 24.9, 24.0, 23.8, 21.0, 14.2, 14.1. HRMS (ESI-TOF) m/z $[M + H]^+$: calcd for $C_{31}H_{44}N_3O_8$ 586.3128, found 586.3142.

Solid-Phase Synthesis of Heptapeptides 9 and 10

Peptides were synthesized manually by standard Fmoc solid-phase peptide synthesis (SPPS) using Wang-Leu resin (0.8 mmol/g). Peptide chain assembly was performed by using a laboratory peptide shaker. The resin was first swollen in DCM (2 mL, 1 h) under gentle agitation, and excess solvent was removed by filtration. Fmoc deprotection was performed with 20% piperidine in DMF (2 × 1 mL, 30 min), followed by thorough washing of the resin with DMF (8

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× 1 mL) and DCM (5 × 2 mL). Coupling reactions were carried out with Fmoc-protected amino acids using HATU as the activating agent and NMM as the base in DMF (1−3 h) under an inert argon atmosphere. After each coupling, the resin was filtered and washed sequentially with DMF (8 × 1 mL) and DCM (5 × 2 mL). Upon completion of chain assembly, the peptide was cleaved from the solid support with 90% aqueous TFA (2 × 1 mL, 30 min). The cleavage mixture was filtered, and the filtrate was precipitated by addition of cold diisopropyl ether. Crude peptides were collected by centrifugation, washed with ether, and dried under vacuum. Further purification was performed by crystallization from methanol/diisopropyl ether,

ASA-Leu-Leu-Leu-Leu-Leu-Leu-OH (9). Yield: 85% (57 mg); white solid; mp = 286 °C (decomp.); t_R = 11 min (gradient elution 10−90% MeOH, λ=215 nm); $[\alpha]_D$= −2.7° (c = 1.0, DMSO). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.97 (s, 3H), 7.96 (s, 1H), 7.94 (d, J = 2.5 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 8.5 Hz, 1H), 6.33 (s, 1H), 4.34−4.32 (m, 1H), 4.31 (d, J = 2.3 Hz, 1H), 4.31−4.30 (m, 1H), 4.30−4.27 (m, 3H), 4.27−4.25 (m, 1H), 4.22−4.18 (m, 2H), 2.41−2.34 (m, 1H), 2.32−2.24 (m, 1H), 1.63−1.52 (m, 9H), 1.45−1.40 (m, 9H), 0.89−0.85 (m, 21H), 0.84−0.81 (m, 15H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 174.3, 172.6, 172.2, 172.0, 171.8, 166.9, 158.9, 158.6, 134.2, 130.2, 67.8, 67.2, 51.9, 51.3, 51.3, 51.0, 50.5, 49.0, 44.2, 41.3, 41.1, 41.0, 40.7, 40.5, 40.3, 40.2, 25.3, 24.8, 24.6, 24.5, 24.4, 24.3, 23.9, 23.6, 23.5, 23.4, 23.3, 23.2, 23.1, 23.0, 22.7, 22.5, 22.4, 22.3, 22.2, 22.1, 22.0, 21.9, 21.8, 21.7. HRMS (ESI-TOF) m/z $[M + H]^+$: calcd for $C_{43}H_{77}N_7O_{10}$ 852.5732, found 852.5749.

H-Leu-Leu-Leu-ASA-Leu-Leu-Leu-OH (10). Yield: 90% (130 mg); white solid; mp = 245 °C (decomp.); t_R = 10.1 min (gradient elution 10−90% MeOH, λ=215 nm); $[\alpha]_D$= −2.5° (c = 1.0, DMSO). ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.59 (d, J = 8.4 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 4.4 Hz, 2H), 7.98 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.1 Hz, 1H), 6.22 (s, 1H), 4.44−4.38 (m, 1H), 4.36−4.28 (m, 3H), 4.23 (s, 1H), 4.21−4.15 (m, 1H), 3.87−3.80 (m, 1H), 3.79−3.73 (m, 1H), 3.68−3.63 (m, 1H), 2.17 (d, J = 7.8 Hz, 2H), 1.64−1.56 (m, 6H), 1.55−1.38 (m, 12H), 0.90−0.85 (m, 22H), 0.83−0.79 (m, 12H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 174.3, 172.4, 172.3, 171.7, 171.5, 169.0, 167.4, 133.9, 132.0, 69.2, 68.6, 51.8, 51.4, 51.2, 51.1, 51.0, 50.5, 47.8, 44.2, 41.3, 41.2, 41.1, 40.8, 40.7, 26.7, 24.8, 24.6, 24.5, 24.4, 23.9, 23.6, 23.5, 23.4, 23.3, 23.2, 23.1, 23.0, 22.5, 22.3, 22.2, 21.9, 21.8, 21.7. HRMS (ESI-TOF) m/z $[M + H]^+$: calcd for $C_{43}H_{77}N_7O_{10}$ 852.5732, found 852.5743.

(3R,4S,5R)-Methyl 5-((*tert*-Butoxycarbonyl)amino)-3,4-dihydroxycyclohex-1-enecarboxylate (11). To compound **5** (309 mg; 1.16 mmol) was added 90% TFA (3 mL). The reaction mixture was stirred at room temperature until full consumption of starting material (1 h). Solvent was evaporated and crude product was dissolved in dry DCM (10 mL), and TEA (324 μL; 2.32 mmol; 2 equiv) was added followed by Boc_2O (400 μL; 1.74 mmol; 1.5 equiv). The reaction mixture was stirred at room temperature for 24 h. Solvent was evaporated under reduced pressure and crude product was dissolved in EtOAc and washed with water and saturated solution of NaCl. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude compound was purified by flash column chromatography with eluent DCM:MeOH = 9:1. Yield: 70% (234 mg); yellow oil; R_f = 0.85 (DCM:MeOH = 9:1); $[\alpha]_D$= −5.5° (c = 0.8, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.91 (s, 1H), 4.72 (d, J = 6.9 Hz, 1H), 4.36 (s, 1H), 3.95 (s, 1H), 3.75 (s, 3H), 3.65 (d, J = 9.7 Hz, 1H), 3.05 (s, 1H), 2.97−2.90 (m, 1H), 2.14−2.05 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 166.5, 146.5, 136.1, 130.9, 80.6, 72.7, 65.8, 53.4, 52.1, 47.9, 28.3. HRMS (ESI-TOF) m/z $[M + H]^+$: calcd for $C_{13}H_{22}NO_6$ 288.1447, found 288.1455.

(1S,2R,6R)-6-((*tert*-Butoxycarbonyl)amino)-4-(methoxycarbonyl)cyclohex-3-ene-1,2-diyl Bis(2-(((benzyloxy)carbonyl)amino)acetate) (12). Cbz-Gly-COOH (0.084 g; 0.4 mmol; 4 equiv) was dissolved in dry DCM (250 μL) together with BOP (0.088 g; 0.2 mmol; 2 equiv), HOBt (0.027 g; 0.2 mmol; 2 equiv), and NMM (17 μL; 0.15 mmol; 1.5 equiv). Reaction was stirred for 15 min at room temperature when solution of compound **11** in dry DCM (250 μL) and NMM (17 μL; 0.15 mmol; 1.5 equiv) was added dropwise. Reaction mixture was stirred at room temperature for 24 h. Solvent was evaporated under reduced pressure and crude compound was purified by flash column chromatography with eluent PE:EtOAc = 1:1. Yield: 64% (43 mg); R_f = 0.55 (PE:EtOAc = 1:1); $[\alpha]_D$ = +2.7° (c = 0.35, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36−7.29 (m, 10H), 6.61 (s, 1H), 5.73 (s, 1H), 5.51 (s, 1H), 5.34 (d, J = 5.4 Hz, 1H), 5.15−5.09 (m, 4H), 4.91 (d, J = 8.2 Hz, 1H), 3.95−3.85 (m, 4H), 3.77 (s, 4H), 2.75 (d, J = 13.1 Hz, 1H), 2.26−2.18 (m, 1H), 1.44 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 169.9, 168.8, 165.7, 156.8, 156.4, 154.9, 136.3, 135.9, 132.9, 131.8, 128.6, 128.5, 128.3, 128.2, 128.0, 70.1, 69.2, 67.4, 67.1, 52.2, 46.6, 42.8, 42.8, 28.3, 27.4. HRMS (ESI-TOF) m/z $[M + H]^+$: calcd for $C_{28}H_{32}N_3O_{10}$ 570.2088, found 570.2095.

(1S,2R,6R)-6-((*tert*-Butoxycarbonyl)amino)-4-(methoxycarbonyl)cyclohex-3-ene-1,2-diyl Bis(8-((*tert*-butyldimethylsilyl)oxy)octanoate) (13). TBDMSO-$(CH_2)_7$COOH (0.412 g; 1.5 mmol; 4 equiv) was dissolved in dry DCM (5 mL) together with BOP (0.336 g; 0.76 mmol; 2 equiv), HOBt (0.103 g; 0.76 mmol; 2 equiv), and NMM (63 μL; 0.57 mmol; 1.5 equiv). Reaction was stirred for 15 min at room temperature when a solution of compound **7** (0.115 g; 0.38 mmol) in dry DCM (5 mL) and NMM (63 μL; 0.57 mmol; 1.5 equiv) was added dropwise. Reaction mixture was stirred at room temperature fo 2 days. Solvent was evaporated under reduced pressure and crude compound was purified by flash column chromatography with eluent PE:EtOAc = 2:1. Yield: 13% (40 mg), R_f = 0.85 (PE:EtOAc = 2:1); $[\alpha]_D$= +1.5° (c = 0.5, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.61 (s, 1H), 5.56 (s, 1H), 5.06 (d, J = 8.7 Hz, 1H), 4.14 (s, 1H), 3.93 (d, J = 6.1 Hz, 1H), 3.75 (s, 3H), 3.61−3.57 (m, 4H), 2.68 (dd, J = 17.6, 5.1 Hz, 1H), 2.41−2.32 (m, 5H), 1.68−1.59 (m, 4H), 1.53−1.48 (m, 4H), 1.44 (s, 9H), 1.32 (s, 12H), 0.89 (s, 18H), 0.04 (s, 12H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 178.3, 172.6, 166.2, 155.5, 137.0, 133.7, 131.7, 80.0, 70.7, 68.2, 63.4, 63.4, 52.2, 48.5, 34.3, 33.9, 32.9, 32.8, 31.4, 29.2, 29.1, 29.0, 28.5, 27.9, 27.0, 26.1, 25.7, 24.9, 24.8, 18.5, −5.1. HRMS (ESI-TOF) m/z $[M + H]^+$: calcd for $C_{41}H_{78}NO_{10}Si_2$ 800.5164, found 800.5173.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are given in the Supporting Information. Raw NMR data are openly available in FULIR data at https://data.fulir.irb.hr/object/irb:856.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.6c00988.

NMR spectra of all synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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