Total Synthesis of a Conformationally Constrained Didemnin B Analog

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The total synthesis of a didemnin B analogue containing a conformationally constrained replacement for the isostatine moiety is reported. Synthetic highlights include an improved preparation of 2-hydroxy-3-cyclohexenecarboxylic acid and a new strategy for accessing the macrocycle.

Introduction

The didemnins, natural products isolated from a marine tunicate,[1] exhibit a variety of biological activities.[2] Most didemnins share a common 23-membered depsipeptide core and differ only in the side chains attached to the nitrogen of threonine.

Investigations of the mechanism of action of didemnin B (**1**) (Figure 1) have identified eEF-1α[3] and palmitoyl protein thioesterase[4,5] as binding proteins. The actions of didemnins A and B on protein biosynthesis in rabbit reticulocyte lysates were found to involve both eEF-1α and EF-2.[6,7] Didemnin B was reported to induce apoptosis in human cells (HL-60) at an extremely high rate.[8−10] Although these results are significant, the understanding of the mechanism of action of the didemnins is still evolving.

Constrained analogues may be used to probe the bioactive conformation of ligands as amply demonstrated by earlier research.[11,12] As the mode of action and biological receptors of the didemnins are still being investigated, a constrained analogue may serve the dual purpose of probing the bioactive conformation and of providing structural information about the protein−ligand complex. Although synthetic routes to a constrained analogue were previously investigated, a stereocontrolled total synthesis could not be achieved, and the resulting diastereomeric mixture could not be separated.[13] At the onset of this work, we realized that the low energy crystal structure of didemnin B[14] was an attractive target to mimic. Therefore, we designed a constrained analogue of didemnin B (**2**, Figure 2) to probe whether the crystal structure was related to the bioactive conformation. In the macrocycle salt of **1**, which is inactive,[15] the isostatine region differs considerably from that of the solid-state structure of didemnin B. Our interest focused on the isostatine portion of the molecule, because the constrained fragment could also be useful to examine the role of β-hydroxy-γ-amino acids present in several bioactive natural products.

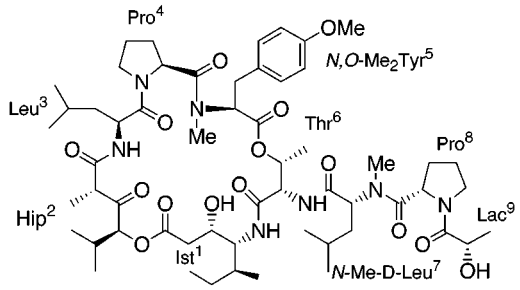

Figure 1. Structure of didemnin B (**1**).

Results and Discussion

The design of an isostatine constrained analogue utilized the X-ray structure of didemnin B as the starting point.[14] The dihedral angles of the isostatine fragment derived from the X-ray structure of didemnin B were matched with those of a hydroxycyclohexane amino acid (**3**) with the stereochemistries shown in Figure 3.

The resulting constrained didemnin B analogue (**2**, Figure 4) was investigated by molecular modeling techniques. Using a combination of MM2 force field mechanics as well as molecular dynamics, a minimized structure of the constrained analogue was obtained. As a control, calculations using Macromodel v3IX and Molecular Dynamics showed no major differences in energy for didem-

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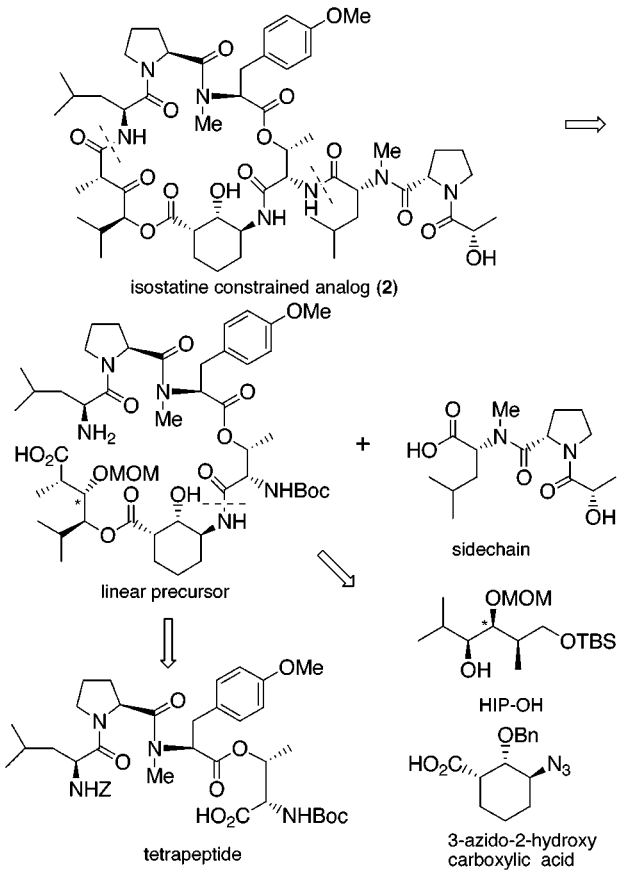


Figure 2. Initial retrosynthesis of the isostatine-constrained analogue (**2**).

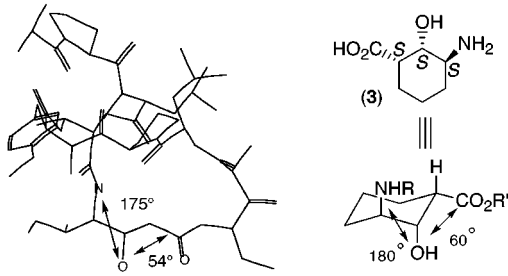
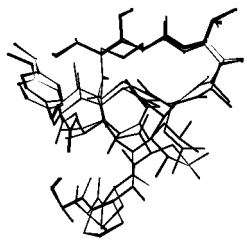


Figure 3. Dihedral angles of the isostatine fragment and hydroxycyclohexane amino acid (**3**).



Dihedral Angles	1	2
ester-hydroxy	54	58
hydroxy-amide	175	172

Figure 4. Comparison of the dihedral angles in didemnin B and the proposed analogue.

nin B,[16] which supports the calculations obtained for the constrained analogue. The minimized structure overlapped well with the X-ray structure of **1**. The calculated dihedral angles of didemnin B and the analogue were well matched. Remarkably, when the other seven possible stereoisomers of the proposed cyclohexane amino acid were incorporated into **1**, none of their minimized structures gave a good overlay with the X-ray structure of **1**. Both chemical intuition and molecular modeling seemed to indicate that this analogue was a good representation of the crystal structure of didemnin B. It is important to note the different configuration at the amine center, which is *S* in the analogue and *R* in didemnin B. This modification is the only way to preserve the conformation of isostatine in the constrained analogue. However, by doing so, the *sec*-butyl moiety was deleted from the proposed analogue for synthetic feasibility. Based on the structure−activity relationships of the didemnins, this modification was believed to have only a minor effect on the biological activity of didemnins.[2]

The initial retrosynthetic analysis (Figure 2) was designed according to the strategy previously developed in our group.[17] The first disconnection was made between the macrocycle and the side chain. Macrocyclization would take place between the Hip acid and the leucine amino group. An important feature of the previous synthesis was the preservation of the β-ketoamide as a protected Hip unit in order to control the stereochemistry of the methyl group located between two carbonyls. The acidity of the proton of the activated keto ester and that of a protonated tertiary amine (which are typical acid scavengers in peptide coupling) are within 2 orders of magnitude. During the long reaction time needed under high dilution cyclization, epimerization of the methyl group was a possibility. Therefore, the length of the synthesis of the Hip unit was justified due to the necessity to secure a stereoselective synthesis. The next disconnection was made between the cyclohexane amine and the known tetrapeptide acid.[17] The lower portion of the molecule was further disconnected through the ester bond to give the known Hip alcohol (Hip-OH) and a fully protected 3-azido-2-hydroxycarboxylic acid.

The major challenge in the synthesis of **2** was to develop an efficient preparation of the proposed (*S*,*S*,*S*)-β-hydroxy-γ-aminocyclohexanecarboxylic acid (**3**, Figure 3).

The synthesis of the desired cyclohexane amino acid began with an auxiliary type Diels−Alder reaction to afford an enantiomerically pure cyclohexene intermediate, which could be manipulated further. Thus, the camphorsultam[18] derived dienophile **4** reacted with an oxygenated diene, 1-acetoxy-1,3-diene, available as a mixture (6:4 ratio, trans:cis). Initial thermal conditions in refluxing toluene nonselectively gave several products (**5**:**5a**:**5b** = 48%:10%:30%) whose structures were characterized by NMR and X-ray crystallography (Scheme 1).[19,20] Attempts to use Lewis acids such as $TiCl_4$ to increase the diastereoselectivity were hampered by the sensitive diene's propensity to polymerize. However, it was found that the desired Diels−Alder reaction could be effected in 4 M lithium perchlorate in ether.[21] Two products were isolated in a ratio of 96:4, in which the

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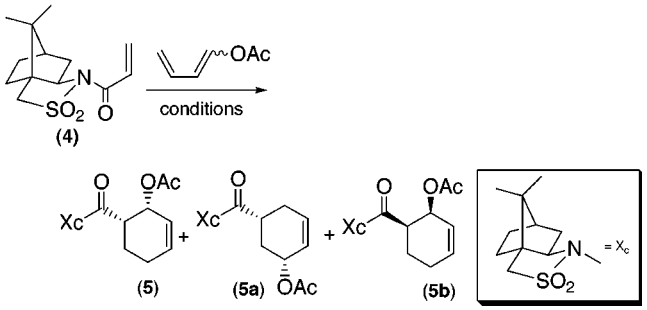
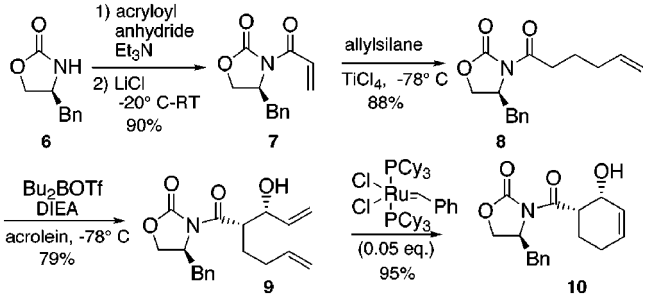
Scheme 1



Scheme 2



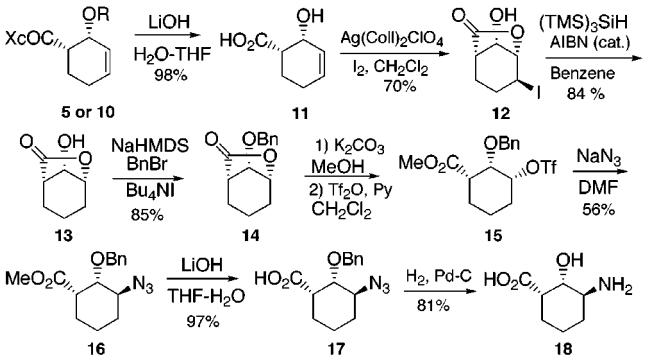
desired endo product **5** predominated with a yield of 82% based on the recovered starting material. No exo product was detected but the minor isomer was identified to be an endo 1,3-regioisomer **5a**.

Although the Diels−Alder reaction was successful, there were two significant drawbacks. The large scale use of lithium perchlorate caused safety concerns, particularly in light of the long reaction time of 10 days to two weeks required to complete the reaction. An attempt to use a catalytic amount of lithium perchlorate as reported by Reetz et al. did not give a good yield.[22] Therefore, an alternative route was sought to provide the desired intermediate (Scheme 2).

We adopted an aldol-metathesis protocol developed by Crimmins and co-workers.[23] An oxazolidinone derived unsaturated imide **7** was chosen as a precursor to the aldol substrate. Compound **7** was synthesized by converting the Evans auxiliary **6** to the corresponding acryloyl derivative.[24] Compound **7** was subjected to a titanium tetrachloride mediated Sakuri reaction to afford the elongated aldol substrate (**8**).[25] The standard aldol conditions[26] afforded diene **9** with excellent stereoselectivity in 79% yield. The cyclohexene ring was then closed (**10**) using Grubbs catalyst to effect the diene metathesis in high yield.[27]

The products from the Diels−Alder reaction or from the aldol-metathesis approach (**5** and **10**) were hydrolyzed to give the corresponding hydroxy acid **11** in nearly quantitative yield (Scheme 3). Introduction of the γ-azido group began with an iodolactonization reaction. Surprisingly, treatment of the hydroxy acid under normal

Scheme 3



conditions, such as Na_2CO_3 or NaH with iodine, did not give rise to the desired transformation. We attributed this lack of reactivity to an intramolecular hydrogen bond between the acid and hydroxyl groups. Using a more reactive electrophilic iodine species, iodonium biscollidine perchlorate,[28] we obtained the desired iodolactonization product **12** in 70% yield (Scheme 3).

Subsequently, the iodine was removed under radical conditions using tris(trimethylsilyl)silane,[29] and the resulting hydroxy group of **13** was then protected as its benzyl ether **14** in 84% yield. The lactone was subjected to transesterification with methanol and K_2CO_3 to free the γ-hydroxyl group. However, very dilute potassium carbonate was required to prevent epimerization of the resulting ester, and under these conditions, methanolysis was incomplete. In addition, the ester was unstable on silica gel and reverted to lactone **14**. Therefore, a mixture of hydroxy ester and starting material was used without purification in the next steps. Inversion of the γ-hydroxyl group with azide was chosen to introduce the nitrogen functionality. The reagents DPPA or $Zn(N_3)_2Py_2$ under Mitsunobu conditions did not afford a product. As the corresponding mesylate was not effectively displaced by azide ion even at elevated temperature, we synthesized a triflate (**15**) which, when subjected to sodium azide in DMF, gave the desired product (**16**) in 56% yield.

With the functionalities and desired stereochemistries secured, synthesis of the required amino acid proceeded uneventfully. The methyl ester **16** was hydrolyzed to afford the corresponding free acid **17** in 97% yield. The stereochemistry of the azido acid was confirmed by an X-ray crystal structure analysis. Subsequently, **17** was treated with hydrogen and Pd on carbon to yield the corresponding amine and to deprotect the β-hydroxyl group in one step to afford **18** in 81% yield (Scheme 3).

The synthesis of the Hip-azidocyclohexane ester fragment utilized a protocol which was developed in the synthesis of **1**.[17] The initial coupling between the protected Hip-OH and **17** was conducted under a variety of standard coupling conditions. Unfortunately, DCC−DMAP, acid chloride, mixed trichlorobenzoic anhydride, 1-methyl-2-chloropyridinium iodide, and tributylamine all failed to give a useful yield of the desired product.

Realizing that the steric demands of both the acid and the alcohol were exceedingly high, we decided to modify the steric environment around the hydroxyl group of the Hip-OH (Scheme 4) by replacing the MOM-protected hydroxyl group with the *epi*-Hip-OH (**22**). As mentioned

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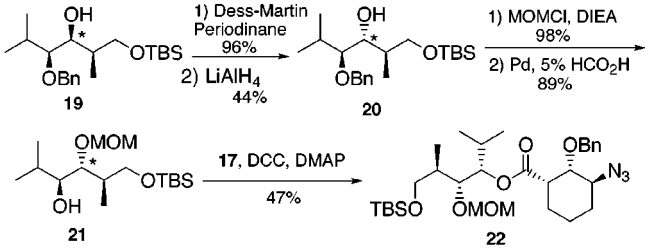
Scheme 4



in the retrosynthetic analysis, oxidation to the ketone was one of the last transformations planned after macrocycle ring closure. Protection of this center as a MOM ether was intended to prevent epimerization during cyclization. Therefore, the chirality of the starred center was irrelevant and a change of stereochemistry might lead to conformational changes and steric reduction of the alcohol substrate. The desired *epi*-Hip alcohol (**22**) was prepared by oxidation of Hip alcohol (**19**) and subsequent reduction of the resultant ketone with $LiAlH_4$ to give alcohol **20**. This alcohol was protected with MOMCl, and the benzyl protecting group was then removed. This intermediate **21** could then be coupled with **17** to give a reasonable 47% yield of the desired product (**22**) (Scheme 4). The strikingly different reactivity between the two epimeric alcohols was not completely understood. It appeared that subtle steric match-up of alcohol substrates with the cyclohexane acid played a role.

In an attempt to understand the different reactivities of the epimeric alcohols, calculations using the CAChe 3.8 program[30] suggested a possible reason. Molecular dynamics simulation of the two alcohols using default parameters gave three stable conformers for the bonds examined. Three Newman projections corresponding to these three conformers can be identified (Figure 5). Of

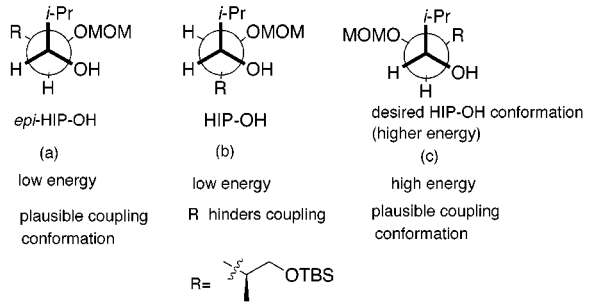
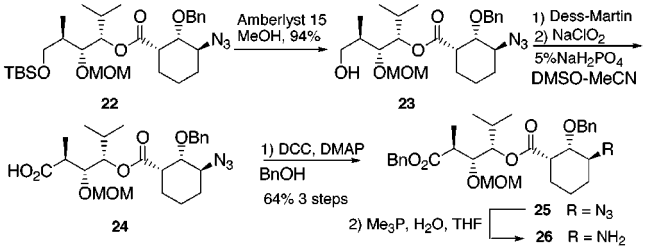


Figure 5. Newman projections of (a) most favorable conformation of *epi*-OH; (b) same conformation of Hip-OH; (c) desired Hip-OH conformation for activated ester attack.

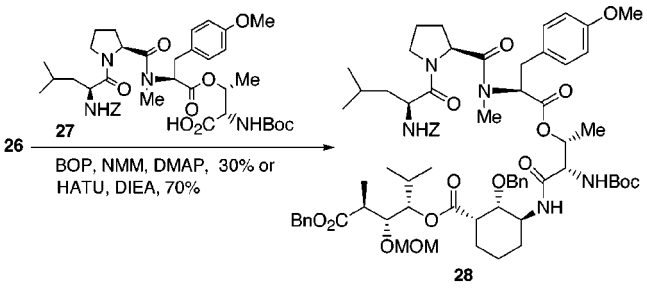
these, the most stable conformation should be the one in which hydrogen bonding between the hydroxyl group and the OMOM group is possible, which occurs when they are in a gauche conformation. Examination of molecular models indicated that for the incoming activated ester to approach the hydroxyl group, it had to avoid the bulky isopropyl and OMOM groups. Figure 5 shows the two preferred conformations, when the hydroxyl group and the OMOM group are in a gauche arrangement. While in the case of the *epi*-Hip alcohol there is room for the approach of the activated ester, the same conformation in the Hip-alcohol shows the hydroxyl group to be sterically hindered.

The next target for the new synthetic strategy required a benzyl-protected azido ester which was obtained as shown in Scheme 5.

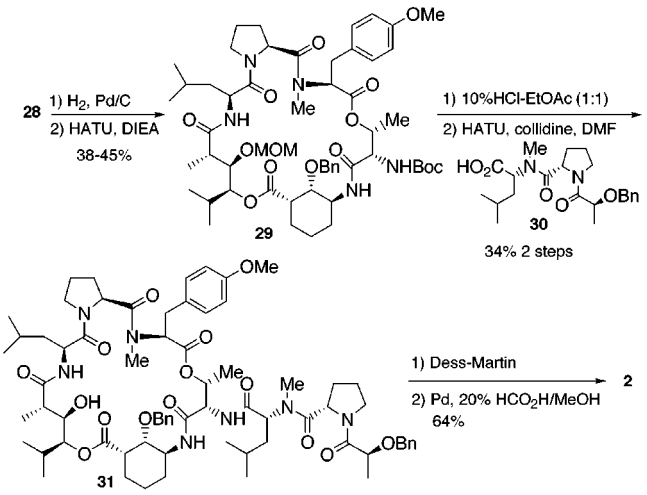
Scheme 5



Scheme 6



Scheme 7



The TBS ether of **22** was removed using Amberlyst 15 to give primary alcohol **23** in 94% yield. This alcohol was subjected to a two-step oxidation protocol: Dess−Martin reagent[31] to convert it to the corresponding aldehyde, followed by a chlorite oxidation[32] to the carboxylic acid **24**. The acid was then esterified with DCC−DMAP and benzyl alcohol to afford the desired benzyl ester (**25**). The azide was reduced to the amine (**26**), using trimethyl phosphine with 2 equiv of water in THF.[33] The amine (**26**) was subsequently coupled with the known tetrapeptide acid[17] (**27**) using HATU to afford the desired coupled product (**28**) in 70% yield (Scheme 6).

With the linear precursor (**28**) in hand, palladium-catalyzed hydrogenation cleanly removed both the benzyloxycarbonyl group and the benzyl ester leaving the cyclohexyl benzyl ether intact (Scheme 7). The amino acid was then cyclized to **29**, using HATU at 0.01 M concentration in 38−45% yield. The macrocycle (**29**) was then

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treated with 10% HCl (aq)−ethyl acetate solution (1:1) to removed both the MOM and Boc protecting groups. The free amine was coupled to a benzyl-protected side chain (**30**) to yield **31**. Subsequent oxidation of **31** by Dess−Martin reagent converted the macrocyclic hydroxyl group to the ketone. Finally, the deprotection of both benzyl ether groups was realized by using 2 equiv of palladium black in 20% formic acid in methanol to afford the desired isostatine-constrained didemnin B analogue (**2**, Figure 2).

The constrained analogue (**2**) was tested for protein biosynthesis inhibition. The assay was conducted in a rabbit reticulocyte lysate.[7] The constrained analogue has an IC_{50} of 99 mM, which is about 20-fold less than didemnin B (IC_{50} = 4.4 mM) in the same assay.

Conclusions

An analogue of **1** in which the isostatine moiety was replaced by a (*S*,*S*,*S*)-β-hydroxy-γ-aminocyclohexanecarboxylic acid (**3**) was synthesized to probe the biological conformation of didemnin B. The synthesis of this analogue (**2**) used an alternative strategy which resulted in a shorter and more efficient approach to the analogue macrocycle. Although changes in the side chains[2,34−36] and in the tyrosine residue[37,38] of **1** resulted in analogues with equal or superior bioactivity to that of the parent compound, changes in the isostatine region reduced the protein biosynthesis inhibition activity. This decrease in potency suggests that the bioactive conformation of **1** may differ from its crystal structure in the isostatine region.

Experimental Section

Acetic Acid (6*S*)-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0.^{1,5}]decane-4-carbonyl)-(1*R*)-cyclohex-2-enyl Ester (5). Method A: To a round-bottomed flask was added anhydrous lithium perchlorate (Aldrich) (51 g, 0.48 mol). The flask was heated at 120 °C under reduced pressure with vigorous stirring for 8 h. The flask was then cooled, and a stream of argon was introduced, followed by addition of 120 mL of freshly distilled ether (Fisher) via a syringe. The mixture was stirred for 1 h. At that time lithium perchlorate dissolved to afford a clear solution. To this solution was introduced sultam **3** (5.9 g, 22 mmol). After stirring for 20 min, freshly distilled acetoxy-1,3-diene (12.3 g, 109 mmol) was introduced through a syringe. The mixture was allowed to stir under argon for 10 days. The mixture was diluted with 600 mL of EtOAc and washed with 200 mL saturated NaS_2O_3 solution and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography using 10−20% EtOAc/petroleum ether gradient yielded starting material (0.885 g) and the title compound **5** (5.81 g, 82% based on the recovered starting material) as well as the minor product **5a** (0.213 g, 3%).

Method B: A round-bottomed flask under argon was charged with freshly distilled toluene (4.6 mL) followed by addition of sultam **3** (124.5 mg, 0.46 mmol) and acetoxy-1,3-diene (260.0 mg, 2.3 mmol). The solution was heated under reflux for 6 h. The solvent was evaporated and the residue was chromatographed using 10−20% EtOAc−petroleum ether to afford **5** (84.6 mg, 48%), **5a** (17.6 mg 10%), and **5b** (52.7 mg, 30%) all as colorless crystals.

5: mp 188−190 °C; R_f 0.40 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (m, 1H), 5.87 (m, 1H), 5.61 (m, 1H), 3.89 (dd, J = 7.5, 5.0 Hz, 1H), 3.42 (d, J = 14.0 Hz, 1H), 3.34 (d, J = 14.0 Hz, 1H), 3.27 (m, 1H), 2.25 (m, 1H), 2.06−1.69 (m, 8H), 1.99 (s, 3H), 1.38 (m, 2H), 1.15 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 170.3, 133.5, 123.6, 66.6, 65.1, 53.1, 48.3, 47.8, 44.7, 44.6, 37.8, 32.8, 26.6, 24.6, 21.0, 20.4, 19.9, 18.8; IR(neat) 1734, 1700, 1238 cm^{-1}; HRMS *m*/*z* calcd for $C_{19}H_{31}N_2O_5S$ (M + NH_4): 399.1954, found 399.1967; $[\alpha]_D^{20}$ −244 (*c* = 2.25, $CHCl_3$). Anal. Calcd for $C_{19}H_{27}NO_5S$: C, 59.82; H, 7.13; N, 3.67. Found: C, 60.17; H, 7.08; N, 3.32.

Acetic acid (5*R*)-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo [5.2.1.0.^{1,5}] decane-4-carbonyl)-(1*S*)-cyclohex-2-enyl ester (5a): mp 136−138 °C; R_f 0.37 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.58 (m, 1H), 5.40 (m, 1H), 3.81 (dd, J = 7.6, 5.0 Hz, 1H), 3.41 (d, J = 14.0 Hz, 1H), 3.36 (d, J = 14.0 Hz, 1H), 3.22 (m, 1H), 2.39 (m, 1H), 2.19 (m, 1H), 2.04 (m, 1H), 1.96 (m, 5H), 1.81 (m, 4H), 1.30 (m, 2H), 1.04 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 170.5, 128.4, 127.3, 69.6, 65.1, 53.0, 48.4, 47.8, 44.6, 39.4, 38.4, 32.8, 29.5, 29.0, 26.4, 21.2, 20.8, 19.8; IR (neat) 2959, 1727, 1696, 1331, 1239; HRMS *m*/*z* calcd for $C_{19}H_{31}N_2O_5S$ (M + NH_4): 399.1954, found 399.1946; $[\alpha]_D^{20}$ −7 (*c* = 1.5, $CHCl_3$).

Acetic acid (6*R*)-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0.^{1,5}]decane-4-carbonyl)-(1*S*)-cyclohex-2-enyl ester (5b): mp 189−191 °C; R_f 0.26 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (m, 1H), 5.79 (m, 1H), 5.74 (m, 2H), 3.89 (dd, J = 7.6, 5.1 Hz, 1H), 3.51 (d, J = 2.2 Hz, 2H), 3.34 (m, 1H), 2.23−2.09 (m, 5H), 1.96−1.84 (m, 4H), 1.47 (m, 1H), 1.37 (m, 1H), 2.08 (s, 3H), 1.19 (s, 1H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 171.1, 132.7, 124.8, 66.0, 65.4, 53.5, 48.8, 48.2, 45.1, 43.9, 39.0, 33.2, 26.8, 24.8, 21.8, 21.7, 21.5, 20.3; IR (neat) 1734, 1699, 1329,-1239 cm^{-1}; HRMS *m*/*z* calcd for $C_{19}H_{27}NO_5SNa$ (M + Na): 404.1507, found 404.1512; $[\alpha]_D^{20}$ +38.0 (*c* = 1.61, $CHCl_3$).

(4*S*)-3-(1-Acryloyl)-4-benzyl-2-oxazolidinone (7). To a solution of acrylic acid (0.634 mL, 9.2 mmol) in 30 mL of THF at −20 °C was added triethylamine (2.39 mL, 17.1 mmol) followed by acryloyl chloride (0.7 mL, 8.6 mmol). The mixture was stirred at that temperature for 2 h. LiCl (0.336 mg, 7.9 mmol) was added followed by oxazolidinone **6** (1.17 g, 6.6 mmol). The mixture was allowed to warm to room temperature and stirred for 8 h. The reaction was quenched by addition of 0.2 N HCl, and THF was removed in vacuo. The residue was partitioned between EtOAc and 0.2 N HCl. The organic layer was washed with half-saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography using 5−20% petroleum ether/EtOAc yielded the title compound as colorless crystals (1.375 g, 90%). **7:** mp 73−74 °C; R_f 0.46 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (m, 1H), 7.44−7.30 (m, 5H), 6.68, (dd, J = 17.1, 1.8 Hz, 1H), 6.00 (dd, J = 10.6, 1.8 Hz, 1H), 4.80 (m, 1H), 4.26 (m, 2H), 3.39 (dd, J = 13.4, 3.3 Hz, 1H), 2.85 (dd, J = 13.5, 9.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 153.3, 135.2, 131.8, 129.4, 129.0, 127.45, 127.38, 66.2, 55.2, 37.8; HRMS *m*/*z* calcd for $C_{13}H_{14}NO_3$ (M + H): 232.0974, found 232.0970; $[\alpha]_D^{20}$ +79.6 (*c* = 1.14, $CHCl_3$).

(4*S*)-3-(1-Oxo-5-hexenyl)-4-benzyl-2-oxazolidinone (8). To a solution of oxazolidinone **7** (1.1 g, 4.76 mmol) in 20 mL of CH_2Cl_2 at −78 °C was added $TiCl_4$ (1 M in CH_2Cl_2, 6.7 mL, 6.7 mmol). After stirring the mixture for 10 min, allyltrimethylsilane (2.48 mL, 14.3 mmol) was added to the dark-brown solution. The mixture was stirred at −78 °C for 3 h and then poured into a saturated $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with ether (25 mL × 3). The combined organic layers were washed

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with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography using 0−10% EtOAc/petroleum ether yielded the title compound as a colorless oil (1.144 g, 88%). **8:** R_f 0.51 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.19 (m, 5H), 5.79 (m, 1H), 5.03−4.94 (m, 2H), 4.62 (m, 1H), 4.11 (m, 2H), 3.23 (dd, J = 13.5, 3.3 Hz, 1H), 2.94−2.81 (m, 2H), 2.69 (dd, J = 13.5, 9.3 Hz, 1H), 2.08 (m, 2H), 1.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 153.5, 137.8, 135.3, 129.4, 129.0, 127.4, 115.3, 66.2, 55.1, 37.9, 34.8, 33.0, 23.4; IR (neat) 3064, 3029, 1772, 1700, 1640 cm^{-1}; HRMS m/z calcd for $C_{16}H_{20}NO_3$ (M + H): 274.1443, found 274.1432; $[\alpha]_D^{20}$ +58.7 (c = 1.08, $CHCl_3$).

(2*S*,3*R*,4*S*)-3-(3-Hydroxy-2-allyl-1-oxo-5-hexenyl)-4-benzyl-2-oxazolidinone (9). To a solution of oxazolidinone **8** (1.0 g, 3.66 mmol) in 9 mL of CH_2Cl_2 at −15 °C was added dropwise Bu_2BOTf (1 M in CH_2Cl_2, 4.03 mL, 4.03 mmol) followed by dropwise addition of triethylamine (0.612 mL, 4.39 mmol). The solution was stirred at 0 °C for 15 min and then cooled to −78 °C. The freshly distilled acrolein (0.269 mL, 4.03 mmol) was then added through a syringe. After stirring at −78 °C for 2 h, the mixture was allowed to warm to 0 °C for 30 min. Then a pH 7 buffer (6 mL) was added, followed by 20 mL of MeOH and dropwise addition of 6 mL of 30% hydrogen peroxide while maintaining the temperature at 0 °C. After stirring for 1 h, the mixture was concentrated and extracted with EtOAc (20 mL × 4). The organic layer was washed with 20 mL of 10% $NaHSO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Further column chromatography using 5−20% EtOAc/petroleum ether yielded the title compound as a colorless oil (0.95 g, 79%). **9:** R_f 0.37 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.20 (m, 5H), 5.89 (m, 1H), 5.78 (m, 1H), 5.30 (dd, J = 17.2, 1.4 Hz, 1H), 5.20 (d, J = 10.5 Hz, 1H), 4.98 (m, 2H), 4.70 (m, 1H), 4.38 (dd, J = 9.4, 4.8 Hz, 1H), 4.18−4.12 (m, 3H), 3.35 (dd, J = 13.3, 3.3 Hz, 1H), 2.68 (dd, J = 13.2, 10.1 Hz, 1H), 2.31 (d, J = 3.5 Hz, 1H), 2.10 (dd, J = 14.5, 7.1 Hz, 2H), 1.98−1.90 (m, 1H), 1.75−1.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 153.6, 137.8, 137.3, 135.2, 129.4, 129.0, 127.4, 116.7, 115.4, 73.8, 66.1, 55.6, 47.5, 38.1, 31.6, 26.7; IR (neat) 3488 (b), 1779 (s), 1692 cm^{-1}; HRMS m/z calcd for $C_{19}H_{24}NO_4$ (M + H): 330.1705, found 330.1697; $[\alpha]_D^{20}$ +35.7 (c = 0.82, $CHCl_3$).

(1*R*,2*R*,4*S*)-4-Benzyl-3-[(2-hydroxy-3-cyclohexen-1-yl)-carbonyl]-2-oxazolidinone (10). To a solution of oxazolidinone **9** (229 mg, 0.696 mmol) in 7 mL of CH_2Cl_2 was added benzylenedine(bistricyclohexylphosphine)ruthenium(II) dichloride (28.6 mg, 0.035 mmol). The solution was stirred for 30 min and then air was bubbled through the mixture for 3 h to oxidize the remaining catalyst. Concentration of the solution followed by chromatography (20−40% EtOAc/petroleum ether gradient) gave the title compound as a colorless crystals (198.1 mg, 95%). **10:** mp 159−161 °C; R_f 0.16 (30% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.20 (m, 5H), 5.96−5.86 (m, 2H), 4.72 (m, 1H), 4.45 (d, J = 3.3 Hz, 1H), 4.21 (m, 2H), 3.75 (m, 1H), 3.29 (dd, J = 13.3, 3.2 Hz, 1H), 2.81 (m, 2H), 2.19 (m, 2H), 2.08−2.00 (m, 1H), 1.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 153.1, 135.1, 131.4, 129.4, 128.9, 127.41, 127.38, 66.3, 63.7, 55.3, 44.4, 37.9, 25.1, 19.8; IR (neat) 3487 (w), 1777 (s), 1699 cm^{-1}; HRMS m/z calcd for $C_{17}H_{20}NO_4$ (M + H): 302.1392, found 302.1382; $[\alpha]_D^{20}$ −48.95 (c = 0.86, $CHCl_3$).

(1*S*,2*R*)-2-Hydroxy-3-cyclohexenecarboxylic Acid (11). Compound **5** (5.23 g, 13.7 mmol) was dissolved in freshly distilled THF followed by addition of distilled water and cooled to 0 °C. The biphasic mixture was treated with one portion of $LiOH·H_2O$ (8.6 g, 204.6 mmol). The reaction was allowed to warm to room temperature and stirred for 2 days. The mixture was concentrated to half of the volume and diluted with ethyl acetate. The pH of the aqueous layer was adjusted to 1 with 1 N $KHSO_4$. The layer was separated, and the aqueous layer was extracted with 100 mL of EtOAc three times. The combined organic solution was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (2%−10% CH_2Cl_2/MeOH) yielded the title compound as a colorless oil (1.908 g, 98%). This identical procedure was applied to compound **10** to obtain the same product. **11:** R_f 0.12 (5% MeOH/ CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91−5.80 (m, 2H), 4.43 (t, = 3.9 Hz, 1H), 2.57 (m, 1H), 2.14 (m, 1H), 1.98 (m, 1H), 1.85 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2, 131.6, 127.2, 63.9, 45.0, 24.8, 19.1; IR (neat) 3407 (b), 1713 (s) cm^{-1}; $[\alpha]_D^{20}$ −270.3 (c = 1.81, $CHCl_3$).

(1*R*,2*S*,5*S*,8*S*)-8-Hydroxy-2-iodo-7-oxa-bicyclo[3.2.1]-octan-6-one (12). To $Ag(collidine)_2ClO_4$ [28] (1.27 g, 2.83 mmol) in 5 mL of CH_2Cl_2 was added iodine (0.717 g, 2.83 mmol) in one portion with vigorous stirring. After 20 min, the iodine was completely dissolved and a white precipitate formed. This suspension was cooled to −20 °C, and then a solution of compound **11** (287 mg, 2.02 mmol) in 10 mL of CH_2Cl_2 was added slowly via cannula into the suspension. The reaction was stirred at that temperature for 3 h. The mixture was diluted with EtOAc and filtered through a pad of Celite. The Celite was washed with EtOAc, and then the combined organic solution was washed with 5% HCl solution, half-saturated $NaHCO_3$, and brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was subject to column chromatography (10−30% EtOAc/petroleum ether) to give rise to colorless crystals (379 mg, 70%). **12:** mp 109−111 °C; R_f 0.15 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.87 (s, 1H), 4.65 (dd, J = 4.5, 1.1 Hz, 1H), 4.47 (dd, J = 5.4, 4.9 Hz, 1H), 2.80 (s, 1H), 2.63 (s, 1H), 2.22−2.14 (m, 1H), 1.95−1.78 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 85.1, 75.6, 47.0, 28.1, 22.18, 22.16; IR (neat) 3473, 1755 cm^{-1}; HRMS m/z calcd for $C_7H_{13}NO_3I$ (M + NH_4): 285.9940, found 285.9946; $[\alpha]_D^{20}$ −64.9 (c = 1.34, $CHCl_3$).

(1*R*,5*S*,8*S*)-8-Hydroxy-7-oxa-bicyclo[3.2.1]octan-6-one (13). To compound **12** (100 mg, 0.37 mmol) in 8 mL of benzene at 60 °C was added tris(trimethylsilyl)silane (0.173 mL, 0.56 mmol) through a syringe followed by addition of AIBN (3.07 mg, 0.019 mmol) in one portion. After refluxing the mixture for 4h, the benzene was removed under reduced pressure, and the resultant oil was dissolved in acetone−water (1:1), followed by treatment with KF (50 mg). After stirring for 20 min, the solution was concentrated down to half of its volume and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was subject to column chromatography using 20−40% EtOAc/petroleum ether to yield title compound as colorless crystals (44.5 mg, 84%) **13:** mp 140−142 °C; R_f 0.16 (5% acetone/$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (d, J = 5.2 Hz, 1H), 3.92 (s, 1H), 3.19 (s, 1H), 2.56 (d, J = 4.6, 1H), 2.01−1.83 (m, 2H), 1.60−1.42 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 83.7, 77.9, 47.4, 27.3, 24.9, 16.7; IR (neat) 3416, 2933, 1770 cm^{-1}; HRMS m/z calcd for $C_7H_{14}NO_3$ (M + NH_4): 160.0973, found 160.0971; $[\alpha]_D^{20}$ −21.8 (c = 2.54, $CHCl_3$). Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found, C, 59.25; H, 7.04.

(1*R*,5*S*,8*S*)-8-Benzyloxy-7-oxa-bicyclo[3.2.1]octan-6-one (14). To compound **13** (1.05 g, 7.4 mmol) in 75 mL of THF at 0 °C was added NaHMDS (1 M in toluene, 8.1 mL, 8.1 mmol). After stirring for 10 min, distilled BnBr (1.3 mL, 11 mmol) was added dropwise, followed by addition of tetrabutylammonium iodide (2.73 g, 7.4 mmol) in one portion with vigorous stirring. After warming the reaction mixture to room temperature, it was stirred for 12 h and then quenched with saturated ammonium chloride. The layers were separated, and the aqueous layer was extracted with EtOAc. The organic layer was washed with half-saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was subject to column chromatography (10−30% EtOAc/petroleum ether) to afford **14** as colorless crystals (1.458 g, 85%). **14:** mp 82−83 °C; R_f 0.28 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5H), 4.76 (m, 1H), 4.52 (s, 2H), 3.62 (s, 1H), 2.72 (t, J = 2.2, 1H), 2.04−1.89 (m, 2H), 1.61−1.42 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 137.3, 128.5, 127.9, 127.5, 84.2, 80.3, 70.2, 44.7, 27.6, 25.2, 17.1; IR (neat) 3020, 1790 cm^{-1}; HRMS m/z calcd for $C_{14}H_{20}NO_3$ (M + NH_4): 250.1443, found 250.1442; $[\alpha]_D^{20}$ −30.8 (c = 0.79, $CHCl_3$).

(1*S*,2*S*,3*S*)-3-Azido-2-benzyloxycyclohexanecarboxylic Acid Methyl Ester (16). To compound **14** (1.071 g, 4.6 mmol) in 150 mL of MeOH (HPLC grade) was added K_2CO_3 (1.27 g, 9.2 mmol) in three portions with vigorous stirring. After 36 h, the reaction mixture was treated with 10% HCl to adjust pH to 7. The methanol was removed on a rotary evaporator, and the residue was dissolved in EtOAc followed by washes with water and brine. The organic layer was dried with Na_2SO_4, filtered, concentrated in vacuo, and pumped under reduced pressure (<5 mmHg). The crude material was dissolved in 70 mL of CH_2Cl_2 and cooled to 0 °C. Subsequent treatment with pyridine (11 mL, 18.4 mmol), trifluoromethanesulfonic anhydride (1.15 mL, 5 mmol) for 2 h at 0 °C yielded the crude triflate solution. This solution was diluted with ether, washed with 5% HCl solution and half-saturated $NaHCO_3$, and brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue (**15**) was dissolved in 100 mL of DMF, followed by addition of NaN_3 (0.3 g, 4.6 mmol) in one portion. After stirring overnight, another 1 equiv of NaN_3 (0.3 g, 4.6 mmol) was added and the reaction mixture stirred further for 8 h. The solvent was distilled, and the crude product was treated with 40 mL of THF and 20 mL of 10% HCl and stirred for 30 min. The aqueous solution was neutralized with 10% KOH and concentrated to half of its original volume. The solution was extracted with 50 mL of EtOAc three times, the organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography using 0−5% EtOAc/petroleum ether yielded the title compound (447.8 mg, 56% based on the recovered starting material). Further elution with 20−30% EtOAc/petroleum ether afforded recovered starting material as a colorless oil (429 mg). **16:** R_f 0.36 (5% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 4.53 (s, 2H), 3.89 (dd, J = 9.3, 5.5 Hz, 1H), 3.71 (t, J = 4.2, 1H), 3.58 (s, 3H), 2.77 (m, 1H), 1.86−1.38 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 138.0, 128.4, 127.8, 127.7, 77.4, 72.3, 59.0, 51.5, 42.5, 25.9, 23.0, 19.2; IR (neat) 2947, 2100, 1738 cm^{-1}; HRMS *m*/*z* calcd for $C_{15}H_{23}N_4O_3$ (M + NH_4): 307.1770, found 307.1776; $[\alpha]_D^{20}$ +43.9 (*c* = 1.06, $CHCl_3$).

(1*S*,2*S*,3*S*)-3-Azido-2-benzyloxy-cyclohexanecarboxylic Acid (17). Compound **16** (220 mg, 0.76 mmol) was dissolved in 40 mL of freshly distilled THF, followed by addition of 20 mL of distilled water. The reaction mixture was cooled to 0 °C. The biphasic mixture was treated with one portion of LiOH·H_2O (366.6 mg, 8.74 mmol). The reaction was allowed to warm to room temperature and stirred for 2 days. The mixture was concentrated to half its volume and diluted with ethyl acetate. The pH of aqueous layer was adjusted to 2 with 1 N $KHSO_4$. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic solution was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Further column chromatography (0−20% EtOAc/petroleum ether) yielded the title compound as colorless crystals (204.1 mg, 97%). **17:** mp 79−81 °C; R_f 0.23 (10% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.24 (m, 5H), 4.58 (s, 2H), 3.84 (dd, J = 9.3, 5.5 Hz, 1H), 3.74 (t, J = 4.1, 1H), 2.80 (m, 1H), 1.86−1.41 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 137.6, 128.4, 127.9, 127.8, 77.4, 72.7, 59.1, 42.6, 26.0, 22.9, 19.2; IR (neat) 3031 (b), 2099, 1704 cm^{-1}; HRMS *m*/*z* calcd for $C_{14}H_{21}N_4O_3$ (M + NH_4): 293.1613, found 293.1619; $[\alpha]_D^{20}$ +44.7 (*c* = 2.46, $CHCl_3$).

(1*S*,2*S*,3*S*)-3-Amino-2-hydroxy-cyclohexanecarboxylic Acid (18). In a Parr hydrogenation tube filled with argon was added compound **17** (40 mg, 0.15 mmol) in 3.5 mL of absolute ethanol followed by addition of 10% Pd on carbon (100 mg). The mixture was subjected to hydrogenation at 50 psi. After 8 h, the reaction mixture was filtered through a pipet plugged with an inert material, and the Pd/C residue was washed with absolute ethanol. The combined ethanol solution was concentrated in vacuo. The crude amino acid was dissolved in 10 mL of distilled water then extracted with 10 mL of EtOAc three times. The aqueous solution was liophilized to yield **18** as an off-white powder (18.8 mg, 81%). **18**: mp 242 °C (dec); ^{1}H NMR (500 MHz, CD_3OD) δ 3.36 (dd, J = 10.2, 5.2 Hz, 1H), 3.12 (m, 1H), 2.59 (d, J = 3.3 Hz, 1H), 1.88−1.85 (m, 1H), 1.78 (d, J = 2.6, 1H), 1.39−1.01 (m, 4H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.5, 71.6, 53.3, 45.4, 28.4, 26.7, 20.3; IR (KBr): 2965 (b), 1580 cm^{-1}; HRMS *m*/*z* calcd for $C_7H_{14}NO_3$ (M + H): 160.0973, found 160.0968; $[\alpha]_D^{20}$ +72.5 (*c* = 1.22, $CHCl_3$).

(2R,3R,4S)-4-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-2,5-dimethyl-3-hexanol (20). Step 1: To compound **19** (2.296 g, 6.26 mmol) in 62 mL of CH_2Cl_2 was added Dess−Martin reagent (3.19 g, 7.5 mmol) with vigorous stirring. After 2 h, the reaction mixture was diluted with 240 mL of ether and then poured into 120 mL of saturated $NaHCO_3$ containing 2 g of NaS_2O_3·$4H_2O$. The mixture was shaken gently until the ether layer became clear. The organic layer was separated, washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography using 0−5% EtOAc/petroleum ether yielded the title compound as a colorless oil (2.18 g, 96%). The title compound: R_f 0.64 (5% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 4.66 (d, J = 11.9 Hz, 1H), 4.26 (d, J = 11.9 Hz, 1H), 3.82 (dd, J = 9.6, 8.3 Hz, 1H), 3.60 (d, J = 5.3 Hz, 1H), 3.44 (dd, J = 9.7, 5.7 Hz, 1H), 3.07 (m, 1H), 2.06 (m, 1H), 0.89−0.84 (m, 9H), 0.77 (s, 9H), −0.08 (d, J = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5, 138.1, 128.3, 127.9, 127.7, 89.0, 72.5, 65.0, 44.2, 30.0, 25.9, 19.5, 17.6, 13.9, −5.5, −5.6; IR (neat) 2934, 1716, 1471, 1095 cm^{-1}; HRMS *m*/*z* calcd for $C_{21}H_{37}O_3Si$ (M + H): 365.2512, found 365.2497; $[\alpha]_D^{20}$ −48.7 (*c* = 2.2, $CHCl_3$).

Step 2: To a suspension of lithium aluminum hydride (193 mg, 5.08 mmol) in 10 mL of Et_2O at −10 °C was added slowly via cannula into a precooled solution (−10 °C) of the above ketone (1.85 g, 5.08 mmol) in 20 mL of Et_2O with vigorous stirring. After 2 h, the reaction temperature was maintained at 0 °C, and H_2O (0.2 mL), 15% NaOH (0.2 mL), and H_2O (0.4 mL) were added dropwise (Caution: reaction is exothermic). The mixture was allowed to stir for 1 h at room temperature and then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed three times using 0−5% EtOAc/petroleum ether to provide the title compound as a colorless oil (819.1 mg, 44%). The (2*R*,3*S*,4*S*) isomer (856 mg, 46%) was recovered and recycled. **20:** R_f 0.48 (5% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.24 (m, 5H), 4.52 (d, J = 12.1 Hz, 1H), 4.47 (d, J = 12.1 Hz, 1H), 3.62 (dd, J = 8.9, 3.8 Hz, 1H), 3.55 (dd, J = 9.0, 5.9 Hz, 1H), 3.50 (dd, J = 5.0, 2.7 Hz, 1H), 3.46 (m, 1H), 2.81 (d, J = 4.5 Hz, 1H), 1.97−1.89 (m, 2H), 1.02−0.90 (m, 9H), 0.89 (s, 9H), 0.05−0.02 (d, J = 9.2, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 128.3, 127.6, 127.5, 77.6, 76.8, 73.3, 73.2, 35.0, 29.4, 26.0, 21.0, 17.2, 14.6, −4.1, −4.4; IR (neat) 3504, 2957, 1090, 1505 cm^{-1}; HRMS *m*/*z* calcd for $C_{21}H_{39}O_3Si$ (M + H): 367.2668, found 367.2673; $[\alpha]_D^{20}$ +2.2 (*c* = 1.5, $CHCl_3$).

(3*S*,4*R*,5*R*)-6-[(*tert*-Butyldimethylsilyl)oxy]-4-(methoxymethoxy)-2,5-dimethyl-3-hexanol (21). Step 1: To compound **20** (0.82 g, 2.2 mmol) in 6.9 mL of CH_2Cl_2 at 0 °C was added sequentially diisopropylethylamine (1.76 mL, 10.1 mmol) and chloromethyl methyl ether (0.515 mL, 6.4 mmol) dropwise through two separate syringes. The mixture was allowed to warm to room temperature and was stirred overnight. The reaction was then diluted with ether followed by washes with 5% HCl solution, half-saturated $NaHCO_3$, and brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography using 0−5% EtOAc/petroleum ether yielded the title compound as a colorless oil (0.9 g, 98%). R_f 0.55 (5% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.30 (m, 5H), 4.72 (d, J = 6.4 Hz, 1H), 4.59 (d, J = 6.4 Hz, 1H), 4.47 (s, 2H), 3.70 (dd, J = 8.9, 3.5 Hz, 1H), 3.51 (dd, J = 5.2, 2.4 Hz, 1H), 3.47 (dd, J = 7.0, 2.4 Hz, 1H), 3.37 (m, 1H), 3.32 (s, 3H), 2.04 (m, 1H), 1.84 (m, 1H), 1.05 (d, J = 6.9 Hz, 3H), 0.94−0.89 (m, 15H), 0.05−0.02 (m, 6H); ^{13}C NMR (125M Hz, $CDCl_3$) δ 139.0, 128.3, 127.5, 127.4, 97.2, 82.7, 78.9, 73.0, 72.9, 56.0, 35.4, 30.3, 26.1, 21.1, 18.6, 15.9, −3.7, −4.8; IR (neat) 2923,

1464 cm^{-1}; HRMS *m/z* calcd for $C_{23}H_{46}NO_4Si$ (M + NH_4): 428.3196, found 428.3191; $[\alpha]_D^{20}$ −49.1 (*c* = 1.19, $CHCl_3$).

Step 2: To the above protected alcohol (0.858 g, 2.09 mmol) in 21 mL of MeOH was added formic acid (0.84 mL) through a syringe, followed immediately by addition of Pd black (0.224 g, 2.1 mmol) in one portion. After stirring for 20 min, the reaction was filtered through a short column contained a plug of inert material. (Caution: Pd black is highly flammable. Care must be taken that the plug is kept moist). The filtrate was added to 20 mL of saturated $NaHCO_3$ and concentrated under reduced pressure. The aqueous solution was extracted with ether, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Further column chromatography using 0−5% EtOAc/petroleum ether yielded the title compound as a colorless oil (669.7 mg, 89%). **21:** R_f 0.63 (10% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (d, *J* = 6.6 Hz, 1H), 4.65 (d, *J* = 6.6 Hz, 1H), 3.93 (dd, *J* = 10.0, 4.3 Hz, 1H), 3.66 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.59 (dd, *J* = 11.4, 5.7 Hz), 3.49 (d, *J* = 6.0 Hz, 1H), 3.37 (s, 3H), 2.06−2.02 (m, 1H), 1.90 (m, 1H), 1.04 (d, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 3.4 Hz, 3H), 0.96 (d, *J* = 3.5 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.4, 83.0, 75.6, 64.2, 56.0, 36.6, 29.9, 25.8, 20.2, 17.3, 15.1, −5.58, −5.62; IR (neat) 3430, 2956, 1036 cm^{-1}; HRMS *m/z* calcd for $C_{16}H_{37}O_4Si$ (M + H): 321.2461, found 321.2464; $[\alpha]_D^{20}$ +11.1 (*c* = 1.5, $CHCl_3$).

(1*S*,2*R*,3*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-2-(methoxymethoxy)-3-methylbutyl (1*S*,2*S*,3*S*)-3-Azido-2-benzyloxy-cyclohexanecarboxylate (22). To azido acid **17** (53.8 mg, 0.2 mmol) and alcohol **21** (202 mg, 0.63 mmol) in 0.49 mL of toluene was added sequentially DCC (67.3 mg, 0.33 mmol) and DMAP (24.9 mg, 0.2 mmol). The mixture was allowed to stir overnight. The reaction was first diluted with ether and then filtered to remove a white precipitate (presumably DCU). The filtrate was concentrated under reduced pressure. After column chromatography (0−5% EtOAc/petroleum ether), the title compound was obtained as a colorless oil (55.5 mg, 47%, based on the azido acid). Further elution recovered the alcohol **21** (158.9 mg). **22:** R_f 0.72 (10% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.24 (m, 5H), 5.01 (dd, *J* = 7.1, 4.5 Hz, 1H), 4.66−4.53 (m, 4H), 3.96 (d, *J* = 4.0 Hz, 1H), 3.81 (s, 1H), 3.76 (dd, *J* = 7.1, 3.2 Hz, 1H), 3.34 (d, *J* = 6.7 Hz, 2H), 3.29 (s, 3H), 2.86 (t, *J* = 4.7 Hz, 1H), 1.91−1.48 (m, 8H), 0.87−0.84 (m, 18H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 138.2, 128.2, 127.7, 127.6, 98.5, 78.7, 78.4, 77.5, 72.8, 65.0, 59.2, 55.9, 43.3, 37.4, 28.8, 25.8, 23.5, 19.8, 19.5, 18.2, 16.2, 10.9, −5.46, −5.54; IR (neat) 2933, 2099, 1728, 1093, 1038 cm^{-1}; HRMS *m/z* calcd for $C_{30}H_{51}N_3O_6SiNa$ (M + Na): 600.3445, found 600.3462; $[\alpha]_D^{20}$ −0.67 (*c* = 0.6, $CHCl_3$).

(1*S*,2*R*,3*R*)-1-Isopropyl-2-(methoxymethoxy)-3-methylbutan-4-ol (1*S*,2*S*,3*S*)-3-azido-2-Benzyloxycyclohexane carboxylate (23). To compound **22** (64.7 mg, 0.11 mmol) in 1.2 mL of MeOH was added Amberlyst-15 (120 mg). After stirring for 20 h, the reaction was filtered and the Amberlyst-15 residue was washed thoroughly with 20 mL of MeOH. The combined methanol solution was concentrated under reduced pressure. Column chromatography using 10−30% EtOAc/petroleum ether yielded the title compound as a colorless oil (51.9 mg, 94%). **23:** R_f 0.4 (20% acetone/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 5.13 (dd, *J* = 8.9, 2.9 Hz, 1H), 4.66−4.60 (m, 3H), 4.42 (d, *J* = 6.8 Hz, 1H), 4.04 (d, *J* = 3.4 Hz, 1H), 3.76 (m, 2H), 3.45 (s, 2H), 3.44 (s, 2H), 3.28 (s, 3H), 2.97 (s, 1H), 2.88 (dd, *J* = 8.6, 4.2 Hz, 1H), 1.98−1.50 (m, 8H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 138.1, 128.3, 127.72, 127.69, 98.8, 78.6, 78.5, 78.1, 73.0, 64.3, 59.3, 56.3, 43.5, 36.3, 28.4, 26.6, 24.1, 19.9, 19.4, 15.5, 9.9; IR (neat) 3495, 2949, 2101, 1727 cm^{-1}; HRMS *m/z* calcd for $C_{24}H_{37}N_3O_6Na$ (M + Na): 4.86.2580, found 486.2570; $[\alpha]_D^{20}$ −16.9 (*c* = 0.91, $CHCl_3$).

(1*S*,2*R*,3*R*)-1-Isopropyl-2-(methoxymethoxy)-3-methylbutanoic Benzyl Ester, Ester with (1*S*,2*S*,3*S*)-3-Azido-2-benzyloxycyclohexanecarboxylate (25). To compound **23** (120 mg, 0.26 mmol) in 2.3 mL of CH_2Cl_2 was added Dess−Martin reagent (128.4 mg, 0.3 mmol) with vigorous stirring. After 4 h, the rectum mixture was diluted with ether and then poured into 20 mL of saturated $NaHCO_3$ containing 1.7% (w/v) $NaS_2O_3{\cdot}4H_2O$. The mixture was shaken gently until the ether layer became clear. The organic layer was separated, washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure to afford a colorless oil. The oil was dissolved in 3 mL of DMSO−MeCN−5% NaH_2PO_4 (1:1:1) followed by addition of solid $NaClO_2$ (280 mg, 3.1 mmol). After stirring overnight, the reaction was concentrated in vacuo to two-thirds of its original volume. The solution was diluted with ether, washed with water and brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to afford an oil, which was used without further purification. The resultant oil was dissolved in 1.4 mL of CH_2Cl_2, followed by sequential addition of benzyl alcohol (45 μL, 0.43 mmol), DCC (85.8 mg, 0.42 mmol), and DMAP (14 mg, 0.11 mmol). The reaction was allowed to stir overnight, at which time it was diluted with ether and filtered to remove a white precipitate. The filtrate was concentrated in vacuo, and the resultant oil was chromatographed using 0−10% acetone/hexanes to yield a colorless oil (94.1 mg, 64%). **25:** R_f 0.48 (20% acetone/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.23 (m, 10H), 5.16 (d, *J* = 12.3 Hz, 1H), 5.07 (d, *J* = 12.3 Hz, 1H), 4.92 (m, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.59−4.56 (m, 2H), 4.51 (d, *J* = 6.7 Hz, 1H), 4.04 (d, *J* = 5.4 Hz, 1H), 3.93 (d, *J* = 3.6 Hz, 1H), 3.78 (s, 1H), 3.28 (s, 3H), 2.97 (m, 1H), 2.88 (m, 1H), 1.95−1.83 (m, 3H), 1.76 (m, 1H), 1.65−1.63 (m, 1H), 1.57−1.48 (m, 2H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 172.5, 138.2, 136.0, 128.5, 128.3, 128.2, 128.1, 127.6, 127.5, 98.3, 79.4, 78.2, 77.7, 72.6, 66.5, 59.2, 56.2, 43.1, 41.4, 28.7, 26.4, 23.7, 19.5, 19.4, 17.2, 11.8; IR (neat) 2940, 2099, 1734 cm^{-1}; HRMS *m/z* calcd for $C_{31}H_{42}N_3O_7$ (M + H): 540.2961, found 540.2940; $[\alpha]_D^{20}$ +8.5 (*c* = 0.6, $CHCl_3$).

***N*-[*N*-[*N*-[(Benzyloxycarbonyl]-L-leucyl]-L-prolyl]-3-(*N*,*O*-dimethyl-tyrosyl Ester with (1*S*,2*S*)-3[(2*S*,3*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-hydroxybutyramido]-2-benzyloxycyclohexanecarboxylic Acid, (1*S*,2*R*,3*S*)-1-Isopropyl-2-(methoxymethoxy)-3-methylbutanoic Acid Benzyl Ester (28).** To compound **25** (63 mg, 0.11 mmol) in 2.5 mL of THF was added one drop (16 μL) of distilled water followed by addition of trimethylphosphine (1 M in toluene, 252 mL, 0.252 mmol). After 1 h, air was bubbled through the reaction mixture for 1 h. The reaction mixture was concentrated under reduced pressure on a rotary evaporator and then pumped under high vacuum (2 mmHg). The crude amine (**26**) was then dissolved in 2 mL of DMF, followed by addition of tetrapeptide acid (**27**, 126 mg, 0.17 mmol), collidine (36 μL, 0.252 mmol) and HATU (67.8 mg, 0.18 mmol). After stirring overnight, DMF was distilled under reduced pressure (2 mmHg). The residue was dissolved in ethyl acetate and washed with 5% HCl, half-saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Further column chromatography using 10−30% acetone/hexanes yielded the title compound as a colorless oil (95 mg, 70%). **28:** R_f 0.49 (30% acetone/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 6.8 Hz, 1H), 7.62−7.79 (m, 1H), 7.36−7.18 (m, 15H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.81(d, *J* = 8.4 Hz, 2H), 6.68 (d, *J* = 9.0 Hz, 1H), 5.16 (dd, *J* = 12.3, 2.9 Hz, 2H), 5.03 (m, 2H), 4.93−4.83 (m, 2H), 4.73−4.41 (m, 6H), 4.32 (d, *J* = 3.1 Hz, 1H), 4.22 (d, *J* = 7.9 Hz, 1H), 4.06−4.00 (m, 2H), 3.78 (S, 3H), 3.67−3.64, (m, 2H), 3.60 (m, 1H), 3.25 (s, 3H), 3.23 (s, 3H), 2.88 (m, 1H), 2.75 (d, *J* = 11.5 Hz, 1H), 2.58 (m, 1H), 2.12 (m, 2H), 2.13 (m, 2H), 2.01−1.31 (m, 12H), 1.40 (s, 3H), 1.35 (s, 9H), 1.14−1.08 (m, 3H), 0.98−0.77 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 173.9, 173.3, 172.6, (dialkylamide rotamer) 171.8, 171.3, 169.5, 168.9, 158.5, 156.7, 155.3, 138.4, 136.8, 136.0, 130.4, 130.2, 130.0, 128.5, 128.4, 128.3, 128.2, 128.18, 128.14, 128.03, 128.01, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 114.3, 114.0, 98.1, 80.3, 78.9, 78.0, 71.8, 71.6, 66.5, 66.4, 66.1, 57.3, 56.1, 56.0, 55.9, 55.4 (rotamer), 55.2, 54.3 (rotamer), 51.8, 51.0, 46.8, 45.7, 43.4, 43.3 (rotamer), 41.6, 41.4 (rotamer), 38.6, 38.2 (rotamer), 33.6, 28.8,

28.7, 28.3, 28.1 (rotamer), 25.4, 24.9, 23.4, 21.0, 19.40, 19.36, 19.2, 16.8, 14.3, 11.6, 11.3; IR (neat) 3323, 2960, 1725 cm^{-1}; HRMS *m/z* calcd for $C_{70}H_{95}N_5O_{17}Na$ (M + Na): 1300.6623, found 1300.6601; $[\alpha]_D^{20}$ −53.6 (*c* = 0.63, $CHCl_3$).

Cyclo-[*N*-(*tert*-butyloxycarbonyl)-*O*-[[*N*-[(2*S*,3*R*,4*S*)-4-[(1*S*,2*S*,3*S*)-3-amino-2-benzyloxycyclohexanecarbonyl]-oxy-3-(methoxymethoxy)-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-*N*,*O*-dimethyl-L-tyrosyl]-L-threonyl] (29). In a Parr hydrogenation tube filled with argon was added compound **28** (17.5 mg, 0.014 mmol) in 0.8 mL of absolute ethanol, followed by addition of 10% Pd on carbon (16.2 mg). The mixture was subjected to hydrogenation at 45−50 psi. After 4−6 h, the reaction mixture was filtered through a column with a plug of inert material, and the Pd/C residue was washed with absolute ethanol. (Care should be taken that the plug will stay moist.) The combined ethanol solution was concentrated in vacuo. The crude amino acid was then dissolved in 1.3 mL of DMF, followed by addition of diisopropylethylamine (7.2 mL, 0.041 mmol) and HATU (6.3 mg, 0.016 mmol). After 24 h, another portion of HATU (3.2 mg, 0.008 mmol) was added, and the reaction was allowed to stir overnight. DMF was distilled under reduced pressure. The residue was dissolved in ethyl acetate and washed with 5% HCl, half-saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography using 20−40% acetone/hexanes yielded the title compound as a clear thick oil (6.4 mg, 45%). **29:** R_f 0.23 (30% acetone/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (m, 1H), 7.36−7.15 (m, 5H), 7.05 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.05 (d, *J* = 9.0 Hz, 1H), 5.31 (d, *J* = 4.9 Hz, 1H), 5.11 (t, *J* = 5.9 Hz, 1H), 4.73 (m, 2H), 4.65−4.61 (m, 2H), 4.58−4.42 (m, 4H), 4.31 (m, 1H), 3.80 (m, 1H), 3.71 (s, 3H), 3.55 (m, 2H), 3.34 (s, 3H), 3.26 (s, 1H), 3.16−3.12 (m, 1H), 2.98 (s, 3H), 2.87 (m, 1H), 2.36 (m, 1H), 2.11 (m, 1H), 1.96 (m, 2H), 1.84−1.07 (m, 15H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.82 (m, 9H), 0.69 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 173.6, 172.9, 172.6, 171.1, 168.6, 168.2, 159.0, 137.5, 130.3, 128.8, 128.3, 128.1, 127.6, 114.3, 98.8, 81.0, 79.1, 78.7, 78.2, 73.8, 71.0, 61.4, 60.3, 56.3, 55.6, 55.3, 52.1, 48.2, 47.4, 43.9, 43.0, 42.7, 34.8, 29.5, 28.9, 28.4, 28.2, 28.1, 27.2, 24.6, 24.0, 22.9, 22.3, 20.5, 19.0, 18.6, 16.6, 14.1; IR (neat) 3318, 2959, 1723, 1631 cm^{-1}; HRMS *m/z* calcd for $C_{55}H_{81}N_5O_{14}Na$ (M + Na):1058.5678, found 1058.5665; $[\alpha]_D^{20}$ −30.6 (*c* = 0.18, $CHCl_3$).

Cyclo-[*N*-(*N*-L-*O*-benzyloxylactyl-L-prolyl-*N*-methyl-D-leucyl)-*O*-[[*N*-[(2*S*,3*R*,4*S*)-4-[(1*S*,2*S*,3*S*)-3-amino-2-benzyloxy-cyclohexanecarbonyl]oxy-3-hydroxy-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-*N*,*O*-dimethyl-L-tyrosyl]-L-threonyl] (31). To a solution of **29** (6.4 mg, 0.006 mmol) in ethyl acetate (0.6 mL) was added a freshly prepared 10% HCl solution (0.6 mL). After stirring for 2 days, the pH of the reaction mixture was adjusted to 9 by addition of 3 N NaOH solution. The resultant solution was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residual amine was dissolved in 0.3 mL of DMF followed by addition of the side chain acid **30** (4.1 mg, 0.01 mmol), collidine (3.6 μL, 0.027 mmol), and HATU (4.2 mg, 0.011 mmol). The solution was allowed to stir overnight. The solvent (DMF) was distilled under reduced pressure, and the crude product was dissolved in 10 mL of ethyl acetate. The organic solution was washed with 5% HCl, half-saturated $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Further column chromatography using 50−80% EtOAc/petroleum ether yielded the title compound as a colorless oil (2.7 mg, 34%). **31:** R_f 0.28 (70% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (m, 1H), 7.49 (s, 1H), 7.47−7.31 (m, 10H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.12 (m, 1H), 6.91 (d, *J* = 8.2 Hz, 2H), 5.16 (m, 2H), 5.13 (m, 1H), 4.93−4.67 (m, 6H), 4.61−4.48 (m, 4H), 4.25 (t, *J* = 6.4 Hz, 1H), 4.16 (m, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.69 (m, 4H), 3.24 (m, 2H), 3.09 (s, 3H), 3.01 (m, 2H), 2.79 (m, 2H), 2.20−1.90 (m, 4H), 1.87−1.81 (m, 4H), 1.70−1.54 (m, 13H), 1.47−1.28 (m, 9H), 1.03−0.81 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 171.3, 170.2, 168.1, 165.8, 161.8, 159.0, 158.6, (dialkylamide rotamer) 156.7, 154.5, 150.4, 149.4, 138.3, 137.9, 137.3, 132.1, 130.3, 130.2, 129.0, 128.96, 128.5, 128.2, 128.0, 127.8, 127.6, 126.0, 121.5, 114.4, 114.1, 78.6, 75.3, 74.0, 72.6, 71.8, 71.0, 70.4, 61.5, 57.2, 56.4, 55.4, 52.4, 48.4, 47.5, 45.3, 44.5, 44.2, 43.6, 43.2, 36.5, 36.3, 34.9, 29.6, 29.1, 28.8, 28.5, 28.1, 26.0, 25.1, 24.7, 24.2, 23.4, 23.2, 22.4, 21.5, 20.7, 19.5, 19.3, 18.7, 17.9, 17.1, 16.6, 14.6; IR (neat) 3311, 2958, 1734, 1635 cm^{-1}; HRMS *m/z* calcd for $C_{70}H_{99}N_7O_{15}Na$ (M + Na): 1300.7097, found 1300.7072; $[\alpha]_D^{20}$ −10.4 (*c* = 0.14, $CHCl_3$).

Cyclo-[*N*-(*N*-L-lactyl-L-prolyl-*N*-methy-D-leucyl)-*O*-[[*N*-[(2*S*,3*R*,4*S*)-4-[(1*S*,2*S*,3*S*)-3-amino-2-benzyloxycyclohexanecarbonyl]oxy-3-oxo-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl-*N*,*O*-dimethyl-L-tyrosyl]-L-threonyl] (2). To a solution of **31** (2.5 mg, 0.002 mmol) in CH_2Cl_2 (0.3 mL) was added Dess−Martin reagent (1.6 mg, 0.003 mmol) with vigorous stirring. After 1 h, the reaction mixture was diluted with 2 mL of ether then poured into 1 mL of saturated $NaHCO_3$ containing 19.2 mg of $NaS_2O_3 \cdot 4H_2O$. The mixture was shaken until the ether layer became clear. The organic layer was separated, and the aqueous layer was extracted with 2 mL of EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure to afford a colorless thin film. The residue was dissolved in HPLC grade MeOH (0.3 mL). Formic acid (15 mL) was added through a syringe followed immediately by addition of Pd black (3.0 mg, 0.028 mmol) in one portion. After stirring for 20 min, the reaction was diluted with absolute ethanol and filtered through a short column with a plug of inert material. (Caution: Pd black is highly flammable; care should be taken to ensure that the plug will remain moist.) The filtrate was concentrated under reduced pressure. The residue was dissolved in chloroform and applied to a short (1 cm) silica gel column. Elution with ethyl acetate afforded the title compound as a semisolid (1.4 mg, 64%). **2:** R_f 0.51 (10% MeOH/ CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 and 8.08 (m, 1H), 7.99 (s, 1H), 7.48−7.44 (m, 1H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.64 (m, 1H), 5.25 (s, 1H), 5.21 (m, 1H), 4.80 (m, 1H), 4.74 (d, *J* = 6.4 Hz, 1H), 4.64 (m, 2H), 4.53 (dd, *J* = 9.7, 4.7 Hz, 1H), 4.32 (m, 1H), 4.26 (m, 1H), 3.83 (m, 1H), 3.74 (s, 3H), 3.71 (m, 2H), 3.55 (m, 4H), 3.27 (m, 1H), 3.11 (m, 1H), 3.01 (s, 3H), 2.76 (s, 3H), 2.11 (m, 2H), 1.96−1.82 (m, 4H), 1.80−1.57 (m, 4H), 1.55−1.39 (m, 4H), 1.35 (m, 3H), 1.24−0.98 (m, 19H), 0.84−0.71 (m, 12H); IR (neat) 3311, 2926, 1734, 1636, 1458 cm^{-1}; HRMS *m/z* calcd for $C_{56}H_{85}N_7O_{15}Na$ (M + Na): 1118.6038, found 1118.6001; $[\alpha]_D^{20}$ −6.7 (*c* = 0.06, $CHCl_3$).

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Supporting Information Available: General procedures, ^{1}H and/or ^{13}C NMR spectra of compounds **2**, **5**, **5a**, **5b**, **7**−**14**, **16**−**23**, **25**, **28**, **29** and **31**, and the X-ray data of compound **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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