Synthetic Routes to a Constrained Ring Analog of Didemnin B

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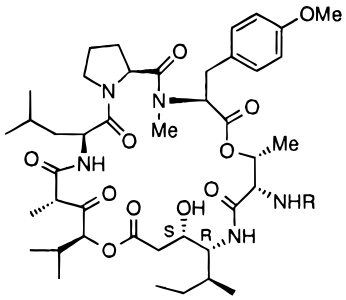
The didemnin class of biologically active cyclodepsipeptides, isolated from a marine tunicate, has shown antitumor, antiviral, and immunosuppressive activities. Synthetic studies were undertaken to prepare a modified analog of one of the most potent congeners, didemnin B (**1**). The side chain of the isostatine unit was tethered into the macrocycle *via* a cyclohexane ring in order to provide a more rigid conformation and determine the importance of this unit in bioactive compounds. This modification created a new macrocycle core and generated a diastereomeric mixture of a constrained analog of didemnin B (**2**).

Introduction

The didemnin class (**1**) of biologically active cyclodepsipeptides, isolated from a marine tunicate,[1] has shown antitumor, antiviral, and immunosuppressive activities.[2−13] To date, the structural features considered essential for activity (the side chains attached to the amino group of threonine, the isostatine hydroxyl group, and the tyrosine unit) were based for the most part on the analysis of the X-ray structure.[14] Although the bioactivity of the most potent member, didemnin B (**1**), has been attributed to its side chain,[5] few other structural features have been examined. Therefore, investigations were undertaken to synthesize a modified macrocycle which tethered the isostatine unit to the macrocycle *via* a cyclohexane ring, to provide a more rigid and structurally stable conformation, a fused ring system (**2**). Such changes should alter the biological activity of the didemnins and help to determine binding site conformation as well as the importance of the isostatine hydroxyl group in active compounds. By using molecular modeling and data from a complex between cyclosporin A and its receptor, cyclophilin, Schreiber designed a bicyclic replacement for two residues of cyclosporin A. Incorporation of a thiazole ring afforded a compound with approximately twice the activity of cyclosporin A, the first structural variant with inhibitory properties greater than the parent compound.[15]



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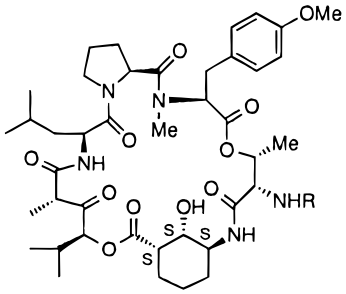

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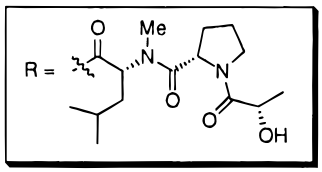

Results and Discussion

A molecular modeling study[16] was conducted for a series of analogs in which the isostatine moiety was

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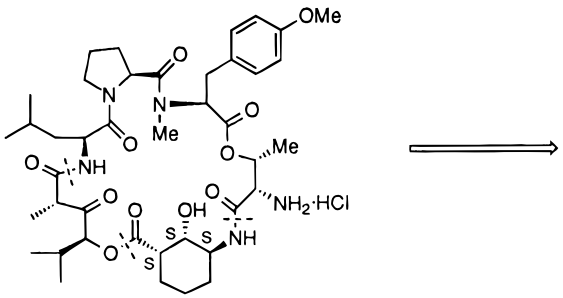
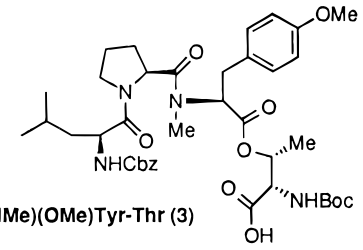
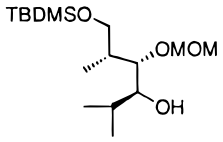
Scheme 1



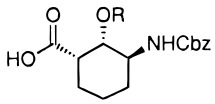
Constrained ring analog macrocycle salt (2a)



Leu-Pro-(NMe)(OMe)Tyr-Thr (3)



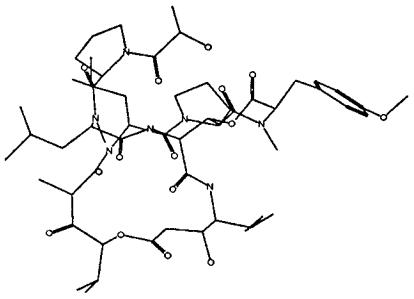
HIP alcohol (4)



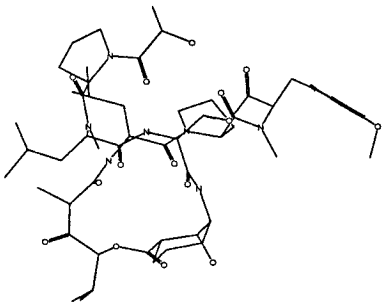
Cyclohexane amino acid (5)

replaced by a cyclohexane β-hydroxy-γ-amino acid. All possible diastereomeric structures were compared to that of didemnin B in order to generate the correct stereochemistry needed for the ring subunit. The minimized molecular modeling structure of **1** was generated from the X-ray coordinates provided by van der Helm and coworkers.[14] The best overlay was obtained for a cyclohexane in which all three contiguous stereogenic centers had the *S* configuration. The stereogenic center to which the nitrogen function is attached had the *R* configuration in didemnin B. However, molecular modeling results showed that an axial amino group with the *S* configuration afforded the closest superimposed overlay as well as being the lowest energy-minimized conformation. A retrosynthetic analysis (Scheme 1) similar to our synthetic approach to the macrocycle[17] was undertaken so that the same methodology could be employed once the cyclohexane amino acid (**5**) was synthesized. This unit would then be esterified with the α-(α-hydroxyisovalery)-propionyl unit (HIP alcohol, **4**) and then coupled with the tetrapeptide **3**.[17]

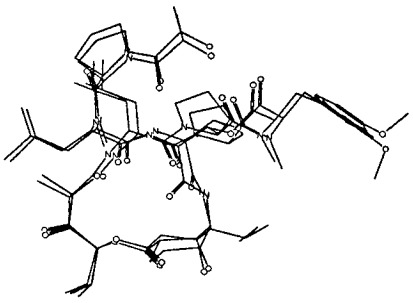
In devising a stereoselective route to **5**, many different synthetic strategies were examined for what appeared to be a trivial project. This deceptively simple substituted cyclohexane amino acid containing three contiguous stereogenic centers proved to be a challenge. The initial stereochemistry for this substructure was obtained by an asymmetric Diels–Alder reaction using the Oppolzer camphorsultam directing group (Scheme 2).[18–23] The



Didemnin B (1)



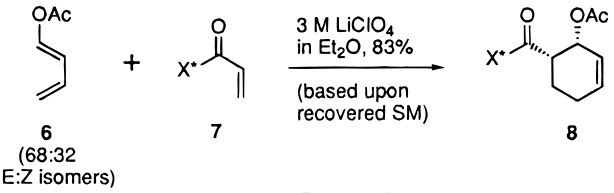
Constrained Ring Analog (2)



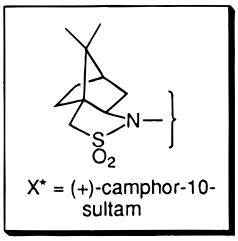
Overlay of Two Structures (1 + 2)

diene **6** was obtained in 57% yield from crotonaldehyde in refluxing Ac_2O under basic conditions (68:32 *E*:*Z* ratio).

Scheme 2



6 (68:32 E:Z isomers) **7** **8**



Only the *E* isomer reacts in the Diels–Alder reaction.[24] Oppolzer's camphorsultam was coupled with acryloyl chloride to generate the dienophile **7** in 70% yield. The

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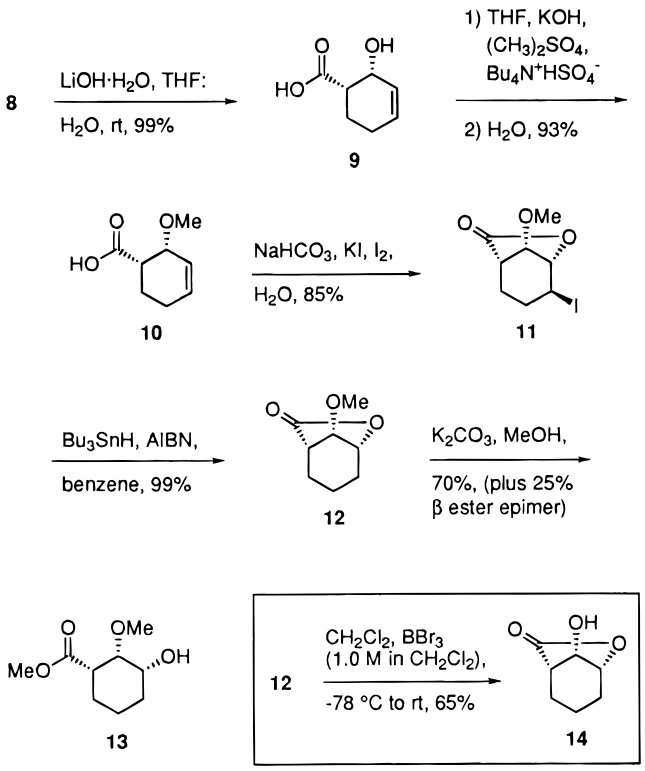
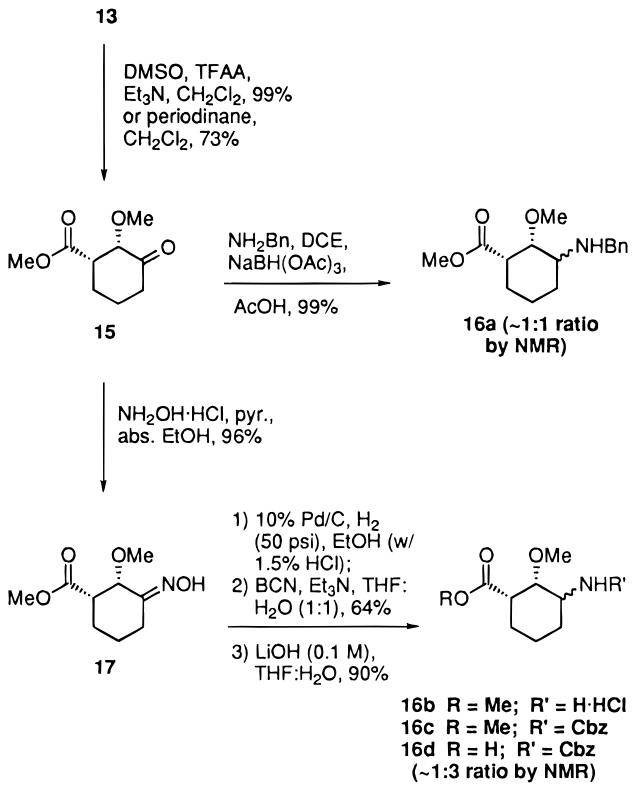
Scheme 3



Scheme 4



best conditions for the Diels−Alder reaction required lithium perchlorate as reported by Grieco.[25,26] This reaction afforded an 83% yield of the major diastereomer **8** and 5% of another diastereomer which could be chromatographically separated (based upon 25% recovered dienophile starting material). These conditions yielded a 5-fold increase in selectivity (3:1 to 17:1) over initial methods.[18] The relative and absolute stereochemistries of this Diels−Alder product were confirmed by single crystal X-ray analysis.[18] At this point, two of the three stereogenic centers were set.

The most practical method for introduction of the third stereogenic center was an iodolactonization of the methoxy acid **10**.[18,27] This compound was prepared by removal of the camphorsultam auxiliary from the Diels−Alder product **8** with aqueous LiOH, followed by protection of the intermediate secondary alcohol (**9**) as its methyl ether **10** (Scheme 3). Originally, several common silyl-protecting groups were investigated, and their steric bulk proved to be a major problem in the subsequent lactonization reaction. Therefore, a methyl group protection was chosen because of its less demanding steric environment even though we realized the difficulty of removing such a group at a later stage in the synthesis. A successful iodolactonization afforded compound **11** in 85% yield. The iodine was removed with Bu_3SnH, and the resulting lactone **12** was opened with methoxide. A 70% yield of compound **13** was obtained with ~25% of a β-ester epimer (determined by NMR) resulting from the basic conditions. At that time, it was found that deprotection of the methyl ether in **12** could be accomplished in 67% yield to provide alcohol **14**.[28] This transformation was to be investigated later in the synthesis because of the need to differentiate between two secondary hydroxyl groups.

After the third stereogenic center had been introduced, an appropriate transformation was needed to incorporate the amino functionality into the ring. Amine formation *via* azide displacement of a mesylate intermediate proved to be an inefficient synthetic pathway.[27] Varying conditions and the use of different azides (sodium, lithium, and trimethylsilyl azides) did not provide the desired transformation. Mitsunobu conditions using diphenylphosphoryl azide and diisopropyl azodicarboxylate also failed.[29,30] Parr bomb reactions with ammonia or benzylamine at 100 °C for 24 h afforded very poor yields of product.[31−35] Amine formation *via* a displacement was inefficient because, regardless of the mechanism (S_N2 or neighboring group assisted S_N1), attack by the nucleophile would be blocked either by steric hindrance or diaxial interactions with the ring hydrogens.[27]

At this stage, it was essential to incorporate the amine function even at the price of destroying previous selectivity. An alternative route *via* reductive amination was employed for amine formation.[27] The alcohol **13** was oxidized to **15** under Swern conditions (Scheme 4).[36] The keto group was then subjected to reductive amination

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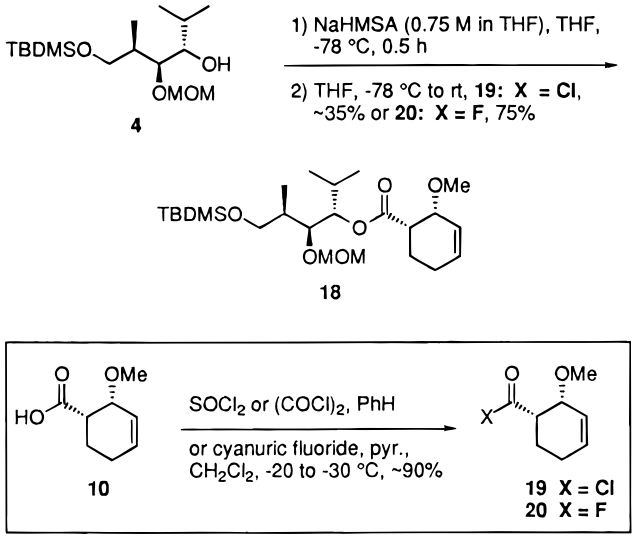
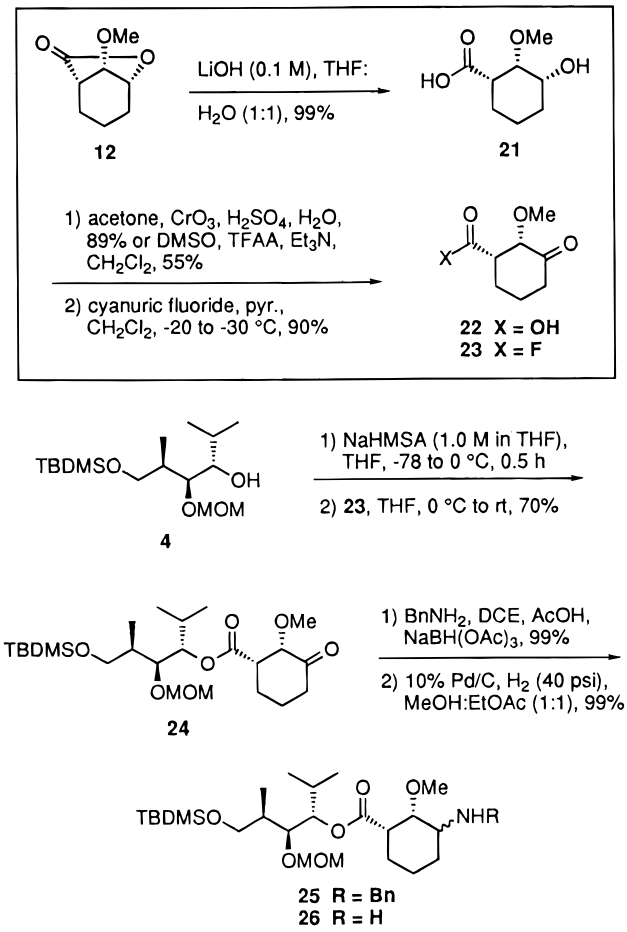
Scheme 5



Scheme 6



with benzylamine and sodium triacetoxyborohydride to afford the secondary amine product (**16a**: ~1:1 ratio by NMR analysis).[37,38] Amine formation through oxime **17** was less effective, giving poorer selectivity (**16d**: ~1:3 ratio by NMR analysis). Although this strategy destroyed the third stereogenic center, if a diastereomeric mixture of amines could be obtained, separation could be accomplished at a later stage such as after esterification with the α-(α-hydroxyisovaleryl)propionyl unit (HIP alcohol, **4**). Both diastereomers could then be used to make two new analogs. In addition, the major diastereomer might be obtainable through equilibrating conditions.

Much time was spent investigating suitable conditions for the esterification of the HIP alcohol **4** with the cyclohexane amino acid **16d** (diastereomeric mixtures—determined by NMR analysis).[39] The best conditions were obtained using Carpino's acid fluoride activation.[40,41] Initially, the alkoxide of the HIP alcohol was added to the acid fluoride **20** of 2-methoxy-3-cyclohexenecarboxylic acid (**10**) to obtain the ester **18** in 75% yield (Scheme 5). To convert the alcohol to its corrresponding alkoxide, several bases were used, but sodium hexamethyldisilazane proved to be the best.

Next, investigations into the coupling of the new synthetic intermediates were undertaken. Lactone **12** could be cleaved with the use of hydroxide instead of methoxide to afford hydroxy acid **21** in quantitative yield as a single diastereomer (Scheme 6). The hydroxyl function in **21** was oxidized to a ketone (**22**), in the presence of the acid group, employing Jones' oxidation conditions.[42] Using Carpino's activation protocol,[40,41] the acid fluoride **23** was added to the alkoxide of **4**, generated from either sodium hexamethylsilazane or *n*-butyllithium, to afford the ester **24** in 70% yield. Introduction of the ester functionality before amine incorporation was chosen with the expectation that the bulkier substituent would induce some selectivity in the reductive amination.

Ketone **24** was subjected to reductive amination conditions incorporating benzylamine and sodium triacetoxyborohydride (Scheme 6).[37,38] The benzyl group of the resulting secondary amine (**25**) was removed by catalytic hydrogenation to afford amine **26** in 99% of a 1:1 diastereomeric mixture. Unfortunately, the bulkier substituent did not induce the selectivity we had hoped for. The inseparable mixture of diastereomers was therefore utilized in the remaining synthetic scheme with the intent of separating the diastereomers at a later stage to obtain two drug candidates for biological testing.

The coupling of the two halves of the macrocycle (**26** + **3**) to give **27** was investigated using our previous methodology as shown in Scheme 7.[17,43] Originally, this transformation was accomplished with isopropenyl chloroformate activation[44,45] to prepare the linear precursor of the constrained ring analog **27** in 55% yield. The yield was increased to 65% by the use of (1*H*-1,3-benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) activation[46] and a catalytic amount of DMAP.

As was the case with our original linear precursor, intermediate **27** had to be functionalized at both ends to

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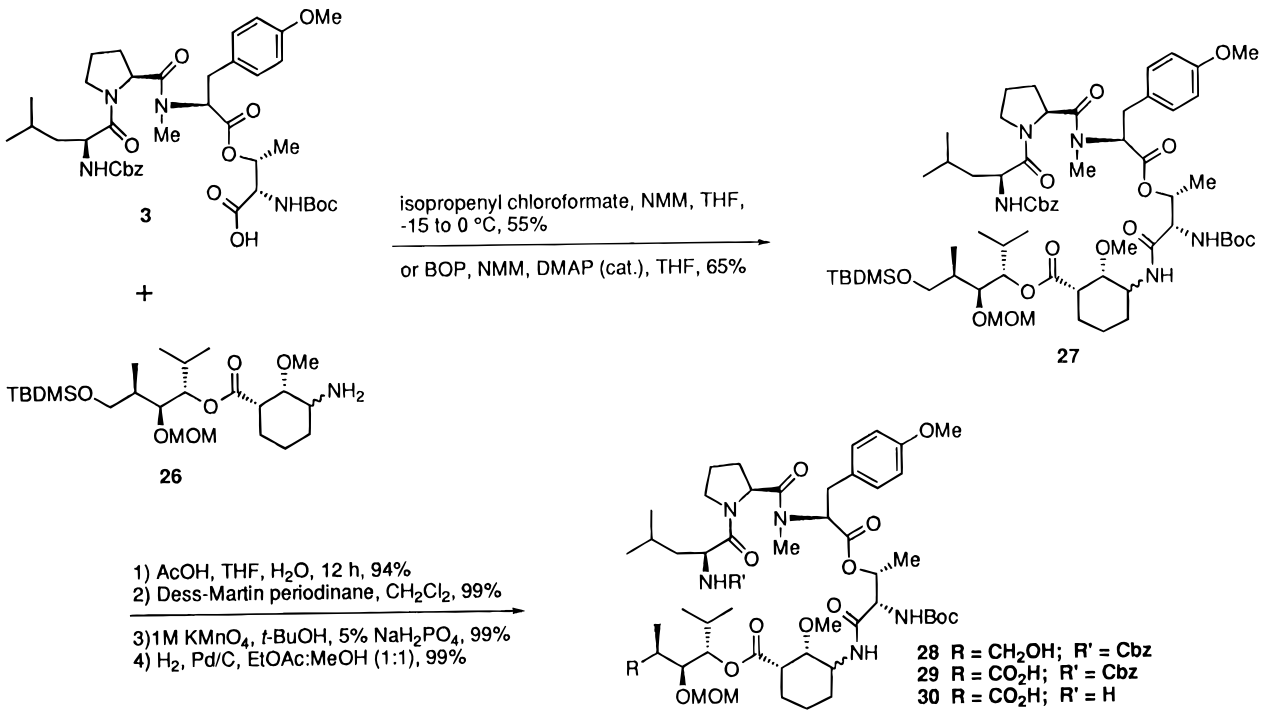
Scheme 7



achieve cyclization (Scheme 7). First, the TBDMS protecting group was removed under acid conditions to afford primary alcohol **28**. This alcohol was then subjected to a two-stage oxidation protocol first to the aldehyde using the Dess−Martin periodinane reagent [1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one][47] and then by Masamune conditions[48] to the acid (**29**) needed for cyclization. Finally, the amino protecting group was removed by catalytic hydrogenation to generate the unprotected linear precursor **30**.

Macrocyclization was originally conducted with pentafluorophenyl diphenylphosphinate (FDPP).[49] However, in contrast with the excellent results obtained in our previous macrocyclizations, yields for this transformation could not be raised above 30%. Using a new derivative of the BOP reagent, *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU),[50] the cyclization yields of **31** were increased to a modest 50% (Scheme 8). The yields of the remaining steps of the synthesis were on the average slightly lower than with the original macrocycle salt. The MOM protecting group of compound **31** was removed with dimethylboron bromide in 77% yield,[51,52] and the subsequent oxidation with periodinane afforded a modest 70% of compound **33**. In the last step of Scheme 8, the protected macrocycle **33** was quantitatively converted to the macrocycle salt of the constrained ring analog **34** when treated with hydrogen chloride in ethyl acetate.[17]

To complete the synthesis of the constrained ring didemnin B analog (**2b**, 1:1 diastereomeric mixture), the macrocycle salt **34** was coupled to the didemnin B side chain[17] (**35**, Scheme 8). Once again, the BOP reagent was used to activate the acid for addition. It was determined by NMR that the reaction was successful in producing a 1:1 diastereomeric mixture of the coupled products; however, thus far yields of this reaction have not been optimized and separation of the diastereomers is currently being pursued using reversed-phase HPLC techniques. The mixture has been submitted for initial biological screening to determine if further investigations are applicable; these results should help clarify the effect of a constrained ring system as well as that of the isostatine hydroxyl protection as no activity was found in other didemnins in which this functionality was not free.[8,13] Currently, we are continuing these investigations with two main goals: to achieve a totally stereocontrolled synthesis of the cyclohexane amino acid **5** and to isolate the optically pure constrained ring analog **2**.

Conclusions

An asymmetric Diels−Alder reaction incorporating an oxygenated diene in the presence of 3.0 M lithium perchlorate−diethyl ether was used to generate the initial stereochemistry for the cyclohexane amino acid, a key intermediate in the preparation of the fused ring didemnin analog **2**.[18] After introduction of the third stereogenic center, some difficult steps were encountered. The deceptively simple transformation of an alcohol to an amino group was finally achieved using the reductive amination of ketones **15** or **24** with sodium triacetoxyborohydride or the hydrogenation of oxime **17** under acidic conditions.[27] Nucleophilic displacement proved to be an impossible synthetic route to the amine function. Incorporation of the amine at a later stage such as from ketone **24** was not as selective as expected. However, the diastereomeric mixture did not present a problem in the latter part of the synthesis and will provide both diastereomers for biological testing.

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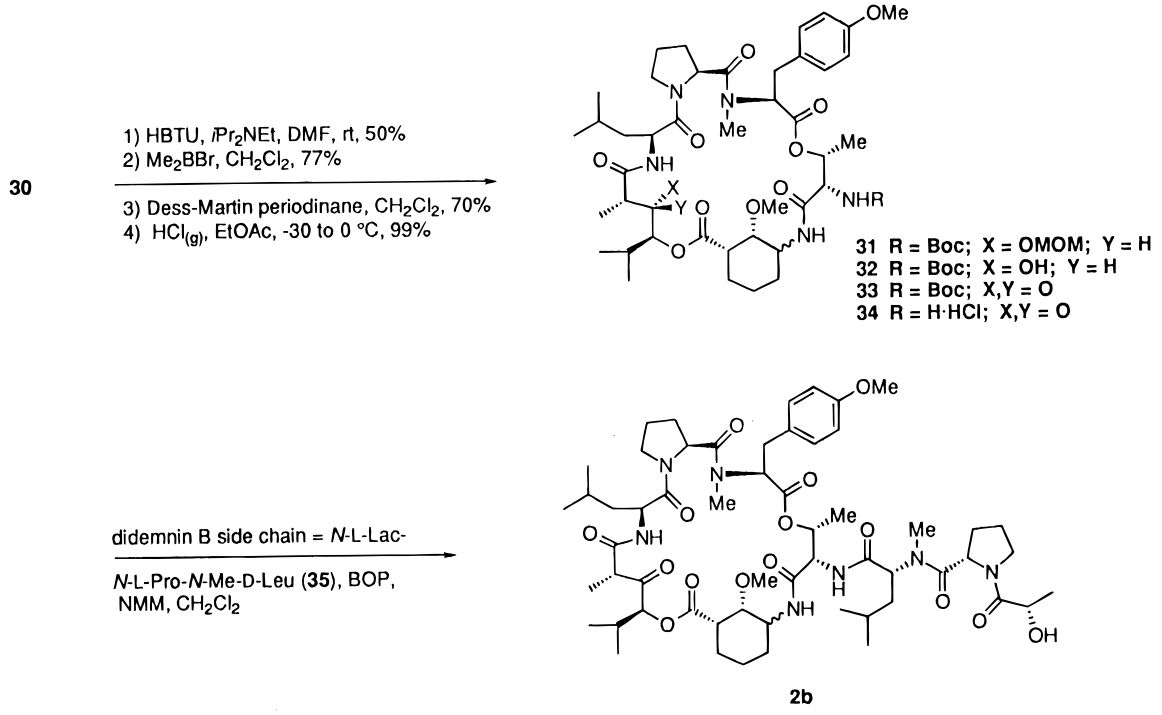
Scheme 8



Esterification of a hindered alcohol (HIP unit, **4**) was accomplished using the acid fluoride coupling method of Carpino.[40,41] Standard coupling procedures were unsuccessful because of the steric bulk and weak nucleophilicity of the secondary alcohol. This recently described strategy[40,41] was superior to all reported esterification procedures and was applied to the coupling of **4** and **22**. The new methodology offers great potential as an alternative to typical activation protocols.[39]

The constrained ring analog **2b** was synthesized, and the separation of the two diastereomers is being investigated *via* HPLC and traditional column chromatography. For the cyclization, HBTU proved to be a better activating agent than FDPP. We are still examining a more stereoselective synthetic route to the ring analog, but before the additional investment of time is made, we would like to see if the final product(s) have any bioactivity and warrant further investigation.

Experimental Section

Provided in the supporting information are the analytical data for the intermediates (**6**−**18**, **3**, and **35**) prepared previously[18,27,39] in our group. All spectroscopic data confirmed the isolation of these important intermediates.

General Procedures. All manipulations were conducted under an inert atmosphere (argon or nitrogen). All solvents were reagent grade. Anhydrous ether, tetrahydrofuran (THF), benzene, and toluene were distilled from sodium and/or benzophenone ketyl. Dichloromethane (CH_2Cl_2) and dichloroethane (DCE) were distilled from calcium hydride (CaH_2). *N*,*N*-Dimethylformamide (DMF) and acetonitrile were distilled from phosphorus pentoxide and calcium hydride. Methanol was distilled from magnesium and iodine. Organic acids and bases were reagent grade. Triethylamine (Et_3N), diisopropylethylamine (*i*-Pr_2NEt), and *N*-methylmorpholine (NMM) were distilled from calcium hydride. All other reagents were commercial compounds of the highest purity available. Analytical purification and structure determination techniques were carried out using previously reported procedures.[43]

(1*S*,2*S*,3*R*)-3-Hydroxy-2-methoxycyclohexanecarboxylic Acid (21). To a mixture of lactone **12** (0.538 g, 3.44 mmol) and THF (35 mL) at 0 °C was added a cooled 0.20 M aqueous solution of LiOH (35 mL) dropwise over a 10 min period. After being stirred at 0 °C for 30 min and rt for 16 h, the solution was concentrated to one-half volume. The resulting aqueous mixture was washed with diethyl ether (Et_2O, 2 × 5 mL). The Et_2O layers were extracted with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layers were combined, acidified to pH 4 with 1 N aqueous $KHSO_4$, and then extracted with ethyl acetate (EtOAc, 3 × 40 mL). The resulting organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to afford the product **21** as a white solid (0.594 g, 99% yield): mp 83−85 °C; R_f 0.29 (10:90 MeOH:$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22−1.26 (m, 1H), 1.61 (dq, J = 3.8, 11.4 Hz, 1H), 1.68−1.75 (m, 3H), 1.78 (ddd, J = 4.2, 8.6, 17.4 Hz, 1H), 2.48 (ddd, J = 2.8, 4.3, 10.8 Hz, 1H), 3.53 (s, 3H), 3.66−3.69 (m, 1H), 3.94 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 21.7, 29.4, 45.5, 60.3, 71.6, 80.4, 178.4; IR (neat) 2760−3620 (br), 2940 (s), 2860 (m), 1705 (s), 1455 (w), 1445 (w), 1370−1420 (m), 1300 (m), 1260 (m), 1215 (m), 1180 (m), 1145 (m), 1105 (m), 1075 (s), 980 (w) cm^{-1}; HRMS m/z calcd for $C_8H_{15}O_4$ ($M + H^+$) 175.0970, found 175.0973; $[\alpha]^{20}_D$ +1.98° (c = 1.42, $CHCl_3$).

(1*S*,2*S*)-2-Methoxy-3-oxocyclohexanecarboxylic Acid (22). To a solution of hydroxy acid **21** (0.432 g, 2.48 mmol) and acetone (15.0 mL) at 0 °C was added a solution of CrO_3 (0.497 g, 4.97 mmol) in H_2SO_4 (0.523 mL) and H_2O (2.02 mL) dropwise over a 20 min period.[42] The reaction was stirred at 0 °C for 1 h and then at rt overnight. Ice/H_2O (∼20 mL) was added to dissolve the precipitate that formed, and the resulting solution was poured into an additional amount of ice/H_2O (∼50 mL). The aqueous layer was extracted with Et_2O (3 × 150 mL). If the organic layer was light green, it was washed with additional volumes of H_2O (50 mL each). The resulting organic solution was washed with saturated aqueous NaCl (30 mL), dried ($MgSO_4$), filtered, and concentrated to afford the product **22** (0.380 g, 89% yield) as a white solid: mp 125−126 °C; R_f 0.36 (10:90 MeOH:$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66−1.73 (m, 1H), 1.97 (dt, J = 4.2, 14.1 Hz, 1H), 2.06−2.20 (m, 3H), 2.25−2.30 (m, 1H), 2.63−2.69 (m, 1H), 2.96−3.00 (m, 1H), 3.39 (s, 3H), 3.86 (d, J = 3.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.9, 23.8, 38.1, 48.4, 58.2, 83.3, 177.0, 208.5; IR (neat) 2360−3580 (b), 2950 (s), 1735 (s), 1700 (s), 1460 (w), 1440 (m), 1420 (m), 1275 (m), 1250 (m), 1215 (m), 1180 (s), 1135 (m), 1110 (s), 1065 (m), 1005 (m), 900 (m) cm^{-1}; HRMS m/z calcd for $C_8H_{12}O_4$ (M^+) 172.0736, found 172.0735; $[\alpha]^{20}_D$ −14.6° (c = 0.445, $CHCl_3$).

(1*S*,2*S*)-2-Methoxy-3-oxocyclohexanecarbonyl Fluoride (23). To a solution of acid **22** (372 mg, 2.16 mmol) in CH_2Cl_2 (10.0 mL) between −20 and −30 °C was added pyridine (175 μL, 2.16 mmol) followed by cyanuric fluoride (0.584 mL, 6.48 mmol) dropwise.[40,41] The reaction was kept at this temperature for 1 h, followed by addition of crushed ice (20 g) and additional CH_2Cl_2 (100 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with ice-cold H_2O (10 mL), dried ($MgSO_4$), filtered, and concentrated to afford the acid fluoride **23** (376 mg, 99% yield), which was immediately utilized in the next step.

(1*S*,2*S*,3*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-2-(methoxymethoxy)-3-methylbutyl (1*S*,2*S*)-2-Methoxy-3-oxocyclohexanecarboxylate (24). A solution of **4** (1.04 g, 3.24 mmol) in THF (32 mL) was prepared and cooled to −78 °C. A solution of either sodium hexamethyldisilazane (NaHMSA, 4.32 mL 0.75 M in THF) or *n*-BuLi (2.03 mL 1.6 M in hexane) was added dropwise and the mixture stirred at −78 °C for 30 min and then at 0 °C for 10 min. The previously prepared acid fluoride (**23**) in THF (2.0 mL) was added at this temperature and the resulting mixture stirred for 10 min and then at rt for 4 h. The solution was concentrated to an oily residue and diluted with EtOAc (200 mL). The organic solution was washed with 5% aqueous HCl (30 mL), 5% aqueous $NaHCO_3$ (30 mL), and saturated NaCl (30 mL), dried ($MgSO_4$), filtered, and concentrated. The crude oil was purified by flash column chromatography, eluting with EtOAc:petroleum ether (5:95) to remove unreacted **4** (2.31 g) and then eluting with EtOAc:petroleum ether (10:90:15:85) to obtain **24** (0.718 g, 70% yield) as a colorless oil: R_f 0.47 (20:80 EtOAc:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.87 (d, J = 7.9 Hz, 3H), 0.88 (s, 9H), 0.89 (d, J = 3.0 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 1.62−1.66 (m, 1H), 1.74−1.77 (m, 1H), 1.94 (ddd, J = 6.9, 11.5, 18.2 Hz, 1H), 1.98−2.00 (m, 1H), 2.01−2.09 (m, 1H), 2.14 (dt, J = 3.6, 13.7 Hz, 1H), 2.24 (dt, J = 5.0, 13.6 Hz, 1H), 2.65−2.70 (m, 1H), 2.88 (dt, J = 4.2, 10.1 Hz, 1H), 3.32 (s, 3H), 3.34 (s, 3H), 3.44−3.53 (m, 2H), 3.80 (dd, J = 3.3, 7.1 Hz, 1H), 3.83 (dd, J = 2.4, 3.4 Hz, 1H), 4.61 (AB, J = 6.5, 13.7 Hz, 2H), 5.02 (dd, J = 4.6, 7.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4, −5.3, 10.9, 16.2, 18.2, 19.7, 23.0, 24.2, 25.9, 28.8, 37.4, 38.0, 49.3, 56.0, 57.8, 65.0, 78.7, 79.2, 83.7, 98.6, 171.0, 209.4; IR (neat) 2940−2970 (s), 2890−2910 (m), 2860 (m), 1730 (s), 1465 (m), 1425 (w), 1390 (m), 1295 (w), 1255 (s), 1210 (m), 1160−1190 (m), 1135 (m), 1100 (s), 1040 (s), 920 (m) cm^{-1}; HRMS m/z calcd for $C_{24}H_{50}NSiO_7$ (M + NH_4^+) 492.3357, found 492.3349; $[\alpha]^{20}_D$ −43.9° (c = 0.900, $CHCl_3$).

(1*S*,2*S*,3*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-2-(methoxymethoxy)-3-methylbutyl (1*S*,2*S*)-3-(*N*-Benzylamino)-2-methoxycyclohexanecarboxylate (25).[37,38] To a solution of ketone **24** (0.575 g, 1.21 mmol) and 1,2-dichloroethane (DCE, 12.1 mL) was added benzylamine (0.145 mL, 1.33 mmol) followed by HOAc (69.3 μL, 1.21 mmol). Sodium triacetoxyborohydride (385 mg, 1.82 mmol) was then added to the mixture. The reaction was stirred at rt for 4 h. The solution was quenched with saturated aqueous $NaHCO_3$ (20 mL), and the product was extracted with EtOAc (3 × 75 mL), dried ($MgSO_4$), filtered, and concentrated to afford **25** (678 mg, 99% yield) as a 1:1 diastereomeric mixture: R_f 0.43 (10:90 MeOH:$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.042 and 0.048 (s, 6H), 0.87−0.94 (m, 9H), 0.889 and 0.893 (s, 9H), 1.35−1.40 (m, 1H), 1.42−1.51 (m, 1H), 1.69−1.88 (m, 6H), 2.24−2.28 (m, 1H), 2.44−2.49 (m, 1H), 2.94 (ddd, J = 4.2, 10.0, 14.1 Hz, 1H), 3.19 and 3.33 (s, 3H), 3.35 and 3.56 (s, 3H), 3.42−3.55 (m, 2H), 3.63−3.96 (m, 4H), 4.57−4.65 (m, 2H), 5.02 and 5.07 (dd, J = 3.9, 7.9 Hz, 1H), 7.22−7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.52, −5.46, 10.6, 11.0, 15.9, 16.0, 18.2, 18.7, 19.2, 19.8, 22.0, 24.0, 25.9, 25.9, 26.9, 27.1, 28.8, 28.9, 29.8, 30.7, 37.4, 37.5, 44.6, 45.2, 47.8, 50.6, 51.0, 51.3, 55.95, 55.98, 56.1, 56.6, 65.0, 65.3, 77.8, 78.2, 78.3, 78.5, 78.6, 98.49, 98.55, 126.8, 126.9, 127.1, 128.0, 128.1, 128.3, 128.4, 141.0, 173.2, 175.0 (diastereomers present in NMR); IR (neat) 3320 (w), 3090 (w), 3070 (w), 3040 (m), 2860−2980 (s), 1730 (s), 1600 (w), 1580 (w), 1525 (w), 1495 (m), 1460 (s), 1405 (m), 1360−1390 (m), 1310 (m), 1215−1255 (s), 1200 (s), 1125−1170 (s), 1085 (s), 1035 (s), 985 (m), 920 (m) cm^{-1}; HRMS m/z calcd for $C_{31}H_{56}SiNO_6$ (M + H^+) 566.3877, found 566.3866; $[\alpha]^{20}_D$ −0.191° (c = 1.70, $CHCl_3$).

(1*S*,2*S*,3*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-2-(methoxymethoxy)-3-methylbutyl (1*S*,2*S*)-3-Amino-2-methoxycyclohexanecarboxylate (26). Under a hydrogen atmosphere (40 psi), secondary amine **25** (0.683 g, 1.21 mmol) was combined with MeOH:EtOAc (1:1, 10.0 mL) and 10% Pd/C (0.444 g, 20.7 mmol) and shaken in a Parr apparatus for 8 h. The slurry was filtered through Celite followed by thorough washing with MeOH:EtOAc. The filtrate was concentrated *in vacuo*, and the residue was azeotroped with toluene several times to give the product **26** as an oil (20.7 mg, 99% yield): R_f 0.11 (10:90 MeOH:$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.048 and 0.051 (s, 6H), 0.88−0.94 (m, 9H), 0.89 and 0.90 (s, 9H), 1.43−1.67 (m, 2H), 1.69−1.83 (m, 3H), 1.85−1.98 (m, 2H), 2.28−2.40 (m, 1H), 2.64−2.68 (m, 1H), 2.77−2.84 (m, 1H), 3.335 and 3.339 (s, 3H), 3.355 and 3.363 (s, 3H), 3.42−3.56 (m, 3H), 3.78−3.83 (m, 1H), 4.59−4.68 (m, 2H), 5.02−5.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.53, −5.47, 10.9, 16.0, 18.2, 19.8, 22.2, 25.8, 28.8, 28.9, 30.7, 37.4, 43.7, 47.8, 56.0, 56.5, 65.0, 78.3, 78.5, 78.6, 98.6, 174.4 (diastereomers present in NMR); IR (neat) 3280−3400 (w), 2930−2970 (s), 2870 (s), 1730 (s), 1670 (w), 1580 (w), 1565 (w), 1545 (w), 1530 (w), 1460 (m), 1355−1385 (m), 1255 (s), 1125−1170 (s), 1095 (s), 1035 (s), 920 (m) cm^{-1}; HRMS m/z calcd for $C_{24}H_{50}SiNO_6$ (M + H^+) 476.3407, found 476.3425; $[\alpha]^{20}_D$ −15.0° (c = 1.26, $CHCl_3$).

***N*-[*N*-[*N*-(Benzyloxycarbonyl)-L-leucyl]-L-prolyl]-3-(*p*-methoxyphenyl)-*N*-methyl-L-alanine, Ester with (1*S*,2*S*)-3-[(2*S*,3*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-hydroxybutyramido]-2-methoxycyclohexanecarboxylic Acid, (1*S*,2*S*,3*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-2-(methoxymethoxy)-3-methylbutyl Ester (27).**[17,43] **Method A.** To acid **3** (1.42 g, 1.88 mmol) in THF (30 mL) at −15 °C was added dropwise NMM (1.88 mL of a 1.0 M solution in THF, 1.88 mmol). To this solution was added isopropenyl chloroformate (IPCF, 1.88 mL of a 1.0 M solution in THF, 1.88 mmol) dropwise.[44,45] The mixture was stirred for 3 min, and then amine **26** (0.815 g, 1.71 mmol) was added in THF (∼2 mL). After the solution was warmed to 0 °C with stirring for 30 min, it was stirred at rt for 3 h. The mixture was then concentrated *in vacuo*. The resulting residue was diluted with Et_2O (150 mL) and washed with 5% aqueous citric acid (15 mL), 5% aqueous $NaHCO_3$ (15 mL), and saturated aqueous NaCl (15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude oil was purified by flash column chromatography eluting with EtOAc:petroleum ether (15:85−60:40) to afford the product (**27**, 1.25 g, 55% yield) as a clear oil.

Method B. Acid **3** (0.888 g, 1.18 mmol) was dissolved in anhydrous THF (25 mL) at 0 °C, and NMM (141 μL, 1.28 mmol) was added with stirring. To this solution was added BOP (0.568 g, 1.28 mmol) and then amine **26** (0.511 g, 1.07 mmol).[46] A catalytic amount of DMAP (26.1 mg, 0.214 mmol) was added, followed by stirring at 0 °C for 30 min. The mixture was stirred at rt overnight and then quenched with saturated aqueous NaCl (5 mL). The mixture was diluted with EtOAc (100 mL), and the layers were separated. The organic layer was washed with 5% aqueous HCl (10 mL), 5% aqueous $NaHCO_3$ (10 mL), and saturated aqueous NaCl (10 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated to an oil. The crude residue was purified by flash column chromatography, eluting with EtOAc:petroleum ether (15:85−60:40). Compound **27** was obtained (0.845 g, 65% yield) as a clear oil: R_f 0.71 (50:50 EtOAc:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.036−0.045 (s, 6H), 0.82−0.99 (m, 15H), 0.890 and 0.892 (s, 9H), 1.22−1.30 (m, 1H), 1.24 and 1.26 (s, 3H), 1.32 and 1.35 (s, 9H), 1.41−1.50 (m, 1H), 1.52−1.63 (m, 2H), 1.64−1.84 (m, 6H), 1.84−1.96 (m, 3H), 2.12−2.25 (m, 2H), 2.32−2.41 (m, 1H), 2.70 and 2.71 (s, 3H), 2.72−2.93 (m, 2H), 3.19 and 3.30 (s, 3H), 3.20−3.29 (m, 1H), 3.32 and 3.35 (s, 3H), 3.42−3.53 (m, 2H), 3.58−3.76 (m, 3H), 3.73 and 3.79 (s, 3H), 3.97−4.02 (m, 1H), 4.23−4.46 (m, 1H), 4.51−4.68 (m, 3H), 4.70−4.76 (m, 1H), 4.83−4.99 (m, 2H), 5.02−5.28 (m, 3H), 5.67−5.70 (m, 1H), 6.68−6.72 (m, 1H), 6.79−6.84 (m, 2H), 7.00−7.05 (m, 1H), 7.06−7.11 (m, 2H), 7.25−

7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.46, −5.52, 10.5, 10.6, 11.0, 11.2, 14.0, 14.6, 15.8, 16.2, 18.15, 18.20, 18.8, 19.3, 19.8, 19.9, 21.0, 21.4, 22.9, 23.4, 23.7, 23.8, 24.5, 24.7, 24.9, 25.2, 25.3, 25.9, 28.0, 28.1, 28.2, 28.7, 28.87, 28.90, 29.5, 29.7, 30.3, 30.4, 33.6, 34.0, 37.4, 38.1, 38.7, 39.2, 44.3, 46.2, 46.9, 47.7, 51.3, 51.7, 54.7, 55.1, 55.2, 55.4, 55.7, 55.9, 56.0, 56.9, 57.3, 61.7, 65.2, 65.5, 66.1, 66.3, 66.8, 68.1, 71.7, 71.9, 78.1, 78.4, 78.65, 78.74, 79.2, 80.1, 80.2, 80.8, 98.5, 98.7, 113.9, 114.0, 127.5, 127.7, 127.8, 128.18, 128.25, 130.1, 130.2, 130.3, 130.5, 136.8, 155.1, 155.3, 156.1, 156.7, 158.4, 158.5, 168.8, 169.1, 169.2, 169.6, 171.2, 171.5, 171.6, 172.0, 172.3, 173.8 (diastereomers present in NMR); IR ($CHCl_3$) 3420 (w), 3330 (w), 2960 (m), 2940 (m), 1725 (s), 1705 (s), 1660 (m), 1640 (s), 1545 (w), 1510 (m), 1450 (m), 1365 (m), 1250 (s), 1160 (m), 1095 (m), 1035 (m) cm^{-1}; HRMS *m/z* calcd for $C_{63}H_{101}N_5SiO_{16}Na$ (M + Na^+) 1234.6910, found 1234.6887; $[\alpha]^{20}_D$ −52.8° (*c* = 0.895, $CHCl_3$).

***N*-[*N*-[*N*-(Benzyloxycarbonyl)-L-leucyl]-L-prolyl]-3-(*p*-methoxyphenyl)-*N*-methyl-L-alanine, Ester with (1*S*,2*S*)-3-[(2*S*,3*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-hydroxybutyramido]-2-methoxycyclohexanecarboxylic Acid, (1*S*,2*S*,3*R*)-4-Hydroxy-1-isopropyl-2-(methoxymethoxy)-3-methylbutyl Ester (28).** To compound **27** (0.822 g, 0.678 mmol) in THF (3.00 mL) was added HOAc:H_2O (3:1, 12.0 mL) dropwise. The reaction was stirred at rt for 24 h and then diluted with toluene (100 mL) and concentrated. The residue was diluted with toluene (100 mL) again and azeotroped until no HOAc remained. The crude oil was purified by flash column chromatography, eluting with EtOAc:petroleum ether (50:50) followed by MeOH:$CHCl_3$ (5:95−10:90) to afford **28** (0.702 g, 94% yield) as a solid: mp 86−88 °C; R_f 0.19 (50:50 EtOAc:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80−0.99 (m, 15H), 1.26 and 1.27 (s, 3H), 1.31 and 1.35 (s, 9H), 1.35−1.50 (m, 2H), 1.52−1.94 (m, 11H), 2.02−2.09 (m, 1H), 2.12−2.41 (m, 2H), 2.70 and 2.71 (s, 3H), 2.74−2.94 (m, 2H), 3.20 and 3.35 (s, 3H), 3.23−3.34 (m, 1H), 3.43−3.52 (m, 2H), 3.395 and 3.403 (s, 3H), 3.57−3.76 (m, 3H), 3.77 and 3.79 (s, 3H), 3.97−4.17 (m, 1H), 4.23−4.43 (m, 1H), 4.49−4.57 (m, 2H), 4.60−4.73 (m, 3H), 4.82−4.96 (m, 2H), 5.07−5.28 (m, 3H), 5.58−5.71 (m, 1H), 6.68−6.85 (m, 1H), 6.79−6.85 (m, 2H), 7.00−7.04 and 7.68−7.73 (m, 1H), 7.05−7.09 (m, 2H), 7.25−7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.9, 10.2, 14.1, 14.6, 14.2, 15.4, 15.5, 18.8, 19.4, 19.9, 20.0, 21.0, 23.4, 23.5, 24.7, 24.8, 24.9, 25.2, 25.4, 26.7, 27.8, 28.1, 28.4, 28.6, 29.0, 29.4, 29.5, 29.7, 33.6, 33.7, 36.3, 38.1, 38.8, 39.1, 39.7, 44.2, 46.3, 46.9, 47.2, 51.0, 51.7, 54.7, 55.1, 55.2, 55.4, 56.4, 56.5, 57.3, 60.4, 64.2, 65.7, 66.1, 66.3, 71.7, 71.9, 78.5, 78.7, 78.9, 79.1, 79.3, 80.2, 98.8, 99.2, 113.9, 114.0, 127.5, 127.7, 127.8, 128.2, 128.3, 130.0, 130.2, 130.3, 130.4, 136.7, 155.1, 155.3, 156.7, 158.4, 158.5, 158.8, 168.7, 169.2, 169.7, 171.1, 171.2, 171.5, 171.6, 172.2, and 173.6 (diastereomers present in NMR); IR ($CHCl_3$) 3420 (w), 3330 (m), 2950 (s), 2930 (s), 2870 (m), 1720 (s), 1700 (s), 1635 (s), 1515 (m), 1505 (s), 1450 (s), 1365 (m), 1300 (m), 1245 (s), 1205 (s), 1155 (s), 1100 (m), 1020 (s) cm^{-1}; HRMS *m/z* calcd for $C_{57}H_{87}N_5O_{16}Na$ (M + Na^+) 1120.6046, found 1120.6083; $[\alpha]^{20}_D$ −53.4° (*c* = 0.810, $CHCl_3$).

***N*-[*N*-[*N*-(Benzyloxycarbonyl)-L-leucyl]-L-prolyl]-3-(*p*-methoxyphenyl)-*N*-methyl-L-alanine, Ester with (1*S*,2*S*)-3-[(2*S*,3*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-hydroxybutyramido]-2-methoxycyclohexanecarboxylic Acid, (1*S*,2*S*,3*S*)-1-Isopropyl-2-(methoxymethoxy)-3-methylbutanoic Acid Ester (29).** To a mixture of the Dess−Martin periodinane reagent (0.702 g, 0.639 mmol)[47] and CH_2Cl_2 (10.0 mL) at rt was added a solution of alcohol **28** (0.352 g, 0.831 mmol) in CH_2Cl_2 (0.763 mL) dropwise. The reaction was stirred for 45 min at this temperature and then diluted with Et_2O (75 mL). This slurry was poured into saturated aqueous $NaHCO_3$ (40 mL) containing $Na_2S_2O_3{\cdot}5H_2O$ (1.65 g). After the mixture was stirred for 5 min, an additional amount of Et_2O (75 mL) was added. The combined organic layers were washed with saturated aqueous $NaHCO_3$ (40 mL) and H_2O (30 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in *t*-BuOH (5.00 mL), keeping the temperature at 25 °C. To this solution was added 5% aqueous NaH_2PO_4 (3.30 mL) followed by 1 M aqueous $KMnO_4$ (5.00 mL) dropwise.[48] The reaction was stirred at 25 °C for 50 min, at which time Et_2O (160 mL) was added. After the solution was cooled to 0 °C, saturated aqueous Na_2SO_3 (274 drops) was added with efficient stirring. A 10% aqueous HCl solution was added until the aqueous layer was pH 3 (use caution not to go below). The aqueous layer was extracted with EtOAc (100 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to obtain the product (704 mg, 99% yield) as a white solid. The crude material (**29**) from this oxidation sequence was used directly in the next step without purification: mp 102−104 °C; R_f 0.55 (10:90 MeOH:$CHCl_3$); ^{1}H NMR (500 MHz, MeOH-d_4) δ 0.83 (d, *J* = 6.7 Hz) and 0.89−1.00 (m, 12H), 1.11 and 1.17 (dd, *J* = 7.1 Hz, 3H), 1.22−1.30 (m, 3H), 1.30−1.38 (m, 1H), 1.38 and 1.40 (s, 9H), 1.42−1.50 (m, 2H), 1.52−1.87 (m, 8H), 1.93−2.10 (m, 2H), 2.11−2.28 (m, 2H), 2.43−2.91 (m, 3H), 2.80 and 2.83 (s, 3H), 3.12−3.24 (m, 1H), 3.24 and 3.30 (s, 3H), 3.29 and 3.37 (s, 3H), 3.45−3.81 (m, 2H), 3.761 and 3.764 (s, 3H), 4.01−4.12 (m, 2H), 4.48−4.68 (m, 4H) and 4.75−4.82 (m, 1H), 4.82−4.92 (m, 3H) 4.92−5.12 (m, 3H), 6.61−6.70 (m, 1H), 6.83−6.91 (m, 2H), 6.68−7.24 and 7.41−7.46 (m, 1H), 7.10−7.18 (m, 2H), 7.24−7.40 (m, 5H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 11.8, 12.3, 15.5, 17.3, 17.5, 19.8, 20.1, 21.3, 21.4, 23.8, 23.9, 25.9, 26.4, 28.66, 28.69, 29.4, 29.9, 30.0, 34.5, 39.3, 40.7, 42.2, 46.2, 46.9, 48.2, 52.7, 53.3, 55.7, 56.3, 57.4, 57.6, 58.6, 62.3, 66.1, 67.48, 67.55, 72.7, 72.9, 79.2, 79.4, 80.1, 80.4, 80.8, 99.1, 114.97, 115.0, 128.71, 128.75, 128.9, 129.36, 129.42, 130.7, 131.0, 131.3, 131.5, 138.0, 157.4, 158.48, 158.54, 160.0, 160.3, 170.8, 171.3, 172.0, 172.8, 173.5, 173.6, 174.2, 176.0, 177.6, 177.7 (diastereomers present in NMR); IR ($CHCl_3$) 3440 (w), 3330 (m), 3010 (m), 2980 (s), 2950 (s), 2880 (m), 1730 (s), 1710 (s), 1645 (s), 1585 (w), 1550 (m), 1530 (m), 1515 (s), 1470 (m), 1455 (s), 1370 (m), 1250 (s), 1165 (s), 1105 (m), 1035 (s) cm^{-1}; HRMS *m/z* calcd for $C_{57}H_{85}N_5O_{17}Na$ (M + Na^+) 1134.5838, found 1134.5892; $[\alpha]^{20}_D$ −53.8° (*c* = 0.960, $CHCl_3$).

***N*-[*N*-(L-Leucyl)-L-prolyl]-3-(*p*-methoxyphenyl)-*N*-methyl-L-alanine, Ester with (1*S*,2*S*)-3-[(2*S*,3*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-hydroxybutyramido]-2-methoxycyclohexanecarboxylic Acid, (1*S*,2*S*,3*S*)-1-Isopropyl-2-(methoxymethoxy)-3-methylbutanoic Acid Ester (30).** Under a hydrogen atmosphere (40 psi), Cbz-protected amine **29** (0.662 g, 0.595 mmol) was combined with MeOH:EtOAc (1:1, 10.0 mL) and 10% Pd/C (0.220 g, 10.3 mmol) and shaken in a Parr apparatus for 24 h. The slurry was filtered through Celite, followed by thorough washing with MeOH:EtOAc. The filtrate was concentrated *in vacuo*, and the residue was azeotroped with toluene several times to give the product **30** as an oil (576 mg, 99% yield): R_f 0.34 (10:90 MeOH:$CHCl_3$); ^{1}H NMR (500 MHz, MeOH-d_4) δ 0.86−1.05 (m, 12H), 1.11−1.19 (m, 3H), 1.28−1.43 (m, 2H), 1.43−1.56 (m, 12H), 1.56−1.96 (m, 10H), 1.99−2.09 (m, 2H), 2.10−2.35 (m, 2H), 2.47−2.56 (m, 2H), 2.78-3.15 (m, 6H), 3.20−3.26 (m, 1H), 3.26−3.37 (m, 3H), 3.42−3.69 (m, 2H), 3.75−3.78 (m, 3H), 4.05−4.18 (m, 2H), 4.23−4.56 (m, 3H), 4.59−4.68 (m, 3H), 4.80−4.97 (m, 3H), 5.02−5.55 (m, 1H), 6.80−6.89 (m, 2H), 7.09−7.17 (m, 2H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 10.8, 10.9, 14.5, 17.4, 19.4, 20.2, 20.9, 21.5, 21.6, 23.8, 25.3, 25.6, 28.5, 28.69, 28.74, 29.4, 30.0, 31.9, 34.4, 41.3, 44.2, 47.1, 51.8, 55.7, 55.8, 56.5, 56.7, 61.5, 70.2, 72.8, 73.7, 80.3, 80.5, 81.1, 81.2, 99.3, 115.0, 115.3, 130.6, 131.1, 131.3, 131.8, 157.8, 160.0, 160.2, 171.0, 171.1, 173.3, 175.8, 176.1, 180.0 (diastereomers present in NMR); IR (neat) 3180−3630 (br), 2960 (s), 2940 (s), 2880 (m), 2830 (w), 1725 (s), 1660 (s), 1635 (s), 1550 (w), 1515 (s), 1440−1470 (m), 1250 (s), 1200−1220 (m), 1165 (s), 1100 (m), 1080 (m), 1035 (s) cm^{-1}; HRMS *m/z* calcd for $C_{49}H_{79}N_5O_{15}Na$ (M + Na^+) 1000.5471, found 1000.5433; $[\alpha]^{20}_D$ −45.4° (*c* = 0.940, $CHCl_3$).

Cyclo[*N*-(*tert*-butyloxycarbonyl)-*O*-[[[*N*-[(2*S*,3*S*,4*S*)-4-[[(1*S*,2*S*)-3-amino-2-methoxycyclohexanecarbonyl]oxy]-3-(methoxymethoxy)-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl]-*N*,*O*-dimethyl-L-tyrosyl]-L-threonyl] (31). The unprotected linear precursor (acid **30**, 0.400 g, 0.409 mmol) was dissolved in DMF (40.5 mL). To this solution was added *i*-Pr_2NEt (0.169 mL, 0.969 mmol) followed by the coupling reagent (HBTU, 0.147 g, 0.388 mmol).[50] The reaction was stirred at rt for 3 h, the solvent distilled, and the residue diluted with EtOAc (100 mL). The ether extract was washed with 5% aqueous HCl (10 mL), 5% aqueous $NaHCO_3$ (10 mL),

and saturated aqueous NaCl (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with acetone:$CHCl_3$ (1:99−25:75) to obtain the product **31** as an oil (0.254 g, 52% yield): R_f 0.33 (20:80 acetone:$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (d, J = 2.6 Hz) and 0.84 (d, J = 4.2 Hz, 3H), 0.82 (d, J = 2.1 Hz) and 0.88 (d, J = 3.1 Hz, 3H), 0.93 (d, J = 3.6 Hz) and 0.97 (d, J = 6.5 Hz, 3H), 1.03 (d, J = 6.6 Hz) and 1.07 (d, J = 6.8 Hz, 3H), 1.17−1.21 (m, 3H), 1.34 (d, J = 6.3 Hz) and 1.37 (d, J = 6.7 Hz, 3H), 1.38−1.50 (m, 3H), 1.42 and 1.53 (s, 9H), 1.55−1.92 (m, 9H), 1.92-2.17 (m, 2H), 2.20−2.34 (m, 1H), 2.63−2.88 (m, 2H), 2.92 and 3.00 (s, 3H), 3.12-3.22 (m, 2H), 3.40 and 3.44 (s, 3H), 3.41 and 3.43 (s, 3H), 3.43−4.59 (m, 1H), 3.63−3.97 (m, 2H), 3.77 and 3.79 (s, 3H), 3.99 (d, J = 10.0 Hz, 1H), 4.18−4.60 (m, 2H), 4.60−5.84 (m, 4H), 4.92−5.06 (m, 2H), 5.40−5.54 (m, 1H), 6.27−6.32 (m) and 6.50 (d, J = 8.1 Hz, 1H), 6.80 (d, J = 8.6 Hz) and 6.84 (d, J = 8.6 Hz, 2H), 6.99−7.19 (m, 2H), 7.35 (d, J = 8.2 Hz) and 8.02−8.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 17.1, 17.5, 19.0, 19.4, 20.7, 21.1, 22.6, 23.7, 24.4, 25.2, 27.7, 28.2, 28.9, 29.3, 29.7, 30.7, 34.8, 41.6, 42.0, 42.5, 46.4, 48.5, 49.6, 55.2, 55.4, 56.4, 57.8, 59.0, 62.1, 72.6, 78.0, 78.8, 79.8, 81.1, 98.9, 113.8, 114.2, 129.1, 129.8, 130.8, 155.4, 158.7, 168.9, 170.4, 172.2, 172.3, 172.7, 174.4 (diastereomers present in NMR); IR (neat) 3326 (m), 2935 (s), 1731 (s), 1645 (s), 1584 (w), 1514 (s), 1456 (m), 1367 (m), 1301 (m), 1249 (m), 1167 (s), 1090 (m), 1044 (m) cm^{-1}; HRMS m/z calcd for $C_{49}H_{77}N_5O_{14}Na$ (M + Na^+) 982.5365, found 982.5379; $[\alpha]^{20}_D$ −17.4° (c = 1.17, $CHCl_3$).

Cyclo[*N*-(*tert*-butoxycarbonyl)-*O*-[[[*N*-[(2*S*,3*S*,4*S*)-4-[(1*S*,2*S*)-3-amino-2-methoxycyclohexanecarbonyl]oxy]-3-hydroxy-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl]-*N*,*O*-dimethyl-L-tyrosyl]-L-threonyl] (32). To a solution of MOM ether **31** (0.254 g, 0.265 mmol) in CH_2Cl_2 (5.8 mL) at −78 °C was added dropwise a solution of dimethylboron bromide (1.5 M, 0.533 mL) in CH_2Cl_2.[51,52] After 1 h at −78 °C, the reaction mixture was transferred *via* cannula into a vigorously stirred mixture of THF (3.7 mL) and saturated aqueous $NaHCO_3$ (1.85 mL). After 5 min, the mixture was diluted with Et_2O (75 mL) and the resulting organic layer washed with H_2O (7.5 mL), 10% aqueous $NaHSO_4$ (7.5 mL), and saturated aqueous NaCl (7.5 mL). The aqueous layers were extracted with Et_2O, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography, eluting with acetone:$CHCl_3$ (2:98−26:74) to afford **32** (186 mg, 77% yield) as an oil: R_f 0.20 (20:80 acetone:$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77−0.98 (m, 9H), 1.02 (d, J = 6.8 Hz, 3H), 1.22−1.28 (m, 1H), 1.30−1.48 (m, 6H), 1.43 and 1.53 (s, 9H), 1.53−1.74 (m, 6H), 1.74−2.02 (m, 4H), 2.02−2.20 (m, 2H), 2.22−2.41 (m, 2H), 2.52−2.80 (m, 1H), 2.91 and 2.99 (s, 3H), 2.93−3.22 (m, 3H), 3.39 and 3.48 (s, 3H), 3.42−3.67 (m, 2H), 3.70−3.94 (m, 1H), 3.78 and 3.79 (s, 3H), 4.01 (d, J = 8.7 Hz, 1H), 4.11−4.51 (m, 2H), 4.53−4.87 (m, 3H), 4.91−5.12 (m, 2H), 5.42−5.60 (m, 1H), 6.24−6.38 (m, 1H), 6.85 (d, J = 8.5 Hz) and 6.91 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 7.9 Hz) and 7.16 (d, J = 6.1 Hz, 2H), 8.06−8.17 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.2, 17.1, 18.9, 19.1, 20.6, 22.4, 23.7, 24.4, 24.7, 25.2, 27.4, 28.3, 29.1, 29.8, 30.6, 35.1, 41.8, 42.6, 43.4, 46.3, 49.5, 55.2, 55.32, 55.34, 57.8, 58.8, 62.0, 71.8, 72.2, 78.3, 79.4, 81.1, 113.1, 114.2, 129.1, 129.7, 130.1, 155.3, 158.7, 168.1, 168.9, 170.5, 171.9, 172.1, 174.3 (diastereomers present in NMR); IR (neat) 3295 (m), 2960 (s), 2873 (m), 1726 (s), 1659 (s), 1650 (s), 1644 (s), 1514 (s), 1454 (m), 1367 (m), 1302 (m), 1249 (s), 1215 (m), 1176 (s), 1088 (m), 1059 (m) cm^{-1}; HRMS m/z calcd for $C_{47}H_{73}N_5O_{13}Na$ (M + Na^+) 938.5103, found 938.5106; $[\alpha]^{20}_D$ −16.9° (c = 0.850, $CHCl_3$).

Cyclo[*N*-(*tert*-butoxycarbonyl)-*O*-[[[*N*-[(2*S*,3*S*,4*S*)-4-[(1*S*,2*S*)-3-amino-2-methoxycyclohexanecarbonyl]oxy]-3-oxo-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl]-*N*,*O*-dimethyl-L-tyrosyl]-L-threonyl] (33). To a mixture of the Dess−Martin periodinane reagent (73.3 mg, 0.173 mmol) and CH_2Cl_2 (3.5 mL) at rt was added a solution of alcohol **32** (122 mg, 0.133 mmol) in CH_2Cl_2 (3.5 mL) dropwise. The reaction was stirred for 2 h at this temperature and then diluted with Et_2O (35 mL). This mixture was poured into a saturated aqueous $NaHCO_3$ solution (7 mL) containing $Na_2S_2O_3{\cdot}5H_2O$ (416 mg) and stirred ∼5 min. Another 35 mL of Et_2O was added, and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (7 mL) and H_2O (7 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by flash column chromatography, eluting with acetone:$CHCl_3$ (1:99−20:80) to afford **33** (85.4 mg, 70% yield) as a clear oil: R_f 0.85 (20:80 acetone:$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75−1.02 (m, 12H), 1.05−1.40 (m, 6H), 1.40−1.78 (m, 8H), 1.43 and 1.46 (s, 9H), 1.80−2.25 (m, 5H), 2.26−2.64 (m, 3H), 2.69 and 2.74 (s, 3H), 2.86−3.24 (m, 2H), 3.24−3.43 (m, 1H), 3.26 and 3.32 (s, 3H), 3.48−3.79 (m, 2H), 3.79 and 3.80 (s, 3H), 3.91−4.46 (m, 2H), 4.49−4.94 (m, 3H), 4.99−5.18 (m, 2H), 5.47−5.69 (m, 1H), 6.05−6.22 (m, 1H), 6.80−6.97 (m, 2H), 7.02−7.15 (m, 2H), 7.33 (d, J = 8.6 Hz) and 8.35 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2, 13.5, 15.1, 16.8, 17.4, 18.0, 18.4, 18.9, 19.0, 21.0, 21.3, 23.4, 23.8, 24.0, 24.3, 24.6, 26.0, 28.1, 28.3, 29.2, 29.7, 30.2, 32.5, 33.2, 38.6, 39.2, 40.3, 43.8, 46.2, 46.5, 46.8, 48.8, 49.0, 50.2, 50.3, 53.3, 55.22, 55.25, 55.3, 55.9, 56.7, 57.7, 57.8, 66.5, 67.3, 70.8, 71.2, 79.3, 79.7, 79.9, 81.0, 81.7, 84.2, 113.8, 114.0, 129.9, 130.0, 130.1, 130.4, 155.1, 158.4, 158.7, 168.9, 169.0, 170.1, 171.1, 171.3, 172.2, 203.4, 204.3 (diastereomers present in NMR); IR (neat) 3306 (m), 2935 (m), 2871 (w), 1741 (s), 1640 (s), 1514 (s), 1452 (m), 1367 (m), 1302 (m), 1248 (s), 1168 (s), 1124 (w), 1098 (m) cm^{-1}; HRMS m/z calcd for $C_{47}H_{71}N_5O_{13}Na$ (M + Na^+) 936.4946, found 936.4930; $[\alpha]^{20}_D$ −80.5° (c = 0.940, $CHCl_3$).

Cyclo[*O*-[[[*N*-[(2*S*,3*S*,4*S*)-4-[(1*S*,2*S*)-3-amino-2-methoxycyclohexanecarbonyl]oxy]-3-oxo-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl]-*N*,*O*-dimethyl-L-tyrosyl]-L-threonyl] Hydrochloride (34). A solution of ketone **33** (70.0 mg, 76.6 μmol) in EtOAc (7.4 mL) was cooled to −30 °C. Gaseous HCl was introduced at such a rate that the temperature of the mixture was maintained between −10 and −20 °C at saturation. After being stirred for 1 h at this temperature, it was stirred at 0 °C for 1 h. The solution was then purged with N_2 for about 30 min, maintaining the temperature at 0 °C. After the solution was concentrated, the residue was triturated and washed by decantation with three 1.0 mL portions of *tert*-butyl methyl ether:hexane (1:4). The product was collected by filtration and dried *in vacuo* after recrystallization from MeOH:toluene to provide the hydrochloride salt (**34**, 58.6 mg, 90% yield) as a white solid: mp 183−185 °C; R_f 0.31 and 0.34 (10:90 MeOH:$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.73−1.11 (m, 12H), 1.11−1.18 (m, 1H), 1.22−1.47 (m, 6H), 1.47−1.97 (m, 10H), 1.97−2.47 (m, 4H), 2.68 (s, 3H), 2.69−2.91(m, 1H), 2.91−3.30 (m, 2H), 3.30 and 3.41 (s, 3H), 3.40−3.63 (m, 3H), 3.63−3.74 (m, 1H), 3.77 and 3.79 (s, 3H), 3.80−4.01 (m, 1H), 4.13−4.98 (m, 4H), 5.03−5.11 (m, 1H), 5.13−5.27 (m, 1H), 6.71−6.88 (m, 2H), 6.94−7.14 (m, 2H), 7.63−7.75 and 8.05−8.20 (m, 1H), 8.20−9.24 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 14.7, 17.6, 17.8, 18.0, 18.3, 18.9, 19.3, 20.4, 20.6, 21.3, 21.5, 22.6, 23.5, 23.8, 24.7, 26.4, 26.9, 28.1, 28.5, 28.9, 29.7, 30.4, 31.2, 31.5, 32.6, 32.9, 33.3, 38.6, 39.5, 41.3, 41.6, 42.2, 43.4, 46.1, 46.8, 47.4, 47.6, 49.4, 49.7, 49.1, 50.2, 52.4, 55.2, 54.0, 55.2, 56.9, 57.9, 58.0, 58.8, 66.3, 69.4, 71.7, 73.0, 79.2, 81.6, 81.8, 83.8, 114.0, 114.2, 129.5, 129.7, 130.0, 130.4, 158.5, 158.9, 166.5, 166.8, 168.6, 169.3, 170.7, 170.9, 171.0, 171.5, 172.4, 172.8, 174.2, 174.5, 203.6, 204.5 (diastereomers present in NMR); IR (neat) 3310 (br), 2960 (s), 1732 (s), 1634 (s), 1558 (m), 1514 (s), 1456 (m), 1388 (w), 1369 (w), 1302 (w), 1248 (m), 1177 (m), 1091 (m) cm^{-1}; HRMS m/z calcd for $C_{42}H_{63}N_5O_{11}$-Na (M − HCl + Na^+) 836.4422, found 836.4438; $[\alpha]^{20}_D$ −91.5° (c = 0.865, $CHCl_3$).

Cyclo[*N*-(*N*-L-lactyl-L-prolyl-*N*-methyl-D-leucyl)-*O*-[[[*N*-[(2*S*,3*S*,4*S*)-4-[(1*S*,2*S*)-3-amino-2-methoxycyclohexanecarbonyl]oxy]-3-oxo-2,5-dimethylhexanoyl]-L-leucyl]-L-prolyl]-*N*,*O*-dimethyl-L-tyrosyl]-L-threonyl] (2b). To a mixture of the constrained macrocycle amine salt (**34**, 30.0 mg, 35.3 μmol) and the didemnin B side chain (**35**, 13.3 mg, 42.4 μmol) in CH_2Cl_2 (2.0 mL) at 0 °C were added BOP (23.4 mg, 53.0 μmol) and NMM (8.9 mg, 9.7 μL, 88.3 μmol).[46] After 30 min at 0 °C, the reaction mixture was allowed to warm to rt and stir for an additional 4 h. The solution was then treated with saturated aqueous NaCl (2 mL) and extracted with EtOAc (10 mL). The organic layer was washed with 5% aqueous HCl (1 mL), 5% aqueous $NaHCO_3$, and saturated aqueous NaCl (1 mL), dried ($MgSO_4$), filtered, and concentrated. The crude

residue was purified by flash column chromatography, eluting with MeOH:$CHCl_3$ (3:97) to afford the product (**2b**, 18.0 mg, 46% yield) as an off-white solid in a 1:1 diastereomeric mixture: R_f 0.30 and 0.46 (20:80 acetone:$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78−1.14 (m, 18H), 1.17−1.28 (m, 6H), 1.28−1.40 (m, 3H), 1.40−1.46 (m, 3H), 1.46−1.65 (m, 5H), 1.65−2.27 (m, 11H), 2.27−2.41 (m, 2H), 2.41−2.54 (m, 1H), 2.63-2.78 (m, 1H), 2.69 and 2.79 (s, 3H), 2.83−2.95 (m, 1H), 2.90 and 3.08 (s, 3H), 3.17−3.43 (m, 1H), 3.30 and 3.33 (s, 3H), 3.48−3.77 (m, 5H), 3.78 and 3.79 (s, 3H), 3.81−4.18 (m, 2H), 4.29−4.52 (m, 2H), 4.52−4.76 (m, 2H), 4.77−4.97 (m, 2H), 4.97−5.22 (m, 2H), 5.22−5.37 (m, 1H), 5.42−5.64 (m, 1H), 6.64−6.73 and 6.88−6.95 (m, 1H), 6.79−6.87 (m, 2H), 7.02 (d, J = 8.5 Hz) and 7.06 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 6.8 Hz) and 7.55−7.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 14.0, 14.8, 16.3, 17.7, 17.9, 18.2, 18.4, 18.8, 18.9, 19.3, 19.4, 20.3, 21.2, 21.65, 21.74, 22.0, 22.3, 22.6, 23.4, 23.7, 23.8, 24.2, 24.5, 24.9, 25.0, 25.3, 25.87, 25.93, 27.5, 28.0, 28.2, 28.3, 29.5, 29.7, 30.1, 30.6, 31.3, 31.6, 32.3, 32.8, 34.1, 34.3, 35.5, 39.3, 39.5, 43.6, 45.2, 45.9, 46.1, 46.8, 47.2, 48.8, 49.2, 49.6, 50.6, 53.1, 54.6, 55.2, 55.29, 55.33, 55.4, 55.8, 56.5, 57.0, 57.1, 57.4, 57.5, 58.8, 59.0, 62.8, 65.6, 65.9, 67.8, 70.4, 71.2, 72.7, 72.8, 75.9, 80.2, 80.9, 83.9, 113.9, 114.2, 129.2, 130.0, 130.1, 130.2, 158.3, 158.7, 168.7, 169.6, 170.5, 170.6, 171.1, 171.2, 172.2, 173.5, 174.8, 203.5 (diastereomers present in NMR); IR (neat) 3386 (br), 2957 (s), 1734 (m), 1635 (s), 1514 (m), 1451 (m), 1369 (w), 1248 (m), 1169 (m), 1098 (m) cm^{-1}; HRMS m/z calcd for $C_{57}H_{87}N_7O_{15}Na$ ($M + Na^+$) 1132.6158, found 1132.6187; $[\alpha]^{20}_D$ −19.8° (c = 0.313, $CHCl_3$).

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Abbreviations: *N*-[(benzyloxy)carbonyl]-5-norbornene-2,3-dicarboximide (BCN); *N*,*N*-bis(2-oxo-3-oxazolidinyl)-phosphonic chloride (BOP-Cl); 1,1-carbonyldiimidazole (CDI); tetrabutylammonium fluoride (TBAF).

Supporting Information Available: Analytical data for intermediates **6**−**18**, **3**, and **35** and copies of NMR spectra of these as well as all new compounds (65 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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